

โพรพราโนลอล ไฮโดรคลอไรด์แคปซูลชนิดออกฤทธิ์นาน ซึ่งเตรียมจากเฟลเสตเคลือบด้วยสาร  
ผสมระหว่างแอมโมนิโอมิธาคริเลต โคโพลีเมอร์ กับเฮซิลเซลลูโลส  
โดยใช้เทคนิคฟลูอิดไดซ์เบด

นางสาว อินทิดา คูวณิชยวงศ์



วิทยานิพนธ์นี้เป็นส่วนหนึ่งของการศึกษาตามหลักสูตรปริญญาเภสัชศาสตรมหาบัณฑิต

ภาควิชาเภสัชอุตสาหกรรม

บัณฑิตวิทยาลัย จุฬาลงกรณ์มหาวิทยาลัย

ปีการศึกษา 2540

ISBN 974-636-276-3

ลิขสิทธิ์ของบัณฑิตวิทยาลัย จุฬาลงกรณ์มหาวิทยาลัย

PROPRANOLOL HYDROCHLORIDE SUSTAINED RELEASE CAPSULES  
PREPARED FROM PELLETS COATED WITH THE MIXTURES OF AMMONIO  
METHACRYLATE COPOLYMER AND ETHYLCELLULOSE USING  
FLUIDIZED BED TECHNIQUE

**Miss Intira Coowanitwong**

สถาบันวิทยบริการ  
จุฬาลงกรณ์มหาวิทยาลัย

**A Thesis Submitted in Partial Fulfillment of the Requirements  
for the Degree of Master of Science in Pharmacy  
Department of Manufacturing Pharmacy**

**Graduate School**

**Chulalongkorn University**

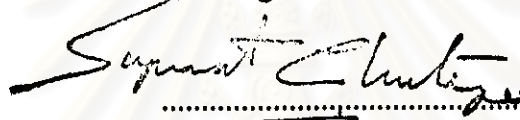
**Academic Year 1997**

**ISBN 974-636-276-3**

Thesis Title            Propranolol Hydrochloride Sustained Release Capsules  
Prepared from Pellets Coated with the Mixture of Ammonio  
Methacrylate Copolymer and Ethylcellulose Using Fluidized  
Bed Technique  
By                            Miss Intira Coowanitwong  
Department            Manufacturing Pharmacy  
Thesis Advisor        Associate Professor Poj Kulvanich, Ph.D.


---


Accepted by the Graduate School, Chulalongkorn University in Partial Fulfillment of  
the Requirements for the Master's Degree.

  
..... Dean of Graduate School  
(Professor Supawat Chutivongse, M.D.)

Thesis Committee

  
..... Chairman  
(Assistant Professor Wichein Thanindratarn, M.Sc.)

  
..... Thesis Advisor  
(Associate Professor Poj Kulvanich, Ph.D.)

  
..... Member  
(Panida Vayumhasuwan, Ph.D.)

  
..... Member  
(Narueporn Nachientung, Ph.D.)

พิมพ์ต้นฉบับบทคัดย่อวิทยานิพนธ์ภายในกรอบสี่เหลี่ยมนี้เพียงแผ่นเดียว

อินทิดา ฤทธิชัยวงศ์ : โพรพรานอลอล ไฮโดรคลอไรด์แคปซูลชนิดออกฤทธิ์นาน ซึ่งเตรียมจากเพลเลต เคลือบด้วยสารผสมระหว่างแอมโมนิโอเมทาคริเลต โคโพลีเมอร์ กับเอธิลเซลลูโลส โดยใช้เทคนิคฟลูอิดโคซ์เบด (PROPRANOLOL HYDROCHLORIDE SUSTAINED RELEASE CAPSULES PREPARED FROM PELLETS COATED WITH THE MIXTURES OF AMMONIO METHACRYLATE COPOLYMER AND ETHYLCELLULOSE USING FLUIDIZED BED TECHNIQUE) อ. ที่ปรึกษา : รศ.ดร. พจน์ ฤควณิช, 224 หน้า. ISBN 974-636-276-3

การเตรียมโพรพรานอลอลไฮโดรคลอไรด์เพลเลตโดยใช้เทคนิคเอกทูชันและสเฟียโรไนเซชัน นำมาเคลือบด้วยสารละลายที่เป็นส่วนผสมระหว่างเอธิลเซลลูโลส กับยูคราจิต อาร์ แอล 100 (แอมโมนิโอ เมทาคริเลต โคโพลีเมอร์ ชนิด A) หรือส่วนผสมระหว่างเอธิลเซลลูโลสกับยูคราจิต อาร์ เอส 100 (แอมโมนิโอ เมทาคริเลต โคโพลีเมอร์ ชนิด B) ซึ่งละลายในสารละลายอินทรีย์ผสมระหว่างอะซีโตนและไอโซโพรพิลแอลกอฮอล์ในอัตราส่วน 1:1 โดยใช้เทคนิคการเคลือบแบบฟลูอิดโคซ์เบดชนิดพ่นจากด้านล่าง เพื่อศึกษาคุณสมบัติทางกายภาพและคุณสมบัติการปลดปล่อยตัวยาจากเพลเลตที่ถูกเคลือบแล้ว พื้นผิวของเพลเลตที่ไม่ได้เคลือบจะมีลักษณะหยาบและมีรูพรุน ส่วนพื้นผิวของเพลเลตที่เคลือบด้วยเอธิลเซลลูโลสจะมีลักษณะขรุขระ แต่เมื่อมีส่วนผสมของยูคราจิต อาร์ แอล 100 หรือ อาร์ เอส 100 ในปริมาณสูงขึ้น ก็ให้พื้นผิวที่เรียบขึ้น การเพิ่มระดับการเคลือบจะทำให้ความหนาของฟิล์มเพิ่มสูงขึ้น ลักษณะการปลดปล่อยตัวยาโพรพรานอลอล ไฮโดรคลอไรด์จากเพลเลตที่เคลือบแล้วจะแตกต่างกันในตัวอย่างที่มีความเป็นกรดและเป็นด่าง อัตราการปลดปล่อยจะช้าลงเมื่อปริมาณสารเคลือบสูงขึ้น อัตราส่วนผสมของโพลีเมอร์จะมีผลต่ออัตราการปลดปล่อยตัวยา ฟิล์มเคลือบที่มีอัตราส่วนของเอธิลเซลลูโลสสูงจะลดอัตราการปลดปล่อยตัวยา และเมื่อเพิ่มอัตราส่วนของยูคราจิต อาร์ แอล 100 หรือยูคราจิต อาร์ เอส 100 จะเพิ่มอัตราการปลดปล่อยตัวยา หลังจากได้ศึกษาวิเคราะห์ลักษณะและปริมาณการปลดปล่อยตัวยาของแต่ละตัวรับแล้วได้คัดเลือกเพลเลตเคลือบที่มีการปลดปล่อยตัวที่เหมาะสมมาผสมกันในอัตราส่วนที่จะให้ลักษณะการปลดปล่อยตัวยาให้ได้ตามข้อกำหนดของยาโพรพรานอลอล ไฮโดรคลอไรด์ชนิดออกฤทธิ์นาน 24 ชั่วโมงของเภสัชตำรับสหรัฐอเมริกา และนำมาเปรียบเทียบกับอินเคอเรล แอล เอ 160 ซึ่งเป็นผลิตภัณฑ์ที่มีจำหน่ายในท้องตลาด

ภาควิชา ..... เภสัชอุตสาหกรรม  
สาขาวิชา ..... เภสัชอุตสาหกรรม  
ปีการศึกษา ..... 2540

ลายมือชื่อนิสิต ..... อินทิดา ฤทธิชัยวงศ์  
ลายมือชื่ออาจารย์ที่ปรึกษา .....  
ลายมือชื่ออาจารย์ที่ปรึกษาร่วม .....

# # C 875223 : MAJOR MANUFACTURING PHARMACY

KEY WORD: PROPRANOLOL HYDROCHLORIDE AMMONIOMETHACRYLATE  
COPOLYMER /FLUIDIZED BED

INTIRA COOWANITWONG : PROPRANOLOL HYDROCHLORIDE  
SUSTAINED RELEASE CAPSULES PREPARED FROM PELLETS COATED  
WITH THE MIXTURES OF AMMONIO METHACRYLATE COPOLYMER AND  
ETHYLCELLULOSE USING FLUIDIZED BED TECHNIQUE. THESIS

ADVISOR : ASSOC. PROF. POJ KULVANICH. Ph. D., 224 PP. ISBN 974-636-276-3

Propranolol hydrochloride pellets were prepared using extrusion and spheronization techniques. Core pellets were coated with the mixtures of ammonio methacrylate copolymer and ethylcellulose in various ratios which were implemented as a film coatings to control the release of the drug. A mixture of acetone and isopropyl alcohol in a ratio of 1:1 was employed as a cosolvents for coating solution.

Pellets were coated using a fluidized bed technique of Wurster type. Physical characteristics and drug release characteristics of uncoated and coated pellets were investigated.

Ethylcellulose gave a rough and porous surface coating film. Nevertheless, when the ethylcellulose film was mixed with either Eudragit® RL100 or Eudragit® RS100, the coating surface becomes smoother. Increasing the amount Eudragit® improved the smoothness of the coating surface. Consequently, with the higher coating levels the thicker film layer was obtained.

The drug release characteristics of coated pellets were affected by dissolution mediums employed. In general, a release rate of coated pellets in an acidic medium was faster than in an alkali medium. At higher coating levels, the release of the drug from the pellets was more retarded. The ratio of polymers affects the drug release characteristics, resulting in the following scenarios: increasing percent of ethylcellulose, decreasing the drug release, increasing either Eudragit® RL100 or Eudragit® RS100, increasing the drug release.

In this study, the coated pellets of various formulations which provided suitable release rates were selected and combined to formulate sustained release propranolol hydrochloride capsules of 24 hour type that could meet the USP XXIII specification. The release profiles of developed formula were comparable to the release characteristic of Inderal® LA160, a wellknown commercial product.

ภาควิชา.....เภสัชอุตสาหกรรม.....

สาขาวิชา.....เภสัชอุตสาหกรรม.....

ปีการศึกษา.....2540.....

ลายมือชื่อนิติกร.....จันทิมา.....ภาควิชาเภสัชฯ.....

ลายมือชื่ออาจารย์ที่ปรึกษา.....

ลายมือชื่ออาจารย์ที่ปรึกษาร่วม.....



## Acknowledgments

I can only begin to express my sincere gratitude to my advisor, Associate Prof. Dr. Poj Kulvanich, for his guidance, and never-ending encouragement during my time working with him. Although it was sometimes a struggle on this work, for both Associate Prof. Dr. Poj and me, I learned a great deal from him. His door was always open and he always had time for discussion with me. I will always admire his work as an educator and a mentor.

To special acknowledgment is given to all the staffs and friends in the Department of Manufacturing Pharmacy for their sincere. They always have supplied me with everlasting laughter. In addition to their advice and refreshing perspective on the general. I would like to thank them for their companionship throughout the years.

I would like to thank Associate Prof. Dr. Karnpimol C. Ritthidej for all her guidance. In addition, I extend my thanks to the three other members of my Master committee, Assistant Prof. Wichain Thanindratarn, Dr. Panida Vayambasuwan, and Dr. Narueporn Nachientung for reading this work and making constructive criticism which have improved its quality.

A special appreciation is given to the Graduate school, Chulalongkorn University for granting partial financial support to fulfill this investigation.

Throughout my graduate work, my family shared with me the best and frustrating moments. Whenever I spoke to them, any discouragement I had was made insignificant. Their confidence and love are inspirational. My love and gratitude go to my mother and my father, who have always given their time and support for all my endeavor. Their love for me are manifested in every way. I am grateful for all things they have done for me for they have given me so much and asked for nothing in return. I am blessed to have this superb family.

## Contents

	Page
Thai Abstract.....	IV
English Abstract.....	V
Acknowledgments.....	VI
List of Tables.....	VII
List of Figures.....	XI
Chapter	
I. General Background.....	1
II. Experimental.....	23
III. Results and Discussion.....	38
IV. Conclusions.....	181
References.....	183
Appendices.....	196
Vitae.....	224

สถาบันวิทยบริการ  
จุฬาลงกรณ์มหาวิทยาลัย

## List of Tables

Table	Page
1. Solubility of ethylcellulose in various solvents.....	9
2. Solubility of polymethacrylate in organic solvents.....	12
3. Comparison of three fluidized-bed coating process.....	22
4. Formulation of core pellets.....	25
5. The spheronizing conditions.....	26
6. Formulation of propranolol hydrochloride pellets.....	27
7. Composition of coating solution in preliminary investigation.....	30
8. Ratio between Eudragit®RL100 and ethylcellulose.....	31
9. Ratio between Eudragit®RS100 and ethylcellulose.....	32
10. The coating conditions using Wurster spray method.....	33
11. Physical properties of uncoated pellets.....	43
12. Physical properties of coated pellets.....	93
13. The time at which most of the drug were release of Formulation 1-16..	143
14. Release pattern of Formulations which gave biphasic release showing initial slow drug release phase (phase 1) and faster drug release phase (phase 2).....	144
15. The release pattern of coated pellets Formulation 22-24 and 33-39....	161
16. The amount of coated pellets formulations selected to formulate sustained release propranolol hydrochloride capsules of 24-hours type..	169
17. Percent release of developed capsule formulation and Inderal®LA160 in pH change method compared with USP XXIII specification.....	179
18. The absorbance value-of the main composition of coated pellets at 289.0 nm.....	198
19. Absorbance of propranolol hydrochloride in acid buffer pH 1.2 at 289.0 nm.....	201



Table (cont.)	Page
20. Absorbance of propranolol hydrochloride in phosphate buffer pH 6.8 at 289.0 nm.....	202
21. Absorbance of propranolol hydrochloride in methanol at 289.0 nm....	202
22. Percent release of propranolol hydrochloride from uncoated pellets and coated pellets formulation 1-3 in acid buffer pH 1.2 and phosphate buffer pH 6.8.....	206
23. Percent release of propranolol hydrochloride from coated pellets formulation 4-7 in acid buffer pH 1.2 and phosphate buffer pH 6.8....	207
24. Percent release of propranolol hydrochloride from coated pellets formulation 8-10 in acid buffer pH 1.2 and phosphate buffer pH 6.8..	208
25. Percent release of propranolol hydrochloride from coated pellets formulation 11-13 in acid buffer pH 1.2 and phosphate buffer pH 6.8....	209
26. Percent release of propranolol hydrochloride from coated pellets formulation 14-16 in acid buffer pH 1.2 and phosphate buffer pH 6.8....	210
27. Percent release of propranolol hydrochloride from coated pellets formulation 17-18 in acid buffer pH 1.2 and phosphate buffer pH 6.8....	211
28. Percent release of propranolol hydrochloride from coated pellets formulation 19-20 in acid buffer pH 1.2 and phosphate buffer pH 6.8....	212
29. Percent release of propranolol hydrochloride from coated pellets formulation 21-22 in acid buffer pH 1.2 and phosphate buffer pH 6.8....	213
30. Percent release of propranolol hydrochloride from coated pellets formulation 23-24 in acid buffer pH 1.2 and phosphate buffer pH 6.8....	214
31. Percent release of propranolol hydrochloride from coated pellets formulation 25-26 in acid buffer pH 1.2 and phosphate buffer pH 6.8....	215
32. Percent release of propranolol hydrochloride from coated pellets formulation 27-28 in acid buffer pH 1.2 and phosphate buffer pH 6.8....	216
33. Percent release of propranolol hydrochloride from coated pellets formulation 29-30 in acid buffer pH 1.2 and phosphate buffer pH 6.8....	217
34. Percent release of propranolol hydrochloride from coated pellets formulation 31-32 in acid buffer pH 1.2 and phosphate buffer pH 6.8....	218

Table (cont.)	Page
35. Percent release of propranolol hydrochloride from coated pellets formulation 33-35 in acid buffer pH 1.2 and phosphate buffer pH 6.8....	219
36. Percent release of propranolol hydrochloride from coated pellets formulation 36-37 in acid buffer pH 1.2 and phosphate buffer pH 6.8...	220
37. Percent release of propranolol hydrochloride from coated pellets formulation 38-39 in acid buffer pH 1.2 and phosphate buffer pH 6.8...	221
38. Percent release of propranolol hydrochloride from Inderal <sup>®</sup> LA160 and sustained release propranolol hydrochloride capsules in acid buffer pH 1.2 and phosphate buffer pH 6.8.....	222
39. Percent release of propranolol hydrochloride from Inderal <sup>®</sup> LA160 and sustained release propranolol hydrochloride capsules by pH change method.....	223

## List of Figures

Figure	Page
1. Chemical structure of propranolol hydrochloride.....	4
2. Chemical structure of ethylcellulose.....	8
3. Chemical structure of Eudragit®RL and RS.....	11
4. Chemical structure of dibutyl phthalate.....	14
5. Classification of pelletization process.....	16
6. Schematic representation of simple extrusion-spheronization process....	17
7. Top spray coater.....	19
8. Wurster (bottom) spray coater.....	20
9. Tangential spray coater.....	22
10. The photograph of spheronizer.....	27
11. The photograph of fluidized bed.....	33
12. Photomicrographs of lactose pellets.....	41
13. Photomicrographs of propranolol hydrochloride pellets.....	42
14. Photomicrographs of coated pellets formulation 1.....	51
15. Photomicrographs of coated pellets formulation 2.....	52
16. Photomicrographs of coated pellets formulation 3.....	53
17. Photomicrographs of coated pellets formulation 4.....	54
18. Photomicrographs of coated pellets formulation 5.....	55
19. Photomicrographs of coated pellets formulation 6.....	56
20. Photomicrographs of coated pellets formulation 7.....	57
21. Photomicrographs of coated pellets formulation 8.....	58
22. Photomicrographs of coated pellets formulation 9.....	60
23. Photomicrographs of coated pellets formulation 10.....	61
24. Photomicrographs of coated pellets formulation 11.....	62
25. Photomicrographs of coated pellets formulation 12.....	63
26. Photomicrographs of coated pellets formulation 13.....	64

Figure (cont.)	Page
27. Photomicrographs of coated pellets formulation 14.....	65
28. Photomicrographs of coated pellets formulation 15.....	66
29. Photomicrographs of coated pellets formulation 16.....	67
30. Photomicrographs of coated pellets formulation 17.....	68
31. Photomicrographs of coated pellets formulation 18.....	69
32. Photomicrographs of coated pellets formulation 19.....	70
33. Photomicrographs of coated pellets formulation 20.....	71
34. Photomicrographs of coated pellets formulation 21.....	73
35. Photomicrographs of coated pellets formulation 22.....	74
36. Photomicrographs of coated pellets formulation 23.....	75
37. Photomicrographs of coated pellets formulation 24.....	76
38. Photomicrographs of coated pellets formulation 25.....	77
39. Photomicrographs of coated pellets formulation 26.....	78
40. Photomicrographs of coated pellets formulation 27.....	79
41. Photomicrographs of coated pellets formulation 28.....	80
42. Photomicrographs of coated pellets formulation 29.....	81
43. Photomicrographs of coated pellets formulation 30.....	82
44. Photomicrographs of coated pellets formulation 31.....	83
45. Photomicrographs of coated pellets formulation 32.....	84
46. Photomicrographs of coated pellets formulation 33.....	85
47. Photomicrographs of coated pellets formulation 34.....	87
48. Photomicrographs of coated pellets formulation 35.....	88
49. Photomicrographs of coated pellets formulation 36.....	89
50. Photomicrographs of coated pellets formulation 37.....	90
51. Photomicrographs of coated pellets formulation 38.....	91
52. Photomicrographs of coated pellets formulation 39.....	92
53. Release profile of uncoated pellets in acid buffer pH 1.2 and phosphate buffer pH 6.8.....	95

Figure (cont.)	Page
54. Release profile of coated pellets formulation 1 in acid buffer pH 1.2 and phosphate buffer pH 6.8.....	97
55. Release profile of coated pellets formulation 2 in acid buffer pH 1.2 and phosphate buffer pH 6.8.....	97
56. Release profile of coated pellets formulation 3 in acid buffer pH 1.2 and phosphate buffer pH 6.8.....	98
57. Release profile of coated pellets formulation 4 in acid buffer pH 1.2 and phosphate buffer pH 6.8.....	98
58. Release profiles of the pellets coating with different levels of Eudragit®RL100 in acid buffer pH 1.2.....	100
59. Release profiles of the pellets coating with different levels of Eudragit®RL100 in phosphate buffer pH 6.8.....	100
60. Release profile of coated pellets formulation 5 in acid buffer pH 1.2 and phosphate buffer pH 6.8.....	101
61. Release profile of coated pellets formulation 6 in acid buffer pH 1.2 and phosphate buffer pH 6.8.....	101
62. Release profile of coated pellets formulation 7 in acid buffer pH 1.2 and phosphate buffer pH 6.8.....	102
63. Release profile of coated pellets formulation 8 in acid buffer pH 1.2 and phosphate buffer pH 6.8.....	102
64. Release profiles of the pellets coating with different levels of EURL80:EC20 in acid buffer pH 1.2.....	104
65. Release profiles of the pellets coating with different levels of EURL80:EC20 in phosphate buffer pH 6.8.....	104
66. Release profile of coated pellets formulation 9 in acid buffer pH 1.2 and phosphate buffer pH 6.8.....	105
67. Release profile of coated pellets formulation 10 in acid buffer pH 1.2 and phosphate buffer pH 6.8.....	105

Figure (cont.)	Page
68. Release profile of coated pellets formulation 11 in acid buffer pH 1.2 and phosphate buffer pH 6.8.....	106
69. Release profile of coated pellets formulation 12 in acid buffer pH 1.2 and phosphate buffer pH 6.8.....	106
70. Release profiles of the pellets coating with different levels of EURL60:EC40 in acid buffer pH 1.2.....	108
71. Release profiles of the pellets coating with different levels of EURL60:EC40 in phosphate buffer pH 6.8.....	108
72. Release profile of coated pellets formulation 13 in acid buffer pH 1.2 and phosphate buffer pH 6.8.....	109
73. Release profile of coated pellets formulation 14 in acid buffer pH 1.2 and phosphate buffer pH 6.8.....	109
74. Release profile of coated pellets formulation 15 in acid buffer pH 1.2 and phosphate buffer pH 6.8.....	110
75. Release profile of coated pellets formulation 16 in acid buffer pH 1.2 and phosphate buffer pH 6.8.....	110
76. Release profiles of the pellets coating with different levels of EURL40:EC60 in acid buffer pH 1.2.....	111
77. Release profiles of the pellets coating with different levels of EURL40:EC60 in phosphate buffer pH 6.8.....	111
78. Release profile of coated pellets formulation 17 in acid buffer pH 1.2 and phosphate buffer pH 6.8.....	113
79. Release profile of coated pellets formulation 18 in acid buffer pH 1.2 and phosphate buffer pH 6.8.....	113
80. Release profile of coated pellets formulation 19 in acid buffer pH 1.2 and phosphate buffer pH 6.8.....	114
81. Release profile of coated pellets formulation 20 in acid buffer pH 1.2 and phosphate buffer pH 6.8.....	114

Figure (cont.)	Page
82. Release profiles of the pellets coating with different levels of EURL20:EC80 in acid buffer pH 1.2.....	115
83. Release profiles of the pellets coating with different levels of EURL80:EC20 in phosphate buffer pH 6.8.....	115
84. Release profile of coated pellets formulation 21 in acid buffer pH 1.2 and phosphate buffer pH 6.8.....	116
85. Release profile of coated pellets formulation 22 in acid buffer pH 1.2 and phosphate buffer pH 6.8.....	116
86. Release profile of coated pellets formulation 23 in acid buffer pH 1.2 and phosphate buffer pH 6.8.....	117
87. Release profile of coated pellets formulation 24 in acid buffer pH 1.2 and phosphate buffer pH 6.8.....	117
88. Release profiles of the pellets coating with different levels of ethylcellulose in acid buffer pH 1.2.....	119
89. Release profiles of the pellets coating with different levels of ethylcellulose in phosphate buffer pH 6.8.....	119
90. Release profile of coated pellets formulation 25 in acid buffer pH 1.2 and phosphate buffer pH 6.8.....	120
91. Release profile of coated pellets formulation 26 in acid buffer pH 1.2 and phosphate buffer pH 6.8.....	120
92. Release profile of coated pellets formulation 27 in acid buffer pH 1.2 and phosphate buffer pH 6.8.....	121
93. Comparison of retardant property on drug release of Eudragit®RS100 and Eudragit®RL100.....	121
94. Release profiles of the pellets coating with different levels of Eudragit®RS100 in acid buffer pH 1.2.....	122
95. Release profiles of the pellets coating with different levels of Eudragit®RS100 in phosphate buffer pH 6.8.....	122

Figure (cont.)	Page
96. Release profile of coated pellets formulation 28 in acid buffer pH 1.2 and phosphate buffer pH 6.8.....	124
97. Release profile of coated pellets formulation 29 in acid buffer pH 1.2 and phosphate buffer pH 6.8.....	124
98. Release profile of coated pellets formulation 30 in acid buffer pH 1.2 and phosphate buffer pH 6.8.....	125
99. Release profiles of the pellets coating with different levels of EURS80:EC20 in acid buffer pH 1.2.....	125
100. Release profiles of the pellets coating with different levels of EURS80:EC20 in phosphate buffer pH 6.8.....	126
101. Release profile of coated pellets formulation 31 in acid buffer pH 1.2 and phosphate buffer pH 6.8.....	126
102. Release profile of coated pellets formulation 32 in acid buffer pH 1.2 and phosphate buffer pH 6.8.....	128
103. Release profile of coated pellets formulation 33 in acid buffer pH 1.2 and phosphate buffer pH 6.8.....	128
104. Release profiles of the pellets coating with different levels of EURS60:EC40 in acid buffer pH 1.2.....	129
105. Release profiles of the pellets coating with different levels of EURS60:EC40 in phosphate buffer pH 6.8.....	129
106. Release profile of coated pellets formulation 34 in acid buffer pH 1.2 and phosphate buffer pH 6.8.....	130
107. Release profile of coated pellets formulation 35 in acid buffer pH 1.2 and phosphate buffer pH 6.8.....	130
108. Release profile of coated pellets formulation 36 in acid buffer pH 1.2 and phosphate buffer pH 6.8.....	131
109. Release profiles of the pellets coating with different levels of EURS40:EC60 in acid buffer pH 1.2.....	131



Figure (cont.)	Page
110. Release profiles of the pellets coating with different levels of EURS40:EC60 in phosphate buffer pH 6.8.....	133
111. Release profile of coated pellets formulation 37 in acid buffer pH 1.2 and phosphate buffer pH 6.8.....	133
112. Release profile of coated pellets formulation 38 in acid buffer pH 1.2 and phosphate buffer pH 6.8.....	134
113. Release profile of coated pellets formulation 39 in acid buffer pH 1.2 and phosphate buffer pH 6.8.....	134
114. Release profiles of the pellets coating with different levels of EURL20:EC80 in acid buffer pH 1.2.....	135
115. Release profiles of the pellets coating with different levels of EURL20:EC80 in phosphate buffer pH 6.8.....	135
116. Photomicrograph of coated pellets formulation 25 after dissolution test in acid buffer pH 1.2.....	137
117. Photomicrograph of coated pellets formulation 25 after dissolution test in phosphate buffer pH 6.8.....	138
118. Photomicrograph of coated pellets formulation 27 after dissolution test in acid buffer pH 1.2.....	139
119. Photomicrograph of coated pellets formulation 27 after dissolution test in phosphate buffer pH 6.8.....	140
120. Photomicrograph of coated pellets formulation 29 after dissolution test in acid buffer pH 1.2.....	141
121. Photomicrograph of coated pellets formulation 29 after dissolution test in phosphate buffer pH 6.8.....	142
122. slow release period of the release profile of coated pellets Formulation 19 in phosphate buffer pH 6.8.....	145
123. The first order plot of coated pellets Formulation 19 in phosphate buffer pH 6.8.....	145

Figure (cont.)	Page
124. The Higuchi plot of coated pellets Formulation 19 in phosphate buffer pH 6.8.....	146
125. slow release period of the release profile of coated pellets Formulation 20 in phosphate buffer pH 6.8.....	146
126. The first-order plot of coated pellets Formulation 20 in phosphate buffer pH 6.8.....	147
127. The Higuchi plot of coated pellets Formulation 20 in phosphate buffer pH 6.8.....	147
128. slow release period of the release profile of coated pellets Formulation 26 in acid buffer pH 1.2.....	148
129. The first-order plot of coated pellets Formulation 26 in acid buffer pH 1.2.....	148
130. The Higuchi plot of coated pellets Formulation 26 in acid buffer pH 1.2.....	149
131. slow release period of the release profile of coated pellets Formulation 26 in phosphate buffer pH 6.8 .....	149
132. The first-order plot of coated pellets Formulation 26 in phosphate buffer pH 6.8.....	150
133. The Higuchi plot of coated pellets Formulation 26 in phosphate buffer pH 6.8.....	150
134. slow release period of the release profile of coated pellets Formulation 27 in acid buffer pH 1.2 .....	151
135. The first-order plot of coated pellets Formulation 27 in acid buffer pH 1.2.....	151
136. The Higuchi plot of coated pellets Formulation 27 in acid buffer pH 1.2.....	152
137. slow release period of the release profile of coated pellets Formulation 27 in phosphate buffer pH 6.8 .....	152
138. The first-order plot of coated pellets Formulation 27 in phosphate buffer pH 6.8.....	153

Figure (cont.)	Page
139. The Higuchi plot of coated pellets Formulation 27 in phosphate buffer pH 6.8.....	153
140. Slow release period of the release profile of coated pellets Formulation 30 in acid buffer pH 1.2 .....	154
141. The first-order plot of coated pellets Formulation 30 in acid buffer pH 1.2.....	154
142. The Higuchi plot of coated pellets Formulation 30 in acid buffer pH 1.2.....	155
143. Slow release period of the release profile of coated pellets Formulation 30 in phosphate buffer pH 6.8 .....	155
144. The first-order plot of coated pellets Formulation 30 in phosphate buffer pH 6.8.....	156
145. The Higuchi plot of coated pellets Formulation 30 in phosphate buffer pH 6.8.....	156
146. Slow release period of the release profile of coated pellets Formulation 32 in phosphate buffer pH 6.8.....	157
147. The first-order plot of coated pellets Formulation 32 in phosphate buffer pH 6.8.....	157
148. The Higuchi plot of coated pellets Formulation 32 in phosphate buffer pH 6.8.....	158
149. Slow release period of the release profile of coated pellets Formulation 33 in acid buffer pH 1.2 .....	158
150. The first-order plot of coated pellets Formulation 33 in acid buffer pH 1.2.....	159
151. The Higuchi plot of coated pellets Formulation 33 in acid buffer pH 1.2.....	159
152. Slow release period of the release profile of coated pellets Formulation 33 in phosphate buffer pH 6.8.....	160

Figure (cont.)	Page
153. The first-order plot of coated pellets Formulation 33 in phosphate buffer pH 6.8.....	160
154. The Higuchi plot of coated pellets Formulation 33 in phosphate buffer pH 6.8.....	161
155. The zero-order plot of coated pellets Formulation 22 in acid buffer pH 1.2.....	162
156. The zero-order plot of coated pellets Formulation 22 in phosphate buffer pH 1.2.....	162
157. The zero-order plot of coated pellets Formulation 23 in acid buffer pH 1.2.....	163
158. The zero-order plot of coated pellets Formulation 23 in phosphate buffer pH 1.2.....	163
159. The zero-order plot of coated pellets Formulation 24 in acid buffer pH 1.2.....	164
160. The zero-order plot of coated pellets Formulation 24 in phosphate buffer pH 1.2.....	164
161. The zero-order plot of coated pellets Formulation 37 in acid buffer pH 1.2.....	165
162. The zero-order plot of coated pellets Formulation 37 in phosphate buffer pH 1.2.....	165
163. The zero-order plot of coated pellets Formulation 38 in acid buffer pH 1.2.....	166
164. The zero-order plot of coated pellets Formulation 38 in phosphate buffer pH 1.2.....	166
165. The zero-order plot of coated pellets Formulation 39 in acid buffer pH 1.2.....	167
166. The zero-order plot of coated pellets Formulation 39 in phosphate buffer pH 1.2.....	167
167. Release profile of developed sustained release propranolol hydrochloride capsules in pH change method.....	169

Figure (cont.)	Page
168. The first order plot of sustained release propranolol hydrochloride capsules in pH change method.....	170
169. The Higuchi plot of sustained release propranolol hydrochloride capsules in pH change method.....	171
170. Release profile of sustained release propranolol hydrochloride capsules in acid buffer pH 1.2 and phosphate buffer pH 6.8.....	172
171. Photomicrographs of sustained release propranolol hydrochloride capsules after dissolution test in pH change method.....	173
172. Photomicrographs of sustained release propranolol hydrochloride capsules after dissolution test in acid buffer pH 1.2.....	174
173. Photomicrographs of sustained release propranolol hydrochloride capsules after dissolution test in phosphate buffer pH 6.8.....	175
174. Release profile of Inderal <sup>®</sup> LA160 in acid buffer pH 1.2 and phosphate buffer pH 6.8.....	176
175. Release profile of Inderal <sup>®</sup> LA160 in pH change method.....	177
176. The first order plot of by Inderal <sup>®</sup> LA160 in pH change method...	178
177. The Higuchi plot of Inderal <sup>®</sup> LA160 in pH change method.....	178
178. Comparison of release profile of Inderal <sup>®</sup> LA160 with developed sustained release propranolol hydrochloride capsules in pH change method .....	179
179. Photomicrographs of Inderal <sup>®</sup> LA160 in pH change method.....	180
180. The sample scan of core lactose.....	199
181. The sample scan of core lactose coated with Eudragit <sup>®</sup> RL100....	199
182. The sample scan of core lactose coated with Eudragit <sup>®</sup> RS100....	200
183. The sample scan of core lactose coated with ethylcellulose.....	200
184. Typical calibration curve of propranolol hydrochloride in acid buffer pH 1.2.....	203
185. Typical calibration curve of propranolol hydrochloride in phosphate buffer pH 6.8.....	203

Figure (cont.)

Page

186. Typical calibration curve of propranolol hydrochloride

in methanol.....

204



สถาบันวิทยบริการ  
จุฬาลงกรณ์มหาวิทยาลัย

## Abbreviations

bar	kg/cm <sup>2</sup>
° C	degree celsius
e.g.	exempli gratia, for example
cm	centimeter
cps	centipoises
et al.	et alii, and others
EC	ethylcellulose
EURL	Eudragit®RL
EURS	Eudragit®RS
gm	gram
hr	hour
HCl	Hydrochloric acid
i.e.	id est, that is
IPA	Isopropyl alcohol
kg	kilogram (s)
l	liter
mg	milligram
min	minute
ml	milliliter
N	normal
nm	nanometer
rpm	revolution per minute
SEM	scanning electron microscope
-SD	standard deviation
soln	solution
USP	The United States Pharmacopoeia
UV	ultraviolet
w/v	weight by volume

w/w	weight by weight
$\mu$ g	microgram
$\mu$ m	micrometer, micrón
% RH	percent of relative humidity



สถาบันวิทยบริการ  
จุฬาลงกรณ์มหาวิทยาลัย