CHAPTER III
RESULTS

I.   Pellets

1. Preliminary Study of Pelletization

In this study, lactose and glycerylmonostearate were used to prepare blank pellet and to investigate proper condition (spheronization speed, time and load) of the experiment. Microcrystalline cellulose, Avicel PH 101®, was used as filler because of its spheronization enhancing property (Harris MR. and Ghebre S.I., 1989). The effect of these parameters could be interpreted clearly from the morphology and sieve analysis of the pellets.

From the preliminary study, the loading amount of each formula was varied from 200-350 grams. The results show that the most suitable amount is 250 grams because of giving adequate yield for spheronization process. The standard condition for next experiment, can give rather good characteristic sphere, is set to 700 RPM at 10 minutes.

2. Physical Properties of Pellets

2.1 Morphology of pellet

Scanning electron photomicrographs of pellets were taken to investigate the surface topography and completeness of the particles. The microscopic images were taken in three magnifications for each formulation.

There was no difference in size, shape and surface topography of the pellets obtained by different loading dose (20, 30, 40, 50%) in the formulations

used Compritol® as matrix forming material. It shows rather smooth surface and irregular cavity at the center of the pellet in every loading dose. The photo micrographs of the formulations using different loading dose are shown in Figures 13 and 14.

Figure 15 shows the photomicrographs of pellets produced by different kinds of common wax at 40 %. Every wax can give rather good sphere especially with glyceryl monostearate and Lubritab®. The roughed moon-like surface was clearly seen, when carnauba wax and Lubritab® were used at the higher magnifications. The same results were also obtained from the formulations containing wax at 20, 30, and 50 %. But those photomicrographs were not shown here.

The photomicrographs of the pellets produced by Gattefosse's wax are shown in Figure 16. Both Precirol® and Compritol® can give rather good sphere. Gelucire® give almost the pellet in long dumbbell shape. All of Gattefosse's wax can shown rather smooth surface and still have the cavity in the center of the pellet.

The effect of the spheronization time and speed are shown in Figure 17. The pellets obtained by the same formulation at different spheronization speed (700, 900 RPM) and spheronization time (10, 15 min) show the same size, shape and surface topography in every magnification.

2.2 Size distribution

The size distribution of the matrix pellets was determined using sieve analysis and the results were shown in Figure 18-25 (Table 82-83, Appendix D). The parameters were as follows
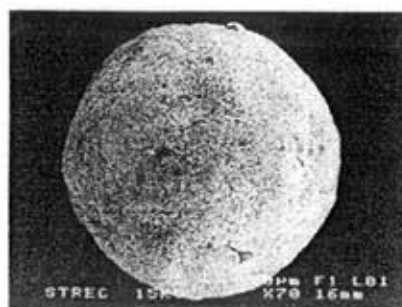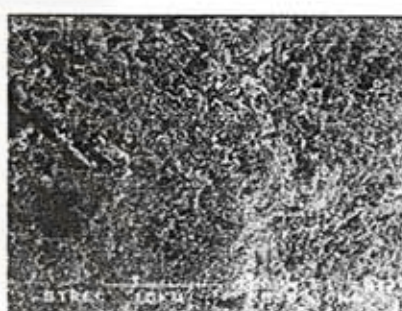
PL 20% × 70   PL 30% × 70

PL 20% × 350   PL 30% × 350

PL 20% × 70 (X-sect.)   PL 30% × 70 (X-sect.)

Figure 13   Scanning electron photomicrographs of matrix pellet from the formulations using Compritol® with various content of propranolol HCl (20%, 30%) at different magnifications.
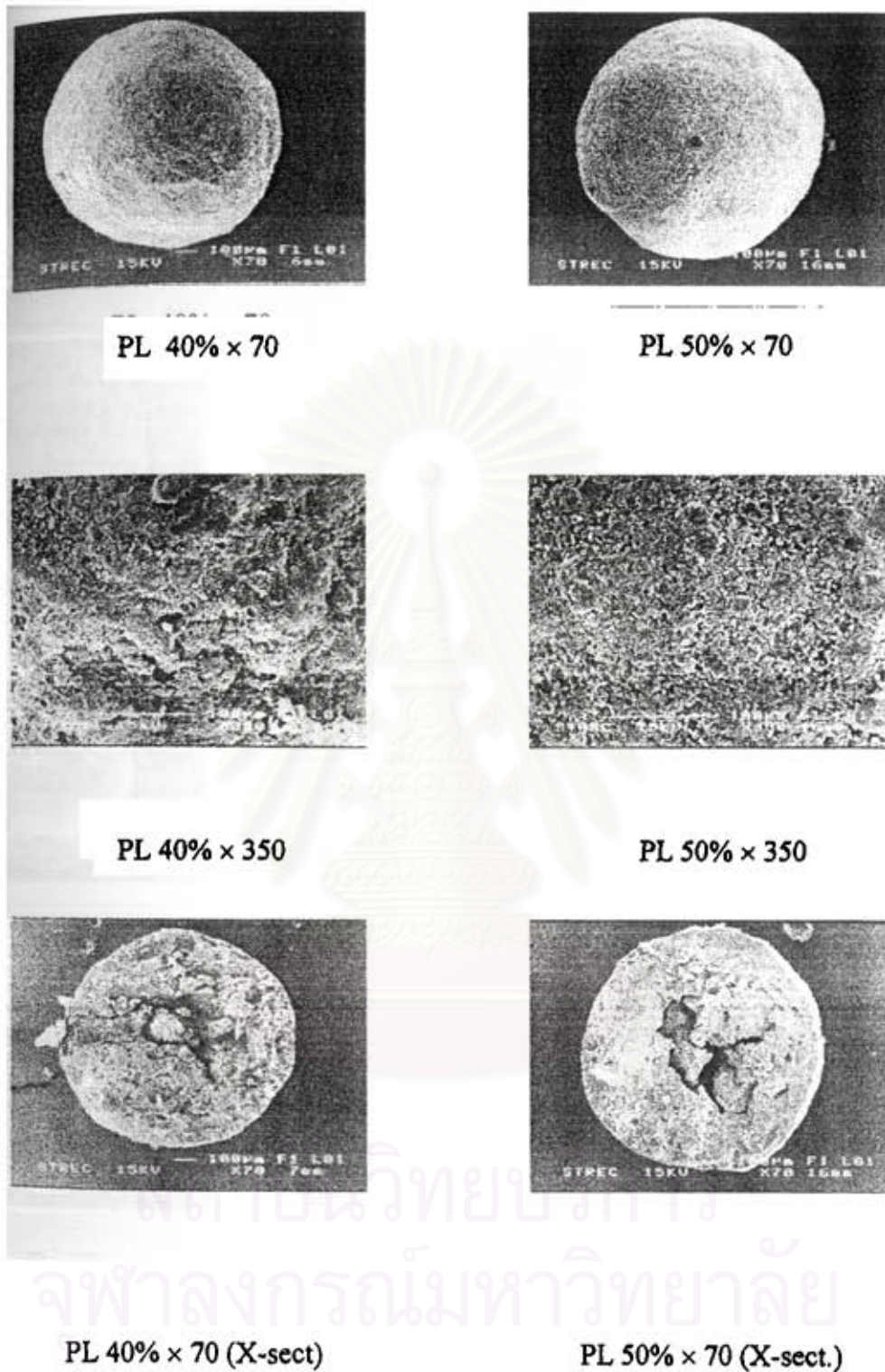
PL 40% × 70

PL 50% × 70

PL 40% × 350

PL 50% × 350

PL 40% × 70 (X-sect)

PL 50% × 70 (X-sect.)

Figure 14   Scanning electron photomicrographs of matrix pellet from the formulations using Compritol® with various content of propranolol HCl (40%, 50%) at different magnifications.

A × 70

A × 350

A × 70 (X-sect.)

B × 70

B × 350

B × 70 (X-sect.)

C × 70

C × 350

C × 70 (X-sect.)
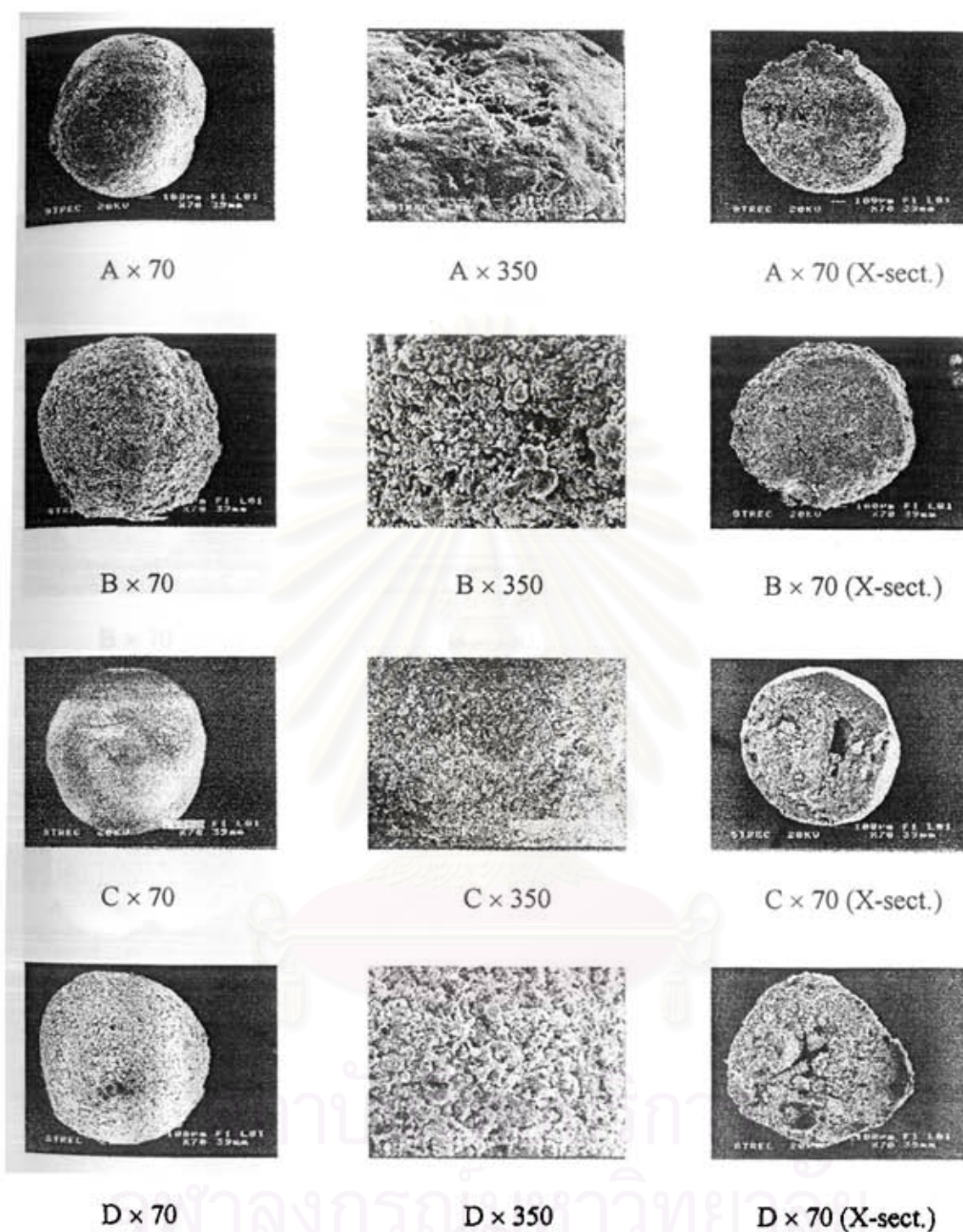
D × 70

D × 350

D × 70 (X-sect.)

Figure 15   Scanning electron photomicrographs of matrix pellet produced from different kinds of wax (40 %) at different magnifications.: A (beeswax), B (carnauba wax), C (glyceryl monostearate), D (Lubritab®).

A × 70   A × 350   A × 70 (X-sect.)

B × 70   B × 350   B × 70 (X-sect.)

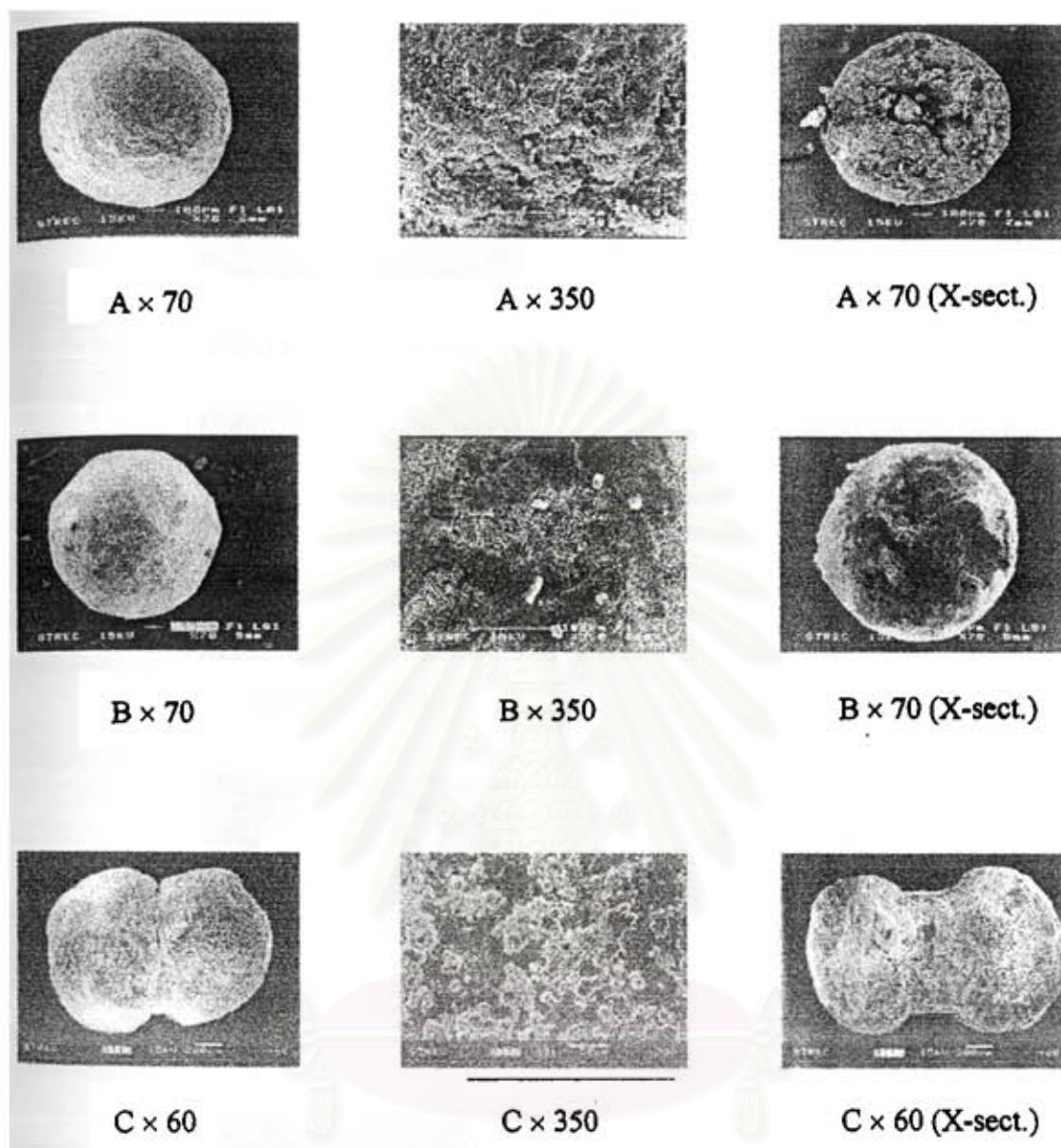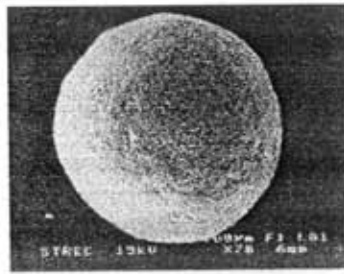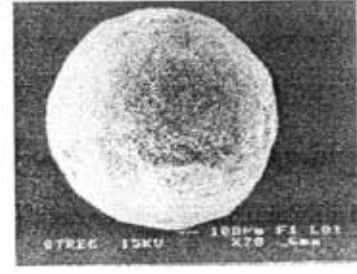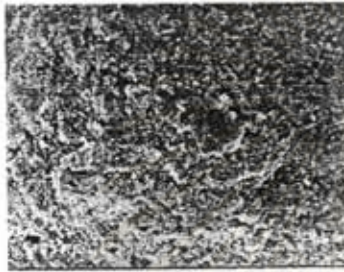C × 60   C × 350   C × 60 (X-sect.)

Figure 16   Scanning electron photomicrographs of matrix pellet produced from different kinds of wax (40 %) at different magnifications.: A (Compritol 888ATO®), B (Precirol ATO5®), C (Gelucire50/02®).
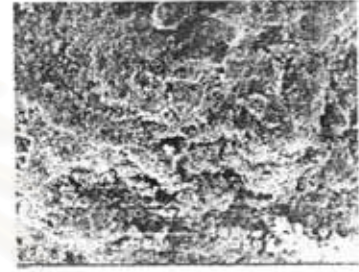
(700 RPM, 10 MIN) × 70

(700 RPM, 15 MIN) × 70

(700 RPM, 10 MIN) × 350

(700 RPM, 15 MIN) × 350

(900 RPM, 10 MIN) × 70
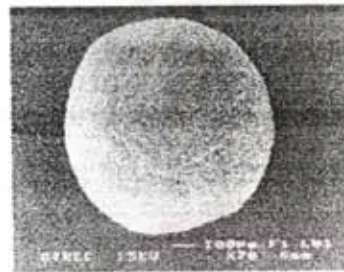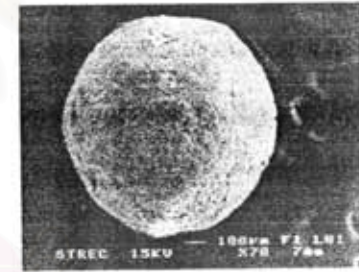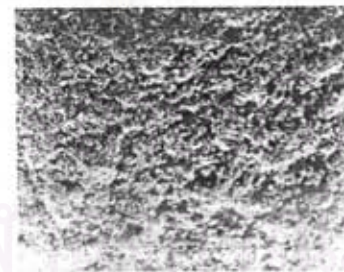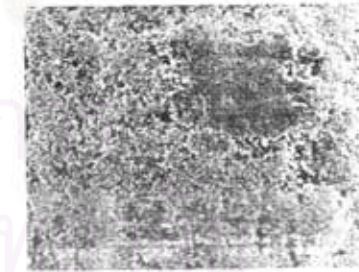
(900 RPM, 15 MIN) × 70

(900 RPM, 10 MIN) × 350

(900 RPM, 15 MIN) × 350

Figure 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.

2.2.1 Amount of diluents

There was no noticeable difference in size distributions of the pellets when different amount of propranolol HCl was used in the formulation in each kind of wax, except carnauba wax and Gelucire®. The results were shown in Figures 22-25 (Table 82, Appendix D) and indicated that more than 65 % of pellets produced were in sieve size range of 14 – 20 mesh, especially of GMS, Compritol®, Precirol® which contained more than 80 % in this size range. The highest portion in the size range of 14 –18 mesh size was attained from every loading dose formulation except for formulations containing carnauba wax and Gelucire®.

2.2.2 Amount and type of wax

The amount of the wax used in the pelletization process was in the range of 20 – 50 %. The size distributions of pellets prepared from different wax content are presented in Figures 18-21 (Table 83, Appendix D)

The highest amount of the pellets obtained from almost wax was retained on sieve size no 18. But formulation containing 50 % beeswax and every level of carnauba wax had wider size distribution than other wax. These waxes cannot control the highest portion of the pellet in sieve size range of 14 – 18 mesh. Only two fractions of the pellets were obtained when the formulation used Gelucire® as matrix forming agent at any levels. The results indicated that approximately more than 70 % of pellets produced were of sieve size of 14 – 20 mesh range except carnauba wax and high level of beeswax.

Figure 18   Size distribution of propranolol HCl pellets produced by various amounts of beeswax and carnauba wax at the same pelletization conditions.

Figure 19   Size distribution of propranolol HCl pellets produced by various amount of GMS and Lubritab® at the same pelletization conditions.

Figure 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.

Figure 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.
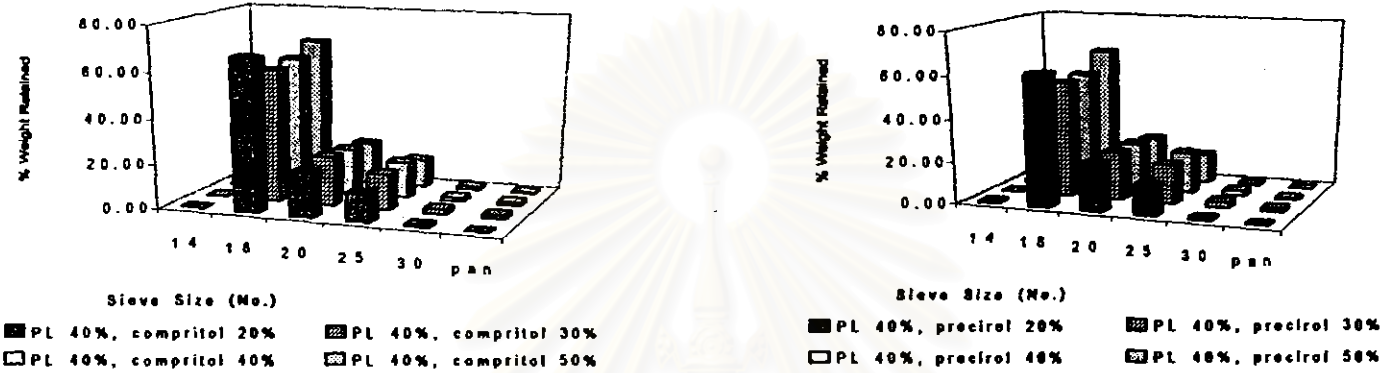
Figure 20   Size distribution of propranolol HCl pellets produced by various amounts of Compritol® and Precirol® at the same pelletization conditions.
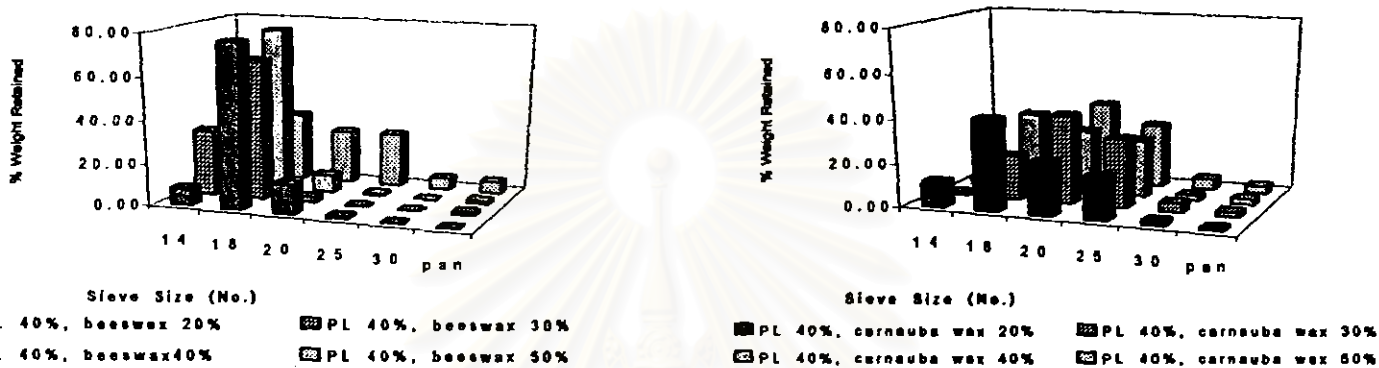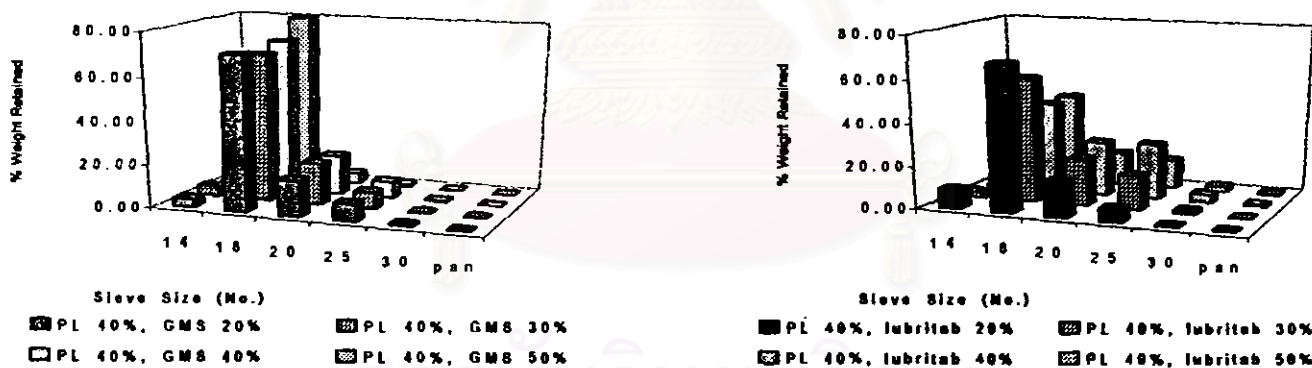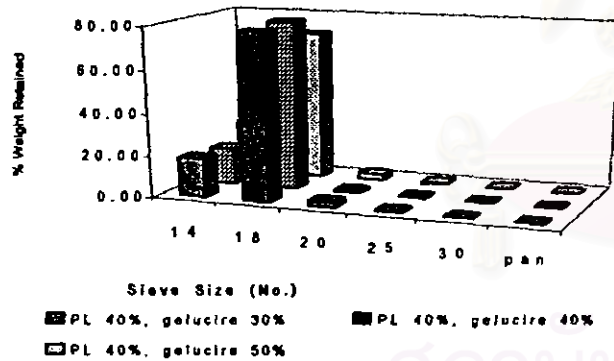

Figure 21   Size distribution of propranolol HCl pellets produced by various amounts of Gelucire® and at the same pelletization conditions.

Figure 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.
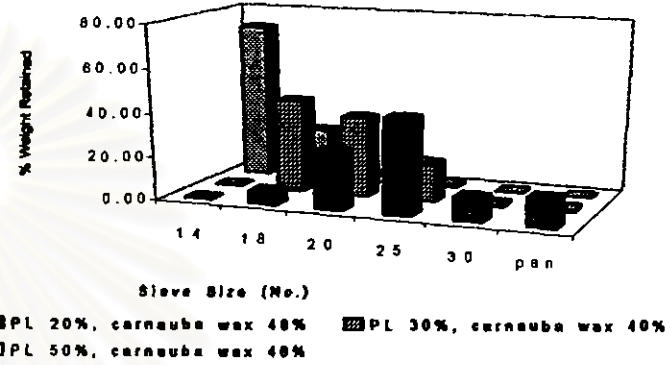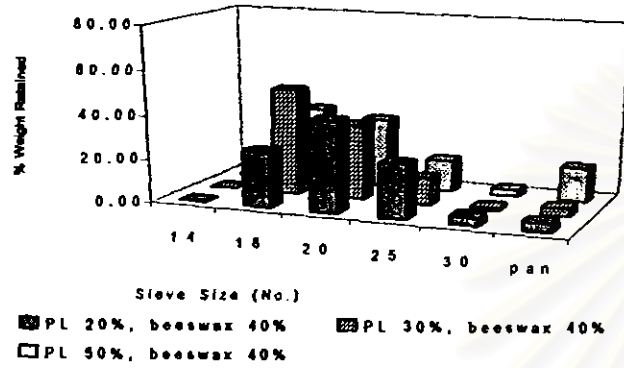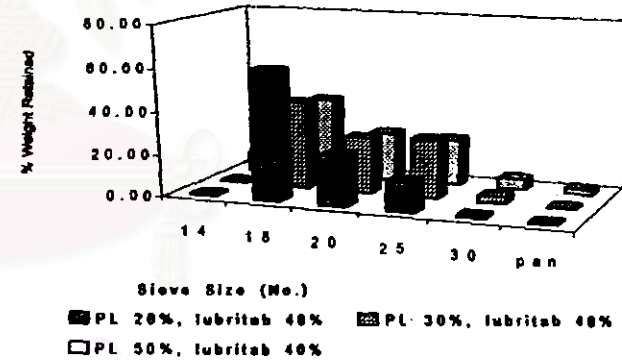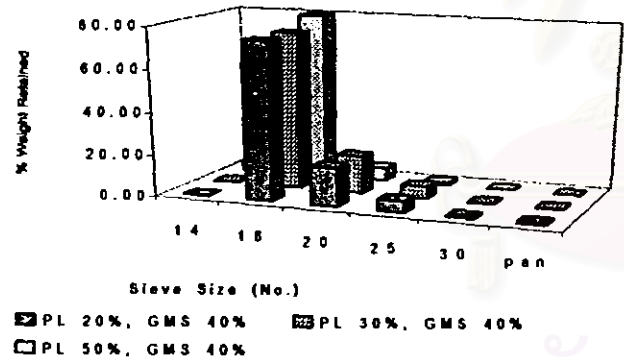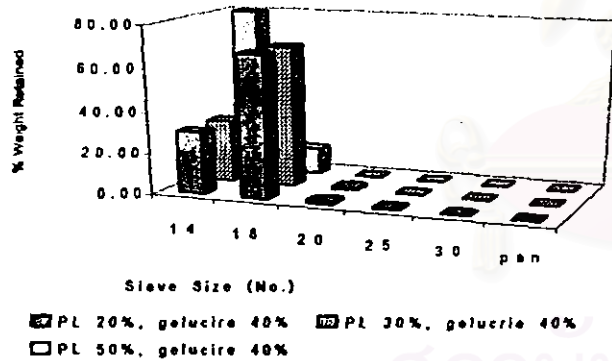

Figure 25   Size distribution of propranolol HCl pellets produced by Gelucire® at 40 % with various amount of propranolol HCl at the same pelletization conditions.
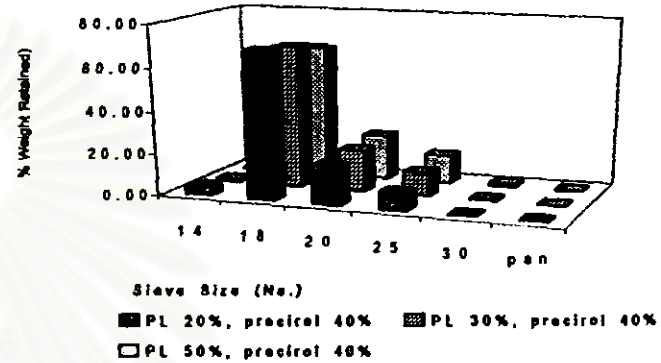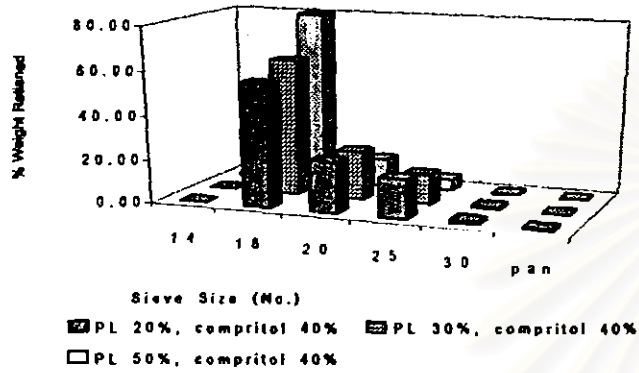
2.3 Angle of repose, bulk density, tapped density, percent compressibility

Angle of repose, flow rate, Bulk density, tapped density and percent compressibiltiy of the matrix pellet from different formulations are shown in Table 7

The bulk and tapped density of all preparations are in the range of 0.58 – 0.70. There is no relationship between wax content and loading dose with bulk and tapped density. The values of the series of the same wax distribute in the narrow range. But in the formulation of 50 % PL with 40 % carnauba wax and 40 % PL with 50 % beeswax show the bulk density out of range, that is 0.7392 and 0.5173, respectively. In addition, the values of the bulk density of all preparations are closely with the tapped density. So every preparations in the form of pellet should give low compressibility.

Percent compressibility values of every preparation could not be clearly concluded. The value is distributed in small range of 2 – 4.5 % compressibility. The data showed no significance difference except of Gelucire® series and high content of beeswax, which give 5 – 6.4 and 6.8 % compressibility, respectively.

Angle of repose from the matrix pellets was tested by funnel method. Highest percent of beeswax, PL 50 % carnauba wax 40 % and series of Gelucire® still showed the parallel effect on the angle of repose and flow rate. They showed rather high angle of repose and low flow rate. During testing, slight tapping the funnel must be applied to initiate the flow of the pellet containing beeswax or Gelucire®. In the case of wax content. When the percent of beeswax and Gelucire® in the formulation increased, there was a tendency to increase angle of repose and decrease in flow rate. Whereas the other wax exhibited no remarkable difference especially GMS, Compritol®, and Precirol® in the series of wax content and loading dose.

Table 7   The angle of repose, flow rate, bulk density, tapped density and percent compressibility of the matrix pellet prepared from each formulations.

Formulations	Angle of repose (funnel method)	Flow rate (g/sec)	Bulk density* (g/ml)	Tapped density* (g/ml)	%compressibility
PL 40%, beeswax 20%	25.59	4.27	0.6742	0.6993	3.5859
PL 40%, beeswax 30%	27.93	3.78	0.6466	0.6536	1.0767
PL 40%, beeswax 40%	25.21	3.86	0.6149	0.6303	2.4422
PL 40%, beeswax 50%	32.83	1.91	0.5173	0.6556	6.8882
PL 40%, carnauba wax 20%	24.86	4.52	0.6727	0.7076	4.9332
PL 40%, carnauba wax 30%	23.34	4.60	0.6772	0.6995	3.1756
PL 40%, carnauba wax 40%	25.22	4.21	0.6250	0.6522	4.1703
PL 40%, carnauba wax 50%	27.65	4.21	0.6303	0.6565	3.9891
PL 40%, GMS 20%	24.49	4.48	0.6882	0.7043	2.2870
PL 40%, GMS 30%	24.85	4.31	0.7060	0.7247	2.5845
PL 40%, GMS 40%	25.19	4.21	0.6757	0.6897	2.0301
PL 40%, GMS 50%	24.59	4.02	0.6439	0.6608	2.5647
PL 40%, lubritab 20%	25.67	4.42	0.6788	0.6961	2.4857
PL 40%, lubritab 30%	25.42	4.07	0.6508	0.6712	3.0280
PL 40%, lubritab 40%	25.16	3.98	0.6135	0.6343	3.2704
PL 40%, lubritab 50%	28.07	3.30	0.5872	0.6122	4.0965
PL 40%, compritol 20%	22.56	5.01	0.6898	0.7160	3.6577
PL 40%, compritol 30%	22.56	4.61	0.6623	0.6865	3.5302
PL 40%, compritol 40%	22.73	4.69	0.6466	0.6682	3.2386
PL 40%, compritol 50%	23.45	4.31	0.6225	0.6522	4.5547
PL 40%, precirol 20%	21.20	4.87	0.6929	0.7143	2.9888
PL 40%, precirol 30%	21.26	4.59	0.6638	0.6742	1.5488
PL 40%, precirol 40%	21.80	4.43	0.6356	0.6537	2.7590
PL 40%, precirol 50%	22.93	4.11	0.6161	0.6356	3.0779
PL 40%, gelucire 30%	24.36	4.00	0.6624	0.7076	6.3870
PL 40%, gelucire 40%	26.47	3.53	0.6522	0.6866	5.0092
PL 40%, gelucire 50%	32.09	2.88	0.6148	0.6551	6.1493

Table 7   (continued.) The angle of repose, flow rate, bulk density, tapped density and percent compressibility of the matrix pellet prepared from each formulations.

Formulations	Angle of repose (funnel method)	Flow rate (g/sec)	Bulk density* (g/ml)	Tapped density* (g/ml)	%compres sibility
PL 20%, beeswax 40%	30.40	3.56	0.6339	0.6642	4.5707
PL 30%, beeswax 40%	30.05	3.48	0.6250	0.6424	2.7067
PL 50%, beeswax 40%	31.83	3.36	0.6098	0.6250	2.4390
PL 20%, carnauba wax 40%	25.93	4.52	0.6558	0.6838	4.0856
PL 30%, carnauba wax 40%	25.22	4.09	0.6317	0.6594	4.2064
PL 50%, carnauba wax 40%	44.43	3.42	0.7392	0.7692	3.9080
PL 20%, GMS 40%	29.75	3.75	0.6684	0.6993	4.4172
PL 30%, GMS 40%	28.64	3.83	0.6579	0.6818	3.5100
PL 50%, GMS 40%	25.65	3.66	0.6356	0.6593	3.5992
PL 20%, lubritab 40%	24.94	4.02	0.6330	0.6652	4.8431
PL 30%, lubritab 40%	25.76	3.90	0.6289	0.6637	5.2395
PL 50%, lubritab 40%	28.53	3.52	0.5826	0.6049	3.6854
PL 20%, compritol 40%	22.38	4.57	0.6550	0.6696	2.1834
PL 30%, compritol 40%	22.84	4.31	0.6397	0.6565	2.5616
PL 50%, compritol 40%	22.49	4.09	0.6186	0.6343	2.4743
PL 20%, precirol 40%	22.91	4.27	0.6682	0.6866	2.6819
PL 30%, precirol 40%	22.14	4.27	0.6383	0.6550	2.5560
PL 50%, precirol 40%	23.02	4.11	0.6263	0.6522	3.9667
PL 20%, gelucire 40%	24.97	3.68	0.6772	0.7042	3.8397
PL 30%, gelucrie 40%	27.32	3.38	0.6565	0.6834	3.9388
PL 50%, gelucire 40%	24.94	3.32	0.6237	0.6466	3.5370

2.4 The amount of water to be used in the formulation and the yield of production

The amount of water used in each formulation is expressed as the percent by weight with respect to the amount of all components. Water is used to make the suitable wet mass for the next step after mixing process, that is extrusion and spheronization. These values are presented in Table 8.

The wax content in the formulations had no significance effect on the amount of water employed. At the highest percentage of beeswax, the amount of water required to attain proper damp mass was decreased. Whereas, Gelucire® used in the formulation as the matrix forming agent remarkably affected the water content demand for making the pellet. The higher amount of Gelucire® used, the lower amount of water was used in making the pellets.

In the contrary, the loading dose of propranolol HCl in the formulations had an effect on the on the amount of water to make the pellet. All kinds of wax showed a tendency to decrease in the amount of water demanded, when the percent of the loading dose in the formulation increased.

The yield of the matrix pellet is expressed as the weight in percent of the final product collected with respect to the initial amount of all components in each formulation. In pelletization process, the wet mass fed through the screw of the extruder, then the extrudate were transferred in the spheronizer. The pellet was collected from the discharged valve and the amount of the pellet was calculated as the percent yield. The yields of the production are shown in Table 8.

Table 8   The water required and percent yield of matrix pellet product.

Formulations	Water required (%)	Percent yield	Formulations	Water required (%)	Percent yield
PL 40%, beeswax 20%	42.0	66.400	PL 20%, beeswax 40%	24.0	67.620
PL 40%, beeswax 30%	42.0	65.396	PL 30%, beeswax 40%	24.0	69.732
PL 40%, beeswax 40%	46.0	65.896	PL 50%, beeswax 40%	22.0	68.016
PL 40%, beeswax 50%	38.0	68.420	PL 20%, carnauba wax 40%	40.0	71.372
PL 40%, carnauba wax 20%	40.0	72.284	PL 30%, carnauba wax 40%	40.0	73.176
PL 40%, carnauba wax 30%	44.8	67.560	PL 50%, carnauba wax 40%	36.0	74.076
PL 40%, carnauba wax 40%	52.0	63.252	PL 20%, GMS 40%	12.0	72.812
PL 40%, carnauba wax 50%	44.0	73.472	PL 30%, GMS 40%	12.0	74.076
PL 40%, GMS 20%	34.0	72.692	PL 50%, GMS 40%	10.0	72.012
PL 40%, GMS 30%	35.0	71.804	PL 20%, lubritab 40%	34.0	71.704
PL 40%, GMS 40%	32.0	71.316	PL 30%, lubritab 40%	34.0	75.320
PL 40%, GMS 50%	34.0	78.512	PL 50%, lubritab 40%	26.0	72.540
PL 40%, lubritab 20%	30.0	75.040	PL 20%, compritol 40%	32.0	72.850
PL 40%, lubritab 30%	32.0	75.400	PL 30%, compritol 40%	32.0	72.800
PL 40%, lubritab 40%	34.0	74.524	PL 50%, compritol 40%	24.0	71.828
PL 40%, lubritab 50%	28.0	70.752	PL 20%, precirol 40%	26.0	73.048
PL 40%, compritol 20%	24.0	73.643	PL 30%, precirol 40%	24.0	73.688
PL 40%, compritol 30%	22.0	72.150	PL 50%, precirol 40%	26.0	70.664
PL 40%, compritol 40%	26.4	74.670	PL 20%, gelucire 40%	12.0	71.284
PL 40%, compritol 50%	27.2	70.592	PL 30%, gelucrie 40%	11.2	71.528
PL 40%, precirol 20%	28.0	70.068	PL 50%, gelucire 40%	10.0	71.168
PL 40%, precirol 30%	24.0	70.404			
PL 40%, precirol 40%	26.0	72.936			
PL 40%, precirol 50%	24.0	74.920			
PL 40%, gelucire 30%	20.0	71.308			
PL 40%, gelucire 40%	17.2	72.284			
PL 40%, gelucire 50%	0.0	67.400			

The result showed that the percent yield from the formulation containing beeswax, some formula containing carnauba wax, formula containing highest percent of Gelucire® was lower than of the other kind of wax. No significance in percent yield was detected in the formulation produced by the other kind of wax. The percent yields of formulation containing these waxes were more than 70-78 % of the initial amount, while the formulation containing the former wax gave only less than 70 % yield. There was no effect from the wax content and loading dose of propranolol HCl on the percent yield of the matrix pellet except Gelucire®.

2.5 Sphericity

In this study, degree of sphericity was derived from some parameters as aspect ratio or form factor which based on two dimensional image of the particle. Image analysis was used to obtain these parameters and the results from various formulations are depicted in Table 9.

The data showed that degree of sphericity from form factor were higher than aspect ratio. Comparison between pellets using waxes with different amount, no significant difference of aspect ratio was found but it was not included those formulations with highest percent of beeswax, carnauba wax, and Gelucire®. Slight difference was observed between aspect ratio of pellets prepared with various amount of carnauba wax. In the case of loading dose, aspect ratio obtained from pellets containing beeswax was clearly lower than other waxes. The difference of aspect ratio at various loading dose in the pellet of all kind of wax was also non significance. The rank of aspect ratio of pellet when using different kind of wax in the case of wax content was in order as: aspect ratio of pellets using Precirol® > Compritol® > Lubritab® > carnauba wax > GMS > bees wax > Gelucire®. And in the

Table 9   Sphericity values of matrix pellets prepared with different wax content and loading dose.

Formulations	Form factor	Aspect ratio
PL 40%, beeswax 20%	0.9693 (0.0196)	0.8809 (0.0656)
PL 40%, beeswax 30%	0.9706 (0.0149)	0.9075 (0.0398)
PL 40%, beeswax 40%	0.9589 (0.0238)	0.8705 (0.0579)
PL 40%, beeswax 50%	0.8019 (0.1234)	0.7767 (0.1271)
PL 40%, carnauba wax 20%	0.9768 (0.0177)	0.8986 (0.0401)
PL 40%, carnauba wax 30%	0.9699 (0.0169)	0.8653 (0.0551)
PL 40%, carnauba wax 40%	0.9753 (0.0130)	0.8534 (0.0400)
PL 40%, carnauba wax 50%	0.9246 (0.0376)	0.8915 (0.0353)
PL 40%, GMS 20%	0.9759 (0.0140)	0.9197 (0.0312)
PL 40%, GMS 30%	0.9701 (0.0241)	0.9032 (0.0369)
PL 40%, GMS 40%	0.9567 (0.0160)	0.8988 (0.0397)
PL 40%, GMS 50%	0.9724 (0.0154)	0.8408 (0.0814)
PL 40%, lubritab 20%	0.9798 (0.0135)	0.9255 (0.0262)
PL 40%, lubritab 30%	0.9813 (0.0110)	0.9247 (0.0276)
PL 40%, lubritab 40%	0.9794 (0.0185)	0.9373 (0.0200)
PL 40%, lubritab 50%	0.9709 (0.0148)	0.8895 (0.0463)
PL 40%, compritol 20%	0.9834 (0.0125)	0.9358 (0.0228)
PL 40%, compritol 30%	0.9818 (0.0113)	0.9313 (0.0220)
PL 40%, compritol 40%	0.9797 (0.0158)	0.9334 (0.0160)
PL 40%, compritol 50%	0.9753 (0.0116)	0.9164 (0.0268)
PL 40%, precirol 20%	0.9785 (0.0146)	0.9346 (0.0189)
PL 40%, precirol 30%	0.9802 (0.0115)	0.9273 (0.0264)
PL 40%, precirol 40%	0.9784 (0.0133)	0.9365 (0.0207)
PL 40%, precirol 50%	0.9833 (0.0118)	0.9395 (0.0187)
PL 40%, gelucire 30%	0.9703 (0.0174)	0.8766 (0.0582)
PL 40%, gelucire 40%	0.9573 (0.0254)	0.8458 (0.0538)
PL 40%, gelucire 50%	0.8813 (0.0712)	0.7142 (0.0244)

Table 9 (continued). Sphericity values of matrix pellets prepared with different wax content and loading dose.

Formulations	Form factor	Aspect ratio
PL 20%, beeswax 40%	0.8903 (0.0472)	0.6700 (0.0884)
PL 30%, beeswax 40%	0.9485 (0.0362)	0.7982 (0.0789)
PL 50%, beeswax 40%	0.9467 (0.0361)	0.8197 (0.0808)
PL 20%, carnauba wax 40%	0.9626 (0.0218)	0.8540 (0.0744)
PL 30%, carnauba wax 40%	0.9691 (0.0219)	0.8693 (0.0807)
PL 50%, carnauba wax 40%	0.9610 (0.0201)	0.8643 (0.0733)
PL 20%, GMS 40%	0.9806 (0.0135)	0.9199 (0.0236)
PL 30%, GMS 40%	0.9737 (0.0114)	0.9133 (0.0324)
PL 50%, GMS 40%	0.9649 (0.0185)	0.8332 (0.0486)
PL 20%, lubritab 40%	0.9749 (0.0322)	0.9325 (0.0197)
PL 30%, lubritab 40%	0.9799 (0.0171)	0.9317 (0.0212)
PL 50%, lubritab 40%	0.9769 (0.0165)	0.9182 (0.0319)
PL 20%, compritol 40%	0.9878 (0.0124)	0.9474 (0.0098)
PL 30%, compritol 40%	0.9850 (0.0112)	0.9420 (0.0163)
PL 50%, compritol 40%	0.9802 (0.0172)	0.9348 (0.0215)
PL 20%, precirol 40%	0.9799 (0.0101)	0.9272 (0.0256)
PL 30%, precirol 40%	0.9804 (0.0112)	0.9432 (0.0201)
PL 50%, precirol 40%	0.9853 (0.0123)	0.9349 (0.0188)
PL 20%, gelucire 40%	0.9695 (0.0147)	0.8337 (0.0450)
PL 30%, gelucrie 40%	0.9657 (0.0234)	0.8705 (0.0615)
PL 50%, gelucire 40%	0.9649 (0.0185)	0.8332 (0.0486)

case of loading dose was ranked as: the aspect ratio of pellets using Compritol® > Precirol® > Lubritab® > GMS > carnauba wax > Gelucire® > beeswax.

The degree of sphericity from form factor had the same characteristic as aspect ratio. But they were closer to unity than the aspect ratio. The rank of form factor of pellet when using different kind of wax in the case of wax content is ranked in the order as: form factors of pellets using Precirol® ≈ Compritol® > Lubritab® > GMS > carnauba wax > beeswax > Gelucire®. And in the case of loading dose was ranked as: the form factor of pellets using Compritol® > Precirol® > Lubritab® ≈ GMS > carnauba wax > Gelucire® > beeswax.

2.6 Friability

Percent friability of matrix pellet with various wax content and loading dose are shown in Table 10. The test method chosen for these experiments put mechanical stress on the pellets.

Percent friability varied between 0.0150 − 0.1970 % and 0.0000 − 0.1720 % for the pellets prepared with series of loading dose and series of wax content, respectively. Form the results, matrix pellets containing wax in the formulations exhibited slightly friable. It could be observed that there was no noticeable difference of friability between each kind of wax or in the series of wax content and loading dose. Furthermore, the percent friability was not related to the kind of wax, series of wax content and series of loading dose.

Table   10   Percent friability of matrix pellets prepared with different wax content and loading dose.

Formulations	% friability	Formulations	% friability
PL 40%, beeswax 20%	0.0530	PL 20%, beeswax 40%	0.0180
PL 40%, beeswax 30%	0.1060	PL 30%, beeswax 40%	0.1360
PL 40%, beeswax 40%	0.0430	PL 50%, beeswax 40%	0.1030
PL 40%, beeswax 50%	0.1420	PL 20%, car. wax 40%	0.0609
PL 40%, car. wax 20%	0.1600	PL 30%, car. wax 40%	0.0150
PL 40%, car. wax 30%	0.0230	PL 50%, car. wax 40%	0.0920
PL 40%, car. wax 40%	0.1720	PL 20%, GMS 40%	0.1450
PL 40%, car. wax 50%	0.1500	PL 30%, GMS 40%	0.0970
PL 40%, GMS 20%	0.1330	PL 50%, GMS 40%	0.1410
PL 40%, GMS 30%	0.1520	PL 20%, lubritab 40%	0.0310
PL 40%, GMS 40%	0.1520	PL 30%, lubritab 40%	0.0850
PL 40%, GMS 50%	0.0930	PL 50%, lubritab 40%	0.1440
PL 40%, lubritab 20%	0.0410	PL 20%, compritol 40%	0.0190
PL 40%, lubritab 30%	0.0790	PL 30%, compritol 40%	0.0220
PL 40%, lubritab 40%	0.0980	PL 50%, compritol 40%	0.1970
PL 40%, lubritab 50%	0.1170	PL 20%, precirol 40%	0.1530
PL 40%, compritol 20%	0.0170	PL 30%, precirol 40%	0.0760
PL 40%, compritol 30%	0.0200	PL 50%, precirol 40%	0.0970
PL 40%, compritol 40%	0.0210	PL 20%, gelucire 40%	0.0590
PL 40%, compritol 50%	0.0000	PL 30%, gelucrie 40%	0.0590
PL 40%, precirol 20%	0.0850	PL 50%, gelucire 40%	0.1640
PL 40%, precirol 30%	0.1290		
PL 40%, precirol 40%	0.0320		
PL 40%, precirol 50%	0.0900		
PL 40%, gelucire 30%	0.0080		
PL 40%, gelucire 40%	0.0160		
PL 40%, gelucire 50%	0.1560		

2.7 drug content

The percent drug contents of the matrix pellet from various formulation are shown in the Table 11.

Percent difference in the range of ± 5% was acceptable that there were no significance differences between percent theoretical and percent experiment drug content. All of matrix pellet formulations had percent drug content in this range (± 5%). So, all values of drug content conform to these former criteria.

2.8 IR (infared spectra)

The IR spectra of propranolol HCl alone, wax and pellets prepared from various formulations are separated into related groups and shown in Figure 26.

The principle peaks of propranolol HCl were observed at the wave numbers of 772, 795, 1103, 1240, 1270, 1580 cm^{-1}. The peaks at 770 and 797 cm^{-1} were resulted from aromatic ring =CH out of plane bending. The IR peaks at 1106 cm^{-1} were resulted from C-OH stretching in secondary alcohol. The IR peaks at 1241 and 1267 cm^{-1} were resulted from aromatic R-O-R asymmetric stretching in ethers. And the IR peaks at 1579 were resulted from C=C cyclic stretching.

The IR spectra of Avicel PH 101$^{®}$ and lactose are displayed in Figure 27 and 28, respectively. They showed broad band of OH stretching at the wave number range of 3300 – 3400 cm^{-1}

Table 11   The percentage of drug content in matrix pellets.

| Formulations	% drug content	Formulations	% drug content
PL 40%, beeswax 20%	97.4051	PL 20%, beeswax 40%	101.2133
PL 40%, beeswax 30%	96.5255	PL 30%, beeswax 40%	101.3694
PL 40%, beeswax 40%	96.0857	PL 50%, beeswax 40%	98.7041
PL 40%, beeswax 50%	97.2794	PL 20%, car. wax 40%	105.8229
PL 40%, car. wax 20%	98.5988	PL 30%, car. wax 40%	104.2393
PL 40%, car. wax 30%	101.2376	PL 50%, car. wax 40%	104.4504
PL 40%, car. wax 40%	99.2271	PL 20%, GMS 40%	102.2865
PL 40%, car. wax 50%	100.6722	PL 30%, GMS 40%	101.1906
PL 40%, GMS 20%	99.0386	PL 50%, GMS 40%	104.5528
PL 40%, GMS 30%	98.8502	PL 20%, lubritab 40%	104.2987
PL 40%, GMS 40%	99.2271	PL 30%, lubritab 40%	104.7678
PL 40%, GMS 50%	98.7245	PL 50%, lubritab 40%	103.1577
PL 40%, lubritab 20%	101.4261	PL 20%, compritol 40%	104.0547
PL 40%, lubritab 30%	100.9863	PL 30%, compritol 40%	104.8572
PL 40%, lubritab 40%	98.5360	PL 50%, compritol 40%	101.7626
PL 40%, lubritab 50%	97.2794	PL 20%, precirol 40%	105.6401
PL 40%, compritol 20%	97.4051	PL 30%, precirol 40%	104.9466
PL 40%, compritol 30%	97.7192	PL 50%, precirol 40%	103.8533
PL 40%, compritol 40%	98.3475	PL 20%, gelucire 40%	104.7011
PL 40%, compritol 50%	96.4627	PL 30%, gelucrie 40%	103.0686
PL 40%, precirol 20%	97.1538	PL 50%, gelucire 40%	102.0846
PL 40%, precirol 30%	98.4732		
PL 40%, precirol 40%	99.8554		
PL 40%, precirol 50%	97.9706		
PL 40%, gelucire 30%	99.2271		
PL 40%, gelucire 40%	98.3475		
PL 40%, gelucire 50%	97.6564		
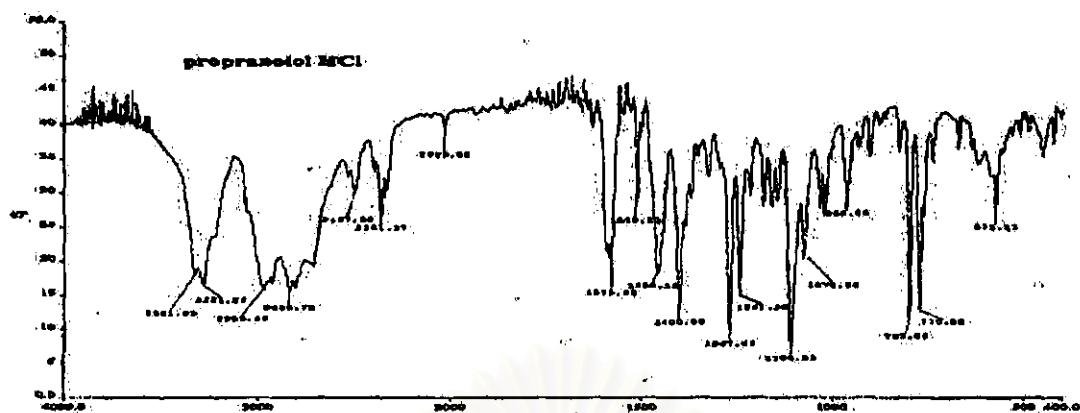
Figure 26   IR spectra of propranolol HCl (PL).
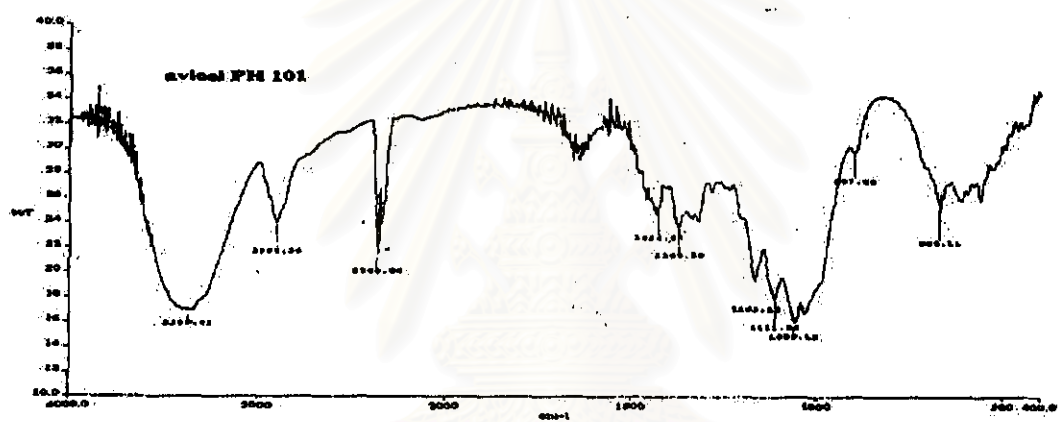
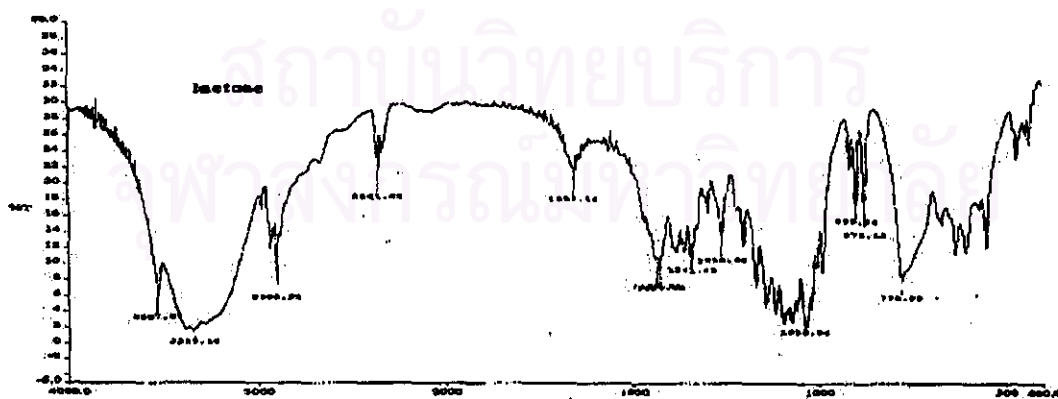Figure 27   IR spectra of Avicel PH 101®
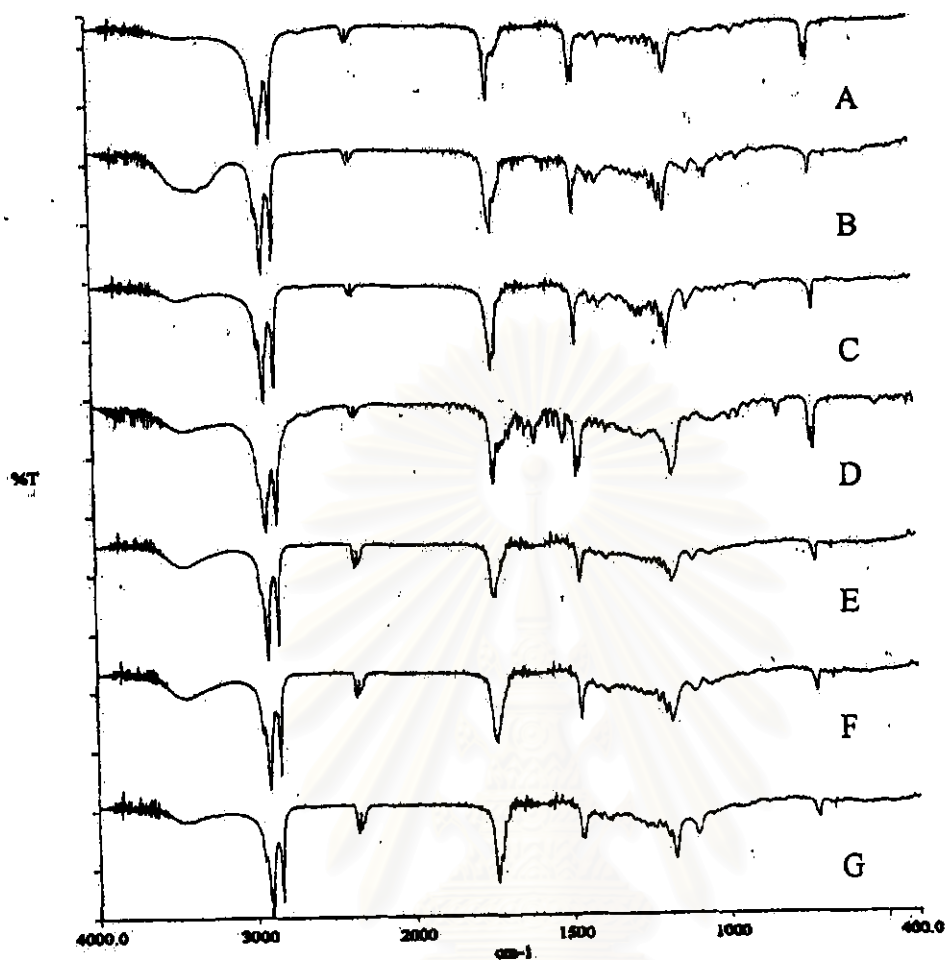
Figure 28   IR spectra of Lactose

Figure 29   IR spectra of various kinds of wax. White beeswax (A), glyceryl monostearate (B), lubritab (C), carnauba wax (D), Compritol 888ATO® (E), Precirol ATO5® (F), Gelucire 50/02® (G)
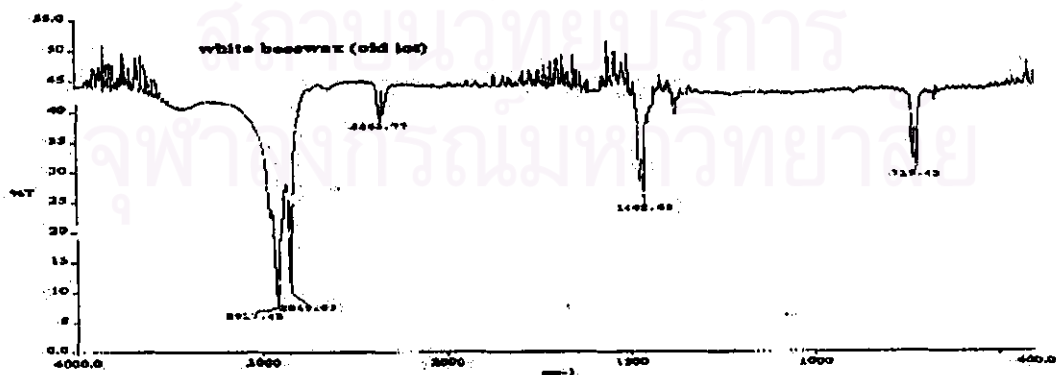

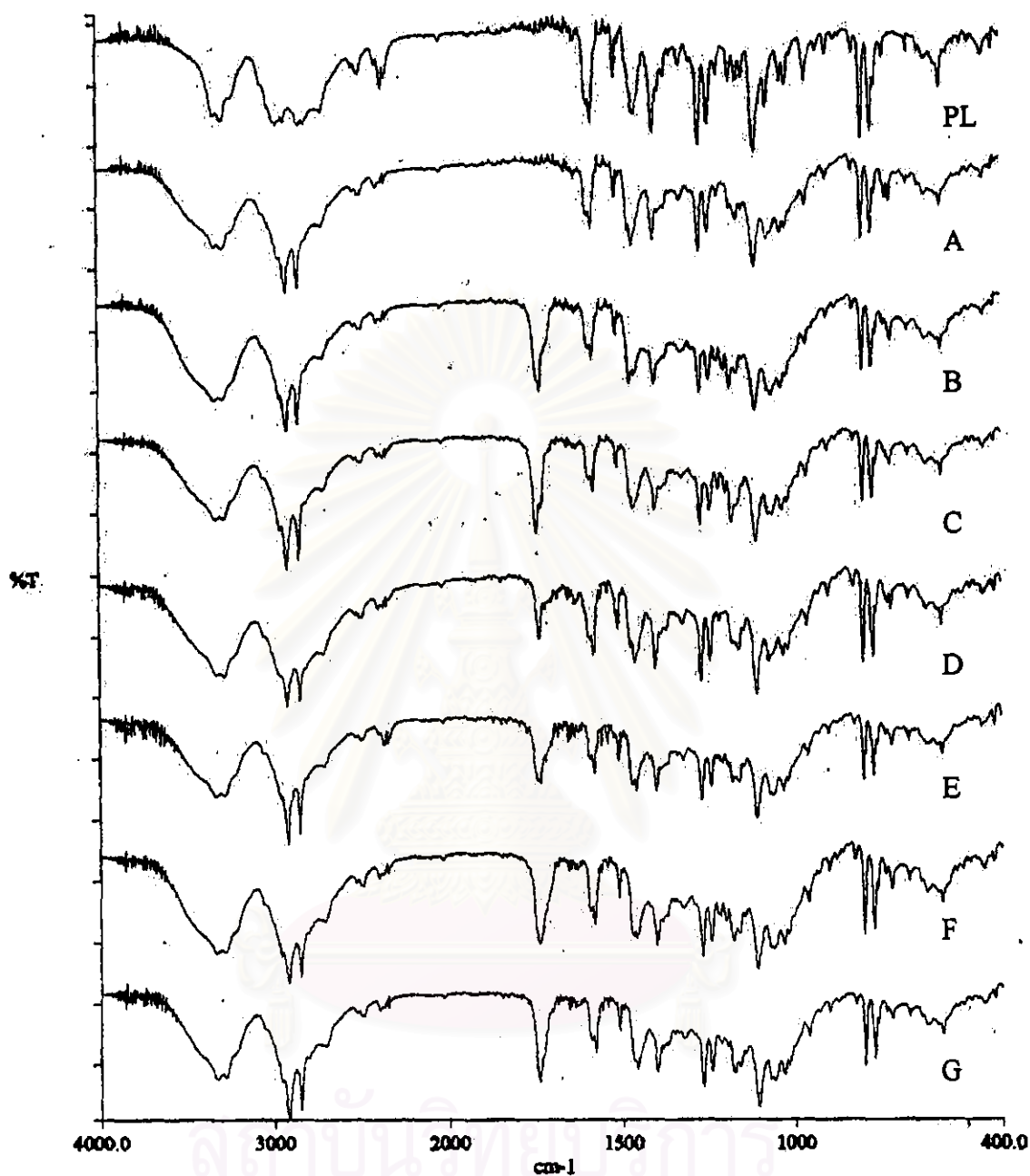Figure 30   IR spectra of white beeswax from first batch.

Figure 31   IR spectra of propranolol HCl (PL) and matrix pellet produced from PL 40% with various kinds of wax 40%. White beeswax (A), glyceryl monostearate (B), Lubritab® (C), carnauba wax (D), Compritol 888ATO® (E), Precirol ATO5® (F), Gelucire 50/02® (G).

Table 12   Characteristic peaks of the IR spectra of matrix pellet products produced by different type of wax.

formulation	Characteristic Peaks (cm^{-1})												
Propranolol HCl	770	797	1106	1241	1267		1579						
Avicel PH101®									2360		2900		3300-3400
Lactose									2361		2900		
White bees wax						1470		1736		2849		2917	
GMS						1471		1731		2849		2915	
Lubritab®						1472		1736		2849		2916	
Carnauba wax						1473		1735		2849		2918	
Compritol 888ATO®						1465		1740		2849		2917	
Precirol ATO5®						1467		1736		2850		2917	
Gelucire 50/02®						1465		1741		2849		2916	
PL40%+ White bees wax	770	797	1107	1241	1267	1470	1578	1736	-	2848	-	2917	3281,3321
PL40%+ GMS	770	797	1107	1241	1267	1469	1579	1730	-	2848	-	2916	3280,3326
PL40%+ Lubritab®	770	797	1107	1241	1268	1470	1578	1741	-	2849	-	2916	3284,3327
PL40%+ Carnauba wax	770	797	1107	1240	1267	1470	1578	1735	-	2848	-	2918	3282,3328
PL40%+ Compritol 888ATO®	770	797	1107	1240	1266	1470	1579	1735	-	2848	-	2917	3280,3327
PL40%+ Precirol ATO5®	770	797	1107	1241	1267	1468	1578	1740	-	2848	-	2916	3280,3329
PL40%+ Gelucire 50/02®	770	797	1107	1241	1266	1466	1578	1741	-	2848	-	2917	3280,3328

The IR spectra of all kinds of wax using in this experiment are illustrated in Figure 29. The C-O stretching peak was represented at 1175 cm^{-1}. The aliphatic CH$_2$ bending was represented at 1470 cm^{-1}. The C=O stretching were represented at 1736 cm^{-1}. The IR peaks at 2849 and 2917 cm^{-1} were resulted from aliphatic CH stretching. There was a little difference in the position of the peaks between these waxes.

The IR spectra of matrix pellets containing 40 % propranolol HCl and 40 % wax are depicted in Figure 31. The IR spectra of matrix pellet showed the combination of propranolol HCl peaks with those of wax, where as the characteristic peaks of both propranolol HCl and waxes were also still revealed. Some positions of the peaks were shifted from single material. But they have no noticeable difference. The characteristic peak of lactose and Avicel PH101® the matrix pellets were disappeared or showed only a small peak. The positions after shifting of characteristic peaks of the matrix pellets are presented in Table 12.

These results indicated that the interaction between drug and wax was hardly seen and amount of the wax had no effect on the IR spectra in this study.

2.9 Powder X-ray diffraction.

The x-ray diffraction patterns of propranolol HCl, waxes, and matrix pellets from various formulations are separated into related groups and illustrated in Figures 32, 33.

The x-ray diffraction patterns of propranolol HCl alone showed characteristic peaks at 9.650° 2θ, 12.400° 2θ, 16.600° 2θ, 19.450° 2θ, 21.000° 2θ,
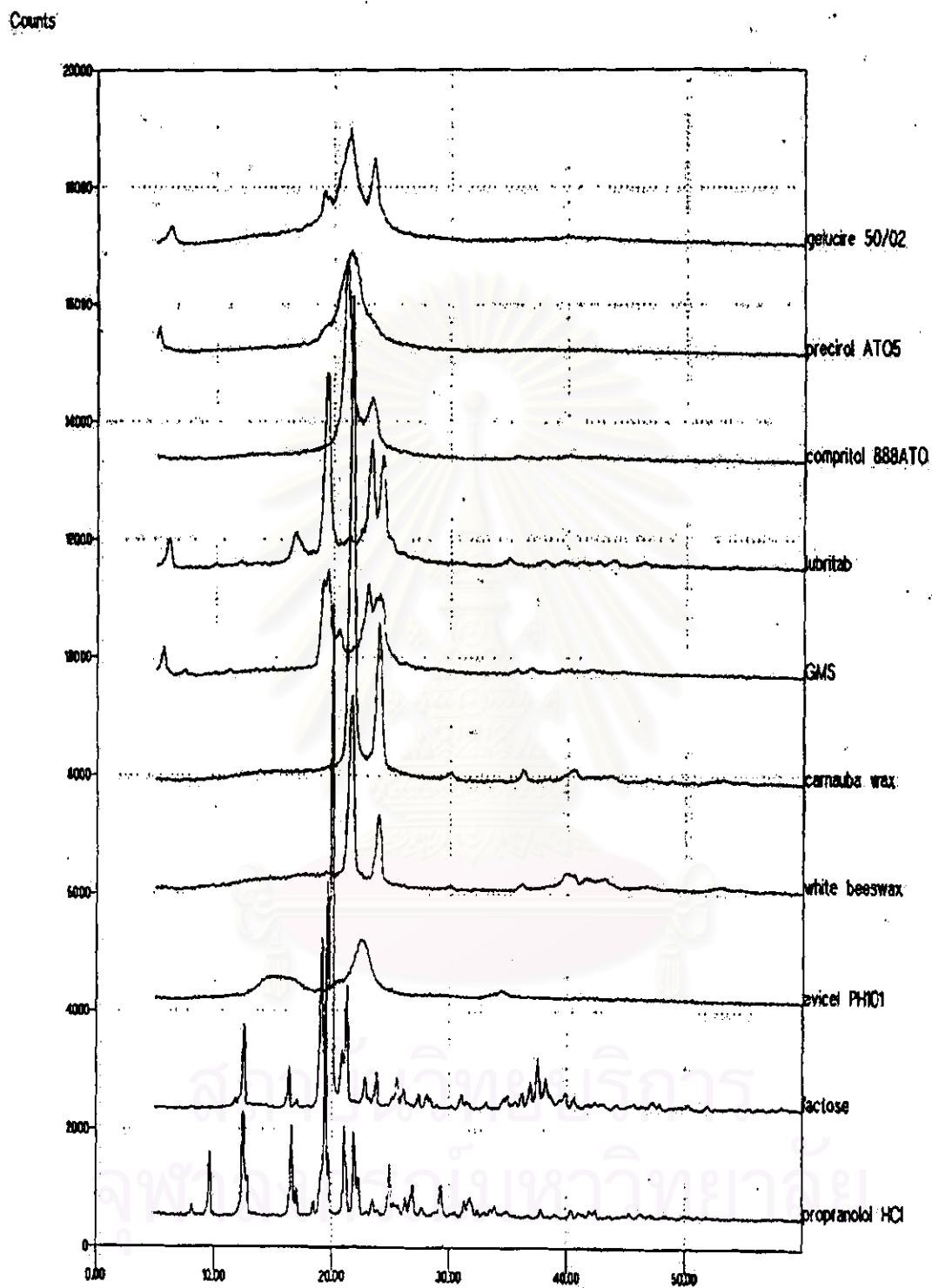
Figure 32   X-ray diffractograms of propranolol HCl, lactose, Avicel PH101®, and various kinds of waxes.
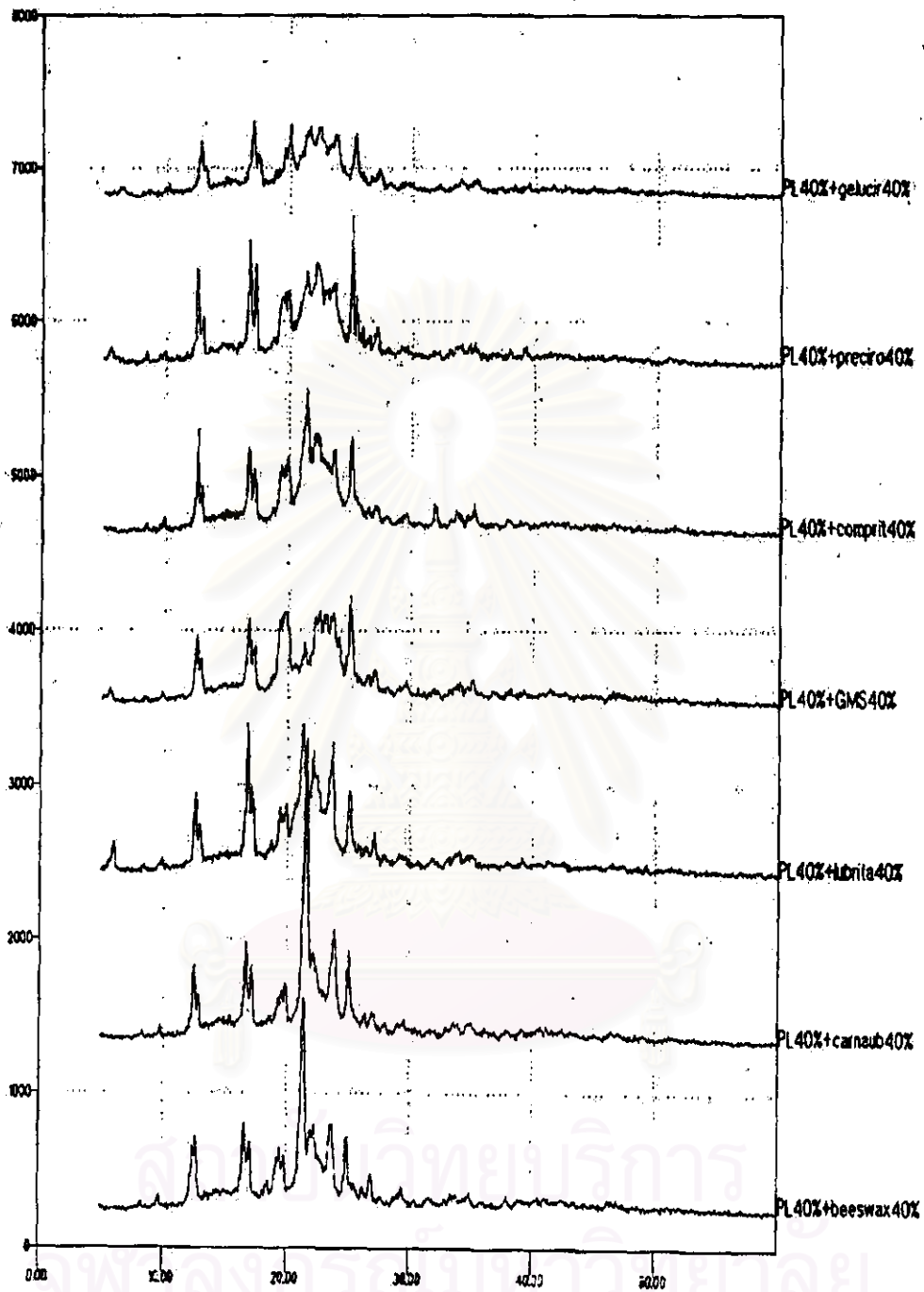
Figure 33   X-ray diffractograms of matrix pellets produced from propranolol HCl at 40 % and various kinds of waxes at 40 %.

Table 13   Characteristic peaks of the X-ray diffraction patterns of matrix pellets produced by different types of waxes.

Formulation	Characteristic Peaks (degree)												
Propranolol HCl	9.650	12.400	-	-	16.600	19.450	-	-	-	-	21.000	-	-
Avicel PH101®	-	-	-	15.000	-	-	-	-	-	-	-	-	-
Lactose	-	-	12.500	-	-	-	-	-	20.000	-	-	21.250	-
White bees wax	-	-	-	-	-	-	-	-	-	-	-	-	-
GMS	-	-	-	-	-	-	-	19.550	-	-	-	-	-
Lubritab®	-	-	-	-	-	-	19.500	-	-	-	-	-	-
Carnauba wax	-	-	-	-	-	-	-	-	-	-	-	-	-
Compritol 888ATO®	-	-	-	-	-	-	-	-	-	20.900	-	-	-
Precirol ATO5®	-	-	-	-	-	-	-	-	-	-	-	-	-
Gelucire 50/02®	-	-	-	-	-	-	-	-	-	-	-	-	21.350
PL40%+ White bees wax	9.750	12.450	-	-	16.650	19.500	-	-	-	-	-	-	-
PL40%+ GMS	9.800	12.600	-	-	16.850	19.250	-	19.600	-	-	20.050	-	-
PL40%+ Lubritab®	9.850	12.550	-	-	16.800	19.400	19.650	-	-	-	21.250	-	-
PL40%+ Carnauba wax	9.800	12.550	-	-	16.750	19.300	-	-	-	-	-	-	-
PL40%+ Compritol 888®	9.900	12.650	-	-	16.800	19.650	-	-	-	20.900	21.150	-	-
PL40%+ Precirol ATO5®	9.800	12.550	-	-	16.800	19.600	-	-	-	-	-	-	-
PL40%+ Gelucire 50/02®	9.800	12.850	-	-	17.050	19.550	-	-	-	-	-	-	21.600

Table 13　　　(continued) Characteristic peaks of the X-ray diffraction patterns of matrix pellets produced by different types of waxes.

formulation	Characteristic Peaks (degree)											
Propranolol HCl	-	-	-	-	-	-	-	-	-	-	-	24.950
Avicel PH101®	-	-	-	22.450	-	-	-	-	-	-	-	-
Lactose	-	-	-	-	-	-	-	-	-	-	-	-
White bees wax	-	21.550	-	-	-	-	-	-	-	-	24.000	-
GMS	-	-	-	-	22.950	-	-	-	-	23.950	-	-
Lubritab®	-	-	-	-	-	23.000	-	-	-	-	24.000	-
Carnauba wax	-	-	21.600	-	-	-	-	-	23.750	-	-	-
Compritol 888ATO®	-	-	-	-	-	-	23.250	-	-	-	-	-
Precirol ATO5®	21.500	-	-	-	-	-	-	-	-	-	-	-
Gelucire 50/02®	-	-	-	-	-	-	-	23.500	-	-	-	-
PL40%+ White bees wax	-	21.450	-	-	-	-	-	-	-	-	23.700	25.050
PL40%+ GMS	-	-	-	-	23.100	-	-	-	-	24.150	-	25.100
PL40%+ Lubritab®	-	-	-	-	-	23.750	-	-	-	-	23.750	25.150
PL40%+ Carnauba wax	-	-	21.600	-	-	-	-	-	23.950	-	-	25.100
PL40%+ Compritol 888®	-	-	-	-	-	-	23.200	-	-	-	-	25.100
PL40%+ Precirol ATO5®	21.400	-	-	-	-	-	-	-	-	-	-	25.150
PL40%+ Gelucire 50/02®	-	-	-	-	-	-	-	23.550	-	-	-	25.450

24.950^0 2θ and small peaks were distributed throughout the diffraction angle of scanning. The diffraction peaks of lactose were still shown crystalline characteristic. The characteristic halo of amorphous of Avicel PH101® was shown at 15.000^0 2θ and 22.450^0 2θ. All kinds of waxes showed only 2 – 4 characteristic peaks. The eminent diffraction peaks of beeswax and carnauba wax were found at 21.550^0 2θ, 24.000^0 2θ. and 21.600^0 2θ, 23.750^0 2θ respectively. The eminent peaks of GMS and Lubritab® were shown at 19.550^0 2θ, 22.950^0 2θ, 23.950^0 2θ, and 19.500^0 2θ. 23.000^0 2θ, 24.000^0 2θ, respectively. The eminent diffraction peaks of Compritol®, Precirol® and Gelucire® were shown at 20.900^0 2θ, 23.250^0 2θ; 21.500^0 2θ; and 21.350^0 2θ, 23.500^0 2θ, respectively. Slightly higher baseline of the diffraction peaks of the wax matrix pellet of every formulation was detected. The intensities of the peaks of every formulation were weaker than those of propranolol HCl, especially the small peaks but the eminent peaks were still found.

There was some difference between the x-ray diffraction patterns of propranolol HCl alone and propranolol HCl matrix pellet prepared from each kind of waxes. It showed the combination of propranolol HCl and waxes diffraction peaks. Therefore, propranolol HCl was still in crystalline form but different degree of crystallinity in all formulations. Some characteristic peaks of all formulations were shifted from that of propranolol HCl and waxes. The shifts of the x-ray diffraction peaks of matrix pellet formulation are shown in Table 13.

The characteristic peak of lactose and Avicel PH101 were not found in the diffractrogram of matrix pellet formulation. The characteristic peak of propranolol HCl at 21.000^0 2θ was disappeared in matrix pellet formulations prepared by white beeswax, carnauba wax, Precirol®, Gelucire®.

2.10   Differential scanning calorimetry.

The DSC thermograms of pure propranolol HCl, Avicel PH 101®, lactose, waxes and matrix pellet prepared from different formulations are shown in Figure 34-38. The endotherm of all components and matrix pellet products are indicated in Table 14.

The thermogram of all components presented only the endotherm characteristic. The melting point of propranolol HCl, Avicel PH 101® were found to be about 165.10^0 C and 87.82^0 C, whereas lactose showed two endotherm peaks at $146.55\ ^0$ C and $212.39\ ^0$ C. Melting points of all waxes were shown at the beginning of scanning range. Their melting points were, $64.50\ ^0$ C for white beeswax, 67.47^0 C for GMS, 68.12^0 C for Lubritab®, $86.07\ ^0$ C for carnauba wax, $74.80\ ^0$ C for Compritol®, $60.76\ ^0$ C for Precirol®, and $53.01\ ^0$ C for Gelucire®.

From Figures 37, 38, there was no difference between the DSC thermograms patterns of propranolol HCl alone and those of the matrix pellet formulation but the different in DSC peak temperature were visible. The melting points of propranolol HCl and all kinds of waxes in the matrix pellet were shifted slightly to lower temperature. As the DSC peak temperature of lactose and Avicel PH 101® were disappeared from the thermogram.
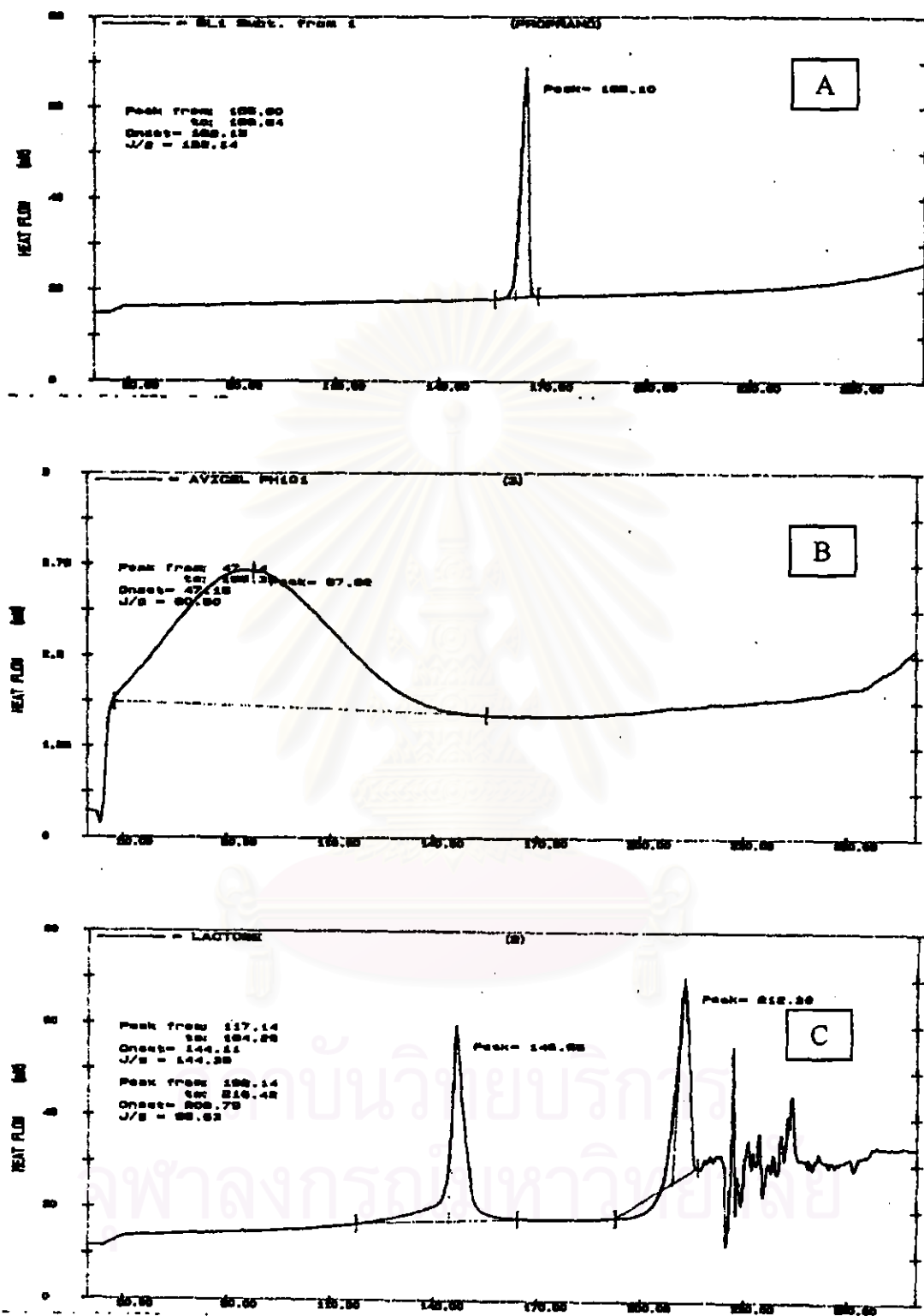
Figure 34   DSC thermograms of propranolol HCl (PL) (A), Avicel PH 101® (B) and lactose (C).
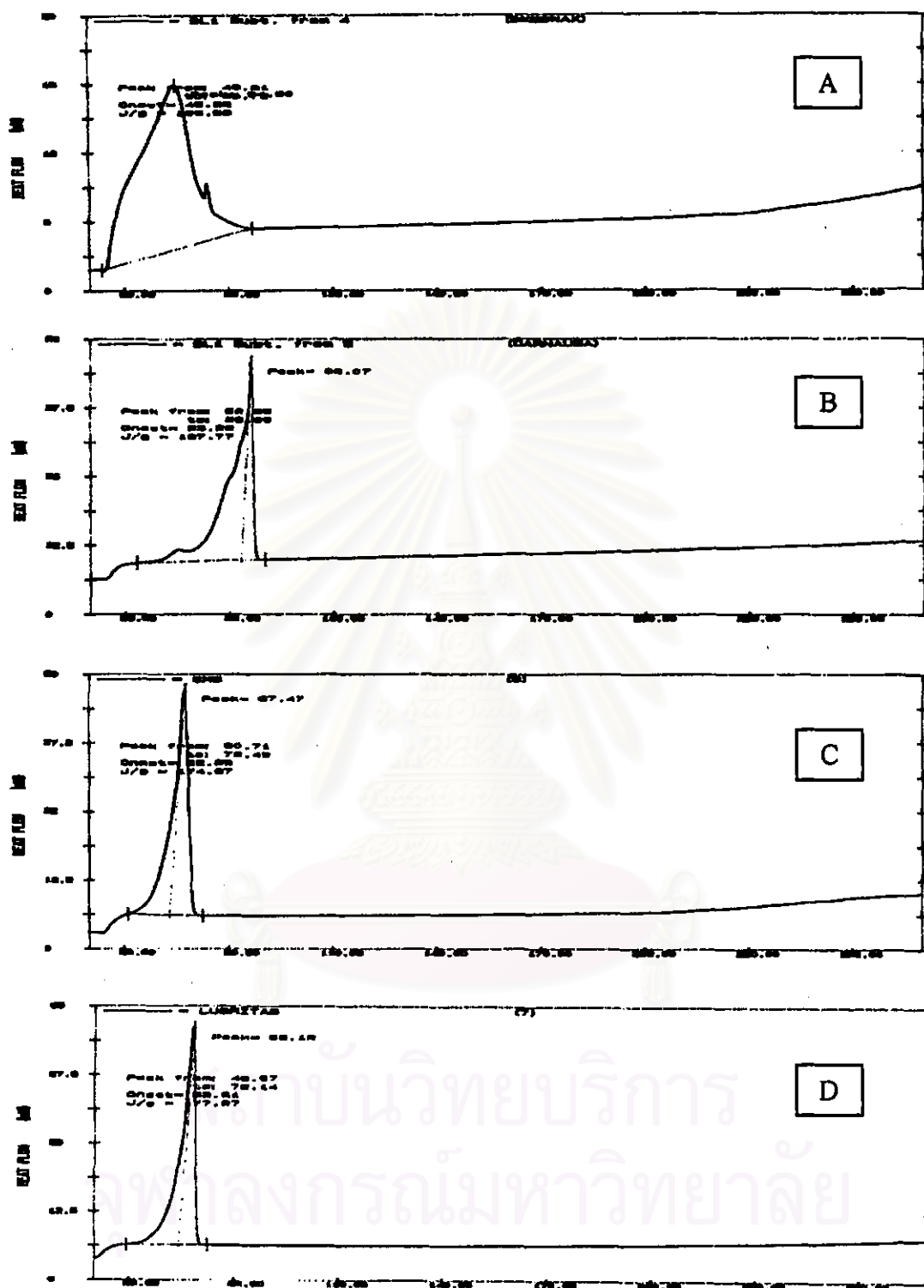
Figure 35   DSC thermograms of white beeswax (A), carnauba wax (B), glyceryl monostearate (C), and Lubritab® (D).
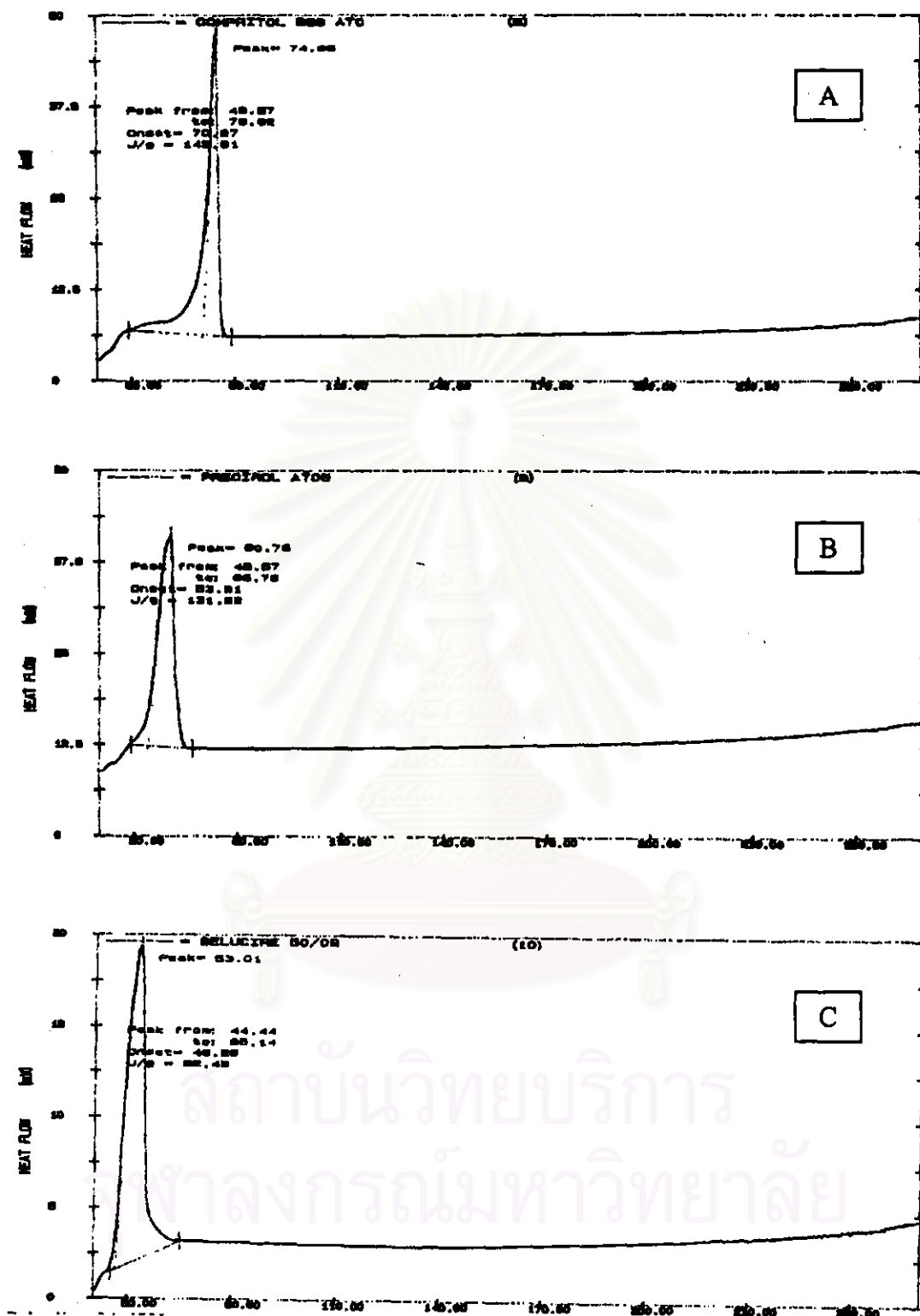
Figure 36   DSC thermograms of Compritol 888ATO® (A), Precirol ATO5® (B), and Gelucire 50/02® (C).
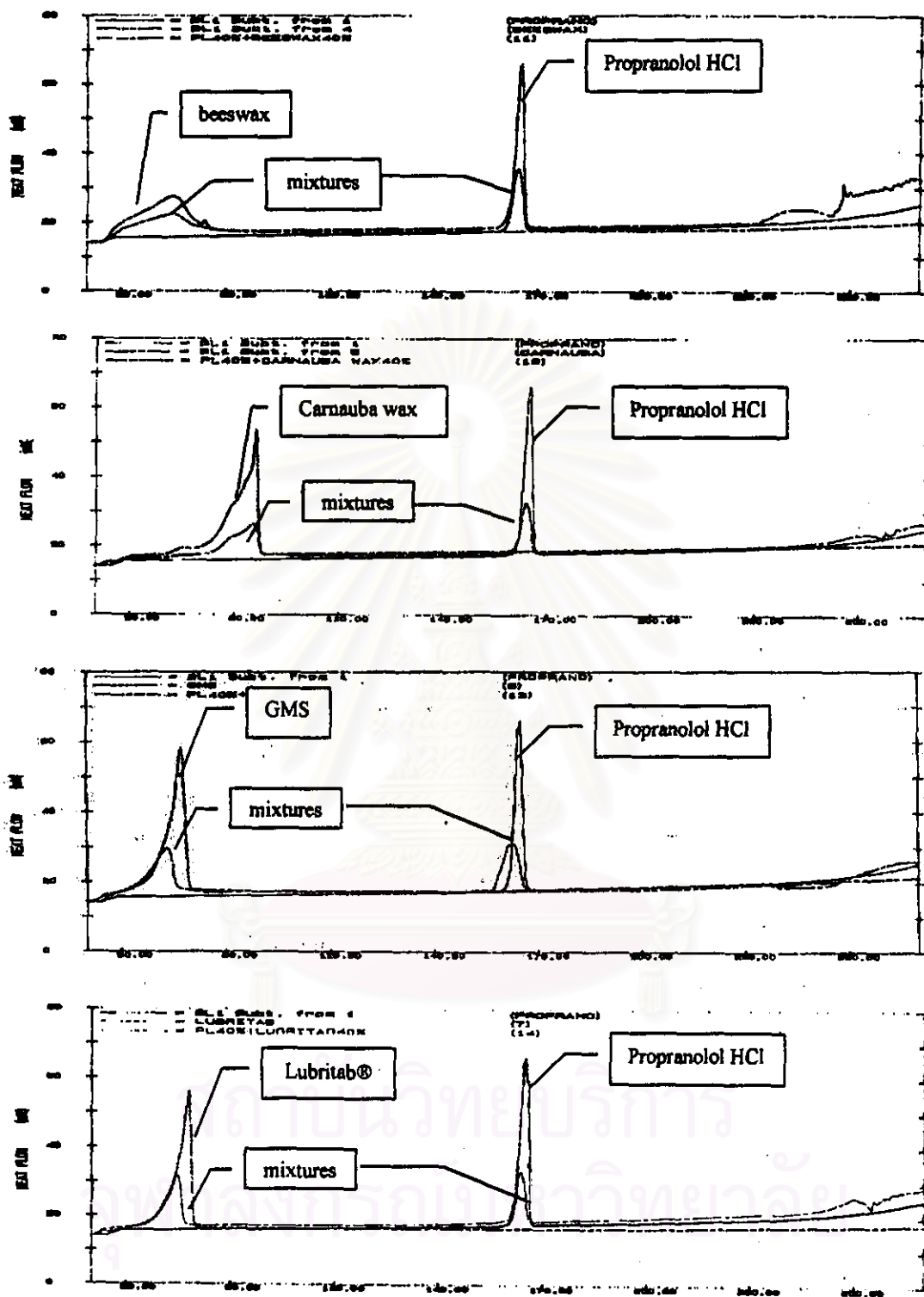
Figure 37   DSC thermograms of matrix pellets prepared from 40% white beeswax, carnauba wax, glyceryl monostearate, and Lubritab® with 40% propranolol HCl .
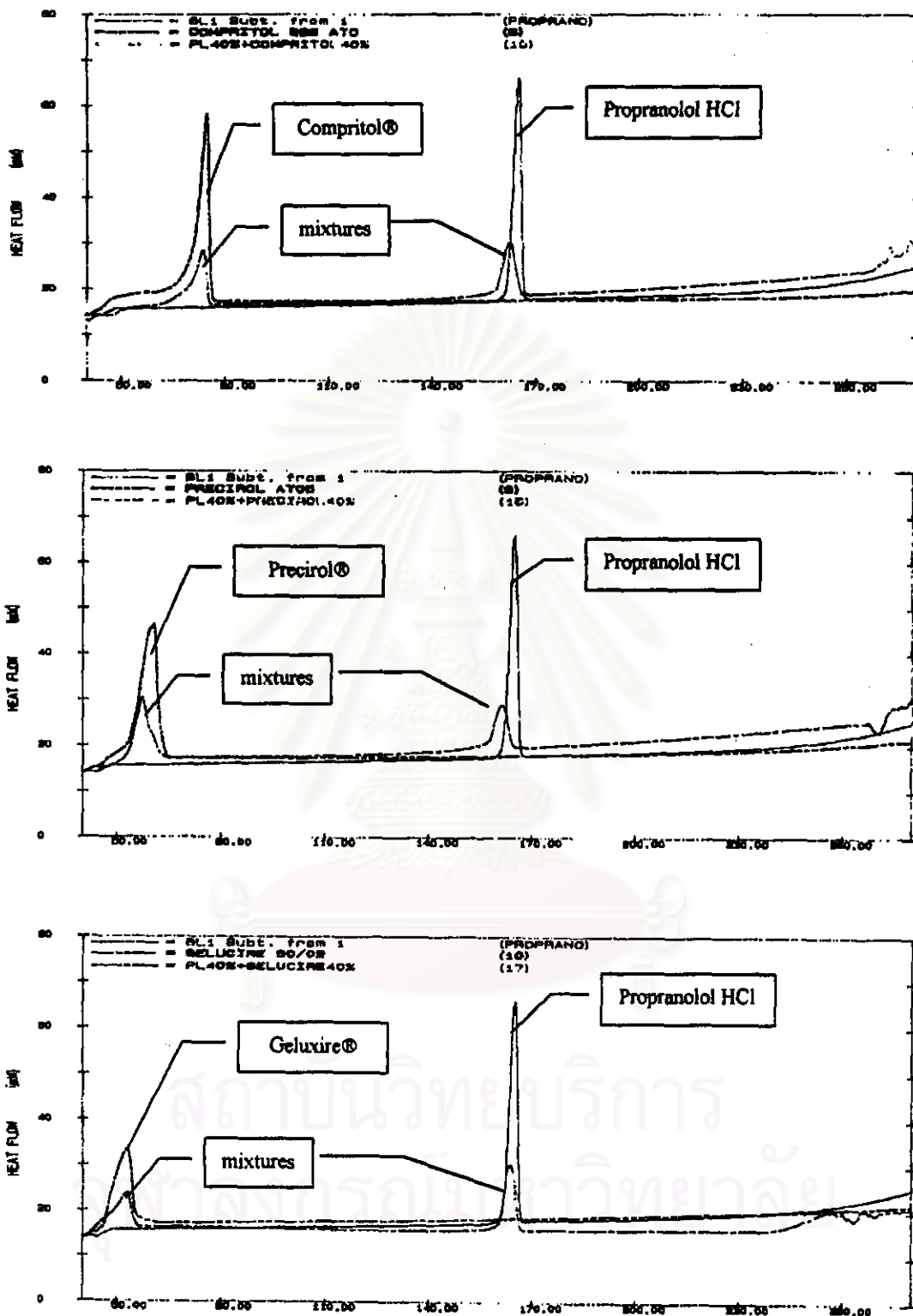
Figure 38   DSC thermograms of matrix pellets prepared from 40% Compritol 888ATO®, Precirol ATO5®, and Gelucire 50/02® with 40%Propranolol HCl.

Table 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 %.

Formulation	DSC Peaks (degree celcious)
	Endotherm
Propranolol HCl	165.10 (155.80-168.64)
Avicel PH101®	87.82 (47.14-155.35)
Lactose	146.55 (117.14-164.28)
	212.39 (192.14-216.42)
White bees wax	64.50 (43.21-86.78)
GMS	67.47 (50.71-72.49)
Lubritab®	68.12 (48.57-72.14)
Carnauba wax	86.07 (52.85-89.99)
Compritol 888ATO®	74.86 (48.57-78.92)
Precirol ATO5®	60.76 (48.57-66.78)
Gelucire 50/02®	53.01 (44.44-65.14)
PL40%+ White bees wax	64.70 (48.73-86.56), 164.24 (153.65-169.36)
PL40%+ GMS	63.26 (48.57-71.42), 162.32 (152.48-168.03)
PL40%+ Lubritab®	64.72 (52.85-69.64), 163.71 (151.42-168.57)
PL40%+ Carnauba wax	85.12 (65.71-90.35), 163.83 (142.85-168.57)
PL40%+ Compritol 888®	73.60 (55.00-77.85), 162.26 (145.71-167.85)
PL40%+ Precirol ATO5®	57.19 (46.59-66.57), 161.08 (134.38-167.57)
PL40%+ Gelucire 50/02®	52.93 (43.21-58.92), 163.70 (147.14-169-64)

II Matrix Tablets.

1. Preliminary Study of Matrix Tablet.

At the beginning of the experiment, the pellet formulation of wax and drug at 40 % using Lubritab® as matrix forming agent was chosen as a model for tabletting process. There was no additional diluent for healing the flow properties or lubricant in the tabletting process. Because of wax matrix pellet properties, it showed good flow in the form of pellet and wax that is in the formulation had self-lubricant properties. Four levels of compression forces were varied from 500 – 2000 pounds. Diameter, weight per tablet, thickness and hardness of this investigation are shown in Table 15.

From the Table 15, when increasing compressional forces, the thickness of matrix tablet was decreased, but the hardness of matrix tablet increased. So, it could be concluded that the compression force had influence on the thickness and the hardness of the matrix tablet.

Table 15   Preliminary study on tabletting properties of pellets compressed at different compression forces.

Parameter	Determination values				Preferred values
Compressional force (pound)	500	1000	1500	2000	-
Diameter (mm)	9.42	9.38	9.41	9.43	9.40
Weight / tablet (mg)	403.2	404.1	399.7	397.3	400.0
Thickness (mm)	4.51	4.44	4.32	4.25	-
Hardness (kp)	8.5 (0.524)	15.9 (0.678)	20.3 (0.462)	23.2 (0.986)	18.0-24.0*

All values are averaged from six determinations.

* (McGinity J.W. et al., 1983.)

The thickness and hardness of matrix tablets at 500 and 1000 pounds of compression forces were out of preferred range. Whereas the compression forces from 2000 pounds gave slightly increasing in hardness and decreasing in thickness. So 1500 pound force was chosen as compression forces for tabletting process for all wax matrix tablet preparations. To preserve energy, it is not necessary to use the force from 2000 pounds although hardness and thickness were also in range.

2. Physical Properties of Matrix Tablets Prepared from Wax Matrix Pellets.

2.1 Morphology of matrix tablets.

The surface topographies of the propranolol HCl matrix tablet was observed both before and after dissolution test by scanning electron photomicrographs process.

The scanning electron photomicrographs of matrix tablet prepared from various kinds of waxes at 40 % as shown in Figures 39 and 40. The upper and lower surfaces of the matrix tablets of all kinds of waxes before dissolution test had similar smooth texture with no holes. There were no detectable differences in surface topographies of the matrix tablet obtained from different kind of waxes. Caranuba wax, Lubritab®, Compritol® still showed fused pellet characteristic at the side surface of the tablet and inside the tablet by cross section.

After dissolution test, the surfaces of the tablets were rougher than those before test. The irregular surface filled with large and deep pores on the upper and lower surfaces of the matrix tablet depicted after 12 hours of dissolution test. The side of the tablets shown smaller pore size and lower number of pore than the
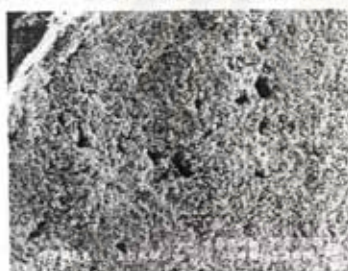
I × 40 (top view)

I × 40 (X-sect)

II × 40 (top view)

II × 40 (X-sect)

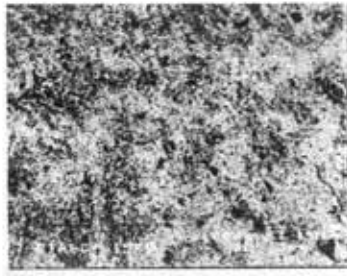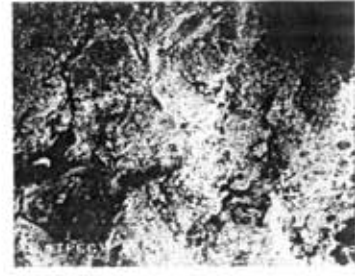III × 40 (top view)

III × 40 (X-sect)

IV × 40 (top view)
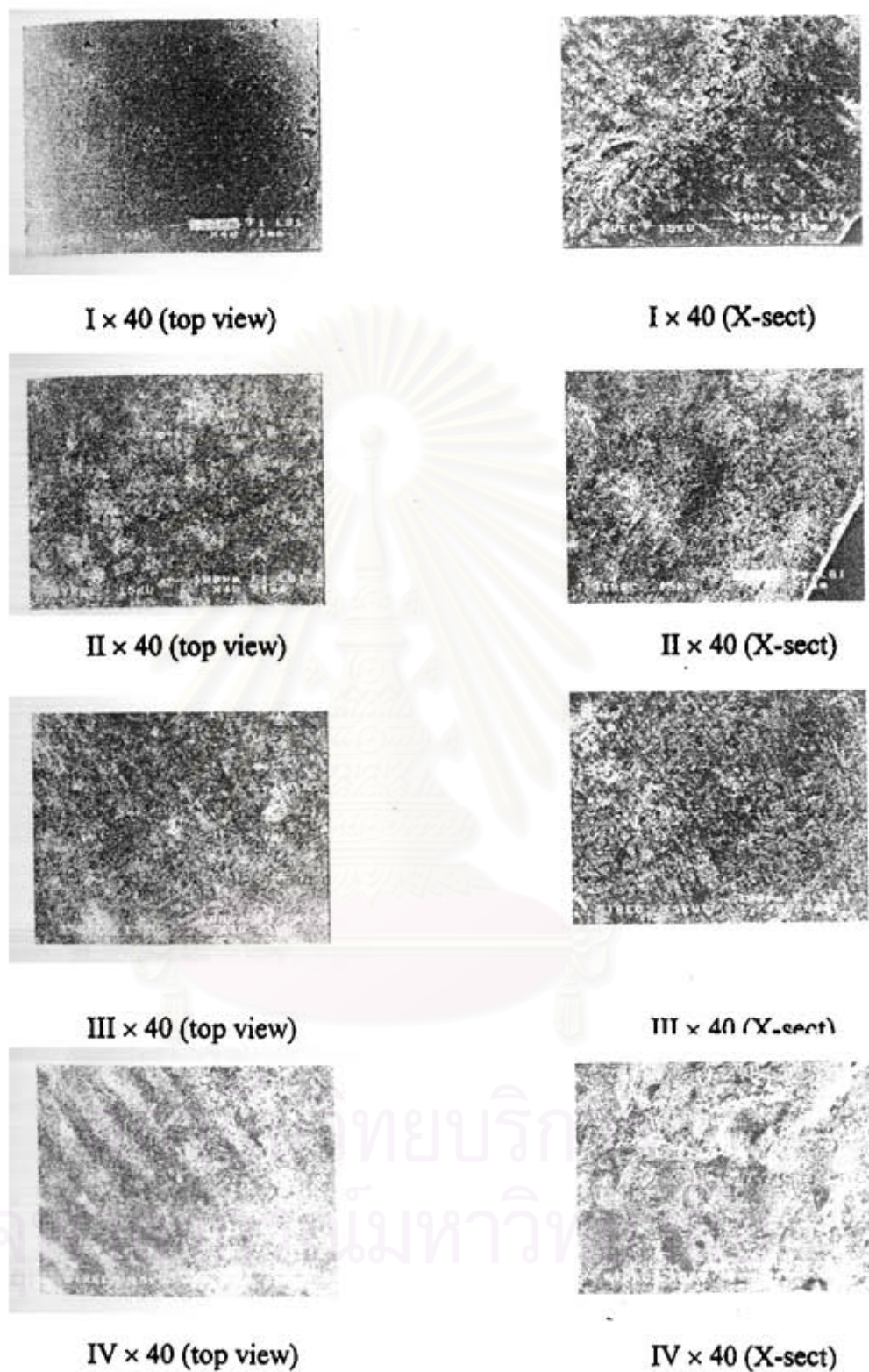
IV × 40 (X-sect)

Figure 39　　Scanning electron photomicrographs of matrix tablet prepared by 40 % commonly used wax (I = beeswax, II = carnauba wax, III = GMS, IV = Lubritab®) and 40 % propranolol HCl before dissolution test.
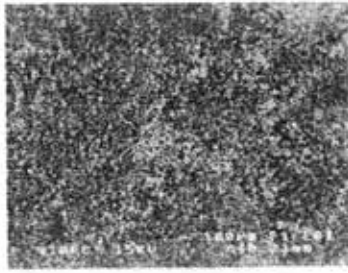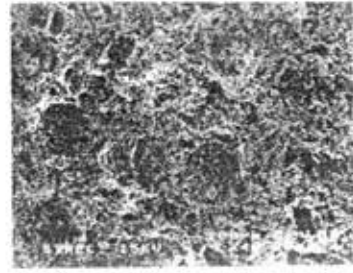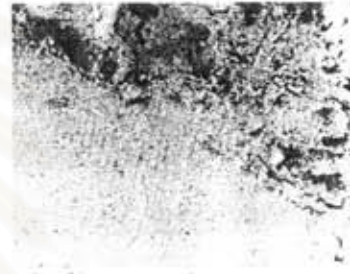
I × 40 (top view)

I × 40 (X-sect)
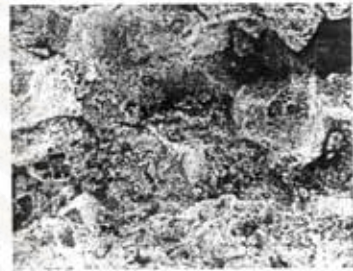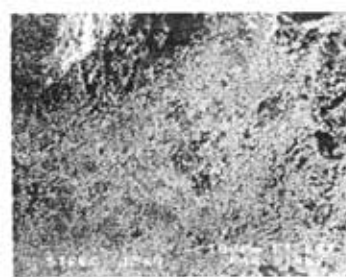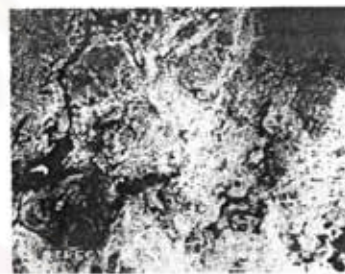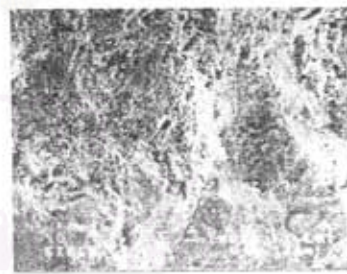
II × 40 (top view)

II × 40 (X-sect)

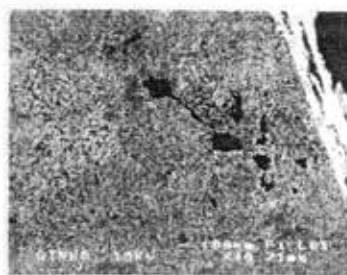III × 40 (top view)

III × 40 (X-sect)

Figure 40　Scanning electron photomicrographs of matrix tablet prepared by 40 % gattefosse's wax (I = Compritol®, II = Precirol®, III = Gelucire®) and 40 % propranolol HCl before dissolution test.
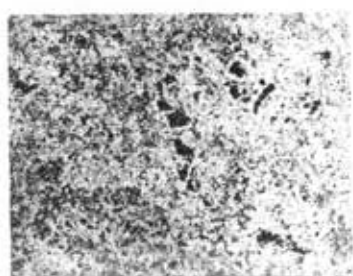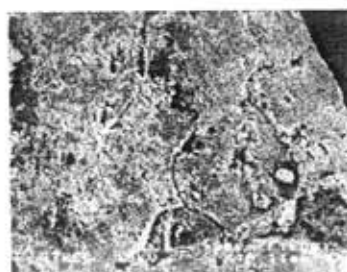
I × 40 (top view)

I × 40 (X-sect)

II × 40 (top view)

II × 40 (X-sect)

III × 40 (top view)

III × 40 (X-sect)

IV × 40 (top view)

IV × 40 (X-sect)

Figure 41   Scanning electron photomicrographs of matrix tablet prepared by 40 % commonly used wax (I = beeswax, II = carnauba wax, III = GMS, IV = Lubritab®) and 40 % propranolol HCl after dissolution test.

I × 40 (top view)

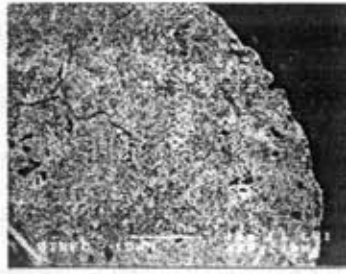

I × 40 (X-sect)

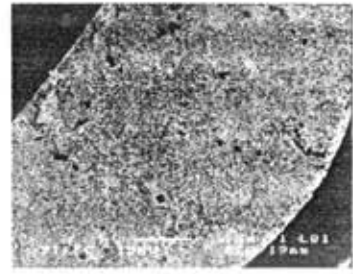II × 40 (top view)

II × 40 (X-sect)

III × 40 (top view)

III × 40 (X-sect)

Figure 42   Scanning electron photomicrographs of matrix tablet prepared by 40 % gattefosse's wax (I = Compritol®, II = Precirol®, III = Gelucire®) and 40 % propranolol HCl after dissolution test.

I × 40 (top view)

I × 40 (X-sect)

II × 40 (top view)

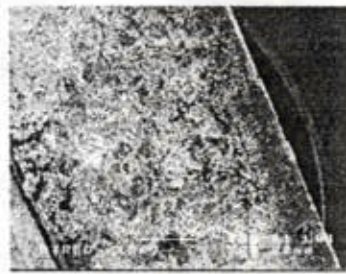II × 40 (X-sect)

III × 40 (top view)

III × 40 (X-sect)

IV × 40 (top view)

IV × 40 (X-sect)

Figure 43   Scanning electron photomicrographs of matrix tablet prepared by Compritol ATO888® (I = 20%, II = 30%, III = 40%, IV = 50%) and 40 % propranolol HCl after dissolution test.

I × 40 (top view)
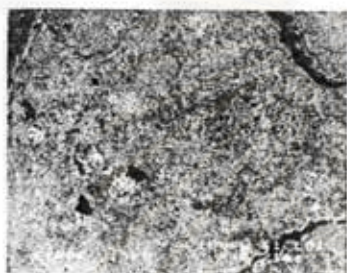
I × 40 (X-sect)

II × 40 (top view)

II × 40 (X-sect)

III × 40 (top view)

III × 40 (X-sect)

Figure 44   Scanning electron photomicrographs of matrix tablet prepared by 40% Compritol ATO888® and propranolol HCl (I = 20%, II = 30%, III = 50%) after dissolution test.
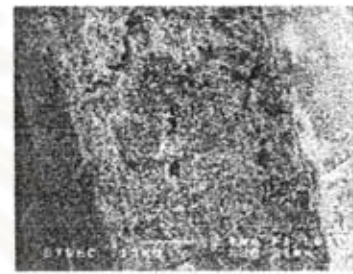
I × 20 (top view)

II × 20 (top view)

I × 20 (X-sect)

II × 20 (X-sect)

I × 40 (X-sect)

II × 40 (X-sect)

Figure 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).

upper and lower surface. By the x-section, there were some small pores connected in canal-like structure inside the tablet. But these characteristics only show at the rim of the tablet. The texture at the center of the tablet is still tightly compacted as the same as before dissolution test.

The upper and lower surface of the wax matrix tablets prepared from carnauba wax was eroded, cracked and clearly shown pellet-like structure. Large numbers of pore are found throughout the texture all around the tablet. Pellet inside the tablet had similar characteristic texture as the outer surface and became looser than those before dissolution test.

Figure 43 illustrated the microscopic appearances of the wax matrix tablets prepared from the formulation containing Compritol® from 20, 30, 40, 50 % and propranolol HCl at 40 % after dissolution test. The larger sized pores on the rough and irregular texture of both upper and lower side of the tablet were produced at the low amount of Compritol®. The small sized pore and smooth texture were found as increasing the amount of Compritol® in the formulation. In addition, the inner part of the matrix tablet was dense and did not show any crack. The crack on the center of the side surface around the tablet was diminished and finally disappeared at high content of Compritol®.

The photomicrographs of the wax matrix tablets obtained from the formulation that composed of 40 % Compritol® with 20, 30, 50 % propranolol HCl after dissolution test are shown in Figure 44. The slightly rough texture occupied with the number of pores was distributed throughout the surface of the tablet when low content of propranolol HCl was used. In contrary, the slightly lesser number and smoother surface of the matrix tablet was observed if propranolol HCl content in the formulation increased. The characterization of inner texture of the tablet was shown and no significance difference was exhibited between the series of loading dose.

The microscopic views of the wax matrix tablet produced from 50 % of Compritol® with 40 % of propranolol HCl after dissolution test in different dissolution medium are shown in Figure 45. The pores of the matrix tablet tested in medium pH 1.2 were slightly higher than those tested in medium pH 6.8. But in general, the texture of the matrix tablets tested in medium pH 1.2 and 6.8 displayed no significance different results.

2.2 Thickness, diameter, hardness and disintegration time of matrix tablet.

Diameter, thickness, hardness and disintegration time of matrix tablet were presented in Table 16.

The diameter of the wax matrix tablets was in the narrow range of 9.35 – 9.44 mm. Because the die of the hydraulic punch for tabletting could control the diameter of all wax matrix tablet.

The thickness value was not in corresponding with the hardness of the matrix tablet especially in the series of wax content and loading dose. The different in wax content and loading dose did not affect the thickness and the hardness of the matrix tablet and this value are in the preferred range. In the different kind of waxes, beeswax and Gelucire® gave the hardness value lower than the preferred value and the thickness value rather higher than the other waxes.

The mean hardness was mostly ranged from 18 – 23 kp. The lowest hardness value at 12.54 kp was obtained from matrix tablet used 50 % of Gelucire® in the formulation. The formulation using 40 % of propranolol HCl with 40 % of carnauba wax produced the lowest thickness value of the matrix tablets at 3.96

Table 16   Thickness, diameter, hardness, and disintegration time of matrix tablets from various matrix pellet formulations.

Formulation	Diameter (mm)	Thickness (mm)	Hardness (kp)	Disintegration time (min)
PL 40%, beeswax 20%	9.35 (0.28)	4.45 (0.49)	15.23 (0.72)	> 120
PL 40%, beeswax 30%	9.37 (0.76)	4.34 (0.14)	14.12 (1.04)	> 120
PL 40%, beeswax 40%	9.40 (0.42)	4.49 (0.52)	14.08 (0.95)	> 120
PL 40%, beeswax 50%	9.38 (0.56)	4.48 (0.16)	13.46 (0.87)	> 120
PL 40%, carnauba wax 20%	9.36 (0.49)	3.98 (0.26)	20.43 (0.89)	> 120
PL 40%, carnauba wax 30%	9.43 (0.12)	4.10 (0.29)	21.11 (1.20)	> 120
PL 40%, carnauba wax 40%	9.41 (0.09)	4.08 (0.21)	22.55 (1.50)	> 120
PL 40%, carnauba wax 50%	9.39 (0.05)	4.12 (0.23)	20.09 (0.86)	> 120
PL 40%, GMS 20%	9.37 (0.19)	4.32 (0.46)	19.87 (1.56)	> 120
PL 40%, GMS 30%	9.35 (0.16)	4.25 (0.09)	18.11 (0.67)	> 120
PL 40%, GMS 40%	9.38 (0.23)	4.21 (0.14)	19.55 (1.28)	> 120
PL 40%, GMS 50%	9.42 (0.42)	4.29 (0.16)	19.75 (0.74)	> 120
PL 40%, lubritab 20%	9.41 (0.33)	4.19 (0.23)	20.18 (0.99)	> 120
PL 40%, lubritab 30%	9.39 (0.18)	4.29 (0.28)	21.26 (0.81)	> 120
PL 40%, lubritab 40%	9.43 (0.19)	4.38 (0.79)	22.18 (1.20)	> 120
PL 40%, lubritab 50%	9.38 (0.41)	4.35 (0.64)	21.13 (1.18)	> 120
PL 40%, compritol 20%	9.36 (0.58)	4.34 (0.43)	22.23 (0.69)	> 120
PL 40%, compritol 30%	9.42 (0.20)	4.29 (0.75)	21.47 (1.43)	> 120
PL 40%, compritol 40%	9.44 (0.13)	4.39 (0.82)	21.89 (0.87)	> 120
PL 40%, compritol 50%	9.35 (0.16)	4.32 (0.95)	23.42 (0.67)	> 120
PL 40%, precirol 20%	9.40 (0.17)	4.15 (0.42)	19.65 (0.92)	> 120
PL 40%, precirol 30%	9.36 (0.31)	4.25 (0.65)	18.43 (0.73)	> 120
PL 40%, precirol 40%	9.43 (0.40)	4.28 (0.09)	19.56 (1.12)	> 120
PL 40%, precirol 50%	9.44 (0.43)	4.31 (0.14)	20.11 (0.97)	> 120
PL 40%, gelucire 30%	9.40 (0.47)	4.32 (0.16)	14.25 (1.87)	> 120
PL 40%, gelucire 40%	9.38 (0.51)	4.38 (0.29)	14.06 (1.96)	> 120
PL 40%, gelucire 50%	9.37 (0.25)	4.50 (0.37)	12.54 (1.93)	> 120

All values of diameter, thickness, hardness are averaged from six determinations

Table 16 (Continued). Thickness, diameter, hardness, and disintegration time of matrix tablets from various matrix pellet formulations.

Formulation	Diameter (mm)	Thickness (mm)	Hardness (kp)	Disintegration time (mm)
PL 20%, beeswax 40%	9.36 (0.43)	4.36 (0.29)	16.54 (1.13)	> 120
PL 30%, beeswax 40%	9.41 (0.15)	4.46 (0.26)	15.26 (0.98)	> 120
PL 50%, beeswax 40%	9.37 (0.16)	4.67 (0.43)	15.38 (1.34)	> 120
PL 20%, carnauba wax 40%	9.38 (0.22)	3.96 (0.15)	19.25 (0.87)	> 120
PL 30%, carnauba wax 40%	9.39 (0.41)	3.97 (0.24)	20.12 (0.79)	> 120
PL 50%, carnauba wax 40%	9.42 (0.46)	4.19 (0.76)	20.23 (0.95)	> 120
PL 20%, GMS 40%	9.40 (0.23)	4.20 (0.51)	18.56 (1.38)	> 120
PL 30%, GMS 40%	9.37 (0.48)	4.21 (0.41)	17.46 (1.20)	> 120
PL 50%, GMS 40%	9.38 (0.19)	4.29 (0.18)	19.23 (1.12)	> 120
PL 20%, lubritab 40%	9.43 (0.43)	4.12 (0.84)	20.78 (0.98)	> 120
PL 30%, lubritab 40%	9.44 (0.56)	4.22 (0.12)	22.12 (0.89)	> 120
PL 50%, lubritab 40%	9.42 (0.19)	4.43 (0.18)	21.29 (1.09)	> 120
PL 20%, compritol 40%	9.42 (0.28)	4.17 (0.28)	20.16 (0.76)	> 120
PL 30%, compritol 40%	9.39 (0.27)	4.29 (0.47)	21.24 (0.67)	> 120
PL 50%, compritol 40%	9.38 (0.65)	4.50 (0.54)	20.78 (1.09)	> 120
PL 20%, precirol 40%	9.39 (0.12)	4.20 (0.14)	18.17 (1.45)	> 120
PL 30%, precirol 40%	9.37 (0.29)	4.20 (0.49)	19.68 (0.46)	> 120
PL 50%, precirol 40%	9.36 (0.68)	4.37 (0.43)	18.99 (0.99)	> 120
PL 20%, gelucire 40%	9.40 (0.21)	4.21 (0.52)	15.14 (1.46)	> 120
PL 30%, gelucrie 40%	9.41 (0.32)	4.34 (0.85)	13.48 (1.54)	> 120
PL 50%, gelucire 40%	9.41 (0.43)	4.47 (0.27)	14.02 (1.39)	> 120

All values of diameter, thickness, hardness are averaged from six determinations

mm. Whereas the highest thickness value at 4.50 mm was produced by the formulation used Gelucire® at 50 %.

All of the preparations had disintegration time that was longer than 2 hours. Wax matrix tablets were still intact after 2 hours of testing.

III Dissolution Study.

The dissolution or the release profiles were constructed by plotting percentage of drug released against time. The change of release rate profile was constructed from the dissolution profile to elucidate the release rate at various time intervals during the course of drug dissolution from the matrix. The dissolution data of each formulation blank propranolol HCl capsule, blank tablet and Inderal® are described in Table 30. (Appendix B)

Three preparations of propranolol HCl were produced by filling 400 mg or propranolol HCl into capsules or compressed into tablet. All preparations were evaluated by testing those preparations both in the acidic state (0.1 N HCl, pH 1.2) and basic state (phosphate buffer, pH 6.8).

The release rate was calculated by dividing the different of percent drug release at various time interval with the time utilized to release that certain amount of the drug (Table 59, Appendix B). Then, the rate was plotted with average time interval. It was found that the rate of release decreased with time increased.

1. The Reference Propranolol HCl Capsule and Tablet.

The drug release data of pure propranolol HCl in capsule and tablet preparations are shown in Table 30 and drug release profiles are shown in Figure 46.

The percentage of drug released both in the acidic stage and basic stage were completely in 0.5 hr. and 1.5 hr., respectively. The release rate of propranolol HCl in 0.1 N HCl was slightly faster than in phosphate buffer pH 6.8 as illustrated in Figure 46. The results indicated that propranolol HCl may be more soluble in 0.1 N HCl than in phosphate buffer pH 6.8. The release rate of both capsule and tablet were faster than other propranolol HCl wax matrices.

2. The Matrix Pellets.

2.1 Wax content.

The dissolution profiles of propranolol HCl from wax matrix pellet with various ratios in 0.1 N HCl and phosphate buffer pH 6.8 were shown in Figures 47-53 (Tables 31-37, Appendix B). Each point represents the average value from three determinations at the given sampling time.

The percent drug released from almost every kinds of wax at 50 % in matrix pellets reached 100 % at about the 4th hour. But at the lower concentration of waxes than 50 % showed faster drug release and completely reached 100 % drug release at the time lower than 4th hour. However, the formulation containing 50 % of Compritol® gradually released the drug from matrix pellet to 100 % at about 8th hour. This formulation showed significance difference in release patterns from the other
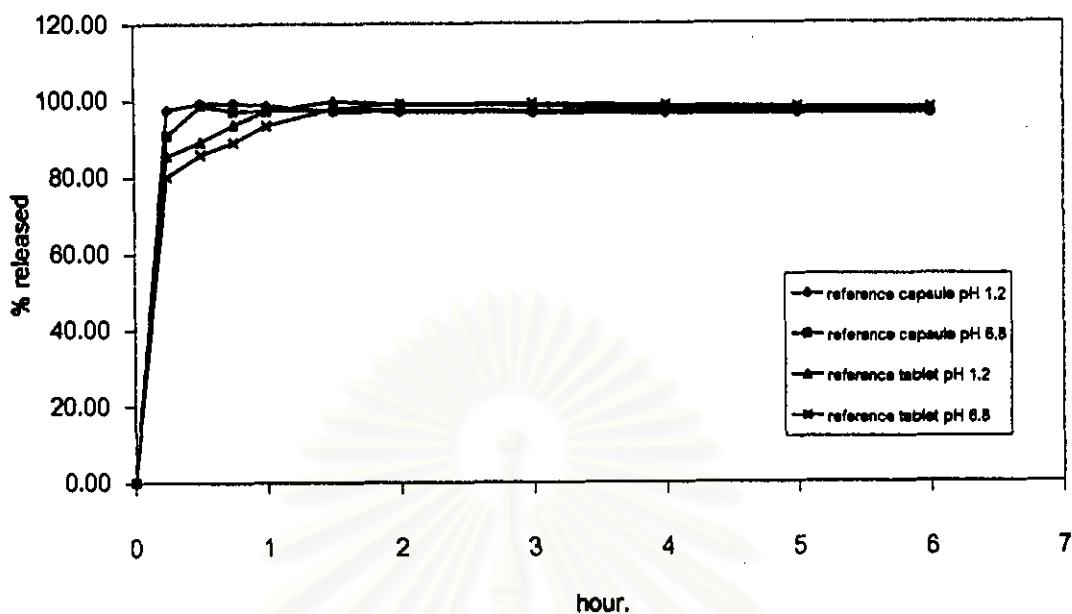
Figure 46   The release profiles of reference propranolol HCl capsules, reference tablets and Inderal® capsule in medium pH1.2 and pH 6.8.
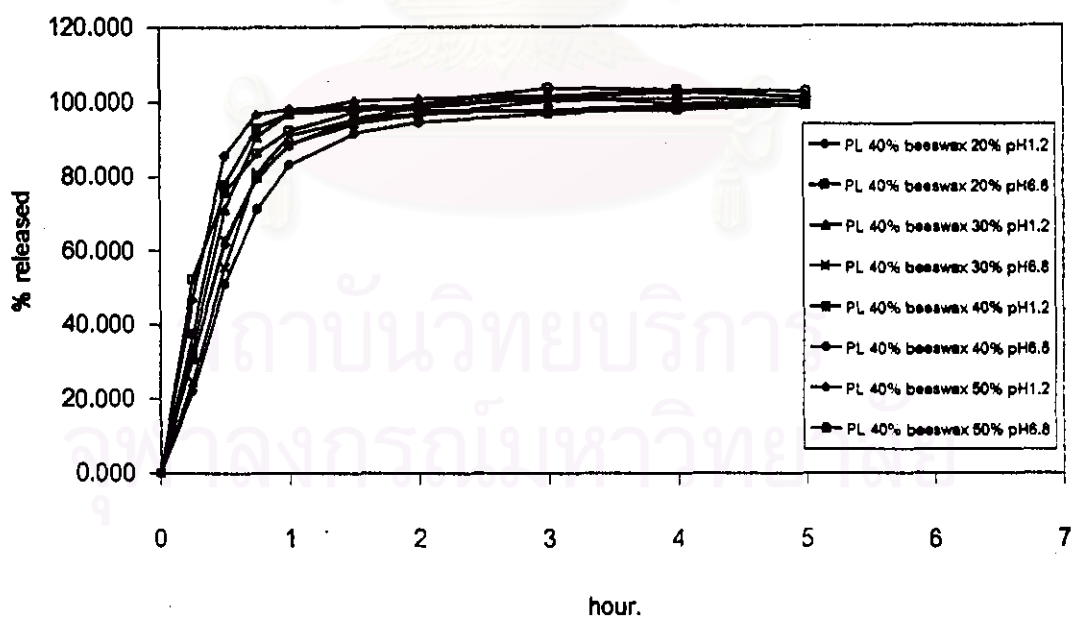
Figure 47   The release profiles of matrix pellet prepared from series of beeswax in medium pH1.2 and pH 6.8.
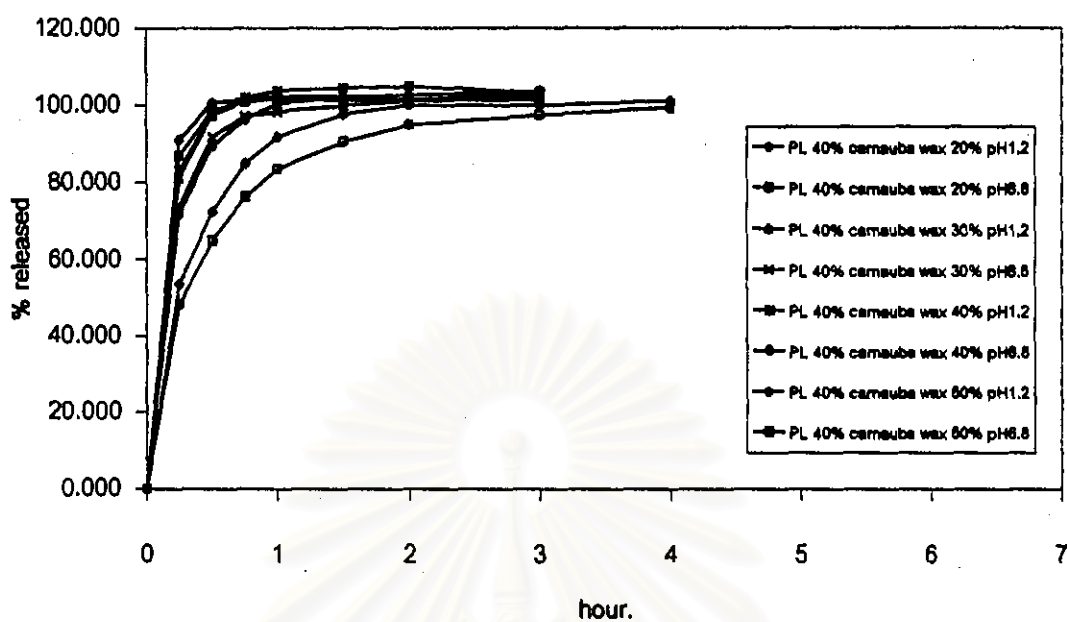
Figure 48   The release profiles of matrix pellet prepared from series of carnauba wax in medium pH1.2 and pH 6.8.
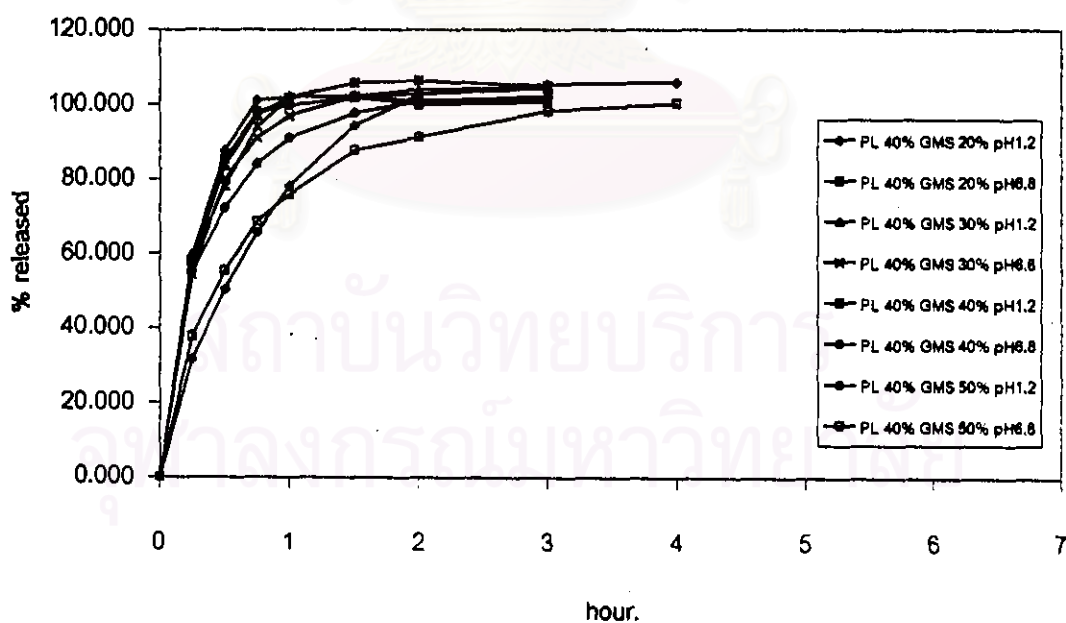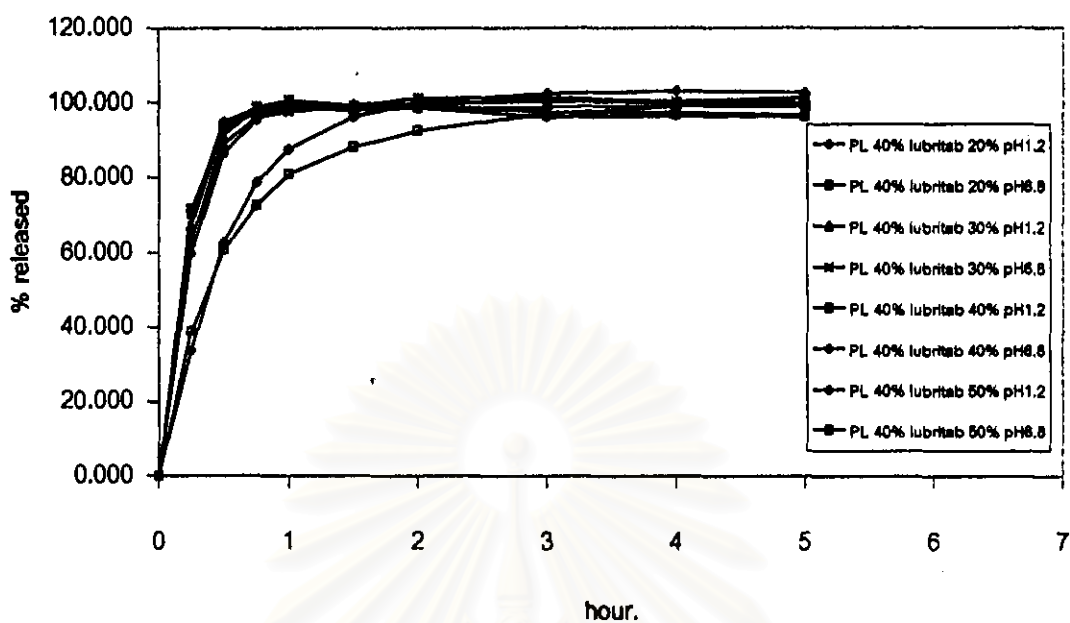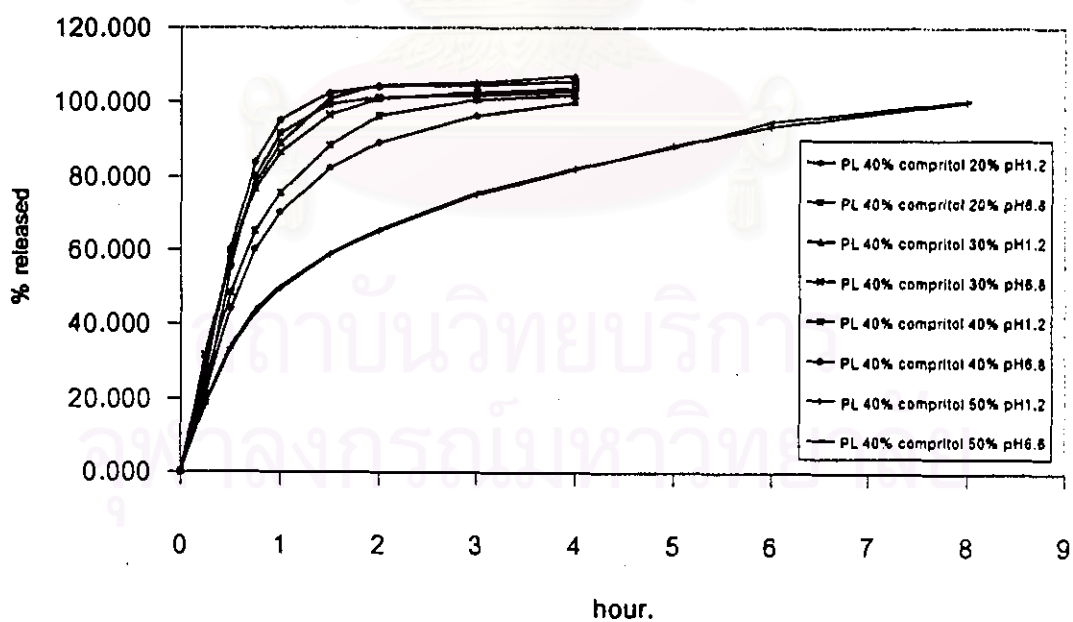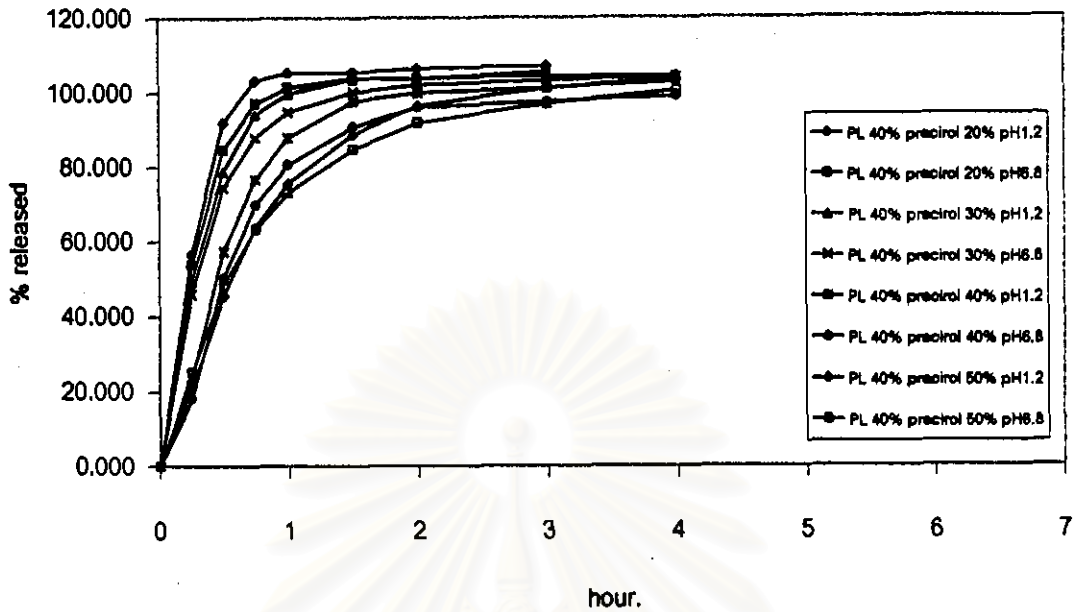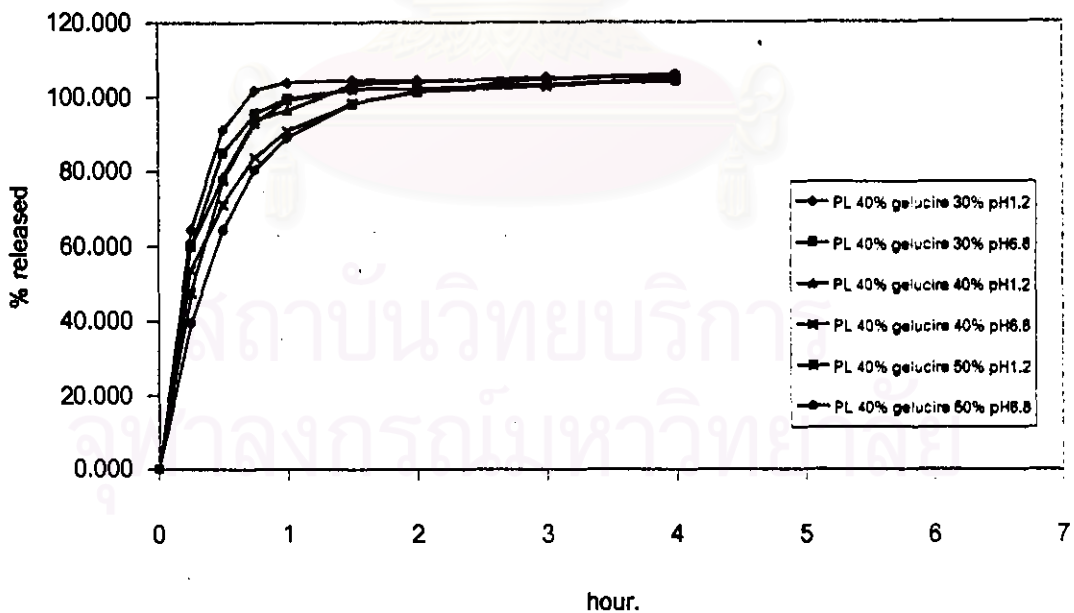

Figure 49   The release profiles of matrix pellet prepared from series of glyceryl monostearate in medium pH1.2 and pH 6.8.

Figure 50   The release profiles of matrix pellet prepared from series of Lubritab®
in medium pH1.2 and pH 6.8.

Figure 51   The release profiles of and matrix pellet prepared from series of
Compritol® in medium pH1.2 and pH 6.8.

Figure 52   The release profiles of matrix pellet prepared from series of Precirol® in medium pH1.2 and pH 6.8.

Figure 53   The release profiles of matrix pellet prepared from series of Gelucire® in medium pH1.2 and pH 6.8.

waxes and exhibited satisfactory controlled released profile of the capsule preparations. No significantly different release pattern was detected from formulations containing other kind of waxes.

Increasing the weight fraction of waxes resulted in a corresponding decrease of the dissolution rate. The concentration of waxes in the formulation was the determining factor in controlling release rate of drug.

The release of drug from these matrix pellets containing various levels of waxes were affected by dissolution medium as shown in Figures 47-53. The amount of propranolol HCl released in 0.1 N HCl was higher than in phosphate buffer pH 6.8. This result may be affected by decrease in propranolol HCl solubility in phosphate buffer pH 6.8.

2.2 loading dose.

The release data of propranolol HCl matrix pellet from the formulations containing waxes at 40 % with various ratio of propranolol HCl are listed in Tables 38-44, Appendix B and release profiles of these preparations are illustrated in Figures 54-60.

All kinds of wax still exhibited fast release of propranolol HCl pellets. The drug dissolved rapidly and release rate was constant after 4 – 5th hour. There was no significance difference in release pattern of the formulations used different kind of waxes at the same drug to wax ratio. Slightly lower in percent drug released was detected in the formulations containing beeswax and Compritol® compared to those containing other waxes.
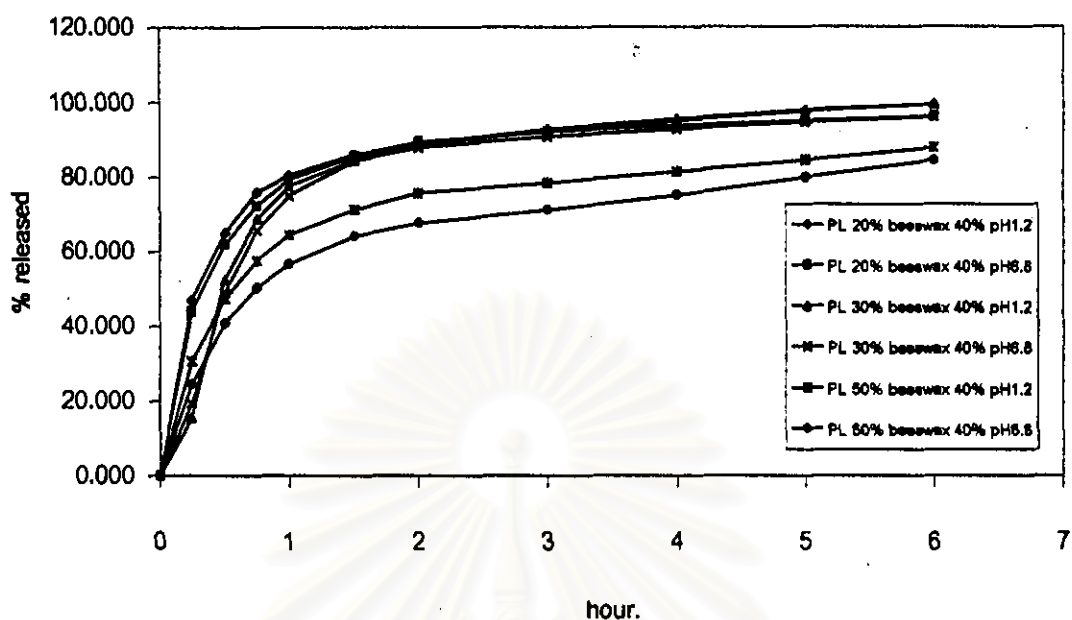
Figure 54   The release profiles of matrix pellets containing 40 % of beeswax with different loading dose in 0.1 N HCl pH 1.2 and phosphate buffer pH 6.8.
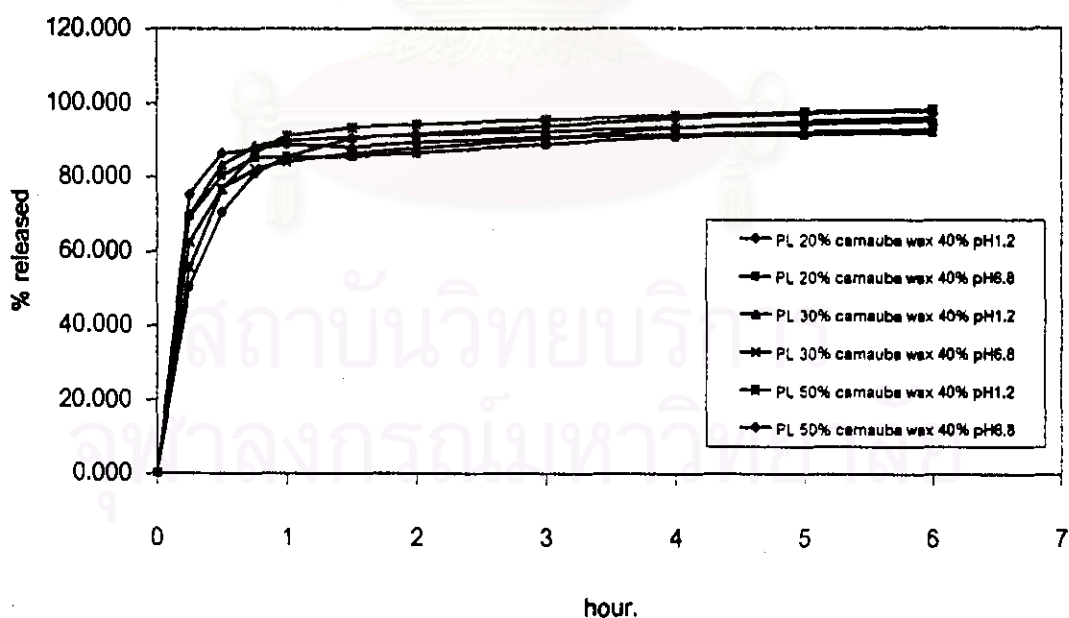

Figure 55   The release profiles of matrix pellets containing 40 % of carnauba wax with different loading dose in 0.1 N HCl pH 1.2 and phosphate buffer pH 6.8.
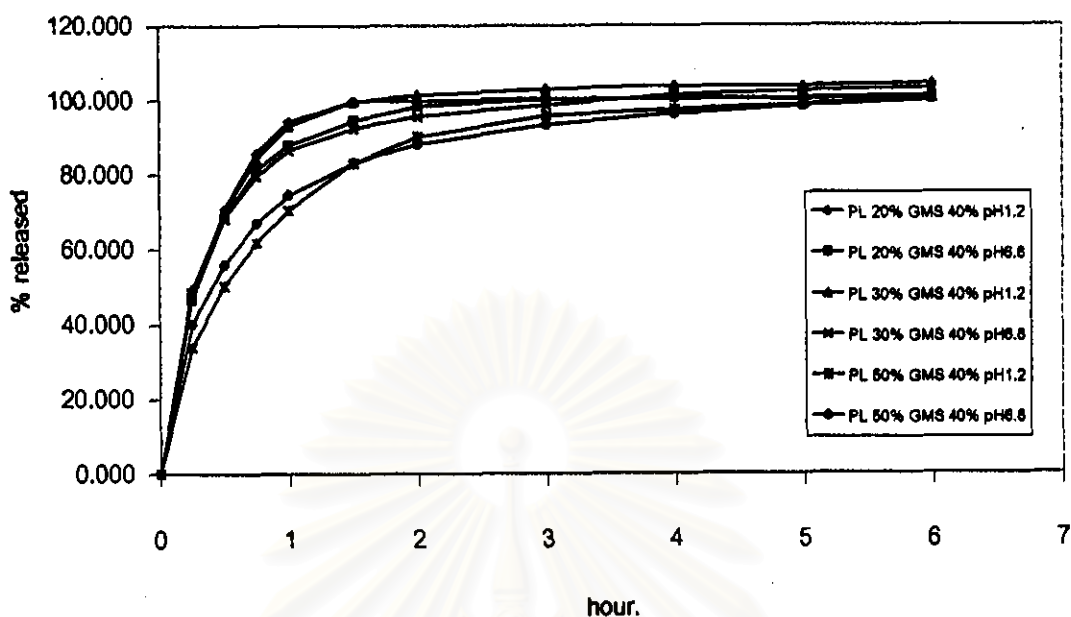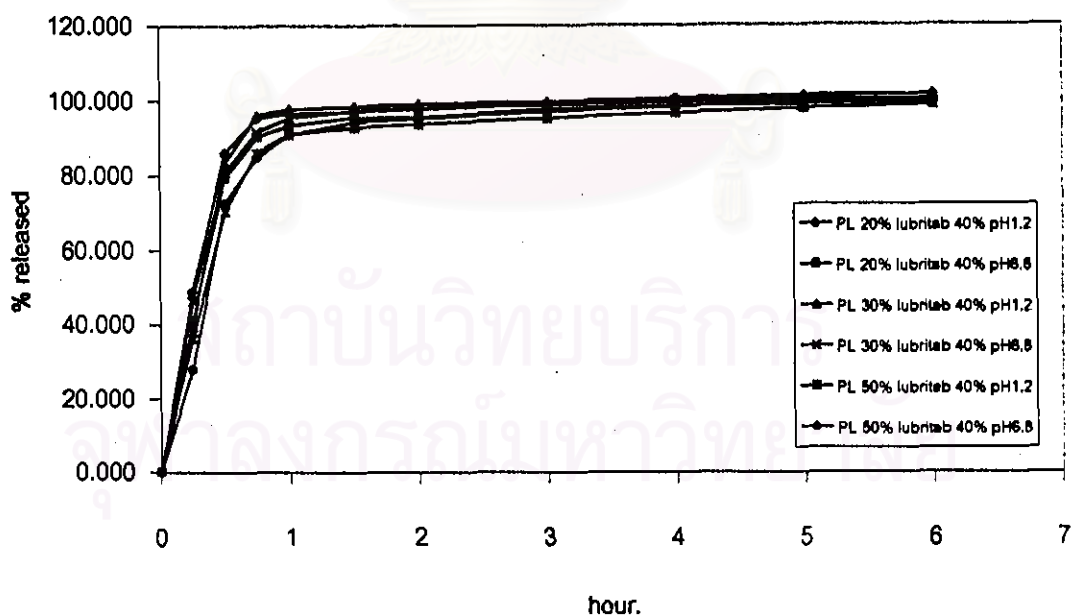
Figure 56   The release profiles of matrix pellets containing 40 % of glyceryl monostearate with different loading dose in 0.1 N HCl pH 1.2 and phosphate buffer pH 6.8.

Figure 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.
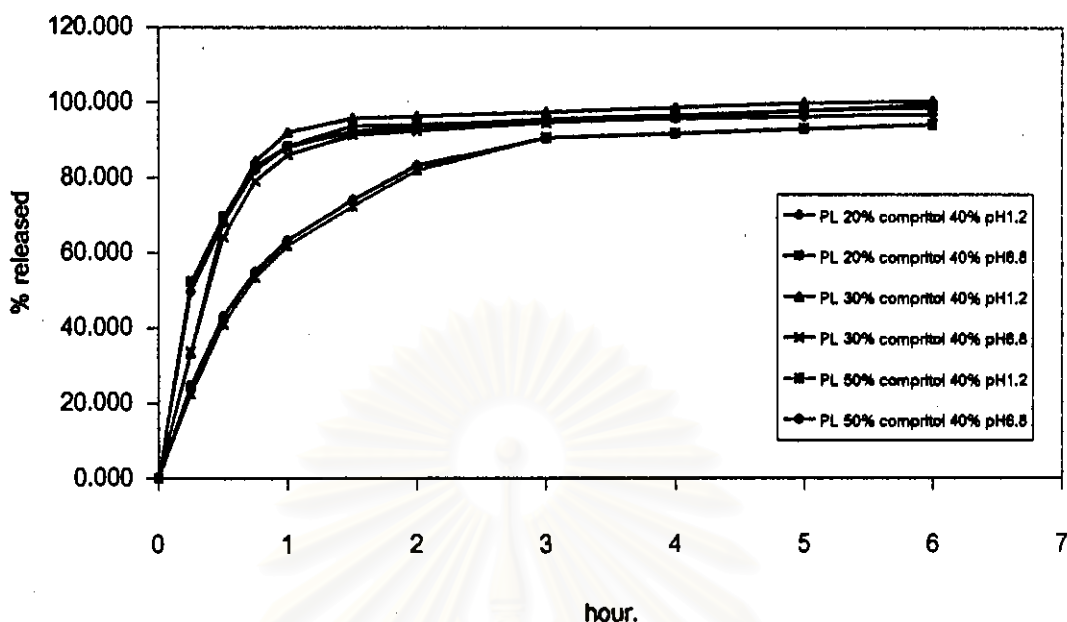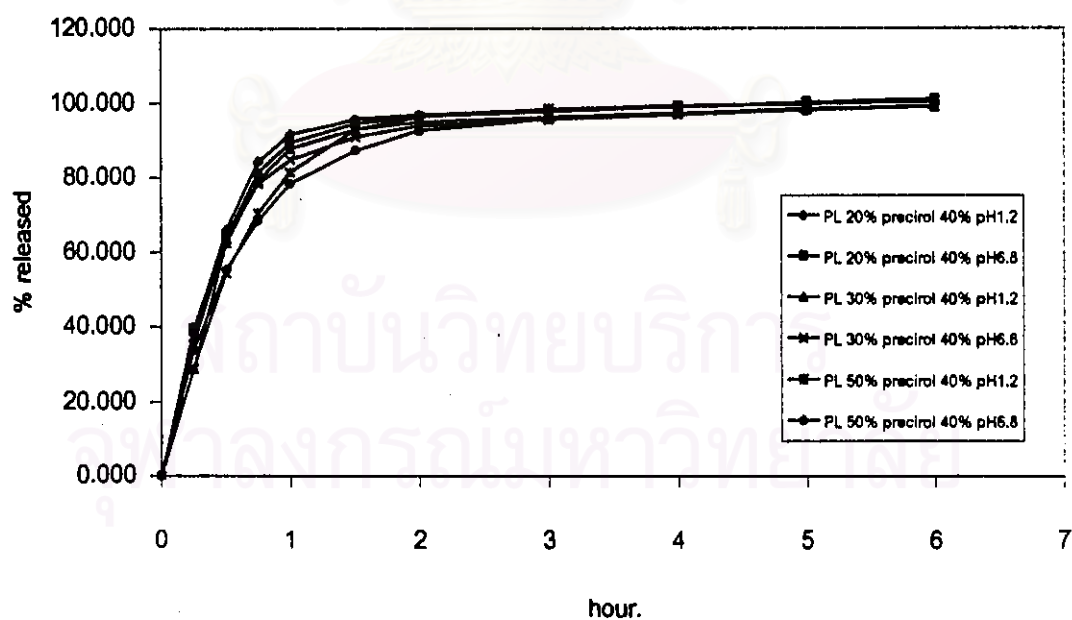
Figure 58   The release profiles of matrix pellets containing 40 % of Compritol®
with different loading dose in 0.1 N HCl pH 1.2 and phosphate buffer pH 6.8.

Figure 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.
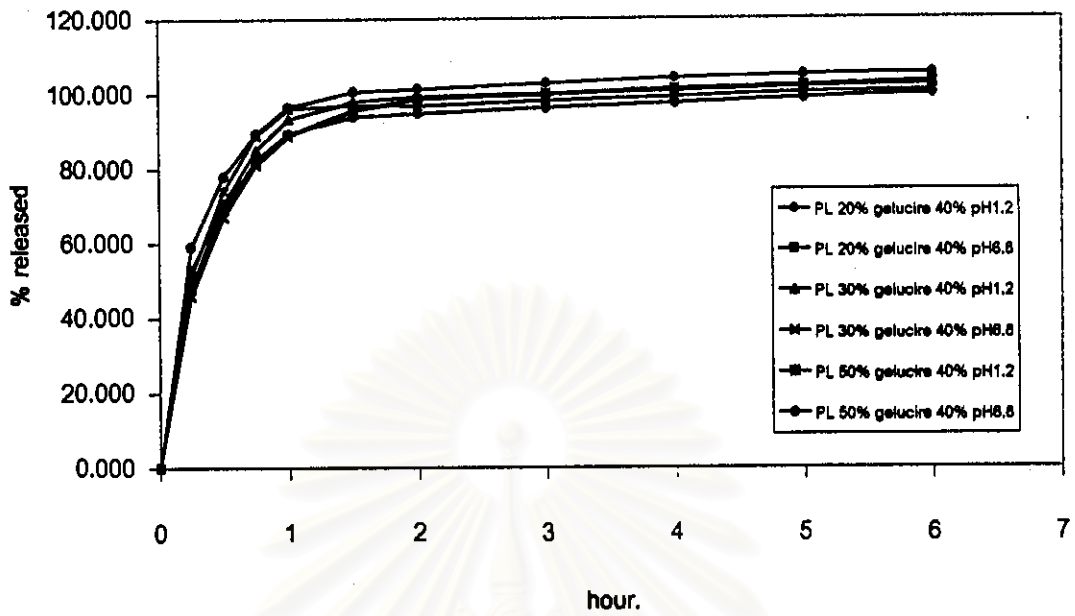
Figure 60   The release profiles of matrix pellets containing 40 % of Gelucire® with different loading dose in 0.1 N HCl pH 1.2 and phosphate buffer pH 6.8.

The formulations using different loading dose of propranolol HCl exhibited the same results as the effect of wax content. The lower in percent released of propranolol HCl was occurred with increasing the amount of propranolol HCl. But this effect was clearly seen by using Compritol® and beeswax in the formulation. However, they still showed high release rate and the drug completely dissolved to 100 % within 6-8 hour although using beeswax or Compritol®. In addition, high release rate could be detected at the first two hours of the release.

The release of propranolol HCl from matrix pellet containing all level of propranolol HCl at 40 % of wax were affected by dissolution medium as displayed in Figures 54-60. The dissolution medium affected the release rate but did not affect the pattern of the drug release. The release rate in 0.1 N HCl was slightly faster than the release rate in phosphate buffer pH 6.8.

From these results, it was indicated the concentration of the waxes obviously affected the percentage of drug released. The pH of the medium had an effect on the release rate profile. The different waxes produced the different drug-released time profile. However, pellet formulation could not exhibit satisfactory controlled release profile and those effects could not be clearly seen.

3. The Matrix Tablets.

The dissolution data and drug release profiles of the matrix tablet were divided into groups depended on the type of wax used in the formulations. The matrix tablet formulations were classified as the following.

3.1 The formulations containing beeswax.

The release data of propranolol HCl wax matrix tablet from the formulations containing beeswax with various ratios are listed in Table 45, Appendix B and released profile of these preparations in 0.1 N HCl and phosphate buffer pH 6.8 are illustrated in Figures 61-62.

The release rate of these formulations decreased with the time increased. If the content of beeswax in the formulation wax increased, the percent of drug release was decreased. At 30 % of beeswax showed slightly lower release rate than 20 % of beeswax. Percent release of both formulations came to the plateau state at 8 and 10 hour in medium pH 1.2 and 6.8, respectively. The percent release of the formulations prepared from the other ratio at the 12th hour was decreased from 104.37 % to 104.12 % to 88.68 % to 56.08 % in medium pH 1.2 and 100.71 % to 101.78 % to 70.18 % to 46.14 % in medium pH 6.8, respectively, when beeswax was changed from 20 – 40 %. As expected, the percent drug releases were decreased with increasing amount of the wax in the formulations.

No difference in release patterns was detected from the formulations produced using different content of beeswax. However, higher percent of beeswax showed rather smooth release profile.

The release of propranolol HCl from these formulations were affected by dissolution medium as shown in Figures 61-62. The release rate in 0.1 N HCl was faster than the release ratio in phosphate buffer pH 6.8.

The release rate was decreased with time as shown in Figures 63-64 and this might be due to an increase diffusional path length for the drug. Increasing the weight fraction of wax resulted in a corresponding decrease of the
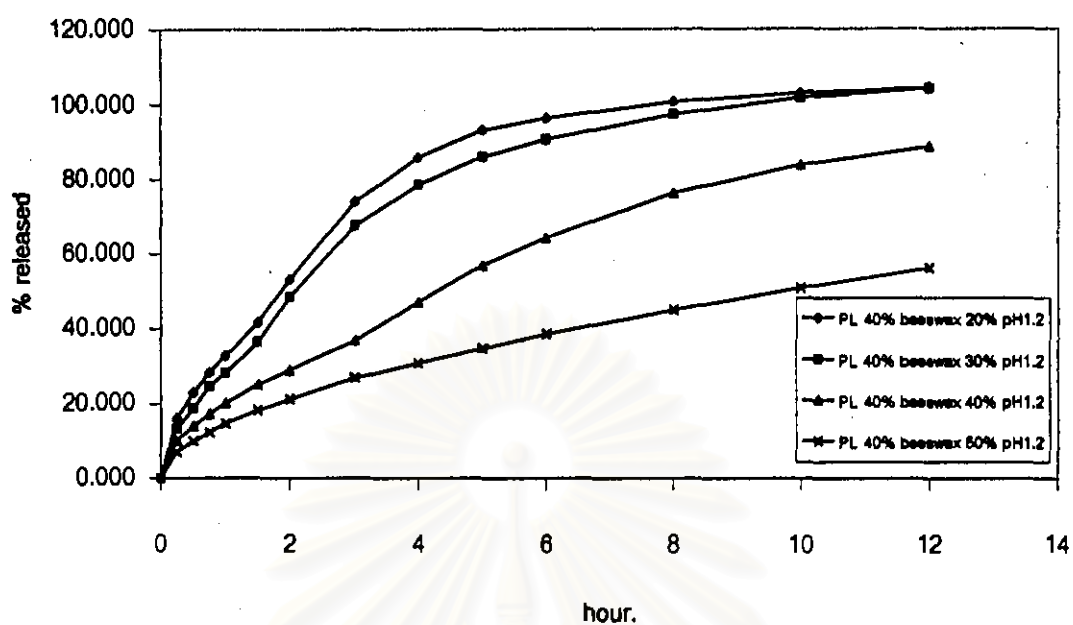
Figure 61   The release profiles of tablets containing matrix pellets of series of beeswax in 0.1 N HCl pH1.2.
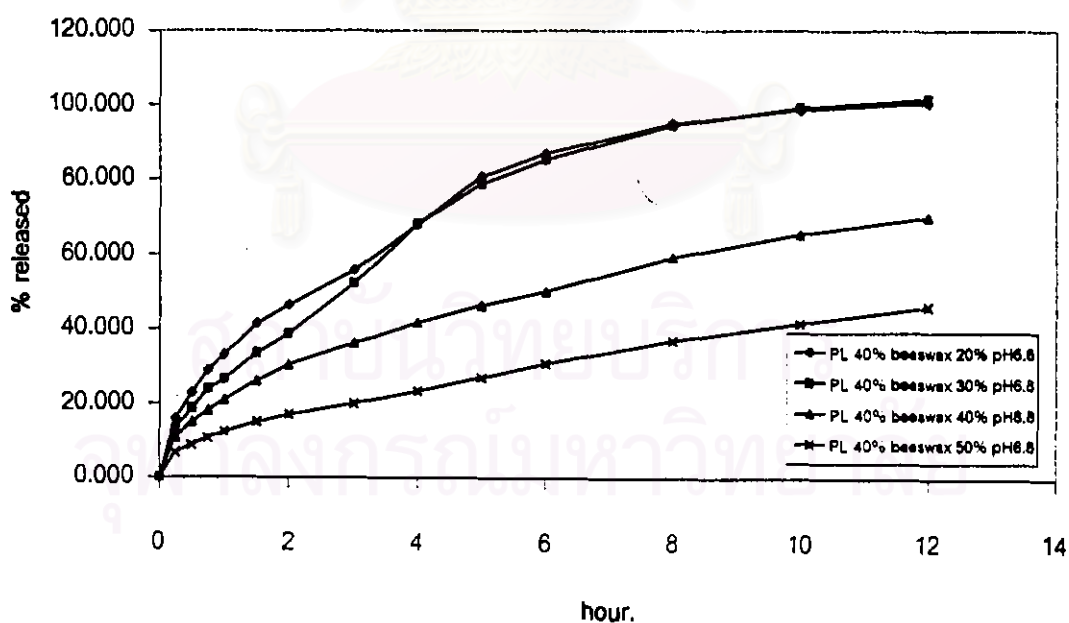

Figure 62   The release profiles of tablets containing matrix pellets of series of beeswax in phosphate buffer pH 6.8.
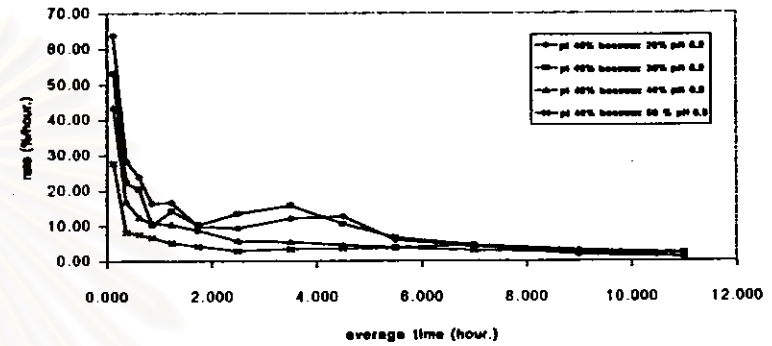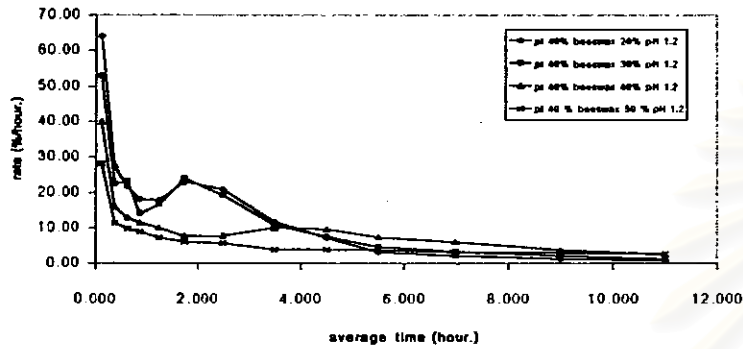
Figure 63   The release rate profiles of propranolol HCl matrix tablet containing various amount of beeswax at different medium.
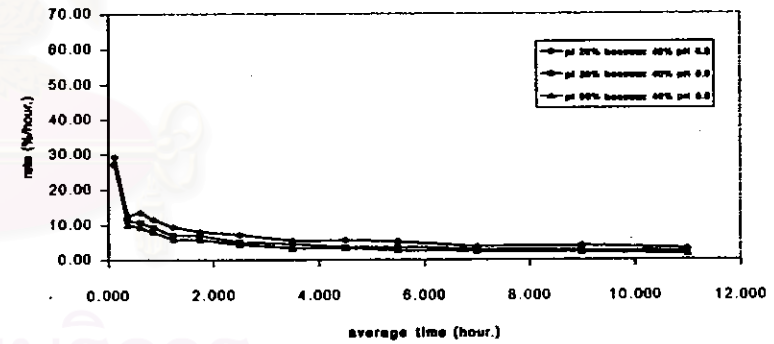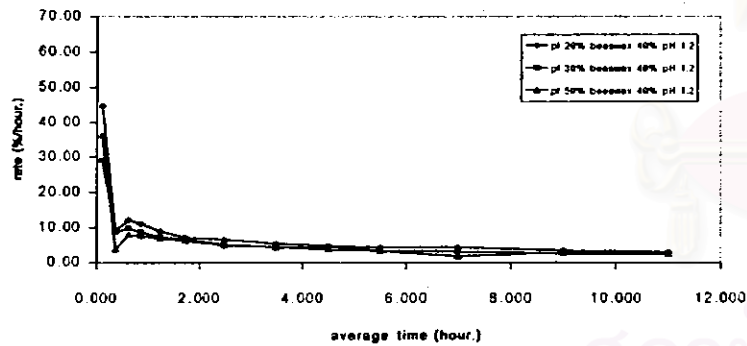

Figure 64   The release rate profiles of propranolol HCl matrix tablet produced by beeswax at 40 % with various amount of propranolol HCl at different medium.

dissolution rate. The concentration of wax in the formulation was the determining factor in controlling release rate of drug. Moreover, the smoother release rate was obtained when using high percentage of wax in the formulation. Decreasing in release rate was also found when increasing loading dose in the formulation. The results of other commonly used waxes were similar to beeswax matrix tablet. But the graphs were not shown here.

The dissolution patterns of matrix tablets prepared from various amount of propranolol HCl with 40 % of beeswax are depicted in Figure 65. (Table 52, Appendix B)

The 40 % beeswax matrix tablet preparation using low percent of propranolol HCl showed higher release rate than those using high percent of propranolol HCl and presented the percent release of 69.84 %, 54.43 %, 45.30 % at 12 [th] hour from the formulation using propranolol HCl of 20, 30 50 %, respectively.

3.2 The formulations containing carnauba wax.

The release profile of tablets containing 40 % of carnauba wax with different amount of propranolol HCl was shown in Figure 66.

With 20 and 30 % of propranolol HCl in the formulations, the drug completely dissolved within 4 – 6 hours in 0.1 N HCl and phosphate buffer pH 6.8. In addition, the release profile of those ratio exhibited into two parts as mention above. Increasing propranolol HCl from 30 to 50 % decreased the release rate of propranolol HCl significantly. The release rate of propranolol HCl from formulation containing carnauba wax in the case of loading dose was still affected by pH of dissolution medium only at highest percent of propranolol HCl.
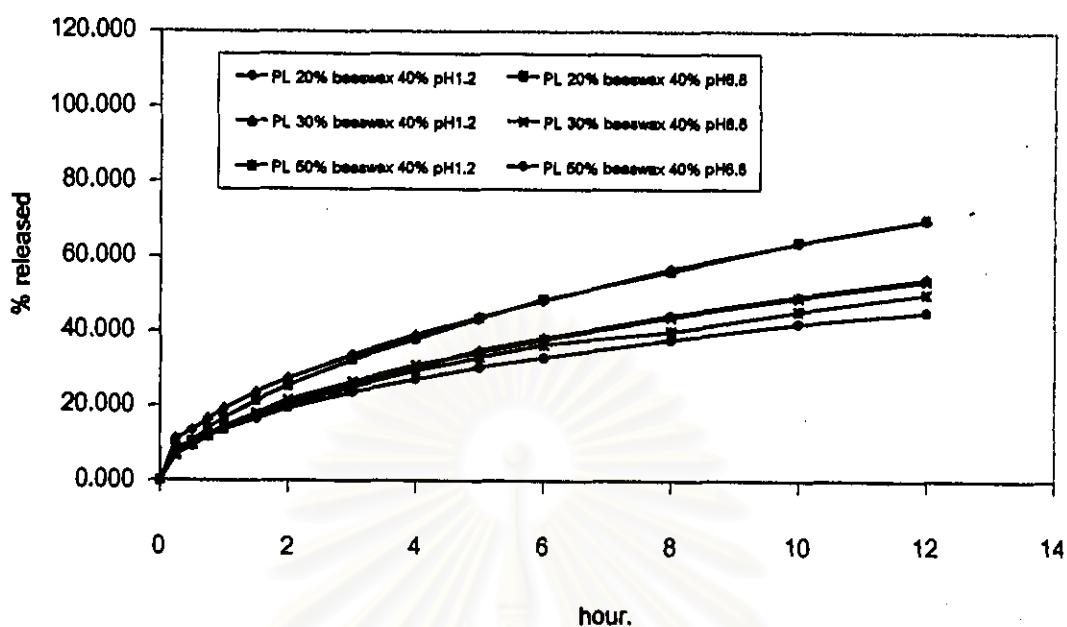
Figure 65   The release profiles of tablets containing 40 % of bees wax with different loading dose in 0.1 N HCl pH 1.2 and phosphate buffer pH 6.8.
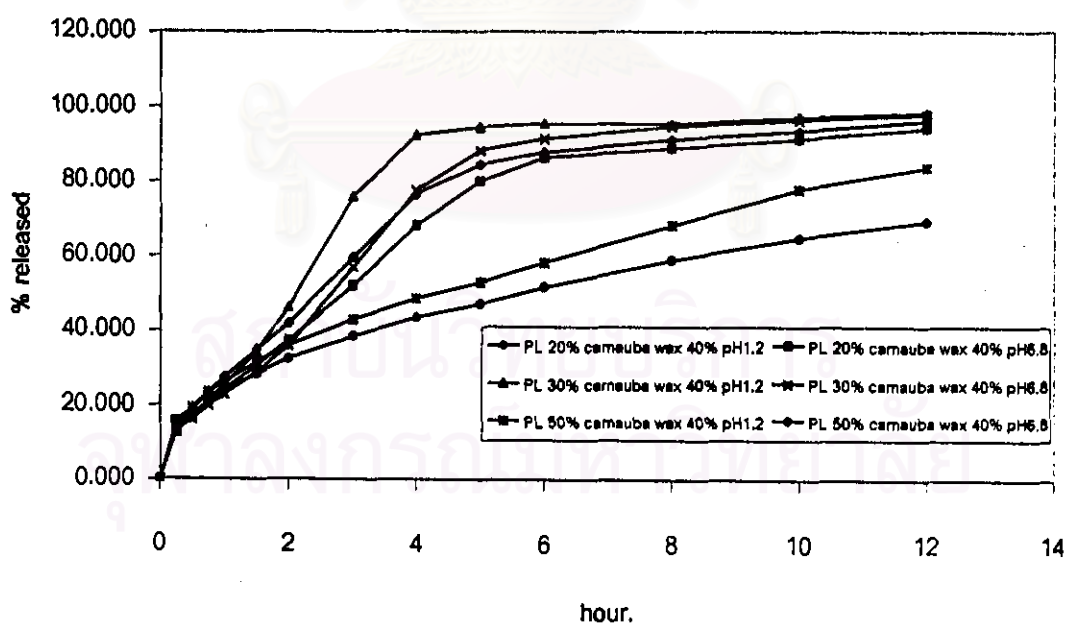

Figure 66   The release profiles of tablets containing 40 % of carnauba wax with different loading dose in 0.1 N HCl pH 1.2 and phosphate buffer pH 6.8.
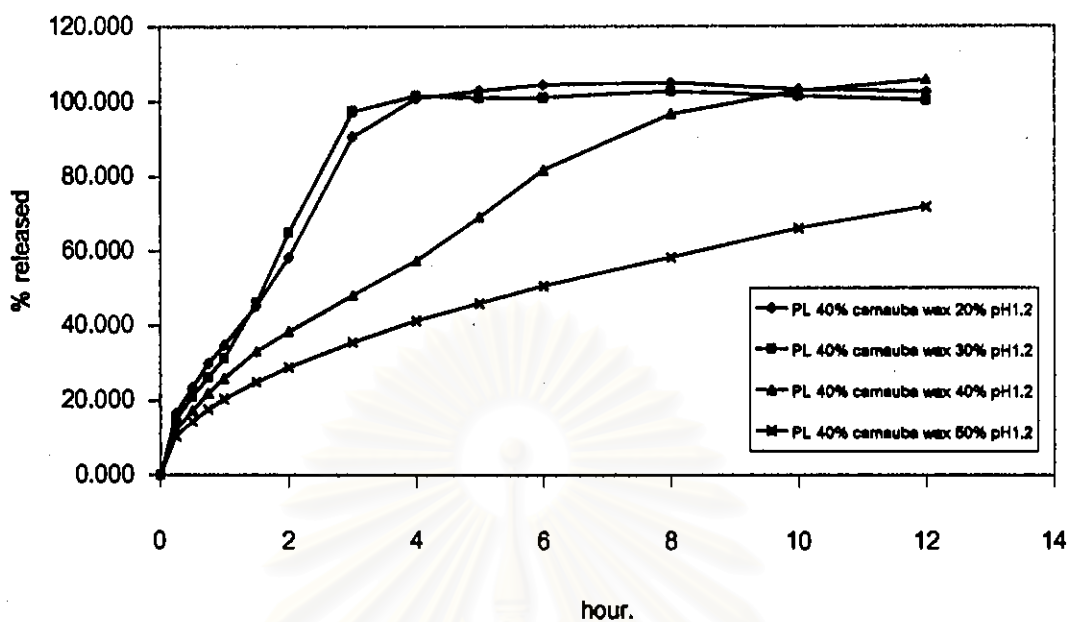
Figure 67   The release profiles of tablets containing matrix pellets of series of carnauba wax in 0.1 N HCl pH1.2.
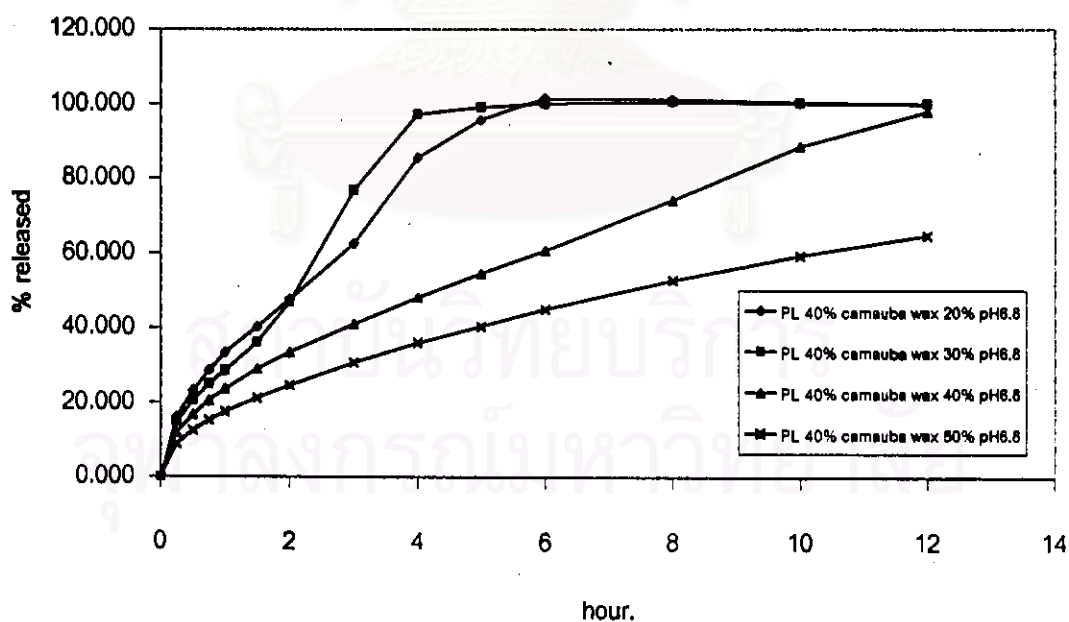

Figure 68   The release profiles of tablets containing matrix pellets of series of carnauba wax in phosphate buffer pH 6.8.

The dissolution profiles of the formulations containing 40 % of propranolol HCl with various amount of carnauba wax in 0.1 N HCl and phosphate buffer pH 6.8 are presented in Figures 67-68 (Table 46, Appendix B).

The propranolol HCl-carnauba wax matrix containing 20 % and 30 % of wax showed the release profile into two parts. The release rate decreased with time within first two hours and showed faster release than those after the 2nd hour of dissolution test. The percent release of both formulations came to the plateau state within 4-5 hours. However, when increasing the percent of carnauba wax in the formulation. The release rate was decreased and the release profile became smoother than the formulation containing low percent of carnauba wax, especially 50 % of carnauba wax in the formulation. The percent release of formulations prepared from 50 % of carnauba wax at 12th hr in 0.1 N HCl pH 1.2 and phosphate buffer were 71.93 and 64.70 %, respectively.

The release of propranolol HCl from matrix tablet containing carnauba wax was affected by pH of dissolution medium as depicted in Figures 67-68. The release rate of the formulation decreased with time increased. But the decreased of release rate was fluctuated with 20 and 30 % of carnauba wax. The release rate in 0.1 N HCl was higher than the release rate in buffer pH 6.8.

3.3 The formulations containing glycerylmonostearate.

As shown in Figures 69 and 70, (Table 47, Appendix B) the release profiles of the matrix tablet formulations prepared from 40 % of propranolol HCl with GMS at various ratio in 0.1 N HCl pH 1.2 was compared to the same formulation in phosphate buffer pH 6.8.
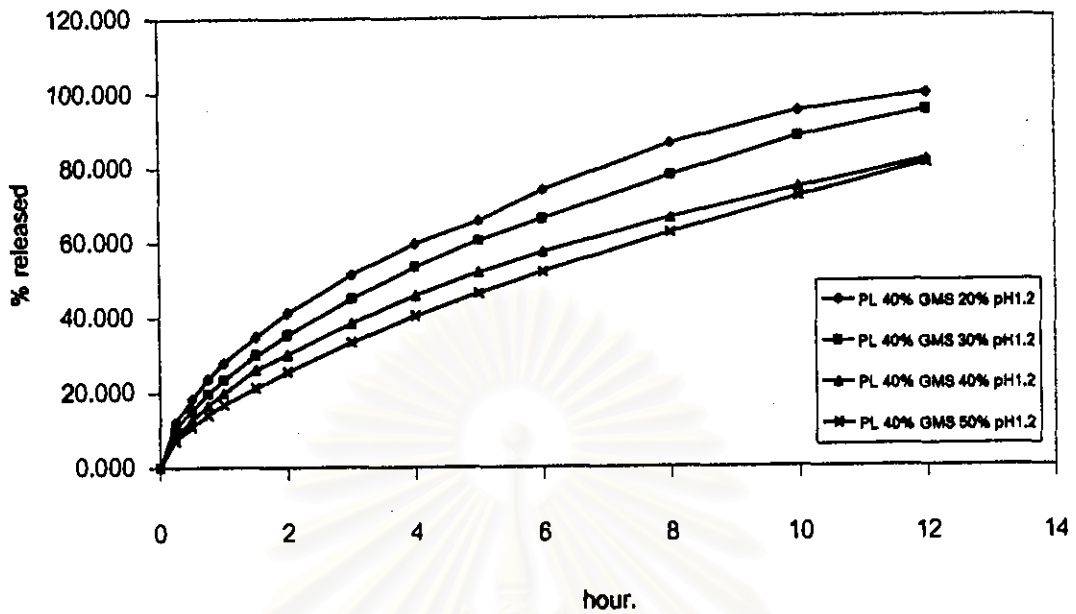
Figure 69   The release profiles of tablets containing matrix pellets of series of glyceryl monostearate in 0.1 N HCl pH 1.2.
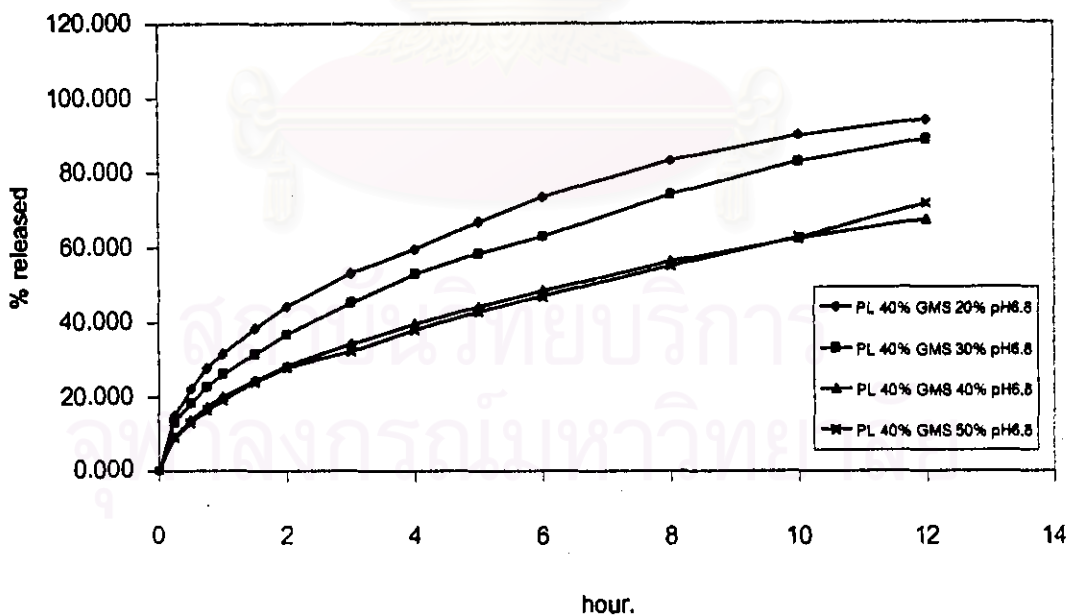

Figure 70   The release profiles of tablets containing matrix pellets of series of glyceryl monostearate in phosphate buffer pH 6.8.

The higher amount of GMS in the formulation showed the lesser percent drug release from the matrix tablet. All of the series of GMS exhibited smooth release profile.

The release of propranolol HCl from formulations containing all levels of GMS were affected by pH of dissolution medium as displayed in Figures 69-70. The release rate in 0.1 N HCl was slightly faster than the release rate in buffer pH 6.8. The release rate of these formulations decreased with the time increased.

The dissolution patterns of wax matrix tablet prepared from various amount of GMS in 0.1 N HCl were similar to those in phosphate buffer pH 6.8. Those results are exhibited in Figures 69-70 (Table 47, Appendix B).

All formulations in medium pH 1.2 showed the higher percent release than those in medium pH 6.8. When increasing the amount of propranolol HCl in the formulation, the lesser the release rate was obtained. Thus, it could indicated that the release of propranolol HCl from these formulations were affected by pH of dissolution medium as depicted in Figure 71. The release rate of these formulations decreased with the time increased.

3.4 The formulations containing Lubritab®.

The dissolution results of the controlled release formulations of 40 % of Lubritab® and various amounts of propranolol HCl are depicted in Figure 72 (Table 55, Appendix B).
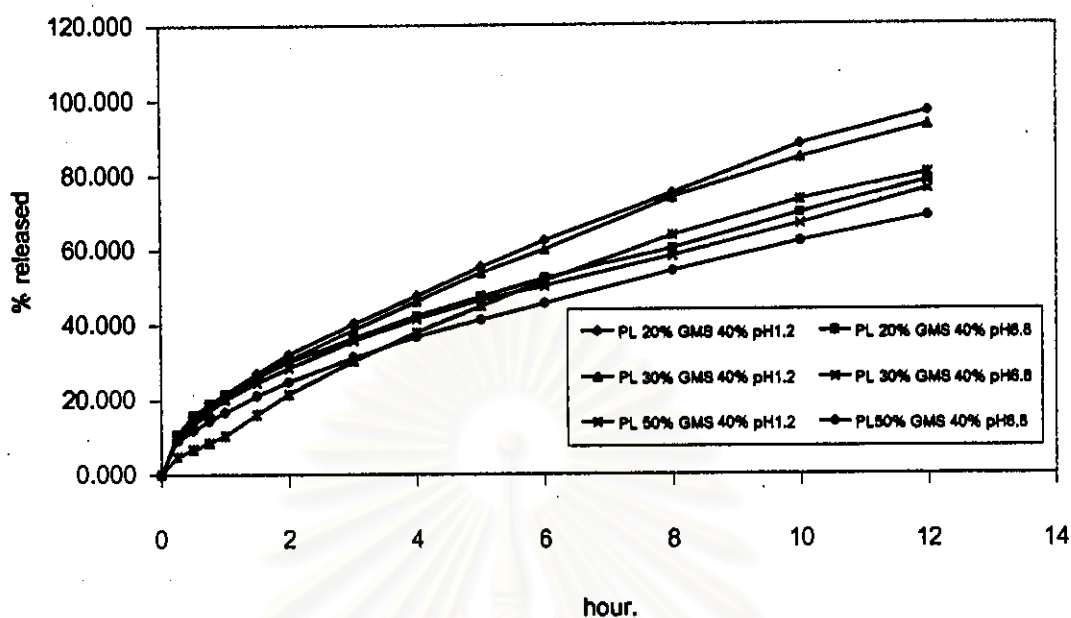
Figure 71   The release profiles of tablets containing 40 % of glycerylmonostearate with different loading dose in 0.1 N HCl pH 1.2 and phosphate buffer pH 6.8.
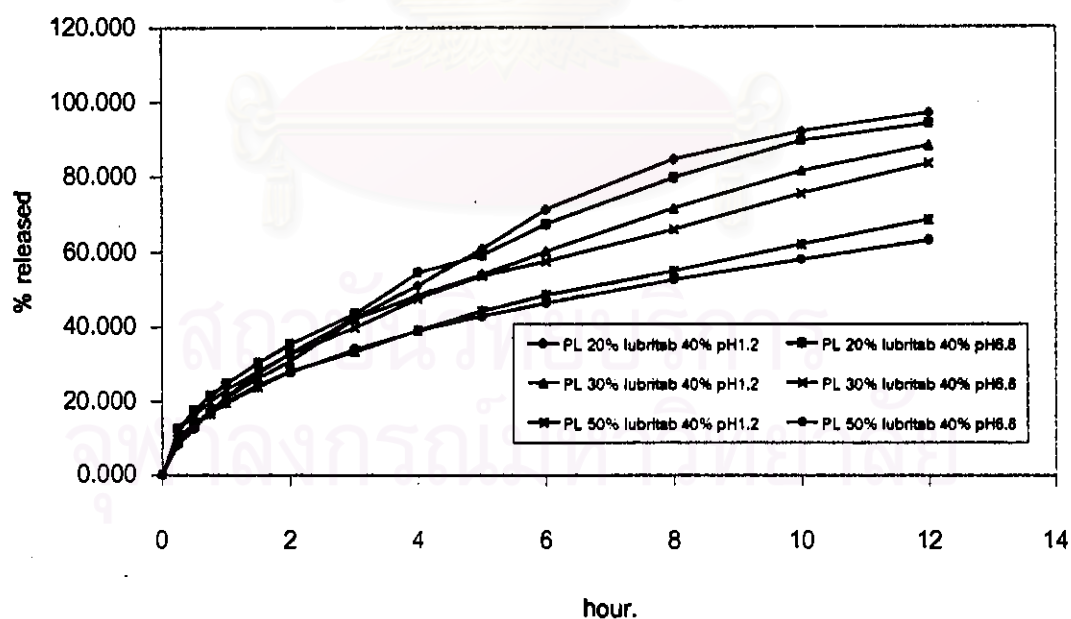

Figure 72   The release profiles of tablets containing 40 % of Lubritab® with different loading dose in 0.1 N HCl pH 1.2 and phosphate buffer pH 6.8.

The highest percent released was obtained from the formulations containing 20 % propranolol HCl. The lowest percent released was obtained from the formulation containing 50 % propranolol HCl.

These formulations containing propranolol HCl-Lubritab®-lactose-Avicel PH101® but the amount of wax and the drug in each formulation was adjusted differently in order to modify the release rate. Those release profiles are illustrated in Figure 73-74. (Table 48, Appendix B).

Lubritab® could decrease the percent released of the matrix tablet, especially when the high amount was used. When the amount of Lubritab® was increased, the propranolol HCl release was decreased. The faster release rate was observed from the matrix tablet containing only 20 or 30 % of Lubritab®. The release of those formulations were completed in 6 and 8 hours in 0.1 N HCl, 8 and 12 hours in phosphate buffer at pH 6.8, respectively. After that time, the release profile came to the plateau state. However, the percent release of the formulations containing Lubritab® at 40 and 50 % both in medium pH 1.2 and pH 6.8 gradually increased to 85.69 and 73.62 %, 57.98 and 51.07 %, respectively.

The release of propranolol HCl from formulations at all concentrations of Lubritab® were affected by type of dissolution medium as shown in Figures 73-74. The release rate of these formulations decreased with the time increased. The release rate in buffer pH 6.8 was slower than the release rate in 0.1 N HCl.

There was no significant difference in release patterns from the formulations produced from any amount of propranolol HCl. But the release rate of these formulations decreased with the time increased. The release of propranolol HCl

Figure 73   The release profiles of tablets containing matrix pellets of series of Lubritab® in 0.1 N HCl pH 1.2.

Figure 74   The release profiles of tablets containing matrix pellets of series of Lubritab® in phosphate buffer pH 6.8.
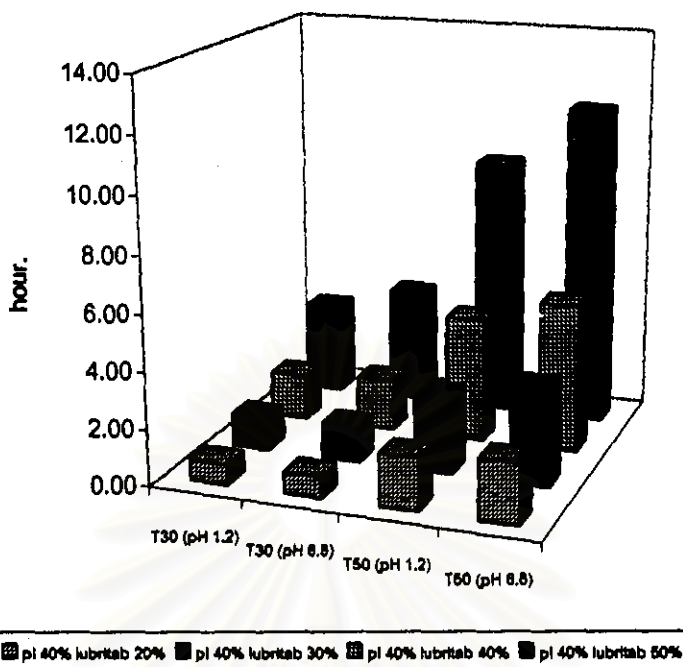
Figure 75   Time to be used for releasing propranolol HCl at 30 and 50 % from formulation containing 40 % of propranolol HCl with various amount of Lubritab® in different medium.
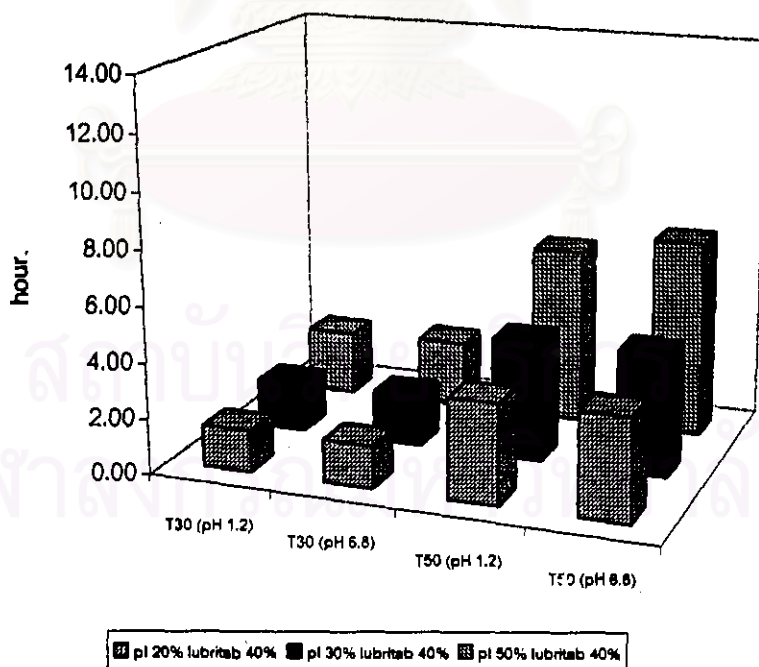
Figure 76   Time to be used for releasing propranolol HCl at 30 and 50 % from formulation containing 40 % of Lubritab® with various amount of propranolol HCl in different medium.

form these formulations were affected by dissolution medium. The release rate in 0.1 N HCl was slightly faster than the release rate in phosphate buffer pH 6.8.

Time period for 30% and 50% release of propranolol HCl from different wax contents and loading doses are presented in Figures 75-76. From the result, when increasing wax content or loading dose in the formulation, the longer time were required to release the same amount of drug release in percent. Slightly longer time were spent for the same amount of drug release when the formulation were in phosphate buffer pH 6.8. Time period for 30 % and 50 % release of drug from other kinds of commonly used waxes were similar to the formulation containing Lubritab®.

3.5 The formulations containing Compritol®.

The release profiles of the wax matrix tablets containing 40 % of propranolol HCl with various amount of Compritol® both in 0.1 N HCl pH 1.2 and phosphate buffer pH 6.8 are displayed in Figures 77-78 (Table 49, Appendix B).

It was evident that the higher in percent released of propranolol HCl was occurred with decreasing the amount of Compritol®. At the 12th hour of the dissolution test, the formulation that used Compritol® from 20 to 50 % exhibited the percent release of 98.60, 79.29, 48.96, 31.52 % in 0.1 N HCl pH 1.2 and 89.01, 64.96, 45.78, 33.53 % in phosphate buffer pH 6.8, respectively. All of the formulations containing Compritol® could give smooth release profile. In addition, Compritol® showed satisfactory controlled release profiles although the low amount was used.

The releases of propranolol HCl from formulations containing Compritol® were affected by dissolution medium as depicted in Figures 77-78. The
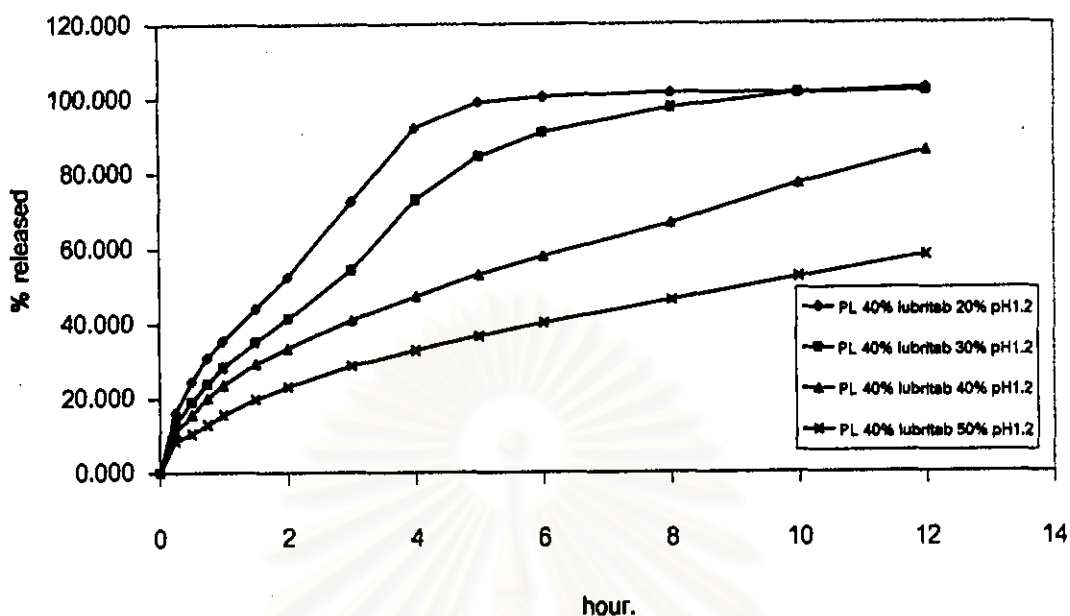
Figure 77   The release profiles of tablets containing matrix pellets of series of Compritol® in 0.1 N HCl pH 1.2.
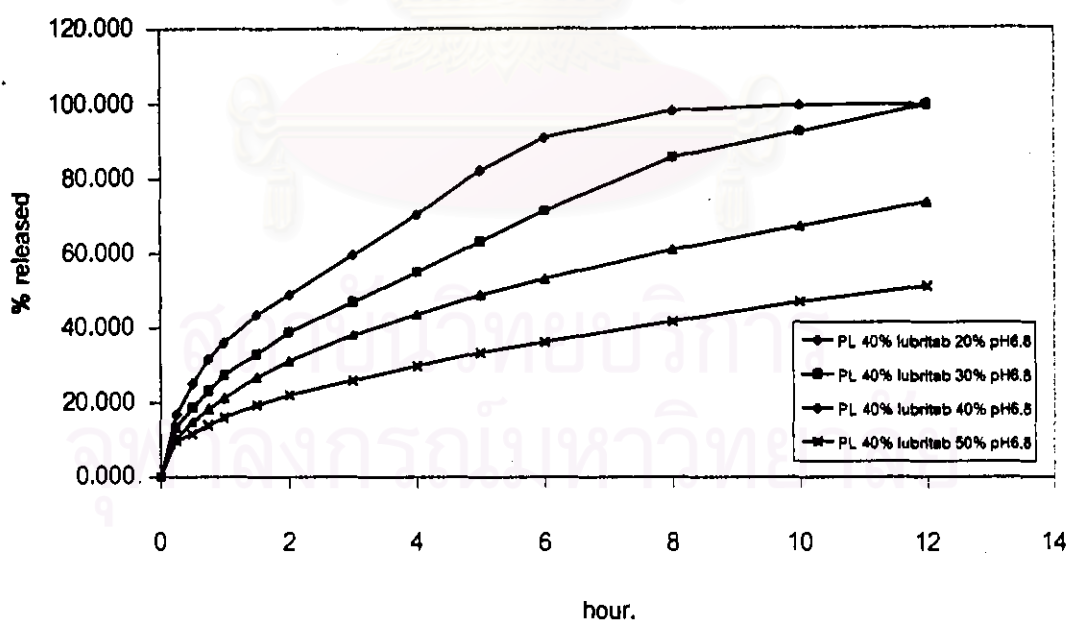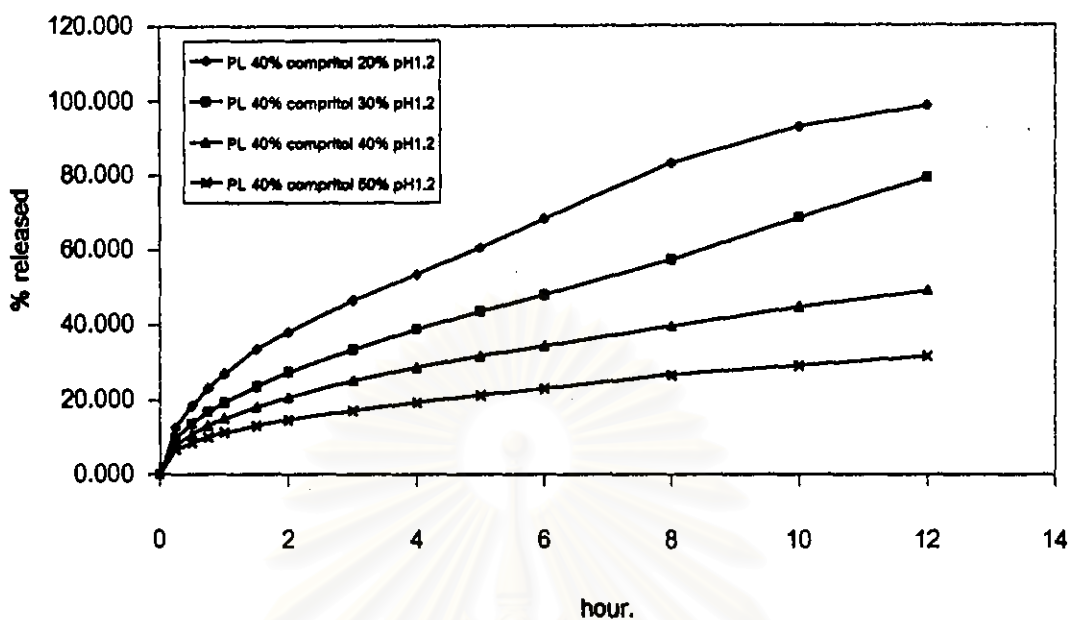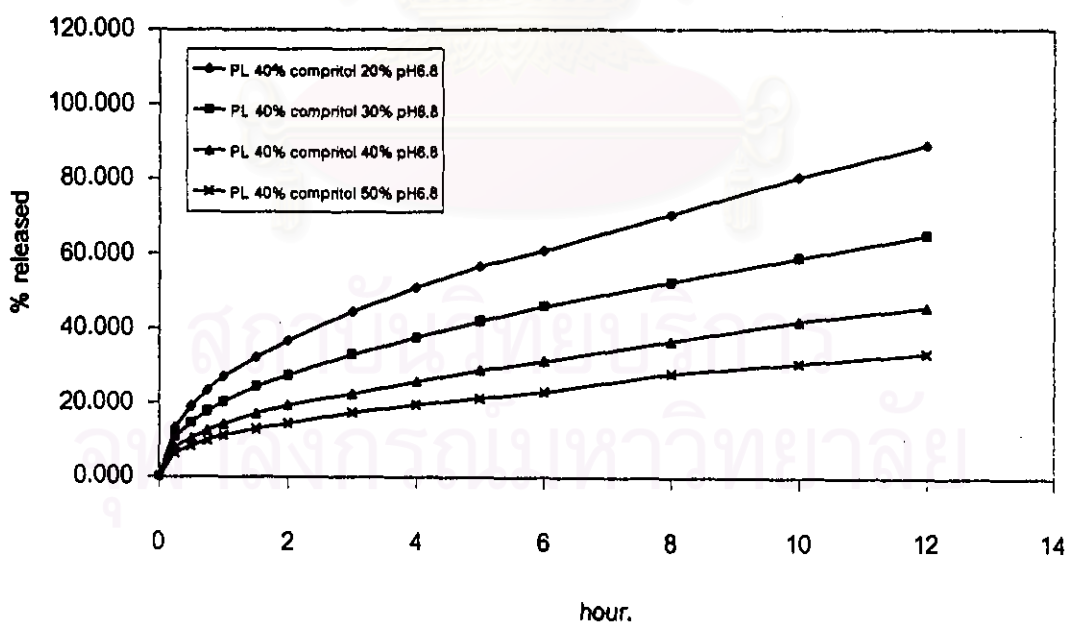

Figure 78   The release profiles of tablets containing matrix pellets of series of Compritol® in phosphate buffer pH 6.8.

release rate of the formulations decreased as the time increased. The release rate in 0.1 N HCl was faster than the release rate in phosphate buffer pH 6.8.

The release data and released profile of propranolol HCl from tablets containing Compritol® 40 % with different loading dose are presented in Figure 83 (Table 56, Appendix B).

The faster release rates were observed from the formulations containing 20 % of propranolol HCl followed by those containing 30 % of propranolol HCl. Whereas the formulation containing 50 % of propranolol HCl showed the lowest drug release of 38.81 % at the 12th hour. The formulation using 40 % of Compritol® with 20 % of propranolol HCl could control the drug release within limit of USP in 12 hours. The release of propranolol HCl from formulations with different loading dose were also affected by dissolution medium. The release rate in 0.1 N HCl was slightly faster than the release rate in buffer pH 6.8. The release rate of these formulations decreased with the time increased as depicted in Figures 79-80.

Time period for releasing propranolol HCl tablet with Compritol® from different wax content and loading dose are shown in Figures 81-82.

Time period for the same percent drug released in acidic state were slightly lower than basic state in all formulations. T_{50} of those formulations containing 50 % of propranolol HCl with 40 % of Compritol® could not be determined from the release profile due to the release lower than 50 % at 12 hours. Longer time period was found for the same percent drug released when increasing wax content or loading dose in the formulations. The other kinds of Gattefosse's wax also give the similar result.
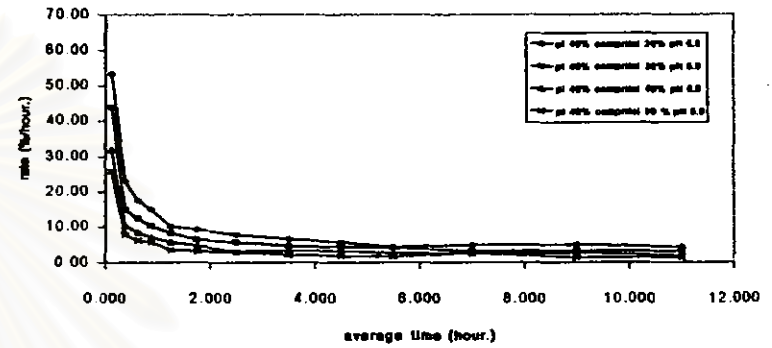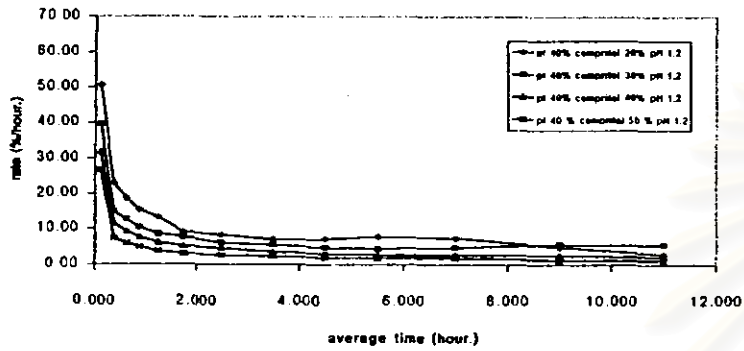
Figure 79   The release rate profiles of propranolol HCl matrix tablet containing various amount of Compritol® at different medium.
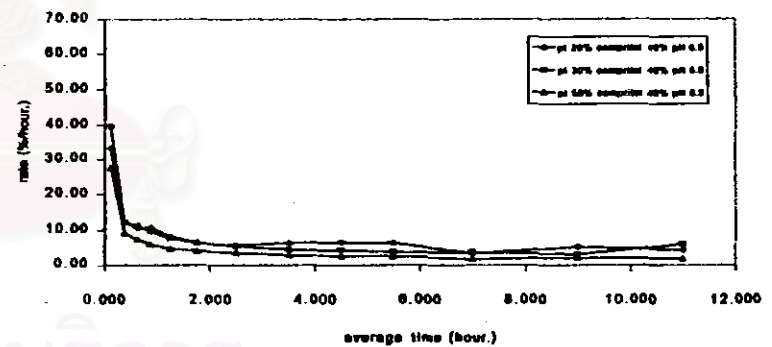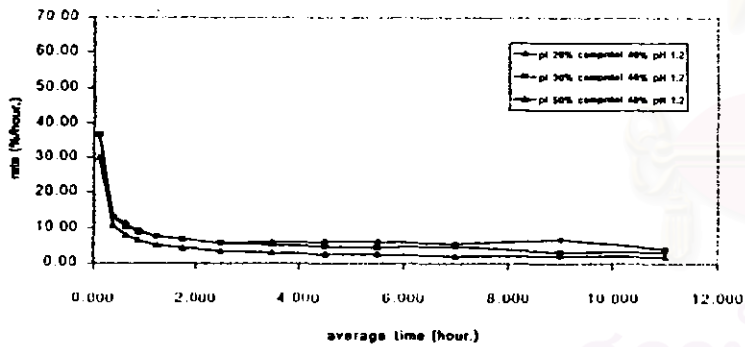
Figure 80   The release rate profiles of propranolol HCl matrix tablet produced by Compritol® at 40 % with various amount of propranolol HCl at different medium.
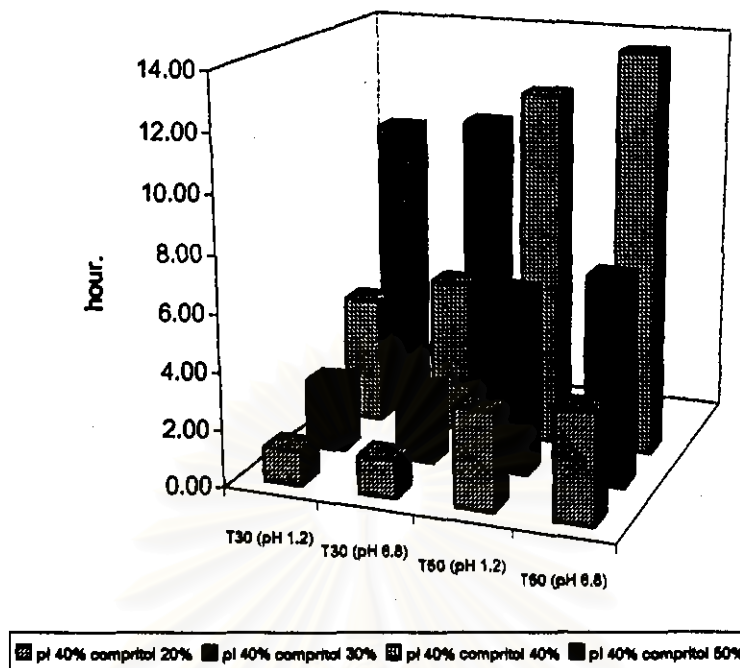
Figure 81   Time to be used for releasing propranolol HCl at 30 and 50 % from formulation containing 40 % of propranolol HCl with various amount of Compritol® in different medium.
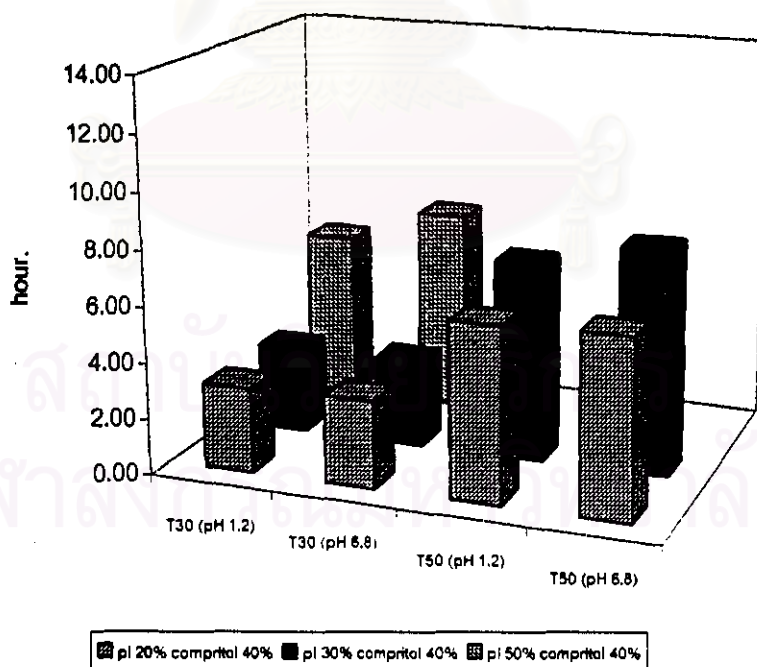
Figure 82   Time to be used for releasing propranolol HCl at 30 and 50 % from formulation containing 40 % of Compritol® with various amount of propranolol HCl in different medium.

3.6 The formulations containing Precirol®.

The dissolution profiles of matrix tablet prepared by 40 % of Precirol® at various ratios of propranolol HCl both in medium pH 1.2 and pH 6.8 were illustrated in Figure 84 (Table 57, Appendix B), respectively.

The release profiles were exhibited the same release pattern as formulations using Compritol®. The higher amount of propranolol HCl in these formulations exhibited the lower percent released.

The release of propranolol HCl from formulations containing Precirol® with different loading dose were affected by dissolution medium. The release rate in 0.1 N HCl was faster than the release rate in buffer pH 6.8.

The drug release data of propranolol HCl from the formulations containing Precirol® at various contents are listed in Table 50 (Appendix B) and drug release profiles in 0.1 N HCl and phosphate buffer pH 6.8 are shown in Figures 85-86.

The percent of drug release at the 12th hour was decreased when the proportion of Precirol® in the formulation was increased. No significantly different release pattern was detected from all series of Precirol® in wax matrix tablet formulations. There was only formulation using 30 % of Precirol® in phosphate buffers pH 6.8 could control the release profile within the limit of USP in 12 hours. The drug release of the other formulations were higher and lower than this limit. The releases of propranolol HCl from various content of Precirol® formulations were affected by dissolution medium. The release rate of these tablet decreased as the time increased. The amount of propranolol HCl released in 0.1 N HCl was higher than in phosphate buffer pH 6.8.

Figure 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.
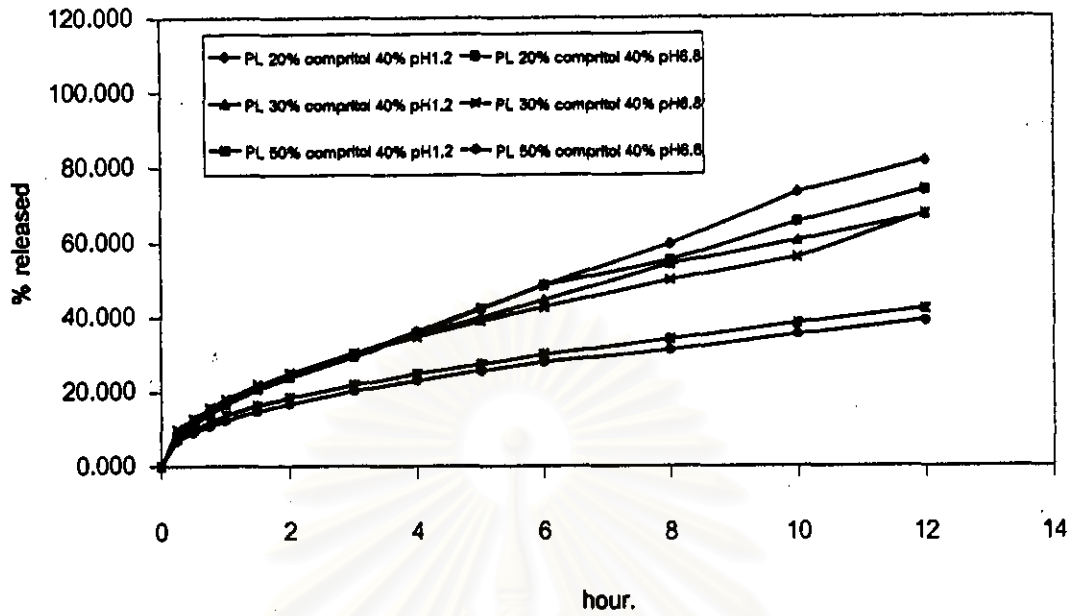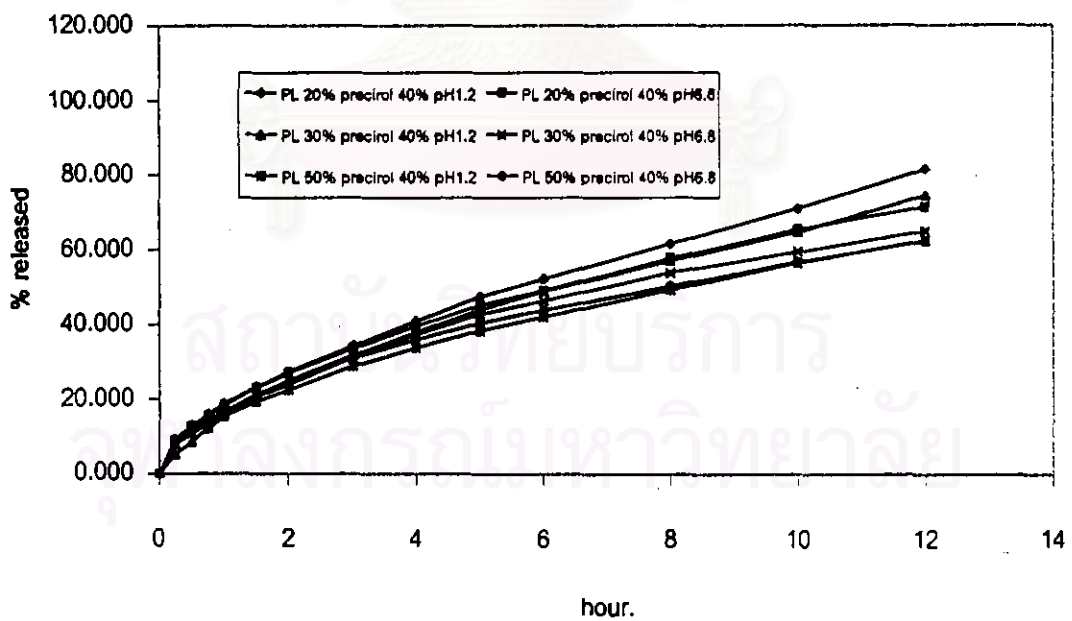

Figure 84   The release profiles of tablets containing 40 % of Precirol® with different loading dose in 0.1 N HCl pH 1.2 and phosphate buffer pH 6.8.

Figure 85   The release profiles of tablets containing matrix pellets of series of
Precirol® in 0.1 N HCl pH 1.2.

Figure 86   The release profiles of tablets containing matrix pellets of series of
Precirol® in phosphate buffer pH 6.8.

3.7 The formulations containing Gelucire®.

The release profiles of the matrix tablet prepared from 40 % of propranolol HCl with various amount of Gelucire® in 0.1 N HCl was compared to the same formulation in buffer pH 6.8. Those release profiles are illustrated in Figures 87-88 (Table 51, Appendix B).

The highest percent released was obtained from the formulations used 30 % of Gelucire® whereas the lowest percent released was obtained from the formulations used 50 % of Gelucire®. At low content of Gelucire® did not show complete smooth release profile. The release rate of these formulation decreased as the time increased. The dissolution medium affected the release rate but did not affect the pattern of drug release. The release rate in 0.1 N HCl was faster than the release rate in buffer pH 6.8.

The dissolution results of the controlled release formulations of Gelucire® at 40 % and various amount of propranolol HCl are depicted in Figure 89 (Table 58, Appendix B).

The propranolol HCl- Gelucire® matrix was swell especially the formulation with low content of propranolol HCl but did not disintegrate into particle during dissolution test. The drug release rate decreased with the time increased in the first two hours after that percent release increased very fast and came to the plateau state within 6th hour. This pattern was found in the formulations containing propranolol HCl 20 and 30 %. Except when 50 % of propranolol HCl was used in phosphate buffer pH 6.8, some delay released was detected. There was no clearly correlation of the drug release with the different of pH medium.
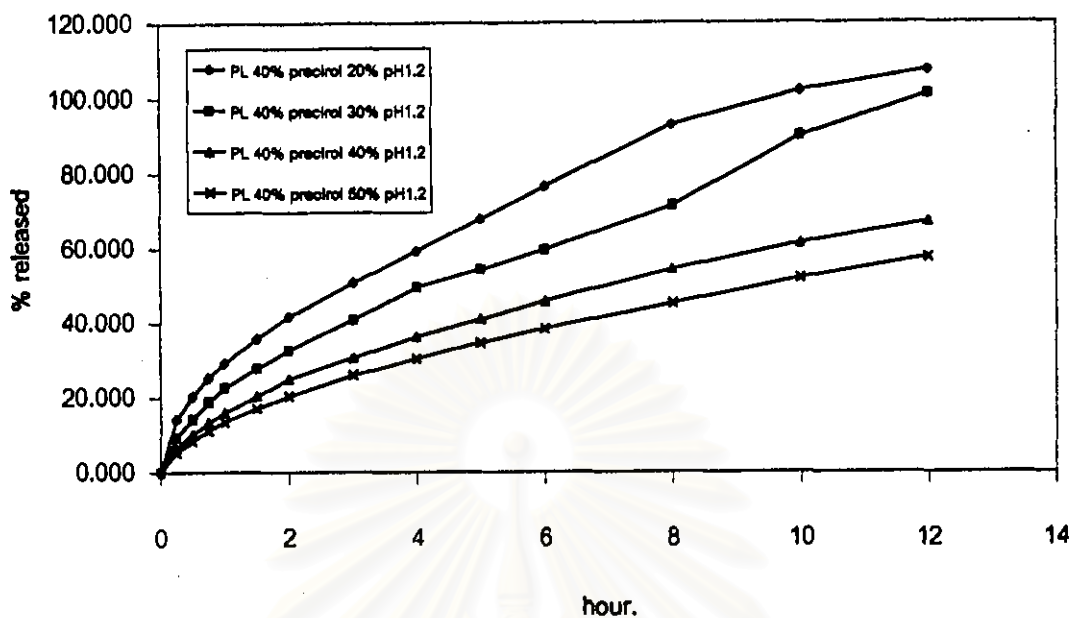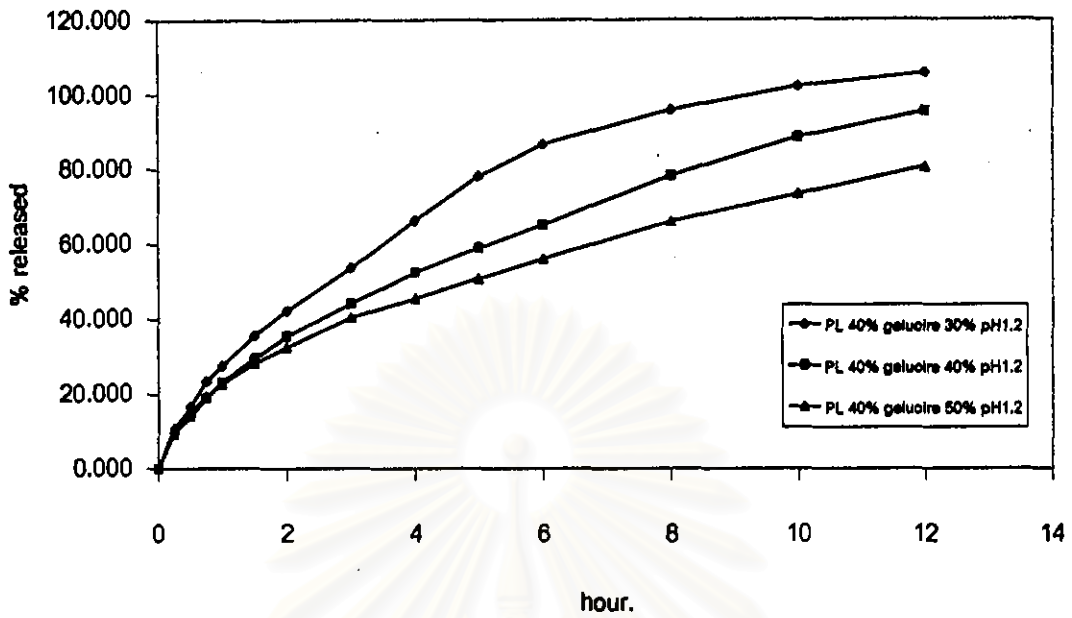
Figure 87   The release profiles of tablets containing matrix pellets of series of Gelucire® in 0.1 N HCl pH 1.2.
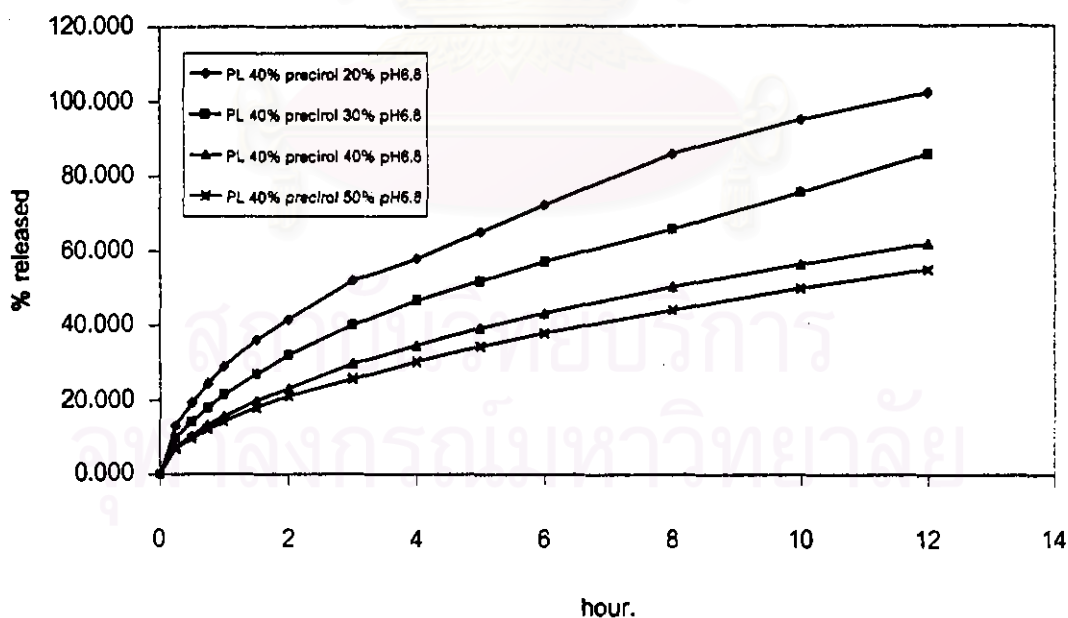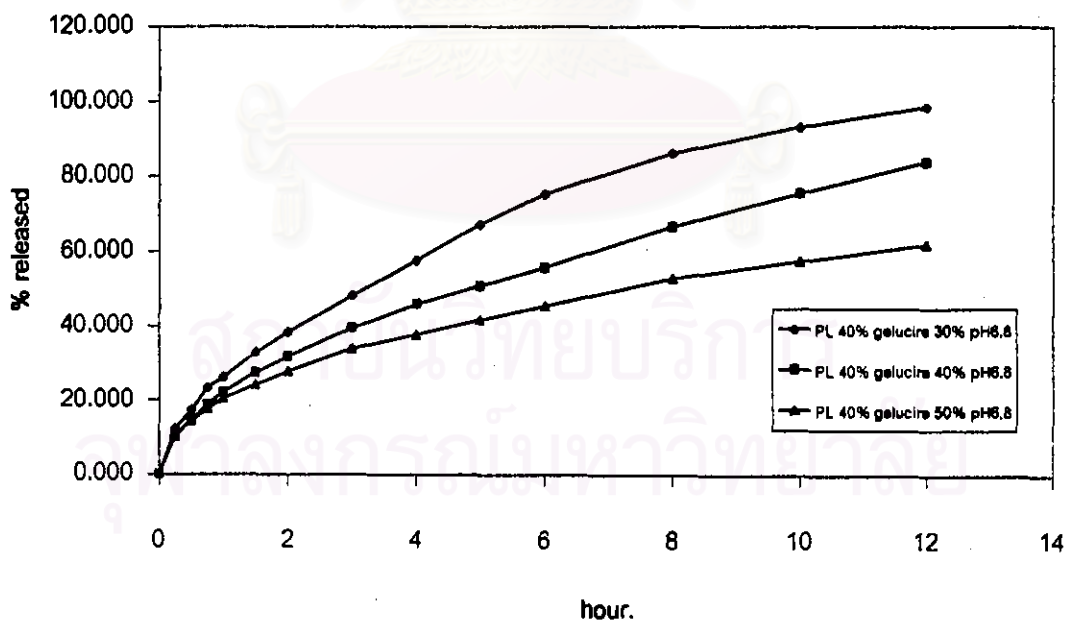

Figure 88   The release profiles of tablets containing matrix pellets of series of Gelucire® in phosphate buffer pH 6.8.
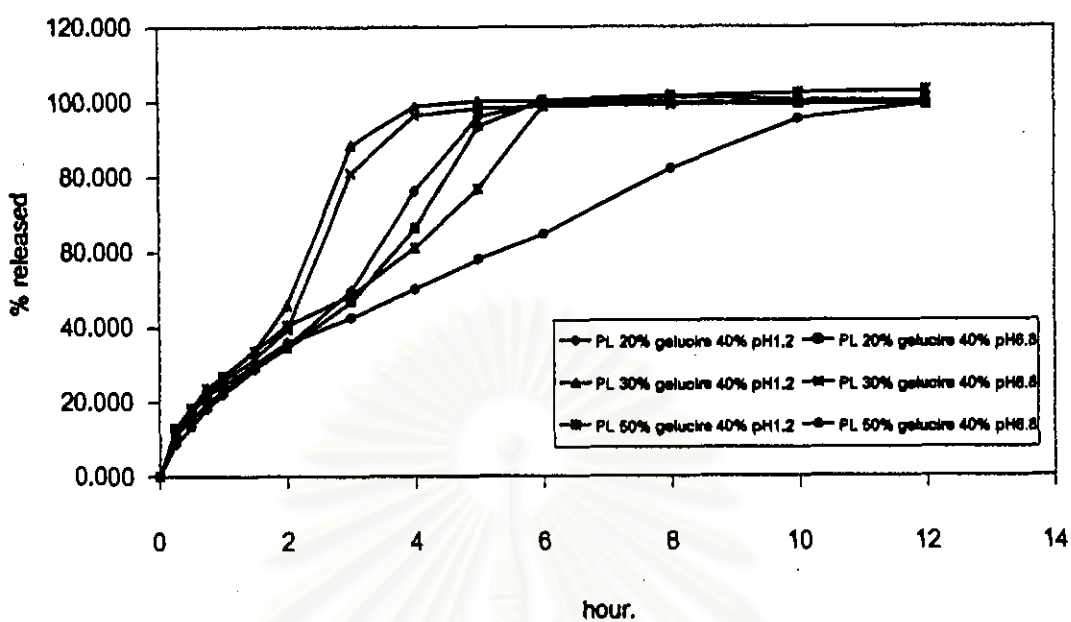
Figure 89   The release profiles of tablets containing Gelucire® 40 % with different loading dose in 0.1 N HCl pH 1.2 and phosphate buffer pH 6.8.

4. Sustained Release Power of Waxes.

The dissolution data and drug released profile of wax matrix tablets containing each wax at 50 % and propranolol HCl at 40 % in 0.1 N HCl pH 1.2 and phosphate buffer pH 6.8 are illustrated in Figures 90-91.

To determine the sustained release power of waxes, highest percent of each waxes in the formulation are chosen to avoid the other factor that can affect the drug release. The release of propranolol HCl were affected by the dissolution medium. The release rate in 0.1 N HCl were slightly faster than the release rate in phosphate buffer pH 6.8. The release rate of these formulations decreased with the time increased. In this present study, the rank order of sustained release power of waxes in 0.1 N HCl pH 1.2 was Compritol® > beeswax ≈ Lubritab® ≈ Precirol® > carnauba wax > GMS > Gelucire®. Whereas the ranked order of sustained release power of waxes in phosphate buffer pH 6.8 was as follows: Sustained release power of waxes with Compritol® > beeswax > Lubritab® > Precirol® > Gelucire® ≈ carnauba wax > GMS.

5. Comparative Studies with Commercial Product.

The dissolution data and drug released profile of commercial product, Inderal® 160 pellets, are presented in Table 30 (Appendix B) and Figures 92-93, respectively. The difference of release profiles of Inderal® in acid and alkali medium was detected. The release of propranolol HCl from Inderal® was affected by dissolution medium. The release profile of Inderal® in phosphate buffer pH 6.8 was faster than that in 0.1 N HCl after 2 hours of dissolution test. The percentage of the drug released at the 12th hour in acidic and basic state were 66.80 and 71.70 %, respectively. The release rate of this pellet decreased with time increased.
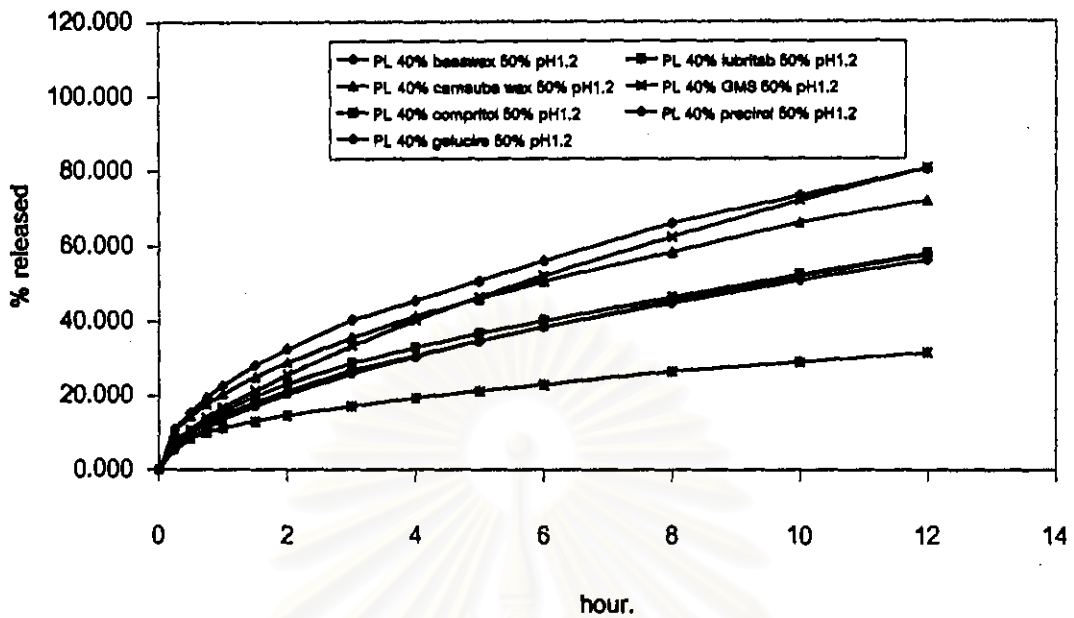
Figure 90   The sustained release power of various kind of waxes from matrix tablet in 0.1 N HCl pH 1.2.
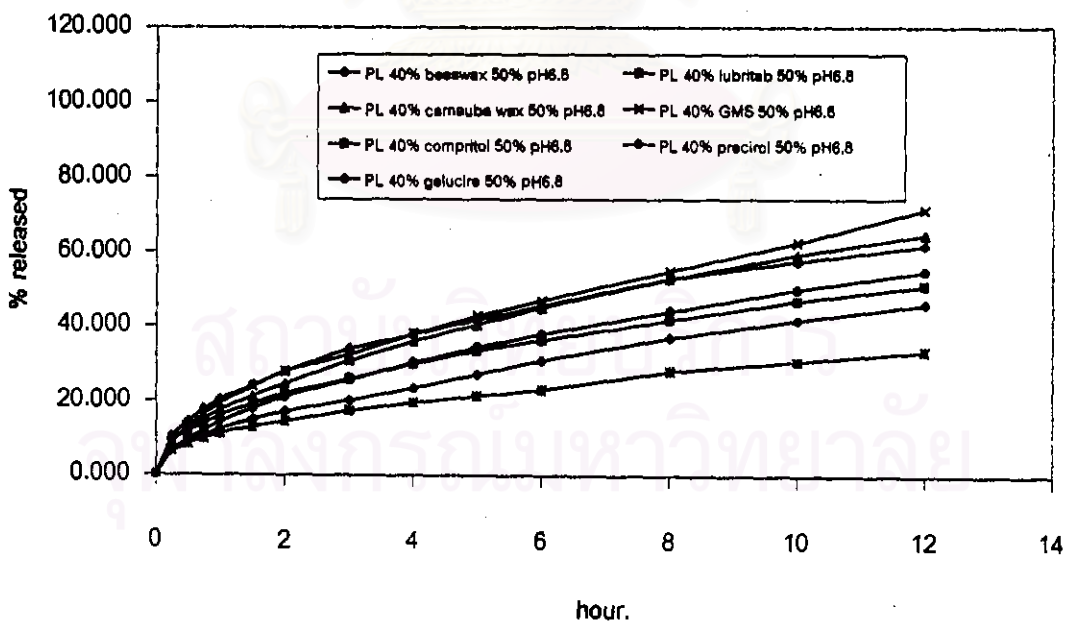
Figure 91   The sustained release power of various kind of waxes from matrix tablet in phosphate buffer pH 6.8.

The release profile of Inderal® and tablet containing 40 % Precirol® which compressed in tablet using hydraulic press and single punch tabletting machine are presented in Figure 92.

No significant difference was found from the formulation containing 40 % of Precirol® that prepared by different compression machine. Slightly lower drug release of the pellets was obtained from Inderal® in the first 2 – 3 hours when compared to the matrix tablet produced from 40 % of Precirol®. After that time, Inderal® showed slightly faster drug release than those formulations.

The percent drug released from Inderal® and matrix tablet containing 40 % of Precriol® prepared by single punch tabletting machine in pH change method are illustrated in Figure 93.

Table 17   Physical properties of wax matrix tablet containing 40 % of propranolol HCl with 40 % of Precirol® prepared from single punch tabletting machine.

Average weight (mg.)	400.005
Weight variation (%)	-4.23%, +4.08%
Hardness *(kp)	15.23 (1.53)
Thickness * (mm.)	4.96 (0.12)
Friability (%)	0.13
Disintegration time (hr)	> 2 hr

* Average from six determination.

The tablets containing Precirol® 40 % exhibited the slightly higher percent released at the first two hours when compared to Inderal®. But after the medium was changed to pH 6.8, slightly faster propranolol HCl release of Inderal® was obtained. These results still showed no remarkable difference.
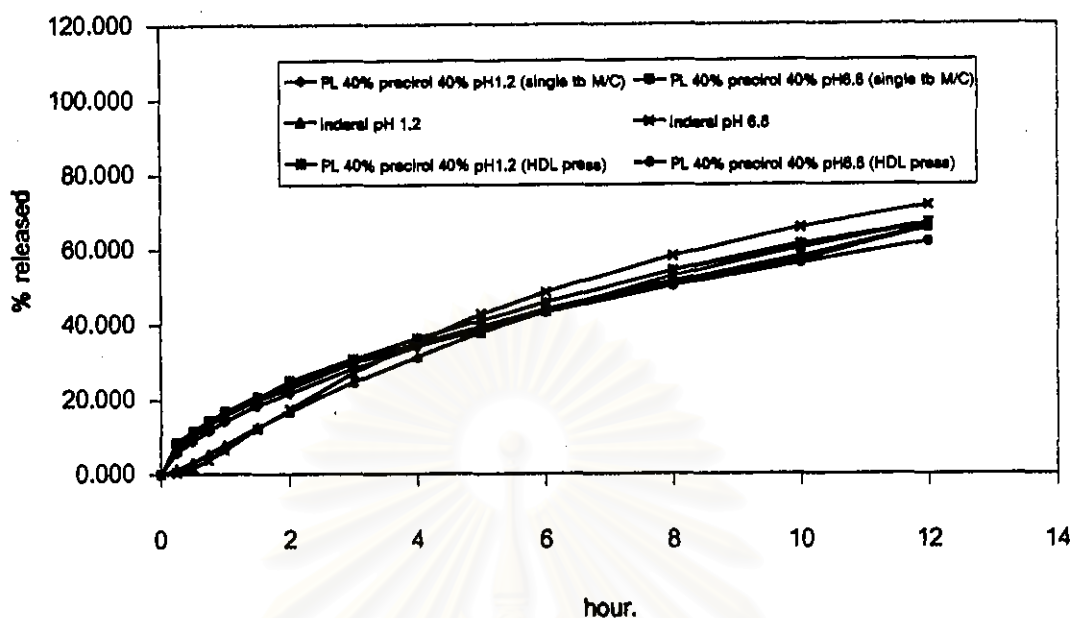
Figure 92   The release profile of Inderal® and matrix tablet prepared from 40% of Precirol® by hydraulic press (HDL press) and single punch tabletting machine (single tb M/C).
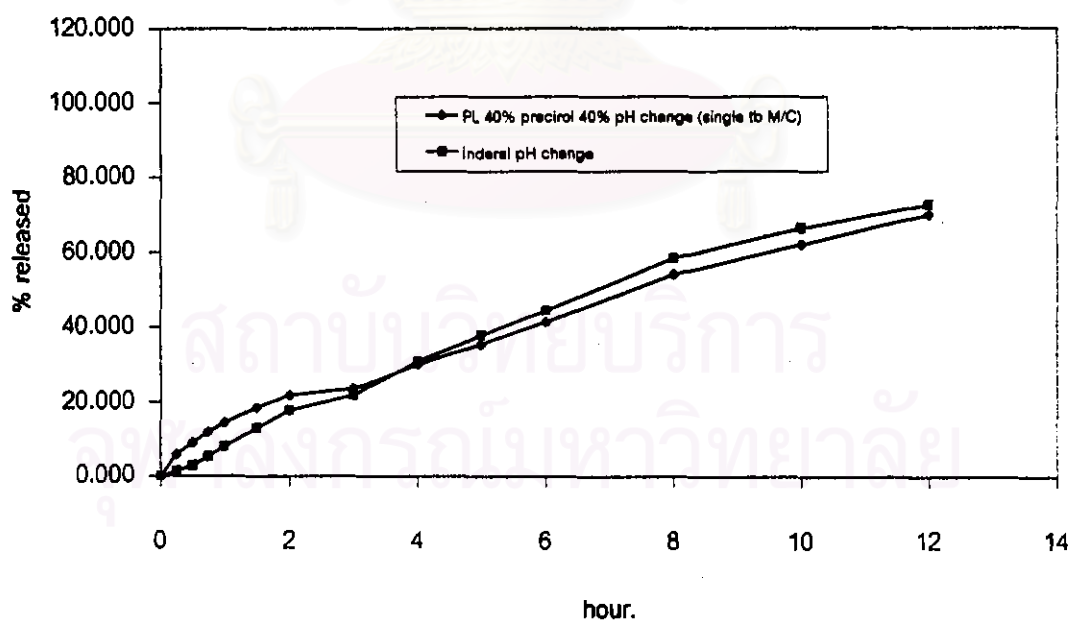
Figure 93   The release profile of Inderal® and matrix tablet containing 40% of Precirol® prepared by single punch tabletting machine (single tb M/C).

IV The Elucidation of Drug Released Model.

In general, the drug-released model of controlled release preparation can be described by using three kinetic models (zero order, first order and Higuchi model) to determine the effect of type, amount of wax and dosage form difference on the model of drug release. Thus, the analysis of all dissolution data was carried out to elucidate the suitable model. The plots between percentage of drug release against time (zero order), log percent drug remained versus time (first order), and percent of drug release versus square root of time (Higuchi model) were constructed. The most linear value was accepted as a model of drug release. The correlation coefficient of zero order, Higuchi, first order were obtained as tabulated in Table 18.

If the coefficients of Higuchi and first order relationships did not clearly show difference between the two release kinetics. The treatment was based upon use of the differential forms of Higuchi and the first order equations (Table 67-81, Appendix C) proposed by Benita and Donbrow (1982); Schwartz J.B. et al., (1967). The release was fitted with the first order model when the plots of rate of release versus Q were linear. If the plots of rate of release versus 1/Q were linear, the Higuchi model was operated. The correlation coefficients of the rate of release against reciprocal amount (1/Q) and amount (Q) are presented in Table 19.

1. Reference Propranolol HCl Capsule,Tablet and Inderal[®]

Since, the Higuchi plot of reference capsule and tablet in medium pH 1.2 and 6.8 were more linearity than first order plot. The correlation coefficent was obtained in the same way as those. Whereas the correlation coefficient of the rate of release versus 1/Q was higher than those of rate versus Q; these indicated

that the trend of propranolol HCl release from the matrix pellet and tablet without additive would probably operated by Higuchi model.

For Inderal®, the highest correlation coefficient was 0.9993 that obtained from first order plot in 0.1 N HCl. In buffer pH 6.8, the highest correlation coefficient was 0.9977 that obtained from first order plot. Therefore, these indicated that first order model would possibly be followed.

2. Matrix Pellet Formulations

For matrix pellet preparations. There was no relationship between two correlation coefficient criteria both in 0.1 N HCl and phosphate buffer pH 6.8. This result are possibly due to the drug release from the slowest formulations are about 6 hours. But from the other formulations are faster than that time. Drug release from matrix pellet cannot be satisfactory controlled. So, the model of matrix pellet could not be specified.

3. Matrix Tablet Preparations.

From the value of correlation coefficient of the relationship shown in Table 18. Figures 94-101 gave the comparison between the linearizations of the first-order model and Higuchi model of the wax matrix tablet in 0.1 N HCl pH 1.2 and phosphate buffer pH 6.8. Almost matrix tablet preparations showed the correlation coefficient of percent drug released versus square root of time higher than those of log percent drug remained versus time. Only few formulations gave the opposite results but these two values of that formulation are so close to each other. The further treatment was based upon use of the differential forms of the first order and Higuchi equations. The correlation coefficient of the rate of release versus 1/Q were higher

Table 18   Correlation coefficient (r) 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.

| formulation | Dissolution medium | | | | | |
| | 0.1 N HCl | | | Phosphate buffer pH 6.8 | | |
	A	B	C	A	B	C
PL 40%, beeswax 20%	0.8874	0.9690	0.9736	0.9305	0.9901	0.9881
PL 40%, beeswax 30%	0.9138	0.9801	0.9922	0.9441	0.9896	0.9720
PL 40%, beeswax 40%	0.9766	0.9941	0.9974	0.9597	0.9996	0.9922
PL 40%, beeswax 50%	0.9718	0.9995	0.9917	0.9784	0.9968	0.9916
PL 40%, carnauba wax 20%	0.8226	0.9285	0.8649	0.8806	0.9607	0.9637
PL 40%, carnauba wax 30%	0.7989	0.9113	0.9058	0.8493	0.9384	0.9326
PL 40%, carnauba wax 40%	0.9663	0.9926	0.9733	0.9848	0.9944	0.9331
PL 40%, carnauba wax 50%	0.9667	0.9999	0.9951	0.9717	0.9994	0.9946
PL 40%, GMS 20%	0.9601	0.9987	0.9510	0.9432	0.9971	0.9969
PL 40%, GMS 30%	0.9711	0.9989	0.9851	0.9623	0.9998	0.9961
PL 40%, GMS 40%	0.9705	0.9989	0.9983	0.9608	0.9998	0.9914
PL 40%, GMS 50%	0.9848	0.9954	0.9964	0.9735	0.9985	0.9940
PL 40%, lubritab 20%	0.8647	0.9557	0.9100	0.9172	0.9855	0.9847
PL 40%, lubritab 30%	0.9290	0.9833	0.9878	0.9696	0.9985	0.9294
PL 40%, lubritab 40%	0.9698	0.9994	0.9924	0.9589	0.9997	0.9934
PL 40%, lubritab 50%	0.9673	0.9996	0.9900	0.9610	0.9993	0.9837
PL 40%, compritol 20%	0.9727	0.9983	0.9547	0.9638	0.9995	0.9897
PL 40%, compritol 30%	0.9835	0.9939	0.9879	0.9607	0.9996	0.9898
PL 40%, compritol 40%	0.9612	0.9997	0.9827	0.9650	0.9988	0.9837
PL 40%, compritol 50%	0.9488	0.9973	0.9649	0.9592	0.9980	0.9740
PL 40%, precirol 20%	0.9706	0.9982	0.9631	0.9652	0.9995	0.9605
PL 40%, precirol 30%	0.9859	0.9921	0.9029	0.9734	0.9988	0.9909
PL 40%, precirol 40%	0.9744	0.9985	0.9965	0.9705	0.9993	0.9933
PL 40%, precirol 50%	0.9769	0.9982	0.9946	0.9719	0.9995	0.9914
PL 40%, gelucire 30%	0.9497	0.9931	0.9846	0.9622	0.9976	0.9724
PL 40%, gelucire 40%	0.9739	0.9984	0.9816	0.9729	0.9992	0.9947
PL 40%, gelucire 50%	0.9661	0.9998	0.9966	0.9517	0.9988	0.9841

Table 18   (Continued) Correlation (r) 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.

formulation	Dissolution medium					
	0.1 N HCl			Phosphate buffer pH 6.8		
	A	B	C	A	B	C
PL 20%, beeswax 40%	0.9706	0.9994	0.9956	0.9741	0.9985	0.9971
PL 30%, beeswax 40%	0.9705	0.9993	0.9904	0.9667	0.9997	0.9881
PL 50%, beeswax 40%	0.9637	0.9989	0.9842	0.9585	0.9997	0.9789
PL 20%, carnauba wax 40%	0.9047	0.9737	0.9870	0.9226	0.9784	0.9854
PL 30%, carnauba wax 40%	0.8572	0.9425	0.9509	0.9079	0.9665	0.9877
PL 50%, carnauba wax 40%	0.9628	0.9989	0.9943	0.9477	0.9975	0.9868
PL 20%, GMS 40%	0.9852	0.9952	0.9568	0.9732	0.9987	0.9940
PL 30%, GMS 40%	0.9848	0.9952	0.9804	0.9726	0.9989	0.9942
PL 50%, GMS 40%	0.9887	0.9879	0.9981	0.9781	0.9982	0.9970
PL 20%, lubritab 40%	0.9745	0.9946	0.9831	0.9713	0.9983	0.9900
PL 30%, lubritab 40%	0.9748	0.9981	0.9955	0.9682	0.9996	0.9952
PL 50%, lubritab 40%	0.9653	0.9997	0.9931	0.9518	0.9990	0.9846
PL 20%, compritol 40%	0.9916	0.9879	0.9875	0.9852	0.9946	0.9965
PL 30%, compritol 40%	0.9783	0.9979	0.9967	0.9749	0.9964	0.9899
PL 50%, compritol 40%	0.9573	0.9991	0.9768	0.9573	0.9992	0.9750
PL 20%, precirol 40%	0.9828	0.9964	0.9927	0.9724	0.9993	0.9968
PL 30%, precirol 40%	0.9792	0.9964	0.9968	0.9665	0.9991	0.9927
PL 50%, precirol 40%	0.9761	0.9987	0.9955	0.9663	0.9996	0.9914
PL 20%, gelucire 40%	0.9040	0.9584	0.8972	0.9145	0.9615	0.9330
PL 30%, gelucrie 40%	0.8294	0.9226	0.8420	0.8490	0.9324	0.9552
PL 50%, gelucire 40%	0.9391	0.9796	0.9290	0.9802	0.9950	0.9285
reference capsule	0.3241	0.5297	0.0166	0.3646	0.5718	0.3114
reference tablet	0.4243	0.6328	0.3982	0.4855	0.6882	0.6842
Inderal 160 mg.	0.9860	0.9868	0.9996	0.9805	0.9839	0.9989

Table 19   Comparison of linearity (r) 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.

| Formulation | Correlation coefficient of dQ/dt | | | |
| | 0.1 N HCl | | Phosphate buffer pH6.8 | |
	versus Q	versus 1/Q	versus Q	versus 1/Q
PL 40%, beeswax 20%	0.8096	0.9089	0.7723	0.9538
PL 40%, beeswax 30%	0.8137	0.8880	0.7144	0.8957
PL 40%, beeswax 40%	0.6528	0.8911	0.7051	0.9293
PL 40%, beeswax 50%	0.7088	0.9421	0.5828	0.8509
PL 40%, carnauba wax 20%	0.7769	0.8460	0.7499	0.9015
PL 40%, carnauba wax 30%	0.7234	0.7259	0.6796	0.7781
PL 40%, carnauba wax 40%	0.6980	0.9064	0.6076	0.9123
PL 40%, carnauba wax 50%	0.6778	0.9145	0.6653	0.9174
PL 40%, GMS 20%	0.8117	0.9882	0.7836	0.9793
PL 40%, GMS 30%	0.7751	0.9740	0.7088	0.9389
PL 40%, GMS 40%	0.8011	0.9836	0.7587	0.9780
PL 40%, GMS 50%	0.7261	0.9709	0.6989	0.9582
PL 40%, lubritab 20%	0.8239	0.9363	0.7987	0.9725
PL 40%, lubritab 30%	0.7547	0.9046	0.7026	0.9367
PL 40%, lubritab 40%	0.7316	0.9698	0.7482	0.9604
PL 40%, lubritab 50%	0.6466	0.8406	0.5847	0.7862
PL 40%, compritol 20%	0.7135	0.9603	0.7038	0.9534
PL 40%, compritol 30%	0.5914	0.9015	0.6613	0.9033
PL 40%, compritol 40%	0.6754	0.9167	0.6302	0.8840
PL 40%, compritol 50%	0.6183	0.8445	0.6188	0.8658
PL 40%, precirol 20%	0.7081	0.9510	0.7662	0.9784
PL 40%, precirol 30%	0.6865	0.9719	0.7226	0.9549
PL 40%, precirol 40%	0.8144	0.9910	0.7262	0.9435
PL 40%, precirol 50%	0.8078	0.9975	0.7129	0.9445
PL 40%, gelucire 30%	0.8738	0.9552	0.7514	0.9439
PL 40%, gelucire 40%	0.8196	0.9865	0.7342	0.9720
PL 40%, gelucire 50%	0.7306	0.9573	0.7147	0.9360

Table 19   (Continued.) Comparison of linearity (r) 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.

| Formulation	Correlation coefficient of dQ/dt			
	0.1 N HCl		Phosphate buffer pH6.8	
	versus Q	versus 1/Q	versus Q	versus 1/Q
PL 20%, beeswax 40%	0.5889	0.7944	0.7672	0.9585
PL 30%, beeswax 40%	0.6720	0.8809	0.7495	0.9577
PL 50%, beeswax 40%	0.5269	0.6754	0.7181	0.9302
PL 20%, carnauba wax 40%	0.7649	0.8859	0.6809	0.8257
PL 30%, carnauba wax 40%	0.6918	0.7232	0.5822	0.6709
PL 50%, carnauba wax 40%	0.5901	0.8127	0.5615	0.7262
PL 20%, GMS 40%	0.6540	0.9224	0.6625	0.9406
PL 30%, GMS 40%	0.6666	0.9164	0.6827	0.9396
PL 50%, GMS 40%	0.6533	0.7053	0.6201	0.8672
PL 20%, lubritab 40%	0.8231	0.9615	0.6710	0.9109
PL 30%, lubritab 40%	0.7327	0.9511	0.6693	0.9112
PL 50%, lubritab 40%	0.6399	0.8463	0.7052	0.9193
PL 20%, compritol 40%	0.5253	0.8546	0.6048	0.8871
PL 30%, compritol 40%	0.6200	0.8883	0.5787	0.8597
PL 50%, compritol 40%	0.6595	0.9045	0.6506	0.8895
PL 20%, precirol 40%	0.6325	0.9096	0.7059	0.9353
PL 30%, precirol 40%	0.8781	0.9463	0.7560	0.9533
PL 50%, precirol 40%	0.6619	0.9105	0.7163	0.9400
PL 20%, gelucire 40%	0.6572	0.7045	0.5550	0.6987
PL 30%, gelucrie 40%	0.6089	0.6773	0.5656	0.6645
PL 50%, gelucire 40%	0.6381	0.8411	0.6386	0.9068
reference capsule	0.0448	0.0489	0.9364	0.9430
reference tablet	0.7818	0.8009	0.7752	0.8064
Inderal 160 mg.	0.7837	0.0485	0.4200	0.4698
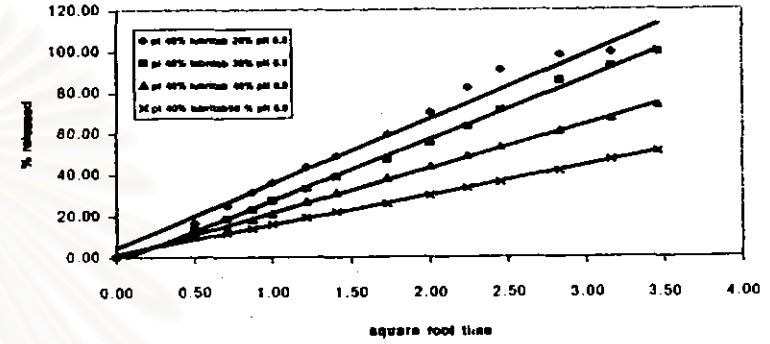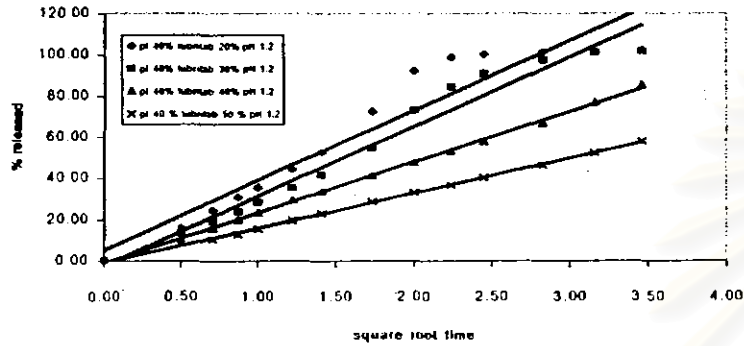
Figure 94   The Higuchi plot of propranolol HCl matrix tablet containing various amount of Lubritab® in different medium.
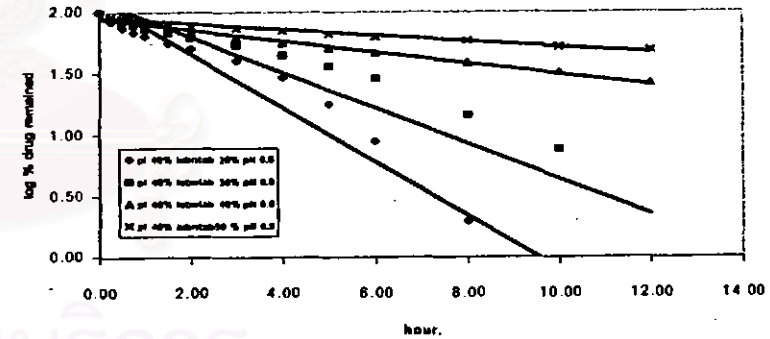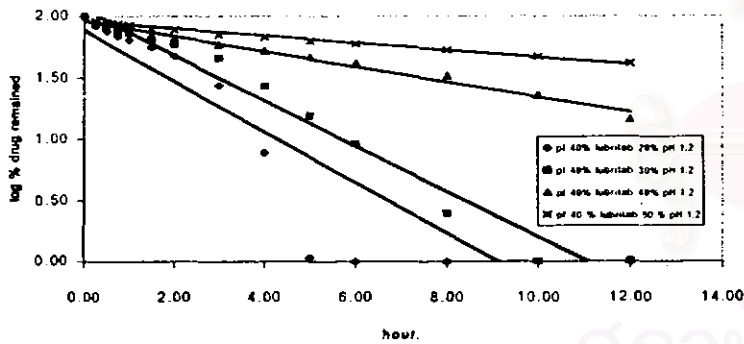

Figure 95   The first order plot of propranolol HCl matrix tablet containing various amount of Lubritab® in different medium.

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Figure 96   The Higuchi plot of propranolol HCl-lubritab® matrix tablet with different loading dose in different medium.
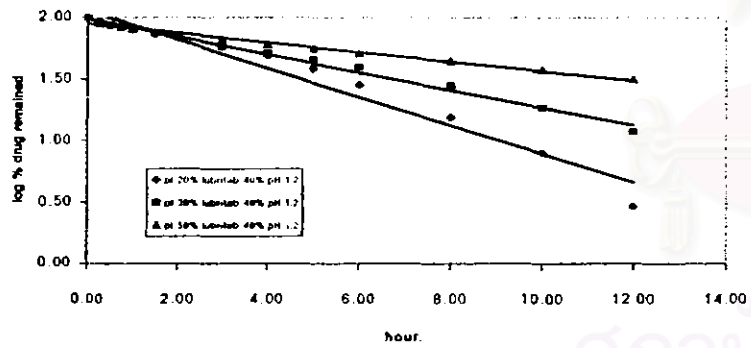
Figure 97   The first order plot of propranolol HCl-lubritab® matrix tablet with different loading dose in different medium.

Figure 98   The Higuchi plot of propranolol HCl matrix tablet containing various amount of Compritol® in different medium.

Figure 99   The first order plot of propranolol HCl matrix tablet containing various amount of Compritol® in different medium.
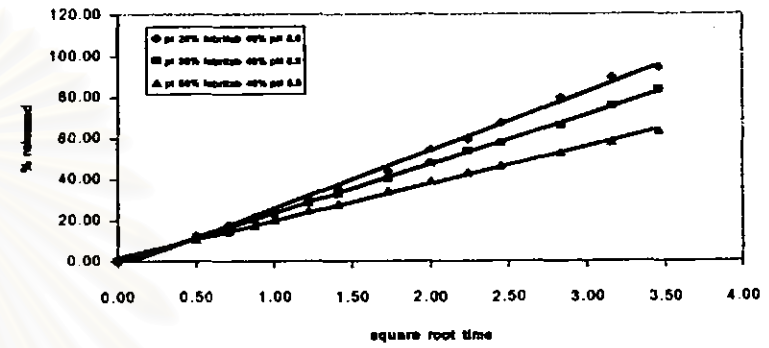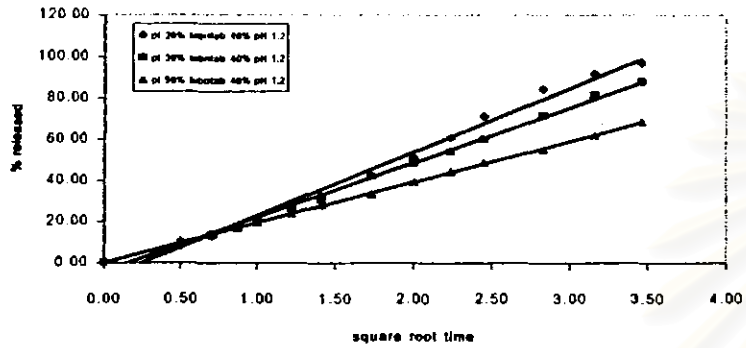
Figure 100   The Higuchi plot of propranolol HCl-compritol® matrix tablet with different loading dose in different medium.
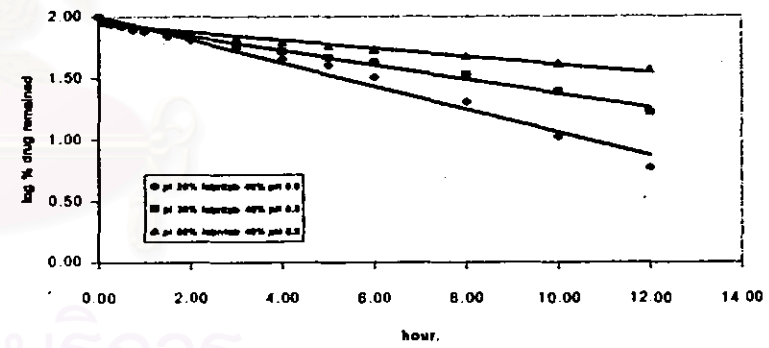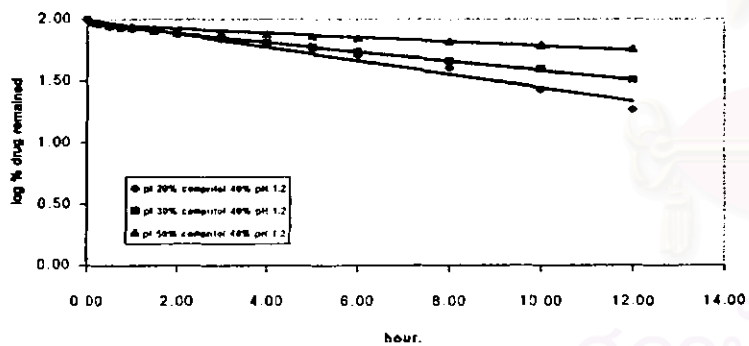

Figure 101   The first order plot of propranolol HCl-comprtiol® matrix tablet with different loading dose in different medium.
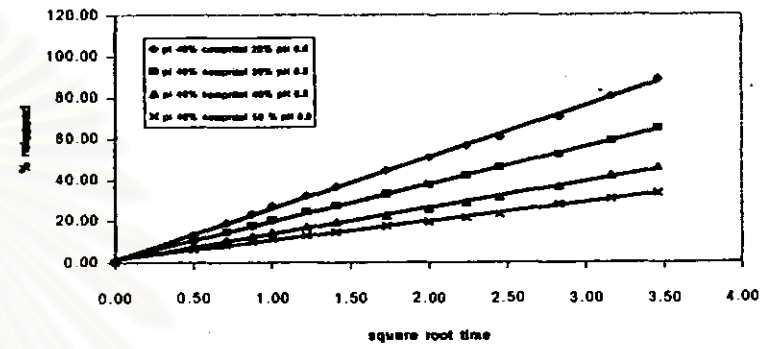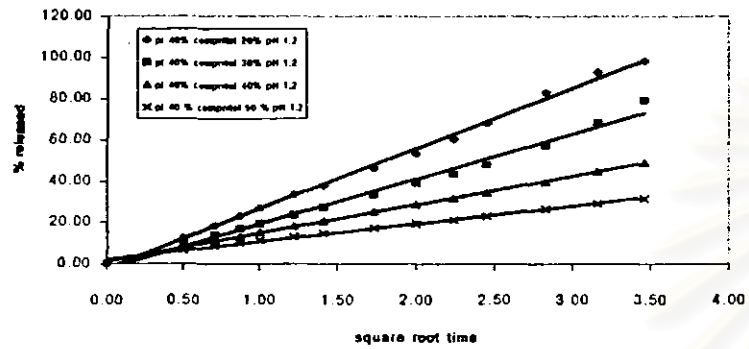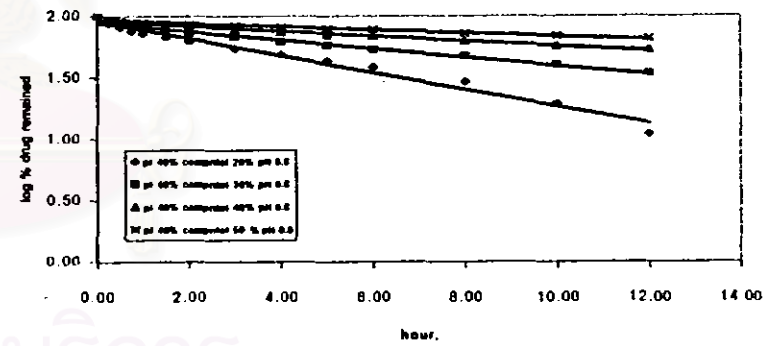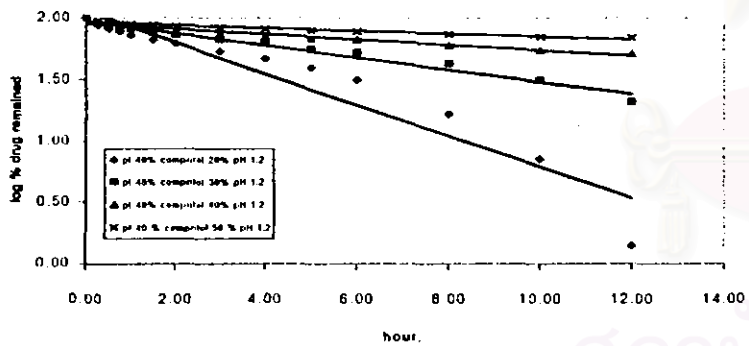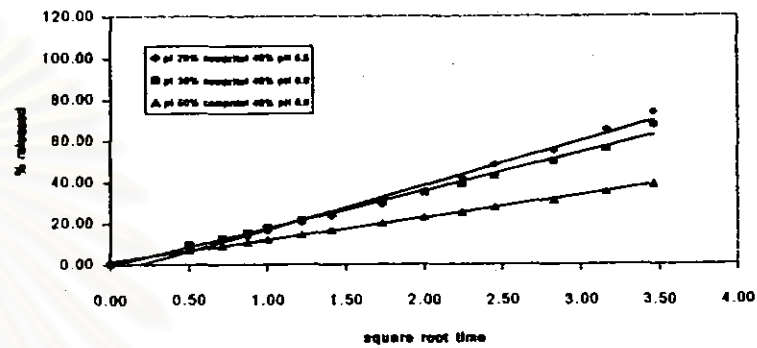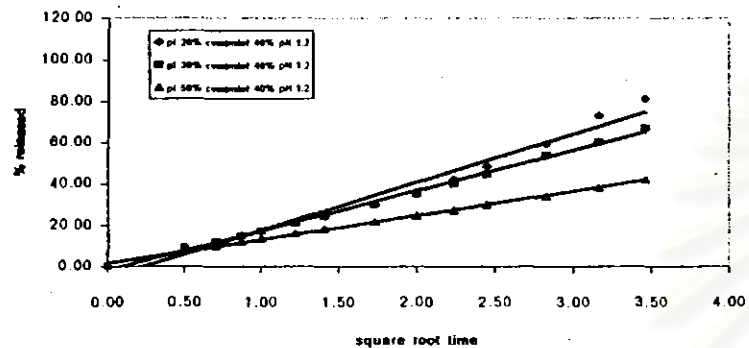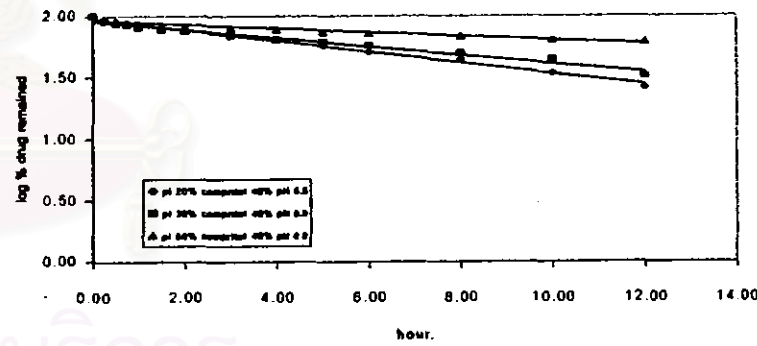
than those of rates versus Q in all formulations of matrix tablet as exhibited in Table 19. This was true for the entire matrix tablet having different drug-wax ratios and indicated that the trend of propranolol HCl release from all wax matrices in this study, Higuchi model would probably be operative.

The dissolution data for the release for propranolol HCl, from the matrices containing the various kind of waxes, when plotted as a function of the square root of time, produced straight line plots (as Ford et al., 1985b). The correlation coefficient for all data were closely to the unity and the release rate, both as $\%F.hr^{-0.5}$ and $mg.hr^{-0.5}$, are given in Tables 20-21.

The lower release rate was obtained when the wax in the formulation increased. This was true with all types of the waxes and in different medium. But the release rate of propranolol HCl in phosphate buffer pH 6.8 was still lower than that in 0.1 N HCl pH1.2. Therefore, increasing the amount of wax in the formulation, and hence the hydrophobic of the system will play the important role in the control of drug release from the matrices. This would result in a more amount of wax and increased system tortuosity. Thus, the diffusional path would become more convulated and the diffusion rate would therefore decrease.

As the content of propranolol HCl in the matrices wax reduced, in matrices containing 160 mg wax, the ability to sustain drug release decreased. In matrices containing Lubritab$^\circledR$, the release rate (estimated as $\%F.hr^{-0.5}$) increased from 19.67 to 30.77 $\%.hr^{-0.5}$ in 0.1 N HCl pH 1.2 and 18.33 to 28.33 $\%.hr^{-0.5}$ in phosphate buffer pH 6.8 as the content of propranolol HCl was lowered from 200 mg to 80 mg. obviously the dissolution rates, as estimated as $mg.hr^{-0.5}$ (Table 22-23) decreased from 39.33 to 24.62 $mg.hr^{-0.5}$ in 0.1 N HCl pH 1.2 and 36.26 to 22.66 $mg.hr^{-0.5}$ in phosphate buffer pH 6.8 over the similar range of the drug. But it must be emphasized that this is about 40 % reduction in release rate was achieved with a 60 % reduction in matrix

Table 20 Linear regression of release rate ($\%F.hr^{-0.5}$) and the percentage of wax (%wax) giving the slope b ($[\%F][hr^{-0.5}][\%wax^{-1}]$) and intercepts a ($[\%F][hr^{-0.5}]$) and correlation coefficient r.

Formulation	0.1 N HCl			Phosphate buffer pH6.8		
	b	a	r	b	a	r
PL 40%, beeswax	-60.30	49.23	0.9228	-70.90	49.34	0.9668
PL 40%, car. wax	-43.34	46.21	0.8184	-54.34	47.93	0.9493
PL 40%, GMS	-22.92	34.91	0.9642	-30.19	33.95	0.9515
PL 40%, lubritab	-60.96	48.63	0.9491	-59.51	45.08	0.9730
PL 40%, compritol	-69.77	42.81	0.9963	-52.85	34.82	0.9902
PL 40%, precirol	-54.01	43.43	0.9809	-48.70	39.39	0.9845
PL 40%, gelucire	-53.94	50.37	0.9999	-63.14	49.40	0.9998

Table 21 Linear regression of release rate ($\%F.hr^{-0.5}$) and the percentage of loading dose (%loading dose) giving the slope b ($[\%F][hr^{-0.5}][\%loading\ dose^{-1}]$) and intercepts a ($[\%F][hr^{-0.5}]$) and correlation coefficient r.

Formulation	0.1 N HCl			Phosphate buffer pH6.8		
	b	a	r	b	a	r
PL, beeswax 40%	-17.53	22.73	0.9104	-24.09	24.70	0.9282
PL, car. wax 40%	-37.51	42.42	0.9937	-50.30	45.01	0.9851
PL, GMS 40%	-10.50	30.70	0.9971	-6.99	23.52	0.9932
PL, lubritab 40%	-36.64	37.87	0.9986	-33.31	34.58	0.9943
PL, compritol 40%	-38.46	30.91	1.0000	-35.19	28.53	0.9991
PL, precirol 40%	-17.71	27.23	0.9927	-8.88	22.59	0.9658
PL, gelucire 40%	-6.58	37.74	0.9768	-22.30	41.11	0.9542

Table 22 The effect of wax content on the release rates (%F.hr$^{-0.5}$ or %F.hr$^{-0.5}$) of propranolol HCl from tablets containing propranolol HCl 160 mg.

formulation	propranolol hydrochloride content (mg)	dissolution rate			
		pH 1.2		pH 6.8	
		% F.hr-0.5	mg.hr-0.5	% F.hr-0.5	mg.hr-0.5
PL 40%, beeswax 20%	160.00	34.25	54.80	33.03	52.85
PL 40%, beeswax 30%	160.00	34.26	54.82	31.55	50.48
PL 40%, beeswax 40%	160.00	27.59	44.14	20.42	32.67
PL 40%, beeswax 50%	160.00	16.38	26.20	13.11	20.98
PL 40%, car. wax 20%	160.00	34.98	55.96	34.96	55.93
PL 40%, car. wax 30%	160.00	34.60	55.37	33.91	54.26
PL 40%, car. wax 40%	160.00	33.76	54.02	27.90	44.64
PL 40%, car. wax 50%	160.00	20.81	33.30	18.85	30.16
PL 40%, GMS 20%	160.00	30.31	48.50	27.80	44.48
PL 40%, GMS 30%	160.00	28.63	45.80	25.93	41.48
PL 40%, GMS 40%	160.00	24.60	39.36	20.14	32.22
PL 40%, GMS 50%	160.00	24.02	38.43	19.67	31.47
PL 40%, lubritab 20%	160.00	33.99	54.38	31.47	50.34
PL 40%, lubritab 30%	160.00	33.88	54.21	29.69	47.50
PL 40%, lubritab 40%	160.00	24.53	39.25	21.48	34.37
PL 40%, lubritab 50%	160.00	16.79	26.86	14.36	22.98
PL 40%, compritol 20%	160.00	29.22	46.75	25.04	40.06
PL 40%, compritol 30%	160.00	21.88	35.00	18.24	29.19
PL 40%, compritol 40%	160.00	13.84	22.14	12.74	20.38
PL 40%, compritol 50%	160.00	8.64	13.83	9.26	14.81
PL 40%, precirol 20%	160.00	32.20	51.53	30.20	48.32
PL 40%, precirol 30%	160.00	28.72	45.95	24.72	39.55
PL 40%, precirol 40%	160.00	20.11	32.18	18.38	29.40
PL 40%, precirol 50%	160.00	17.07	27.31	16.08	25.73
PL 40%, gelucire 30%	160.00	34.16	54.65	30.40	48.63
PL 40%, gelucire 40%	160.00	28.86	46.18	24.26	38.81
PL 40%, gelucire 50%	160.00	23.37	37.39	17.77	28.43

Table 23   The effect of propranolol HCl content on the release rates (%F.hr$^{-0.5}$ or %F.hr$^{-0.5}$) of propranolol HCl from tablets containing 160 mg wax.

| Formulation	propranolol hydrochloride content (mg)	dissolution rate			
		pH 1.2		pH 6.8	
		% F.hr-0.5	mg.hr-0.5	% F.hr-0.5	mg.hr-0.5
PL 20%, beeswax 40%	80.00	20.15	16.12	21.00	16.80
PL 30%, beeswax 40%	120.00	16.09	19.31	15.81	18.97
PL 50%, beeswax 40%	200.00	14.43	28.85	13.22	26.43
PL 20%, car. wax 40%	80.00	34.43	27.54	33.94	27.15
PL 30%, car. wax 40%	120.00	31.90	38.28	31.44	37.73
PL 50%, car. wax 40%	200.00	23.42	46.84	19.35	38.71
PL 20%, GMS 40%	80.00	28.51	22.81	22.02	17.62
PL 30%, GMS 40%	120.00	27.69	33.23	21.60	25.92
PL 50%, GMS 40%	200.00	25.41	50.81	19.97	39.94
PL 20%, lubritab 40%	80.00	30.77	24.62	28.33	22.66
PL 30%, lubritab 40%	120.00	26.54	31.85	23.97	28.77
PL 50%, lubritab 40%	200.00	19.67	39.33	18.13	36.26
PL 20%, compritol 40%	80.00	23.21	18.57	21.32	17.05
PL 30%, compritol 40%	120.00	19.38	23.25	18.23	21.88
PL 50%, compritol 40%	200.00	11.68	23.35	10.85	21.69
PL 20%, precirol 40%	80.00	23.44	18.75	21.09	16.87
PL 30%, precirol 40%	120.00	22.29	26.74	19.52	23.42
PL 50%, precirol 40%	200.00	18.25	36.49	18.29	36.58
PL 20%, gelucire 40%	80.00	36.59	29.27	35.84	28.67
PL 30%, gelucrie 40%	120.00	35.51	42.62	35.63	42.75
PL 50%, gelucire 40%	200.00	34.53	69.06	29.55	59.11
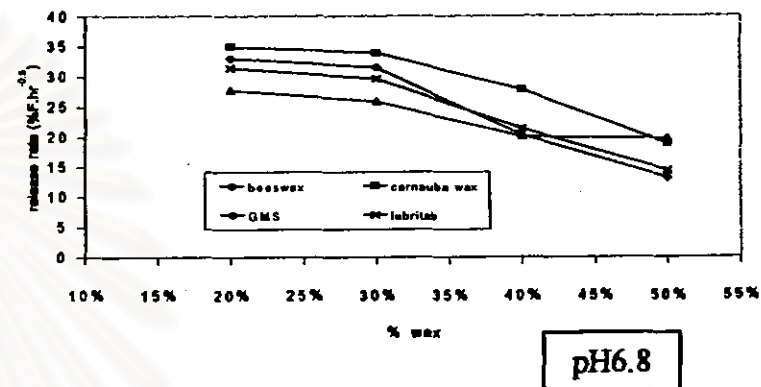
Figure 102   Relationship between release rate of propranolol HCl (%F.hr$^{-0.5}$) and the percentage of commonly used wax contained in the formulation in different medium.

Figrue 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.
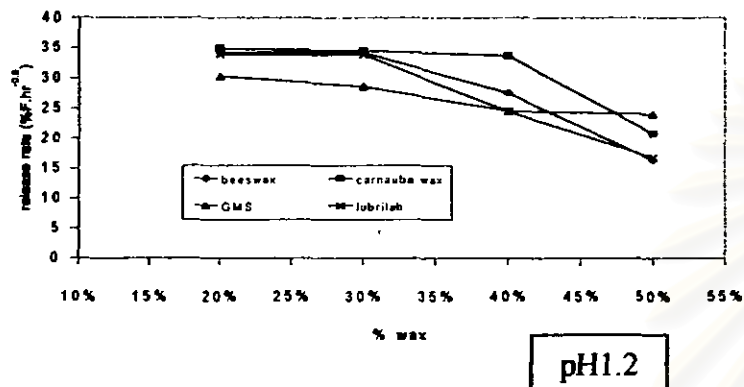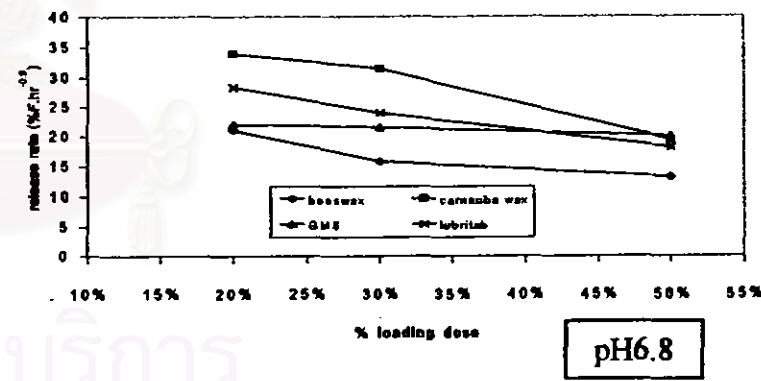
Figure 104   Relationship between release rate of propranolol HCl (%F.hr$^{-0.5}$) and the percentage of Gattefosse wax contained in the formulation in different medium.
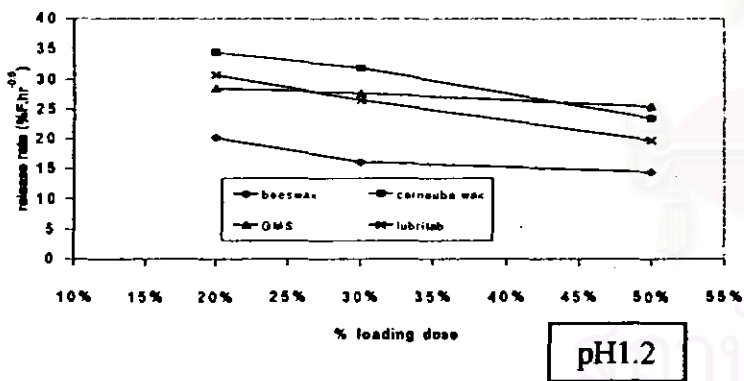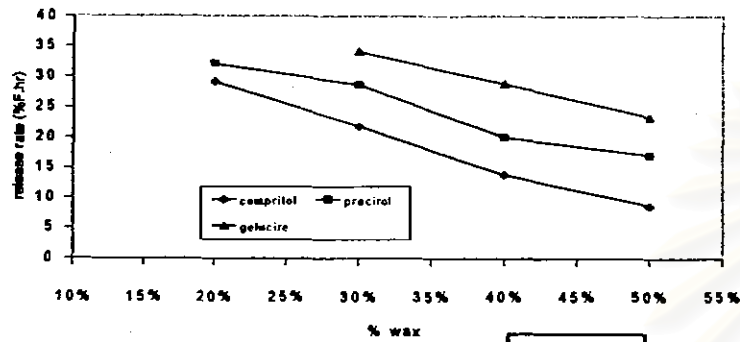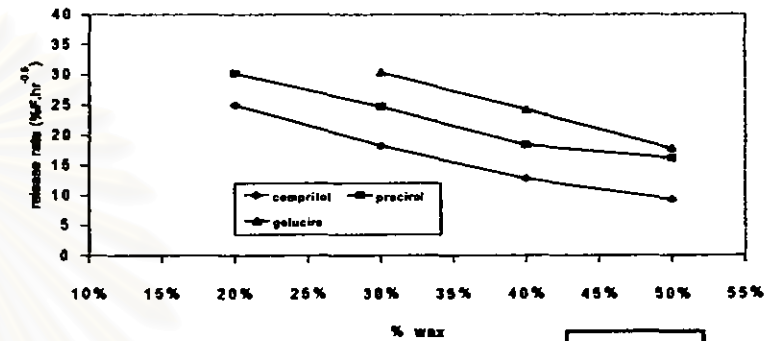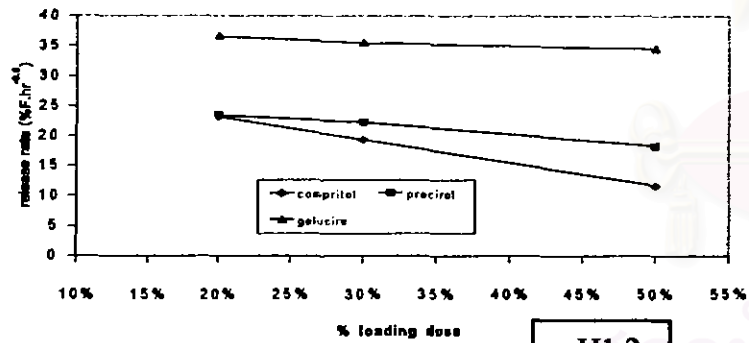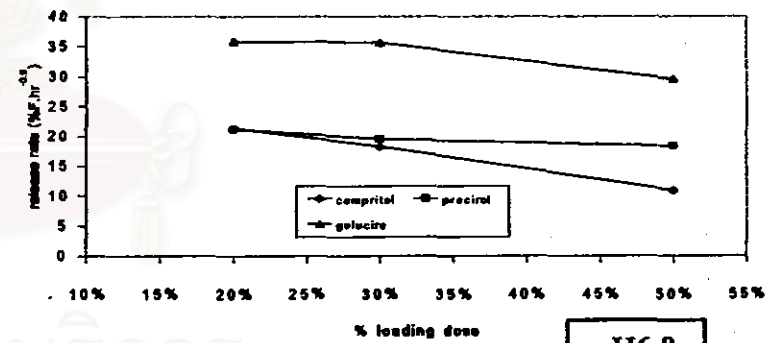

Figure 105   Relationship between release rate of propranolol HCl (%F.hr$^{-0.5}$) and the percentage of loading dose in the formulation containing 40 % of Gattefosse wax in different medium.

content of propranolol HCl and the overall release rate of drug from the matrix, considering the reduction in dose, increased. Over the similar drug contents, the matrices containing other kind of waxes also displayed the same result.

The general relationship, Equation 2, between release rate and matrix wax content or loading dose could be expressed as

$$R \quad = \quad M(W) + C \quad\quad\quad 2)$$

Where
$$R \quad = \text{higuchian release rate } (\%F.hr^{-0.5})$$
$$M \quad = \text{derived slope of line (b)}$$
$$W \quad = \text{percentage of wax or loading dose in the formulation}$$
$$C \quad = \text{constant (a)}$$

Tables 20-21 gave values of M and C, which are presented from previously derived data. This indicated that equation 2 is valid when apply to any kind of waxes studied especially Compritol®, provided that $time^{-0.5}$ release kinetic are approximately followed except carnauba wax that showed rather value of correlation coefficient.

Release mechanism from wax matrix tablets.

The general form of a simple, semiempirical equation that can be used to analyze data of controlled release of drugs under perfect conditions is

$$M_t / M_\infty \quad = \quad kt^n \quad\quad\quad 3)$$

Where M_t / M_∞ is the fractional release of the drug, t is the release time, k is a constant incorporating structural and geometric characteristics of the controlled release device, and n is the release exponent, indicative of the mechanism of drug release.

The results of each constant in equation of all wax matrix tablet formulations were shown in Table 26. These exponent values were compared with the value of cylindrical samples in Equation 3.

Table 24   Diffusional exponent and mechanism of diffusional drug release from non swellable controlled release system.

Diffusinal exponent, n			Drug release mechanism
Thin film	Cylindrical sample	Spherical sample	
0.5	0.45	0.43	Fickian diffusion
0.5 < n < 1.00	0.45 < n < 1.00	0.43 < n < 1.00	Anomalous transport (non Fickian)
1.0	1.0	1.0	Zero-order release

Table 25   Diffusional exponent and mechanism of diffusional drug release from swellable controlled release system.

Diffusinal exponent, n			Drug release mechanism
Thin film	Cylindrical sample	Spherical sample	
0.5	0.45	0.43	Fickian diffusion
0.5 < n < 1.00	0.45 < n < 0.89	0.43 < n < 0.85	Anomalous transport (non Fickian)
1.0	0.89	0.85	Zero-order release

The propranolol HCl wax matrix tablets were not dissolved but slightly swelled. The release exponent value tended to be decreased when the amount of wax or propranolol HCl in the formulation was increased. These values were in the range of 0.45 – 0.89. Thus, the release mechanism was seemed to be anomalous tmasport (non-fickian diffusion) in both mediums.

Table 26 The value of kinetic constant (k), release exponent (n) and correlation coefficient (r) following linear regression of dissolution data for values of M_t/M_∞ in 0.1 N HCl and phosphate buffer pH6.8.

formulation	0.1 N HCl			Phosphate buffer pH6.8		
	n	r	k	n	r	k
PL 40%, beeswax 20%	0.61	0.9976	0.3346	0.49	0.9993	0.3315
PL 40%, beeswax 30%	0.68	0.9963	0.2871	0.58	0.9980	0.2669
PL 40%, beeswax 40%	0.67	0.9967	0.1814	0.49	0.9997	0.2114
PL 40%, beeswax 50%	0.54	0.9999	0.1465	0.58	0.9983	0.1051
PL 40%, carnauba wax 20%	0.65	0.9974	0.3567	0.52	0.9998	0.3302
PL 40%, carnauba wax 30%	0.71	0.9944	0.3285	0.60	0.9956	0.2937
PL 40%, carnauba wax 40%	0.57	0.9999	0.2590	0.52	0.9998	0.2331
PL 40%, carnauba wax 50%	0.51	0.9999	0.2014	0.54	0.9998	0.1691
PL 40%, GMS 20%	0.56	0.9998	0.2778	0.47	0.9994	0.3171
PL 40%, GMS 30%	0.60	1.0000	0.2326	0.50	0.9999	0.2623
PL 40%, GMS 40%	0.59	0.9998	0.2019	0.50	0.9999	0.1988
PL 40%, GMS 50%	0.64	0.9999	0.1649	0.51	0.9995	0.1887
PL 40%, lubritab 20%	0.55	0.9998	0.3582	0.48	0.9992	0.3552
PL 40%, lubritab 30%	0.59	0.9994	0.2783	0.51	0.9998	0.2705
PL 40%, lubritab 40%	0.51	0.9998	0.2345	0.51	0.9998	0.2155
PL 40%, lubritab 50%	0.52	0.9997	0.1586	0.48	0.9995	0.1519
PL 40%, compritol 20%	0.50	0.9997	0.2698	0.47	0.9998	0.2665
PL 40%, compritol 30%	0.53	0.9996	0.1850	0.47	0.9998	0.1967
PL 40%, compritol 40%	0.48	0.9998	0.1463	0.49	0.9988	0.1309
PL 40%, compritol 50%	0.43	0.9994	0.1057	0.46	0.9984	0.1037
PL 40%, precirol 20%	0.51	0.9999	0.2922	0.52	0.9991	0.2896
PL 40%, precirol 30%	0.55	0.9994	0.2275	0.54	0.9997	0.2203
PL 40%, precirol 40%	0.58	0.9997	0.1638	0.55	0.9998	0.1611
PL 40%, precirol 50%	0.58	0.9999	0.1370	0.54	0.9999	0.1438
PL 40%, gelucire 30%	0.62	0.9994	0.2758	0.56	0.9996	0.2635
PL 40%, gelucire 40%	0.59	0.9996	0.2324	0.52	0.9997	0.2226
PL 40%, gelucire 50%	0.50	0.9997	0.2305	0.46	0.9998	0.2005

Table 26 (continued) The value of kinetic constant (k), release exponent (n) and correlation coefficient (r) following linear regression of dissolution data for values of M_t/M_∞ in 0.1 N HCl and phosphate buffer pH6.8.

Formulation	0.1 N HCl			Phosphate buffer pH6.8		
	n	r	k	n	r	k
PL 20%, beeswax 40%	0.52	0.9994	0.1889	0.58	0.9997	0.1711
PL 30%, beeswax 40%	0.54	0.9997	0.1439	0.52	0.9998	0.1494
PL 50%, beeswax 40%	0.50	0.9988	0.1441	0.48	0.9998	0.1398
PL 20%, car. wax 40%	0.68	0.9964	0.2674	0.65	0.9954	0.2401
PL 30%, car. wax 40%	0.74	0.9938	0.2593	0.82	0.9853	0.2073
PL 50%, car. wax 40%	0.46	0.9996	0.2669	0.46	0.9991	0.2362
PL 20%, GMS 40%	0.59	0.9997	0.2104	0.49	0.9984	0.2150
PL 30%, GMS 40%	0.61	0.9998	0.1989	0.51	0.9998	0.2033
PL 50%, GMS 40%	0.83	0.9990	0.1180	0.56	0.9997	0.1664
PL 20%, lubritab 40%	0.64	0.9998	0.2123	0.55	0.9988	0.2435
PL 30%, lubritab 40%	0.60	0.9990	0.2092	0.52	0.9996	0.2276
PL 50%, lubritab 40%	0.50	0.9995	0.1957	0.46	0.6971	0.2041
PL 20%, compritol 40%	0.64	0.9976	0.1481	0.61	0.9986	0.1539
PL 30%, compritol 40%	0.56	0.9989	0.1620	0.50	0.9997	0.1737
PL 50%, compritol 40%	0.46	0.9996	0.1308	0.46	0.9997	0.1215
PL 20%, precirol 40%	0.58	0.9996	0.1830	0.55	0.9999	0.1843
PL 30%, precirol 40%	0.61	0.9991	0.1669	0.54	0.9994	0.1768
PL 50%, precirol 40%	0.56	0.9998	0.1541	0.52	0.9997	0.1728
PL 20%, gelucire 40%	0.74	0.9987	0.2151	0.63	0.9982	0.2262
PL 30%, gelucrie 40%	0.66	0.9944	0.2739	0.55	0.9984	0.2609
PL 50%, gelucire 40%	0.54	0.9995	0.2719	0.52	0.9993	0.2463