

ลักษณะการปลดปล่อยด้วยยาแบบออกฤทธิ์เนิ่นนานของเพลเลท และ
เพลเลทที่ผ่านการตอกอัด ซึ่งประกอบขึ้นจากสารกลุ่มไขมัน หรือขี้ผึ้ง

นาย มนต์ชัย สีอุไรย์



สถาบันวิทยบริการ
จุฬาลงกรณ์มหาวิทยาลัย
วิทยานิพนธ์นี้เป็นส่วนหนึ่งของการศึกษาตามหลักสูตรปริญญาเภสัชศาสตรมหาบัณฑิต
สาขาวิชาเภสัชอุตสาหกรรม ภาควิชาเภสัชอุตสาหกรรม
คณะเภสัชศาสตร์
จุฬาลงกรณ์มหาวิทยาลัย
ปีการศึกษา 2542
ISBN 974-332-906-4
ลิขสิทธิ์ของจุฬาลงกรณ์มหาวิทยาลัย

**SUSTAINED RELEASE CHARACTERISTICS OF PELLETS AND
COMPRESSED PELLETS CONTAINING LIPIDIC
OR WAXY SUBSTANCES**

Mr. Monchai Siurai

สถาบันวิทยบริการ
จุฬาลงกรณ์มหาวิทยาลัย

**A Thesis Submitted in Partial Fulfillment of the Requirements
for the Degree of Master of Science in Pharmacy
Department of Manufacturing Pharmacy
Faculty of Pharmaceutical Sciences
Chulalongkorn University
Academic Year 1999
ISBN 974-332-906-4**

Thesis Titles Sustained Release Characteristics of Pellets and Compressed Pellets Containing Lipidic or Waxy Substances
By Mr. Monchai Siurai
Department Manufacturing Pharmacy
Thesis advisor Associate Professor Poj Kulvanich, Ph.D.

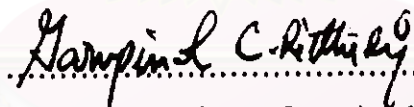
Accepted by the Faculty of Pharmaceutical Sciences,
Chulalongkorn University in Partial Fulfillment of the Requirements for the Master's
Degree



.....
(Associate Professor Sunibhond Pummangura, Ph.D.)

Dean of Faculty of Pharmaceutical Sciences

Thesis Committee



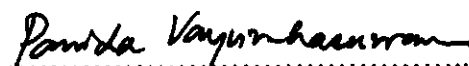
..... Chairman
(Associate Professor Gampimol C. Ritthidej, Ph.D.)



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



..... Member
(Assistant Professor Wichein Thanindratarn, M.Sc.in Pharm.)



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



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

มนต์ชัย ลีอุไรย์ : ลักษณะการปลดปล่อยด้วยยาแบบออกฤทธิ์เนิ่นนานของเพลเลทและเพลเลท
ที่ผ่านการดกอัด ซึ่งประกอบขึ้นจากสารกลุ่มไขมัน หรือขี้ผึ้ง (SUSTAINED RELEASE
CHARACTERISTICS OF PELLETS AND COMPRESSED PELLETS
CONTAINING LIPIDIC OR WAXY SUBSTANCES.) อ.ที่ปรึกษา : รศ.ดร. พงษ์
กุลวานิช, 264 หน้า. ISBN 974-332-906-4.

โพรพราโนลอล ไฮโดรคลอไรด์ขี้ผึ้งเมทริกซ์เพลเลท เตรียมขึ้นด้วยเทคนิคเอกทูล
ชั้นสเฟียร์โรโนซ์เซชัน โดยการนำสารจำพวกขี้ผึ้งชนิดต่าง ๆ มาเป็นสารก่อเมทริกซ์ และแลคโตสที่อยู่
ในสูตรตำรับจะทำหน้าที่เป็นแซแนลลิ่งเอเจนท์ ชนิด และปริมาณของส่วนประกอบในเมทริกซ์ จะมี
ผลต่อสภาวะการเตรียมโดยเอกทูลชั้นสเฟียร์โรโนซ์เซชัน และคุณสมบัติทางกายภาพของเมทริกซ์เพล
เลทที่เตรียมได้ ลักษณะการปลดปล่อยโพรพราโนลอล ไฮโดรคลอไรด์จากขี้ผึ้งเมทริกซ์เพลเลทไม่ได้
ถูกยึดออกเพียงพอที่จะมีคุณสมบัติออกฤทธิ์เนิ่นนานอย่างที่ต้องการ ยกเว้นเมื่อใช้คอมไพร์ดอลที่
ปริมาณสูง ดังนั้น การดกอัดเมทริกซ์เพลเลท ให้เป็นยาเม็ดเมทริกซ์ จึงเป็นวิธีที่มีประสิทธิภาพในการ
ลดอัตราเร็วในการปลดปล่อยด้วยยาให้อยู่ในระดับที่ต้องการ อัตราเร็วในการปลดปล่อยด้วยยาจะลดลง
เมื่อปริมาณของขี้ผึ้ง หรือโพรพราโนลอล ไฮโดรคลอไรด์เพิ่มขึ้น ขณะที่การเพิ่มแลคโตส มีแนวโน้ม
ในการเพิ่มการปลดปล่อยด้วยยา ลักษณะการปลดปล่อยโพรพราโนลอล ไฮโดรคลอไรด์จากทุกสูตร
ตำรับจะขึ้นอยู่กับสภาวะแวดล้อมความเป็นกรด ต่างของตัวกลาง พบว่า ภูบริแทบ® คอมไพร์ดอล®
พริซิริล® เป็นขี้ผึ้งที่เหมาะสมที่สุดในระหว่างกระบวนการผลิต และให้รูปแบบการปลดปล่อยยาที่น่า
พอใจที่สุด การปรับปริมาณของขี้ผึ้งเหล่านี้ หรือสารอื่น ๆ สามารถทำให้การปลดปล่อยโพรพรา
โนลอล ไฮโดรคลอไรด์จากยาเม็ดเมทริกซ์ สามารถเทียบเคียง ได้กับผลิตภัณฑ์ในท้องตลาด

อินฟราเรดสเปกตรัมของเมทริกซ์ที่เตรียมได้แสดงให้เห็นว่าไม่มีปฏิกิริยาระหว่างกัน
ของยา ขี้ผึ้ง และสารอื่น ๆ ที่อยู่ในสูตรตำรับ โพรพราโนลอล ไฮโดรคลอไรด์ยังอยู่ในลักษณะที่เป็น
ผลึก และจากผลการศึกษาทางด้านเอกซ์เรย์ พบว่า พิกที่เป็นลักษณะเฉพาะของโพรพราโนลอล ไฮโดร
คลอไรด์ ยังคงอยู่ และมีการเปลี่ยนตำแหน่งอย่างไม่มีนัยสำคัญ ตำแหน่งของพิกหลักจากการศึกษา
ด้วยดีเอสซีพบว่าเกือบจะไม่เปลี่ยนแปลง

ภาควิชา.....เภสัชอุตสาหกรรม.....ลายมือชื่อนิสิต.....
สาขาวิชา.....เภสัชอุตสาหกรรม.....ลายมือชื่ออาจารย์ที่ปรึกษา.....
ปีการศึกษา.....2542.....ลายมือชื่ออาจารย์ที่ปรึกษาร่วม.....

4076521333 : Major INDUSTRIAL PHARMACY
KEY WORD: PROPRANOLOL HYDROCHLORIDE / LIPIDIC MATRIX / WAX
MATRIX / MELTING SOLVENT / SUSTAINED RELEASE
MONCHAI SIURAI : SUSTAINED RELEASE CHARACTERISTICS OF
PELLETS AND COMPRESSED PELLETS CONTAINING LIPIDIC OR
WAXY SUBSTANCES. THESIS ADVISOR : ASSOC.PROF. POJ
KULVANICH, Ph.D., 264 pp. ISBN 974-332-906-4.

Propranolol HCl wax matrix pellets were prepared by extrusion-spheronization technique. Various kinds of waxy material were used as matrix forming agent. Lactose was chosen as channeling agent in the formulation. The type and amount of matrix additives affected the condition of extrusion-spheronization process and the physical properties of matrix pellets. The release characteristics of propranolol HCl form wax matrix pellet were not prolonged enough to have sustained release properties as required except those containing highest percent of Compritol[®]. Thus, compaction of matrix pellets in to matrix tablet was very effective way for reducing drug release rate as required. The release rate was decreased with an increase in the content of wax or propranolol HCl, whereas increasing lactose tended to increase the drug release. The release characteristics of propranolol HCl from all formulations depended on environmental pH medium. Lubritab[®], Compritol[®], and Precirol[®] were found to be the most suitable waxes during the production process and exhibited the most satisfactory release profiles. Adjusting the level of these waxes or other additives could provide the release of propranolol HCl matrix tablet in compliance with commercial products.

The IR spectra of the obtained matrices indicated no interaction between drug, wax, and other additives in the formulation. Propranolol HCl was still in crystalline form and characteristic peaks of propranolol HCl were observed and negligibly shifted by x-ray diffractometry investigation. The position of the major peaks remained relatively unchanged by DSC investigation.

ภาควิชา.....เภสัชอุตสาหกรรม.....ลายมือชื่อนิสิต.....
สาขาวิชา.....เภสัชอุตสาหกรรม.....ลายมือชื่ออาจารย์ที่ปรึกษา.....
ปีการศึกษา.....2542.....ลายมือชื่ออาจารย์ที่ปรึกษาร่วม.....

ACKNOWLEDGEMENTS



I would like to express my grateful and sincere thankfulness to my thesis advisor, Associate Professor Poj Kulvanich, Ph.D. for his invaluable attention, guidance, encouragement and support throughout this research. His generosity and helpfulness are really appreciated.

Special acknowledgements are given to Mr. Paisan Setsuwan, Ph.D. National Metal and Material Center (MTEC), Ministry of Science, Technology and Environment, Thailand. For his helpfulness and supporting in X-ray diffractometry evaluations. The other special acknowledgements is extended to Assistant Professor Phongsak Kunluan, Department of Physiology, Faculty of Pharmaceutical Sciences, Chulalongkorn University for his thoughtful advices and support for Image Analyzer in my work. A special acknowledgement is extended to Thai Powder Technology Center, Faculty of Engineer, Chulalongkorn University for supplying a momentous instrument, Xtruder[®], in this research.

A special appreciation is also given to Graduate school, Chulalongkorn University for granting partial financial support to fulfill this investigation and being the place for learning, participating academic activities, which is one of the valuable experiences in my life.

My special thanks is send to all staffs and members in the department of Manufacturing Pharmacy and all of my friends in Master's degree for their encouragement and assistance.

Finally, I would like to express my tremendous gratitude to my parents. Their endless love and encouragement given to me are immeasurable and contributed me to finish this work.

CONTENTS

	Page
Thai Abstract.....	iv
English Abstract.....	v
Acknowledgements.....	vi
List of Tables.....	viii
List of Figures.....	xv
List of Abbreviations.....	xxiv
Chapter	
I Introduction.....	1
II Experimental.....	43
III Results	62
IV Discussion and Conclusions.....	176
References.....	196
Appendices.....	206
Vita.....	264

สถาบันวิทยบริการ
จุฬาลงกรณ์มหาวิทยาลัย

LIST OF TABLES

Table		Page
1	Critical factors in extrusion-spheronization.....	13
2	Material used as retardants in matrix tablet formulations.....	34
3	Formulation of core pellets.....	47
4	The pelletization conditions for preliminary study and suitable conditions.....	47
5	Compositions of propranolol HCl matrix pellets at different percentage of wax content.....	48
6	Compositions of propranolol HCl matrix pellets at different percentage of loading dose.....	50
7	The angle of repose, flow rate, bulk density, tapped density and percent compressibility of the matrix pellet prepared from each formulations.....	75
8	The water required and percent yield of matrix pellet product.....	78
9	Sphericity values of matrix pellets prepared with different wax content and loading dose.....	80
10	Percent friability of matrix pellets prepared with different wax content and loading dose.....	83
11	The percentage of drug content in matrix pellets.....	85
12	Characteristic peaks of the IR spectra of matrix pellet products produced by different type of wax.....	89
13	Characteristic peaks of the X-ray diffraction patterns of matrix pellets produced by different types of waxes.....	93
14	The endotherm and exotherm of thermal analysis of propranolol HCl, waxes, and matrix pellet products produced by different types of waxes at 40 % and propranolol HCl at 40 %.....	102
15	Preliminary study on tableting properties of pellets compressed at different compression forces.....	103

Table (cont.)

Page

16	Thickness, diameter, hardness, and disintegration time of matrix tablets from various matrix pellet formulations.....	114
17	Physical properties of wax matrix tablet containing 40 % of propranolol HCl With 40 % of Precirol® prepared from single punch tableting machine.....	154
18	Correlation coefficient of the relationships between percent drug released versus time (A), percent drug released versus square root time (B), and log percent drug remained versus time (C) of matrix tablet formulations.....	158
19	Comparison of linearity between plots of rate of release against reciprocal amount (1/Q) and amount (Q) of propranolol HCl released from matrix tablet in 0.1 N HCl and phosphate buffer pH 6.8.....	160
20	Linear regression of release rate ($\%F \cdot \text{hr}^{-0.5}$) and the percentage of wax ($\%wax$) giving the slope b ($[\%F][\text{hr}^{-0.5}][\%wax^{-1}]$) and intercepts a ($[\%F][\text{hr}^{-0.5}]$) and correlation coefficient r	167
21	Linear regression of release rate ($\%F \cdot \text{hr}^{-0.5}$) and the percentage of loading dose ($\%loading\ dose$) giving the slope b ($[\%F][\text{hr}^{-0.5}][\%loading\ dose^{-1}]$) and intercepts a ($[\%F][\text{hr}^{-0.5}]$) and correlation coefficient r	167
22	The effect of wax content on the release rates ($\%F \cdot \text{hr}^{-0.5}$ or $\%F \cdot \text{hr}^{-0.5}$) of propranolol HCl from tablets containing propranolol HCl 160 mg.....	168
23	The effect of propranolol HCl content on the release rates ($\%F \cdot \text{hr}^{-0.5}$ or $\%F \cdot \text{hr}^{-0.5}$) of propranolol HCl from tablets containing 160 mg wax.....	169
24	Diffusional exponent and mechanism of diffusional drug release from non swellable controlled release system.....	173
25	Diffusional exponent and mechanism of diffusional drug release from swellable controlled release system.....	173

Table (cont.)

Page

26	The value of kinetic constant (k), release exponent (n) and correlation coefficient (r^2) following linear regression of dissolution data for values of M_t/M_∞ in 0.1 N HCl and phosphate buffer pH6.8.....	174
27	Absorbance of propranolol HCl in methanol at 290 nm.....	207
28	Asorbance of propranolol HCl in HCl acid pH 1.2 at 289 nm.....	208
29	Absorbance of propranolol HCl in phosphate buffer pH 6.8 at 289 nm.....	209
30	Percentage amount of propranolol HCl release from reference capsules, reference tablets, and commercial product (Inderal [®]).....	214
31	Percentage amount of propranolol HCl matrix pellet release from series of beeswax.....	215
32	Percentage amount of propranolol HCl matrix pellet release from series of carnauba wax.....	216
33	Percentage amount of propranolol HCl matrix pellet release from series of glyceryl monostearate.....	217
34	Percentage amount of propranolol HCl matrix pellet release from series of Lubritab [®]	218
35	Percentage amount of propranolol HCl matrix pellet release from series of Compritol [®]	219
36	Percentage amount of propranolol HCl matrix pellet release from series of Precirol [®]	220
37	Percentage amount of propranolol HCl matrix pellet release from series of Gelucire 50/02 [®]	221
38	Percentage amount of propranolol HCl matrix pellet release from various concentration of propranolol HCl and beeswax at 40 %.....	222
39	Percentage amount of propranolol HCl matrix pellet release from various concentration of propranolol HCl and carnauba wax at 40 %.....	223
40	Percentage amount of propranolol HCl matrix pellet release from various concentration of propranolol HCl and glyceryl monostearate at 40 %.....	224

Table (cont.)	Page
41 Percentage amount of propranolol HCl matrix pellet release from various concentration of propranolol HCl and Lubritab [®] at 40 %.....	225
42 Percentage amount of propranolol HCl matrix pellet release from various concentration of propranolol HCl and Compritol [®] at 40 %.....	226
43 Percentage amount of propranolol HCl matrix pellet release from various concentration of propranolol HCl and Precirol [®] at 40 %.....	227
44 Percentage amount of propranolol HCl matrix pellet release from various concentration of propranolol HCl and Gelucire [®] at 40 %.....	228
45 Percentage amount of propranolol HCl matrix tablet release from series of beeswax.....	229
46 Percentage amount of propranolol HCl matrix tablet release from series of carnauba wax.....	230
47 Percentage amount of propranolol HCl matrix tablet release from series of glyceryl monostearate.....	231
48 Percentage amount of propranolol HCl matrix tablet release from series of Lubritab [®]	232
49 Percentage amount of propranolol HCl matrix tablet release from series of Compritol [®]	233
50 Percentage amount of propranolol HCl matrix tablet release from series of Precirol [®]	234
51 Percentage amount of propranolol HCl matrix tablet release from series of Gelucire [®]	235
52 Percentage amount of propranolol HCl matrix tablet release from various concentration of propranolol HCl and beeswax at 40 %.....	236
53 Percentage amount of propranolol HCl matrix tablet release from various concentration of propranolol HCl and carnauba wax at 40 %.....	237
54 Percentage amount of propranolol HCl matrix tablet release from various concentration of propranolol HCl and glyceryl monostearate at 40 %.....	238

Table (cont.)	Page
55 Percentage amount of propranolol HCl matrix tablet release from various concentration of propranolol HCl and Lubritab [®] at 40 %.....	239
56 Percentage amount of propranolol HCl matrix tablet release from various concentration of propranolol HCl and Compritol [®] at 40 %.....	240
57 Percentage amount of propranolol HCl matrix tablet release from various concentration of propranolol HCl and Precirol [®] at 40 %.....	241
58 Percentage amount of propranolol HCl matrix tablet release from various concentration of propranolol HCl and Gelucire [®] at 40 %.....	242
59 The release rate of propranolol HCl from matrix tablet produced from propranolol HCl at 40 % with various concentration of beeswax in 0.1 N HCl.....	243
60 The release rate of propranolol HCl from matrix tablet produced from propranolol HCl at 40 % with various concentration of beeswax in phosphate buffer pH 6.8.....	243
61 The release rate of propranolol HCl from matrix tablet produced from beeswax at 40 % with various concentration of propranolol HCl in 0.1 N HCl.....	244
52 The release rate of propranolol HCl from matrix tablet produced from beeswax at 40 % with various concentration of propranolol HCl in phosphate buffer pH 6.8.....	244
63 The release rate of propranolol HCl from matrix tablet produced from propranolol HCl at 40 % with various concentration of Compritol [®] in 0.1 N HCl.....	245
64 The release rate of propranolol HCl from matrix tablet produced from propranolol HCl at 40 % with various concentration of Compritol [®] in phosphate buffer pH 6.8.....	245

Table (cont.)	Page
65 The release rate of propranolol HCl from matrix tablet produced from Compritol [®] at 40 % with various concentration of propranolol HCl in 0.1 N HCl.....	246
66 The release rate of propranolol HCl from matrix tablet produced from Compritol [®] at 40 % with various concentration of propranolol HCl in phosphate buffer pH 6.8.....	246
67 Values for rate, amount released, and the corresponding reciprocal for the release blank propranolol HCl matrix and Inderal [®]	247
68 Values for rate, amount released and the corresponding reciprocal for the release of propranolol HCl tablet containing various amounts of beeswax.....	248
69 Values for rate, amount released and the corresponding reciprocal for the release of propranolol HCl tablet containing various amounts of carnauba wax.....	249
70 Values for rate, amount released and the corresponding reciprocal for the release of propranolol HCl tablet containing various amounts of GMS.....	250
71 Values for rate, amount released and the corresponding reciprocal for the release of propranolol HCl tablet containing various amounts of Lubritab [®]	251
72 Values for rate, amount released and the corresponding reciprocal for the release of propranolol HCl tablet containing various amounts of Compritol [®]	252
73 Values for rate, amount released and the corresponding reciprocal for the release of propranolol HCl tablet containing various amounts of Precirol [®]	253
74 Values for rate, amount released and the corresponding reciprocal for the release of propranolol HCl tablet containing various amounts of Gelucire [®]	254
75 Values for rate, amount released and the corresponding reciprocal for the release of propranolol HCl tablet with series of beeswax at different loading dose.....	255

Table (cont.)	Page
76 Values for rate, amount released and the corresponding reciprocal for the release of propranolol HCl tablet with series of car. wax at different loading dose.....	256
77 Values for rate, amount released and the corresponding reciprocal for the release of propranolol HCl tablet with series of GMS at different loading dose.....	257
78 Values for rate, amount released and the corresponding reciprocal for the release of propranolol HCl tablet with series of Lubritab® at different loading dose.....	258
79 Values for rate, amount released and the corresponding reciprocal for release of propranolol HCl tablet with series of Compritol® at different loading dose.....	259
80 Values for rate, amount released and the corresponding reciprocal for the release of propranolol HCl tablet with series of Precirol® at different loading dose.....	260
81 Values for rate, amount released and the corresponding reciprocal for the release of propranolol HCl tablet with series of Gelucire® at different loading dose.....	261
82 Sieve analysis of each pellet formulation from different loading dose.....	262
83 Sieve analysis of each pellet formulation from different wax content.....	263

จุฬาลงกรณ์มหาวิทยาลัย

LIST OF FIGURES

Figure	Page
1 Pellet-forming mechanism.....	9
2 Geometry of the spheronization plate.....	9
3 Diagrammatic representation of the stages of compaction.....	15
4 Lipid classification and structure.....	18
5 Outline of pellmix PL 1/8 high shear mixer.....	24
6 Impeller with changeable impeller blades.....	24
7 The destructive nucleation growth mechanism of high shear pelletization.....	26
8 Granulation formation mechanisms in melt agglomeration.....	27
9 Schematic representation of a twin screw compounding extruder.....	30
10 Scheme of CF granulator (CF-360S).....	31
11 Schematic representation of principle of TMG method.....	32
12 Niro-fielder, Model S320.....	46
13 Scanning electron photomicrographs of matrix pellet from the formulations using Compritol [®] with various content of propranolol HCl (20%, 30%) at different magnifications.....	64
14 Scanning electron photomicrographs of matrix pellet from the formulations using Compritol [®] with various content of propranolol HCl (40%, 50%) at different magnifications.....	65
15 Scanning electron photomicrographs of matrix pellet produced from different kinds of wax (40 %) at different magnifications.....	66
16 Scanning electron photomicrographs of matrix pellet produced from different kinds of wax (40 %) at different magnifications.....	67
17 Scanning electron photomicrographs of matrix pellet with propranolol HCl to Compritol [®] ratio of 1:1 (40 %:40 %) prepared from different spheronization speed (700 and 900 RPM) and different spheronization time (10 and 15 min) at different magnifications.....	68

Figure (cont.)	Page
18 Size distribution of propranolol HCl pellets produced by various amounts of beeswax and carnauba wax at the same pelletization conditions.....	70
19 Size distribution of propranolol HCl pellets produced by various amount of GMS and lubritab [®] at the same pelletization conditions.....	70
20 Size distribution of propranolol HCl pellets produced by various amounts of Compritol [®] and Precirol [®] at the same pelletization conditions.....	71
21 Size distribution of propranolol HCl pellets produced by various amounts of Gelucire [®] and at the same pelletization conditions.....	71
22 Size distribution of propranolol HCl pellets produced by beeswax and carnauba wax at 40 % with various amount of propranolol HCl at the same pelletization conditions.....	72
23 Size distribution of propranolol HCl pellets produced by GMS and Lubritab [®] at 40% with various amount of propranolol HCl at the same pelletization conditions.....	72
24 Size distribution of propranolol HCl pellets produced by Compritol [®] and Precirol [®] at 40 % with various amount of propranolol HCl at the same pelletization conditions.....	73
25 Size distribution of propranolol HCl pellets produced by Gelucire [®] at 40 % with various amount of propranolol HCl at the same pelletization conditions.....	73
26 IR spectra of propranolol HCl.....	86
27 IR spectra of Avicel PH 101 [®]	86
28 IR spectra of Lactose.....	86
29 IR spectra of various kinds of wax.....	87
30 IR spectra of white beeswax from first batch.....	87
31 IR spectra of propranolol HCl (PL) and matrix pellet produced from 40% PL with various kinds of 40%wax	88

Figure (cont.)	Page
32 X-ray diffractograms of propranolol HCl, Avicel PH 101 [®] , lactose, and various kinds of waxes.....	91
33 X-ray diffractograms of matrix pellets produced from propranolol HCl at 40% and various kinds of waxes at 40%.....	92
34 DSC thermograms of propranolol HCl, Avicel PH 101 [®] , lactose.....	97
35 DSC thermograms of white beeswax, carnauba wax, glyceryl monostearate and Lubritab [®]	98
36 DSC thermograms of Compritol 888ATO [®] , Precirol ATO5 [®] , Gelucire 50/02 [®]	99
37 DSC thermograms of matrix pellets prepared from 40% white beeswax, carnauba wax, glyceryl monostearate, and Lubritab [®] with 40% propranolol HCl.....	100
38 DSC thermograms of matrix pellets prepared from 40% Compritol 888ATO [®] , Precirol ATO5 [®] , and Gelucire 50/02 [®] with 40% Propranolol HCl.....	101
39 Scanning electron photomicrographs of matrix tablet prepared by 40 % commonly used wax and 40 % propranolol HCl before dissolution test.....	105
40 Scanning electron photomicrographs of matrix tablet prepared by 40 % gattefosse's wax and 40 % propranolol HCl before dissolution test.....	106
41 Scanning electron photomicrographs of matrix tablet prepared by 40 % common wax and 40 % propranolol HCl after dissolution test.....	107
42 Scanning electron photomicrographs of matrix tablet prepared by 40 % gattefosse's wax and 40 % propranolol HCl after dissolution test.....	108
43 Scanning electron photomicrographs of matrix tablet prepared by (20%, 30%, 40%, 50%) Compritol ATO888 [®] and 40 % propranolol HCl after dissolution test.....	109

Figure (cont.)

Page

44	Scanning electron photomicrographs of matrix tablet prepared by 40% Compritol ATO888 [®] and (20%, 30%, 50%) propranolol HCl after dissolution test.....	110.
45	Scanning electron photomicrographs of matrix tablet prepared by 50 % Compritol ATO888 [®] and 40% propranolol HCl after dissolution test in different dissolution medium (I = pH 1.2, II = pH 6.8).....	111
46	The release profiles of reference propranolol HCl capsules, reference tablets and Inderal [®] capsule in medium pH1.2 and pH 6.8.....	118
47	The release profiles of matrix pellet prepared from series of beeswax in medium pH1.2 and pH 6.8.....	118
48	The release profiles of matrix pellet prepared from series of carnauba wax in medium pH1.2 and pH 6.8.....	119
49	The release profiles of matrix pellet prepared from series of glyceryl monostearate in medium pH1.2 and pH 6.8.....	119
50	The release profiles of matrix pellet prepared from series of Lubritab [®] in medium pH1.2 and pH 6.8.....	120
51	The release profiles of matrix pellet prepared from series of Compritol [®] in medium pH1.2 and pH 6.8.....	120
52	The release profiles of matrix pellet prepared from series of Precirol [®] in medium pH1.2 and pH 6.8.....	121
53	The release profiles of matrix pellet prepared from series of Gelucire [®] in medium pH1.2 and pH 6.8.....	121
54	The release profiles of matrix pellets containing 40 % of beeswax with different loading dose in 0.1 N HCl pH 1.2 and phosphate buffer pH 6.8.....	123
55	The release profiles of matrix pellets containing 40 % of carnauba wax with different loading dose in 0.1 N HCl pH 1.2 and phosphate buffer pH 6.8.....	123

Figure (cont.)

Page

56	The release profiles of matrix pellets containing 40 % of glyceryl monostearate with different loading dose in 0.1 N HCl pH 1.2 and phosphate buffer pH 6.8.....	124
57	The release profiles of matrix pellets containing 40 % of Lubritab [®] with different loading dose in 0.1 N HCl pH 1.2 and phosphate buffer pH 6.8.....	124
58	The release profiles of matrix pellets containing 40 % of Compritol [®] with different loading dose in 0.1 N HCl pH 1.2 and phosphate buffer pH 6.8.....	125
59	The release profiles of matrix pellets containing 40 % of Precirol [®] with different loading dose in 0.1 N HCl pH 1.2 and phosphate buffer pH 6.8.....	125
60	The release profiles of matrix pellets containing 40 % of Gelucire [®] with different loading dose in 0.1 N HCl pH 1.2 and phosphate buffer pH 6.8.....	126
61	The release profiles of tablets containing matrix pellets of series of beeswax in 0.1 N HCl pH1.2.....	129
62	The release profiles of tablets containing matrix pellets of series of beeswax in phosphate buffer pH 6.8.....	129
63	The release rate profiles of propranolol HCl matrix tablet containing various amount of beeswax at different medium.....	130
64	The release rate profiles of propranolol HCl matrix tablet produced by beeswax at 40 % with various amount of propranolol HCl at different medium.....	130
65	The release profiles of tablets containing 40 % of beeswax with different loading dose in 0.1 N HCl pH 1.2 and phosphate buffer pH 6.8.....	132
66	The release profiles of tablets containing 40 % of carnauba wax with different loading dose in 0.1 N HCl pH 1.2 and phosphate buffer pH 6.8.....	132
67	The release profiles of tablets containing matrix pellets of series of carnauba wax in 0.1 N HCl pH1.2.....	133
68	The release profiles of tablets containing matrix pellets of series of carnauba wax in phosphate buffer pH 6.8.....	133

Figure (cont.)	Page
69 The release profiles of tablets containing matrix pellets of series of glyceryl monostearate in 0.1 N HCl pH 1.2.....	135
70 The release profiles of tablets containing matrix pellets of series of glyceryl monostearate in phosphate buffer pH 6.8.....	135
71 The release profiles of tablets containing 40 % of glycerylmonostearate with different loading dose in 0.1 N HCl pH 1.2 and phosphate buffer pH 6.8.....	137
72 The release profiles of tablets containing 40 % of Lubritab [®] with different loading dose in 0.1 N HCl pH 1.2 and phosphate buffer pH 6.8.....	137
73 The release profiles of tablets containing matrix pellets of series of Lubritab [®] in 0.1 N HCl pH 1.2.....	139
74 The release profiles of tablets containing matrix pellets of series of Lubritab [®] in phosphate buffer pH 6.8.....	139
75 Time to be used for releasing propranolol HCl at 30 and 50 % from formulation containing 40 % of propranolol HCl with various amount of Lubritab [®] in different medium.....	140
76 Time to be used for releasing propranolol HCl at 30 and 50 % from formulation containing 40 % of Lubritab [®] with various amount of propranolol HCl in different medium.....	140
77 The release profiles of tablets containing matrix pellets of series of Compritol [®] in 0.1 N HCl pH 1.2.....	142
78 The release profiles of tablets containing matrix pellets of series of Compritol [®] in phosphate buffer pH 6.8.....	142
79 The release rate profiles of propranolol HCl matrix tablet containing various amount of Compritol [®] at different medium.....	144
80 The release rate profiles of propranolol HCl matrix tablet produced by Compritol [®] at 40 % with various amount of propranolol HCl at different medium.....	144

Figure (cont.)

Page

81	Time to be used for releasing propranolol HCl at 30 and 50 % from formulation containing 40 % of propranolol HCl with various amount of Compritol [®] in different medium.....	145
82	Time to be used for releasing propranolol HCl at 30 and 50 % from formulation containing 40 % of Compritol [®] with various amount of propranolol HCl in different medium.....	145
83	The release profiles of tablets containing 40 % of Compritol [®] with different loading dose in 0.1 N HCl pH 1.2 and phosphate buffer pH 6.8.....	147
84	The release profiles of tablets containing 40 % of Precirol [®] with different loading dose in 0.1 N HCl pH 1.2 and phosphate buffer pH 6.8.....	147
85	The release profiles of tablets containing matrix pellets of series of Precirol [®] in 0.1 N HCl pH 1.2.....	148
86	The release profiles of tablets containing matrix pellets of series of Precirol [®] in phosphate buffer pH 6.8.....	148
87	The release profiles of tablets containing matrix pellets of series of Gelucire [®] in 0.1 N HCl pH 1.2.....	150
88	The release profiles of tablets containing matrix pellets of series of Gelucire [®] in phosphate buffer pH 6.8.....	150
89	The release profiles of tablets containing 40 % of Gelucire [®] with different loading dose in 0.1 N HCl pH 1.2 and phosphate buffer pH 6.8.....	151
90	The sustained release power of various kind of waxes from matrix tablet in 0.1 N HCl pH 1.2.....	153
91	The sustained release power of various kind of waxes from matrix tablet in phosphate buffer pH 6.8.....	153
92	The release profile of Inderal [®] and matrix tablet prepared from 40% of Precirol [®] by hydraulic press and single punch tableting machine.....	155
93	The release profile of Inderal [®] and matrix tablet containing 40% of Precirol [®] prepared by single punch tableting machine.....	155

Figure (cont.)	Page
94 The Higuchi plot of propranolol HCl matrix tablet containing various amount of Lubritab [®] in different medium.....	162
95 The first order plot of propranolol HCl matrix tablet containing various amount of Lubritab [®] in different medium.....	162
96 The Higuchi plot of propranolol HCl-lubritab matrix tablet with different loading dose in different medium	163
97 The first order plot of propranolol HCl-lubritab matrix tablet with different loading dose in different medium.....	163
98 The Higuchi plot of propranolol HCl matrix tablet containing various amount of Compritol [®] in different medium	164
99 The first order plot of propranolol HCl matrix tablet containing various amount of Compritol [®] in different medium	164
100 The Higuchi plot of propranolol HCl-compritol matrix tablet with different loading dose in different medium	165
101 The first order plot of propranolol HCl-compritol matrix tablet with different loading dose in different medium.....	165
102 Relationship between release rate of propranolol HCl (%F.hr ^{-0.5}) and the percentage of commonly used wax contained in the formulation in different medium	170
103 Relationship between release rate of propranolol HCl (%F.hr ^{-0.5}) and the percentage of loading dose in the formulation containing 40 % of commonly used wax in different medium.....	170
104 Relationship between release rate of propranolol HCl (%F.hr ^{-0.5}) and the percentage of Gattefosse wax contained in the formulation in different medium	171
105 Relationship between release rate of propranolol HCl (%F.hr ^{-0.5}) and the percentage of loading dose in the formulation containing 40 % of Gattefosse wax in different medium.....	171

Figure (cont.)	Page
106 Calibration curve of propranolol HCl in methanol at 290 nm.....	207
107 Calibration curve of propranolol HCl in HCl acid pH 1.2 at 289 nm.....	208
108 Calibration curve of propranolol HCl in phosphate buffer pH 6.8 at 289 nm	209
109 Absorbance scanning of beeswax blank pellet in 0.1 N HCl pH 1.2 and phosphate buffer pH 6.8	210
110 Absorbance scanning of carnauba wax blank pellet in 0.1 N HCl pH 1.2 and phosphate buffer pH 6.8.....	210
111 Absorbance scanning of glyceryl monostearate blank pellet in 0.1 N HCl pH 1.2 and phosphate buffer pH 6.8	211
112 Absorbance scanning of Lubritab [®] blank pellet in 0.1 N HCl pH 1.2 and phosphate buffer pH 6.8	211
113 Absorbance scanning of Compritol [®] blank pellet in 0.1 N HCl pH 1.2 and phosphate buffer pH 6.8	212
114 Absorbance scanning of Precirol [®] blank pellet in 0.1 N HCl pH 1.2 and phosphate buffer pH 6.8	212
115 Absorbance scanning of Gelucire [®] blank pellet in 0.1 N HCl pH 1.2 and phosphate buffer pH 6.8.	213
116 Absorbance scanning of propranolol HCl in 0.1 N HCl pH 1.2, phosphate buffer pH 6.8 and methanol	213

LIST OF ABBREVIATIONS

%	percentage
µg	microgram (s)
°C	degree celcius (centigrade)
°	degree
cm	centimeter (s)
cm ³	cube centimeter (s)
CMC	carboxy methyl cellulose
DSC	differential scanning calorimetry
e.g.	exempli gratia, for example
et al.	Et alli, and others
g	gram (s)
GMS	glyceryl monostearate
HCl	hydrochloric acid or hydrochloride salt
hr	hour (s)
IR	infared
kg	kilogram (s)
kp	kilopound (s)
MCC	microcrystalline cellulose
mg	milligram (s)
min	minute (s)
ml	milliliter (s)
nm	nanometer (s)
No.	number
pH	the negative logarithm of the hydrogen ion concentration

pKa	the negative logarithm of the dissociation constant
PL	propranolol HCl
psi	pound per square inch
PVC	polyvinyl chloride
q.s.	make to volume
RPM	round per minute
SD	standard deviation
SEM	scanning electron microscopy
UV	ultraviolet
w/v	weight by volume
w/w	weight by weight



สถาบันวิทยบริการ
จุฬาลงกรณ์มหาวิทยาลัย