CHAPTER III

RESULTS AND DISCUSSION

I Evaluation of pellets

1. Morphology of Pellets

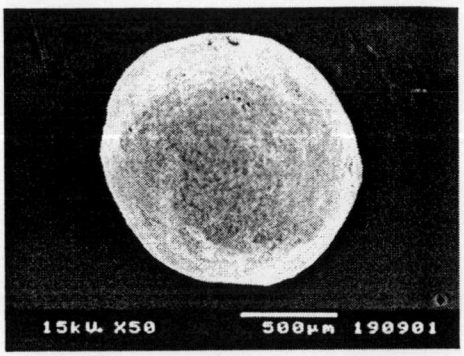
The surface morphology of pellets was observed by using scanning electron microscope (SEM) at different magnifications (×50, ×350, ×50).

Figures 11-13 presented the photomicrographs of propranolol hydrochloride matrix pellets produced by three kinds of glycerides (Glyceryl monostearate, Lubritab®, and Compritol® ATO 888) at 40% loading dose.

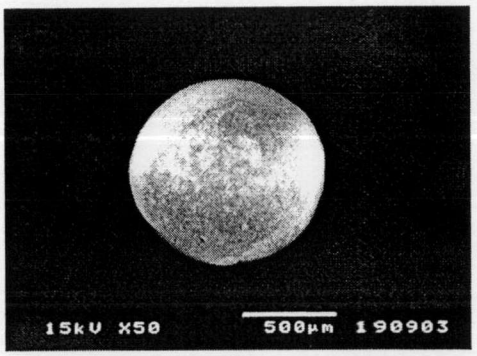
The surface of propranolol hydrochloride matrix pellets shown clearly moon-like in formulation which composed GMS, whereas the formulation, which contained Lubritab,® and Compritol® ATO 888 are depicted as rough surfaces similar to an orange-peel.

Figures 14-16 presented the photomicrographs of diclofenac sodium matrix pellets produced by glyceryl monostearate, Lubritab®, and Compritol® ATO 888 at 40% loading dose. The roughed surface that was seen in the formulation of diclofenac sodium matrix pellets that containing Lubritab® and Compritol® ATO 888. Except the formulation which containing glyceryl monostearate is shown clearly moon like surfaces.

On their surfaces, a random aggregation of filament micro-crystal creates a high internal porosity. The cross-section of all formulation is shown the small holes inside the pellets that bonding not condensed. They are usually hollow spheres. From this result it may be affected to the release of drug from the matrix pellets.

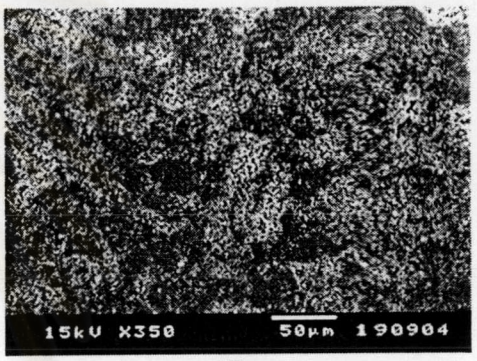


A_1

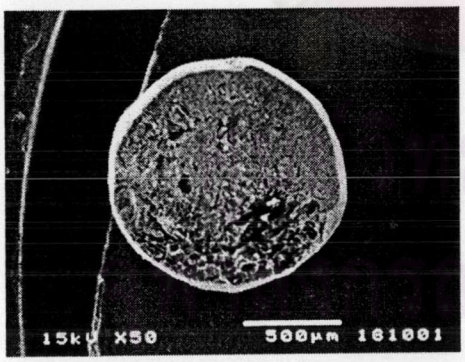


B_1

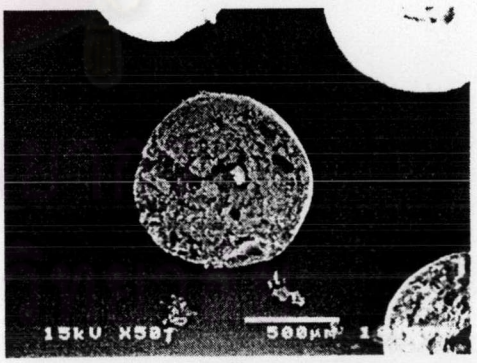
A_2



B_2

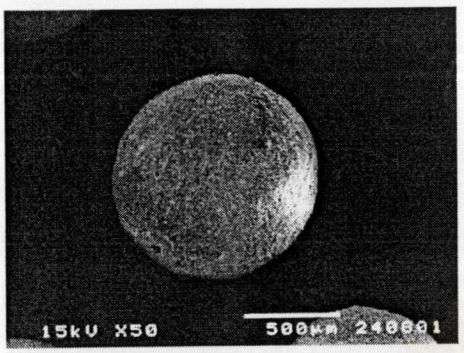


A_3

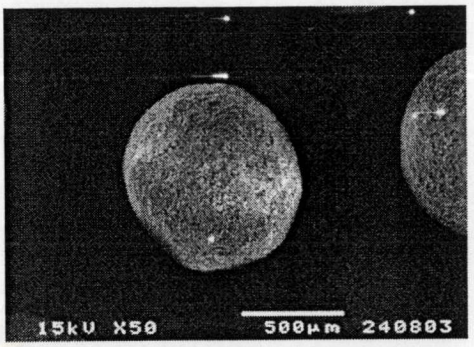


B_3

Figure 11 Scanning electron photomicrographs of 40% propranolol hydrochloride matrix pellets from the initial formulation using 40% GMS A: pellets mesh cut 14/18 (A_1, A_2; at ×50, ×350 magnification, respectively, A_3: cross-section at ×50 magnification); B: pellets mesh cut 18/20 (B_1, B_2, at × 50, ×350 magnification, respectively B_3: cross-section at ×50 magnification).

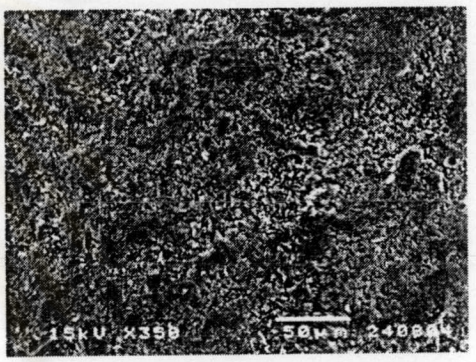


A_1

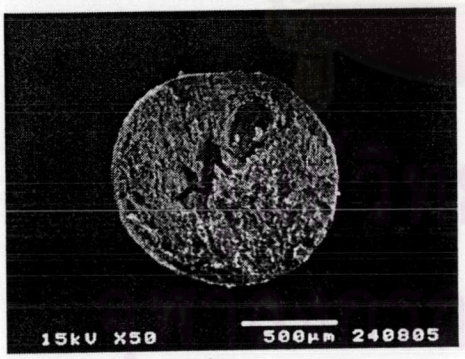


B_1

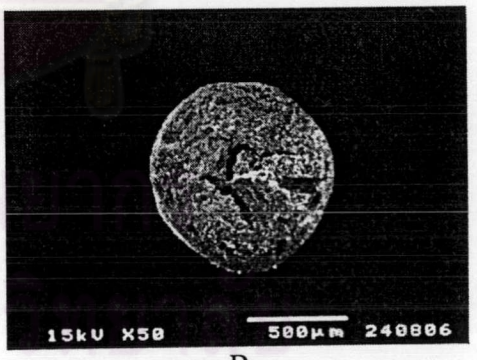
A_2



B_2

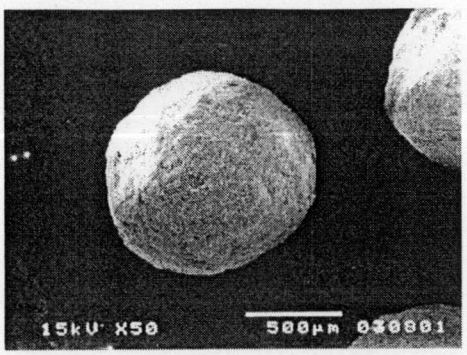


A_3

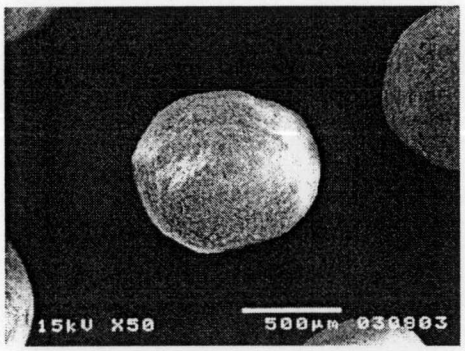


B_3

Figure 12 Scanning electron photomicrographs of 40% propranolol hydrochloride matrix pellets from the initial formulation using 40% Lubritab® A: pellets mesh cut 14/18 (A_1, A_2; at ×50, ×350 magnification, respectively, A_3: cross-section at ×50 magnification); B: pellets mesh cut 18/20 (B_1, B_2, at × 50, ×350 magnification, respectively; B_3: cross-section at ×50 magnification).

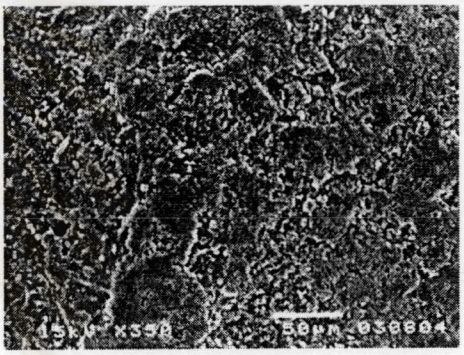


A_1

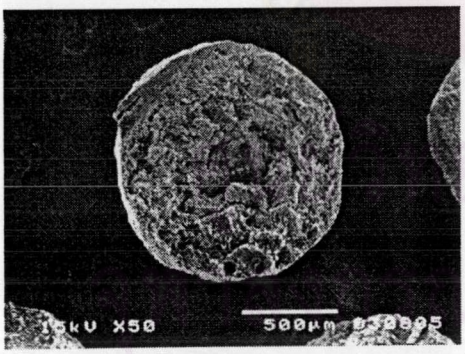


B_1

A_2



B_2



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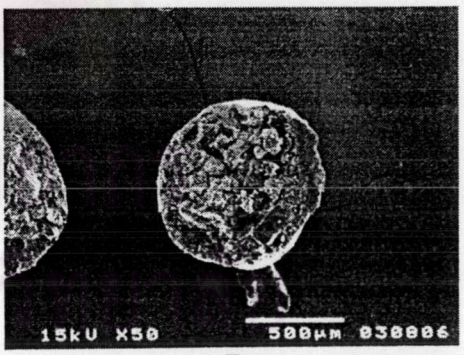
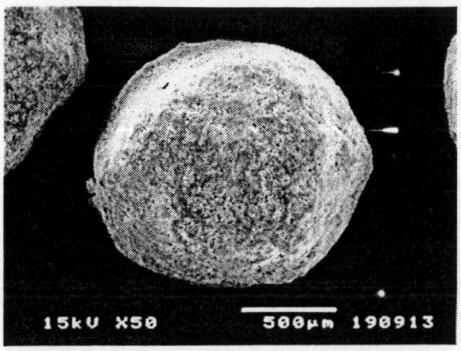
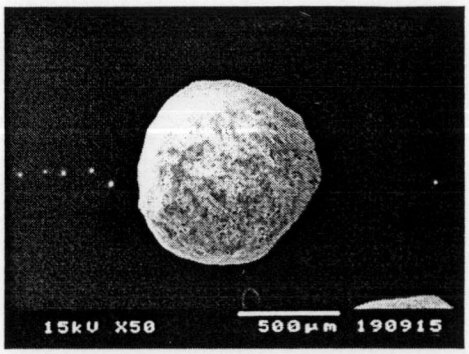


B_3

Figure 13 Scanning electron photomicrographs of 40% propranolol hydrochloride matrix pellets from the initial formulation using 40% Compritol®ATO 888 A: pellets mesh cut 14/18 (A_1, A_2; at ×50, ×350 magnification, respectively, A_3: cross-section at ×50 magnification); B: pellets mesh cut 18/20 (B_1, B_2, at ×50, ×350 magnification, respectively B_3: cross-section at ×50 magnification).

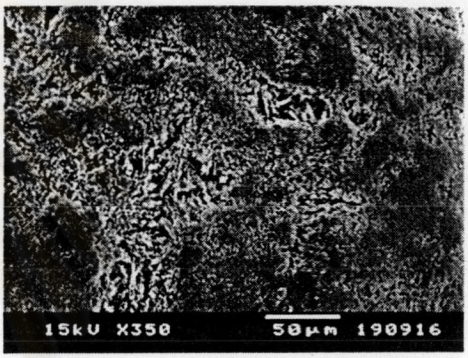


A_1

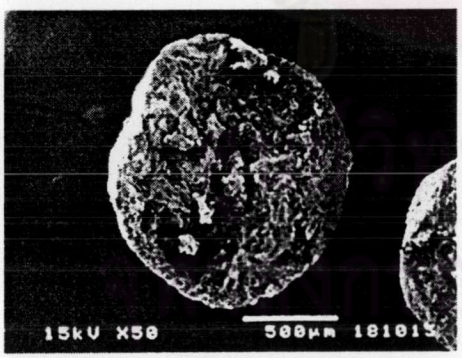


B_1

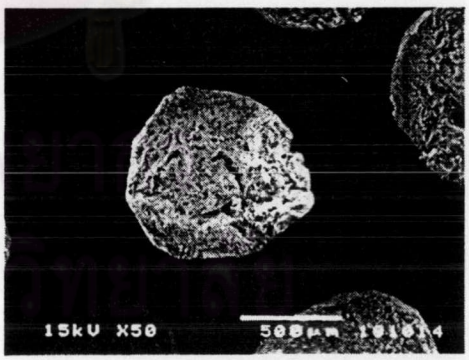
A_2



B_2

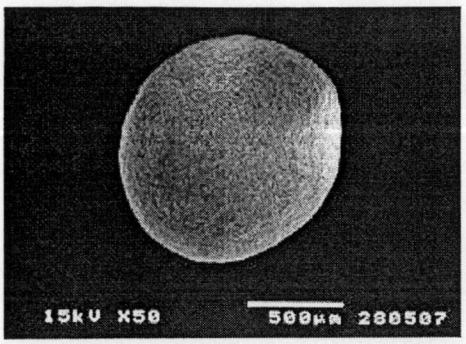


A_3

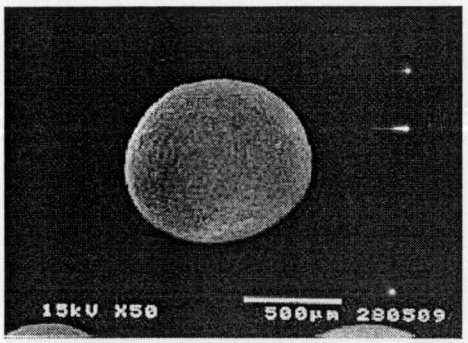


B_3

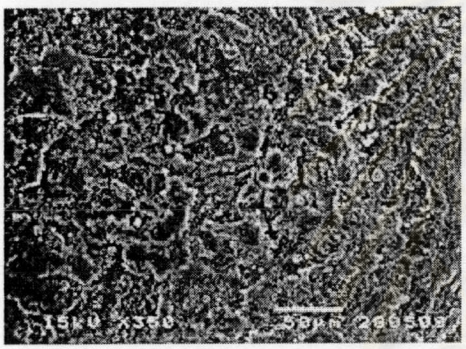
Figure 14 Scanning electron photomicrographs of 40% diclofenac sodium matrix pellets from the initial formulation using 40% GMS A: pellets mesh cut 14/18 (A_1, A_2; at ×50, ×350 magnification, respectively, A_3: cross-section at ×50 magnification); B: pellets mesh cut 18/20 (B_1, B_2, at ×50, ×350 magnification, respectively B_3: cross-section at ×50 magnification).



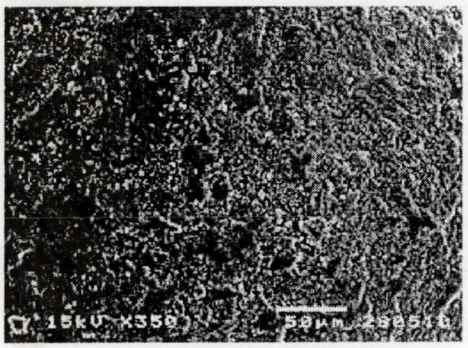
A_1



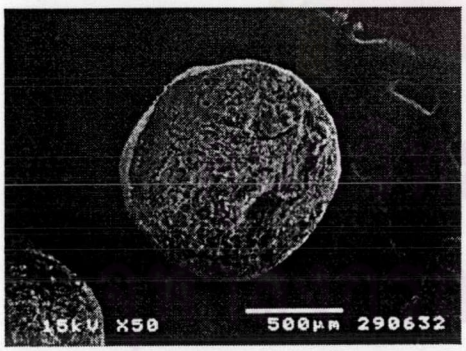
B_1



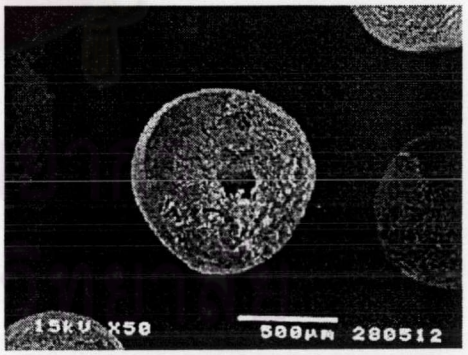
A_2



B_2

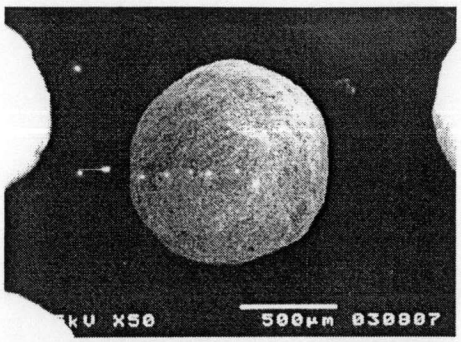


A_3

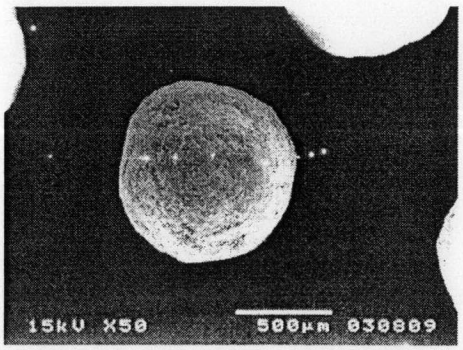


B_3

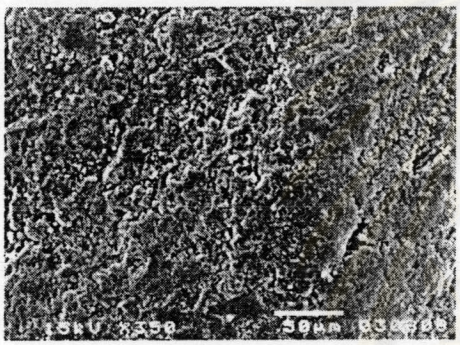
Figure 15 Scanning electron photomicrographs of 40% diclofenac sodium matrix pellets from the initial formulation using 40% Lubritab® A: pellets mesh cut 14/18 (A_1, A_2; at ×50, ×350 magnification, respectively, A_3: cross-section at ×50 magnification); B: pellets mesh cut 18/20 (B_1, B_2, at ×50, × 350 magnification, respectively B_3: cross-section at ×50 magnification).



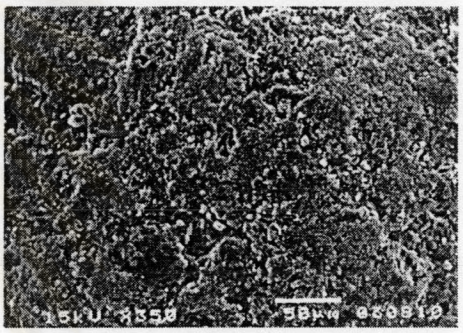
A_1



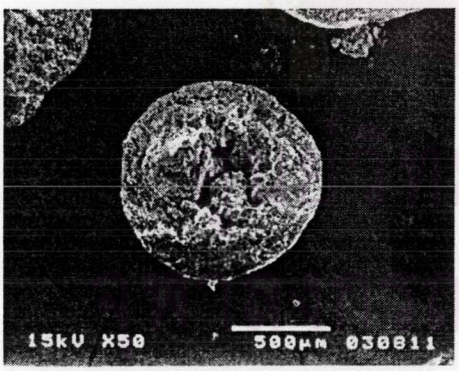
B_1



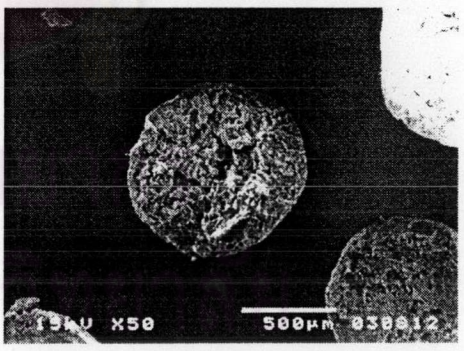
A_2



B_2



A_3



B_3

Figure 16 Scanning electron photomicrographs of 40% diclofenac sodium matrix pellets from the initial formulation using 40% Compritol®ATO 888 A: pellets mesh cut 14/18 (A_1, A_2; at ×50, ×350 magnification, respectively, A_3: cross-section at ×50 magnification); B: pellets mesh cut 18/20 (B_1, B_2, at ×50, ×350 magnification, respectively B_3: cross-section at ×50 magnification).

2. Size Distribution

The size distribution of the matrix pellets is determined using sieve analysis method (Blandque et al., 1995) and the results are shown in Table 11-12. All formulations showed that the highest amount of pellets is retained on sieve size No.18.

In fact, the particle size distribution should be as narrow as possible (Harris and Ghebre, 1989). Because narrow particles size distribution from the same formulation should give the same release profile and release rate. In addition, this could eliminate surface area variation of the particle in dissolution studies.

On the other hand, different amount of glycerides and drug in pellet formulation showed no effect on pellets size. The results demonstrated the feasibility of using pelletization condition adopted in this work to produce pellets of relatively narrow particle size from three glycerides.

3. Bulk Density, Tapped Density, and Percent Compressibility

The bulk density, tapped density, and Carr's compressibility index of pellets are presented in Table 13. The values of density of all formulations are in the range of 0.58-0.71. Except propranolol hydrochloride matrix pellets, which have Lubritab® as matrix forming agent showed the lowest density than the other formulations.

If bulk volume is higher than a tapped volume, a bulk density will be less than tapped density. A high Carr's compressibility implied a loosen of particles. If the Carr's compressibility equal to zero, bulks density, and tapped density would be equal. The difference between the minimum and maximum bulk density of the pellets is generally very small indicating free flowing behavior (Chopra et al., 2001).

In addition, the values of bulk density of all formulation are close to tapped density. So all formulations in the form of pellets should give low compressibility.

Table 11 Sieve analysis of propranolol hydrochloride matrix pellets formulation from different component.

Formulations	Percent retained on each sieves sizes*					
	14	18	20	25	30	pan
PL 40% GMS 40%	20.19	73.23	5.20	1.35	0.02	0.01
PL 40% GMS 50%	15.73	71.51	9.16	3.28	0.30	0.02
PL 20% GMS 60%	7.53	86.25	4.12	1.72	0.35	0.03
PL 30% GMS 60%	5.66	87.14	4.92	1.88	0.27	0.13
PL 40% Lubritab 40%	0.00	43.76	21.20	22.45	6.74	5.85
PL 40% Lubritab 50%	0.19	27.92	16.61	24.74	10.53	20.01
PL 20% Lubritab 60%	1.94	27.97	20.27	26.90	10.47	12.45
PL 30% Lubritab 60%	0.29	33.93	13.36	28.28	15.03	9.11
PL 40% Compritol 40%	3.17	77.46	13.56	5.14	0.22	0.45
PL 40% Compritol 50%	0.05	35.71	19.87	25.77	8.90	9.70
PL 20% Compritol 60%	0.77	41.80	22.36	26.01	6.44	2.62
PL 30% Compritol 60%	10.62	53.24	20.28	13.15	1.42	1.29

*underlined the highest percent yield of sieve analysis.

Table 12 Sieve analysis of diclofenac sodium matrix pellets formulation from different component.

Formulations	Percent retained on each sieves sizes*					
	14	18	20	25	30	pan
DS 40% GMS 40%	40.08	57.44	2.01	0.29	0.07	0.00
DS 40% GMS 50%	17.11	75.92	4.45	2.04	0.35	0.13
DS 20% GMS 60%	4.38	89.87	4.28	1.34	0.04	0.09
DS 30% GMS 60%	3.64	87.07	4.83	2.49	0.53	1.44
DS 40% Lubritab 40%	0.84	48.27	11.48	18.51	10.16	10.74
DS 40% Lubritab 50%	0.85	66.14	8.58	12.34	6.24	5.85
DS 20% Lubritab 60%	38.73	57.84	2.48	0.55	0.07	0.33
DS 30% Lubritab 60%	0.48	75.39	6.10	6.69	4.47	6.87
DS 40% Compritol 40%	0.49	68.65	15.89	11.60	2.42	0.95
DS 40% Compritol 50%	10.03	63.21	14.92	8.62	1.55	1.67
DS 20% Compritol 60%	1.10	71.20	18.16	8.47	0.92	0.15
DS 30% Compritol 60%	0.25	44.26	19.15	21.65	6.49	8.20
DS 40% GMS 40% PEG1%	2.4	90.51	4.35	1.68	0.33	0.73
DS 40% GMS 40% PEG1%Tween 1%	4.48	79.14	10.34	4.33	1.06	0.65
DS 40% GMS 40% PEG0.5% Tween 0.5%	23.49	70.40	4.07	1.87	0.10	0.07
DS 40% GMS 40% PEG0.2% Tween 0.2%	27.55	68.21	3.46	0.72	0.05	0.01

*underlined the highest percent yield of sieve analysis.

Table 13 Bulk density, tapped density, and percent Carr's compressibility of the matrix pellets prepared from each formulation.

Formulation	Bulk density	Tapped density	% Carr's
PL40% GMS40%	0.6637	0.6732	1.8486
PL40% GMS50%	0.6757	0.6849	1.3433
PL20%GMS60%	0.6122	0.6173	0.8262
PL30% GMS60%	0.6148	0.6224	1.2211
PL40% Lubritab40%	0.5859	0.5906	0.7958
PL40% Lubritab50%	0.5515	0.5555	0.7201
PL20% Lubritab60%	0.5357	0.5435	1.4351
PL30% Lubritab60%	0.5172	0.5245	1.3918
PL40% Compritol40%	0.6276	0.6410	2.0905
PL40% Compritol50%	0.6024	0.6148	2.0169
PL20% Compritol60%	0.6224	0.6224	0
PL30% Compritol60%	0.5769	0.5837	1.1650
DS40% GMS40%	0.7075	0.7109	0.4783
DS40% GMS50%	0.6881	0.6881	0
DS20% GMS60%	0.6494	0.6522	0.4293
DS30% GMS60%	0.6494	0.6608	1.7252
DS40% Lubritab40%	0.6494	0.6666	2.5803
DS40% Lubritab50%	0.6550	0.6666	1.7402
DS20% Lubritab60%	0.6073	0.6148	1.2199
DS30% Lubritab60%	0.6329	0.6494	2.5408
DS40% Compritol40%	0.6881	0.6944	0.9073
DS40% Compritol50%	0.6787	0.6944	2.2609
DS20% Compritol60%	0.6073	0.6148	1.2199
DS30% Compritol60%	0.6383	0.6494	1.7093
DS40% GMS40% PEG1%	0.7246	0.7353	1.4552
DS40% GMS40% PEG1% Tween1%	0.6912	0.7075	2.3039
DS40% GMS40% PEG0.5% Tween0.5%	0.6944	0.7177	3.2465
DS40% GMS40% PEG0.2% Tween0.2%	0.6881	0.6977	1.3760

Carr's compressibility is distributed in a narrow range 0-3%. The value of all formulation could not be clearly concluded. The data showed no cleary difference value.

As a result of the low value of bulk, tapped density and percent Carr's compressibility index. All pellets seem to have good flow characteristics.

4. Angle of Repose and Flowability

The angle of repose indicated the flowability of mass. Lower angle of repose is obtained from the mass with better flowability (Aiache and Beyssac, 1995).

In this study, angle of repose and flowability of pellets prepared from various formulations could not be determined. Because the pellet can not form a conical heap when flow from the glass funnel glass. The height and the radius of the cone could not be measured. From this result, all matrix pellets seem to have good flow characteristic.

5. Friability

Percent friability of matrix pellets with various components is shown in Table 14.

The value varied between 0.0012-0.1730%. It could be observed that there was no noticeable difference of friability between each kind of glycerides or in the series of glycerides content and loading dose.

In this experiment, the kind of glycerides, series of glycerides content, and series of loading dose showed no clear difference on the percent friability of pellets. The friability of these matrix pellets was extremely low, indicating that the extrusion/spheronization technique is an acceptable technique for producing matrix pellets.

Table 14 Percent friability of matrix pellets prepared with different glycerides content and loading dose.

Formulations	% Friability
PL40% GMS40%	0.0171
PL40% GMS50%	0.0346
PL20%GMS60%	0.0093
PL30% GMS60%	0.0203
PL40% Lubritab40%	0.0167
PL40% Lubritab50%	0.0072
PL20% Lubritab60%	0.0355
PL30% Lubritab60%	0.0058
PL40% Compritol40%	0.0345
PL40% Compritol50%	0.0341
PL20% Compritol60%	0.0206
PL30% Compritol60%	0.0196
DS40% GMS40%	0.0070
DS40% GMS50%	0.0650
DS20% GMS60%	0.0400
DS30% GMS60%	0.0350
DS40% Lubritan40%	0.0720
DS40% Lubritab50%	0.0140
DS20% Lubritab60%	0.0399
DS30% Lubritab60%	0.0220
DS40% Compritol40%	0.0412
DS40% Compritol50%	0.1730
DS20% Compritol60%	0.0400
DS30% Compritol60%	0.0700
DS40% GMS40% PEG 1%	0.0470
DS40% GMS40% PEG 1% Tween1%	0.0480
DS40% GMS40% PEG 0.5% Tween 0.5%	0.0040
DS40% GMS40% PEG 0.2% Tween 0.2%	0.0101

Pellets that showed friability less than 1% were mechanically acceptable for the next process. The friability is an indicator of pellets strength or hardness that is the lesser the friability, the greater the hardness. The glyceride matrix pellets prepared from the above mentioned process showed low and narrow range percent friability in all formulation. This could be due to the glycerides in the formulation would induce the hardness of the pellets by forming the matrix in the pellets. These matrix pellets should be stronger than the pellets with hydrophilic polymer as additives.

6. Drug Content

The percent drug contents of the matrix pellets from various formulations are shown in Table 15.

There was no clearly different between percent theoretical and percent experimental drug content. All of matrix pellets formulation had percent drug content in the range of 90-110%.

The uniformity of percent drug content was observed. They are not effected by the method of preparation. This result indicated that mixing all ingredients by planetary mixer could produce a homogeneous mass.

7. Sphericity of Pellets

In this study, degree of sphericity was derived from parameter that based on two-dimensional image of the particles by using Image analyzer. Hellen et al. (1993) reported that the roundness parameter was more sensitive and could classify the pellets clearly according to visual observation. The roundness parameter increased as pellets shape became more spherical and the value was close to 1.0. The pellips parameter increased as the shape of pellets became more spherical like circularity and roundness parameter.

Table 16 showed the value of sphericity of represent pellets (n=30), the aspect ratio is closed to 1. Indicating, the shape of pellets is nearest to spheres in all formulations and also referred to good flow property of pellets.

The average size of pellets was also investigated, the illustrated that pellets had an averages size in the range of 1.0-1.4 mm and 0.9-1.0 mm for pellets mesh cut #14/18 and # 18/20, respectively. This average size is correlated to the range of the U.S. Standard ASTME 11-61 (Ghibre-Sellassie, 1989).

Table 15 The percentage of drug content in matrix pellets.

Formulation	1	2	3	Average
PL40% GMS40%	97.88	96.96	97.51	97.45
PL40% GMS50%	98.07	98.07	98.07	98.07
PL20%GMS60%	94.29	93.18	96.88	94.79
PL30% GMS60%	92.24	93.48	93.72	93.15
PL40% Lubritab40%	98.07	98.07	98.07	98.07
PL40% Lubritab50%	97.88	98.07	98.07	98.01
PL20% Lubritab60%	95.40	96.98	98.00	96.76
PL30% Lubritab60%	96.19	96.44	94.96	95.86
PL40% Compritol40%	92.88	93.25	92.14	92.76
PL40% Compritol50%	93.81	92.70	91.03	92.51
PL20% Compritol60%	98.00	95.40	100.22	97.87
PL30% Compritol60%	96.44	99.70	96.93	97.59
DS40% GMS40%	100.19	100.39	100.59	100.39
DS40% GMS50%	99.80	103.39	102.79	101.99
DS20% GMS60%	105.24	103.84	102.44	103.84
DS30% GMS60%	101.22	102.28	100.95	101.48
DS40% Lubritab40%	96.01	98.20	96.81	97.00
DS40% Lubritab50%	96.41	96.81	96.61	96.61
DS20% Lubritab60%	103.98	102.59	103.78	103.45
DS30% Lubritab60%	99.36	98.69	98.43	98.83
DS40% Compritol40%	97.20	96.61	97.00	96.94
DS40% Compritol50%	97.00	97.00	96.01	96.67
DS20% Compritol60%	94.61	94.01	95.09	94.57
DS30% Compritol60%	102.15	101.22	99.89	101.09
DS40% GMS40% PEG1%	93.02	91.42	96.81	93.75
DS40% GMS40% PEG1% Tween1%	93.22	91.62	96.81	93.88
DS40% GMS40% PEG0.5% Tween0.5%	93.22	91.62	96.81	93.88
DS40% GMS40% PEG0.2% Tween0.2%	93.02	94.81	96.81	94.88

Table 16 Sphericity values of matrix pellets prepared with different drug and glycerides content.

Formulations	Aspect Ratio	Average Size (mm)
PL 40% GMS 40% #14/18	0.9834 (0.0557)	1.1922 (0.1057)
PL 40% GMS 40% #18/20	0.9726 (0.0600)	1.0056 (0.0489)
DS 40% GMS 40% #14/18	0.9815 (0.1043)	1.2328 (0.1172)
DS 40% GMS 40% #18/20	1.0000 (0.0772)	1.0180 (0.0580)
PL 40% Lubritab 40% #14/18	0.9694 (0.0690)	1.1288 (0.0661)
PL 40% Lubritab 40% #18/20	0.9866 (0.0599)	0.9843 (0.1300)
DS 40% Lubritab 40% #14/18	0.9961 (0.0950)	1.0670 (0.1077)
DS 40% Lubritab 40% #18/20	0.9634 (0.0821)	0.9553 (0.0749)
PL 40% Compritol 40% #14/18	1.0000 (0.0770)	1.1474 (0.0968)
PL 40% Compritol 40% #18/20	0.9745 (0.0843)	0.9884 (0.0608)
DS 40% Compritol 40% #14/18	1.0000 (0.0697)	1.1318 (0.0836)
DS 40% Compritol 40% #18/20	0.9823 (0.1120)	1.0002 (0.1411)

8. Infrared Spectra (IR)

The IR spectra of three glycerides, lactose and Avicel® PH 101 are shown in Figure 17. The IR spectra of Avicel® PH 101 showed broad band of O-H stretching at the wavenumbers range of 3300-3400 cm^{-1}. The IR spectra of three glycerides are shown the same characteristics because of having the same structures bone. 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 peak at 2849 and 2917 cm^{-1} were resulted from aliphatic C-H stretching. There are a little different in the position of the peaks.

The principal peaks of propranolol hydrochlorides were observed at the wavenumbers of 773, 790, 1108, 1243, 1269, and 1151 cm^{-1} (Table 1D, Appendix D). The peaks at 770, and 797 cm^{-1} were resulted from aromatic ring =CH out of plane blending. 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

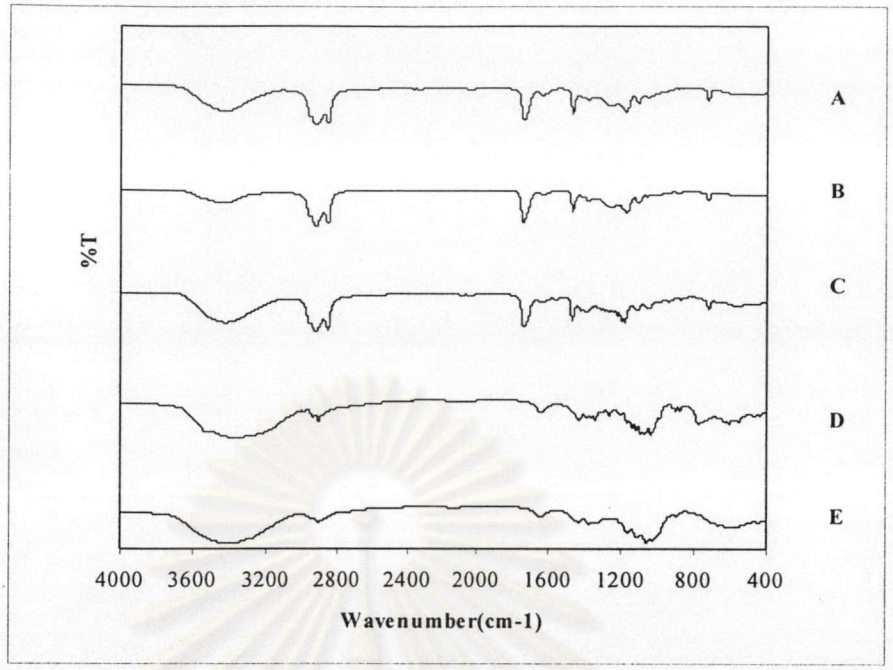


Figure 17 IR spectra of Compritol®ATO 888 (A); Lubritab® (B); GMS (C); Lactose (D); and Avicel® PH 101 (E).

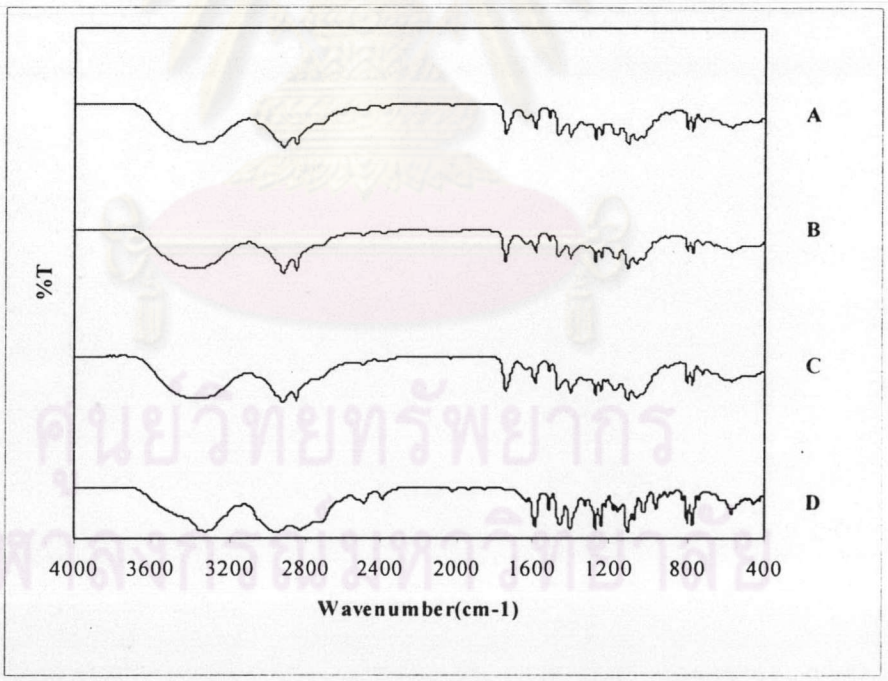


Figure 18 IR spectra of 40% propranolol hydrochloride 40% Compritol®ATO 888 (A); 40% propranolol hydrochloride 40% Lubritab®(B); 40% propranolol hydrochloride 40% GMS (C); and propranolol hydrochloride (D).

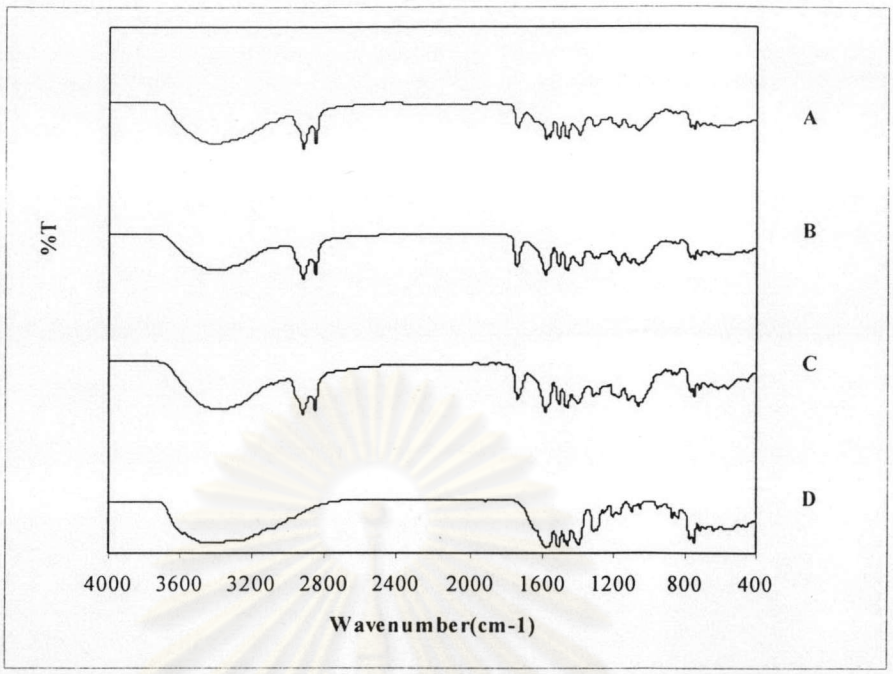


Figure 19 IR spectra of 40% diclofenac sodium 40% Compritol®ATO 888 (A); 40% diclofenac sodium 40% Lubritab® (B); 40% diclofenac sodium 40% GMS (C); and diclofenac sodium.

asymmetric stretching in ethers. And the IR peaks at 1579 cm^{-1} were resulted from C=C cyclic stretching.

The principal peaks of diclofenac sodium were observed at wavenumbers of 749, 771, 1287, 1308, 1500, and 1576 cm^{-1}. The peaks at 756 and 775 cm^{-1} were resulted from C-H out of plane bending. The IR absorption bands at 1286 and 1308 cm^{-1} were resulted from C-N stretching. The peaks at 1504 and 1572 cm^{-1} were resulted from C=C stretching.

The IR spectra of matrix pellets containing 40% of two drug and 40% of glycerides are depicted in Figures 18 and 19 (for propranolol hydrochloride and diclofenac sodium, respectively). The IR spectra of matrix pellets showed the combination of drug peaks with glycerides, whereas the principal peaks of both drug and glycerides were also still revealed. Some positions of the peaks were slightly shifted from the original material. The characteristic peak of lactose and Avicel® PH 101 was disappeared because there was a small quantity in the formulations. It could

be concluded that interaction between drug and glycerides was unlikely to occur and types of glycerides had no effect on the IR spectra.

9. Powder X-ray Diffraction

The powder X-ray diffraction patterns of pure substances (Lubritab®, GMS, Compritol®ATO 888, lactose, and Avicel® PH 101, respectively) are shown in Figure 20. And the matrix pellets, which were produced from various formulations, are illustrated in Figure 21 and 22.

The X-ray diffraction patterns of lactose are shown crystalline characteristics at 12.470°, 19.950°, and 21.190° 2θ. Avicel®PH 101 is shown halo of amorphous characteristics. The X-ray diffraction patterns show the characteristics peaks at 19.470°, 22.870°, 23.430°, and 19.270°, 23.070°, 23.990° 2θ for GMS and Lubritab®, respectively. Only two characteristic peaks appear at 21.030°, and 22.950° 2θ for Compritol®ATO 888.

The X-ray diffraction pattern of propranolol hydrochloride alone shows characteristics peaks at 9.670°, 12.430°, 16.630°, 19.470°, 21.150°, and 25.030° 2θ (Table 2D, Appendix D). There was some difference between the X-ray diffraction pattern of propranolol hydrochloride alone and propranolol hydrochloride matrix pellets prepared from three kind of glycerides. They showed the combination of propranolol hydrochloride and each glycerides diffraction peaks. Therefore, propranolol hydrochloride was still in crystalline form but some characteristic peaks of each formulation were shifts from the original crystalline pattern.

The X-ray diffraction patterns of diclofenac sodium alone are shown to have characteristics peaks at 6.630°, 8.550°, 15.230°, 17.150°, 19.910°, 23.510°, and 27.910° 2θ (Table 2D, Appendix D). They are combination peaks of 40% diclofenac sodium and all 40% glycerides. The eminent peak was still shown but the percent crystallinity were less than those original crystals.

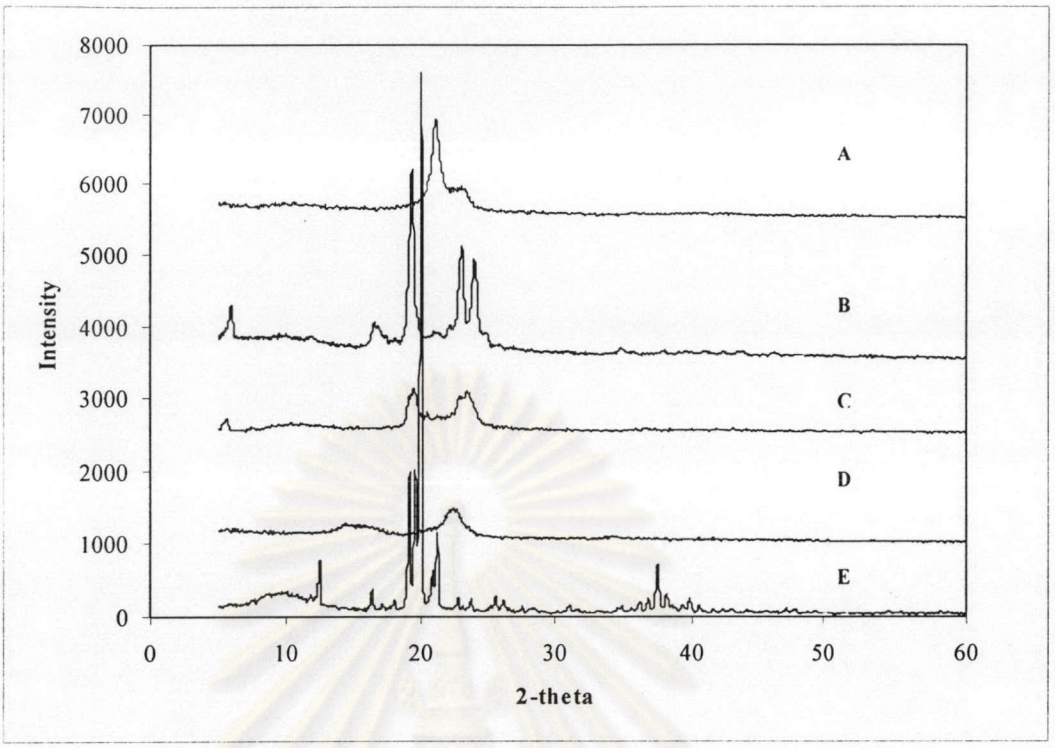


Figure 20 X-ray diffractograms of Compritol®ATO 888 (A); Lubritab® (B); Glyceryl monostearate (C); Avicel®PH 101 (D); and Lactose (E).

It might be the small change of some characteristic peaks position occurred due to the pack processing of substances into the quartz slide. There are difficult to pack a smooth surface in the quartz slide. If the surface in quartz slide are roughed, the exposed of X-ray beam would affect to the intensity of crystalline but not affect to the pattern of diffractograms.

Lactose and Avicel® PH 101 disappeared from the diffractograms of matrix pellets formulation. It might be due to the low amount, which were used in the formulation.

The X-ray diffractograms of propranolol hydrochloride and diclofenac sodium matrix pellets are stilled exhibits the crystalline form.

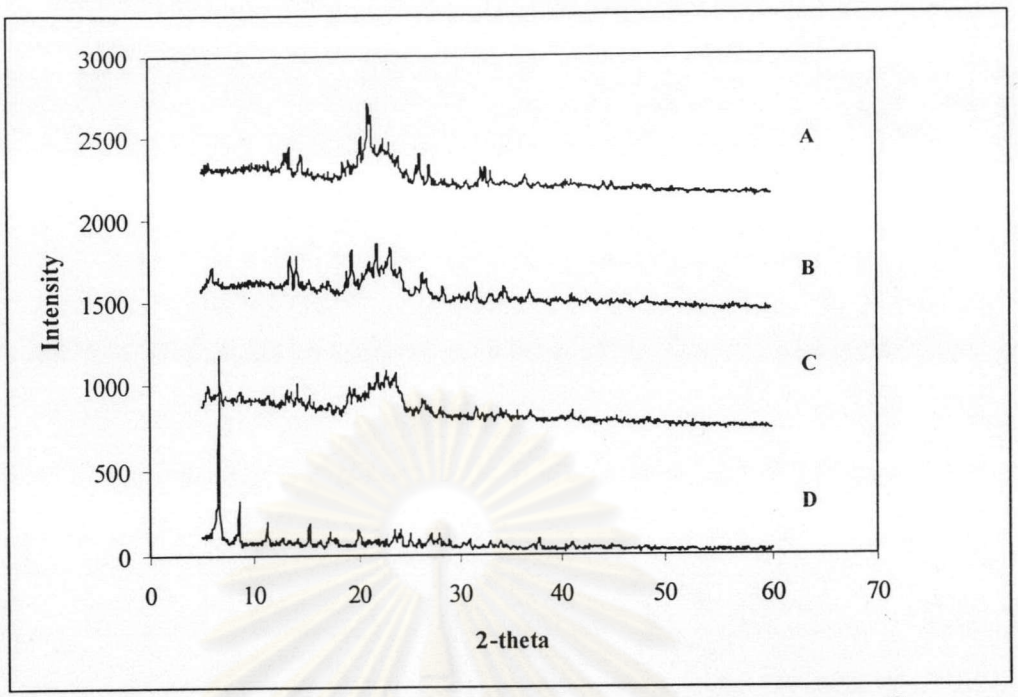


Figure 21 X-ray diffractograms of 40% diclofenac sodium 40% Compritol®ATO 888 (A); 40% diclofenac sodium 40% Lubritab® (B); 40% diclofenac sodium 40% GMS (C), diclofenac sodium (D).

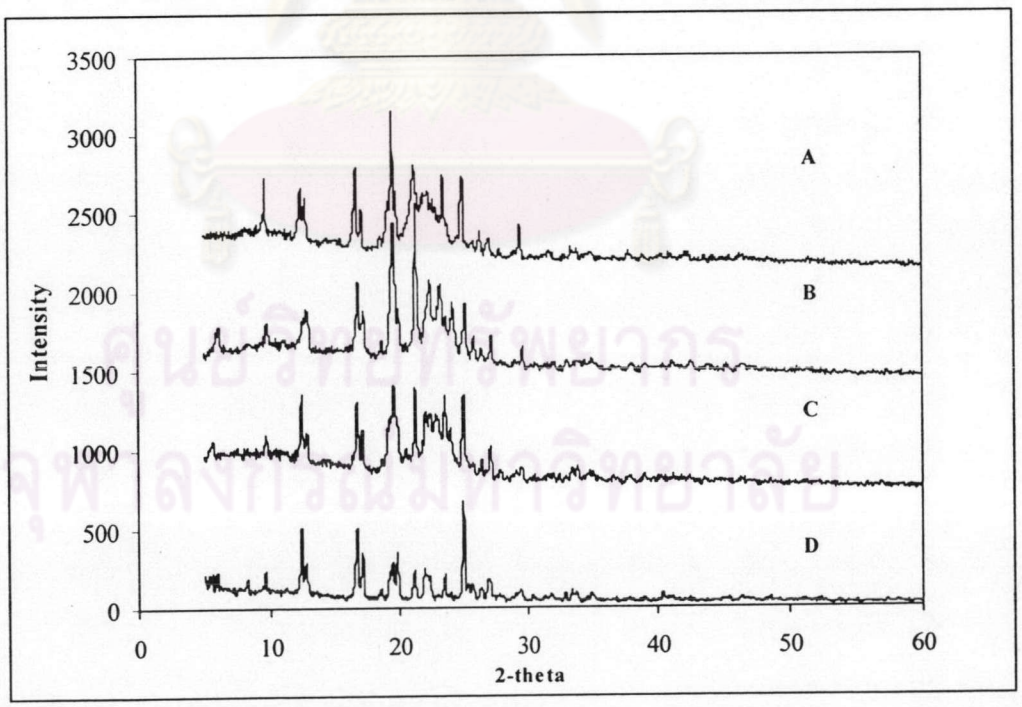


Figure 22 X-ray diffractograms of 40% propranolol hydrochloride 40% Compritol® ATO 888 (A); 40% propranolol hydrochloride 40% Lubritab® (B); 40% propranolol hydrochloride 40% GMS (C), propranolol hydrochloride (D).

10. Differential Scanning Calorimetry (DSC)

The DSC thermograms of pure propranolol hydrochloride, diclofenac sodium, Avicel PH 101, lactose, GMS, Lubritab®, Compritol® ATO 888, and matrix pellets prepared from different formulations are shown in Figures 23-26. The endothermic peak of all components and matrix pellets products are indicated in Table 3D and Appendix D.

The thermograms of almost pure component presented only the endotherm characteristic. Except lactose showed two endothermic peaks at 149.4°C and 217.4°C and pure diclofenac sodium reveal presented the exothermic then followed by endothermic peaks at 288.7°C. The melting point of propranolol hydrochloride was 164.3°C. Melting point of GMS, Lubritab®, and Compritol® ATO 888 was shown to be at 60.8°C, 64.1°C and 71.5°C, respectively.

From Figure 25, there was no clearly difference between the DSC thermograms pattern of propranolol hydrochloride alone and those product pellets but the difference in DSC peak temperature were visible. The melting points of propranolol hydrochloride in GMS and Compritol® ATO 888 were slightly shifted to lower temperature, while propranolol hydrochloride in Lubritab® was slightly shifted to higher temperature. The DSC peak temperature of Avicel® PH 101 disappeared from the thermograms. There was no indication of interaction, since the position of the major peaks remained relatively unchanged.

Figure 26 shows the DSC thermograms of diclofenac sodium alone and the formulation of diclofenac sodium pellets, which contained three glycerides. The thermograms of product still have the characteristic peaks of diclofenac sodium and glycerides similar to those of propranolol hydrochloride pellets. But the characteristic peak of active ingredient in all formulation was slightly shifted to the lower temperature. The lower in melting point indicated the presence of amorphous or polymorphic form of diclofenac sodium products. Surprisingly, unless diclofenac sodium and glycerides peak are depicted new two peaks occurring between the peak of glycerides (in range 55-70°C).

These results could be confirmed by TGA method for checking the temperature peaks and percent weight loss of the substances. Figure 27 showed the TGA thermograms of diclofenac sodium 40% and Compritol® ATO 888 40%. The weight loss occurred at temperature 65.9°, 102.3 °C. It might be expected that the weight lost at 65.9° C is the peak in front of peak of glycerides and at temperature 102.3 °C it may be the peak behind glycerides peak.

The weight loss at 65.9°C appears at lower temperature of melting point of glycerides. In addition, the another peak appeared at higher temperature (102.3°C). At 259.6°C should be the weight loss of diclofenac sodium indicated the temperature is nearest the melting point of it. Because of the melting of diclofenac sodium and glycerides are approximately 300°C the temperature that we seen at 350°C would be degradation of them.

For the scale up process, should be aware the residue of chloroform in the preparations. That is a good idea to check the remained residue of chloroform before the next process by Gas Chromatography (GC).

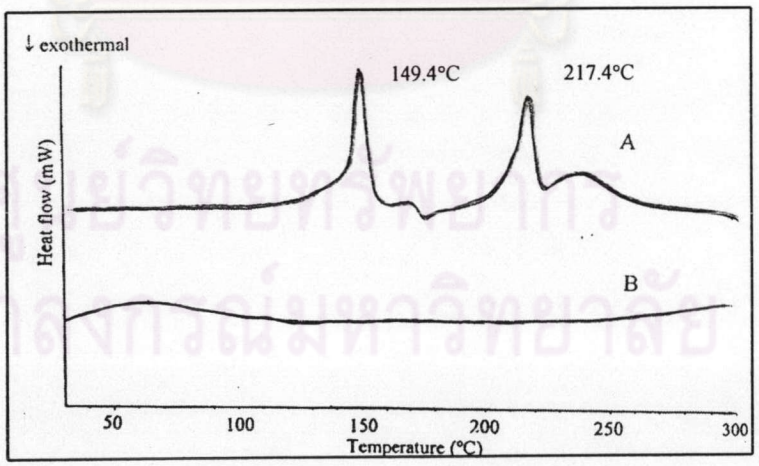


Figure 23 DSC thermograms of lactose (A); and Avicel®PH 101 (B).

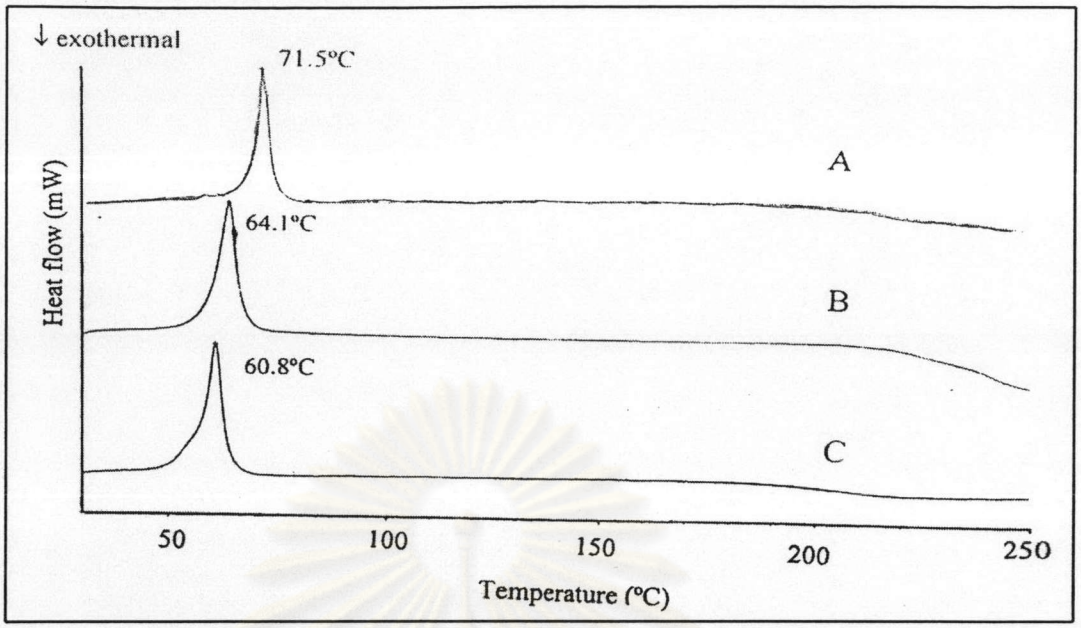


Figure 24 DSC thermograms of Compritol®ATO 888 (A); Lubritab® (B); and Glyceryl monostearate (C).

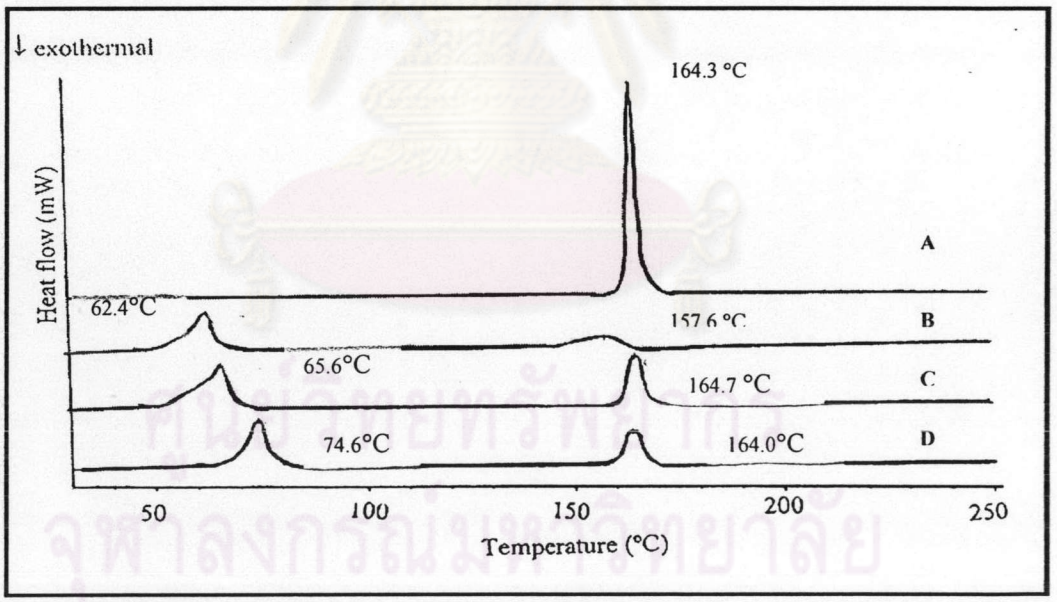


Figure 25 DSC thermograms of propranolol hydrochloride (A); and matrix pellets prepared from 40% of GMS (B); Lubritab® (C); and Compritol®ATO 888 (D) with 40% propranolol hydrochloride.

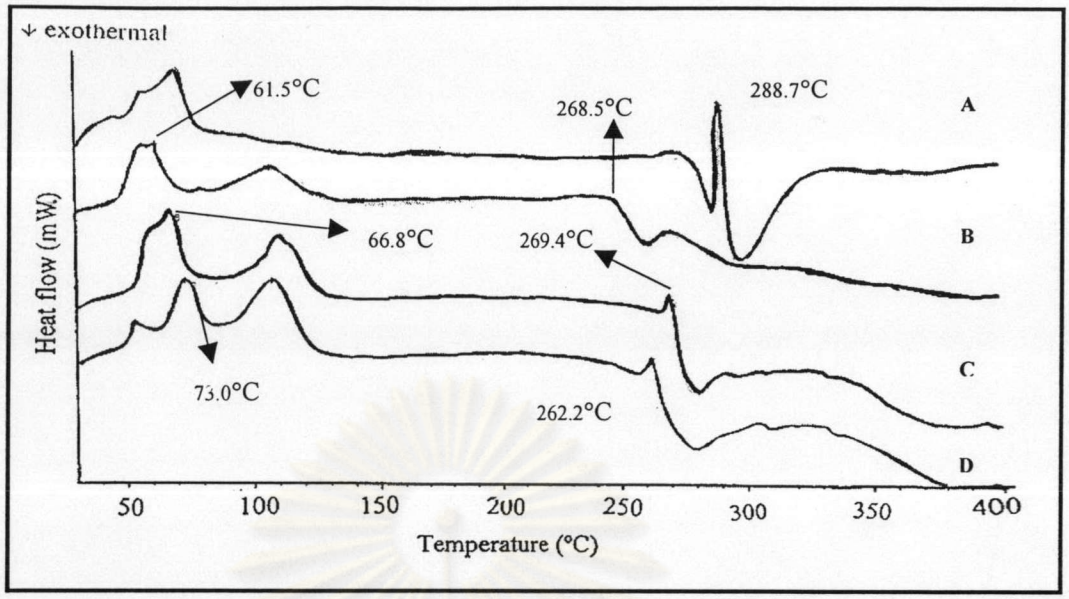


Figure 26 DSC thermograms of diclofenac sodium (A); and matrix pellets prepared from 40% of GMS (B); Lubritab® (C); and Compritol®ATO 888 (D) with 40% diclofenac sodium.

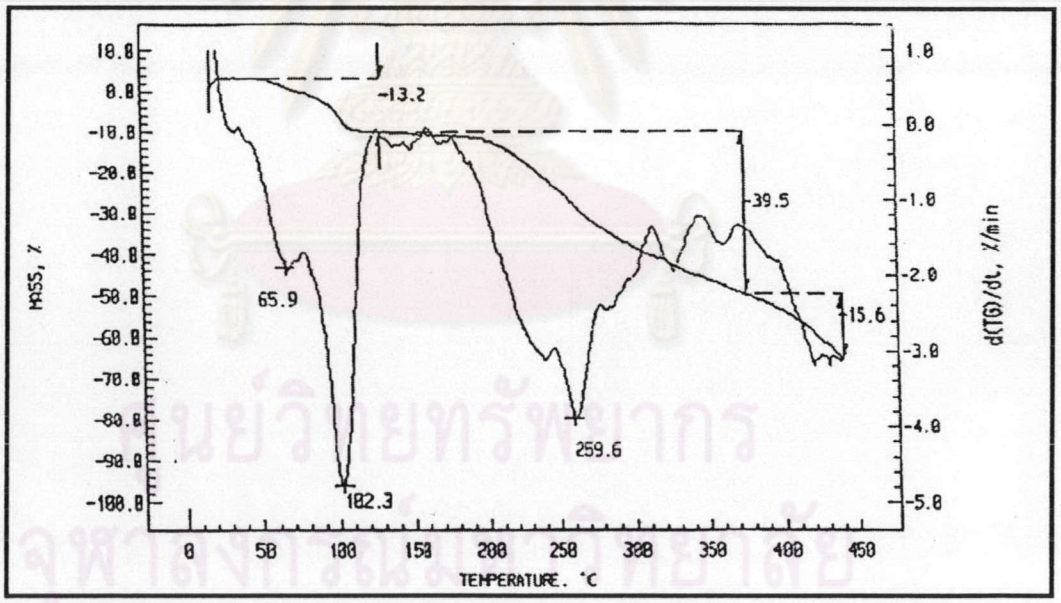


Figure 27 The TGA thermogram of pellets that containing 40% diclofenac sodium and 40% Compritol®ATO 888.

II Dissolution Study

The preparations were produced by filling 400 mg of pellets equivalent to each drug of 160 mg into hard gelatin capsules. They were evaluated by testing in both acid (0.1 N HCl, pH 1.2) and basic media (phosphate buffer pH 6.8). The dissolution data of each formulation are presented in Tables 1B-16B (Appendix B).

1. Drug Release of Pellets

1.1 Pellets without glycerides

The preparations of pellets without glycerides were composing drug, lactose, and microcrystalline cellulose (Avicel®PH 101). It use as controlled formulation.

1.1.1 Propranolol Hydrochloride Capsule

The drug release data of propranolol hydrochloride blank pellets in both acidic and basic stage is listed in Table 1B and Appendix B, and the drug release profiles are shown in Figure 28.

The release profiles of blank propranolol hydrochloride pellets exhibited rapid release of active drug, approximately 100% of propranolol hydrochloride was released completely in 0.25 hour.

1.1.2 Diclofenac Sodium Capsules

In earlier work (Adeyeye and Li, 1990), it was shown that the solubility of diclofenac sodium highly depend on the pH of the media used. At low pH values, the solubility of the drug was very poor (< 1 mg/ml at pH 1.1). With increasing pH, the solubility of the drug improved dramatically. Hence, it is not suprising that these dissolution studies reveal this result (Figure 29). The drug dissolution rates increased greatly with pH over 1.2. Therefore, the pH of the dissolution media is a critical factor in determining the dissolution rate of diclofenac sodium.

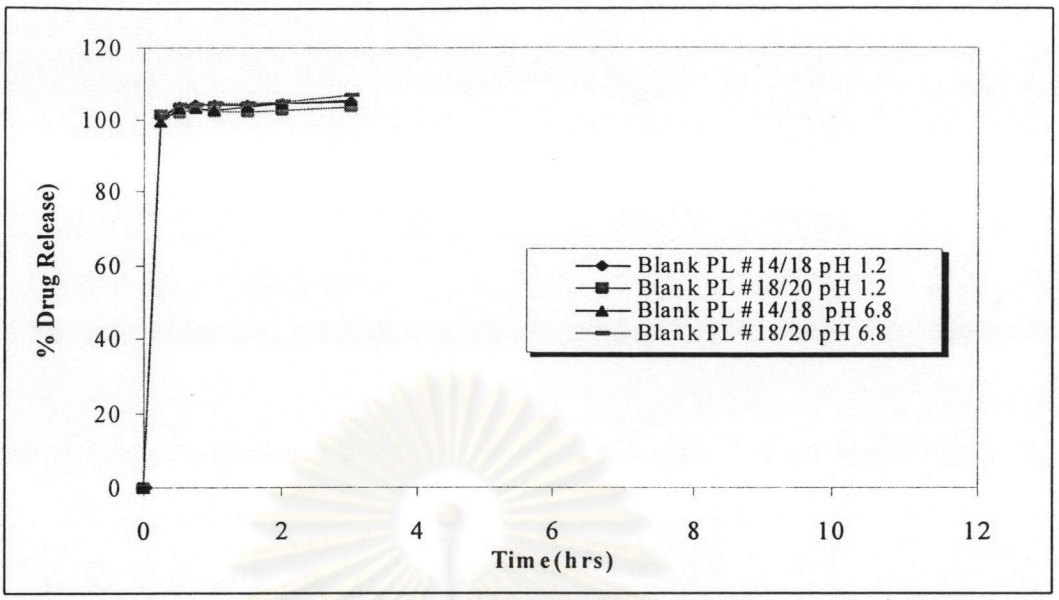


Figure 28 The release profiles of blank propranolol hydrochloride pellets in media pH 1.2 and pH 6.8 (#14/18 and #18/20 indicated the size of pellets).

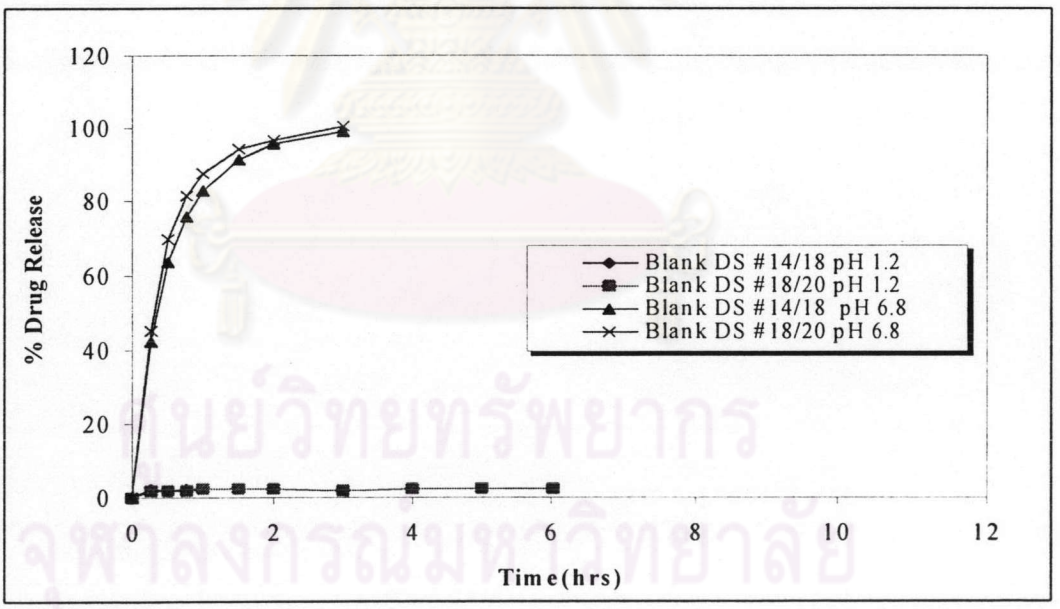


Figure 29 The release profiles of blank diclofenac sodium pellets in media pH 1.2 and pH 6.8.

The drug release data of blank diclofenac sodium in both acidic and basic media are listed in Table 1B and Appendix B.

The release profile of diclofenac sodium was affected by the dissolution medium. In 0.1 N HCl, the percentage of diclofenac sodium release in 6 hours was 3%. Whereas in phosphate buffer pH 6.8 system, it was completely dissolved within 3 hours. This result indicated that diclofenac sodium was more soluble in phosphate buffer pH 6.8 than in 0.1 N HCl (Sheu et al., 1992; Liu et al., 1995).

Due to low solubilities of diclofenac sodium in 0.1 N HCl, the absorbance of solution is also very low. Thus the limit of quantitative of UV-visible spectrophotometer should be investigated. From the studied, the lowest quantitative that UV-visible spectrophotometer is read are 0.4 μg/mL. The % CV is in the range of ± 5% (see Table 7A, Appendix A).

1.2 The Matrix Pellets

The dissolution data and drug release profiles of the matrix pellets were divided into three groups depending on the type of glycerides used in the formulations.

1.2.1 Influence of Glyceride Concentrations

A. Glyceryl Monostearate (GMS)

The dissolution profiles of 40% propranolol hydrochloride from 40% and 50% GMS matrix pellets in 0.1 N HCl and phosphate buffer pH 6.8 are shown in Figures 30 and 31. The dissolution data are presented in Table 2B and Appendix B.

The percent of propranolol hydrochloride release from GMS matrix pellets reached 100% in 2 hours. The formulas that composed of 50% GMS showed slightly slower release than those of 40% GMS. Increasing the fraction of GMS resulted in a corresponding decrease of the dissolution rate. The concentration of glycerides in the

formulation was the determining factor in control release rate of drug. They are exhibited the similar release profiles from different concentration of GMS.

In 0.1 N HCl, the release of propranolol hydrochloride was faster than in phosphate buffer pH 6.8. It could be explained that the different solubilities of drug in two media. The mean equilibrium solubilities of propranolol hydrochloride at 37 ± 0.5°C are reported by Rekhi et al., (1989). Propranolol hydrochloride, a basic drug with pK_a of 9.45, should be more soluble in acidic solutions (in which the ionized form of drug is dominant) than in alkaline solutions (in which it is predominantly unionized). Therefore, more drugs release was found in 0.1 N HCl when compared to phosphate buffer pH 6.8.

The dissolution profiles of diclofenac sodium from 40% and 50% GMS matrix pellets in both dissolution media are shown in Figure 32. The dissolution data are presented in Table 5B and Appendix B.

The percentage of diclofenac sodium release from GMS matrix pellets in 0.1 N HCl was less than 3 % similar to blank diclofenac sodium capsules. While the release of diclofenac sodium in phosphate buffer pH 6.8 was slower than blank capsules. They were released about 80% in 12 hours. The release of diclofenac sodium was decreased when the concentration of GMS in the formulation was increased (Saraiya and Botton, 1990). And could be explained that Avicel®PH 101 in the formulations reduced. Due to the porous particles of Avicel®PH 101 (Wade and Weller, 1994), the decreased of Avicel®PH 101 result in decreased porous of sphere and also decreased drug release.

From this study, the release of diclofenac sodium containing GMS as matrix forming agent had capacity to retard drug release for 12 hours. The first order plots were found to be best fit to release data as shown in Figure 33. The coefficients of determination (r^2) of these parameters are tabulated in Tables 2E and Appendix E.

The size of pellets appeared to be an important factor to determine the release of drug. For this study, varying the particle size of pellets would dramatically affect

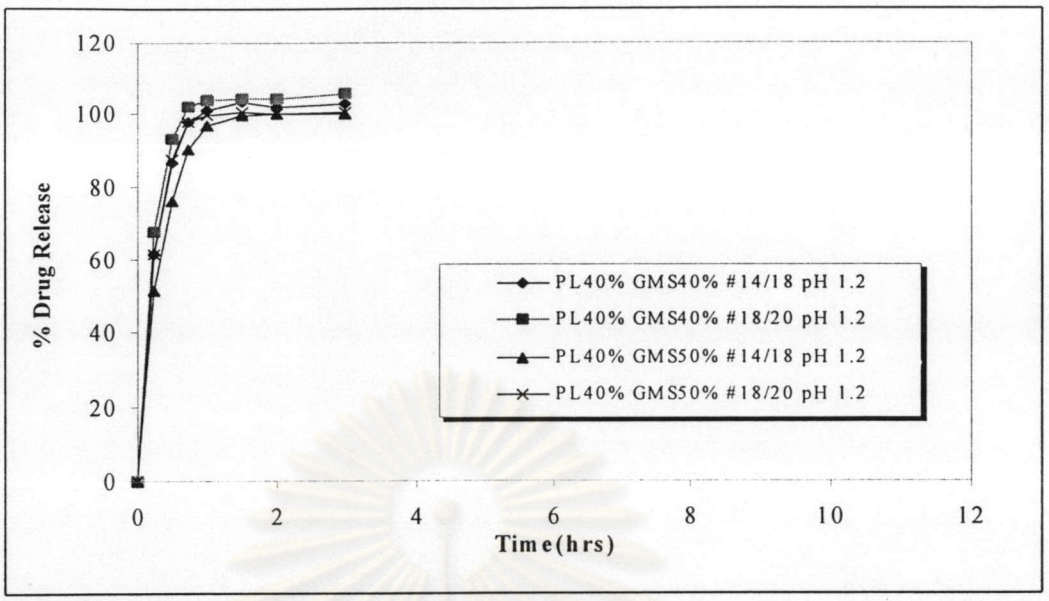


Figure 30 The release profiles of propranolol hydrochloride matrix pellets prepared from series of GMS in medium pH 1.2.

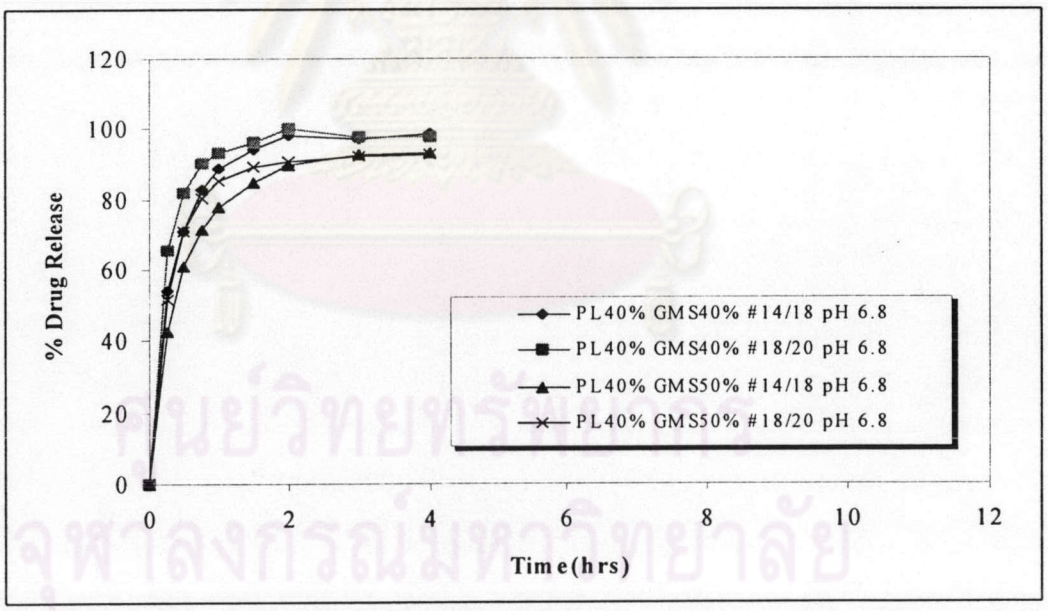


Figure 31 The release profiles of propranolol hydrochloride matrix pellets prepared from series of GMS in medium pH 6.8.

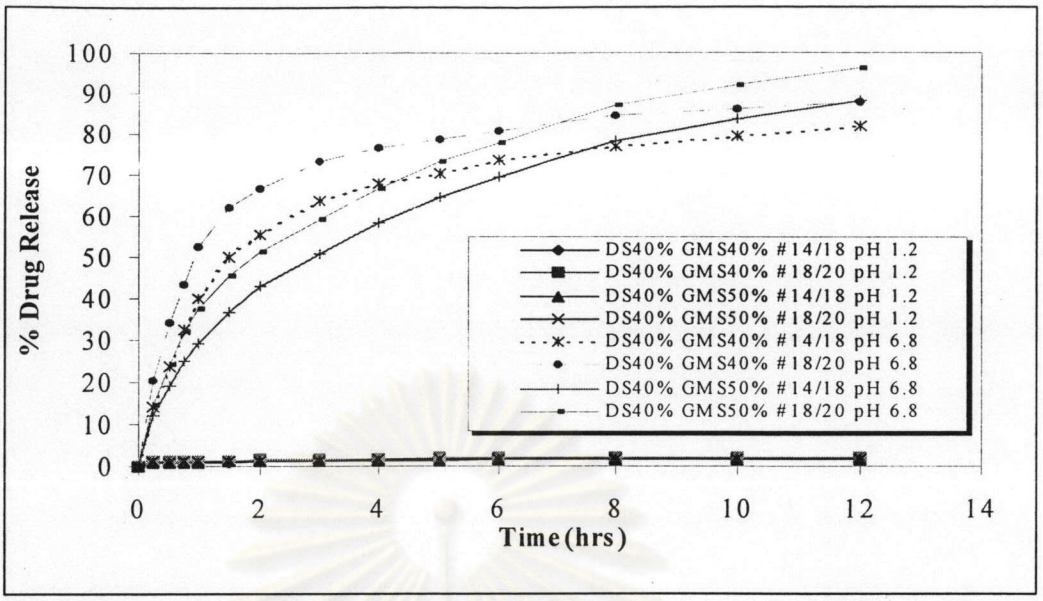


Figure 32 The release profiles of diclofenac sodium matrix pellets prepared from series of GMS in media pH 1.2 and pH 6.8.

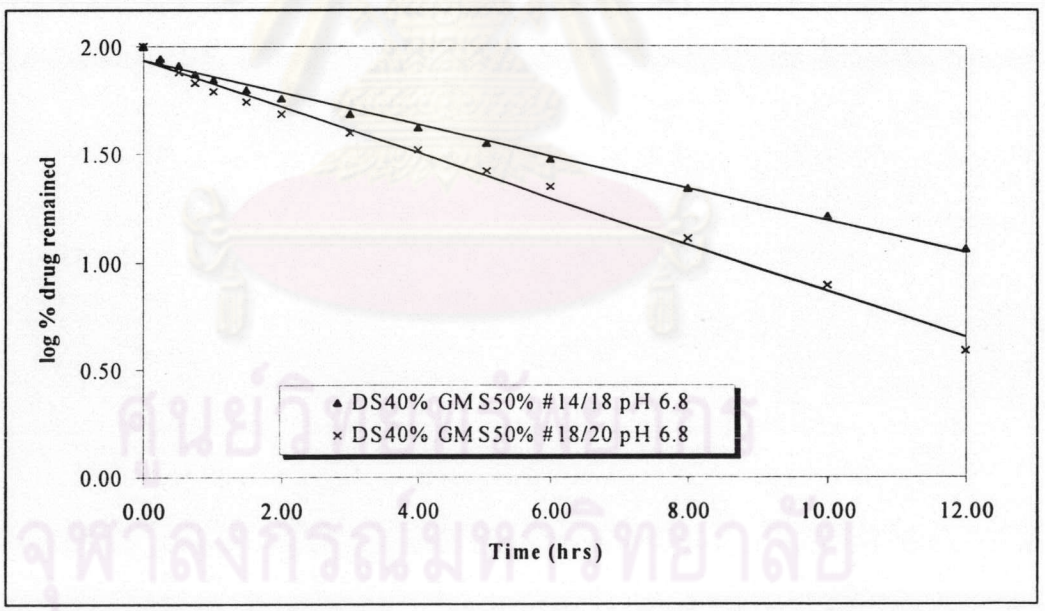
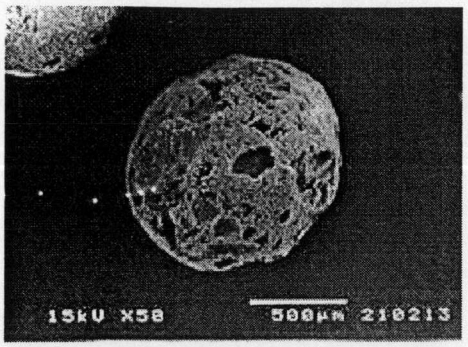
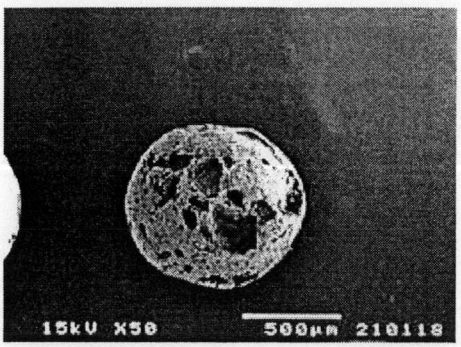


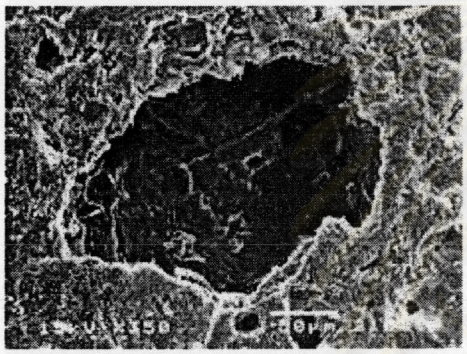
Figure 33 The first order plot of diclofenac sodium matrix pellets prepared from series of GMS in medium pH 6.8.



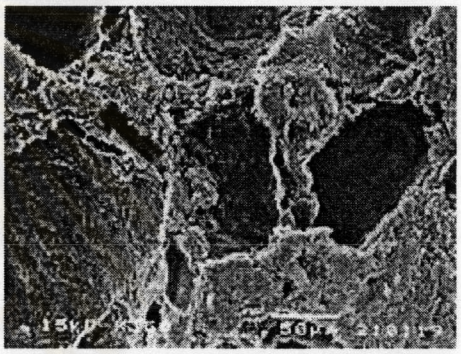
A_1



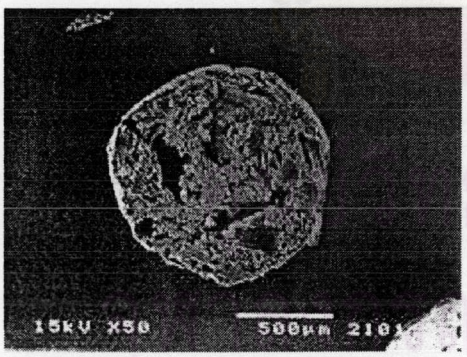
B_1



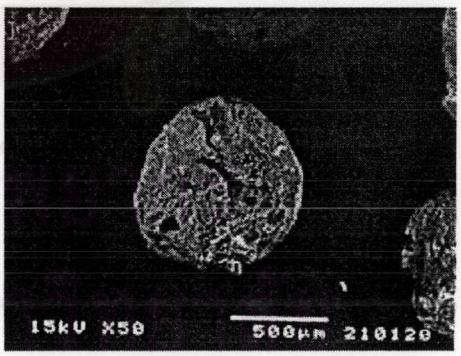
A_2



B_2

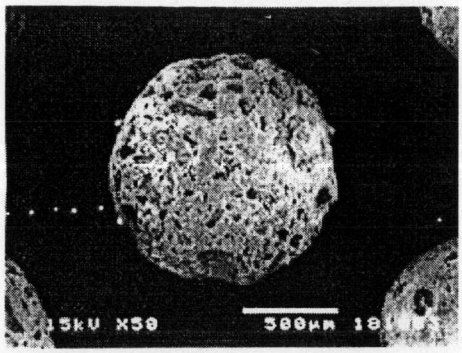


A_3

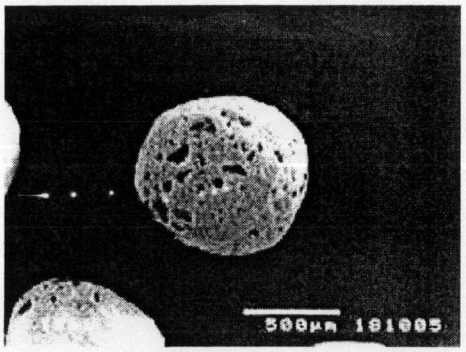


B_3

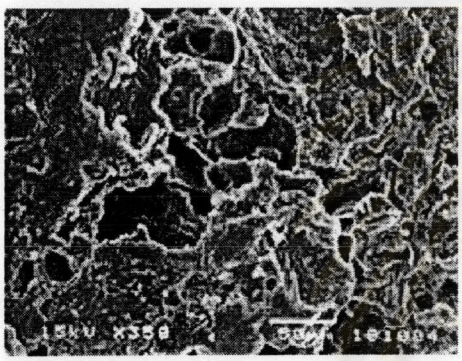
Figure 34 Scanning electron photomicrographs of 40% propranolol hydrochloride matrix pellets from the formulation using GMS (A_1, A_2; pellets size 14/18 mesh cut at ×50, ×350 magnification, A_3; cross-section at ×50 magnification; B_1, B_2; pellets size 18/20 mesh cut at ×50, ×350 magnification, B_3; cross-section at ×50 magnification) after dissolution in 0.1 N HCl.



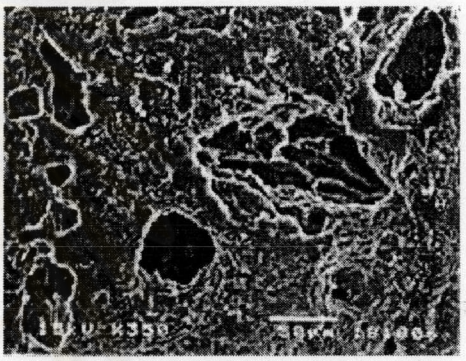
A_1



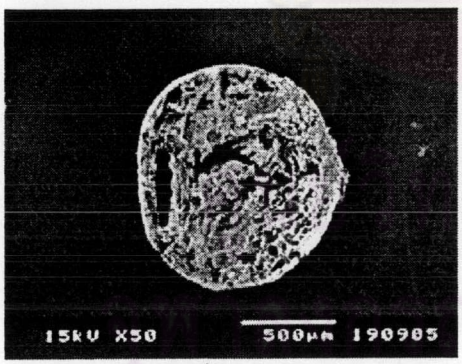
B_1



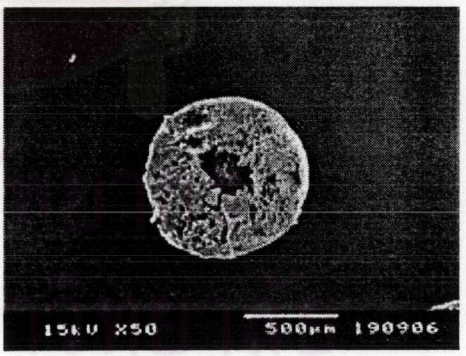
A_2



B_2

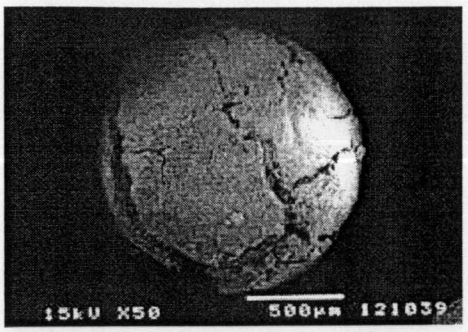


A_3

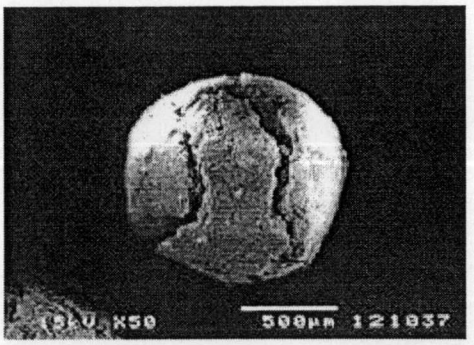


B_3

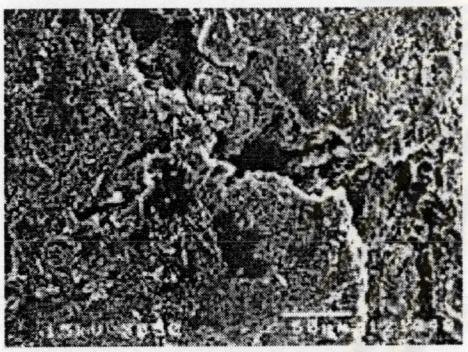
Figure 35 Scanning electron photomicrographs of 40% propranolol hydrochloride matrix pellets from the formulation using GMS (A_1, A_2; pellets size 14/18 mesh cut at ×50, ×350 magnification, A_3; cross-section at ×50 magnification; B_1, B_2; pellets size 18/20 mesh cut at ×50, ×350 magnification, B_3; cross-section at ×50 magnification) after dissolution in phosphate buffer pH 6.8.



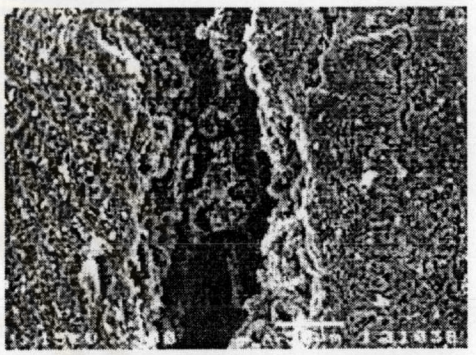
A_1



B_1

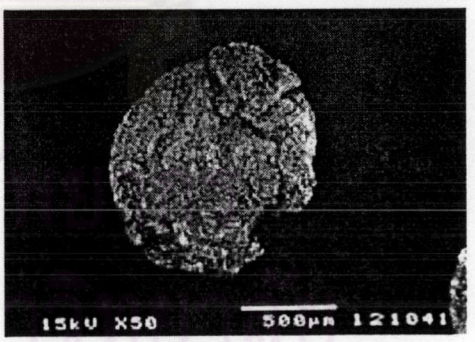


A_2



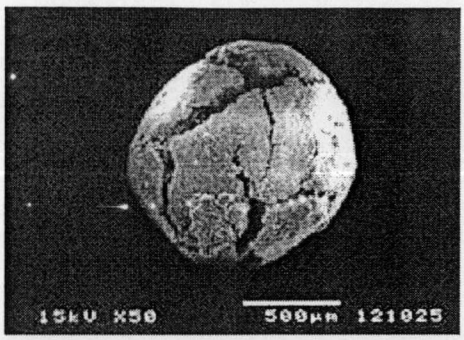
B_2

A_3

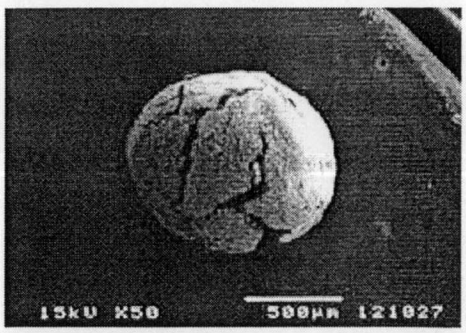


B_3

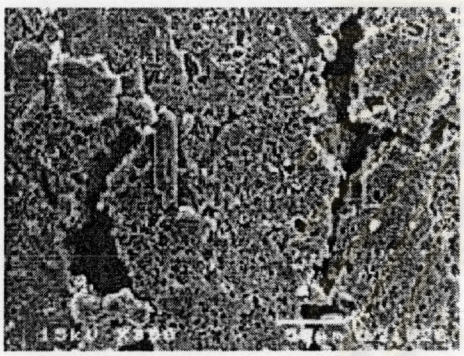
Figure 36 Scanning electron photomicrographs of 40% diclofenac sodium matrix pellets from the formulation using GMS (A_1, A_2; pellets size 14/18 mesh cut at ×50, ×350 magnification, A_3; cross-section at ×50 magnification; B_1, B_2; pellets size 18/20 mesh cut at ×50, ×350 magnification, B_3; cross-section at ×50 magnification) after dissolution in 0.1 N HCl.



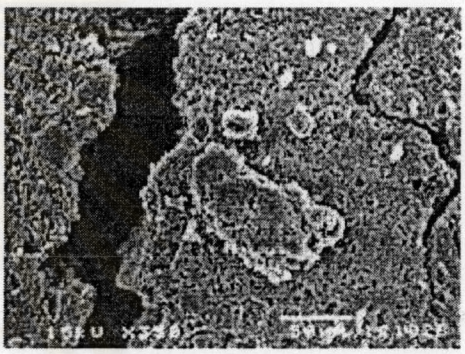
A_1



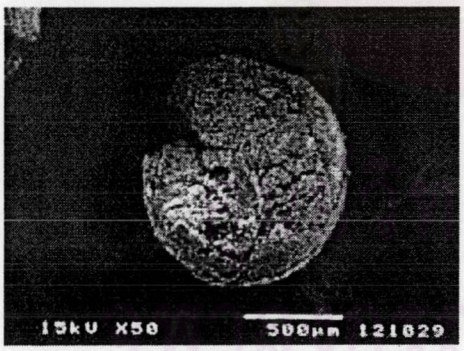
B_1



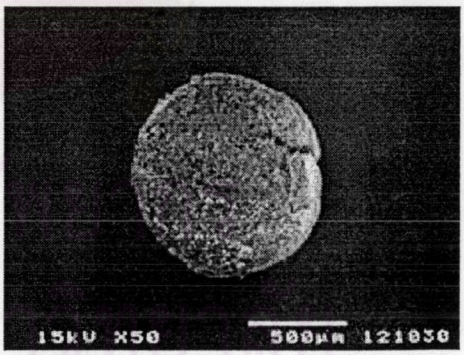
A_2



B_2



A_3



B_3

Figure 37 Scanning electron photomicrographs of 40% diclofenac sodium matrix pellet from the formulation using GMS (A_1, A_2; pellets size 14/18 mesh cut at ×50, ×350 magnification; A_3; cross-section at ×50 magnification; B_1, B_2; pellets size 18/20 mesh cut at ×50, ×350 magnification, B_3; cross-section at ×50 magnification after dissolution in phosphate buffer pH 6.8.

the release of drug from pellets. Figures 30-32 showed difference in the release profiles of propranolol hydrochloride and diclofenac sodium, respectively. The dissolution profiles from two sizes of pellets showed that the release of diclofenac sodium decreased with increasing pellets size (#14/18 mesh cut). An increase in drug release was observed with fraction #18/20 mesh cut. So, diclofenac sodium release from matrix pellets was apparently depend on the size of pellets (Wang et al., 1997) similar to propranolol hydrochloride matrix pellets.

After the release study in both media, propranolol hydrochloride matrix pellets still remained their integrity (see Figures 34 and 35). The surfaces of pellets were rougher than those before test and filled with larger and deeper pores. By the cross-section, there were some small pores connected in the channel-like structure at the center of the pellets. While the surfaces of diclofenac sodium matrix pellets showed cracks and pores on the surfaces of pellets as presented in Figures 36 and 37. Although small cracks were obtained from pellets tested in 0.1 N HCl, the release of diclofenac sodium was still less than 2% in 12 hours. But in phosphate buffer pH 6.8, the surfaces of diclofenac sodium matrix pellets had a large cracks and small pores and also affected the release of drug from pellets.

B. Lubritab® (Hydrogenated Cottonseed Oil)

The release data of propranolol hydrochloride matrix pellets from the formulations containing 40% and 50% Lubritab® are listed in Table 3B and Appendix B. The release profiles of these preparations in 0.1 N HCl and phosphate buffer pH 6.8 are illustrated in Figures 38 and 39, respectively.

The release of these formulations were completed in two hours both in 0.1 N HCl and phosphate buffer pH 6.8. It noted that the release of propranolol hydrochloride in phosphate buffer pH 6.8 was slightly slower than the release in 0.1 N HCl similar to the release study of drug that containing GMS as matrix forming agent. But the release profiles of the formulation that comprised 50% Lubritab® were almost superimpose with 40% Lubritab® in both media and there were not apparently different among release patterns between 0.1 N HCl and phosphate buffer pH 6.8.

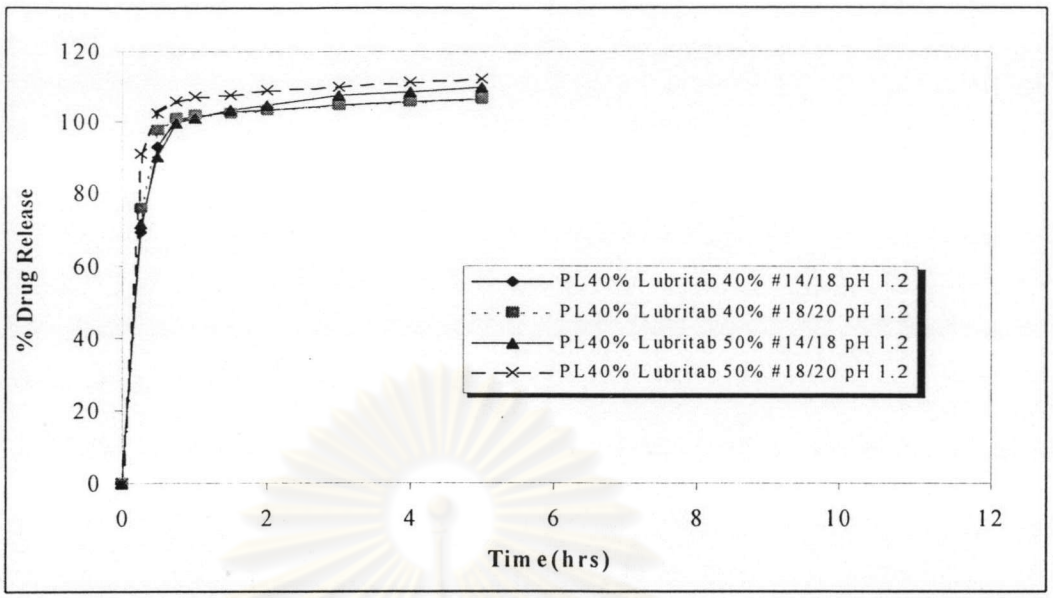


Figure 38 The release profiles of propranolol hydrochloride matrix pellets prepared from series of Lubritab® in medium pH 1.2.

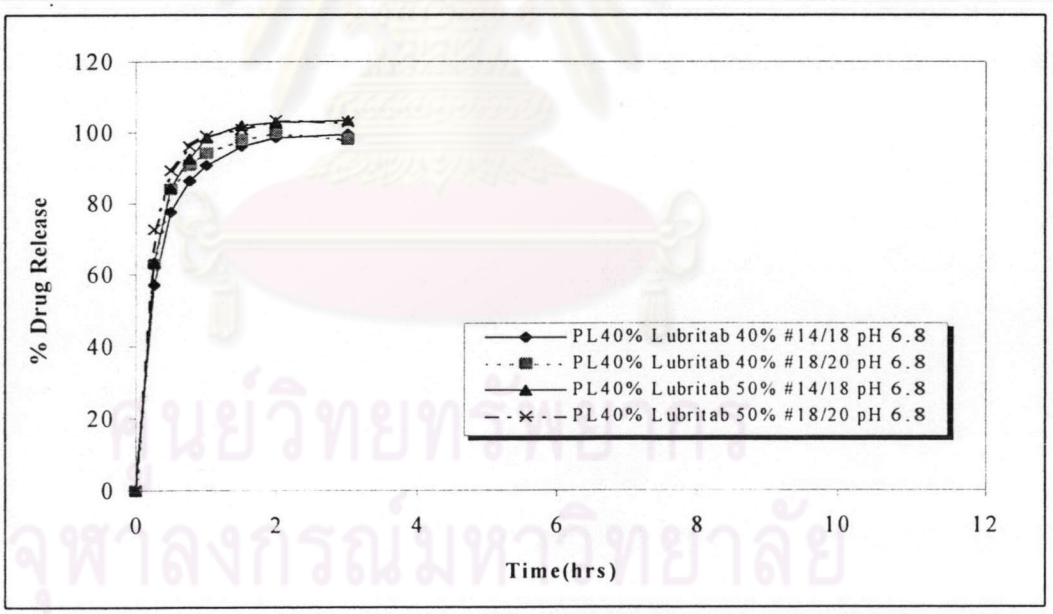


Figure 39 The release profiles of propranolol hydrochloride matrix pellets prepared from series of Lubritab® in medium pH 6.8.

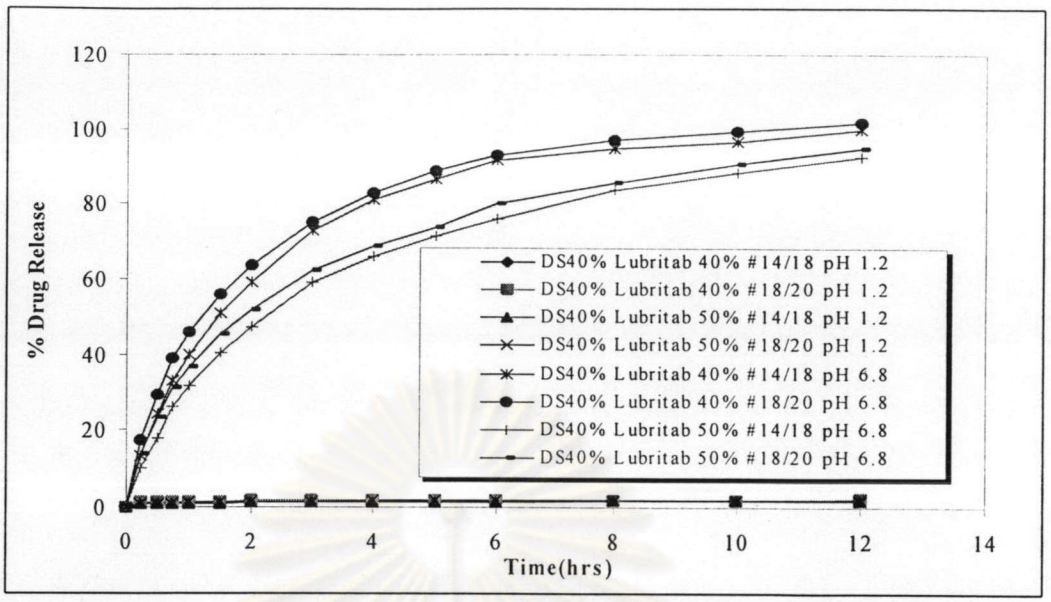


Figure 40 The release profiles of diclofenac sodium matrix pellets prepared from series of Lubritab® in media pH 1.2 and pH 6.8.

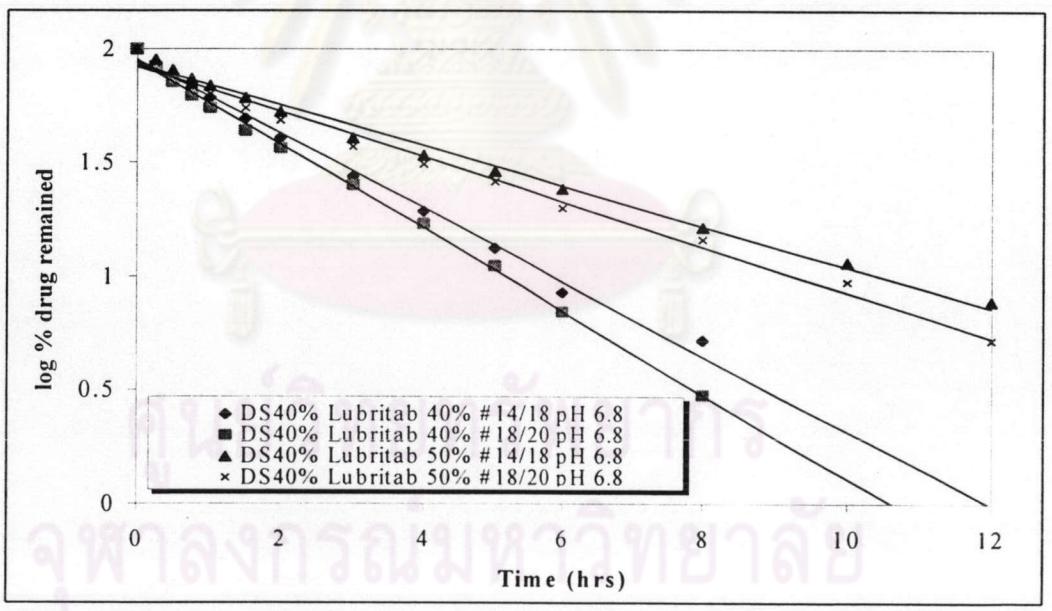


Figure 41 The first order plots of diclofenac sodium matrix pellets prepared from series of Lubritab® in medium pH 6.8.

After dissolution test, pellets remained intact but pore formations on the surfaces in both 0.1 N HCl and phosphate buffer pH 6.8 were similar to the previous study.

The release data of diclofenac sodium matrix pellets from the formulation consisted of 40% and 50% Lubritab® are listed in Table 6B and Appendix B and the release profiles of these preparations in 0.1 N HCl and phosphate buffer pH 6.8 are displayed in Figure 40.

The release of diclofenac sodium not only decreased when the concentration of Lubritab® was increased from 40% to 50% but also decreased the release rate of drug from the matrix. It was apparent that no difference in release pattern from the formulations produced from varying amount of glycerides. These studies revealed that Lubritab® had capacity to control diclofenac sodium release for up to 12 hours because the lipophilicity of Lubritab® obstructs the medium penetration into the pellets. The pellets after tested in 0.1 N HCl remained its integrity while in phosphate buffer pH 6.8 the pellets eroded and broke into the smaller pieces. It could be explained that the less binding property of Lubritab® for remaining intact pellets during dissolution test. This phenomenon implies that if the pellets are not broken, the release of diclofenac sodium could be slower than those obtained in this study.

The first order profiles of release of diclofenac sodium in phosphate buffer pH 6.8 were also depicted in Figure 41. It could be seen that a relatively linear relationship was obtained. The coefficient of determination (r^2) are presented in Table 2E (Appendix E).

C. Compritol® ATO 888 (Glyceryl Behenate)

Compritol® ATO 888, the lipophilic substances, has been shown to be able to retard the drug dissolution of a dosage form. Thus, the ability of Compritol® ATO 888 to retard the rate of drug release from the pellets may be attributed to its lipophilicity property. Incorporation of Compritol® ATO 888 caused an increase in the lipophilic of the pellet matrix, leading to a decrease in the effective interfacial wetability.

Consequently, there is a slower rate of water penetration and dissolution of the drug within the pellets and hence a slower rate of drug releases.

The drug release pattern of 40% propranolol hydrochloride from 40% and 50% Compritol® ATO 888 matrix pellets in 0.1 N HCl and phosphate buffer pH 6.8 are shown in Figures 42 and 44. The dissolution data of each formulation are presented in Table 4B and Appendix B. In 0.1 N HCl the release of propranolol hydrochloride from matrix pellets was seem to be faster than in phosphate buffer pH 6.8.

The percentage of propranolol hydrochloride released from Compritol® ATO 888 matrix pellets in both media was complete within 8 hours. This formulation was slower in drug release pattern than of GMS and Lubritab® matrix pellets. A formula with 50% Compritol® ATO 888 was slower release than the formulation with 40% Compritol® ATO 888. No clearly different release pattern was observed from the formulation with 40% and 50% Compritol® ATO 888 in both media.

The first order plots of propranolol hydrochloride in 0.1 N HCl and phosphate buffer pH 6.8 are graphically in Figures 43 and 45, respectively. The coefficient of determination (r^2) between time and log % drug remained of propranolol hydrochloride matrix pellets in both media are not clearly different as presented in Tables 1E and 2E, Appendix E. Thus, the treatment was based upon use of the differential forms of Higuchi and first order equations. And the result was determined to fit Anomalous transport.

After dissolution test, the microscopic appearances of propranolol hydrochloride matrix pellets showed that there were some small pores on the surfaces of pellets. The pores of pellets in medium pH 1.2 were slightly higher than those tested in medium pH 6.8 as seen in Figures 34 and 35.

The release of diclofenac sodium matrix pellets in 0.1 N HCl was less than 2% similar to the blank capsule and another glycerides. But the release rate in phosphate buffer pH 6.8 was slower than that of blank capsule. The release profiles was

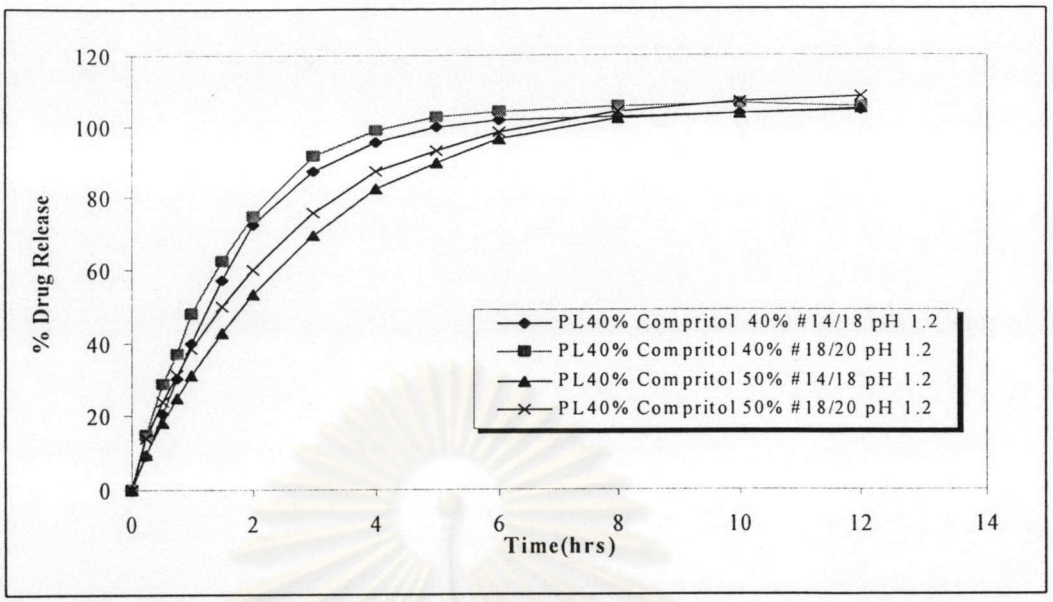


Figure 42 The release profiles of propranolol hydrochloride matrix pellets prepared from series of Compritol®ATO 888 in medium pH 1.2.

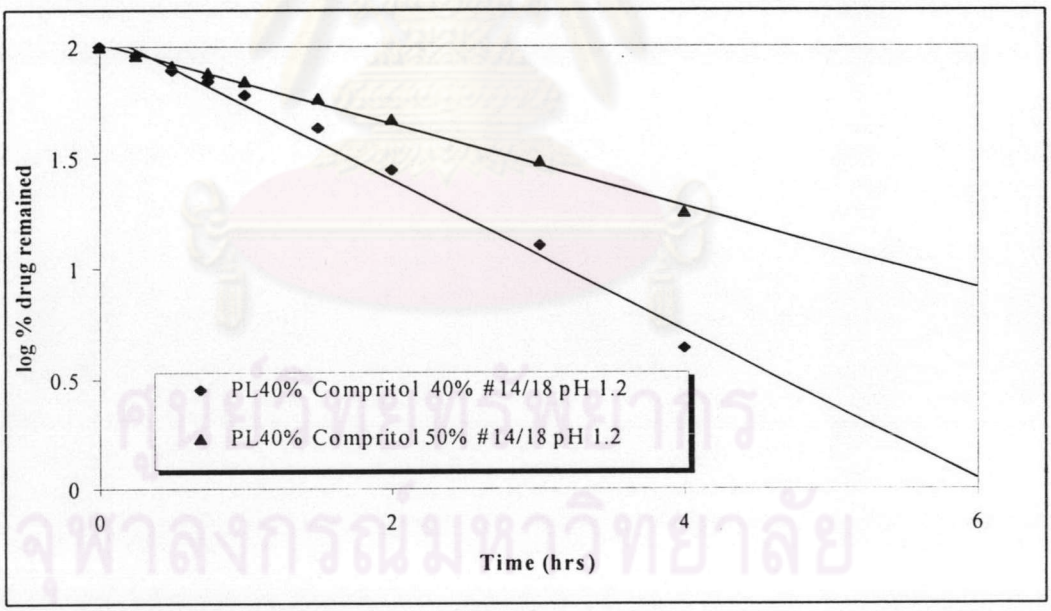


Figure 43 The first order plot of propranolol hydrochloride matrix pellets prepared from series of Compritol®ATO 888 in medium pH 1.2.

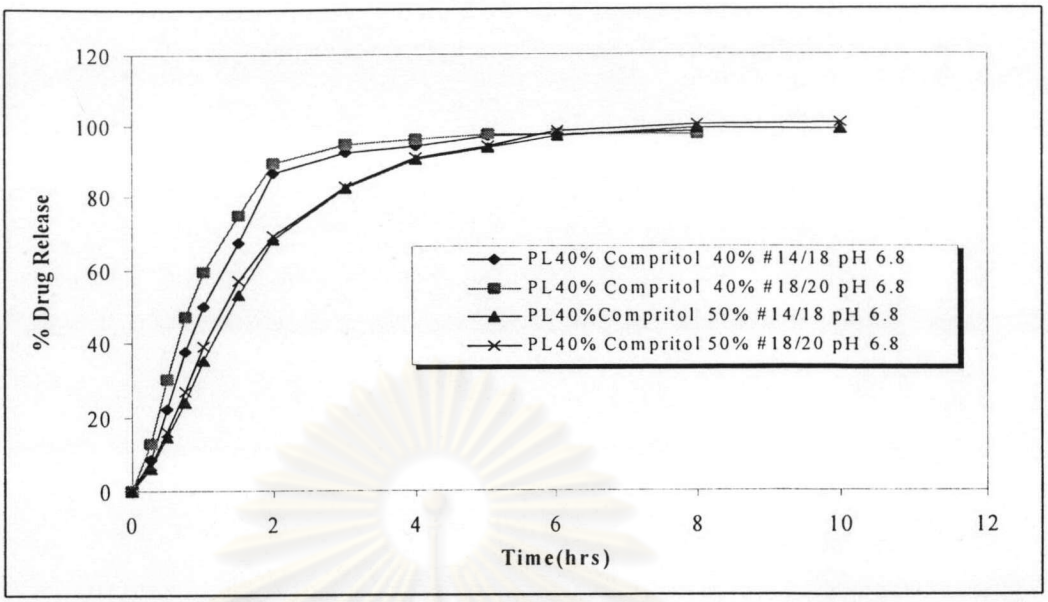


Figure 44 The release profiles of propranolol hydrochloride matrix pellets prepared from series of Compritol®ATO 888 in medium pH 6.8.

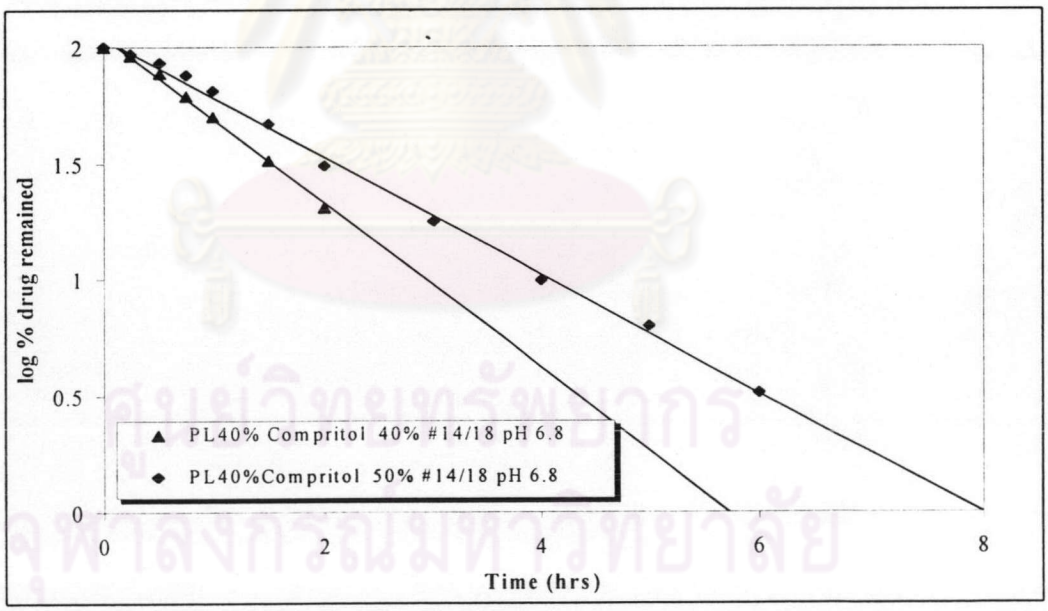


Figure 45 The first order plots of propranolol hydrochloride matrix pellets prepared from series of Compritol®ATO 888 in medium pH 6.8.

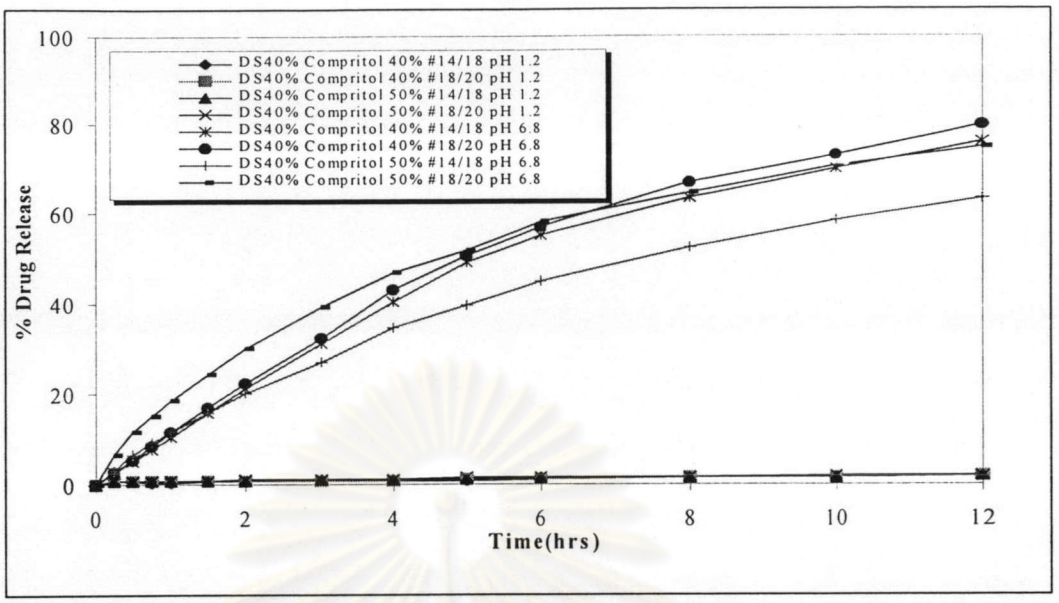


Figure 46 The release profiles of diclofenac sodium matrix pellets prepared from series of Compritol®ATO 888 in media pH 1.2 and pH 6.8.

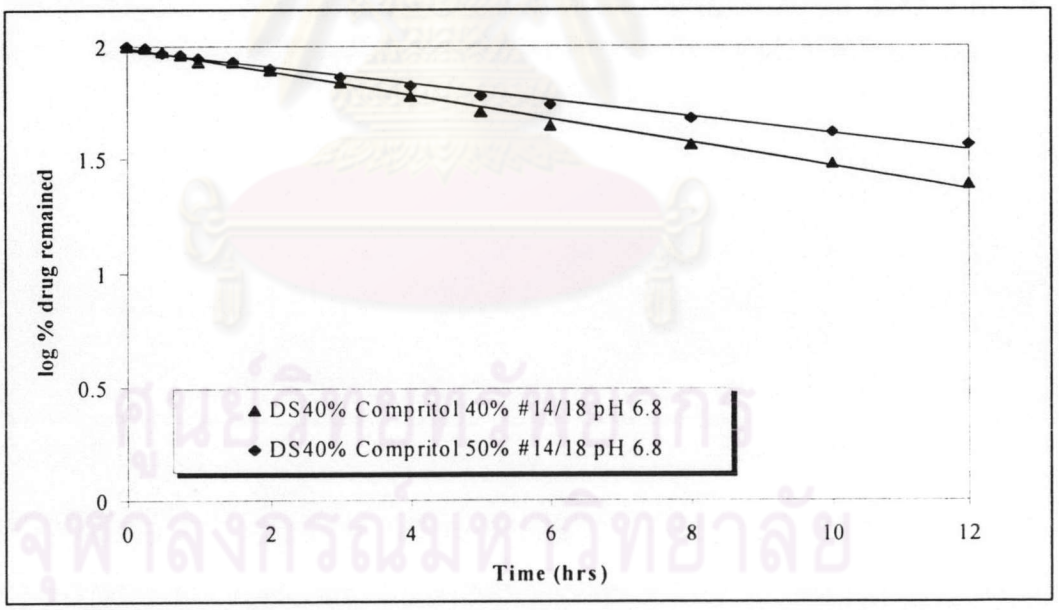


Figure 47 The first order plots of diclofenac sodium matrix pellets prepared from series of Compritol®ATO 888 in medium pH 6.8.

completed in 12 hours. It was shown that no different in the release pattern between 40% and 50% of Compritol® ATO 888 containing pellets.

The drug release profile of 40% diclofenac sodium from 40% and 50% Compritol® ATO 888 matrix pellets in 0.1 N HCl and phosphate buffer pH 6.8 are shown in Figure 46. The release data are presented in Table 7B and Appendix B.

The first order plots are depicted in Figure 47. The coefficient of determination (r^2) and k-value of the formulation in phosphate buffer pH 6.8 are tabulated in Table 2E, Appendix E. The release mechanism of diclofenac sodium matrix pellets could expected to be Anomalous transport similar to those of propranolol hydrochloride matrix pellets.

The microscopic views of diclofenac sodium matrix pellets after dissolution test in 0.1 N HCl and phosphate buffer pH 6.8 are shown some cracks and small pores on the surfaces of pellets similar to the study in pellets containing GMS. They exhibited different from propranolol hydrochloride matrix pellets as presented in previous study.

In this study, the dissolution tests were performed on two fractions (both 14/18 and 18/20 meshes) of pellets. Table 17 is shown the value of specific surface area of propranolol hydrochloride and diclofenac sodium containing Compritol®ATO 888 as matrix forming agent in both size range 14/18 and #18/20 mesh. The data referred that surface area of 14/18 pellet mesh is less than the 18/20 pellets mesh in both propranolol hydrochloride and diclofenac sodium.

Table 17 The specific surface area of pellets in different mesh cut.

Formulations	Mesh cut	Specific surface area (m^2/g)
PL 40% Compritol® 40%	14/18	0.81
	18/20	0.84
DS 40% Compritol® 40%	14/18	1.03
	18/20	1.32

The results indicated that pellets mesh cut 18/20 had a higher specific surface area than pellets mesh cut 14/18. The result indicated that smaller particles possessed higher dissolution rates than larger particles due to the forming possessing a greater available surface area and less diffusion path length (Adeyeye and James, 1994). It was thus proposed that the available surface area of drug generated might control the release of drug from matrix pellets. There are corresponding to the fact that the spheres in different particle size will have different surface area and also result in different dissolution rates (Tapia et al., 1993). From these results, we can propose that the specific surface area had a greatest effect on the release of drug from the matrix pellet.

The concentration of glycerides in the formulation was determining factor in controlled release rate of drug. Decreasing the fraction of glycerides resulted in a corresponding increase of the dissolution rate. Matrix pellets containing 40% drug load were prepared with 40% and 50% GMS, Lubritab®, and Compritol® ATO 888 as matrix forming agents. When Lubritab® was used as the matrix-forming agent, the release rate of drug was the fastest, while it was the slowest when Compritol® ATO 888 was chosen as matrix forming agent. From the study of Shaikh et al., (1991), the drug release seemed to be related to the lipophilicity of glycerides and correlated inversely with the melting point of glycerides. That is, the higher melting point of glycerides, the slower the drug release rate. The release is expected to be regulated by selecting appropriate glycerides. However, it may be difficult to predict the release pattern since it differs from glycerides to glycerides.

Brabander et al. (2000) reported that the amount of drug release was correlated with the melting range of glycerides: the higher the melting range, the fewer drugs were release similar results were obtained by Zhou et al. (1996).

But in this study, Lubritab® could not provided slower release than GMS. It is due to Lubritab® had less binding property to remained intact pellet structure after dissolution test. Only Lubritab® is broken into a small piece while the other glycerides still remained integrity. Thus Lubritab® could not provide prolonged release for matrix pellets.

The drug release was primilary a function of the composition of the glycerides matrix pellets. It is expected that the drug release increase with decreasing glyceride concentration, this observation became more pronounced with decreasing levels of lactose.

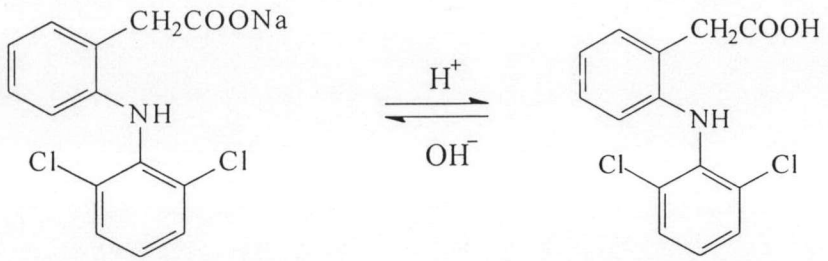
1.2.2 Influence of Drug Solubility

As shown in previous chapter, the release of drug from various glyceride matrices increased when the drug solubility increased. The release of diclofenac sodium seemed to be much slower than propranolol hydrochloride and could prolonged the release for 12 hours.

Propranolol hydrochloride, a basic drug with a pK_a of 9.45, should be more soluble in acidic solution (in which the ionized form of the drug is predominant) than in alkaline solution (in which the unionized form of the drug is dominant). But in the present study, there was only a slight difference between the dissolution behavior in two-dissolution system. All formulation of propranolol hydrochloride matrix pellets gave the release rate in 0.1 N HCl was slightly faster than in phosphate buffer pH 6.8. According to the study by Rekhi et al., 1989, the release property of propranolol hydrochloride coated bead by aqueous polymeric dispersion was found to be faster in 0.1 N HCl compared in phosphate buffer pH 6.8.

Furthermore, the solubility of diclofenac sodium depends on pH, solubility is poor at low pH but when the pH rise above the pK_a (pK_a = 4), rapid increases in the solubility occur (Maitani et al, 1991; Herzfeldt and Kummel, 1983).

In 0.1 N HCl diclofenac sodium release was less than 3% in 12 hours, it might be expected that diclofenac sodium converted to diclofenac which had lower solubility than diclofenac sodium. Whereas in alkaline medium (phosphate buffer pH 6.8), the sodium salt was remained as follow:



Diclofenac sodium **Diclofenac**

Sheu et al (1992) reported that the additions of sodium or potassium chloride to the dissolution medium reduced the solubility of drug and the dissolution rate decreased. The result was attributed to the salting out effect. However, in our study, sodium chloride in the dissolution medium had only slightly affected to the solubility of diclofenac sodium, because the very small quantity of sodium chloride in the dissolution system.

In phosphate buffer pH 6.8, diclofenac sodium was released immediately from all formulation even when the formulation contained 60% glycerides. More than 50% of diclofenac sodium released in the first 2 hours when glyceryl monostearate and Lubritab® are used as matrix forming agent. In this system, pellets did not have the capacity to control the release for up to 12 hours. As expected, it was due to diclofenac sodium was more soluble in alkali medium and coupled with the drug that located on surface of pellets. Whereas the formulation that contained Compritol® ATO 888 as matrix forming agent released about 20% in the first 2 hours. This phenomenon occured due to the effect of lipophillicity and high melting point of Compritol® ATO 888 according to the part of glycerides concentration.

Porter (1989) reported that the solubility of drug and effect of pH on drug solubility would affect the rate at which the drugs release. Blandque et al. (1995) suggested that the release of drug from pellets is also delayed by decreasing the solubility of the drug. The solubility of lactose was detected to cause the greatest effect on the value of the mean dissolution time, followed by the solubility of the drug. Maejima et al (1997) also depicted that the release rates of drug seemed to increase with an increase in the solubility of drug.

1.2.3 Influence of Loading Dose on Drug Release

The influence of loading dose was performed on pellets that comprised 60% glycerides and then varying percent of loading drug dose between 20-30% of propranolol hydrochloride or diclofenac sodium.

A. Glyceryl Monostearate (GMS)

The release data of propranolol hydrochloride matrix pellet from the formulations containing 60% GMS are listed in Table 8B and Appendix B. The release profiles of the formulations in 0.1 N HCl and phosphate buffer pH 6.8 are shown in Figures 48 and 49, respectively.

The formulation using 20% and 30% loading dose of propranolol hydrochloride comprise GMS depicted that loading dose had slight effect on the dissolution of drug in both acidic and basic media. The release profiles of propranolol hydrochloride in 0.1 N HCl is slightly faster than in phosphate buffer pH 6.8. It was clear that the smaller size of pellets shown the faster release than the bigger one in accordance with the study of Tapia et al., (1993).

The release data of diclofenac sodium matrix pellets from the formulation containing 60% GMS are listed in Table 11B, Appendix B, and graphically in Figure 50. In 0.1 N HCl, the release of diclofenac sodium was less than 3% similar to the previous study while the release in phosphate buffer pH 6.8 were able to control the release of drug for 12 hours. The patterns of diclofenac sodium release from 20% and 30% loading dose were not slightly different.

The first order plots of 60% GMS matrix pellets with 30% diclofenac sodium in phosphate buffer pH 6.8 are shown in Figure 51. The coefficient of determination (r^2) of pellet size range 14/18 and 18/20 mesh is 0.9872 and 0.9883, respectively. And value of release exponent (n) are in the range $0.43<n<0.85$, indicating that release mechanism are very close to Anomalous transport. The value of kinetic constant, release exponential and coefficient of determination (r^2) of these pellets are presented in Table 5E, Appendix E.

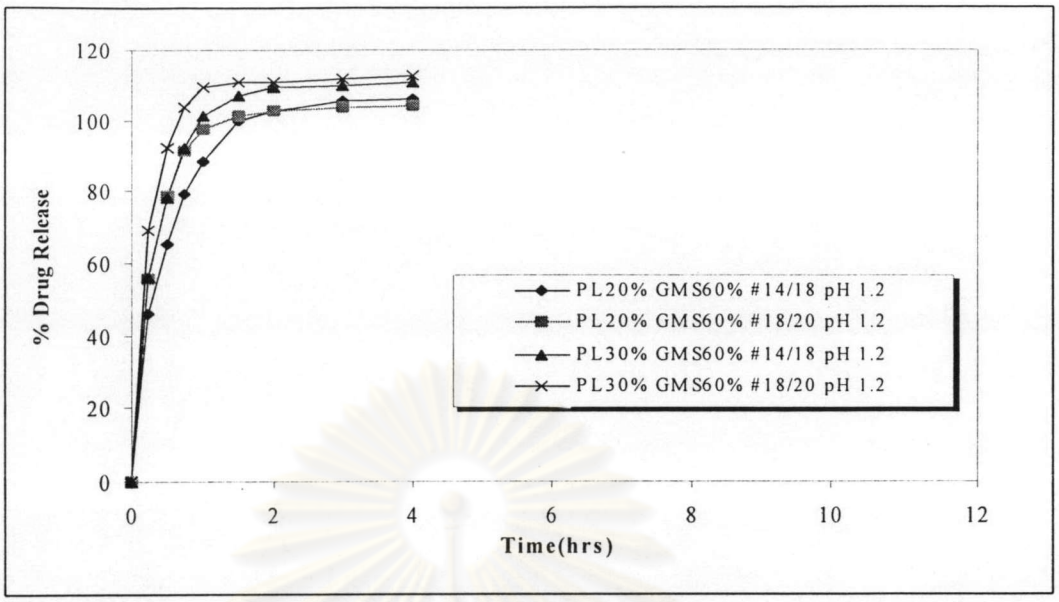


Figure 48 The release profiles of 60% GMS matrix pellets with 20% and 30% propranolol hydrochloride loading in medium pH 1.2.

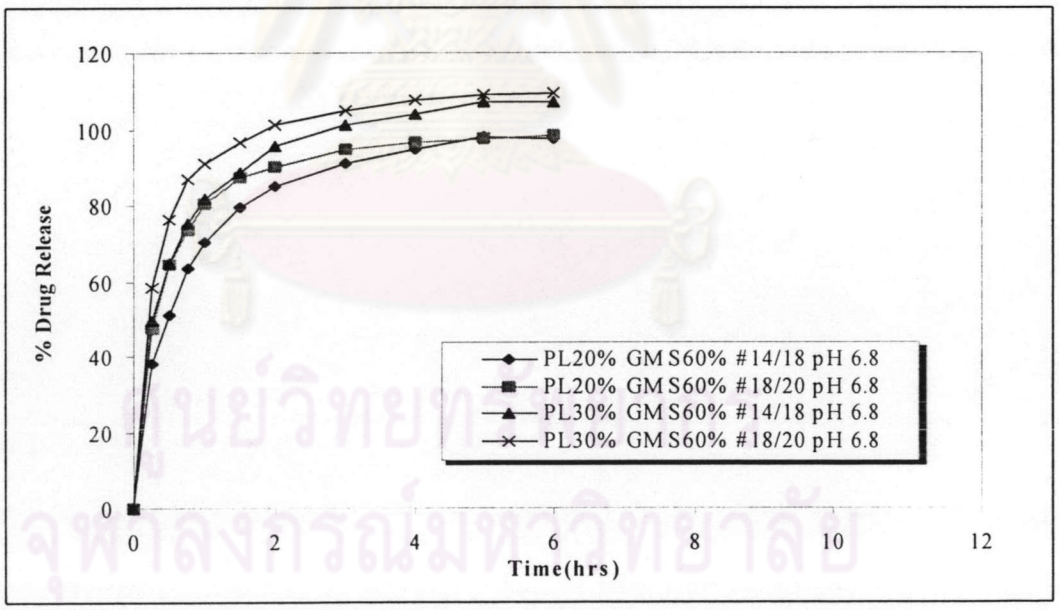


Figure 49 The release profiles of 60% GMS matrix pellets with 20% and 30% propranolol hydrochloride loading in medium pH 6.8.

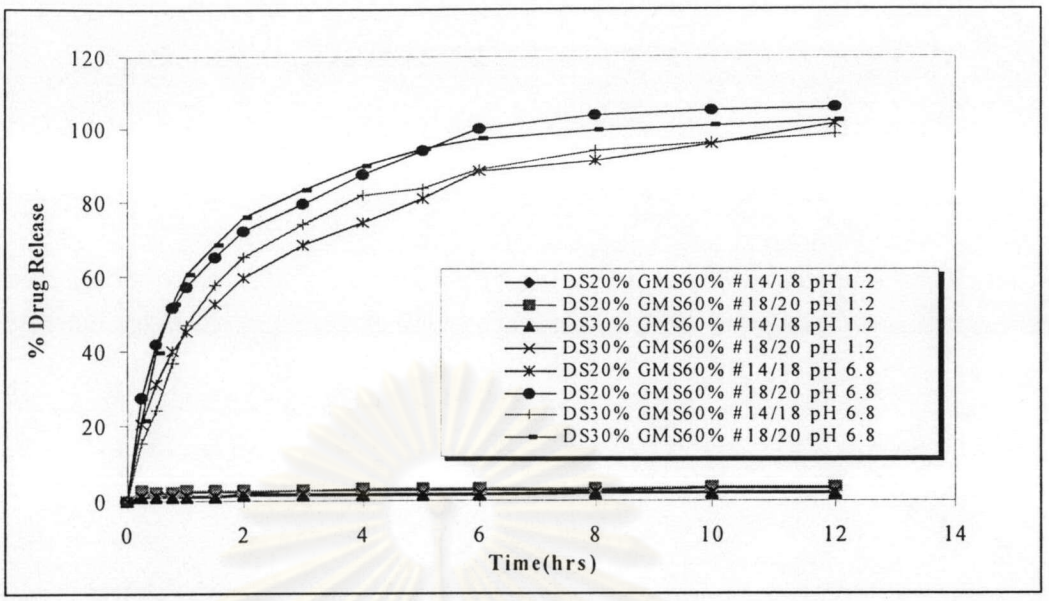


Figure 50 The release profiles of 60% GMS matrix pellets with 20% and 30% diclofenac sodium loading in media pH 1.2 and pH 6.8.

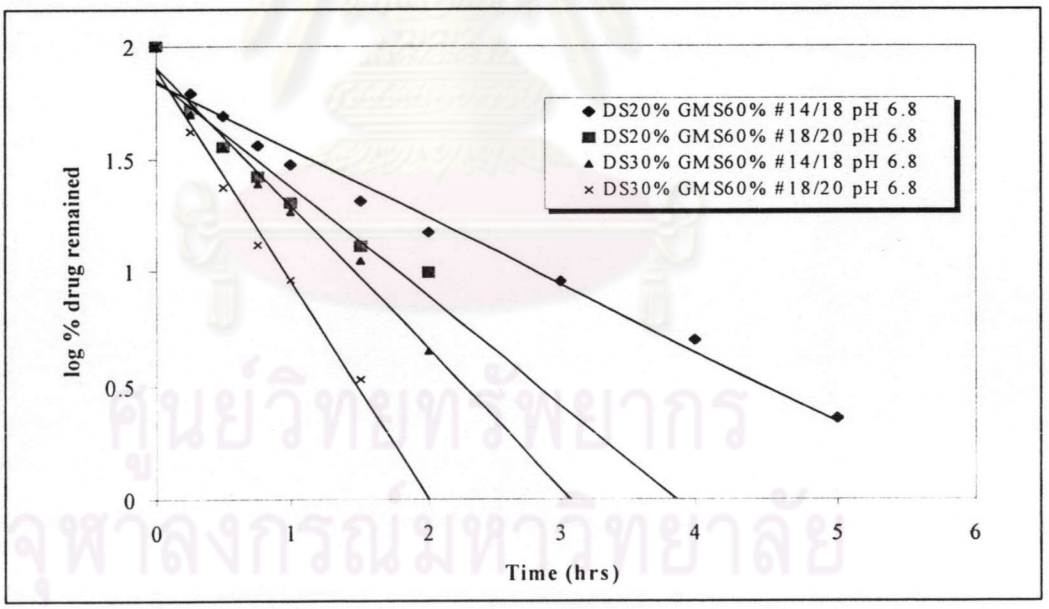


Figure 51 The first order plots of 60% GMS matrix pellets with 20% and 30% diclofenac sodium loading in medium pH 6.8.

B. Lubritab® (Hydrogenated Cottonseed Oil)

The drug release patterns of propranolol hydrochloride matrix pellets at 20% and 30% drug loading in 0.1 N HCl and phosphate buffer pH 6.8 are displayed in Figures 52 and 53, the release data are shown in Table 9B (Appendix B). The release rate of drug in acidic medium was faster than in phosphate buffer pH 6.8.

When the proportion of drugs in the formulation were decreased, the percentage of drug release from 20% drug loading slightly faster than 30% loading. But they were not clearly different in 0.1 N HCl medium. It could be explained that propranolol hydrochloride pellets is freely soluble in 0.1 N HCl in which the ionized form of the drug is predominant (Rekhi et al., 1989).

Figure 54 revealed no different in drug release pattern profiles between the 20% and 30% loading of diclofenac sodium formulation, When the release of diclofenac sodium in pH 6.8 was strongly medium dependent, drug release in 0.1 N HCl was less than 3% in 12 hours. In phosphate buffer pH 6.8,30% diclofenac sodium load seemed to be slower release than that of 20% drug load. These are probably due to lower concentration of lactose in the formulation of 30% drug loading.

The coefficient of determination (r^2) of drug was closed to 1, when the first order and Higuchi plots constructed. But, it was not clearly different among two mechanisms. Therefore, they were treated by the different between two mechanisms. The coefficient of determination between the release rate (dQ/dt) and amount (Q) of release are higher than the coefficient of determination (r^2) between the release rate (dQ/dt) and reciprocal amount (Q) of release of drug, the data are presented in Table 5E and Appendix E. The release profiles of this series might be the first order release model as shown in Figure 55. And the mechanism of this formulation are range in 0.43-0.85, thus the release mechanism could be Anomalous transport. The kinetic constant (n) are tabulated in Table 6E and Appendix E.

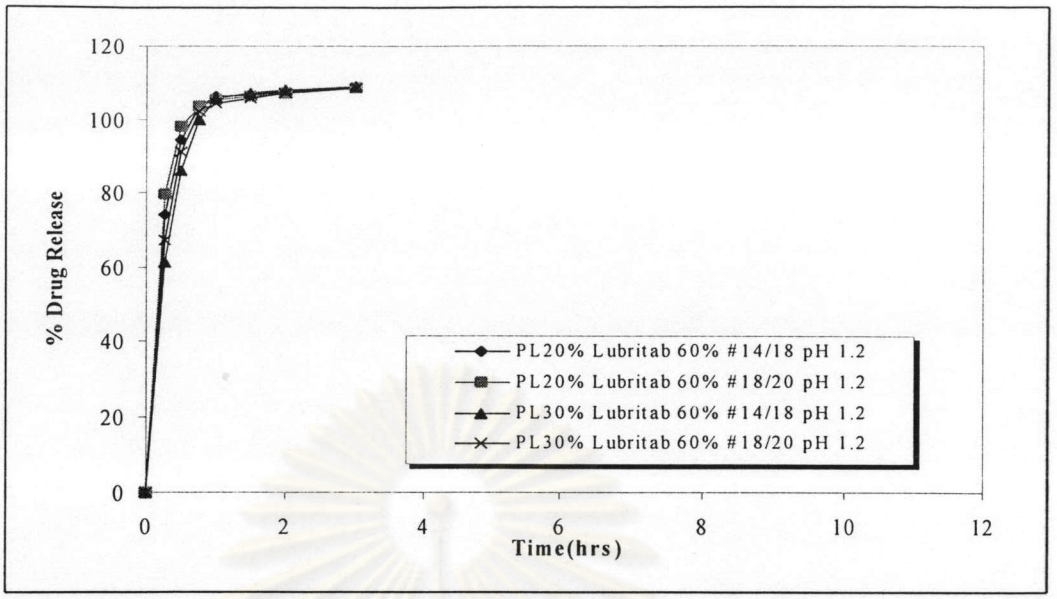


Figure 52 The release profiles of 60% Lubritab® matrix pellets with 20% and 30% propranolol hydrochloride loading in medium pH 1.2.

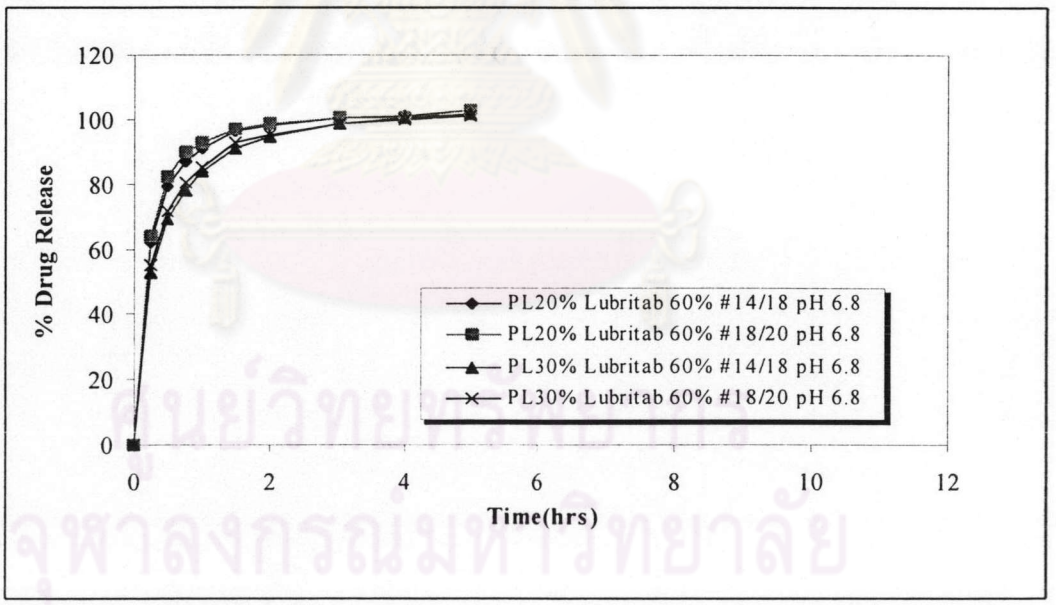


Figure 53 The release profiles of 60% Lubritab® matrix pellets with 20% and 30% propranolol hydrochloride loading in medium pH 6.8.

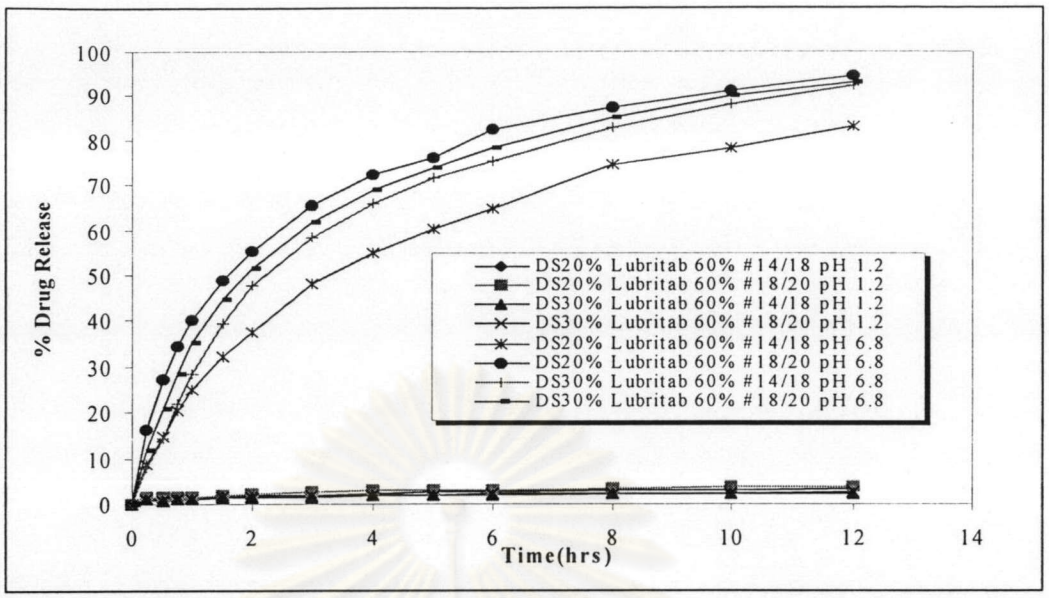


Figure 54 The release profiles of 60% Lubritab® matrix pellets with 20% and 30% diclofenac sodium loading in media pH 1.2 and pH 6.8.

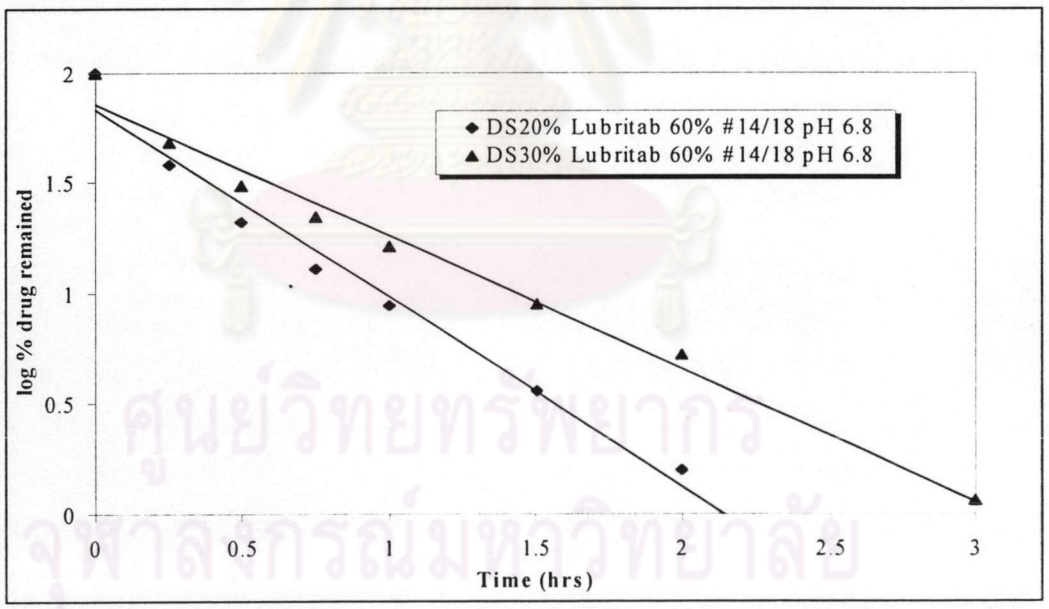


Figure 55 The first order plots of 60% Lubritab® matrix pellets with 20% and 30% diclofenac sodium loading in medium pH 6.8.

C. Compritol®ATO 888 (Glyceryl Behenate)

The release of 20% and 30% propranolol hydrochloride load from matrix pellets with 60% Compritol®ATO 888 in 0.1 N HCl and phosphate buffer pH 6.8 are exhibited in Figures 56 and 58, respectively. The release data are presented in Table 10B and Appendix B. It revealed that no difference in drug release pattern between the 20% and 30% drug load when Compritol®ATO 888 was kept constant at 60% in both media.

The coefficient of determination (r^2) of first order and Higuchi plots are vicinity, thus the release model was determined by using the value of coefficient of determination (r^2) between the release rate (dQ/dt) and amount (Q) or reciprocal amount (1/Q) of drug release. The higher coefficient of determination (r^2) value are obtained from the plots of dQ/dt and Q. Therefore the release model of propranolol hydrochloride is closed to first order than Higuchi model. Release mechanism still is Anomalous transport that was similar to the previous study.

Figure 60 displayed the dissolution profiles of diclofenac sodium 20% and 30% load with 60% Compritol®ATO 888 in 0.1 N HCl and phosphate buffer pH 6.8.

For diclofenac sodium pellets produced with Compritol®ATO 888 was in phosphate buffer pH 6.8, the release profiles was closely related to first order model because the best linearity was achieved using the first order model (Figure 61). The high coefficient of determination (r^2) was obtained with other kinetics models as depicted in Table 2E and Appendix E.

Less than 3% of diclofenac sodium release from matrix pellets in 0.1 N HCl. The release of diclofenac sodium in phosphate buffer pH 6.8 could be controlled for 12 hours. The release rate of 30% of diclofenac sodium was slower than 20% diclofenac sodium. These are agree with the evaluated of Mehta et al. (2000), reported that poorly soluble drug dissolution was found to decrease with increasing drug loading due to the total polymer content in the formulation is low. The number of pore reduced, thus the total pore surface area was reduced, too.

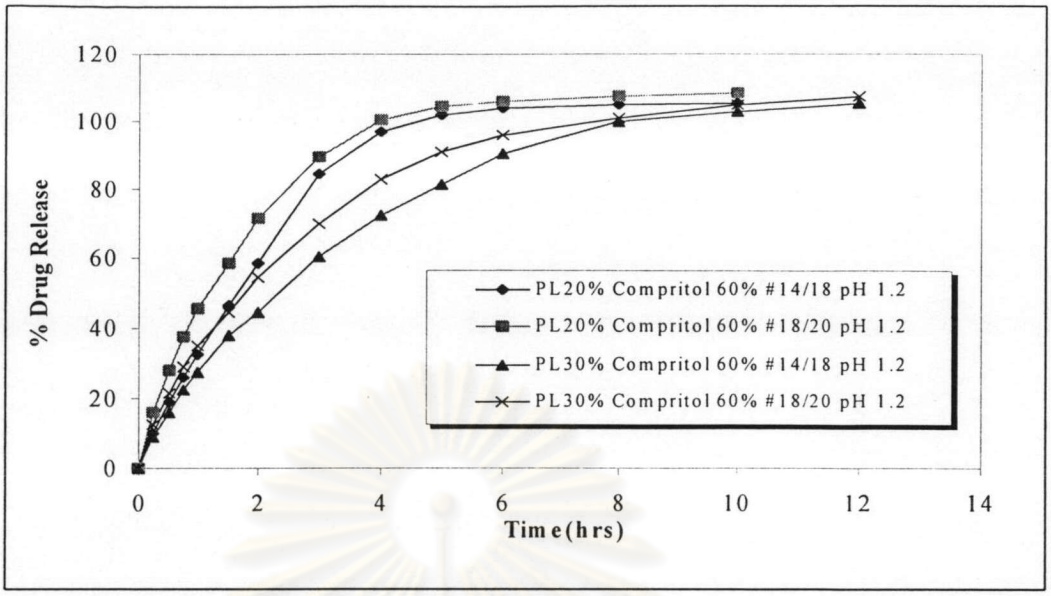


Figure 56 The release profiles of 60% Compritol®ATO 888 matrix pellets with 20% and 30% propranolol hydrochloride loading in medium pH 1.2.

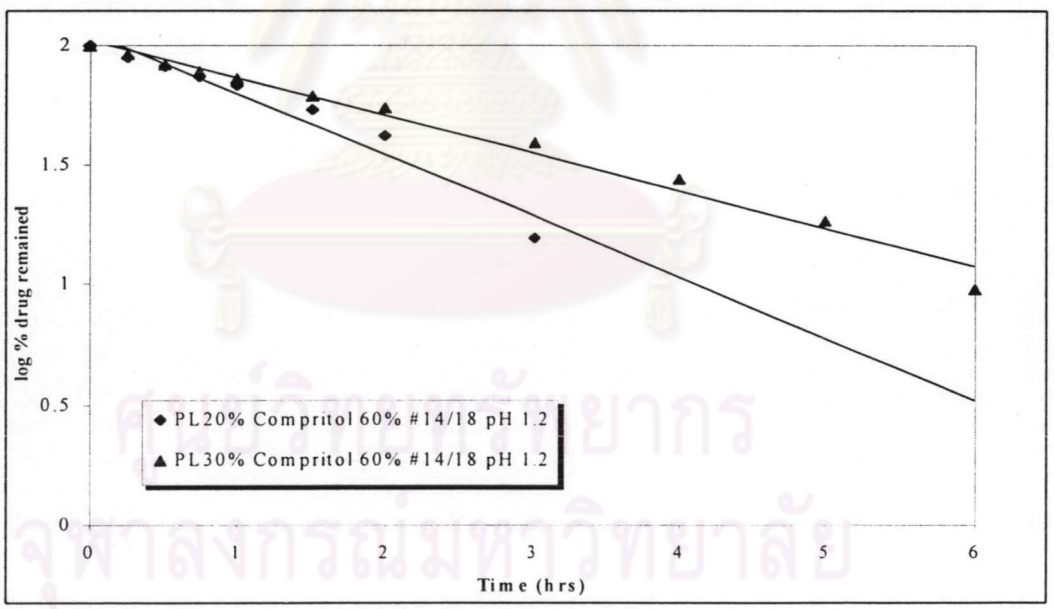


Figure 57 The first order plots of 60% Compritol®ATO 888 matrix pellets with 20% and 30% propranolol hydrochloride loading in medium pH 1.2.

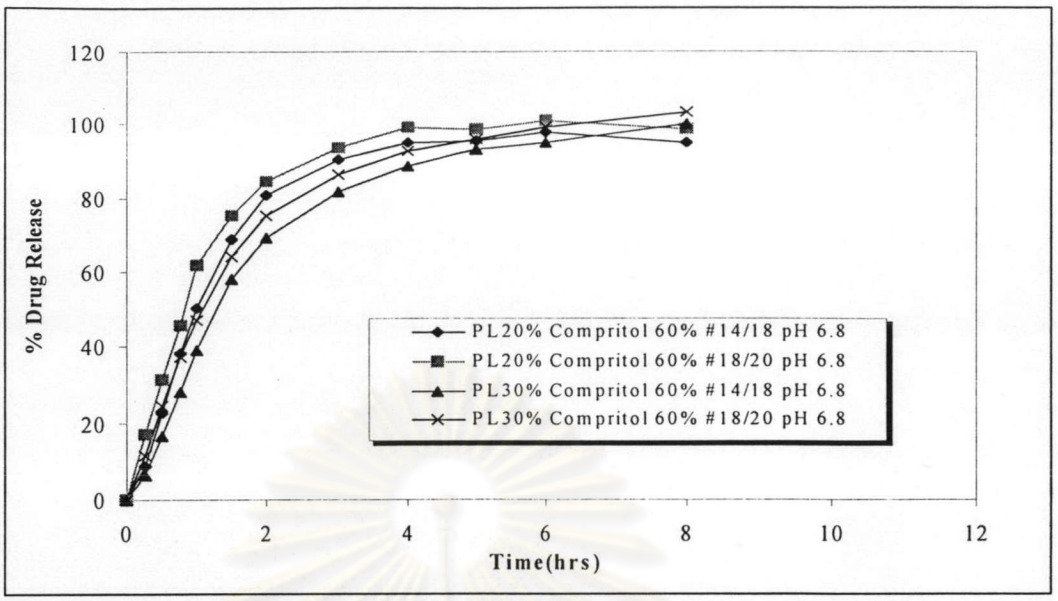


Figure 58 The release profiles of 60% Compritol®ATO 888 matrix pellets with 20% and 30% propranolol hydrochloride loading in medium pH 6.8.

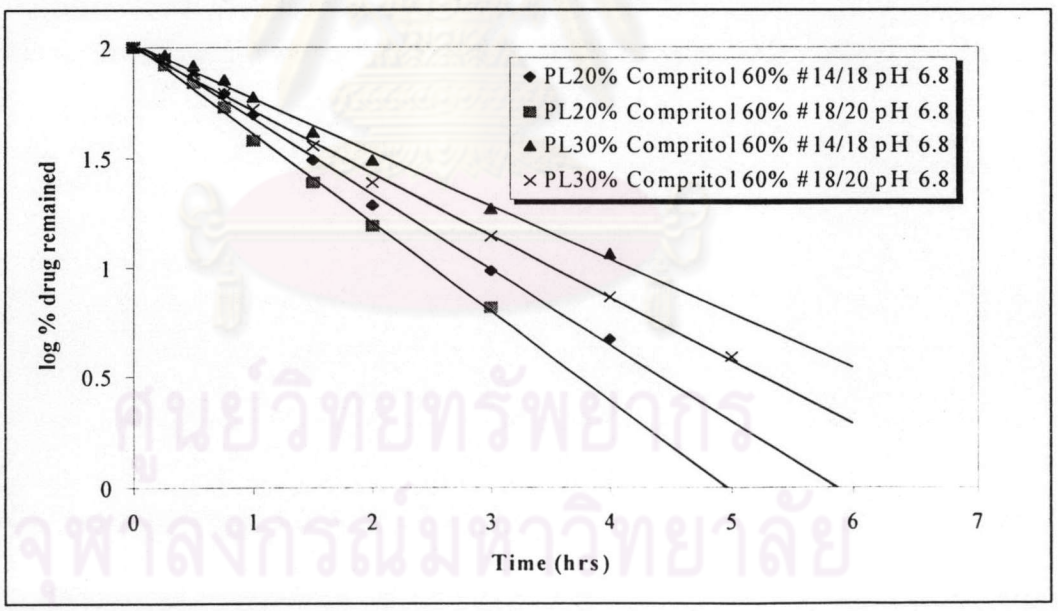


Figure 59 The first order plots of 60% Compritol®ATO 888 matrix pellets with 20% and 30% propranolol hydrochloride loading in medium pH 6.8.

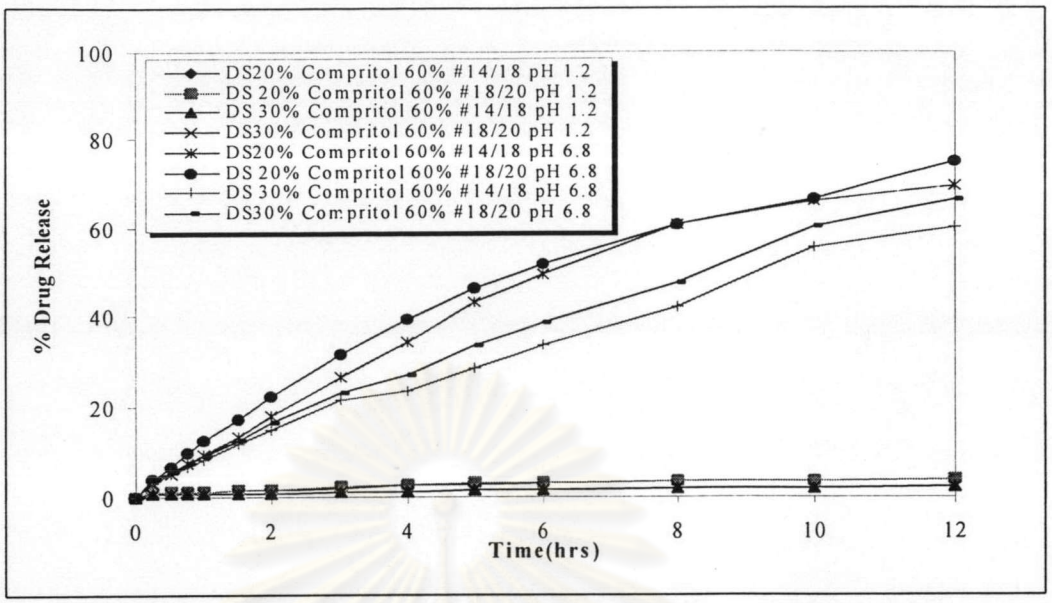


Figure 60 The release profiles of 60% Compritol®ATO 888 matrix pellets with 20% and 30% diclofenac sodium loading in media pH 1.2 and pH 6.8.

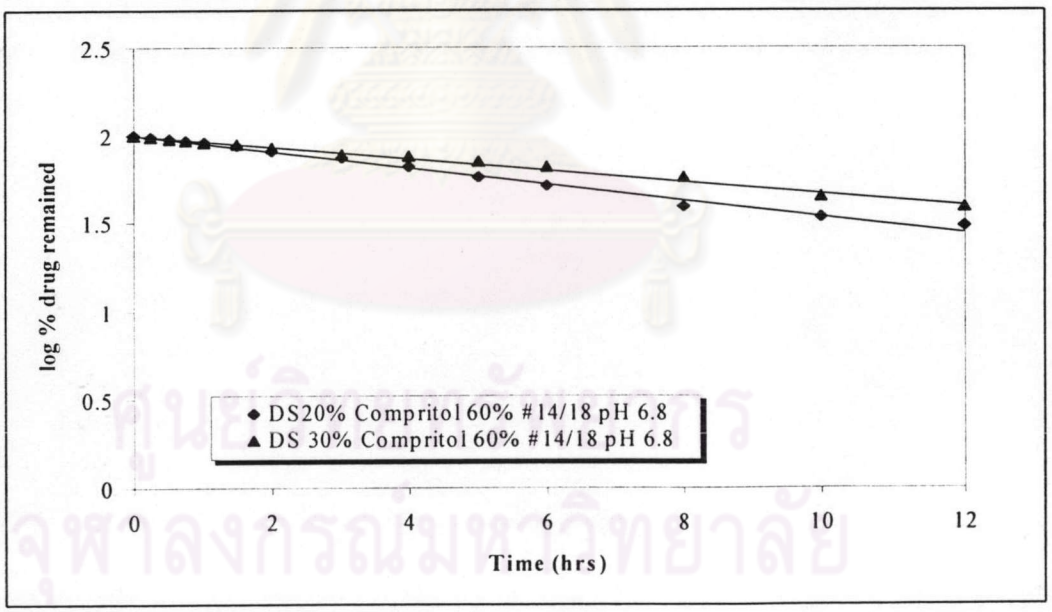


Figure 61 The first order plots of 60% Compritol®ATO 888 matrix pellets with 20% and 30% diclofenac sodium loading in medium pH 6.8.

In the formulations containing 20% and 30% of propranolol hydrochloride and Compritol®ATO 888 kept constant at 60% revealed decreased of release rate when drug load increased accordant with the previous study.

The high solubility of the lactose provides the possibility of highly porous spheres during the dissolution process, which allows the drug substances to be release quickly. The release of drug from matrix pellets would increase when the higher amount of lactose was embedded in the formulation. Lactose dissolved and released from the matrix, as the result channels were formed and the porosity was increased. The channels would increase in release rate.

1.2.4 Effect of Additives on the Release of Diclofenac Sodium from Matrix Pellet.

Due to the solubility of diclofenac sodium is suppressed when it surround with acidic environment. Whereas propranolol hydrochloride is freely soluble in both medias. Thus in this part of study, the effect of polyethylene glycol 1450 (PEG 1450) and polysorbate 80 (Tween 80) as the additives (Kenneth et al., 1992) in the formulation of diclofenac sodium on drug release was investigated.

The pellets matrix of 40% diclofenac sodium and 40% GMS which containing 0.2% PEG 1450 and 0.2% Tween 80 are depicted in Figure 62.

The release profiles of diclofenac sodium from matrix pellets containing various amount of additive are presented in Figure 63. The release data are presented in Table 14B and 15B, (Appendix B). From the result, it was found that the additives did not increase the release of diclofenac sodium in 0.1 N HCl. Whereas, the release of diclofenac sodium in phosphate buffer pH 6.8 is completed in the first hours. The release of diclofenac sodium containing additives in all concentration in phosphate buffer pH 6.8 release 100% in the first hour while pellets without additives release 82.12% of drug after 12 hours (see Figure 32).

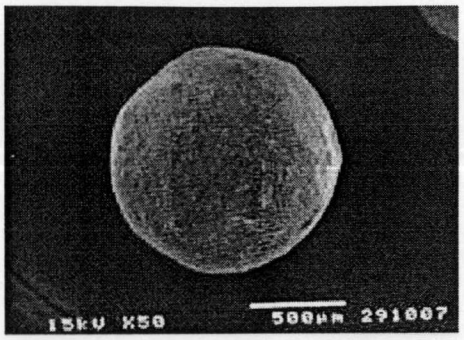
The various amount of PEG 1450 and Tween 80 at all concentration above had a greatest effect on the release of diclofenac sodium matrix pellets in phosphate buffer pH 6.8. They produced the faster release of diclofenac sodium in all concentration. The pellets was fragmented to a small piece during tested phosphate buffer pH 6.8 around 15 minutes (see Figure 64). It due to pellets was cracked. Whereas in 0.1 N HCl, pellets still remained intact with visible swelling (see Figure 65). But the release of diclofenac sodium from matrix pellets were not increased, it could be due to the solubility of diclofenac was much depended on the pH of dissolution medium. The additives could not increase the release of diclofenac sodium release in 0.1 N HCl.

1.2.5 The Effect of Curing Temperature and Time on the Release of Propranolol Hydrochloride

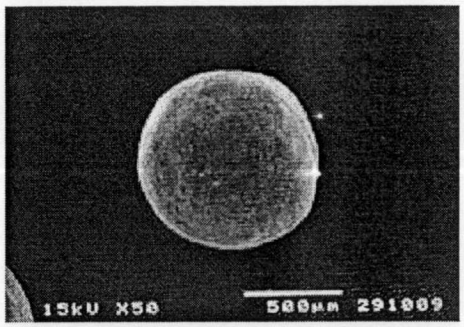
The drug release data from pellets using Lubritab® treated at 55°, 60° and 65° C at various time intervals is presented in Table 16B, Appendix B. Increasing the temperature and duration of curing slightly reduced the drug release as shown in Figures 64-67.

It was also observed that at 65°C curing temperature, the beads were sticky, leading to agglomeration of the beads in the fluid bed dryer, talcum and Cab-O-Sil® was added as anti-sticking agent (Wesseling et al., 1999). Interestingly, the rate of drug release of the pellets was found to be slower than other formulation. In particular when talcum was used as illustrated in Figures 70-71.

The pellets that curing at 65°C resulting in decrease drug release when compared to the release of uncured beads. Ghali et al., 1989 reported that thermal treatment of water soluble drug have apparently resulted in a redistribution of glycerides throughout the beads and possible change in nature of the pores within the beads.

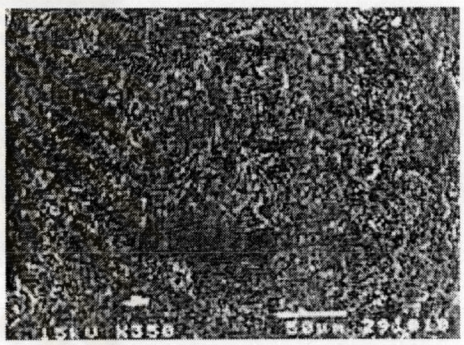


A_1

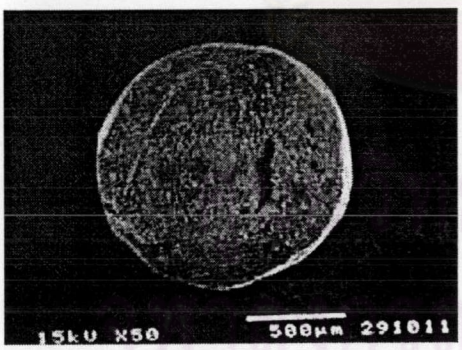


B_1

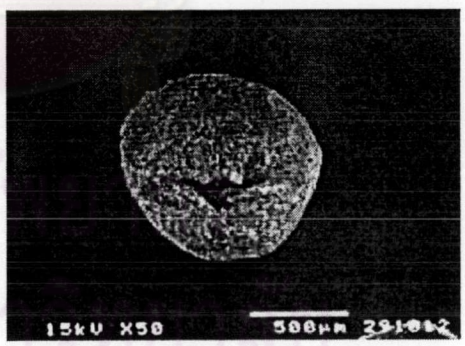
A_2



B_2



A_3



B_3

Figure 62 Scanning electron photomicrographs of 40% diclofenac sodium and 40% GMS matrix pellets that containing 0.2 % PEG 1450 and 0.2% Tween 80 (A_1, A_2; pellets size of 14/18 mesh at ×50, ×350 magnification, A_3; cross-section at ×50 magnification; B_1, B_2; pellets size of 18/20mesh at ×50, × 350 magnification, B_3; cross-section ×50 magnification).

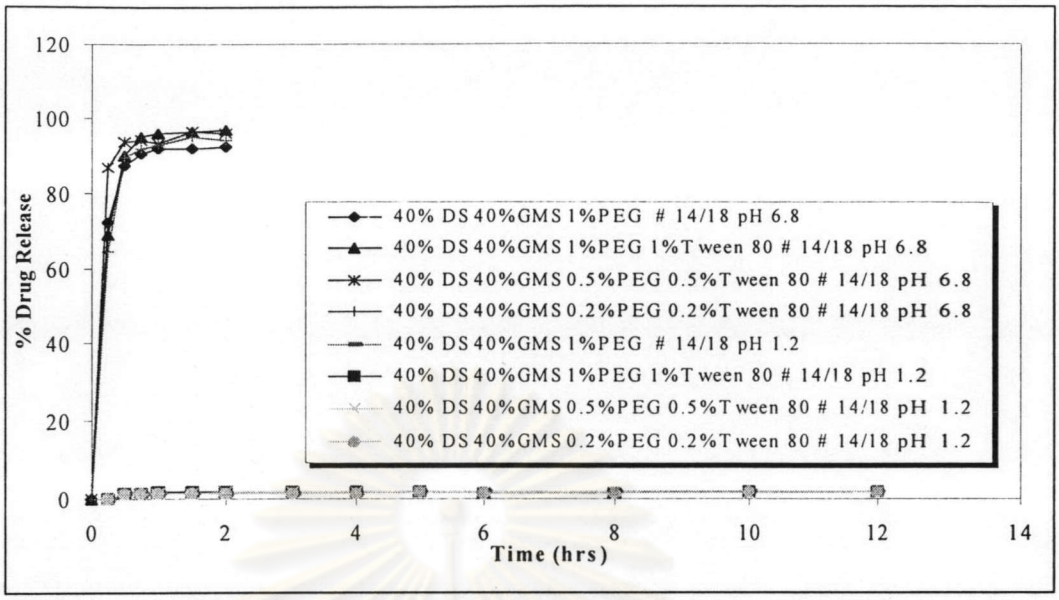
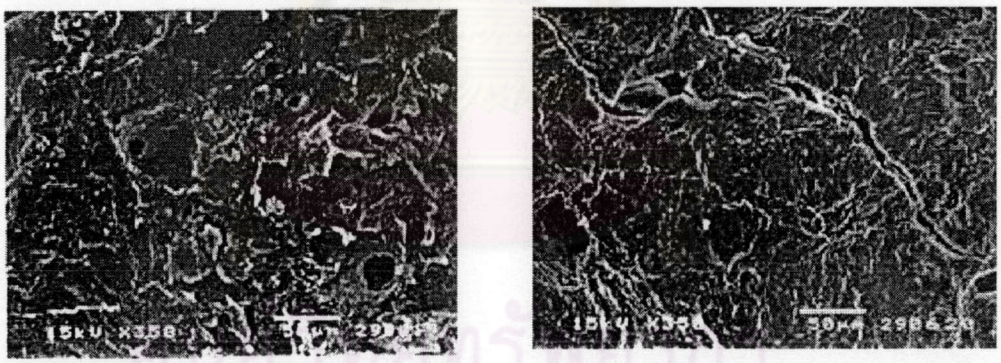
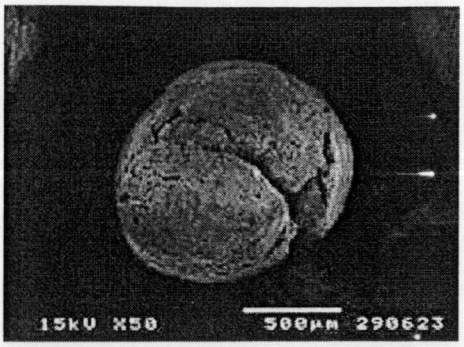


Figure 63 Release profiles of 40% diclofenac sodium and 40% GMS from matrix pellets containing various amount of additives in media pH 1.2 and pH 6.8.

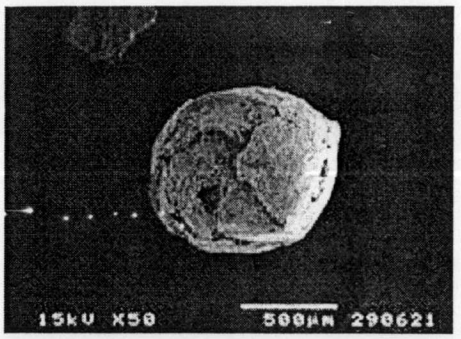


A_1 B_1

Figure 64 Scanning electron photomicrographs of 40% diclofenac sodium and 40% GMS matrix pellets containing 0.2 % PEG 1450 and 0.2% Tween 80 (A_1; pellets size of 14/18 mesh at ×350 magnification; B_1; pellets size of 18/20 mesh at ×350 magnification) after dissolution in phosphate buffer pH 6.8.

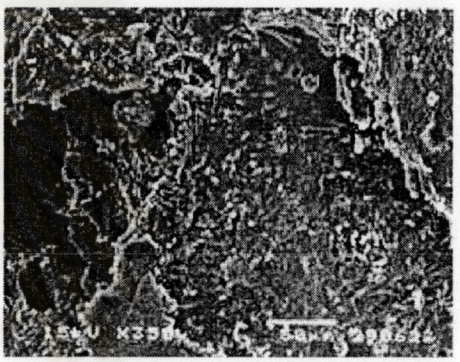


A_1

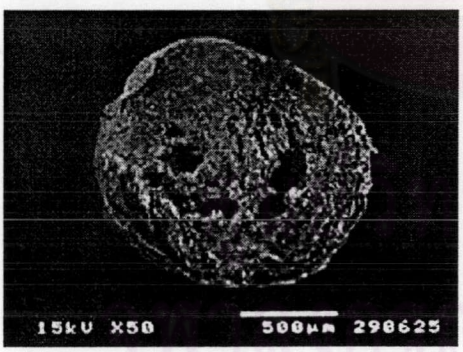


B_1

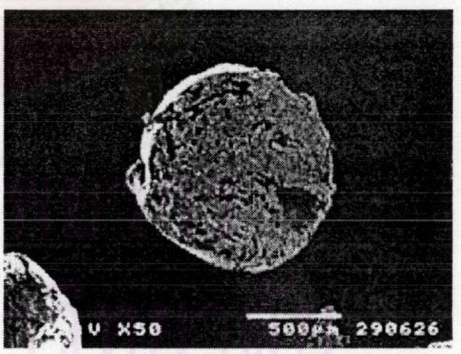
A_2



B_2



A_3



B_3

Figure 65 Scanning electron photomicrographs of 40% diclofenac sodium and 40% GMS matrix containing 0.2 % PEG 1450 and 0.2% Tween 80 (A_1, A_2; pellets size of 14/18 mesh at ×50, ×350 magnification, A_3; cross-section at ×50 magnification; B_1, B_2; pellets size of 18/20 mesh at ×50, ×350 magnification, B_3; cross-section at ×50 magnification) after dissolution in 0.1 N HCl.

Blending the beads with talcum or Cab-O-Sil® prior to curing avoid the fusion of the beads into an agglomeration, the beads remained free flowing during curing and therefore, the surface of pellets was not mechanically damaged. The topography of pellets with anti-sticking agent was slightly different between the pellets that not blend with anti-sticking agent as shown in Figure 70. The surface of pellets was enveloped with anti-sticking agent. There were slightly rougher than the pellets that did not blend with anti-sticking agent.

After dissolution test, the pellets had small pores on the surface and cross-section exhibited that there are some holes at the center of pellets as shown in Figures 73-75.

The drug release data of pellets using GMS treated at different temperature and duration of curing are shown in Table 16B, Appendix B. It seem to be that the drug release profiles of curing pellets at 50°, 55°, and 58°C for different durations were not changed. It is indicated that the rate of drug release was not affected by both curing temperature and the duration of curing (Ghali et al., 1989), even though the formulation that using high temperature with anti-sticking agent (Figures 76-77).

The dissolution release data for pellets using Compritol®ATO 888 treated at 65°, 70° and 75°C for 7 minutes are shown in Table 16B, Appendix B. The release rate of drug from pellets was found to be faster than other formulation even though the formulation that using anti-sticking agent before curing at high temperature as shown in Figures 78-79, indicated that the rate of drug release was affected by both curing temperature and the duration of curing. Increasing in both temperature and duration for curing of pellets apparently increased in release of propranolol hydrochloride from Compritol®ATO 888 matrix pellets (see dissolution data in Table 16B, Appendix B).

As it was seen from the previous study, Lubritab® had less binding property to remained intact pellet structure after dissolution test. But in this study, pellets comprising Lubritab® as matrix forming agent revealed the slowest release. It expected that after curing process, Lubritab® should be melted and repacked to form

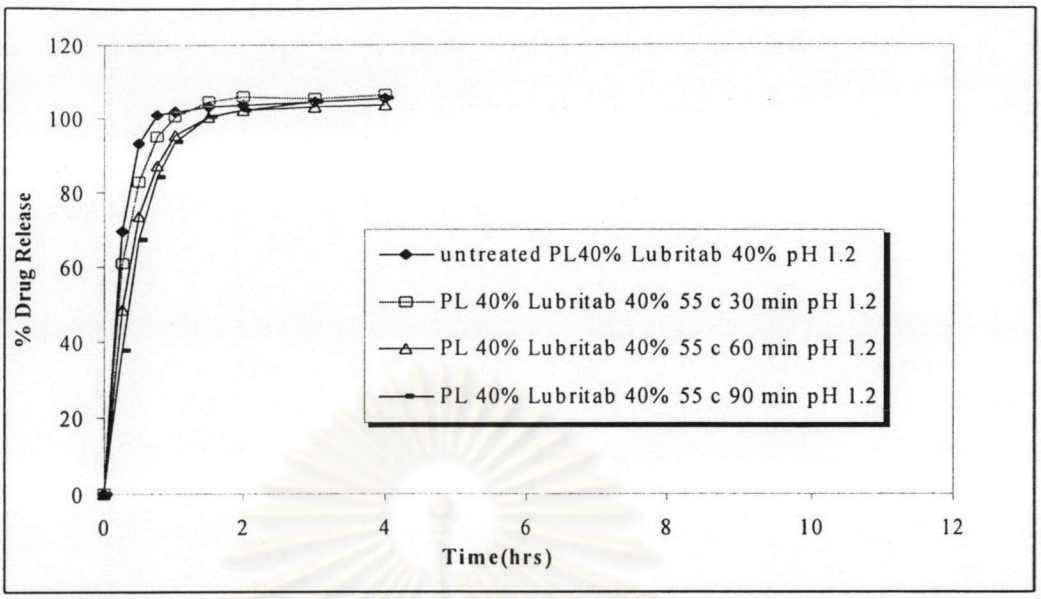


Figure 66 The release profiles of propranolol hydrochloride matrix pellets containing Lubritab® in pH 1.2 when curing at 55°C at various time intervals.

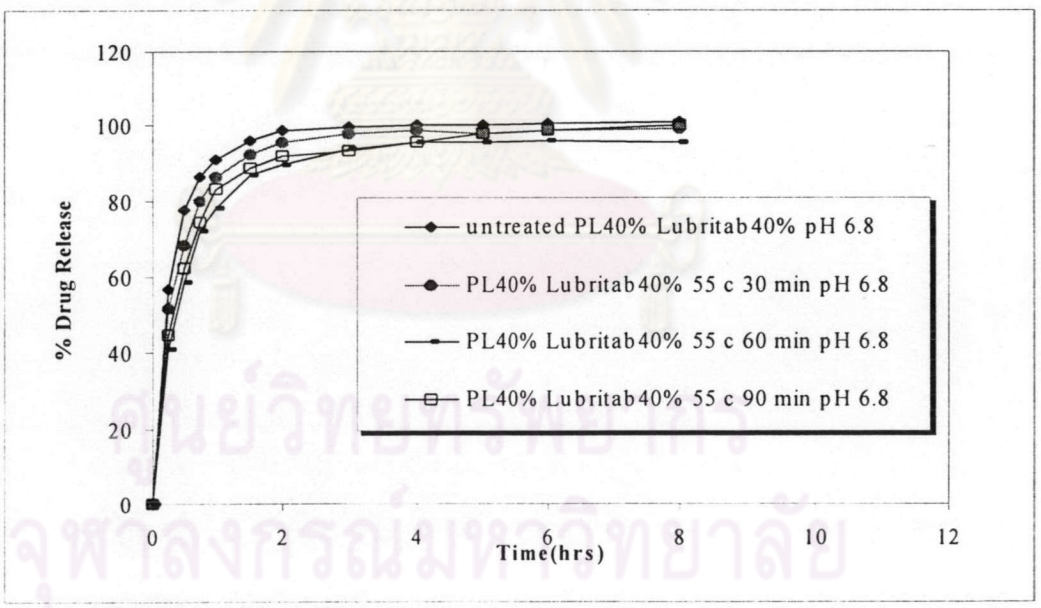


Figure 67 The release rate profiles of propranolol hydrochloride matrix pellets containing Lubritab® in pH 6.8 when curing at 55°C at various time intervals.

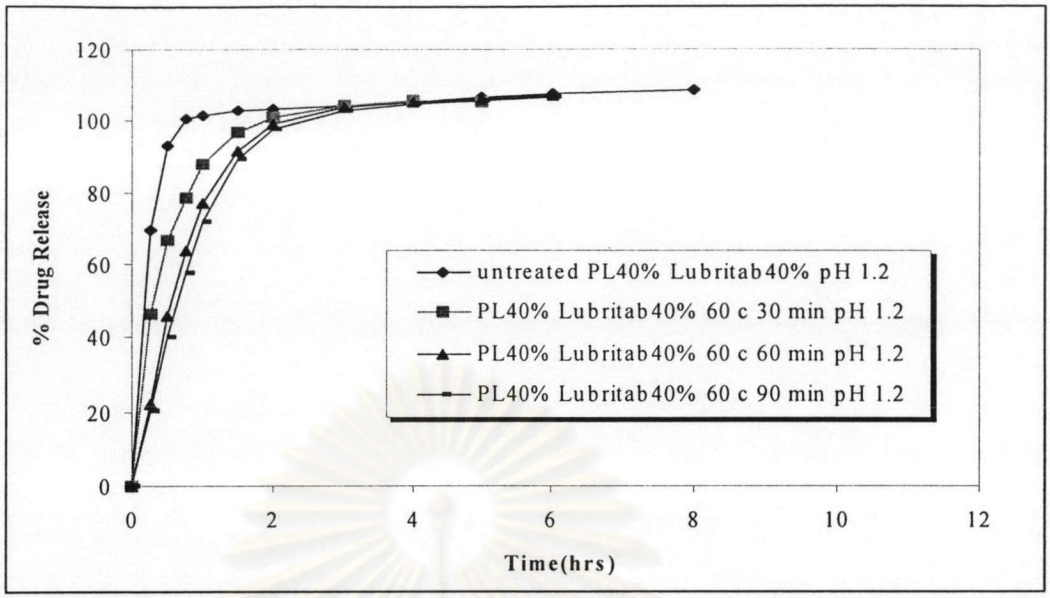


Figure 68 The release profiles of propranolol hydrochloride matrix pellets containing Lubritab® in pH 1.2 when curing at 60° C at various time intervals.

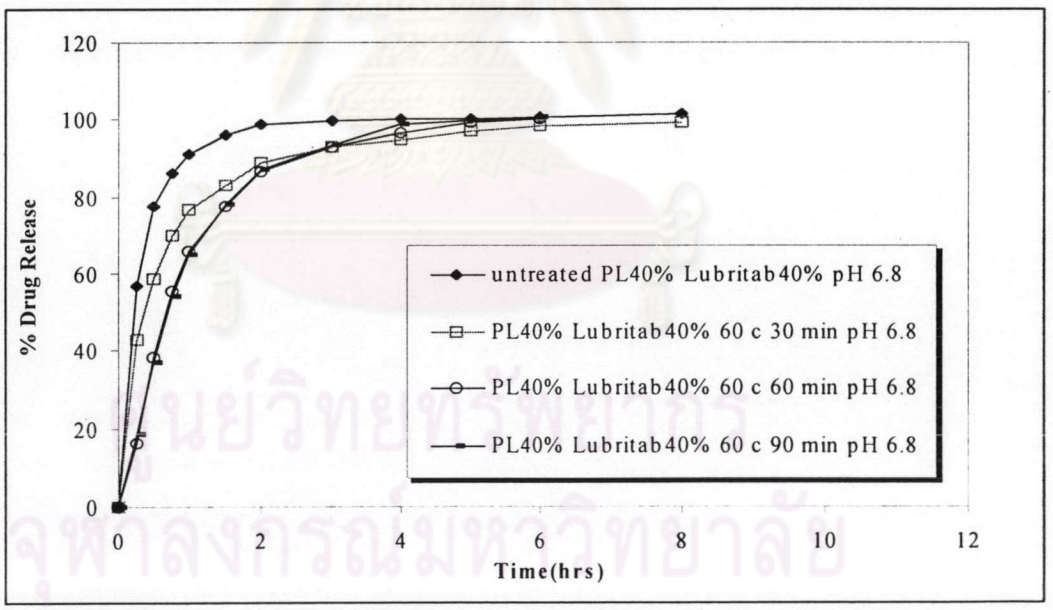


Figure 69 The release rate profiles of propranolol hydrochloride matrix pellets containing Lubritab® in pH 6.8 when curing at 60° C at various time intervals.

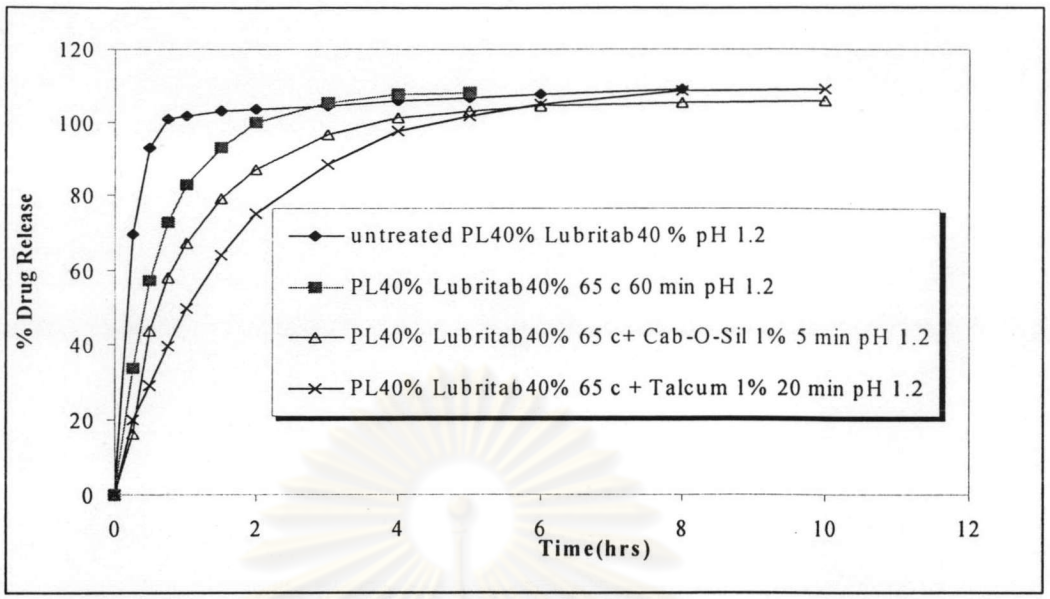


Figure 70 The release profiles of propranolol hydrochloride matrix pellets containing Lubritab® in pH 1.2 at 65°C at various time intervals when using talcum and Cab-O-Sil® as anti-sticking agent.

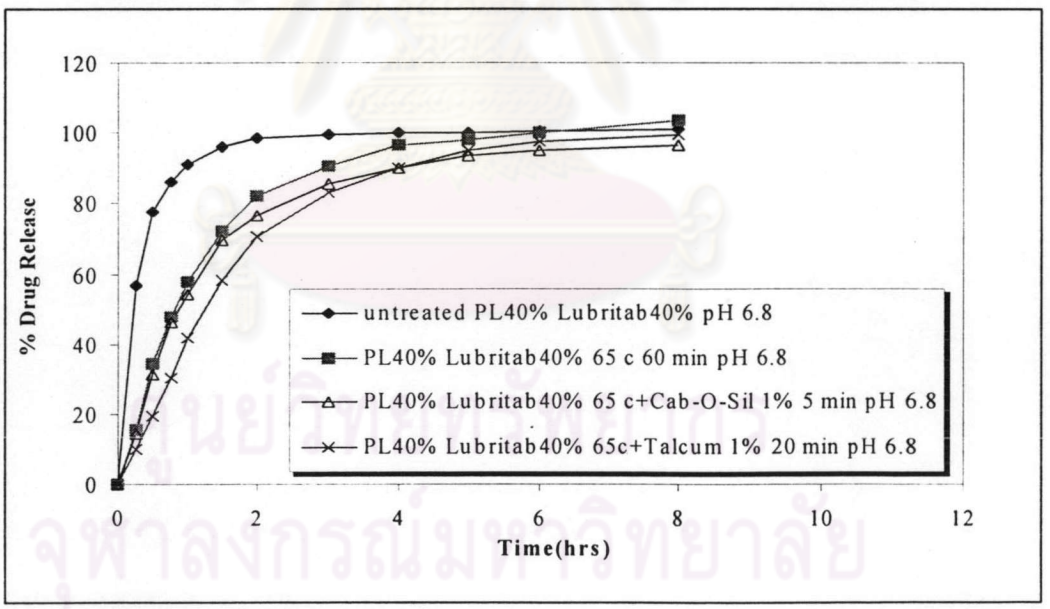
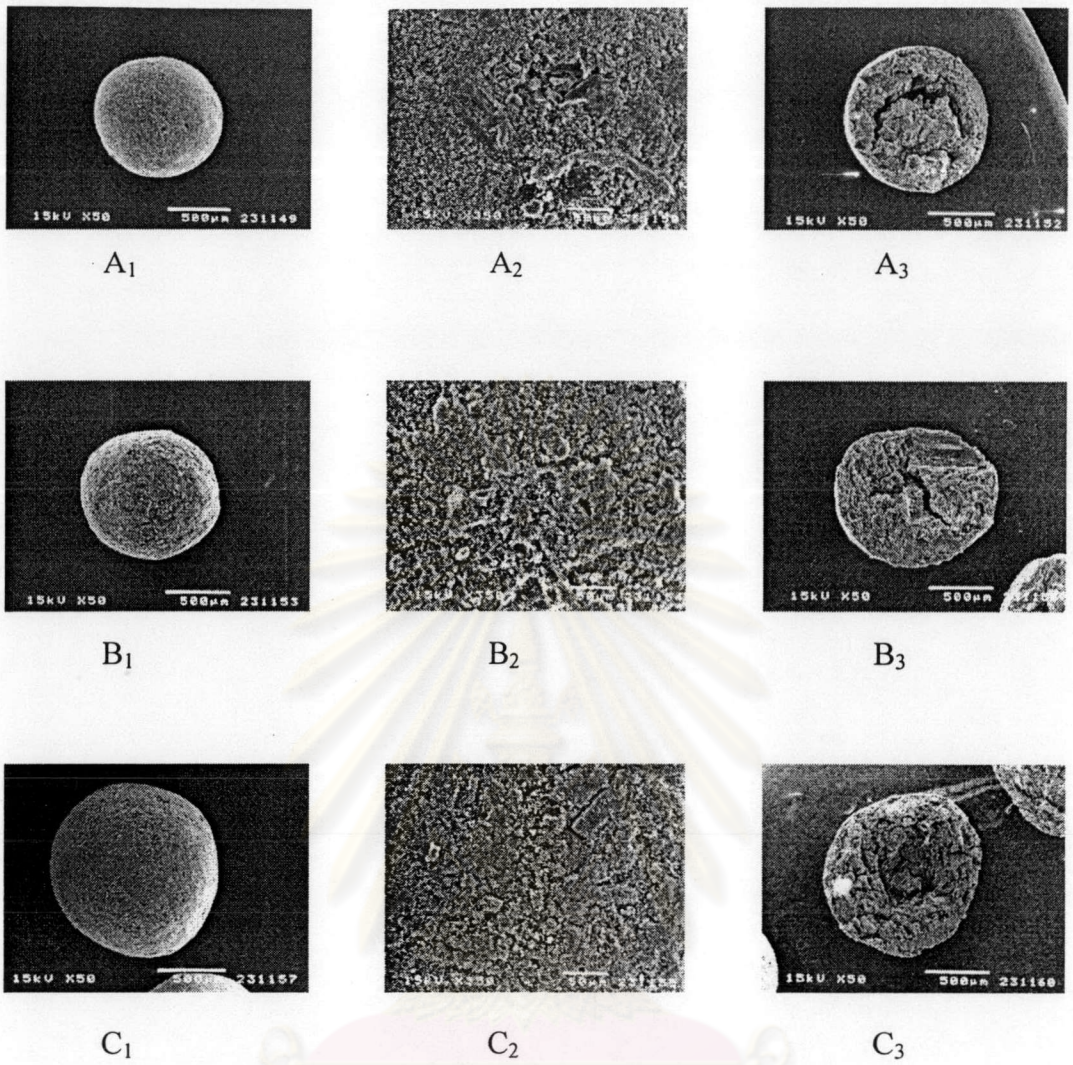


Figure 71 The release rate profiles of propranolol hydrochloride matrix pellets containing Lubritab® in pH 6.8 at 65°C at various time intervals when using talcum and Cab-O-Sil® as anti-sticking agent.

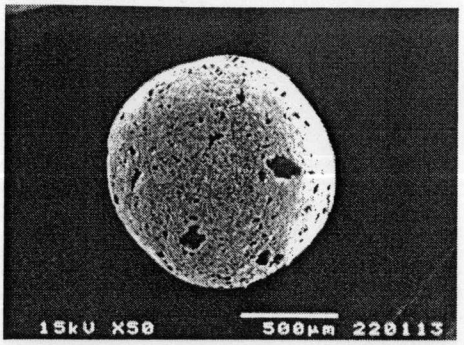


A_1 A_2 A_3

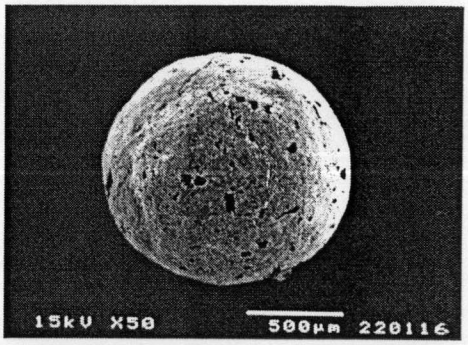
B_1 B_2 B_3

C_1 C_2 C_3

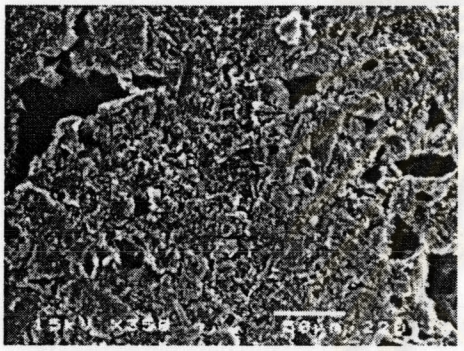
Figure 72 Scanning electron photomicrographs of curing 40% propranolol hydrochloride with Lubritab® at different temperature and time (A_1, A_2; pellets cure at 65°C 60 minutes at ×50, ×350 magnification A_3; cross-section at ×50 magnification; B_1, B_2; pellets cure at 65°C + 1% Cab-O-Sil® 5 minutes at ×50, ×350 magnification B_3; cross-section at × 50 magnification; C_1, C_2; pellets cure at 65°C + 1% talcum 20 minutes at ×50, ×350 magnification C_3; cross-section at ×50 magnification.



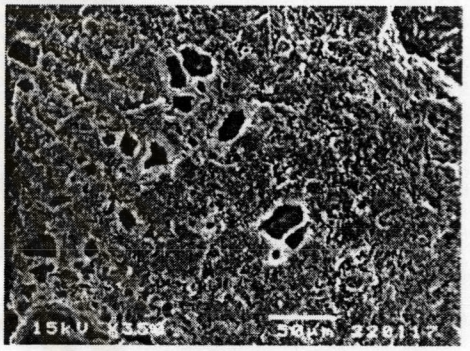
A_1



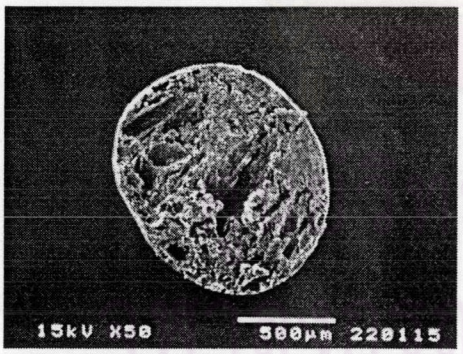
B_1



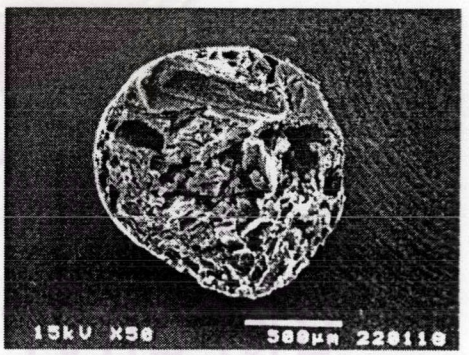
A_2



B_2

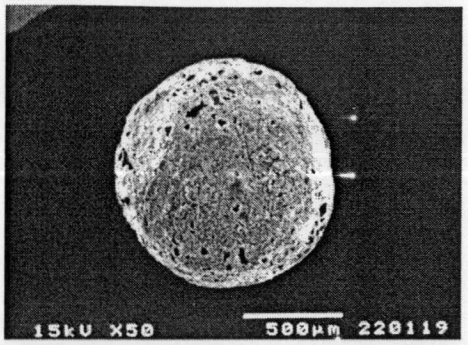


A_3

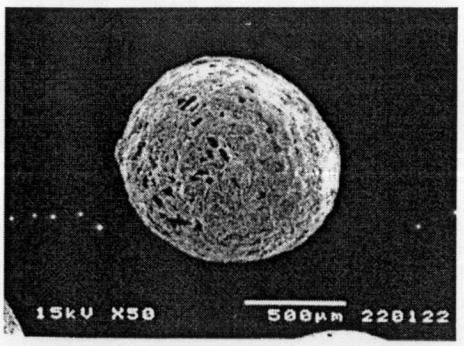


B_3

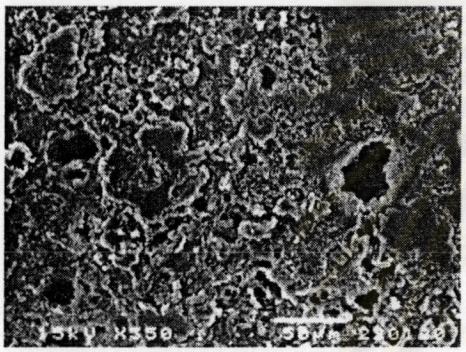
Figure 73 Scanning electron photomicrographs of 40% propranolol hydrochloride matrix pellets from the formulation using Lubritab® at 65°C 60 minutes (A_1, A_2; pellets at ×50, ×350 magnification, A_3; pellets cross-section at × 50 magnification after dissolution in 0.1 N HCl; B_1, B_2; pellets at ×50, × 350 magnification, B_3; pellets cross-section at ×50 magnification after dissolution in phosphate buffer pH 6.8).



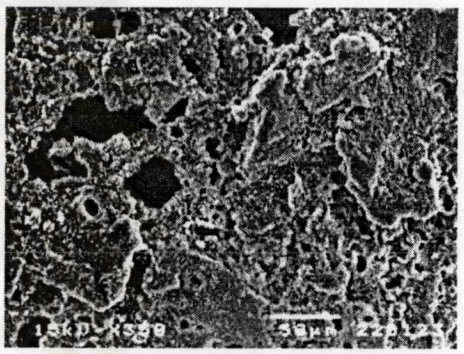
A_1



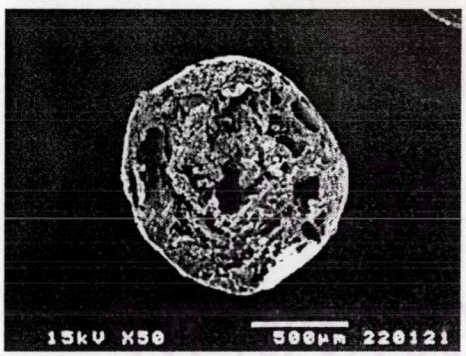
B_1



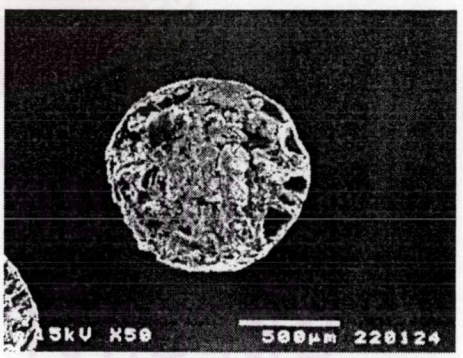
A_2



B_2

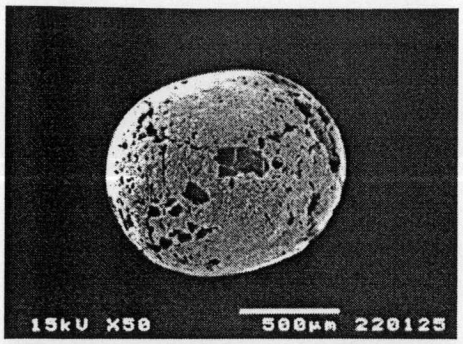


A_3

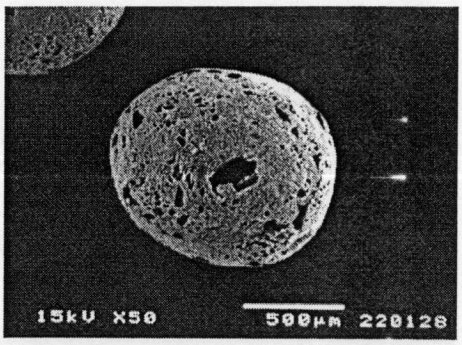


B_3

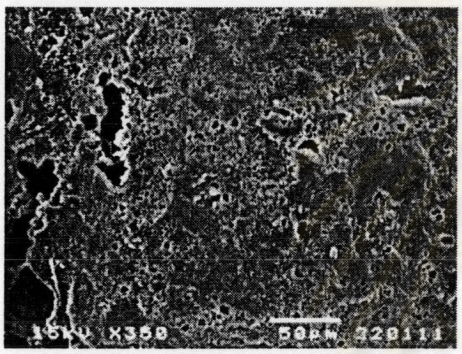
Figure 74 Scanning electron photomicrographs of 40% propranolol hydrochloride matrix pellets from the formulation using Lubritab® at 65°C +1% Cab-O-Sil® 5 minutes (A_1, A_2; pellets at ×50, ×350 magnification, A_3; pellets cross-section at ×50 magnification after dissolution in 0.1 N HCl; B_1, B_2; pellets at ×50, ×350 magnification, B_3; pellets cross-section at ×50 magnification after dissolution in phosphate buffer pH 6.8).



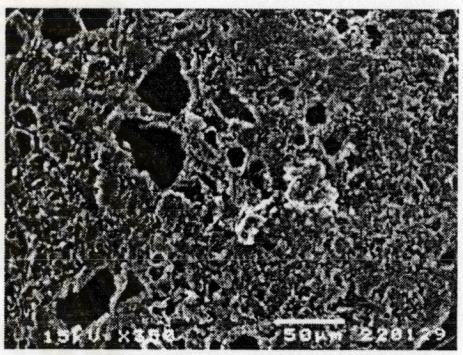
A_1



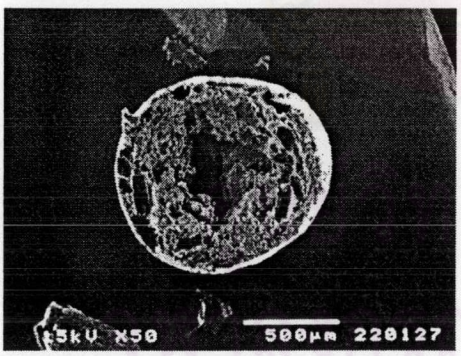
B_1



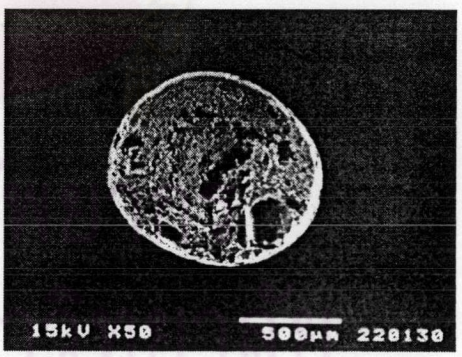
A_2



B_2



A_3



B_3

Figure 75 Scanning electron photomicrographs of 40% propranolol hydrochloride matrix pellets from the formulation using Lubritab® at 65°C +1% talcum 20 minutes (A_1, A_2; pellets at ×50, ×350 magnification, A_3; pellets cross-section at ×50 magnification after dissolution in 0.1 N HCl; B_1, B_2; pellets at ×50, ×350 magnification, B_3; pellets cross-section at ×50 magnification after dissolution in phosphate buffer pH 6.8).

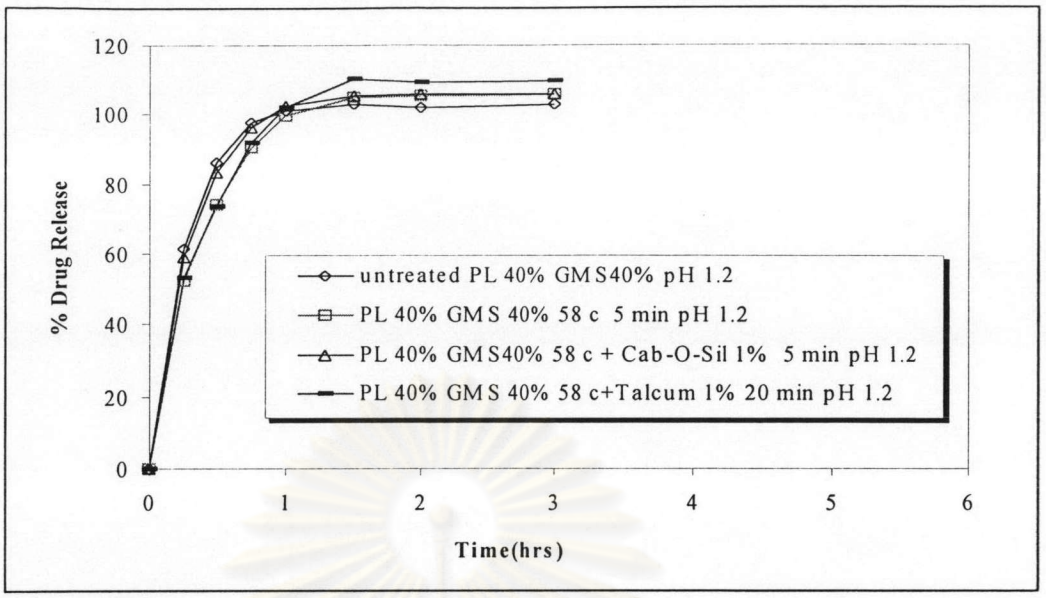


Figure 76 The release profiles of propranolol hydrochloride matrix pellets containing GMS in pH 1.2 at 58°C at various time intervals when using talcum and Cab-O-Sil® as anti-sticking agent.

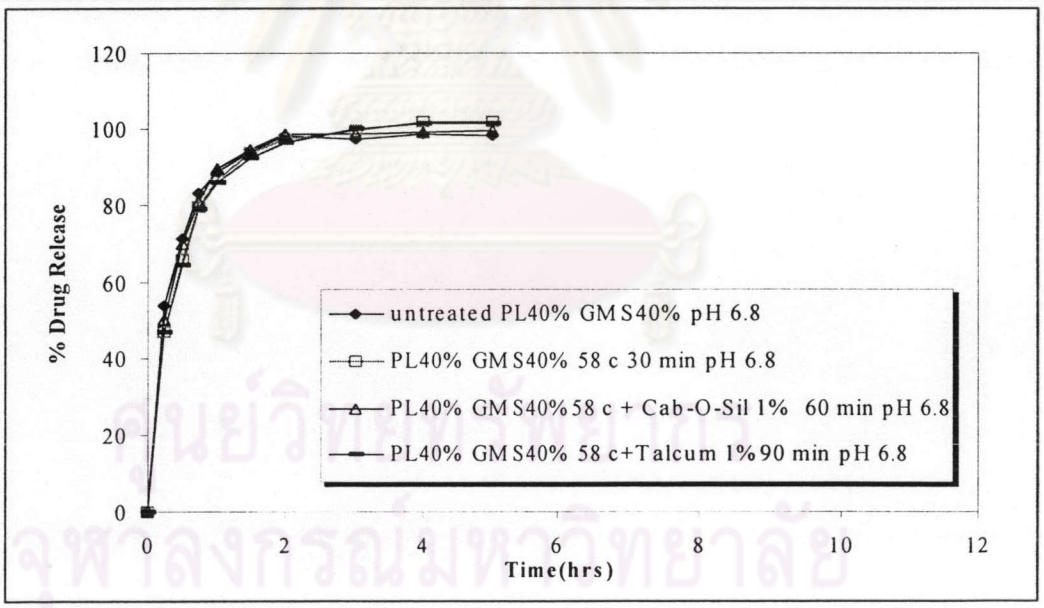


Figure 77 The release rate profiles of propranolol hydrochloride matrix pellets containing GMS in pH 6.8 at 58°C at various time intervals when using talcum and Cab-O-Sil® as anti-sticking agent.

pellet that had more binding property to result in slower release than before curing. Whereas the fastest release occurred in pellets consisted of Compritol®ATO 888 as matrix forming agent. This unexpected increase was caused by the mechanical damage done to the pellets during curing as shown in Figure 80 (Wesseling et al., 1999).

1.3 Glycerides Matrix Tablets

The study of this part was investigated the compression of pellets into tablets matrix would be prolonged the release of drug in the pH-change system.

A. Propranolol Hydrochloride Matrix Tablets

The dissolution data and drug release profiles of commercial product Inderal® LA 80 mg and our preparations that equivalent to 80 mg of drug in pH-change system are presented in Table 17B (Appendix B) and Figure 81.

Among three glycerides, only propranolol hydrochloride pellets containing 40% Lubritab® and 40% Compritol®ATO 888 could be compressed into matrices. Pellets containing 40% GMS could not be compacted to form the matrices. The release patterns of 40% Lubritab® and 40% Compritol®ATO 888 matrices were resemble to the release pattern of Inderal®LA 80. The release in 12 hours is not more than 75% in all formulations.

From the previous study, the best pellets formulation could give prolonged propranolol hydrochloride release for 12 hours is the formulation that comprising 60% Compritol®ATO 888 and 30% propranolol hydrochloride. Thus, the release of this formulation was also tested in pH-change system. The study revealed that this formulation could not prolonged release of propranolol hydrochloride for 12 hours. The release of drug was completed in 5 hours.

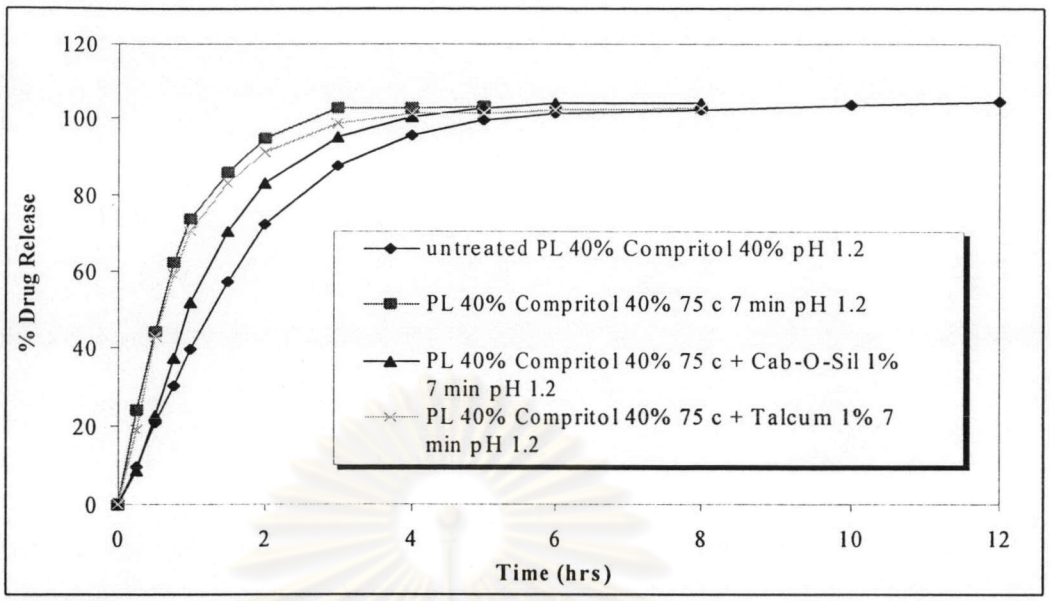


Figure 78 The release profiles of propranolol hydrochloride matrix pellets containing Compritol®ATO 888 in pH 1.2 at 75°C when using talcum and Cab-O-Sil® as anti-sticking agent.

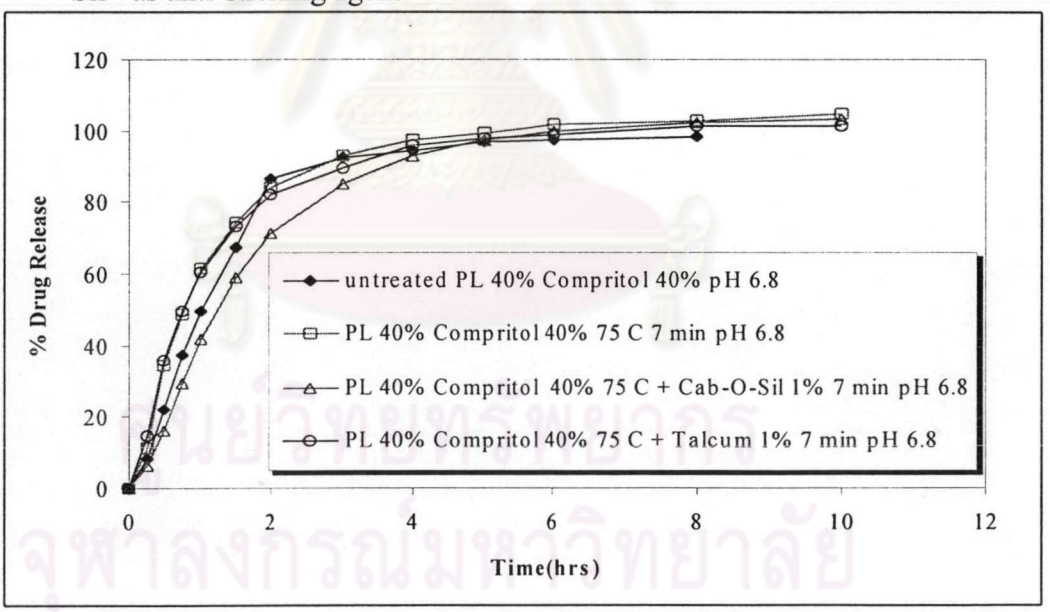


Figure 79 The release rate profiles of propranolol hydrochloride matrix pellets containing Compritol®ATO 888 in pH 6.8 at 75°C when using talcum and Cab-O-Sil® as anti-sticking agent.

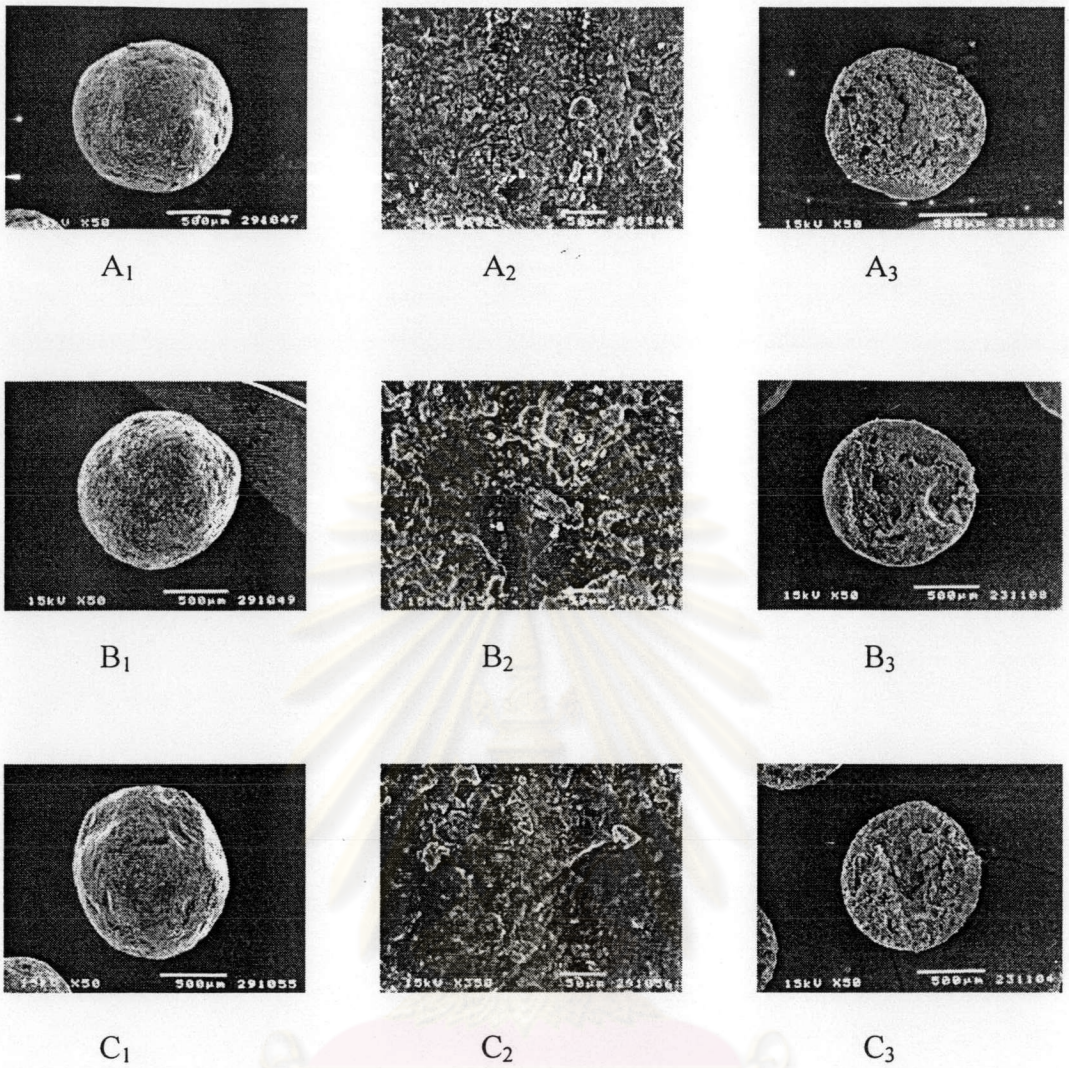


Figure 80 Scanning electron photomicrographs of curing 40% propranolol hydrochloride pellets with Compritol®ATO 888 at different curing (A_1, A_2; pellet curing at 75°C for 7 minutes at ×50, ×350, respectively, A_3; cross-section at ×50 magnification; B_1, B_2; pellets curing at 75°C + 1% Cab-O-Sil® for 7 minutes at ×50, ×350, respectively, B_3; cross-section at ×50 magnification; C_1, C_2; pellets curing at 75°C + 1% talcum for 7 minutes at ×50, ×350, respectively, C_3; cross-section at ×50 magnification.

B. Diclofenac Sodium Matrix Tablets

The release behavior of 40% diclofenac sodium pellets containing 40% of GMS, Lubritab®, and Compritol®ATO 888 when compressed into tablets are presented in Figure 82. The release patterns of GMS and Compritol®ATO 888 compared to Voltaren®SR 100 while the tablets containing Lubritab® exhibited the faster release when compared to the other formulations. Because of Lubritab® matrix tablet was disintegrated into the smaller pieces during release testing.

In comparison of drug release from three glycerides that compressed at 1000 psi revealed that drug release was fastest from tablet containing Lubritab® followed by those containing GMS and Compritol®ATO 888. When the pellets were compress to form the matrix, the compression force constituted an effective sustained release action. In the case of hard gelatin capsules containing matrix pellets, available dissolution area was much increased because of the greater number of individual particles exposed to the dissolution fluid, and results in a shorter diffusional path length, which facilitate release.

The release test of the diclofenac sodium pellets containing 60% Compritol® ATO 888 is also shown in Figure 83 for comparison with those pellet formulations when compressed into matrices. It was seem that at 12 hours the release of diclofenac sodium from Compritol®ATO 888 containing pellets was 66.63%.

Tablets showed a greater sustained release effect compared with pellets in capsule, in both propranolol hydrochloride and diclofenac sodium matrix.

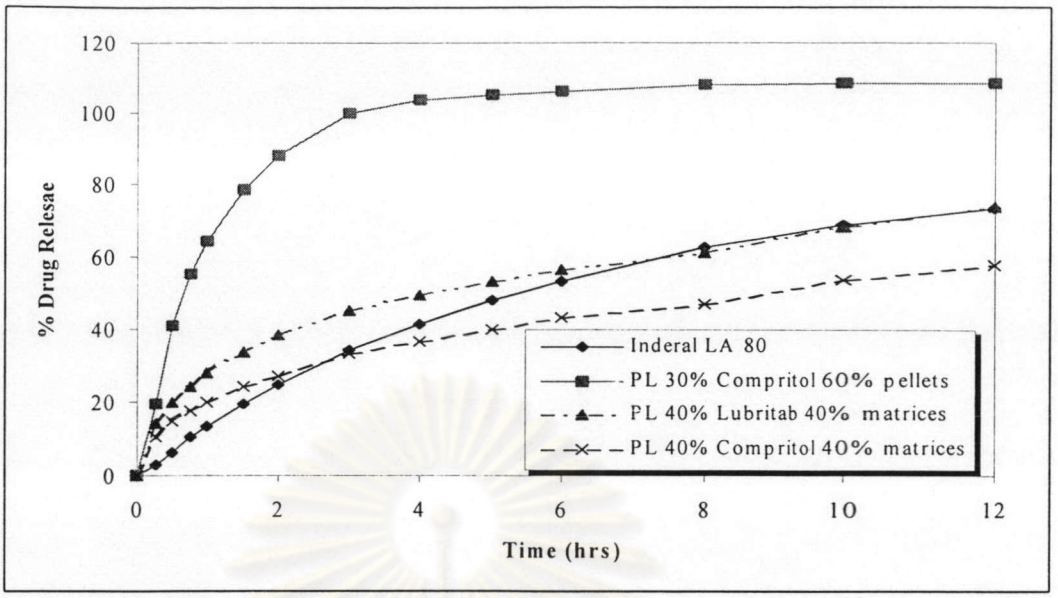


Figure 81 The release profiles in pH-change system of propranolol hydrochloride matrix tablets prepared from pellets containing Lubritab® and Compritol® ATO 888 in comparing with Inderal® LA 80.

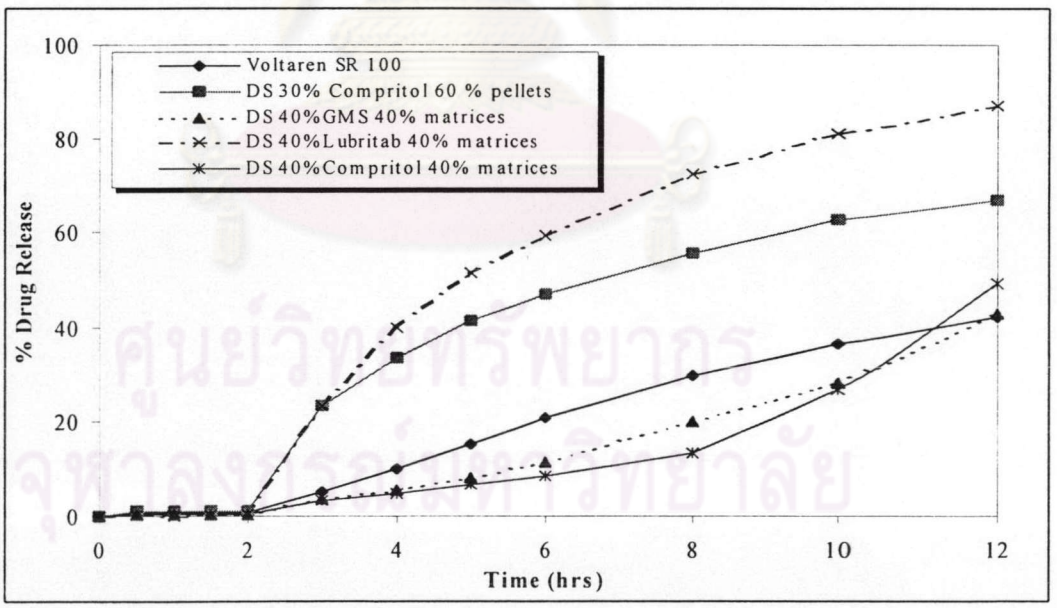


Figure 82 The release profiles in pH-change system of diclofenac sodium matrix tablets prepared from pellets containing GMS, Lubritab® and Compritol® ATO 888 in comparing with Voltaren® SR 100.