

CHAPTER III

RESULTS

1. Preliminary Investigation on Suitable Coating Conditions

Suitable coating conditions were investigated by coating theophylline granules with aqueous polymeric coating which had composition as previously presented in Table 3 and 4. The suitable coating conditions using top spray method was previously described in Table 5.

The theophylline granules of various sizes (16/18, 18/20m 20/25 and 25/30 mesh) were coated with various levels of Surelease[®] and Eudragit[®] NE 30D. The levels of coating were calculated on the basis of Surelease[®] and Eudragit[®] NE 30D content in aqueous polymeric coating used and were shown as percent of polymer coated based on weight of granules. The percent coating levels of Surelease[®] and Eudragit[®] NE 30D are presented in Table 8 and 9.

Table 8 The Percent Coating Levels of Surelease[®] on Granules of Different Sizes.

Size of Granules (mesh)	% Coating Levels of Surelease [®]			
16/18	1.92	3.05	3.87	6.29
18/20	2.04	3.29	7.61	9.00
20/25	4.48	3.86	8.39	12.12
25/30	7.84	12.18	13.40	17.05

Table 9 The Percent Coating Levels of Eudragit® NE 30D on Granules of Different Sizes.

Size of Granules (mesh)	% Coating Levels of Eudragit® NE 30D			
	16/18	2.51	5.96	8.53
18/20	4.04	6.75	10.93	19.12
20/25	5.56	11.46	15.00	20.76
25/30	8.83	14.57	17.68	22.37

2. Physical Properties of Theophylline Granules

2.1 Morphology of Theophylline Granules

The theophylline granules were examined using scanning electron microscope (SEM) at different magnifications (x35 and x500). The cross-section of theophylline granules was also observed for the film morphology at x2000 magnification.

2.1.1 Uncoated Granules

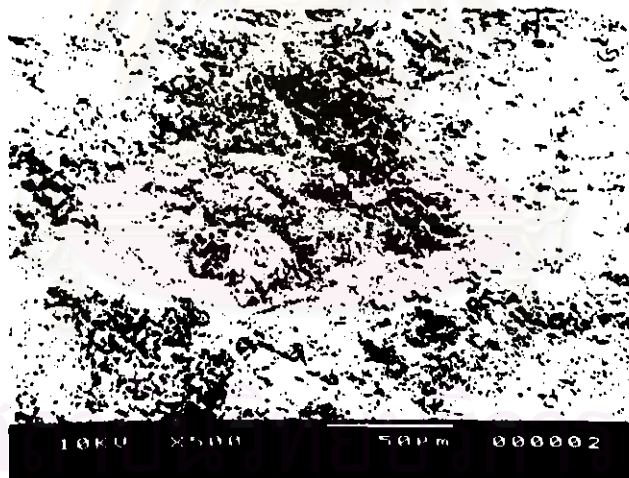
The surface and cross-sectioned morphology of uncoated granules of various sizes are shown in Figures 9-12 representing 16/18 mesh size, 18/20 mesh size, 20/25 mesh size and 25/30 mesh size respectively. All uncoated granules of various sizes exhibited rough surface and irregular shape

2.1.2 Surelease® Coated Granules

The surface and cross-sectioned morphology of theophylline granules of various sizes coated with various percent coating levels of



A



B

Figure 9. The photomicrographs of uncoated theophylline granules of 16/18 mesh size (Key : A. theophylline granules x35, B. theophylline surface x500)

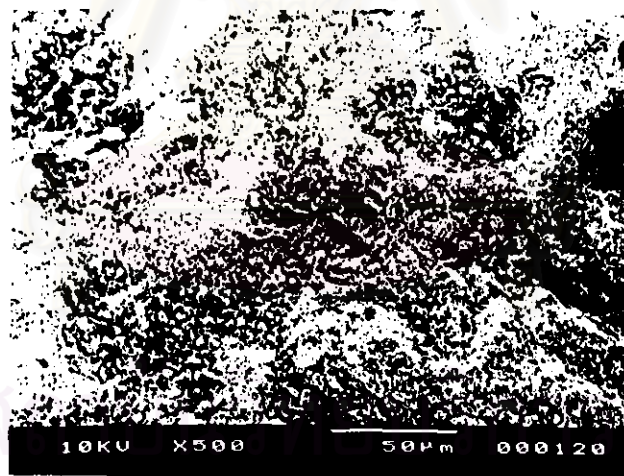
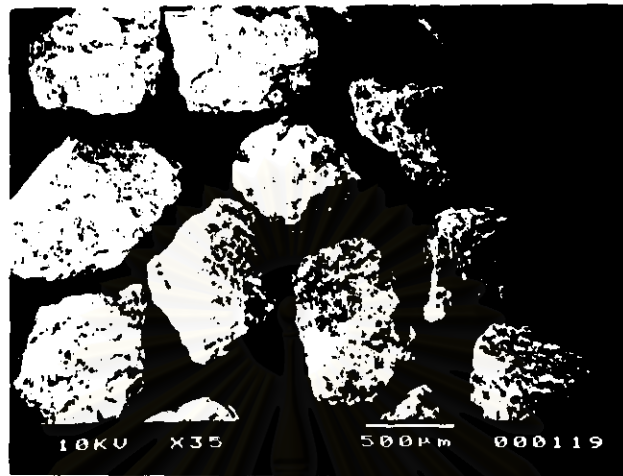


Figure 10 The photomicrographs of uncoated theophylline granules of 18/20 mesh size (Key : A. theophylline granules x35, B. theophylline surface x500)

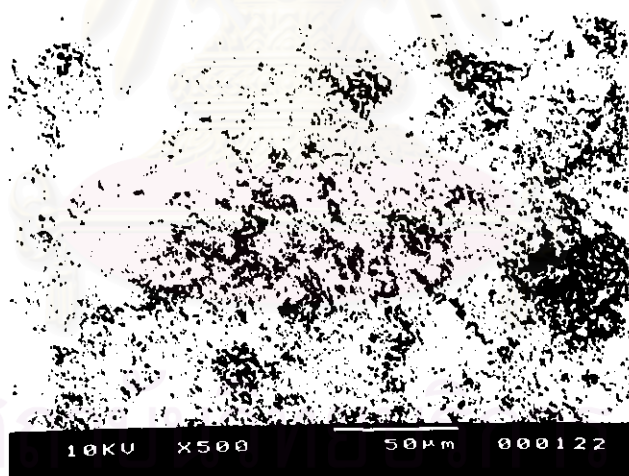


Figure 11 The photomicrographs of uncoated theophylline granules of 20/25 mesh size (Key : A. theophylline granules x35, B. theophylline surface x500)

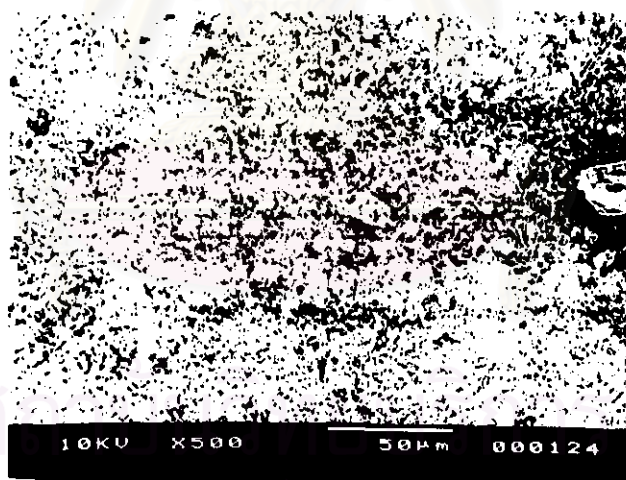
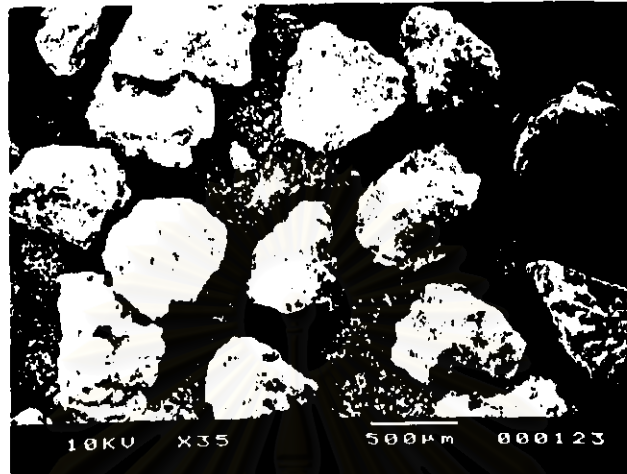


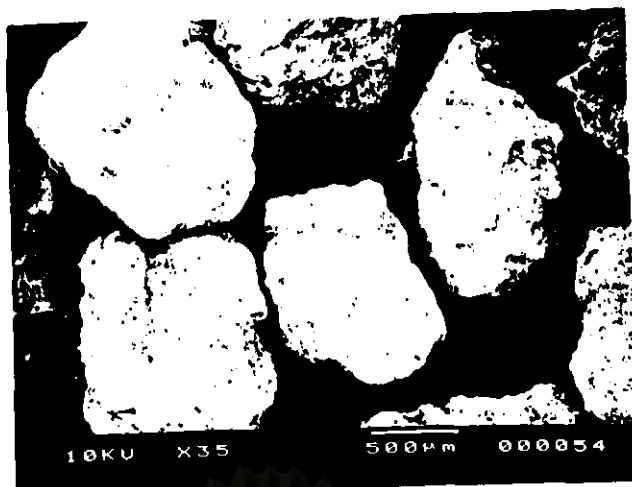
Figure 12 The photomicrographs of uncoated theophylline granules of 25/30 mesh size (Key : A. theophylline granules x35, B. theophylline surface x500)

Surelease[®] are shown in Figures 13-28. Figures 13-16 illustrate granules of 16/18 mesh size which were coated with 1.92%, 3.05%, 3.87% and 6.29% coating levels of Surelease[®] respectively. Figures 17-20 shows granules of 18/20 mesh size which were coated with 2.04%, 3.29%, 7.61 and 9.00% coating levels respectively. Figures 21-24 are granules of 20/25 mesh size which were coated with 2.48%, 3.86%, 8.39% and 12.12% coating levels respectively whereas Figures 25-28 are granules of 25/30 mesh size which were coated with 7.84%, 12.18%, 13.40% and 17.05% coating levels respectively.

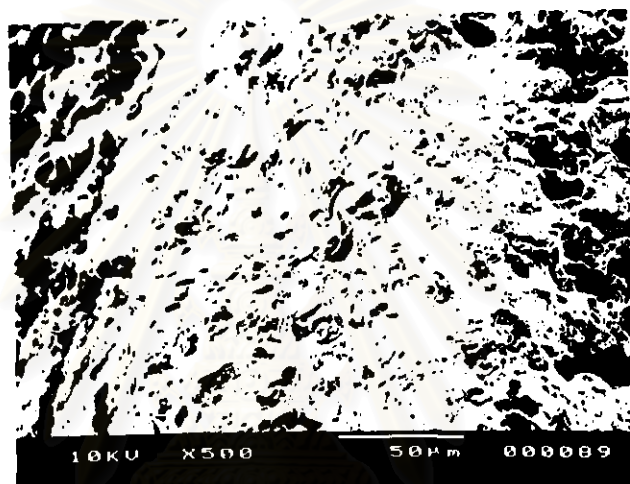
The photomicrographs of all Surelease[®] coated granules were notable that granules coated with lower percent coating level exhibited thinner film than those with higher percent coating level of Surelease[®]. Edge and corner of theophylline granules were decreased with the increasing of the percent coating level of Surelease[®].

2.1.3 Eudragit[®] NE 30D Coated Granules

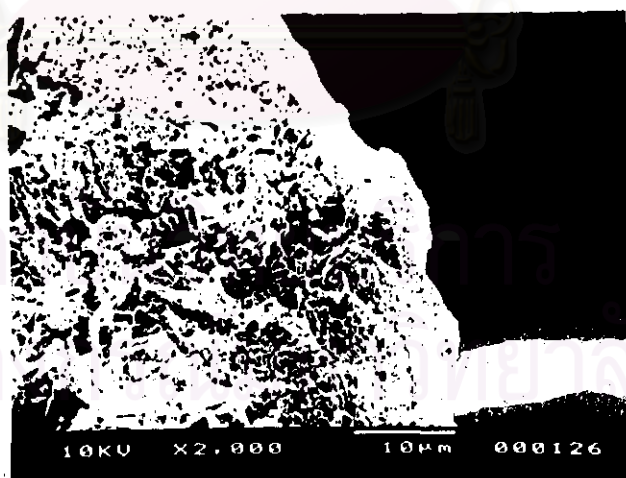
The surface and cross-sectioned morphology of theophylline granules of various sizes coated with various percent coating levels of Eudragit[®] NE 30D are shown in Figures 29-44. Figures 29-32 are granules of 16/18 mesh size which were coated with 2.51%, 5.96%, 8.53% and 14.76% coating levels of Eudragit[®] NE 30D respectively. Figures 33-36 are granules of 18/20 mesh size which were coated with 4.04%, 6.75%, 10.93% and 19.12% coating levels respectively. Figures 37-40 are granules of 20/25 mesh size which were coated with 5.56%, 11.46%, 15.00% and 20.76% coating levels respectively whereas Figures 41-44 are granules of 25/30 mesh size which were coated with 8.83%, 14.57%, 17.68% and 22.37% coating levels respectively.



A



B



C

Figure 13 The photomicrographs of 1.92% Surelease[®] coated granules of 16/18 mesh size (Key : A.coated granules x35, B. coated surface x500, C. cross-section x2000)

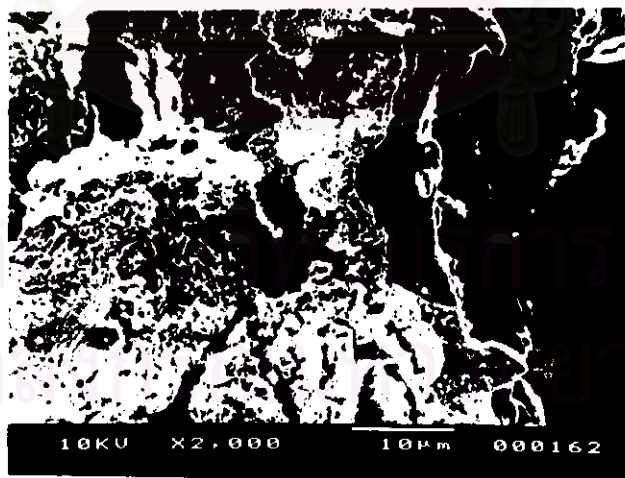
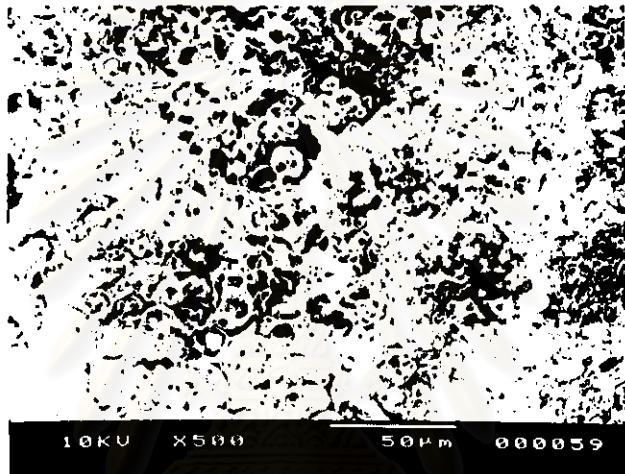
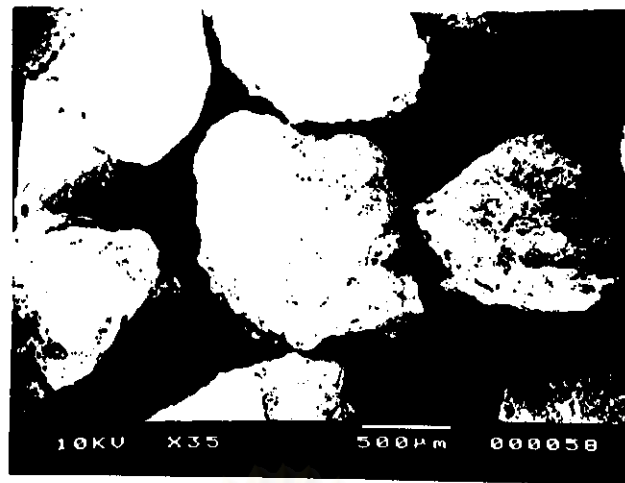
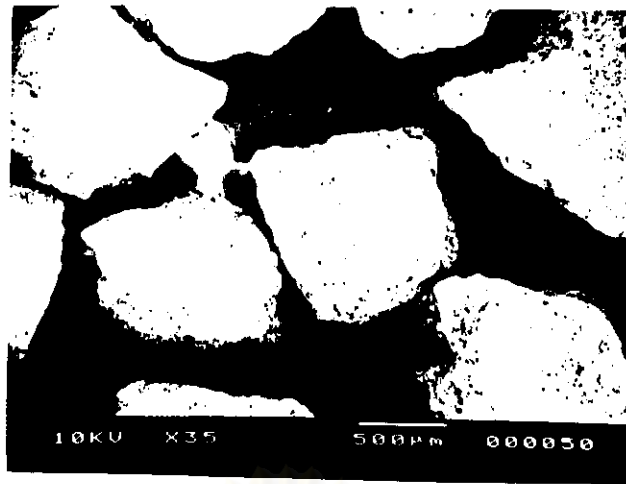
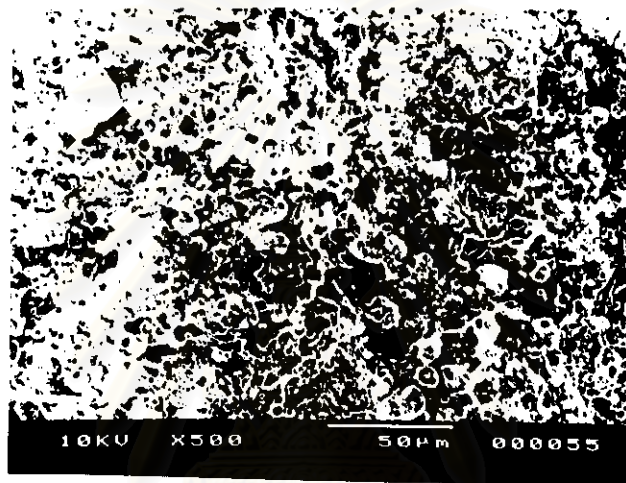


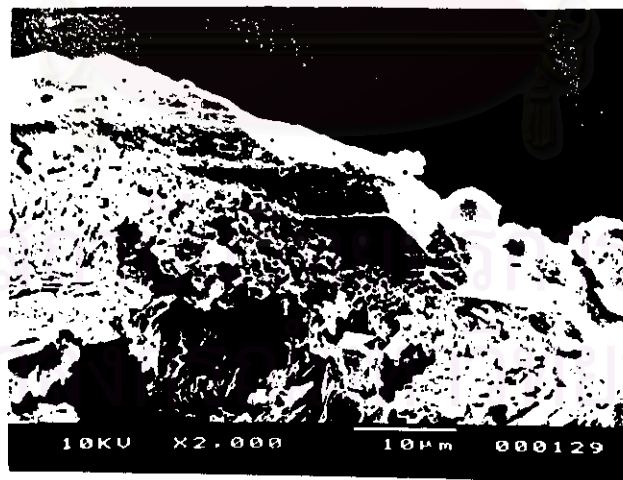
Figure 14 The photomicrographs of 3.05% Surelease[®] coated granules of 16/18 mesh size (Key : A coated granules x35, B. coated surface x500, C. cross-section x2000)



A

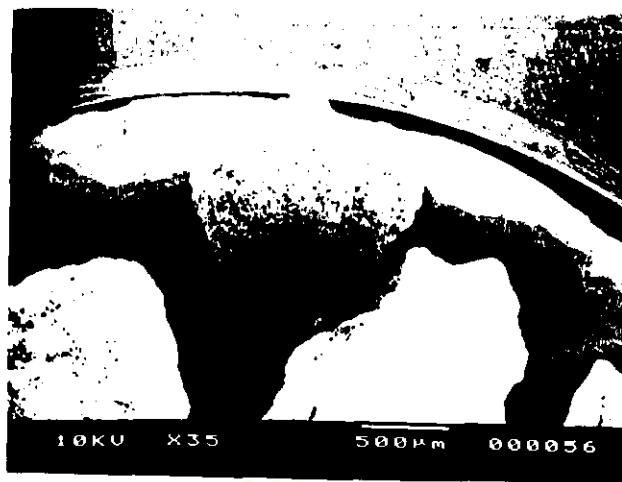


B

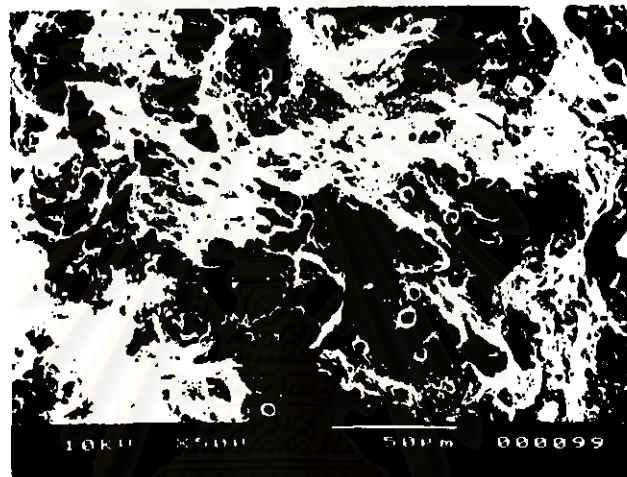


C

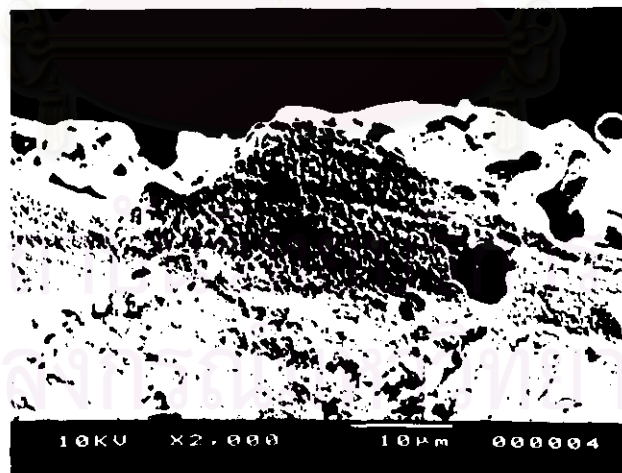
Figure 15 The photomicrographs of 3.87% Surelease[®] coated granules of 16/18 mesh size (Key : A coated granules x35, B. coated surface x500, C. cross-section x2000)



A



B



C

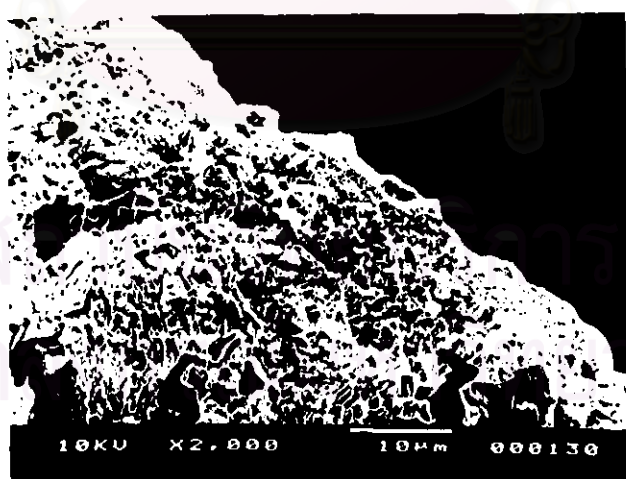
Figure 16 The photomicrographs of 6.29% Surelease[®] coated granules of 16/18 mesh size (Key : A coated granules x35, B. coated surface x500, C. cross-section x2000)



A

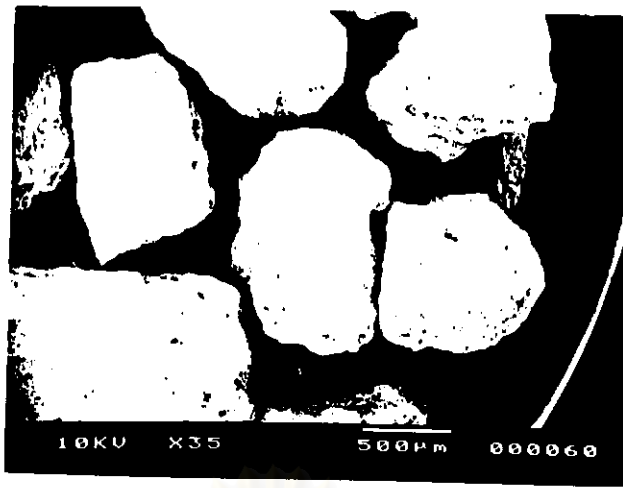


B

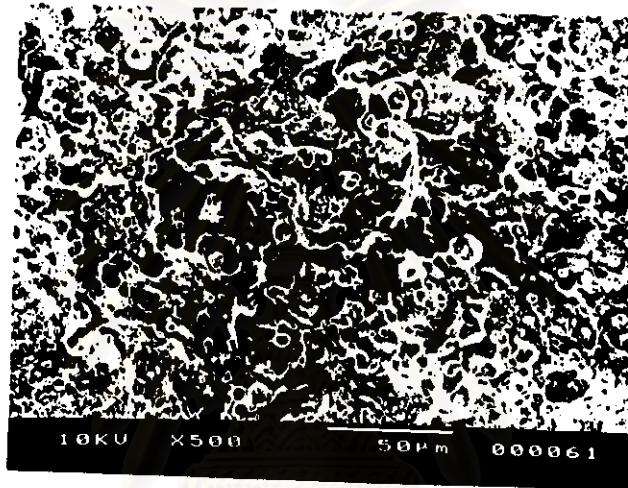


C

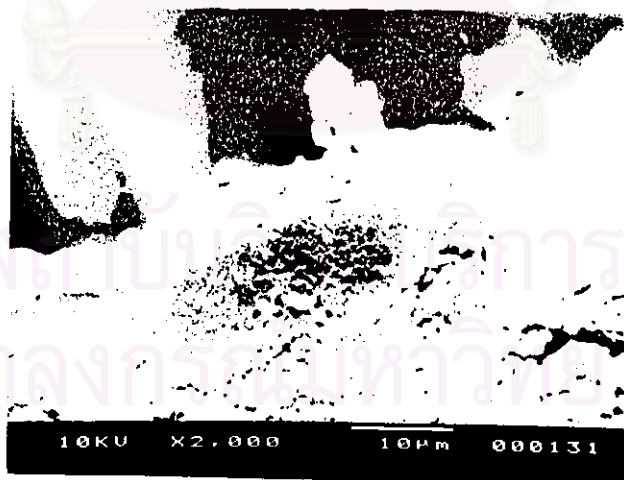
Figure 17 The photomicrographs of 2.04% Surelease[®] coated granules of 18/20 mesh size (Key : A coated granules x35, B. coated surface x500, C. cross-section x2000)



A

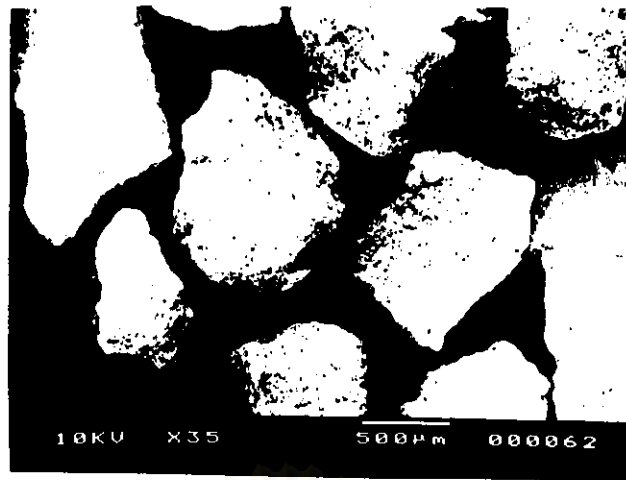


B

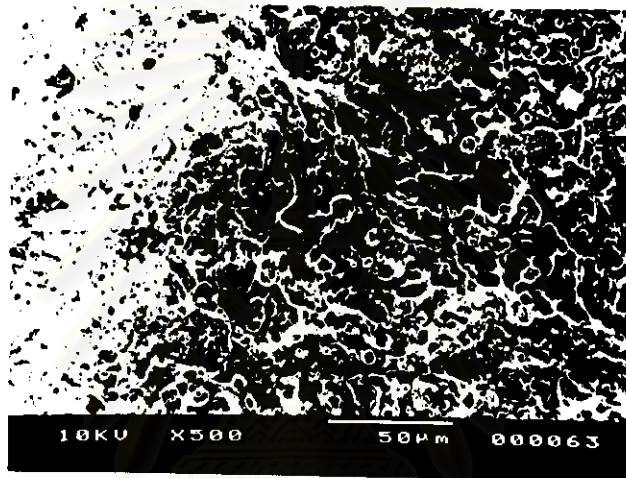


C

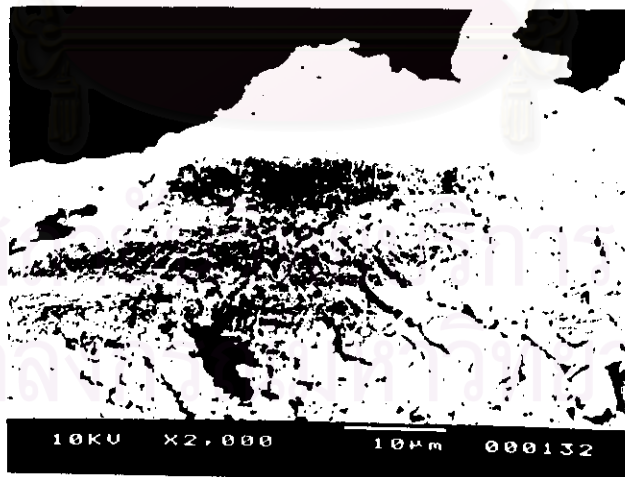
Figure 18 The photomicrographs of 3.29% Surelease[®] coated granules of 18/20 mesh size (Key : A coated granules x35, B. coated surface x500, C. cross-section x2000)



A



B

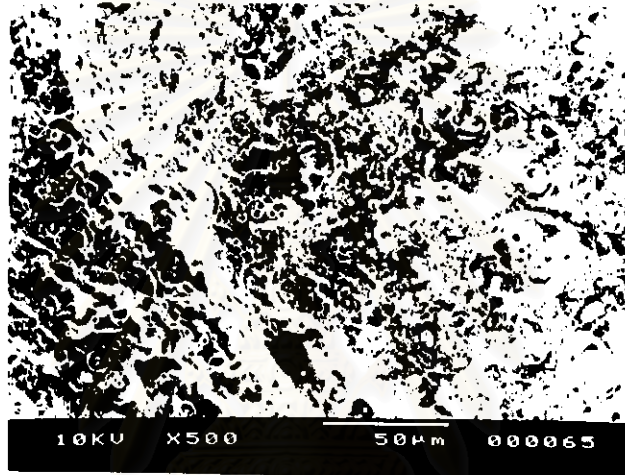


C

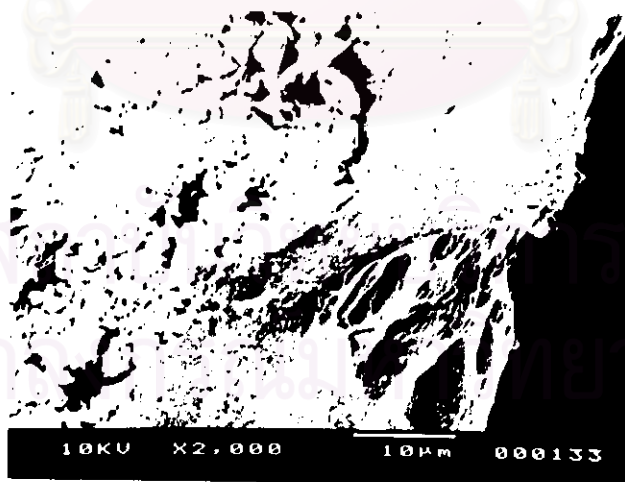
Figure 19 The photomicrographs of 7.61% Surelease[®] coated granules of 18/20 mesh size (Key : A coated granules x35, B. coated surface x500, C. cross-section x2000)



A

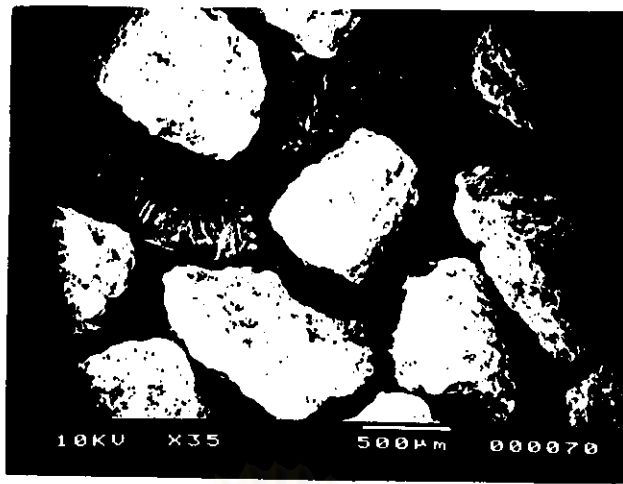


B

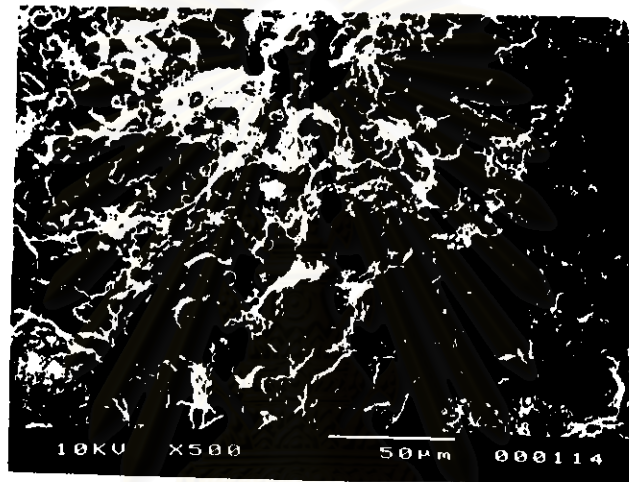


C

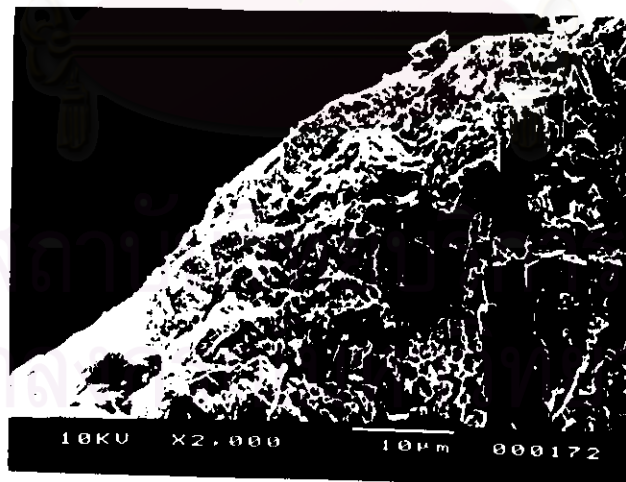
Figure 20 The photomicrographs of 9.00% Surelease[®] coated granules of 18/20 mesh size (Key : A coated granules x35, B. coated surface x500, C. cross-section x2000)



A

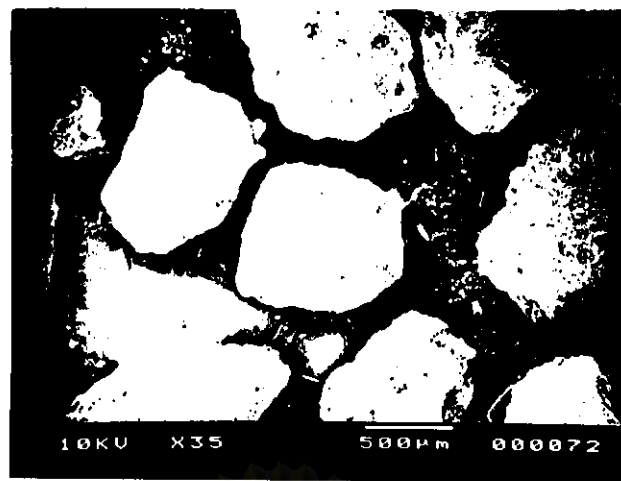


B

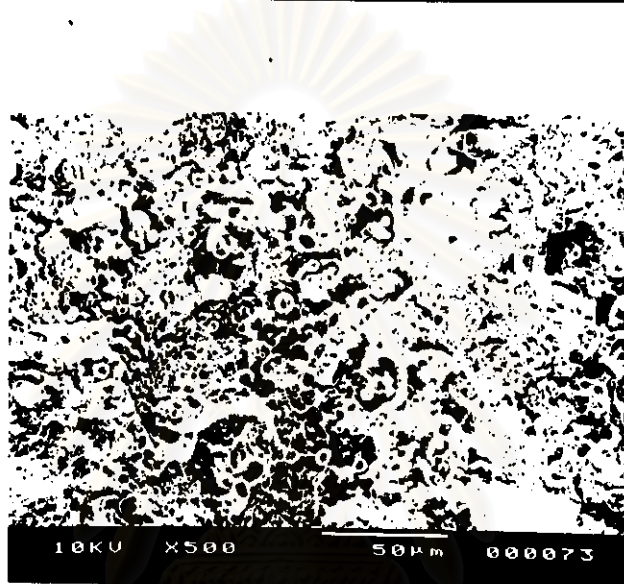


C

Figure 21 The photomicrographs of 2.48% Surelease[®] coated granules of 20/25 mesh size (Key : A coated granules x35, B. coated surface x500, C. cross-section x2000)



A



B



C

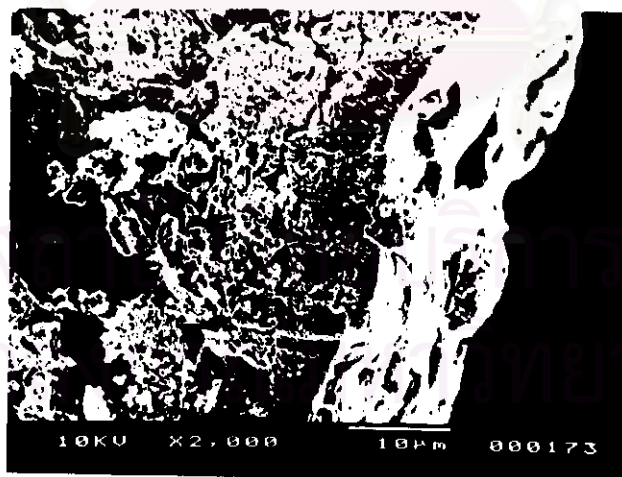
Figure 22 The photomicrographs of 3.86% Surelease[®] coated granules of 20/25 mesh size (Key : A coated granules x35, B. coated surface x500, C. cross-section x2000)



A

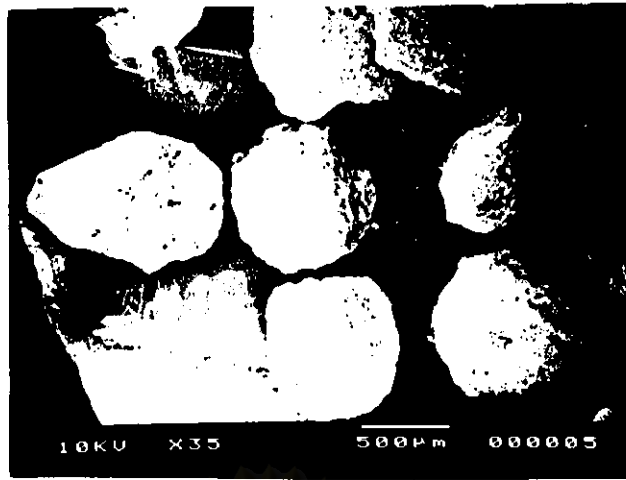


B

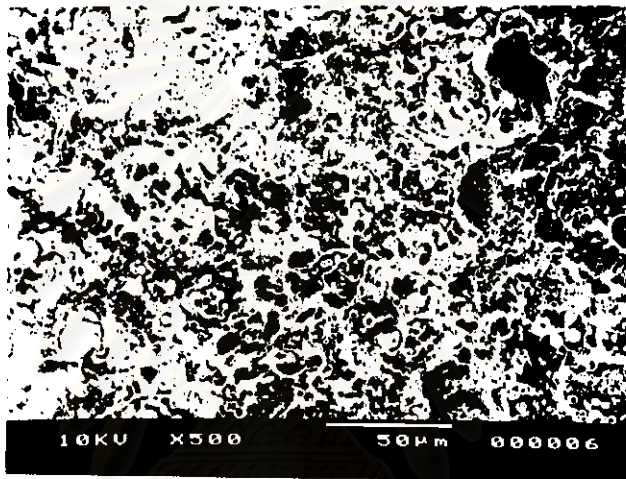


C

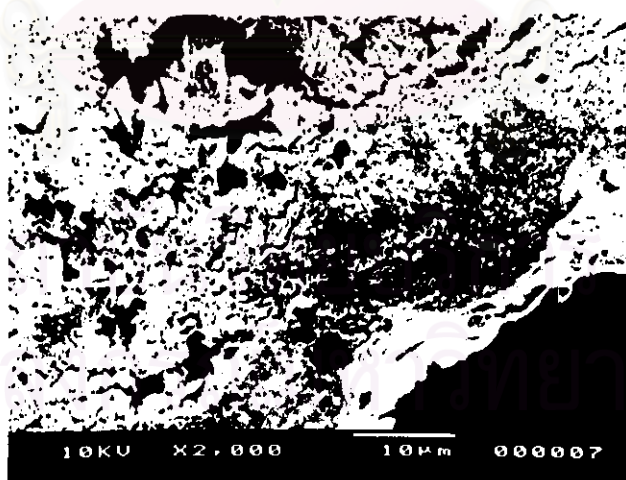
Figure 23 The photomicrographs of 8.39% Surelease[®] coated granules of 20/25 mesh size (Key : A coated granules x35, B. coated surface x500, C. cross-section x2000)



A

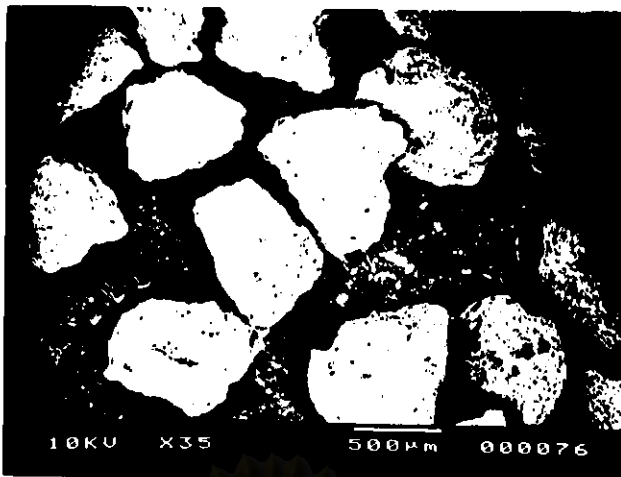


B

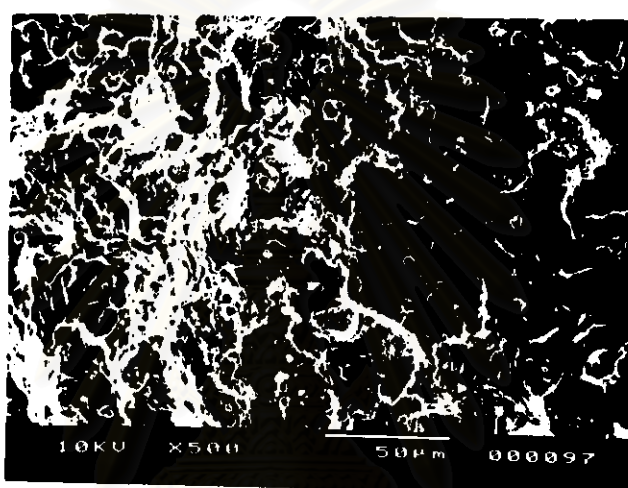


C

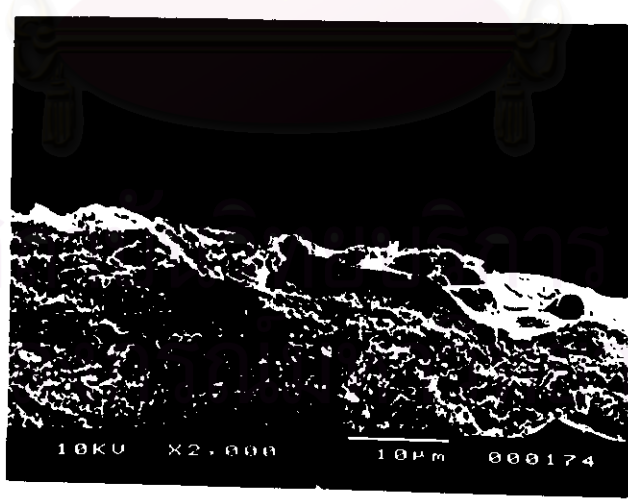
Figure 24 The photomicrographs of 12.12% Surelease[®] coated granules of 20/25 mesh size (Key : A coated granules x35, B. coated surface x500, C. cross-section x2000)



A



B

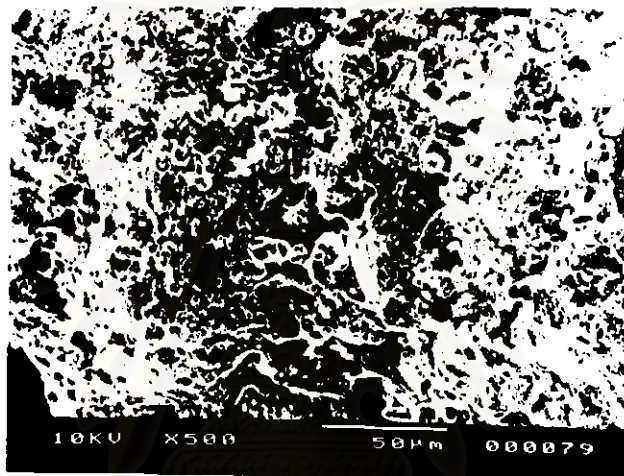


C

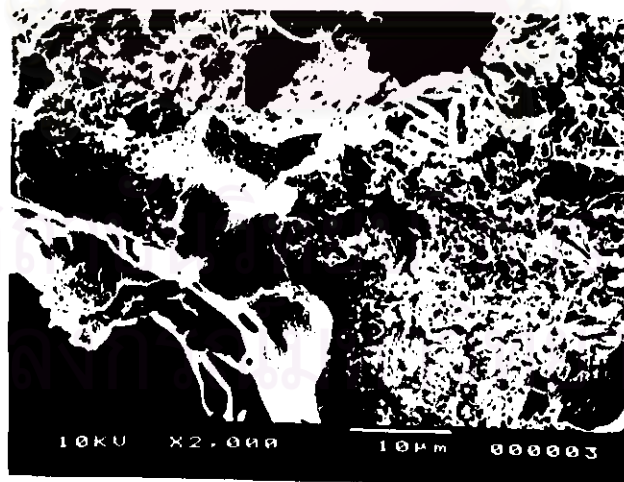
Figure 25 The photomicrographs of 7.84% Surelease[®] coated granules of 25/30 mesh size (Key : A coated granules x35, B. coated surface x500, C. cross-section x2000)



A



B



C

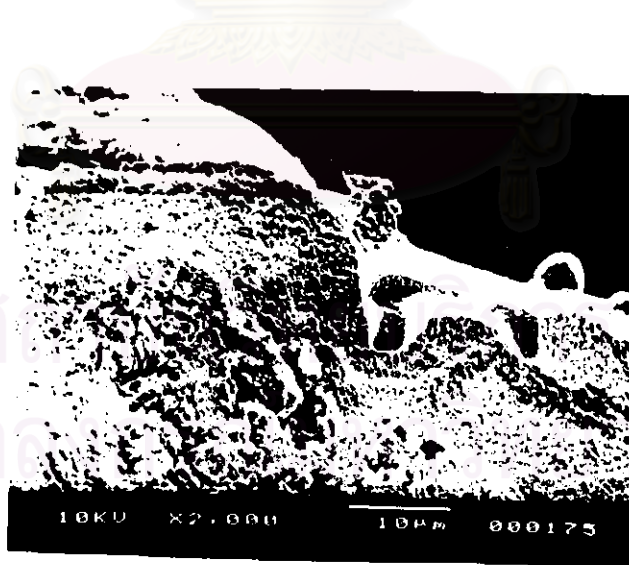
Figure 26 The photomicrographs of 12.18% Surelease[®] coated granules of 25/30 mesh size (Key : A coated granules x35, B. coated surface x500, C. cross-section x2000)



A



B

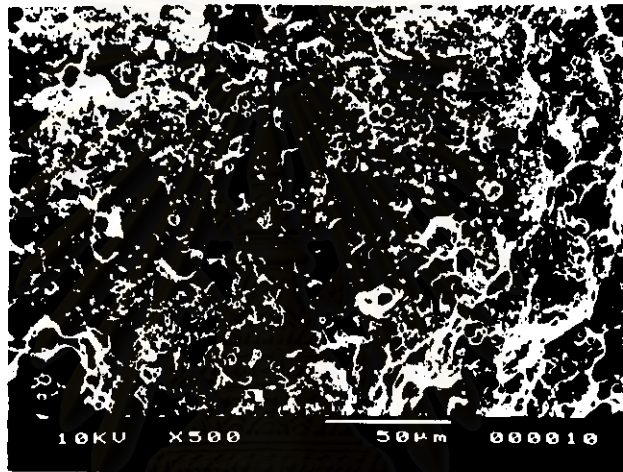


C

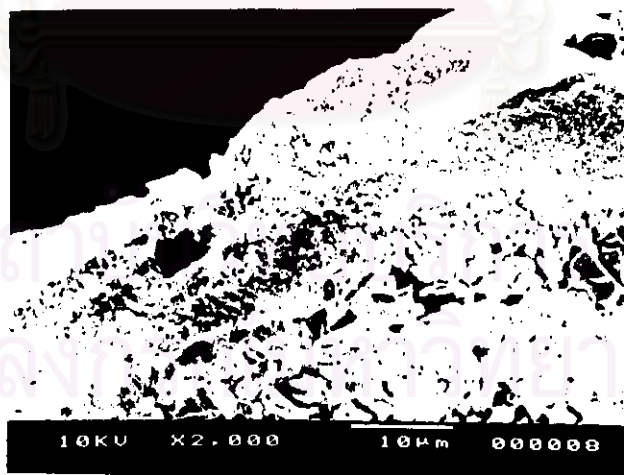
Figure 27 The photomicrographs of 13.40% Surelease[®] coated granules of 25/30 mesh size (Key : A coated granules x35, B. coated surface x500, C. cross-section x2000)



A

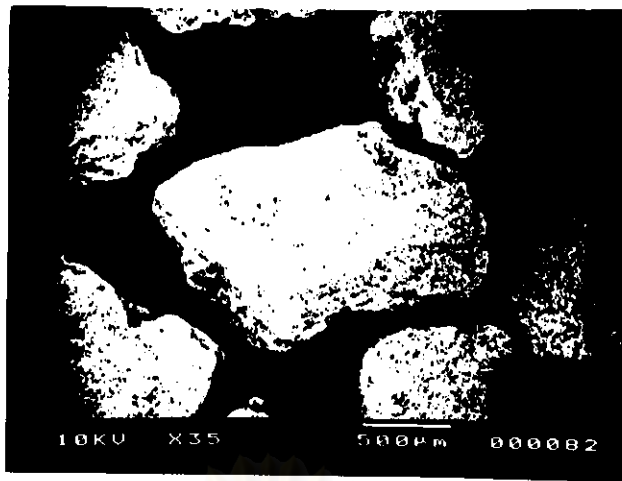


B

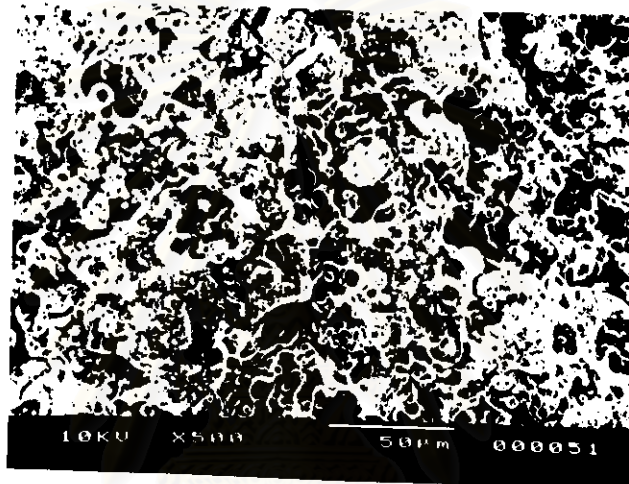


C

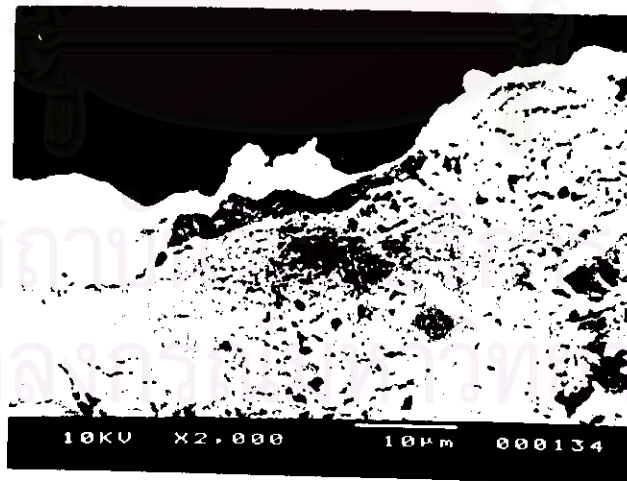
Figure 28 The photomicrographs of 17.05% Surelease[®] coated granules of 25/30 mesh size (Key : A coated granules x35, B. coated surface x500, C. cross-section x2000)



A



B



C

Figure 29 The photomicrographs of 2.51% Eudragit[®] NE 30D coated granules of 16/18 mesh size (Key : A coated granules x35, B. coated surface x500, C. cross-section x2000)

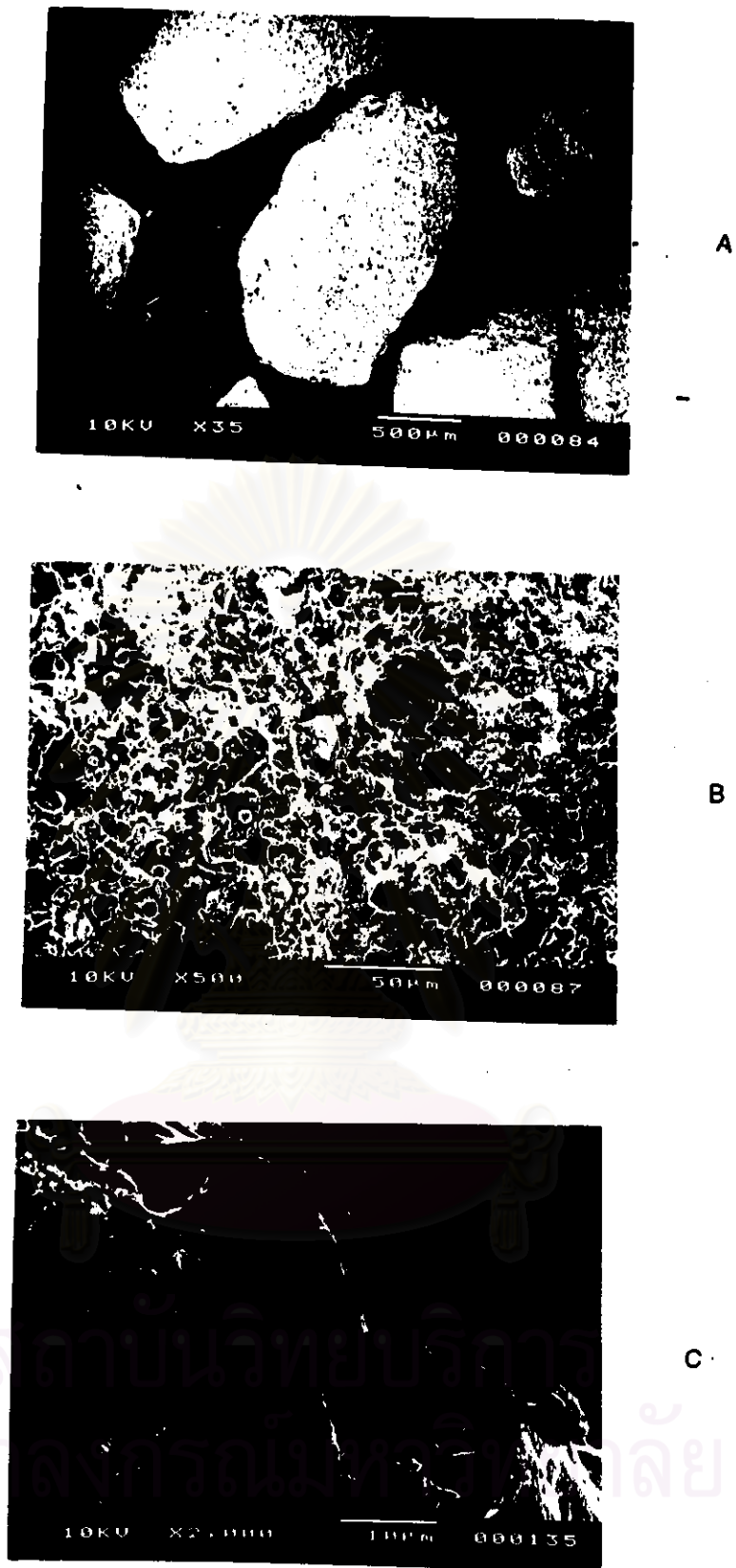
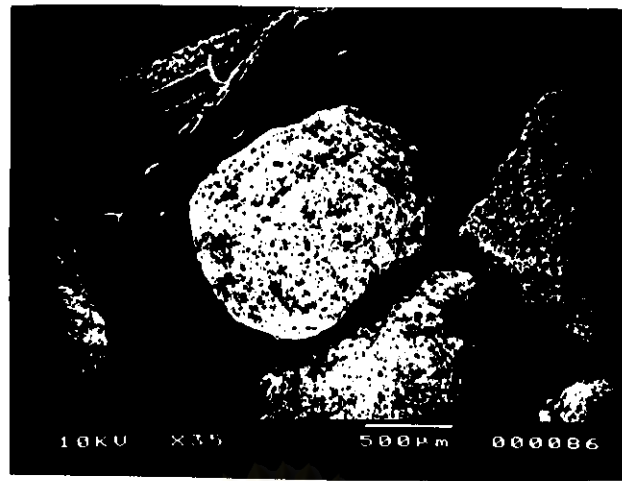


Figure 30 The photomicrographs of 5.96% Eudragit® NE 30D coated granules of 16/18 mesh size (Key : A coated granules x35, B. coated surface x500, C. cross-section x2000)



A

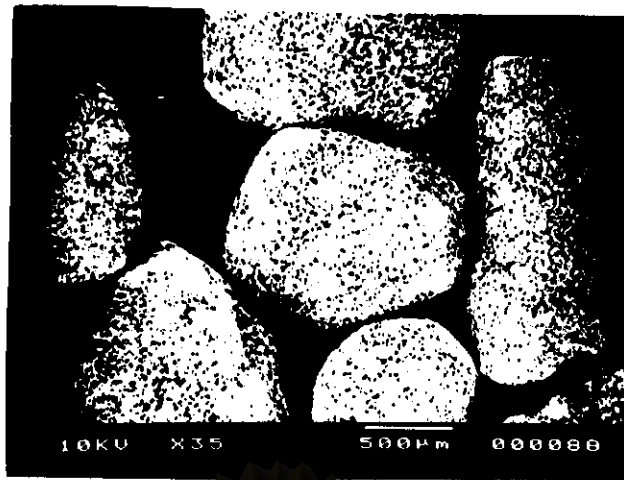


B

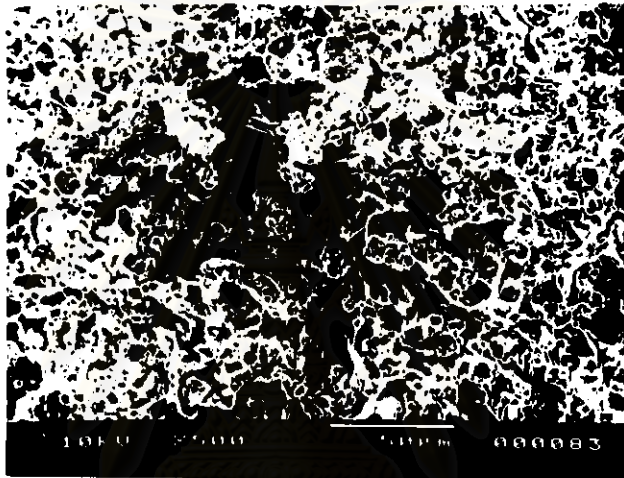


C

Figure 31 The photomicrographs of 8.53% Eudragit® NE 30D coated granules of 16/18 mesh size (Key : A coated granules x35, B. coated surface x500, C. cross-section x2000)



A

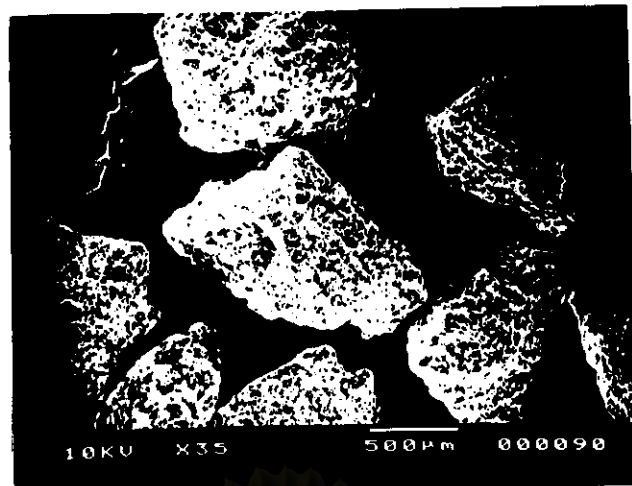


B

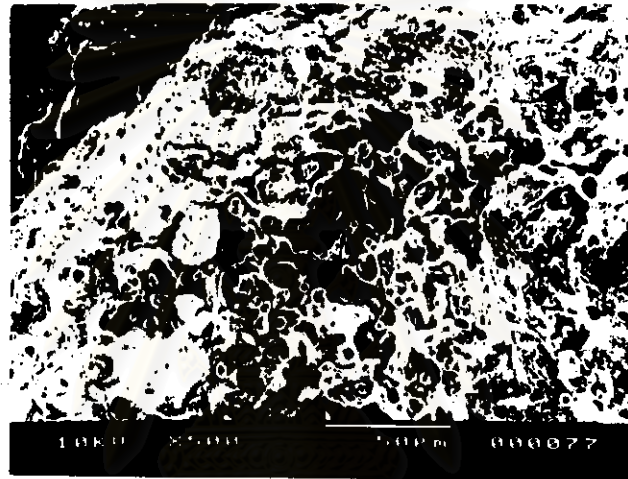


C

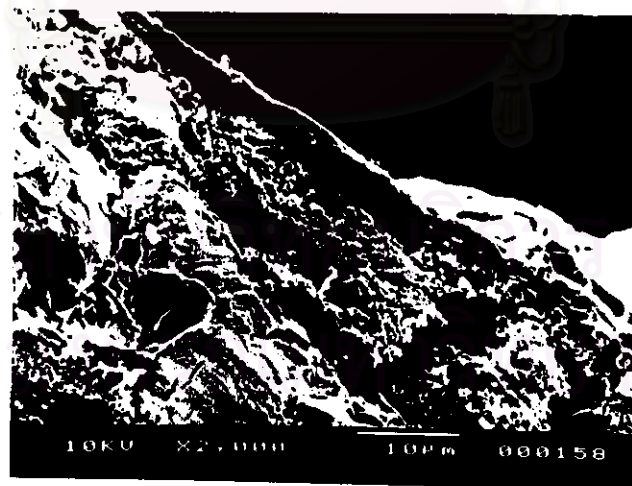
Figure 32 The photomicrographs of 14.76% Eudragit® NE 30D coated granules of 16/18 mesh size (Key : A coated granules x35, B. coated surface x500, C. cross-section x2000)



A



B



C

Figure 33 The photomicrographs of 4.04% Eudragit® NE 30D coated granules of 18/20 mesh size (Key : A coated granules x35, B. coated surface x500, C. cross-section x2000)

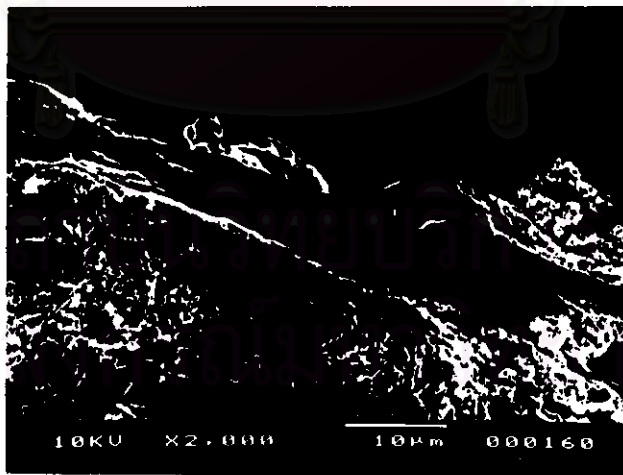
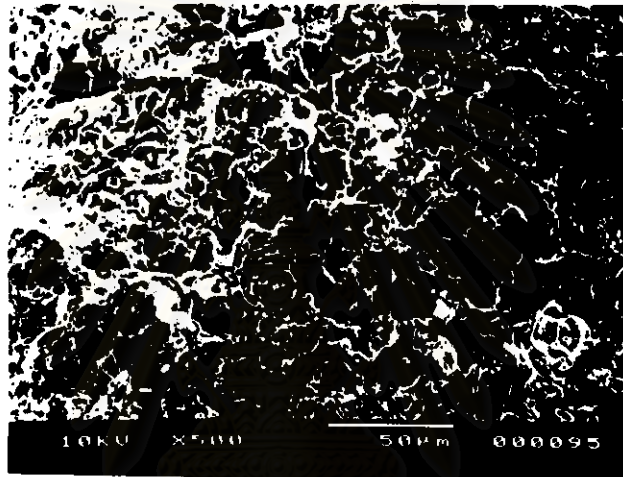
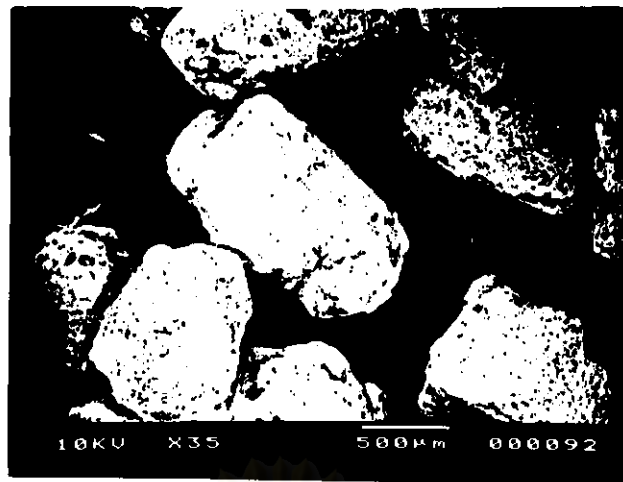
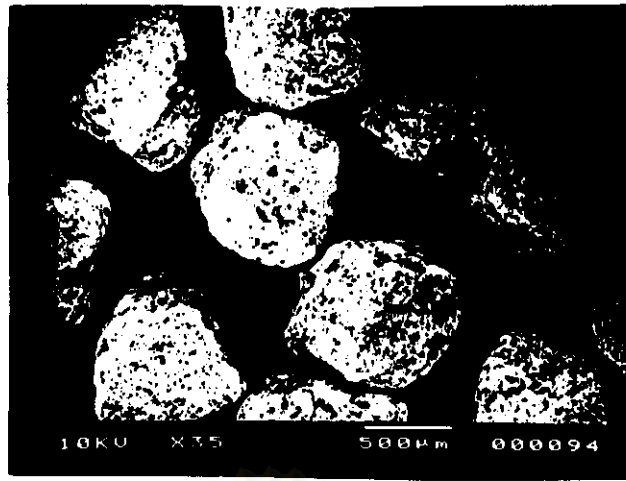
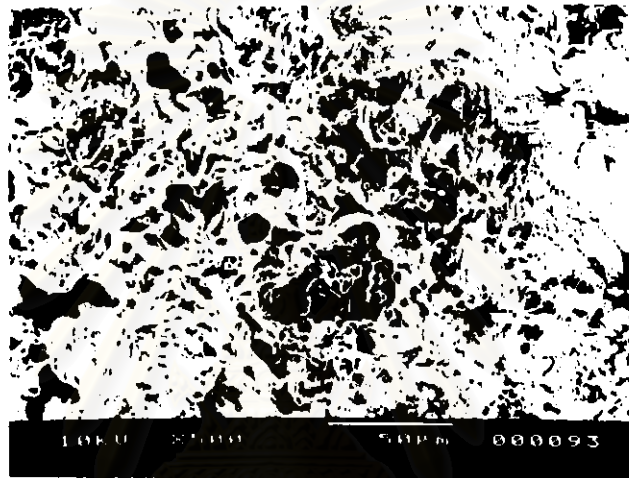


Figure 34 The photomicrographs of 6.75% Eudragit® NE 30D coated granules of 18/20 mesh size (Key : A coated granules x35, B. coated surface x500, C. cross-section x2000)



A

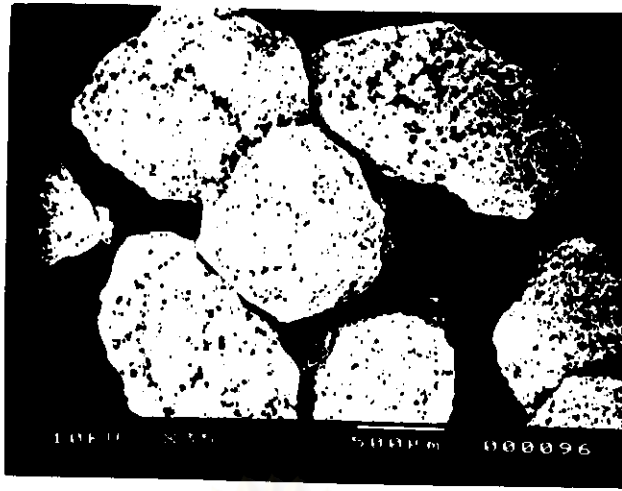


B



C

Figure 35 The photomicrographs of 10.93% Eudragit® NE 30D coated granules of 18/20 mesh size (Key : A coated granules x35, B. coated surface x500, C. cross-section x2000)



A



B

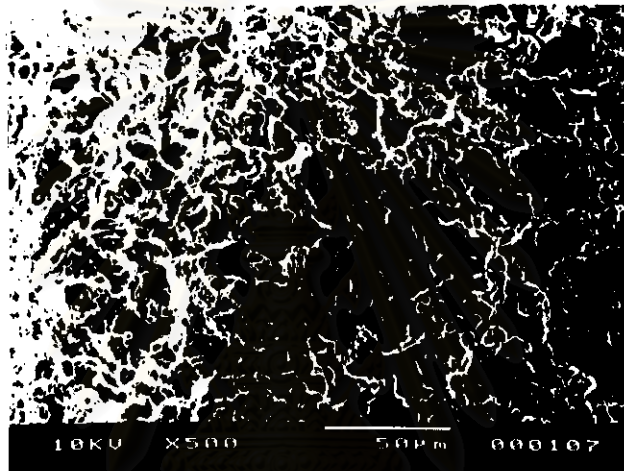


C

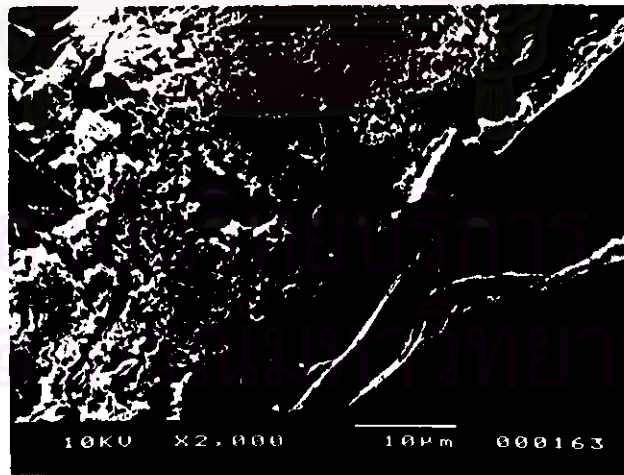
Figure 36 The photomicrographs of 19.12% Eudragit® NE 30D coated granules of 18/20 mesh size (Key : A coated granules x35, B. coated surface x500, C. cross-section x2000)



A



B

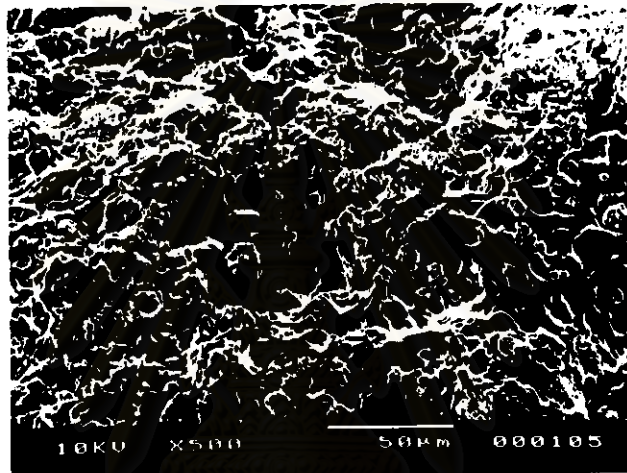


C

Figure 37 The photomicrographs of 5.56% Eudragit® NE 30D coated granules of 20/25 mesh size (Key : A coated granules x35, B. coated surface x500, C. cross-section x2000)



A

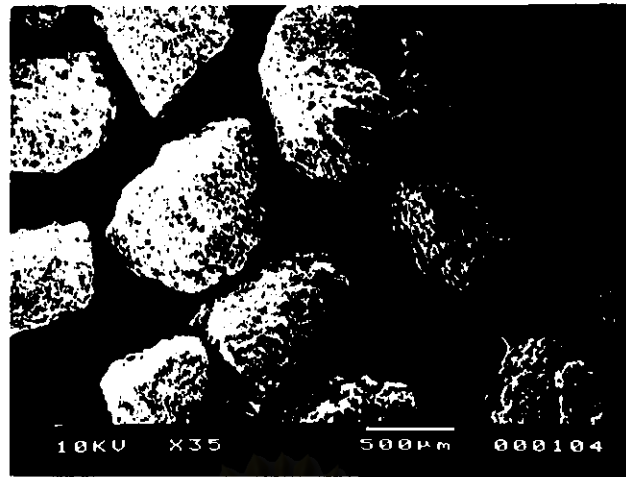


B

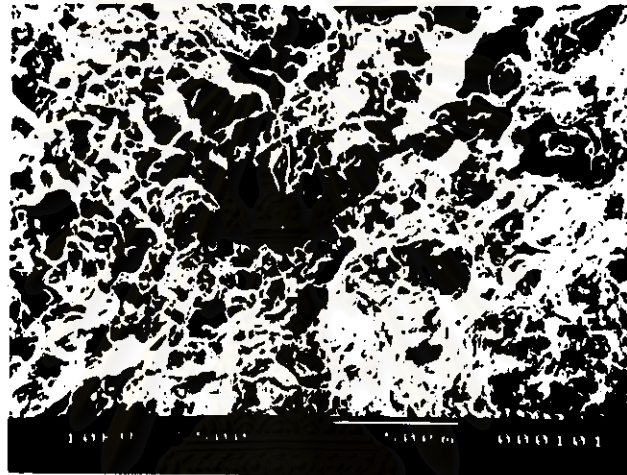


C

Figure 38 The photomicrographs of 11.46% Eudragit[®] NE 30D coated granules of 20/25 mesh size (Key : A coated granules x35, B. coated surface x500, C. cross-section x2000)



A

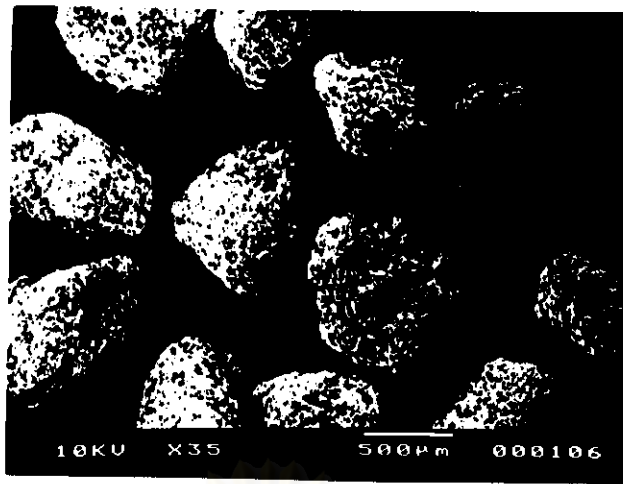


B

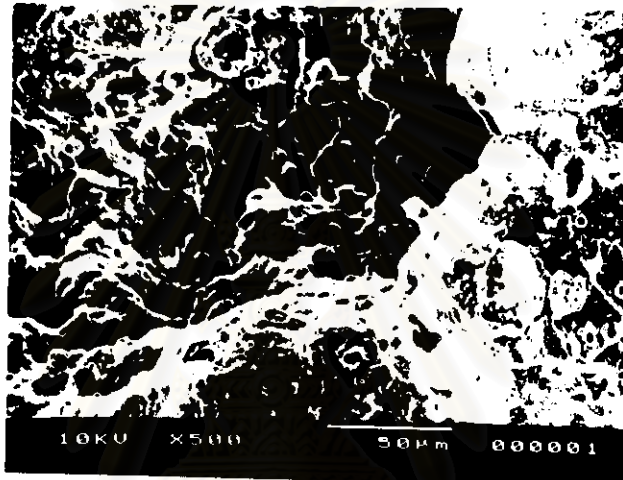


C

Figure 39 The photomicrographs of 15.00% Eudragit® NE 30D coated granules of 20/25 mesh size (Key : A coated granules x35, B. coated surface x500, C. cross-section x2000)



A

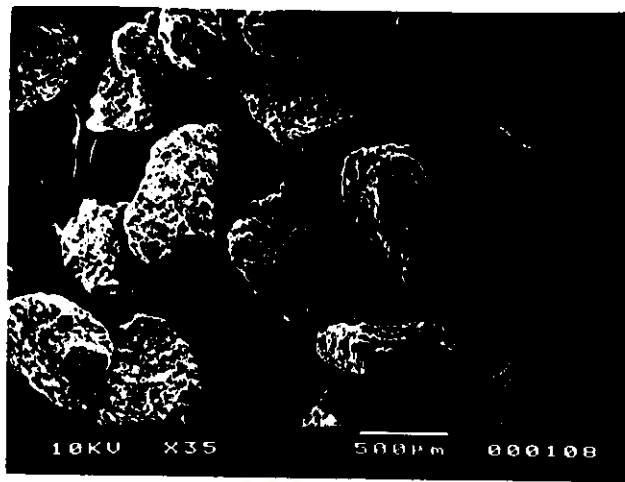


B

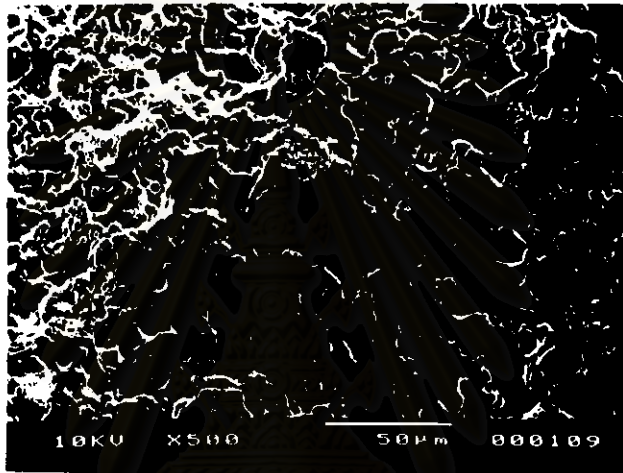


C

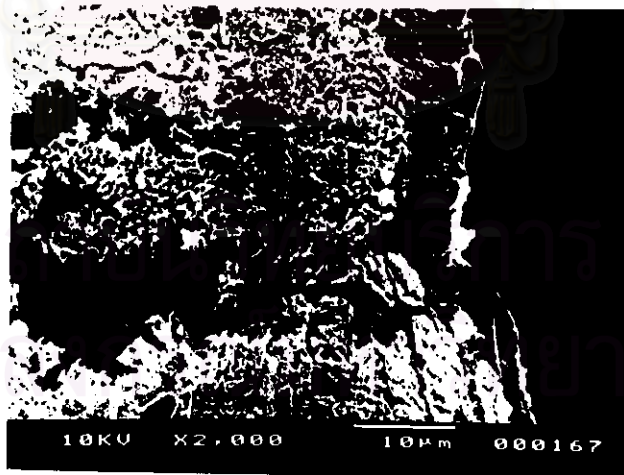
Figure 40 The photomicrographs of 20.76% Eudragit® NE 30D coated granules of 20/25 mesh size (Key : A coated granules x35, B. coated surface x500, C. cross-section x2000)



A

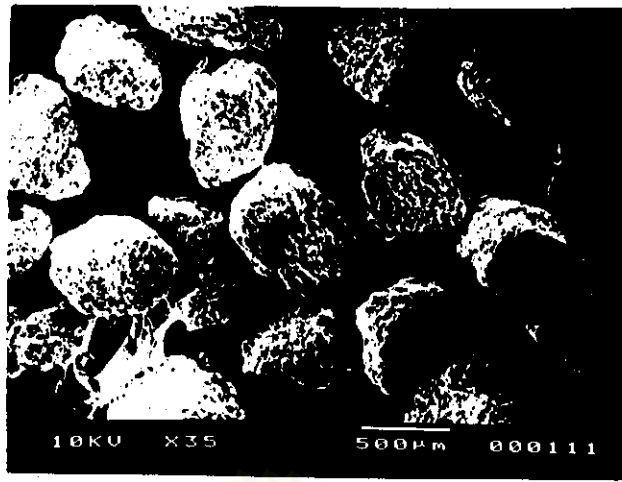


B

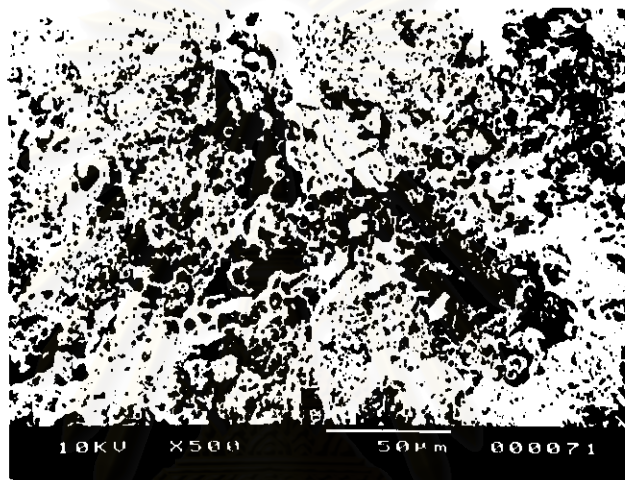


C

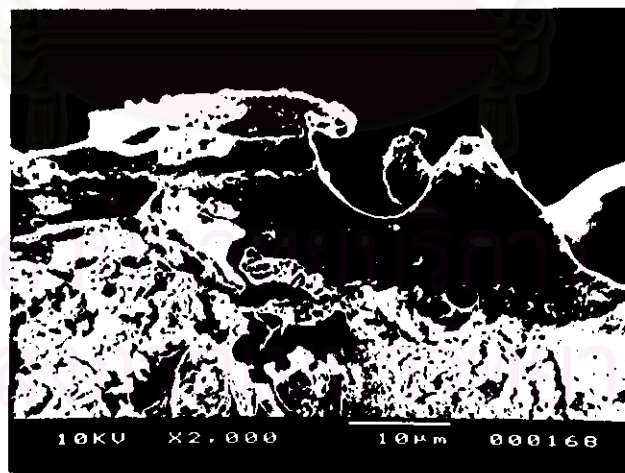
Figure 41 The photomicrographs of 8.83% Eudragit[®] NE 30D coated granules of 25/30 mesh size (Key : A coated granules x35, B. coated surface x500, C. cross-section x2000)



A

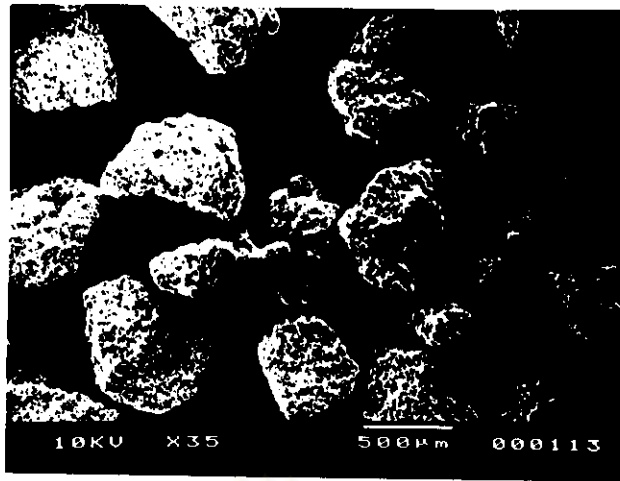


B

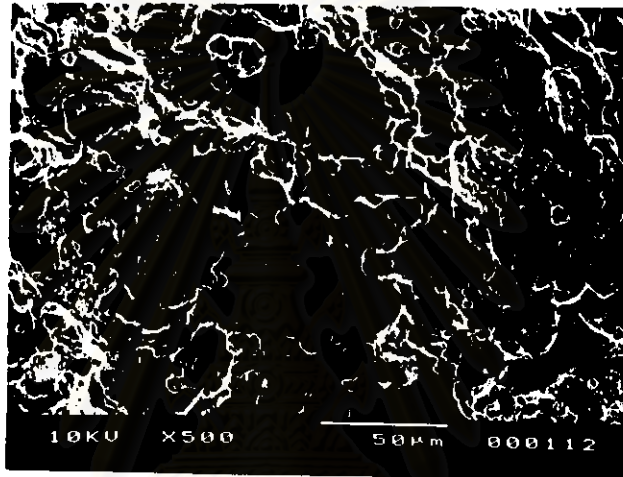


C

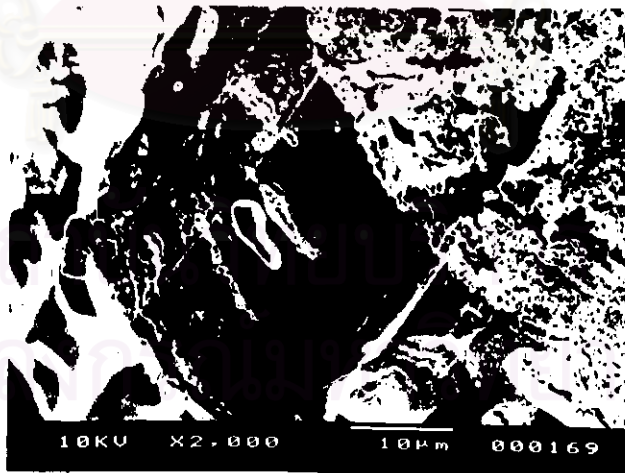
Figure 42 The photomicrographs of 14.57% Eudragit® NE 30D coated granules of 25/30 mesh size (Key : A coated granules x35, B. coated surface x500, C. cross-section x2000)



A

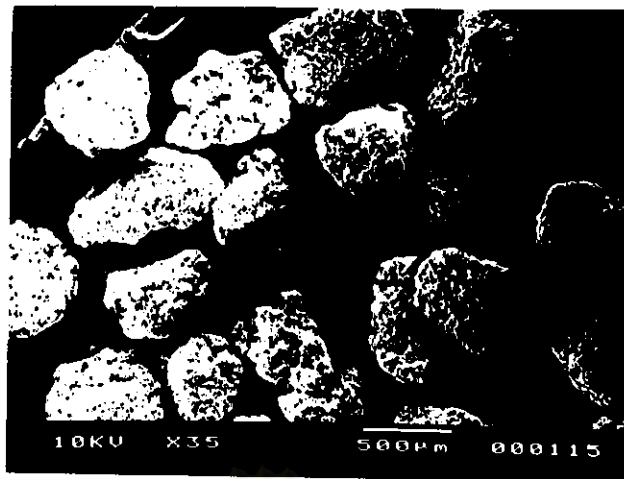


B

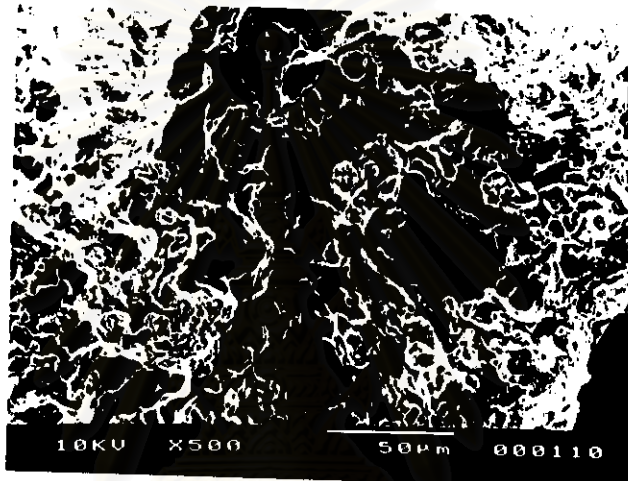


C

Figure 43 The photomicrographs of 17.68% Eudragit® NE 30D coated granules of 25/30 mesh size (Key : A coated granules x35, B. coated surface x500, C. cross-section x2000)



A



B



C

Figure 44 The photomicrographs of 22.37% Eudragit[®] NE 30D coated granules of 25/30 mesh size (Key : A coated granules x35, B. coated surface x500, C. cross-section x2000)

The photomicrographs of all Eudragit® NE 30D coated granules were notable that granules coated with higher percent coating level exhibited thicker film than those with lower percent coating level. Edge and corner of theophylline granules were decreased with the increasing of the percent coating level of Eudragit® NE 30D. Some formulations of them had fine particles of theophylline granules embedding into the layers of the films.

2.2 Mean Sizes of Theophylline Granules

The mean sizes of uncoated granules are shown in Table 10. The mean sizes of each uncoated granules (16/18, 18/20, 20/25 and 25/30 mesh) were 922.57, 866.56, 762.08 and 650.13 μm , respectively.

The mean sizes of all Surelease® coated granules are shown in Table 11. From the obtained data the mean sizes of all Surelease® coated granules obviously increased when increasing the percent coating level of Surelease®. The mean sizes of theophylline granules of various sizes (16/18, 18/20, 20/25 and 25/30 mesh) which were coated with various levels of Surelease® dispersion were within the range of 930-960, 880-900, 780-800 and 670-700 μm , respectively and they were slightly larger than the mean sizes of each uncoated granules (922.57, 866.56, 762.08 and 650.13 μm) respectively.

Similarly, the mean sizes of Eudragit® NE 30D coated granules obviously increased when increasing the percent coating level of Eudragit® NE 30D and their mean sizes were also larger than the mean sizes of uncoated granules as shown in Table 12.

2.3 Bulk Densities, Tapped Densities and Carr's Compressibilities of Theophylline Granules

For uncoated granules, the bulk densities of all uncoated granules were about 0.5 g/ml as shown in Table 10. When coated with different levels of Surelease® or Eudragit® NE 30D, their bulk densities were not much affected as shown in Tables 13 and 14.

The Tapped densities of all uncoated and coated granules shown in Tables 10, 15 and 16 were also not apparently different.

For uncoated granules, higher percentage of compressibility was obtained from larger granules as shown in Table 10. When coated with various levels of Surelease® or Eudragit® NE 30D, their compressibility could not be concluded. The F-Ratio of them are shown in Tables 96 and 97.

2.4 Flow Rates and Angles of Repose of Theophylline Granules

The larger size of uncoated granules showed slower flow rate than smaller granules as shown in Table 10 and the F-Ratio of uncoated granules are shown in Table 79.

The flow rates of all Surelease® coated granules are shown in Table 19. It is notable that coating level had no effect on flow rate. The F-Ratio of them are shown in Table 98.

The flow rates of all Eudragit® NE 30D coated granules were not much different as shown in Table 20. The F-Ratio of them are shown in Table 99.

The angles of repose of uncoated and coated granules are shown in Tables 10, 21 and 22. They were not much different and were within the range of 30-38° which indicated good flow as shown in Table 25.

2.5 Moisture Contents of Theophylline Granules

The moisture contents of uncoated and coated granules are reported in Tables 10, 23 and 24. They were not much different and were in the range of 0.74-0.86%

2.6 Specific surface area of Theophylline Granules

2.6.1 Uncoated Granules

Specific surface area of uncoated granules was different among each size as shown in Table 26. Smaller granules exhibited specific surface area.

2.6.2 Surelease® Coated Granules

The satisfactory formulations of Surelease® coated granules which showed drug release profiles within the range at various time intervals as required by the USP XXIII standard were selected to determine their specific surface area as shown in Table 27. The specific surface area of satisfactory formulations were not very different except the specific surface area of 6.29% Surelease® coated granules of 16/18 mesh. Comparison to the uncoated granules of each size, the specific surface area of Surelease® coated granules were lower than that of the uncoated granules except 6.29% coated granules

which exhibited higher specific surface area than its corresponding uncoated granules.

2.6.3 Eudragit® NE 30D Coated Granules

The satisfactory formulations of Eudragit® NE 30D coated granules which showed drug release profiles within the range at various time intervals as required by the USP XXIII standard were selected to determine their specific surface area as shown in Table 28. The specific surface area of satisfactory formulations were not very different except the specific surface area of 14.76% Eudragit® NE 30D coated granules of 16/18 mesh. Comparison to the uncoated granules of each sizes, the specific surface area of Eudragit® NE 30D coated granules were higher than that of the uncoated granules.

3. Physical Properties of Aqueous Polymeric Films.

For preparation of the Surelease® film, it was found that addition of dibutyl phthalate as plasticizer in the polymeric film was necessary otherwise the Surelease® film could not be peeled off from the glass plate. However for preparation of the Eudragit® NE 30D film, plasticizer was not needed.

3.1 Percent Elongation at Break and Tensile Strength of Aqueous Polymeric Films.

3.1.1 Surelease® Films

From the data in Table 29, the profiles could be plotted between the percentage of dibutyl phthalate against percent elongation at break

and between the percentage of dibutyl phthalate against tensile strength as shown in Figures 45 and 46, respectively. Extrapolation to the Y-axis, the ultimate percent elongation at break and the tensile strength of Surelease[®] film without dibutyl phthalate could be obtained.

The percent elongation at break was increased while the tensile strength was decreased when increasing of the percentage of dibutyl phthalate. The amount of dibutyl phthalate between 10, 15 and 20% had no effect on the tensile strength.

3.1.2 Eudragit[®] NE 30D Film

The percent elongation at break and tensile strength of Eudragit[®] NE 30D film with 30% of cab-o-sil are shown in Table 29. It could be seen that the percent elongation at break and the tensile strength of Eudragit[®] NE 30D film were much higher than those of the Surelease[®] film.

3.2 Water Sorption of Aqueous Polymeric Films

3.2.1 Surelease[®] Films

The percent water sorption of Surelease[®] film are shown in Table 30. From the data in Table 30, the profile could be plotted between percentage of dibutyl phthalate against percent water sorption as shown in Figure 47. The result indicated that the percent water sorption was decreased then increased with the decreasing of the amount of dibutyl phthalate. The lowest water sorption was from Surelease[®] film containing 10% dibutyl phthalate

3.2.2 Eudragit® NE 30D Film

The percentage water sorption of Eudragit® NE 30D film containing cab-o-sil are shown in Table 30. They were higher than those of the Surelease® film except at 25% of dibutyl phthalate which exhibited equal water sorption. The t-Values of them are shown in Table 73 (Appendix).

Table 10 Physical Properties of Uncoated Theophylline Granules

Size of Granules	Mean Size (μ)	Bulk Density (g/ml)	Tapped Density (g/ml)	Carr's Index (%)	Flow Rate (g/sec.)	Angle of Repose (x°)	Moisture Content (%)
16/18	922.57	0.50	0.57	11.66	7.01	32.01	0.80
18/20	866.56	0.52	0.56	6.93	8.50	32.01	0.78
20/25	762.08	0.50	0.53	5.84	8.67	30.47	0.80
25/30	650.13	0.51	0.54	5.08	8.98	30.47	0.85

Table 11 Mean Sizes of Surelease® Coated Granules

Size of Granules (mesh)							
16/18		18/20		20/25		25/30	
Percent Coated	Mean Size (μ)	Percent Coated	Mean Size (μ)	Percent Coated	Mean Size (μ)	Percent Coated	Mean Size (μ)
1.92	939.72	2.04	881.05	2.48	788.86	7.84	672.98
3.05	944.06	3.29	885.12	3.86	790.68	12.18	687.07
3.87	950.60	7.61	887.16	8.39	794.33	13.40	691.83
6.29	954.99	9.00	891.25	12.12	796.16	17.05	699.84

Table 12 Mean Sizes of Eudragit® NE 30D Coated Granules

Size of Granules (mesh)							
16/18		18/20		20/25		25/30	
Percent Coated	Mean Size (μ)	Percent Coated	Mean Size (μ)	Percent Coated	Mean Size (μ)	Percent Coated	Mean Size (μ)
2.51	954.99	4.04	885.12	5.56	792.50	8.83	687.07
5.96	959.40	6.75	887.16	11.46	799.83	14.57	693.43
8.53	966.05	10.93	891.25	15.00	805.38	17.68	696.63
14.76	977.24	19.12	912.01	20.76	810.96	22.37	701.46

Table 13 Bulk Densities of Surelease® Coated Granules

Size of Granules (mesh)							
16/18		18/20		20/25		25/30	
Percent Coated	Bulk Density (g/ml)	Percent Coated	Bulk Density (g/ml)	Percent Coated	Bulk Density (g/ml)	Percent Coated	Bulk Density (g/ml)
1.92	0.50	2.04	0.50	2.48	0.53	7.84	0.50
3.05	0.48	3.29	0.52	3.86	0.52	12.18	0.48
3.87	0.50	7.61	0.52	8.39	0.50	13.40	0.49
6.29	0.48	9.00	0.52	12.12	0.51	17.05	0.50

Table 14 Bulk Densities of Eudragit® NE 30D Coated Granules

Size of Granules (mesh)							
16/18		18/20		20/25		25/30	
Percent Coated	Bulk Density (g/ml)	Percent Coated	Bulk Density (g/ml)	Percent Coated	Bulk Density (g/ml)	Percent Coated	Bulk Density (g/ml)
2.51	0.50	4.04	0.49	5.56	0.51	8.83	0.50
5.96	0.51	6.75	0.48	11.46	0.49	14.57	0.48
8.53	0.49	10.93	0.46	15.00	0.49	17.68	0.52
14.76	0.46	19.12	0.50	20.76	0.46	22.37	0.49

Table 15 Tapped Densities of Surelease[®] Coated Granules

Size of Granules (mesh)							
16/18		18/20		20/25		25/30	
Percent Coated	Tapped Density (g/ml)	Percent Coated	Tapped Density (g/ml)	Percent Coated	Tapped Density (g/ml)	Percent Coated	Tapped Density (g/ml)
1.92	0.53	2.04	0.53	2.48	0.55	7.84	0.52
3.05	0.51	3.29	0.55	3.86	0.55	12.18	0.51
3.87	0.53	7.61	0.55	8.39	0.53	13.40	0.52
6.29	0.52	9.00	0.54	12.12	0.54	17.05	0.53

Table 16 Tapped Densities of Eudragit[®] NE 30D Coated Granules

Size of Granules (mesh)							
16/18		18/20		20/25		25/30	
Percent Coated	Tapped Density (g/ml)	Percent Coated	Tapped Density (g/ml)	Percent Coated	Tapped Density (g/ml)	Percent Coated	Tapped Density (g/ml)
2.51	0.54	4.04	0.52	5.56	0.56	8.83	0.55
5.96	0.56	6.75	0.52	11.46	0.53	14.57	0.53
8.53	0.53	10.93	0.50	15.00	0.54	17.68	0.55
14.76	0.49	19.12	0.55	20.76	0.50	22.37	0.52

Table 17 Carr's Compressibilities of Surelease[®] Coated Granules

Size of Granules (mesh)							
16/18		18/20		20/25		25/30	
Percent Coated	Carr's Index (%)	Percent Coated	Carr's Index (%)	Percent Coated	Carr's Index (%)	Percent Coated	Carr's Index (%)
1.92	5.00	2.04	5.00	2.48	4.41	7.84	4.96
3.05	6.35	3.29	5.19	3.86	5.19	12.18	5.88
3.87	5.84	7.61	5.19	8.39	5.00	13.40	5.67
6.29	6.46	9.00	4.33	12.12	5.08	17.05	5.84

Table 18 Carr's Compressibilities of Eudragit® NE 30D Coated Granules

Size of Granules (mesh)							
16/18		18/20		20/25		25/30	
Percent Coated	Carr's Index (%)	Percent Coated	Carr's Index (%)	Percent Coated	Carr's Index (%)	Percent Coated	Carr's Index (%)
2.51	7.66	4.04	8.90	5.56	7.69	8.83	8.41
5.96	8.48	6.75	7.21	11.46	7.93	14.57	8.06
8.53	7.93	10.93	7.68	15.00	8.19	17.68	7.67
14.76	9.45	19.12	8.41	20.76	7.68	22.37	8.90

Table 19 Flow Rates of Surelease® Coated Granules

Size of Granules (mesh)							
16/18		18/20		20/25		25/30	
Percent Coated	Flow Rate (g/sec.)	Percent Coated	Flow Rate (g/sec.)	Percent Coated	Flow Rate (g/sec.)	Percent Coated	Flow Rate (g/sec.)
1.92	6.67	2.04	7.30	2.48	7.50	7.84	8.50
3.05	6.50	3.29	7.47	3.86	7.67	12.18	8.36
3.87	6.40	7.61	6.70	8.39	7.30	13.40	8.88
6.29	6.24	9.00	6.42	12.12	7.70	17.05	8.43

Table 20 Flow Rates of Eudragit® NE 30D Coated Granules

Size of Granules (mesh)							
16/18		18/20		20/25		25/30	
Percent Coated	Flow Rate (g/sec.)	Percent Coated	Flow Rate (g/sec.)	Percent Coated	Flow Rate (g/sec.)	Percent Coated	Flow Rate (g/sec.)
2.51	6.19	4.04	6.85	5.56	6.74	8.83	6.71
5.96	6.67	6.75	6.67	11.46	6.36	14.57	6.44
8.53	6.24	10.93	6.42	15.00	6.67	17.68	6.85
14.76	6.44	19.12	6.49	20.76	6.32	22.37	6.74

Table 21 Angles of Repose of Surelease® Coated Granules

Size of Granules (mesh)							
16/18		18/20		20/25		25/30	
Percent Coated	Angle of Repose (x°)	Percent Coated	Angle of Repose (x°)	Percent Coated	Angle of Repose (x°)	Percent Coated	Angle of Repose (x°)
1.92	32.01	2.04	32.01	2.48	32.01	7.84	32.01
3.05	33.69	3.29	33.69	3.86	32.01	12.18	30.47
3.87	32.01	7.61	32.85	8.39	35.22	13.40	32.01
6.29	35.22	9.00	32.01	12.12	32.85	17.05	32.85

Table 22 Angles of Repose of Eudragit® NE 30D Coated Granules

Size of Granules (mesh)							
16/18		18/20		20/25		25/30	
Percent Coated	Angle of Repose (x°)	Percent Coated	Angle of Repose (x°)	Percent Coated	Angle of Repose (x°)	Percent Coated	Angle of Repose (x°)
2.51	30.47	4.04	33.69	5.56	32.01	8.83	30.47
5.96	32.01	6.75	30.47	11.46	33.69	14.57	32.85
8.53	33.69	10.93	32.01	15.00	32.01	17.68	32.01
14.76	30.47	19.12	32.01	20.76	30.47	22.37	32.01

Table 23 Moisture Contents of Surelease® Coated Granules

Size of Granules (mesh)							
16/18		18/20		20/25		25/30	
Percent Coated	Moisture Content (%)	Percent Coated	Moisture Content (%)	Percent Coated	Moisture Content (%)	Percent Coated	Moisture Content (%)
1.92	0.84	2.04	0.80	2.48	0.78	7.84	0.79
3.05	0.80	3.29	0.82	3.86	0.81	12.18	0.81
3.87	0.85	7.61	0.79	8.39	0.82	13.40	0.85
6.29	0.74	9.00	0.86	12.12	0.80	17.05	0.84

Table 24 Moisture Contents of Eudragit® NE 30D Coated Granules

Size of Granules (mesh)							
16/18		18/20		20/25		25/30	
Percent Coated	Moisture Content (%)	Percent Coated	Moisture Content (%)	Percent Coated	Moisture Content (%)	Percent Coated	Moisture Content (%)
2.51	0.82	4.04	0.81	5.56	0.74	8.83	0.81
5.96	0.80	6.75	0.78	11.46	0.79	14.57	0.78
8.53	0.81	10.93	0.78	15.00	0.82	17.68	0.82
14.76	0.78	19.12	0.74	20.76	0.84	22.37	0.83

Table 25 The Angle of Repose of the Granules

Angle of Repose (x°)	Flowability
25 - 30	excellent flow
30 - 38	good flow
38 - 45	fair flow
45 - 55	poor flow
55 - 70	very poor flow
> 70	very very poor flow

Table 26 Specific Surface Area of Uncoated Granules

Size of Granules	Specific Surface Area (m ² /g)
16 - 18	0.00112
18 - 20	0.00117
20 - 25	0.00129
25 - 30	0.00185

Table 27 Specific Surface Area of Surelease® Coated Granules

Percent Coated	Size of Granules	Specific Surface Area (m ² /g)
6.29	16/18	0.00154
7.61	18/20	0.00084
8.39	20/25	0.00071
12.18	25/30	0.00082
13.40	25/30	0.00089

Table 28 Specific Surface Area of Eudragit® NE 30D Coated Granules

Percent Coated	Size of Granules	Specific Surface Area (m ² /g)
14.76	16/18	0.00173
19.12	18/20	0.00230
20.76	20/25	0.00222
22.37	25/30	0.00242

Table 29 Percent Elongation at Break and Tensile Strength of Aqueous Polymeric Films

Type of Polymer	Percent Dibutyl Phthalate	Percent Elongation at Break	Tensile Strength (N/Cm ²)
Surelease®	0.00	11.00 *	13.55 *
	5.00	15.00 ± 5.00	12.09 ± 0.69
	10.00	20.00 ± 0.00	9.12 ± 0.98
	15.00	21.67 ± 2.89	9.76 ± 1.95
	20.00	26.67 ± 2.89	9.14 ± 1.94
	25.00	31.67 ± 2.89	4.30 ± 0.70
Eudragit® NE 30D	-	370 ± 5.00	67.5 ± 2.11

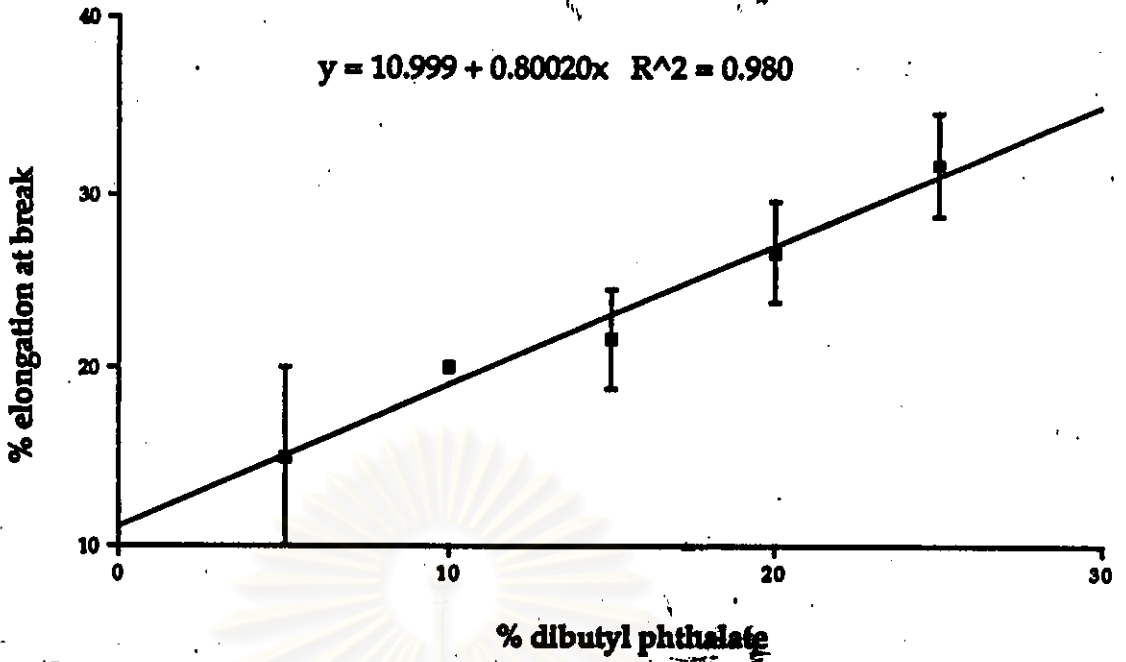


Figure 45 Influence of dibutyl phthalate concentration on percent elongation at break of Surelease® films

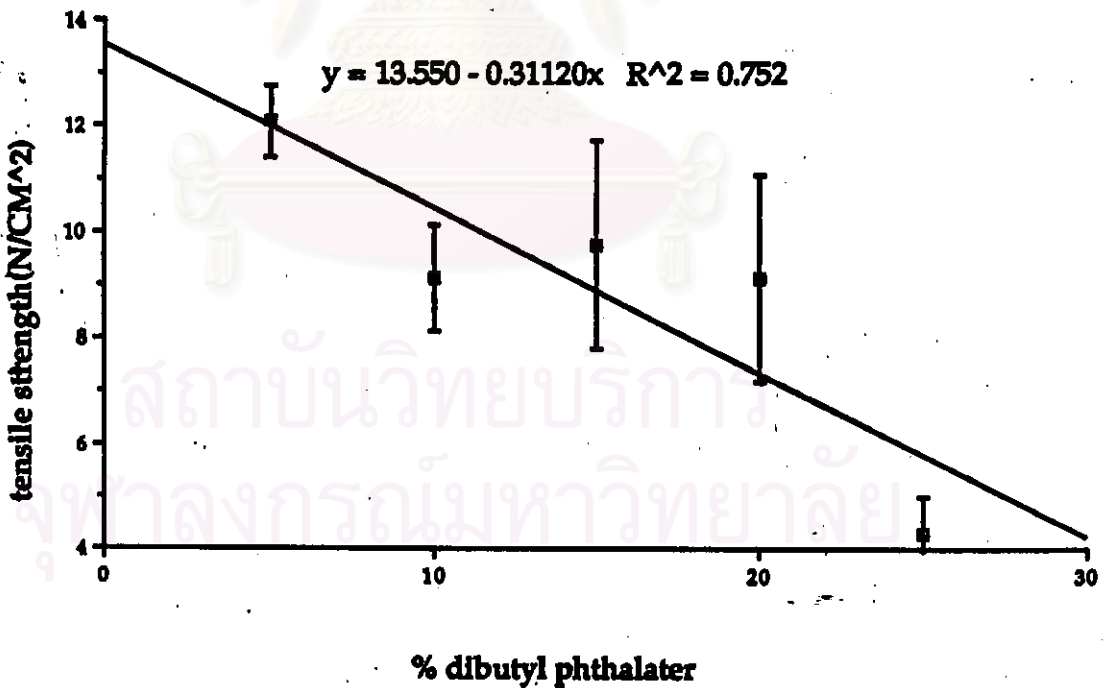


Figure 46 Influence of dibutyl phthalate concentration on tensile strength of Surelease® films

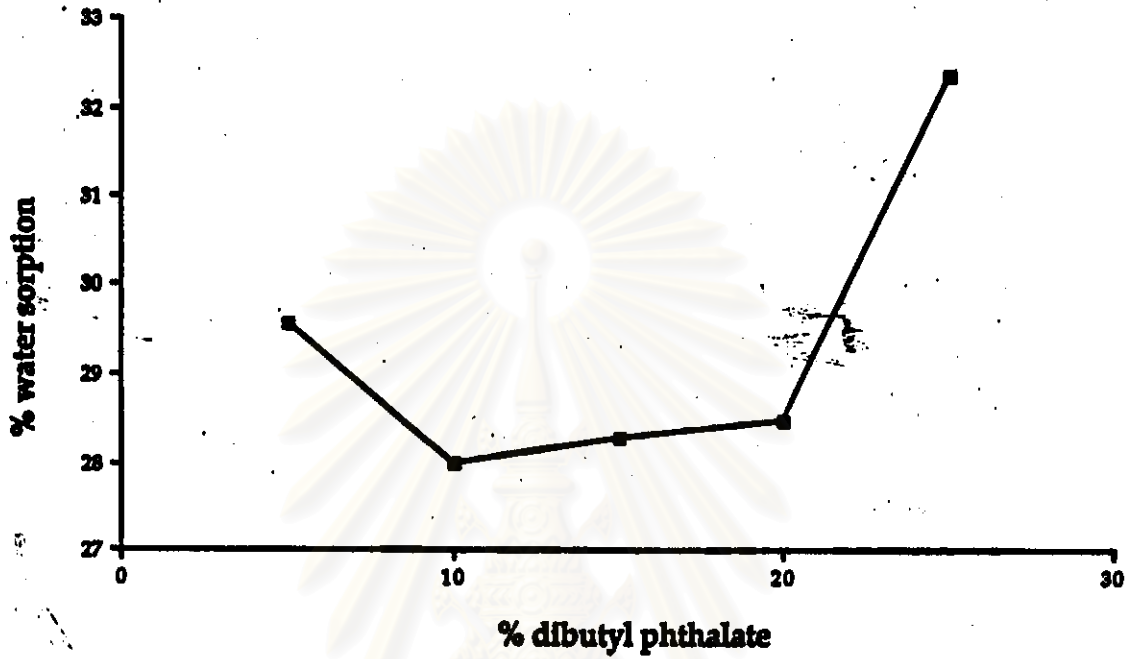


Figure 47 Influence of dibutyl phthalate concentration on percentage of water sorption of Surelease® films

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Table 30 Percent Water of Aqueous Polymeric Films

Type of Polymer	Percent Dibutyl Phthalate	Percent Water Sorption
Surelease®	5.00	29.58 ± 2.76
	10.00	27.98 ± 2.82
	15.00	28.28 ± 2.60
	20.00	28.48 ± 3.68
	25.00	32.37 ± 3.00
Eudragit® NE 30D	-	35.31 ± 2.24

4. Dissolution Study

4.1 Uncoated Granules

The uncoated granules of various sizes investigated included 16/18, 18/20, 20/25 and 25/30 mesh. The dissolution data of theophylline from the uncoated granules are tabulated in Table 42 (Appendix) and are shown graphically in Figure 48 A. The release rate profiles of all uncoated granules are tabulated in Table 52 (Appendix) and the release rate of these uncoated granules decreased with the time increased as shown in Figure 48B. For the first 10 minutes, the highest release rate was obtained from 25/30 mesh size followed by 20/25 mesh size, 18/20 mesh size and 16/18 mesh size. Then the granules of 16/18 mesh size exhibited the highest release rate.

Influence of Various Sizes on the Dissolution Profiles of Uncoated Granules

The release of drug from uncoated granules was different among each size of granules. In the first 30 minutes, higher release of drug was obtained

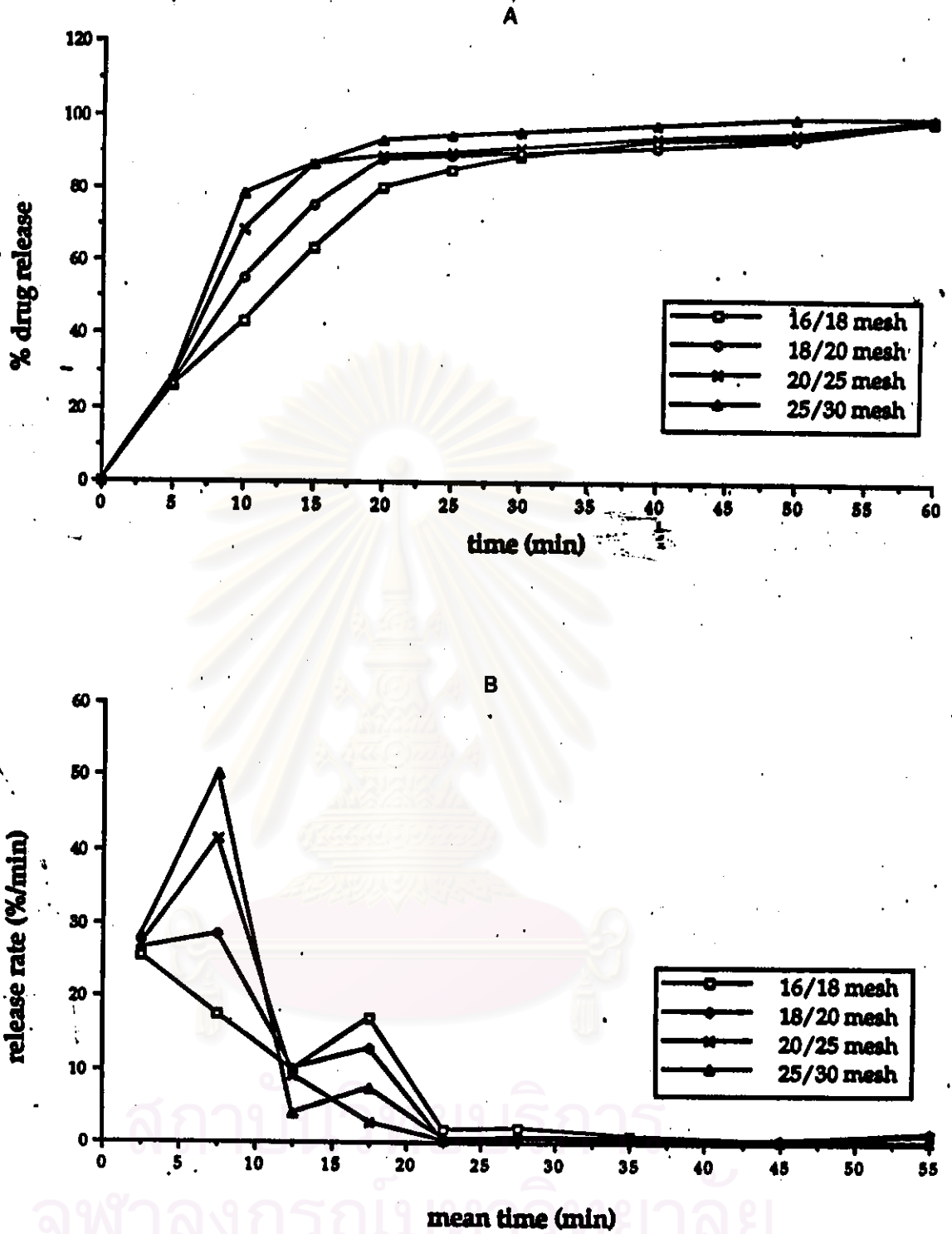


Figure 48 A. The release profiles of uncoated theophylline granules of various sizes
 B. The release rate profiles of uncoated theophylline granules of various sizes

from uncoated granules of smaller sizes. The uncoated granules of 25/30 mesh size released the drug approximately 96% in the first 30 minutes while only 89% of theophylline was released from uncoated granules having a particle size range of 16/18 mesh. After 30 minutes, more than 90% of the dose was released from every size of uncoated granules.

4.2 Surelease® Coated Granules

The dissolution data of theophylline granules of various sizes coated with various levels of Surelease® are described in Tables 43-46 (Appendix) and are shown graphically in Figures 49A-52A. The release rate profiles of all Surelease® coated granules are tabulated in Tables 53-56 (Appendix) and are shown graphically in Figures 49B-52B. These release rate profiles decreased as the time increased.

A. Influence of Coating Level on the Drug Release Profiles of Surelease® Coated Granules

From the obtained data increasing the percent coating level of Surelease® resulted in a corresponding decrease of the release of drug. The dissolution profiles between 3.05% and 3.87% coated granules of 16/18 mesh, 2.48% and 3.86% coated granules of 20/25 mesh and 12.18% and 13.40% coated granules of 25/30 mesh showed no statistical significance difference as shown in Table 74 (Appendix).

B. Influence of Various Sizes on the Dissolution Profiles of Surelease® Coated Granules

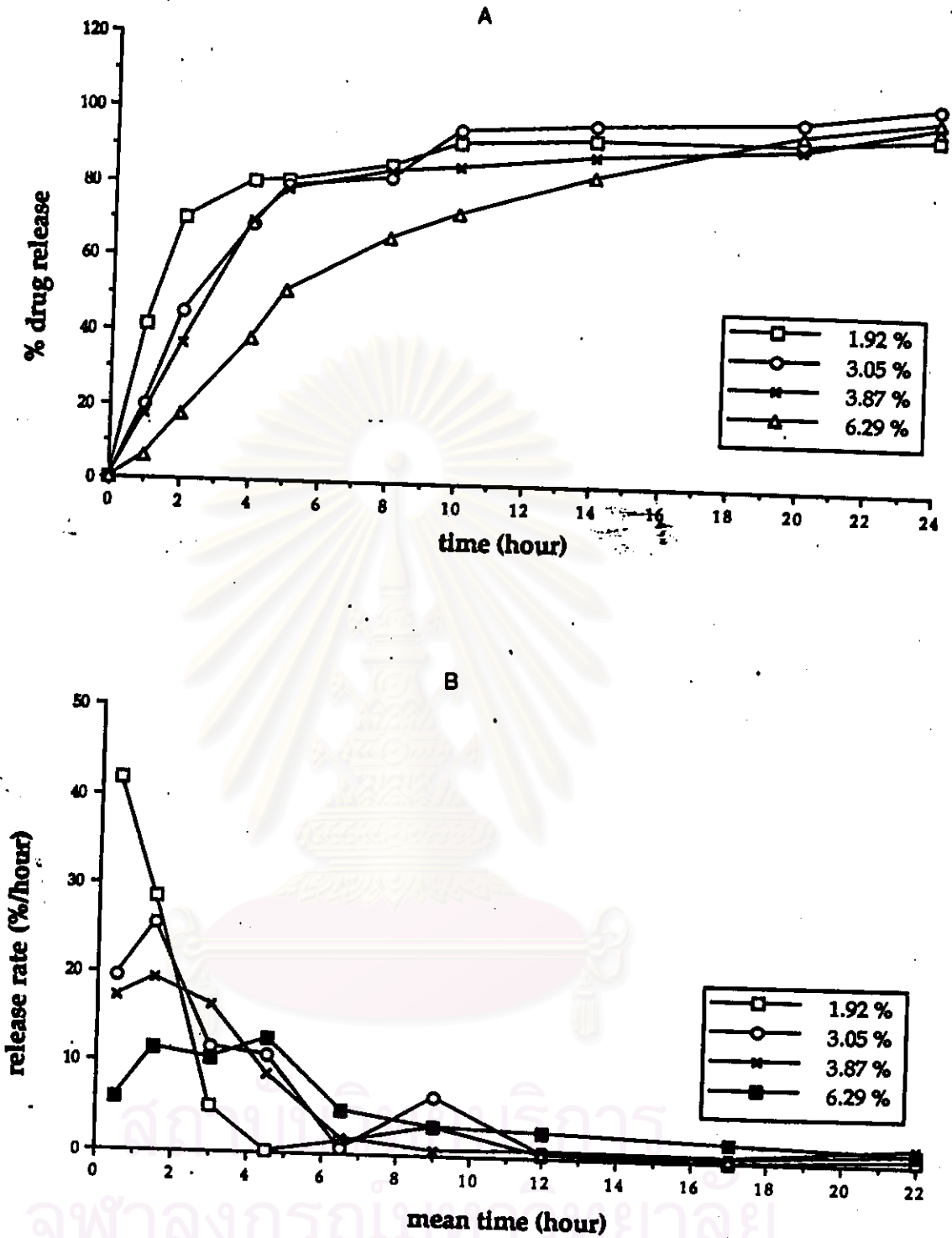


Figure 49 A. The release profiles of Surelease[®] coated granules of 16/18 mesh sizes
 B. The release rate profiles of Surelease[®] coated granules of 16/18 mesh sizes

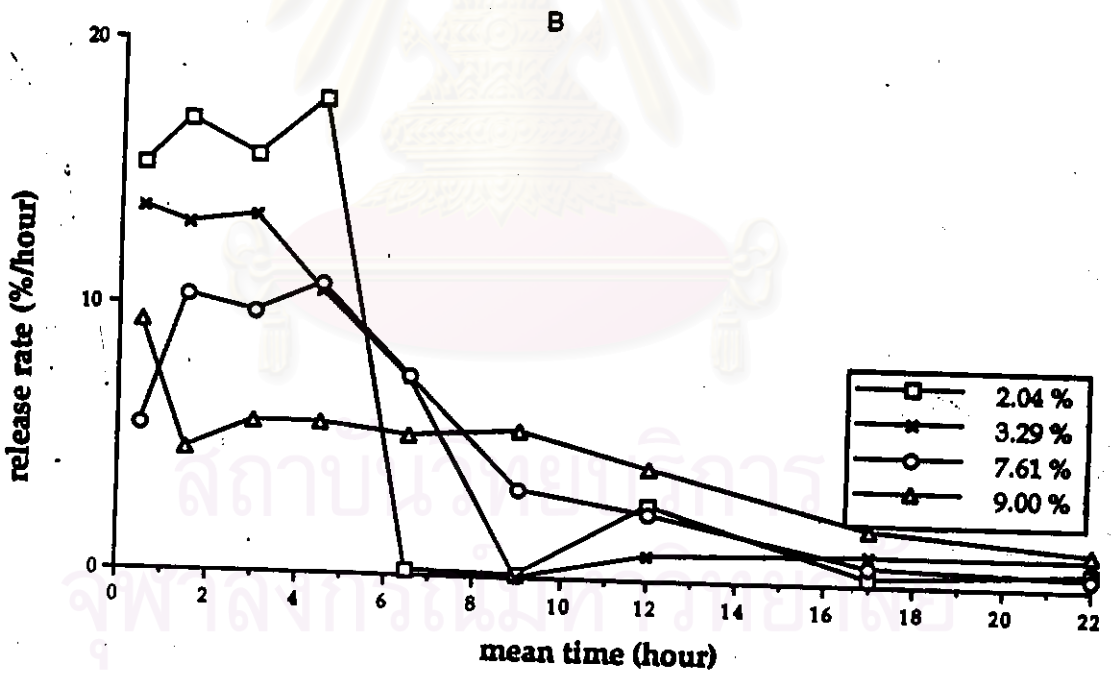
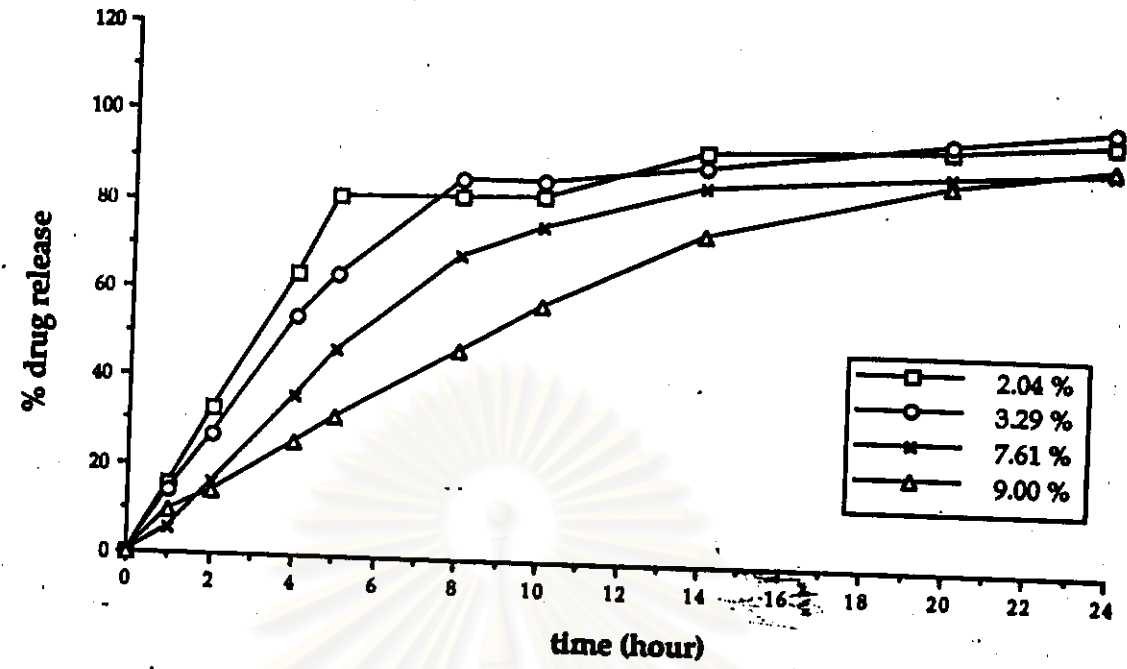


Figure 50 A. The release profiles of Surelease[®] coated granules of 18/20 mesh sizes
 B. The release rate profiles of Surelease[®] coated granules of 18/20 mesh sizes

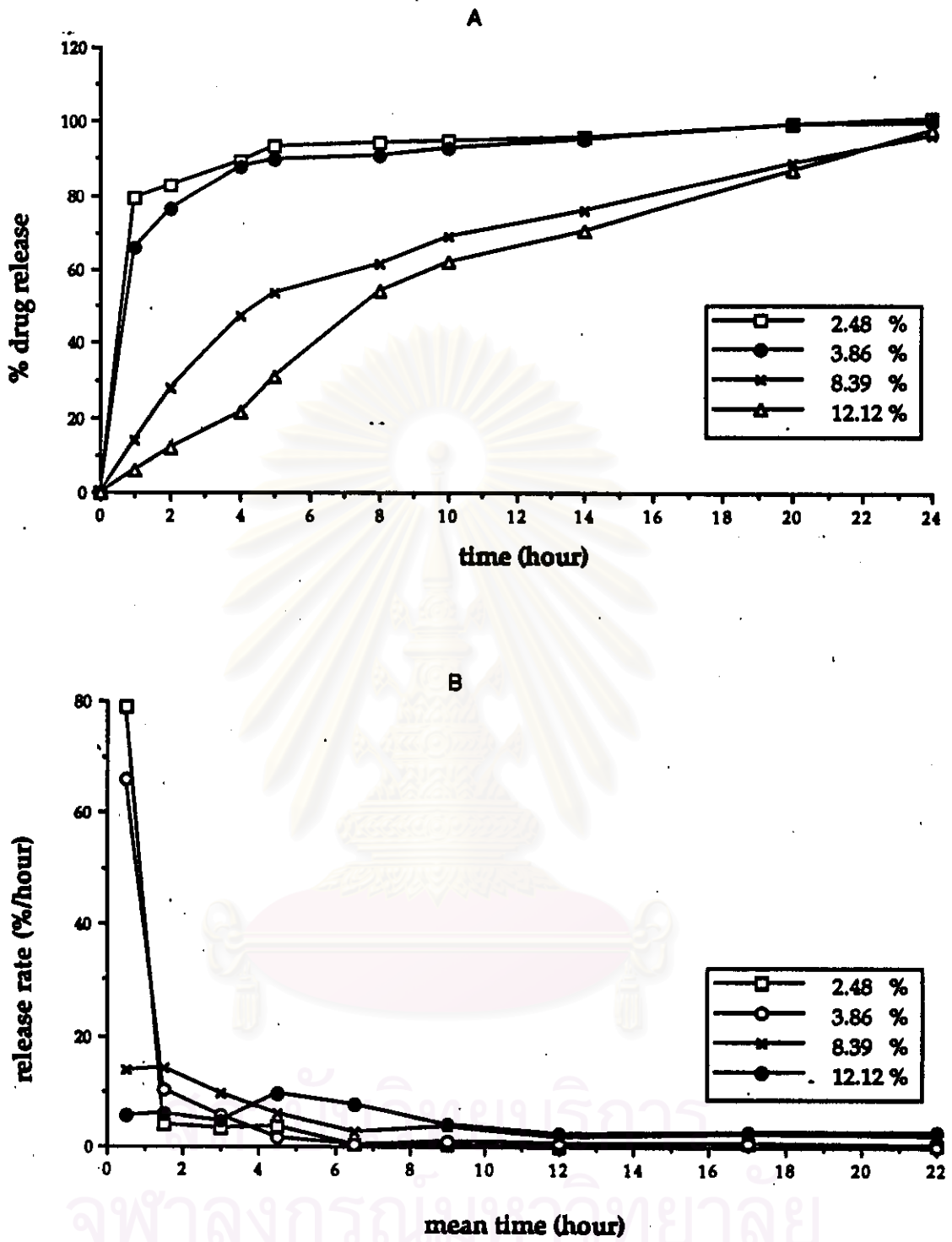


Figure 51 A. The release profiles of Surelease[®] coated granules of 20/25 mesh sizes
 B. The release rate profiles of Surelease[®] coated granules of 20/25 mesh sizes

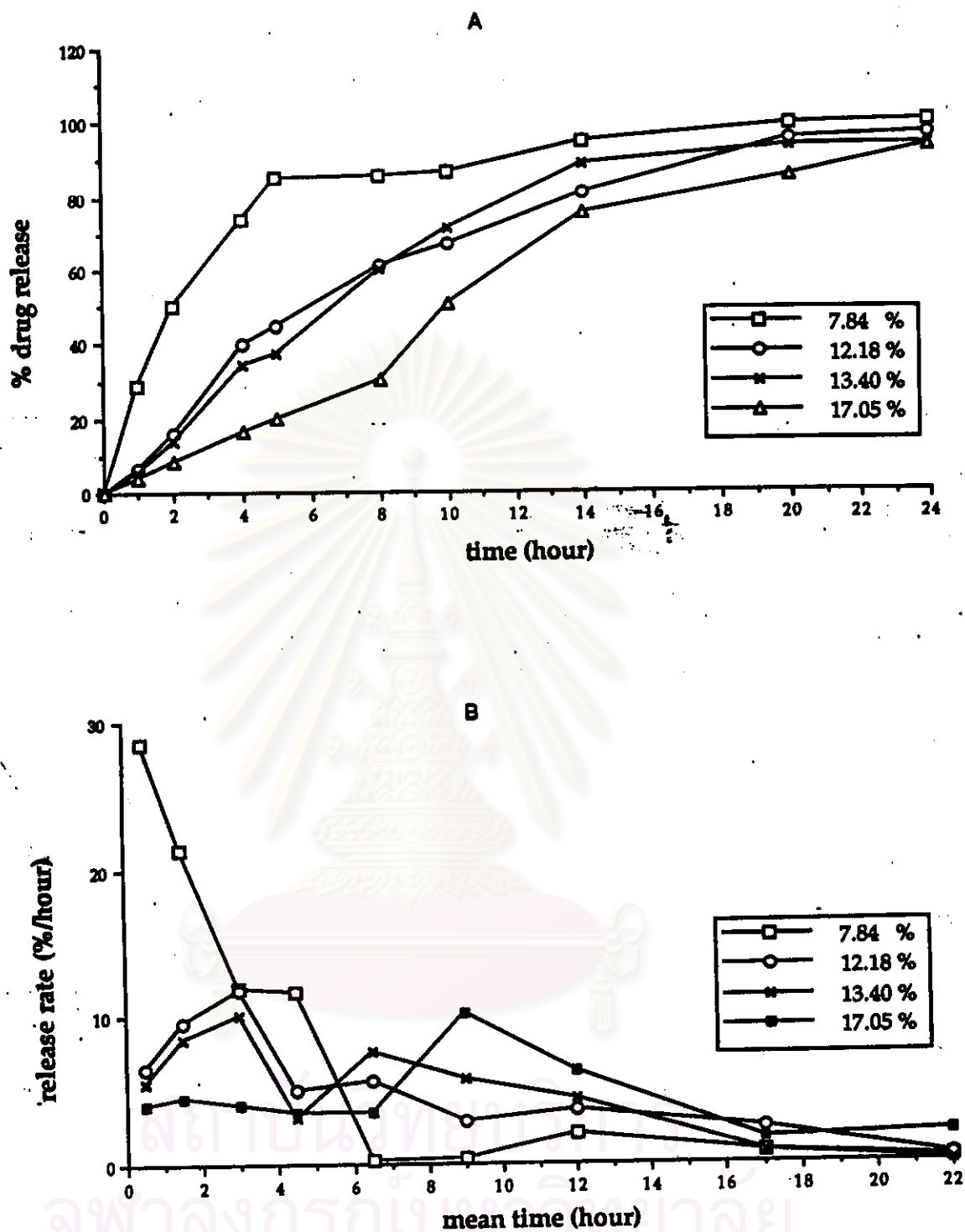


Figure 52 A. The release profiles of Surelease[®] coated granules of 25/30 mesh sizes
 B. The release rate profiles of Surelease[®] coated granules of 25/30 mesh sizes

Several size of theophylline granules (16/18, 18/20, 20/25 and 25/30 mesh) were evaluated for their influence on release profiles of the same level of Surelease[®] coated granules. The comparative release profiles for various sizes at the same level are shown graphically in Figures 58-61. Figure 58 shows release profiles of theophylline granules of 18/20 and 20/25 mesh coated with approximately 2% coating level (2.04% and 2.48%), Figure 59 shows release profiles of theophylline granules of 16/18, 18/20 and 20/25 mesh at approximately 3% coating level (3.87%, 3.29% and 3.86%), Figure 60 shows release profiles of theophylline granules of 18/20 and 25/30 mesh at approximately 7% coating level (7.61% and 7.84%) and Figure 61 for about 12% coating level (12.12% and 12.18%) of 20/25 and 25/30 mesh.

From the obtained results, slower release profile was obtained from theophylline granules of larger size. These results were similar to the results obtained from uncoated granules except the coating level about 3%, the granules of 16/18 mesh exhibited higher release profile than the 18/20 mesh as shown in Figure 59.

4.3 Eudragit[®] NE 30D Coated Granules

The dissolution data of theophylline granules of various sizes which were coated with various levels of Eudragit[®] NE 30D are listed in Tables 47-50 (Appendix) and are shown graphically in Figures 53A-56A. The release rate profiles of all Eudragit[®] NE 30D coated granules are tabulated in Tables 57-60 (Appendix) and are shown graphically in Figures 53B-56B.

A

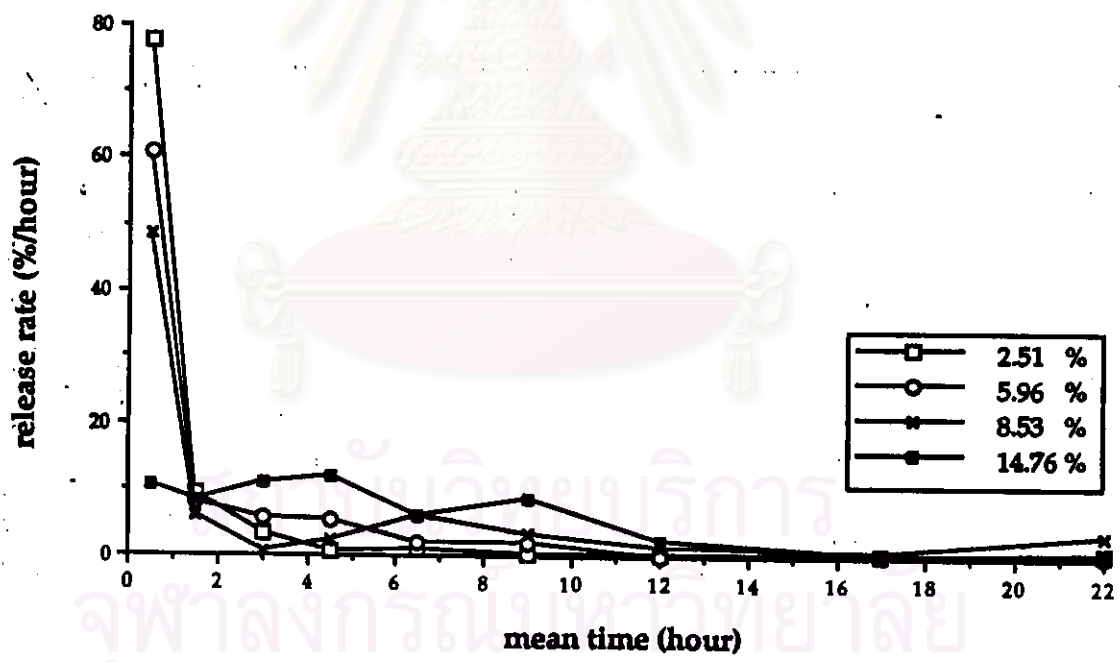
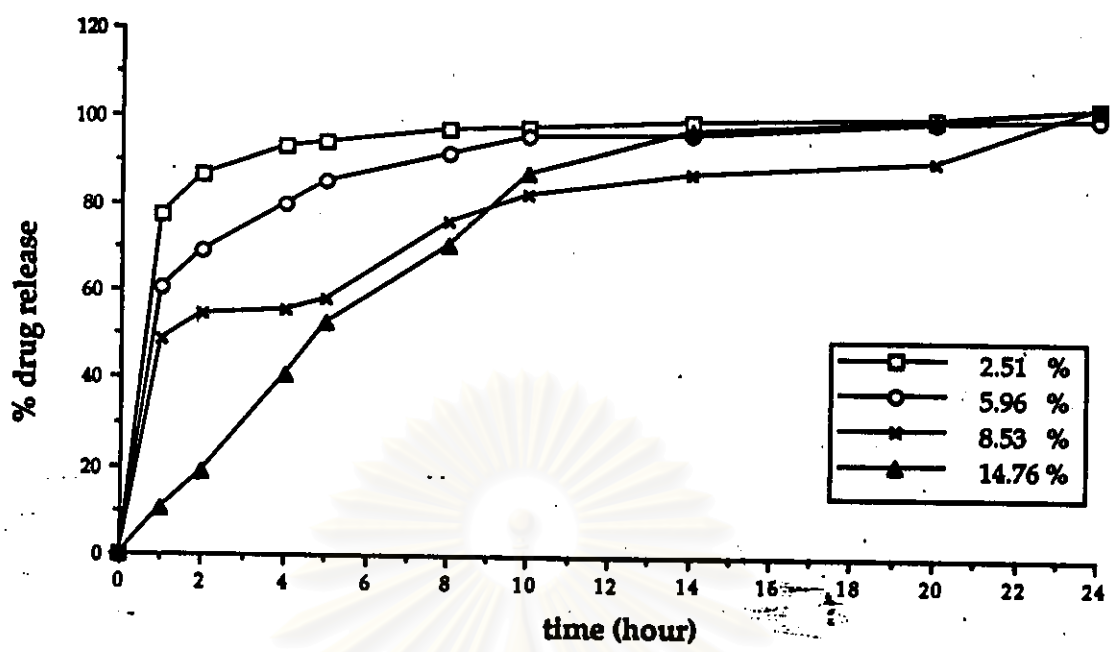


Figure 53 A. The release profiles of Eudragit® NE 30D coated granules of 16/18 mesh sizes
 B. The release rate profiles of Eudragit® NE 30D coated granules of 16/18 mesh sizes

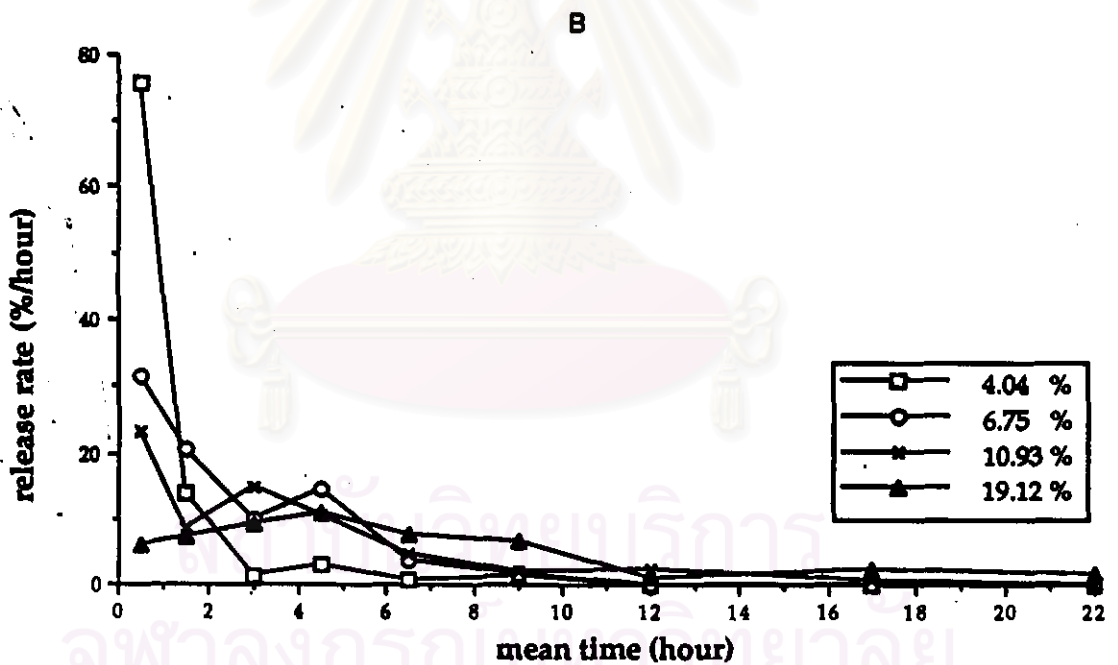
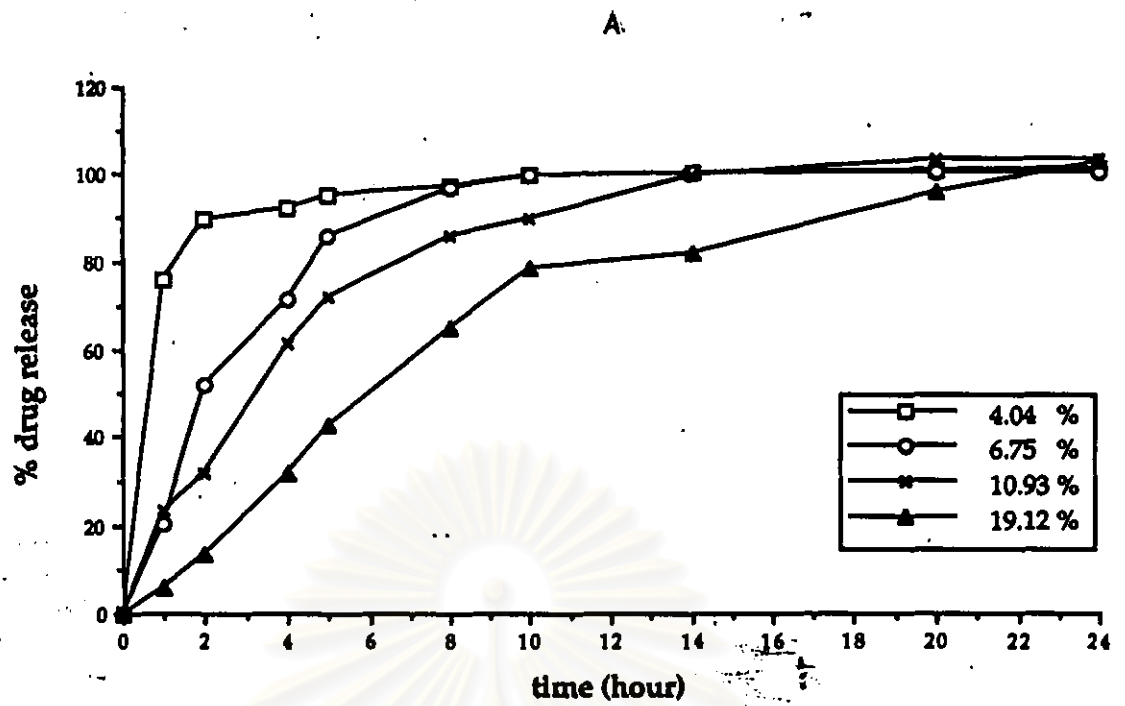


Figure 54 A. The release profiles of Eudragit® NE 30D coated granules of 18/20 mesh sizes
 B. The release rate profiles of Eudragit® NE 30D coated granules of 18/20 mesh sizes

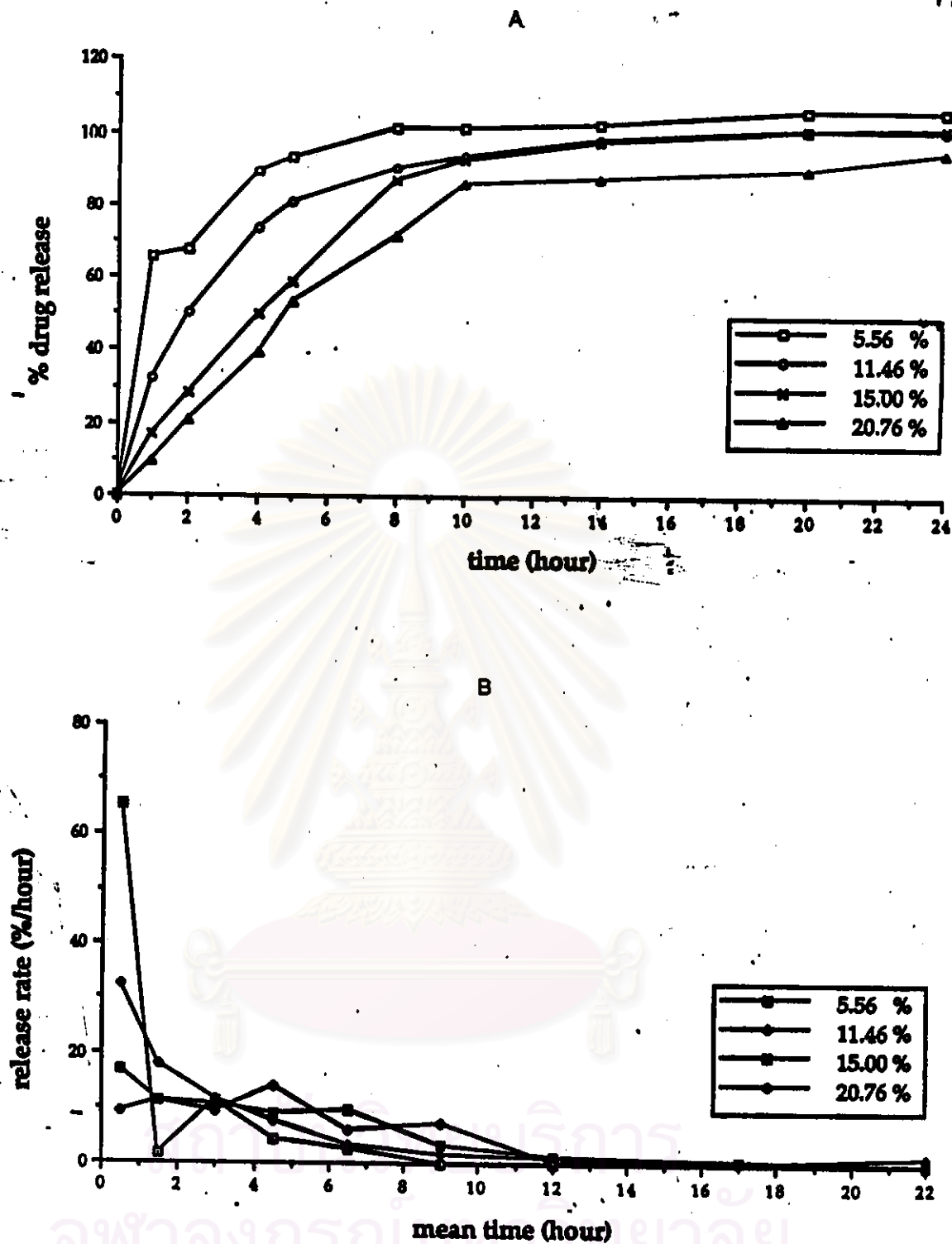


Figure 55 A. The release profiles of Eudragit[®] NE 30D coated granules of 20/25 mesh sizes
 B. The release rate profiles of Eudragit[®] NE 30D coated granules of 20/25 mesh sizes

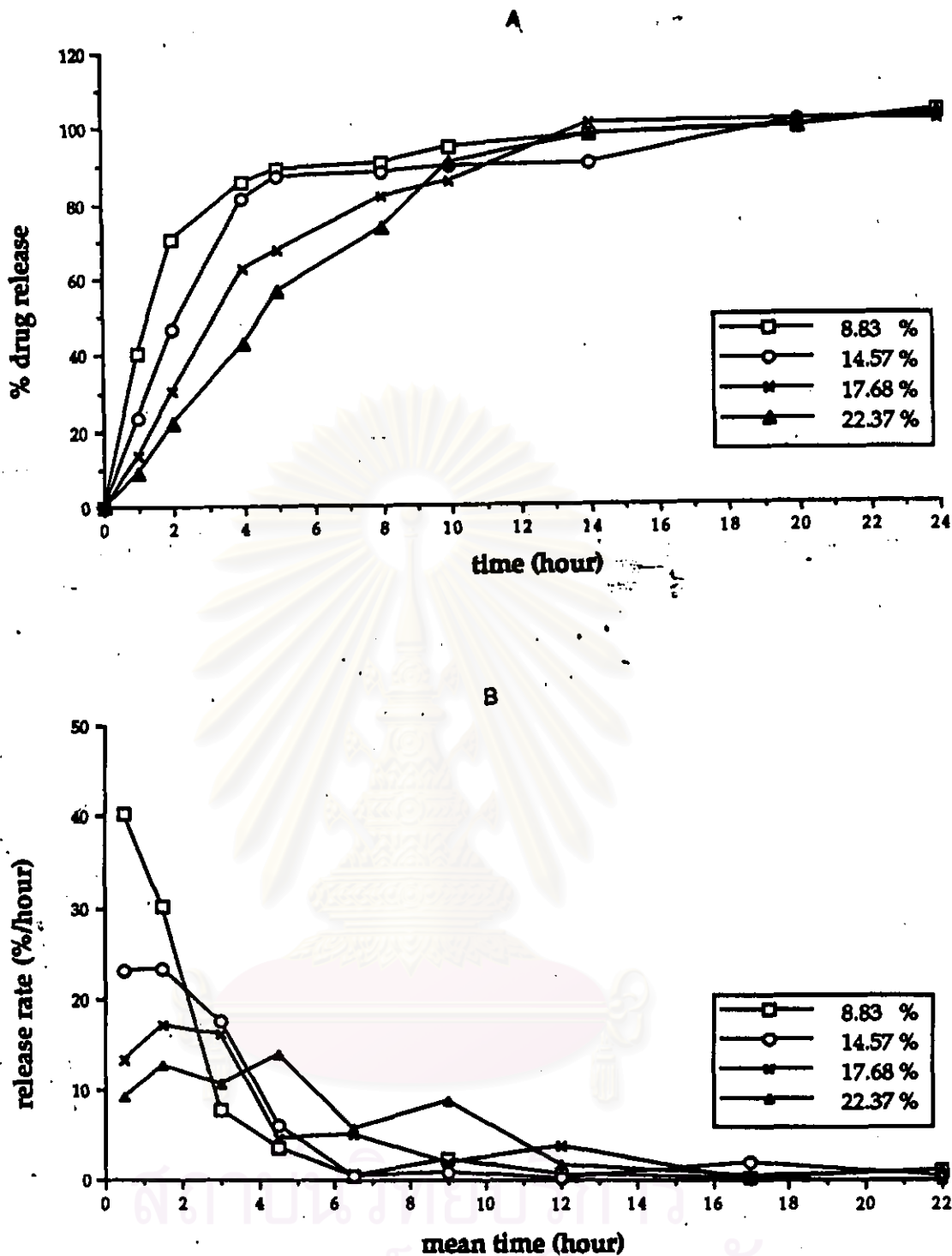


Figure 56 A. The release profiles of Eudragit® NE 30D coated granules of 25/30 mesh sizes
 B. The release rate profiles of Eudragit® NE 30D coated granules of 25/30 mesh sizes

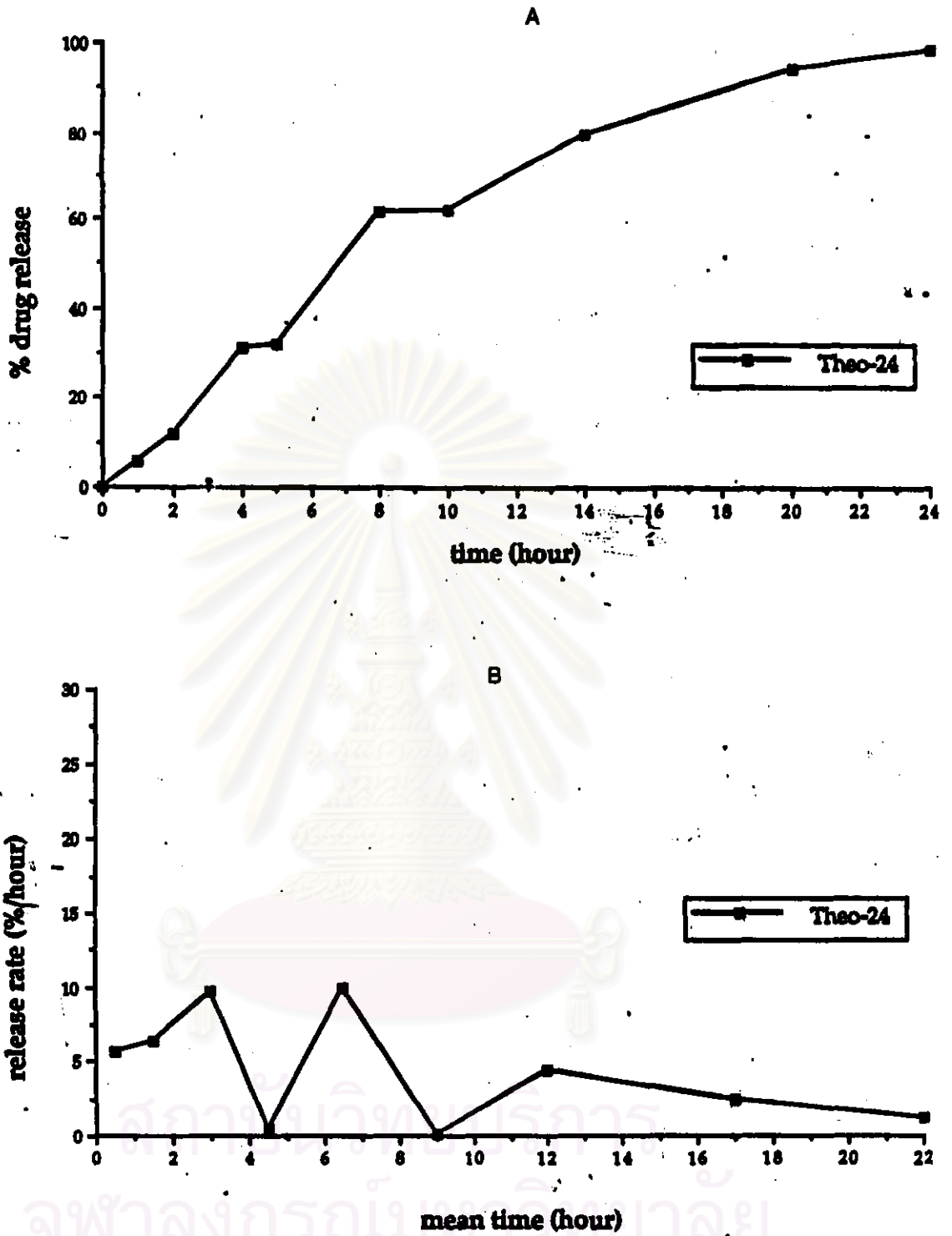


Figure 57 A. The release profiles of Theo-24[®]
 B. The release rate profiles of Theo-24[®]

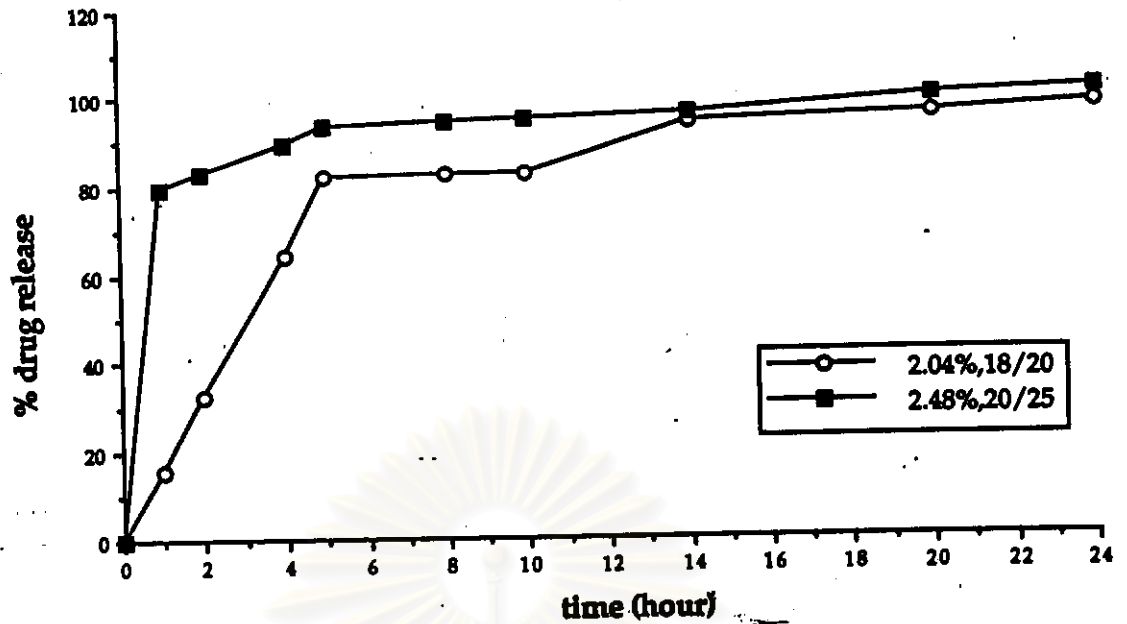


Figure 58 Influence of various sizes (18/20 and 20/25 mesh) in about 2% coating level of Surelease® on the theophylline release profiles from coated granules

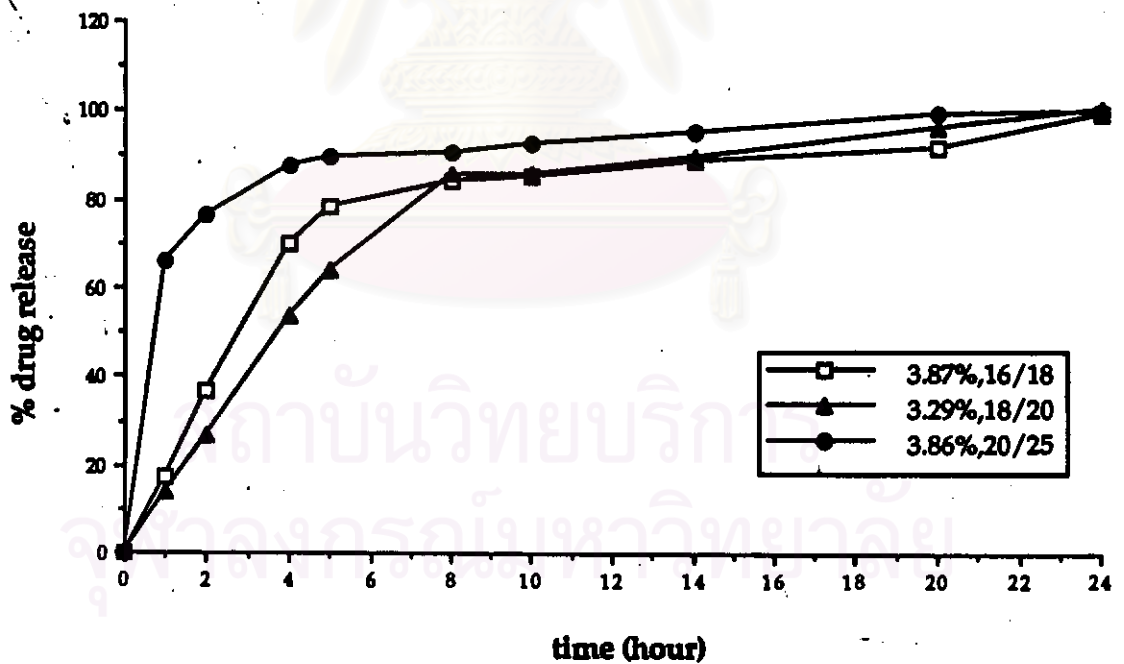


Figure 59 Influence of various sizes (16/18, 18/20 and 20/25 mesh) in about 3% coating level of Surelease® on the theophylline release profiles from coated granules

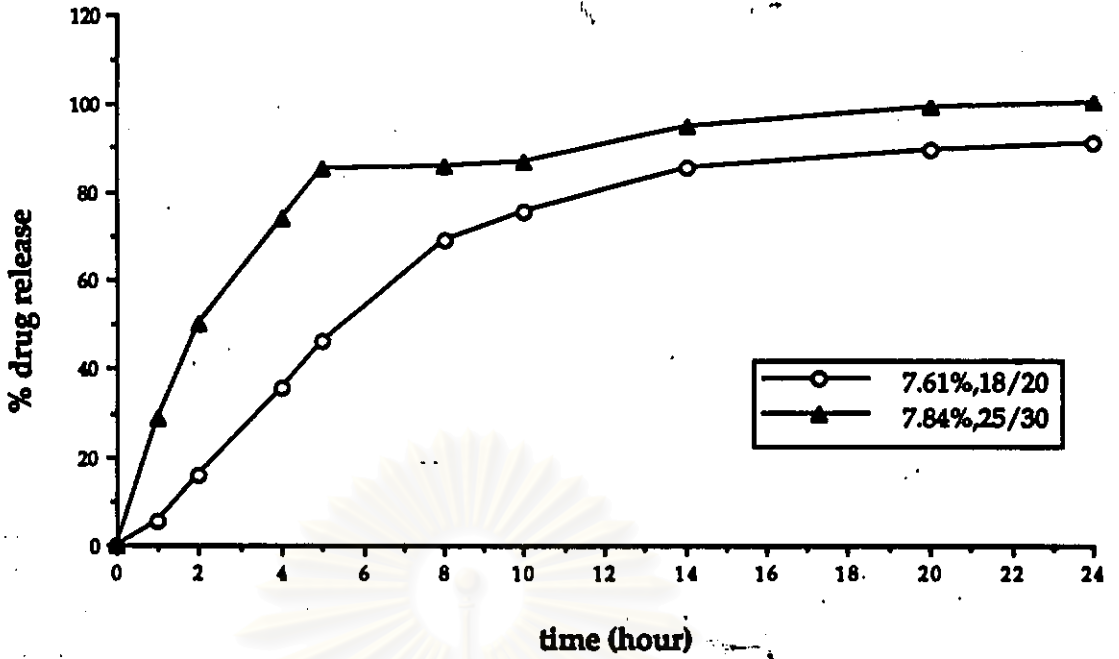


Figure 60 Influence of various sizes (18/20 and 25/30 mesh) in about 7% coating level of Surelease® on the theophylline release profiles from coated granules

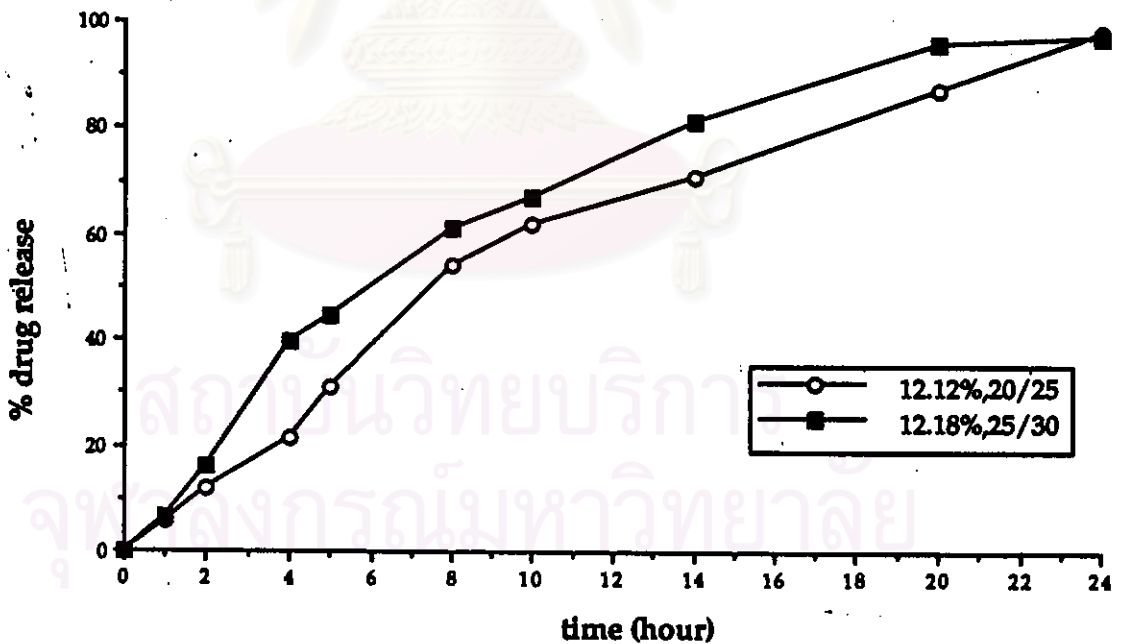


Figure 61 Influence of various sizes (20/25 and 25/30 mesh) in about 12% coating level of Surelease® on the theophylline release profiles from coated granules

Eudragit® NE 30D coated granules exhibited release profiles similar to the Surelease® coated granules that the release rate profiles of Eudragit® NE 30D coated granules decreased as the time increased.

A. Influence of Coating Level on the Drug Release Profiles of Eudragit® NE 30D Coated Granules

The obtained results from Eudragit® NE 30D coated granules were similar to the results from Surelease® coated granules. Increasing the percent coating level of Eudragit® NE 30D resulted in corresponding decrease of the release of drug (Figures 53A-56A).

B. Influence of Various Sizes on the Dissolution Profiles of Eudragit® NE 30D Coated Granules

Several size of theophylline granules (16/18, 18/20, 20/25 and 25/30 mesh) were evaluated for their influence on release profiles of the same level of Eudragit® NE 30D coated granules. The comparative release profiles for various sizes at the same level are shown graphically in Figures 62-64. Figure 62 shows release profiles of theophylline granules of 16/18 and 20/25 mesh coated with approximately 5% coating level (5.96% and 5.56%), Figure 63 shows release profiles of theophylline granules of 16/18 and 25/30 mesh at about 8% coating level (8.53% and 8.83%) and Figure 64 shows release profiles of theophylline granules of 16/18 and 25/30 mesh at about 14% coating level (14.76% and 14.57%).

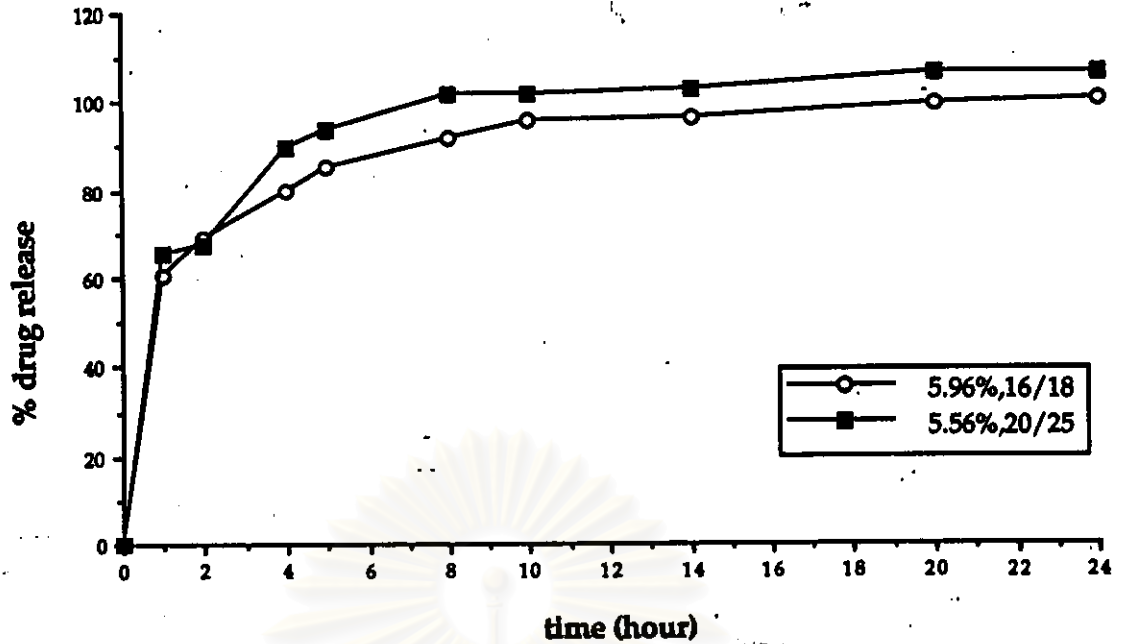


Figure 62 Influence of various sizes (16/18 and 20/25 mesh) in about 5% coating level of Eudragit® NE 30D on the theophylline release profiles from coated granules

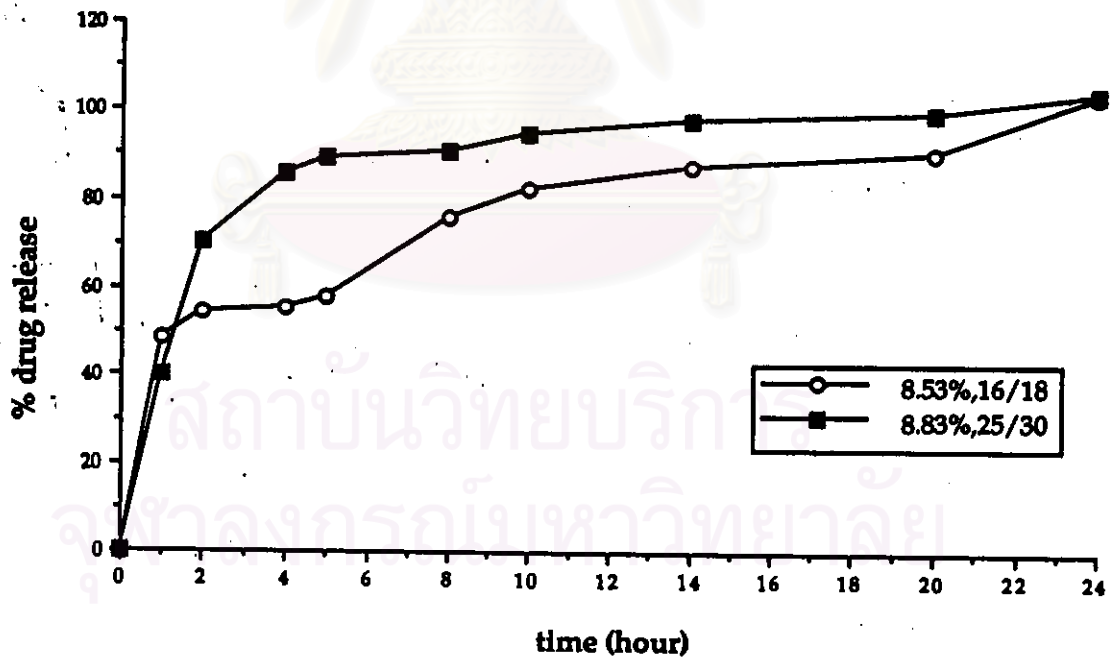


Figure 63 - Influence of various sizes (16/18 and 25/30 mesh) in about 8% coating level of Eudragit® NE 30D on the theophylline release profiles from coated granules

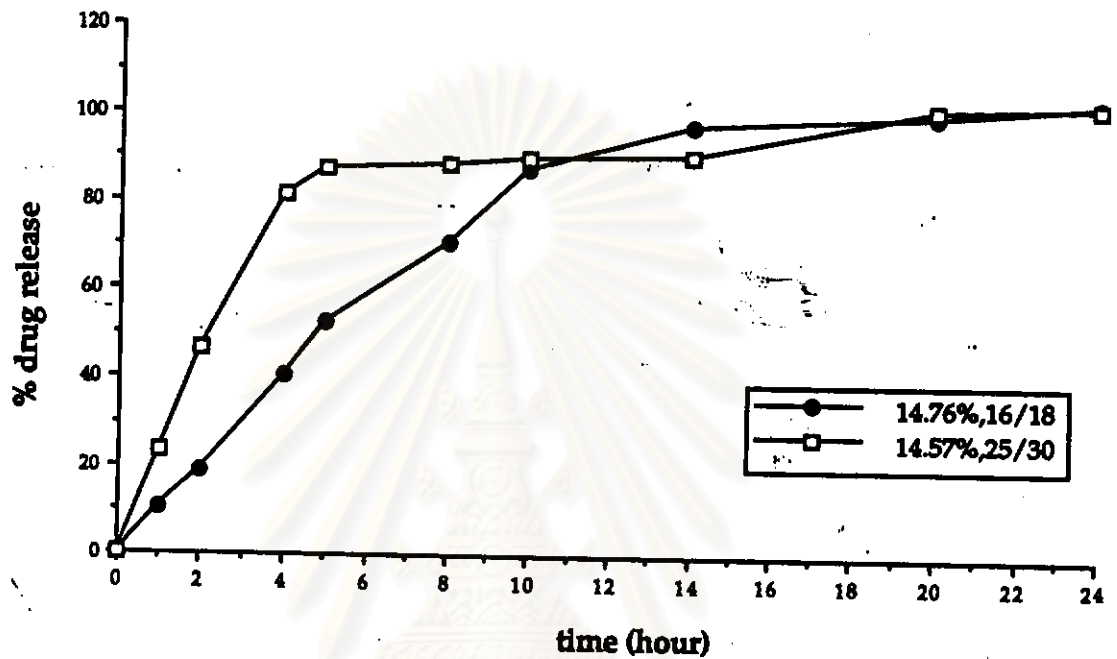


Figure 64 Influence of various sizes (16/18 and 25/30 mesh) in about 14% coating level of Eudragit® NE 30D on the theophylline release profiles from coated granules

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The Eudragit[®] NE 30D coated granules exhibited results similarly to the Surelease[®] coated granules. Lower release profile was obtained from larger size of granules. These results were similar to the results of uncoated granules.

4.4 Theo-24[®] (Commercial Product)

The dissolution data of Theo-24[®] are tabulated in Table 51 (Appendix) and are shown graphically in Figure 57A. The convex curves were turned to the x-axis and had three step.

The release rate profile of Theo-24[®] are tabulated in Table 61 (Appendix) and are shown graphically in Figure 57B. The release rate of this product decreased as the time increased but the decrease of release rate was fluctuated.

5. Comparison of the Percent Coating Level between Surelease[®] and Eudragit[®] NE 30D

For each size of theophylline granules, the equal drug release profiles of Surelease[®] and Eudragit[®] NE 30D coated granules were selected and their percent coating levels were compared. The comparative percent coating levels between Surelease[®] and Eudragit[®] NE 30D are shown graphically in Figures 65-68. Figure 65 shows release profiles of theophylline granules of 16/18 mesh coated with 6.29% of Surelease[®] and 14.76% of Eudragit[®] NE 30D, Figure 66 shows release profiles of theophylline granules of 18/20 mesh coated with 7.61% of Surelease[®] and 19.12% of Eudragit[®] NE 30D, Figure 67 shows release profiles of theophylline granules of 20/25 mesh coated with 3.86% of Surelease[®] and 5.56% of Eudragit[®] NE 30D and Figure 68 shows release

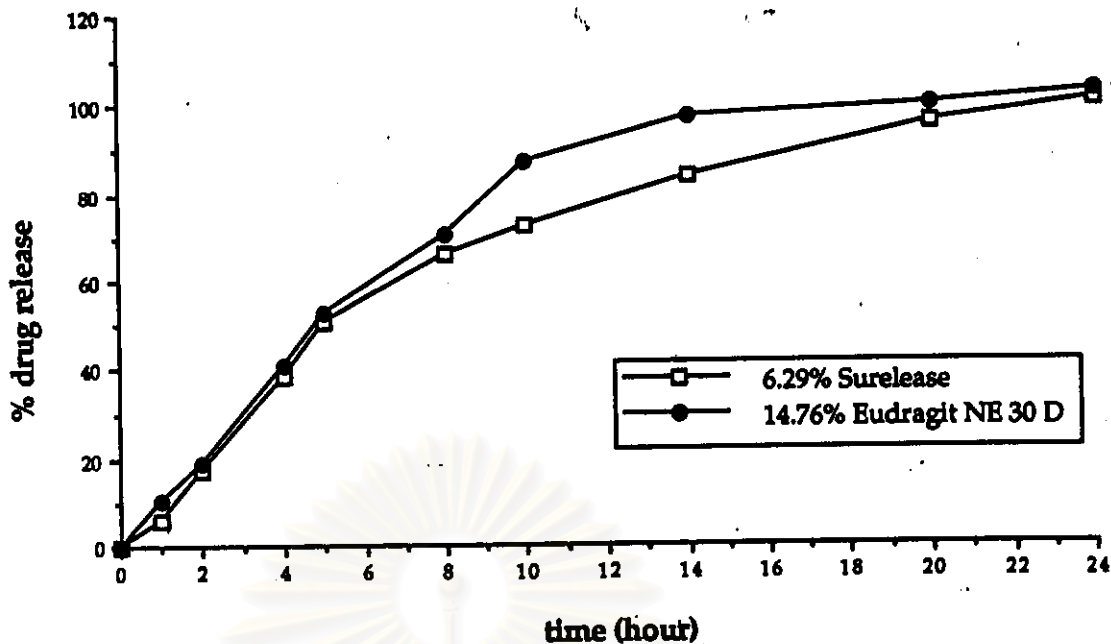


Figure 65 The release profiles between 6.29% Surelease[®] coated granules and 14.76% Eudragit[®] NE 30D coated granules for granules of 16/18 mesh

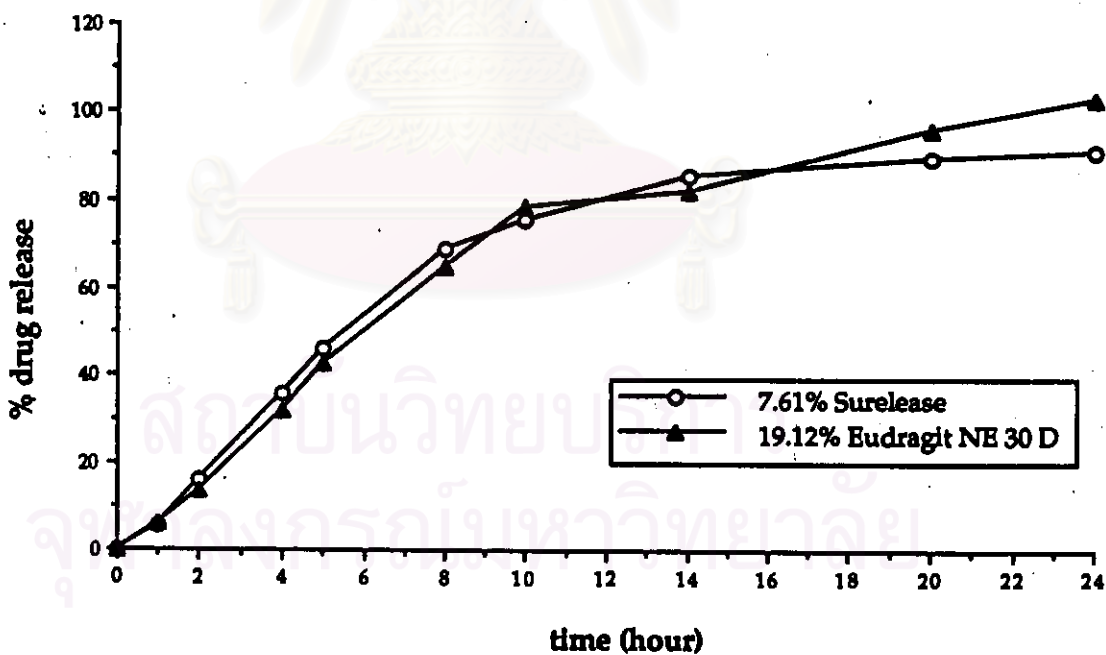


Figure 66 The release profiles between 7.61% Surelease[®] coated granules and 19.12% Eudragit[®] NE 30D coated granules for granules of 18/20 mesh

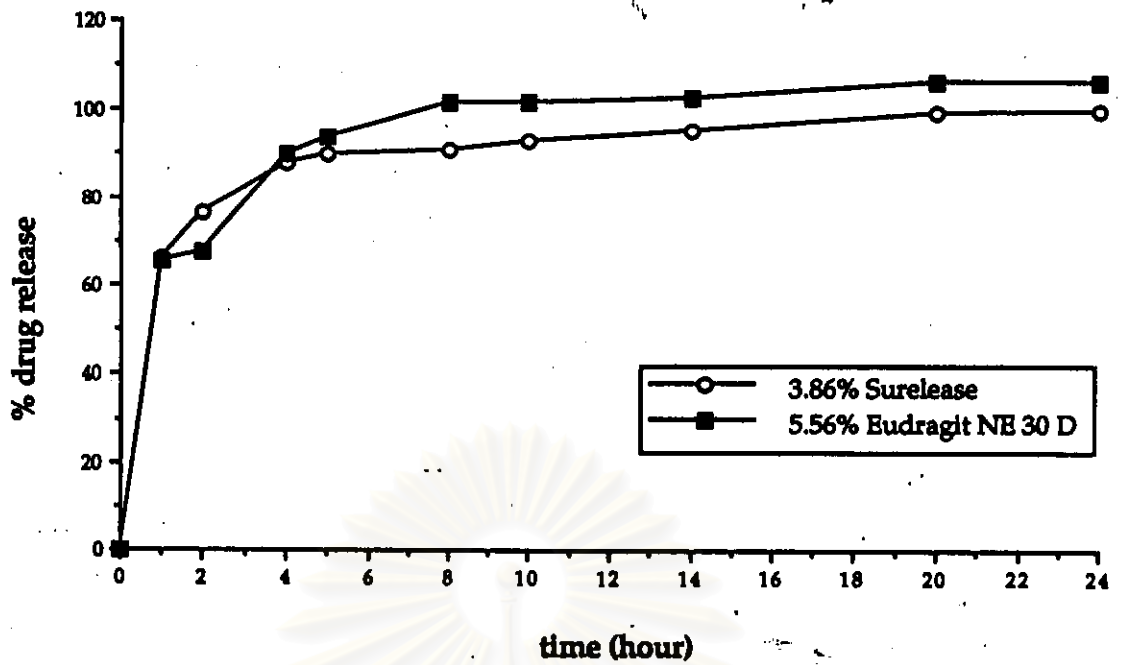


Figure 67 The release profiles between 3.86% Surelease[®] coated granules and 5.56% Eudragit[®] NE 30D coated granules for granules of 20/25 mesh

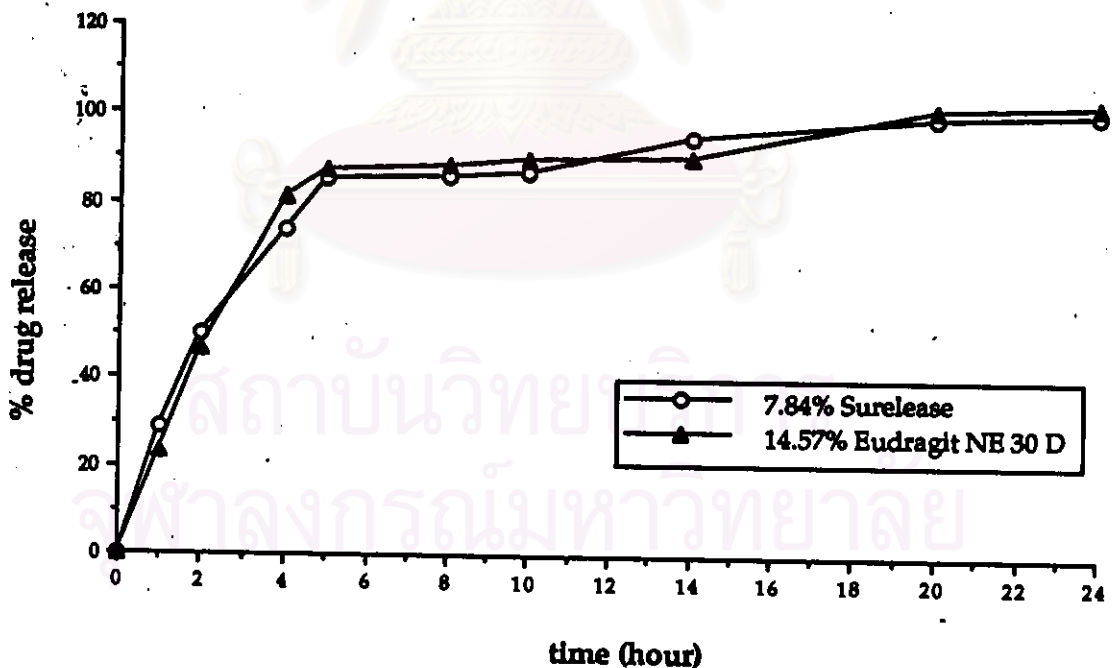


Figure 68 -The release profiles between 7.84% Surelease[®] coated granules and 14.57% Eudragit[®] NE 30D coated granules for granules of 25/30 mesh

profiles of theophylline granules of 25/30 mesh coated with 7.84% of Surelease® and 14.57% of Eudragit® NE 30D.

Each pair of drug release profiles showed no statistical significance difference as shown in Table 75 (Appendix). From the obtained results, for equal drug release the amount of Eudragit® NE 30D used was higher than that of the Surelease®.

6. Dissolution Profiles of Selected Formulations Compared with Commercial Product

The satisfactory formulation were selected and compared their dissolution profiles with available commercial product, Theo-24®. The selections of formulations were based on the drug release at 24 hours interval of not less than 80% with small standard deviation and cumulative percent release of drug conforming to the USP XXIII requirement for the theophylline extended release capsules as shown in Tables 31 and 32.

Figure 69 shows the profiles of all selected formulations of Surelease® coated granules were 6.29% coated granules of 16/18 mesh, 7.61% coated granules of 18/20 mesh, 8.39% coated granules of 20/25 mesh, 12.18% and 13.40% coated granules of 25/30 mesh. Figures 70-73 show the release profiles of them when compared with Theo-24®, respectively.

Figure 74 shows the profiles of all selected formulations of Eudragit® NE 30D coated granules and commercial product. The selected formulation of Eudragit® NE 30D coated granules were 14.76% coated granules of 16/18 mesh, 19.12% coated granules of 18/20 mesh, 20.76% coated granules of 20/25

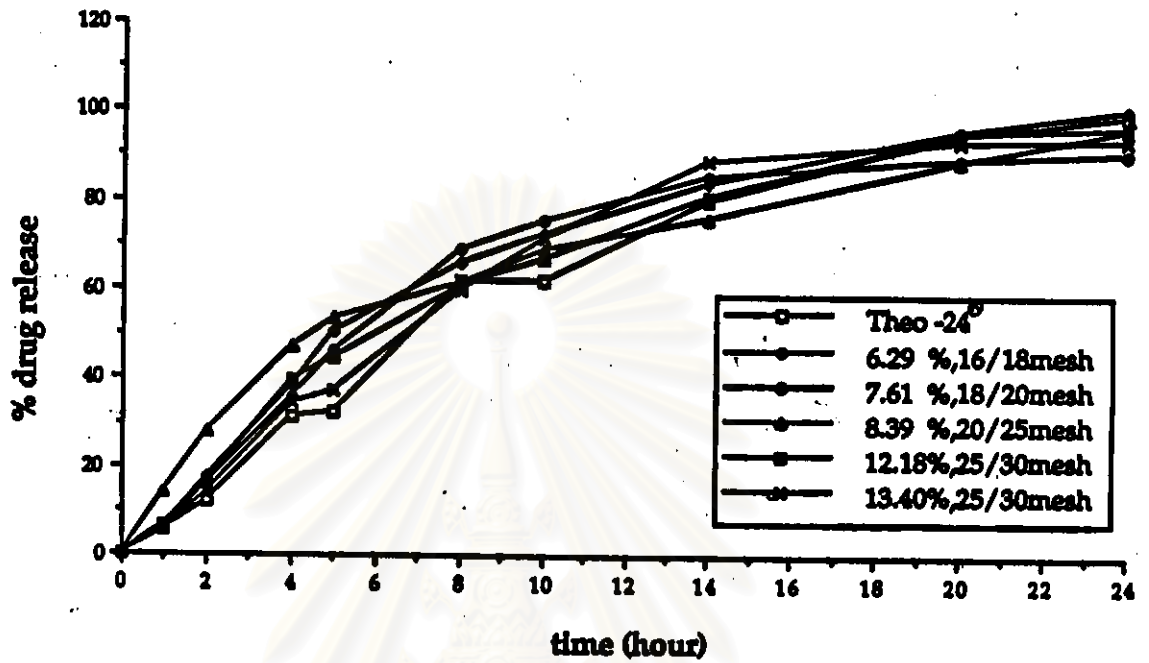


Figure 69 The release profiles from all selected formulations of Surelease[®] coated granules compared with Theo-24[®]

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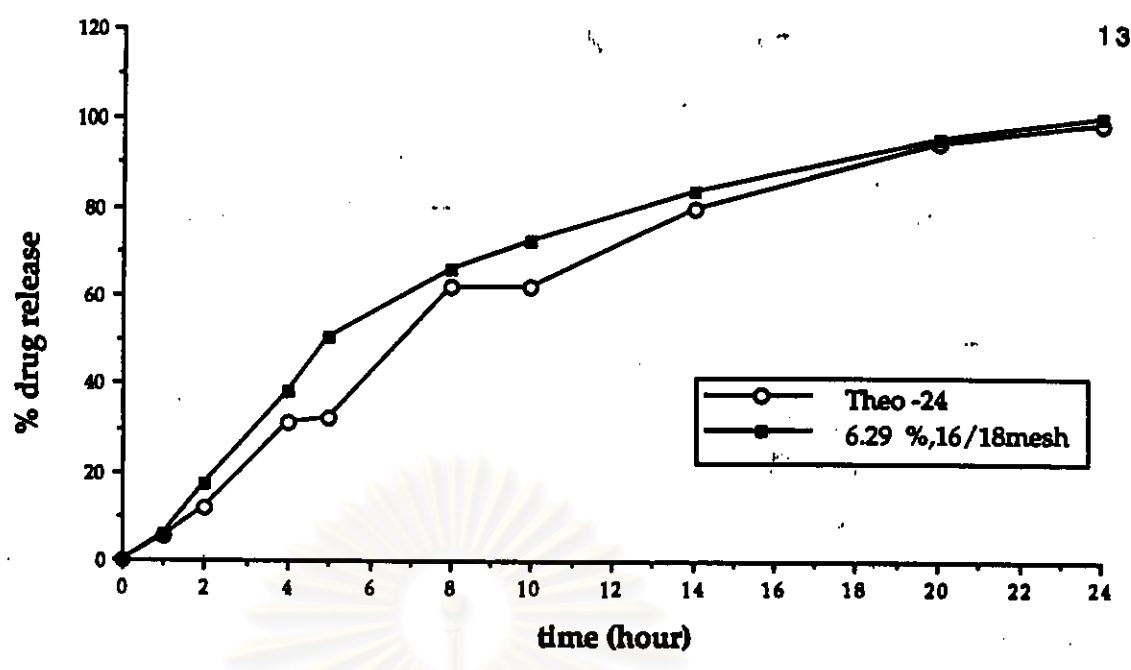


Figure 70 The release profiles from 6.29% Surelease[®] coated granules of 16/18 mesh compared with Theo-24[®]

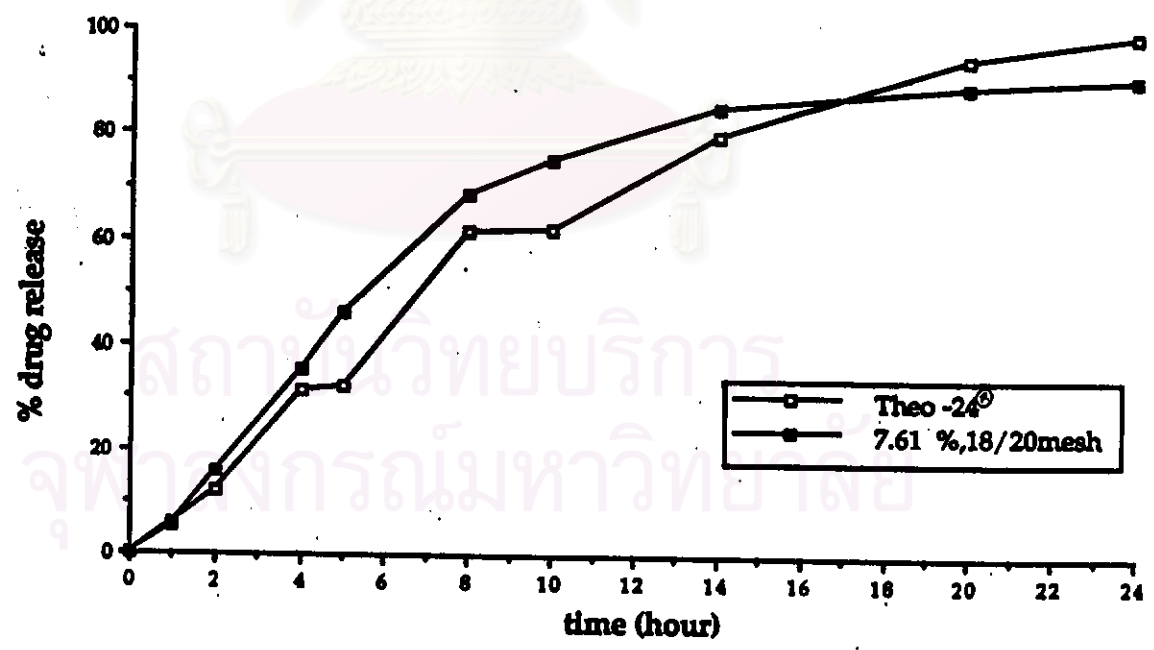


Figure 71 The release profiles from 7.61% Surelease[®] coated granules of 18/20 mesh compared with Theo-24[®]

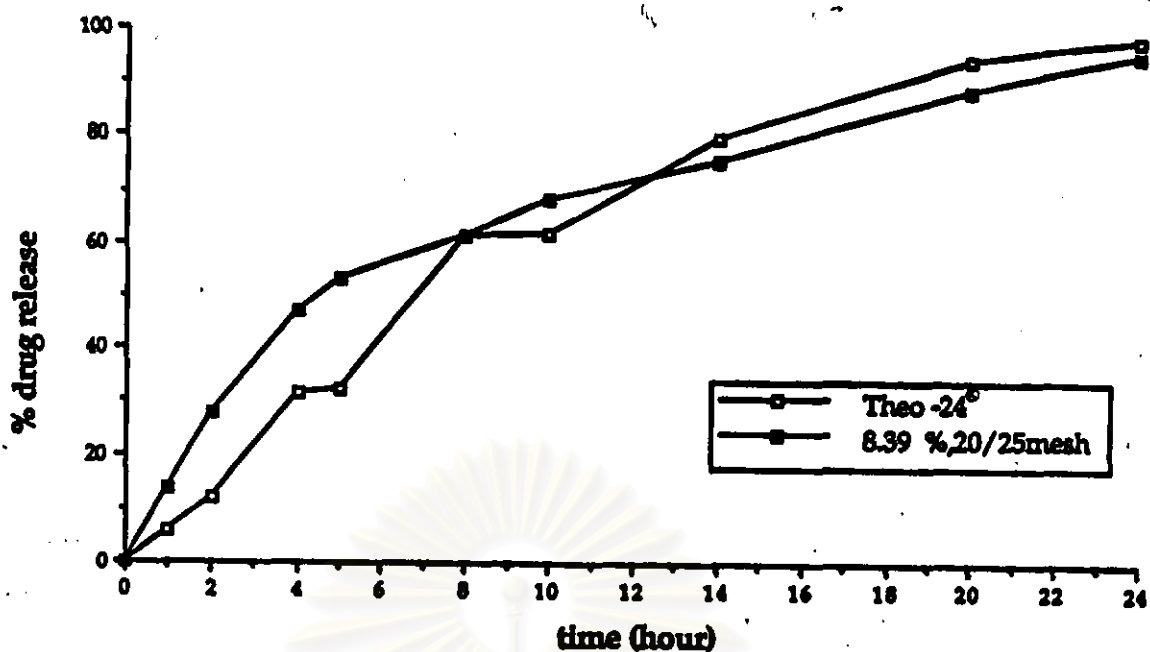


Figure 72 The release profiles from 8.39% Surelease[®] coated granules of 20/25 mesh compared with Theo-24[®]

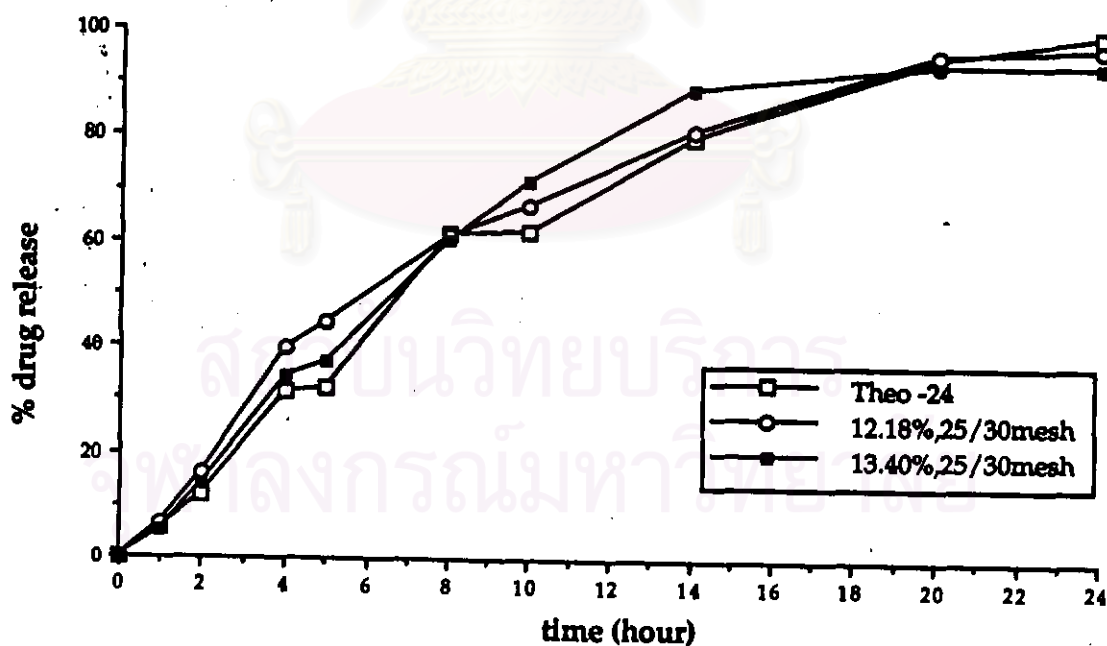


Figure 73 The release profiles from 12.18% and 13.40% Surelease[®] coated granules of 25/30 mesh compared with Theo-24[®]

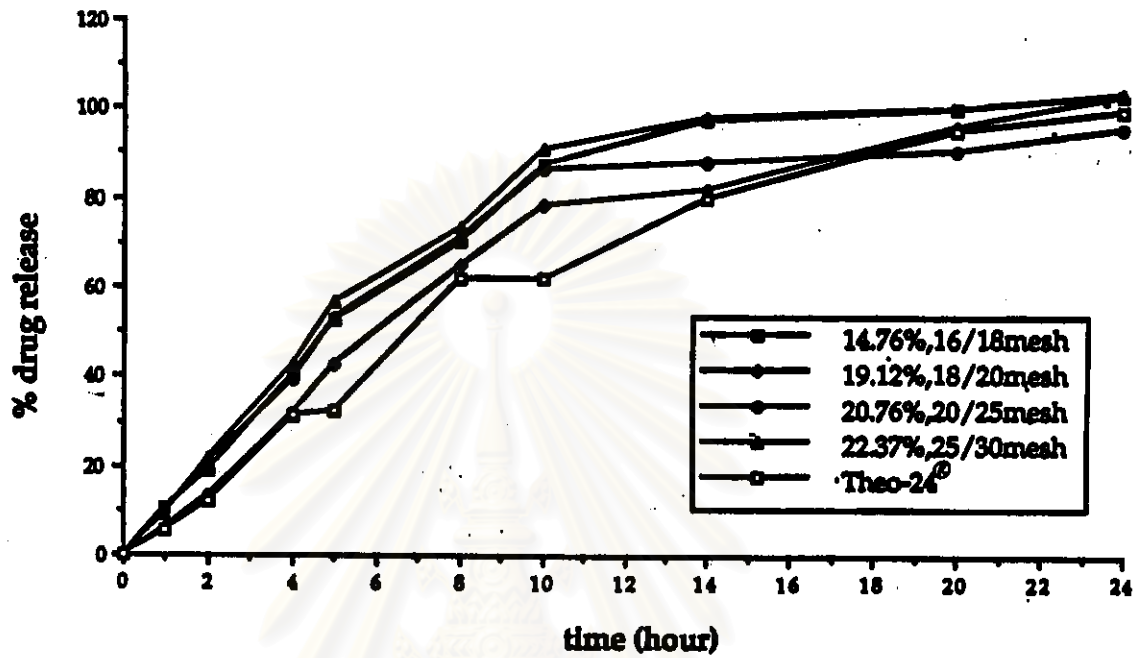


Figure 74 The release profiles from all selected formulations of Eudragit® NE 30D coated granules compared with Theo-24®

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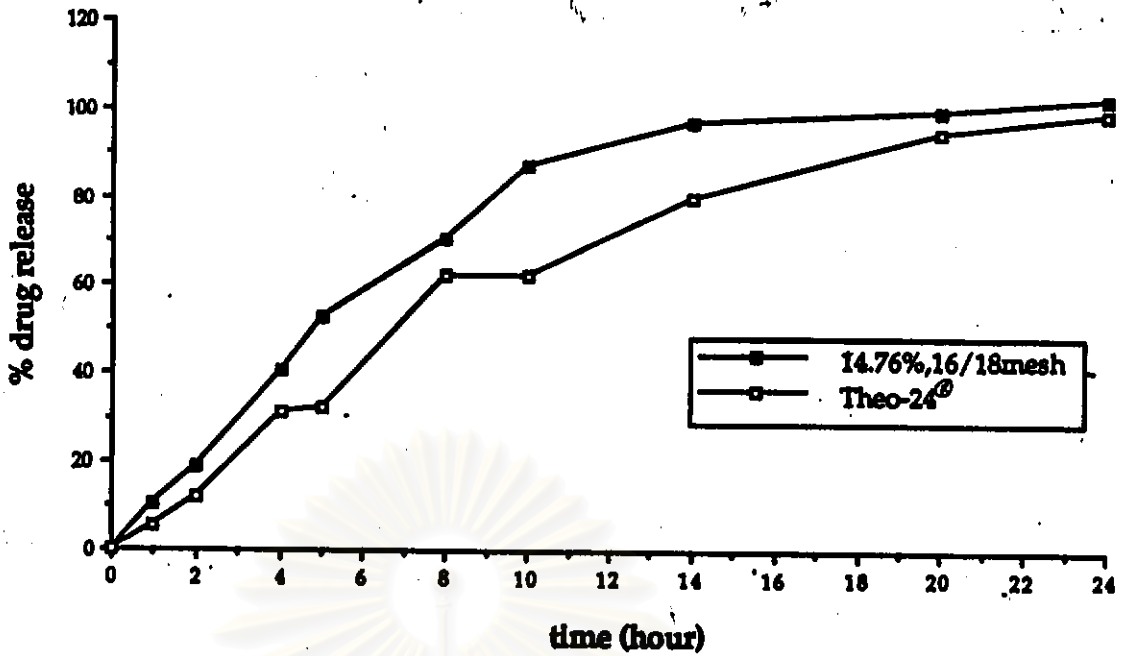


Figure 75 The release profiles from 14.76% Eudragit® NE 30D coated granules of 16/18 mesh compared with Theo-24®

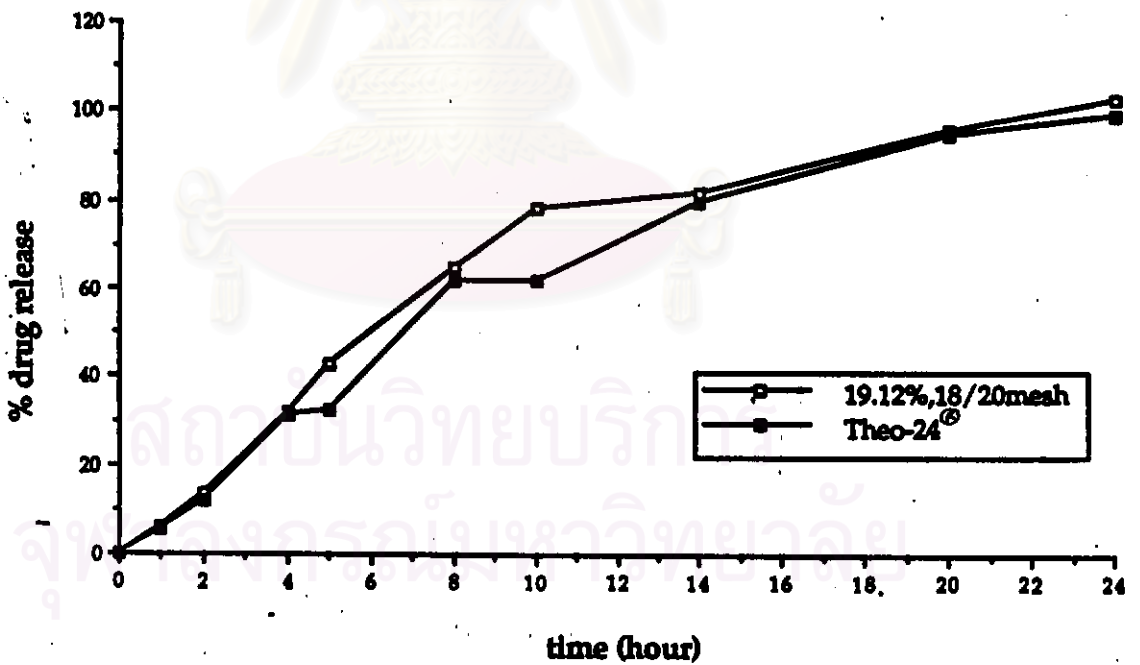


Figure 76 The release profiles from 19.12% Eudragit® NE 30D coated granules of 18/20 mesh compared with Theo-24®

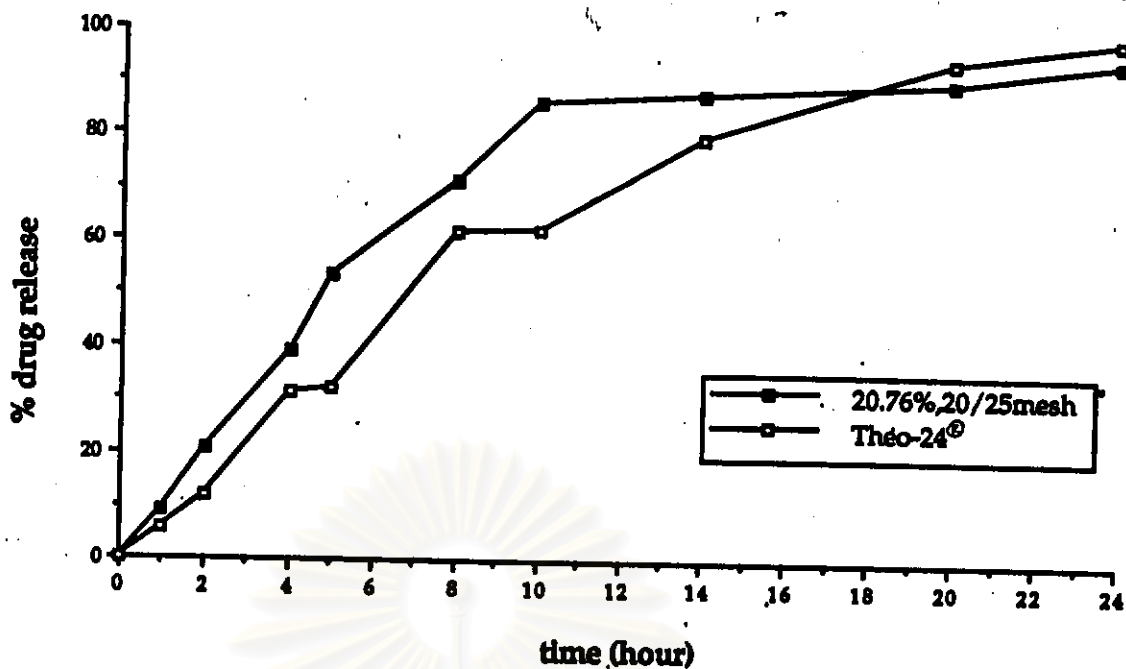


Figure 77 The release profiles from 20.76% Eudragit® NE 30D coated granules of 20/25 mesh compared with Theo-24®

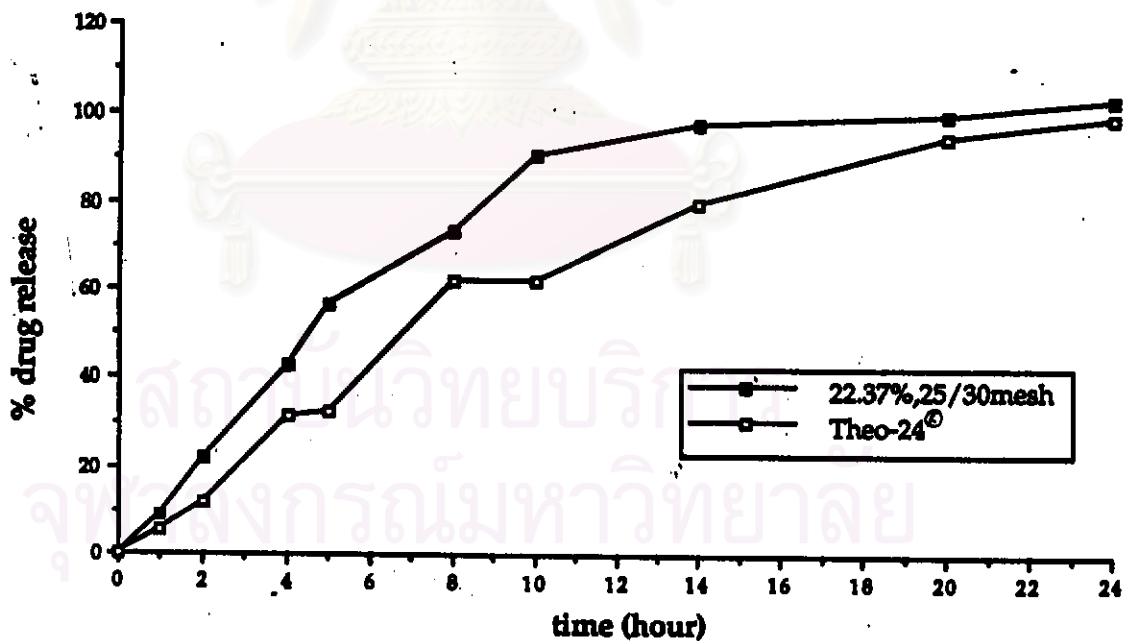


Figure 78 The release profiles from 22.37% Eudragit® NE 30D coated granules of 25/30 mesh compared with Theo-24®

mesh and 22.37% coated granules of 25/30 mesh. Their release profiles are shown in Figures 75-78.

All selected formulations exhibited higher release profiles than Theo-24[®]. Their drug release at 24 hours interval were not less than 80%. The release profiles which were closed to Theo-24[®] were 13.40% Surelease[®] coated granules and 19.12% Eudragit[®] NE 30D coated granules. The statistical significance difference between each selected formulation and Theo-24[®] showed no statistical significance difference (Table 76, Appendix)

7. The Elucidation of Drug Release Model

In order to determine the effect of type of polymer and formulation difference on the model of drug release. Therefore, analysis of all dissolution data were carried out to elucidate the drug release model. The plots between percentage of drug against time (zero-order), log percent of drug remained versus time (first-order), and percentage of drug versus square root of time (Higuchi model) were constructed. The most linear plot was accepted as the model of drug release.

7.1 Uncoated Granules

The correlation coefficient of uncoated granules of various sizes are tabulated in Table 33.

For uncoated granules of various sizes (16/18, 18/20, 20/25 and 25/30 mesh), the highest correlation coefficient were 0.8664, 0.7563, 0.8046 and 0.8721 from the plot of log percent of drug remained versus time respectively.

These results indicated that the theophylline release from all uncoated granules were likely to be first order model.

7.2 Surelease® Coated Granules

The correlation coefficient of Surelease® coated granules are tabulated in Table 34. The highest correlation coefficient of 1.92% and 3.05% coated granules of 16/18 mesh and 7.84% coated granules of 25/30 mesh were obtained from first-order model. High correlation coefficients of other granules were indifferiated between first-order and Higuchi model. Then, it was necessary to distinguish between the models. Further treatment was based upon use of the differential forms of the first order and Higuchi equations (data in Tables 62-65, Appendix). The correlation coefficients of release rate versus Q were higher than those of rates versus $1/Q$ as exhibited in Table 37. Therefore, the theophylline release from these granules were likely to be first-order model.

7.3 Eudragit® NE 30D Coated Granules

The correlation coefficient of Eudragit® NE 30D coated granules are tabulated in Table 35. The highest correlation coefficient of 5.96% coated granules of 16/18 mesh and 14.57% coated granules of 25/30 mesh were obtained from Higuchi model. For 2.51% coated granules of 16/18 mesh, 4.04% and 6.75% coated granules of 18/20 mesh, 5.56% and 11.46% coated granules of 20/25 mesh and 8.83% coated granules of 25/30 mesh, the highest correlation coefficient were obtained from first-order model. Other coated granules exhibited similarly high correlation coefficient in both first-order and Higuchi model. The further treatment revealed that the correlation coefficient of release rate versus Q were higher than those of rates versus $1/Q$ except the

result of 8.53% coated granules of 16/18 mesh which were contrary to the above mentioned as exhibited in Table 38 (data in Tables 66-69, Appendix). It was indicated that theophylline release from these coated granules were first-order model except 8.53% coated granules of 16/18 mesh which was Higuchi model.

7.4 Theo-24[®] (Commercial Product)

The correlation coefficient of Theo-24[®] was tabulated in Table 36. The correlation coefficient of the relationship for first-order and Higuchi model were interested. Further treatment as exhibited in Table 39 indicated that theophylline release from Theo-24[®] was first-order model.

Table 31 USP XXIII Requirement and Cumulative Percent Release of Drug from Selected Formulations of Surelease[®] Coated Granules

Time (hr.)	% Release (Surelease [®])					
	USP range	Size of Granules (mesh)				
		Percent Coated	16/18	18/20	20/25	25/30
		6.29	7.61	8.39	12.18	13.40
1	5-15	5.89	5.50	13.72	6.50	5.46
2	12-30	17.32	15.86	27.83	15.99	13.95
4	25-50	38.15	35.51	47.31	39.48	34.14
5	30-60	50.81	46.36	53.33	44.48	37.30
8	55-75	65.91	68.73	61.73	61.11	60.16
10	—	72.38	75.38	68.75	66.78	71.45
14	—	83.59	85.29	75.80	80.99	88.87
20	—	95.73	89.13	88.75	95.26	93.43
24	—	100.54	90.75	96.43	96.60	93.50

Table 32 USP XXIII Requirement and Cumulative Percent Release of Drug from Selected Formulations of Eudragit® NE 30D Coated Granules

Time (hr.)	% Release (Surelease®)				
	USP range	Size of Granules (mesh)			
		Percent Coated			
		16/18 14.76	18/20 19.12	20/25 20.76	25/30 22.37
1	5-15	10.46	5.89	9.25	9.17
2	12-30	18.68	13.30	20.61	21.80
4	25-50	40.49	31.65	39.37	42.84
5	30-60	52.44	42.54	53.29	56.74
8	55-75	70.23	65.08	71.47	73.18
10	—	87.29	78.26	86.17	90.59
14	—	96.99	81.74	87.96	97.44
20	—	99.65	95.86	90.37	99.48
24	—	102.84	102.67	95.14	103.20

Table 33 Correlation Coefficient of the Relationships between Percent Drug Released versus Time (A), Percent Drug Released versus Square Root Time (B), and Log Percent Drug Remained versus Time (C) from Uncoated Granules

Size of Granules (mesh)	A	B	C
16/18	0.6384	0.2464	0.8664
18/20	0.5328	0.2109	0.7563
20/25	0.4594	0.4594	0.8046
25/30	0.4233	0.1475	0.8721

Table 34 Correlation Coefficient of the Relationships between Percent Drug Released versus Time (A), Percent Drug Released versus Square Root Time (B), and Log Percent Drug Remained versus Time (C) from Theophylline Granules Coating with Surelease®.

Size of Granules (mesh)	Percent Coated	A	B	C
16/18	1.92	0.4667	0.7337	0.8178
	3.05	0.6560	0.8746	0.9837
	3.87	0.6240	0.8442	0.8714
	6.29	0.8708	0.9666	0.9840
18/20	2.04	0.6407	0.8514	0.9259
	3.29	0.7317	0.9095	0.9575
	7.61	0.8117	0.9334	0.9534
	9.00	0.9516	0.9727	0.9912
20/25	2.48	0.2990	0.5458	0.8124
	3.86	0.3793	0.6416	0.9356
	8.39	0.8516	0.9788	0.9615
	12.12	0.9032	0.9633	0.9136
25/30	7.84	0.5988	0.8388	0.9509
	12.18	0.8907	0.9736	0.9619
	13.40	0.8704	0.9503	0.9676
	17.05	0.9169	0.9638	0.9839

Table 35 Correlation Coefficient of the Relationships between Percent Drug Released versus Time (A), Percent Drug Released versus Square Root Time (B), and Log Percent Drug Remained versus Time (C) from Theophylline Granules Coating with Eudragit® NE 30D .

Size of Granules (mesh)	Percent Coated	A	B	C
16/18	2.51	0.2972	0.5486	0.8906
	5.96	0.4605	0.7276	0.5218
	8.53	0.7137	0.8995	0.9186
	14.76	0.8260	0.9435	0.9649
18/20	4.04	0.2831	0.5362	0.9042
	6.75	0.5536	0.7999	0.9258
	10.93	0.7210	0.9151	0.9030
	19.12	0.8853	0.9576	0.9763
20/25	5.56	0.3779	0.7131	0.9633
	11.46	0.6033	0.8493	0.9419
	15.00	0.7457	0.9150	0.9809
	20.76	0.7798	0.9227	0.9940
25/30	8.83	0.4857	0.7491	0.9427
	14.57	0.5720	0.8073	0.7561
	17.68	0.7239	0.9086	0.9850
	22.37	0.8007	0.9343	0.9792

Table 36 Correlation Coefficient of the Relationships between Percent Drug Released versus Time (A), Percent Drug Released versus Square Root Time (B), and Log Percent Drug Remained versus Time (C) from Theo-24[®] (Commercial Product)

Formulation	A	B	C
Theo-24 [®]	0.9251	0.9648	0.9222

Table 37 Comparison of Linearity between Plots of Rate of Release Against Reciprocal Amount ($1/Q$) and Amount (Q) of Theophylline Release from Theophylline Granules Coating with Surelease[®]

Size of Granules (mesh)	Percent Coated	Correlation Coefficient of Rate dQ/dt	
		Versus Q	Versus $1/Q$
16/18	3.87	0.7394	0.4388
	6.29	0.5150	0.0352
18/20	3.29	0.7758	0.4383
	7.61	0.5271	0.0349
	9.00	0.6769	0.5712
20/25	8.39	0.8631	0.6754
	12.12	0.3784	0.0686
25/30	12.18	0.5903	0.1271
	13.40	0.4094	0.0531
	17.05	0.0112	0.0053

Table 38 Comparison of Linearity between Plots of Rate of Release Against Reciprocal Amount ($1/Q$) and Amount (Q) of Theophylline Release from Theophylline Granules Coating with Eudragit[®] NE 30D

Size of Granules (mesh)	Percent Coated	Correlation Coefficient of Rate dQ/dt	
		Versus Q	Versus $1/Q$
16/18	8.53	0.2415	0.3856
	14.76	0.6113	0.2095
18/20	10.93	0.7500	0.6740
	19.12	0.4296	0.0489
20/25	15.00	0.8503	0.6815
	20.76	0.5666	0.1761
25/30	17.68	0.7053	0.3405
	22.37	0.5782	0.1441

Table 39 Comparison of Linearity between Plots of Rate of Release Against Reciprocal Amount ($1/Q$) and Amount (Q) of Theophylline Release from Theo-24[®], 200 mg

Product	Correlation Coefficient of Rate dQ/dt	
	Versus Q	Versus $1/Q$
Theo-24 [®]	0.1444	0.0489