

**(19)**  
**(12)**

**(KR)**  
**(A)**

(51) . Int. Cl.<sup>7</sup>  
A61K 9/28  
A61K 9/32

(11)  
(43) 10-2004-0065989  
2004 07 23

|      |                   |      |                |
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|      | 2003 08 18        |      |                |
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|      |           |            |      |
|------|-----------|------------|------|
| (30) | 0104327-2 | 2001 12 19 | (SE) |
|      | 0104328-0 | 2001 12 19 | (SE) |

(71) 151 85

(72) , , ,  
-431 83

, -  
-431 83

,  
-431 83

,  
-431 83

(74)

(54)

a) , b) , c) - , ,

, ,

가

가

1 가

[Langer and Wise (Eds)  
 'Medical applications of controlled release', vols I and II, CRC Press Inc, Boca Raton, 1984; Robinson and Le e (Eds) 'Controlled drug delivery - fundamentals and applications', Marcel Dekker, NY 1987; Bogentoft and Sjogren, in 'Towards better safety of drugs and pharmaceutical products' (Ed: Braimer), Elsevier, 1980; Sandberg 'Extended-release metoprolol', Thesis, Uppsala University, 1994]

(extended-release, ER) 가 (Sandberg)(1994)  
 가 (ER)  
 (reservoir)

가

가

가

(metoprolol)

가 (Ragnarsson, *Drug Develop Ind Pharmacy* 13, 1495 (1987); Sandberg, *Eur J Clin Pharmacol* 33, S3 91988) S9 (1988); Ragnarsson, *Int J Pharmaceutics* 79, 223 (1992); Sandberg, 68, 167 (1991); Sandberg, *Pharmaceutcl Res* 10, 28 (1993); Sandberg, *Drug Invest* 6, 320 (1993); Sandberg, *Thesis* Uppsala University, 1994).  
 가 (Ragnarsson, *Drug Dev Ind Pharmacy* 13, 1495 (1987)) 가

가

가 가

가  
가

가

10 1000 nm

가

(Tg)

80

가 (, Aquacoat (R), FMC Corp.; Eudragit (R) NE30D, Rohm Pharma; Kollicoat (R) EMM30D, BASF AG). 가 (Peteriet and Weisbrod, *Eur J Pharmaceutics and Biopharm* 47, 15 (1999); Peteriet, 41, 219(1995); Amighi and Moes, *STP Pharma Sci* 7, 141(1997); Bodmeier and Paeratakul, *Pharm Res* 11, 882 (1994); Ozturk, *J Controlled Release* 14, 203 (1990); Goodhart, *Pharmaceutical Tech* April, 64(1984); Bodmeier and Paeratakul / *Int J Pharmaceutics* 152, 17 (1997); Bodmeier and Paeratakul *Drug Develop Ind Pharmacy* 20, 1517 (1994))

Tg ) 1.5% w/w , 28.5% w/w  
 ( tenside) (N

onoxytol) 100 (Eudragit (R) NE30D . E  
udragit (R) NE30D Kollicoat (R) EMM30D(BASF AG, Ludwigshafen, Germany) .  
(Petereit Weisbrod, 19  
95) 가 가 .

가 , 가 , , .  
 icoat (R) SR30D (BASF), Kollicoat (R) SR30D . Koll  
 27% w/w 2.7% w/w , 0.3% w/w SDS ( )  
 )  
 (TEC) 가 , (Kolter, K , Proc. Int. Symp. Controlled Relea  
 se Bioact. Mater., 27 , 425 (2000)).  
 가 , , 가 ,  
 가 ,

4,871,546

EP 431 877 ( ) pH 가 . . . ( ) pH

4,975,283

4,800,087 - 가 Eudr  
agit (R) L30D Eudragit (R) NE30D .

가 가 가

(0- ) 가

- a)
- b)
- c)

d)

1

a)

b)

c)

d)

1 ( 15 KD ) / 1 ( 15 kD ) /  
 4% w/w 0.5% w/w 가

가  
가

15 kD , 4% w/w /  
 0.5% w/w

a)

b)

c)

가 가 가 , 가

1

a)

b)

c)

m

D

15 kD  
 3%) /  
 0.3%)

100 μm , 5 50 μm , 10 30 μ (15 K

(15 KD ) / 0.5% w/w ( 0.05 0.5% 4%, 1  
 4% w/w ( 0.05 0.5% , 0.1



18 22

3 10 24

a)

1

b)

가

1

S-

(enantiomer)

Tq가

Ta가

|    |       |       |   |      |      |    |          |          |       |
|----|-------|-------|---|------|------|----|----------|----------|-------|
|    |       | (AP)  |   |      | (VP) |    | 0.1/99.9 | 99.9/0.1 |       |
|    | AP    | VP    |   | 5/95 | 95/5 |    |          | AP       |       |
| VP | 20/80 | 80/20 | 가 |      |      | AP | VP       | 30/70    | 70/30 |

pH  
가

: 2

Eudragit (R) NE30D / Kollicoat (R) EMM30D  
/ 2/1

, Kollicoat<sup>(R)</sup> SR30D (BASF AG, Ludwigshafen, Germany)

Eudragit (R) NE30D / Kollicoat (R) EMM30D, Kollicoat (R) SR30D onoxynol 100 / (SDS).

.5 %w/w , 15 kD 4 %w/w / 0 %w/w . 15 kD 0

가

가

M C Wilkinson , *Advances in Colloid and Interface Science* 81 , 77 (1999)],

가

(Handbook of Pharmaceutical Excipients, sec  
ess, London 1994). 가

가 0.005 0.5 %, 0.01 0.1 % 가  
20 % 0

- 가  
- . 가 , Euragit (R) NE30D (Rohm Pharma) / Kollicoat (R) EMM30D  
(BASF), Kollicoat (R) SR30D (BASF)  
- . 가  
- . .

, 0 100 , 10 100

(top) (bottom)  
hman, Lea and Feabiger, 1986 3rd ed.] ['Theory and Practice in Industrial Pharmacy', Lac  
Glatt), , (Accela-cota), , (가 .

가

가

1: Eudragit (R) NE30D      Kollicoat (R) SR30D

Kollicoat® SR30D / Eudragit® NE30D : 2  
 . 가 Eudragit® NE30D : A: 20%, B: 30%,  
 C: 50%, D: 70%. 10 ml (10 x 10 cm<sup>2</sup>)  
 . , 25 / 60% 19

1: GMS/PS80/Eudragit (R) NE30D

GMS, PS80 Eudragit (R) NE30D 3 가 GMS PS80 E, F G GMS, PS80 NE30D  
 80 . , . . . . . . . .  
 (R) Eudragit (R) NE30D 가 . . . . . . . .  
 E, F G . . . . . . . .  
 GMS(GMS/ = 5%) . . . . . . . . [Peterleit and Weisbrod 1995]

E: 1 . 6000 rpm : 65

E: 20 . 3000 rpm : 65

G: 4 . . . . . : 65

2:

가 , 250 N Hounsfield H5K-S  
 B, C G 1(B C) 1(G) ,  
 40 mm, 10 mm , 250  $\mu$ m 4 m  
 m/min , 23-24 , 28 30% 3

1

[ 1 ]

|                      | B     | C     | G    |
|----------------------|-------|-------|------|
| (kJ/m <sup>3</sup> ) | 10693 | 20335 | 6550 |
| SD (%)               | 27.6  | 10.2  | 28.6 |

가

2:

1( A, B, C D)      1( E, F G)  
 teborg 1998).      (tritiated water)      A-G  
 (Hjartstam, Thesis, Chalmers University of Technology, Go  
 가

2

[ 2 ]

|                                       | A    | B    | C   | D   | E    | F    | G    |
|---------------------------------------|------|------|-----|-----|------|------|------|
| (10 <sup>-12</sup> m <sup>2</sup> /s) | 22.3 | 19.6 | 5.4 | 2.3 | 30.1 | 40.5 | 51.0 |

NE30D      가      (A      D),      ,      (G  
 E).

4:

( 0.40      0.63 mm)  
 Wurster      A, B, C      D

200 g

~ 170 g

4.6 g/min

2.5

35 m<sup>3</sup>/h

30

20

40 ( 20 ) , 20 m<sup>3</sup>/h ,  
 1 .

5:

4 100 mg USP No. 2( 100 rpm  
 가 . pH 6.8, 500 ml (bath) 3  
 7 . (1 cm 274 nm 0.1 M )  
 . . . . . . . . . .

[ 3 ]

| /hrs   | 1    | 2    | 4    | 6    | 8    | 10   | 12   | 16   | 20   |
|--------|------|------|------|------|------|------|------|------|------|
| (A) %  | 2.2  | 4.4  | 12.2 | 29.4 | 55.8 | 75.1 | 85.9 | ---  | 99.9 |
| SD (%) | 0    | 0    | 0    | 0    | 0    | 0    | 0    | ---  | 0    |
| (B) %  | 20.0 | 24.0 | 33.7 | 52.0 | 72.3 | 86.0 | 93.0 | 96.3 | 99.3 |
| SD (%) | 2.4  | 2.4  | 1.8  | 2.0  | 2.1  | 1.0  | 1.0  | 0.58 | 0.73 |
| (C) %  | 2.0  | 4.0  | 16.0 | 41.0 | 66.0 | 83.0 | 91.0 | 97.0 | 99.0 |
| SD (%) | 0    | 0    | 0    | 0    | 0    | 0    | 0    | 0    | 0    |
| (D) %  | 13.0 | 19.3 | 31.3 | 48.0 | 63.3 | 76.3 | 85.0 | 90.3 | 95.3 |
| SD (%) | 1.0  | 0.58 | 0.58 | 0    | 0.58 | 0.58 | 1.0  | 0.58 | 0.58 |

3 20

6:

4 C , Avicel PH102 (Turbul  
 a) T2C(Willy A. Bachofen, Switzerland) 4 . 0.15%  
 가 . 2 (excenter) (Kilian SP30  
 0, Germany) 8 kN 200 mg . . . . .

가

7:

6 USP No.2 ( 10  
 0 rpm, 37 0.1 M, pH = 6.8 )  
 . . . . . . . . . .  
 (1 cm 274 nm ) . . . . .

4

3( C)

가

[ 4]

| /hrs | 1 | 2  | 4  | 6  | 8  | 10 | 12 | 16 | 20 |
|------|---|----|----|----|----|----|----|----|----|
| %    | 0 | 18 | 31 | 47 | 66 | 79 | 88 | 95 | 98 |

8:

30% Eudragit (R) NE30D (Rohn Pharma) 70% Kollicoat (R) SR30D (BASF) Spectra/P  
 or (R) (ELGA ) (cut-off) .  
 , , , , , .  
 . NE30D NF100 276 nm UV - . Kollicoat  
 SDS PVP ( = 11.1% w/w SDS = 12.6% w/w PVP)  
 / LC-MS( - ) .  
 : .

[ I]

|        | D1-4,7 a)                   | D2-4,4 a)                    |
|--------|-----------------------------|------------------------------|
|        | 14 000 D                    | 100 000 D                    |
|        | 21.2 %w/w b) (29.8 %w/w) c) | 17.3 %w/w b) (29.8 %w/w) c)  |
| NF 100 | 0.24 %w/w b) (0.45 %w/w) c) | 0.28 %w/w b) (0.45 %w/w) c)  |
| SDS    | 0.04 %w/w b) (0.14 %w/w) c) | 0.007 %w/w b) (0.14 %w/w) c) |
| PVP    | 2.0 %w/w b) (2.2 %w/w) c)   | 1.3 %w/w b) (2.2 %w/w) c)    |
| a)     | ,                           | .                            |
| b)     |                             |                              |
| c)     |                             |                              |
| d)     | UV, LC-MS                   | ; 29.8% 21.2 17.3%           |

Eudragit (R) NE30D Kollicoat (R) SR30D

9:

10 ml 8 D1 D2 (10 x 10 cm<sup>2</sup>)  
 , 25 / 60% 19  
 (D0) D0, D1 D2  
 F0, F1 F2 II SDS PVP I II  
 : .

[ II]

|          | F0  | F1   | F2   |
|----------|---|--|--|
| NF100    | 1.5%w/w <sup>a)</sup>                             | 0.80 %w/w <sup>a)</sup>                              | 0.94 %w/w <sup>a)</sup>                              |
| SDS      | 0.47 %w/w <sup>a)</sup><br>1.7 %w/w <sup>b)</sup> | 0.13 %w/w <sup>a)</sup><br>< 0.45 %w/w <sup>b)</sup> | 0.02 %w/w <sup>a)</sup><br>< 0.45 %w/w <sup>b)</sup> |
| PVP      | 8.1 %w/w <sup>a)</sup><br>6.2 %w/w <sup>b)</sup>  | 6.7 %w/w <sup>a)</sup><br>5.8 %w/w <sup>b)</sup>     | 4.4 %w/w <sup>a)</sup><br>3.4 %w/w <sup>b)</sup>     |
| a)<br>b) | ( I )   |  |  |

F0  
~4000 D) SDS( $M_w \sim 300$  D) . (SDS  
.)

10:

9 F0, F1 F2  
(Hjartstam, Thesis, Chalmers University of Technology, Goteborg 1998). (tritiated  
water) が / 60% 2  
가

[ III ]

|                         | F0          | F1         | F2        |
|-------------------------|-------------|------------|-----------|
| P( $m^{-12} m^2/s$ ):   | 19.6        | 9.8        | 2.6       |
| P( $m^{-12} m^2/s$ ): 2 | 10.4 (-47%) | 7.0 (-29%) | 2.4 (-7%) |

( ) ,

11:

( 0.40 0.63 mm) D2  
14 % w/w Wurster

200 g

~ 340 g

4.6 g/min

2.5

35  $m^3/h$

50

28

12:

|                   |          |                  |                   |       |          |                           |              |
|-------------------|----------|------------------|-------------------|-------|----------|---------------------------|--------------|
| 11<br>0 rpm<br>37 | 가<br>. . | 100 mg<br>(1 cm) | pH 6.8,<br>274 nm | 0.1 M | USP<br>) | No. 2( )<br>500 ml<br>. . | 10<br>(bath) |
|                   |          |                  |                   |       |          |                           |              |
|                   |          | (0 ),            | 2                 | /     | 60%      |                           |              |

## [ IV]

| /hrs  | 1  | 2  | 4  | 6  | 8  | 10 | 12 | 16 | 20 |
|-------|----|----|----|----|----|----|----|----|----|
| % - 0 | 12 | 18 | 26 | 34 | 41 | 48 | 54 | 70 | 84 |
| % - 2 | 9  | 14 | 22 | 31 | 37 | 44 | 51 | 66 | 80 |

(0      20      )

0      2

2

(57)

1.

a)

b)

c)

2.

1      , d)

3.

1

a)

b)

4.

3      , c)

5.

- 4                  2                  ,                  가 15 kD                  가                  ,  
     4 %w/w                  /                  0.5 %w/w
- 6.**  
 a)                  1  
 b) i)                  ,  
 ii)                  ,                  ,
- 7.**  
 6                  , iii)  
 4                  ,                  가 15 kD                  가                  ,                  4 %w/w                  /  
     0.5 %w/w
- 8.**  
 1                  ,                  3                  5
- 9.**  
 6                  9                  ,
- 10.**  
 10                  ,
- 11.**  
 11                  ,
- 12.**  
 12                  ,                  ,                  ,
- 13.**  
 1                  2                  ,                  가
- 14.**  
 1                  14                  ,                  가                  /
- 15.**  
 1                  15                  ,                  가 Eudragit (R) NE30D                  /                  Kollicoat (R) EMM30D
- 16.**  
 1                  16                  ,                  가 Kollicoat (R) SR30D                  ,
- 17.**  
 1                  17                  ,                  가 20/80  
     80/20                  ,
- 18.**  
 1                  15                  18                  0                  100
- 19.**  
 1                  2                  15                  18

**20.**

|    |    |    |
|----|----|----|
| 1  | 15 | 18 |
| 15 | 18 |    |

|   |   |   |
|---|---|---|
| , | 3 | 5 |
|---|---|---|

**21.**

|   |   |    |    |    |    |
|---|---|----|----|----|----|
|   | 1 | 3  | 13 | 15 | 18 |
| , | 6 | 13 |    | 15 | 18 |

**22.**

|   |   |    |   |    |    |
|---|---|----|---|----|----|
|   | 1 | ,  | 2 | 15 | 18 |
| , | 6 | 13 |   | 15 | 18 |