

(19)  
(12)

(KR)  
(A)

(51) 。 Int. Cl. 7  
A61K 31/485

(11)  
(43)

2002 - 0071032  
2002 09 11

(21) 10 - 2002 - 7010121  
(22) 2002 08 06  
      2002 08 06  
(86) PCT/US2001/04347  
(86) 2001 02 08

(87) WO 2001/58447  
(87) 2001 08 16

(30) 60/181,369 2000 02 08 (US)

(71) - 122

(72) NY 10028 351 84

06851. 가 1

(74)

(54)

8

가

8

(Merck Manual, 16th Ed., 1992).

ing), (pruritus), (urinary retention) (respiratory depression)  
 Gan, Anesthesiology, vol. 87, No.5, 1075 - 1081, (1997)).  
 가 가 (S  
 hen, Brain Res., Vol.597, 74 - 83(1992)).

$\text{kg}^{-1} \cdot \text{h}^{-1}$ , Gan (naloxone, ) 0.25 $\mu\text{g}$   
 $1\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$  가 (Anesthesiology, vol.87, No.5, 1075 - 1081(1997)).

가

가

(intranasal)

(oral mucosal)

(hyperexcitability), /

가

5,512,578 , 5,472,943 , 5,580,876 5,767,125 (Crain )

가

가

가

" (controlled - release dosage form)"

, ( ) ( )가 ( " MEAC" )

( ) 가

Crain

( ,

37

(pH 1.6 7.2) 900Mℓ 100rpm

U

SP Paddle Method(U.S.Pharmacopeia XXII(1990))

8

가 ( ,

가 ). , ( 12 ), 1 - 1 ( 24 ) 3 . ,

/ 5 , 7

, ( ) ,

가

가 - , , , , /

가

( )가 가

가

Crain (1995, 1996) has shown that the relationship between the number of species and area is often non-linear, with a positive slope that decreases as area increases.

10 100

가

가

가 . 가 ( ),  
가

/

15mg

1

[ 1]

	(mg)
	13.5
	90.0
	15.0
	3.375
	1.8
	135.0
	9.0
	27.0

(bimodally action opioid agonists)" (inhibitory and excitatory o  
pioid receptor) (nociceptive neuron)

가

(opioid agonist)" "

(stereoisomer),

,"

(opioid antagonist)"

,

, N,N'

-

(enantiomer),

(diastreomer),

가

(asymmetric center)

(tautomer)

E Z

가

가 ( )

(chiral center)"

(eantiomer)"

(resolution)"

가

가

(Transdermal delivery system)

가

( ) , 48 72 (2 3 ) , Duragesic ( )

( ) ( ) ,

50 100 ,

가

(Wallenstein SL , Crossover Trials in Clinical Analgesic Assays; Studied of Buprenorphin and Morphine , Pharmacotherapy, G(5): 225 - 235, 1986).

5,069,909(Sharma )

가

4,806,341 (Chien )

)

(

5,026,556 (Drust )  
 3 4 , 3 6 ,  
 , , ;  
 ;  
 : 60:40 99:1  
 4,588,580 (Gale ) 5 100cm<sup>2</sup>  
 가  
 47 95%, 1 10%, 0.1 50 % 0.1 10%,

가

/ 1 , 0 , 1 0  
 , " 1 " 가  
 . " 0 " 30% 48

" (delivers)" 가 "

g /cm<sup>2</sup>/hr , 72 1.2mg  
 가 16.67g/hr ,  
 , " (flux rate)"

, 5,968,547  
 ; 72 3 8  
 6g/hr ; 72 120 0.3 9g/hr

20 % , 20 90 % , 0.1 30 % , 0.1 , 30 % , 0.1 가

0 150% A:B ( , A B )가 1.0:5.0 ,  
B 5 0.001 3.0μm, (b) 가 ;

8 85g/mm,  
, 1.0 % .

: (1) 0.5 4.9μm,  
, A (a) 1.

(2)(a) , (a)  
2 60 $\mu$ m

; . : (a) 2 25  
; (b) %  
% 1 12 %  
, 10 100cm<sup>2</sup> 1 100μg/hr

; (b) : (a) 가

99:1

(Oral mucosal delivery system)

MxQuinn, R.L. ( Sustained Oral Mucosal Delivery in Human Volunteers J.Controlled Release ; (34 1995(240 - 250)).  
 8%, Carbopol 934 52%, 35% 5% 2 -  
 ( )  
 (0.5cm<sup>2</sup>) 0.6mm  
 2.9mg 12 ( 25pg/Mℓ)  
 가 가 가 ,  
 24 0.42 ± 0.18mg

Carbopol 934,

(Suppositories)

( )

5,215,758

pH,  
Ka,

pH, p

18

12

Novata TM(AB, AB, B, BC, BD, BBC,  
E, BCF, C, D 299 ) Witepsol TM(H5, H12, H15, H175, H185, H19, H32, H35, H39, H42, W25, W31,  
W35, W45, S55, S58, E75, E76 E85 ) 12 18

65 80 %

( , ),  
20 90 %

가

가

가

가

(Compositions for intranasal administraion)

282 PCT WO8203768( )  
 205  
 - 6 - , 가 ) 5,629,011 ( - 6 -  
 가

( Modified Starches: Properties and Uses, O.B. Wurzburg, CRC Press Bo  
 ca Raton(1986)).

(DEAE - ),

( Davis , " Microspheres and Drug Ther  
 apy" , Elsevier Biomedical Press, 1984).

B 1 518 121 EP 223 303

(coacervation)

G

( Florence and Attwood, Physicochemical Principles of Pharmacy 2en E  
d., MacMillan Press, 1988, Chapter 8).

( Fisons Lomudal System).

가

( Bell. A. Intranasal Delivery Devices, in Drug Delivery Devices Fundamentals and Applications, Tyle P.(ed), Dekker, New York, 1988).

가

가 (Injectable formulations)

가 5,942,241 (Chasin )

가

가

가

/

가 5 200  
20 120

가 가

가 1 . , 6 50% 가  
2 , 100% 1 3  
2 .  
,'

4,293,539  
가  
( Dowex HCR - W2 - H ).  
0.01 20  
100 2502

가 가

가  
WO 95/13799

1 , 2  
1 2

??  
2

(Wurster air suspension coating apparatus)

가  
가

가

(Controlled release oral dosage forms)

가

" (release rate)"

U.S.P. Paddle(  
100rpm)

1:1

100:1 40:1 50:1 20:1  
100 100

가

가

가 , , 가

pH -  
가  
pH  
(CAP), (PVAP),

) (i) ; (ii) ; (iii)

2	25	%
5,273,760	5,286,493	

5,472,712                  .                  5,324,351    ,    5,356,467

#### (Alkylcellulose Polymers)

, / 가

가 Aquacoat (FMC Corp., , , )  
Aquacoat

Aquacoat . 가 가

Surelase (Colorcon, Inc., ), 가 ( ), ), . ( )

(Acrylic polymers)

, , ( ), ( ), , , ( ), , .

NF XVII

4

4  
가

pH -

nc) . Eudragit . Eudragit E  
. Eudragit L pH 5.7 pH 6  
. Eudragit S pH 6.5 pH 7 , Eudragit RL Eudragit RS  
. pH , Eudragit RL RS pH -

Eudragit RL30D Eudragit RS30D . Eudragit RL30D Eudragit RS30D Rhom Pharma

4 가 Eudragit RL30D 1:20 , Eudragit RS30D 1:40 . 150,000 . RL( ) RS( ) . Eudragit RL/RS 가 가

Eudragit® RL /RS

100% Eudragit® RL 50% Eudragit® RL

50% Eudragit RS 10% Eudragit RL: 90% Eudragit RS

Eudragit L

가

74

가

가

2

nu pariel 18/20

, Aquacoat Surelease 가 Eudragi  
Surelease , 가 가

( , )  
가

가

가 가 Aquacoat

가

가 . 가

Opadry

가

가

3,845,70 , 3,916,889 , 4,063,064 4,088,864

가

pH pH -

가

/

가

( 8 50,

12 40)

가

Eudragit RSPO -

1 80 %

25 90

가 60 %  
60 %

20 50 % , .

1

/ 가 1:2 1:4  
1:3 1:4 .

1,000      15,000,      1,500      12,000

( ), 12 36

2

(a) ; (b)

/ ; (c) , / , 가

12	36		
,	,	,	,
1.5	5	1.75	3.5

가 . Avicel PH 101(FMC )

가 . 가 ( )

(a)

; (b)

가 , 4.861.598

가

가

1:5,000 %

50 % 가

Handbook of Pharmaceutical Excipients (American Pharmaceutical Association (1986))

가

가

0.1      5mm      8      24

0.1 12mm

12mm

0.1 5mm

가,

0.1

)  
- 1593(1980))

Remington's Pharmaceutical Science (Arthur Osol ), 1553

4,957,681 (Klimesche )

2 30 %

( )

가 , 가 ,

가  
/

1  
2  
1 2

가

가 (Additional Drugs)

가

가

, ; N - D - (NMDA) - II (" COX - II " ); /

## NSAID      COX - 2

가

N - - D - (NMDA)  
 , , , d -  
 , " NMDA " NMDA -  
 ,  
 556,838 ( Mayer ) 가  
 . NMDA Mayer

5,514,680 (Webe

7g

, 가  
(antitussive), (expectorant), (decongestant),

4 325 650mg, 24 가 4g  
1000mg .

4

mg,	325mg	15mg,	325mg	300
mg	325mg	60mg		300
	7.5mg,	300mg	15mg,	300mg
	30g,	300mg	60mg	

500mg / 가 . / 5mg( ) 500mg  
           2.5mg, 500mg 5mg,  
   500mg 7.5mg, 7.5mg 650 750mg,  
           10m 500, 650, 660mg 가 .  
   / ( ) 5mg 500mg  
           , 5mg 325mg 가

가

가

(antitussive), (expectorant), (decongestant),

1: /

( )

( )

/

(MSCR) NXCR

(NXCR)

[ 2]

1A. NXCR		/ (mg)	/ (g)
1. (Drug layering)	HCl	2.0	14.0
	nu pariel (30/35 )	96.0	672.0
	C30	1.0	7.0
		1.0	7.0
			280
2. (seal coat)	Opadry Clear( )	5.0	35.0
			315.0
3.	Eudragit RS30D( )	13.23	92.61
		3.51	24.57
	Tween 80	0.03	0.21
		13.23	92.61
			624.0
4.	Opadry Clear( )	5.0	35.0
			315.0
		140	980

(NXCR )

1. HCl nu pariel

. Opadry Clear

2. Opadry Clear

3. Eudragit RS30D, , Tween 80

4. Opadry Clear

6. 60 24

(Dissolution method)

1. - USP Type II(paddle), 50rmp, 37
  2. - 1, 2, 4, 12, 24, 36
  3. - pH 6.5 900Mℓ
  4. - (HPLC)
- :

NXCR

3

[ 3]

(hr)	1	4	8	12	18
(%)	10	13	24	40	75

가 24

[ 4]

1B( - MSCR )	/ (mg)	/ (kg)
1.	60.0	45.0
	12.0	9.0
Eudragit RS 30D( )	2.0	1.5
	3.5	2.63
nu pariel PG 30/35	16.8	12.6
Opadry Blue	4.9	3.68
		31.5
2.	99.2	74.41
MSIR ( 1)	4.712	3.53
Eudragit RS 30D( )	0.248	0.19
Eudragit RL 30D( )	0.992	0.74
	1.884	1.49
Opadry Blue	5.639	4.23
		q.s.
	112.675	159

(MSCR )

1. Eudragit RS30D

2. (Rotor processor)

3.

4. Eudragit RS30D, RL30D,

5.

(Dissolution method)

1. - USP Type II(paddle), 100rmp, 37

2. - 1, 2, 4, 12, 24, 36

3. - 55 700Mℓ , 900Mℓ

4. - (HPLC)

:

MSCR 5

[ 5 ]

(hr)	1	2	4	8	12	18	24
(%)	4	8	23	49	70	83	85

가 24

1C. CR/ CR

[ 6 ]

		/ (mg)	/ (kg)
1.	CR	112.675	159
	HCl CR	140.0	105
		232.675	264

(MSCR/NXCR )

MSCR ( 1B) 112.675mg CR ( 1A) 140mg

2: /

HCl (HHCR) CR

2A: HCl

[ 7]

	/ (mg)	/ (gm)
HCl	2.0	33.3
Eudragit RSPO	70.0	1166.7
Eudragit RLPO	8.0	133.3
	40.0	666.7
	120.0	2000.0

1. HCl, Eudragit RSPO, Eudragit RLPO

2.

3.

4.

5.

(Dissolution method)

1. - USP Type I(Basket), 75rmp, 37

2. - 1, 2, 4, 8, 12

3. - 1 700Mℓ , 900Mℓ

4. - (HPLC)

HCl 8

[ 8]

(hr)	1	2	4	8	12
(%)	13.9	20.3	27.3	37.6	45.3

2B( HCl )

[ 9]

	/ (mg)	/ (kg)
HCl	12.0	3.2
Eudragit RSPO	76.5	20.4
	4.5	1.2
	27.0	7.2
	120.0	32.0

1.

2. HCl, Eudragit RSPO,

3.

4.

5.

6.

(Dissolution method)

1. - USP Type I(Basket), 75rmp, 37

2. - 1, 2, 4, 8, 12, 18, 24

3. - 900Mℓ+3g NaCl/L

4. - (HPLC)

HCl 10

[ 10]

(hr)	1	2	4	8	12	18	24
(%)	12.6	23.8	43.2	69.5	84.7	96.5	100.8

2C:

HCl CR/

CR

[ 11]

	/ (mg)	/ (kg)
HCl	120.0	12.0
HCl	120.0	12.0
	240.0	24.0

1. HCl ( 2B) HCl ( 2A)

3: / ( ) ( HCl) ( HCl)

( ) ,

[ 12]

	/ (mg)	/ (kg)
HCl	10.00	11.00
HCl	0.50	0.55
	68.75	75.62
	5.00	5.50
Eudragit RS 30D( )	10.00	11.00
	2.00	2.20
	25.00	27.50
	2.50	2.75
	1.25	1.38
Opadry White	5.00	5.50
		31.16*
	130.00	143.00
*		

1. - Eudragit 가 HCl 가

2. : HCl,

3. :

4. :

5. : , 가

6. :

7. :

8. :

9. :

10. :

Opadry

4: / ( )

( ) ( HCl )

( ) ,

[ 13]

	/ (mg)	/ (kg)
( )	30.00	108.0
HCl	0.50	1.8
	69.5	250.2
	10.0	36.0
		75.9*
	35.0	126.0
	3.0	10.8
	2.0	7.2
Opadry Purple	3.0	10.8
		61.2*
	153.0	550.8
*		

1. : HCl

2. : HCl , ,

3. :

4. :

5. :

6. : , , が

7. :

8. :

9. : ,

10. : ,

11. : Opadry ,

5: /

( HCl) ( )  
Eudragit

[ 14]

	/ (mg)	/ (gm)
HCl	12.0	120.0
Eudragit RSPO	76.0	760.0
	4.5	45.0
	27.0	270.0
HCl	0.5	5.0
	120.0	1200.0

1. :

2. : HCl, Eudragit, , HCl

3. :

4. :

5. :

6. :

7. : 120mg

6: /

( ) ( HCl)

[ 15]

	/ (mg)	/ (gm)
	30.0	15.0
HCl	0.5	0.25
	44.0	22.0
( )	62.0	31.0
	62.0	31.0
	20.0	10.0
	2.0	1.0
Opadry Red	10.0	5.0
		28.4*
	230.5	115.25
*		

1. :

2. : , HCl, , ,

3. :

4. :

5. :

6. :

7. :

8. : Opadry

7: / ( )

( ) ( HCl)

(Eudragit

RS 30D)

[ 16]

	/ (mg)	/ (kg)
HCl	0.50	1.80
Eudragit RS 30D( )	0.03	0.10
	0.01	0.04
( )	30.00	108.00
	69.46	250.06
	10.00	36.00
		75.90*
	35.00	126.00
	3.00	10.80
	2.00	7.20
Opadry Purple	3.00	10.80
		61.20*
	153.0	550.8
*		

1. : Eudragit 가

2. : HCl

3. : HCl , , ,

4. :

5. :

6. :

7. : 가

8. :

9. :

10. : ,

11. :

12. : Opadry

8:

WO96/19975

1

: 2 -

0

9 WO 96/19975 3 . . 10%  
 ( ), 10%, 10%, 1  
 0%, . 1 . 25µg/hr  
 , 10mg , 12.5cm<sup>2</sup>  
 30.6cm<sup>2</sup>

7

10mg, 0.1mg

10:

, 80 ; M, 100g 20 . (Cole - Parmer Company ) 100rpm 382 80

, DC - 360 20 M 가 20 ( 100g )( )  
)- 가 . . . . .

, 0.2 3mm .

3 20cm<sup>2</sup> 3M Company

Scotchpak 1006  
w Corning DC - 355

, 100 , : 30 , 6.5 ; 30 ;  
 DC - 355 Dow - Corning 6.5  
 100

가

5 200

, 3. , 4.

: 1. , 2.

10cm<sup>2</sup>

: 1 -

- 2 - ( Azone),

P.R. Keshary Y.W. Chien

(Drug Develop. &amp; Ind. Pharm., 10(6) 883 - 913(1984))

11:

(5 %) 2 - , Carbopol 934(52%), (35%)  
 ( ) , (0.5cm<sup>2</sup>) , 0.6mm  
 3mg

12 - 14:

17

가

[ 17]

( : mg)	1	2	3
	30.0	30.0	30.0
HCl	0.5	0.5	0.5
( LF )	327	409	450
	32.5	40.5	45.0
-B(Novata - B)	1410.0	1320.0	1275.0
	1800.0	1800.0	1800.0

- B (33.4 25.5 ) 12 18

, - . ,

, HCl , #200

- B 60

( 50 ) 가 40  
(filing kettle)

38

, 37 ( 36 38 )

15 - 19:

15 - 19 , 5,629,011

15 , - 6 - 가  
 EP 223302 1  
 100µm 75mg 30Mℓ 1g

16 , 15 가  
 (LPG) LPG 100mg 가

17 , 가 : - 6 - 150  
 mg (Chitosan) 0.5% (80%) , Protan Limite  
 d ) - - (Sigma Chemical Corp )  
 5% 가

18 , 17  
 50mg/Mℓ 가

19 , 16  
EDTA 50mg

EDTA  
가 15

20: (Microspheres for injection)

20 , /  
50 % 50 % 50:50 (D,L) co -  
( ) 가 . 가

5,512,578 , 5,472,943 , 5,580,876 5,767,125 (Crain , " Crain " )

가 ,

가

8

(57)

1.

8

2.

1 , .

3.

1 , 100 1000

4.

1 3 , .

5.

1 3 , , , , ,

6.

1 3 , ,

7.

1 3 , .

8.

1 3 , ㅏ

9.

1 3 , .

10.

1 3 , , , ,

11.

4 , ㅏ ,

12.

4 , , 가 가

13.

4 , 1  
2 , 1 2

14.

1 3 ,  
, 가

15.

1 14 , , , , , ,  
,

16.

15 , , , , , , ,  
,

17.

6 , 12

18.

6 , 24

19.

; ; ;  
,

8

20.

19 , 100  
1000 .

21.

19            20            ,            ,            ,            ,  
,            ,            .

22.

21            ,            ,            ,            ,            ,  
,

23.

22            ,            ,            ,            ,            ,  
,            ,

24.

;            ;  
가            8

25.

;            ;  
가            8

26.

24            25            ,  
100          1000

27.

24            ,            ,            ,            ,  
,

28.

24 26

29.

28

30.

24 26

31.

가

32.

가

3

가

33.

32 ,  
가

34.

34  
1000 ,