

Señor

SUPERINTENDENTE DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES

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SUPERINDUSTRIA Y COMERCIO
Radacion : 00016006 00000001
Fecha (AMD): 2000-03-23 15:44:44
Tramite : 002 PATENTES D 1 REGISTRO/ 029 COMPLEMEN
Dependencia: 0029 DIVISION DE NUEVAS CREACIONES

E. _____ S _____ D. _____

Re: P1.- MERCK & CO, INC.-Solicitud de Patente de Invención para
"ACIDO ABIERTO DIHIDROXI Y SALES DE INHIBIDORES
DE REDUCTASA DE HMG-CO-A".-Clase A61.-Expediente
número 00-016.006.-

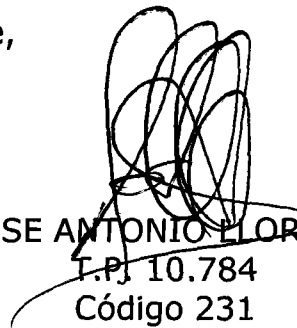
1. Me refiero a mi solicitud arriba nombrada de 6 de Marzo de 2000.
2. Anexos me permito presentar a usted:
 - (1) Copias autenticas (3) de las primeras solicitudes de patente presentadas para el invento arriba nombrado **respecto de las cuales reclamo prioridad**, a saber:
 - (a) La solicitud estadinense número 60/123.247 del 8 de Marzo de 1999, junto con su traducción oficial No. LLC-040-2000, **correspondiente a las legalizaciones y reivindicaciones de dicho documento;**
 - (b) La solicitud estadinense número 09/264.745 del 9 de Marzo de 1999, junto con su traducción oficial No. LLC-039-2000, **correspondiente a las legalizaciones y reivindicaciones de dicho documento;**
 - (c) La solicitud estadinense número PCT/US00/2627 del 2 de Febrero de 2000, junto con su traducción oficial No. LLC-056-2000, **correspondiente a las legalizaciones y reivindicaciones de dicho documento;**

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(2) Copia debidamente autenticada por el Notario Sexto del Circulo de Bogotá, de los documentos que acreditan la calidad de Traductor Oficial del señor Gabriel Rueda Chadid quien elaboró la traducción de las solicitudes estadinenses número 60/123.247 , 09/264.745 y PCT/US00/02627, respecto de las cuales se reivindica prioridad en el presente caso.

3. Ruego a usted tomar atenta nota de lo anterior y proceder de conformidad.

Señor Superintendente,


JOSE ANTONIO FLOREDA
T.P. 10.784
Código 231

EL SUSCRITO JEFE DEL AREA DE
LEGALIZACIONES DE MINISTERIO DE
RELACIONES EXTERIORES

HACE CONSTAR

que el señor Gabriel Rueda, se encuentra debidamente
registrado ante este Ministerio, como traductor e
intérprete oficial para los idiomas INGLES -ESPAÑOL,
ESPAÑOL - INGLES.

Para efectos de ésta certificación el interesado presentó
copia autenticada de la certificación del Ministerio de
Justicia acerca de la vigencia de la resolución
1982.

Dada en Santafé de Bogotá, D.C., a 19 de octubre de 1994
(19) del mes de diciembre de 1994

Neibón Sánchez Torres
Jefe Área de Legalizaciones

COMO NOTARIO SEXTO ENCARGADO
DE SANTAFÉ DE BOGOTÁ
HAGO CONSTAR

QUE LA FOTOCOPIA COINCIDE CON LA FOTOCOPIA
AUTÉNTICA QUE HE TENIDO A LA VISTA

SANTAFÉ DE BOGOTÁ, 03 SEI 1998

PABLO MENDEZ BARAJAS

NST/gtm.

COMO NOTARIO SEXTO DE
SANTAFÉ DE BOGOTÁ
HAGO CONSTAR

QUE LA FOTOCOPIA COINCIDE CON LA FOTOCOPIA
AUTÉNTICA QUE HE TENIDO A LA VISTA

JUAN MANUEL BOTERO MEDINA
NOTARIO

20 APR 1999

COMO NOTARIO SEXTO DE
SANTAFÉ DE BOGOTÁ
HAGO CONSTAR

QUE LA FOTOCOPIA COINCIDE CON LA FOTOCOPIA
AUTÉNTICA QUE HE TENIDO A LA VISTA

JUAN MANUEL BOTERO MEDINA
NOTARIO

08 MAR 1999

COMO NOTARIO SEXTO ENCARGADO
DE SANTAFÉ DE BOGOTÁ
HAGO CONSTAR

QUE LA FOTOCOPIA COINCIDE CON LA FOTOCOPIA
AUTÉNTICA QUE HE TENIDO A LA VISTA

SANTAFÉ DE BOGOTÁ, 21 AGO 1998

COMO NOTARIO SEXTO ENCARGADO
DE SANTAFÉ DE BOGOTÁ
HAGO CONSTAR

QUE LA FOTOCOPIA COINCIDE CON LA FOTOCOPIA
AUTÉNTICA QUE HE TENIDO A LA VISTA

SANTAFÉ DE BOGOTÁ, 10 AGO 1999

PABLO MENDEZ BARAJAS

COMO NOTARIO SEXTO DE
SANTAFÉ DE BOGOTÁ
HAGO CONSTAR

QUE LA FOTOCOPIA COINCIDE CON LA FOTOCOPIA
AUTÉNTICA QUE HE TENIDO A LA VISTA

SANTAFÉ DE BOGOTÁ, 05 ENE 1999

COMO NOTARIO SEXTO ENCARGADO DE
SANTAFÉ DE BOGOTÁ
HAGO CONSTAR

QUE LA FOTOCOPIA COINCIDE CON LA FOTOCOPIA
AUTÉNTICA QUE HE TENIDO A LA VISTA

SANTAFÉ DE BOGOTÁ, 01 JUL 1998

JUAN MANUEL BOTERO MEDINA
NOTARIO

COMO NOTARIO SEXTO DE
SANTAFÉ DE BOGOTÁ
HAGO CONSTAR

QUE LA FOTOCOPIA COINCIDE CON LA FOTOCOPIA
AUTÉNTICA QUE HE TENIDO A LA VISTA

SANTAFÉ DE BOGOTÁ, 23 NOV 1998

JUAN MANUEL BOTERO MEDINA
NOTARIO

República de Colombia



Ministerio de Justicia y del Derecho

EL SECRETARIO GENERAL DEL MINISTERIO DE
JUSTICIA Y DEL DERECHO

CERTIFICA:

Se por Resolución 5996 del 29 de noviembre de 1982, le fue expedida
cencia para ejercer funciones de Traductor e Intérprete Oficial en los
idiomas INGLES-ESPAÑOL, ESPAÑOL-INGLES a GABRIEL RUEDA
CHADID, identificado con la cédula de ciudadanía No. 17.124.145
expedida en Bogotá. Que dicha resolución se encuentra vigente en la
fecha.

A solicitud del interesado, en Santafé de Bogotá, los 10
mes de noviembre de 1994.

JORGE LOIS SARRAL SARRAL

COMO NOTARIO SEXTO ENCARGADO
DE SANTAFE DE BOGOTA
HAGO CONSTAR
QUE LA FOTOCOPIA COINCIDE CON LA FOTOCOPIA
AUTENTICA QUE HE TENIDO A LA VISTA.
SANTAFE DE BOGOTA.

PAOLO MENEZ BARAJAS

COMO NOTARIO SEXTO DE
SANTAFE DE BOGOTA
HAGO CONSTAR
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SANTAFE DE BOGOTA.

JUAN MANUEL BOTERO MEDINA
NOTARIO

COMO NOTARIO SEXTO DE
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SANTAFE DE BOGOTA.

JUAN MANUEL BOTERO MEDINA
NOTARIO

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HAGO CONSTAR
QUE LA FOTOCOPIA COINCIDE CON LA FOTOCOPIA
AUTENTICA QUE HE TENIDO A LA VISTA.
SANTAFE DE BOGOTA.

10 AGO 1999

PAOLO MENEZ BARAJAS

COMO NOTARIO SEXTO DE
SANTAFE DE BOGOTA
HAGO CONSTAR
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AUTENTICA QUE HE TENIDO A LA VISTA.
SANTAFE DE BOGOTA.

11 AGO 1998

COMO NOTARIO SEXTO DE
SANTAFE DE BOGOTA
HAGO CONSTAR
QUE LA FOTOCOPIA COINCIDE CON LA FOTOCOPIA
AUTENTICA QUE HE TENIDO A LA VISTA.
SANTAFE DE BOGOTA.

13 NOV 1998

JUAN MANUEL BOTERO MEDINA
NOTARIO

SECRETARIO
GENERAL

COMO NOTARIO SEXTO DE
SANTAFE DE BOGOTA
HAGO CONSTAR
QUE LA FOTOCOPIA COINCIDE CON LA FOTOCOPIA
AUTENTICA QUE HE TENIDO A LA VISTA.
SANTAFE DE BOGOTA.

06 ENE 1999

JUAN MANUEL BOTERO MEDINA
NOTARIO

01 JUL 1998

PAOLO MENEZ BARAJAS

13 SET 1998

TRIBUNAL SUPERIOR DEL DISTRITO JUDICIAL DE SANTAFE DE BOGOTÁ
SECRETARIA GENERAL

LA SUSCRITA SECRETARIA DEL H. TRIBUNAL SUPERIOR DEL DISTRITO JUDICIAL
DE SANTAFE DE BOGOTÁ,

CERTIFICA:

que el Acuerdo No. 183 de diciembre 3 de 1982 emanado de esta Corporación, por medio del cual dió posesión al señor GABRIEL RUEDA CHADID, identificado con Cédula de Ciudadanía No. 9990, de Bogotá, como TRADUCTOR E INTERPRETE OFICIAL de los Idiomas INGLÉS-ESPAÑOL, ESPAÑOL-INGLÉS, en virtud de la Resolución No. 9990, de 1990, se encuentra VIGENTE.

Se expide en Santafé de Bogotá D.C. a dieciseis (16) de noviembre de mil novecientos noventa y cuatro (1994).

MARIA INES RODRIGUEZ TORRES

SECRETARIA

crm./

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COMO NOTARIO SEXTO DE
SANTAFE DE BOGOTÁ
HAGO CONSTAR
QUE LA FOTOCOPIA COINCIDE CON LA FOTOCOPIA
AUTENTICA QUE HE TENIDO A LA VISTA
SANTAFE DE BOGOTÁ

28 ABR. 1999

JUAN MANUEL BOTERO MEDINA
NOTARIO

COMO NOTARIO SEXTO DE
SANTAFE DE BOGOTÁ
HAGO CONSTAR
QUE LA FOTOCOPIA COINCIDE CON LA FOTOCOPIA
AUTENTICA QUE HE TENIDO A LA VISTA
SANTAFE DE BOGOTÁ

08 MAR. 1999

JUAN MANUEL BOTERO
NOTARIO

COMO NOTARIO SEXTO DE
SANTAFE DE BOGOTÁ
HAGO CONSTAR
QUE LA FOTOCOPIA COINCIDE CON LA FOTOCOPIA
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SANTAFE DE BOGOTÁ

10 AGO. 1998

PABLO MENDEZ BARAJAS

COMO NOTARIO SEXTO DE
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QUE LA FOTOCOPIA COINCIDE CON LA FOTOCOPIA
AUTENTICA QUE HE TENIDO A LA VISTA
SANTAFE DE BOGOTÁ

06 ENI. 1999

JUAN MANUEL BOTERO MEDINA
NOTARIO

01 JUL 1998

PABLO MENDEZ BARAJAS
COMO NOTARIO SEXTO DE
SANTAFE DE BOGOTÁ

COMO NOTARIO SEXTO DE
SANTAFE DE BOGOTÁ
HAGO CONSTAR

QUE LA FOTOCOPIA COINCIDE CON LA FOTOCOPIA
AUTENTICA QUE HE TENIDO A LA VISTA
SANTAFE DE BOGOTÁ

02 SET. 1998

PABLO MENDEZ BARAJAS

HAGO CONSTAR
QUE LA FOTOCOPIA COINCIDE CON LA FOTOCOPIA
AUTENTICA QUE HE TENIDO A LA VISTA
SANTAFE DE BOGOTÁ

23 NOV. 1998

JUAN MANUEL BOTERO MEDINA
NOTARIO

Merick 8 CO 300
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C-203574

REF: LLC-040-2000. La presente es Traducción Oficial de un documento presentado originalmente en inglés. Esta traducción es elaborada por Gabriel Rueda Chadid (Traductor Oficial).

ESTADOS UNIDOS DE AMERICA
A TODOS AQUELLOS QUE LLEGAREN A LEER EL CONTENIDO DEL
PRESENTE DOCUMENTO LES CERTIFICAMOS:
DEPARTAMENTO DE LOS ESTADOS UNIDOS

Oficina de Marcas y Patentes de los Estados Unidos

Diciembre 28 de 1999

Se certifica que anexo se encuentra fiel copia de los Registros de la Oficina de Marcas y Patentes de los Estados Unidos correspondientes a los documentos de la patente solicitada y cuya identificación aparece más adelante, la cual cumplió con los requerimientos exigidos para que se otorgue una fecha de presentación de acuerdo con los dispuesto en la Sección 35 USC 111.

Número de Solicitud: 60/123.247
Fecha de presentación: Marzo 8 de 1999

Por autorización del
COMISIONADO DE MARCAS REGISTRADAS Y PATENTES

L. EDELEN

Funcionario Encargado de Certificaciones(Hay firma y sello)

GABRIEL RUEDA CHADID
TRADUCTOR OFICIAL
Resolución 5996 de Nov. 29/82
Ministerio de Justicia

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REIVINDICACIONES

1. Un compuesto que es una forma hidratada de la sal de calcio de la simvastatina de ácido abierto dihidroxi en forma cristalina.

2. El compuesto de la reivindicación 1 que tiene un patrón de difracción de polvos de rayos X que se obtienen utilizando la radiación $\text{CuK}\alpha$ caracterizada por reflexiones en los espacios "d" correspondientes a 30.7, 24.6, 15.9, 11.2, 8.58, 7.31, 6.74, 6.06, 5.35, 5.09, 4.93, 4.60, 3.93, 3.84, 3.67, 3.51 y 3.28Å.

3. El compuesto de la reivindicación 2 que tiene una curva termogravimétrica caracterizada por una pérdida de peso de 6.3% de temperatura ambiente hasta alcanzar un nivel de pérdida de peso a los 175°C aproximadamente que se obtienen bajo un flujo de nitrógeno a un promedio de calefacción de 10°C/minuto.

4. El compuesto de la reivindicación 2 que tiene una curva de calorimetría de escaneo diferencial que se caracteriza por endotermos de temperatura baja con temperaturas pico de 52, 77 y 100°C y calores asociados de 48, 90 y 21J/g, respectivamente, y endotermos de temperatura mas alta en razón de la descomposición a temperaturas pico de 222 y 241°C y calores asociados de 163 y 92J/g que se obtienen bajo un flujo de nitrógeno burbujeante a través de agua a 16.0°C a un promedio de calefacción de 10°C/minuto en copa abierta.


GABRIEL RUEDA CHADID
TRADUCTOR OFICIAL
Resolución 5996 de Nov. 29/82
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5. Un método para inhibir la reductasa HMG-CoA que comprende la administración a un paciente que necesite de dicho tratamiento de una cantidad inhibitoria eficaz del compuesto de la reivindicación 1.

6. El método de la reivindicación 5 donde el compuesto se administra por vía oral.

7. El método de la reivindicación 6 donde el compuesto se administra en forma de dosificación farmacéutica de liberación retardada.

8. El método de la reivindicación 7 donde el compuesto se administra en una forma de dosificación farmacéutica entérica y revestida.

9. El método de la reivindicación 6 donde el compuesto se administra en forma de dosis farmacéutica de liberación en tiempo controlado.

10. El método de la reivindicación 6 donde el compuesto se administra en un instrumento de aplicación de medicamento conformado por:

(A) Un núcleo comprimido que se prepara a partir de una mezcla conformada por:

(i) una cantidad terapéuticamente eficaz del compuesto;

y

(ii) un polímero que en el momento de la hidratación forma partículas microscópicas gelatinosas; y

(B) un revestimiento polimérico insoluble al agua e impermeable a ésta que comprende un polímero y un plastificador, que rodea y se adhiere al núcleo, donde el revestimiento tiene una serie de aperturas formadas que exponen entre 1 y 75% aproximadamente de la superficie del núcleo:

y donde la tasa de liberación del compuesto que sale del instrumento está en función del número y tamaño de aberturas.

11. Un método para, el tratamiento de la hipercolesterolemia que comprende la administración a un paciente que necesite de dicho tratamiento una cantidad terapéuticamente eficaz del compuesto de la reivindicación 1.

12. Un método para prevenir o reducir el riesgo de desarrollo de la enfermedad aterosclerótica que comprende la administración de una cantidad profilácticamente eficaz del compuesto de la reivindicación 1 a una persona que se encuentre en riesgo de desarrollar la mencionada enfermedad aterosclerótica.

13. El método de la reivindicación 12 donde la enfermedad aterosclerótica se selecciona del grupo de enfermedades cardiovasculares, cerebrovasculares y de los vasos periféricos.

14. El método de la reivindicación 13 donde la enfermedad cardiovascular es una enfermedad coronaria cardíaca.

15. Un método para prevenir o reducir el riesgo de desarrollo de la enfermedad aterosclerótica que comprende la administración de una cantidad profilacticamente eficaz del compuesto de la reivindicación 2 a una persona que se encuentre en riesgo de desarrollar la mencionada enfermedad aterosclerótica.

16. Un método para el tratamiento de la enfermedad aterosclerótica que comprende la administración de una cantidad terapéuticamente eficaz del compuesto de la reivindicación 1 a una persona que padezca la mencionada enfermedad aterosclerótica.

17. El método de la reivindicación 16 donde la enfermedad aterosclerótica se selecciona del grupo de enfermedades cardiovasculares, cerebrovasculares y de vasos periféricos.

18. El método de la reivindicación 17 donde la enfermedad cardiovascular es una enfermedad cardíaco coronaria.

19. Un método para el tratamiento de la enfermedad aterosclerótica que comprende la administración de una cantidad terapéuticamente eficaz del compuesto de la reivindicación 2 a una persona que padezca de la enfermedad aterosclerótica.

20. Un método para prevenir o reducir el riesgo de ocurrencia o recurrencia de un evento de enfermedad aterosclerótica que comprende la administración de una

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cantidad terapéuticamente eficaz del compuesto de la reivindicación 1 a una persona que se encuentre en riesgo de padecer un evento de enfermedad aterosclerótica.

21. El método de la reivindicación 20 donde la persona que recibe el compuesto padece la enfermedad aterosclerótica.

22. El método de la reivindicación 20 donde la persona que recibe el compuesto se encuentra en riesgo de desarrollar la enfermedad aterosclerótica.

23. El método de la Reivindicación 20, donde el evento de la enfermedad aterosclerótica se selecciona del grupo de eventos de enfermedad cardíaco coronaria, eventos cerebrovascular y claudicación intermitente.

24. El método de la Reivindicación 23 donde el evento de enfermedad cardíaco coronaria se selecciona a partir de la muerte por enfermedad cardíaco coronaria, infarto del miocardio y procedimientos de revascularización coronaria.

25. El método de la Reivindicación 23 donde el evento cerebrovascular se selecciona a partir de un accidente cerebrovascular y de un ataque isquémico transitorio.

26. Un método para prevenir o reducir el riesgo de ocurrencia o recurrencia de un evento de enfermedad aterosclerótica que comprende la administración de una cantidad terapéuticamente eficaz del compuesto de la

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GABRIEL RUEDA CHADID
TRADUCTOR OFICIAL
Resolución 5996 de Nov. 29/82
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Reivindicación 2 a una persona que se encuentre en riesgo de padecer un evento de enfermedad aterosclerótica.

27. Una composición farmacéutica que comprende una cantidad terapéuticamente eficaz del compuesto de la Reivindicación 1 y un portador farmacéuticamente aceptable.

28. La composición farmacéutica de la reivindicación 27 que se formula para administración por vía oral.

29. La Composición farmacéutica de la reivindicación 28 que se formula en forma de dosificación de liberación retardada donde la liberación del compuesto proveniente de la forma de dosificación se retarda hasta un momento posterior al paso de la forma de la dosificación a través del estómago.

30. La composición farmacéutica de la Reivindicación 29 donde la forma de dosificación tiene revestimiento entérico.

31. La composición farmacéutica de la Reivindicación 28 que se formula en forma de dosificación de liberación con tiempo controlado.

32. La composición farmacéutica de la reivindicación 28 que se formula en un dispositivo para aplicación del medicamento que consiste en:


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TRADUCTOR OFICIAL
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(A) Un núcleo comprimido que se prepara a partir de una mezcla conformada por:

(i) una cantidad terapéuticamente eficaz del compuesto;

y

(ii) un polímero que en el momento de la hidratación forma partículas microscópicas gelatinosas; y

(B) un revestimiento polimérico insoluble al agua e impermeable a ésta que comprende un polímero y un plastificador, que rodea y se adhiere al núcleo, donde el revestimiento tiene una serie de aperturas formadas que exponen entre 1 y 75% aproximadamente de la superficie del núcleo;

y donde la tasa de liberación del compuesto que sale del instrumento está en función del número y tamaño de aberturas.

33. Un proceso para la preparación de una composición farmacéutica que comprende la combinación del compuesto de la reivindicación 1 con un portador farmacéuticamente aceptable.

34. Un proceso para la preparación de una composición farmacéutica que comprende la combinación del compuesto de la reivindicación 2 con un portador farmacéuticamente aceptable.

35. Una composición farmacéutica que se hace mediante la combinación de una cantidad terapéuticamente eficaz del compuesto de la reivindicación 1 y un portador

G. Rueda Chadid
GABRIEL RUEDA CHADID
TRADUCTOR OFICIAL
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farmacéuticamente aceptable.

36. Una composición farmacéutica que se hace mediante la combinación de una cantidad terapéuticamente eficaz del compuesto de la reivindicación 2 y un portador farmacéuticamente aceptable.

37. Un proceso para la elaboración del compuesto de la reivindicación 2 que comprende los siguientes pasos:

38. Un proceso para elaborar el compuesto de la reivindicación 2 que comprende los siguientes pasos:

A) La combinación de una mezcla de una sal de simvastatina de ácido abierto dihidroxi en un solvente acuoso con hidrato de acetato de calcio para formar una sal amorfa de calcio de simvastatina de ácido abierto dihidroxi, donde el solvente acuoso se selecciona a partir del agua, de una mezcla de solvente orgánico acuso-prótico y una mezcla de solvente orgánico acuoso-aprótico.

B) El envejecimiento de la mezcla resultante a una temperatura hasta de 50°C hasta cuando se produzca la rotación de la sal de calcio amorfa de la simvastatina del ácido abierto dihidroxi hasta formar la sal de calcio cristalina en forma completa de la simvastatina del ácido abierto dihidroxi.

C) La recuperación del sal de calcio cristalina de la simvastatina del ácido abierto dihidroxi por medio de la filtración por succión; y

D) Secado por succión de los cristales recuperados bajo una atmósfera de humedad.

39. El proceso de la reivindicación 38 donde los pasos se cumplen bajo una atmósfera inerte.

40. El proceso de la reivindicación 38 donde el solvente acuoso se selecciona a partir de una mezcla de solvente orgánico acuoso-prótico y de una mezcla de solvente orgánico acuoso-aprótico.

41. El proceso de la reivindicación 40 donde el solvente orgánico prótico se selecciona a partir del grupo conformado por etanol, isopropil alcohol, propanol, tetrahidrofurano, y donde el solvente aprótico se selecciona a partir del grupo conformado por metil eter tert-butilo y tolueno.

42. El proceso de la reivindicación 38 donde el solvente acuoso es una mezcla acuosa de etanol.

43. El proceso de la reivindicación 38 donde en el paso (A), el pH de la mezcla de sal de la simvastatina del ácido abierto dihidroxi en un solvente acuoso se ajusta a 6 y hasta 9 antes de combinarse con el hidrato de acetato de calcio.

44. El proceso de la reivindicación 43 donde el pH se ajusta a un rango de 7 a 8.5.

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45. El proceso de la reivindicación 43 donde el pH se ajusta mediante adición de un ácido mineral a la mezcla.

46. El proceso de la reivindicación 38 donde en el paso (A), el hidrato de acetato de calcio se adiciona en porciones a la mezcla de la sal de la simvastatina del ácido abierto dihidroxi.

47. El proceso de la reivindicación 38 donde en el paso (B), la mezcla se envejece a una temperatura dentro del rango de 10°C hasta 50°C.

48. El proceso de la reivindicación 38 donde en el paso (B), la mezcla se envejece a una temperatura que comprende desde la temperatura ambiente hasta 50°C.

49. El proceso de la reivindicación 38 donde en el paso (B), la mezcla se envejece a una temperatura desde 30°C hasta 35°C.

50. El proceso de la reivindicación 38 donde en el paso (D), la atmósfera de humedad es inerte y tiene una humedad relativa de 40 a 70%.

51. El proceso de la reivindicación 38 donde con posterioridad al paso (C) y con anterioridad al paso (D), se combina un antioxidante con la sal de calcio cristalina recuperada de la simvastatina del ácido abierto dihidroxi en una mezcla de solvente acuoso-aprótico y el material resultante se recupera por medio de la filtración por succión.

gabriel rueda chadid
GABRIEL RUEDA CHADID
TRADUCTOR OFICIAL
Resolución 5996 de Nov. 29/82
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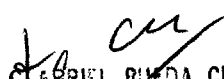
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52. El proceso de la reivindicación 51 donde el paso final del secado por succión se realiza bajo una atmósfera húmeda inerte.

53. El producto elaborado a partir del proceso descrito en la reivindicación 38.

La anterior es Traducción Oficial de un documento presentado originalmente en inglés. Esta traducción fue realizada por GABRIEL RUEDA CHADID (Traductor Oficial). Resolución 5996 del Minjusticia, por lo cual estampo mi Sello y Firmo.

Santafé de Bogotá D.C., Febrero 28 del 2000.


GABRIEL RUEDA CHADID
TRADUCTOR OFICIAL
Resolución 5996 de Nov. 29/82
Ministerio de Justicia



THE UNITED STATES OF AMERICA

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UNITED STATES DEPARTMENT OF COMMERCE

United States Patent and Trademark Office

December 28, 1999

THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM THE RECORDS OF THE UNITED STATES PATENT AND TRADEMARK OFFICE OF THOSE PAPERS OF THE BELOW IDENTIFIED PATENT APPLICATION THAT MET THE REQUIREMENTS TO BE GRANTED A FILING DATE UNDER 35 USC 111.

APPLICATION NUMBER: 60/123,247

FILING DATE: March 08, 1999



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PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53 (C).

03/08/99
1c490 U.S. PTO

CASE NUMBER		20357PV	
INVENTOR(S)			
Given Name (first and middle [if any])	Family Name or Surname	Residence (City and Either State or Foreign Country)	
Paul J. Richard D. Jose M. Feng Edward J. J.	Reider Tillyer Vega Xu Grabowski	Westfield, NJ 07090 Cranford, NJ 07016 Trappe, PA 19426 Staten Island, NY 10310 Westfield, NJ 07090	
☐ Additional inventors are being named on the __ separately numbered sheets attached hereto			
TITLE OF THE INVENTION (280 characters max)			
DIHYDROXY OPEN-ACID AND SALTS OF HMG-CO-A REDUCTASE INHIBITORS			
CORRESPONDENCE ADDRESS			
Merck & Co., Inc. Patent Department - RY60-30 P.O. Box 2000 Rahway			
STATE	New Jersey	ZIP CODE	07065
COUNTRY		U.S.A.	
ENCLOSED APPLICATION PARTS (check all that apply)			
☒ Specification	Number of Pages	35	☐ Small Entity Statement
☒ Drawing(s)	Number of Sheets	3	☐ Other (specify)
METHOD OF PAYMENT OF FILING FEES FOR THIS PROVISIONAL APPLICATION FOR PATENT (check one)			
☐ A check or money order is enclosed to cover the filing fees		FILING FEE AMOUNT (\$)	\$150.00
☒ The Commissioner is hereby authorized to charge filing fees or credit to Deposit Account Number: 13-2755			

1c541 U.S. PTO
60/123247
03/08/99

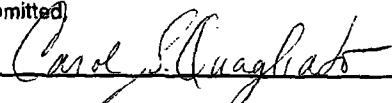
The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

☒ No.

☐ Yes, the name of the U.S. Government agency and the Government contract number are: _____

Respectfully submitted,

SIGNATURE



Date 3/8/99

TYPED or PRINTED NAME

Carol S. Quagliato

REGISTRATION NO.
(if appropriate)

35,330

TELEPHONE 732-594-3809

EXPRESS MAIL CERTIFICATE
DATE OF DEPOSIT March 8, 1999
EXPRESS MAIL NO. 20357PV
I HEREBY CERTIFY THAT THIS CORRESPONDENCE IS
BEING DEPOSITED WITH THE UNITED STATES POSTAL
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ADDRESSEE" BEFORE 5 P.M. ON THE ABOVE DATE IN
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FOR PATENTS, WASHINGTON, D.C. 20590
MAILED BY Carol S. Quagliato
DATE March 8, 1999

InTriplicate



generated form No. P11, Merck & Co., Inc., 12/1/97

TITLE OF THE INVENTION

DIHYDROXY OPEN-ACID AND SALTS OF HMG-CO-A REDUCTASE
INHIBITORS

5 FIELD OF THE INVENTION

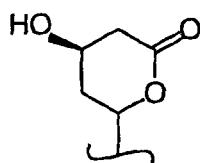
The instant invention relates to the use of dihydroxy open
acid statins and salts thereof, which are inhibitors of 3-hydroxy-3-
methylglutaryl coenzyme A (HMG-CoA) reductase, in a delayed-release
dosage formulation, and to a particular crystalline hydrated form of the
10 calcium salt of dihydroxy open acid simvastatin referred to herein as
compound I.

BACKGROUND OF THE INVENTION

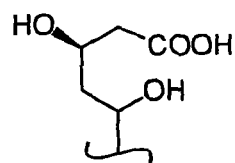
It has been clear for several decades that elevated blood
15 cholesterol is a major risk factor for coronary heart disease (CHD), and
many studies have shown that the risk of CHD events can be reduced by
lipid-lowering therapy. Prior to 1987, the lipid-lowering
armamentarium was limited essentially to a low saturated fat and
cholesterol diet, the bile acid sequestrants (cholestyramine and
20 colestipol), nicotinic acid (niacin), the fibrates and probucol.
Unfortunately, all of these treatments have limited efficacy or
tolerability, or both. With the introduction of lovastatin (MEVACOR®;
see US Patent No. 4,231,938), the first inhibitor of HMG-CoA reductase to
become available for prescription in 1987, for the first time physicians
25 were able to obtain comparatively large reductions in plasma cholesterol
with very few adverse effects.

In addition to the natural fermentation products,
mevastatin and lovastatin, there are now a variety of semi-synthetic and
totally synthetic HMG-CoA reductase inhibitors, including simvastatin
30 (ZOCOR®; see US Patent No. 4,444,784), pravastatin sodium salt
(PRAVACHOL®; see US Patent No. 4,346,227), fluvastatin sodium salt
(LESCOL®; see US Patent No. 5,354,772), atorvastatin calcium salt
(LIPITOR®; see US Patent No. 5,273,995) and cerivastatin sodium salt
(also known as rivastatin; see US Patent No. 5,177,080). The structural
35 formulas of these and additional HMG-CoA reductase inhibitors, are

described at page 87 of M. Yalpani, "Cholesterol Lowering Drugs", Chemistry & Industry, pp. 85-89 (5 February 1996). The HMG-CoA reductase inhibitors described above belong to a structural class of compounds which contain a moiety which can exist as either a 3-hydroxy lactone ring or as the corresponding ring opened dihydroxy open-acid, and are often referred to as "statins." An illustration of the lactone portion of a statin and its corresponding open-acid form is shown below.



Lactone

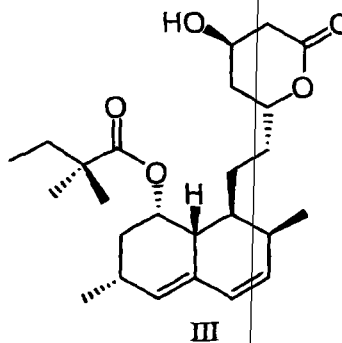
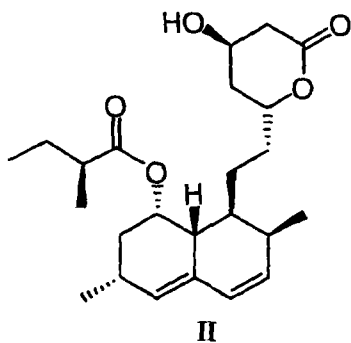


Dihydroxy Open-Acid

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Salts of the dihydroxy open-acid can be prepared, and in fact, as noted above, several of the marketed statins are administered as the dihydroxy open acid salt forms. Lovastatin and simvastatin are marketed worldwide in their lactonized form. Lovastatin is shown as structural formula II, and simvastatin is shown as structural formula III, below.

15



The lactonized forms of the statins are not active inhibitors of HMG-CoA reductase, but the dihydroxy open acid forms are. It is known that

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condensation of the dihydroxy open acid form of statins to the corresponding lactonized form occurs under acidic conditions, that is at about pH 4 or under.

Therefore, due to the low gastric pH of the stomach, a statin conventionally administered by oral dosing in its lactone form will remain largely in its lactone form in the stomach. The vast majority of the drug will still be in the lactone form at the time of absorption from the intestine following oral dosing with the lactone. After absorption, the lactone enters the liver and it is in the hepatocytes that the lactone can be metabolized to the active open acid form, a reaction catalyzed by two hepatic esterases or "lactonases," one which is in the cytosolic and the other in the microsomal fraction. Once in the blood there is an additional plasma esterase which can also hydrolyze the lactone to the open acid. There may be some minimal chemical, i.e., non-enzymatic, hydrolysis that occurs in blood or in the liver; however, at the pH in blood and liver, there should not be any lactonization, i.e., conversion of open acid back to the lactone.

A statin conventionally administered by oral dosing in its dihydroxy open acid form or a pharmaceutically acceptable salt or ester thereof will tend to convert to its lactone form in the acidic environment of the stomach, so that a mixture of the open ring and the corresponding closed ring forms will co-exist there. For example, see M.J. Kaufman, International Journal of Pharmaceutics, 1990, 66(Dec 1), p. 97-106, which provides hydrolysis data that are used to simulate the extent of drug degradation that occurs in acidic gastric fluids following oral administration of several structurally related hypocholesterolemic agents, including simvastatin and lovastatin. Therefore, even after conventional oral dosing with a dihydroxy open acid statin or a salt or ester thereof, a mixture of the open acid and the corresponding lactone form of the drug would exist by the time of absorption from the intestine.

The preparation of the naturally occurring compound lovastatin and the semi-synthetic analog simvastatin leads to a mixture of the lactone and the open-ring dihydroxy acid forms. Several procedures have been published describing ways to make simvastatin from lovastatin, and most proceed through a lactone ring opening step at

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some point in the process and sometimes formation of a salt at the resulting carboxy acid, and end with a ring-closing step in order to make the final simvastatin product. For example, U.S. Patent No. 4,820,850 describes a process for making simvastatin which involves opening the lactone ring of lovastatin and forming an alkyl-amide at the resulting carboxy acid, followed by protection of the two hydroxy groups and methylation of the 8' acyl sidechain. After the methylation step, the hydroxy protecting groups are removed, the amide is hydrolyzed to the free acid and an ammonium salt of the free acid is formed, followed by a step to re-lactonize the ring. In U.S. Patent No. 4,444,784, the 8'-acyl sidechain of lovastatin is removed and the lactone ring opened in the first step, followed by re-lactonization of the ring and protection of its hydroxy group. Next, the 8' position is acylated to introduce the simvastatin sidechain and a deprotection step is performed to obtain the simvastatin final product. In another process disclosed in U.S. Patent No. 4,582,915, the potassium salt of the ring opened form of lovastatin is methylated at the 8' acyl sidechain, the free acid is then re-generated, and the dihydroxy open acid moiety is re-lactonized.

Several pharmaceutically acceptable salt forms of dihydroxy open acid statins are known in the art, as shown by the marketed salt forms of pravastatin, fluvastatin, atorvastatin and cerivastatin described above. Some salt forms of dihydroxy open acid simvastatin have been previously described, for example the ammonium salt and the potassium salt which were used as intermediates in the synthetic processes described above. Chemical Abstracts also discloses a variety of salt forms of dihydroxy open acid simvastatin, including a calcium salt having Registry No. 151006-18-7, which was referenced from a genus disclosed in U.S. Patent No. 5,223,415, assigned to Merck & Co., Inc. Although there are no calcium salts exemplified in the patent, the general description of salt preparation taught in this patent would lead to an amorphous calcium salt product.

Since becoming available, millions of doses of simvastatin have been administered and these drugs have developed an excellent safety record. However, as noted in the Physician's Desk Reference (PDR), in rare instances myopathy has been associated with the use of

all statins, including simvastatin. The mechanism for statin-related myopathy is currently poorly understood. It is also known that many drugs, including certain statins such as simvastatin, are metabolised in the liver and intestine by the cytochrome P450 3A4 (CYP 3A4) enzyme system. As also noted in the PDR, there are adverse drug interaction concerns if a potent inhibitor of CYP3A4, such as itraconazole, and a CYP3A4-metabolized statin are used together, and some cases of myopathy were found to have occurred in patients taking such a drug combination. Simvastatin has been administered to over 20 million patients worldwide in the past 11 years and has been demonstrated to be remarkably safe. However, the very low risk of myopathy is substantially increased when simvastatin is given together with potent inhibitors of CYP3A4. This increased risk is believed to be related to the increased plasma levels of HMG-CoA reductase inhibitory activity resulting from the reduced metabolic elimination of simvastatin in the presence of a potent inhibitor of CYP3A4. While the overall safety record for simvastatin is exceptional, it would be desirable to further optimize its safety profile by reducing the potential for drug interactions with inhibitors of CYP3A4. It would also be desirable to further reduce the already low rate of occurrence of myopathy associated with the use of all statins.

Applicants have now discovered that dihydroxy open acid statins may be less reliant on CYP3A4 metabolism than their closed ring lactonized counterparts. The instant invention involves methods and pharmaceutical compositions for orally administering open-ring dihydroxy open acid statins and salts and esters thereof, which are HMG-CoA reductase inhibitors, in such a way so as to minimize conversion to their lactonized counterparts. This allows for delivery of a dihydroxy open acid statin without its lactone counterpart directly to the absorptive mucosa of the small intestine thus allowing for absorption of the open acid statin into the portal circulation, penetration by active open acid statin into hepatocytes to achieve enhanced efficacy, and systemic exposure consisting of open acid moieties. More particularly, delayed-release of an orally administered dihydroxy open acid statin or a pharmaceutically acceptable salt or ester thereof, for example dihydroxy

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open acid simvastatin or a salt thereof, until after passage through the stomach reduces the amount of lactone formed and absorbed in the body. Maintaining the statin in its open acid form in the body thereby reduces the potential for drug interactions between statins whose metabolism is CYP34A-mediated and other active agents which inhibit the CYP34A enzymatic pathway. Moreover, maintaining the statin in its open acid form in the body may have additional clinical benefits for all statins, even for those statins that are not significantly metabolized by the CYP34A enzymatic pathway.

In addition, a novel crystalline hydrated form of the calcium salt of dihydroxy open acid simvastatin has now been discovered to be a pharmaceutically suitable salt form having desirable physical properties for formulation into an anti-hypercholesterolemic drug composition.

SUMMARY OF THE INVENTION

One object of the instant invention is to provide a method for inhibiting HMG-CoA reductase, as well as for treating and/or reducing the risk for diseases and conditions affected by inhibition of HMG-CoA reductase, comprising orally administering a therapeutically effective amount of a compound selected from a dihydroxy open acid statin and a pharmaceutically acceptable salt or ester thereof in a delayed-release pharmaceutical dosage form to a patient in need of such treatment wherein substantial release of the compound from the dosage form is delayed until after passage of the dosage form through the stomach.

One embodiment of the first object is to provide the above-described method wherein the delayed-release pharmaceutical dosage form is a gel extrusion module (GEM) drug delivery device.

Another embodiment of the first object is to provide the above-described method wherein the delayed-release pharmaceutical dosage form is an enterically coated pharmaceutical dosage form. An additional aspect of this embodiment is to provide the above-described method wherein the delayed-release pharmaceutical dosage form is an enterically coated time controlled-release pharmaceutical dosage form. Yet another aspect of this embodiment is to provide the above-described

method wherein the delayed-release pharmaceutical dosage form is an enterically coated gel extrusion module (GEM) drug delivery device.

The compound used for the above-described object and embodiments may particularly be dihydroxy open acid simvastatin and the pharmaceutically acceptable salts thereof, and more particularly a pharmaceutically acceptable salt thereof.

A second object of the instant invention is to provide novel HMG-CoA reductase inhibitors which are crystalline hydrated forms of the calcium salt of dihydroxy open acid simvastatin, and particularly the compound referred to herein as compound I.

Additional objects are to provide the use of the crystalline hydrated forms of the calcium salt of dihydroxy open acid simvastatin, particularly compound I, for inhibiting HMG-CoA reductase, as well as for treating and/or reducing the risk for diseases and conditions affected by inhibition of HMG-CoA reductase, and also to provide pharmaceutical formulations, including conventional rapid-release, delayed-release and time controlled-release formulations, including the GEM drug delivery device and enterically coated dosage forms, that can be used with the compounds. A further object is to provide a process for making compound I. Additional objects will be evident from the following detailed description.

BRIEF DESCRIPTION OF THE DRAWINGS

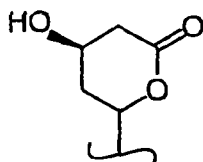
Figure 1 is a thermogravimetry (TG) weight loss curve for compound I obtained under a nitrogen flow at a heating rate of 10°C/minute.

Figure 2 is a differential scanning calorimetry (DSC) curve for compound I obtained under a nitrogen flow bubbled through 16.0°C water at a heating rate of 10°C/minute in an open cup.

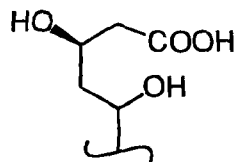
Figure 3 is an x-ray powder diffraction (XRPD) pattern for compound I. The XRPD pattern was obtained using CuK α radiation. The ordinate or Y-axis is x-ray intensity (cpm) and the abscissa or X-axis is the angle two-theta (2 θ) in degrees.

DETAILED DESCRIPTION OF THE INVENTION

- The term "statin(s)" as used herein is intended to be defined as inhibitors of HMG-CoA reductase which belong to a structural class of compounds that contain a moiety which can exist as either a 3-hydroxy lactone ring or as the corresponding ring opened dihydroxy open acid, wherein the lactone portion of the statin and its corresponding dihydroxy open-acid form is shown below.



Lactone



Dihydroxy Open-Acid

- All hydrates, solvates and polymorphic crystalline forms of HMG-CoA reductase inhibitors having the above-described lactone/dihydroxy open acid moiety are included within the scope of the term "statin(s)". Pharmaceutically acceptable salts and esters of the dihydroxy open-acid statins are included within the scope of the term "statin(s)".
- Statins inhibit HMG-CoA reductase in their dihydroxy open acid form. Compounds which have inhibitory activity for HMG-CoA reductase can be readily identified by using assays well-known in the art. For example, see the assays described or cited in U.S. Patent 4,231,938 at col. 6, and WO 84/02131 at pp. 30-33.
- The term "dihydroxy open acid statin(s)" is intended to be defined as statins which contain the dihydroxy open acid moiety, including pharmaceutically acceptable salts and esters thereof. The phrases "dihydroxy open acid statin(s)" and "dihydroxy open acid statin(s) and the pharmaceutically acceptable salts and esters thereof" are used interchangeably herein and are both intended to encompass the open acid and salt and ester forms of the open acid of the statin, unless otherwise indicated. All hydrates, solvates and polymorphic crystalline forms are encompassed within the the scope of the term "dihydroxy open acid statin(s)."

Examples of dihydroxy open acid statins that may be used with the present invention include but are not limited to the dihydroxy open acid forms and pharmaceutically acceptable salts and esters thereof of: lovastatin (see US Patent No. 4,342,767); simvastatin (see US
5 Patent No. 4,444,784), pravastatin, particularly the sodium salt thereof; fluvastatin particularly the sodium salt thereof; atorvastatin, particularly the calcium salt thereof; cerivastatin, particularly the sodium salt thereof, and nisvastatin also referred to as NK-104 (see PCT international publication number WO 97/23200). Pharmaceutically
10 acceptable salts of dihydroxy open acid simvastatin, particularly the crystalline hydrated forms of the calcium salt of dihydroxy open acid simvastatin, and more particularly the hydrated calcium salt of dihydroxy open acid simvastatin referred to herein as compound I, are preferred for use in the methods and compositions of this invention.

15 Herein, the term "pharmaceutically acceptable salts" shall mean non-toxic salts of the compounds employed in this invention which are generally prepared by reacting the free acid with a suitable organic or inorganic base, particularly those formed from cations such as sodium, potassium, aluminum, calcium, lithium, magnesium, zinc
20 and tetramethylammonium, as well as those salts formed from amines such as ammonia, ethylenediamine, N-methylglucamine, lysine, arginine, ornithine, choline, N,N'-dibenzylethylenediamine, chloroprocaine, diethanolamine, procaine, N-benzylphenethylamine, 1-p-chlorobenzyl-2-pyrrolidine-1'-yl-methylbenzimidazole, diethylamine,
25 piperazine, morpholine, 2,4,4-trimethyl-2-pentamine and tris(hydroxymethyl)aminomethane. Pharmaceutically acceptable esters at the carboxylic acid group can be made by treating a dihydroxy open acid statin with an alcohol. Examples of pharmaceutically acceptable esters of dihydroxy open acid statins include, but are not limited to, -C1-
30 4 alkyl and -C1-4 alkyl substituted with phenyl-, dimethylamino-, and acetylamino. "C1-4 alkyl" herein includes straight or branched aliphatic chains containing from 1 to 4 carbon atoms, for example methyl, ethyl, n-propyl, n-butyl, iso-propyl, sec-butyl and tert-butyl.

An object of this invention is to provide methods for
35 reducing the amount of lactonized statin formed and absorbed in the

body after oral administration of a dihydroxy open acid statin in order to achieve enhanced clinical benefits. A way to achieve this is to administer the dihydroxy open acid statin in a delayed-release pharmaceutical dosage form. A delayed-release pharmaceutical dosage form as defined herein is an orally administerable pharmaceutical dosage form or device that does not release a substantial amount of the active compound until after the dosage form has passed through the stomach. Therefore, substantial release of the active compound would initially occur after entry into the duodenum. By "substantial release," it is intended that 90% or more by weight of the active agent in the delayed-release dosage form is released after entry into the duodenum, and that 10% or less by weight of the active agent in the delayed-release dosage form is released in the stomach. Particularly, the amount of active compound released in the stomach before entry into the duodenum is 5% or less by weight and more particularly 1% or less by weight.

It is to be understood that metabolism of the dihydroxy open acid statins will occur, primarily in the liver, after orally dosing in a delayed-release dosage form. However, since lactonization of the dihydroxy open acid statin would have been substantially avoided by use of a delayed release dosage form, the active and inactive metabolites that are formed will also be in the dihydroxy open acid form. In essence, if the dihydroxy open acid statin is administered in a delayed release dosage form, the internal exposure to lactonized parent compound and also to lactonized active and inactive metabolites will be minimized.

One example of a delayed-release dosage form is an enterically coated dosage form. The enteric coating will not dissolve in the acidic gastric environment, but will dissolve in the higher pH environment of the duodenum. An enterically coated dosage form will therefore not permit release of any significant amount of the active compound from the dosage form in the stomach, but, once the enteric coating dissolves in the duodenum, the active compound will be released. Suitable compositions for enteric coatings that can be used with the present invention are known to those of ordinary skill in the pharmaceutical arts; for example, see L. Lachman, The Theory and Practice of Industrial Pharmacy, 3rd Ed., H. Liebermann and J. Kanig

contributors (Lea & Febiger, 1986). The pharmaceutical dosage form that is enterically coated can be a conventional rapid release dosage form or it can be a time controlled-release dosage form. Time controlled-release dosage forms are also well known in the pharmaceutical art, and are designed so as to slowly release the active compound in the body over a period of time, for example over a period of from about 6 to 24 hours. Use of a time controlled-release dosage form is preferred so as to lower the systemic exposure to the active statin.

An example of a delayed-release dosage form that also functions as a time controlled-release dosage form is described in U.S. Patent No. 5,366,738, herein incorporated by reference in its entirety. The controlled-release drug delivery device described in U.S. Patent No. 5,366,738 is known as a gel extrusion module (GEM) delivery device. The GEM device is a drug delivery device for the controlled in situ production and release of a dispersion containing a beneficial agent such as a pharmaceutical drug comprising:

- (A) a compressed core prepared from an admixture comprising:
 - (i) a therapeutically effective amount of the beneficial agent; and
 - (ii) a polymer which upon hydration forms gelatinous microscopic particles; and
- (B) a water insoluble, water impermeable polymeric coating comprising a polymer and a plasticizer, which surrounds and adheres to the core, the coating having a plurality of formed apertures exposing between about 1 and about 75% of the core surface;

and wherein the release rate of the beneficial agent from the device is a function of the number and size of the apertures.

In the GEM device, the polymer inside the compressed core is preferably selected from sodium polyacrylate, carboxypolymethylenes, and the pharmaceutically acceptable salts thereof, wherein the carboxypolymethylenes are prepared from acrylic acid crosslinked with allylethers of sucrose or pentaerythritol, and more preferably it is selected from carboxypolymethylenes prepared from acrylic acid crosslinked with allylethers of sucrose or pentaerythritol, and the

pharmaceutically acceptable salts thereof. Most preferably, CARBOPOL® 974P is used as the polymer inside the compressed core. In addition, the compressed core may also contain one or more polymer hydration modulating agents, anti-oxidants, lubricants, fillers and excipients. An optional subcoating may be applied to the compressed core prior to application of the water insoluble coating as an aid in the manufacturing process. The subcoating may be comprised of, for example, hydroxypropyl cellulose and hydroxypropylmethylcellulose.

The water insoluble, water impermeable polymeric coating is preferably comprised of (1) a polymer selected from polyvinyl chloride, cellulose acetate, cellulose acetate butyrate, ethylcellulose and combinations of these polymers; and (2) a plasticizer selected from diethylphthalate, dibutylsebacate and triethylcitrate. More preferably, the polymeric coating is comprised of cellulose acetate butyrate and triethyl citrate. The GEM device does not function as an osmotic drug delivery device, hence the release function of the device depends on passage of fluids from the external environment of the body to the internal environment of the compressed core through the formed apertures. It is intended that the terms "water insoluble, water impermeable" used to describe the polymeric coating define a coating which is essentially water insoluble and water impermeable, meaning that the polymeric coating allows minimal to no passage of water through the coating from the external environment of the body to the internal environment of the compressed core, except for the fluid passage that occurs through the drilled apertures, during the period of time the drug is being released from the GEM device in the body. Any minimal amount of water that does pass through the water insoluble, water impermeable polymeric coating is insubstantial and does not significantly contribute to the function of the GEM device, i.e. the release rate of the drug through the apertures. Rather the release rate of the drug from the GEM device is a function of the number and size of the apertures on the device.

For an elegant, aesthetically pleasing final product, an overcoat may finally be applied to the GEM delivery device containing colorants, waxes, and the like. The GEM device can also be enterically

coated. Even without enteric coating, extrusion of the polymer which carries the drug out from inside the compressed core of the GEM device does not occur to a substantial extent in the acidic pH of the stomach, therefore substantial release of the drug does not occur in the stomach.

- 5 Further details and examples of the GEM delivery device are described in US Patent No. 5,366,738.

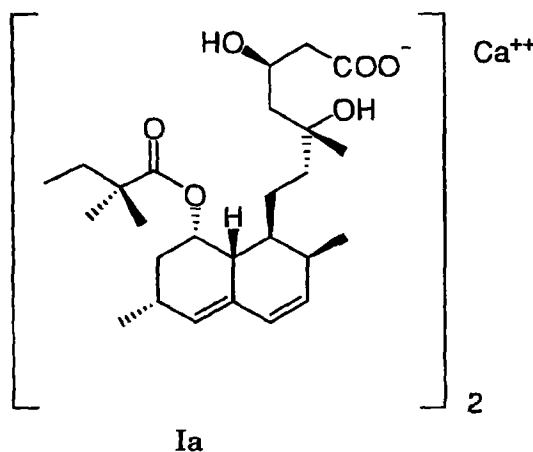
The term "patient" includes mammals, especially humans, who take compound I for the prevention or treatment of a medical condition. Administering of the drug to the patient includes both self-
10 administration and administration to the patient by another person. The patient may be in need of treatment for an existing disease or medical condition, or may desire prophylactic treatment to prevent or reduce the risk for diseases and medical conditions affected by inhibition of HMG-CoA reductase.

15 The term "therapeutically effective amount" is intended to mean that amount of a drug or pharmaceutical agent that will elicit the biological or medical response of a tissue, a system, animal or human that is being sought by a researcher, veterinarian, medical doctor or other clinician. The term "prophylactically effective amount" is
20 intended to mean that amount of a pharmaceutical drug that will prevent or reduce the risk of occurrence of the biological or medical event that is sought to be prevented in a tissue, a system, animal or human by a researcher, veterinarian, medical doctor or other clinician.

Particularly, the dosage a patient receives can be selected so as to
25 achieve the amount of LDL (low density lipoprotein) cholesterol lowering desired; the dosage a patient receives may also be titrated over time in order to reach a target LDL level. The dosage regimen utilizing a dihydroxy open acid statin is selected in accordance with a variety of factors including type, species, age, weight, sex and medical condition of
30 the patient; the severity of the condition to be treated; the potency of the compound chosen to be administered; the route of administration; and the renal and hepatic function of the patient. A consideration of these factors is well within the purview of the ordinarily skilled clinician for the purpose of determining the therapeutically effective or

prophylactically effective dosage amount needed to prevent, counter, or arrest the progress of the condition.

The novel compounds of this invention are the crystalline hydrated forms of the calcium salt of dihydroxy open acid. A particular crystalline hydrated calcium salt of dihydroxy open acid is the one having an x-ray powder diffraction (XRPD) pattern obtained using CuK α radiation characterized by reflections at d-spacings of 30.7, 24.6, 15.9, 11.2, 8.58, 7.31, 6.74, 6.06, 5.35, 5.09, 4.93, 4.60, 3.93, 3.84, 3.67, 3.51 and 3.28Å. For convenience, the crystalline hydrated form of the calcium salt of dihydroxy open acid simvastatin having the above-defined XRPD pattern will also be referred to herein as compound I. Compound I can be represented two-dimensionally as a hydrated form of the following structural formula Ia:



In addition to the XRPD pattern described above, compound I of the instant invention is further characterized by the thermogravimetry (TG) curve shown in Figure I. The TG curve for compound I was obtained under a nitrogen flow at a heating rate of 10°C/minute and is characterized by a 6.3% weight loss from ambient room temperature to a stable weight loss plateau at about 175°C. Additional weight losses due to the onset of decomposition of the compound are observed above about 190°C.

Compound I is still further characterized by the differential scanning calorimetry (DSC) curve shown in Figure 2. The DSC curve for compound I was obtained under a nitrogen flow bubbled through 16.0°C water at a heating rate of 10°C/minute in an open cup, and is characterized by three lower temperature endotherms with peak temperatures of 52, 77 and 100°C and associated heats of 48, 90 and 21 J/g, respectively, and two higher temperature endotherms due to decomposition with peak temperatures of 222 and 241°C and associated heats of 163 and 92 J/g.

Compound I of the instant invention is still further characterized by the ¹H NMR, ¹³C NMR and mass spectral data as given in Example 1 herein.

In the methods of treatment and prophylaxis described herein, as well as the pharmaceutical compositions and medicaments, a dihydroxy open acid statin or a pharmaceutically acceptable salt or ester thereof is employed. Preferably the compound employed is a pharmaceutically acceptable salt of a dihydroxy open acid statin, more preferably it is a pharmaceutically acceptable salt of dihydroxy open acid simvastatin, particularly a crystalline hydrated form of the calcium salt of dihydroxy open acid simvastatin, and most preferably it is compound I. All hydrates, solvates and polymorphic crystalline forms of the above-described compounds and their use are encompassed within scope of the instant invention.

The instant invention provides methods for inhibiting HMG-CoA reductase, and for treating lipid disorders including hypercholesterolemia, hypertriglyceridemia and hyperlipidemia, comprising administering a therapeutically effective amount of a dihydroxy open acid statin to a person in need of such treatment. Further provided are methods for preventing or reducing the risk of developing atherosclerosis, as well as for halting or slowing the progression of atherosclerotic disease once it has become clinically evident, comprising the administration of a prophylactically or therapeutically effective amount, as appropriate, of a dihydroxy open acid statin to a mammal who is at risk of developing atherosclerosis or who already has atherosclerotic disease.

Atherosclerosis encompasses vascular diseases and conditions that are recognized and understood by physicians practicing in the relevant fields of medicine. Atherosclerotic cardiovascular disease, coronary heart disease (also known as coronary artery disease or ischemic heart disease), cerebrovascular disease and peripheral vessel disease are all clinical manifestations of atherosclerosis and are therefore encompassed by the terms "atherosclerosis" and "atherosclerotic disease."

A dihydroxy open acid statin may be administered to prevent or reduce the risk of occurrence, or recurrence where the potential exists, of a coronary heart disease event, a cerebrovascular event, and/or intermittent claudication. Coronary heart disease events are intended to include CHD death, myocardial infarction (i.e., a heart attack), and coronary revascularization procedures. Cerebrovascular events are intended to include ischemic or hemorrhagic stroke (also known as cerebrovascular accidents) and transient ischemic attacks. Intermittent claudication is a clinical manifestation of peripheral vessel disease. The term "atherosclerotic disease event" as used herein is intended to encompass coronary heart disease events, cerebrovascular events, and intermittent claudication. It is intended that persons who have previously experienced one or more non-fatal atherosclerotic disease events are those for whom the potential for recurrence of such an event exists.

Accordingly, the instant invention also provides a method for preventing or reducing the risk of a first or subsequent occurrence of an atherosclerotic disease event comprising the administration of a prophylactically effective amount of a dihydroxy open acid statin to a patient at risk for such an event. The patient may already have atherosclerotic disease at the time of administration, or may be at risk for developing it.

Persons to be treated with the instant therapy include those at risk of developing atherosclerotic disease and of having an atherosclerotic disease event. Standard atherosclerotic disease risk factors are known to the average physician practicing in the relevant fields of medicine. Such known risk factors include but are not limited

to hypertension, smoking, diabetes, low levels of high density lipoprotein (HDL) cholesterol, and a family history of atherosclerotic cardiovascular disease. Published guidelines for determining those who are at risk of developing atherosclerotic disease can be found in: National Cholesterol Education Program, Second report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel II), National Institute of Health, National Heart Lung and Blood Institute, NIH Publication No. 93-3095, September 1993; abbreviated version: Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults, Summary of the second report of the national cholesterol education program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel II), JAMA, 1993, 269, pp. 3015-23. People who are identified as having one or more of the above-noted risk factors are intended to be included in the group of people considered at risk for developing atherosclerotic disease. People identified as having one or more of the above-noted risk factors, as well as people who already have atherosclerosis, are intended to be included within the group of people considered to be at risk for having an atherosclerotic disease event.

The oral dosage amount of the dihydroxy open acid statin, particularly a salt of a dihydroxy open acid statin such as simvastatin, and more particularly a crystalline hydrated form of the calcium salt of dihydroxy open acid simvastatin such as compound I, is from about 1 to 200 mg/day, and more preferably from about 5 to 160 mg/day. However, dosage amounts will vary depending on factors as noted above, including the potency of the particular compound. Although the active drug of the present invention may be administered in divided doses, for example from one to four times daily, a single daily dose of the active drug is preferred.. As examples, the daily dosage amount may be selected from, but not limited to, 5 mg, 10 mg, 20 mg, 25 mg, 40 mg, 50 mg, 75 mg, 80 mg, 150 mg and 160 mg.

The active drug employed in the instant therapy can be administered in such oral forms as tablets, capsules, pills, powders,

granules, elixirs, tinctures, suspensions, syrups, and emulsions. Oral formulations are preferred.

Oral delayed-release formulations are employed with the dihydroxy open acid statins. Examples of suitable formulations include
5 but are not limited to enterically coated pharmaceutical dosage forms such as enterically coated conventional pharmaceutical dosage forms and enterically coated time-controlled release dosage forms, the GEM delivery device, and an enterically coated GEM delivery device.

For the crystalline hydrated forms of the calcium salt of
10 dihydroxy open acid simvastatin, for example compound I, administration of the active drug can be via any pharmaceutically acceptable route and in any pharmaceutically acceptable dosage form. This includes the use of oral conventional rapid-release, time controlled-release and delayed-release (such as described above) pharmaceutical
15 dosage forms. An oral time controlled-release dosage formulation of the instant drug is preferred, and particularly the GEM controlled-release drug delivery device described in U.S Patent No. 5,366,738, herein incorporated by reference in its entirety. Additional suitable
20 pharmaceutical compositions for use with the present invention are known to those of ordinary skill in the pharmaceutical arts; for example, see Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, PA.

In the methods of the present invention, the active drug is typically administered in admixture with suitable pharmaceutical
25 diluents, excipients or carriers (collectively referred to herein as "carrier" materials) suitably selected with respect to the intended form of administration, that is, oral tablets, capsules, elixirs, syrups and the like, and consistent with conventional pharmaceutical practices.

For instance, for oral administration in the form of a tablet
30 or capsule, the active drug component can be combined with a non-toxic, pharmaceutically acceptable, inert carrier such as lactose, starch, sucrose, glucose, modified sugars, modified starches, methyl cellulose and its derivatives, dicalcium phosphate, calcium sulfate, mannitol, sorbitol and other reducing and non-reducing sugars, magnesium
35 stearate, steric acid, sodium stearyl fumarate, glyceryl behenate,

calcium stearate and the like. For oral administration in liquid form, the drug components can be combined with non-toxic, pharmaceutically acceptable inert carrier such as ethanol, glycerol, water and the like. Moreover, when desired or necessary, suitable binders, lubricants, 5 disintegrating agents and coloring and flavoring agents can also be incorporated into the mixture. Stabilizing agents such as antioxidants, for example butylated hydroxyanisole (BHA), 2,6-di-tert-butyl-4-methylphenol (BHT), propyl gallate, sodium ascorbate, citric acid, and calcium metabisulphite, can also be added to stabilize the dosage forms; 10 the use of at least one stabilizing agent is preferred with the instant composition, and preferably an antioxidant is employed with dihydroxy open acid simvastatin or a salt thereof, and particularly compound I. Other suitable components include gelatin, sweeteners, natural and synthetic gums such as acacia, tragacanth or alginates, 15 carboxymethylcellulose, polyethylene glycol, waxes and the like.

The active drug can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, 20 stearylamine or phosphatidylcholines.

Active drug may also be delivered by the use of monoclonal antibodies as individual carriers to which the compound molecules are coupled. Active drug may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinyl- 25 pyrrolidone, pyran copolymer, polyhydroxy-propyl-methacrylamide-phenol, polyhydroxy-ethyl-aspartamide-phenol, or polyethyleneoxide-polylysine substituted with palmitoyl residues. Furthermore, active drug may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, 30 polyglycolic acid, copolymers of polylactic and polyglycolic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates and cross linked or amphipathic block copolymers of hydrogels.

The instant invention also encompasses a process for 35 preparing a pharmaceutical composition comprising combining a

dihydroxy open acid statin with a pharmaceutically acceptable carrier. Also encompassed is the pharmaceutical composition which is made by combining a dihydroxy open acid statin with a pharmaceutically acceptable carrier.

- 5 Additional active agents may be used in combination with the dihydroxy open acid statin in a single dosage formulation, or may be administered to the patient in a separate dosage formulation, which allows for concurrent or sequential administration of the active agents. One or more additional active agents may be administered with a
- 10 dihydroxy open acid statin. The additional active agent or agents can be cholesterol lowering compounds. Examples of additional active agents which may be employed include but are not limited to HMG-CoA synthase inhibitors; squalene epoxidase inhibitors; squalene synthetase inhibitors (also known as squalene synthase inhibitors), acyl-coenzyme
- 15 A: cholesterol acyltransferase (ACAT) inhibitors; microsomal triglyceride transfer protein (MTP) inhibitors; probucol; niacin; fibrates such as clofibrate, fenofibrate, including micronized fenofibrate, and gemfibrozil; cholesterol absorption inhibitors; bile acid sequestrants; LDL (low density lipoprotein) receptor inducers; platelet aggregation
- 20 inhibitors, for example glycoprotein IIb/IIIa fibrinogen receptor antagonists and aspirin; human peroxisome proliferator activated receptor gamma (PPAR γ) agonists including the compounds commonly referred to as glitazones, including those compounds included within the structural class known as thiazolidinediones as well as those PPAR γ
- 25 agonists outside the thiazolidinedione structural class; PPAR dual α/γ agonists; vitamin B₆ (also known as pyridoxine) and the pharmaceutically acceptable salts thereof such as the HCl salt; vitamin B₁₂ (also known as cyanocobalamin); beta-blockers; folic acid or a pharmaceutically acceptable salt or ester thereof such as the sodium salt
- 30 and the methylglucamine salt; and anti-oxidant vitamins such as vitamin C and E and beta carotene.

- A therapeutically effective amount of a crystalline hydrated form of the calcium salt of dihydroxy open acid simvastatin, for example compound I, can be used for the preparation of a medicament useful for
- 35 inhibiting HMG-CoA reductase, as well as for treating and/or reducing

the risk for diseases and conditions affected by inhibition of HMG-CoA reductase, such as preventing or reducing the risk of developing atherosclerotic disease, halting or slowing the progression of atherosclerotic disease once it has become clinically manifest, and preventing or reducing the risk of a first or subsequent occurrence of an atherosclerotic disease event. For example, the medicament may be comprised of about 1 mg to 200 mg of a crystalline hydrated form of dihydroxy open acid simvastatin, or more particularly about 5 mg to 160 mg.

A therapeutically effective amount of a dihydroxy open acid statin can be used for the preparation of a medicament adapted for delayed-release that is useful for inhibiting HMG-CoA reductase, as well as for treating and/or reducing the risk for diseases and conditions affected by inhibition of HMG-CoA reductase, as described above.

The medicament comprised of a dihydroxy open acid statin, for example compound I, may also be prepared with one or more additional active agents, such as those described supra.

Simvastatin is a semi-synthetic product which can be made from the natural product lovastatin. Processes for preparing lovastatin and simvastatin are well documented in the published literature. For example, U.S. Patent No. 4,231,938, herein incorporated by reference, describes a fermentation and isolation process for obtaining lovastatin using the microorganism *Aspergillus terreus*. U.S. Patent No.'s 4,444,784, 4,820,850, 4,916,239 and 4,582,915, herein all incorporated by reference, describe methods for making simvastatin.

Preparation of Compound I

Compound I of the instant invention can generally be prepared as follows. Simvastatin and its dihydroxy open acid counterpart, including compound I, tend to form oxidative by-products; therefore, to minimize the formation of such by-products, it is preferred that the procedures used to make compound I are performed under an inert atmosphere such as nitrogen. Although compound I can be obtained without using an inert atmosphere, the purity of the desired product will not be optimized.

Hydrolysis of the lactone ring of simvastatin can be accomplished by treating simvastatin with at least one equivalent, and preferably a slight excess of one equivalent, of an aqueous base. If more than a slight excess of base is used, the excess base is preferably neutralized before proceeding to the salt formation step in order to prevent formation of insoluble calcium hydroxide or calcium carbonate by-product. The base employed for the hydrolysis can be an aqueous solution of a metal hydroxide or metal carbonate, for example but not limited to sodium hydroxide, potassium hydroxide, lithium hydroxide, sodium carbonate and potassium carbonate. Sodium hydroxide is preferred. The hydrolysis can be performed in water, an aqueous-protic organic solvent mixture, or an aqueous-aprotic organic solvent mixture. Suitable protic organic solvents include but are not limited to methanol (MeOH), ethanol (EtOH), isopropyl alcohol, propanol and tetrahydrofuran (THF). Examples of suitable aprotic organic solvents include but are not limited to *tert*-butyl methyl ether (MTBE) and toluene. An aqueous ethanol solvent mixture is preferred.

After the hydrolysis reaction is complete, the pH of the reaction mixture is adjusted to 6 to 9, preferably 7 to 8.5, by addition of an acid. In this pH range, the dihydroxy open acid simvastatin will exist as a metal salt, for example as the sodium salt if the base used in the hydrolysis step is sodium hydroxide or sodium carbonate. Any acid that is capable of forming a soluble calcium salt such as calcium chloride or calcium citrate, is suitable. A soluble calcium salt is intended to be a salt that is soluble in the solvent system employed in the instant process. Preferably a mineral acid is employed, particularly HCl.

The resulting pH-adjusted reaction mixture containing the metal salt of dihydroxy open acid simvastatin is next combined with a solution of about 0.50 to 0.55 equivalents of calcium acetate hydrate $[\text{Ca}(\text{OAc})_2 \cdot \text{Ca} \cdot x\text{H}_2\text{O}]$ in an aqueous-protic organic solvent mixture, such as water-EtOH. The pH-adjusted reaction mixture can be added to the calcium acetate hydrate solution, or the calcium acetate hydrate solution can be added to the pH-adjusted reaction mixture. The addition can occur all at once, or optionally it can be performed in portions over time with periods of aging. For example, a small portion, e.g., about one-

quarter, of the calcium acetate hydrate solution can be added to the pH-adjusted reaction mixture over a short period of time, for example over about 30 minutes, and then the resulting mixture can be allowed to age for an additional short period of time at room temperature, optionally
5 followed by a further period of aging at a temperature up to about 50°C, for example from about 10°C up to about 50°C, particularly from room temperature up to about 50°C, and more particularly from about 30 to 35°C, after which the remaining calcium acetate hydrate solution can be added in portions over several hours at a temperature up to about 50°C,
10 for example from about 10°C up to about 50°C, particularly from room temperature up to about 50°C, and more particularly from about 30 to 35°C.

Whether the pH-adjusted reaction mixture and the calcium acetate hydrate solution are combined at once or in portions, the
15 resulting slurry must be aged until turnover of the resulting amorphous calcium salt of dihydroxy open acid simvastatin to the crystalline product is complete, usually for at least several hours. Complete turnover to the crystalline product can be assessed by standard techniques in the art, for example, by examining a sample of the product
20 under a microscope. This aging step can be performed at a temperature up to about 50°C, for example from about 10°C up to about 50°C, particularly from room temperature up to about 50°C, and more particularly from about 30 to 35°C. During the aging period or periods, the use of lower temperatures will lead to crystallized product; however,
25 it has been found that as the temperature drops, the rate of crystal turnover becomes slower, making the procedure less time-efficient.

If necessary, the slurry is then allowed to cool to room temperature and is collected by suction filtration, and the recovered solid is suction dried under a moist atmosphere (about 40 to 70% relative
30 humidity), preferably a moist inert atmosphere such as nitrogen. The final step of suction filtration in the recovery of compound I should be done under a moist atmosphere, and preferably a moist inert atmosphere in order to minimize oxidative by-products. If an additional step of adding an antioxidant to compound I is performed, as described

below, then the final suction filtration is the one performed after combining the antioxidant with compound I.

As noted above, compound I has a tendency to oxidize upon contact with air, and one way to minimize oxidation is to perform the reaction sequence under an inert atmosphere. Additionally, an antioxidant such as BHA, BHT, ascorbic acid, or calcium metabisulphite can be combined with compound I. This is simply done by agitating a slurry of compound I with the antioxidant and recovering the resulting solid by suction filtration.

Abbreviations which may appear herein are as follows: EtOH is ethanol; HPLC is high performane liquid chromatography; min. is minutes; h is hour(s); D.I. is de-ionized; NMR is nuclear magnetic resonance; EI MS is electron impact mass spectrum; HR-EI MS is high resolution electron impact mass spectrum; RH is relative humidity.

EXAMPLE 1

Preparation of crystalline hydrated calcium salt of dihydroxy open acid simvastatin (Compound I)

A 22 L four-necked round bottom flask was equipped with a temperature probe, a N₂ inlet, an addition funnel, and an overhead stirrer. 8.0 L of 15% EtOH-H₂O was added and the solution was purged with N₂ for 10 min. Simvastatin (396 g, 0.946 mol) was added, and the slurry was purged with N₂ for 5 min. Then 5N NaOH (198 mL) was added at room temperature. After about 1 hour, the hydrolysis reaction was complete as analyzed by HPLC (> 99.9% conversion). The pH of the reaction solution was adjusted to 7 to 8.5 by addition of 1 N HCl (approx. 65 mL). A solution of Ca(OAc)₂·H₂O (116.6 g, 0.662 mol) in 4.0 L of 60% EtOH-H₂O was purged with nitrogen for 5 min. A 1.0 L portion of this solution was added to solution of the sodium salt over 30 min. The resulting slurry was aged at room temperature for 30 min, and then at 30 to 35°C for 1-2 h.

The rest of Ca(OAc)₂ in EtOH-water was added over approx. 30 min at 30 to 35°C. The slurry was aged at 30 to 35 °C for 5 hours under

atmosphere of N₂. The slurry was cooled to room temperature and was collected by suction-filtration. The wet cake was washed with 4 L 30% EtOH-H₂O, 4 L 20% EtOH-H₂O, followed by 6 L x 3 of D.I. water. The solid was suction dried under an atmosphere of moist N₂ (40 to 70%

- 5 relative humidity) at room temperature for 4 days. Crystalline hydrated calcium salt of dihydroxy open acid simvastatin was obtained as a white powder.

The calcium salt was delumped with a single pass through a cleaned QUADRO™ COMIL® (Model 197S).

10

HPLC CONDITIONS

Column: YMC Basic 4.6 mm x 25 cm
 Detector: ABS 757 1AU/volt output
 15 Sample solvent: EtOH/CH₃CN/H₂O (1:1:1)
 Column temp: 25 °C (Anal. Dept. runs samples at 5 °C to prevent formation of simvastatin on column).
 Flow rate: 1.5 mL / min.
 Wavelength: 238 and 210 nm

20

Gradient:	%H ₂ O (10 mM K ₂ HPO ₄ - KH ₂ PO ₄ pH = 6.5)		
	<u>Time (min.)</u>	<u>%CH₃CN</u>	
	0.00	30	70
	20.00	45	55
25	34.00	70	30
	39.00	70	30
	39.50	30	70
	43.00	30	70

30

Retention time of simvastatin open acid: 17.07 min.
 Retention time of simvastatin: 32.90 min.

SPECTRAL DATA

35

203
123

¹H NMR (400 MHz, CD₃OD), δ 5.97 (d, J = 9.6 Hz, 1 H), 5.77 (dd, J = 9.6, 5.2 Hz, 1 H), 5.49 (m, 1 H), 5.33 (m, 1 H), 4.17 (m, 1 H), 3.70 (m, 1 H), 2.44 - 2.35 (m, 2 H), 2.42 (dd, J = 15.7, 3.6 Hz, 1 H), 2.31 - 2.27 (m, 1 H), 2.29 (dd, J = 15.7, 8.4 Hz, 1 H), 2.00 (ddd, J = 15.7, 7.6, 2.4 Hz, 1 H), 1.93 (m, 1 H),
5 1.68 (m, 1 H), 1.61 - 1.55 (m, 2 H), 1.55 (m, 2 H), 1.42 (m, 1 H), 1.32 (m, 1 H), 1.19 (m, 1 H), 1.12 (s, 6 H), 1.08 (d, J = 7.2 Hz, 3 H), 0.89 (d, J = 7.2 Hz, 3 H), 0.84 (t, J = 7.6 Hz, 3 H) ppm.

¹³C NMR (100.55 MHz, CD₃OD), δ 182.3, 179.3, 134.1, 133.2, 130.3, 129.6,
10 72.5, 69.8, 45.1, 44.4, 44.1, 38.8, 38.3, 36.4, 34.3, 33.9, 32.0, 28.6, 25.9, 25.37, 25.36, 23.7, 14.3, 9.9 ppm

EI MS: m/e: 437 (M+H), 419 (M+H-H₂O), 303.

HR-EI MS: Calcd. for C₂₅H₃₈O₅ 418.2719; Found: 418.2712.

15

EXAMPLE 2

Preparation of crystalline hydrated calcium salt of dihydroxy open acid
simvastatin (Compound I) with BHA

A 22 L three-necked round bottom flask was equipped with a
20 temperature probe, a N₂ inlet, an additional funnel, and an overhead stirrer. 8.0 L of 15% EtOH-H₂O was added and purged with N₂ for 10 min. Simvastatin (396 g, 0.946 mol) was added, and the slurry purged with N₂ for 5 min. 198 mL of 5N NaOH (0.993 mol, 1.05 equiv.) was then added at room temperature. The hydrolysis reaction is usually complete
25 in 1 h. as analyzed by HPLC (> 99.9% conversion). The pH of the reaction solution was adjusted to 7 to 8.5 by addition of 1 N HCl (about 65 mL).

A solution of Ca(OAc)₂·H₂O (91.7 g, 0.520 mol, 0.55 equiv.) in 4.0 L of
60% EtOH- H₂O was purged with nitrogen for 5 min. 1.0 L of this solution was added to reaction solution over 30 min. The slurry was aged at room
30 temperature for 30 min, and then at 30 to 35 °C for 1-2 h. The rest of the Ca(OAc)₂ in EtOH-water was added in portions over 3h hours at 30-35°C. The slurry was allowed to age at 30 to 35 °C for 5 h under an atmosphere of N₂. The slurry was allowed to cool to room temperature and was

collected by suction-filtration. The wet cake was washed with 4 L 30% EtOH-H₂O, 4 L 20% EtOH-H₂O, followed by 6 L x 3 of D.I. water. The solid was suction dried under atmosphere of moist N₂ (40 to 70% RH) at room temperature to give 1.7 Kg of wet cake.

5 The above wet cake was placed in a clean 20 L three necked flask under atmosphere of nitrogen. A solution of BHA (2.603 g, 0.2 wt % equiv) in degassed 15% EtOH H₂O (8.5 L) was added, followed by addition of degassed water (2.55 L), and the slurry was agitated at room temperature for 1 to 2 h. The solid was collected by suction filtration
10 under atmosphere of moist N₂ with no washing to give 1.49 Kg wet cake. The solid was suction dried under atmosphere of moist N₂ (40 to 70% RH) at room temperature for 4 days. The calcium salt was obtained as a white powder (94% yield. 99.4%A at 238 nm, 0.2wt% BHA, KF = 7.3 %wt).

15 While the invention has been described and illustrated with reference to certain particular embodiments thereof, those skilled in the art will appreciate that various changes, modifications and substitutions can be made therein without departing from the spirit and scope of the invention. For example, effective dosages other than the particular
20 dosages as set forth herein above may be applicable as a consequence of variations in the responsiveness of the mammal being treated for any of the indications for the active agents used in the instant invention as indicated above. Likewise, the specific pharmacological responses observed may vary according to and depending upon the particular
25 active compound selected or whether there are present pharmaceutical carriers, as well as the type of formulation employed, and such expected variations or differences in the results are contemplated in accordance with the objects and practices of the present invention. It is intended, therefore, that the invention be defined by the scope of the claims which
30 follow and that such claims be interpreted as broadly as is reasonable.

WHAT IS CLAIMED IS:

1. A compound which is a hydrated form of the calcium salt of dihydroxy open acid simvastatin in crystalline form.
- 5
2. The compound of claim 1 having an x-ray powder diffraction pattern obtained using CuK α radiation characterized by reflections at d-spacings of 30.7, 24.6, 15.9, 11.2, 8.58, 7.31, 6.74, 6.06, 5.35, 5.09, 4.93, 4.60, 3.93, 3.84, 3.67, 3.51 and 3.28Å.
- 10
3. The compound of claim 2 having a thermogravimetry curve characterized by a 6.3% weight loss from ambient room temperature to a stable weight loss plateau at about 175°C obtained under a nitrogen flow at a heating rate of 10°C/minute.
- 15
4. The compound of claim 2 having a differential scanning calorimetry curve characterized by lower temperature endotherms with peak temperatures of 52, 77 and 100°C and associated heats of 48, 90 and 21 J/g, respectively, and higher temperature endotherms due to decomposition with peak temperatures of 222 and 241°C and associated heats of 163 and 92 J/g obtained under a nitrogen flow bubbled through 16.0°C water at a heating rate of 10°C/minute in an open cup.
- 20
5. A method of inhibiting HMG-CoA reductase comprising administering to a patient in need of such treatment an effective inhibitory amount of the compound of claim 1.
- 25
6. The method of claim 5 wherein the compound is administered orally.
- 30
7. The method of claim 6 wherein the compound is administered in a delayed-release pharmaceutical dosage form.

8. The method of claim 7 wherein the compound is administered in an enteric coated pharmaceutical dosage form.

5 9. The method of claim 6 wherein the compound is administered in a time controlled-release pharmaceutical dosage form.

10. The method of claim 6 wherein the compound is administered in a drug delivery device comprised of:

(A) a compressed core prepared from an admixture comprising:

10 (i) a therapeutically effective amount of the compound; and

(ii) a polymer which upon hydration forms gelatinous microscopic particles; and

15 (B) a water insoluble, water impermeable polymeric coating comprising a polymer and a plasticizer, which surrounds and adheres to the core, the coating having a plurality of formed apertures exposing between about 1 and about 75% of the core surface;

20 and wherein the release rate of the compound from the device is a function of the number and size of the apertures.

25 11. A method of treating hypercholesterolemia comprising administering to a patient in need of such treatment a therapeutically effective amount of the compound of claim 1.

30 12. A method for preventing or reducing the risk of developing atherosclerotic disease comprising the administration of a prophylactically effective amount of the compound of claim 1 to a person at risk of developing atherosclerotic disease.

13. The method of Claim 12 wherein the atherosclerotic disease is selected from cardiovascular disease, cerebrovascular disease and peripheral vessel disease.

14. The method of Claim 13 wherein the cardiovascular disease is coronary heart disease.

5 15. A method for preventing or reducing the risk of developing atherosclerotic disease comprising the administration of a prophylactically effective amount of the compound of claim 2 to a person at risk of developing atherosclerotic disease.

10 16. A method for treating atherosclerotic disease comprising the administration of a therapeutically effective amount of the compound of claim 1 to a person who has atherosclerotic disease.

15 17. The method of Claim 16 wherein the atherosclerotic disease is selected from cardiovascular disease, cerebrovascular disease and peripheral vessel disease.

18. The method of Claim 17 wherein the cardiovascular disease is coronary heart disease.

20 19. A method for treating atherosclerotic disease comprising the administration of a therapeutically effective amount of the compound of claim 2 to a person who has atherosclerotic disease.

25 20. A method for preventing or reducing the risk of occurrence or recurrence of an atherosclerotic disease event comprising the administration of a therapeutically effective amount the compound of claim 1 to a person at risk of having an atherosclerotic disease event.

30 21. The method of Claim 20 wherein the person receiving the compound has atherosclerotic disease.

22. The method of Claim 20 wherein the person receiving the compound is at risk of developing atherosclerotic disease.

23. The method of Claim 20 wherein the atherosclerotic disease event is selected from a coronary heart disease event, a cerebrovascular event and intermittent claudication.
- 5 24. The method of Claim 23 wherein the coronary heart disease event is selected from coronary heart disease death, myocardial infarction, and coronary revascularization procedures.
- 10 25. The method of Claim 23 wherein the cerebrovascular event is selected from a cerebrovascular accident and a transient ischemic attack.
- 15 26. A method for preventing or reducing the risk of occurrence or recurrence of an atherosclerotic disease event comprising the administration of a therapeutically effective amount of the compound of claim 2 to a person at risk of having an atherosclerotic disease event.
- 20 27. A pharmaceutical composition comprising a therapeutically effective amount of the compound of claim 1 and a pharmaceutically acceptable carrier.
28. The pharmaceutical composition of claim 27 formulated for oral administration.
- 25 29. The pharmaceutical composition of claim 28 formulated in a delayed-release dosage form wherein release of the compound from the dosage form is delayed until after passage of the dosage form through the stomach.
- 30 30. The pharmaceutical composition of claim 29 wherein the dosage form has an enteric coating.
- 35 31. The pharmaceutical composition of claim 28 formulated in a time controlled-release dosage form.

32. The pharmaceutical composition of claim 28 formulated in a drug delivery device comprised of:

(A) a compressed core prepared from an admixture comprising:

- 5 (i) a therapeutically effective amount of the compound;
and
(ii) a polymer which upon hydration forms gelatinous
microscopic particles; and

10 (B) a water insoluble, water impermeable polymeric coating comprising a polymer and a plasticizer, which surrounds and adheres to the core, the coating having a plurality of formed apertures exposing between about 1 and about 75% of the core surface;

and wherein the release rate of the compound from the device is a function of the number and size of the apertures.

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33. A process for preparing a pharmaceutical composition comprising combining the compound of claim 1 with a pharmaceutically acceptable carrier.

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34. A process for preparing a pharmaceutical composition comprising combining the compound of claim 2 with a pharmaceutically acceptable carrier.

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35. A pharmaceutical composition made by combining a therapeutically effective amount of the compound of claim 1 and a pharmaceutically acceptable carrier.

30

36. A pharmaceutical composition made by combining a therapeutically effective amount of the compound of claim 2 and a pharmaceutically acceptable carrier.

37. A process for making the compound of claim 2 comprising the steps of :

38. A process for making the compound of claim 2 comprising the steps of:

- 5 A) combining a mixture of a salt of dihydroxy open acid simvastatin in an aqueous solvent with calcium acetate hydrate to form an amorphous calcium salt of dihydroxy open acid simvastatin, wherein the aqueous solvent is selected from water, an aqueous-protic organic solvent mixture and an aqueous-aprotic organic solvent mixture;
- 10 B) aging the resulting mixture at a temperature up to 50°C until turnover of the amorphous calcium salt of dihydroxy open acid simvastatin to the crystalline calcium salt of dihydroxy open acid simvastatin is complete;
- C) recovering the crystalline calcium salt of dihydroxy open acid simvastatin by suction filtration; and
- 15 D) suction drying the recovered crystals under a moist atmosphere.

39. The process of claim 38 wherein the steps are performed under an inert atmosphere.

20 40. The process of claim 38 wherein the aqueous solvent selected from an aqueous-protic organic solvent mixture and an aqueous-aprotic organic solvent mixture.

25 41. The process of claim 40 wherein the protic organic solvent is selected from the group consisting of ethanol, isopropyl alcohol, propanol, tetrahydrofuran, and the aprotic solvent is selected from the group consisting of *tert*-butyl methyl ether and toluene.

30 42. The process of claim 38 wherein the aqueous solvent is an aqueous ethanol mixture.

35 43. The process of claim 38 wherein in step (A), the pH of the mixture of the salt of dihydroxy open acid simvastatin in an aqueous solvent is adjusted to 6 to 9 prior to combining it with the calcium acetate hydrate.

44. The process of claim 43 wherein the pH is adjusted to 7 to 8.5.

5 45. The process of claim 43 wherein the pH is adjusted by addition of a mineral acid to the mixture.

10 46. The process of claim 38 wherein in step (A), the calcium acetate hydrate is added in portions to the mixture of the salt of dihydroxy open acid simvastatin.

47. The process of claim 38 wherein in step (B), the mixture is aged at a temperature from about 10°C to 50°C.

15 48. The process of claim 38 wherein in step (B), the mixture is aged at a temperature from room temperature to 50°C.

20 49. The process of claim 38 wherein in step (B), the mixture is aged at a temperature from about 30°C to 35°C.

50. The process of claim 38 wherein in step (D), the moist atmosphere is an inert atmosphere having a relative humidity of 40 to 70%.

25 51. The process of claim 38 wherein after step (C) and prior to step (D), an anti-oxidant is combined with the recovered crystalline calcium salt of dihydroxy open acid simvastatin in an aqueous-aprotic solvent mixture and the resulting material is recovered by suction filtration.

30 52. The process of claim 51 wherein the final step of suction drying is performed under an inert moist atmosphere.

35 53. The product produced from the process of claim 38.

TITLE OF THE INVENTION
DIHYDROXY OPEN-ACID AND SALTS OF HMG-CO-A REDUCTASE
INHIBITORS

5 ABSTRACT OF THE DISCLOSURE

The instant invention provides crystalline hydrates of the calcium salt of dihydroxy open acid simvastatin which are useful for inhibiting HMG-CoA reductase, and for treating and/or reducing the risk for diseases and conditions affected by inhibition of HMG-CoA reductase. A process for making a specific crystalline hydrate of the calcium salt of dihydroxy open acid simvastatin is described. Conventional rapid-release, time controlled-release and delayed-release formulations of the active agents are also provided.

15

Result: ΔY 8/ 5/98 1: 46 PM
CaSimvastatin 98669-146

Point	Temperature (°C)	Weight (Wt. %)
X1	20.611	99.866
X2	173.337	93.563
Y1	20.611	99.866
Y2	173.337	93.563
ΔY		-6.303

10CPM

TEMP1: 20.0 °C
TEMP2: 300.0 °C

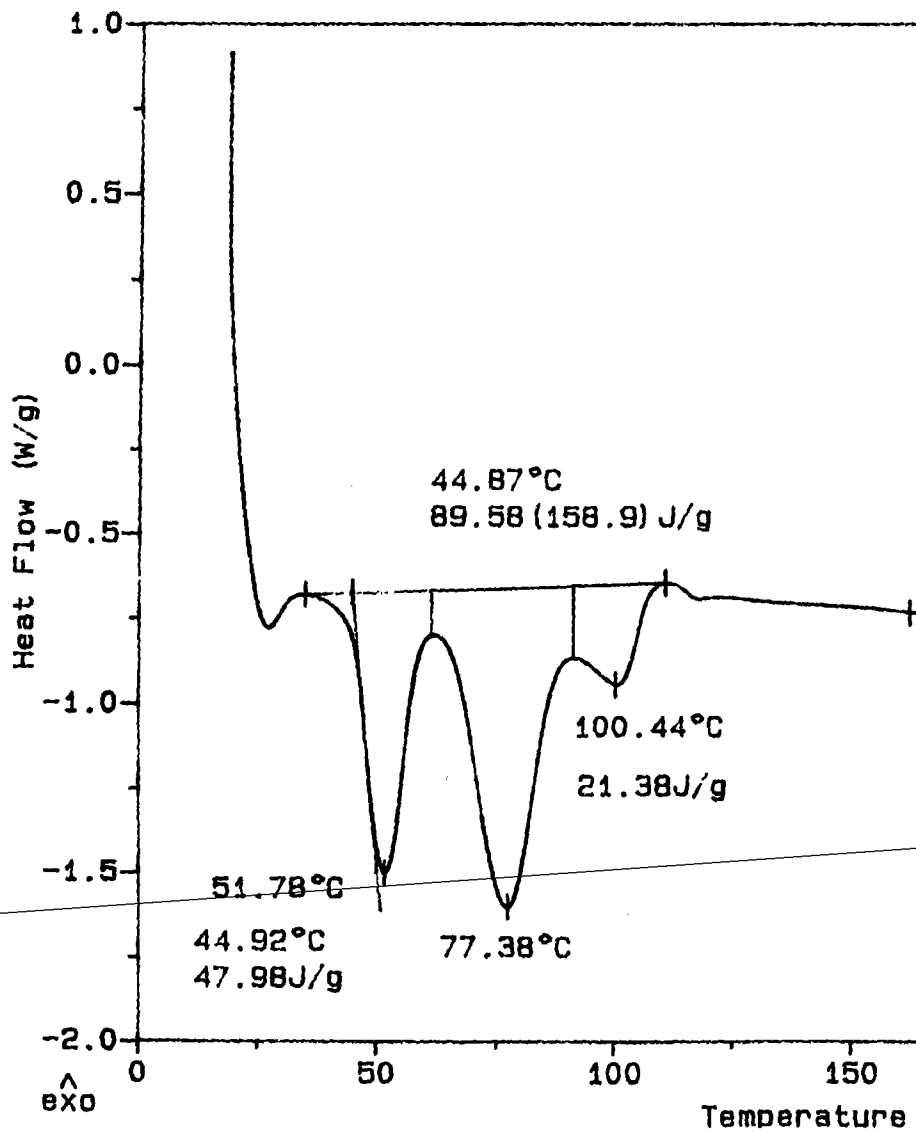
TIME1: 0.0 min RATE1: 10.0 °/min

VRM
PERKIN-ELMER
7 Series Thermal Analysis System

Figure 1.

2/5

Figure 2.



222.49°C
162.8 (254.3) J/g

204.74°C

241.37°C
91.57 J/g

200

250

300

(°C)

Universal V1.6I TA Instruments

214
131

668020" 2122209

$\times 10^2$

2.20

1.98

1.76

1.54

1.32

1.10

0.88

0.66

0.44

0.22

0.0

5.0

10.0

15.0

20.0

25.0

30.0

35.0

40.0

Figure 3.

245
135

Meich 800 37 C
20 357 Y 248
136

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C-203574

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Número de Solicitud: 09/264.745
Fecha de presentación: Marzo 9 de 1999

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REIVINDICACIONES

1. Un compuesto que es una forma hidratada de la sal de calcio de la simvastatina de ácido abierto dihidroxi en forma cristalina.

2. El compuesto de la reivindicación 1 que tiene un patrón de difracción de polvos de rayos X que se obtienen utilizando la radiación CuK α caracterizada por reflexiones en los espacios "d" correspondientes a 30.7, 24.6, 15.9, 11.2, 8.58, 7.31, 6.74, 6.06, 5.35, 5.09, 4.93, 4.60, 3.93, 3.84, 3.67, 3.51 y 3.28Å.

3. El compuesto de la reivindicación 2 que tiene una curva termogravimétrica caracterizada por una pérdida de peso de 6.3% de temperatura ambiente hasta alcanzar un nivel de pérdida de peso a los 175°C aproximadamente que se obtienen bajo un flujo de nitrógeno a un promedio de calefacción de 10°C/minuto.

4. El compuesto de la reivindicación 2 que tiene una curva de calorimetría de escaneo diferencial que se caracteriza por endotermos de temperatura baja con temperaturas pico de 52, 77 y 100°C y calores asociados de 48, 90 y 21J/g, respectivamente, y endotermos de temperatura mas alta en razón de la descomposición a temperaturas pico de 222 y 241°C y calores asociados de 163 y 92J/g que se obtienen bajo un flujo de nitrógeno burbujeante a través de agua a 16.0°C a un promedio de calefacción de 10°C/minuto en copa abierta.

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5. Un método para inhibir la reductasa HMG-CoA que comprende la administración a un paciente que necesite de dicho tratamiento de una cantidad inhibitoria eficaz del compuesto de la reivindicación 1.

6. El método de la reivindicación 5 donde el compuesto se administra por vía oral.

7. El método de la reivindicación 6 donde el compuesto se administra en forma de dosificación farmacéutica de liberación retardada.

8. El método de la reivindicación 7 donde el compuesto se administra en una forma de dosificación farmacéutica entérica y revestida.

9. El método de la reivindicación 6 donde el compuesto se administra en forma de dosis farmacéutica de liberación en tiempo controlado.

10. El método de la reivindicación 6 donde el compuesto se administra en un instrumento de aplicación de medicamento conformado por:

(A) Un núcleo comprimido que se prepara a partir de una mezcla conformada por:

(i) una cantidad terapéuticamente eficaz del compuesto;
y

(ii) un polímero que en el momento de la hidratación forma partículas microscópicas gelatinosas; y

(B) un revestimiento polimérico insoluble al agua e impermeable a ésta que comprende un polímero y un plastificador, que rodea y se adhiere al núcleo, donde el revestimiento tiene una serie de aperturas formadas que exponen entre 1 y 75% aproximadamente de la superficie del núcleo;

y donde la tasa de liberación del compuesto que sale del instrumento está en función del número y tamaño de aberturas.

11. Un método para el tratamiento de la hipercolesterolemia que comprende la administración a un paciente que necesite de dicho tratamiento una cantidad terapéuticamente eficaz del compuesto de la reivindicación 1.

12. Un método para prevenir o reducir el riesgo de desarrollo de la enfermedad aterosclerótica que comprende la administración de una cantidad profilácticamente eficaz del compuesto de la reivindicación 1 a una persona que se encuentre en riesgo de desarrollar la mencionada enfermedad aterosclerótica.

13. El método de la reivindicación 12 donde la enfermedad aterosclerótica se selecciona del grupo de enfermedades cardiovasculares, cerebrovasculares y de los vasos periféricos.

14. El método de la reivindicación 13 donde la enfermedad cardiovascular es una enfermedad coronaria cardíaca.

15. Un método para prevenir o reducir el riesgo de desarrollo de la enfermedad aterosclerótica que comprende la administración de una cantidad profilacticamente eficaz del compuesto de la reivindicación 2 a una persona que se encuentre en riesgo de desarrollar la mencionada enfermedad aterosclerótica.

16. Un método para el tratamiento de la enfermedad aterosclerótica que comprende la administración de una cantidad terapéuticamente eficaz del compuesto de la reivindicación 1 a una persona que padezca la mencionada enfermedad aterosclerótica.

17. El método de la reivindicación 16 donde la enfermedad aterosclerótica se selecciona del grupo de enfermedades cardiovasculares, cerebrovasculares y de vasos periféricos.

18. El método de la reivindicación 17 donde la enfermedad cardiovascular es una enfermedad cardíaco coronaria.

19. Un método para el tratamiento de la enfermedad aterosclerótica que comprende la administración de una cantidad terapéuticamente eficaz del compuesto de la reivindicación 2 a una persona que padezca de la enfermedad aterosclerótica.

20. Un método para prevenir o reducir el riesgo de ocurrencia o recurrencia de un evento de enfermedad aterosclerótica que comprende la administración de una

cantidad terapéuticamente eficaz del compuesto de la reivindicación 1 a una persona que se encuentre en riesgo de padecer un evento de enfermedad aterosclerótica.

21. El método de la reivindicación 20 donde la persona que recibe el compuesto padece la enfermedad aterosclerótica.

22. El método de la reivindicación 20 donde la persona que recibe el compuesto se encuentra en riesgo de desarrollar la enfermedad aterosclerótica.

23. El método de la Reivindicación 20. donde el evento de la enfermedad aterosclerótica se selecciona del grupo de eventos de enfermedad cardíaco coronaria, eventos cerebrovascular y claudicación intermitente.

24. El método de la Reivindicación 23 donde el evento de enfermedad cardíaco coronaria se selecciona a partir de la muerte por enfermedad cardíaco coronaria, infarto del miocardio y procedimientos de revascularización coronaria.

25. El método de la Reivindicación 23 donde el evento cerebrovascular se selecciona a partir de un accidente cerebrovascular y de un ataque isquémico transitorio.

26. Un método para prevenir o reducir el riesgo de ocurrencia o recurrencia de un evento de enfermedad aterosclerótica que comprende la administración de una cantidad terapéuticamente eficaz del compuesto de la

Reivindicación 2 a una persona que se encuentre en riesgo de padecer un evento de enfermedad aterosclerótica.

27. Una composición farmacéutica que comprende una cantidad terapéuticamente eficaz del compuesto de la Reivindicación 1 y un portador farmacéuticamente aceptable.

28. La composición farmacéutica de la reivindicación 27 que se formula para administración por vía oral.

29. La Composición farmacéutica de la reivindicación 28 que se formula en forma de dosificación de liberación retardada donde la liberación del compuesto proveniente de la forma de dosificación se retarda hasta un momento posterior al paso de la forma de la dosificación a través del estómago.

30. La composición farmacéutica de la Reivindicación 29 donde la forma de dosificación tiene revestimiento entérico.

31. La composición farmacéutica de la Reivindicación 28 que se formula en forma de dosificación de liberación con tiempo controlado.

32. La composición farmacéutica de la reivindicación 28 que se formula en un dispositivo para aplicación del medicamento que consiste en:

(A) Un núcleo comprimido que se prepara a partir de una mezcla conformada por:

(i) una cantidad terapéuticamente eficaz del compuesto;

y

(ii) un polímero que en el momento de la hidratación forma partículas microscópicas gelatinosas; y

(B) un revestimiento polimérico insoluble al agua e impermeable a ésta que comprende un polímero y un plastificador, que rodea y se adhiere al núcleo, donde el revestimiento tiene una serie de aperturas formadas que exponen entre 1 y 75% aproximadamente de la superficie del núcleo;

y donde la tasa de liberación del compuesto que sale del instrumento está en función del número y tamaño de aberturas.

33. Un proceso para la preparación de una composición farmacéutica que comprende la combinación del compuesto de la reivindicación 1 con un portador farmacéuticamente aceptable.

34. Un proceso para la preparación de una composición farmacéutica que comprende la combinación del compuesto de la reivindicación 2 con un portador farmacéuticamente aceptable.

35. Una composición farmacéutica que se hace mediante la combinación de una cantidad terapéuticamente eficaz del compuesto de la reivindicación 1 y un portador

farmacéuticamente aceptable.

36. Una composición farmacéutica que se hace mediante la combinación de una cantidad terapéuticamente eficaz del compuesto de la reivindicación 2 y un portador farmacéuticamente aceptable.

37. Un proceso para la elaboración del compuesto de la reivindicación 2 que comprende los siguientes pasos:

38. Un proceso para elaborar el compuesto de la reivindicación 2 que comprende los siguientes pasos:

A) La combinación de una mezcla de una sal de simvastatina de ácido abierto dihidroxi en un solvente acuoso con hidrato de acetato de calcio para formar una sal amorfa de calcio de simvastatina de ácido abierto dihidroxi, donde el solvente acuoso se selecciona a partir del agua, de una mezcla de solvente orgánico acuso-prótico y una mezcla de solvente orgánico acuoso-aprótico.

B) El envejecimiento de la mezcla resultante a una temperatura hasta de 50°C hasta cuando se produzca la rotación de la sal de calcio amorfa de la simvastatina del ácido abierto dihidroxi hasta formar la sal de calcio cristalina en forma completa de la simvastatina del ácido abierto dihidroxi.

C) La recuperación del sal de calcio cristalina de la simvastatina del ácido abierto dihidroxi por medio de la filtración por succión; y


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D) Secado por succión de los cristales recuperados bajo una atmósfera de humedad.

39. El proceso de la reivindicación 38 donde los pasos se cumplen bajo una atmósfera inerte.

40. El proceso de la reivindicación 38 donde el solvente acuoso se selecciona a partir de una mezcla de solvente orgánico acuoso-prótico y de una mezcla de solvente orgánico acuoso-aprótico.

41. El proceso de la reivindicación 40 donde el solvente orgánico prótico se selecciona a partir del grupo conformado por etanol, isopropil alcohol, propanol, tetrahidrofurano, y donde el solvente aprótico se selecciona a partir del grupo conformado por metil eter tert-butilo y tolueno.

42. El proceso de la reivindicación 38 donde el solvente acuoso es una mezcla acuosa de etanol.

43. El proceso de la reivindicación 38 donde en el paso (A), el pH de la mezcla de sal de la simvastatina del ácido abierto dihidroxi en un solvente acuoso se ajusta a 6 y hasta 9 antes de combinarse con el hidrato de acetato de calcio.

44. El proceso de la reivindicación 43 donde el pH se ajusta a un rango de 7 a 8.5.


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45. El proceso de la reivindicación 43 donde el pH se ajusta mediante adición de un ácido mineral a la mezcla.

46. El proceso de la reivindicación 38 donde en el paso (A), el hidrato de acetato de calcio se adiciona en porciones a la mezcla de la sal de la simvastatina del ácido abierto dihidroxi.

47. El proceso de la reivindicación 38 donde en el paso (B), la mezcla se envejece a una temperatura dentro del rango de 10°C hasta 50°C.

48. El proceso de la reivindicación 38 donde en el paso (B), la mezcla se envejece a una temperatura que comprende desde la temperatura ambiente hasta 50°C.

49. El proceso de la reivindicación 38 donde en el paso (B), la mezcla se envejece a una temperatura desde 30°C hasta 35°C.

50. El proceso de la reivindicación 38 donde en el paso (D), la atmósfera de humedad es inerte y tiene una humedad relativa de 40 a 70%.

51. El proceso de la reivindicación 38 donde con posterioridad al paso (C) y con anterioridad al paso (D), se combina un antioxidante con la sal de calcio cristalina recuperada de la simvastatina del ácido abierto dihidroxi en una mezcla de solvente acuoso-aprótico y el material resultante se recupera por medio de la filtración por succión.

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52. El proceso de la reivindicación 51 donde el paso final del secado por succión se realiza bajo una atmósfera húmeda inerte.

53. El producto elaborado a partir del proceso descrito en la reivindicación 38.

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Santafé de Bogotá D.C., Febrero 28 del 2000.

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Reivindicación 2 a una persona que se encuentre en riesgo de padecer un evento de enfermedad aterosclerótica.

27. Una composición farmacéutica que comprende una cantidad terapéuticamente eficaz del compuesto de la Reivindicación 1 y un portador farmacéuticamente aceptable.

28. La composición farmacéutica de la reivindicación 27 que se formula para administración por vía oral.

29. La Composición farmacéutica de la reivindicación 28 que se formula en forma de dosificación de liberación retardada donde la liberación del compuesto proveniente de la forma de dosificación se retarda hasta un momento posterior al paso de la forma de la dosificación a través del estómago.

30. La composición farmacéutica de la Reivindicación 29 donde la forma de dosificación tiene revestimiento entérico.

31. La composición farmacéutica de la Reivindicación 28 que se formula en forma de dosificación de liberación con tiempo controlado.

32. La composición farmacéutica de la reivindicación 28 que se formula en un dispositivo para aplicación del medicamento que consiste en:

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(A) Un núcleo comprimido que se prepara a partir de una mezcla conformada por:

(i) una cantidad terapéuticamente eficaz del compuesto;

y

(ii) un polímero que en el momento de la hidratación forma partículas microscópicas gelatinosas; y

(B) un revestimiento polimérico insoluble al agua e impermeable a ésta que comprende un polímero y un plastificador, que rodea y se adhiere al núcleo, donde el revestimiento tiene una serie de aperturas formadas que exponen entre 1 y 75% aproximadamente de la superficie del núcleo;

y donde la tasa de liberación del compuesto que sale del instrumento está en función del número y tamaño de aberturas.

33. Un proceso para la preparación de una composición farmacéutica que comprende la combinación del compuesto de la reivindicación 1 con un portador farmacéuticamente aceptable.

34. Un proceso para la preparación de una composición farmacéutica que comprende la combinación del compuesto de la reivindicación 2 con un portador farmacéuticamente aceptable.

Una composición farmacéutica que se hace combinación de una cantidad terapéuticamente eficaz del compuesto de la reivindicación 1 y un portador

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farmacéuticamente aceptable.

36. Una composición farmacéutica que se hace mediante la combinación de una cantidad terapéuticamente eficaz del compuesto de la reivindicación 2 y un portador farmacéuticamente aceptable.

37. Un proceso para la elaboración del compuesto de la reivindicación 2 que comprende los siguientes pasos:

38. Un proceso para elaborar el compuesto de la reivindicación 2 que comprende los siguientes pasos:

A) La combinación de una mezcla de una sal de simvastatina de ácido abierto dihidroxi en un solvente acuoso con hidrato de acetato de calcio para formar una sal amorfa de calcio de simvastatina de ácido abierto dihidroxi, donde el solvente acuoso se selecciona a partir del agua, de una mezcla de solvente orgánico acuso-prótico y una mezcla de solvente orgánico acuoso-aprótico.

B) El envejecimiento de la mezcla resultante a una temperatura hasta de 50°C hasta cuando se produzca la rotación de la sal de calcio amorfa de la simvastatina del ácido abierto dihidroxi hasta formar la sal de calcio cristalina en forma completa de la simvastatina del ácido abierto dihidroxi.

C) La recuperación del sal de calcio cristalina de la simvastatina del ácido abierto dihidroxi por medio de la filtración por succión; y


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D) Secado por succión de los cristales recuperados bajo una atmósfera de humedad.

39. El proceso de la reivindicación 38 donde los pasos se cumplen bajo una atmósfera inerte.

40. El proceso de la reivindicación 38 donde el solvente acuoso se selecciona a partir de una mezcla de solvente orgánico acuoso-prótico y de una mezcla de solvente orgánico acuoso-aprótico.

41. El proceso de la reivindicación 40 donde el solvente orgánico prótico se selecciona a partir del grupo conformado por etanol, isopropil alcohol, propanol, tetrahidrofurano, y donde el solvente aprótico se selecciona a partir del grupo conformado por metil eter tert-butilo y tolueno.

42. El proceso de la reivindicación 38 donde el solvente acuoso es una mezcla acuosa de etanol.

43. El proceso de la reivindicación 38 donde en el paso (A), el pH de la mezcla de sal de la simvastatina del ácido abierto dihidroxi en un solvente acuoso se ajusta a 6 y hasta 9 antes de combinarse con el hidrato de acetato de calcio.

44. El proceso de la reivindicación 43 donde el pH se ajusta a un rango de 7 a 8.5.


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45. El proceso de la reivindicación 43 donde el pH se ajusta mediante adición de un ácido mineral a la mezcla.

46. El proceso de la reivindicación 38 donde en el paso (A), el hidrato de acetato de calcio se adiciona en porciones a la mezcla de la sal de la simvastatina del ácido abierto dihidroxi.

47. El proceso de la reivindicación 38 donde en el paso (B), la mezcla se envejece a una temperatura dentro del rango de 10°C hasta 50°C.

48. El proceso de la reivindicación 38 donde en el paso (B), la mezcla se envejece a una temperatura que comprende desde la temperatura ambiente hasta 50°C.

49. El proceso de la reivindicación 38 donde en el paso (B), la mezcla se envejece a una temperatura desde 30°C hasta 35°C.

50. El proceso de la reivindicación 38 donde en el paso (D), la atmósfera de humedad es inerte y tiene una humedad relativa de 40 a 70%.

51. El proceso de la reivindicación 38 donde con posterioridad al paso (C) y con anterioridad al paso (D), se combina un antioxidante con la sal de calcio cristalina recuperada de la simvastatina del ácido abierto dihidroxi en una mezcla de solvente acuoso-aprótico y el material resultante se recupera por medio de la filtración por succión.

F. Cu
FABRIEL RUEDA CHADID
TRADUCTOR OFICIAL
Resolución 5996 de Nov. 29/82
Ministerio de Justicia

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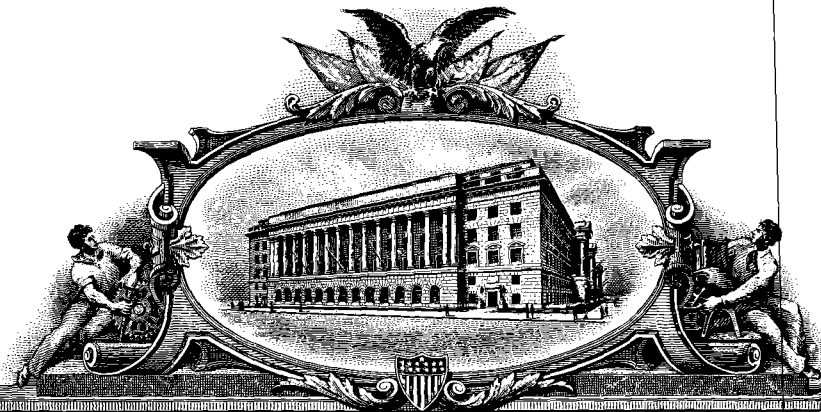
52. El proceso de la reivindicación 51 donde el paso final del secado por succión se realiza bajo una atmósfera húmeda inerte.

53. El producto elaborado a partir del proceso descrito en la reivindicación 38.

La anterior es Traducción Oficial de un documento presentado originalmente en inglés. Esta traducción fue realizada por **GABRIEL RUEDA CHADID (Traductor Oficial)**. Resolución 5996 del Minjusticia, por lo cual estampo mi Sello y Firmo.

Santafé de Bogotá D.C., Febrero 28 del 2000.


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Resolución 5996 de Nov. 29/82
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December 28, 1999

THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM THE RECORDS OF THE UNITED STATES PATENT AND TRADEMARK OFFICE OF THOSE PAPERS OF THE BELOW IDENTIFIED PATENT APPLICATION THAT MET THE REQUIREMENTS TO BE GRANTED A FILING DATE UNDER 35 USC 111.

APPLICATION NUMBER: 09/264,745

FILING DATE: March 09, 1999



**By Authority of the
COMMISSIONER OF PATENTS AND TRADEMARKS**

H. Phillips
H. PHILLIPS
Certifying Officer

03/09/99



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PTO/SB/05 (12/97)

**UTILITY
PATENT
APPLICATION
TRANSMITTAL**

(Only for new nonprovisional applications under 37 CFR 1.53(b))

Attorney Docket No. 20357

Total Pages 40

First Named Inventor or Application Identifier

Richard D. Tillyer et al.

Express Mail Label No.

BM358363506US

**APPLICATION ELEMENTS**

See MPEP chapter 600 concerning utility patent application contents.

1. ☒ Fee Transmittal Form
(Submit an original, and a duplicate for fee processing)
2. ☒ Specification [Total Pages 35]
3. ☒ Drawing(s) (35 USC 113) [Total Sheets 3]
4. Oath or Declaration [Total Pages 1]
- a. ☐ Newly executed (original or copy)
- b. ☐ Copy from a prior application (37 CFR 1.63(d))
(for continuation/divisional with Box 14 completed)
[Note Box 5 below]
- i. ☐ **DELETION OF INVENTOR(S)**
Signed statement attached deleting inventor(s) named in the prior application, see 37 CFR 1.63(d)(2) and 1.33 (b).
5. ☐ Incorporation By Reference (useable if Box 4b is checked). The entire disclosure of the prior application, from which a copy of the oath or declaration is supplied under Box 4b, is considered as being part of the disclosure of the accompanying application and is hereby incorporated by reference therein.
6. Nucleotide and/or Amino Acid Sequence Submission (if applicable, all necessary)
- a. ☐ Computer Readable Copy
- b. ☐ Paper Copy (identical to computer copy)
- c. ☐ Statement verifying identity of above copies

ADDRESS TO: Assistant Commissioner for Patents
Box Patent Application
Washington, DC 20231**ACCOMPANYING APPLICATION PARTS**

7. ☐ Assignment papers (cover sheet & document(s))
8. ☐ 37 CFR 3.73(b) Statement (when there is an assignee) ☐ Power of Attorney
9. ☐ Information Disclosure Statement (IDS)/PTO-1449 ☐ Copies of IDS Citations
10. ☐ Preliminary Amendment
11. ☒ Return Receipt Postcard (MPEP 503)
(Should be specifically itemized)
12. ☐ Certified Copy of Priority Document(s)
(if foreign priority is claimed)
13. ☒ Other:
Declaration (unsigned)

14. If a CONTINUING APPLICATION, check appropriate box and supply the requisite information:☐ Continuation ☐ Divisional ☐ Continuation-in-part (CIP) of prior application No. _____**15. CORRESPONDENCE ADDRESS**☒ Customer Number or Bar Code Label

Customer No. 000210

(Insert Customer No. or Attach bar code here)

NAME	Carol S. Quagliato				
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COUNTRY	USA	TELEPHONE	732-594-3809	FAX	732-594-4720

(computer generated form No. U6 - Merck & Co., Inc., 12/97)

EXPRESS MAIL CERTIFICATE

DATE OF DEPOSIT March 9, 1999

EXPRESS MAIL NO. BM358363506US

I HEREBY CERTIFY THAT THIS CORRESPONDENCE IS BEING DEPOSITED WITH THE UNITED STATES POSTAL SERVICE AS EXPRESS MAIL "POST OFFICE TO ADDRESSEE" BEFORE 5 P.M. ON THE ABOVE DATE IN AN ENVELOPE ADDRESSED TO ASSISTANT COMMISSIONER FOR PATENTS, BOX PATENT APPLICATION, WASHINGTON, D.C. 20231.

MAILED BY

Diane Samuels

DATE

March 9, 1999

TITLE OF THE INVENTION**DIHYDROXY OPEN-ACID AND SALTS OF HMG-CO-A REDUCTASE INHIBITORS****5 FIELD OF THE INVENTION**

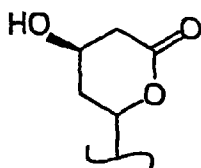
The instant invention relates to the use of dihydroxy open acid statins and salts thereof, which are inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, in a delayed-release dosage formulation, and to a particular crystalline hydrated form of the calcium salt of dihydroxy open acid simvastatin referred to herein as compound I.

BACKGROUND OF THE INVENTION

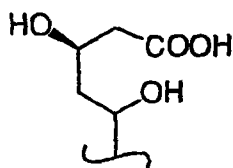
It has been clear for several decades that elevated blood cholesterol is a major risk factor for coronary heart disease (CHD), and many studies have shown that the risk of CHD events can be reduced by lipid-lowering therapy. Prior to 1987, the lipid-lowering armamentarium was limited essentially to a low saturated fat and cholesterol diet, the bile acid sequestrants (cholestyramine and colestipol), nicotinic acid (niacin), the fibrates and probucol. Unfortunately, all of these treatments have limited efficacy or tolerability, or both. With the introduction of lovastatin (MEVACOR®; see US Patent No. 4,231,938), the first inhibitor of HMG-CoA reductase to become available for prescription in 1987, for the first time physicians were able to obtain comparatively large reductions in plasma cholesterol with very few adverse effects.

In addition to the natural fermentation products, mevastatin and lovastatin, there are now a variety of semi-synthetic and totally synthetic HMG-CoA reductase inhibitors, including simvastatin (ZOCOR®; see US Patent No. 4,444,784), pravastatin sodium salt (PRAVACHOL®; see US Patent No. 4,346,227), fluvastatin sodium salt (LESCOL®; see US Patent No. 5,354,772), atorvastatin calcium salt (LIPITOR®; see US Patent No. 5,273,995) and cerivastatin sodium salt (also known as rivastatin; see US Patent No. 5,177,080). The structural formulas of these and additional HMG-CoA reductase inhibitors, are

described at page 87 of M. Yalpani, "Cholesterol Lowering Drugs", Chemistry & Industry, pp. 85-89 (5 February 1996). The HMG-CoA reductase inhibitors described above belong to a structural class of compounds which contain a moiety which can exist as either a 3-hydroxy lactone ring or as the corresponding ring opened dihydroxy open-acid, and are often referred to as "statins." An illustration of the lactone portion of a statin and its corresponding open-acid form is shown below.

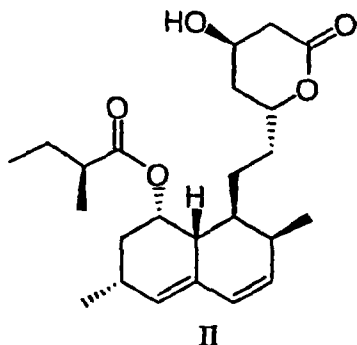


Lactone

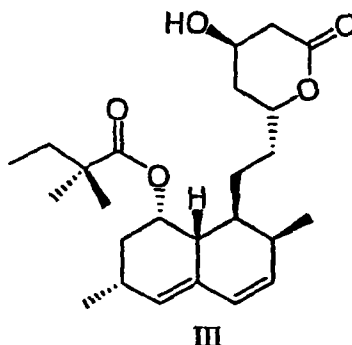


Dihydroxy Open-Acid

Salts of the dihydroxy open-acid can be prepared, and in fact, as noted above, several of the marketed statins are administered as the dihydroxy open acid salt forms. Lovastatin and simvastatin are marketed worldwide in their lactonized form. Lovastatin is shown as structural formula II, and simvastatin is shown as structural formula III, below.



II



III

The lactonized forms of the statins are not active inhibitors of HMG-CoA reductase, but the dihydroxy open acid forms are. It is known that

condensation of the dihydroxy open acid form of statins to the corresponding lactonized form occurs under acidic conditions, that is at about pH 4 or under.

Therefore, due to the low gastric pH of the stomach, a statin conventionally administered by oral dosing in its lactone form will remain largely in its lactone form in the stomach. The vast majority of the drug will still be in the lactone form at the time of absorption from the intestine following oral dosing with the lactone. After absorption, the lactone enters the liver and it is in the hepatocytes that the lactone can be metabolized to the active open acid form, a reaction catalyzed by two hepatic esterases or "lactonases," one which is in the cytosolic and the other in the microsomal fraction. Once in the blood there is an additional plasma esterase which can also hydrolyze the lactone to the open acid. There may be some minimal chemical, i.e., non-enzymatic, hydrolysis that occurs in blood or in the liver; however, at the pH in blood and liver, there should not be any lactonization, i.e., conversion of open acid back to the lactone.

A statin conventionally administered by oral dosing in its dihydroxy open acid form or a pharmaceutically acceptable salt or ester thereof will tend to convert to its lactone form in the acidic environment of the stomach, so that a mixture of the open ring and the corresponding closed ring forms will co-exist there. For example, see M.J. Kaufman, International Journal of Pharmaceutics, 1990, 66(Dec 1), p. 97-106, which provides hydrolysis data that are used to simulate the extent of drug degradation that occurs in acidic gastric fluids following oral administration of several structurally related hypocholesterolemic agents, including simvastatin and lovastatin. Therefore, even after conventional oral dosing with a dihydroxy open acid statin or a salt or ester thereof, a mixture of the open acid and the corresponding lactone form of the drug would exist by the time of absorption from the intestine.

The preparation of the naturally occurring compound lovastatin and the semi-synthetic analog simvastatin leads to a mixture of the lactone and the open-ring dihydroxy acid forms. Several procedures have been published describing ways to make simvastatin from lovastatin, and most proceed through a lactone ring opening step at

some point in the process and sometimes formation of a salt at the resulting carboxy acid, and end with a ring-closing step in order to make the final simvastatin product. For example, U.S. Patent No. 4,820,850 describes a process for making simvastatin which involves opening the lactone ring of lovastatin and forming an alkyl-amide at the resulting carboxy acid, followed by protection of the two hydroxy groups and methylation of the 8' acyl sidechain. After the methylation step, the hydroxy protecting groups are removed, the amide is hydrolyzed to the free acid and an ammonium salt of the free acid is formed, followed by a step to re-lactonize the ring. In U.S. Patent No. 4,444,784, the 8'-acyl sidechain of lovastatin is removed and the lactone ring opened in the first step, followed by re-lactonization of the ring and protection of its hydroxy group. Next, the 8' position is acylated to introduce the simvastatin sidechain and a deprotection step is performed to obtain the simvastatin final product. In another process disclosed in U.S. Patent No. 4,582,915, the potassium salt of the ring opened form of lovastatin is methylated at the 8' acyl sidechain, the free acid is then re-generated, and the dihydroxy open acid moiety is re-lactonized.

Several pharmaceutically acceptable salt forms of dihydroxy open acid statins are known in the art, as shown by the marketed salt forms of pravastatin, fluvastatin, atorvastatin and cerivastatin described above. Some salt forms of dihydroxy open acid simvastatin have been previously described, for example the ammonium salt and the potassium salt which were used as intermediates in the synthetic processes described above. Chemical Abstracts also discloses a variety of salt forms of dihydroxy open acid simvastatin, including a calcium salt having Registry No. 151006-18-7, which was referenced from a genus disclosed in U.S Patent No. 5,223,415, assigned to Merck & Co., Inc. Although there are no calcium salts exemplified in the patent, the general description of salt preparation taught in this patent would lead to an amorphous calcium salt product.

Since becoming available, millions of doses of simvastatin have been administered and these drugs have developed an excellent safety record. However, as noted in the Physician's Desk Reference (PDR), in rare instances myopathy has been associated with the use of

all statins, including simvastatin. The mechanism for statin-related myopathy is currently poorly understood. It is also known that many drugs, including certain statins such as simvastatin, are metabolised in the liver and intestine by the cytochrome P450 3A4 (CYP 3A4) enzyme system. As also noted in the PDR, there are adverse drug interaction concerns if a potent inhibitor of CYP3A4, such as itraconazole, and a CYP3A4-metabolized statin are used together, and some cases of myopathy were found to have occurred in patients taking such a drug combination. Simvastatin has been administered to over 20 million patients worldwide in the past 11 years and has been demonstrated to be remarkably safe. However, the very low risk of myopathy is substantially increased when simvastatin is given together with potent inhibitors of CYP3A4. This increased risk is believed to be related to the increased plasma levels of HMG-CoA reductase inhibitory activity resulting from the reduced metabolic elimination of simvastatin in the presence of a potent inhibitor of CYP3A4. While the overall safety record for simvastatin is exceptional, it would be desirable to further optimize its safety profile by reducing the potential for drug interactions with inhibitors of CYP3A4. It would also be desirable to further reduce the already low rate of occurrence of myopathy associated with the use of all statins.

Applicants have now discovered that dihydroxy open acid statins may be less reliant on CYP3A4 metabolism than their closed ring lactonized counterparts. The instant invention involves methods and pharmaceutical compositions for orally administering open-ring dihydroxy open acid statins and salts and esters thereof, which are HMG-CoA reductase inhibitors, in such a way so as to minimize conversion to their lactonized counterparts. This allows for delivery of a dihydroxy open acid statin without its lactone counterpart directly to the absorptive mucosa of the small intestine thus allowing for absorption of the open acid statin into the portal circulation, penetration by active open acid statin into hepatocytes to achieve enhanced efficacy, and systemic exposure consisting of open acid moieties. More particularly, delayed-release of an orally administered dihydroxy open acid statin or a pharmaceutically acceptable salt or ester thereof, for example dihydroxy

open acid simvastatin or a salt thereof, until after passage through the stomach reduces the amount of lactone formed and absorbed in the body. Maintaining the statin in its open acid form in the body thereby reduces the potential for drug interactions between statins whose metabolism is CYP34A-mediated and other active agents which inhibit the CYP3A4 enzymatic pathway. Moreover, maintaining the statin in its open acid form in the body may have additional clinical benefits for all statins, even for those statins that are not significantly metabolized by the CYP3A4 enzymatic pathway.

In addition, a novel crystalline hydrated form of the calcium salt of dihydroxy open acid simvastatin has now been discovered to be a pharmaceutically suitable salt form having desirable physical properties for formulation into an anti-hypercholesterolemic drug composition.

SUMMARY OF THE INVENTION

One object of the instant invention is to provide a method for inhibiting HMG-CoA reductase, as well as for treating and/or reducing the risk for diseases and conditions affected by inhibition of HMG-CoA reductase, comprising orally administering a therapeutically effective amount of a compound selected from a dihydroxy open acid statin and a pharmaceutically acceptable salt or ester thereof in a delayed-release pharmaceutical dosage form to a patient in need of such treatment wherein substantial release of the compound from the dosage form is delayed until after passage of the dosage form through the stomach.

One embodiment of the first object is to provide the above-described method wherein the delayed-release pharmaceutical dosage form is a gel extrusion module (GEM) drug delivery device.

Another embodiment of the first object is to provide the above-described method wherein the delayed-release pharmaceutical dosage form is an enterically coated pharmaceutical dosage form. An additional aspect of this embodiment is to provide the above-described method wherein the delayed-release pharmaceutical dosage form is an enterically coated time controlled-release pharmaceutical dosage form. Yet another aspect of this embodiment is to provide the above-described

method wherein the delayed-release pharmaceutical dosage form is an enterically coated gel extrusion module (GEM) drug delivery device.

The compound used for the above-described object and embodiments may particularly be dihydroxy open acid simvastatin and the pharmaceutically acceptable salts thereof, and more particularly a pharmaceutically acceptable salt thereof.

A second object of the instant invention is to provide novel HMG-CoA reductase inhibitors which are crystalline hydrated forms of the calcium salt of dihydroxy open acid simvastatin, and particularly the compound referred to herein as compound I.

Additional objects are to provide the use of the crystalline hydrated forms of the calcium salt of dihydroxy open acid simvastatin, particularly compound I, for inhibiting HMG-CoA reductase, as well as for treating and/or reducing the risk for diseases and conditions affected by inhibition of HMG-CoA reductase, and also to provide pharmaceutical formulations, including conventional rapid-release, delayed-release and time controlled-release formulations, including the GEM drug delivery device and enterically coated dosage forms, that can be used with the compounds. A further object is to provide a process for making compound I. Additional objects will be evident from the following detailed description.

BRIEF DESCRIPTION OF THE DRAWINGS

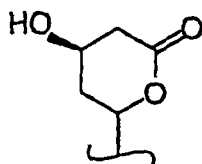
Figure 1 is a thermogravimetry (TG) weight loss curve for compound I obtained under a nitrogen flow at a heating rate of 10°C/minute.

Figure 2 is a differential scanning calorimetry (DSC) curve for compound I obtained under a nitrogen flow bubbled through 16.0°C water at a heating rate of 10°C/minute in an open cup.

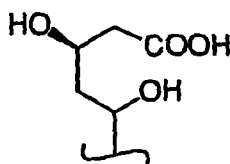
Figure 3 is an x-ray powder diffraction (XRPD) pattern for compound I. The XRPD pattern was obtained using CuK α radiation. The ordinate or Y-axis is x-ray intensity (cpm) and the abscissa or X-axis is the angle two-theta (2 θ) in degrees.

DETAILED DESCRIPTION OF THE INVENTION

The term "statin(s)" as used herein is intended to be defined as inhibitors of HMG-CoA reductase which belong to a structural class of compounds that contain a moiety which can exist as either a 3-hydroxy lactone ring or as the corresponding ring opened dihydroxy open acid, wherein the lactone portion of the statin and its corresponding dihydroxy open-acid form is shown below.



Lactone



Dihydroxy Open-Acid

All hydrates, solvates and polymorphic crystalline forms of HMG-CoA reductase inhibitors having the above-described lactone/dihydroxy open acid moiety are included within the scope of the term "statin(s)". Pharmaceutically acceptable salts and esters of the dihydroxy open-acid statins are included within the scope of the term "statin(s)".

Statins inhibit HMG-CoA reductase in their dihydroxy open acid form. Compounds which have inhibitory activity for HMG-CoA reductase can be readily identified by using assays well-known in the art. For example, see the assays described or cited in U.S. Patent 4,231,938 at col. 6, and WO 84/02131 at pp. 30-33.

The term "dihydroxy open acid statin(s)" is intended to be defined as statins which contain the dihydroxy open acid moiety, including pharmaceutically acceptable salts and esters thereof. The phrases "dihydroxy open acid statin(s)" and "dihydroxy open acid statin(s) and the pharmaceutically acceptable salts and esters thereof" are used interchangeably herein and are both intended to encompass the open acid and salt and ester forms of the open acid of the statin, unless otherwise indicated. All hydrates, solvates and polymorphic crystalline forms are encompassed within the the scope of the term "dihydroxy open acid statin(s)."

Examples of dihydroxy open acid statins that may be used with the present invention include but are not limited to the dihydroxy open acid forms and pharmaceutically acceptable salts and esters thereof of: lovastatin (see US Patent No. 4,342,767); simvastatin (see US Patent No. 4,444,784), pravastatin, particularly the sodium salt thereof; fluvastatin particularly the sodium salt thereof; atorvastatin, particularly the calcium salt thereof; cerivastatin, particularly the sodium salt thereof, and nisvastatin also referred to as NK-104 (see PCT international publication number WO 97/23200). Pharmaceutically acceptable salts of dihydroxy open acid simvastatin, particularly the crystalline hydrated forms of the calcium salt of dihydroxy open acid simvastatin, and more particularly the hydrated calcium salt of dihydroxy open acid simvastatin referred to herein as compound I, are preferred for use in the methods and compositions of this invention.

Herein, the term "pharmaceutically acceptable salts" shall mean non-toxic salts of the compounds employed in this invention which are generally prepared by reacting the free acid with a suitable organic or inorganic base, particularly those formed from cations such as sodium, potassium, aluminum, calcium, lithium, magnesium, zinc and tetramethylammonium, as well as those salts formed from amines such as ammonia, ethylenediamine, N-methylglucamine, lysine, arginine, ornithine, choline, N,N'-dibenzylethylenediamine, chloroprocaine, diethanolamine, procaine, N-benzylphenethylamine, 1-p-chlorobenzyl-2-pyrrolidine-1'-yl-methylbenzimidazole, diethylamine, piperazine, morpholine, 2,4,4-trimethyl-2-pentamine and tris(hydroxymethyl)aminomethane. Pharmaceutically acceptable esters at the carboxylic acid group can be made by treating a dihydroxy open acid statin with an alcohol. Examples of pharmaceutically acceptable esters of dihydroxy open acid statins include, but are not limited to, -C₁₋₄ alkyl and -C₁₋₄ alkyl substituted with phenyl-, dimethylamino-, and acetyl amino. "C₁₋₄ alkyl" herein includes straight or branched aliphatic chains containing from 1 to 4 carbon atoms, for example methyl, ethyl, n-propyl, n-butyl, *iso*-propyl, *sec*-butyl and *tert*-butyl.

An object of this invention is to provide methods for reducing the amount of lactonized statin formed and absorbed in the

body after oral administration of a dihydroxy open acid statin in order to achieve enhanced clinical benefits. A way to achieve this is to administer the dihydroxy open acid statin in a delayed-release pharmaceutical dosage form. A delayed-release pharmaceutical dosage form as defined herein is an orally administerable pharmaceutical dosage form or device that does not release a substantial amount of the active compound until after the dosage form has passed through the stomach. Therefore, substantial release of the active compound would initially occur after entry into the duodenum. By "substantial release," it is intended that 90% or more by weight of the active agent in the delayed-release dosage form is released after entry into the duodenum, and that 10% or less by weight of the active agent in the delayed-release dosage form is released in the stomach. Particularly, the amount of active compound released in the stomach before entry into the duodenum is 5% or less by weight and more particularly 1% or less by weight.

It is to be understood that metabolism of the dihydroxy open acid statins will occur, primarily in the liver, after orally dosing in a delayed-release dosage form. However, since lactonization of the dihydroxy open acid statin would have been substantially avoided by use of a delayed release dosage form, the active and inactive metabolites that are formed will also be in the dihydroxy open acid form. In essence, if the dihydroxy open acid statin is administered in a delayed release dosage form, the internal exposure to lactonized parent compound and also to lactonized active and inactive metabolites will be minimized.

One example of a delayed-release dosage form is an enterically coated dosage form. The enteric coating will not dissolve in the acidic gastric environment, but will dissolve in the higher pH environment of the duodenum. An enterically coated dosage form will therefore not permit release of any significant amount of the active compound from the dosage form in the stomach, but, once the enteric coating dissolves in the duodenum, the active compound will be released. Suitable compositions for enteric coatings that can be used with the present invention are known to those of ordinary skill in the pharmaceutical arts; for example, see L. Lachman, The Theory and Practice of Industrial Pharmacy, 3rd Ed., H. Liebermann and J. Kanig

contributors (Lea & Febiger, 1986). The pharmaceutical dosage form that is enterically coated can be a conventional rapid release dosage form or it can be a time controlled-release dosage form. Time controlled-release dosage forms are also well known in the pharmaceutical art, and are designed so as to slowly release the active compound in the body over a period of time, for example over a period of from about 6 to 24 hours. Use of a time controlled-release dosage form is preferred so as to lower the systemic exposure to the active statin.

An example of a delayed-release dosage form that also functions as a time controlled-release dosage form is described in U.S. Patent No. 5,366,738, herein incorporated by reference in its entirety. The controlled-release drug delivery device described in U.S. Patent No. 5,366,738 is known as a gel extrusion module (GEM) delivery device. The GEM device is a drug delivery device for the controlled in situ production and release of a dispersion containing a beneficial agent such as a pharmaceutical drug comprising:

- (A) a compressed core prepared from an admixture comprising:
 - (i) a therapeutically effective amount of the beneficial agent; and
 - (ii) a polymer which upon hydration forms gelatinous microscopic particles; and
- (B) a water insoluble, water impermeable polymeric coating comprising a polymer and a plasticizer, which surrounds and adheres to the core, the coating having a plurality of formed apertures exposing between about 1 and about 75% of the core surface;

and wherein the release rate of the beneficial agent from the device is a function of the number and size of the apertures.

In the GEM device, the polymer inside the compressed core is preferably selected from sodium polyacrylate, carboxypolymethylenes, and the pharmaceutically acceptable salts thereof, wherein the carboxypolymethylenes are prepared from acrylic acid crosslinked with allylethers of sucrose or pentaerythritol, and more preferably it is selected from carboxypolymethylenes prepared from acrylic acid crosslinked with allylethers of sucrose or pentaerythritol, and the

pharmaceutically acceptable salts thereof. Most preferably, CARBOPOL® 974P is used as the polymer inside the compressed core. In addition, the compressed core may also contain one or more polymer hydration modulating agents, anti-oxidants, lubricants, fillers and excipients. An optional subcoating may be applied to the compressed core prior to application of the water insoluble coating as an aid in the manufacturing process. The subcoating may be comprised of, for example, hydroxypropyl cellulose and hydroxypropylmethylcellulose.

The water insoluble, water impermeable polymeric coating is preferably comprised of (1) a polymer selected from polyvinyl chloride, cellulose acetate, cellulose acetate butyrate, ethylcellulose and combinations of these polymers; and (2) a plasticizer selected from diethylphthalate, dibutylsebacate and triethylcitrate. More preferably, the polymeric coating is comprised of cellulose acetate butyrate and triethyl citrate. The GEM device does not function as an osmotic drug delivery device, hence the release function of the device depends on passage of fluids from the external environment of the body to the internal environment of the compressed core through the formed apertures. It is intended that the terms "water insoluble, water impermeable" used to describe the polymeric coating define a coating which is essentially water insoluble and water impermeable, meaning that the polymeric coating allows minimal to no passage of water through the coating from the external environment of the body to the internal environment of the compressed core, except for the fluid passage that occurs through the drilled apertures, during the period of time the drug is being released from the GEM device in the body. Any minimal amount of water that does pass through the water insoluble, water impermeable polymeric coating is insubstantial and does not significantly contribute to the function of the GEM device, i.e. the release rate of the drug through the apertures. Rather the release rate of the drug from the GEM device is a function of the number and size of the apertures on the device.

For an elegant, aesthetically pleasing final product, an overcoat may finally be applied to the GEM delivery device containing colorants, waxes, and the like. The GEM device can also be enterically

coated. Even without enteric coating, extrusion of the polymer which carries the drug out from inside the compressed core of the GEM device does not occur to a substantial extent in the acidic pH of the stomach, therefore substantial release of the drug does not occur in the stomach.

- 5 Further details and examples of the GEM delivery device are described in US Patent No. 5,366,738.

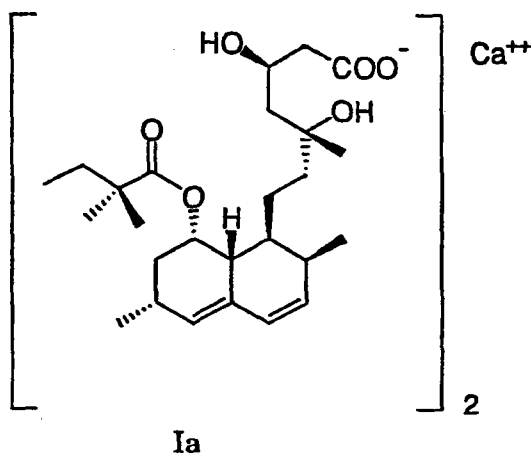
The term "patient" includes mammals, especially humans, who take compound I for the prevention or treatment of a medical condition. Administering of the drug to the patient includes both self-
10 administration and administration to the patient by another person. The patient may be in need of treatment for an existing disease or medical condition, or may desire prophylactic treatment to prevent or reduce the risk for diseases and medical conditions affected by inhibition of HMG-CoA reductase.

15 The term "therapeutically effective amount" is intended to mean that amount of a drug or pharmaceutical agent that will elicit the biological or medical response of a tissue, a system, animal or human that is being sought by a researcher, veterinarian, medical doctor or other clinician. The term "prophylactically effective amount" is
20 intended to mean that amount of a pharmaceutical drug that will prevent or reduce the risk of occurrence of the biological or medical event that is sought to be prevented in a tissue, a system, animal or human by a researcher, veterinarian, medical doctor or other clinician.

Particularly, the dosage a patient receives can be selected so as to
25 achieve the amount of LDL (low density lipoprotein) cholesterol lowering desired; the dosage a patient receives may also be titrated over time in order to reach a target LDL level. The dosage regimen utilizing a dihydroxy open acid statin is selected in accordance with a variety of factors including type, species, age, weight, sex and medical condition of
30 the patient; the severity of the condition to be treated; the potency of the compound chosen to be administered; the route of administration; and the renal and hepatic function of the patient. A consideration of these factors is well within the purview of the ordinarily skilled clinician for the purpose of determining the therapeutically effective or

prophylactically effective dosage amount needed to prevent, counter, or arrest the progress of the condition.

The novel compounds of this invention are the crystalline hydrated forms of the calcium salt of dihydroxy open acid. A particular crystalline hydrated calcium salt of dihydroxy open acid is the one having an x-ray powder diffraction (XRPD) pattern obtained using CuK α radiation characterized by reflections at d-spacings of 30.7, 24.6, 15.9, 11.2, 8.58, 7.31, 6.74, 6.06, 5.35, 5.09, 4.93, 4.60, 3.93, 3.84, 3.67, 3.51 and 3.28Å. For convenience, the crystalline hydrated form of the calcium salt of dihydroxy open acid simvastatin having the above-defined XRPD pattern will also be referred to herein as compound I. Compound I can be represented two-dimensionally as a hydrated form of the following structural formula Ia:



In addition to the XRPD pattern described above, compound I of the instant invention is further characterized by the thermogravimetry (TG) curve shown in Figure I. The TG curve for compound I was obtained under a nitrogen flow at a heating rate of 10°C/minute and is characterized by a 6.3% weight loss from ambient room temperature to a stable weight loss plateau at about 175°C. Additional weight losses due to the onset of decomposition of the compound are observed above about 190°C.

Compound I is still further characterized by the differential scanning calorimetry (DSC) curve shown in Figure 2. The DSC curve for compound I was obtained under a nitrogen flow bubbled through 16.0°C water at a heating rate of 10°C/minute in an open cup, and is characterized by three lower temperature endotherms with peak temperatures of 52, 77 and 100°C and associated heats of 48, 90 and 21 J/g, respectively, and two higher temperature endotherms due to decomposition with peak temperatures of 222 and 241°C and associated heats of 163 and 92 J/g.

Compound I of the instant invention is still further characterized by the ^1H NMR, ^{13}C NMR and mass spectral data as given in Example 1 herein.

In the methods of treatment and prophylaxis described herein, as well as the pharmaceutical compositions and medicaments, a dihydroxy open acid statin or a pharmaceutically acceptable salt or ester thereof is employed. Preferably the compound employed is a pharmaceutically acceptable salt of a dihydroxy open acid statin, more preferably it is a pharmaceutically acceptable salt of dihydroxy open acid simvastatin, particularly a crystalline hydrated form of the calcium salt of dihydroxy open acid simvastatin, and most preferably it is compound I. All hydrates, solvates and polymorphic crystalline forms of the above-described compounds and their use are encompassed within scope of the instant invention.

The instant invention provides methods for inhibiting HMG-CoA reductase, and for treating lipid disorders including hypercholesterolemia, hypertriglyceridemia and hyperlipidemia, comprising administering a therapeutically effective amount of a dihydroxy open acid statin to a person in need of such treatment. Further provided are methods for preventing or reducing the risk of developing atherosclerosis, as well as for halting or slowing the progression of atherosclerotic disease once it has become clinically evident, comprising the administration of a prophylactically or therapeutically effective amount, as appropriate, of a dihydroxy open acid statin to a mammal who is at risk of developing atherosclerosis or who already has atherosclerotic disease.

Atherosclerosis encompasses vascular diseases and conditions that are recognized and understood by physicians practicing in the relevant fields of medicine. Atherosclerotic cardiovascular disease, coronary heart disease (also known as coronary artery disease or ischemic heart disease), cerebrovascular disease and peripheral vessel disease are all clinical manifestations of atherosclerosis and are therefore encompassed by the terms "atherosclerosis" and "atherosclerotic disease."

A dihydroxy open acid statin may be administered to prevent or reduce the risk of occurrence, or recurrence where the potential exists, of a coronary heart disease event, a cerebrovascular event, and/or intermittent claudication. Coronary heart disease events are intended to include CHD death, myocardial infarction (i.e., a heart attack), and coronary revascularization procedures. Cerebrovascular events are intended to include ischemic or hemorrhagic stroke (also known as cerebrovascular accidents) and transient ischemic attacks. Intermittent claudication is a clinical manifestation of peripheral vessel disease. The term "atherosclerotic disease event" as used herein is intended to encompass coronary heart disease events, cerebrovascular events, and intermittent claudication. It is intended that persons who have previously experienced one or more non-fatal atherosclerotic disease events are those for whom the potential for recurrence of such an event exists.

Accordingly, the instant invention also provides a method for preventing or reducing the risk of a first or subsequent occurrence of an atherosclerotic disease event comprising the administration of a prophylactically effective amount of a dihydroxy open acid statin to a patient at risk for such an event. The patient may already have atherosclerotic disease at the time of administration, or may be at risk for developing it.

Persons to be treated with the instant therapy include those at risk of developing atherosclerotic disease and of having an atherosclerotic disease event. Standard atherosclerotic disease risk factors are known to the average physician practicing in the relevant fields of medicine. Such known risk factors include but are not limited

- to hypertension, smoking, diabetes, low levels of high density lipoprotein (HDL) cholesterol, and a family history of atherosclerotic cardiovascular disease. Published guidelines for determining those who are at risk of developing atherosclerotic disease can be found in: National Cholesterol Education Program, Second report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel II), National Institute of Health, National Heart Lung and Blood Institute, NIH Publication No. 93-3095, September 1993; abbreviated version: Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults, Summary of the second report of the national cholesterol education program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel II), JAMA, 1993, 269, pp. 3015-23. People who are identified as having one or more of the above-noted risk factors are intended to be included in the group of people considered at risk for developing atherosclerotic disease. People identified as having one or more of the above-noted risk factors, as well as people who already have atherosclerosis, are intended to be included within the group of people considered to be at risk for having an atherosclerotic disease event.

- The oral dosage amount of the dihydroxy open acid statin, particularly a salt of a dihydroxy open acid statin such as simvastatin, and more particularly a crystalline hydrated form of the calcium salt of dihydroxy open acid simvastatin such as compound I, is from about 1 to 200 mg/day, and more preferably from about 5 to 160 mg/day. However, dosage amounts will vary depending on factors as noted above, including the potency of the particular compound. Although the active drug of the present invention may be administered in divided doses, for example from one to four times daily, a single daily dose of the active drug is preferred.. As examples, the daily dosage amount may be selected from, but not limited to, 5 mg, 10 mg, 20 mg, 25 mg, 40 mg, 50 mg, 75 mg, 80 mg, 150 mg and 160 mg.

The active drug employed in the instant therapy can be administered in such oral forms as tablets, capsules, pills, powders,

granules, elixirs, tinctures, suspensions, syrups, and emulsions. Oral formulations are preferred.

Oral delayed-release formulations are employed with the dihydroxy open acid statins. Examples of suitable formulations include but are not limited to enterically coated pharmaceutical dosage forms such as enterically coated conventional pharmaceutical dosage forms and enterically coated time-controlled release dosage forms, the GEM delivery device, and an enterically coated GEM delivery device.

For the crystalline hydrated forms of the calcium salt of dihydroxy open acid simvastatin, for example compound I, administration of the active drug can be via any pharmaceutically acceptable route and in any pharmaceutically acceptable dosage form. This includes the use of oral conventional rapid-release, time controlled-release and delayed-release (such as described above) pharmaceutical dosage forms. An oral time controlled-release dosage formulation of the instant drug is preferred, and particularly the GEM controlled-release drug delivery device described in U.S Patent No. 5,366,738, herein incorporated by reference in its entirety. Additional suitable pharmaceutical compositions for use with the present invention are known to those of ordinary skill in the pharmaceutical arts; for example, see Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, PA.

In the methods of the present invention, the active drug is typically administered in admixture with suitable pharmaceutical diluents, excipients or carriers (collectively referred to herein as "carrier" materials) suitably selected with respect to the intended form of administration, that is, oral tablets, capsules, elixirs, syrups and the like, and consistent with conventional pharmaceutical practices.

For instance, for oral administration in the form of a tablet or capsule, the active drug component can be combined with a non-toxic, pharmaceutically acceptable, inert carrier such as lactose, starch, sucrose, glucose, modified sugars, modified starches, methyl cellulose and its derivatives, dicalcium phosphate, calcium sulfate, mannitol, sorbitol and other reducing and non-reducing sugars, magnesium stearate, steric acid, sodium stearyl fumarate, glyceryl behenate,

calcium stearate and the like. For oral administration in liquid form, the drug components can be combined with non-toxic, pharmaceutically acceptable inert carrier such as ethanol, glycerol, water and the like.

- Moreover, when desired or necessary, suitable binders, lubricants, 5 disintegrating agents and coloring and flavoring agents can also be incorporated into the mixture. Stabilizing agents such as antioxidants, for example butylated hydroxyanisole (BHA), 2,6-di-tert-butyl-4-methylphenol (BHT), propyl gallate, sodium ascorbate, citric acid, and calcium metabisulphite, can also be added to stabilize the dosage forms; 10 the use of at least one stabilizing agent is preferred with the instant composition, and preferably an antioxidant is employed with dihydroxy open acid simvastatin or a salt thereof, and particularly compound I. Other suitable components include gelatin, sweeteners, natural and synthetic gums such as acacia, tragacanth or alginates, 15 carboxymethylcellulose, polyethylene glycol, waxes and the like.

- The active drug can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, 20 stearylamine or phosphatidylcholines.

- Active drug may also be delivered by the use of monoclonal antibodies as individual carriers to which the compound molecules are coupled. Active drug may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinyl- 25 pyrrolidone, pyran copolymer, polyhydroxy-propyl-methacrylamide-phenol, polyhydroxy-ethyl-aspartamide-phenol, or polyethyleneoxide-polylysine substituted with palmitoyl residues. Furthermore, active drug may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, 30 polyglycolic acid, copolymers of polylactic and polyglycolic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates and cross linked or amphipathic block copolymers of hydrogels.

- The instant invention also encompasses a process for 35 preparing a pharmaceutical composition comprising combining a

dihydroxy open acid statin with a pharmaceutically acceptable carrier. Also encompassed is the pharmaceutical composition which is made by combining a dihydroxy open acid statin with a pharmaceutically acceptable carrier.

5 Additional active agents may be used in combination with the dihydroxy open acid statin in a single dosage formulation, or may be administered to the patient in a separate dosage formulation, which allows for concurrent or sequential administration of the active agents. One or more additional active agents may be administered with a
10 dihydroxy open acid statin. The additional active agent or agents can be cholesterol lowering compounds. Examples of additional active agents which may be employed include but are not limited to HMG-CoA synthase inhibitors; squalene epoxidase inhibitors; squalene synthetase inhibitors (also known as squalene synthase inhibitors), acyl-coenzyme A: cholesterol acyltransferase (ACAT) inhibitors; microsomal triglyceride transfer protein (MTP) inhibitors; probucol; niacin; fibrates such as clofibrate, fenofibrate, including micronized fenofibrate, and gemfibrozil; cholesterol absorption inhibitors; bile acid sequestrants; LDL (low density lipoprotein) receptor inducers; platelet aggregation inhibitors, for example glycoprotein IIb/IIIa fibrinogen receptor antagonists and aspirin; human peroxisome proliferator activated receptor gamma (PPAR γ) agonists including the compounds commonly referred to as glitazones, including those compounds included within the structural class known as thiazolidinediones as well as those PPAR γ
25 agonists outside the thiazolidinedione structural class); PPAR dual α/γ agonists; vitamin B₆ (also known as pyridoxine) and the pharmaceutically acceptable salts thereof such as the HCl salt; vitamin B₁₂ (also known as cyanocobalamin); beta-blockers; folic acid or a pharmaceutically acceptable salt or ester thereof such as the sodium salt and the methylglucamine salt; and anti-oxidant vitamins such as
30 vitamin C and E and beta carotene.

A therapeutically effective amount of a crystalline hydrated form of the calcium salt of dihydroxy open acid simvastatin, for example compound I, can be used for the preparation of a medicament useful for
35 inhibiting HMG-CoA reductase, as well as for treating and/or reducing

the risk for diseases and conditions affected by inhibition of HMG-CoA reductase, such as preventing or reducing the risk of developing atherosclerotic disease, halting or slowing the progression of atherosclerotic disease once it has become clinically manifest, and preventing or reducing the risk of a first or subsequent occurrence of an atherosclerotic disease event. For example, the medicament may be comprised of about 1 mg to 200 mg of a crystalline hydrated form of dihydroxy open acid simvastatin, or more particularly about 5 mg to 160 mg.

A therapeutically effective amount of a dihydroxy open acid statin can be used for the preparation of a medicament adapted for delayed-release that is useful for inhibiting HMG-CoA reductase, as well as for treating and/or reducing the risk for diseases and conditions affected by inhibition of HMG-CoA reductase, as described above.

The medicament comprised of a dihydroxy open acid statin, for example compound I, may also be prepared with one or more additional active agents, such as those described supra.

Simvastatin is a semi-synthetic product which can be made from the natural product lovastatin. Processes for preparing lovastatin and simvastatin are well documented in the published literature. For example, U.S. Patent No. 4,231,938, herein incorporated by reference, describes a fermentation and isolation process for obtaining lovastatin using the microorganism *Aspergillus terreus*. U.S. Patent No.'s 4,444,784, 4,820,850, 4,916,239 and 4,582,915, herein all incorporated by reference, describe methods for making simvastatin.

Preparation of Compound I

Compound I of the instant invention can generally be prepared as follows. Simvastatin and its dihydroxy open acid counterpart, including compound I, tend to form oxidative by-products; therefore, to minimize the formation of such by-products, it is preferred that the procedures used to make compound I are performed under an inert atmosphere such as nitrogen. Although compound I can be obtained without using an inert atmosphere, the purity of the desired product will not be optimized.

Hydrolysis of the lactone ring of simvastatin can be accomplished by treating simvastatin with at least one equivalent, and preferably a slight excess of one equivalent, of an aqueous base. If more than a slight excess of base is used, the excess base is preferably neutralized before proceeding to the salt formation step in order to prevent formation of insoluble calcium hydroxide or calcium carbonate by-product. The base employed for the hydrolysis can be an aqueous solution of a metal hydroxide or metal carbonate, for example but not limited to sodium hydroxide, potassium hydroxide, lithium hydroxide, sodium carbonate and potassium carbonate. Sodium hydroxide is preferred. The hydrolysis can be performed in water, an aqueous-protic organic solvent mixture, or an aqueous-aprotic organic solvent mixture. Suitable protic organic solvents include but are not limited to methanol (MeOH), ethanol (EtOH), isopropyl alcohol, propanol and tetrahydrofuran (THF). Examples of suitable aprotic organic solvents include but are not limited to *tert*-butyl methyl ether (MTBE) and toluene. An aqueous ethanol solvent mixture is preferred.

After the hydrolysis reaction is complete, the pH of the reaction mixture is adjusted to 6 to 9, preferably 7 to 8.5, by addition of an acid. In this pH range, the dihydroxy open acid simvastatin will exist as a metal salt, for example as the sodium salt if the base used in the hydrolysis step is sodium hydroxide or sodium carbonate. Any acid that is capable of forming a soluble calcium salt such as calcium chloride or calcium citrate, is suitable. A soluble calcium salt is intended to be a salt that is soluble in the solvent system employed in the instant process. Preferably a mineral acid is employed, particularly HCl.

The resulting pH-adjusted reaction mixture containing the metal salt of dihydroxy open acid simvastatin is next combined with a solution of about 0.50 to 0.55 equivalents of calcium acetate hydrate $[\text{Ca}(\text{OAc})_2 \cdot \text{Ca} \cdot x\text{H}_2\text{O}]$ in an aqueous-protic organic solvent mixture, such as water-EtOH. The pH-adjusted reaction mixture can be added to the calcium acetate hydrate solution, or the calcium acetate hydrate solution can be added to the pH-adjusted reaction mixture. The addition can occur all at once, or optionally it can be performed in portions over time with periods of aging. For example, a small portion, e.g., about one-

quarter, of the calcium acetate hydrate solution can be added to the pH-adjusted reaction mixture over a short period of time, for example over about 30 minutes, and then the resulting mixture can be allowed to age for an additional short period of time at room temperature, optionally
5 followed by a further period of aging at a temperature up to about 50°C, for example from about 10°C up to about 50°C, particularly from room temperature up to about 50°C, and more particularly from about 30 to 35°C, after which the remaining calcium acetate hydrate solution can be added in portions over several hours at a temperature up to about 50°C,
10 for example from about 10°C up to about 50°C, particularly from room temperature up to about 50°C, and more particularly from about 30 to 35°C.

Whether the pH-adjusted reaction mixture and the calcium acetate hydrate solution are combined at once or in portions, the
15 resulting slurry must be aged until turnover of the resulting amorphous calcium salt of dihydroxy open acid simvastatin to the crystalline product is complete, usually for at least several hours. Complete turnover to the crystalline product can be assessed by standard techniques in the art, for example, by examining a sample of the product
20 under a microscope. This aging step can be performed at a temperature up to about 50°C, for example from about 10°C up to about 50°C, particularly from room temperature up to about 50°C, and more particularly from about 30 to 35°C. During the aging period or periods, the use of lower temperatures will lead to crystallized product; however,
25 it has been found that as the temperature drops, the rate of crystal turnover becomes slower, making the procedure less time-efficient.

If necessary, the slurry is then allowed to cool to room temperature and is collected by suction filtration, and the recovered solid is suction dried under a moist atmosphere (about 40 to 70% relative
30 humidity), preferably a moist inert atmosphere such as nitrogen. The final step of suction filtration in the recovery of compound I should be done under a moist atmosphere, and preferably a moist inert atmosphere in order to minimize oxidative by-products. If an additional step of adding an antioxidant to compound I is performed, as described

below, then the final suction filtration is the one performed after combining the antioxidant with compound I.

As noted above, compound I has a tendency to oxidize upon contact with air, and one way to minimize oxidation is to perform the reaction sequence under an inert atmosphere. Additionally, an antioxidant such as BHA, BHT, ascorbic acid, or calcium metabisulphite can be combined with compound I. This is simply done by agitating a slurry of compound I with the antioxidant and recovering the resulting solid by suction filtration.

Abbreviations which may appear herein are as follows: EtOH is ethanol; HPLC is high performane liquid chromatography; min. is minutes; h is hour(s); D.I. is de-ionized; NMR is nuclear magnetic resonance; EI MS is electron impact mass spectrum; HR-EI MS is high resolution electron impact mass spectrum; RH is relative humidity.

EXAMPLE 1

Preparation of crystalline hydrated calcium salt of dihydroxy open acid simvastatin (Compound I)

A 22 L four-necked round bottom flask was equipped with a temperature probe, a N₂ inlet, an addition funnel, and an overhead stirrer. 8.0 L of 15% EtOH-H₂O was added and the solution was purged with N₂ for 10 min. Simvastatin (396 g, 0.946 mol) was added, and the slurry was purged with N₂ for 5 min. Then 5N NaOH (198 mL) was added at room temperature. After about 1 hour, the hydrolysis reaction was complete as analyzed by HPLC (> 99.9% conversion). The pH of the reaction solution was adjusted to 7 to 8.5 by addition of 1 N HCl (approx. 65 mL). A solution of Ca(OAc)₂·H₂O (116.6 g, 0.662 mol) in 4.0 L of 60% EtOH-H₂O was purged with nitrogen for 5 min. A 1.0 L portion of this solution was added to solution of the sodium salt over 30 min. The resulting slurry was aged at room temperature for 30 min, and then at 30 to 35°C for 1-2 h.

The rest of Ca(OAc)₂ in EtOH-water was added over approx. 30 min at 30 to 35°C. The slurry was aged at 30 to 35 °C for 5 hours under

atmosphere of N₂. The slurry was cooled to room temperature and was collected by suction-filtration. The wet cake was washed with 4 L 30% EtOH-H₂O, 4 L 20% EtOH-H₂O, followed by 6 L x 3 of D.I. water. The solid was suction dried under an atmosphere of moist N₂ (40 to 70%

5 relative humidity) at room temperature for 4 days. Crystalline hydrated calcium salt of dihydroxy open acid simvastatin was obtained as a white powder.

The calcium salt was delumped with a single pass through a cleaned QUADRO™ COMIL® (Model 197S).

10 HPLC CONDITIONS

Column: YMC Basic 4.6 mm x 25 cm
 Detector: ABS 757 1AU/volt output
 15 Sample solvent: EtOH/CH₃CN/H₂O (1:1:1)
 Column temp: 25 °C (Anal. Dept. runs samples at 5 °C to prevent formation of simvastatin on column).
 Flow rate: 1.5 mL / min.
 Wavelength: 238 and 210 nm

20 Gradient:

Time (min.)	%CH ₃ CN	%H ₂ O (10 mM K ₂ HPO ₄ -KH ₂ PO ₄ pH = 6.5)
0.00	30	70
20.00	45	55
25 34.00	70	30
39.00	70	30
39.50	30	70
43.00	30	70

30 Retention time of simvastatin open acid: 17.07 min.
 Retention time of simvastatin: 32.90 min.

35 SPECTRAL DATA

¹H NMR (400 MHz, CD₃OD), δ 5.97 (d, J = 9.6 Hz, 1 H), 5.77 (dd, J = 9.6, 5.2 Hz, 1 H), 5.49 (m, 1 H), 5.33 (m, 1 H), 4.17 (m, 1 H), 3.70 (m, 1 H), 2.44 - 2.35 (m, 2 H), 2.42 (dd, J = 15.7, 3.6 Hz, 1 H), 2.31 - 2.27 (m, 1 H), 2.29 (dd, J = 15.7, 8.4 Hz, 1 H), 2.00 (ddd, J = 15.7, 7.6, 2.4 Hz, 1 H), 1.93 (m, 1 H), 1.68 (m, 1 H), 1.61 - 1.55 (m, 2 H), 1.55 (m, 2 H), 1.42 (m, 1 H), 1.32 (m, 1 H), 1.19 (m, 1 H), 1.12 (s, 6 H), 1.08 (d, J = 7.2 Hz, 3 H), 0.89 (d, J = 7.2 Hz, 3 H), 0.84 (t, J = 7.6 Hz, 3 H) ppm.

¹³C NMR (100.55 MHz, CD₃OD), δ 182.3, 179.3, 134.1, 133.2, 130.3, 129.6, 72.5, 69.8, 45.1, 44.4, 44.1, 38.8, 38.3, 36.4, 34.3, 33.9, 32.0, 28.6, 25.9, 25.37, 25.36, 23.7, 14.3, 9.9 ppm

EI MS: m/e: 437 (M+H), 419(M+H-H₂O), 303.

HR-EI MS: Calcd. for C₂₅H₃₈O₅ 418.2719; Found: 418.2712.

EXAMPLE 2

Preparation of crystalline hydrated calcium salt of dihydroxy open acid simvastatin (Compound I) with BHA

A 22 L three-necked round bottom flask was equipped with a temperature probe, a N₂ inlet, an additional funnel, and an overhead stirrer. 8.0 L of 15% EtOH-H₂O was added and purged with N₂ for 10 min. Simvastatin (396 g, 0.946 mol) was added, and the slurry purged with N₂ for 5 min. 198 mL of 5N NaOH (0.993 mol, 1.05 equiv.) was then added at room temperature. The hydrolysis reaction is usually complete in 1 h. as analyzed by HPLC (> 99.9% conversion). The pH of the reaction solution was adjusted to 7 to 8.5 by addition of 1 N HCl (about 65 mL).

A solution of Ca(OAc)₂·H₂O (91.7 g, 0.520 mol, 0.55 equiv.) in 4.0 L of 60% EtOH- H₂O was purged with nitrogen for 5 min. 1.0 L of this solution was added to reaction solution over 30 min. The slurry was aged at room temperature for 30 min, and then at 30 to 35 °C for 1-2 h. The rest of the Ca(OAc)₂ in EtOH-water was added in portions over 3h hours at 30-35°C. The slurry was allowed to age at 30 to 35 °C for 5 h under an atmosphere

of N₂. The slurry was allowed to cool to room temperature and was collected by suction-filtration. The wet cake was washed with 4 L 30% EtOH-H₂O, 4 L 20% EtOH-H₂O, followed by 6 L x 3 of D.I. water. The solid was suction dried under atmosphere of moist N₂ (40 to 70% RH) at room temperature to give 1.7 Kg of wet cake.

The above wet cake was placed in a clean 20 L three necked flask under atmosphere of nitrogen. A solution of BHA (2.603 g, 0.2 wt % equiv) in degassed 15% EtOH H₂O (8.5 L) was added, followed by addition of degassed water (2.55 L), and the slurry was agitated at room temperature for 1 to 2 h. The solid was collected by suction filtration under atmosphere of moist N₂ with no washing to give 1.49 Kg wet cake. The solid was suction dried under atmosphere of moist N₂ (40 to 70% RH) at room temperature for 4 days. The calcium salt was obtained as a white powder (94% yield. 99.4%A at 238 nm, 0.2wt% BHA, KF = 7.3 %wt).

While the invention has been described and illustrated with reference to certain particular embodiments thereof, those skilled in the art will appreciate that various changes, modifications and substitutions can be made therein without departing from the spirit and scope of the invention. For example, effective dosages other than the particular dosages as set forth herein above may be applicable as a consequence of variations in the responsiveness of the mammal being treated for any of the indications for the active agents used in the instant invention as indicated above. Likewise, the specific pharmacological responses observed may vary according to and depending upon the particular active compound selected or whether there are present pharmaceutical carriers, as well as the type of formulation employed, and such expected variations or differences in the results are contemplated in accordance with the objects and practices of the present invention. It is intended, therefore, that the invention be defined by the scope of the claims which follow and that such claims be interpreted as broadly as is reasonable.

WHAT IS CLAIMED IS:

1. A compound which is a hydrated form of the calcium salt of dihydroxy open acid simvastatin in crystalline form.

5

2. The compound of claim 1 having an x-ray powder diffraction pattern obtained using $\text{CuK}\alpha$ radiation characterized by reflections at d-spacings of 30.7, 24.6, 15.9, 11.2, 8.58, 7.31, 6.74, 6.06, 5.35, 5.09, 4.93, 4.60, 3.93, 3.84, 3.67, 3.51 and 3.28Å.

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3. The compound of claim 2 having a thermogravimetry curve characterized by a 6.3% weight loss from ambient room temperature to a stable weight loss plateau at about 175°C obtained under a nitrogen flow at a heating rate of 10°C/minute.

15

4. The compound of claim 2 having a differential scanning calorimetry curve characterized by lower temperature endotherms with peak temperatures of 52, 77 and 100°C and associated heats of 48, 90 and 21 J/g, respectively, and higher temperature endotherms due to decomposition with peak temperatures of 222 and 241°C and associated heats of 163 and 92 J/g obtained under a nitrogen flow bubbled through 16.0°C water at a heating rate of 10°C/minute in an open cup.

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5. A method of inhibiting HMG-CoA reductase comprising administering to a patient in need of such treatment an effective inhibitory amount of the compound of claim 1.

30

6. The method of claim 5 wherein the compound is administered orally.

7. The method of claim 6 wherein the compound is administered in a delayed-release pharmaceutical dosage form.

8. The method of claim 7 wherein the compound is administered in an enteric coated pharmaceutical dosage form.

5 9. The method of claim 6 wherein the compound is administered in a time controlled-release pharmaceutical dosage form.

10. The method of claim 6 wherein the compound is administered in a drug delivery device comprised of:

(A) a compressed core prepared from an admixture comprising:

10 (i) a therapeutically effective amount of the compound; and

(ii) a polymer which upon hydration forms gelatinous microscopic particles; and

15 (B) a water insoluble, water impermeable polymeric coating comprising a polymer and a plasticizer, which surrounds and adheres to the core, the coating having a plurality of formed apertures exposing between about 1 and about 75% of the core surface;

20 and wherein the release rate of the compound from the device is a function of the number and size of the apertures.

25 11. A method of treating hypercholesterolemia comprising administering to a patient in need of such treatment a therapeutically effective amount of the compound of claim 1.

30 12. A method for preventing or reducing the risk of developing atherosclerotic disease comprising the administration of a prophylactically effective amount of the compound of claim 1 to a person at risk of developing atherosclerotic disease.

13. The method of Claim 12 wherein the atherosclerotic disease is selected from cardiovascular disease, cerebrovascular disease and peripheral vessel disease.

14. The method of Claim 13 wherein the cardiovascular disease is coronary heart disease.

5 15. A method for preventing or reducing the risk of developing atherosclerotic disease comprising the administration of a prophylactically effective amount of the compound of claim 2 to a person at risk of developing atherosclerotic disease.

10 16. A method for treating atherosclerotic disease comprising the administration of a therapeutically effective amount of the compound of claim 1 to a person who has atherosclerotic disease.

15 17. The method of Claim 16 wherein the atherosclerotic disease is selected from cardiovascular disease, cerebrovascular disease and peripheral vessel disease.

18. The method of Claim 17 wherein the cardiovascular disease is coronary heart disease.

20 19. A method for treating atherosclerotic disease comprising the administration of a therapeutically effective amount of the compound of claim 2 to a person who has atherosclerotic disease.

25 20. A method for preventing or reducing the risk of occurrence or recurrence of an atherosclerotic disease event comprising the administration of a therapeutically effective amount the compound of claim 1 to a person at risk of having an atherosclerotic disease event.

30 21. The method of Claim 20 wherein the person receiving the compound has atherosclerotic disease.

22. The method of Claim 20 wherein the person receiving the compound is at risk of developing atherosclerotic disease.

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23. The method of Claim 20 wherein the atherosclerotic disease event is selected from a coronary heart disease event, a cerebrovascular event and intermittent claudication.

5 24. The method of Claim 23 wherein the coronary heart disease event is selected from coronary heart disease death, myocardial infarction, and coronary revascularization procedures.

10 25. The method of Claim 23 wherein the cerebrovascular event is selected from a cerebrovascular accident and a transient ischemic attack.

15 26. A method for preventing or reducing the risk of occurrence or recurrence of an atherosclerotic disease event comprising the administration of a therapeutically effective amount of the compound of claim 2 to a person at risk of having an atherosclerotic disease event.

20 27. A pharmaceutical composition comprising a therapeutically effective amount of the compound of claim 1 and a pharmaceutically acceptable carrier.

25 28. The pharmaceutical composition of claim 27 formulated for oral administration.

30 29. The pharmaceutical composition of claim 28 formulated in a delayed-release dosage form wherein release of the compound from the dosage form is delayed until after passage of the dosage form through the stomach.

35 30. The pharmaceutical composition of claim 29 wherein the dosage form has an enteric coating.

 31. The pharmaceutical composition of claim 28 formulated in a time controlled-release dosage form.

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32. The pharmaceutical composition of claim 28 formulated in a drug delivery device comprised of:

- (A) a compressed core prepared from an admixture comprising:
- (i) a therapeutically effective amount of the compound; and
 - (ii) a polymer which upon hydration forms gelatinous microscopic particles; and
- (B) a water insoluble, water impermeable polymeric coating comprising a polymer and a plasticizer, which surrounds and adheres to the core, the coating having a plurality of formed apertures exposing between about 1 and about 75% of the core surface;

and wherein the release rate of the compound from the device is a function of the number and size of the apertures.

33. A process for preparing a pharmaceutical composition comprising combining the compound of claim 1 with a pharmaceutically acceptable carrier.

34. A process for preparing a pharmaceutical composition comprising combining the compound of claim 2 with a pharmaceutically acceptable carrier.

35. A pharmaceutical composition made by combining a therapeutically effective amount of the compound of claim 1 and a pharmaceutically acceptable carrier.

36. A pharmaceutical composition made by combining a therapeutically effective amount of the compound of claim 2 and a pharmaceutically acceptable carrier.

37. A process for making the compound of claim 2 comprising the steps of :

38. A process for making the compound of claim 2 comprising the steps of:

- 5 A) combining a mixture of a salt of dihydroxy open acid simvastatin in an aqueous solvent with calcium acetate hydrate to form an amorphous calcium salt of dihydroxy open acid simvastatin, wherein the aqueous solvent is selected from water, an aqueous-protic organic solvent mixture and an aqueous-aprotic organic solvent mixture;
- 10 B) aging the resulting mixture at a temperature up to 50°C until turnover of the amorphous calcium salt of dihydroxy open acid simvastatin to the crystalline calcium salt of dihydroxy open acid simvastatin is complete;
- C) recovering the crystalline calcium salt of dihydroxy open acid simvastatin by suction filtration; and
- 15 D) suction drying the recovered crystals under a moist atmosphere.

39. The process of claim 38 wherein the steps are performed under an inert atmosphere.

- 20 40. The process of claim 38 wherein the aqueous solvent selected from an aqueous-protic organic solvent mixture and an aqueous-aprotic organic solvent mixture.

- 25 41. The process of claim 40 wherein the protic organic solvent is selected from the group consisting of ethanol, isopropyl alcohol, propanol, tetrahydrofuran, and the aprotic solvent is selected from the group consisting of *tert*-butyl methyl ether and toluene.

- 30 42. The process of claim 38 wherein the aqueous solvent is an aqueous ethanol mixture.

- 35 43. The process of claim 38 wherein in step (A), the pH of the mixture of the salt of dihydroxy open acid simvastatin in an aqueous solvent is adjusted to 6 to 9 prior to combining it with the calcium acetate hydrate.

44. The process of claim 43 wherein the pH is adjusted to 7 to 8.5.

45. The process of claim 43 wherein the pH is adjusted by addition of a mineral acid to the mixture.

46. The process of claim 38 wherein in step (A), the calcium acetate hydrate is added in portions to the mixture of the salt of dihydroxy open acid simvastatin.

47. The process of claim 38 wherein in step (B), the mixture is aged at a temperature from about 10°C to 50°C.

48. The process of claim 38 wherein in step (B), the mixture is aged at a temperature from room temperature to 50°C.

49. The process of claim 38 wherein in step (B), the mixture is aged at a temperature from about 30°C to 35°C.

50. The process of claim 38 wherein in step (D), the moist atmosphere is an inert atmosphere having a relative humidity of 40 to 70%.

51. The process of claim 38 wherein after step (C) and prior to step (D), an anti-oxidant is combined with the recovered crystalline calcium salt of dihydroxy open acid simvastatin in an aqueous-aprotic solvent mixture and the resulting material is recovered by suction filtration.

52. The process of claim 51 wherein the final step of suction drying is performed under an inert moist atmosphere.

53. The product produced from the process of claim 38.

TITLE OF THE INVENTION
DIHYDROXY OPEN-ACID AND SALTS OF HMG-CO-A REDUCTASE
INHIBITORS

5 ABSTRACT OF THE DISCLOSURE

The instant invention provides crystalline hydrates of the calcium salt of dihydroxy open acid simvastatin which are useful for inhibiting HMG-CoA reductase, and for treating and/or reducing the risk for diseases and conditions affected by inhibition of HMG-CoA reductase. A process for making a specific crystalline hydrate of the calcium salt of dihydroxy open acid simvastatin is described. Conventional rapid-release, time controlled-release and delayed-release formulations of the active agents are also provided.

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191IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
DECLARATION AND POWER OF ATTORNEYAssistant Commissioner for Patents
Washington, D.C. 20231

As a below-named inventor, I hereby declare that I believe I am:

- ☐ the original, first and sole inventor; or
- ☒ an original, first and joint inventor along with the other inventors listed below, of the subject matter which is claimed and for which a patent is sought on the invention entitled
- DIHYDROXY OPEN-ACID AND SALTS OF HMG-CO-A REDUCTASE INHIBITORS

the specification of which ☒ is attached hereto;

☐ was filed on _____ as Application

Serial No. _____ and was amended

through _____ (if applicable).

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended as indicated above.

I acknowledge the duty to disclose to the Patent and Trademark Office all information known to me to be material to the patentability of this application in accordance with Title 37, Code of Federal Regulations, §1.56.

Foreign Priority

I hereby claim foreign priority benefits under Title 35, United States Code, §119 (a)-(d) of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate for the same invention having a filing date before that of the application on which priority is claimed:

Prior Foreign Application(s)

Country	Number	Date Filed	Attorney Docket

Country	Number	Date Filed	Attorney Docket

Priority Claimed

☐ ☐
Yes No

☐ ☐
Yes No

22A
192**Prior United States Filing**

I hereby claim the benefit under Title 35, United States Code, §119(e) of any United States provisional application(s) listed below.

To Be Assigned	March 8, 1999	20357PV
Appln. Ser. No.	Filing Date	Attorney Docket
Appln. Ser. No.	Filing Date	Attorney Docket
Appln. Ser. No.	Filing Date	Attorney Docket
Appln. Ser. No.	Filing Date	Attorney Docket

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application(s) in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, §1.56 which occurred between the filing date(s) of the prior application(s) and the national or PCT international filing date of this application:

Appln. Ser. No.	Filing Date	Status	Attorney Docket
Appln. Ser. No.	Filing Date	Status	Attorney Docket
Appln. Ser. No.	Filing Date	Status	Attorney Docket
Appln. Ser. No.	Filing Date	Status	Attorney Docket
Appln. Ser. No.	Filing Date	Status	Attorney Docket
Appln. Ser. No.	Filing Date	Status	Attorney Docket

And I hereby appoint

Carol S. Quagliato

Melvin Winokur

Reg. No. 35,330

Reg. No. 32,763

Reg. No. _____

respectively and individually, as my attorneys or agents with full power of substitution and revocation, to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith. Please address all communications to:

Carol S. Quagliato
Patent Department
Merck & Co., Inc.
P.O. Box 2000
Rahway, NJ 07065-0907

Telephone No. (732) 594- 3809

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I hereby declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

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Full name of joint inventor	
Inventor's Signature	
Date	
Residence	
Citizenship	
Post Office Address (if different from above)	

Full name of joint inventor		
Inventor's Signature		
Date		
Residence		
Citizenship		
Post Office Address (if different from above)		

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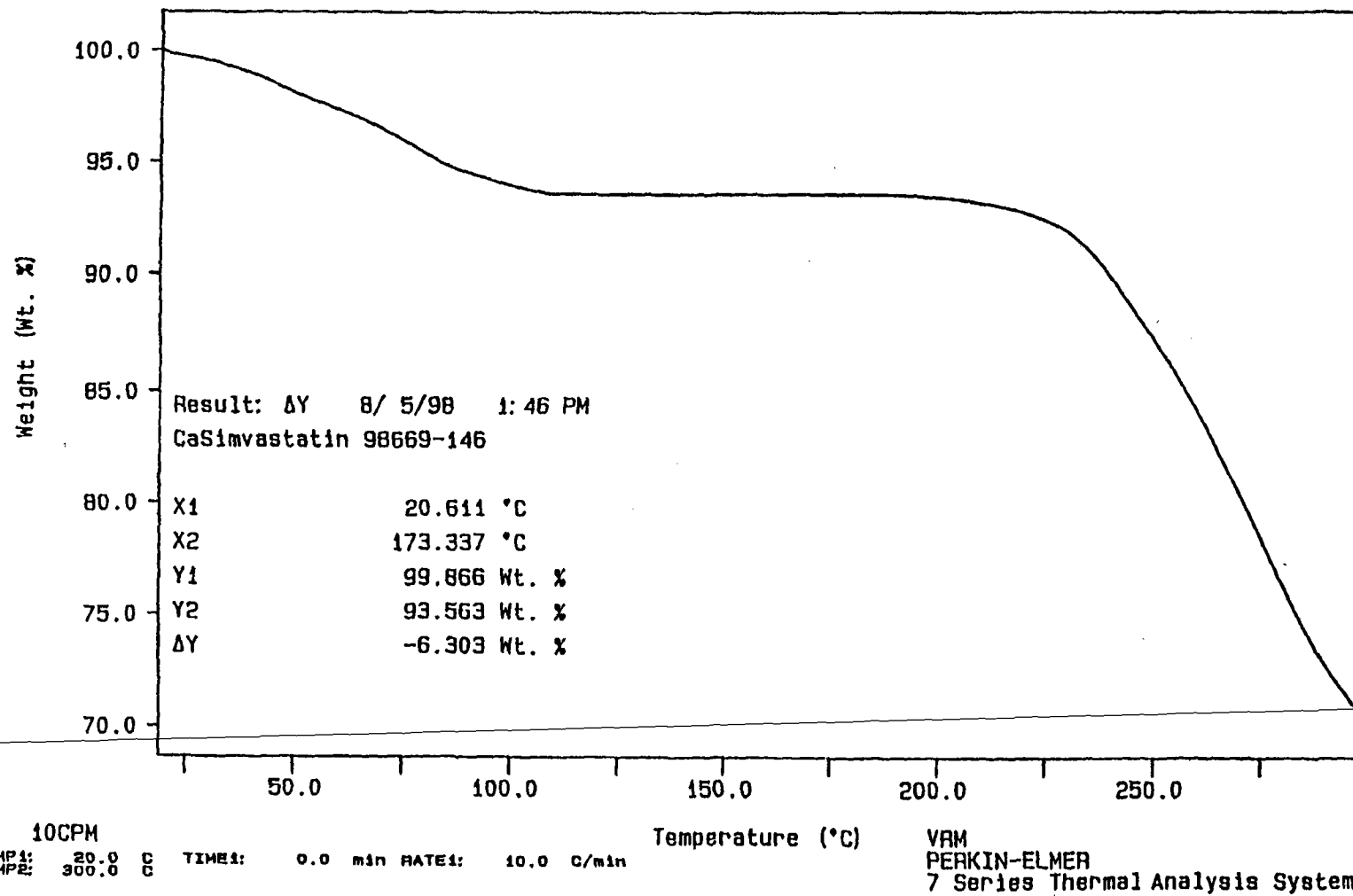
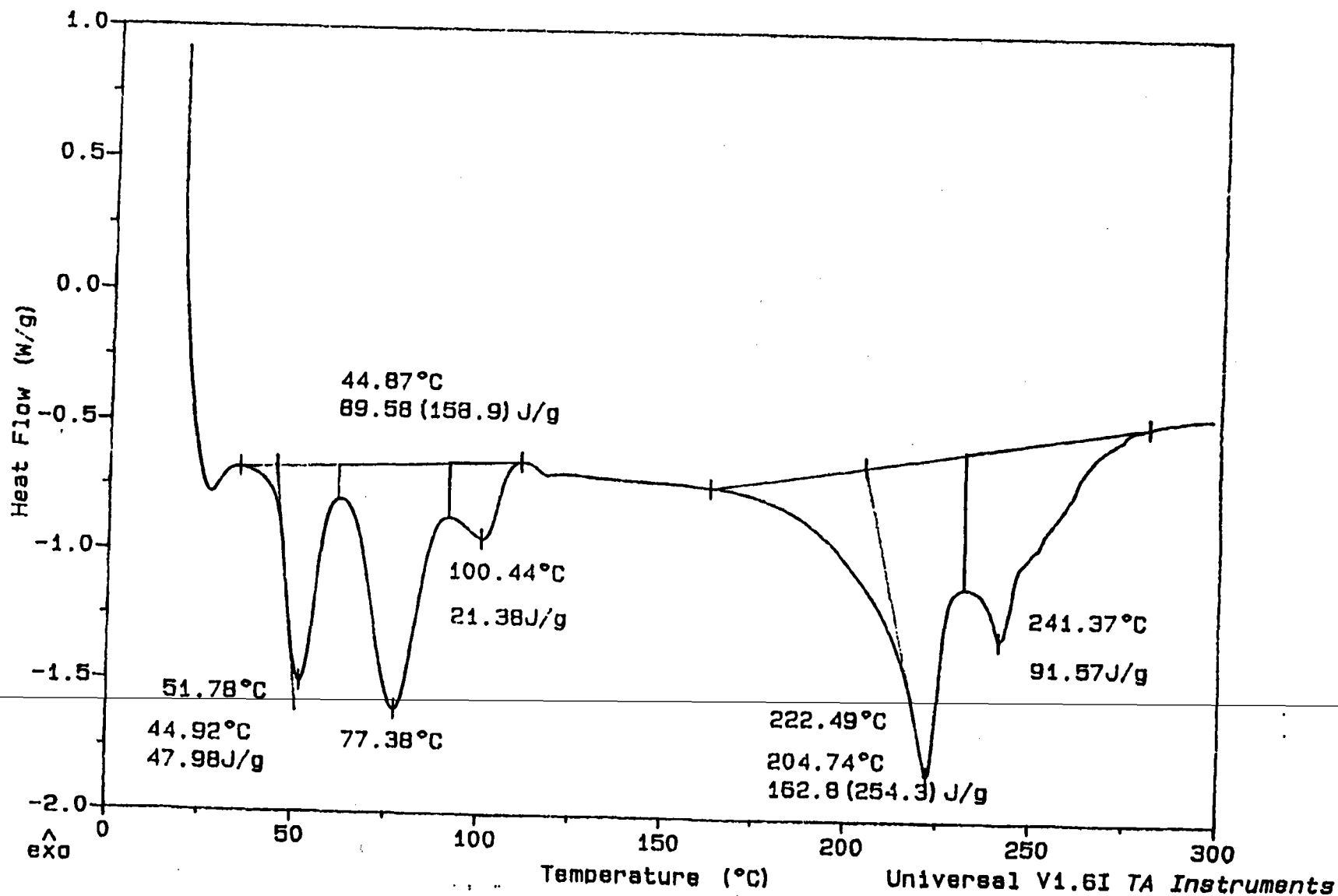


Figure 1.

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Figure 2.

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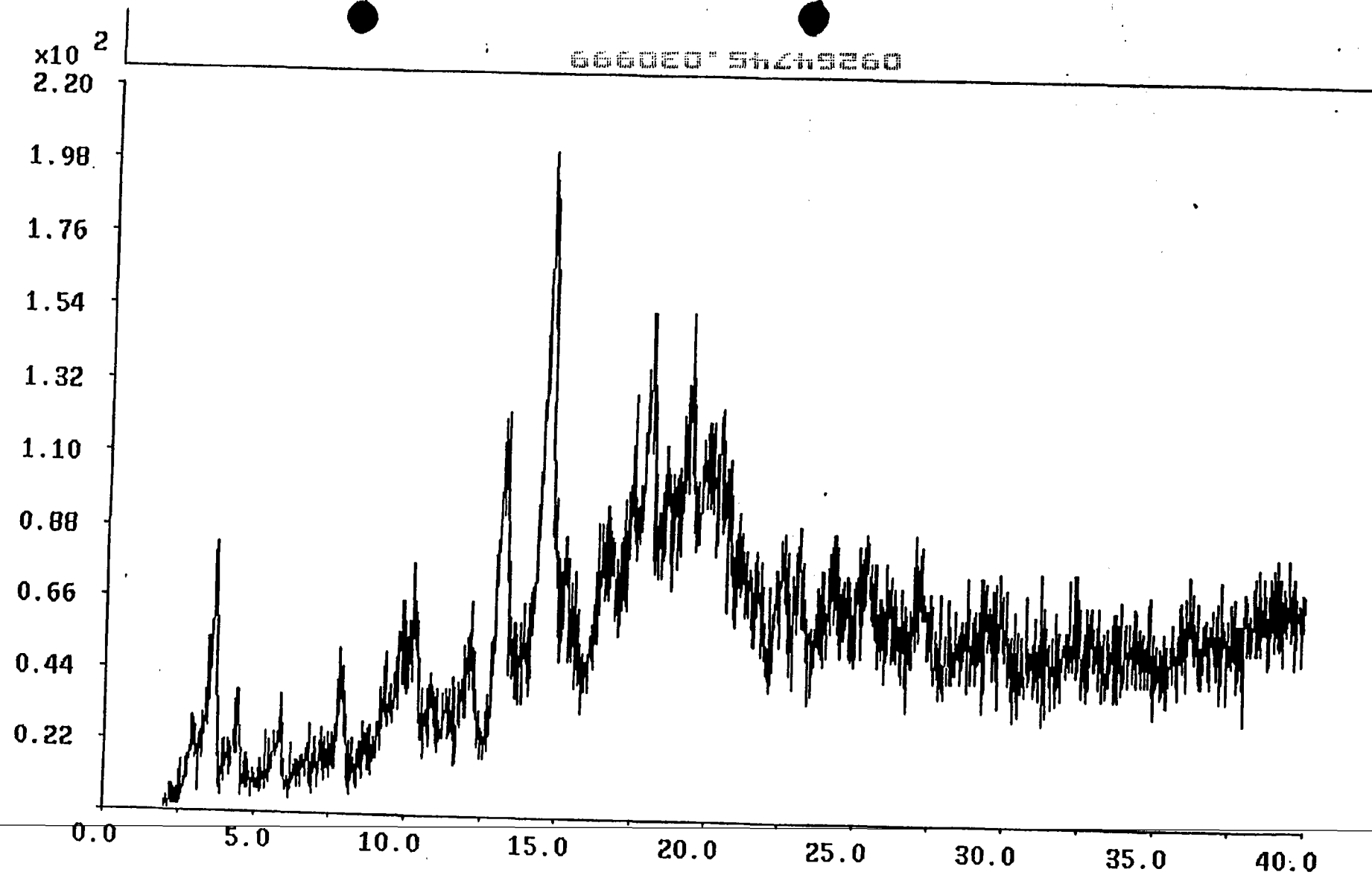


Figure 3.

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

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RADICACIÓN: 0-16006

EDICTO No. 15261

LA SECRETARÍA GENERAL AD-HOC HACE SABER:

Que esta Superintendencia profirió **Resolución No. 29808 de 30-NOV-2004**. Que el contenido de la parte resolutive es como sigue: El Superintendente de Industria y Comercio.

RESUELVE

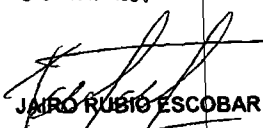
ARTICULO PRIMERO: Declarar abandonada la solicitud de privilegio de patente de invención contenida en el expediente de la referencia.

ARTICULO SEGUNDO: Notificar personalmente el contenido de la presente resolución a la doctora Alicia Lloreda Ricaurte, o a quien haga sus veces, quien actúa como apoderada de Merck & Co., Inc., entregándole copia de la misma, advirtiéndole que contra ella procede el recurso de reposición interpuesto ante el Superintendente de Industria y Comercio, al momento de la notificación o dentro de los 5 días hábiles siguientes a ella.

NOTIFÍQUESE Y CUMPLASE

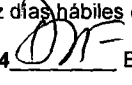
Dada en Bogotá, D.C., a los **30 NOV. 2004**

EL SUPERINTENDENTE DE INDUSTRIA Y COMERCIO,


JAIRO RUBIO ESCOBAR

Para notificar a los interesados, se fija el presente EDICTO en lugar visible al público en la SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO, por el término de (10) diez días hábiles contados a partir de las 8:30 a.m. de hoy.

Secretaría General Ad-Hoc **14-DIC-2004**
Secretaría General Ad-Hoc
EDICTO No. 15261

 Este edicto se desfija hoy **27-DIC-2004** a las cinco (5:00 p.m.) 