

**(19) AUSTRALIAN PATENT OFFICE**

(54) Title  
Crystalline forms of 'R-(R\*,R\*)!-2-(4-Fluorophenyl)-BETA,  
DELTA-dihydroxy-5-(1-methylethyl)-3-Phenyl-4-'phenylamino)carbonyl!-1H-pyrrole-1-heptanoic  
acid calcium salt (2:1)(atorvastatin)

(51)<sup>6</sup> International Patent Classification(s)  
**C07D** 207/34 OBMJP **A61P**  
(2006.01) 3/06  
**A61K** 31/40 (2006.01) 20060101ALI2005122  
**A61P** 3/06 (2006.01) OBMJP **A61P**  
**A61P** 19/10 (2006.01) 19/10  
**A61P** 25/28 (2006.01) 20060101ALI2005122  
**C07D** 207/34 OBMJP **A61P**  
20060101AFI2005100 25/28  
**8BMEP** **A61K** 20060101ALI2005122  
31/40 OBMJP  
20060101ALI2005122 PCT/IB02/01796

(21) Application No: 2002258092 (22) Application Date: 2002 .05 .21

(87) WIPO No: W003/004470

(30) Priority Data

(31) Number	(32) Date	(33) Country
60/302,049	2001 .06 .29	US

(43) Publication Date : 2003 .01 .21

(43) Publication Journal Date : 2003 .05 .22

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(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization  
International Bureau



(43) International Publication Date  
16 January 2003 (16.01.2003)

PCT

(10) International Publication Number  
WO 03/004470 A1

- (51) International Patent Classification: C07D 207/34, A61K 31/40 Pfizer Global Research and Development, Eastern Point Road, Groton, CT 06340 (US). KRZYZYANIAK, Joseph, Francis [US/US]; Pfizer Global Research and Development, Eastern Point Road, Groton, CT 06340 (US).
- (21) International Application Number: PCT/IB02/01796
- (22) International Filing Date: 21 May 2002 (21.05.2002) (74) Agents: LUMB, J., Trevor et al.; Pfizer Inc., 201 Tabor Road, Morris Plains, NJ 07950 (US).
- (25) Filing Language: English (81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.
- (26) Publication Language: English
- (30) Priority Data: 60/302,049 29 June 2001 (29.06.2001) US (84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).
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- Published:  
— with international search report
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.



WO 03/004470 A1

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

(57) Abstract: Novel crystalline forms of [R-(R\*,R\*)]-2-(4-fluorophenyl)- $\beta$ ,  $\Delta$ ;-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid hemi calcium salt atorvastatin designated Form V, Form VI, Form VII, Form VIII, Form IX, Form X, Form XI, Form XII, Form XIII, Form XIV, Form XV, Form XVI, Form XVII, Form XVIII, and Form XIX are characterized by their X-ray powder diffraction, solid-state NMR, and/or Raman spectroscopy are described, as well as methods for the preparation and pharmaceutical composition of the same, which are useful as agents for treating hyperlipidemia, hypercholesterolemia, osteoporosis, and Alzheimer's disease.

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

5 FIELD OF THE INVENTION

The present invention relates to novel crystalline forms of atorvastatin which is known by the chemical name [R-(R\*,R\*)-2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid hemi calcium salt useful as pharmaceutical agents, to methods for their production and  
10 isolation, to pharmaceutical compositions which include these compounds and a pharmaceutically acceptable carrier, as well as methods of using such compositions to treat subjects, including human subjects, suffering from hyperlipidemia, hypercholesterolemia, osteoporosis, and Alzheimer's disease.

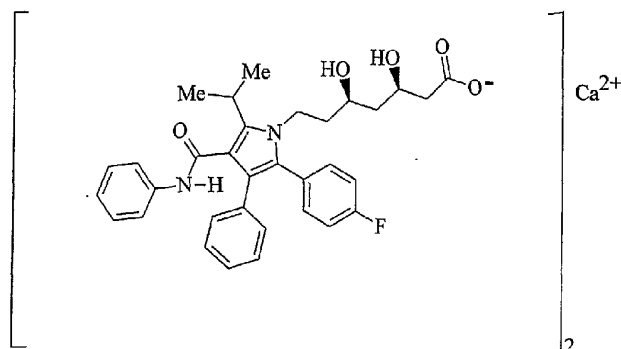
BACKGROUND OF THE INVENTION

15 Any discussion of the prior art throughout the specification should in no way be considered as an admission that such prior art is widely known or forms part of common general knowledge in the field.

The conversion of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) to mevalonate is an early and rate-limiting step in the cholesterol biosynthetic pathway.  
20 This step is catalyzed by the enzyme HMG-CoA reductase. Statins inhibit HMG-CoA reductase from catalysing this conversion. As such, statins are collectively potent lipid lowering agents.

Atorvastatin calcium, disclosed in United States Patent No. 5,273,995, which is incorporated herein by reference, is currently sold as Lipitor® having the chemical name  
25 [R-(R\*,R\*)-2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid calcium salt (2:1) trihydrate and the formula

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Atorvastatin calcium is a selective, competitive inhibitor of HMG-CoA reductase. As such, atorvastatin calcium is a potent lipid lowering compound and is thus useful as a hypolipidemic and/or hypocholesterolemic agent.

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

10 United States Patent Number 5,273,995, which is herein incorporated by reference, discloses the enantiomer having the R form of the ring-opened acid of *trans*-5-(4-fluorophenyl)-2-(1-methylethyl)-N, 4-diphenyl-1-[(2-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3-carboxamide, ie, [R-(R\*,R\*)]-2-(4-fluorophenyl)- $\beta,\delta$ -dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)-carbonyl]-1H-pyrrole-1-heptanoic acid which is atorvastatin.

15 United States Patent Numbers 5,003,080; 5,097,045; 5,103,024; 5,124,482; 5,149,837; 5,155,251; 5,216,174; 5,245,047; 5,248,793; 5,280,126; 5,397,792; 5,342,952; 5,298,627; 5,446,054; 5,470,981; 5,489,690; 5,489,691; 5,510,488; 5,998,633; and 6,087,511, which are herein incorporated by reference, disclose  
20 various processes and key intermediates for preparing amorphous atorvastatin. Amorphous atorvastatin has unsuitable filtration and drying characteristics for large-scale production and must be protected from heat, light, oxygen, and moisture.

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Crystalline forms of atorvastatin calcium are disclosed in United States Patent Numbers 5,969,156 and 6,121,461 which are herein incorporated by reference.

International Published Patent Application Number WO 01/36384  
5 allegedly discloses a polymorphic form of atorvastatin calcium.

Stable oral formulations of atorvastatin calcium are disclosed in United States Patent Numbers 5,686,104 and 6,126,971.

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

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

We have now surprisingly and unexpectedly found novel crystalline forms of atorvastatin. Thus, the present invention provides atorvastatin in new crystalline forms designated Forms V, VI, VII, VIII, IX, X, XI, XII, XIII, XIV, XV, XVI, XVII, XVIII, and XIX. The new crystalline forms of atorvastatin are purer, more  
25 stable, or have advantageous manufacturing properties than the amorphous product.

#### SUMMARY OF THE INVENTION

Accordingly, the present invention is directed to crystalline Form V atorvastatin and hydrates thereof characterized by the following X-ray powder  
30 diffraction pattern expressed in terms of the  $2\theta$  and relative intensities with a

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relative intensity of >10% measured on a Shimadzu diffractometer with CuK $\alpha$  radiation:

2 $\theta$	Relative Intensity (>10%) <sup>a</sup>
4.9 (broad)	9
6.0	15
7.0	100
8.0 (broad)	20
8.6	57
9.9	22
16.6	42
19.0	27
21.1	35

<sup>a</sup> Relative intensity of 4.9 (broad) 2 $\theta$  is 9.

Additionally, the following X-ray powder diffraction pattern of crystalline Form V atorvastatin expressed in terms of the 2 $\theta$  values was measured on an Inel (capillary) diffractometer:

5

2 $\theta$
5.0
6.1
7.5
8.4 (broad)
8.7 (broad)
9.9
16.7
19.0
21.2

-5-

Further, the present invention is directed to crystalline Form V atorvastatin and hydrates thereof characterized by the following solid-state  $^{13}\text{C}$  nuclear magnetic resonance (ssNMR) spectrum wherein chemical shift is expressed in parts per million:

Assignment	Chemical Shift
C12 or C25	185.7
C12 or C25	176.8
C16	166.9
<u>Aromatic Carbons</u>	138.7
C2-C5, C13-C18, C19-C24, C27-C32	136.3
	133.0
	128.4
	122.0
	117.0
	116.3
C8, C10	68.0
<u>Methylene Carbons</u>	43.1
C6, C7, C9, C11	
C33	25.6
C34	19.9

5 Additionally, the present invention is directed to crystalline Form V atorvastatin and hydrates thereof characterized by the following Raman spectrum having peaks expressed in  $\text{cm}^{-1}$ :

-6-

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3062  
1652  
1604  
1528  
1478  
1440  
1413  
1397  
1368  
1158  
1034  
1001  
825  
245  
224  
130

---

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

In a second aspect, the present invention is directed to crystalline Form VI atorvastatin and hydrates thereof characterized by the following X-ray powder  
5 diffraction pattern expressed in terms of the  $2\theta$  and relative intensities with a relative intensity of >10% measured on a Shimadzu diffractometer with  $\text{CuK}\alpha$  radiation:



-7-

2 $\theta$	Relative Intensity (>10%) <sup>a</sup>
7.2	11
8.3	77
11.0	20
12.4	11
13.8	9
16.8	14
18.5	100
19.7 (broad)	22
20.9	14
25.0 (broad)	15

<sup>a</sup> Relative intensity of 13.8 (broad) 2 $\theta$  is 9.

Additionally, the following X-ray powder diffraction pattern of crystalline Form VI atorvastatin expressed in terms of the 2 $\theta$  values was measured on an Inel (capillary) diffractometer:

2 $\theta$
7.3
8.5
11.2
12.7
14.0
17.1 (broad)
18.7
19.9
21.1 (broad)
25.2 (broad)

5 Further, the present invention is directed to crystalline Form VI atorvastatin and hydrates thereof characterized by the following solid-state

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$^{13}\text{C}$  nuclear magnetic resonance spectrum wherein chemical shift is expressed in parts per million:

Assignment	Chemical Shift
C12 or C25	176.5
C16 or C12 or C25	168.2
C16 or C12 or C25	163.1
C16 or C12 or C25	159.8
<u>Aromatic Carbons</u>	136.8
C2-C5, C13-C18, C19-C24, C27-C32	127.8
	122.3
	118.8
	113.7
C8, C10	88.2
C8, C10	79.3
	70.5
<u>Methylene Carbons</u>	43.3
C6, C7, C9, C11	36.9
	31.9
C33, C34	25.9
C33, C34	22.5

In a third aspect, the present invention is directed to crystalline Form VII atorvastatin and hydrates thereof characterized by the following X-ray powder diffraction pattern expressed in terms of the  $2\theta$  and relative intensities with a relative intensity of >10% measured on a Shimadzu diffractometer with  $\text{CuK}\alpha$  radiation:

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$2\theta$	Relative Intensity (>10%)
8.6	76
10.2	70
12.4 (broad)	12
12.8 (broad)	15
17.6	20
18.3 (broad)	43
19.3	100
22.2 (broad)	14
23.4 (broad)	23
23.8 (broad)	26
25.5 (broad)	16

Additionally, the following X-ray powder diffraction pattern of crystalline Form VII atorvastatin expressed in terms of the  $2\theta$  values was measured on an Inel (capillary) diffractometer:

$2\theta$
8.7
10.2
12.4
12.9
17.6
18.4
19.4
22.2
23.5
23.9
25.6

-10-

Further, the present invention is directed to crystalline Form VII atorvastatin and hydrates thereof characterized by the following solid-state  $^{13}\text{C}$  nuclear magnetic resonance spectrum wherein chemical shift is expressed in parts per million:

Assignment	Chemical Shift
C12 or C25	186.5
C12 or C25	183.3
C12 or C25	176.8
C16	166.5
	159.2
<u>Aromatic Carbons</u>	137.6
C2-C5, C13-C18, C19-C24, C27-C32	128.3
	122.3
	119.2
C8, C10	74.5
C8, C10	70.3
C8, C10	68.3
C8, C10	66.2
<u>Methylene Carbons</u>	43.5
C6, C7, C9, C11	40.3
C33, C34	26.3
C33, C34	24.9
C33, C34	20.2

5 Additionally, the present invention is directed to crystalline Form VII atorvastatin and hydrates thereof characterized by the following Raman spectrum having peaks expressed in  $\text{cm}^{-1}$ :

-11-

Raman Spectrum
3060
2927
1649
1603
1524
1476
1412
1397
1368
1159
1034
998
824
114

In a preferred embodiment of the third aspect of the invention, crystalline Form VII atorvastatin is a sesquihydrate.

In a fourth aspect, the present invention is directed to crystalline Form VIII atorvastatin and hydrates thereof characterized by the following X-ray powder diffraction pattern expressed in terms of the  $2\theta$  and relative intensities with a relative intensity of >10% measured on a Shimadzu diffractometer with  $\text{CuK}\alpha$  radiation:

-12-

2 $\theta$	Relative Intensity (>10%) <sup>a</sup>
7.5	61
9.2	29
10.0	16
12.1	10
12.8	6
13.8	4
15.1	13
16.7 (broad)	64
18.6 (broad)	100
20.3 (broad)	79
21.2	24
21.9	30
22.4	19
25.8	33
26.5	20
27.4 (broad)	38
30.5	20

<sup>a</sup> Relative intensity of 12.8 2 $\theta$  is 6 and  
13.8 2 $\theta$  is 4.

Additionally, the following X-ray powder diffraction pattern of crystalline Form VIII atorvastatin expressed in terms of the 2 $\theta$  values was measured on an Inel (capillary) diffractometer:

2 $\theta$
7.5
9.3
10.1
12.2
12.8

-13-

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20

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13.8

15.1

16.6-16.9

18.5-18.9

20.2-20.6

21.3

22.0

22.5

25.9

26.5

27.4 (broad)

30.6

---

Further, the present invention is directed to crystalline Form VIII atorvastatin and hydrates thereof characterized by the following solid-state  $^{13}\text{C}$  nuclear magnetic resonance spectrum wherein chemical shift is expressed in parts per million:

Assignment	Chemical Shift
C12 or C25	186.1
C12 or C25	179.5
C16	167.9
C16	161.0
<u>Aromatic Carbons</u>	139.4
C2-C5, C13-C18, C19-C24, C27-C32	132.9
	128.7
	124.7
	121.8
	116.6
C8, C10	67.0

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Assignment	Chemical Shift
<u>Methylene Carbons</u> C6, C7, C9, C11	43.3
C33, C34	26.7
C33, C34	24.7
C33, C34	20.9
C33, C34	20.1

Additionally, the present invention is directed to crystalline Form VIII atorvastatin and hydrates thereof characterized by the following Raman spectrum having peaks expressed in  $\text{cm}^{-1}$ :

Raman Spectrum
3065
2923
1658
1603
1531
1510
1481
1413
997
121

5 In a preferred embodiment of the fourth aspect of the invention, crystalline Form VIII atorvastatin is a dihydrate.

10 In a fifth aspect, the present invention is directed to crystalline Form IX atorvastatin and hydrates thereof characterized by the following X-ray powder diffraction pattern expressed in terms of the  $2\theta$  and relative intensities with a relative intensity of >10% measured on a Shimadzu diffractometer with  $\text{CuK}\alpha$  radiation:



-15-

2 $\theta$	Relative Intensity (>10%)
8.8	50
9.4 (broad)	32
11.2-11.7 (broad)	26
16.7	59
17.5 (broad)	33
19.3 (broad)	55
21.4 (broad)	100
22.4 (broad)	33
23.2 (broad)	63
29.0 (broad)	15

Additionally, the following X-ray powder diffraction pattern of crystalline Form IX atorvastatin expressed in terms of the 2 $\theta$  values was measured on an Inel (capillary) diffractometer:

2 $\theta$
9.0
9.4
10.0 - 10.5 (broad)
11.8 - 12.0 (broad)
16.9
17.5 (broad)
19.4 (broad)
21.6 (broad)
22.6 (broad)
23.2 (broad)
29.4 (broad)

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

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diffraction pattern expressed in terms of the  $2\theta$  and relative intensities with a relative intensity of >10% measured on a Shimadzu diffractometer with  $\text{CuK}\alpha$  radiation:

$2\theta$	Relative Intensity (>10%)
4.7	35
5.2	24
5.8	11
6.9	13
7.9	53
9.2	56
9.5	50
10.3 (broad)	13
11.8	20
16.1	13
16.9	39
19.1	100
19.8	71
21.4	49
22.3 (broad)	36
23.7 (broad)	37
24.4	15
28.7	31

5 Additionally, the following X-ray powder diffraction pattern of crystalline Form X atorvastatin expressed in terms of the  $2\theta$  values was measured on an Inel (capillary) diffractometer:

-17-

2θ
4.7
5.2
5.8
6.9
7.9
9.2
9.6
10.2-10.4
11.9
16.2
16.9
19.1
19.9
21.5
22.3-22.6
23.7-24.0 (broad)
24.5
28.8

Further, the present invention is directed to crystalline Form X atorvastatin and hydrates thereof characterized by the following solid-state  $^{13}\text{C}$  nuclear magnetic resonance spectrum wherein chemical shift is expressed in parts per million:

Assignment	Chemical Shift
C12 or C25	187.0
C12 or C25	179.5
C16	165.5
C16	159.4

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Assignment	Chemical Shift
<u>Aromatic Carbons</u>	137.9
C2-C5, C13-C18,	134.8
C19-C24, C27-C32	129.4
	127.9
	123.2
	119.9
C8, C10	71.1
<u>Methylene Carbons</u>	43.7
C6, C7, C9, C11	40.9
C33	26.4
	25.3
C34	20.3
	18.3

Additionally, the present invention is directed crystalline Form X atorvastatin and hydrates thereof characterized by the following Raman spectrum having peaks expressed in  $\text{cm}^{-1}$ :

Raman Spectrum
3062
2911
1650
1603
1525
1478
1411
1369
1240
1158
1034
999

-19-

Raman Spectrum
824
116

In a preferred embodiment of the sixth aspect of the invention, crystalline Form X atorvastatin is a trihydrate.

In a seventh aspect, the present invention is directed to crystalline Form XI atorvastatin and hydrates thereof characterized by the following X-ray powder diffraction pattern expressed in terms of the 2 $\theta$  and relative intensities with a relative intensity of >10% measured on a Shimadzu diffractometer with CuK $\alpha$  radiation:

2 $\theta$	Relative Intensity (>10%)
10.8 (broad)	58
12.0	12
13.5	11
16.5	52
17.6-18.0 (broad)	35
19.7	82
22.3	100
23.2	26
24.4	28
25.8	17
26.5	30
27.3	31
28.7	19
29.5	12
30.9 (broad)	17
32.8 (broad)	11
33.6 (broad)	15
36.0 (broad)	15
38.5 (broad)	14

-20-

In an eighth aspect, the present invention is directed to crystalline Form XII atorvastatin and hydrates thereof characterized by the following X-ray powder diffraction pattern expressed in terms of the  $2\theta$  and relative intensities with a relative intensity of >10% measured on a Shimadzu diffractometer with

5  $\text{CuK}\alpha$  radiation:

$2\theta$	Relative Intensity (>10%) <sup>a</sup>
5.4	11
7.7	24
8.0	25
8.6	42
8.9	25
9.9	36
10.4 (broad)	24
12.5	18
13.9 (broad)	9
16.2	10
17.8	70
19.4	100
20.8	51
21.7	13
22.4-22.6 (broad)	18
24.3	19
25.5	24
26.2	11
27.1	8

<sup>a</sup> Relative intensity of 13.9 (broad)  $2\theta$  is 9 and 27.1  $2\theta$  is 8.

Additionally, the following X-ray powder diffraction pattern of crystalline Form XII atorvastatin expressed in terms of the  $2\theta$  values was measured on an Inel (capillary) diffractometer:

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2θ
5.4
7.7
8.1
8.6
8.9
10.0
10.5
12.6
14.0 (broad)
16.2
17.9
19.4
20.9
21.8
22.5 - 22.8 (broad)
24.4
25.6
26.4
27.2

---

Additionally, the present invention is directed crystalline Form XII atorvastatin and hydrates thereof characterized by the following Raman spectrum having peaks expressed in  $\text{cm}^{-1}$ :

---

Raman Spectrum
3064
2973
2926
1652
1603
1527

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-22-

Raman Spectrum
1470
1410
1367
1240
1159
1034
1002
823

In a ninth aspect, the present invention is directed to crystalline Form XIII atorvastatin and hydrates thereof characterized by the following X-ray powder diffraction pattern expressed in terms of the  $2\theta$  and relative intensities with a relative intensity of >10% measured on a Shimadzu diffractometer with  $\text{CuK}\alpha$  radiation:

$2\theta$	Relative Intensity (>10%)
8.4	100
8.9	82
15.7 (broad)	45
16.4 (broad)	46
17.6 (broad)	57
18.1 (broad)	62
19.7 (broad)	58
20.8 (broad)	91
23.8 (broad)	57

In a tenth aspect, the present invention is directed to crystalline Form XIV atorvastatin and hydrates thereof characterized by the following X-ray powder diffraction pattern expressed in terms of the  $2\theta$  and relative intensities with a



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relative intensity of >10% measured on a Bruker D5000 diffractometer with  
CuK $\alpha$  radiation:

2 $\theta$	Relative Intensity (>10%)
5.4	41
6.7	31
7.7	100
8.1	35
9.0	65
16.5 (broad)	15
17.6 (broad)	17
18.0 – 18.7 (broad)	21
19.5 (broad)	18

In an eleventh aspect, the present invention is directed to crystalline  
Form XV atorvastatin and hydrates thereof characterized by the following X-ray  
5 powder diffraction pattern expressed in terms of the 2 $\theta$  and relative intensities  
with a relative intensity of >10% measured on a Bruker D5000 diffractometer  
with CuK $\alpha$  radiation:

2 $\theta$	Relative Intensity (>10%)
5.7	26
6.1	21
6.8	18
7.5	39
8.1	39
8.5	42
9.5	33
10.5 (broad)	18
19.1 - 19.6 (broad)	32

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In a twelfth aspect, the present invention is directed to crystalline Form XVI atorvastatin and hydrates thereof characterized by the following X-ray powder diffraction pattern expressed in terms of the  $2\theta$  and relative intensities with a relative intensity of >10% measured on a Bruker D5000 diffractometer with  $\text{CuK}\alpha$  radiation:

5

$2\theta$	Relative Intensity (>10%)
5.2	37
6.4	34
7.5	100
8.7	79
10.5 (broad)	19
12.0 (broad)	10
12.7 (broad)	17
16.7	26
18.3 (broad)	27
19.5	23
20.1 - 20.4 (broad)	37
21.2 - 21.9 (broad)	32
22.9 - 23.3 (broad)	38
24.4 - 25.0 (broad)	35

Additionally, the following X-ray powder diffraction pattern of crystalline Form XVI atorvastatin expressed in terms of the  $2\theta$  values was measured on a Shimadzu diffractometer with  $\text{CuK}\alpha$  radiation:

$2\theta$
7.6
8.8
10.2
12.5

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2 $\theta$
16.8
18.2
19.3
20.5
23.0
24.8

In addition, the following X-ray powder diffraction pattern of crystalline Form XVI atorvastatin expressed in terms of the 2 $\theta$  values was measured on an Inel (capillary) diffractometer:

2 $\theta$
5.1
6.2
7.3
8.7
10.2 (broad)
12.0 (broad)
12.7 (broad)
16.7
18.0 (broad)
19.5 (broad)
20.0 - 20.5 (broad)
21.5 - 21.6 (broad)
22.9 - 23.3 (broad)
24.0 - 25.0 (broad)

5 In a thirteenth aspect, the present invention is directed to crystalline Form XVII atorvastatin and hydrates thereof characterized by the following X-ray powder diffraction pattern expressed in terms of the 2 $\theta$  and relative intensities

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with a relative intensity of >10% measured on a Bruker D5000 diffractometer  
with  $\text{CuK}\alpha$  radiation:

$2\theta$	Relative Intensity (>10%)
5.0	27
6.1	33
7.3	100
7.9	30
8.5	29
9.1	22
10.0	45
12.1 (broad)	24
14.8	17
16.0 - 16.5 (broad)	20
17.5 (broad)	28
19.0 (broad)	46
19.5	65
20.2 (broad)	47
21.3	64
21.6	55
22.0	45

In a fourteenth aspect, the present invention is directed to crystalline  
Form XVIII atorvastatin and hydrates thereof characterized by the following  
5 X-ray powder diffraction pattern expressed in terms of the  $2\theta$  and relative  
intensities with a relative intensity of >10% measured on a Bruker D5000  
diffractometer with  $\text{CuK}\alpha$  radiation:

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2 $\theta$	Relative Intensity (>10%)
8.0	100
9.2 (broad)	52
9.7 (broad)	40
12.1	24
16.6 (broad)	48
18.5	67

Additionally, the following X-ray powder diffraction pattern of crystalline Form XVIII atorvastatin expressed in terms of the 2 $\theta$  values was measured on a Shimadzu diffractometer with CuK $\alpha$  radiation:

2 $\theta$
7.7
9.3
9.9
12.2
16.8
18.5

5 In addition, the following X-ray powder diffraction pattern of crystalline Form XVIII atorvastatin expressed in terms of the 2 $\theta$  values was measured on an Inel (capillary) diffractometer:

2 $\theta$
7.9
9.2 (broad)
9.8 (broad)
12.2 (broad)
16.7 (broad)
18.5

In a fifteenth aspect, the present invention is directed to crystalline Form XIX atorvastatin and hydrates thereof characterized by the following X-ray powder diffraction pattern expressed in terms of the  $2\theta$  and relative intensities with a relative intensity of >10% measured on a Bruker D5000 diffractometer with  $\text{CuK}\alpha$  radiation:

$2\theta$	Relative Intensity (>10%)
5.2	32
6.3	28
7.0	100
8.6	74
10.5	34
11.6 (broad)	26
12.7 (broad)	35
14.0	15
16.7 (broad)	30
18.9	86
20.8	94
23.6 (broad)	38
25.5 (broad)	32

5

Unless the context clearly requires otherwise, throughout the description and the claims, the words "comprise", "comprising", and the like are to be construed in an inclusive sense as opposed to an exclusive or exhaustive sense; that is to say, in the sense of "including, but not limited to".

10 As inhibitors of HMG-CoA reductase, the novel crystalline forms of atorvastatin are useful hypolipidemic and hypocholesterolemic agents as well as agents in the treatment of osteoporosis and Alzheimer's disease.

A still further embodiment of the present invention is a pharmaceutical composition for administering an effective amount of crystalline Form V, Form VI,  
15 Form VII, Form VIII, Form IX, Form X, Form XI, Form XII, Form XIII, Form XIV, Form XV, Form XVI, Form XVII, Form XVIII, or Form XIX atorvastatin in unit dosage form in the treatment methods mentioned above. Finally, the present invention is

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directed to methods for production of Form V, Form VI, Form VII, Form VIII, Form IX,  
Form X, Form XI, Form XII, \_\_\_\_\_

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Form XIII, Form XIV, Form XV, Form XVI, Form XVII, Form XVIII, or  
Form XIX atorvastatin.

#### BRIEF DESCRIPTION OF THE DRAWINGS

5 The invention is further described by the following nonlimiting examples  
which refer to the accompanying Figures 1 to 35, short particulars of which are  
given below.

Figure 1

Diffractiongram of Form V atorvastatin carried out on Shimadzu XRD-6000  
diffractometer.

10 Figure 2

Diffractiongram of Form VI atorvastatin carried out on Shimadzu  
XRD-6000 diffractometer.

Figure 3

15 Diffractiongram of Form VII atorvastatin carried out on Shimadzu  
XRD-6000 diffractometer.

Figure 4

Diffractiongram of Form VIII atorvastatin carried out on Shimadzu  
XRD-6000 diffractometer.

Figure 5

20 Diffractiongram of Form IX atorvastatin carried out on Shimadzu  
XRD-6000 diffractometer.

Figure 6

Diffractiongram of Form X atorvastatin carried out on Shimadzu XRD-6000  
diffractometer.

25 Figure 7

Diffractiongram of Form XI atorvastatin carried out on Shimadzu  
XRD-6000 diffractometer.



Figure 8

Diffractiongram of Form XII atorvastatin carried out on Shimadzu XRD-6000 diffractometer.

Figure 9

5 Diffractiongram of Form XIII atorvastatin carried out on Shimadzu XRD-6000 diffractometer.

Figure 10

Diffractiongram of Form XIV atorvastatin carried out on Bruker D 5000 diffractometer.

10 Figure 11

Diffractiongram of Form XV atorvastatin carried out on Bruker D 5000 diffractometer.

Figure 12

15 Diffractiongram of Form XVI atorvastatin carried out on Bruker D 5000 diffractometer.

Figure 13

Diffractiongram of Form XVII atorvastatin carried out on Bruker D 5000 diffractometer.

Figure 14

20 Diffractiongram of Form XVIII atorvastatin carried out on Bruker D 5000 diffractometer.

Figure 15

Diffractiongram of Form XIX atorvastatin carried out on Bruker D 5000 diffractometer.

25 Figure 16

Diffractiongram of Form V atorvastatin carried out on Inel XRG-3000 diffractometer.

Figure 17

Diffractogram of Form VI atorvastatin carried out on Inel XRG-3000 diffractometer.

Figure 18

5 Diffractogram of Form VII atorvastatin carried out on Inel XRG-3000 diffractometer.

Figure 19

Diffractogram of Form VIII atorvastatin carried out on Inel XRG-3000 diffractometer.

10 Figure 20

Diffractogram of Form IX atorvastatin carried out on Inel XRG-3000 diffractometer.

Figure 21

15 Diffractogram of Form X atorvastatin carried out on Inel XRG-3000 diffractometer.

Figure 22

Diffractogram of Form XII atorvastatin carried out on Inel XRG-3000 diffractometer.

Figure 23

20 Diffractogram of Form XVI atorvastatin carried out on Inel XRG-3000 diffractometer.

Figure 24

Diffractogram of Form XVIII atorvastatin carried out on Inel XRG-3000 diffractometer.

25 Figure 25

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

Figure 26

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

Figure 27

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

Figure 28

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

10 Figure 29

Solid-state  $^{13}\text{C}$  nuclear magnetic resonance spectrum of Form X atorvastatin.

Figure 30

Raman spectrum of Form V.

15 Figure 31

Raman spectrum of Form VI.

Figure 32

Raman spectrum of Form VII.

Figure 33

20 Raman spectrum of Form VIII.

Figure 34

Raman spectrum of Form X.

Figure 35

Raman spectrum of Form XII.

25 DETAILED DESCRIPTION OF THE INVENTION

Crystalline Form V, Form VI, Form VII, Form VIII, Form IX, Form X, Form XI, Form XII, Form XIII, Form XIV, Form XV, Form XVI, Form XVII,

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Form XVIII, and Form XIX atorvastatin may be characterized by their X-ray powder diffraction patterns, by their solid state nuclear magnetic resonance spectra (NMR), and/or their Raman spectra.

#### X-RAY POWDER DIFFRACTION

5 Forms V, VI, VII, VIII, IX, X, XI, XII, XIII, XIV, XV, XVI, XVII, XVIII, and XIX

Forms V, VI, VII, VIII, IX, X, XI, XII, XIII, XIV, XV, XVI, XVII, XVIII, or XIX atorvastatin were characterized by their X-ray powder diffraction pattern. Thus, the X-ray diffraction patterns of Forms V, VI, VII, VIII, IX, X, XI, XII, or Form XIII atorvastatin were carried out on a Shimadzu XRD-6000 X-ray powder diffractometer using  $\text{CuK}\alpha$  radiation. The instrument is equipped with a fine-focus X-ray tube. The tube voltage and amperage were set at 40 kV and 40 mA, respectively. The divergence and scattering slits were set at 1°, and the receiving slit was set at 0.15 mm. Diffracted radiation was detected by a NaI scintillation detector. A theta-two theta continuous scan at 3°/min (0.4 sec/0.02° step) from 2.5 to 40 °2θ was used. A silicon standard was analyzed each day to check the instrument alignment. The X-ray diffraction patterns of Forms XIV, XV, XVI, XVII, XVIII, and XIX were carried out on a Bruker D5000 diffractometer using copper radiation, fixed slits (1.0, 1.0, 0.6 mm), and a Kevex solid state detector. Data was collected from 3.0 to 40.0 degrees in 2θ using a step size of 0.04 degrees and a step time of 1.0 seconds. It should be noted that Bruker Instruments purchased Siemens; thus, a Bruker D 5000 instrument is essentially the same as a Siemens D 5000.

25 The X-ray diffraction patterns of Forms V, VI, VII, VIII, IX, X, XII, XVI, and XVIII were also carried out on an Inel diffractometer. X-ray diffraction analyses were carried out on an Inel XRG-3000 diffractometer, equipped with a Curved Position Sensitive (CPS) detector with a 2θ range of 120 degrees. Real time data were collected using  $\text{CuK}\alpha$  radiation starting at approximately 4 °2θ at a resolution of 0.03 °2θ. The tube voltage and amperage were set to 40 kV and

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30 mA, respectively. Samples were prepared for analysis by packing them into thin-walled glass capillaries. Each capillary was mounted onto a goniometer head that is motorized to permit spinning of the capillary during data acquisition. Instrument calibration was performed daily using a silicon reference standard. The Inel diffractograms for the available forms are shown in the figures without baseline subtraction. Calculating the intensities from these diffractograms is within the skill of the art and involves using baseline subtraction to account for background scattering (e.g., scattering from the capillary).

To perform an X-ray powder diffraction measurement on a Shimadzu or Bruker instrument like the ones used for measurements reported herein, the sample is typically placed into a holder which has a cavity. The sample powder is pressed by a glass slide or equivalent to ensure a random surface and proper sample height. The sample holder is then placed into the instrument (Shimadzu or Bruker). The source of the X-ray beam is positioned over the sample, initially at a small angle relative to the plane of the holder, and moved through an arc that continuously increases the angle between the incident beam and the plane of the holder. Measurement differences associated with such X-ray powder analyses result from a variety of factors including: (a) errors in sample preparation (e.g., sample height), (b) instrument errors (e.g., flat sample errors), (c) calibration errors, (d) operator errors (including those errors present when determining the peak locations), and (e) preferred orientation. Calibration errors and sample height errors often result in a shift of all the peaks in the same direction and by the same amount. Small differences in sample height on a flat holder lead to large displacements in XRPD peak positions. A systematic study showed that, using a Shimadzu XRD-6000 in the typical Bragg-Brentano configuration, sample height differences of 1 mm led to peak shifts as high as  $1^\circ 2\theta$  (Chen, *et al.*, *J. Pharmaceutical and Biomedical Analysis*, 2001;26:63). These shifts can be identified from the X-ray diffractogram and can be eliminated by compensating for the shift (applying a systematic correction factor to all peak position values) or recalibrating the instrument. In contrast, the Inel instrument used herein places the sample in a capillary which is positioned at the center of the instrument. This minimizes sample height errors (a) and preferred orientation (e). Since, when

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using capillaries, the sample height is not established manually, the peak locations from the Inel measurements are typically more accurate than those from the Shimadzu or the Bruker instrument. As mentioned above, it is possible to rectify measurements from the various machines by applying a systematic correction factor to bring the peak positions into agreement. In general, this correction factor will bring the peak positions from the Shimadzu and Bruker into agreement with the Inel and will be in the range of 0 to  $0.2^\circ 2\theta$ .

Table 1 lists the  $2\theta$  and relative intensities of all lines in the sample with a relative intensity of  $>10\%$  for crystalline Forms V-XIX atorvastatin. The numbers listed in this table are rounded numbers.

Table 1. Intensities and Peak Locations of All Diffraction Lines With Relative Intensity Greater Than 10%<sup>a</sup> for Forms V to XIX  
(Measured on Shimadzu Diffractometer)

(Page 1 of 3)

2θ	Form V		Form VI		Form VII		Form VIII		Form IX		Form X		Form XI		Form XII		
	Relative Intensity (>10%)	2θ	Relative Intensity (>10%)	2θ	Relative Intensity (>10%)	2θ	Relative Intensity (>10%)	2θ	Relative Intensity (>10%)	2θ	Relative Intensity (>10%)	2θ	Relative Intensity (>10%)	2θ	Relative Intensity (>10%)	2θ	Relative Intensity (>10%)
4.9*	9	7.2	11	8.6	7.5	61	8.8	50	4.7	35	10.8*	58	5.4	11			
6.0	15	8.3	77	10.2	7.0	29	9.4*	32	5.2	24	12.0	12	7.7	24			
7.0	100	11.0	20	12.4*	12	10.0	16	11.2-11.7*	26	5.8	11	13.5	11	8.0	25		
8.0*	20	12.4	11	12.8*	15	12.1	10	16.7	59	6.9	13	16.5	52	8.6	42		
8.6	57	13.8	9	17.6	20	12.8	6	17.5*	33	7.9	53	17.6-18.0*	35	8.9	25		
9.9	22	16.8	14	18.3*	43	13.8	4	19.3*	55	9.2	56	19.7	82	9.9	36		
16.6	42	18.5	100	19.3	100	15.1	13	21.4*	100	9.5	50	22.3	100	10.4*	24		
19.0	27	19.7*	22	22.2*	14	16.7*	64	22.4*	33	10.3*	13	23.2	26	12.5	18		
21.1	35	20.9	14	23.4*	23	18.6*	100	23.2*	63	11.8	20	24.4	28	13.9*	9		
		25.0*	15	23.8*	26	20.3*	79	29.0*	15	16.1	13	25.8	17	16.2	10		
				25.5*	16	21.2	24			16.9	39	26.5	30	17.8	70		
						21.9	30										
						22.4	19			19.1	100	27.3	31				

\* Broad

<sup>a</sup> Relative intensity for Form V 4.9 (broad) 2θ is 9; Form VI 13.8 2θ is 9; Form VII 12.8 2θ is 6 and 13.8 2θ is 4; and Form VIII 13.9 (broad) 2θ is 9 and 27.1 2θ is 8.

Table 1. Intensities and Peak Locations of All Diffraction Lines With Relative Intensity Greater Than 10%<sup>a</sup> Forms V to XIX  
(Measured on Shimadzu Diffractometer)

(Page 2 of 3)

Form V	Form VI	Form VII	Form VIII	Form IX	Form X	Form XI	Form XII
2θ	2θ	2θ	2θ	2θ	2θ	2θ	2θ
Relative Intensity (>10%)	Relative Intensity (>10%)	Relative Intensity (>10%)	Relative Intensity (>10%)	Relative Intensity (>10%)	Relative Intensity (>10%)	Relative Intensity (>10%)	Relative Intensity (>10%)
	25.8	33	19.8	71	28.7	19.4	100
	26.5	20	21.4	49	29.5	12	51
	27.4*	38	22.3*	36	30.9*	17	13
	30.5	20	23.7*	37	32.8*	11	22.4-22.6*
			24.4	15	33.6*	15	24.3
			28.7	31	36.0*	15	25.5
					38.5*	14	26.2
							27.1
							8

\* Broad

<sup>a</sup> Relative intensity for Form V 4.9 (broad) 2θ is 9; Form VI 13.8 2θ is 9; Form VIII 12.8 2θ is 6 and 13.8 2θ is 4; and Form XII 13.9 (broad) 2θ is 9 and 27.1 2θ is 8.



Table 1. Intensities and Peak Locations of All Diffraction Lines With Relative Intensity Greater Than 10%<sup>a</sup> for Forms V to XIX (Measured on Shimadzu Diffractometer)

(Page 3 of 3)

Form XIII		Form XIV		Form XV		Form XVI		Form XVII		Form XVIII		Form XIX	
2θ	Relative Intensity (>10%)	2θ	Relative Intensity (>10%)	2θ	Relative Intensity (>10%)	2θ	Relative Intensity (>10%)	2θ	Relative Intensity (>10%)	2θ	Relative Intensity (>10%)	2θ	Relative Intensity (>10%)
8.4	100	5.4	41	5.7	26	5.2	37	5.0	27	8.0	100	5.2	32
8.9	82	6.7	31	6.1	21	6.4	34	6.1	33	9.2*	52	6.3	28
15.7*	45	7.7	100	6.8	18	7.5	100	7.3	100	9.7*	40	7.0	100
16.4*	46	8.1	35	7.5	39	8.7	79	7.9	30	12.1	24	8.6	74
17.6*	57	9.0	65	8.1	39	10.5*	19	8.5	29	16.6*	48	10.5	34
18.1*	62	16.5*	15	8.5	42	12.0*	10	9.1	22	18.5	67	11.6*	26
19.7*	58	17.6*	17	9.5	33	12.7*	17	10.0	45			12.7*	35
20.8*	91	18.0-18.7*	21	10.5*	18	16.7	26	12.1*	24			14.0	15
23.8*	57	19.5*	18	19.1-19.6*	32	18.3*	27	14.8	17			16.7*	30
						19.5	23	16.0-16.5*	20			18.9	86
						20.1-20.4*	37	17.5*	28			20.8	94
						21.2-21.9*	32	19.0*	46			23.6*	38
						22.9-23.3*	38	19.5	65			25.5*	32
						24.4-25.0*	35	20.2*	47				
								21.3	64				
								21.6	55				
								22.0	45				

\* Broad

Forms XIV, XV, XVI, XVII, XVIII, and XIX were measured on Bruker D-5000 Diffractometer.

<sup>a</sup> Relative intensity for Form V 4.9 (broad) 2θ is 9; Form VI 13.8 2θ is 9; Form VIII 12.8 2θ is 6 and 13.8 2θ is 4; and Form XII 13.9 (broad) 2θ is 9 and 27.1 2θ is 8.

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Because only 19 crystalline forms of atorvastatin are known, each form can be identified and distinguished from the other crystalline forms by either a combination of lines or a pattern that is different from the X-ray powder diffraction of the other forms.

- 5 For example, Table 2 lists combination of 2 $\theta$  peaks for Forms V to XIX atorvastatin, i.e., a set of X-ray diffraction lines that are unique to each form. Forms I to IV atorvastatin disclosed in United States Patent Numbers 5,969,156 and 6,121,461 are included for comparison.

Table 2. Forms I to XIX Unique Combination of 20 Peaks

Form I	Form II	Form III	Form IV	Form V	Form VI	Form VII	Form VIII	Form IX	Form X
9.0	8.5	8.3	4.7	6.0	7.2	8.6	7.5	8.8	4.7
9.3	9.0	16.4	5.2	7.0	8.3	10.2	9.2	9.4*	6.9
10.1	17.1-17.4	19.9	7.7	8.0*	11.0	12.8*	10.0	16.7	7.9
10.4	20.5	24.2	9.4	9.9	18.5	17.6	16.7*	17.5*	9.2
11.7			10.1	16.6		18.3*	18.6*	19.3*	9.5
12.0						19.3	20.3*	21.4*	19.1
16.8								29.0*	19.8
								30.0	

Form XI	Form XII	Form XIII	Form XIV	Form XV	Form XVI	Form XVII	Form XVIII	Form XIX
10.8*	7.7	8.4	5.4	5.7	5.2	6.1	8.0	5.5
16.5	8.0	8.9	6.7	6.1	6.4	7.3	9.2*	7.0
19.7	8.6	20.8*	7.7	7.5	7.5	7.9	16.6*	8.6
22.3	8.9	23.8*	8.1	8.1	8.7	10.0	18.5	10.5
	9.9		9.0	8.5	16.7	19.0*		12.7*
	17.8			9.5	20.1-20.4*	19.5		18.9
	19.4			19.1-19.6*	22.9-23.3*	21.3		20.8
						21.6		

\* Broad

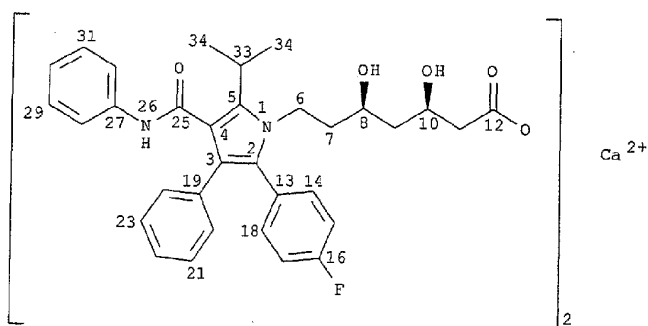
Forms I to XIII were measured on Shimadzu XRD-6000 diffractometer. Forms XIV to XIX were measured on Bruker D 5000I diffractometer. Form II 20 peaks from US Patent Number 5,969,156.

## SOLID STATE NUCLEAR MAGNETIC RESONANCE (NMR)

Methodology

Solid-state  $^{13}\text{C}$  NMR spectra were obtained at 270 or 360 MHz Tecmag instruments. High-power proton decoupling and cross-polarization with magic-angle spinning at approximately 4.7 and 4.2 kHz or 4.6 and 4.0 kHz were used for 5  
68 MHz ( $^{13}\text{C}$  frequency) data acquisition, 4.9 and 4.4 kHz were used for 91 MHz ( $^{13}\text{C}$  frequency) data acquisition. The magic angle was adjusted using the Br signal of KBr by detecting the side bands. A sample was packed into a 7 mm Doty rotor and used for each experiment. The chemical shifts were referenced 10  
externally to adamantane except for Form X where the chemical shifts are arbitrary.

Table 3 shows the solid-state NMR spectrum for crystalline Forms V, VI, VII, VIII, and X atorvastatin.



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Table 3. Chemical Shifts for Forms V, VI, VII, VIII, and X Atorvastatin

Chemical Shift				
V	VI	VII	VIII	X
185.7		186.5	186.1	187.0
		183.3	179.5	
176.8	176.5	176.8		179.5
166.9	168.2	166.5	167.9	165.5
	163.1		161.0	
	159.8	159.2		159.4
138.7	136.8	137.6	139.4	137.9
136.3			132.9	134.8
133.0				
				129.4
128.4	127.8	128.3	128.7	127.9
			124.7	123.2
122.0	122.3	122.3		
			121.8	
	118.8	119.2		119.9
117.0				
116.3			116.6	
	113.7			
	88.2	74.5		
	79.3			
	70.5	70.3		71.1
68.0		68.3	67.0	
		66.2		
43.1	43.3	43.5	43.3	43.7
		40.3		
	36.9			40.9
	31.9			

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Table 3. Chemical Shifts for Forms V, VI, VII, VIII and X Atorvastatin (cont)

Chemical Shift				
V	VI	VII	VIII	X
25.6	25.9	26.3	26.7	26.4
		24.9	24.7	25.3
	22.5	20.2	20.9	20.3
19.9			20.1	
				18.3

Forms V, VI, VII, VIII, and X: Relative peak intensity over 20 are shown here (4.5, 4.6, 4.7, or 4.9 kHz CPMAS). Spectra were obtained using two different magic-angle spinning rates to determine spinning sidebands.

Form X: Relative peak intensity over 20 are shown here (5.0 kHz CPMAS).

Table 4 shows unique solid-state NMR peaks for Forms V, VI, VII, VIII and X atorvastatin, ie, peaks within  $\pm 1.0$  ppm. Forms I to IV atorvastatin are included for comparison.

Table 4. Forms I to VIII and X Unique Solid-State NMR Peaks

Form I	Form II	Form III	Form IV	Form V	Form VI	Form VII	Form VIII	Form X
182.8	181.0	161.0	181.4	176.8	163.1	183.3	132.9	18.3
131.1	163.0	140.1	63.5		36.9	176.8		
73.1	161.0	131.8	17.9		31.9	74.5		
64.9	140.5	69.8						
		35.4						

## RAMAN SPECTROSCOPY

Methodology

The Raman spectrum was obtained on a Raman accessory interfaced to a Nicolet Magna 860 Fourier transform infrared spectrometer. The accessory  
5 utilizes an excitation wavelength of 1064 nm and approximately 0.45 W of neodymium-doped yttrium aluminum garnet (Nd:YAG) laser power. The spectrum represents 64 or 128 co-added scans acquired at 4  $\text{cm}^{-1}$  resolution. The sample was prepared for analysis by placing a portion into a 5-mm diameter glass tube and positioning this tube in the spectrometer. The spectrometer was  
10 calibrated (wavelength) with sulfur and cyclohexane at the time of use.

Table 5 shows the Raman spectra for Forms V, VI, VII, VIII, X, and XII atorvastatin.



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Table 5. Raman Peak Listing for Forms V, VI, VII, VIII, X and XII  
Atorvastatin

Form V	Form VI	Form VII	Form VIII	Form X	Form XII
3062	3058	3060	3065	3062	3064
					2973
	2935	2927	2923	2911	2926
1652	1651	1649	1658	1650	1652
1604	1603	1603	1603	1603	1603
1528	1556	1524	1531	1525	1527
	1525		1510		
			1481		
1478	1478	1476		1478	1470
1440					
1413	1412	1412	1413	1411	1410
1397		1397			
1368		1368		1369	1367
				1240	1240
1158	1157	1159		1158	1159
1034		1034		1034	1034
1001	997	998	997	999	1002
825		824		824	823
245					
224					
130					
		114	121	116	

Relative peak intensity over 20 are shown.

Table 6 lists unique Raman peaks for Forms V, VI, VII, VIII, X, and XII atorvastatin, ie, only one other form has a peak with  $\pm 4 \text{ cm}^{-1}$ . In the case of Forms VI and X, it is a unique combination of peaks. Forms I to IV atorvastatin are included for comparison.

Table 6. Forms I to VIII, X and XII Unique Raman Peaks

Form I	Form II	Form III	Form IV	Form V	Form VI*	Form VII	Form VIII	Form X*	Form XII
3080	1663	2938	423	1440	3058	1397	1510	3062	2973
1512	359	1660	215	1397	2935		1481	2911	
1439		1510	132	130	1556		1413	1525	
142		1481			1525		121	1240	
		1427							
		1182							
		859							

\* Unique combination of Raman peaks

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Crystalline Forms V to XIX atorvastatin of the present invention may exist in anhydrous forms as well as hydrated and solvated forms. In general, the hydrated forms are equivalent to unhydrated forms and are intended to be encompassed within the scope of the present invention. Crystalline Form XIV contains about 6 mol of water. Preferably, Form XIV contains 6 mol of water. Crystalline Forms V, X, and XV atorvastatin contain about 3 mol of water. Preferably, Forms V, X, and XV atorvastatin contain 3 mol of water.

Crystalline Form VII contains about 1.5 mol of water. Preferably, Form VII atorvastatin contains 1.5 mol of water. Crystalline Form VIII contains about 2 mol of water. Preferably, Form VIII atorvastatin contains 2 mol of water.

Crystalline Forms XVI-XIX may exist as a solvate.

Crystalline forms of atorvastatin of the present invention, regardless of the extent of hydration and/or solvation having equivalent x-ray powder diffractograms, ssNMR, or Raman spectra are within the scope of the present invention.

Crystalline forms, in general, can have advantageous properties. A polymorph, solvate, or hydrate is defined by its crystal structure and properties. The crystal structure can be obtained from X-ray data or approximated from other data. The properties are determined by testing. The chemical formula and chemical structure does not describe or suggest the crystal structure of any particular polymorphic or crystalline hydrate form. One cannot ascertain any particular crystalline form from the chemical formula, nor does the chemical formula tell one how to identify any particular crystalline solid form or describe its properties. Whereas a chemical compound can exist in three states—solid, solution, and gas-crystalline solid forms exist only in the solid state. Once a chemical compound is dissolved or melted, the crystalline solid form is destroyed and no longer exists (Wells J.I., Aulton M.E. *Pharmaceutics. The Science of Dosage Form Design. Reformulation*, Aulton M.E. ed., Churchill Livingstone, 1988;13:237).

The new crystalline forms of atorvastatin described herein have advantageous properties. Form VII has good chemical stability, which is comparable to Form I (disclosed in United States Patent Number 5,969,156).

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Since noncrystalline forms of atorvastatin are not chemically stable, this is a significant advantage, which would translate into enhanced shelf life and longer expiration dating. Form VII can be prepared from acetone/water, whereas Form I is prepared from the more toxic methanol/water system. Form VII is the  
5 sesquihydrate and contains less water, meaning that a unit weight of Form VII contains more atorvastatin molecules, meaning it is of higher potency.

The ability of a material to form good tablets at commercial scale depends upon a variety of drug physical properties, such as the Tableting Indices described in Hiestand H. and Smith D., *Indices of Tableting Performance, Powder*  
10 *Technology*, 1984;38:145-159. These indices may be used to identify forms of atorvastatin calcium which have superior tableting performance. One such index is the Brittle Fracture Index (BFI), which reflects brittleness, and ranges from 0 (good - low brittleness) to 1 (poor - high brittleness). For example, Form VII has a  
15 BFI value 0.09, while Form I has a BFI value 0.81. Thus, Form VII is less brittle than Form I. This lower brittleness indicates greater ease of manufacture of tablets.†

Form VIII also has less water than Form I (dihydrate vs trihydrate) and thus a gram of Form VIII contains more atorvastatin molecules.

Form X is advantageous in that it can be prepared from the less toxic  
20 isopropanol (IPA):water system, thus avoiding the more toxic methanol:water system.

Form XII has the highest melting point (210.6). Since high melting point correlates with stability at high temperature, this means this form is most stable at  
25 temperatures near the melting point. High melting forms can be advantageous when process methods involving high temperatures are used. Form XII is also prepared from the less toxic tetrahydrofuran (THF) water system.

Form XIV is prepared using the less toxic THF/water system.

The present invention provides a process for the preparation of crystalline  
30 Forms V to XIX atorvastatin which comprises crystallizing atorvastatin from a solution in solvents under conditions which yield crystalline Forms V to XIX atorvastatin.

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

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

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

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

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

The powders and tablets preferably contain from two or ten to about seventy percent of the active compound. Suitable carriers are magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting wax,  
30 cocoa butter, and the like. The term "preparation" is intended to include the formulation of the active compound with encapsulating material as a carrier providing a capsule in which the active component, with or without other carriers,

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is surrounded by a carrier, which is thus in association with it. Similarly, cachets and lozenges are included. Tablets, powders, capsules, pills, cachets, and lozenges can be used as solid dosage forms suitable for oral administration.

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

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

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

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

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

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

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

5 In therapeutic use as hypolipidemic and/or hypocholesterolemic agents and agents to treat osteoporosis and Alzheimer's disease, the crystalline Forms V to XIX atorvastatin utilized in the pharmaceutical method of this invention are administered at the initial dosage of about 2.5 mg to about 80 mg daily. A daily dose range of about 2.5 mg to about 20 mg is preferred. The dosages, however, 10 may be varied depending upon the requirements of the patient, the severity of the condition being treated, and the compound being employed. Determination of the proper dosage for a particular situation is within the skill of the art. Generally, treatment is initiated with smaller dosages which are less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the 15 optimum effect under the circumstance is reached. For convenience, the total daily dosage may be divided and administered in portions during the day if desired.

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

## EXAMPLE 1

20 [R-(R\*,R\*)]-2-(4-Fluorophenyl)- $\beta$ , $\delta$ -dihydroxy-5-(1-methylethyl)-3-phenyl-4-  
[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid hemi calcium salt  
(Forms V-XIX atorvastatin)

**Form V Atorvastatin**Method A

25 Amorphous atorvastatin calcium (United States Patent Number 5,273,995) was slurried in a mixture of acetonitrile/water (9:1) to afford crystalline Form V atorvastatin.

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Method B

Crystalline Form I atorvastatin calcium (United States Patent Number 5,969,156) was slurried in a mixture of acetonitrile/water (9:1) at 60°C overnight, filtered, and air dried to afford crystalline Form V atorvastatin.

5 Method C

Amorphous atorvastatin calcium (United States Patent Number 5,273,995) was stressed under vapors of acetonitrile/water (9:1) to afford crystalline Form V atorvastatin.

Method D

10 Acetonitrile was added to a solution of amorphous atorvastatin calcium (United States Patent Number 5,273,995) in tetrahydrofuran/water (9:1) and cooled to afford crystalline Form V atorvastatin.

Method E

15 Acetonitrile was added to a solution of amorphous atorvastatin calcium (United States Patent Number 5,273,995) in dimethylformamide/water and fast evaporation affords crystalline Form V atorvastatin.

Method F

20 Amorphous atorvastatin calcium (United States Patent Number 5,273,995) diffused in a vapor of acetonitrile/water (9:1) to afford crystalline Form V atorvastatin.

Crystalline Form V atorvastatin, mp 171.4°C, trihydrate  
Karl Fischer 4.88% (3 mol of water).

**Form VI Atorvastatin**Method A

25 Amorphous atorvastatin calcium (United States Patent Number 5,273,995) was placed into a vapor jar containing dimethylformamide/water (9:1) for 20 days to afford crystalline Form VI atorvastatin.



Method B

Fast evaporation of a dimethylformamide/water solution of amorphous atorvastatin calcium (United States Patent Number 5,273,995) afforded crystalline Form VI atorvastatin.

5 Method C

Fast evaporation of a dimethylformamide/water (saturated) solution of amorphous atorvastatin calcium (United States Patent Number 5,273,995) seeded with crystalline Form VI afforded crystalline Form VI atorvastatin.

Crystalline Form VI atorvastatin, mp 145.9°C.

10 **Form VII Atorvastatin**Method A

A solution of amorphous atorvastatin calcium (United States Patent Number 5,273,995) in acetone/water (1:1) (5.8 mg/mL) was stirred overnight. A solid formed which was filtered to afford crystalline Form VII atorvastatin.

15 Method B

A solution of amorphous atorvastatin calcium (United States Patent Number 5,273,995) in acetone/water (1:1) was evaporated at 50°C to afford crystalline Form VII atorvastatin.

Method C

20 A saturated solution of amorphous atorvastatin calcium (United States Patent Number 5,273,995) in acetone/water (1:1) was seeded with crystalline Form VII atorvastatin to afford crystalline Form VII atorvastatin.

Method D

25 Fast evaporation of a saturated solution of amorphous atorvastatin calcium (United States Patent Number 5,273,995) in acetone/water (1:1) was seeded with crystalline Form VII to afford crystalline Form VII atorvastatin.

Crystalline Form VII atorvastatin, mp 195.9°C, 1.5 hydrate  
Karl Fischer 2.34% (1.5 mol of water).

**Form VIII Atorvastatin**Method A

5 A solution of amorphous atorvastatin calcium (United States Patent Number 5,273,995) in dimethylformamide/water (saturated) (9:1), was seeded with crystalline Form VII and evaporated to afford crystalline Form VIII atorvastatin.

Method B

10 Fast evaporation of a solution of amorphous atorvastatin calcium (United States Patent Number 5,273,995) in dimethylformamide/water (9:1) affords crystalline Form VIII atorvastatin.

Crystalline Form VIII atorvastatin, mp 151°C, dihydrate  
Karl Fischer 2.98% (2 mol of water).

**Form IX Atorvastatin**Method A

15 A solution of amorphous atorvastatin calcium (United States Patent Number 5,273,995) in acetone/water (6:4) (3.4 mg/mL) was evaporated on a rotary evaporator to afford crystalline Form IX atorvastatin.

Method B

20 A solution of amorphous atorvastatin calcium (United States Patent Number 5,273,995) in acetone/water (6:4) was filtered, seeded with crystalline Form IX evaporated on a rotary evaporator to afford crystalline Form IX atorvastatin.

Method C

25 A solution of amorphous atorvastatin calcium (United States Patent Number 5,273,995) in acetone/water (6:4) was stirred for 0.5 hours, filtered, evaporated on rotary evaporator to concentrate the solution, and dried in a vacuum oven to afford crystalline Form IX atorvastatin.

**Form X Atorvastatin**Method A

5 A slurry of amorphous atorvastatin calcium (United States Patent Number 5,273,995) in isopropanol/water (9:1) was stirred for a few days, filtered, and air dried to afford crystalline Form X atorvastatin.

Method B

A slurry of amorphous atorvastatin calcium (United States Patent Number 5,273,995) in isopropanol/water (9:1) was stirred for 5 days, filtered, and air dried to afford crystalline Form X atorvastatin.

10 Method C

A saturated solution of amorphous atorvastatin calcium (United States Patent Number 5,273,995) in isopropanol/water (9:1) was stirred for 2 days, filtered, and air dried to afford crystalline Form X atorvastatin.

15 Crystalline Form X atorvastatin, mp 180.1°C, trihydrate  
Karl Fischer 5.5% (3.5 mol of water).

**Form XI Atorvastatin**

A solution of amorphous atorvastatin calcium (United States Patent Number 5,273,995) in acetonitrile/water (9:1) was filtered and allowed to evaporate slowly to afford crystalline Form XI atorvastatin.

20 **Form XII Atorvastatin**

Crystalline Form I atorvastatin calcium (United States Patent Number 5,969,156) was slurried in tetrahydrofuran/water (2:8) at 90°C for 5 days, filtered, and air dried to afford crystalline Form XII atorvastatin.

Crystalline Form XII atorvastatin, mp 210.6°C.

25 **Form XIII Atorvastatin**

Crystalline Form I atorvastatin calcium (United States Patent Number 5,969,156) was added to 10 mL 2:8 water:methanol to leave a layer of solid on the bottom of a vial. The slurry was heated to about 70°C for 5 days. The supernatant was removed, and the solid air dried to afford crystalline Form XIII atorvastatin.

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**Form XIV Atorvastatin**

Amorphous atorvastatin calcium (United States Patent Number 5,273,995), 1 g, was slurried for 3 weeks in 45 mL of isopropyl alcohol/5 mL of water (9:1) at ambient temperature. The mixture was filtered to afford crystalline Form XIV atorvastatin after drying at ambient temperature.

Differential scanning calorimetry (DSC) indicates a low desolvation event at about 60°C (peak) followed by a melt at about 150°C. Combustion analysis indicates that the compound is a hexahydrate. Thermographic infrared spectroscopy (TG-IR) shows the compound contains water. Karl Fischer shows the compound contains 5.8% water.

**Form XV Atorvastatin**

Amorphous atorvastatin calcium (United States Patent Number 5,273,995), 1 g, was slurried for 3 weeks in 45 mL acetonitrile/5 mL of water (9:1) at ambient temperature. The mixture was filtered to afford crystalline Form XV atorvastatin after drying at ambient temperature. DSC indicates a low desolvation event at about 78°C (peak) followed by a melt at about 165°C. Combustion analysis indicates that the compound is a trihydrate. TG-IR shows the compound contains water.

**Form XVI Atorvastatin**

Amorphous atorvastatin calcium (United States Patent Number 5,273,995), 1 g, was slurried for about 1 day in 9:1 acetonitrile/water at room temperature. The mixture was filtered to afford crystalline Form XVI atorvastatin after drying at ambient temperature. DSC indicates a broad endotherm at peak temperature of 72°C and an endotherm with onset temperature of 164°C. The weight loss profile by thermographic analysis (TGA) indicates a total weight loss of about 7% at 30°C to 160°C. Combustion analysis indicates that TGA and Karl Fischer analysis (shows 7.1% water) indicates the compound is a tetrahydrate/acetonitrile solvate.

**Form XVII Atorvastatin**

Amorphous atorvastatin calcium (United States Patent Number 5,273,995), 0.5 g, was slurried for about 2 days in 5 mL of 9:1 dimethylformamide (DMF)/water containing 25 mL of acetonitrile at room temperature. The mixture

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was filtered to afford crystalline Form XVII atorvastatin after drying at ambient temperature. DSC showed multiple broad endotherms indicating the compound was a solvate.

**Form XVIII Atorvastatin**

5           Crystalline Form XVI atorvastatin, 0.5 g, was dried for about 1 day at room temperature to afford crystalline Form XVIII atorvastatin. DSC showed a broad endotherm at low temperature indicating the compound was a solvate. Karl Fischer analysis showed the compound contained 4.4% water.

**Form XIX Atorvastatin**

10           Amorphous atorvastatin calcium (United States Patent Number 5,273,995), 0.4 g, was slurried for about 7 days in 4 mL methyl ethyl ketone at room temperature. The mixture was filtered to afford crystalline Form XIX atorvastatin after drying at ambient temperature. DSC indicated a low desolvation event at about 50°C (peak) followed by a melt at about 125°C. TGA analysis indicates that  
15           the compound is a solvate that desolvates at low temperature.

## CLAIMS

What is claimed is:

1. A crystalline Form V atorvastatin or a hydrate thereof having an X-ray powder diffraction containing the following  $2\theta$  values measured using  
5  $\text{CuK}\alpha$  radiation: 4.9 (broad), 6.0, 7.0, 8.0 (broad), 8.6, 9.9, 16.6, 19.0, and 21.1.
2. A crystalline Form VI atorvastatin or a hydrate thereof having an X-ray powder diffraction containing the following  $2\theta$  values measured using  
10  $\text{CuK}\alpha$  radiation: 7.2, 8.3, 11.0, 12.4, 13.8, 16.8, 18.5, 19.7 (broad), 20.9, and 25.0.
3. A crystalline Form VII atorvastatin or a hydrate thereof having an X-ray powder diffraction containing the following  $2\theta$  values measured using  
 $\text{CuK}\alpha$  radiation: 8.6, 10.2, 12.4 (broad), 12.8 (broad), 17.6, 18.3 (broad),  
15 19.3, 22.2 (broad), 23.4 (broad), 23.8 (broad), and 25.5 (broad).
4. A crystalline Form VIII atorvastatin or a hydrate thereof having an X-ray powder diffraction containing the following  $2\theta$  values measured using  
 $\text{CuK}\alpha$  radiation: 7.5, 9.2, 10.0, 12.1, 12.8, 13.8, 15.1, 16.7 (broad), 18.6  
20 (broad), 20.3 (broad), 21.2, 21.9, 22.4, 25.8, 26.5, 27.4 (broad), and 30.5.
5. A crystalline Form IX atorvastatin or a hydrate thereof having an X-ray powder diffraction containing the following  $2\theta$  values measured using  
 $\text{CuK}\alpha$  radiation: 8.8, 9.4 (broad), 11.2-11.7 (broad), 16.7, 17.5 (broad),  
19.3 (broad), 21.4 (broad), 22.4 (broad), 23.2 (broad), and 29.0 (broad).
6. A crystalline Form X atorvastatin or a hydrate thereof having an X-ray powder diffraction containing the following  $2\theta$  values measured using

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CuK $\alpha$  radiation: 4.7, 5.2, 5.8, 6.9, 7.9, 9.2, 9.5, 10.3 (broad), 11.8, 16.1, 16.9, 19.1, 19.8, 21.4, 22.3 (broad), 23.7 (broad), 24.4, and 28.7.

7. A crystalline Form XI atorvastatin or a hydrate thereof having an X-ray powder diffraction containing the following  $2\theta$  values measured using CuK $\alpha$  radiation: 10.8 (broad), 12.0, 13.5, 16.5, 17.6-18.0 (broad), 19.7, 22.3, 23.2, 24.4, 25.8, 26.5, 27.3, 28.7, 29.5, 30.9 (broad), 32.8 (broad), 33.6 (broad), 36.0 (broad), and 38.5 (broad).
8. A crystalline Form XII atorvastatin or a hydrate thereof having an X-ray powder diffraction containing the following  $2\theta$  values measured using CuK $\alpha$  radiation: 5.4, 7.7, 8.0, 8.6, 8.9, 9.9, 10.4 (broad), 12.5, 13.9 (broad), 16.2, 17.8, 19.4, 20.8, 21.7, 22.4-22.6 (broad), 24.3, 25.5, 26.2, and 27.1.
9. A crystalline Form XIII atorvastatin or a hydrate thereof having an X-ray powder diffraction containing the following  $2\theta$  values measured using CuK $\alpha$  radiation: 8.4, 8.9, 15.7 (broad), 16.4 (broad), 17.6 (broad), 18.1 (broad), 19.7 (broad), 20.8 (broad), and 23.8 (broad).
10. A crystalline Form XIV atorvastatin or a hydrate thereof having an X-ray powder diffraction containing the following  $2\theta$  values measured using CuK $\alpha$  radiation: 5.4, 6.7, 7.7, 8.1, 9.0, 16.5 (broad), 17.6 (broad), 18.0-18.7 (broad), and 19.5 (broad).
11. A crystalline Form XV atorvastatin or a hydrate thereof having an X-ray powder diffraction containing the following  $2\theta$  values measured using CuK $\alpha$  radiation: 5.7, 6.1, 6.8, 7.5, 8.1, 8.5, 9.5, 10.5 (broad), and 19.1-19.6 (broad).

12. A crystalline Form XVI atorvastatin or a hydrate thereof having an X-ray powder diffraction containing the following  $2\theta$  values measured using  $\text{CuK}\alpha$  radiation: 5.2, 6.4, 7.5, 8.7, 10.5 (broad), 12.0 (broad), 12.7 (broad), 16.7, 18.3 (broad), 19.5, 20.1-20.4 (broad), 21.2-21.9 (broad), 22.9-23.3 (broad), and 24.4-25.0 (broad).
- 5 13. A crystalline Form XVII atorvastatin or a hydrate thereof having an X-ray powder diffraction containing the following  $2\theta$  values measured using  $\text{CuK}\alpha$  radiation: 5.0, 6.1, 7.3, 7.9, 8.5, 9.1, 10.0, 12.1 (broad), 14.8, 16.0-16.5 (broad), 17.5 (broad), 19.0 (broad), 19.5, 20.2 (broad) 21.3, 21.6 and 22.0.
- 10 14. A crystalline Form XVIII atorvastatin or a hydrate thereof having an X-ray powder diffraction containing the following  $2\theta$  values measured using  $\text{CuK}\alpha$  radiation: 8.0, 9.2 (broad), 9.7 (broad), 12.1, 16.6 (broad) and 18.5.
- 15 15. A crystalline Form XIX atorvastatin or a hydrate thereof having an X-ray powder diffraction containing the following  $2\theta$  values measured using  $\text{CuK}\alpha$  radiation: 5.2, 6.3, 7.0, 8.6, 10.5, 11.6 (broad), 12.7 (broad), 14.0, 16.7 (broad), 18.9, 20.8, 23.6 (broad), and 25.5 (broad).
16. Crystalline atorvastatin or a hydrate thereof, substantially as herein described with reference to any one of the examples but excluding comparative examples.



**FIG. 1**

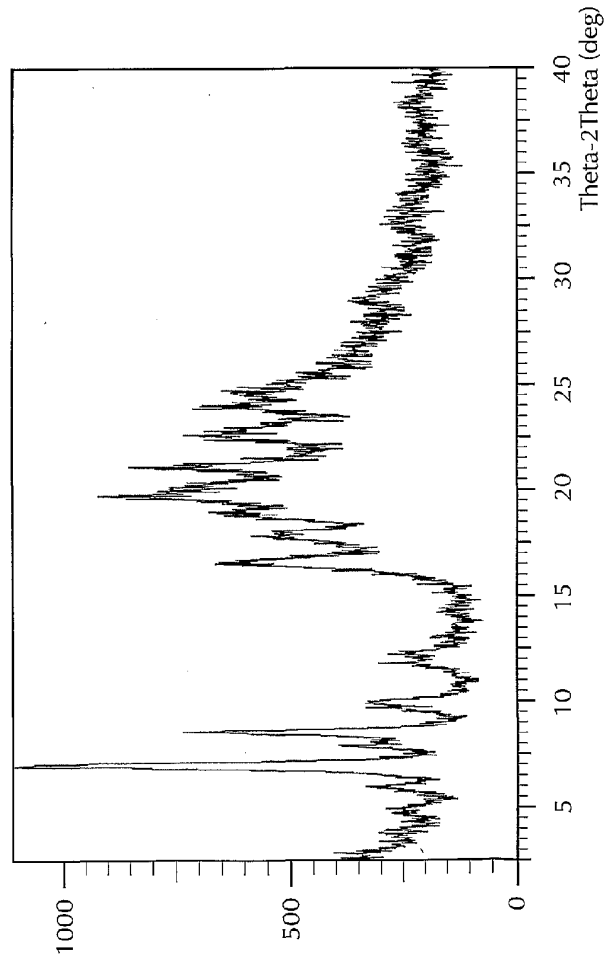


FIG. 2

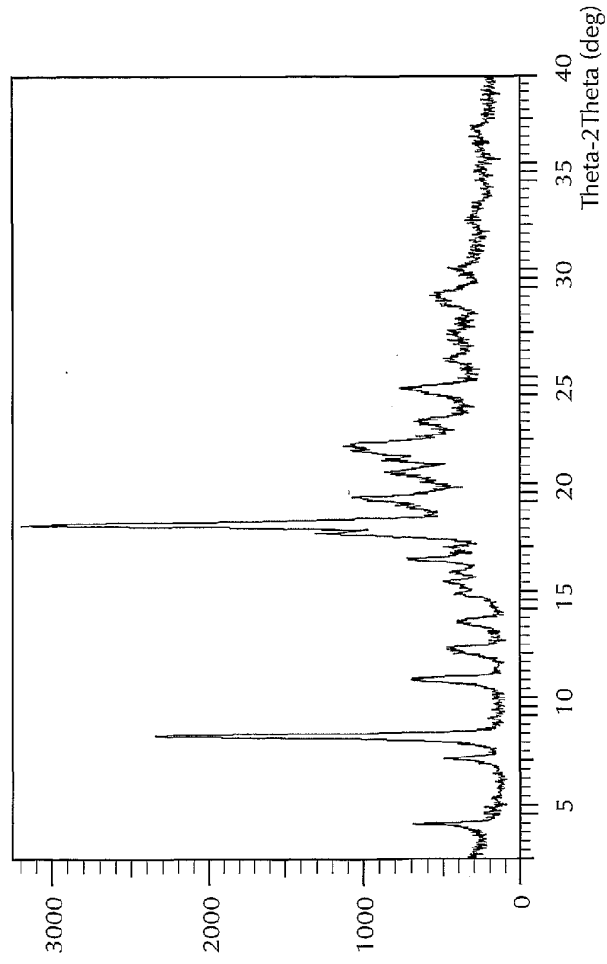
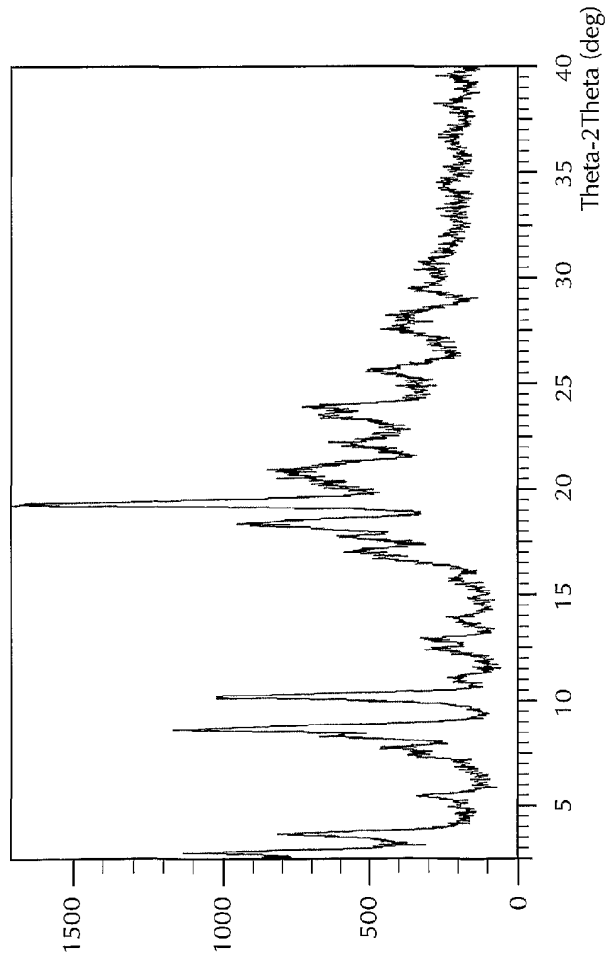


FIG. 3



**FIG. 4**

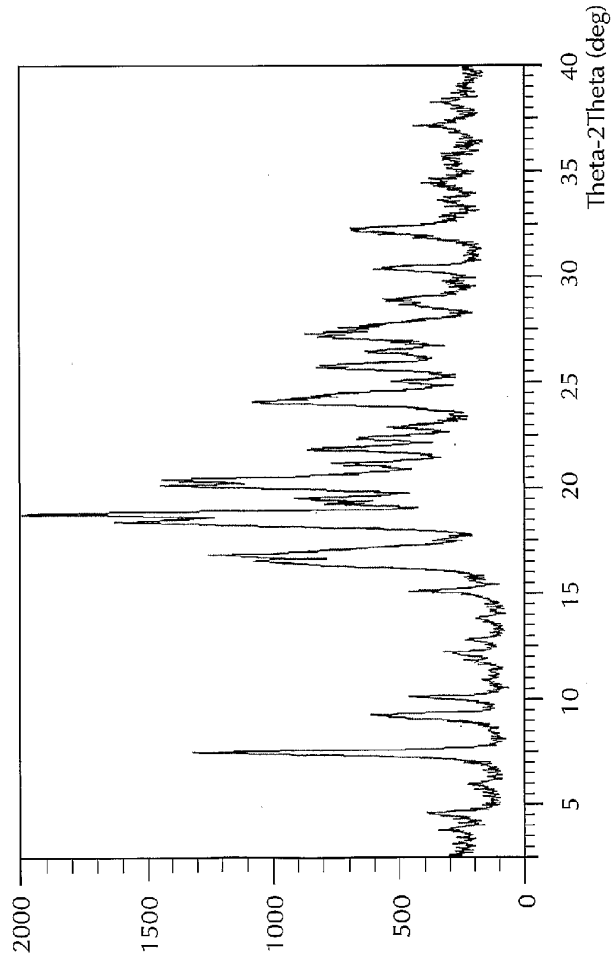


FIG. 5

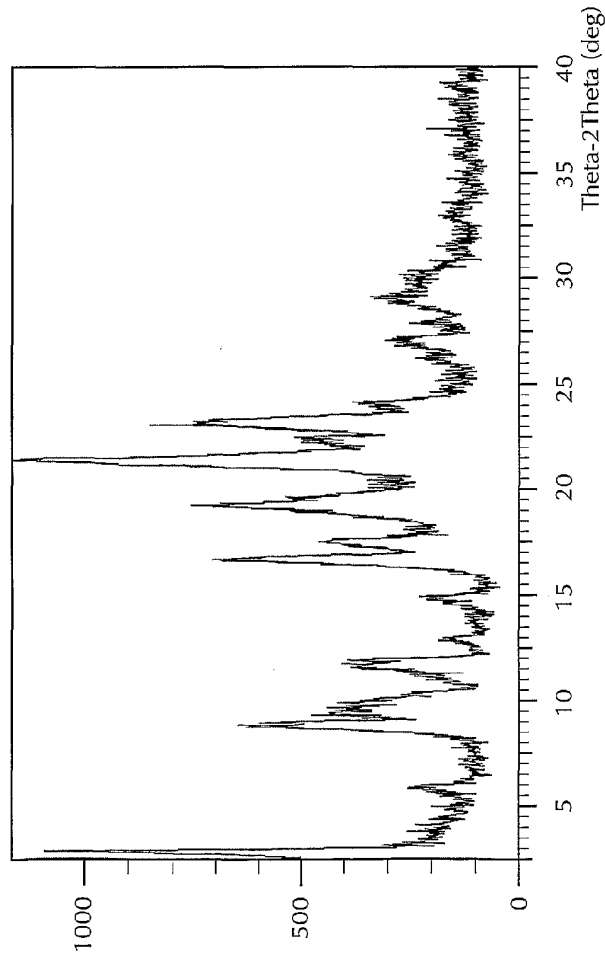


FIG. 6

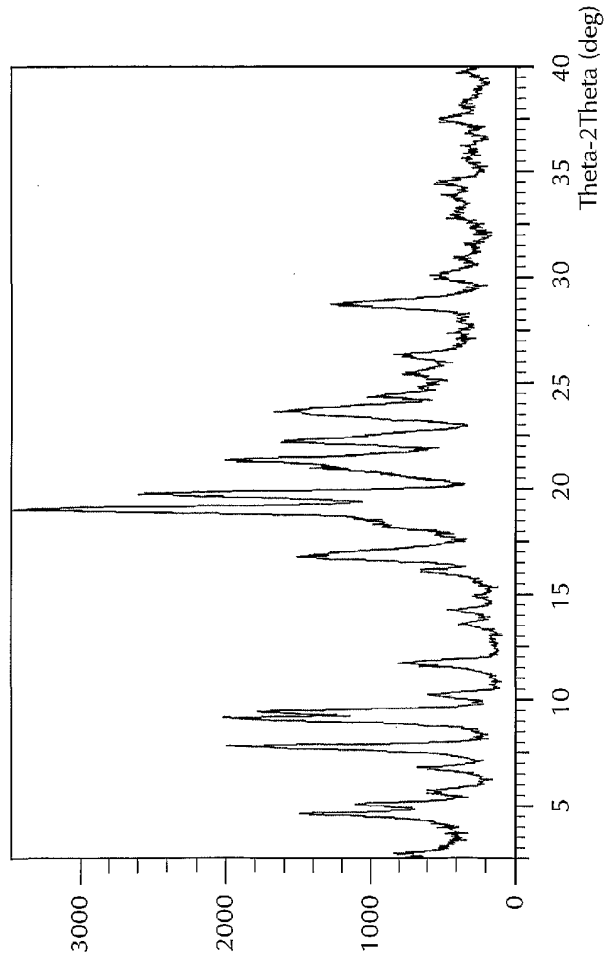


FIG. 7

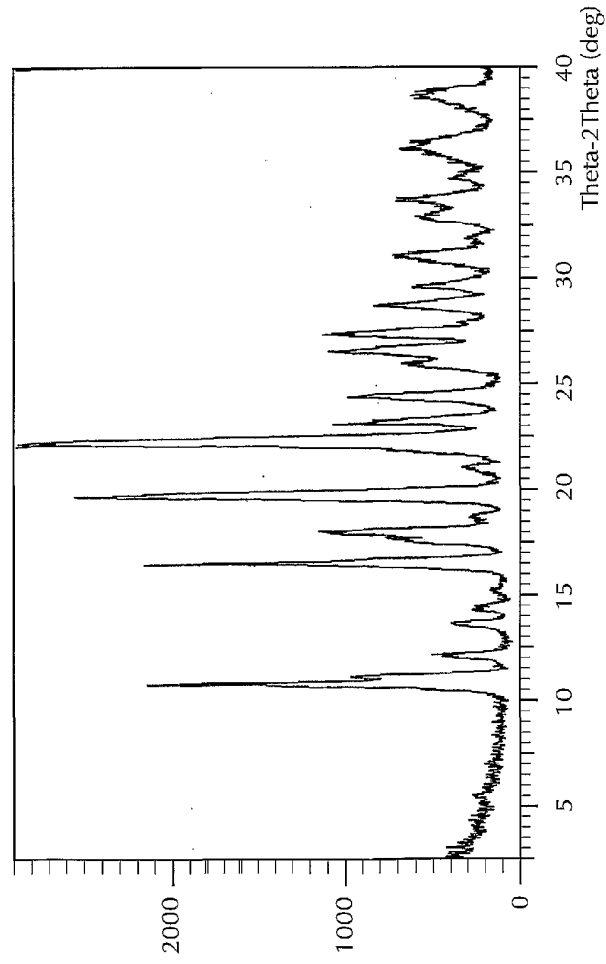


FIG. 8

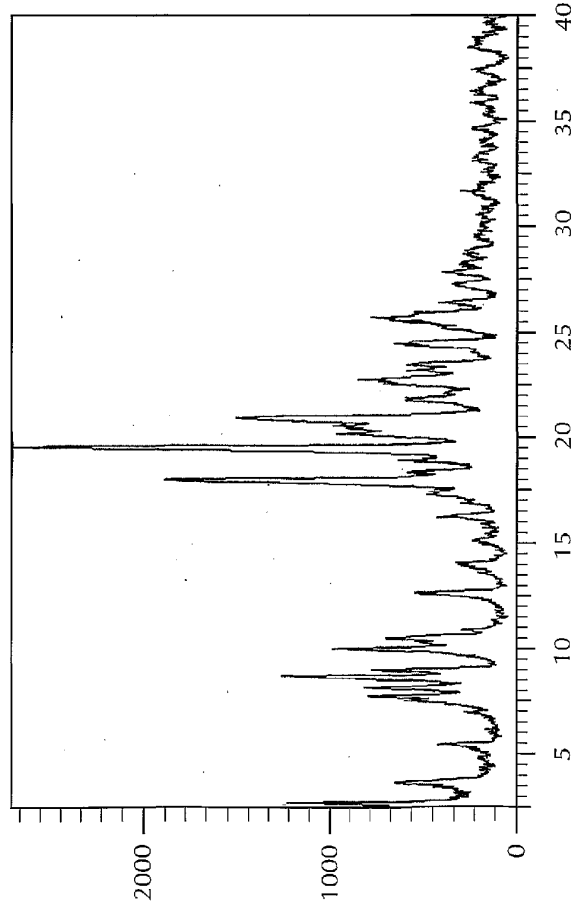
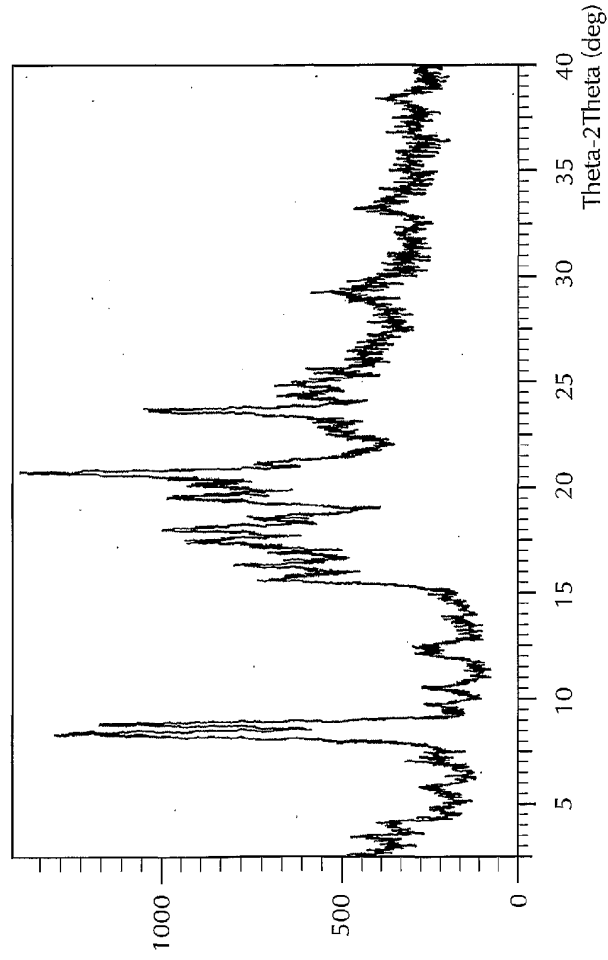
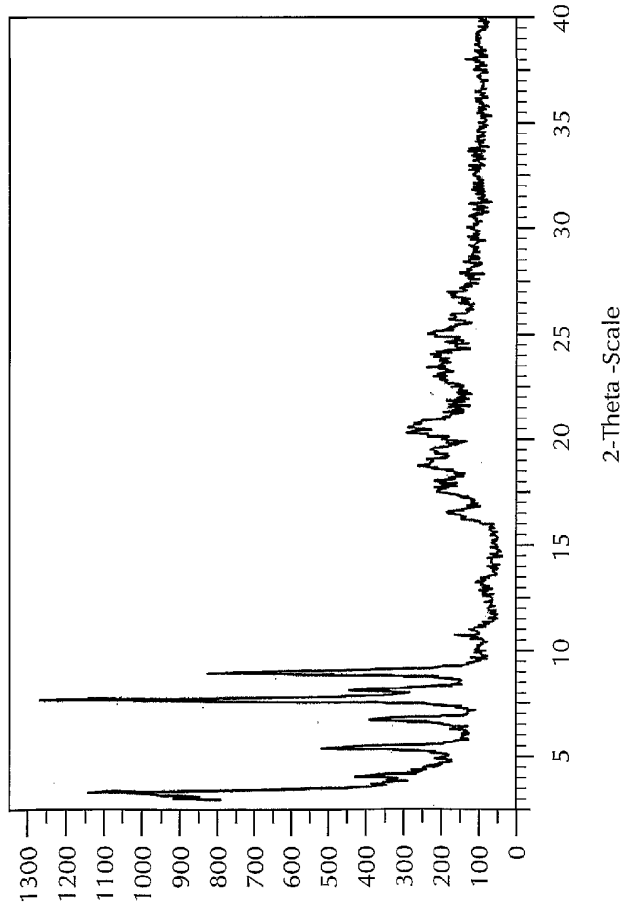




FIG. 9



**FIG. 10**



**FIG. 11**

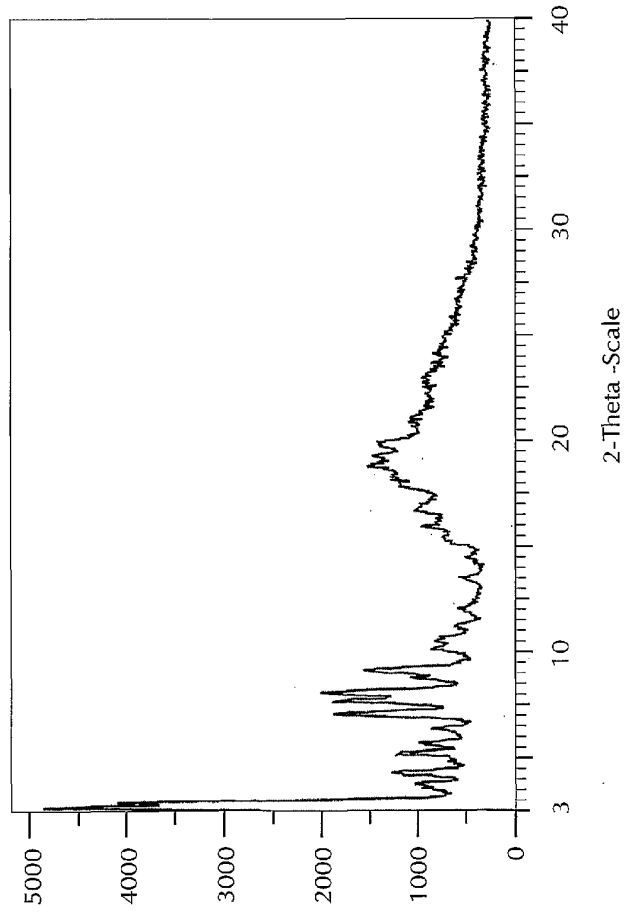
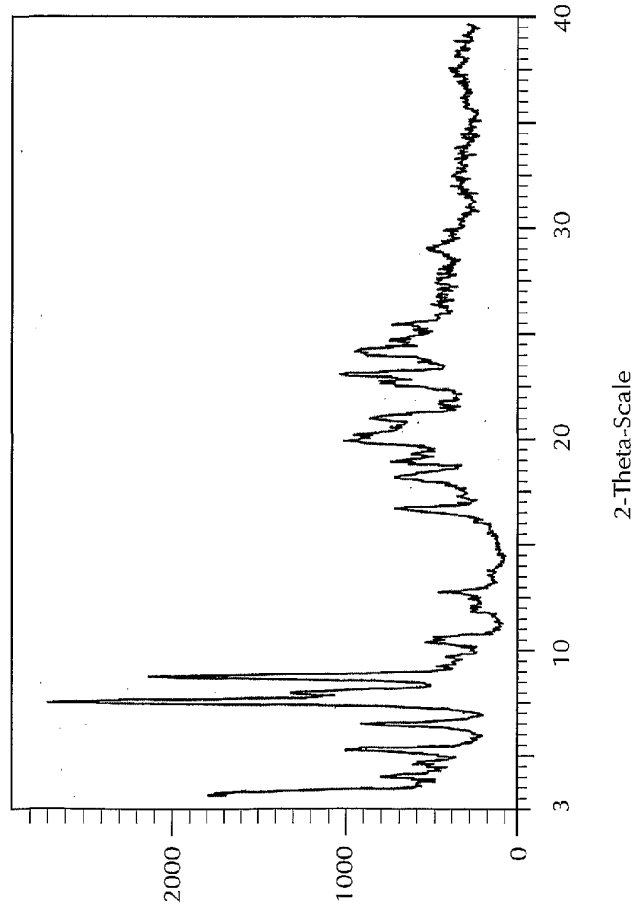


FIG. 12



**FIG. 13**

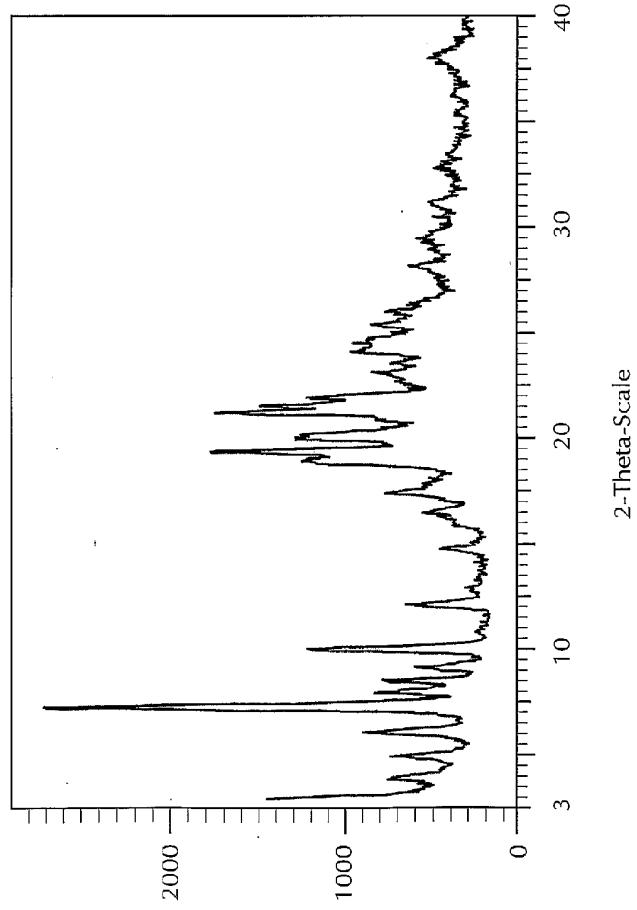


FIG. 14

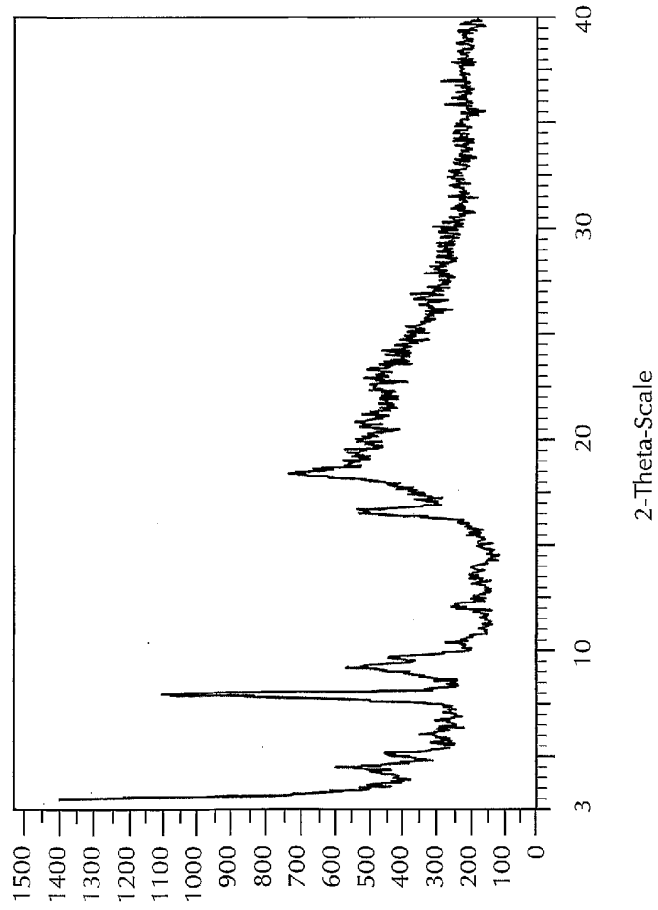
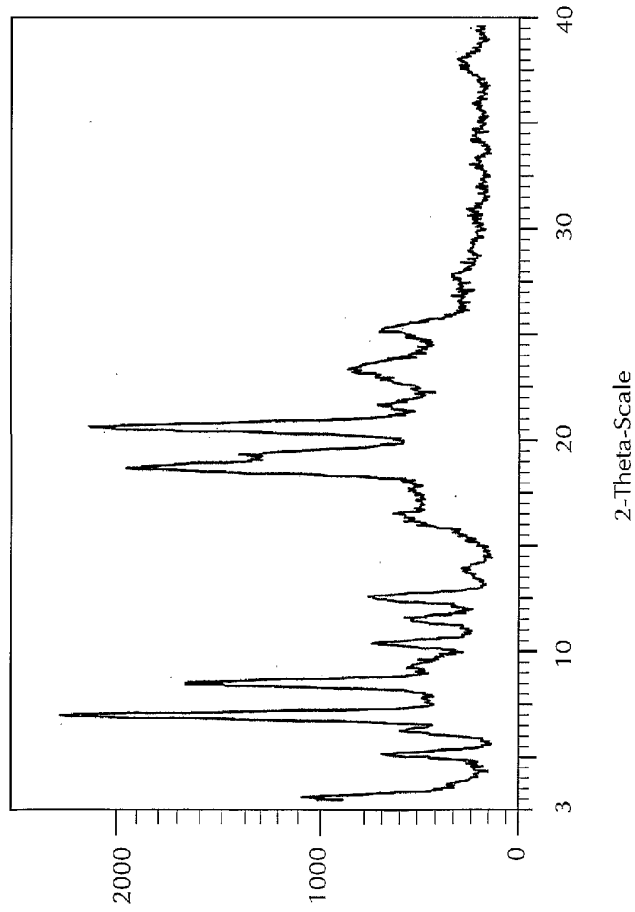
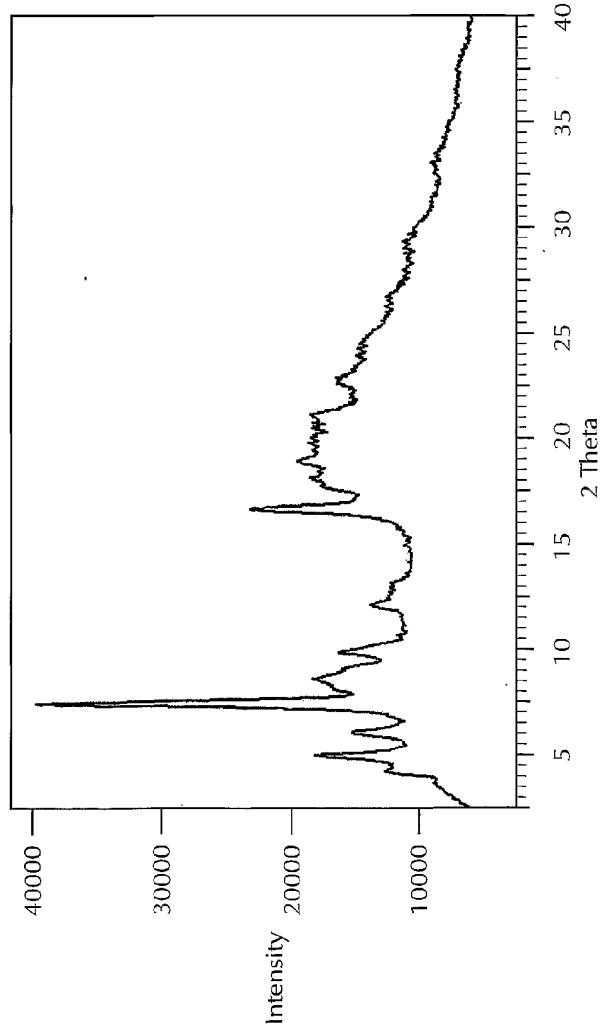


FIG. 15



**FIG. 16**





**FIG. 17**

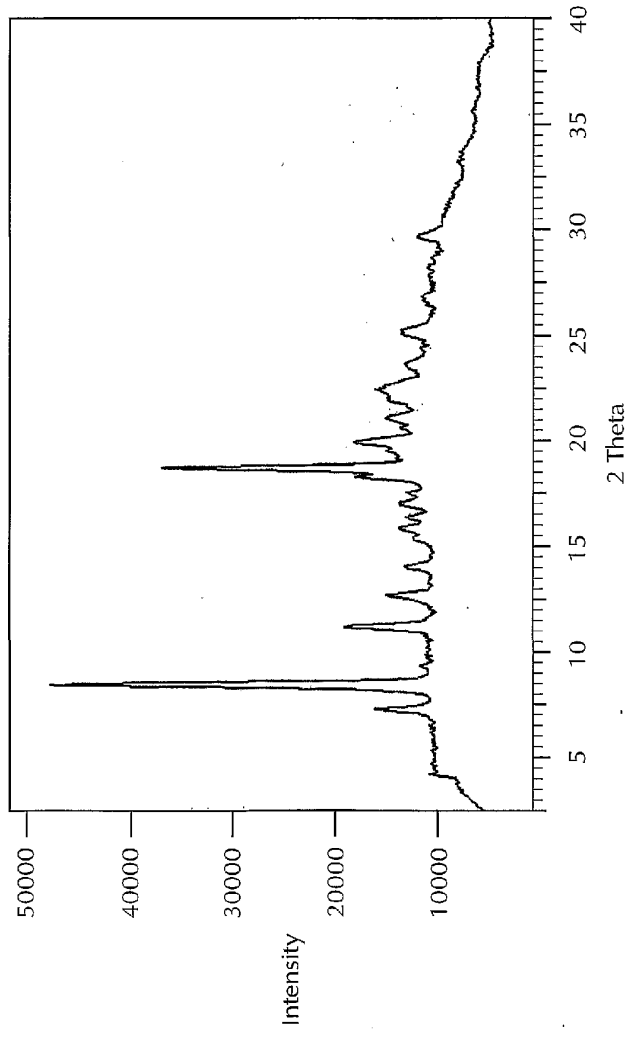
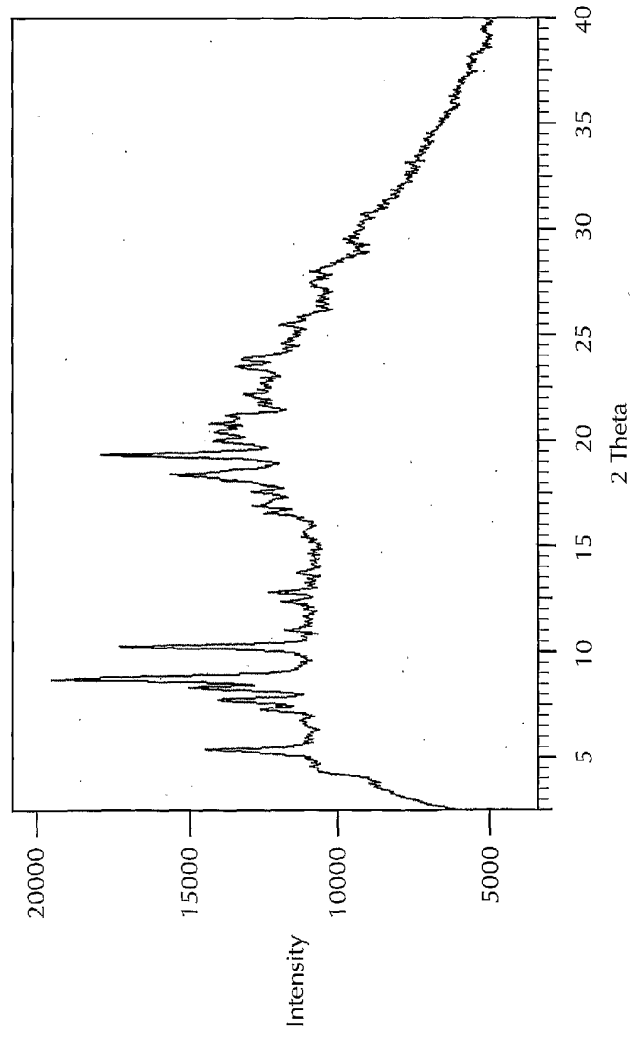
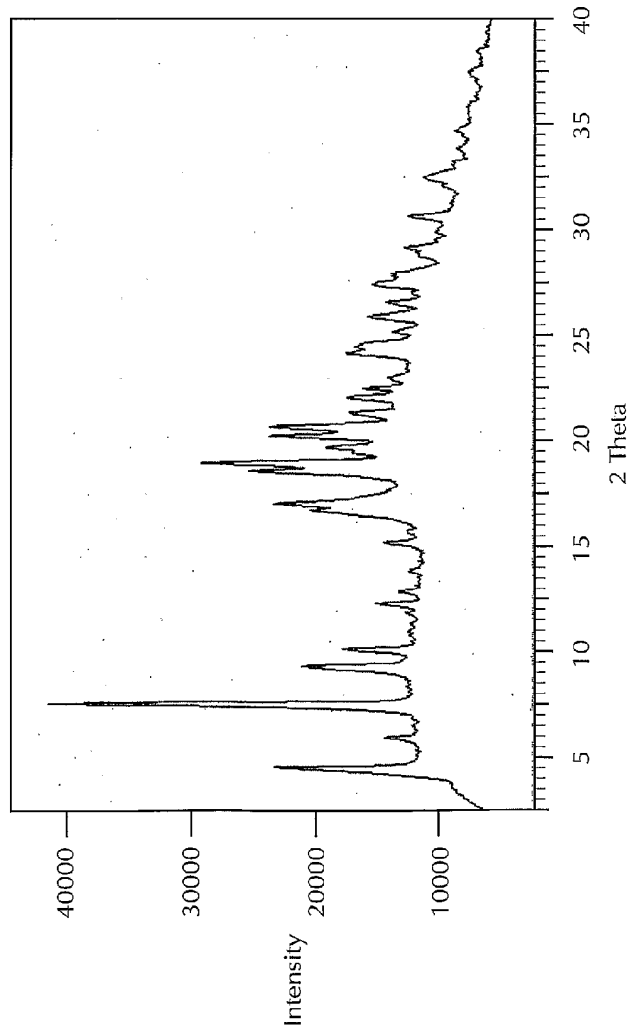
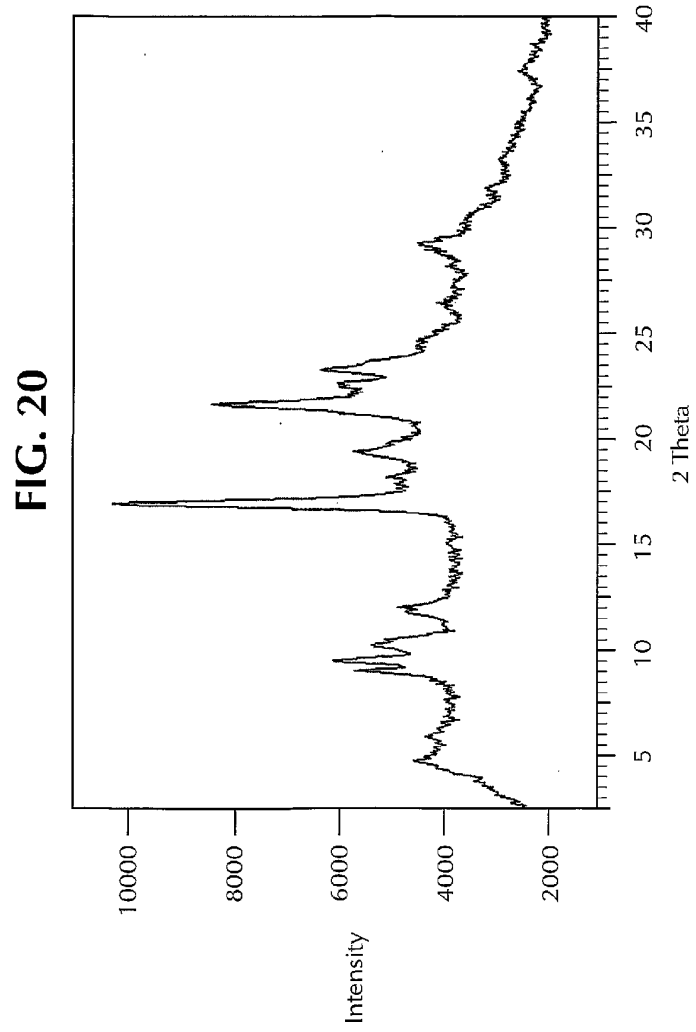


FIG. 18



**FIG. 19**





**FIG. 21**

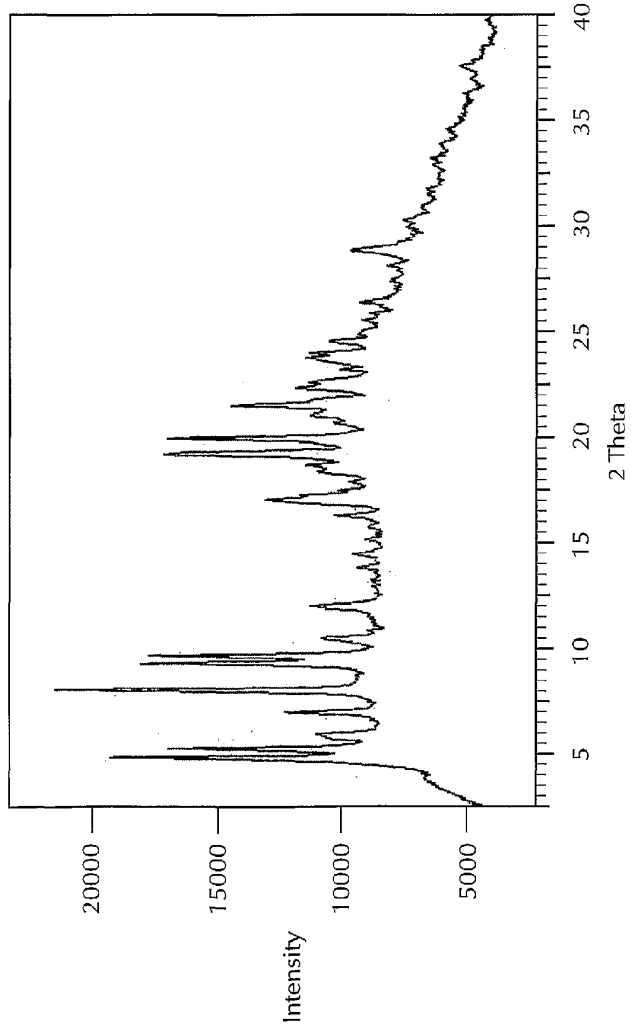
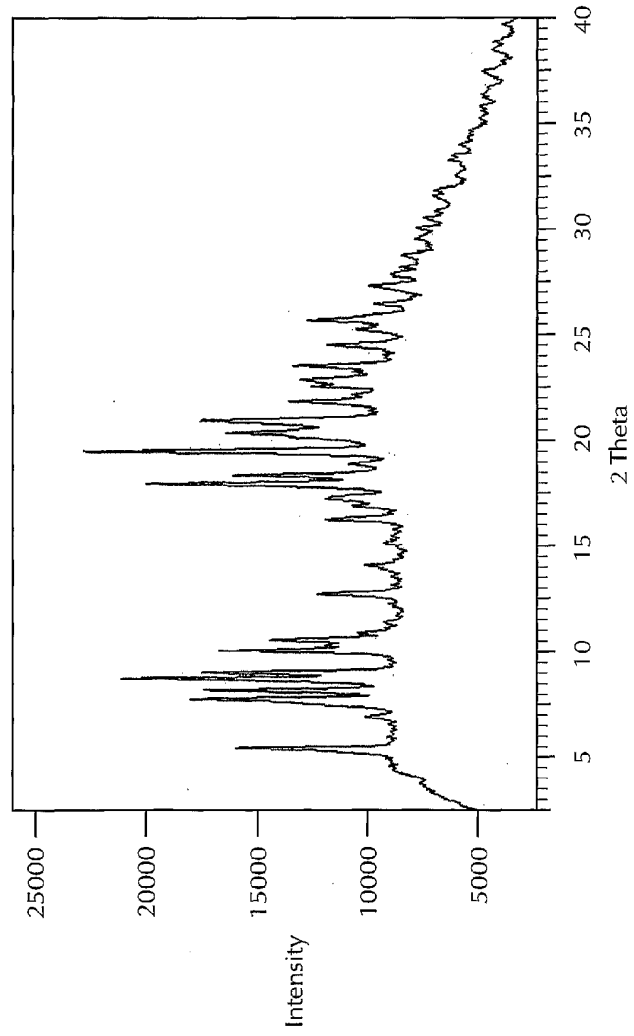
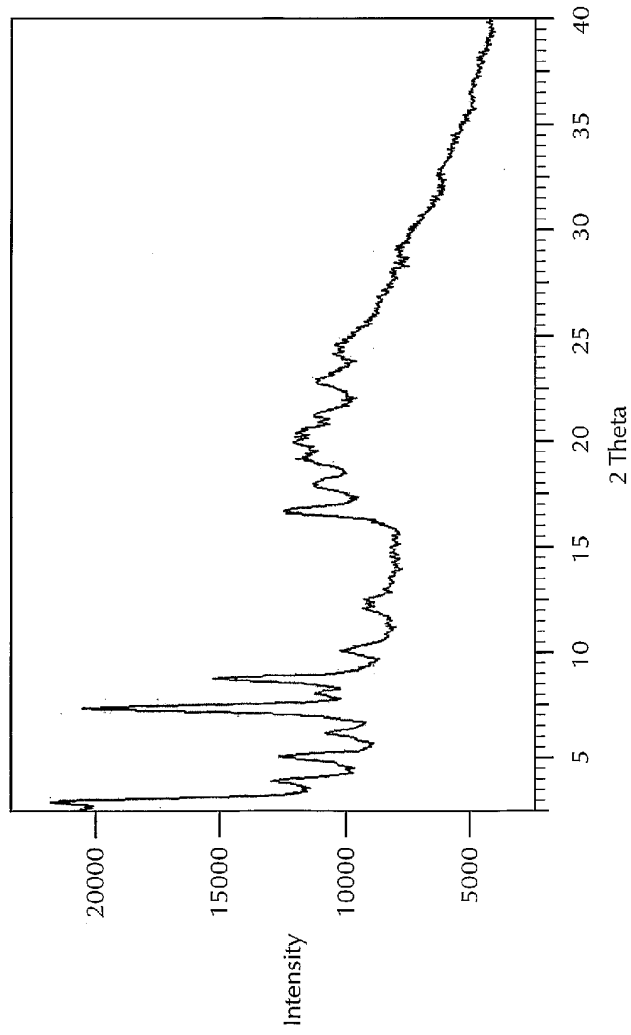


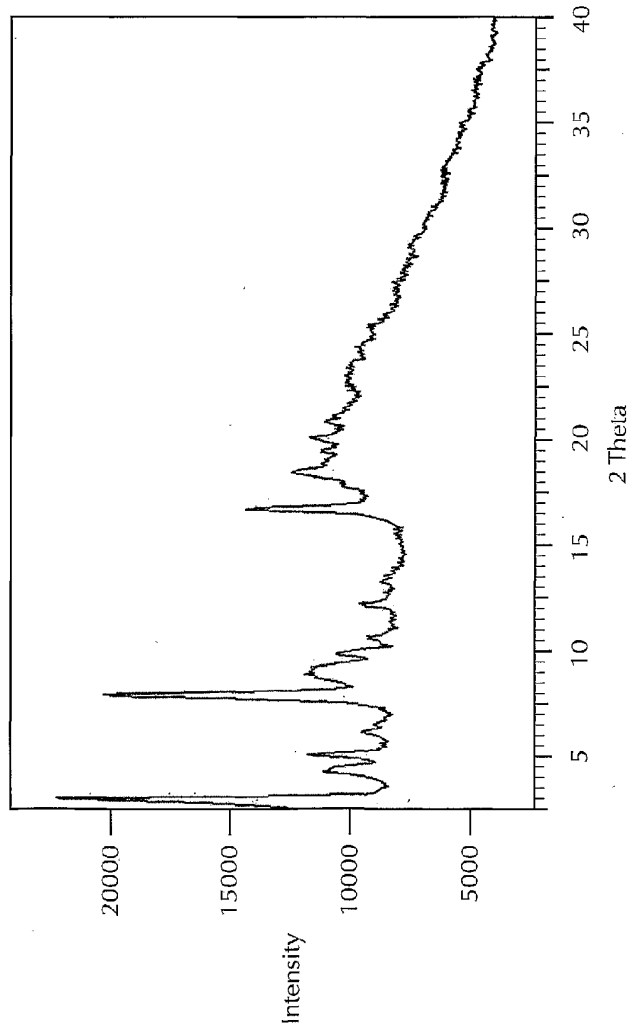
FIG. 22



**FIG. 23**



**FIG. 24**





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**FIG. 25**

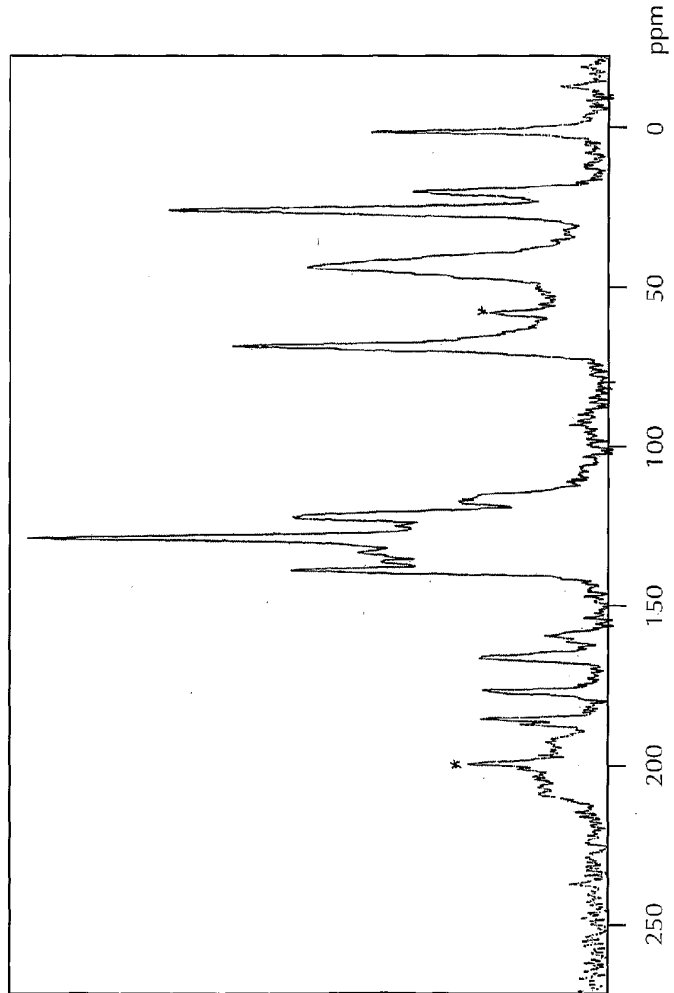
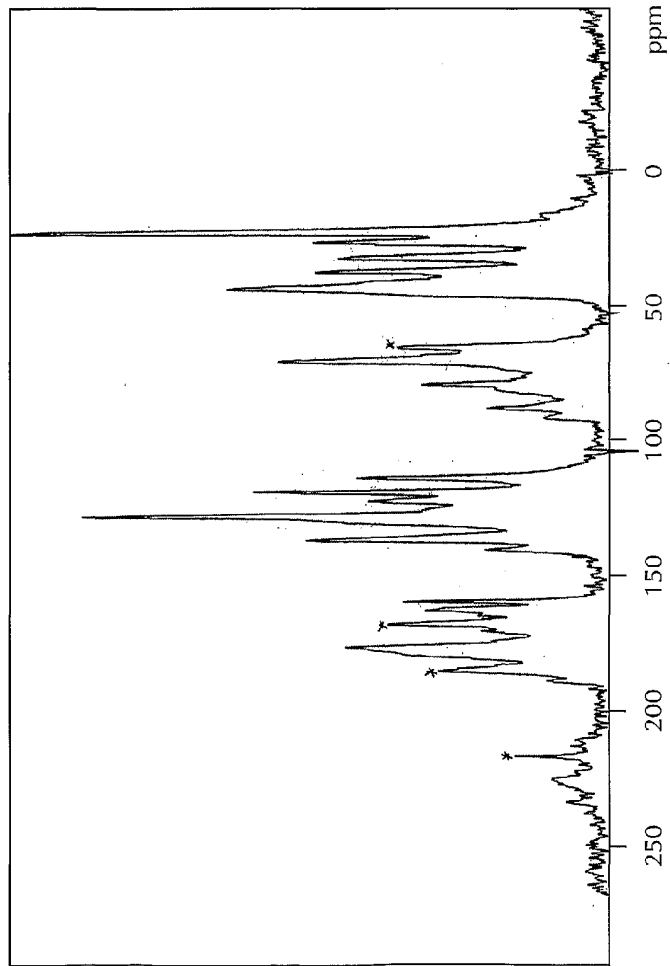
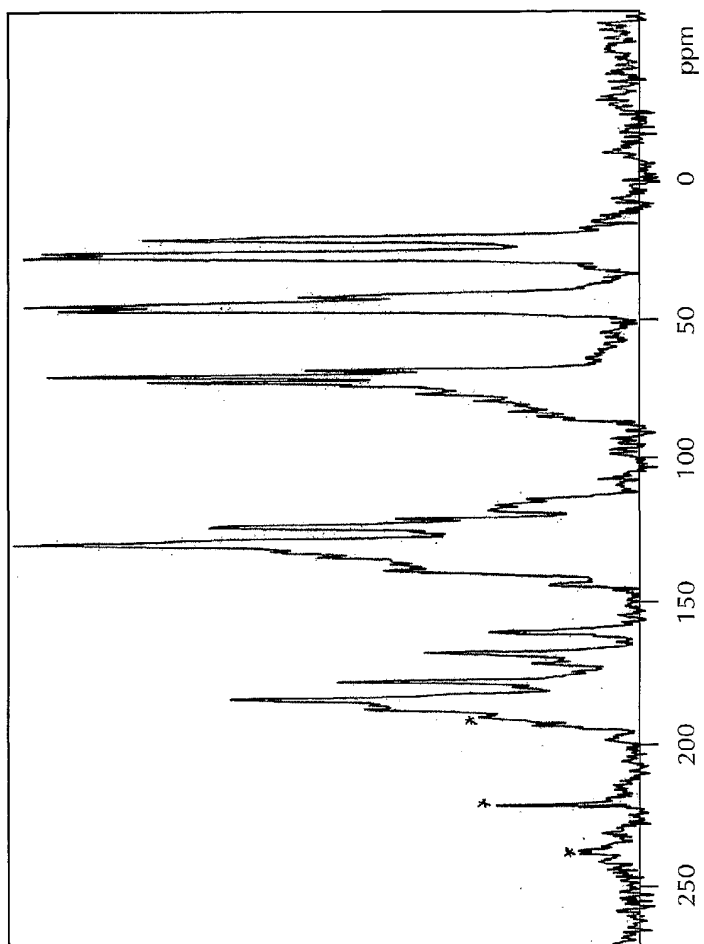


FIG. 26

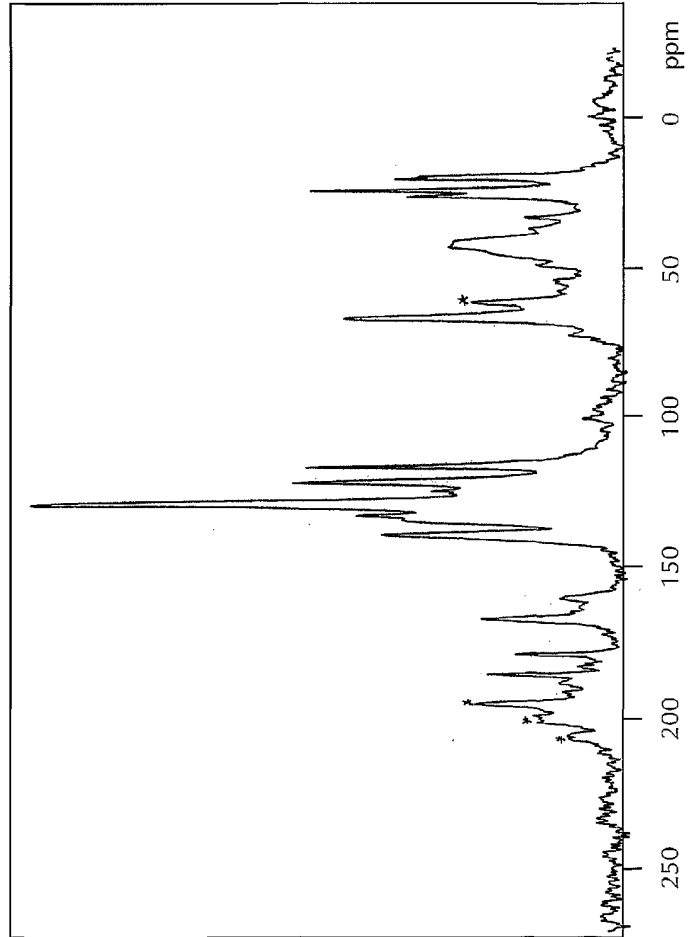


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FIG. 27

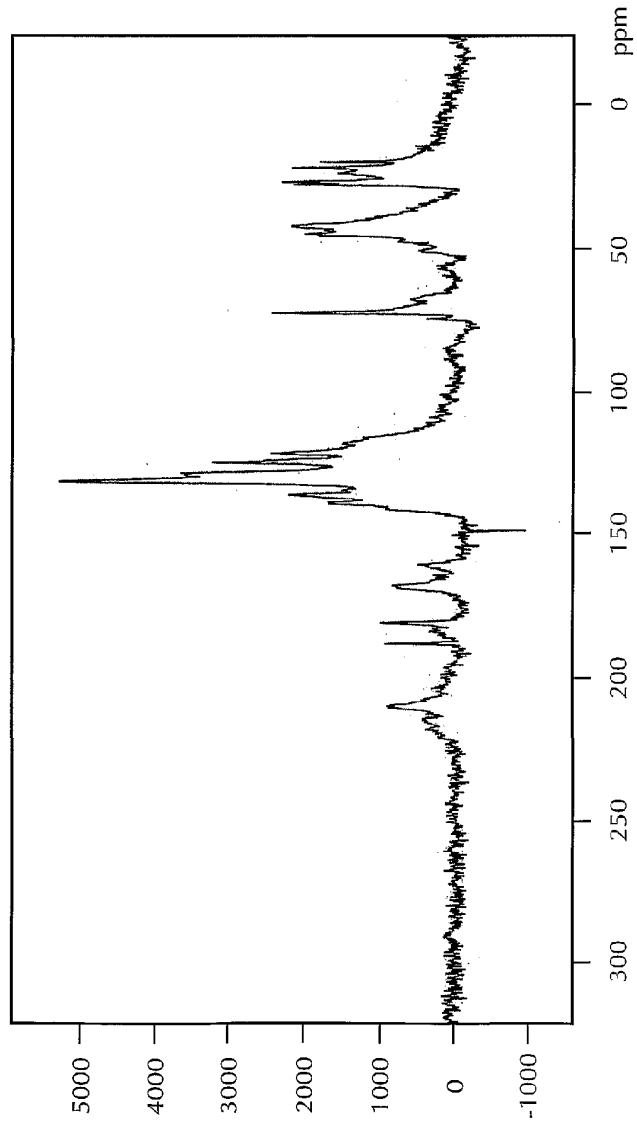


**FIG. 28**



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FIG. 29



**FIG. 30**

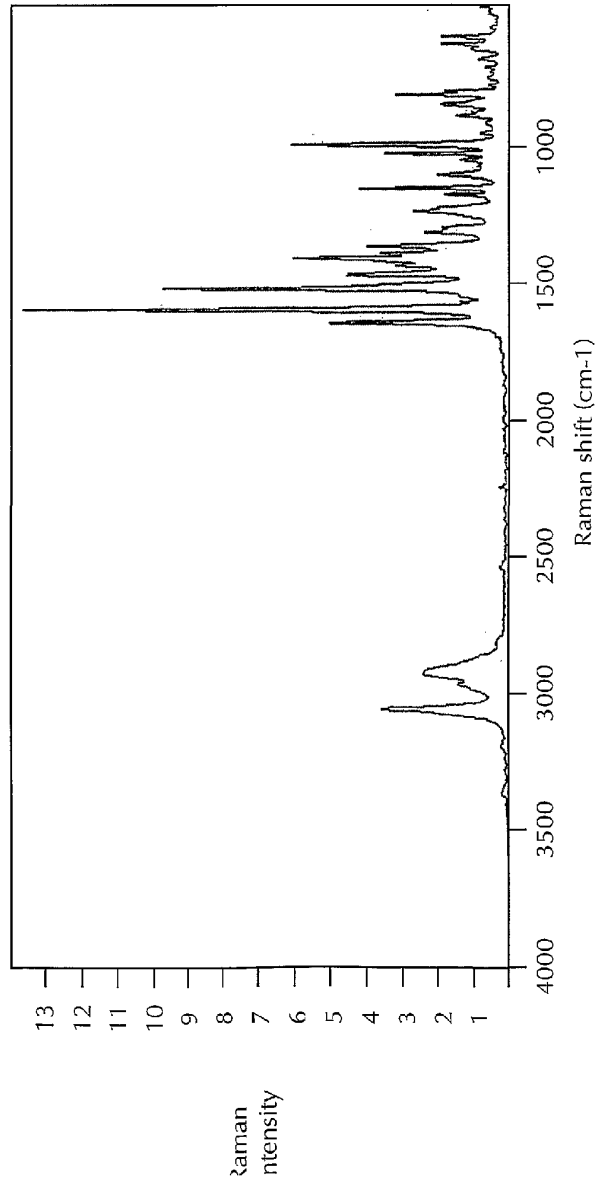


FIG. 31

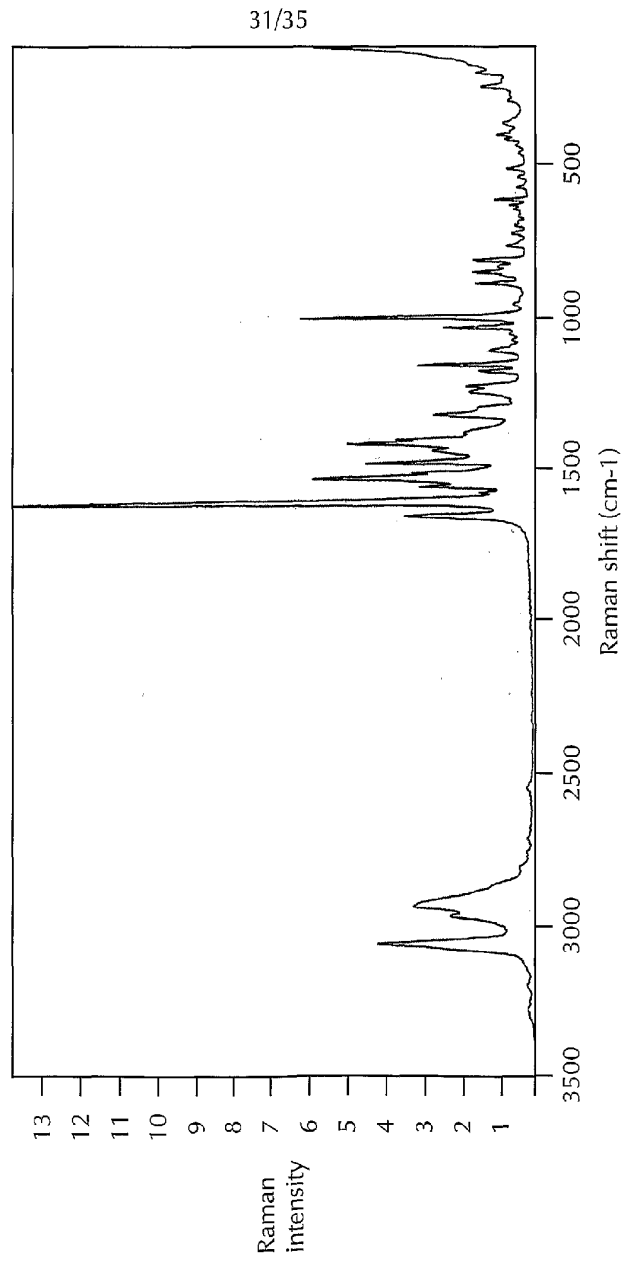
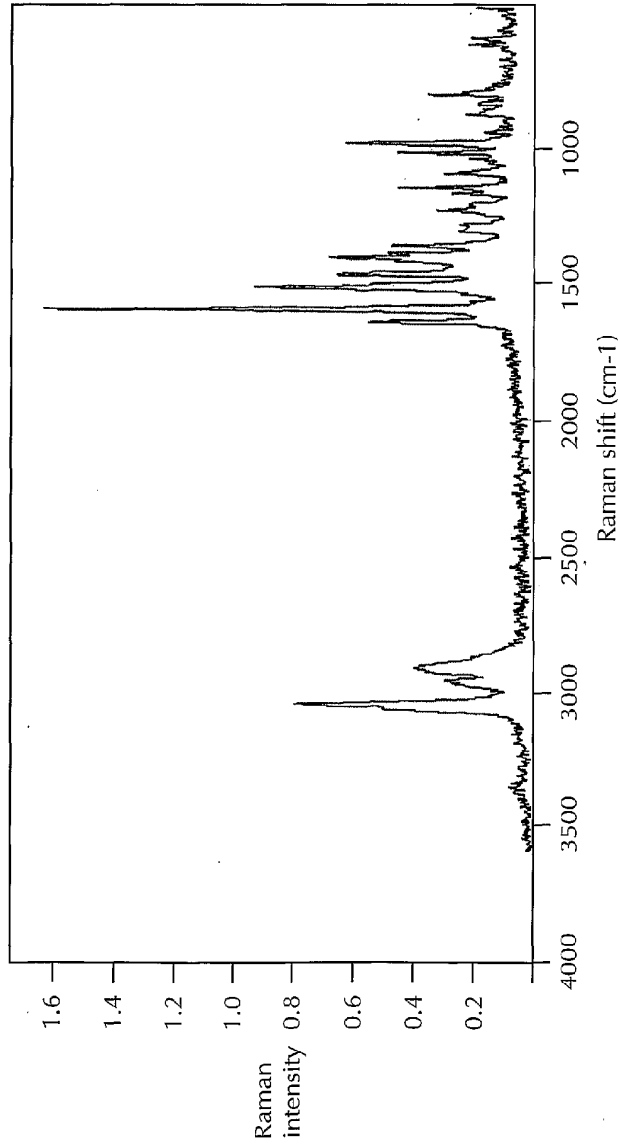


FIG. 32





**FIG. 33**

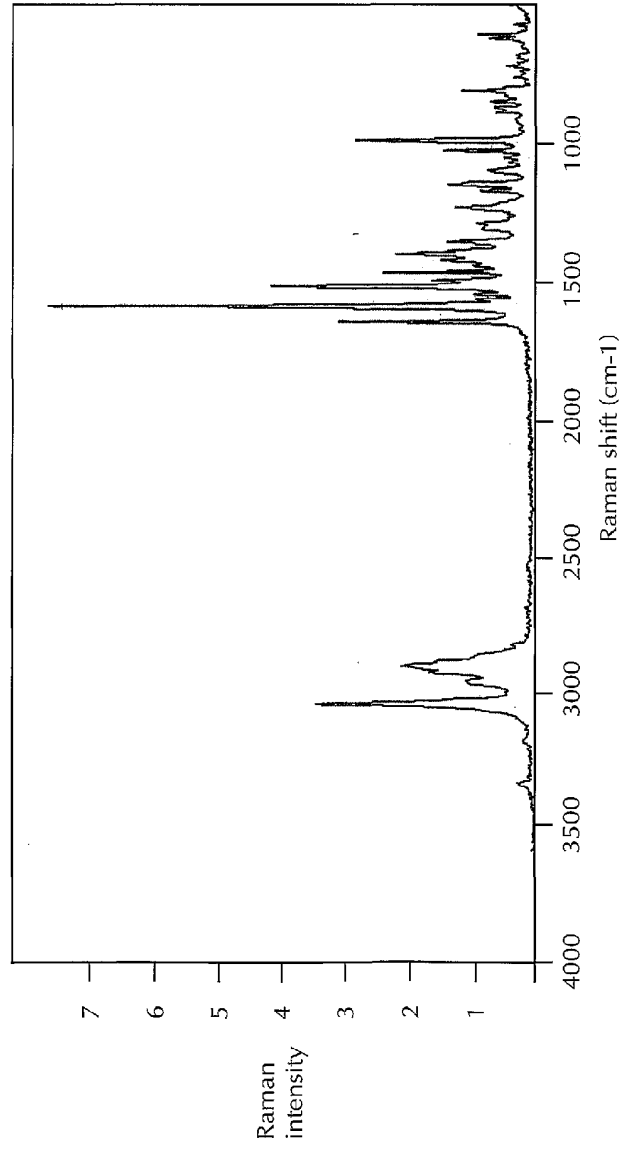


FIG. 34

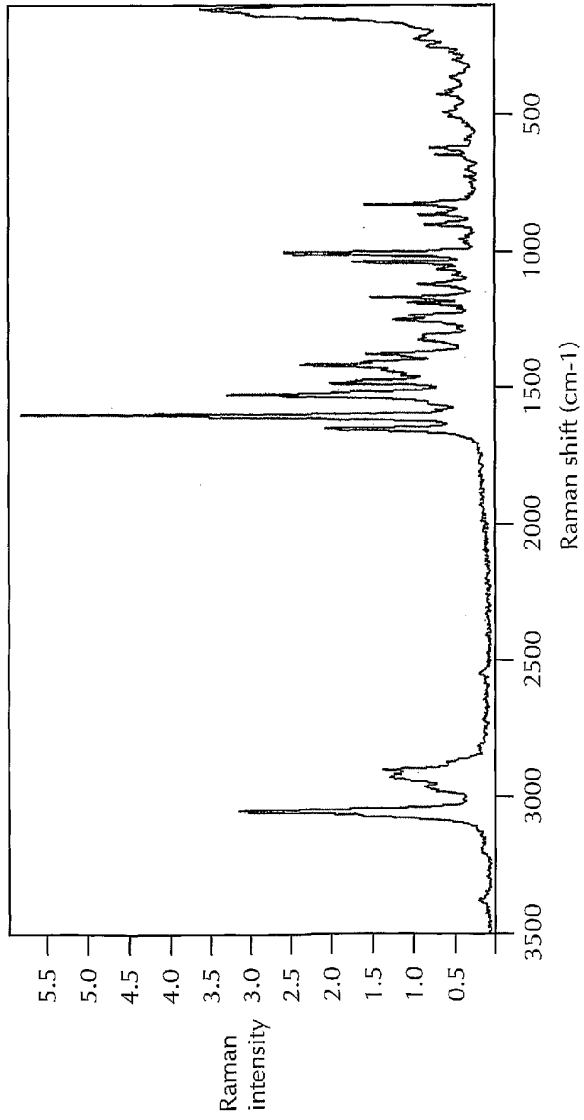


FIG. 35

