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(30) 60/358,497 2002 02 19 (US)
(71) - 49131 . . 3190 5
(72) 76217 5
- 2556 50
(74) :
(54) -

-
가 , 가 , 가
가 1%
- , -
- , , ,

2002 2 19 가 60/358,497 .

(atorvastatin)

(solvate)

(highly branched)

(solvate)

([R-(R*,R*)]-2-(4-

-5-(1-

)-3-

-4-[(

)

]-1H-

-1-

3

5,273,995

(HPLC)

2

(CaCl₂ · 2H₂O)

1

5,298,627

N,N-

(workup)
(Ca(OAc)₂)

가

5,969,156

I, II III

. '156

1

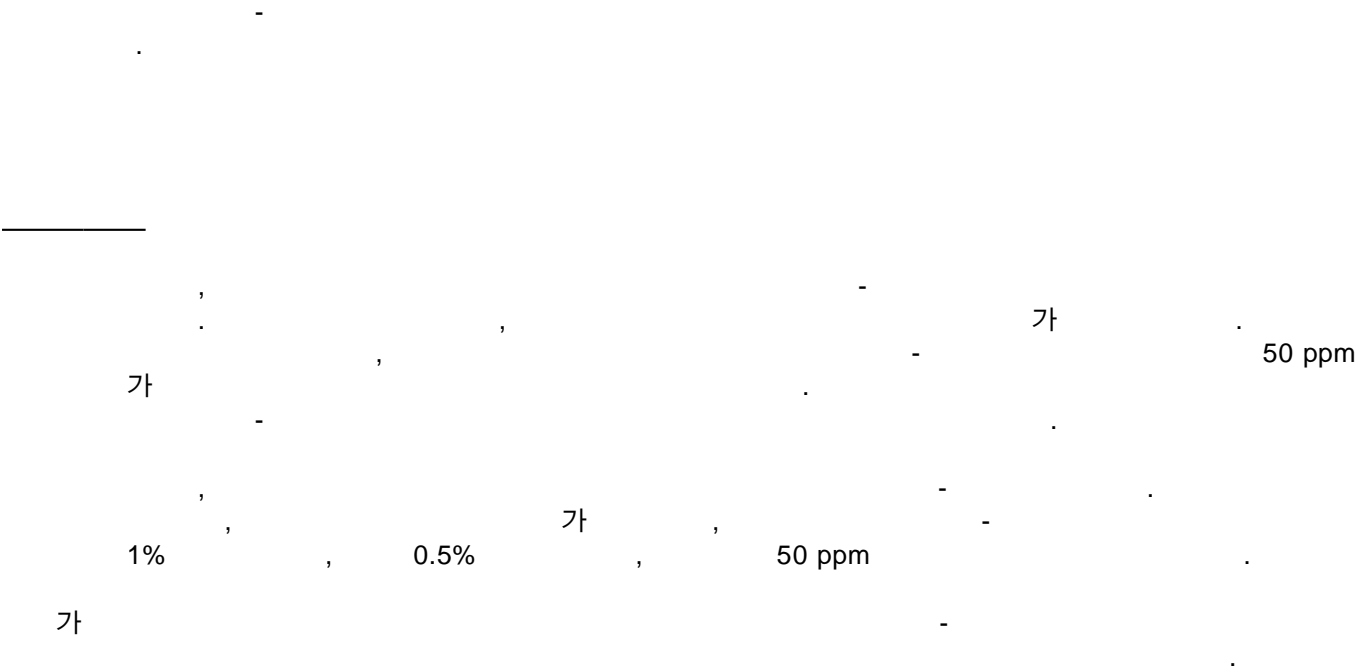
(seeding)

1 51-57 가 15-40 ,
4 60-70 'I ' (- ,) 2 , I

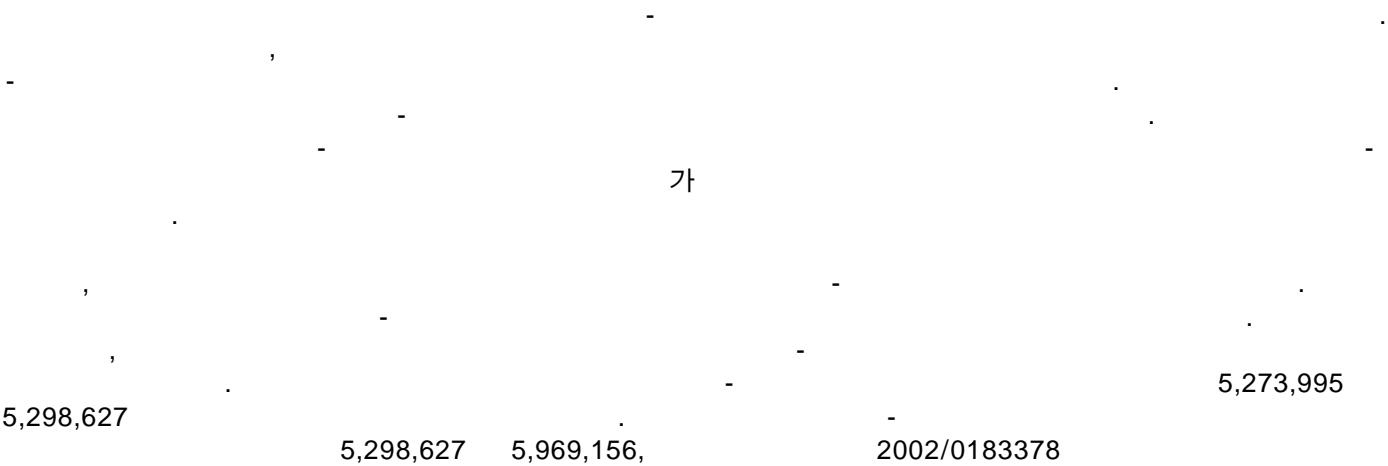
IV II 3 I
 IV
 6,121,461 , '461 3 , II 95% 11
 III
 2002/0183378 VI, VIII-
 XII 가
 VI
 VII (polymorph)
 VIII 가
 , 6.9, 9.3, 9.6, 16.
 3, 17.1, 19.2, 20.0, 21.6, 22.4, 23.9, 24.7, 25.6, 26.5 ± 0.2 2 X- VII
 I VIII ; a = 18.55-18.7 , b = 5.52-5.53 , c = 31.0-31.2 a c
 97.5-99.5 ° (monoclinic) (cross-polarized)/
 (magic angle spinning) ('CP/MAS') ^{13}C 17.8, 20.0, 24.8, 25.2, 26.1,
 40.3, 40.8, 41.5, 43.4, 44.1, 46.1, 70.8, 73.3, 114.1, 116.0, 119.5, 120.1, 121.8, 122.8, 126.6, 128.8, 129.2, 1
 34.2, 135.1, 137.0, 138.3, 139.8, 159.8, 166.4, 178.8, 186.5 ppm VIII
 NMR
 VIII ppm
 가; 2.2, 7.0, 7.4, 8.3, 22.5, 23.0, 23.7, 25.6, 26.3, 28.3, 53.0, 55.5, 96.3, 98.2, 101.7, 102.3, 104.0,
 105.0, 108.8, 111.0, 111.4, 116.4, 117.3, 119.2, 120.5, 122.0, 142.0, 148.6, 161.0 168.7 ppm
 , '378
 IX X
 XI
 XII
 '995, '627 , '156 '378
 -1-
 1 % 5 %
 가 / , 가 /
 (가,
 , 가
 /
 가
 6,080,759 (-)- -4-(4'-)-3-(3',4'-
)- ()
 '759
 1 , 13% -2-
 20 A
 '759
 가
 6,002,011
 1% 가

1% 가
966, 18, 190S-197S

. Carless, J.E. et.al *J. Pharm. amp; Pharmacol.* 1



1 - VIII CP/MAS ¹³ C NMR
0-60 ppm
2 1 (lot) - VIII
CP/MAS ¹³ C NMR 0-60 ppm 100%
18 가 15.9 ppm 57.4 ppm 1
3 - V
III X-



25 1
-1- ; t- -1- ; N,N- -2- -1- 2-
N,N

- ; N,N- ; ;

III IX , V

가

1% , 0.5% , 50 ppm (ppm = $10^5 \times (\text{wt.}\%)$)

(milling) 가

60% 100%

20 100 , 40 60

ppm 6

(100% RH), 4 18 , 25 ± 3

2.5% 50 ppm

가

^{13}C CP/MAS 가 1 VIII

CH_2OH CH_3 CH_2OH 15.9 57.4 ppm CH_3CH

100% 2 18

ce) 1-3 , 가 (head spa

2 4 , 가

50 ppm

(polymorphic transition)

VIII 3 , 3 wt.%

PXRD PXRD가

VIII PXRD

95% 6,121,461 3

II III 1 '156 2 VII

I, IX, IV

II ,

가

가

(bed)

/

/

, VIII IX

4,444,129 4,624,058

가

가

(flux).

0.2%

30

70

3- 5%

-1-

40

60

6-8

, 24

I

1 wt.%

4.5 ± 1 wt.%

2 wt.%

50 ppm

3

HMG-CoA

() 가 ,
가

1

가

가

(Avicel?),

2

2

3

(Eudragit?),

Methocel?),

(Kollidon?, Plasdone?),

(Klucel?),

(

e?),

(croscarmellose)

(Ac-Di-Sol?, Primellose?),

(Kollidon?, Polyplasdon
(polacrillin)

(Explotab?)

(glidants)

가 가

3

(die)

가

2 2

가

10 80 mg

g ml⁻¹ 가 (Hewlett Packard) HP-5890 HP-6890 가 100 m
 (megabore) USP G43 FID Combi Pal-CTC PEG 가 가
 7694 / 가

FT NMR BL-4CP/MAS / ¹H 가 Bruker DMX-500
 5.0 kHz ¹³C CP/MAS NMR 125.76 MHz . 4 mm
 SELTICS

가 SCINTAG X- X'TRA =1.4518 2-
 40 ° 2 PXRD 3 -l

_____1

2.5 wt.% VIII (500 mg)
 100% 18 , 4 cm
 50 ppm 가

_____2

2.5 wt.% VIII (500 mg)
 100% 4 , 4 cm

_____3

3% 0 5 - VIII (30 g) , 가 , 4
 - VIII 0.7% .

4

50 wt.% - VIII (18 g) 60 7
 가
 - VIII .

5

3% 0.2% - VIII (50 g) 40 6 VIII
 3.1% .

6

4.5 wt.% - 1- - IX (12 g) 55 IX 24
 1.5 wt.% - 1- .

7

5.5 wt.% - 1- - IX (12 g) 50 IX 6
 3.8 wt.% - 1- .

(57)

1.

a) - ,

b) 가 ,

c) -

- .

2.

1 , 1 5 % .

3.

1 , 5 % .

4.

1 , 가 , , N,N- , ,

5.

4 , 가 , -1- , -2- , -1- , 2- -1- ,
 , t- ; N,N- , N,N- , ,

- 4 6. , 가 C₁ -C₆ .
- 6 7. , C₁ -C₆ , , -1- , -2- , -1- 2- -1
- .
- 1 8. , 가 60% 100% .
- 1 9. , - 1 %
.
- 9 10. , 50 ppm
.
- 1 11. , - 3
.
- 1 12. , -
.
- 12 13. , - II .
- 13 14. , - I, III, IV, V, VI, VII, VIII, IX, X, XI, XII
.
- 14 15. , - VIII .
- 15 16. , - IX .
- 1 17. 1 % - .
- 1 18. 0.5 % - .
- a) 19. -
.
- b) 가 ,
- c) -
.
- 20.

- 19 , - .
- 21.**
- 20 , - - II .
- 22.**
- 21 , - I, III, IV, V, VI, VII, VIII, IX, X, XI, XII .
- 23.**
- 22 , - VIII .
- 24.**
- 22 , - IX .
- 25.**
- 19 , .
- 26.**
- 25 , 1 4 % .
- 27.**
- 19 , 5 % .
- 28.**
- 19 , 가 , , N,N- , , .
- 29.**
- 28 , 가 , , -1- , -2- , -1- , 2- -1- ,
 , t- ; N,N- , N,N- , , .
- 30.**
- 28 , 가 C₁-C₆ .
- 31.**
- 30 , 가 , , -1- , -2- , -1- 2- -1- .
- 32.**
- 19 , 가 40% 100% .
- 33.**
- 32 , 가 20 100 .
- 34.**
- 33 , 6 20 가 .
- 35.**
- 19 , - 1 % .
- 36.**
- 35 , - 5

0 ppm

37.

19 , -
- 3 .

38.

19 1 % - .

39.

38 , 50 ppm - .

40.

a) - ,

b) ,

c) 1 % -

- .

41.

a) - ,

b) ,

c) 1 % -

- .

42.

41 , - VIII
- VIII .

43.

41 , - IX
- IX .

44.

41 , 가 , , N,N- , ,

45.

44 , 가 , , -1- , -2- , -1- , 2- -1- ,
, t- ; N,N- , N,N- , ,

46.

44 , 가 C₁-C₆ .

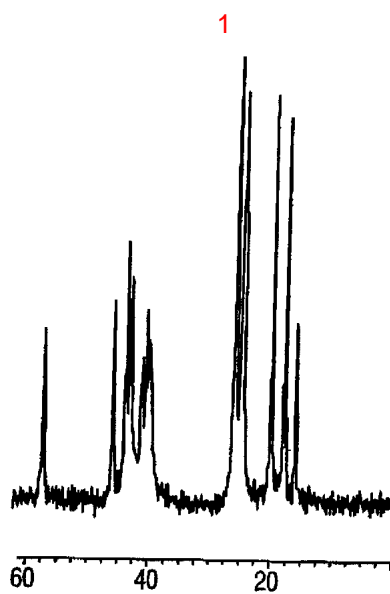
47.

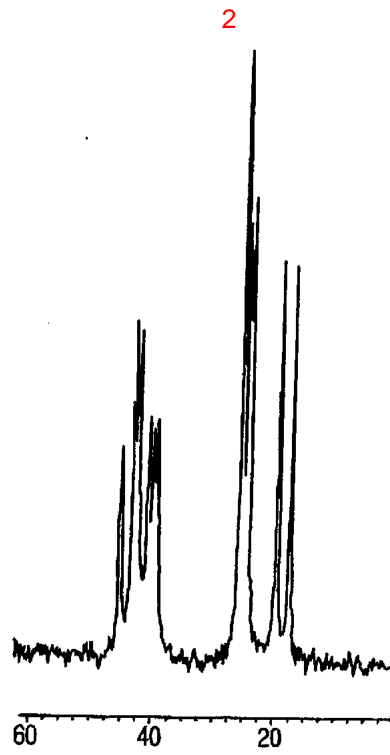
46 , 가 , , -1- , -2- , -1- 2- -1-

48.

41 , 가 40 60 .

41	49.		
1 %	50.		
50	51.	, 50 ppm	
50	52.		
	53.	가	52
52	54.		
	55.	가	54
HMG-CoA	56.	, 가	50
	57.		
		, 50	





3

