CHAPTER III

RESULTS

Preliminary Investigation on Suitable Coating Conditions

Suitable coating conditions were investigated by coating sucrose crystals with coating solution which had composition as previously presented in Table 2. The suitable coating conditions using top spray method was previously described in Table 4 .

Uniform coating of polymer on sugar crystals was simply tested by observation of smooth color of erythrosine and loss of sucrose sweetened taste. Finally, erythrosine dye was substituted by propranolol hydrochloride.

Evaluation of the Beads Coated with Drug and Various Coating Formulation

The result of evaluation of the coated beads are described according to the following formulations of the coating solution.

FORMULATIONS 1-10

The sucrose crystals were coated with coating solution having composition as previously described in Table 3 but only the amount and type of plasticizers were varied as presented in the following Table 5 and 6.

Table 5 Composition of Coating Formulations 1-4

Component (% w/v)	Formulation 1	2	3	4
Propranolol HCl	5	5	5	5
Ethylcellulose	5	5	5	5
Glycerylmonostearate	-	1	2	3
Ethanol qs.	100	100	100	100

Table 6 Composition of Coating Formulations 5-10

Component (%w/v)	Formulation 5	6	7	8	9	10
Propranolol HCl	5	5	5	5	5	5
Ethylcellulose	5	5	5	5	5	5
Castor oil	1	2	3	-	-	-
PEG 4000	-	-	-	1	2	3
Ethanol qs.	100	100	100	100	100	100

Physical property evaluation of beads coated with formulation 1-10

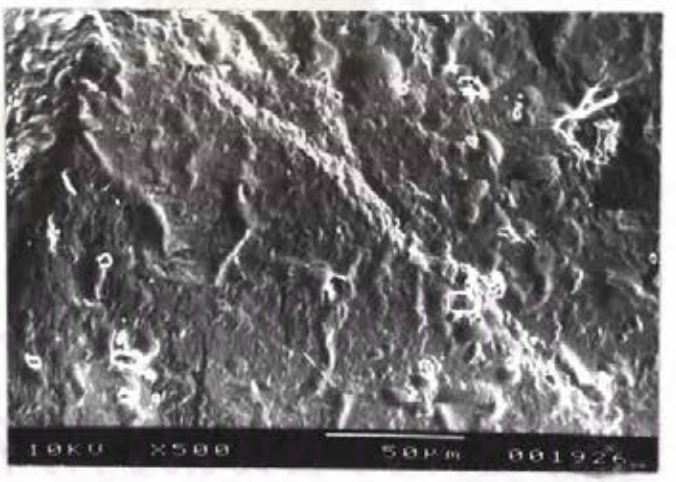
The sucrose crystals coated with different formulation of coating solution were examined using scanning electron microscope (SEM) at different maginification (x 35 and x 500). The cross-section of the coated beads was also observed for the film morphology at x 100 magnification.

Figure 11 showed the scanning electron photomicrograph of uncoated sucrose crystals. The shape and surface topography of coated sucrose beads prepared at different type and content of plasticizers is shown in Figure 12-21. The surface of beads was covered with rough coating porous layer but some of them had rather smooth surface.

Formulation 1 (no plasticizer) gave rather smooth surface and uniformity of coating (Figure 12). More rough and porous coating surface of the beads were obtained when using coating solution of formulation 2-4 which containing 1-3% glycerylmonosterate as shown in Figure 13-15. Formulations 5-7 (1-3% castor oil) gave thinner coating film than formulations 2-4 and more rough surface was observed when content of castor oil was increased (Figure 16-18). Formulation 8-10 (1-3% PEG 4000) provided the thickest coating film and when PEG 4000 content was increased, more rough surface was observed (Figure 19-21).

The physical properties of the beads formulation 1-10 are shown in Table 7. The mean size of the coated beads using formulation 1-10 was about 700 μm. Size of sucrose beads

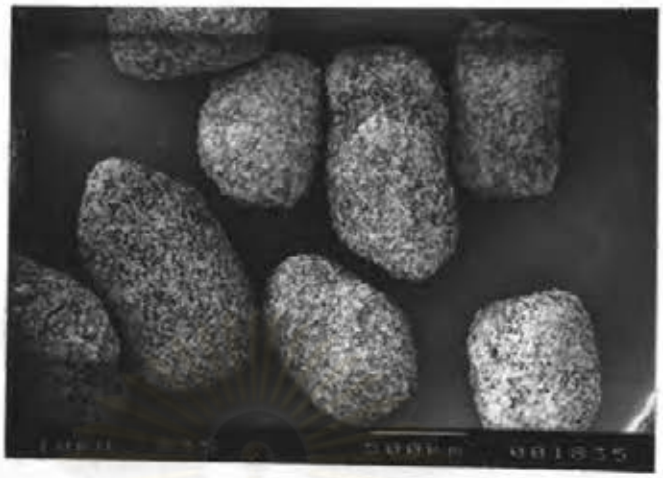
A



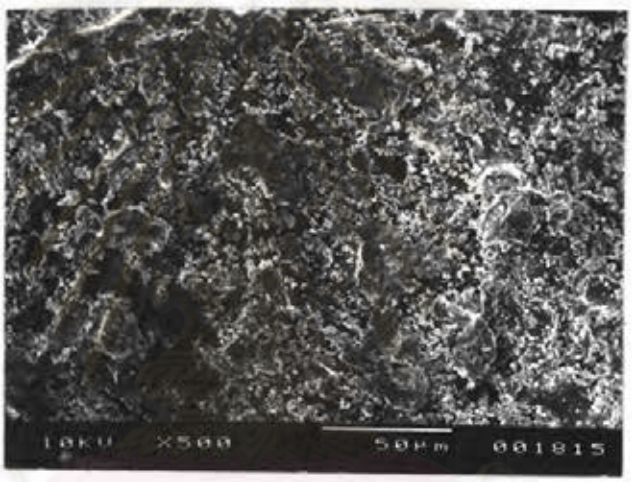
B

Figure 11 Photomicrographs of uncoated sucrose crystal

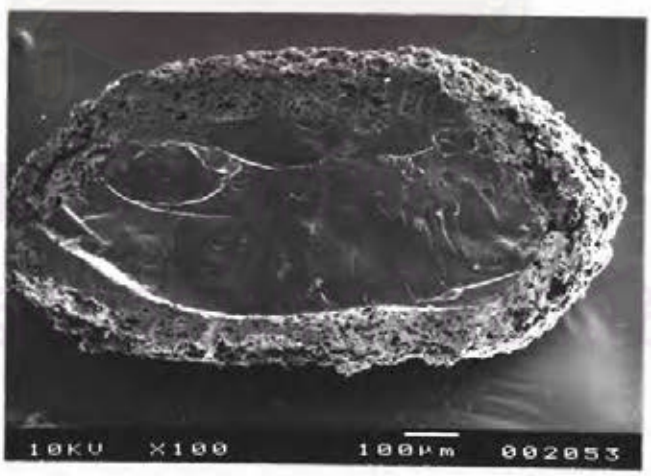
(Key: A sucrose beads x100 , B sucrose surface x 500)



A



B

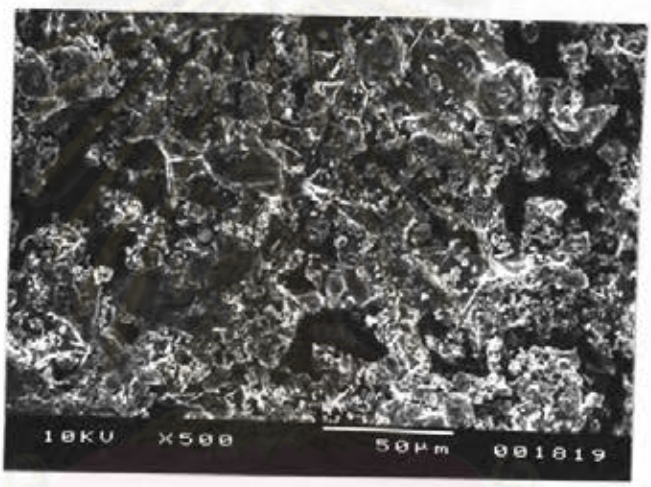


C

Figure 12 Photomicrographs of coated sucrose beads formulation 1 (Key: A coated beads x 35 , B coating surface x 500 , C cross-section x 100)

Figure 13 Photomicrographs of coated sucrose beads formulation 2 (Key: A coated beads x 35 , B coating surface x 500 , C cross-section x 100)

A



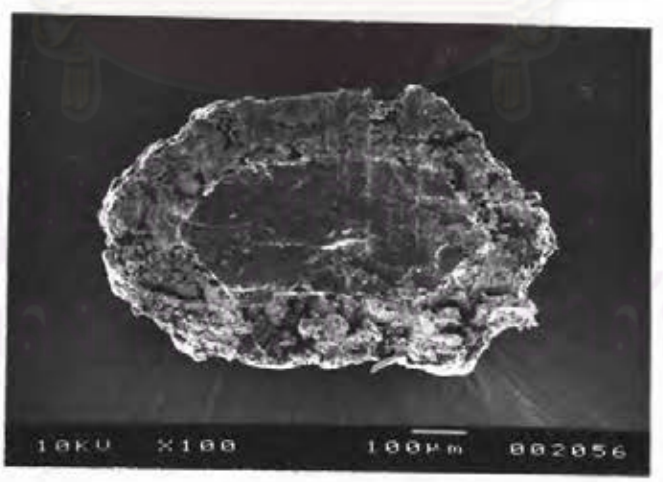
B

C

Figure 14 Photomicrographs of coated sucrose beads formulation 3 (Key: A coated beads x 35 , B coating surface x 500 , C cross-section x 100)

A

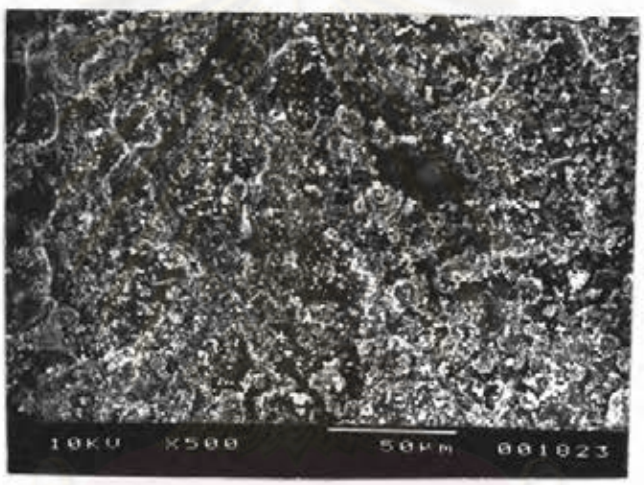
B



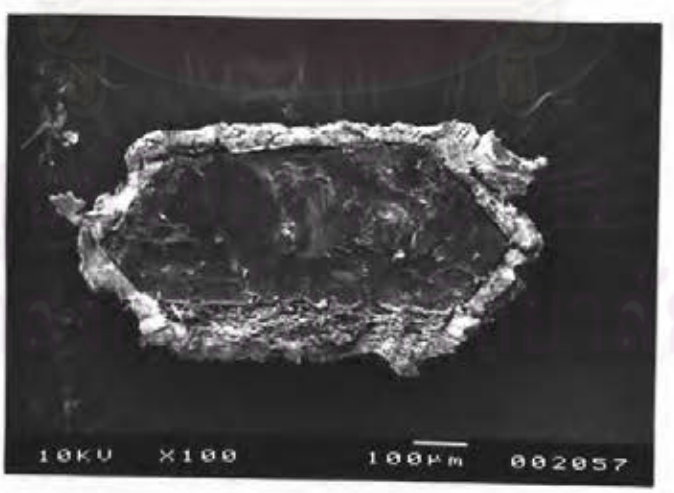
C

Figure 15 Photomicrographs of coated sucrose beads formulation 4 (Key: A coated beads x 35 , B coating surface x 500 , C cross-section x 100)

A



B



C

Figure 16 Photomicrographs of coated sucrose beads formulation 5 (Key: A coated beads x 35 , B coating surface x 500 , C cross-section x 100)

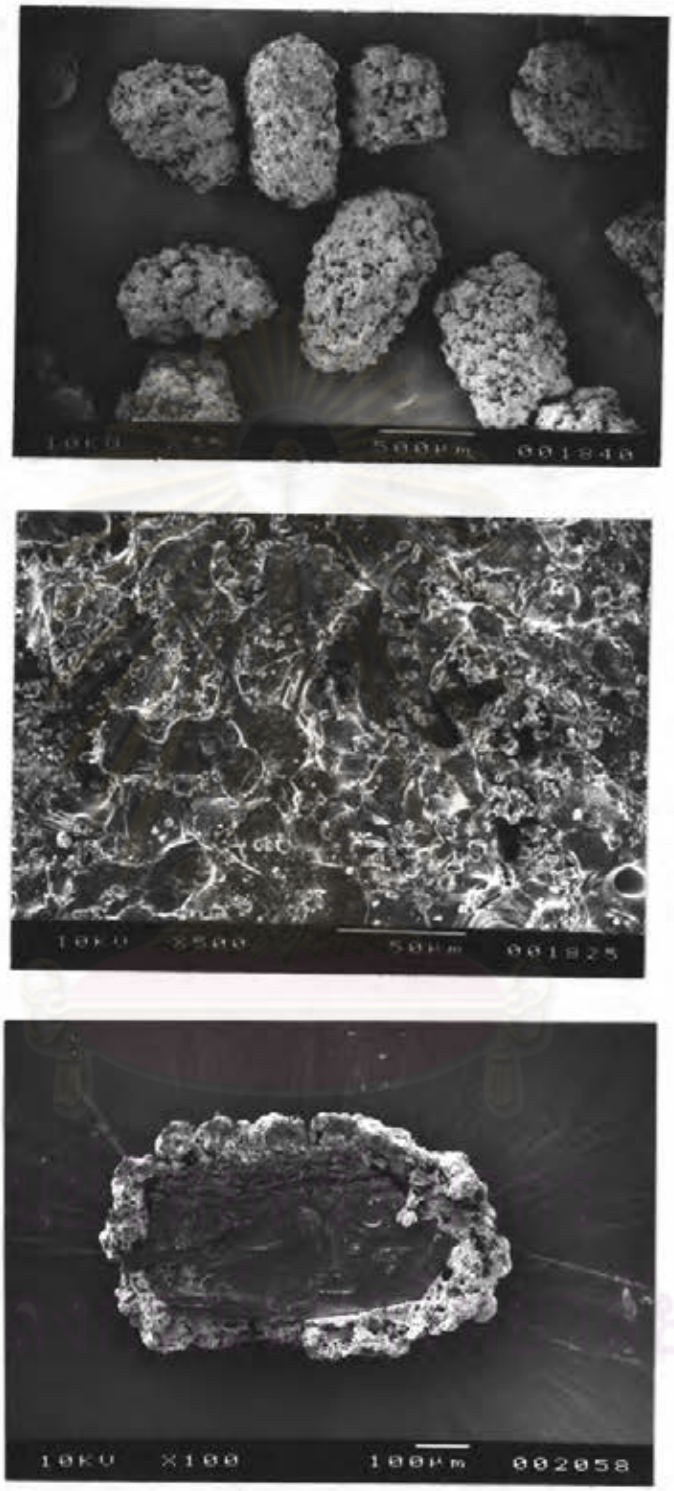
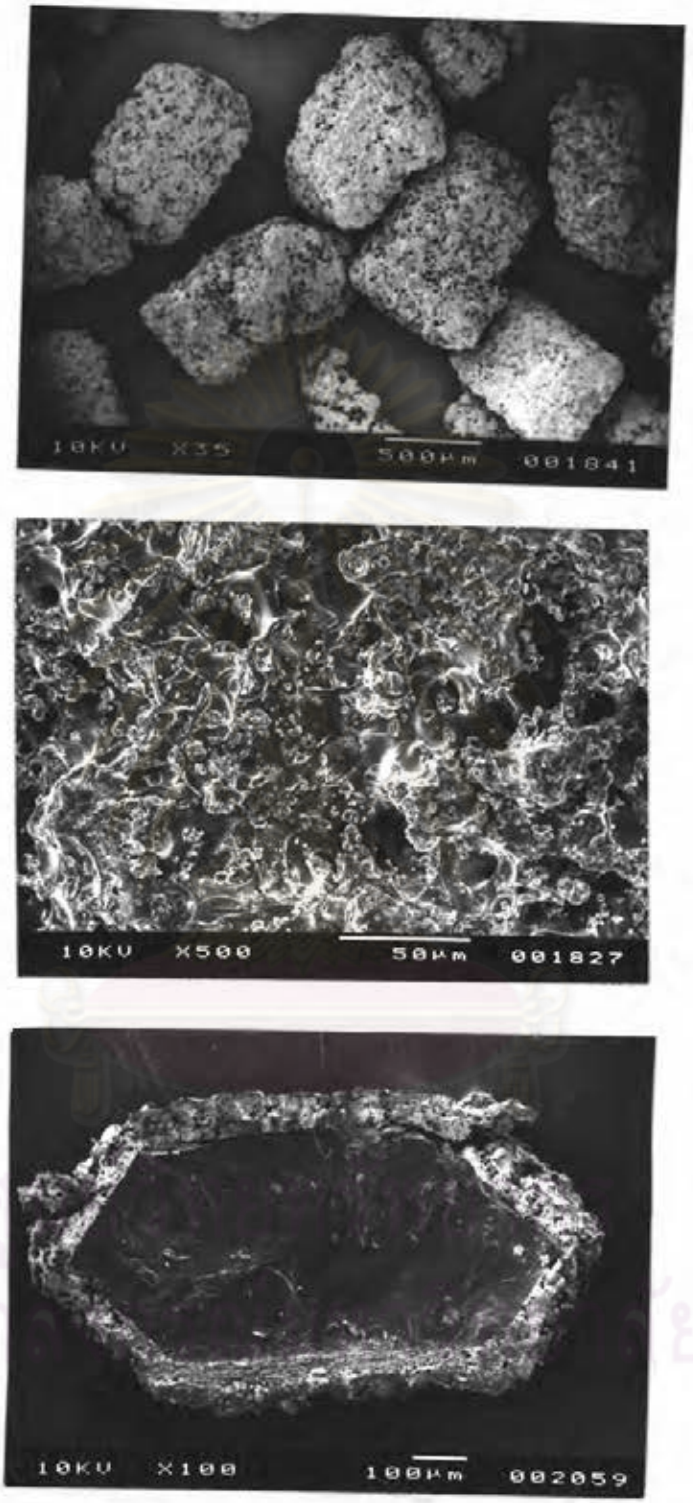


Figure 17 Photomicrographs of coated sucrose beads formulation 6 (Key: A coated beads x 35 , B coating surface x 500 , C cross-section x 100)



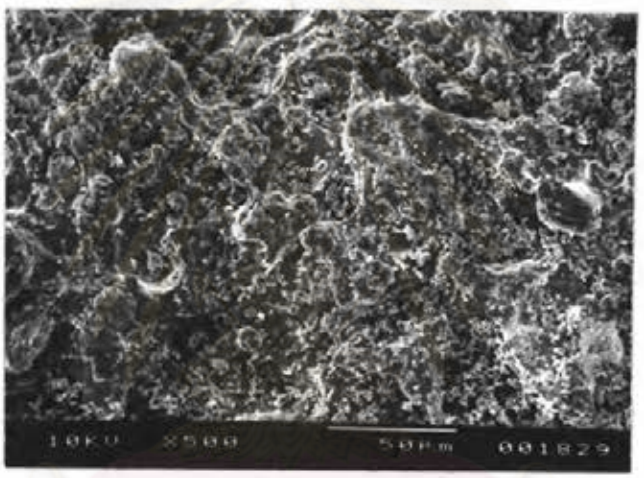
A

B

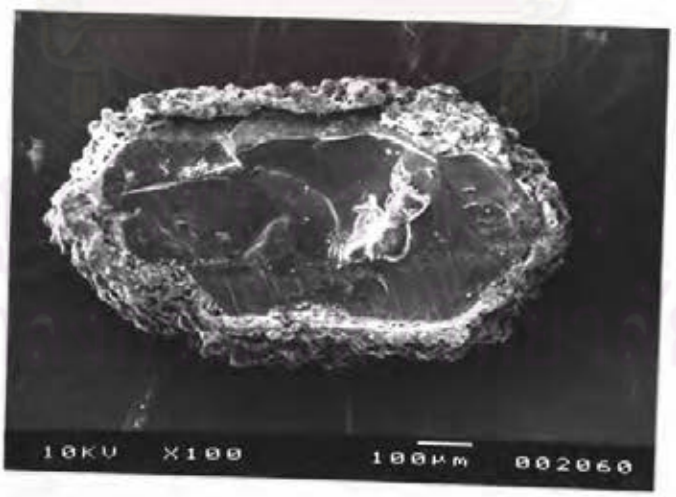
C

Figure 18 Photomicrographs of coated sucrose beads formulation 7 (Key: A coated beads x 35 , B coating surface x 500 , C cross-section x 100)

A

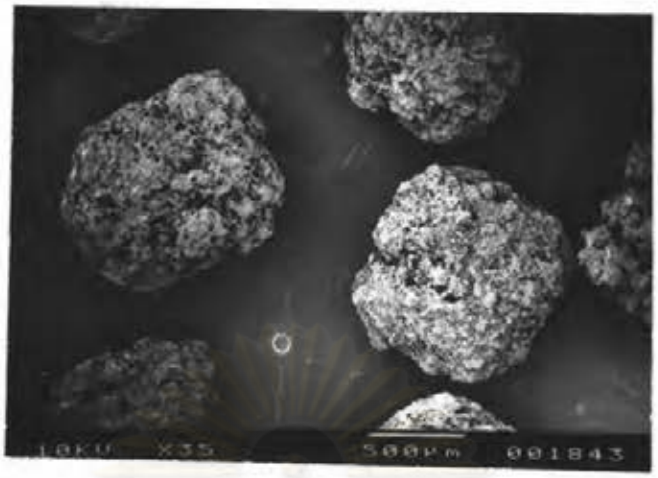


B

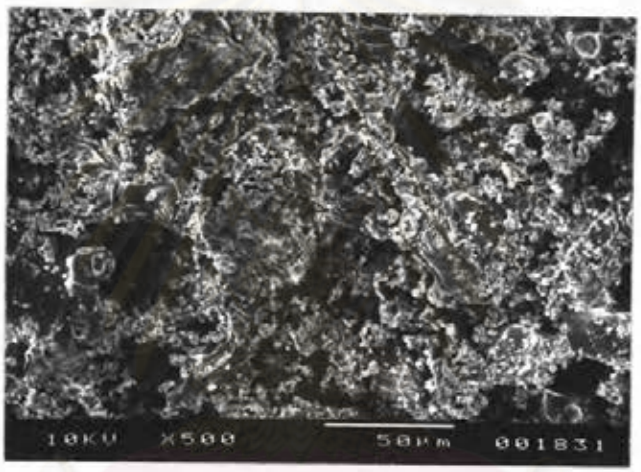


C

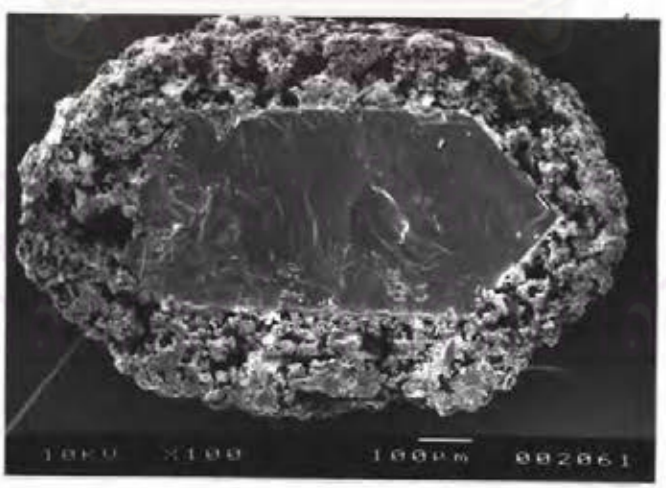
Figure 19 Photomicrographs of coated sucrose beads formulation 8 (Key: A coated beads x 35 , B coating surface x 500 , C cross-section x 100)



A

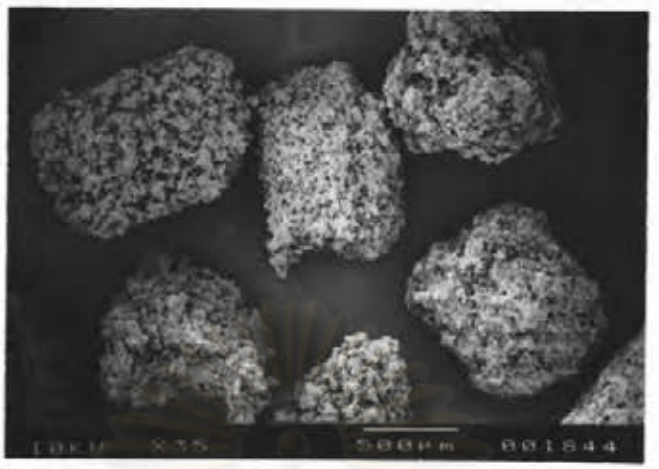


B

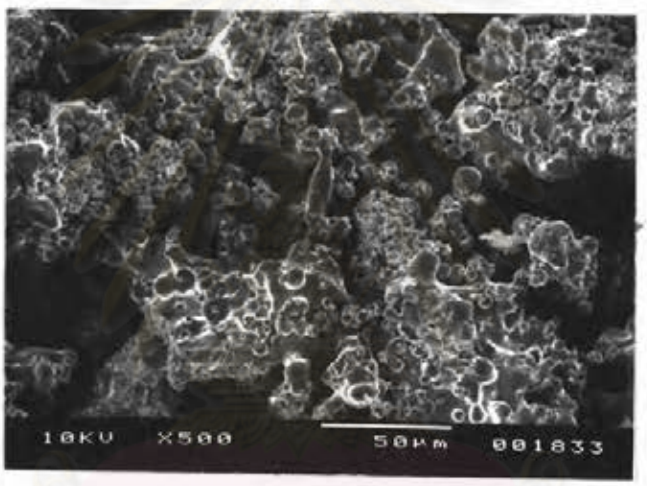


C

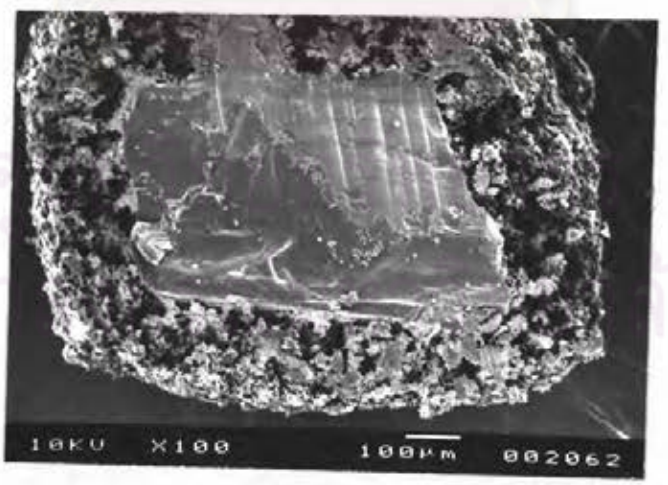
Figure 20 Photomicrographs of coated sucrose beads formulation 9 (Key: A coated beads x 35 , B coating surface x 500 , C cross-section x 100)



A



B



C

Figure 21 Photomicrographs of coated sucrose beads formulation 10 (Key: A coated beads x 35 , B coating surface x 500 , C cross-section x 100)

Table 7 The Physical Properties of the Beads Formulations 1-10

Formulation	Mean Size (μ)	Bulk Density (g/ml)	Tapped Density (g/ml)	Carr's Index	Friability (%)
1	689.97	0.59	0.64	6.93	0.60
2	708.09	0.61	0.65	6.12	0.60
3	703.05	0.56	0.59	5.56	0.50
4	689.29	0.56	0.60	7.41	0.40
5	692.32	0.55	0.57	3.64	0.60
6	701.91	0.53	0.56	5.26	0.50
7	702.58	0.57	0.61	7.55	0.60
8	705.15	0.53	0.57	7.02	0.90
9	703.54	0.59	0.64	7.84	0.70
10	691.54	0.53	0.58	8.85	0.90

coated by coating solution which composed of several plasticizers was not apparently different.

The bulk density , tapped density and Carr's compressibility index of coated beads are also presented in Table 7. The compressibility was interpreted to predict the flowability of the beads. The lower compressibility was obtained from beads with better flowability. For sucrose beads, it was observed that there was not apparently different among formulation 1-10. The products prepared according to the formulations 1-10 were not apparently different in bulk density.

The friability of beads are presented in Table 7. Formulations 8-10, using PEG 4000 as plasticizer showed tendency to increase friability.

Dissolution study evaluation of formulations 1-10

The release profiles of coated beads were studied by basket method in different media as 0.1 N HCl, phosphate buffer pH 6.8 and pH change method. The dissolution data of the beads coated by the individual formulations are presented in Tables 31-42 (see Appendix A).

The type of plasticizers was investigated including glycerylmonostearate , castor oil and polyethylene glycol 4000. The dissolution rates of the coated beads which were composed of plasticizer and non-plasticizer and were studied by basket method in 0.1 N HCl, phosphate buffer pH 6.8 and pH change method are tabulated in Tables 29-32, 33-36 and 37-40 (Appendix A) and are

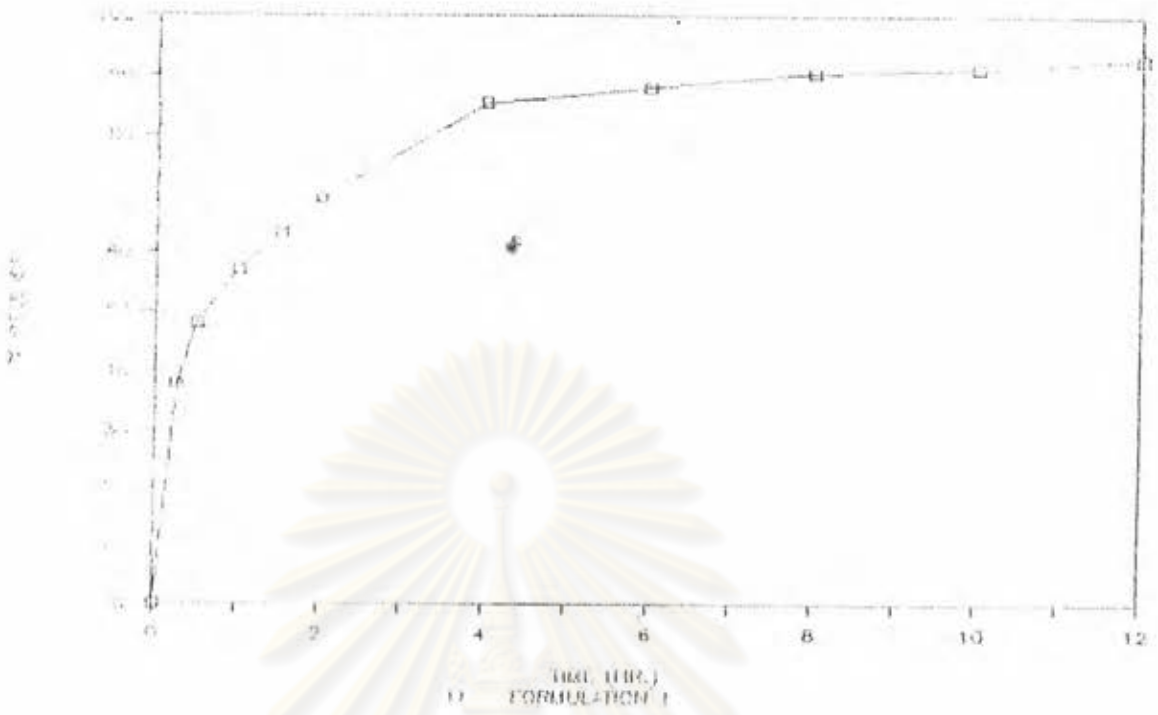


Figure 22 Release profile of coated sucrose beads formulation 1 in 0.1 N HCl

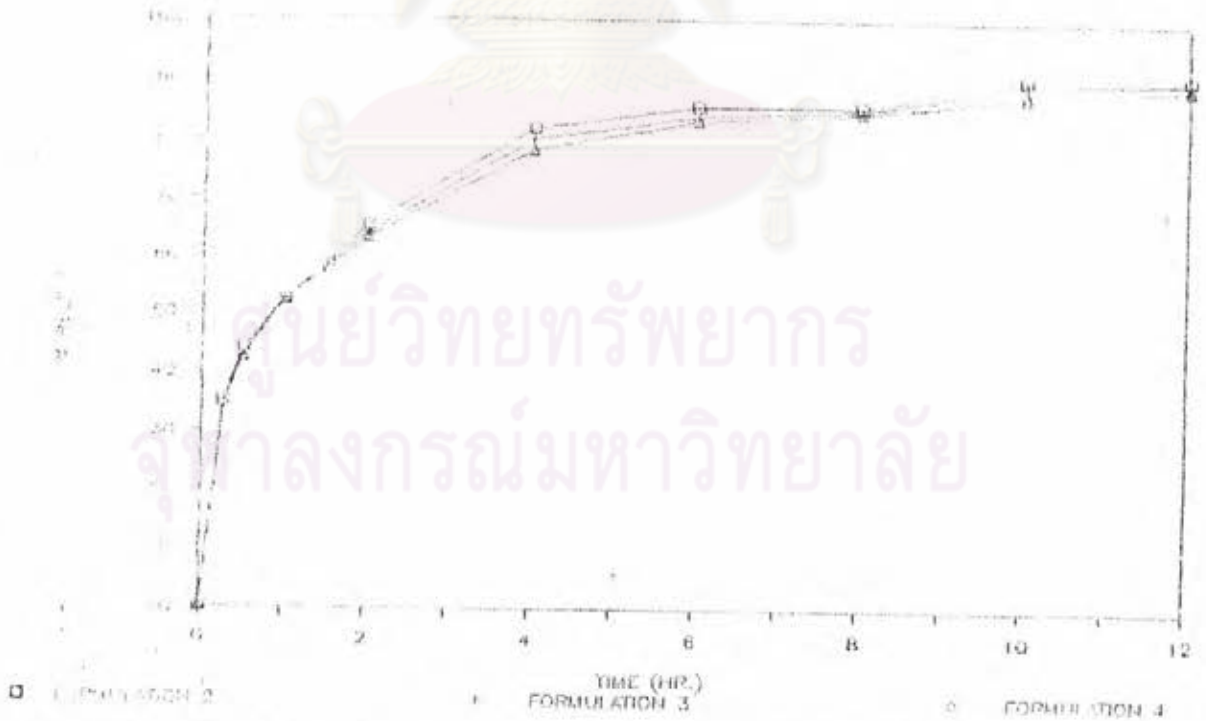


Figure 23 Release profile of coated sucrose beads formulation 2-4 in 0.1 N HCl

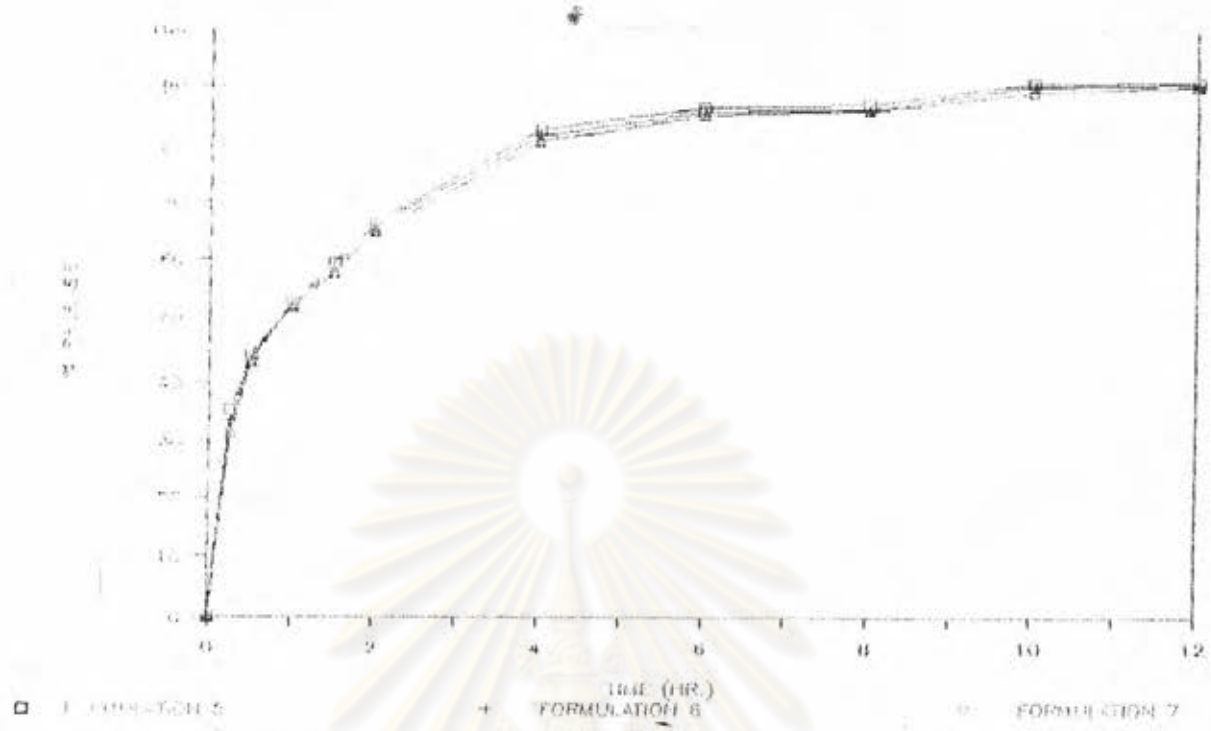


Figure 24 Release profile of coated sucrose beads formulation 5-7 in 0.1 N HCl

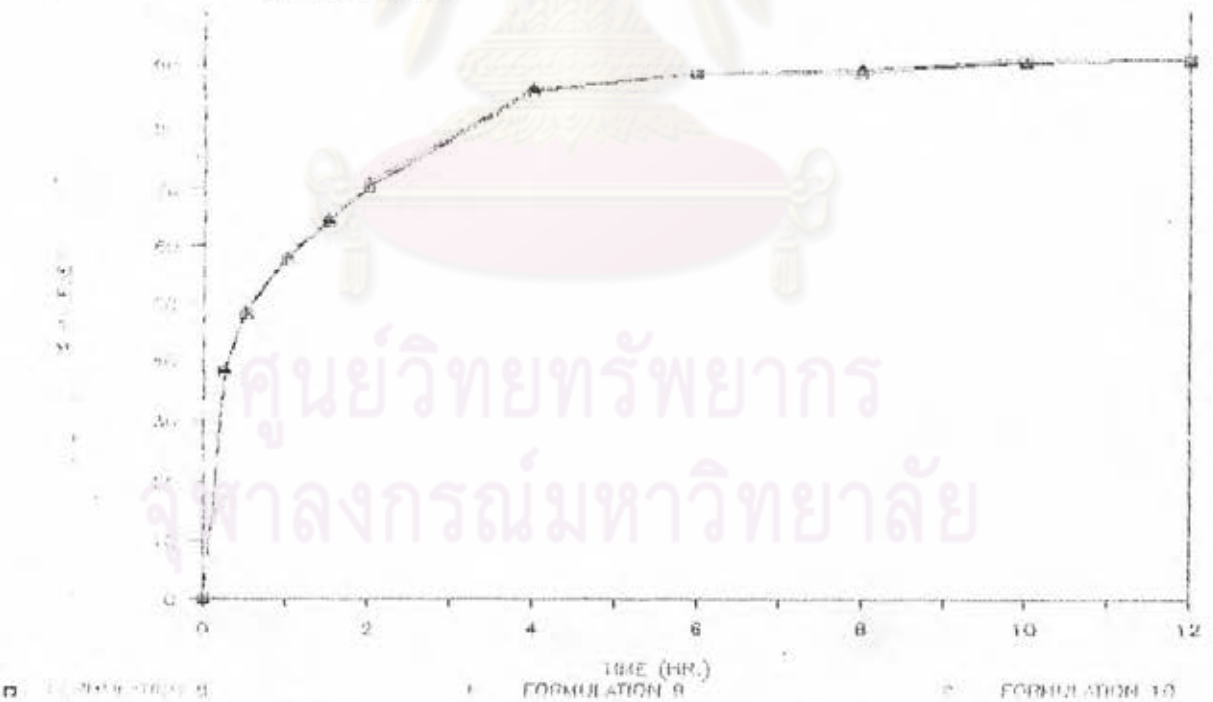


Figure 25 Release profile of coated sucrose beads formulation 8-10 in 0.1 N HCl

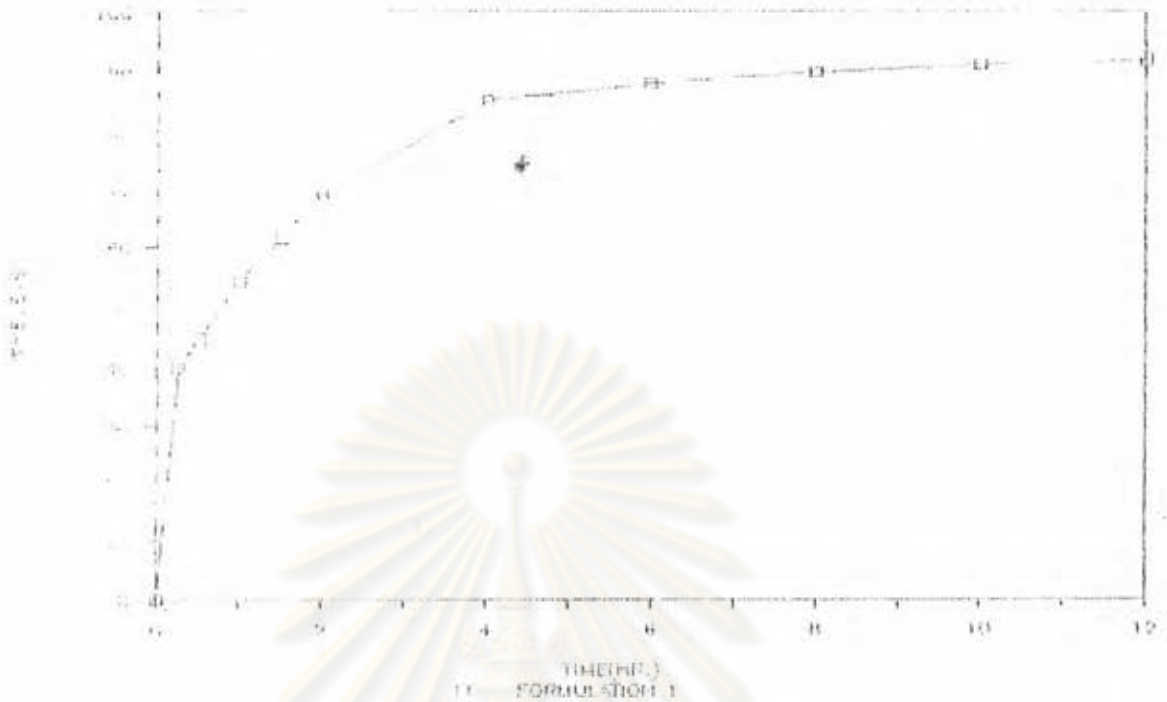


Figure 26 Release profile of coated sucrose beads formulation 1 in phosphate buffer pH 6.8

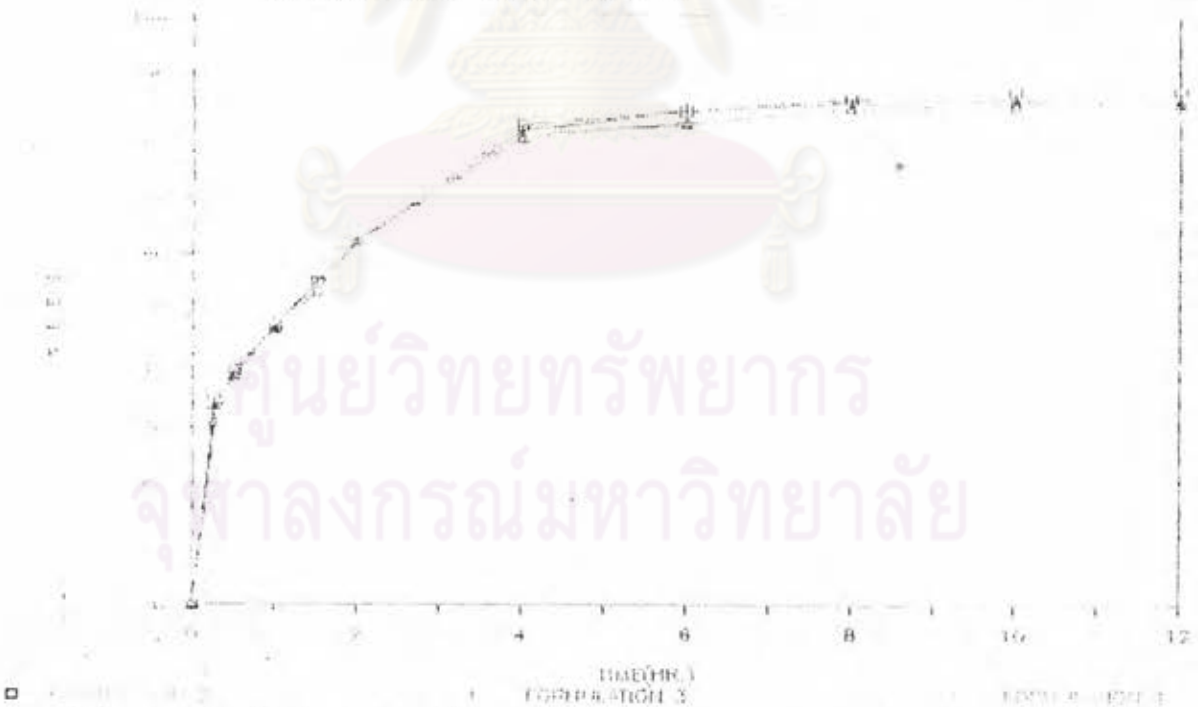


Figure 27 Release profile of coated sucrose beads formulation 2-4 in phosphate buffer pH 6.8

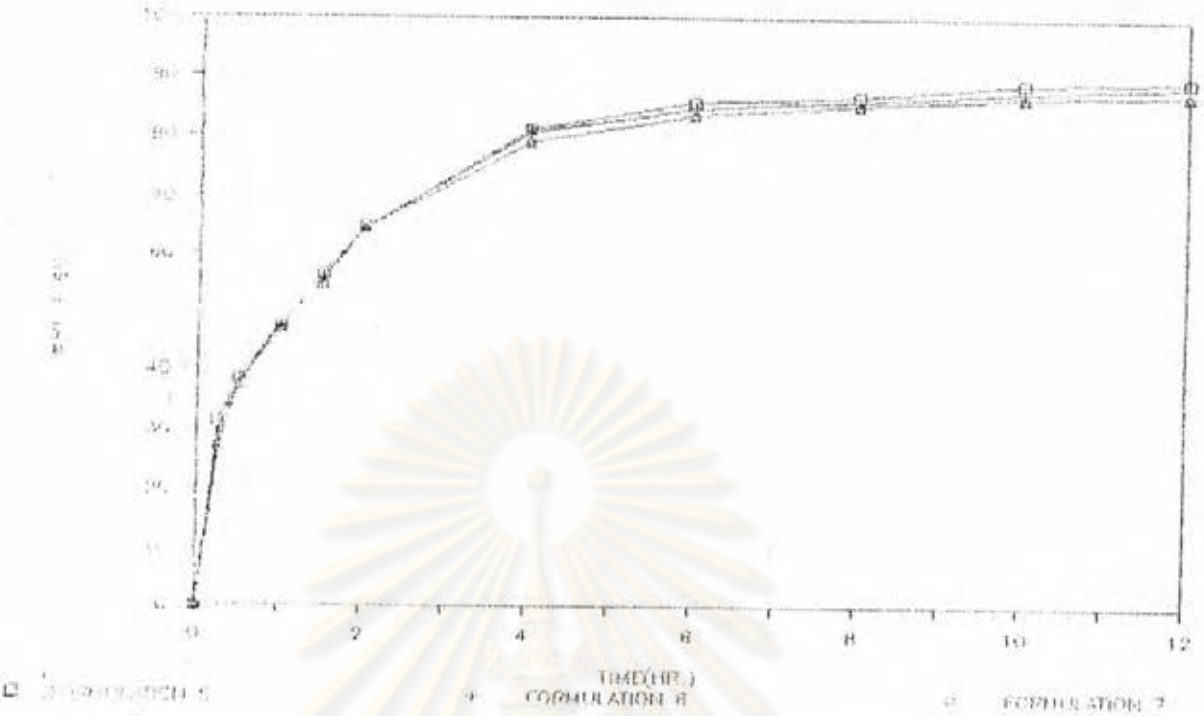


Figure 28 Release profile of coated sucrose beads formulation 5-7 in phosphate buffer pH 6.8

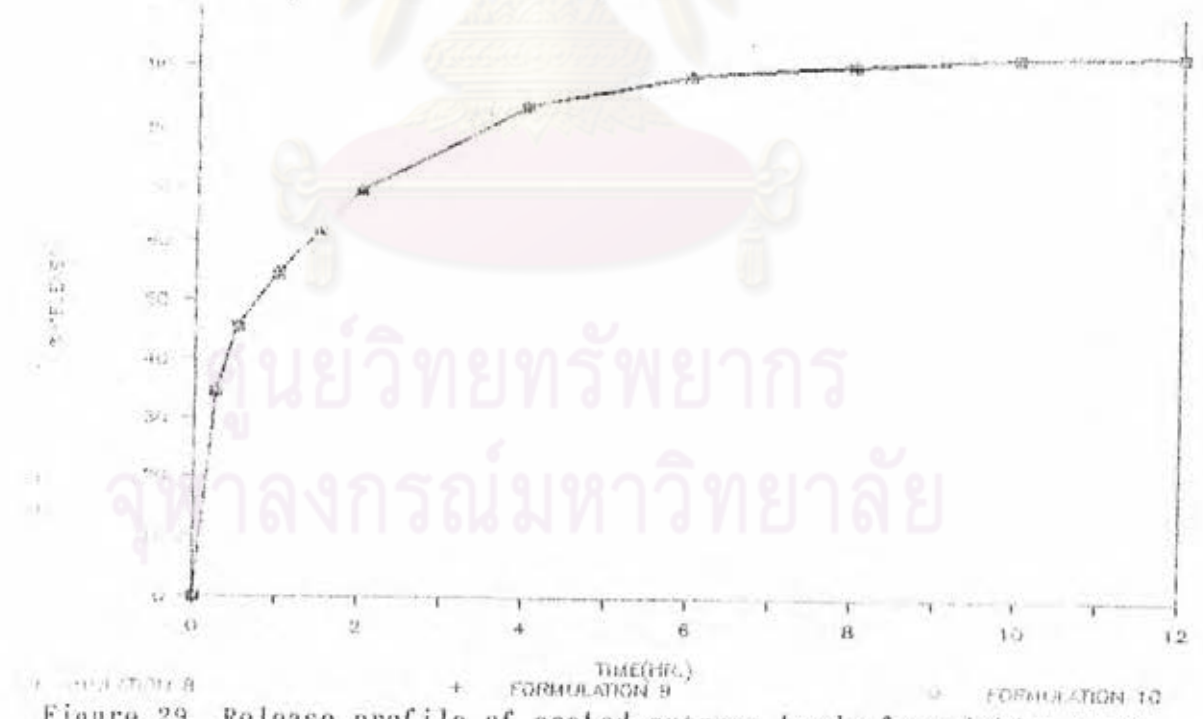


Figure 29 Release profile of coated sucrose beads formulation 8-10 in phosphate buffer pH 6.8

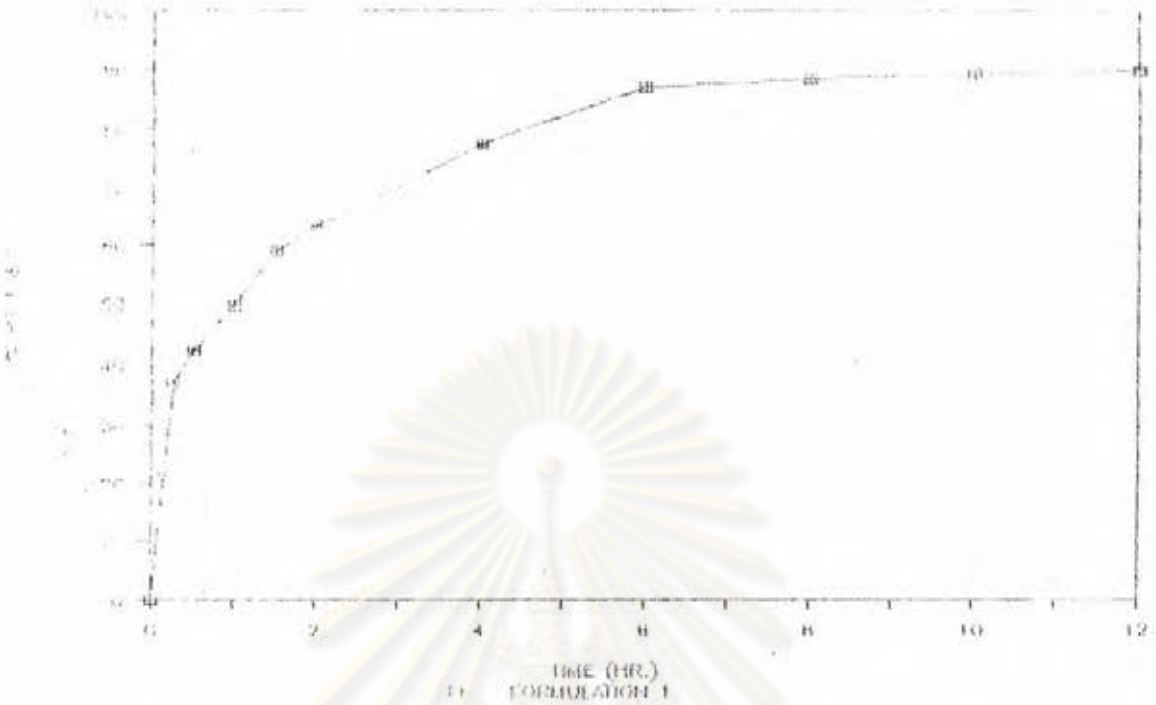


Figure 30 Release profile of coated sucrose beads formulation 1 in pH change method

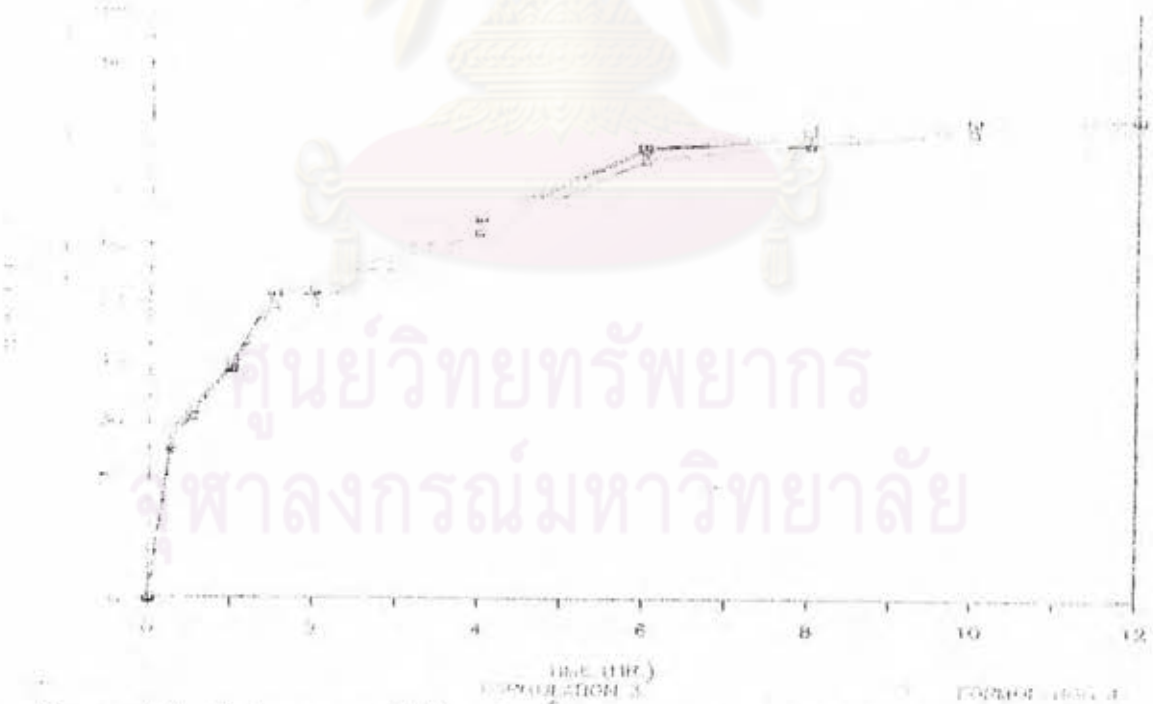


Figure 31 Release profile of coated sucrose beads formulation 2-4 in pH change method

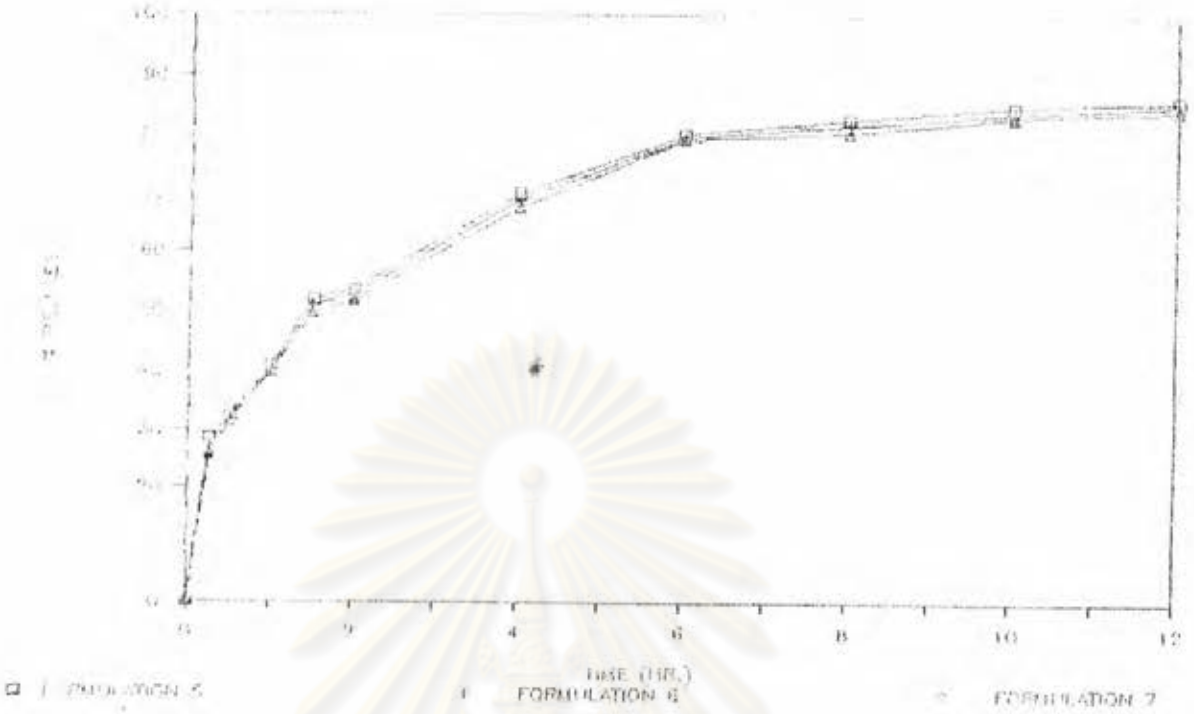


Figure 32 Release profile of coated sucrose beads formulation 5-7 in pH change method

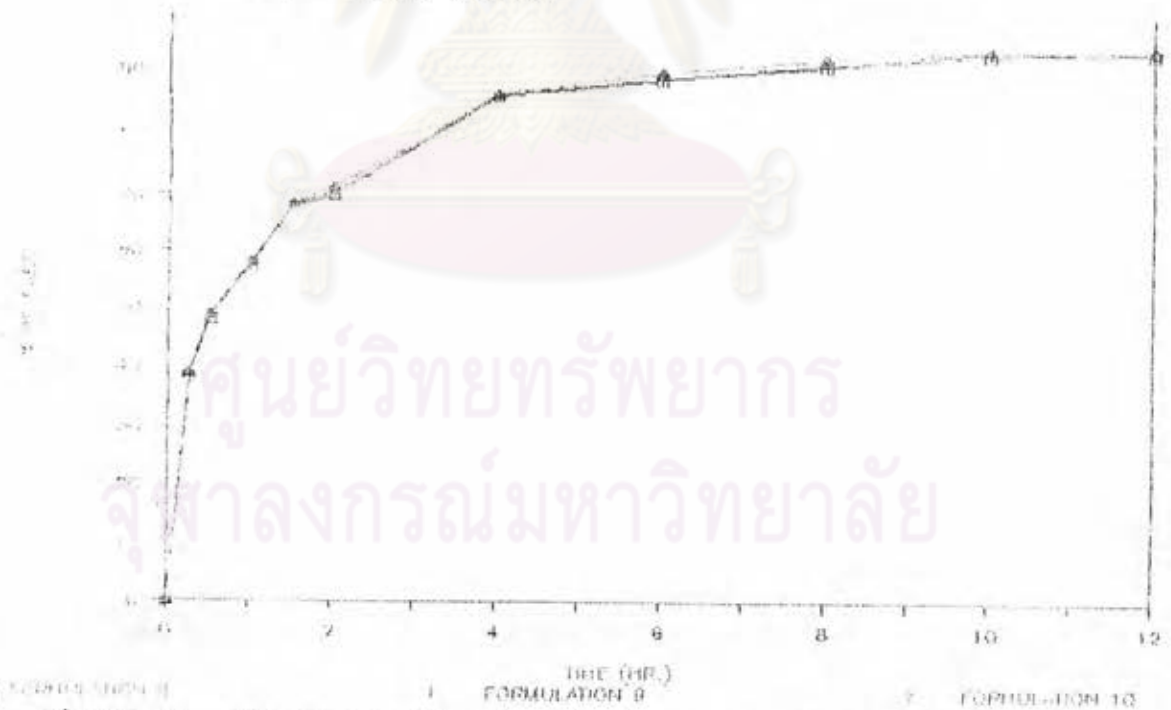


Figure 33 Release profile of coated sucrose beads formulation 8-10 in pH change method

shown graphically in Figures 22-25, 26-29 and 30-33.

Coated beads containing glycerylmonostearate and castor oil as plasticizer when using 0.1 N HCl as the medium released approximately 58 % of the drug in 1.5 hr. (Figure 23, 24 Table 30, 31). Non-plasticizer coated beads release 64 % of the drug in 1.5 hrs which was similar to the beads using PEG 4000 (Figures 22, 25 Table 28, 31). Hence, the coated beads can be classified in 2 groups according to the release rate in 0.1 N HCl.

The influence of plasticizers on drug release from coated beads were also studied in phosphate buffer pH 6.8 and pH change method for 12 hrs. The release data in pH change method of coated beads containing glycerylmonostearate, castor oil and non-plasticizer were lower than in buffer pH 6.8 and the release rate in phosphate buffer was lower than in acid medium.

On the other hand , the drug release of coated beads which contained PEG 4000 in pH change method were higher than the dissolution in phosphate buffer pH 6.8 and 0.1 N HCl medium.

The content of each plasticizer type were investigated in 3 levels as 1%, 2% and 3%. It was found that an increase in the content of glycerylmonostearate and castor oil showed tendency to decrease drug release. PEG 4000 increased release rate of propranolol hydrochloride when its amount in coating formulation was increased. The effect of plasticizer content on the drug release were not different when using different dissolution media.

The release profiles in pH change method exhibited biphasic curves which could be seperated in 2 period between 0-2 hr. and 2-12 hr. And it was observed that it had reflective

point to be a plateau phase at 1.5-2 hr.

From the drug release profiles, the coated beads which contained 3% glycerylmonostearate gave the lowest release profile. So, this formulation was used for further modification of release characteristic to comply with the USP standard for drug release of propranolol hydrochloride sustained release capsules by outercoating the coated beads with the coating solution which was composed of the polymer without addition of the drug as shown in Table 8 to have the coated beads of formulations 11-13.

FORMULATIONS 11-13

Physical property evaluation of formulations 11-13

Coated beads of formulation 11 exhibited rough surface and thinner film than of formulation 12 (Figure 34-35). When coated beads of formulation 12 were outercoated with coating solution contained mixed polymer of EC + 5% HPMC and 1% PG (formulation 13, Figure 36), they were founded to have more smooth surface and more thickness of the film than of formulation 12. In the outercoated formulation, drug release could be retard and more smoothly coated surface was attained.

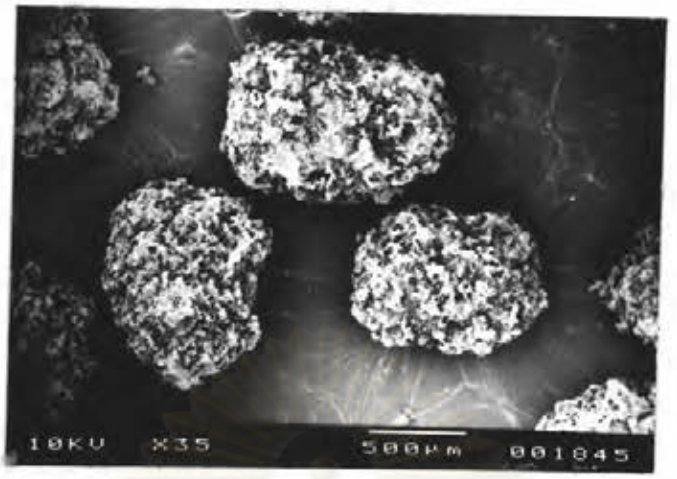
Mean size of coated beads were increased in all formulations which prepared by outercoating process. It was found that the outercoated formulation have a trend to decrease the compressibility. However, after outercoating process, it was found that bulk density had tendency to decline, and higher friability was observed, except formulations 12 and 13. (see Table 9)

Table 8 Composition of Coating Formulations 11-13

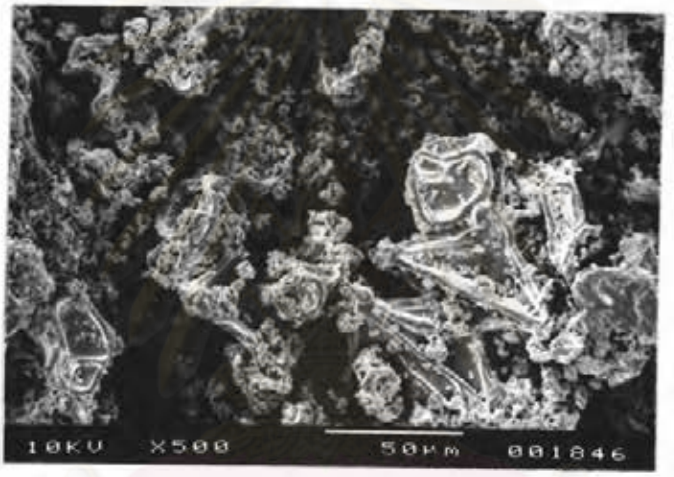
Component (%w/v)	Formulation 11	12	13
Propranolol HCl	5	5	5
Ethylcellulose	5	5	5
Glycerylmonostearate	-	3	3
Ethanol qs.	100	100	100
Outercoated			
Ethylcellulose	10	10	10
HPMC	-	-	5
PG	-	-	1
Ethanol qs.	100	100	100

Table 9 The Physical Properties of the Beads Formulations 11-13

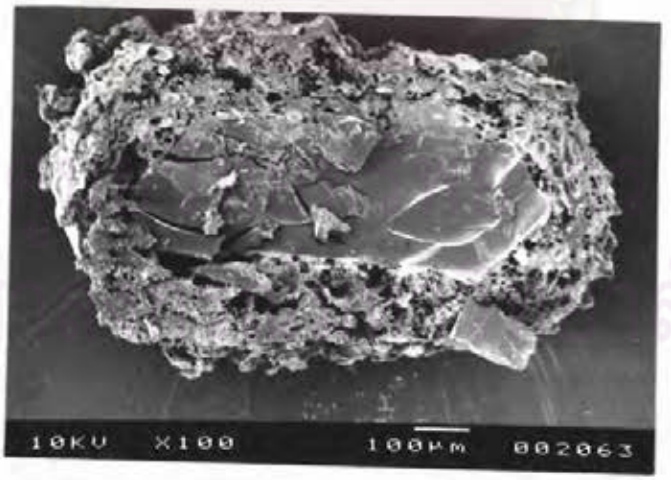
Formulation	Mean Size (μ)	Bulk Density (g/ml)	Tapped Density (g/ml)	Carr's Index	Friability (%)
11	792.11	0.37	0.39	5.59	0.80
12	838.05	0.35	0.37	5.20	0.30
13	839.27	0.39	0.42	6.49	0.20



A

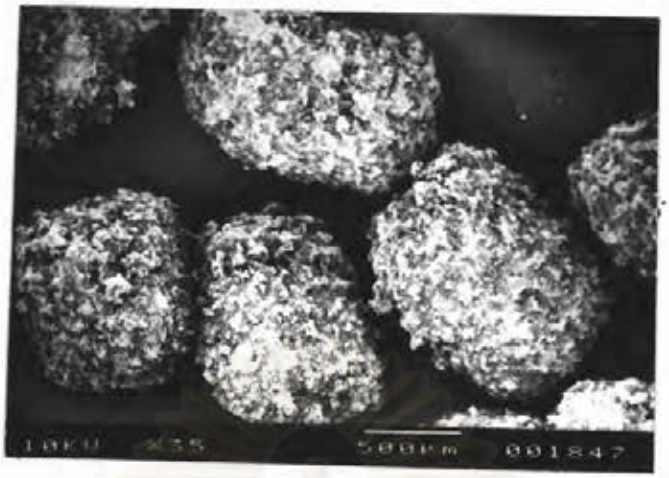


B

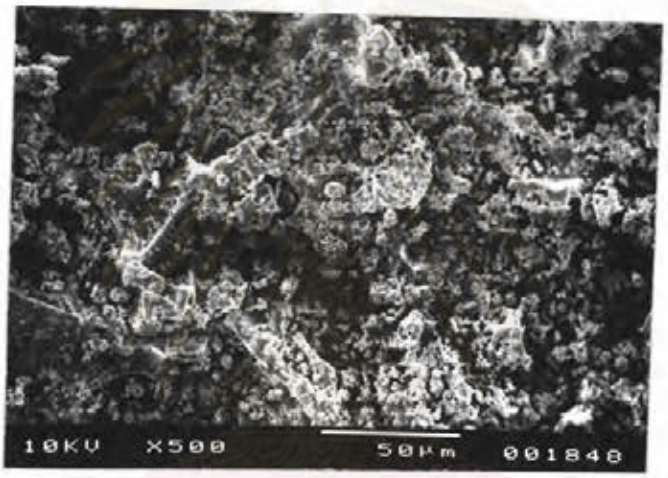


C

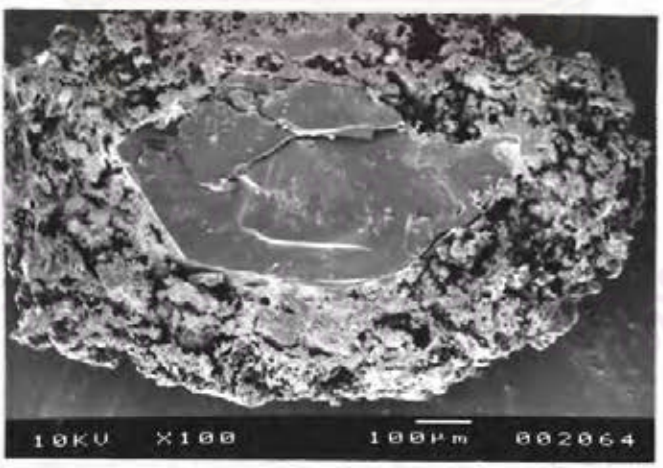
Figure 34 Photomicrographs of coated sucrose beads formulation 11 (Key: A coated beads x 35 , B coating surface x 500 , C cross-section x 100)



A

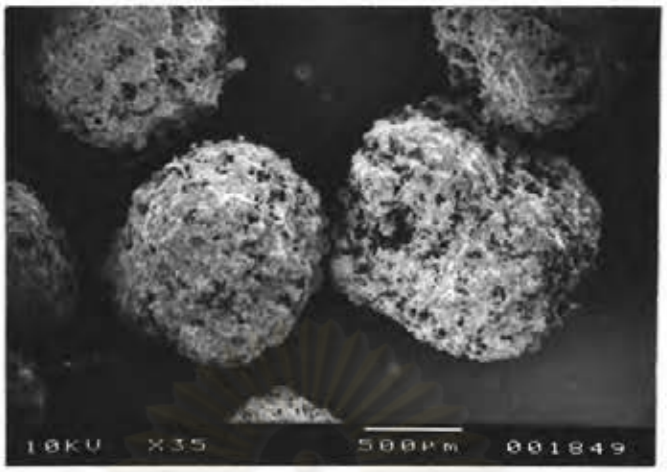


B

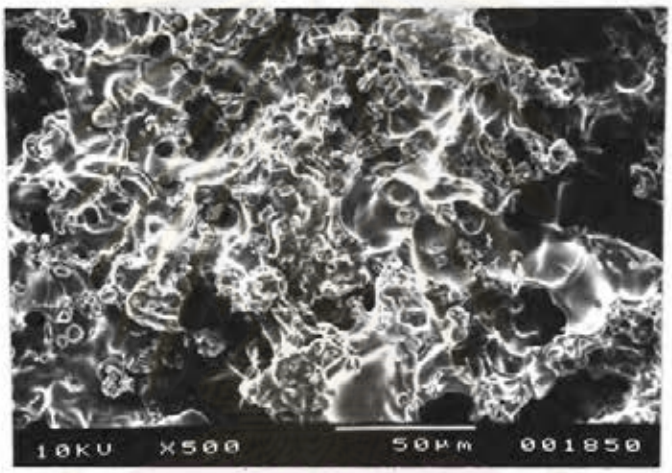


C

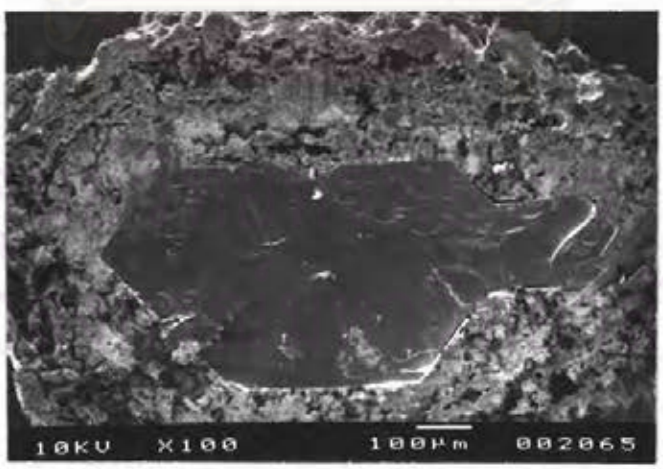
Figure 35 Photomicrographs of coated sucrose beads formulation 12 (Key: A coated beads x 35 , B coating surface x 500 , C cross-section x 100)



A



B



C

Figure 36 Photomicrographs of coated sucrose beads formulation 13 (Key: A coated beads x 35 , B coating surface x 500 , C cross-section x 100)

Dissolution study evaluation of formulations 11-13

The dissolution profiles (in pH change method) of the coated beads of formulation 1, 4 when outercoated with outercoating solution as presented in Table 8 were illustrated in Figure 37.

The dissolution data of formulation 11(outercoating on formulation 1) was given 85% release in 1.5 hr.but formulation 12 (outercoating on formulation 4) was shown 35% release in the same time period (Figure 37 Table 41).

To investigate a role of hydrophillic film former on drug release profiles, formulation 4 were coated by 10% EC coating solution and the mixture of 10% EC, 5% HPMC and 1% PG as plasticizer as described in formulation 12 and 13, respectively. It was seen that the release rate of formulation 12 was 35% release at 1.5 hr but formulation 13 coating with hydrophillic film former gave 42 % release (Figure 37 Table 41).

FORMULATIONS 14-17

The coated beads of formulation 4 were outercoated with the outercoating solutions 14-16 which contained different concentration of ethylcellulose in the range 5, 7, 15 % , respectively as presented in Table 10. The composition of coating solution formulation 17 was shown in Table 10.

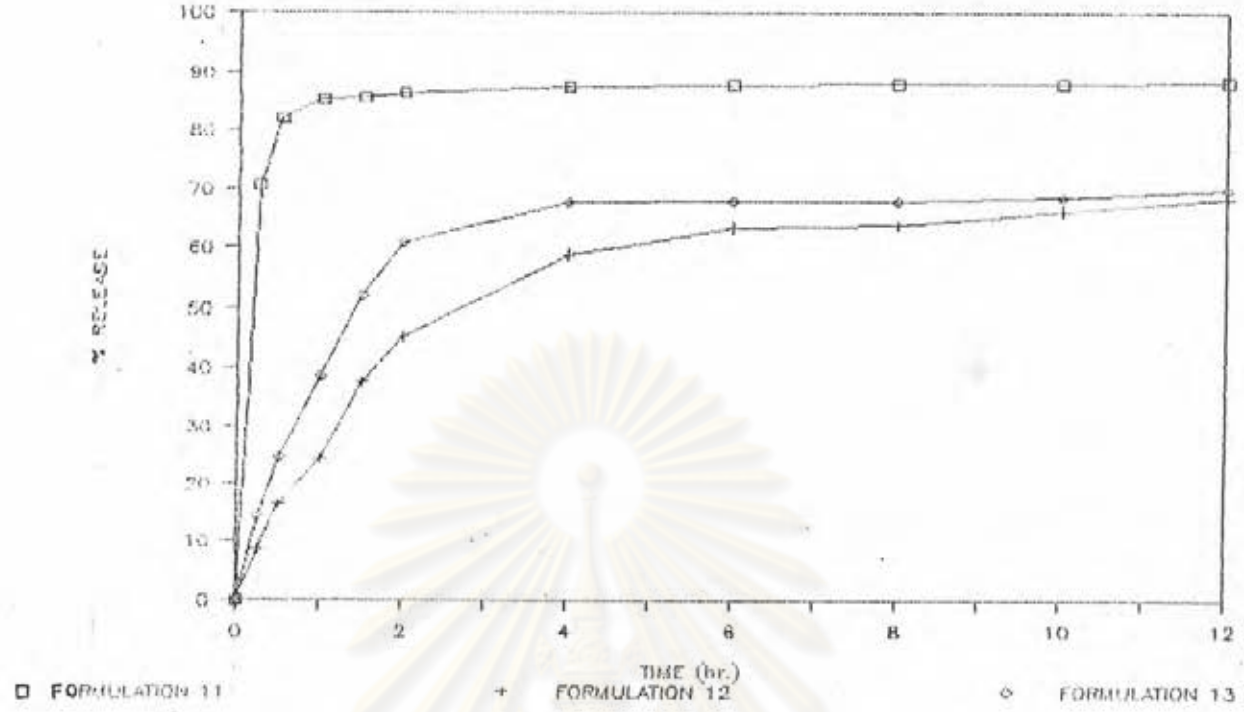


Figure 37 Release profile of coated sucrose beads formulation 11-13 in pH change method

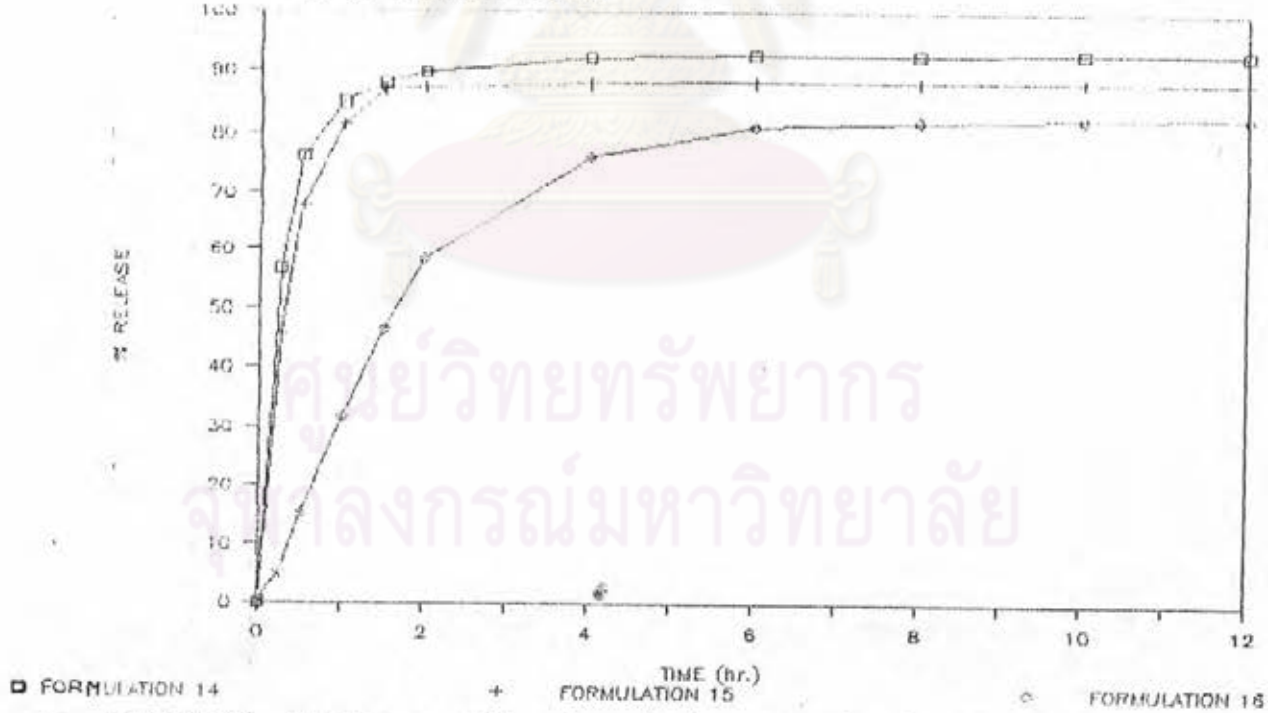


Figure 38 Release profile of coated sucrose beads formulation 14-16 in pH change method

Table 10 Composition of Coating Formulations 14-17

Component (%w/v)	Formulation 14	15	16	17
Propranolol HCl	5	5	5	10
Ethylcellulose	5	5	5	10
Glycerylmonostearate	3	3	3	3
Ethanol qs.	100	100	100	100
Outercoated				
Ethylcellulose	5	7	15	10
Ethanol qs.	100	100	100	100

Table 11 The Physical Properties of the Beads Formulations 14-17

Formulation	Mean Size (μ)	Bulk Density (g/ml)	Tapped Density (g/ml)	Carr's Index	Friability (%)
14	666.83	0.50	0.56	10.24	0.30
15	651.84	0.40	0.43	10.00	0.50
16	729.75	0.34	0.37	6.90	0.70
17	764.13	0.32	0.34	6.45	0.70

Physical property evaluation of formulations 14-17

Comparison of the coated beads from formulation 14, 15, 12 and 16 prepared by outercoating the beads of formulaton 4 with outercoating solution containing ethylcellulose at 5, 7, 10 and 15% respectively, more rough surface and more thickness of coated film were seen (Figure 39, 40, 35 and 41).

Bulk and tapped density of the coated beads of formulation 14-16 decreased and Carr's compressibility index decrease in corresponding with the increase of the EC content in outercoating solution. It was apparent that the friability of coated beads of formulation 14-16 increased (see Table 11).

Dissolution study evaluation of formulations 14-17

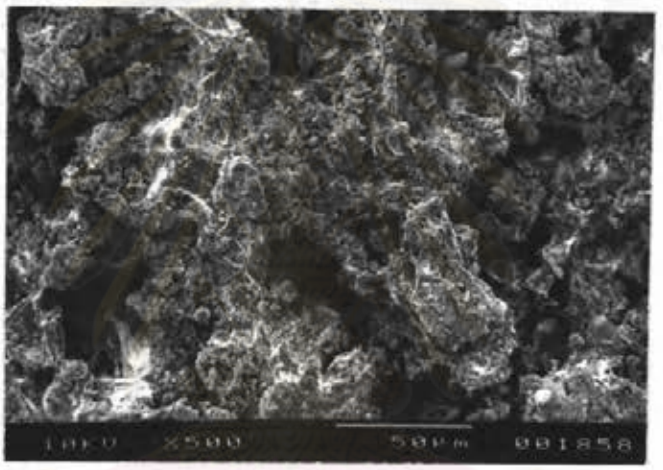
To investigate the effect of film former content on drug release profiles while drug contents was kept at 5 % Formulations 14, 15, 12 and 16 were modified from formulation 4 by coating with 5, 7, 10 and 15% EC , respectively.

The release data of formulation 14, 15, 12 and 16 in pH change method at 1.5 hr was 88.11, 87.08, 37.68 and 46.42 % release, respectively (Figure 37 and 38 Table 42, 41 and 43).

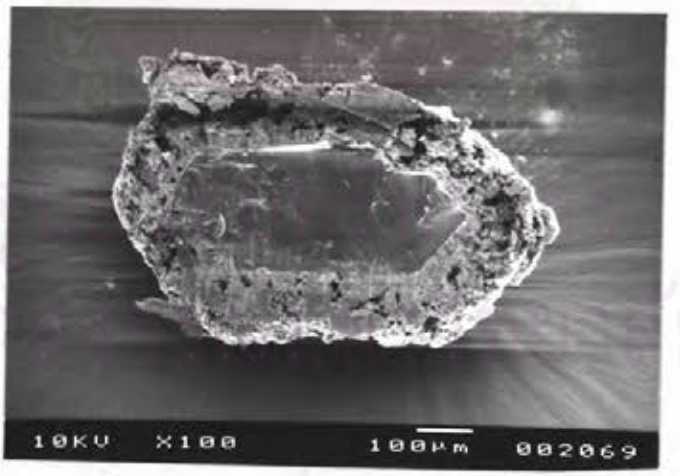
The coated beads of formulaton 12 gave the slowest drug release, followed by the beads of formulation 16, 15 and 14, respectively.

In order to show that the content of drugs and film former had an effect on drug release, coating solution according

A



B



C

Figure 39 Photomicrographs of coated sucrose beads formulation 14 (Key: A coated beads x 35 , B coating surface x 500 , C cross-section x 100)

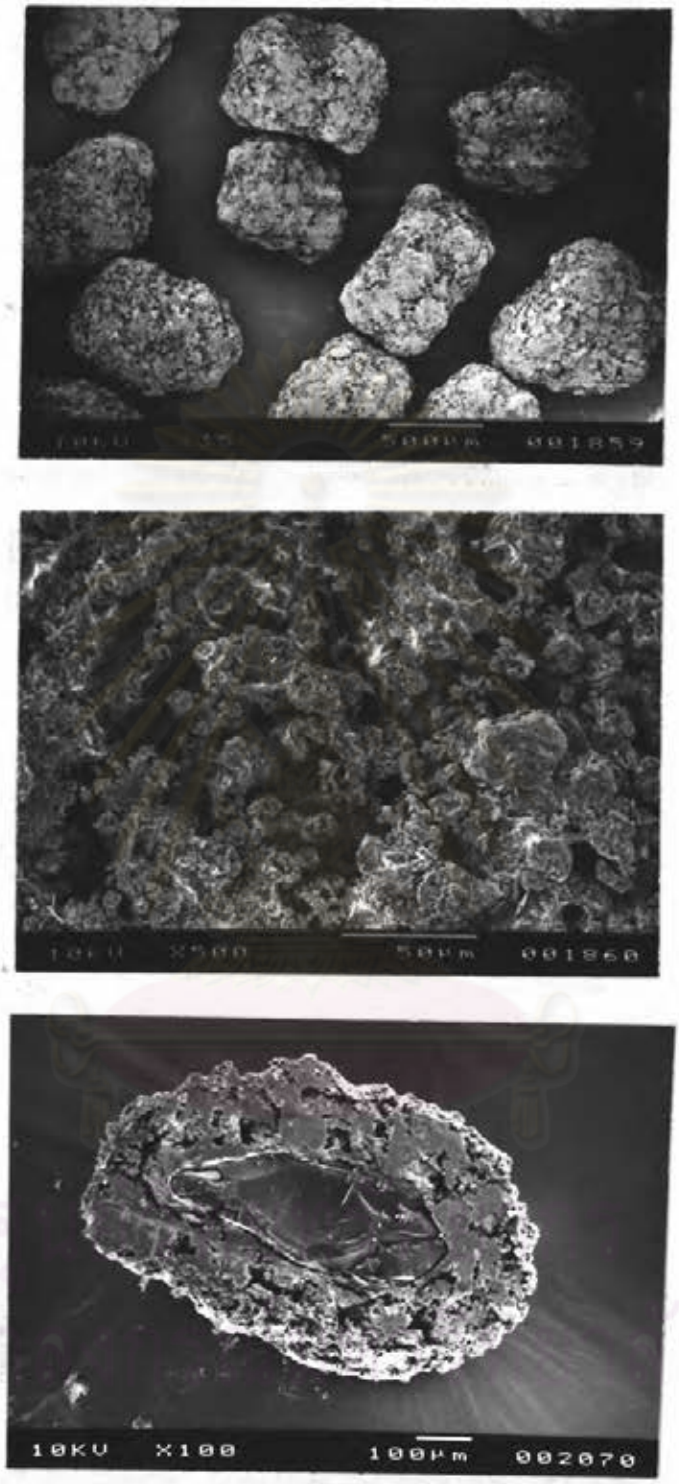
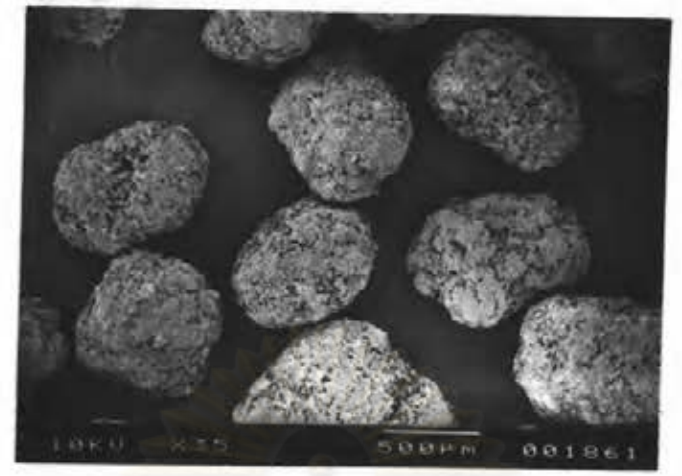
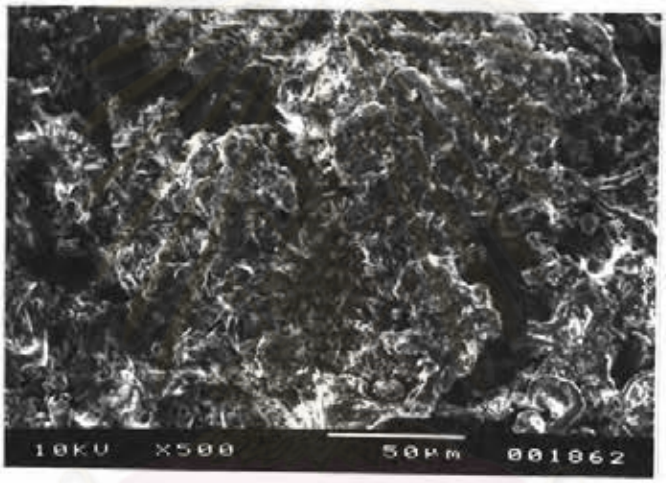


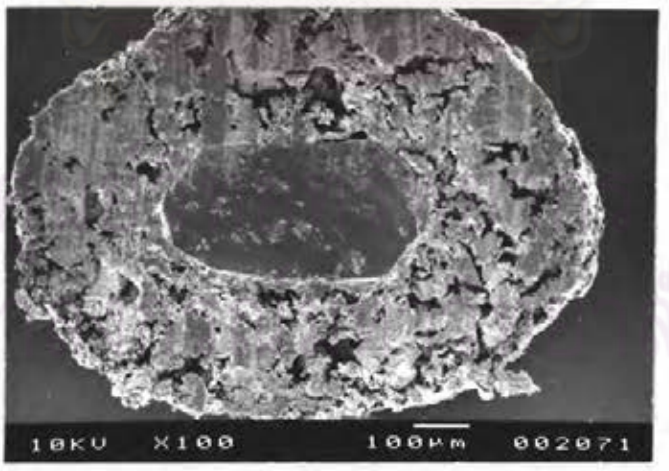
Figure 40 Photomicrographs of coated sucrose beads formulation 15 (Key: A coated beads x 35 , B coating surface x 500 , C cross-section x 100)



A

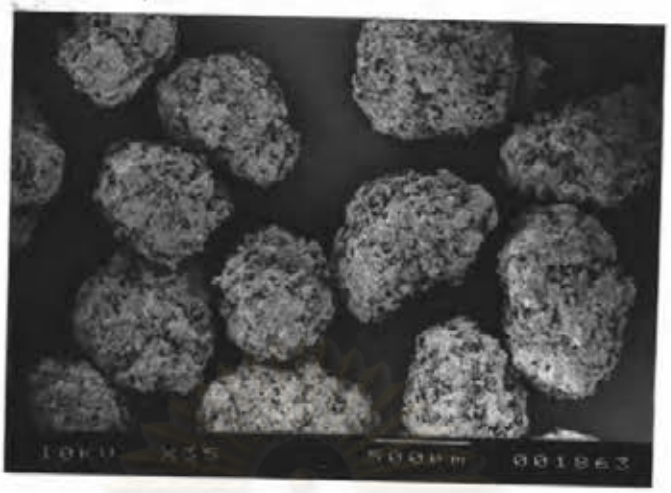


B

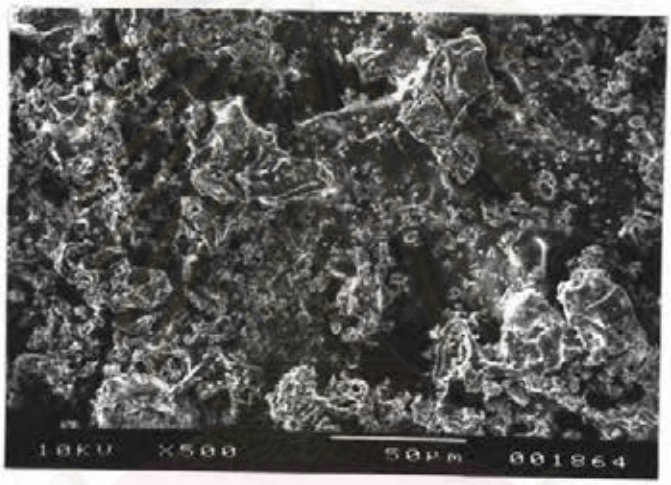


C

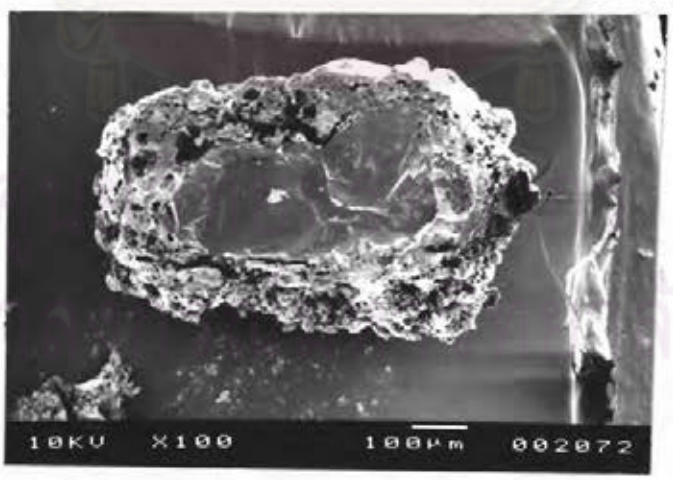
Figure 41 Photomicrographs of coated sucrose beads formulation 16 (Key: A coated beads x 35 , B coating surface x 500 , C cross-section x 100)



A



B



C

Figure 42 Photomicrographs of coated sucrose beads formulation 17 (Key: A coated beads x 35 , B coating surface x 500 , C cross-section x 100)

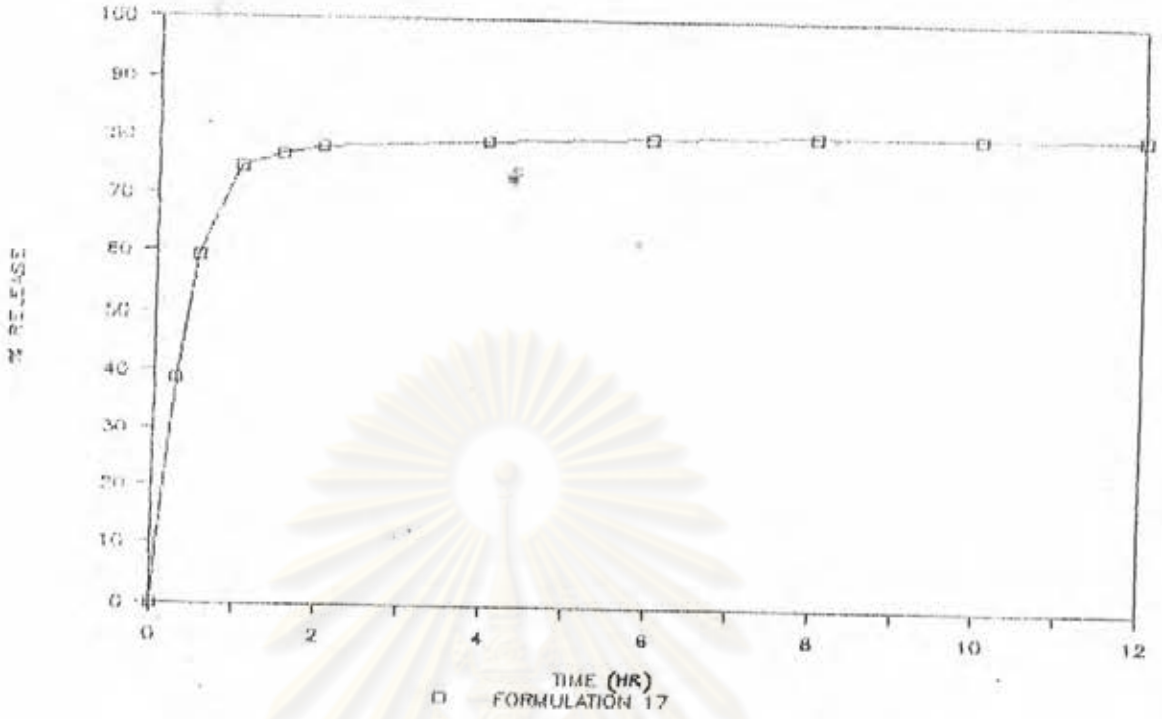


Figure 43 Release profile of coated sucrose beads formulation 17 in pH change method

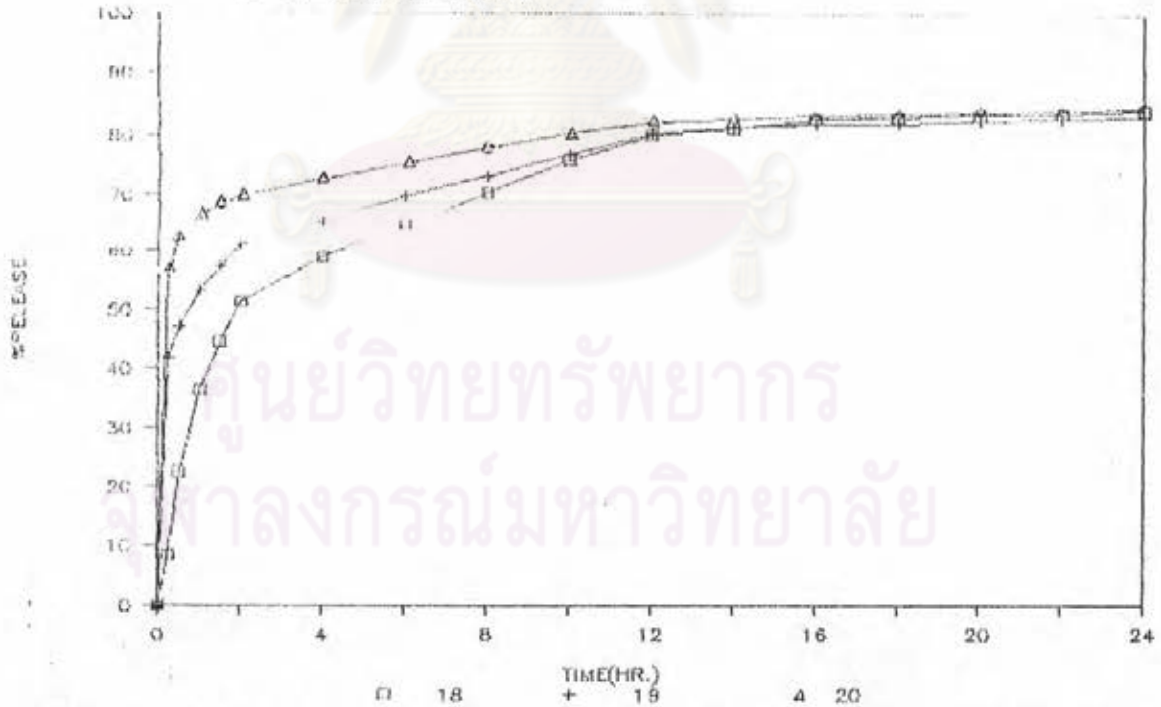


Figure 44 Release profile of coated sucrose beads formulation 18-20 in pH change method

to formulation 17 was developed by increasing the amount of the drug and film former from 5% up to 10% and after that outercoating by 10% EC coating solution was performed as shown in Table 10.

It was observed that when the amount of drugs and EC were increased, more smooth surface and higher thickness was found as shown in Figure 35(Formulation 12) and Figure 42(Formulation 17).

The release rate of formulation 17 was 76.69% in pH change method at 1.5 hr while the coating beads of formulation 12 was only 41.73% release (Figure 43, 37 Table 42, 40). The release rate of formulation 17 was higher than formulation 12 in pH change method, 0.1 N HCl and phosphate buffer pH 6.8. This indicated the effect of the drug and ethylcellulose content in the inner coating solution on the drug release from the film.

FORMULATIONS 18-20

In order to decrease the drug release of the coated beads in formulation 14, 12 and 16, so additional outercoating procedure was performed on the coated beads with the same amount of 5% EC coating solution (1200 ml.) as described in formulations 18, 19 and 20 (see Table 12).

Physical property evaluation of formulations 18-20

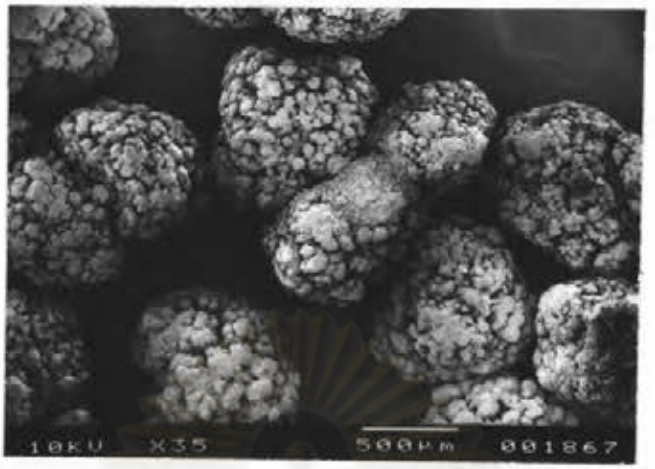
Formulations 18,19 and 20 gave rough surface and more thickness coated film, so the double overcoating might not be suitable in preparing the product (Figure 45-47).

Table 12 Composition of Coating Formulations 18-20

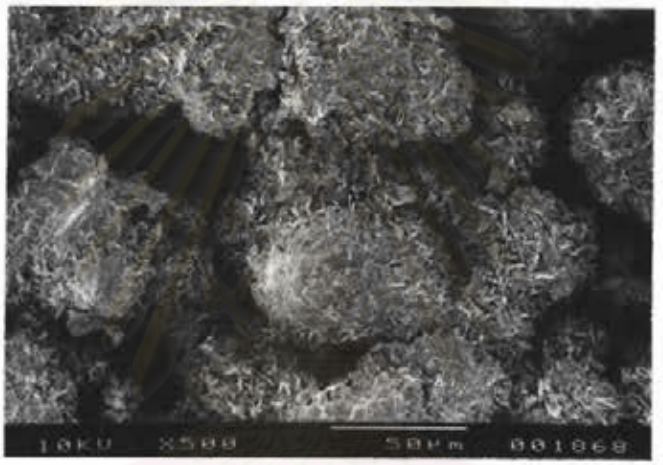
Component (%w/v)	Formulation 18	19	20
Propranolol HCl	5	5	5
Ethylcellulose	5	5	5
Glycerylmonostearate	3	3	3
Ethanol qs.	100	100	100
Outercoated			
Ethylcellulose	5	10	15
Ethanol qs.	100	100	100
Outercoated			
Ethylcellulose	5	5	5
Ethanol qs.	100	100	100

Table 13 The Physical Properties of the Beads Formulations 18-20

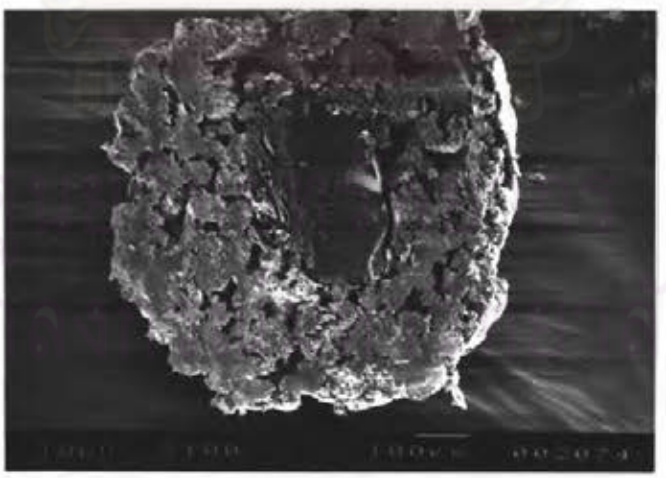
Formulation	Mean Size (μ)	Bulk Density (g/ml)	Tapped Density (g/ml)	Carr's Index	Friability (%)
18	666.83	0.43	0.45	6.38	0.60
19	651.84	0.41	0.43	5.48	0.90
20	729.75	0.39	0.41	4.58	1.00



A



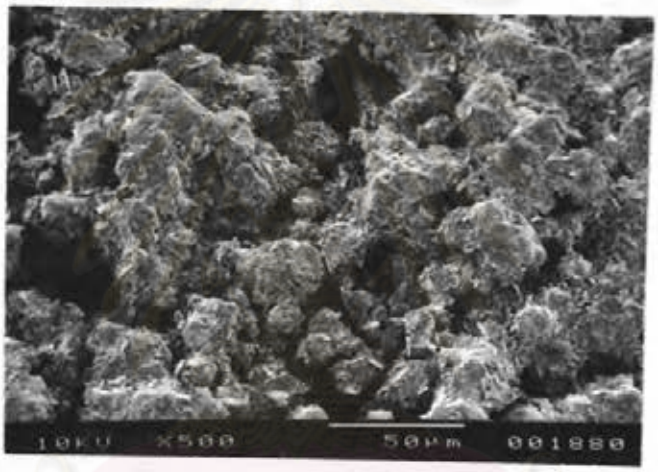
B



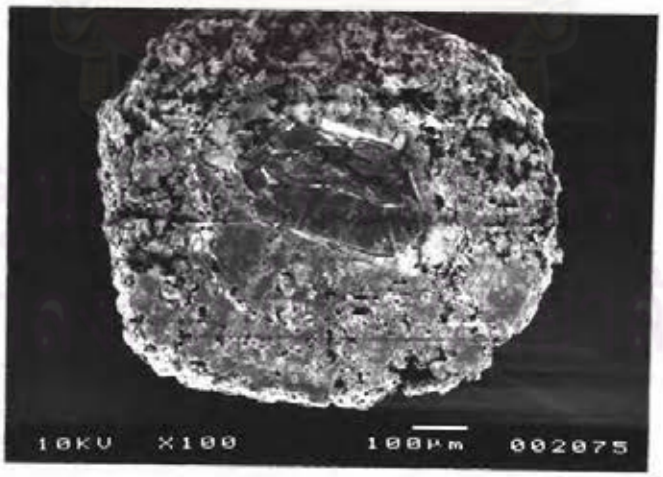
C

Figure 45 Photomicrographs of coated sucrose beads formulation 18 (Key: A coated beads x 35 , B coating surface x 500 , C cross-section x 100)

A



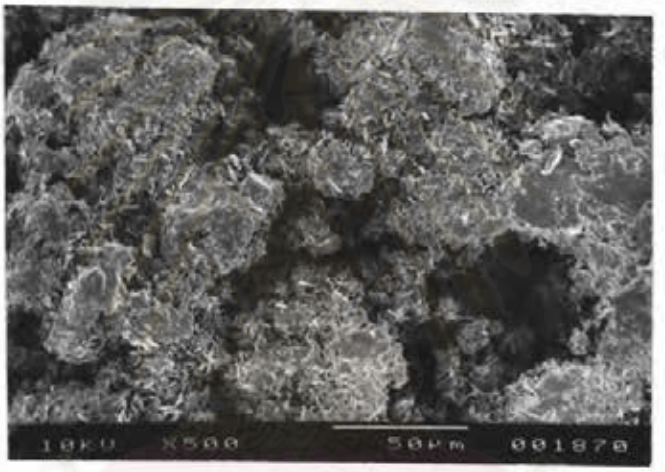
B



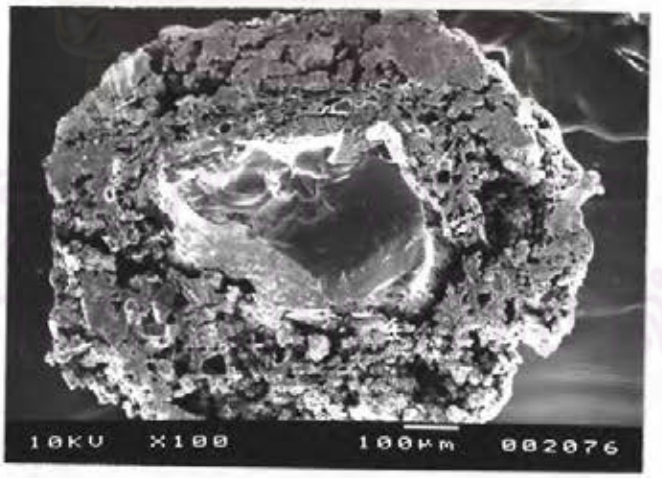
C

Figure 46 Photomicrographs of coated sucrose beads formulation 19 (Key: A coated beads x 35 , B coating surface x 500 , C cross-section x 100)

A



B



C

Figure 47 Photomicrographs of coated sucrose beads formulation 20 (Key: A coated beads x 35 , B coating surface x 500 , C cross-section x 100)

In double outercoating process, bulk and tapped density as well as the compressibility was further decreased. The friability of the coated beads increased (formulation 18-20), formulation 20 gave highest friability coated beads.

Dissolution study evaluation of formulations 18-20

The release data of the beads in formulations 18, 19 and 20 at the time of 1.5 hr were 44.61, 57.26 and 68.21%, respectively (Figure 44 Table 43, 44, 45). The dissolution rate of formulation 18 was the lowest and the release data of formulation 19 was lower than of formulation 20.

FORMULATIONS 21-22

To investigate the effect of type of plasticizer on the release rate of the drug, the castor oil was incorporated in the coating solution replacing glycerylmonostearate as presented in formulation 21 and 22 (Table 14).

Dissolution study evaluation of formulations 21-22

It was found that the castor oil could reduce the release rate of the drug when compared with glycerylmonostearate, the release of coated beads in formulation 21 at 1.5 hr was 37.68% The coated beads of formulation 21, was further otercoated with 5% EC coating solution containing 1% castor oil as shown in

Table 14 Composition of Coating Formulations 21-22

Component (%W/V)	Formulation 21	22
Propranolol HCl	5	5
Ethylcellulose	5	5
Castor oil	5	5
Ethanol qs.	100	100
Outercoated		
Ethylcellulose	-	5
Castor oil	-	1
Ethanol qs.	-	100

Table 15 The Physical Properties of the Beads Formulations 21-22

Formulation	Mean Size (μ)	Bulk Density (g/ml)	Tapped Density (g/ml)	Carr's Index	Friability (%)
21	705.50	0.28	0.33	16.67	0.10
22	734.10	0.30	0.32	4.57	0.20

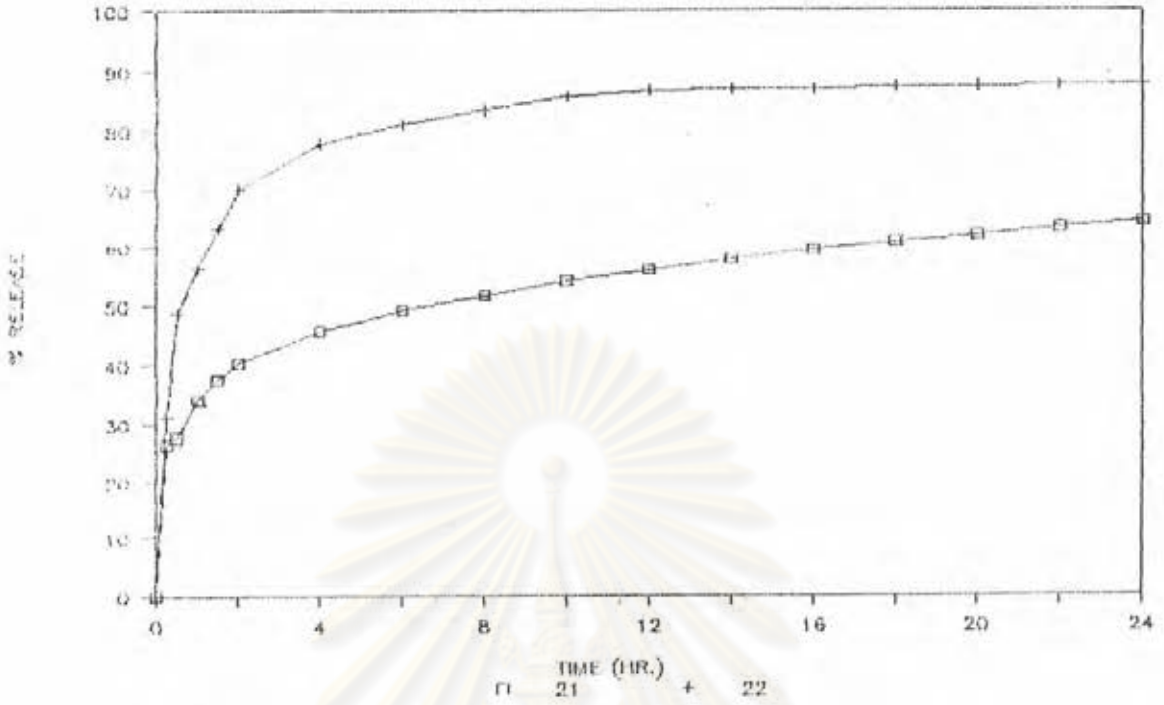


Figure 48 Release profile of coated sucrose beads formulation 21-22 in pH change method

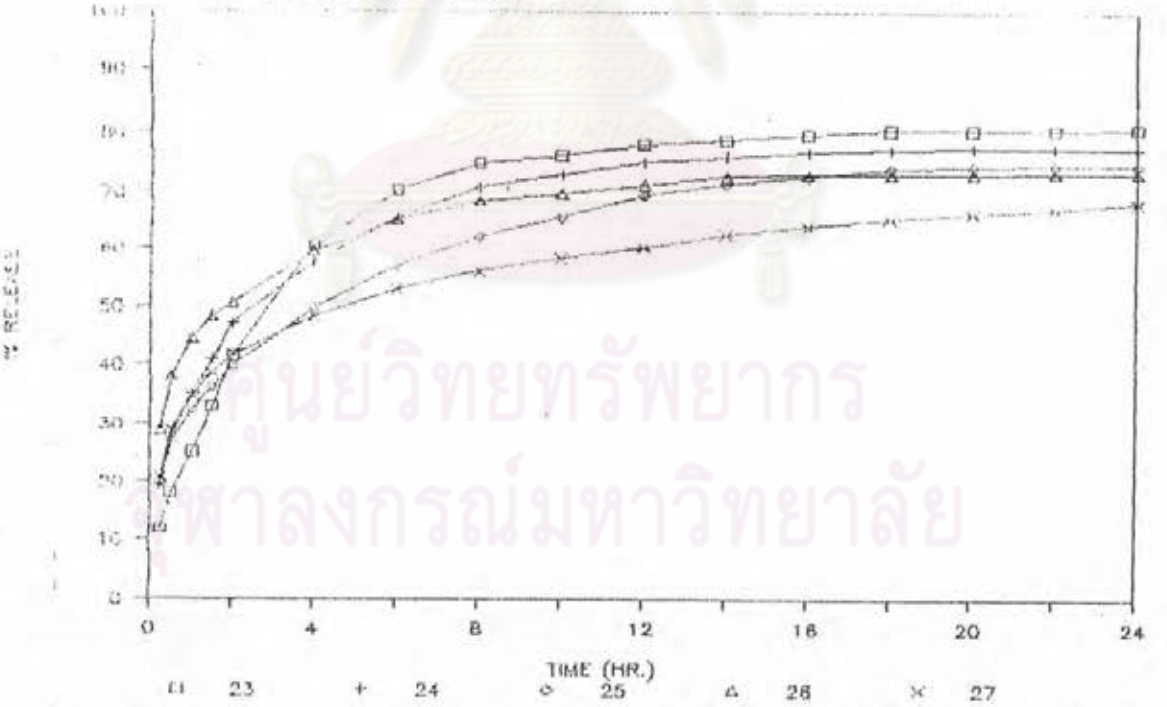
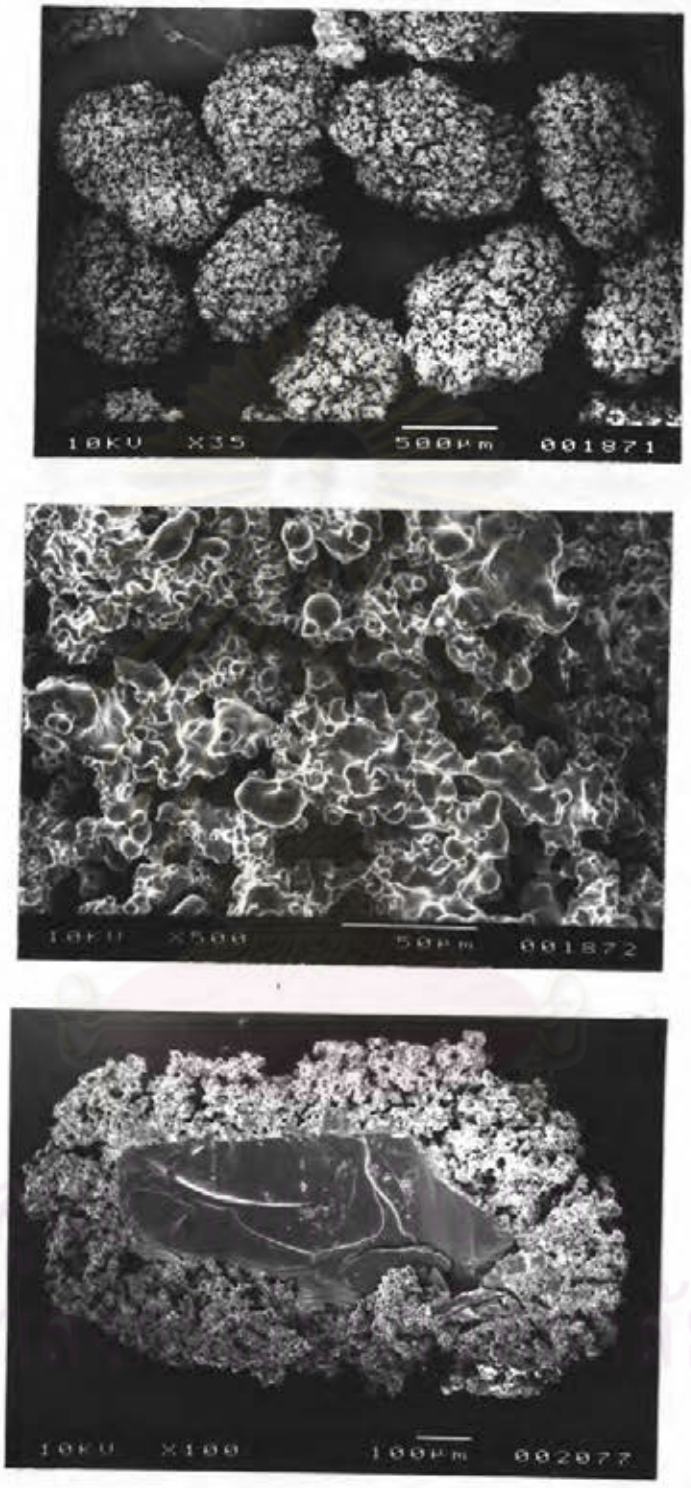


Figure 49 Release profile of coated sucrose beads formulation 23-27 in pH change method



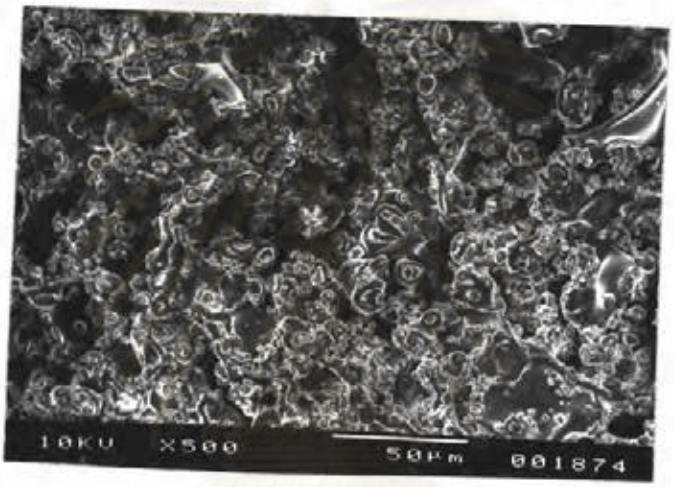
A

B

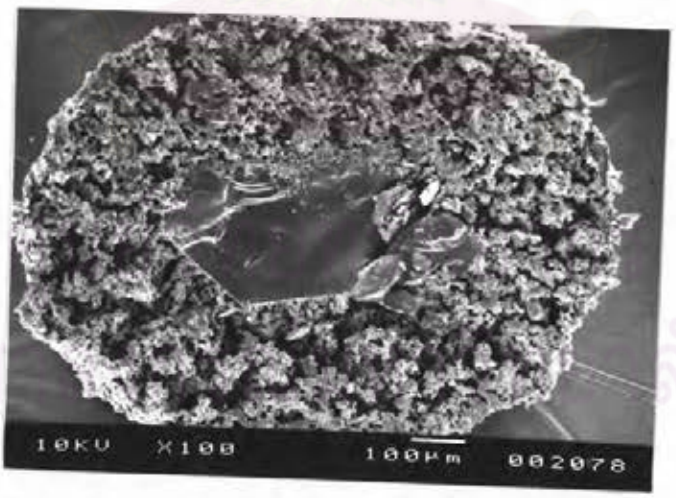
C

Figure 50 Photomicrographs of coated sucrose beads formulation 21 (Key: A coated beads x 35 , B coating surface x 500 , C cross-section x 100)

A



B



C

Figure 51 Photomicrographs of coated sucrose beads formulation 22 (Key: A coated beads x 35 , B coating surface x 500 , C cross-section x 100)

formulation 22. But it was found that the release of the drug was increase to 63.23% in 1.5 hr. (Figure 48 Table 47).

Physical property evaluation of formulations 21-22

Table 15 present the physical property of the coated beads obtained from formulation 21 and 22.

Formulation 21 and 22 gave porous and bulk film (Figure 50, 51). The change of plasticizer from glycerylmonostearate to 5% castor oil (formulation 21) gave the highest compressibility value but after outercoated process, the compressibility was much decreased. When glycerylmonostearate was substituted by castor oil as plasticizer, the coated beads showed the lowest friability (formulation 21 and Table 15).

FORMULATIONS 23-31

In order to adjust the release rate of the propranolol hydrochloride, the combination of the beads having different release characteristics was investigated. As formulation 21 gave the lowest drug release. So that, the formulation 21 was combined with other formulations (such as Formulations 12 and 17) which had satisfactory drug release approaching the USP specification at the first 2 hrs. (not more than 30% release).

The coated beads of formulation 12 and 21 were combined in the ratio of 1:1, 1:2, 1:3, 1:4, 1:5, 2:1, 3:1, 4:1 and 5:1 (as presented in Formulations 23-31 Table 16).

Table 16 Composition of Coating Formulations 23-31

Combination ratio between Formulation	Formulation								
Formulation	23	24	25	26	27	28	29	30	31
12 and 21	1:1	1:2	1:3	1:4	1:5	2:1	3:1	4:1	5:1

Table 17 Composition of Coating Formulations 32-36

Combination ratio between Formulation	Formulation				
Formulation	32	33	34	35	36
17 and 21	1:1	1:3	1:5	1:7	1:9

Dissolution study evaluation of formulations 23-31

The release rates at 1.5 hr of the formulations 23-31 were 33.04, 41.03, 36.30, 48.24, 38.82, 39.66, 41.95, 41.25 and 38.70%, respectively (Figure 49, 52-55 Table 48-52). The release rate of formulations 23, 24, 25, 26 and 27 at 4 hrs were 60.39, 57.47, 49.68, 59.44 and 48.36%, but the amount of the drug release given by formulations 28, 29, 30 and 31 were not apparently different, approximately, 68% at 4 hrs. Coated beads of formulation 28-31 showed no difference of drug release at 14 and 24 hr.

FORMULATIONS 32-36

The coated beads of formulation 17 and 21 were combined in the ratio of 1:1, 1:3, 1:5, 1:7 and 1:9 (as presented in Formulations 32-36 Table 17).

Dissolution study evaluation of formulations 32-36

The release rate of the coated beads of formulation 32-36 at 1.5 hr were 56.62, 52.15, 50.21, 47.44 and 38.47 % (Figure 56 Table 52-54). It was found that as the ratio of formulation 21 was increased, the percentage of drug release tended to decline at 4, 14 and 24 hrs.

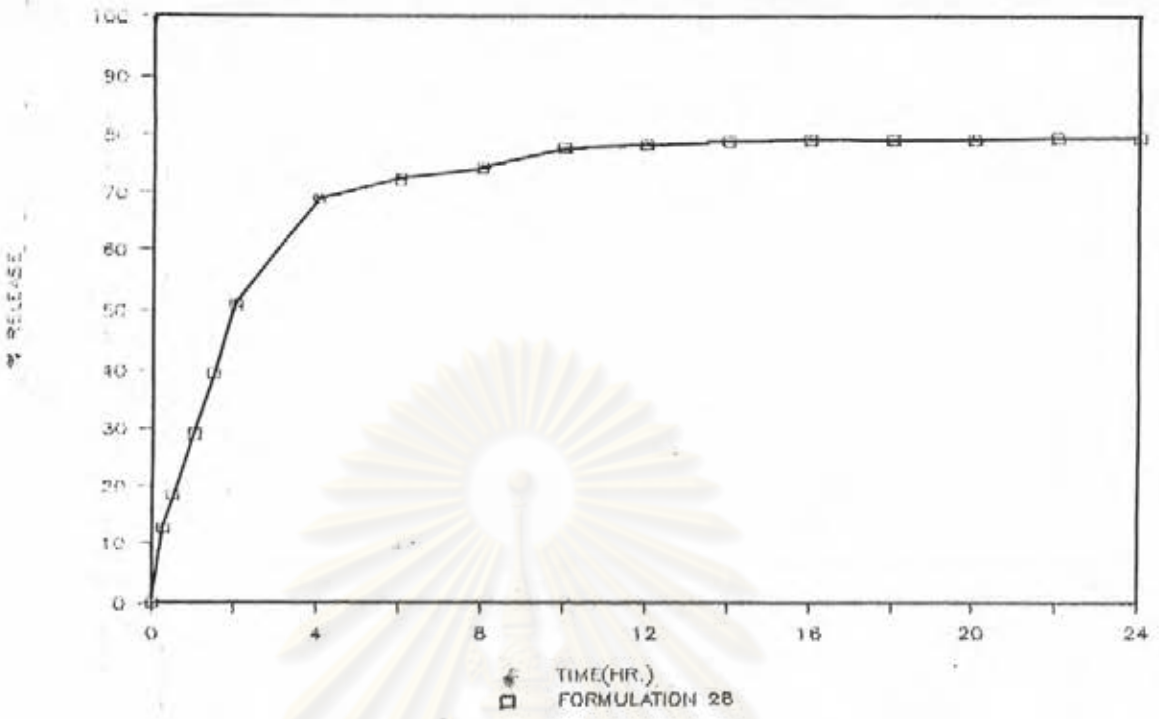


Figure 52 Release profile of coated sucrose beads formulation 28 in pH change method

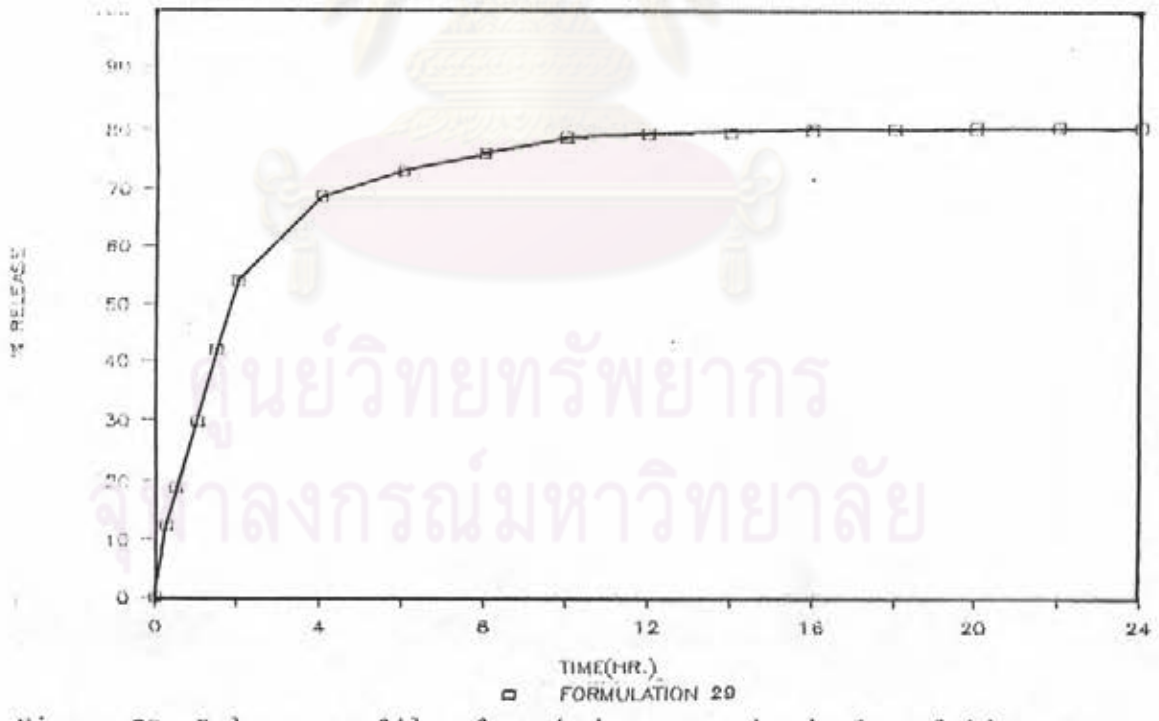


Figure 53 Release profile of coated sucrose beads formulation 29 in pH change method

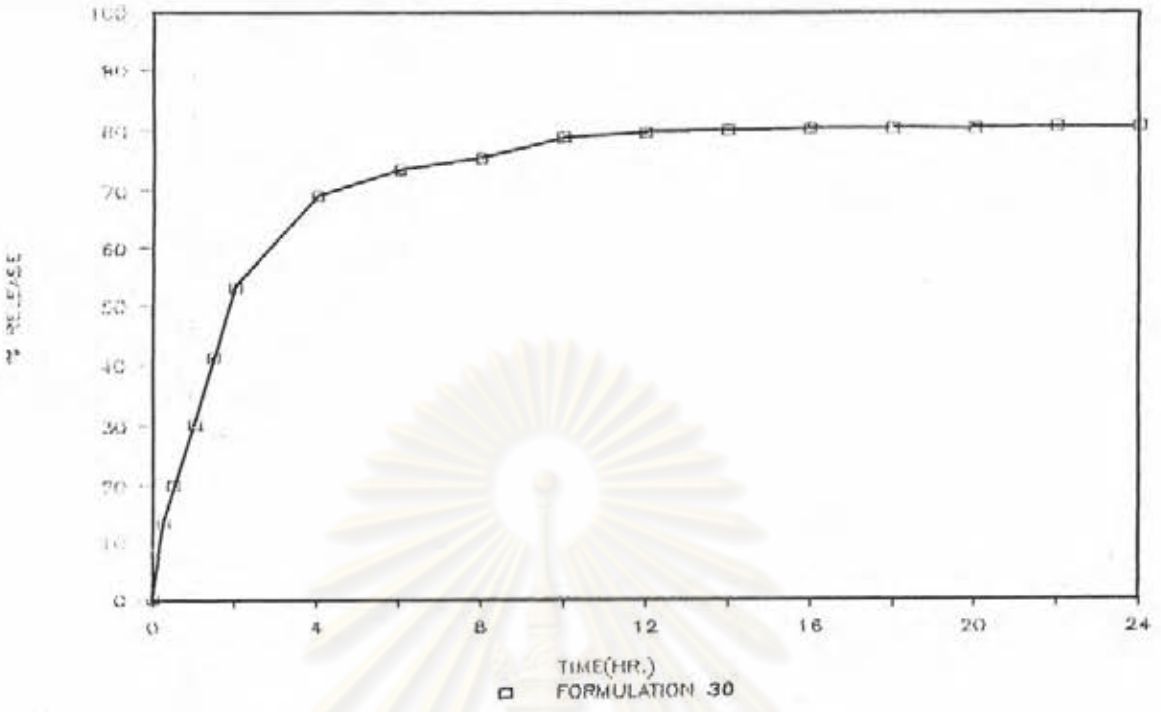


Figure 54 Release profile of coated sucrose beads formulation 30 in pH change method

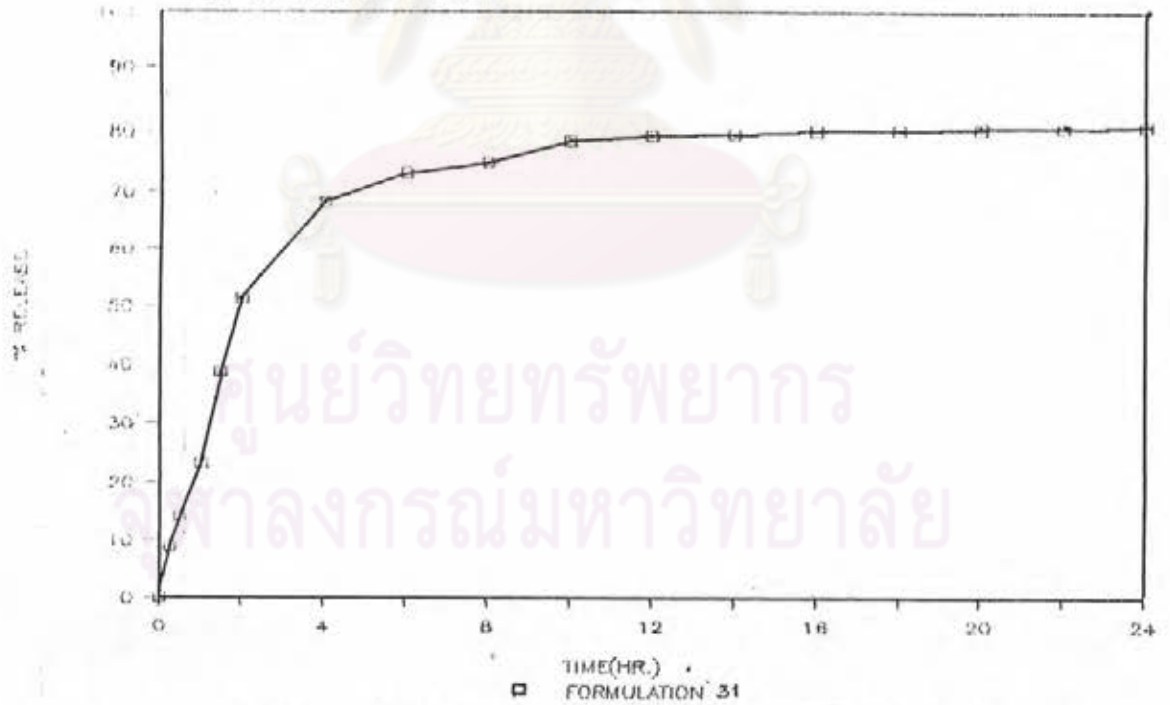


Figure 55 Release profile of coated sucrose beads formulation 31 in pH change method

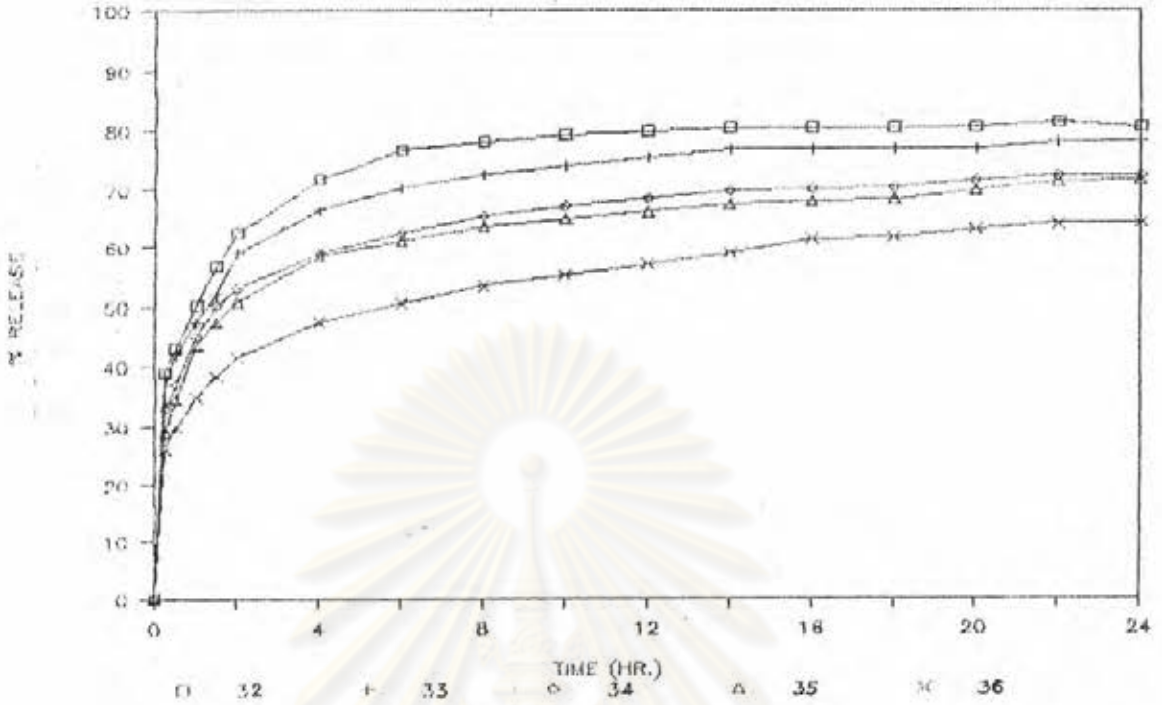


Figure 56 Release profile of coated sucrose beads formulation 32-36 in pH change method

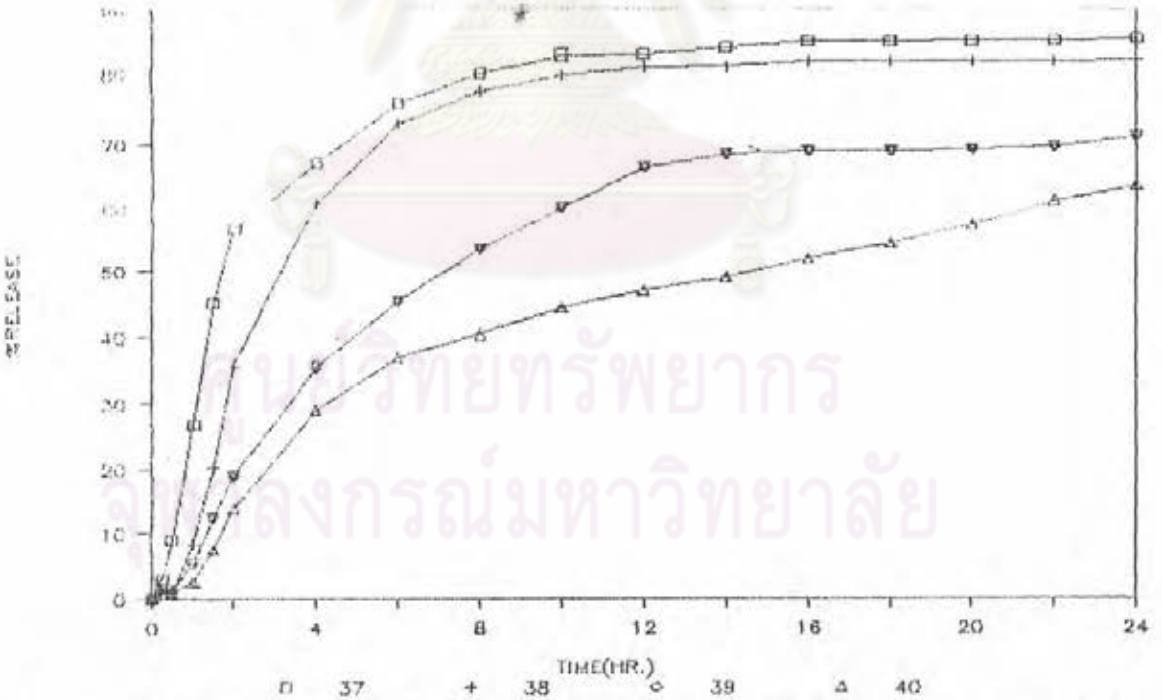


Figure 57 Release profile of coated sucrose beads formulation 37-40 in pH change method

FORMULATIONS 37-44

As castor oil was found to retard the release of the drug so it was investigated by incorporation into outercoating solution in combination with ethylcellulose.

Formulation 4 was chosen to be outercoated by outercoating solution which composed of 5% EC and 3% castor oil at the volume of 500, 1000, 1500 and 2000 ml as shown in formulation 37, 38, 39 and 40, respectively (see Table 18).

The volume of outercoating solution had an effect on the thickness of film which had influenced drug release profile. The release rate of the coated beads of formulation 37 to 40 at 1.5 hr were 45.08, 20.30, 12.43 and 7.58 % , respectively (Figure 57, Table 55, 56). In the same ways at 4, 8, 14 and 24 hr, it was found that as the volume of outercoating solution was increased, the release rates tended to decrease.

Comparison of the release data among formulations 37-40 and the USP XXII requirement for propranolol hydrochloride extended release capsules are shown in Table 20 . The release profile of formulation 38 was found to be higher than USP XXII standard while the release of formulation 39 was lower than USP XXII requirement. So that, the volume of outercoating solution between 1000-1500 ml were expected to be suitable overcoating in order to have the release rates conform to the USP standard. So the formulation 4 was outercoated with same outercoating solution in the range 1100, 1200, 1300 and 1400 ml. (as presented in Formulations 41-44 Table 19).

Table 18 Composition of Coating Formulations 37-40

Component (%W/V)	Formulation 37	38	39	40
Propranolol HCl	5	5	5	5
Ethylcellulose	5	5	5	5
Glycerylmonostearate	3	3	3	3
Ethanol qs.	100	100	100	100
Outercoated				
Ethylcellulose	5	5	5	5
Castor oil	3	3	3	3
Ethanol qs.	100	100	100	100
Outercoating Volume (ml.)	500	1000	1500	2000

Table 19 Composition of Coating of Formulations 41-44

Component (%w/v)	Formulation 41	42	43	44
Propranolol HCl	5	5	5	5
Ethylcellulose	5	5	5	5
Glycerylmonostearate	3	3	3	3
Ethanol qs.	100	100	100	100
Outercoated				
Ethylcellulose	5	5	5	5
Castor oil	3	3	3	3
Ethanol qs.	100	100	100	100
Outercoating Volume (ml.)	1100	1200	1300	1400

The release rate of the coated beads of formulation 41 to 44 at 1.5 hr were 16.11, 14.49, 16.35 and 11.19%, respectively (Figure 58 Tables 58 and 59). All formulations gave the release rate in limit of USP standard except the release rate at 24 hr of formulation 42, 43 and 44 were lower than that of the USP XXII standrad (Tables 35 and 36 see Appendix A)

So that, the formulation 41 was found to be the most similar. The coated beads of formulation 41 gave the release of the drug within the range at various time intervals as required by the USP XXII standard. The three lots of formulation 41 were prepared in order to observe the reproducibility and variation of coating process and the release pattern was shown in Figure 59 and Table 20.

Table 20 Comparison among USP XXII Requirement and Three Lots of Formulation 41

TIME (hr.)	% RELEASE			
	USP range	41 lot 1	41 lot 2	41 lot 3
1.5	< 30	16.11	14.53	17.27
4	35-60	52.03	55.56	57.42
8	55-80	73.30	75.90	73.98
14	70-95	80.85	81.02	82.23
24	81-110	81.43	82.12	83.09

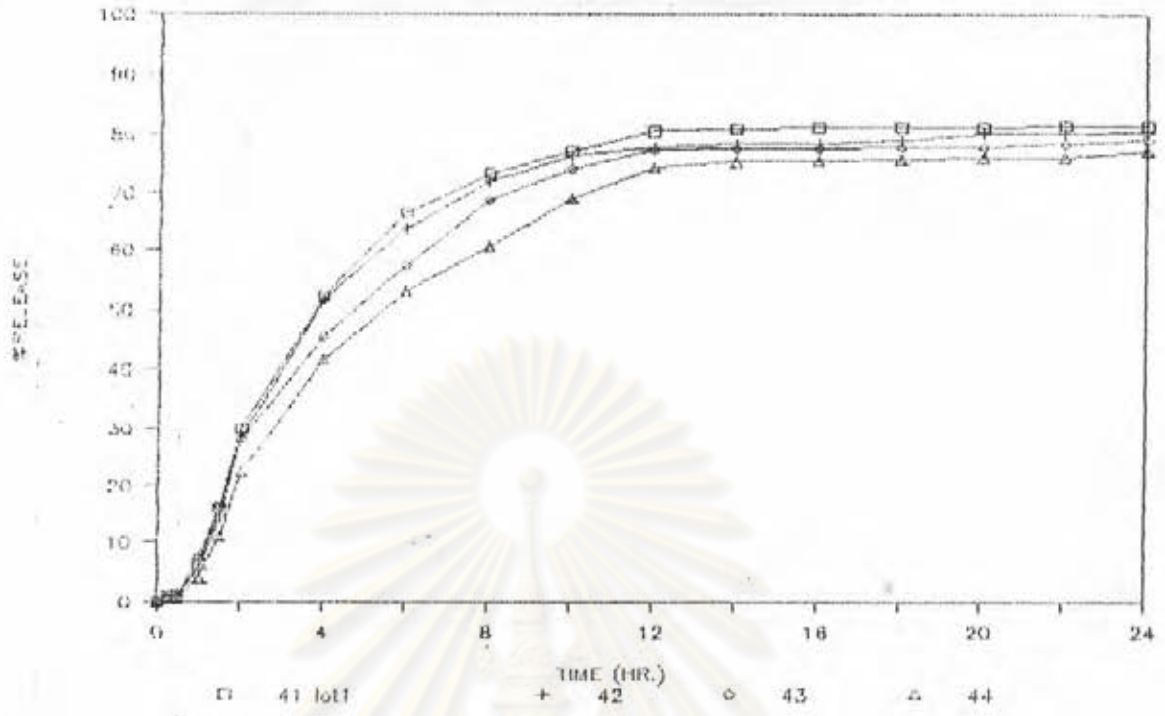


Figure 58 Release profile of coated sucrose beads formulation 41-44 in pH change method

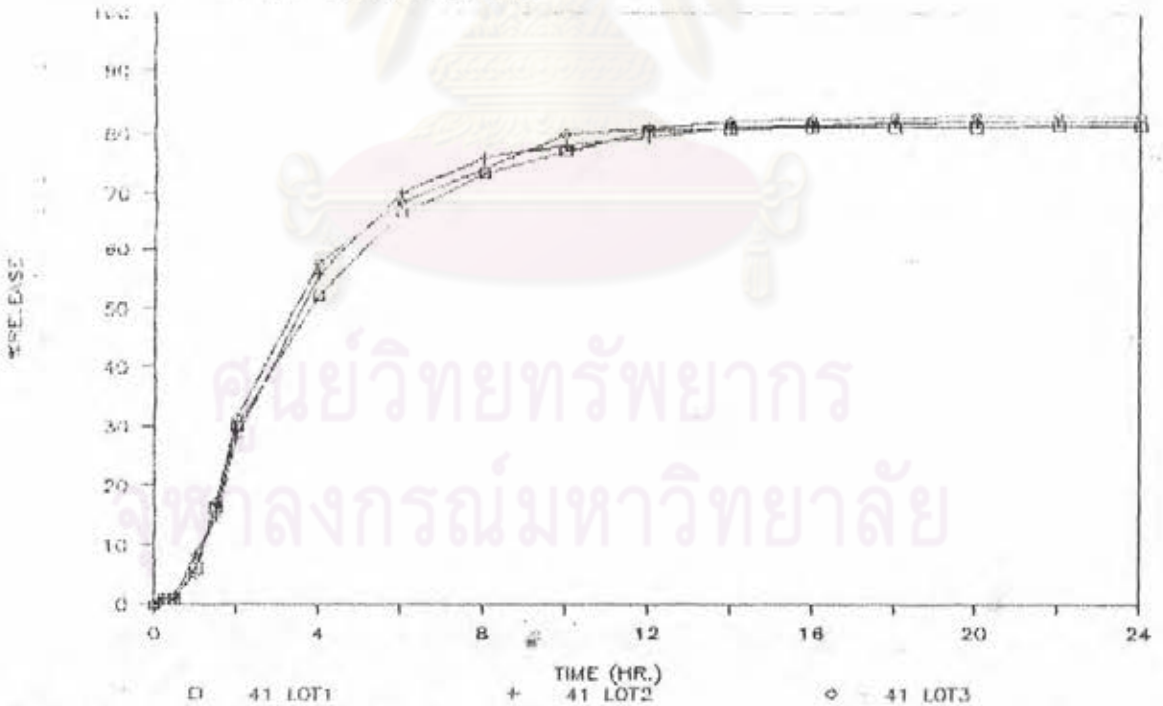
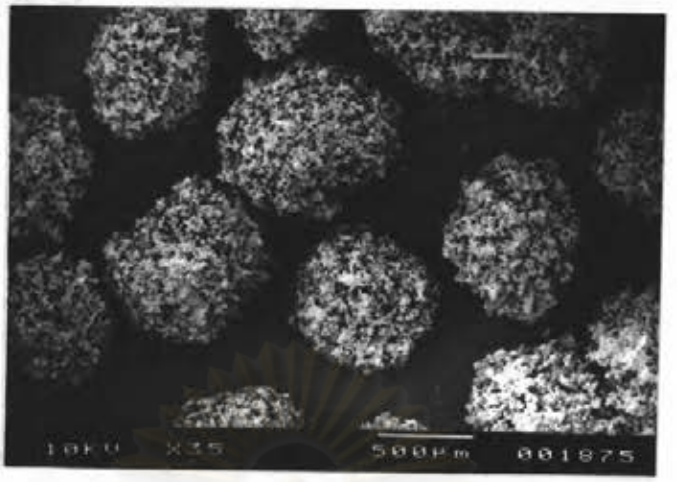
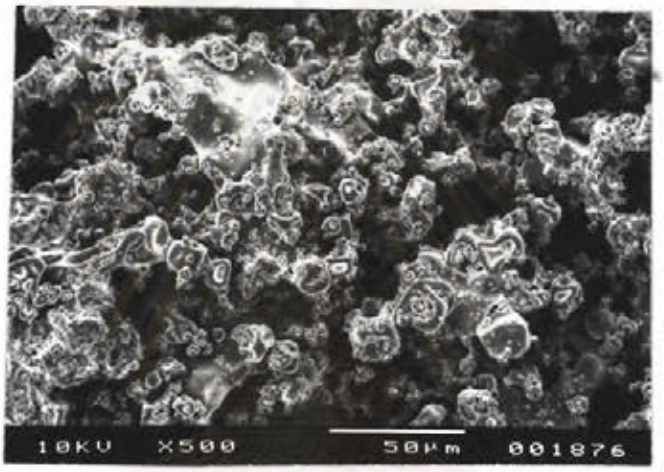


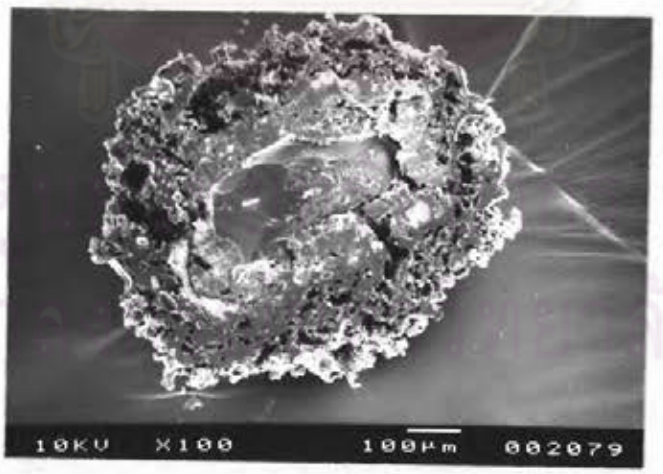
Figure 59 Release profile of coated sucrose beads formulation 41 lot1- 41 lot3 in pH change method



A

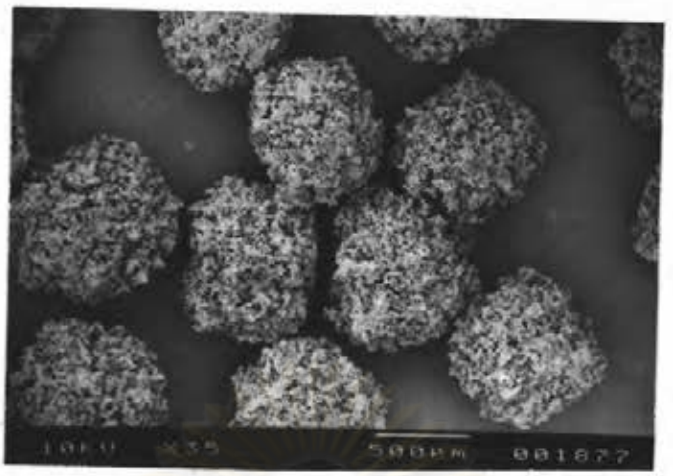


B

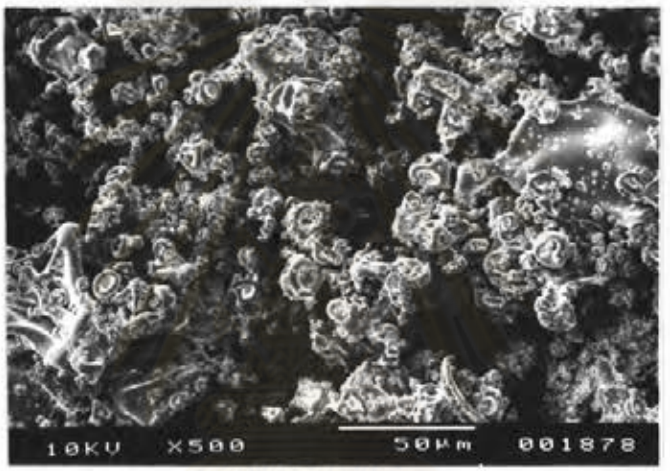


C

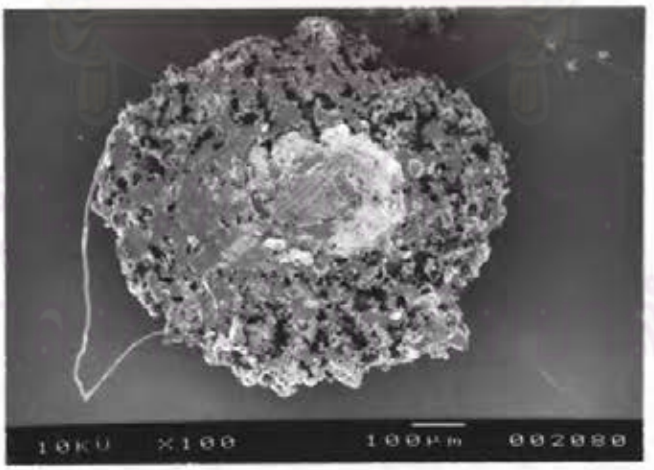
Figure 60 Photomicrographs of coated sucrose beads formulation 41 lot.1 (Key: A coated beads x 35 , B coating surface x 500 , C cross-section x 100)



A

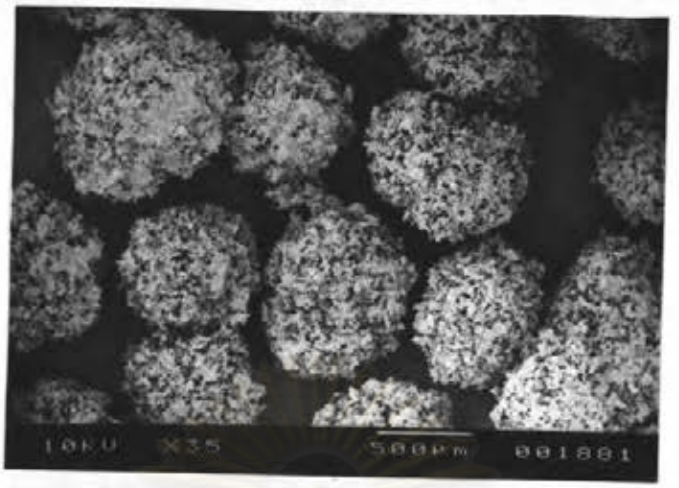


B

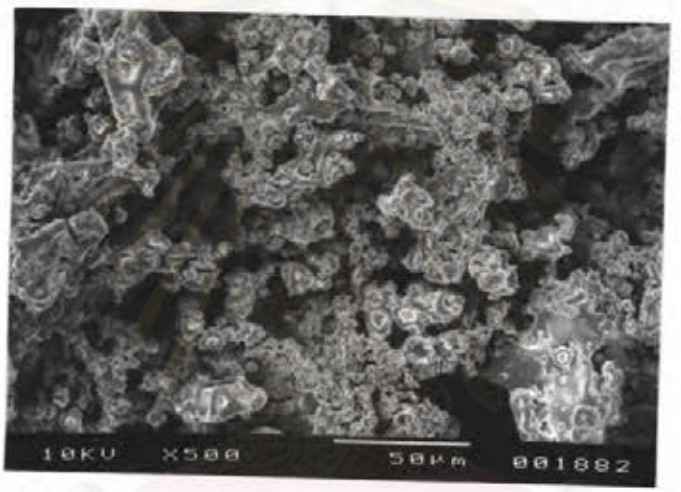


C

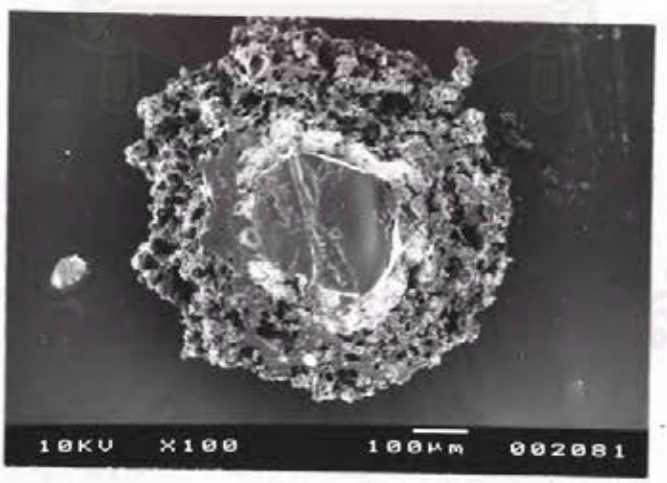
Figure 61 Photomicrographs of coated sucrose beads formulation 41 lot.2 (Key: A coated beads x 35 , B coating surface x 500 , C cross-section x 100)



A

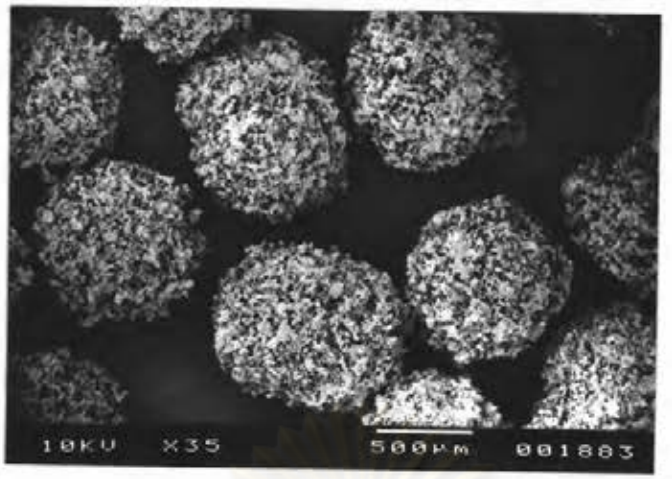


B

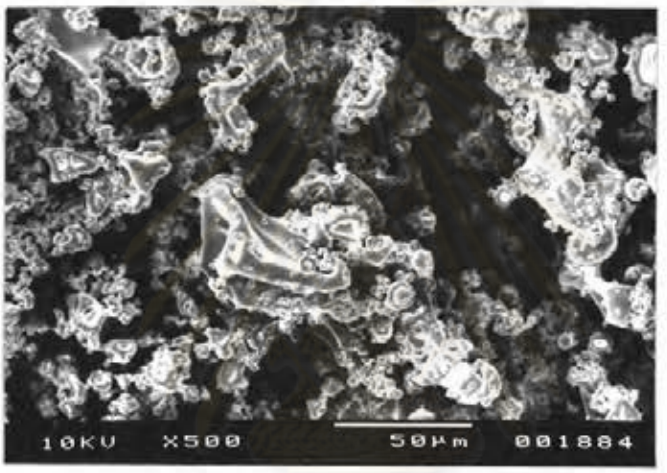


C

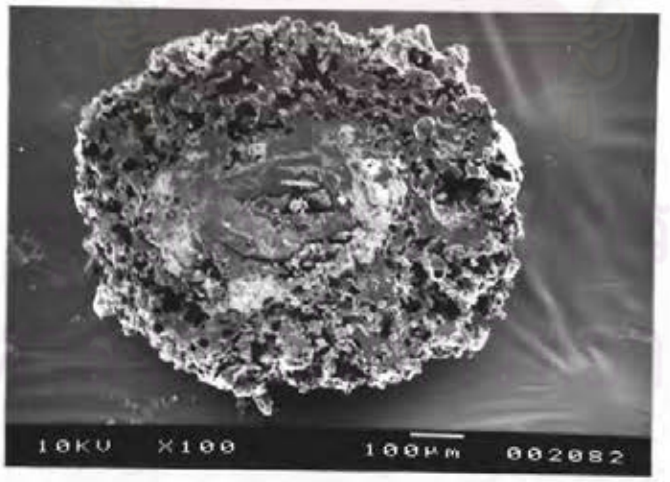
Figure 62 Photomicrographs of coated sucrose beads formulation 41 lot.3 (Key: A coated beads x 35 , B coating surface x 500 , C cross-section x 100)



A

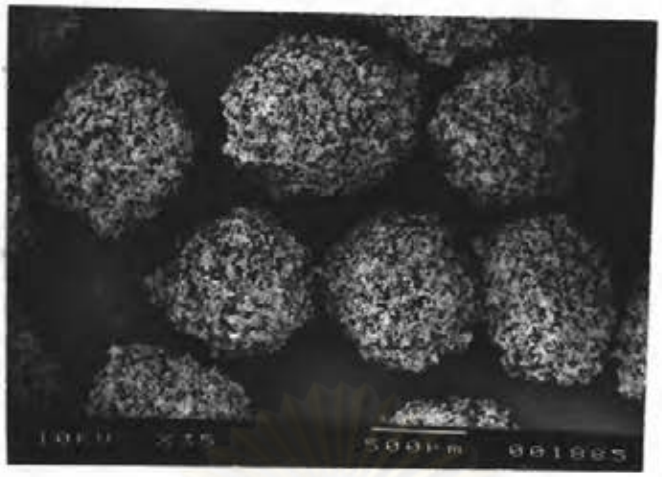


B

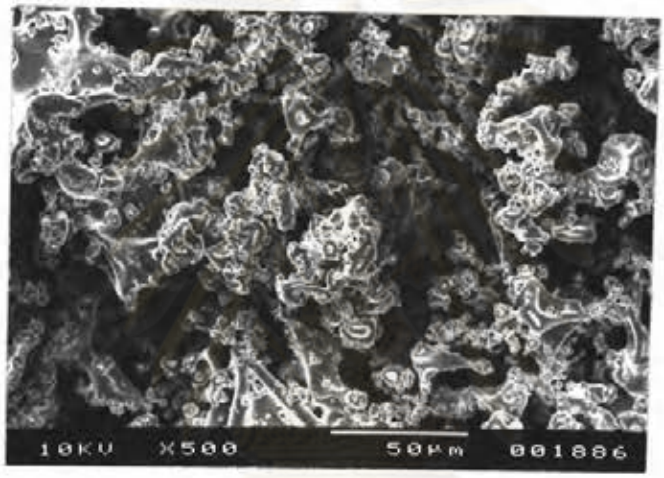


C

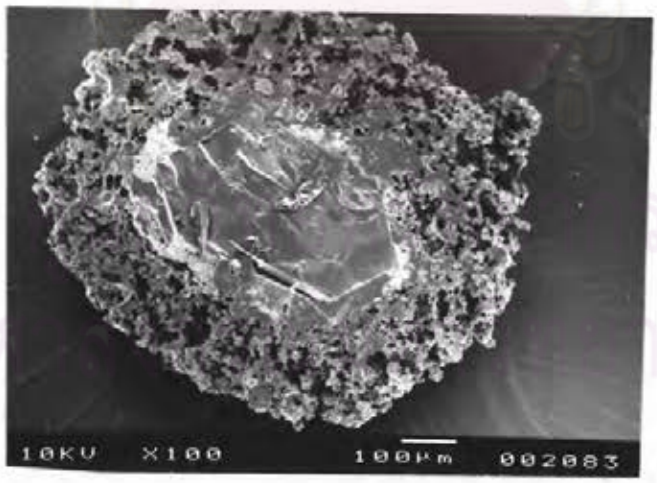
Figure 63 Photomicrographs of coated sucrose beads formulation 42 (Key: A coated beads x 35 , B coating surface x 500 , C cross-section x 100)



A



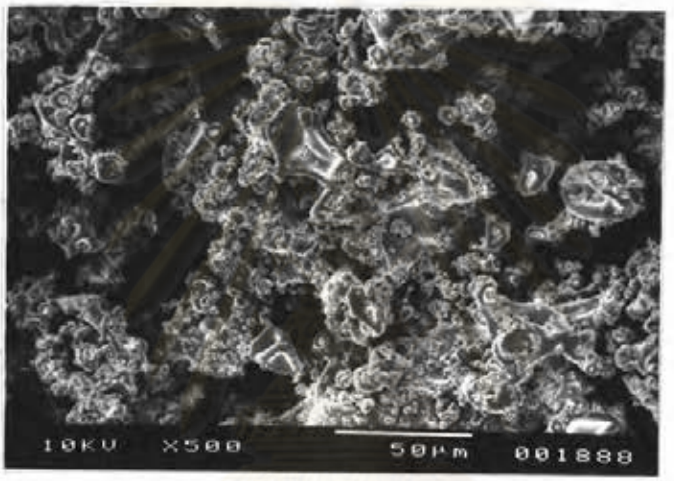
B



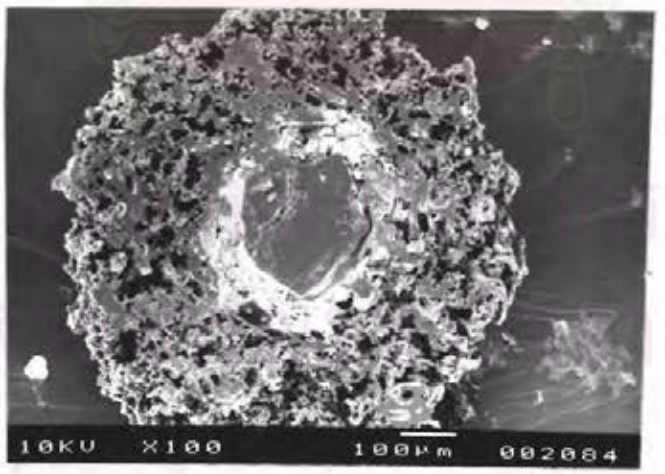
C

Figure 64 Photomicrographs of coated sucrose beads formulation 43 (Key: A coated beads x 35 , B coating surface x 500 , C cross-section x 100)

A



B



C

Figure 65 Photomicrographs of coated sucrose beads formulation 44 (Key: A coated beads x 35 , B coating surface x 500 , C cross-section x 100)

Physical property evaluation of formulations 37-44

For formulations 41-44, it was found that there were likely surface but the thickness of coated film was increased when the volume of outercoating solution was raised (Figure 60-65).

For variation of outercoating solution volume in formulations 37-44, there were not apparently different between each formulation with respect to bulk density and friability (see Table 21).

FORMULATIONS 45-54

In these experimental formulation, the pellets were used as the cores instead of sucrose crystal in order to observe the difference in release behaviors between two types of the coated cores. The studies and experiment were in the same procedures as previously described for sucrose crystal.

The amount and type of plasticizer were varied as presented in the following Table 22 and 23 in the same composition as formulations 1-10.

Physical property evaluation of formulations 45-54

The scanning electron photomicrographs of uncoated pellets were shown in Figure 66. The shape and surface topography of coated pellets which prepared at different type and content of plasticizers were seen in Figures 67-70.

Table 21 The Physical Properties of the Beads Formulations 37-44

Formulation	Mean Size (μ)	Bulk Density (g/ml)	Tapped Density (g/ml)	Carr's Index	Friability (%)
37	690.23	0.29	0.31	4.90	0.30
38	771.62	0.29	0.30	4.81	0.30
39	813.31	0.28	0.29	4.59	0.60
40	831.75	0.29	0.30	4.29	0.70
41	781.52	0.29	0.30	4.83	0.40
42	792.58	0.29	0.30	4.78	0.50
43	798.36	0.29	0.30	4.76	0.50
44	809.15	0.28	0.29	4.67	0.50

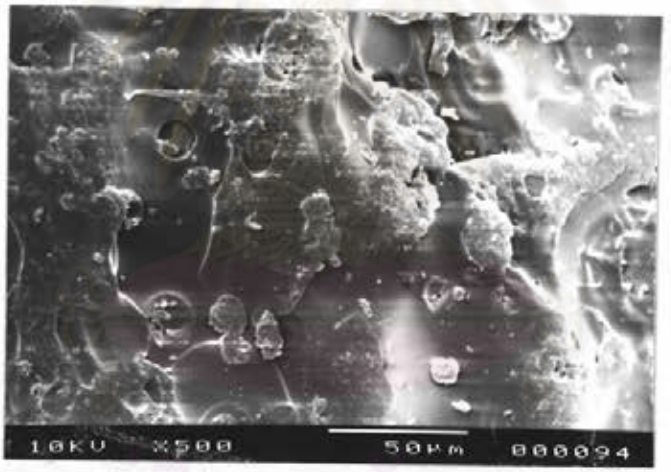
Table 22 Composition of Coating Formulations 45-48

Component (%w/v)	Formulation 45	46	47	48
Propranolol HCl	5	5	5	5
Ethylcellulose	5	5	5	5
Glycerylmonostearate	-	1	2	3
Ethanol qs.	100	100	100	100

Table 23 Composition of Coating Formulations 49-54

Compoonent (%w/v)	Formulation 49	50	51	52	53	54
Propranolol HCl	5	5	5	5	5	5
Ethylcellulose	5	5	5	5	5	5
Castor oil	1	2	3	-	-	-
PEG 4000	-	-	-	1	2	3
Ethanol qs.	100	100	100	100	100	100

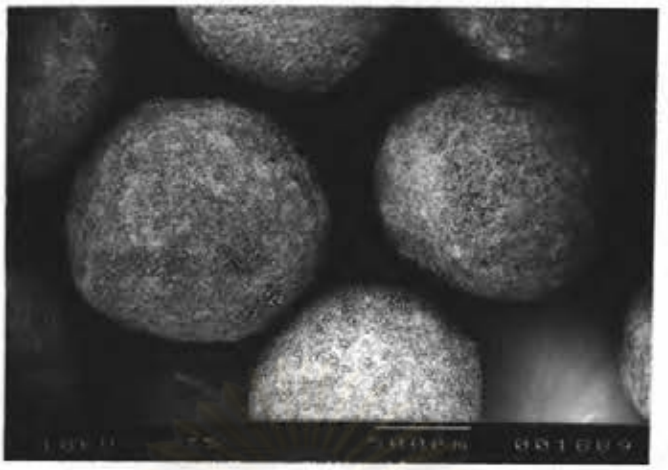
A



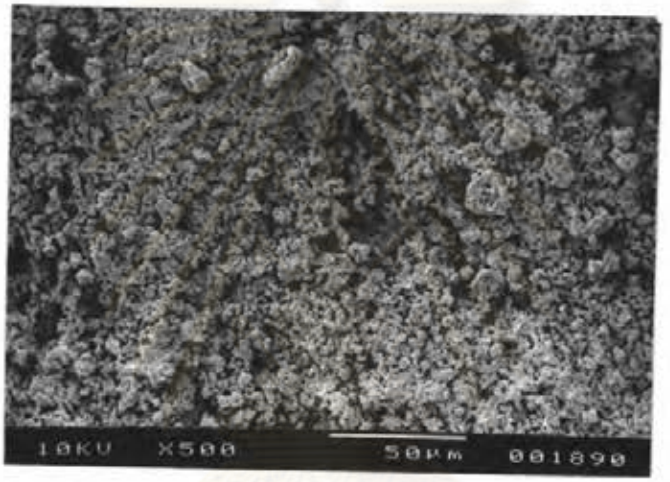
B

Figure 66 Photomicrographs of uncoated pellets

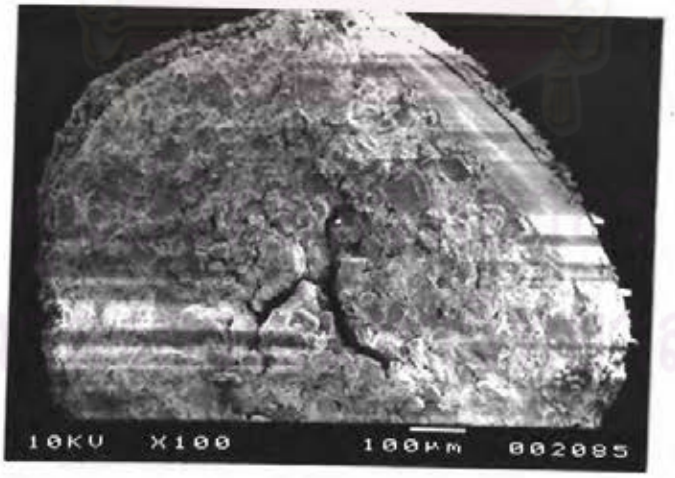
(Key: A beads x 100 , B beads surface x 500)



A



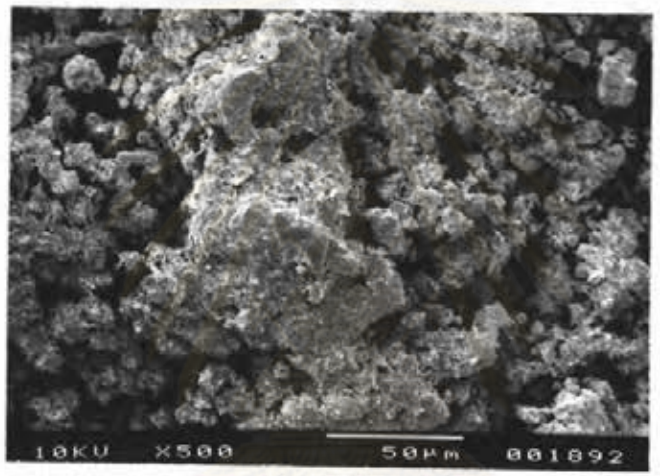
B



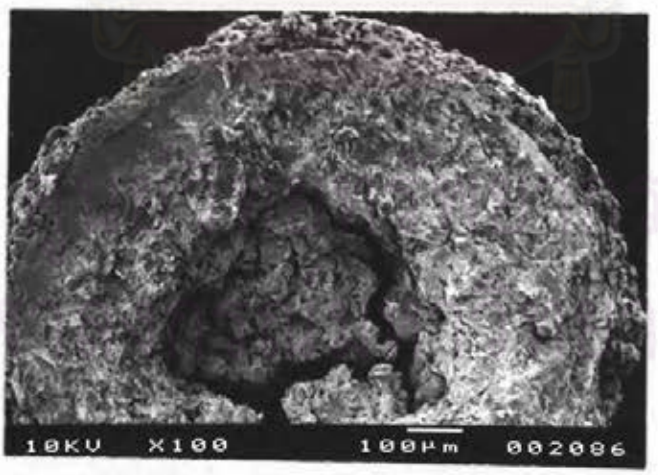
C

Figure 67 Photomicrographs of coated pellets formulation 45 (Key: A coated beads x 35 , B coating surface x 500 , C cross-section x 100)

A

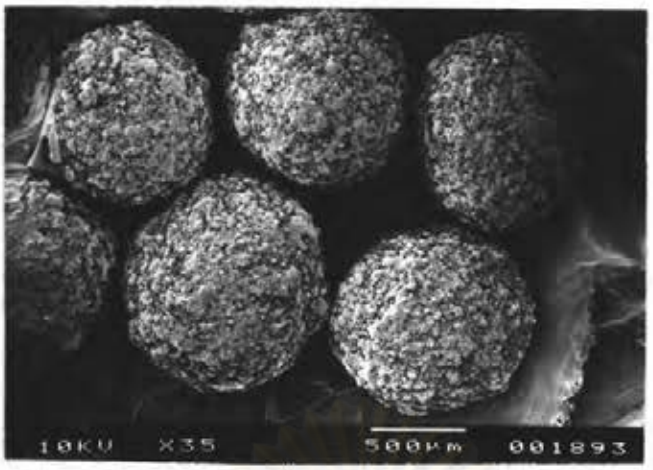


B

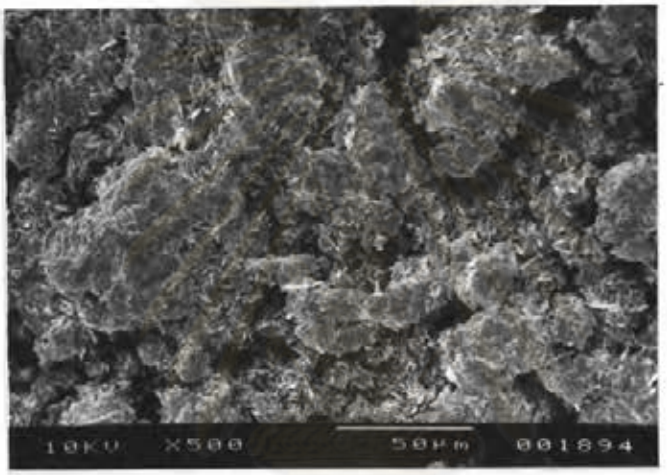


C

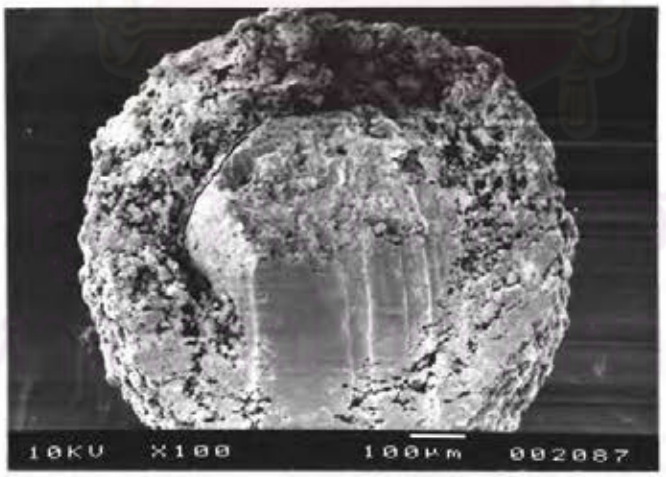
Figure 68 Photomicrographs of coated pellets formulation 46 (Key: A coated beads x 35 , B coating surface x 500 , C cross-section x 100)



A



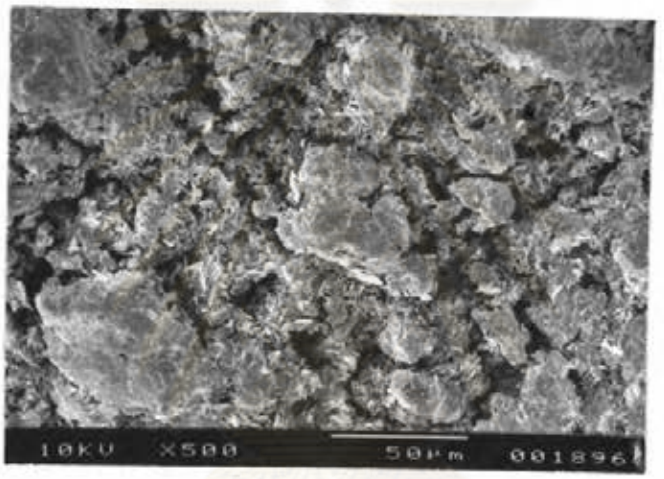
B



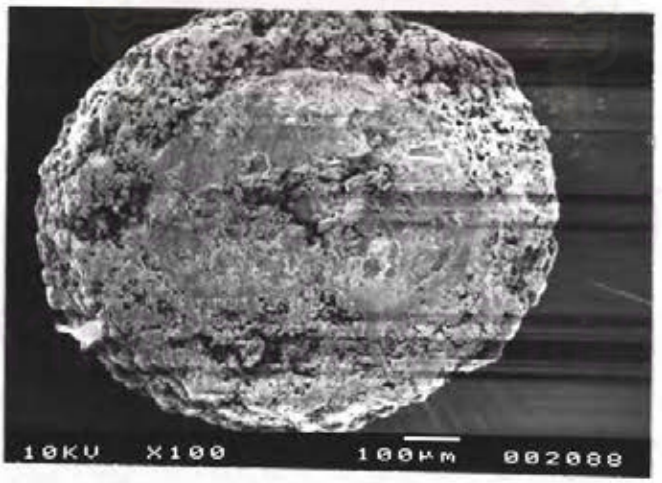
C

Figure 69 Photomicrographs of coated pellets formulation 47 (Key: A coated beads x 35 , B coating surface x 500 , C cross-section x 100)

A



B



C

Figure 70 Photomicrographs of coated pellets formulation 48 (Key: A coated beads x 35 , B coating surface x 500 , C cross-section x 100)

Formulation 45 gave smooth surface and uniformity of coating (Figure 67). For formulations 46-48, there were more rough surface when glycerylmonostearate content was increased (Figure 68-70).

Mean size of the beads using formulations 45-54 was about 830 μ. Size of the coated pellets with different plasticizers were not apparently different. When comparing with sucrose crystal, the average size of coated pellets was larger than of coated sucrose. The compressibility was not apparently different among the coated pellets of formulations 45-54 except formulation 47 which gave the lowest compressibility. And, the compressibility of coated pellets was lower than of coated sucrose. It thus indicated a better flowability. There were not apparently different in bulk density and friability of all formulations, and it was lower than coated sucrose (see Table 24).

Dissolution study evaluation of formulations 45-54

The dissolution rate of the coated pellets which composed of plasticizer and non-plasticizer were studied by basket method in 0.1 N HCl, phosphate buffer pH 6.8 and pH change method. Data are tabulated in Tables 67-70, 71-74 and 75-78 (Appendix A). and are illustrated graphically in Figures 71-74, 75-78 and 79-82.

The release rate in 0.1 N HCl and buffer pH 6.8 could be classified into 2 groups. The first was composed of glycerylmonostearate and castor oil. The other was composed of

Table 24 The Physical Properties of the Beads Formulations 45-54

Formulation	Mean Size (μ)	Bulk Density (g/ml)	Tapped Density (g/ml)	Carr's Index	Friability (%)
45	828.49	0.50	0.52	3.36	0.30
46	830.11	0.52	0.53	2.59	0.20
47	830.30	0.53	0.54	1.75	0.40
48	830.57	0.51	0.53	3.39	0.20
49	829.23	0.52	0.54	2.61	0.30
50	829.35	0.52	0.53	2.59	0.20
51	829.48	0.51	0.52	2.54	0.10
52	829.77	0.52	0.54	2.61	0.20
53	829.92	0.52	0.54	3.45	0.30
54	830.13	0.51	0.53	3.39	0.40

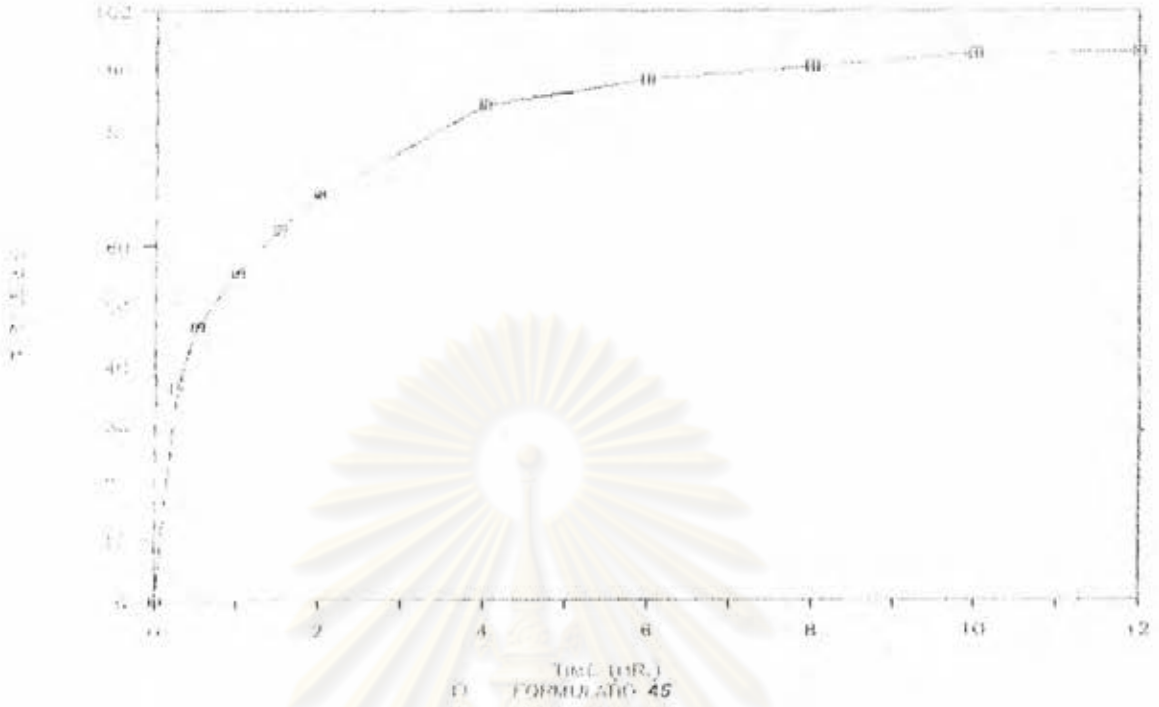


Figure 71 Release profile of coated pellets formulation 45 in 0.1 N HCl

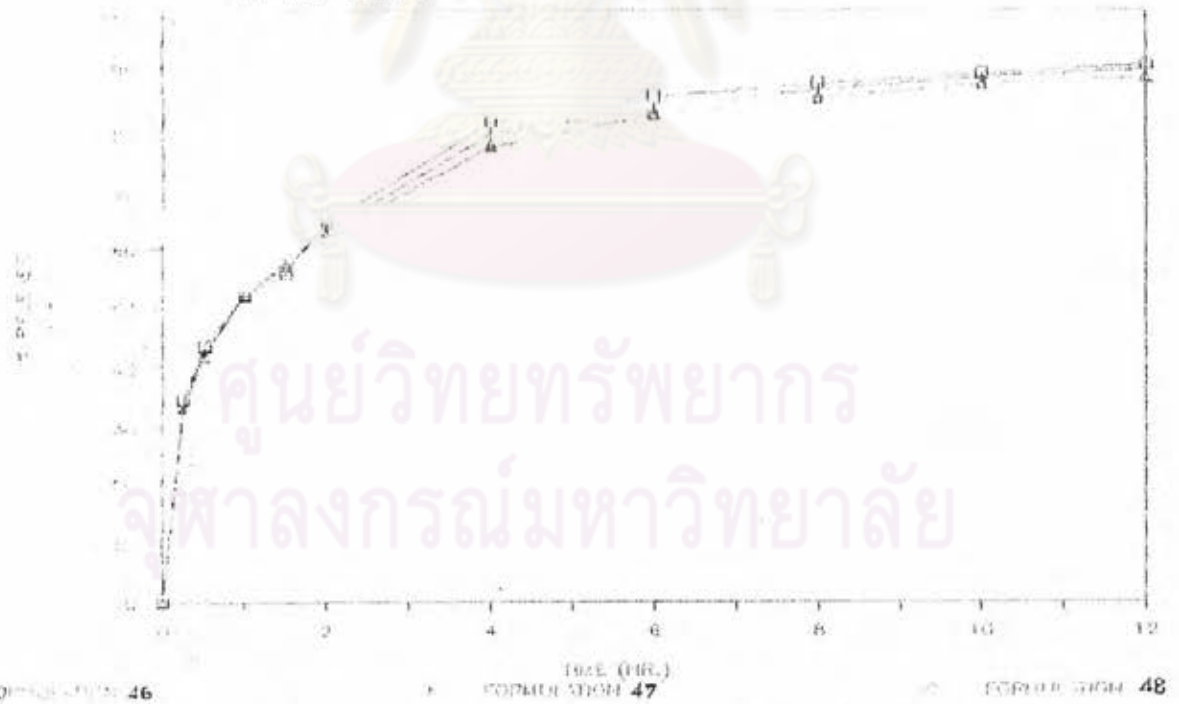


Figure 72 Release profile of coated pellets formulation 46-48 in 0.1 N HCl

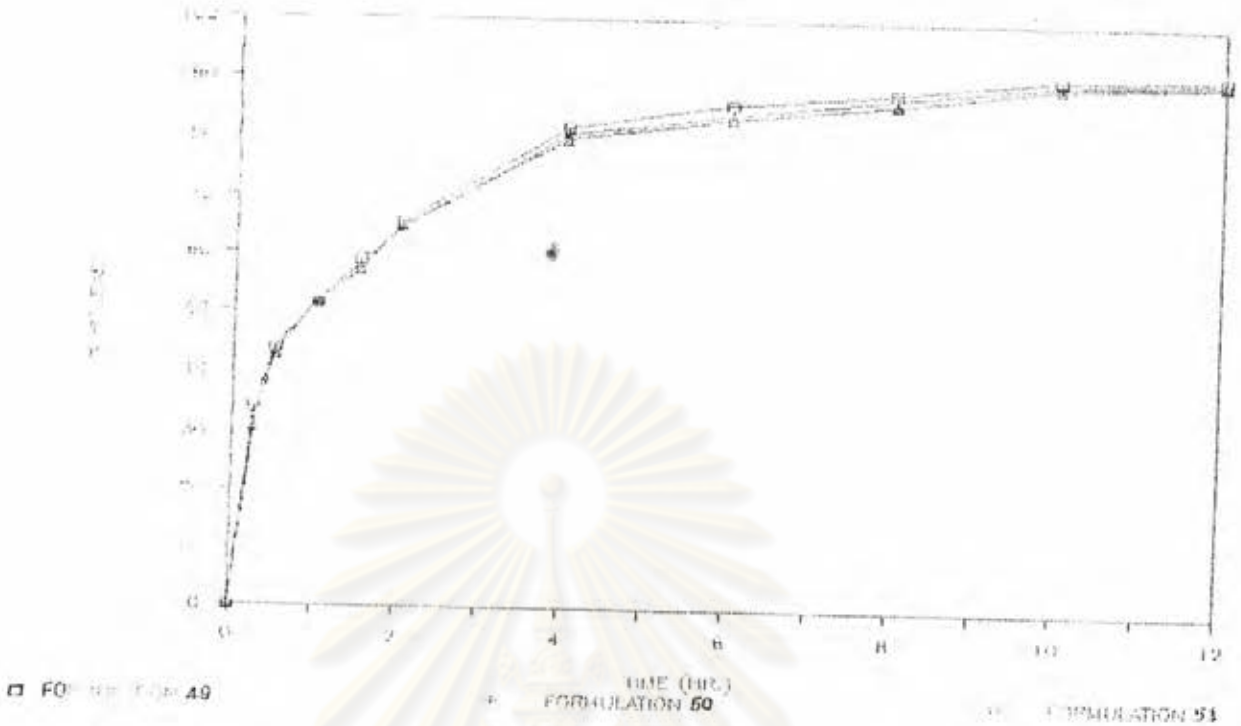


Figure 73 Release profile of coated pellets formulation 49-51 in 0.1 N HCl

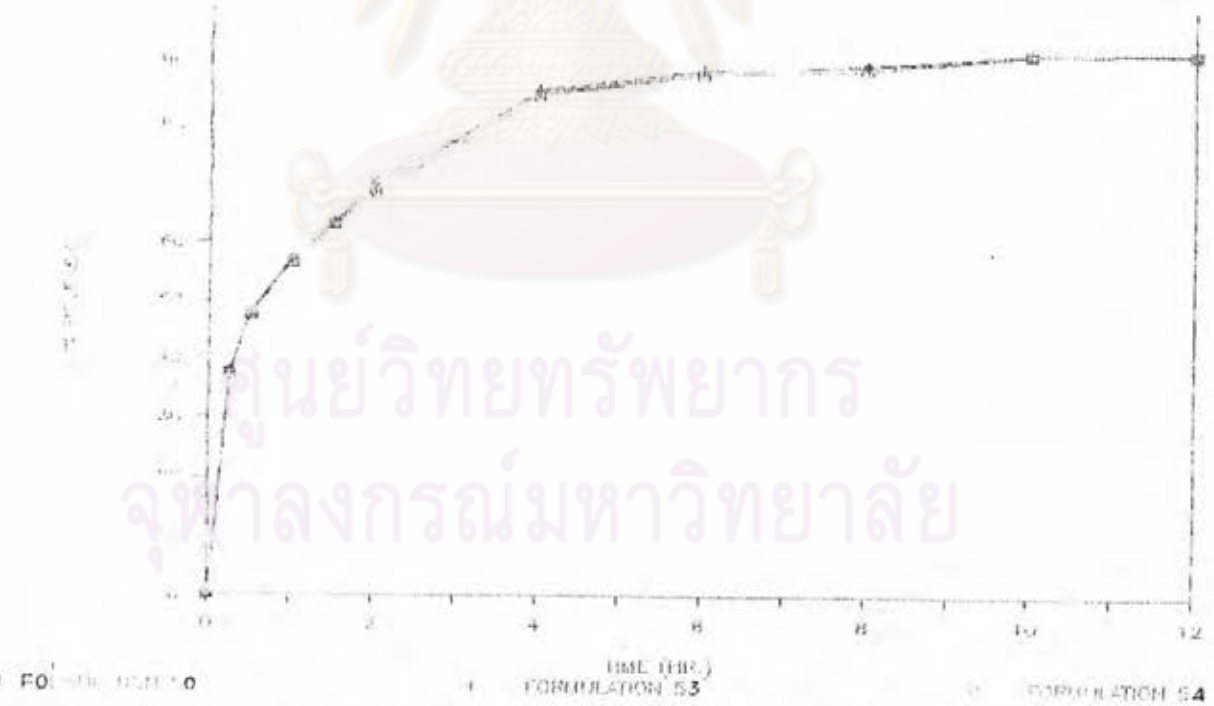


Figure 74 Release profile of coated pellets formulation 52-54 in 0.1 N HCl

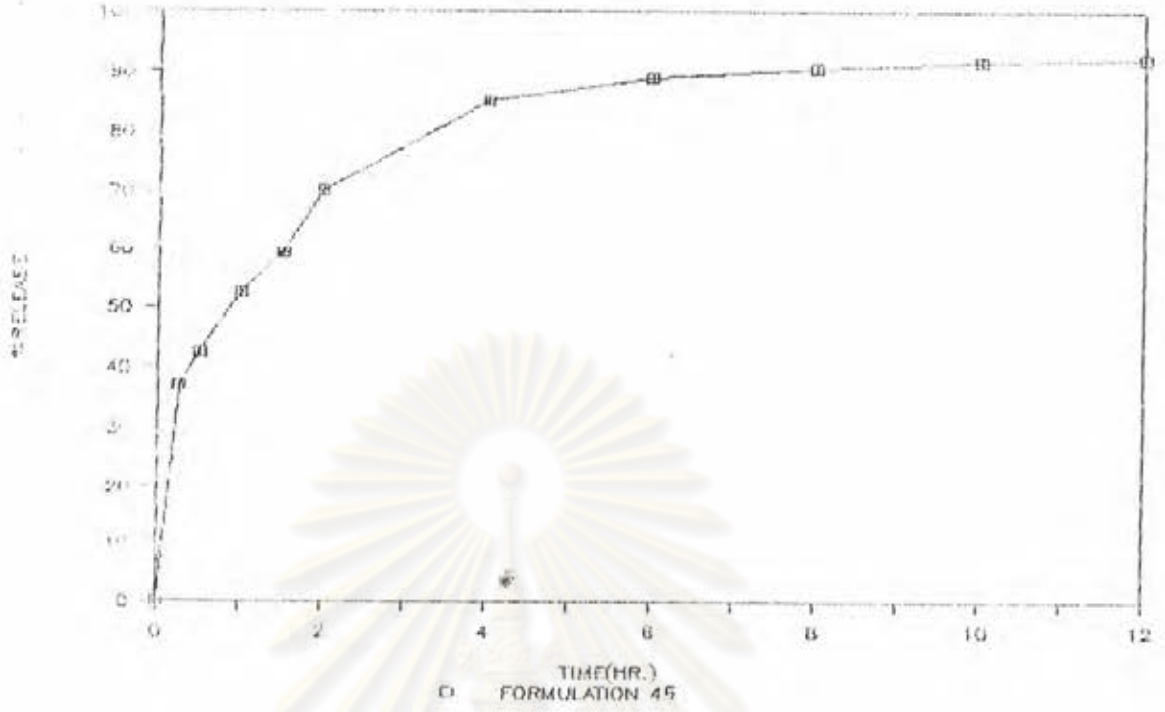


Figure 75 Release profile of coated pellets formulation 45 in phosphate buffer pH 6.8

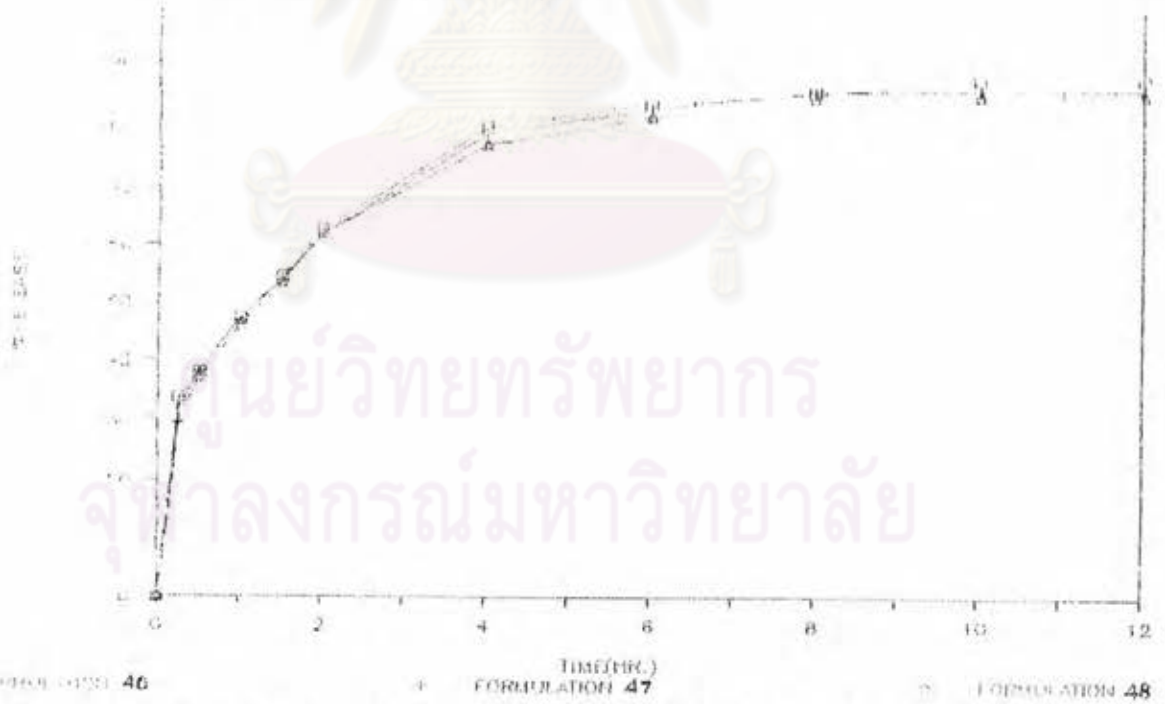


Figure 76 Release profile of coated pellets formulation 46-48 in phosphate buffer pH 6.8

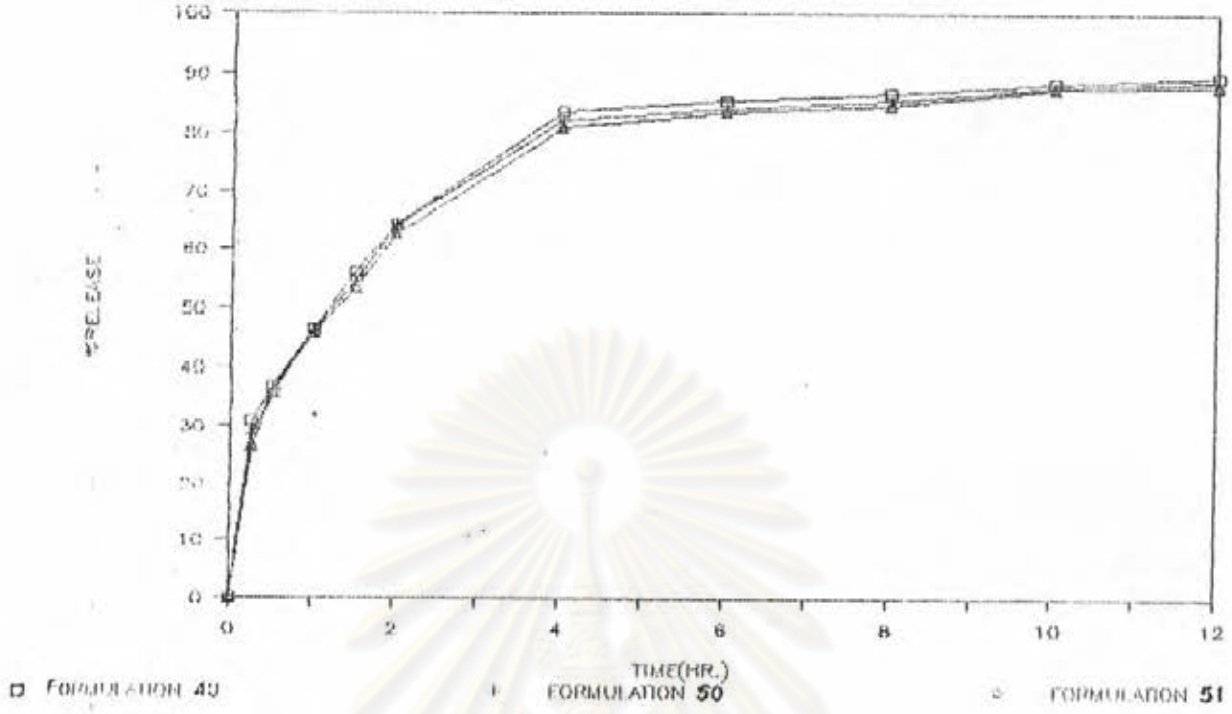


Figure 77 Release profile of coated pellets formulation 49-51 in phosphate buffer pH 6.8

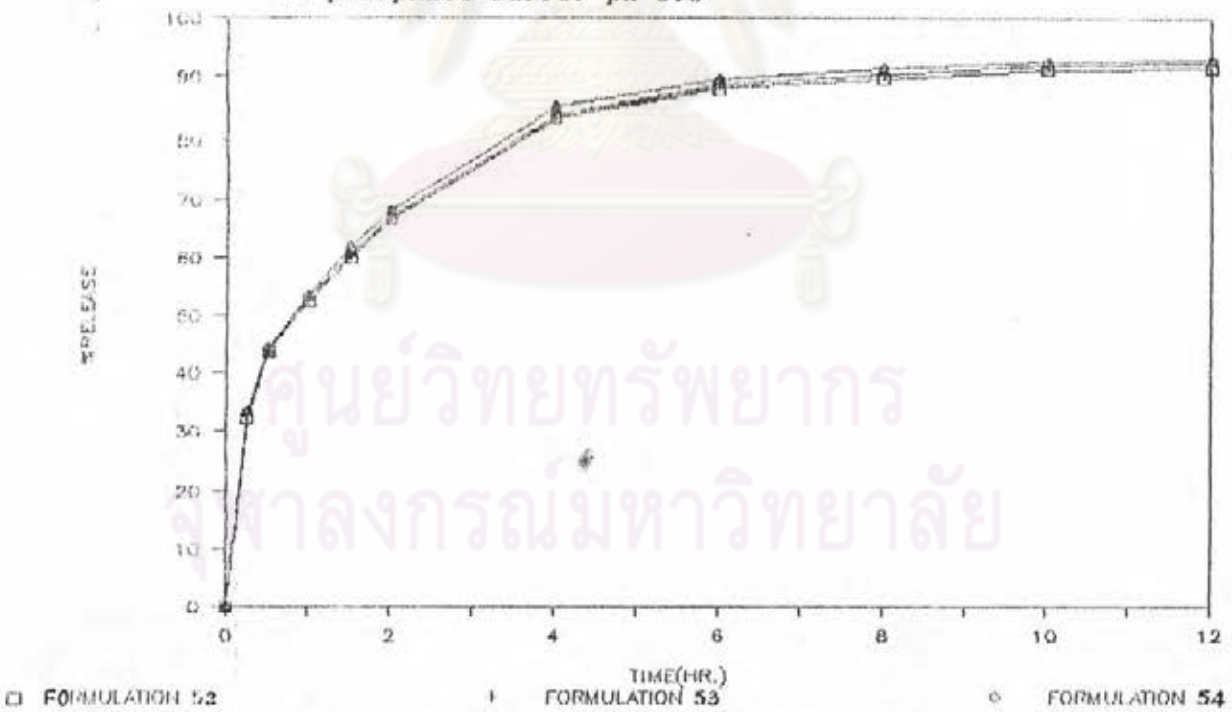


Figure 78 Release profile of coated pellets formulation 52-54 in phosphate buffer pH 6.8

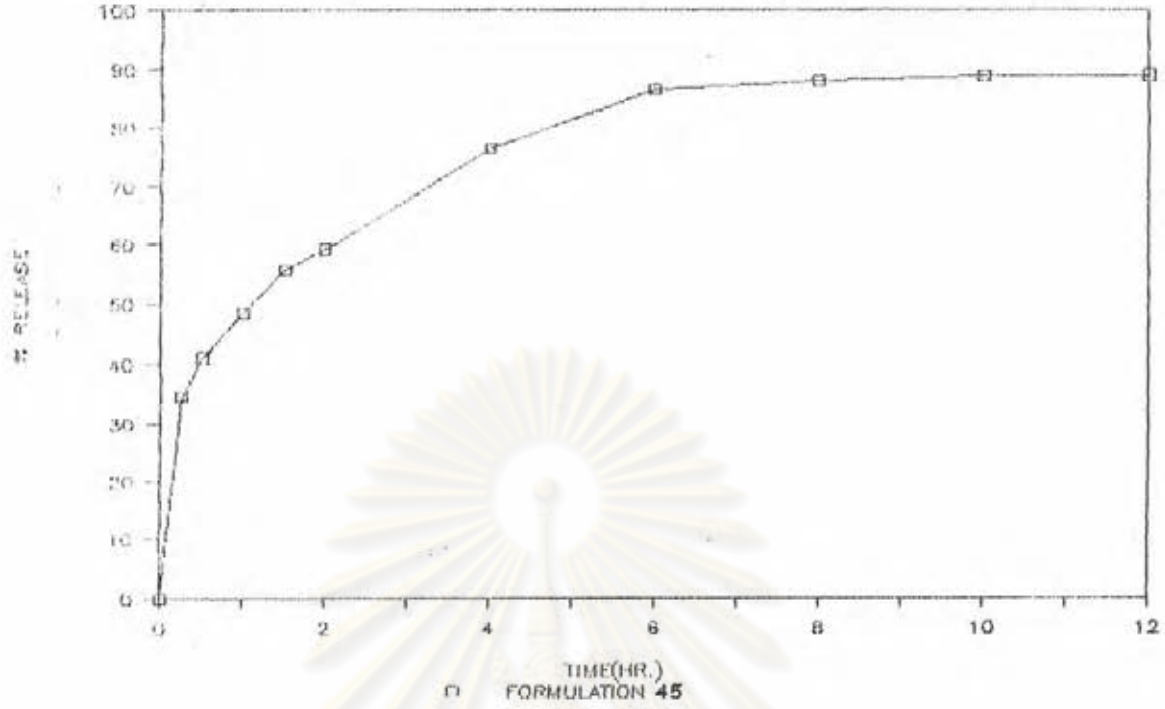


Figure 79 Release profile of coated pellets formulation 45 in pH change method

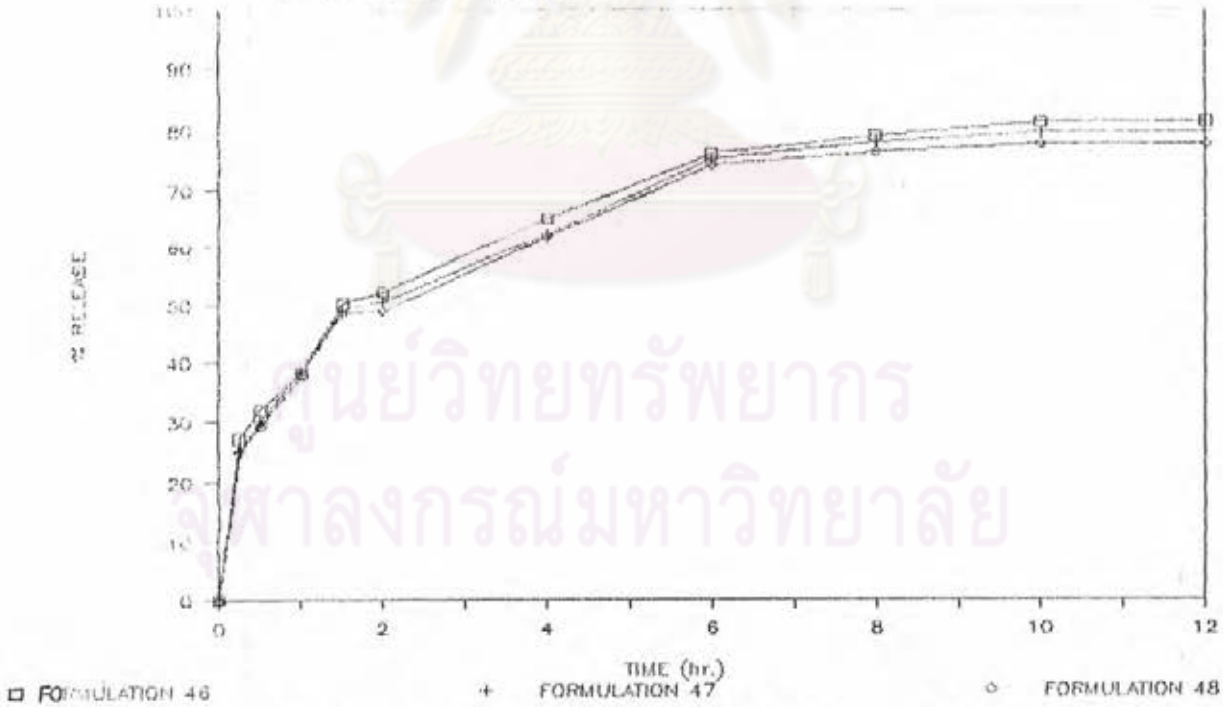


Figure 80 Release profile of coated pellets formulation 46-48 in pH change method

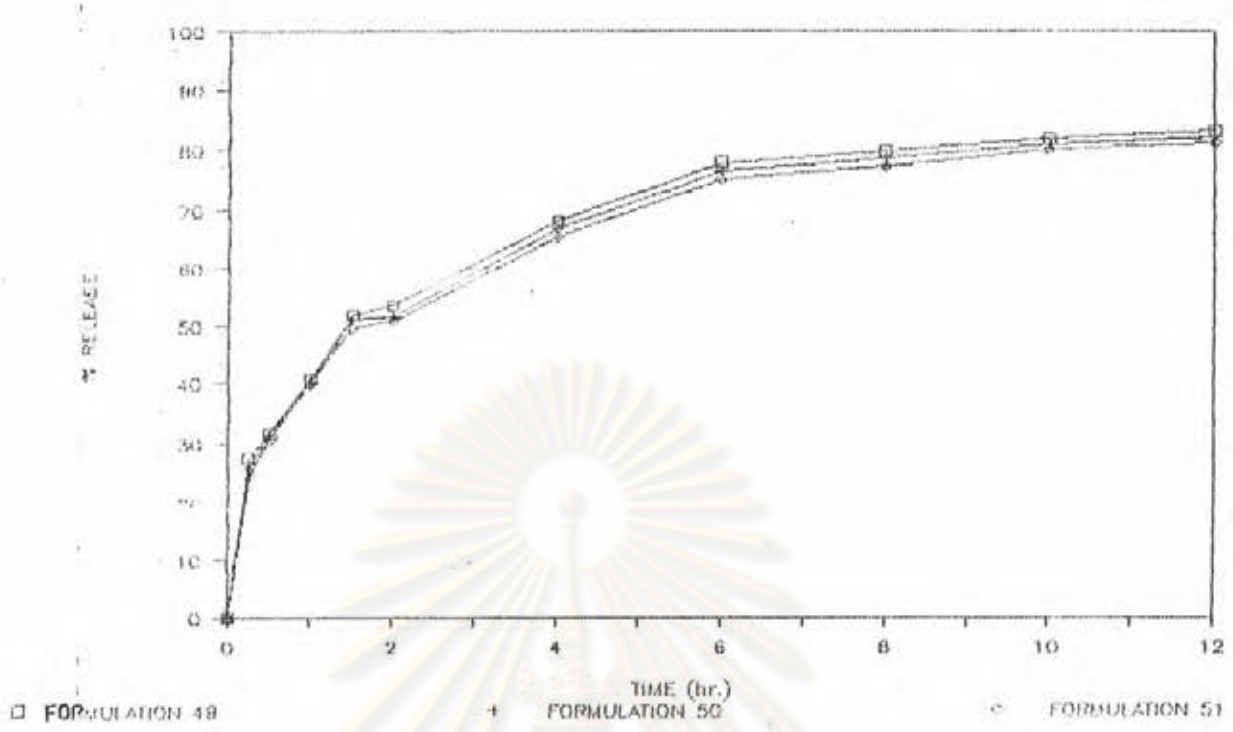


Figure 81 Release profile of coated pellets formulation 49-51 in pH change method

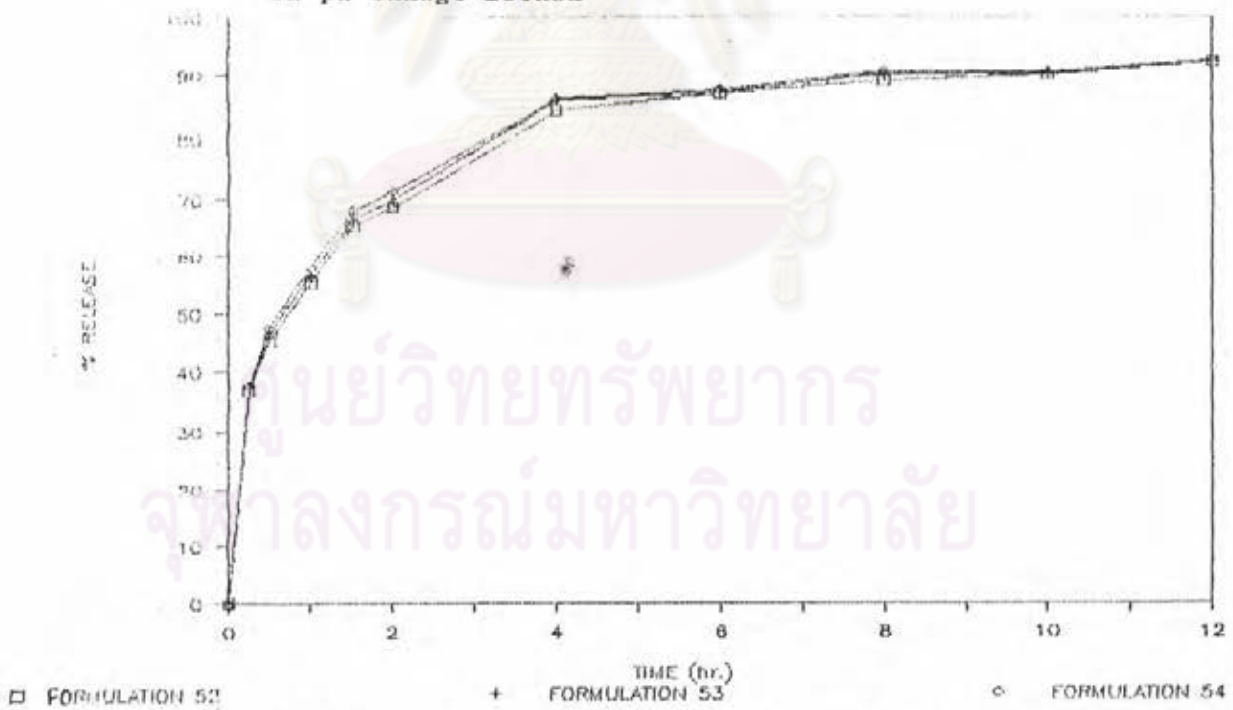


Figure 82 Release profile of coated pellets formulation 52-54 in pH change method

PEG 4000 and non-plasticizer. It gave the similar profiles of release data in each group and at various time intervals (1.5, 4, 8 and 12 hr).

On the other hand, the release data in pH change method can be classified in 3 groups. The first were glycerylmonostearate and castor oil. The other was composed of PEG 4000. The last one was non-plasticizer at 1.5, 4, 8 and 12 hr.

The three types of plasticizer were investigated at 3 levels of 1%, 2% and 3%. An increasing content of plasticizer, glycerylmonostearate and castor oil, showed a trend to decrease drug release. But PEG 4000 gave faster drug release. And the same results could be found in all release media, at all sampling time and all levels of PEG 4000.

The release profiles of pellets(in pH change medium) exhibited biphasic curves, having reflective point at 1.5-2 hr. Formulation 48 gave the lowest release profiles. So, it was chosen for modification to have slower release product.

FORMULATIONS 55-57

To investigate the effect of concentration of ethylcellulose in outercoating solution on drug release profiles, formulation 48 was chosen to be coated with outercoating solution contains 5%, 7% and 10% EC (as presented in Formulations 55, 56 and 57 Table 25).

Table 25 Composition of Coating Formulations 55-57

Component (%w/v)	Formulation 55	56	57
Propranolol HCl	5	5	5
Ethylcellulose	5	5	5
Glycerylmonostearate	3	3	3
Ethanol qs.	100	100	100
Outercoated			
Ethycellulose	5	7	10
Ethanol qs.	100	100	100

Table 26 The Physical Properties of the Beads Formulations 55-57

Formulation	Mean Size (μ)	Bulk Density (g/ml)	Tapped Density (g/ml)	Carr's Index	Friability (%)
55	832.52	0.50	0.52	3.33	0.40
56	833.41	0.49	0.50	3.25	0.60
57	834.10	0.48	0.49	3.17	0.80

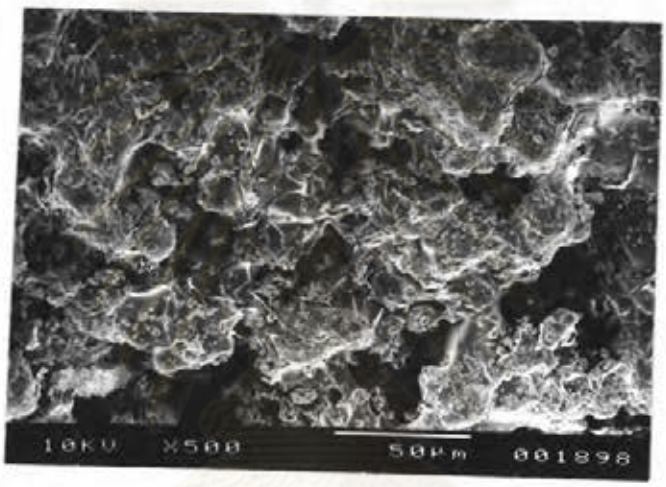
Physical property evaluation of formulations 55-57

It was found that as the ethylcellulose content in outercoating solution was increased, coating surface had more rough but the thickness of film was not apparently different (Figures 83-85). The highest friability was attained when formulation 57 was used (see Table 26). The density and compressibility had a trend to decrease corresponding to the increase of EC content in outercoating solution.

Dissolution study evaluation of formulations 55-57

The dissolution rate at 1.5 hr of these coated pellets of formulations 55, 56 and 57 were 59.54, 77.62 and 84.64 %, respectively (Figure 86, Table 60). The coated pellets formulation 57 exhibited the highest release rate and the coated pellets formulation 56 gave higher rate than of formulation 55.

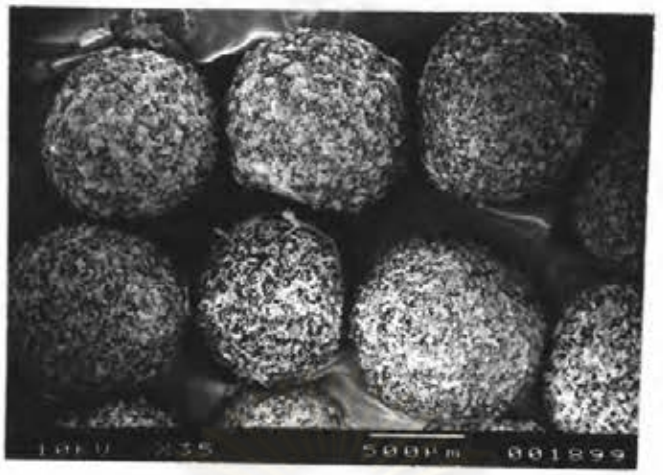
A



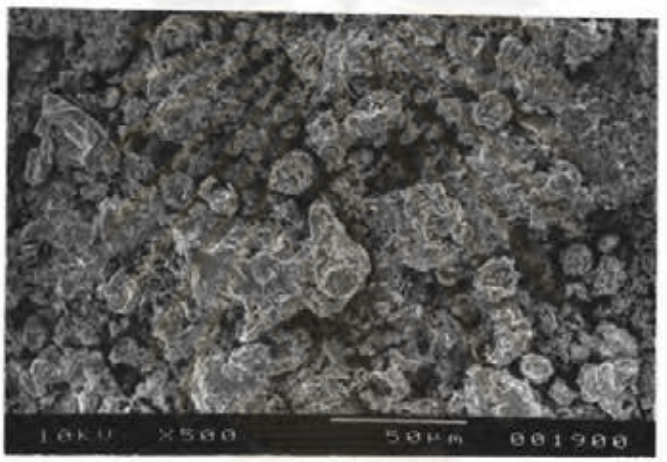
B

C

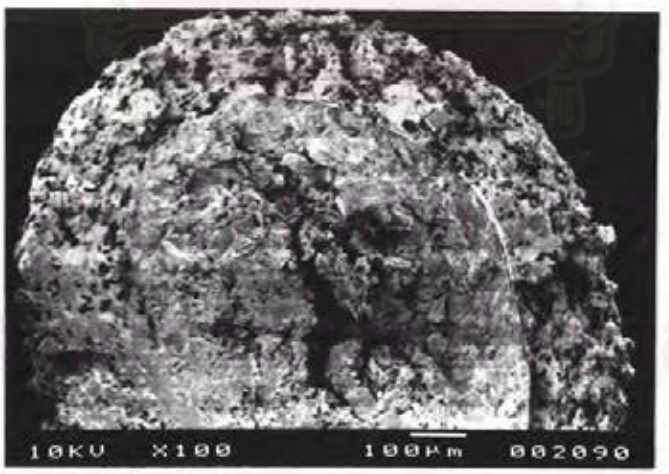
Figure 83 Photomicrographs of coated pellets formulation 55 (Key: A coated beads x 35 , B coating surface x 500 , C cross-section x 100)



A

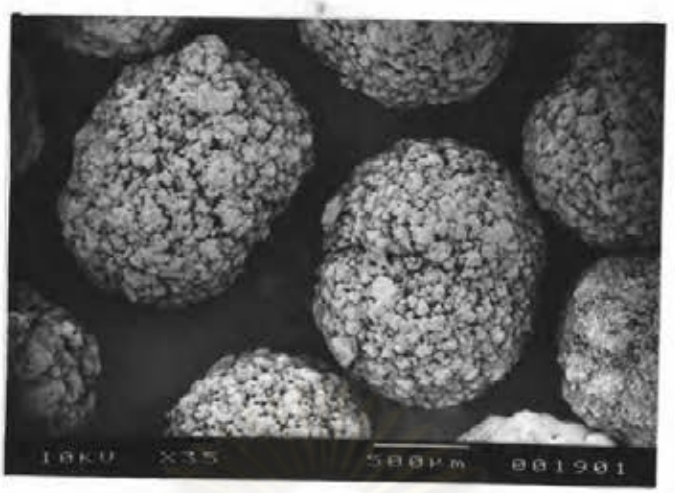


B

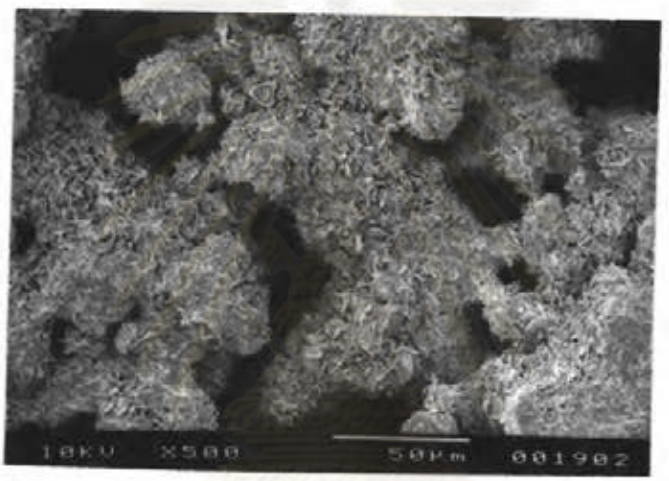


C

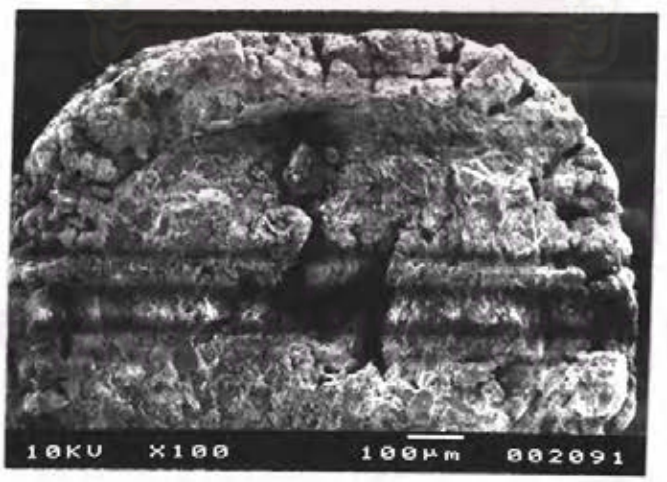
Figure 84 Photomicrographs of coated pellets formulation 56 (Key: A coated beads x 35 , B coating surface x 500 , C cross-section x 100)



A



B



C

Figure 85 Photomicrographs of coated pellets formulation 57 (Key: A coated beads x 35 , B coating surface x 500 , C cross-section x 100)

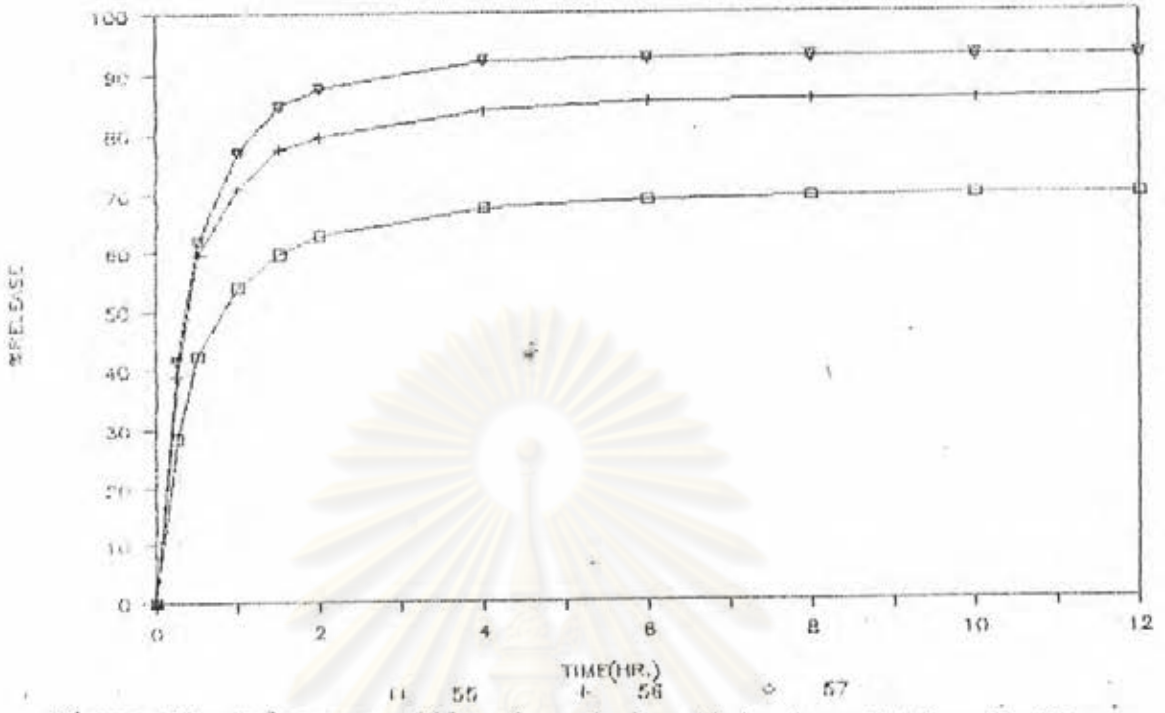


Figure 86 Release profile of coated pellets formulation 55-57 in pH change method

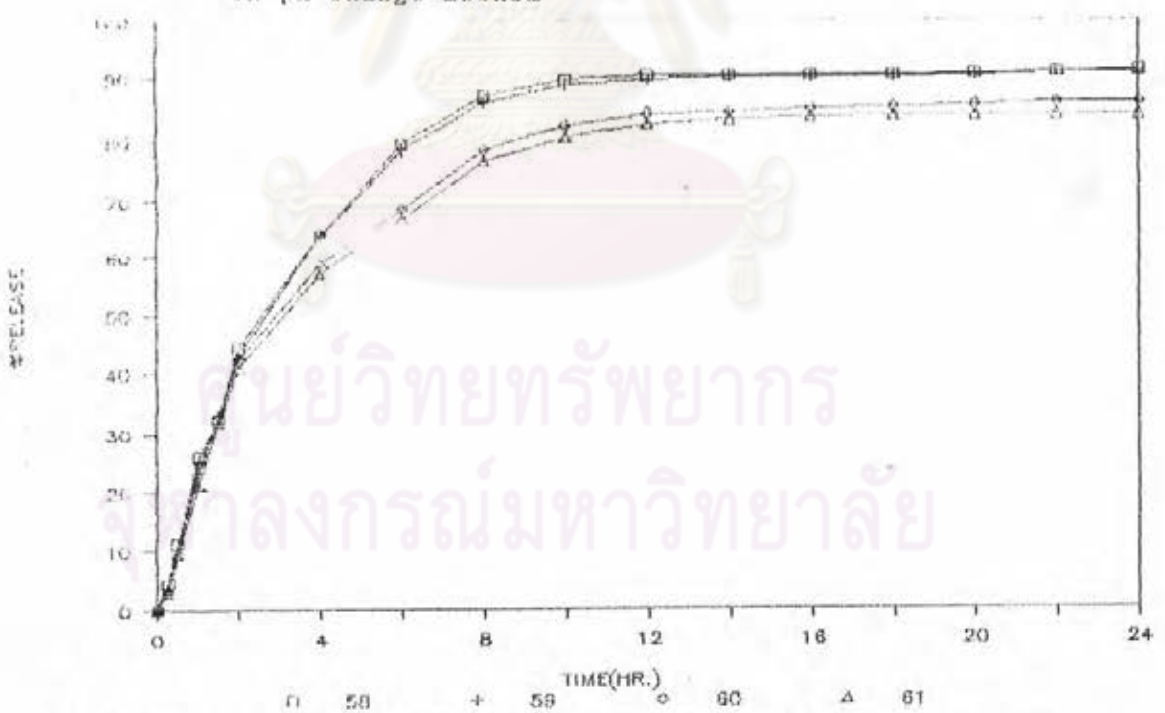


Figure 87 Release profile of coated pellets formulation 58-61 in pH change method

FORMULATIONS 58-65

Formulation 48 was overcoated by coating solution which composed of 5% EC and 3% castor oil at the volume of 500, 1000, 1500 and 2000 ml as shown in formulation 58, 59, 60 and 61, respectively (see Table 27). And it was outercoated by coating solution which composed of 5% EC and 3% castor oil at the volume of 1100, 1200, 1300 and 1400 ml as shown in formulations 62, 63, 64 and 65, respectively (see Table 28).

Physical property evaluation of formulations 58-65

It was found that increasing the volume of outercoating solution resulted in film with more rough surface and thickness. Formulation 63 gave the lowest friability coated pellets.

Mean size of the coated pellets was about 830 μ and increased in size when the volume of outercoating solution increased, and it had larger mean size than coated sucrose. The coated pellets of formulation 63 exhibited tendency to decrease in the compressibility and friability (see Table 29).

When comparing to the coated sucrose beads , density and compressibility of the coated pellets were lower than of coated sucrose. It means an increase in flowability. The coated pellets were less friable than coated sucrose.

Table 27 Composition of Coating Formulations 58-61

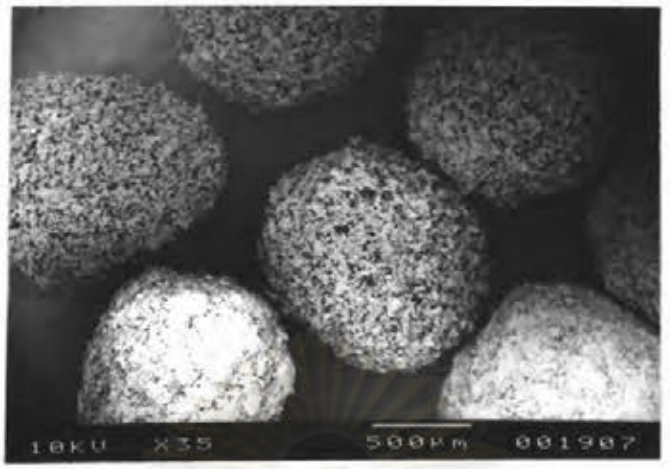
Component	Formulation			
	58	59	60	61
Propranolol	5	5	5	5
Ethylcellulose	5	5	5	5
Glycerylmonostearate	3	3	3	3
Ethanol qs.	100	100	100	100
Outercoated				
Ethylcellulose	5	5	5	5
Castor oil	3	3	3	3
Ethanol qs.	100	100	100	100
Outercoating Volume (ml.)	500	1000	1500	2000

Table 28 Composition of Coating Formulations 62-65

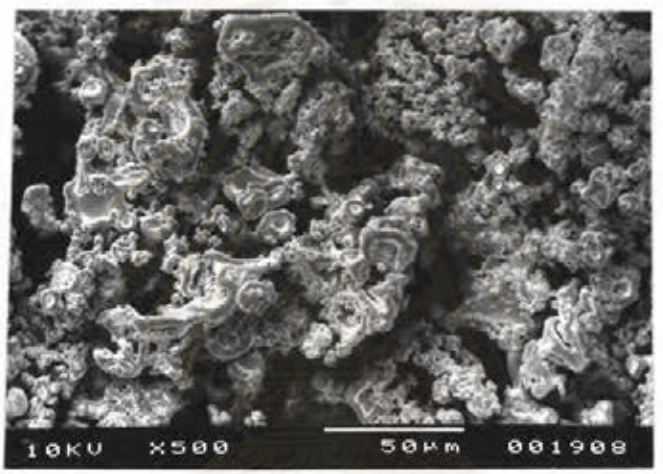
Component	Formulation			
	62	63	64	65
Propranolol	5	5	5	5
Ethylcellulose	5	5	5	5
Glycerylmonostearste	3	3	3	3
Ethanol qs.	100	100	100	100
Outercoated				
Ethylcellulose	5	5	5	5
Castor oil	3	3	3	3
Ethanol qs.	100	100	100	100
Outercoating Volume (ml.)	1100	1200	1300	1400

Table 29 The Physical Properties of the Beads Formulations 58-65

Formulation	Mean Size (μ)	Bulk Density (g/ml)	Tapped Density (g/ml)	Carr's Index	Friability (%)
58	830.30	0.54	0.56	3.57	0.60
59	831.11	0.53	0.55	3.54	0.50
60	835.07	0.55	0.56	2.73	0.20
61	835.30	0.53	0.54	2.63	0.10
62	832.31	0.53	0.55	3.54	0.50
63	833.20	0.53	0.55	3.54	0.40
64	834.18	0.56	0.57	2.78	0.40
65	834.88	0.56	0.57	2.78	0.30



A



B

C

Figure 88 Photomicrographs of coated pellets formulation 60 (Key: A coated beads x 35 , B coating surface x 500 , C cross-section x 100)

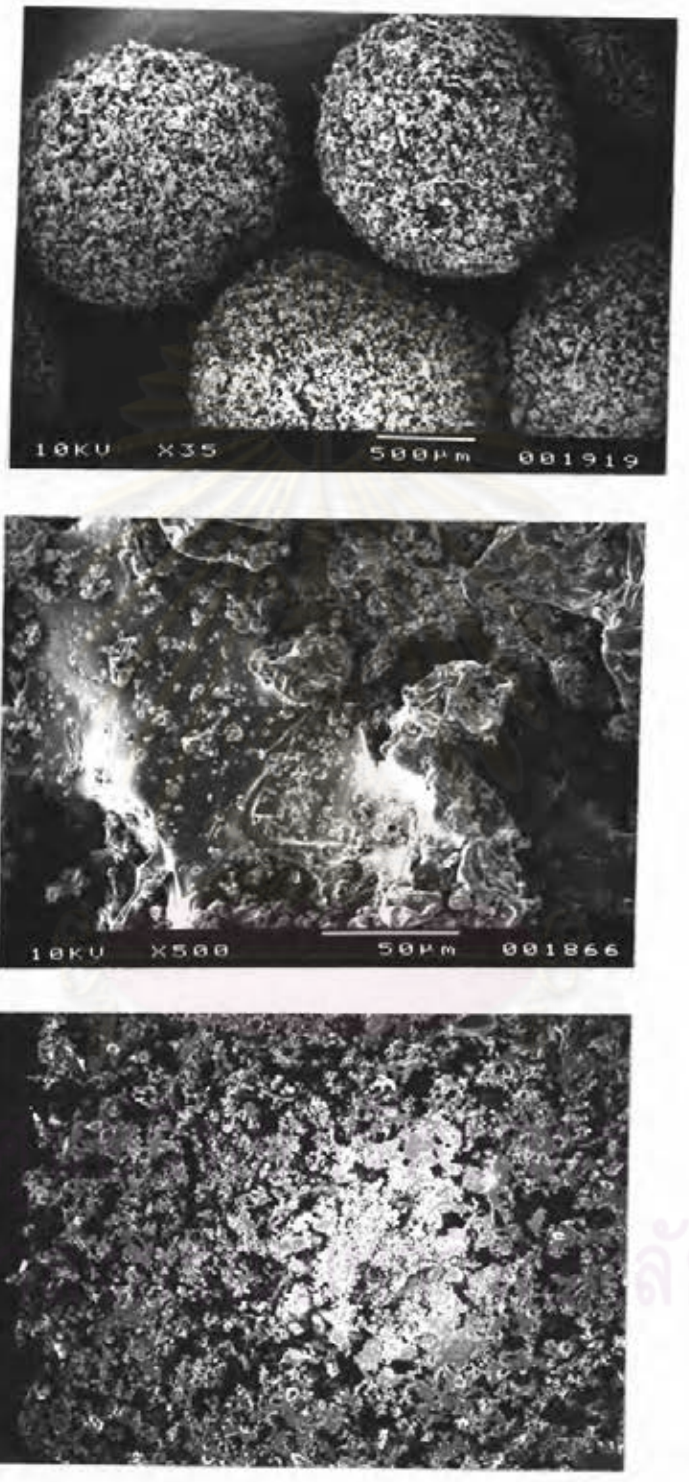
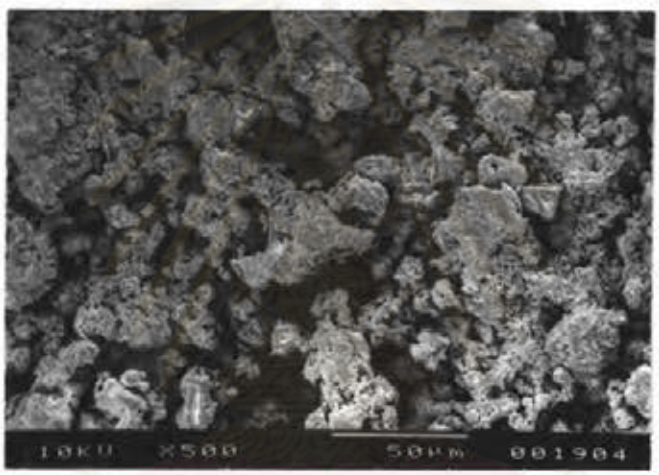
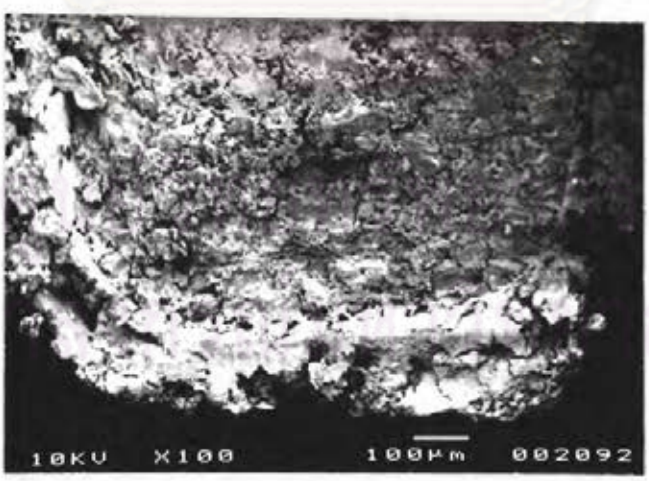


Figure 89 Photomicrographs of coated pellets formulation 61 (Key: A coated beads x 35 , B coating surface x 500 , C cross-section x 100)

A



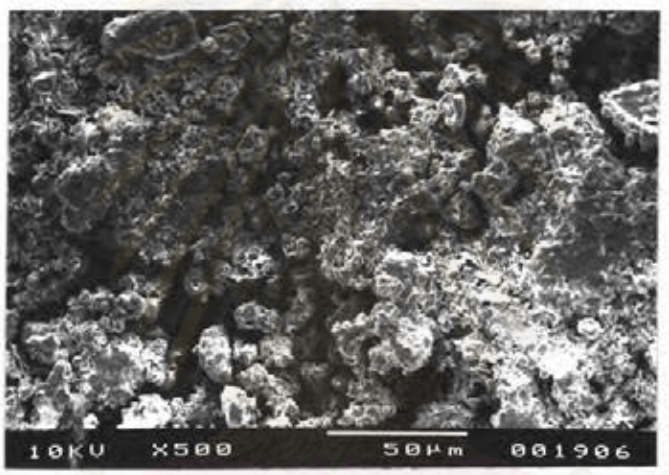
B

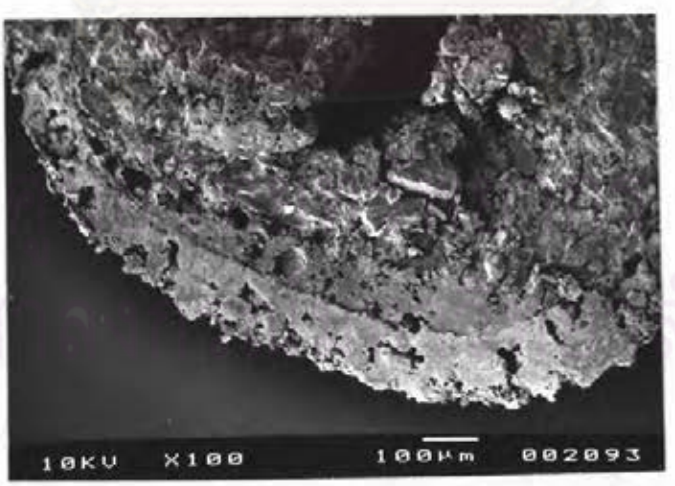


C

Figure 90 Photomicrographs of coated pellets formulation 62 lot.1 (Key: A coated beads x 35 , B coating surface x 500 , C cross-section x 100)

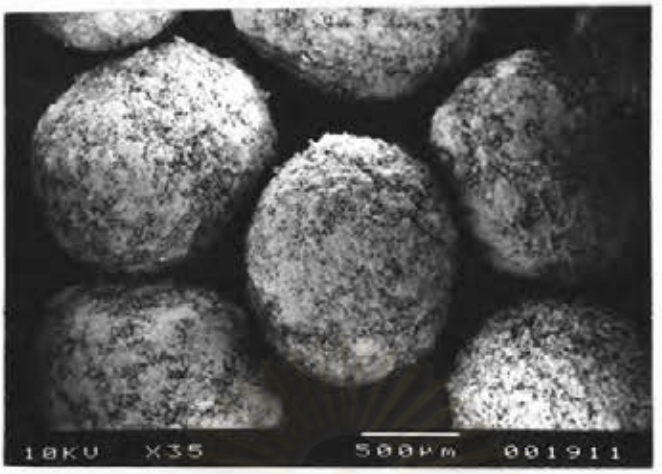
A



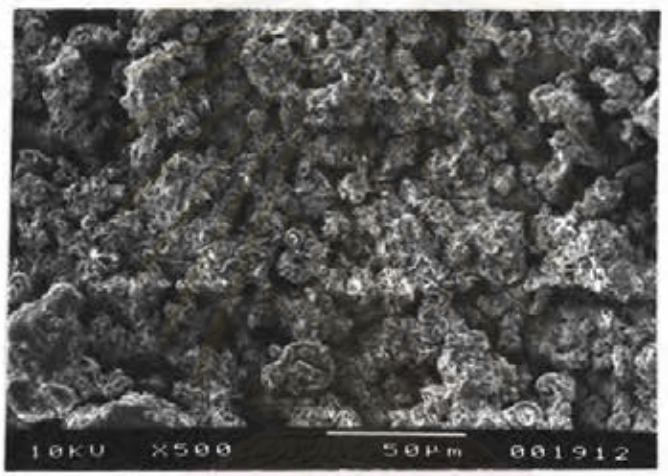


C

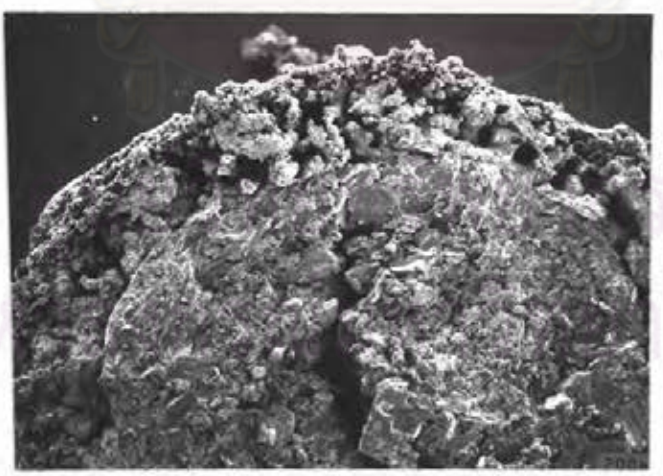
Figure 91 Photomicrographs of coated pellets formulation 62 lot.2 (Key: A coated beads x 35 , B coating surface x 500 , C cross-section x 100)



A

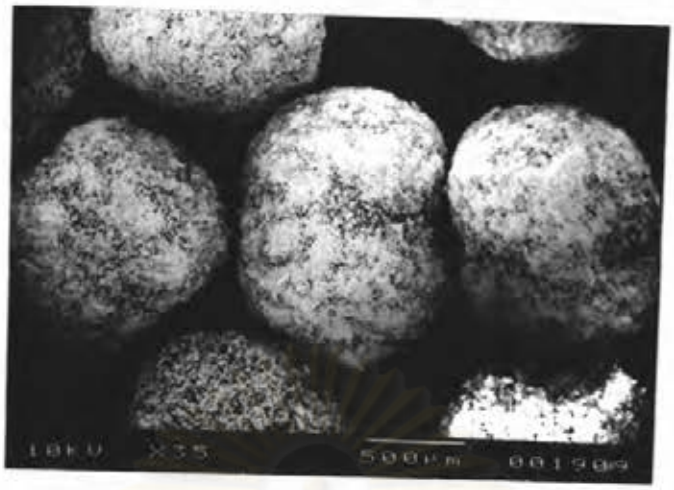


B

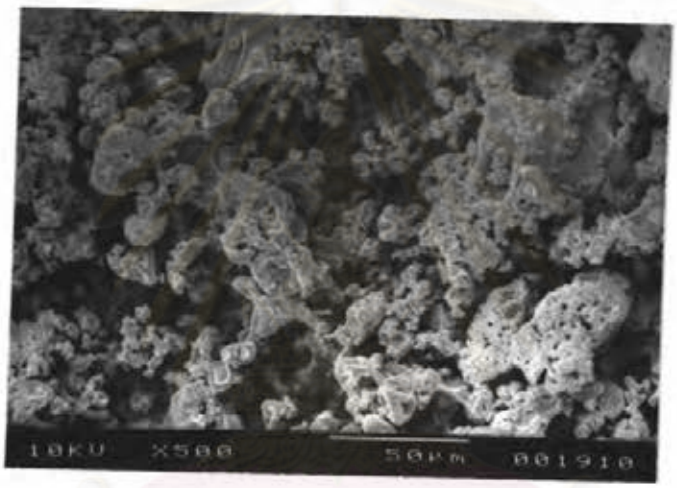


C

Figure 92 Photomicrographs of coated pellets formulation 62 lot.3 (Key: A coated beads x 35 , B coating surface x 500 , C cross-section x 100)



A

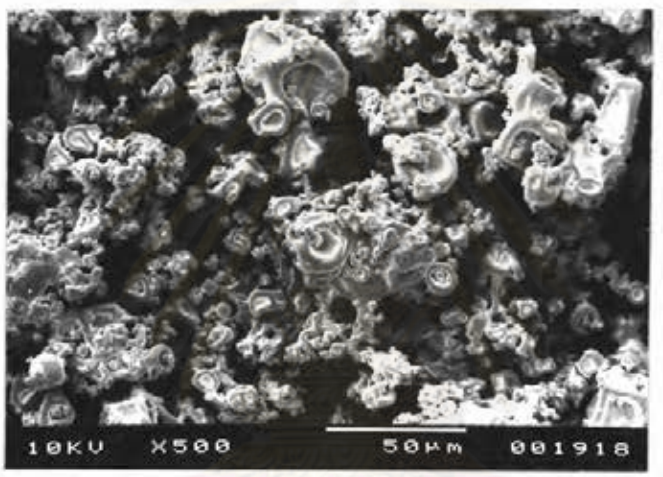


B

C

Figure 93 Photomicrographs of coated pellets formulation 63 (Key: A coated beads x 35 , B coating surface x 500 , C cross-section x 100)

A

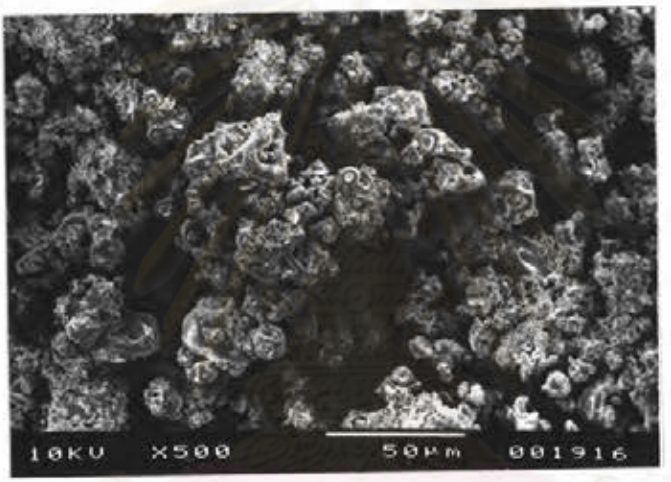


B

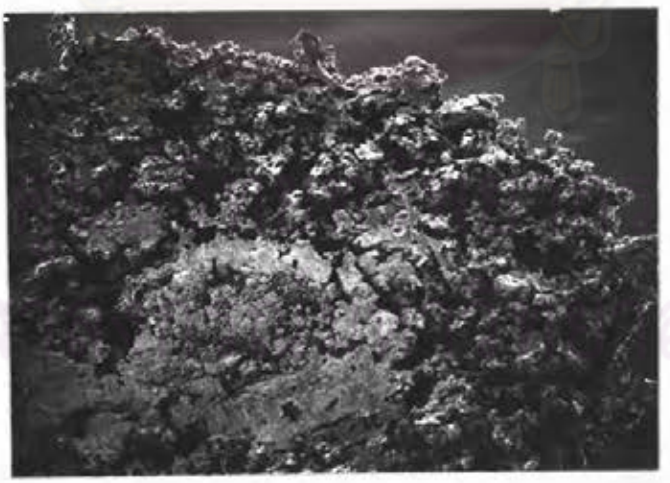
C

Figure 94 Photomicrographs of coated pellets formulation 64 (Key: A coated beads x 35 , B coating surface x 500 , C cross-section x 100)

A



B



C

Figure 95 Photomicrographs of coated pellets formulation 65 (Key: A coated beads x 35 , B coating surface x 500 , C cross-section x 100)

Dissolution study evaluation of formulations 58-65

From the release data of formulations 58 to 61, it was found that as the volume of the outercoating solution was increased, the release rate was decreased (Figure 87 Tables 60-61).

Comparison of the release rate among formulations 58-61 with the USP XXII requirement for propranolol hydrochloride extented release capsules, the release profile of formulation 59 was found to be higher than USP XXII standard while the release of formulation 60 was lower than USP XXII requirement. Therefore, the volume of outercoating solution between 1000-1500 ml. were expected to be suitable for outercoating in order to have the release rate conformed to the USP XXII standard.

The release at 1.5 hr of formulations 62 to 65 were 27.07, 24.40, 24.98 and 21.19 % (Figure 96 Tables 62-64), respectively. The release rate of them were in the limit of the USP XXII standrad except the release data at 24 hr of formulation 63, 64 and 65 which were lower than of the USP XXII standard (Table 30). Thus, formulation 62 was chosen to be the most suitable formulation in compliance with the USP standard. After that, three experimental formulations 62 were repeated in order to observe the reproducibility and variation of coating process, which might affect the release pattern as shown in Figure 97.

Table 30 Comparison among USP XXII Requirement and Three Lots of Formulation 62

TIME (hr.)	% RELEASE			
	USP range	62 lot 1	62 lot 2	62 lot 3
1.5	< 30	27.07	27.01	27.21
4	35-60	54.01	54.20	53.89
8	55-80	73.21	73.69	73.02
14	70-95	80.09	80.19	80.29
24	81-110	81.15	81.69	81.03

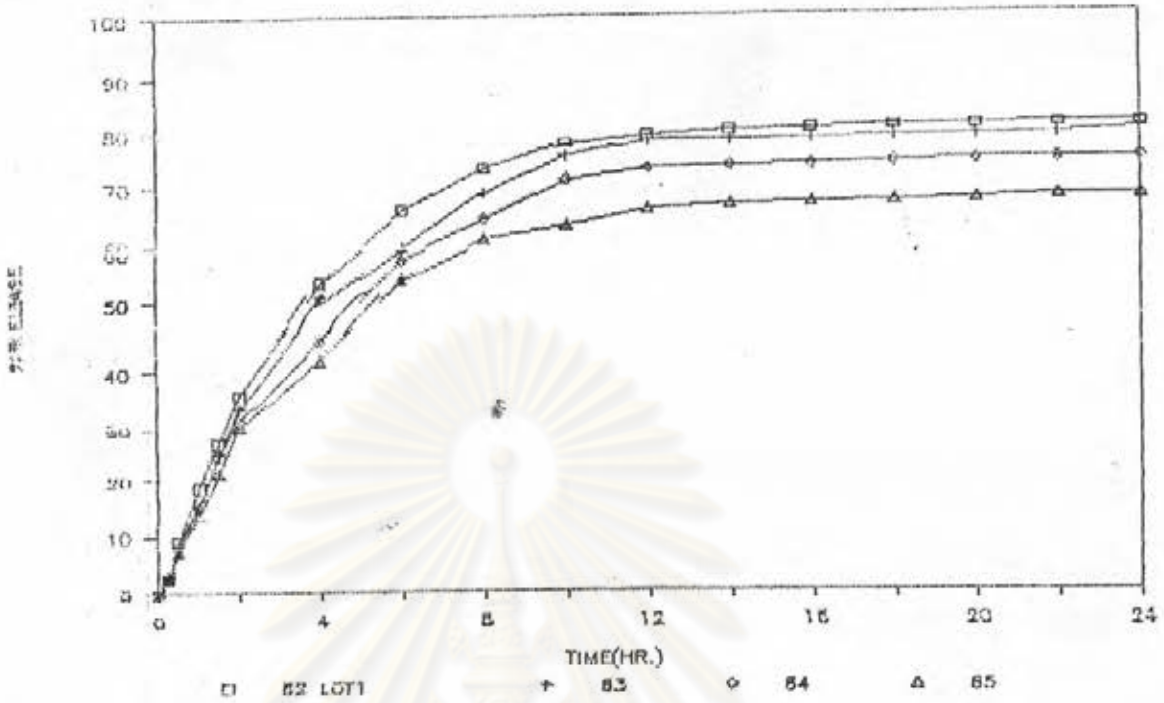


Figure 96 Release profile of coated pellets formulation 62-65 in pH change method

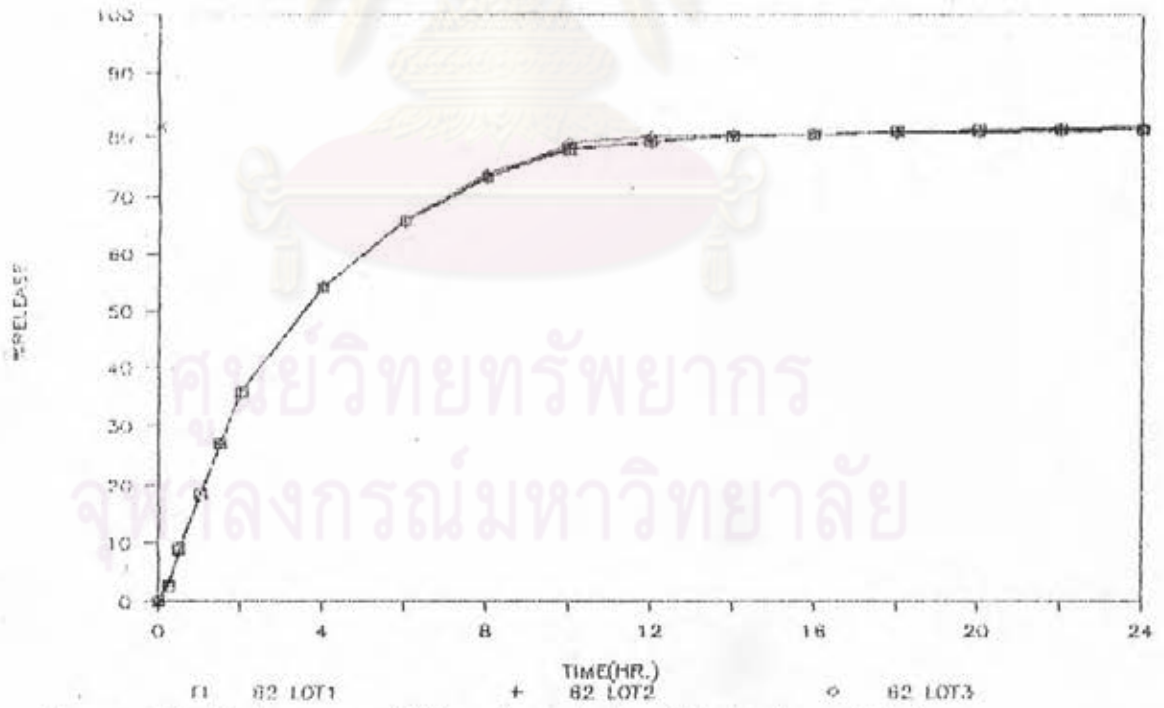


Figure 97 Release profile of coated pellets formulation 62 lot1 - 62 lot3 in pH change method