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(A)

(51) 。 Int. Cl.⁷
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(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 Lee (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]

(Sandberg)(1994)

(extended-release, ER)

가

ER

가

:

(

)

(

)

(reservoir)

;

가

가

가

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, *Pharmaceut Res* 10, 28 (1993); Sandberg, *Drug Invest* 6, 320 (1993); Sandberg, *Thesis* Uppsala University, 1994).

가 (Ragnarsson, *Drug Dev Ind Pharm* 13, 1495 (1987))

가

(Ragnarsson, *Drug Dev Ind Pharm* 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 (Petereit and Weisbrod, *Eur J Pharmaceutics and Biopharm* 47, 15 (1999); Petereit, 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

onoxynol) 100 () Eudragit (R) NE30D . E
udragit (R) NE30D Kollicoat (R) EMM30D(BASF AG, Ludwigshafen, Germany) .
- (Petereit Weisbrod, 19

95) 가 가 .
(GMS)가 . [Wolff , WO 00/13687; Wolff , W
O 00/13686; Nagy , WO 99/42087; Lee , WO 99/30685; Eichel , US 5,529,790; Eichel US 5,478,573; C
hen, US 5,260,068; Petereit , EP 403,959] () Eudragit
가 , 가

가 , 가 , 가 ,

(BASF) , Kollicoat^(R) SR30D . Koll
icoat^(R) SR30D 27% w/w 2.7% w/w , 0.3% w/w SDS (

)

(TEC) 가 (Kolter, K , *Proc. Int. Symnp. Controlled Relea*
se Bioact. Mater. , 27 , 425 (2000)). 가 ,

가 , 가

가 (a)

Tg 가 , (b) Tg

가 가

4,871,546

가

EP 431 877 () pH 가 , pH () pH

4,975,283 pH pH

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

가 가 , 가 ,

(0-) 가 ,

b) _____,

d)

a)

b)

c) -

d)

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

a)

b)

c) -

가 가 가 , 가

1

a)

b)

c) -

1 100 μ m 5 50 μ m 10 30 μ m
 m D) / 1 (15 KD) 1 (15 K
 15 kD 가 4% w/w (0.5 4%, , 1
 3%) / 0.5% w/w (0.05 0.5% , 0.1
 0.3 %)

가 (sachet) 가

가

(

0.01 2 mm 0.05 0.5 mm 0.1 0.3 mm

00 kJ/m³ 500 20000 kJ/m³ 10000 20000 kJ/m³ 2500 200

a) 1

b) i)

ii)

iii)

15 kD) / 1 (15 kD) 1 (

15 kD 4% w/w /

0.5% w/w

a) 1

b) i)

ii)

가 (sachet) 가

가

(

0.01 2 mm 0.0 0.1 0.7 mm

0.01 2 mm 0.05 0.5 mm 0.1 0.3 mm

00 kJ/m³ 500 20000 kJ/m³ 10000 20000 kJ/m³ 2500 200

3

가

10

24

18 22

a)

1

b)

가

1

S_-

(enantiomer)

T_g가

T_g가

		(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

•

$$: 2$$

pH
가

Eudragit[®] NE30D / Kollicoat[®] EMM30D
/ 2/1 .

[illegible]

Kolliccoat[®] SR30D (BASF AG, Ludwigshafen, Germany)

Eudragit[®] NE30D / Kollicoat[®] EMM30D, Kollicoat[®] SR30D
onoxynol 100 / (SDS),

N

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

(Brij ,), (Span), (Tween);
(Triton Igepal ,)
, (,), (,), (SDS)
, ;
, (bile) (,
) , (,
) ;
(, ,), 가
(, ,), , ,
, (,), , , ,

, 가 .

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

가 : , , , , (Handbook of Pharmaceutical Excipients, second ed., Eds. A. Wade and P.J. Weller, The Pharmaceutical Press, London 1994). 가

[illegible]

(BASF), Kollicoat^(R) SR30D (BASF) , Euragit^(R) NE30D (Rohm Pharma) / Kollicoat^(R) EMM30D

-

, 0 100 , 10 100

, -

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

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

Kollicoat^(R) SR30D / Eudragit^(R) NE30D 가 Eudragit^(R) NE30D : A: 20%, B: 30%,
C: 50%, D: 70%. 10 ml (10 x 10 cm²)
25 / 60% 19

1: GMS/PS80/Eudragit^(R) NE30D

GMS, PS80 Eudragit^(R) NE30D 3 가 GMS PS80 E, F G GMS PS
80 Eudragit^(R) NE30D 가 GMS, PS80 NE30D
(R) E, F G , 0.225 g GMS, 0.090 g PS80 15.0 g NE30D^(R) 1.5% w/w
GMS(GMS/ = 5%) [Petereit and Weisbrod 1995]

E: 1 , 6000 rpm ; 65

F: 20 , 3000 rpm ; 65

G: 4 , ; 65

10 ml 3 (10 x 10 cm²)
25 / 60% 18

2:

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

:
1 .

[1]

	B	C	G
(kJ/m3)	10693	20335	6550
SD (%)	27.6	10.2	28.6

가 .

2:

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

:
2 .

[2]

	A	B	C	D	E	F	G
(10 ⁻¹² m ² /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) A, B, C D .
Wurster .
200 g
~ 170 g
4.6 g/min
2.5
35 m³ /h
30

20

40 (20) . , 20 m³/h ,
1 .

:

5:

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

:

[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)

, , 가 .
. 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 ²)
. , 25 / 60% 19 .
(D0) D0, D1 D2
F0, F1 F2 I .
II . SDS PVP II .

:

[II]

	F0	F1	F2
NF100	1.5%w/w ^{a)}	0.80 %w/w ^{a)}	0.94 %w/w ^{a)}
SDS	0.47 %w/w ^{a)} 1.7 %w/w ^{b)}	0.13 %w/w ^{a)} < 0.45 %w/w ^{b)}	0.02 %w/w ^{a)} < 0.45 %w/w ^{b)}
PVP	8.1 %w/w ^{a)} 6.2 %w/w ^{b)}	6.7 %w/w ^{a)} 5.8 %w/w ^{b)}	4.4 %w/w ^{a)} 3.4 %w/w ^{b)}
a) (I) b)			

~4000 D) SDS(M_w ~300 D) F0 . (SDS NF100(M_w ~4000 D) F0, F1 F2 (Hjartstam, Thesis, Chalmers University of Technology, Goteborg 1998). (tritiated water) 가 / 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 . Wurster
14 % w/w .
:

200 g

~ 340 g

4.6 g/min

2.5

35 m³ /h

50
28

:

12:

11 100 mg USP No. 2() 10
0 rpm 가 . pH 6.8, 0.1 M 500 ml . (bath)
37 (1 cm 274 nm)
(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) 2
10

0 ' 2 ' .

(57)

1.

- a) ,
b)
c) - ,

2.

1 , d) .

3.

1 ,

a)

b)

4.

3 , c) .

5.

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

20.

1 15 18
 15 18

, 3 5

21.

 1 3 13 15
 , 6 13 15 18

22.

 1 , 2 15 18
 , 6 13 15 18