CHAPTER III

RESULTS

Physical Properties of Lactose-Avicel PH101^{R} Placebo Pellets Prepared with Various Spheronization Times, Binder Types and Concentrations

1 Determination of Placebo Pellets Appearance

1.1 Methocel E-15LV^{R}

The microscopic appearance of lactose-Avicel PH101^{R} pellets using Methocel E-15LV^{R} as a binder are illustrated in Figures 12 and 13. At 414 rpm of spheronizer speed, pellets appeared to be rod shape. Shorter rod shape combined with a little sphere pellets with smooth surface were received when spheronization time was increased.In the case of binder concentration increased, the pellets of longer rod shape with more smooth surface were obtained. At spheronizer speed of 951 rpm,pellets were quite sphere shape. Increasing in sphericity with more smooth surface of pellets were obtained when spheronization time was increased. The binder concentration increased, the pellets were slightly increased in size, more smooth surface but decreased in sphericity.

1.2 HPC-L^{R}

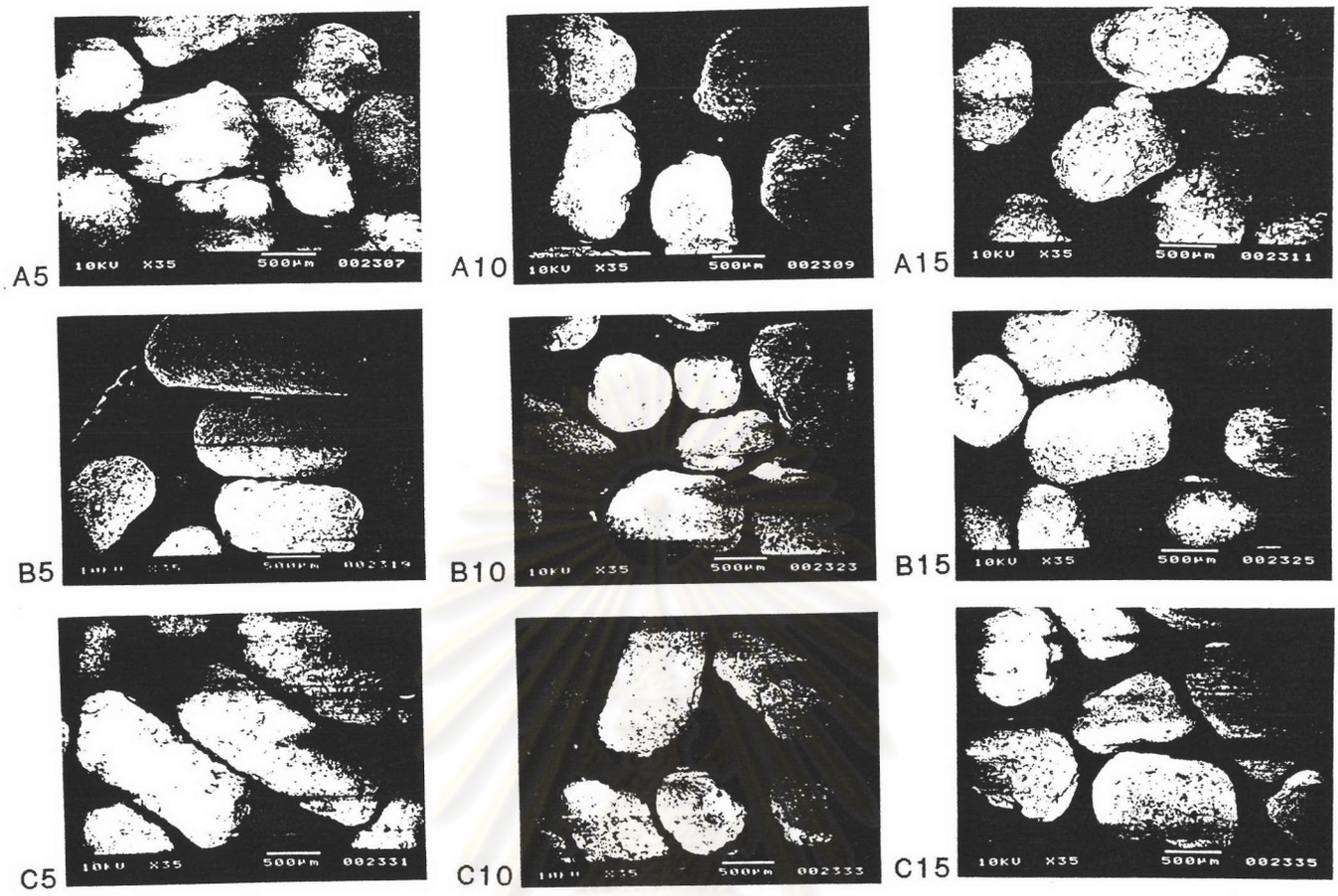

Figure 12 Photomicrographs of lactose-Avicel PH101^{R} pellets using various concentrations of Methocel E-15LV^{R} as a function of spheronization times at spheronizer speed of 414 rpm (x35) (A5,A10,A15 are 1.33 % w/w of binder concentration at 5,10, 15 min of spheronization time; B5,B10,B15 are 1.67 % w/w of binder concentration at 5,10,15 min of spheronization time and C5,C10,C15 are 2.00 % w/w of binder concentration at 5, 10,15 min of spheronization time)

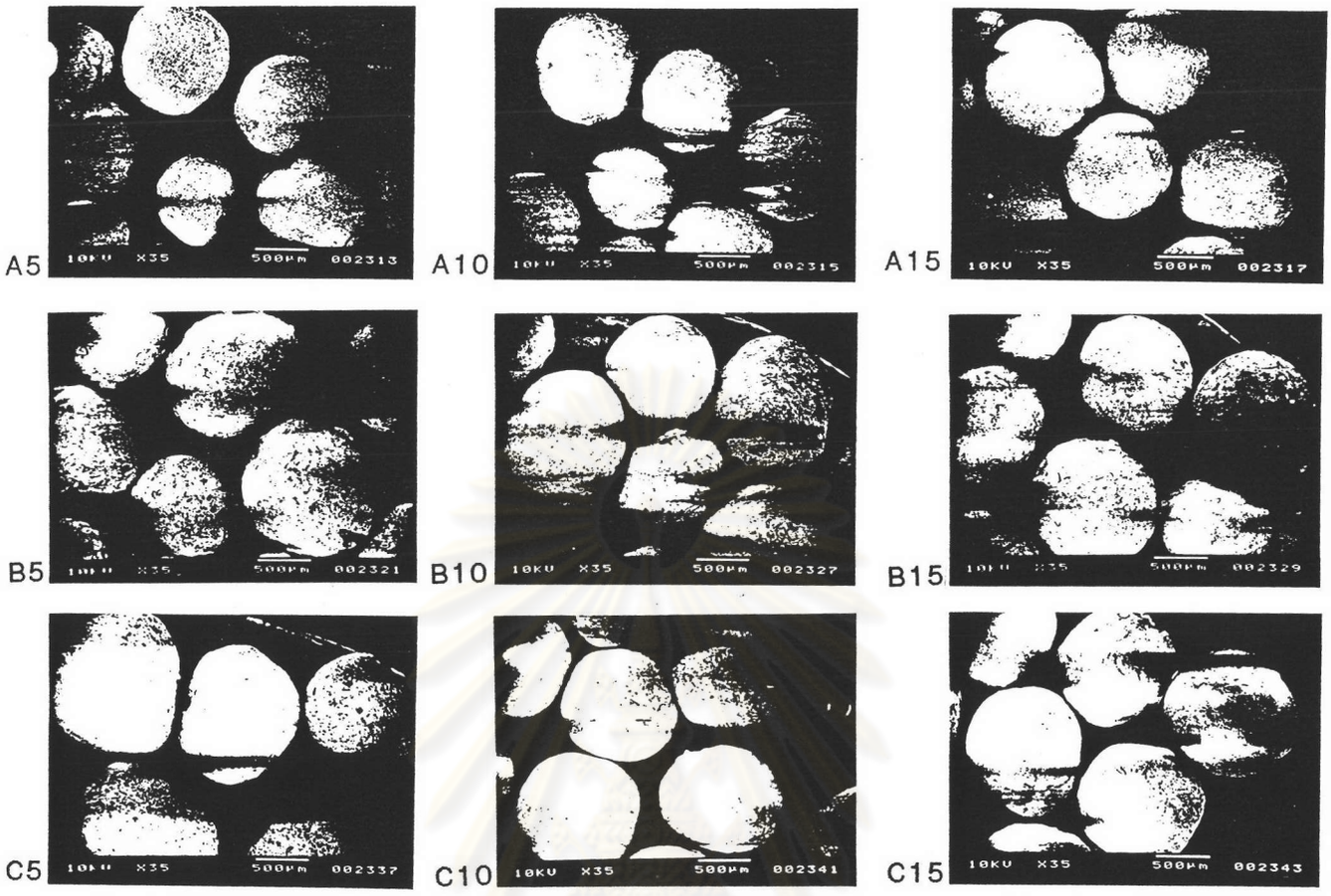

Figure 13 Photomicrographs of lactose-Avicel PH101^{R} pellets using various concentrations of Methocel E-15LV^{R} as a function of spheronization times at spheronizer speed of 951 rpm (x35) (A5,A10,A15 are 1.33 % w/w of binder concentration at 5,10, 15 min of spheronization time; B5,B10,B15 are 1.67 % w/w of binder concentration at 5,10,15 min of spheronization time; and C5,C10,C15 are 2.00 % w/w of binder concentration at 5, 10,15 min of spheronization time)

The microscopic appearance of lactose-Avicel PH101^{R} pellets using HPC-L^{R} as a binder are presented in Figures 14 and 15. At spheronizer speed of 414 rpm, rod shape of pellets were observed. Increasing spheronization time gave more smooth surface. In addition, increasing binder concentration had slightly increased in size of pellets. The orders of smooth surface appearance of pellets were as followed : binder concentration 1.67 % w/w > 2.00 % w/w > 1.33 % w/w. At 951 rpm of spheronizer speed, sphere shape pellets were obtained. Increasing in sphericity with more smooth surface of pellets were obtained from increasing spheronization time. Increasing in rough surface of pellets were received from increasing binder concentration.

1.3 Methocel A4M^{R}

The microscopic appearance of lactose-Avicel PH101^{R} pellets using Methocel A4M^{R} as a binder are shown in Figures 16 and 17. At 414 rpm of spheronizer speed, rod shape pellets were also observed. Combination of shorter rod shape and sphere pellets with smooth surface were increased with increasing spheronization time. Longer rod shape with rough surface pellets were increased with increasing binder concentration. At speed of 951 rpm, pellets were quite sphere shape. Sphericity with smooth surface of pellets were increased with increasing spheronization time. Increasing binder concentration had decreased in sphericity, increased in size and increased in rough surface of pellets.

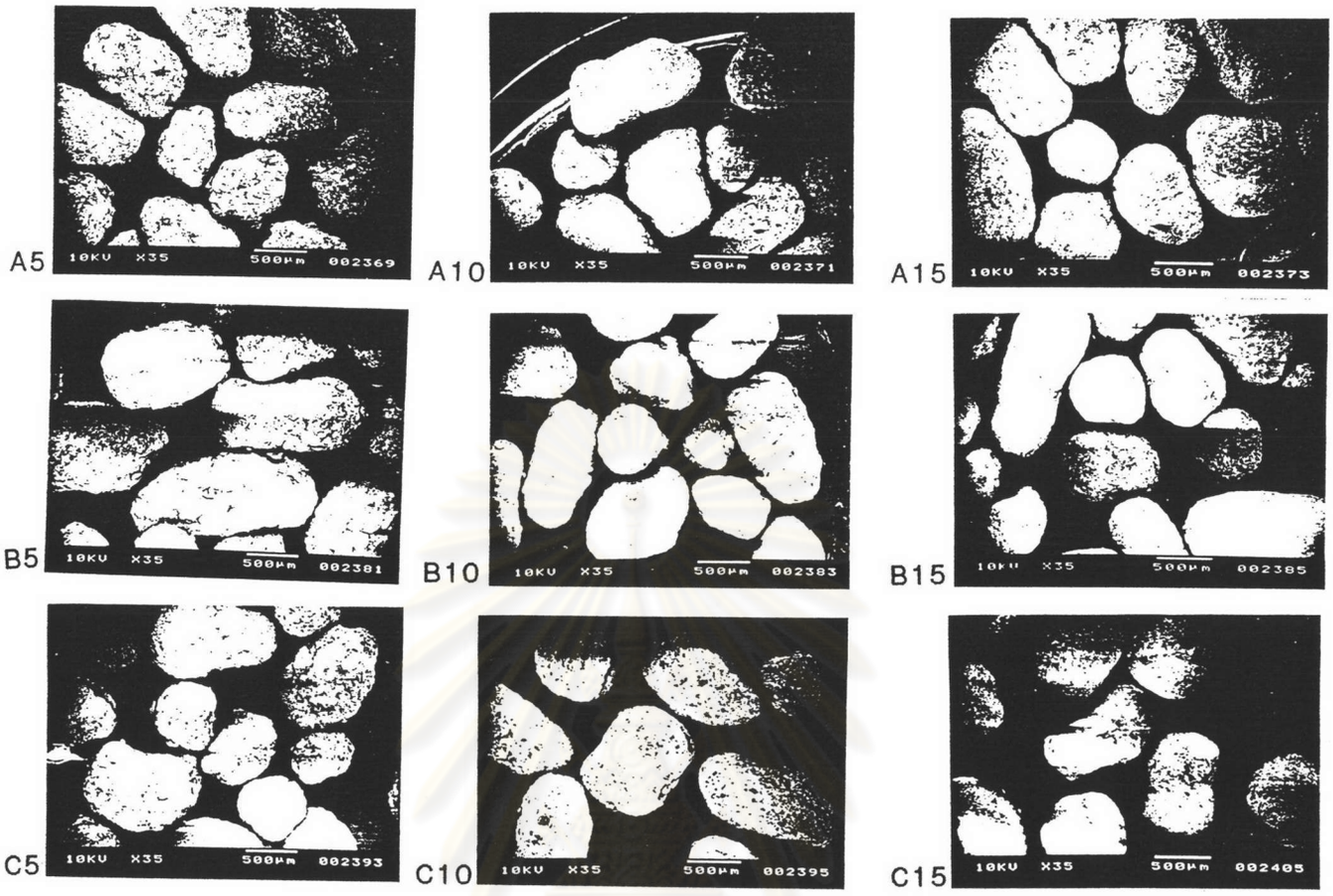

Figure 14 Photomicrographs of lactose-Avicel PH101^{R} pellets using various concentration of HPC-L^{R} as a function of spheronization times at spheronizer speed of 414 rpm (x35)
(A5,A10,A15 are 1.33 % w/w of binder concentration at 5,10, 15 min of spheronization time; B5,B10,B15 are 1.67 % w/w of binder concentration at 5,10,15 min of spheronization time; and C5,C10,C15 are 2.00 % w/w of binder concentration at 5, 10,15 min of spheronization time)

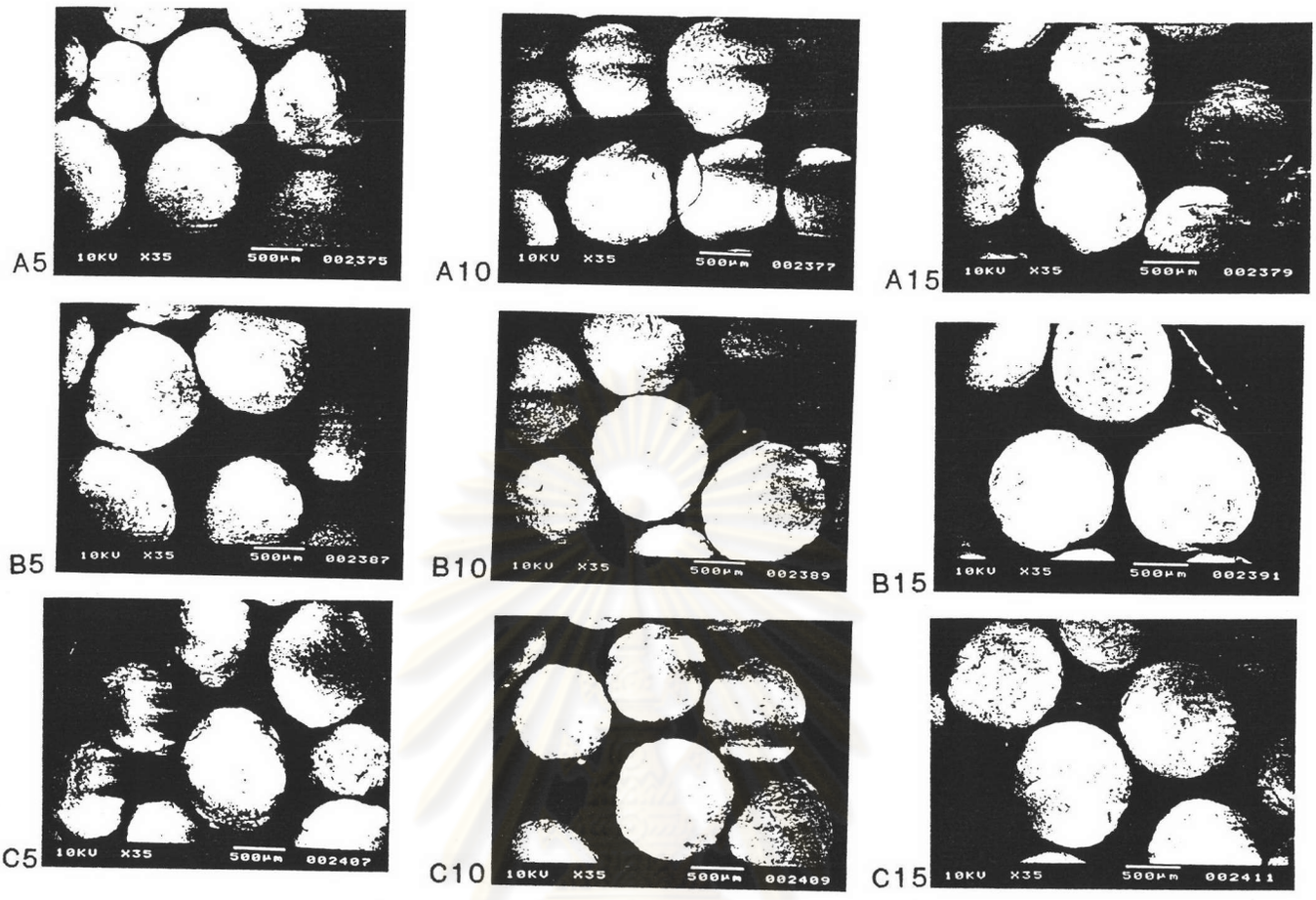

Figure 15 Photomicrographs of lactose-Avicel PH101^{R} pellets using various concentration of HPC-L^{R} as a function of spheronization times at spheronizer speed of 951 rpm (x35)
(A5,A10,A15 are 1.33 % w/w of binder concentration at 5,10, 15 min of spheronization time; B5,B10,B15 are 1.67 % w/w of binder concentration at 5,10,15 min of spheronization time; and C5,C10,C15 are 2.00 % w/w of binder concentration at 5, 10,15 min of spheronization time)

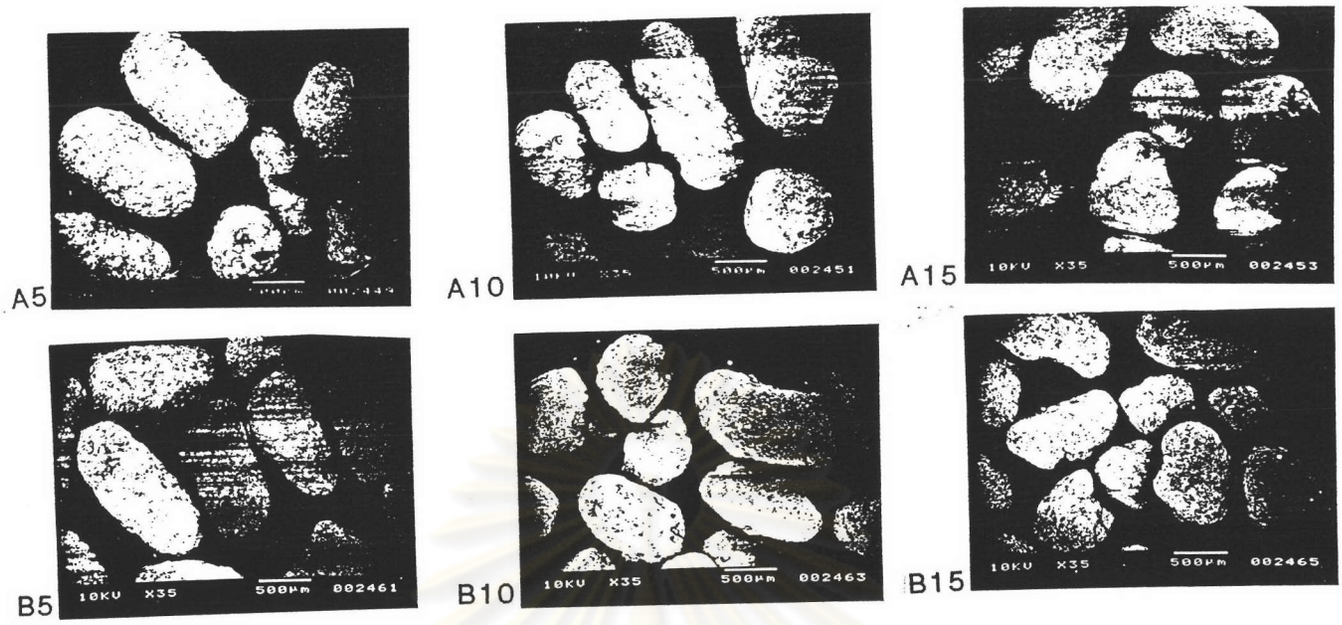

Figure 16 Photomicrographs of lactose-Avicel PH101^{R} pellets using various concentration of Methocel A4M^{R} as a function of spheronization times at spheronizer speed of 414 rpm (x35) (A5,A10,A15 are 0.33 % w/w of binder concentration at 5,10, 15 min of spheronization time; B5,B10,B15 are 0.67 % w/w of binder concentration at 5,10,15 min of spheronization time)

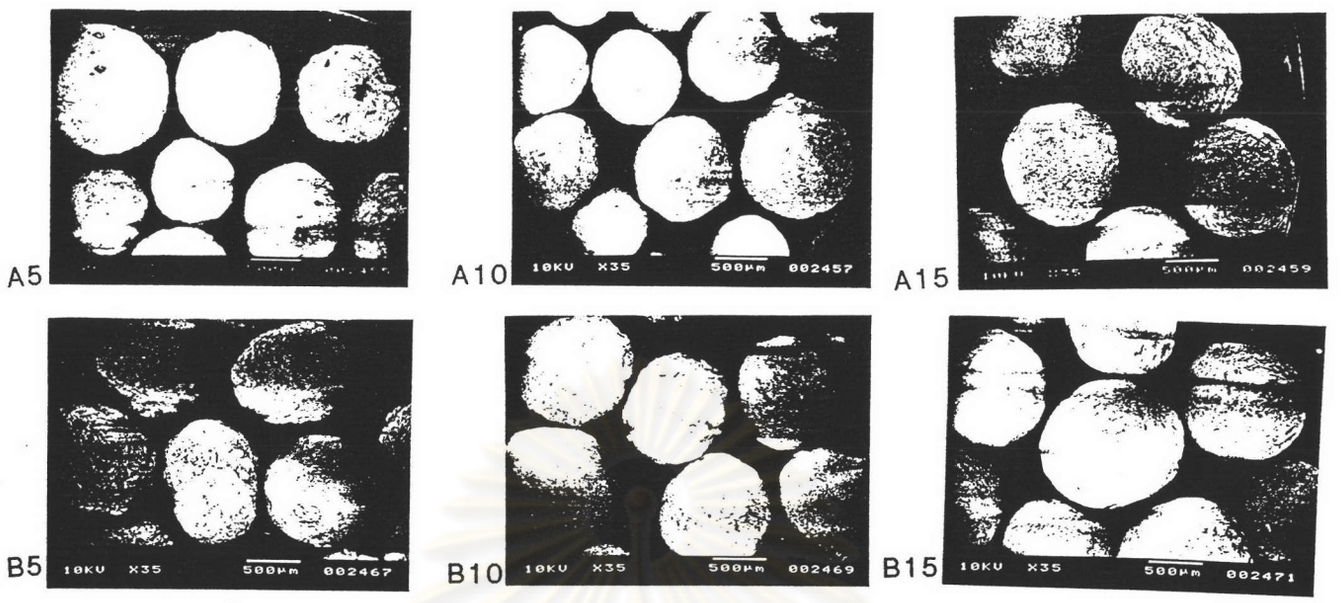

Figure 17 Photomicrographs of lactose-Avicel PH101^{R} pellets using various concentration of Methocel A4M^{R} as a function of spheronization times at spheronizer speed of 951 rpm (x35) (A5,A10,A15 are 0.33 % w/w of binder concentration at 5,10, 15 min of spheronization time; B5,B10,B15 are 0.67 % w/w of binder concentration at 5,10,15 min of spheronization time)

1.4 HPC-M^R

The microscopic appearance of lactose-Avicel PH101^R pellets using HPC-M^R as a binder are presented in Figures 18 and 19. At 414 rpm of spheronizer speed, rod shape pellets were obtained. Combination of shorter rod shape and sphere pellets with more smooth surface were also obtained from increasing spheronization time.However, longer rod shape with smooth surface of pellets were increased with increasing binder concentration. At 951 rpm of spheronizer speed, pellets were quite sphere shape. Sphericity with smooth surface of pellets were increased with increasing spheronization time.In different binder concentration, the highest sphericity with smooth surface of placebo pellets were obtained from 1.67 % w/w of binder concentration.

1.5 Compared Type of Binders at Different Concentrations and Spheronization Times on Microscopic Appearance of Placebo Pellets

At spheronizer speed of 951 rpm, pellets using HPC-M^R as a binder were more sphericity with smooth surface than pellets using HPC-L^R or Methocel E-15LV^R as binder.

2 Particle Size Distribution

Particle size distribution of lactose-Avicel PH101^R pellets are presented in Tables 6-9 and Figures 20-31. Pellets using HPC-M^R as a binder were more narrow size distribution than pellets using the other binders.

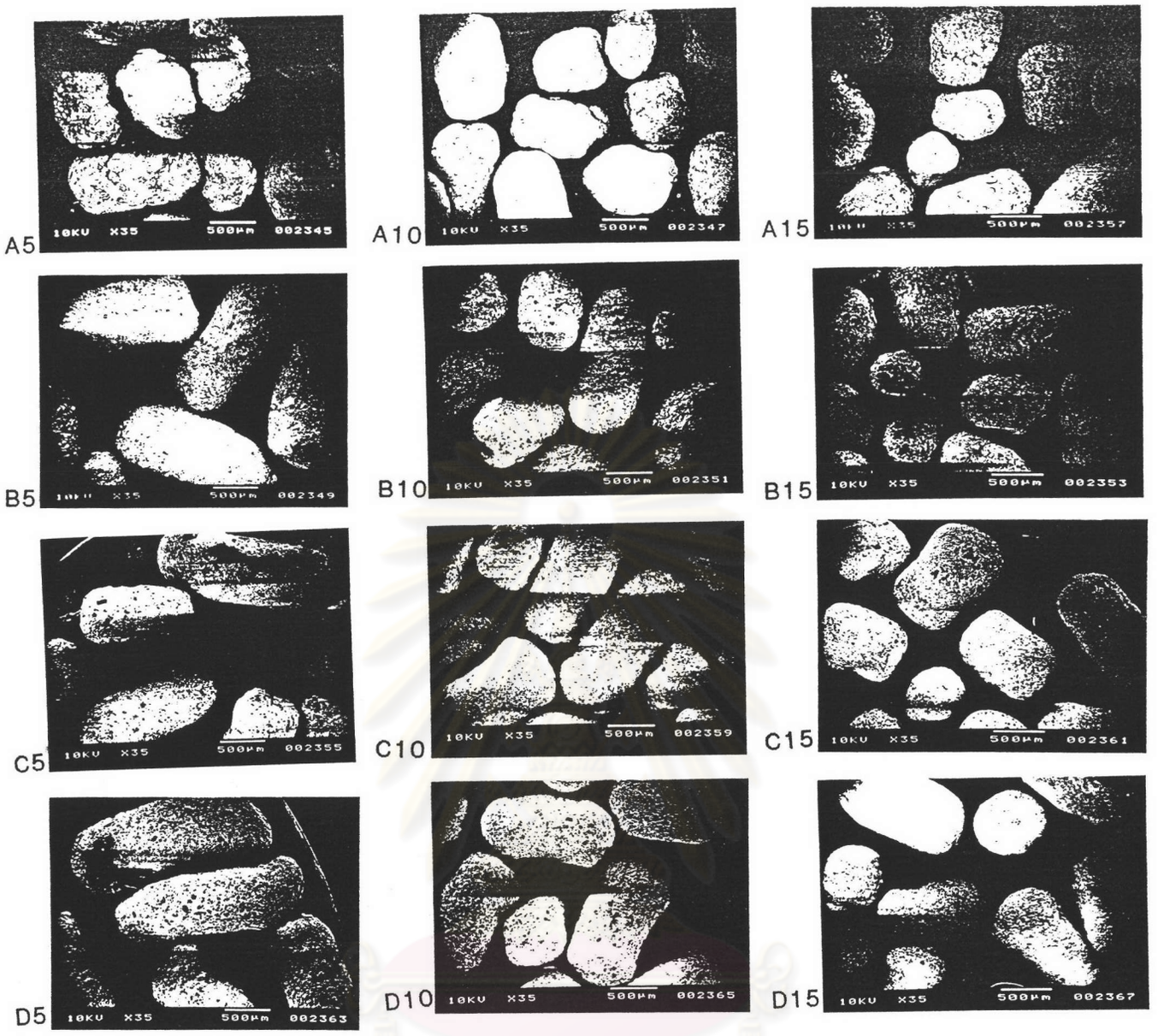

Figure 18 Photomicrographs of lactose-Avicel PH101^{R} pellets using various concentration of HPC-M^{R} as a function of spheronization times at spheronization speed of 414 rpm (x35)
(A5,A10,A15 are 1.33 % w/w of binder concentration at 5,10, 15 min of spheronization time; B5,B10,B15 are 1.67 % w/w of binder concentration at 5,10,15 min of spheronization time; C5,C10,C15 are 2.00 % w/w of binder concentration at 5,10, 15 min of spheronization time and D5,D10,D15 are 2.33 % w/w of binder concentration at 5,10,15 min of spheronization time)

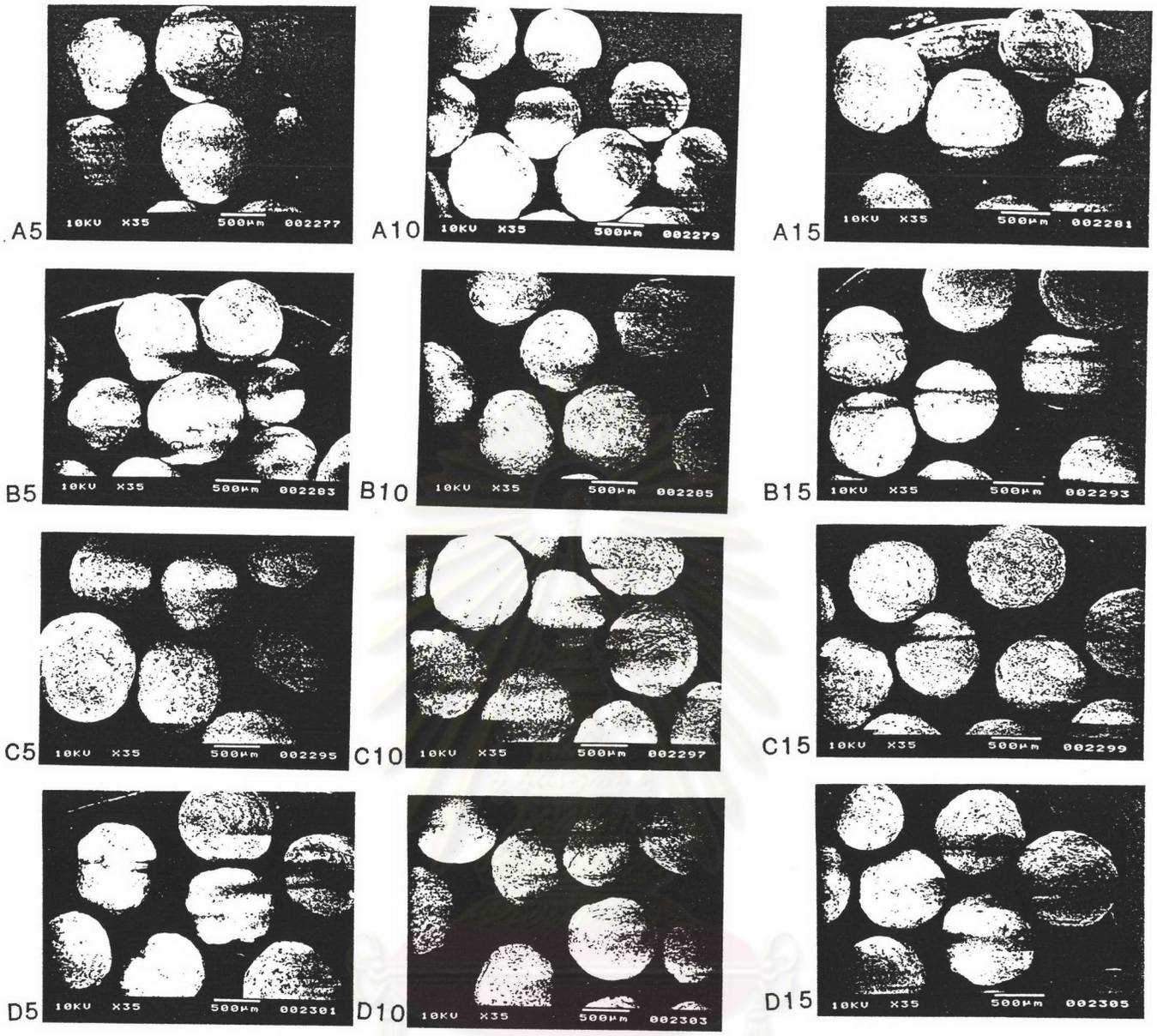

Figure 19 Photomicrographs of lactose-Avicel PH101^{R} pellets using various concentration of HPC-M^{R} as a function of spheronization times at spheronization speed of 951 rpm (x35)
(A5,A10,A15 are 1.33 % w/w of binder concentration at 5,10, 15 min of spheronization time; B5,B10,B15 are 1.67 % w/w of binder concentration at 5,10,15 min of spheronization time; C5,C10,C15 are 2.00 % w/w of binder concentration at 5,10, 15 min of spheronization time and D5,D10,D15 are 2.33 % w/w of binder concentration at 5,10,15 min of spheronization time)

Table 6 Sieve analysis of lactose-Avicel PH101^{R} pellets prepared with various spheronization times and concentrations of hydroxypropyl methylcellulose (Methocel E-15LV^{R})

Concentration (% w/w)	Spheronization Time (min)	% Weight Retained (a) Sieve No. 14	18	20	40	60	Pan
1.33	5	6.44	25.71	32.90	33.30	1.62	0.02
	10	11.72	27.19	29.61	30.16	1.31	0.01
	15	10.04	28.16	32.66	28.83	0.32	0.00
1.67	5	43.20	30.21	13.02	10.03	2.84	0.70
	10	47.59	27.47	12.98	9.30	2.35	0.31
	15	54.26	26.73	11.70	6.06	1.14	0.10
2.00	5	29.99	29.96	17.23	18.90	3.74	0.18
	10	37.55	26.63	15.26	17.96	2.57	0.05
	15	32.53	24.52	16.50	23.71	2.65	0.08

(a) averaged from two determinations

Table 7 Sieve analysis of lactose-Avicel PH101^{R} pellets prepared with various spheronization times and concentrations of hydroxypropyl cellulose (HPC-L^{R})

Concentration (% w/w)	Spheronization Time (min)	% Weight Retained (a) Sieve No. 14	18	20	40	60	Pan
1.33	5	13.01	30.25	22.68	24.29	7.98	1.80
	10	19.54	30.74	20.57	19.42	8.81	0.91
	15	24.77	34.11	22.34	15.86	2.76	0.40
1.67	5	22.00	33.31	17.13	15.22	8.92	3.42
	10	40.85	30.72	12.93	8.74	5.90	0.86
	15	54.62	29.18	10.01	4.53	1.51	0.15
2.00	5	14.94	35.79	20.65	16.76	8.82	3.06
	10	27.97	32.29	18.60	14.19	6.38	0.58
	15	40.23	34.04	17.29	7.86	0.56	0.02

(a) averaged from two determinations

Table 8 Sieve analysis of lactose-Avicel PH101^{R} pellets prepared with various spheronization times and concentrations of hydroxypropyl methylcellulose (Methocel A4M^{R})

Concentration (% w/w)	Spheronization Time (min)	% Weight Retained (a) Sieve No. 14	18	20	40	60	Pan
0.33	5	13.22	31.77	24.41	26.30	4.38	0.21
	10	16.97	32.02	22.81	24.66	3.51	0.03
	15	16.48	33.39	22.42	24.82	2.69	0.17
0.67	5	21.89	37.59	15.91	16.89	5.41	4.69
	10	36.56	34.27	14.28	9.03	4.23	1.62
	15	41.57	33.12	14.02	7.17	3.03	1.05

(a) averaged from two determinations

Table 9 Sieve analysis of lactose-Avicel PH101^{R} pellets prepared with various spheronization times and concentrations of hydroxypropyl cellulose (HPC-M^{R})

Concentration (% w/w)	Spheronization Time (min)	% Weight Retained (a) Sieve No.					
		14	18	20	40	60	Pan
1.33	5	5.60	35.27	29.01	21.97	6.21	1.91
	10	11.65	38.02	24.83	16.75	7.38	1.37
	15	16.92	37.14	22.22	14.34	7.68	1.57
1.67	5	8.73	40.48	27.13	15.03	7.25	1.38
	10	9.92	39.39	24.57	17.36	7.08	1.40
	15	10.72	41.11	24.39	14.12	8.03	1.63
2.00	5	2.09	30.40	40.78	21.75	4.22	0.75
	10	5.72	32.75	38.16	18.58	4.42	0.38
	15	7.84	38.09	36.09	15.94	1.88	0.03
2.33	5	2.12	27.59	50.03	19.13	1.01	0.03
	10	3.17	33.83	48.25	14.57	1.15	0.02
	15	3.99	34.80	45.13	15.49	0.62	0.01

(a) averaged from two determinations

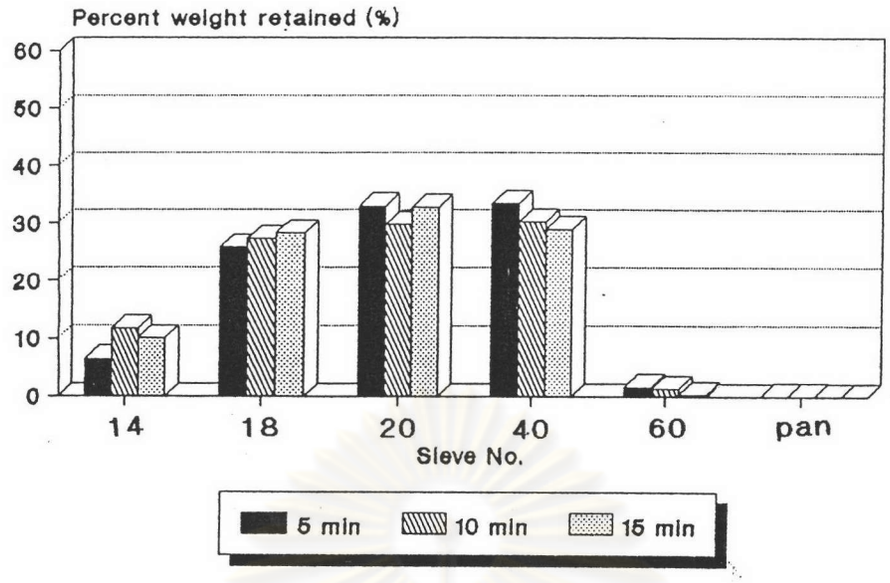

Figure 20 Percent retained on sieve of lactose-Avicel PH101^{R} pellets using 1.33 % w/w of Methocel E-15LV^{R} as a function of spheronization times.

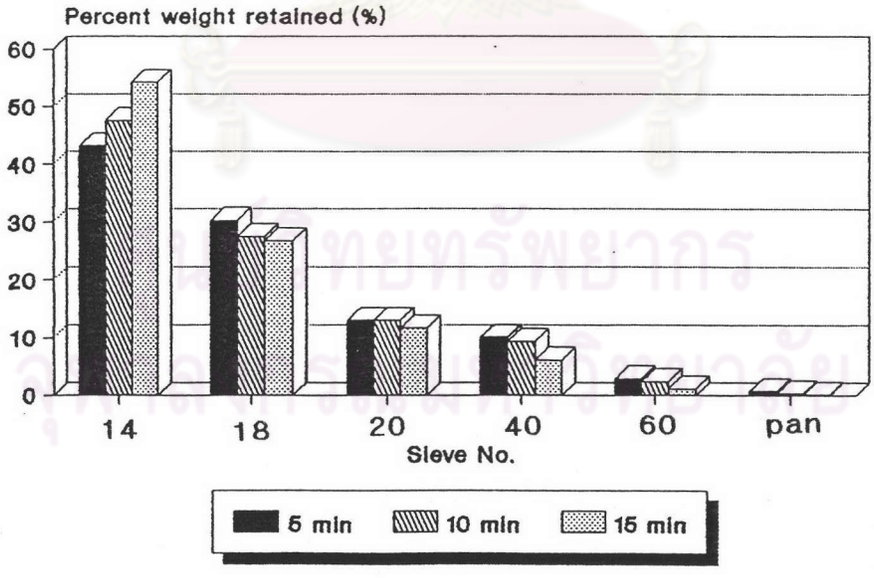

Figure 21 Percent retained on sieve of lactose-Avicel PH101^{R} pellets using 1.67 % w/w of Methocel E-15LV^{R} as a function of spheronization times

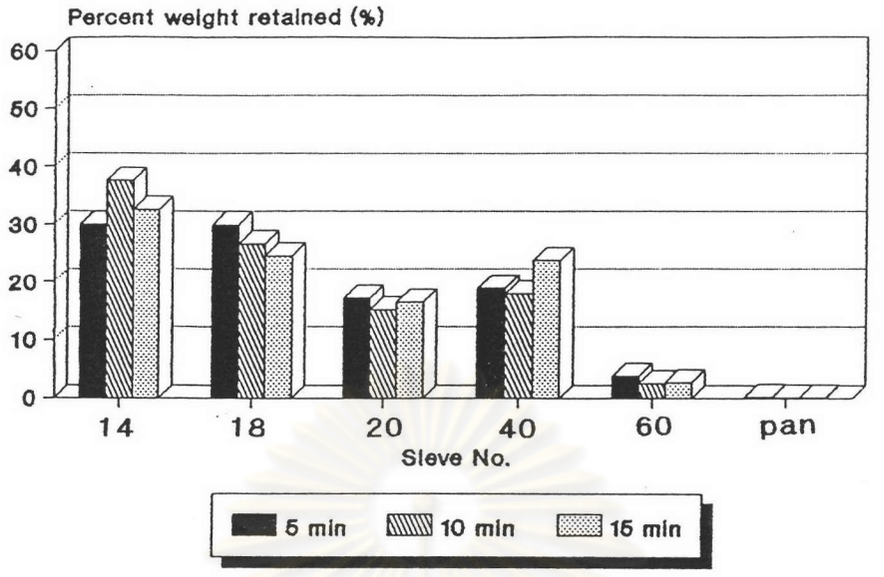

Figure 22 Percent retained on sieve of lactose-Avicel PH101^{R} pellets using 2.00 % w/w of Methocel E-15LV^{R} as a function of spheronization times

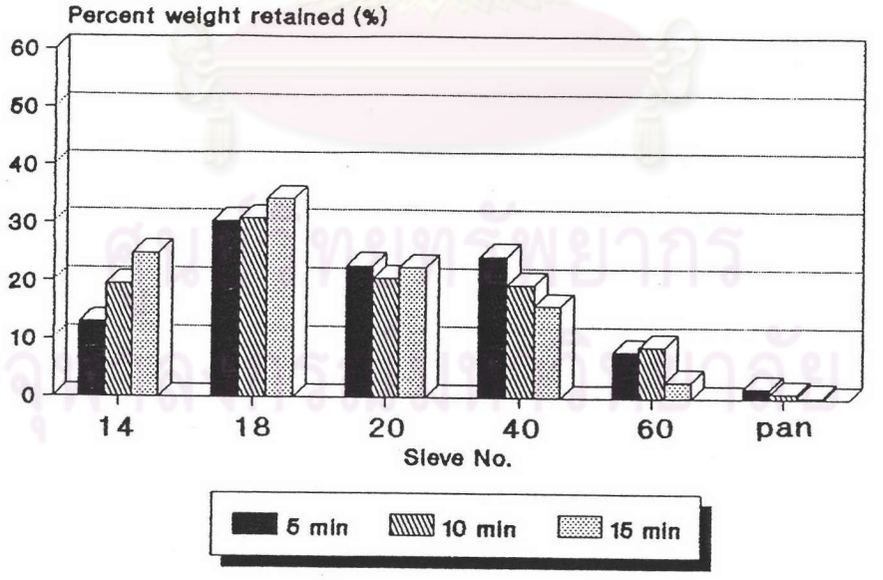

Figure23 Percent retained on sieve of lactose-Avicel PH101^{R} pellets using 1.33 % w/w of HPC-L^{R} as a function of spheronization times

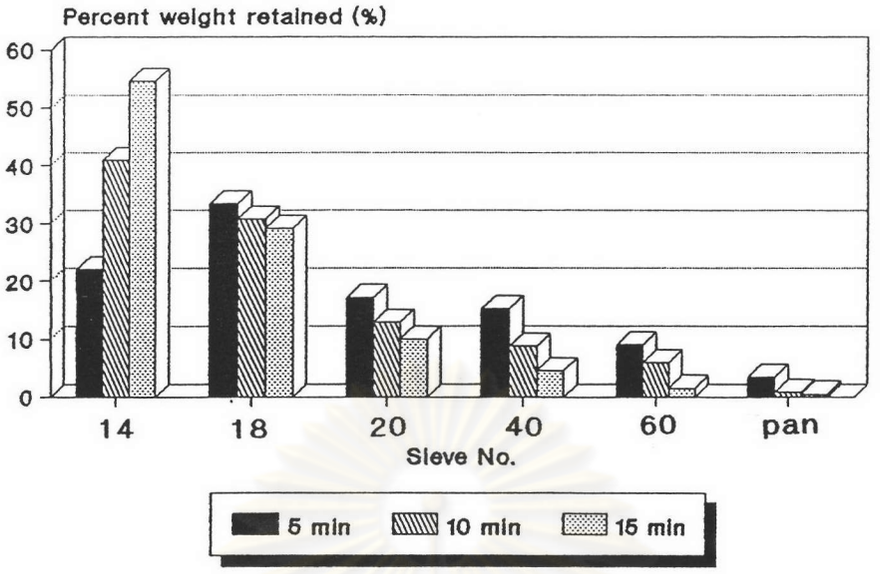

Figure 24 Percent retained on sieve of lactose-Avicel PH101^{R} pellets using 1.67 % w/w of HPC-L^{R} as a function of spheronization times

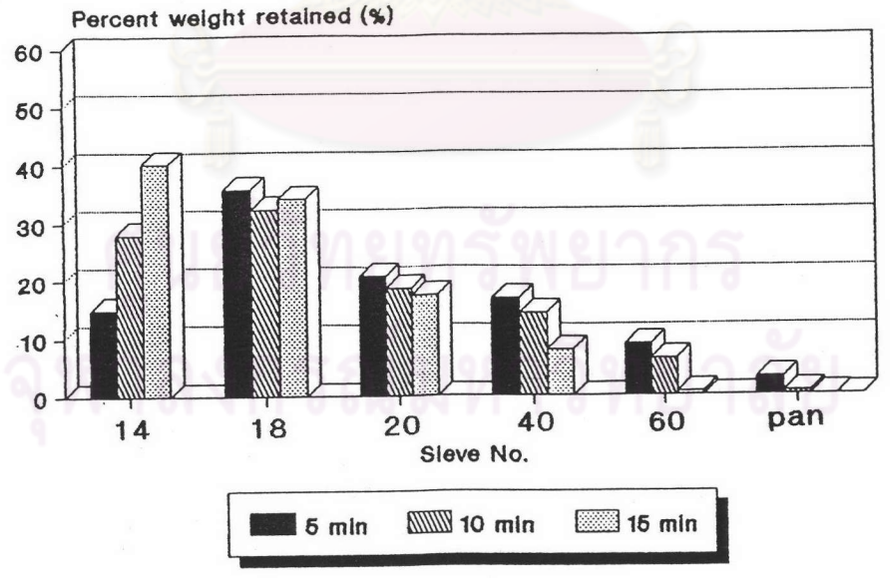

Figure 25 Percent retained on sieve of lactose-Avicel PH101^{R} pellets using 2.00 % w/w of HPC-L^{R} as a function of spheronization times

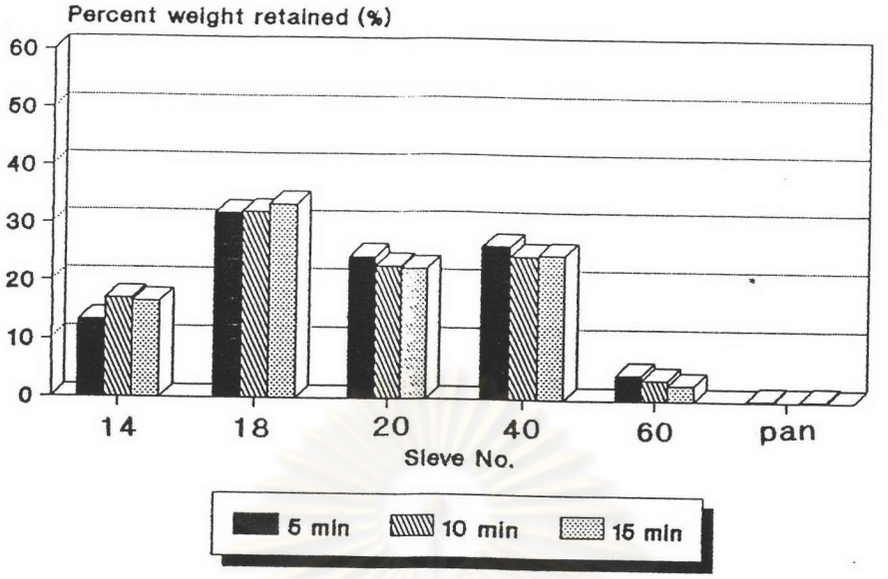

Figure 26 Percent retained on sieve of lactose-Avicel PH101^{R} pellets using 0.33 % w/w of Methocel A4M^{R} as a function of spheronization times

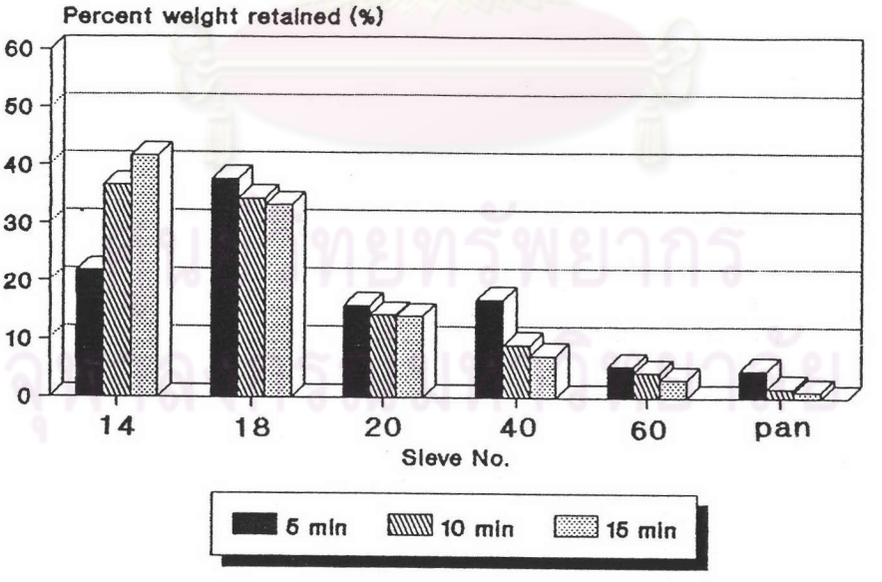

Figure 27 Percent retained on sieve of lactose-Avicel PH101^{R} pellets using 0.67 % w/w of Methocel A4M^{R} as a function of spheronization times

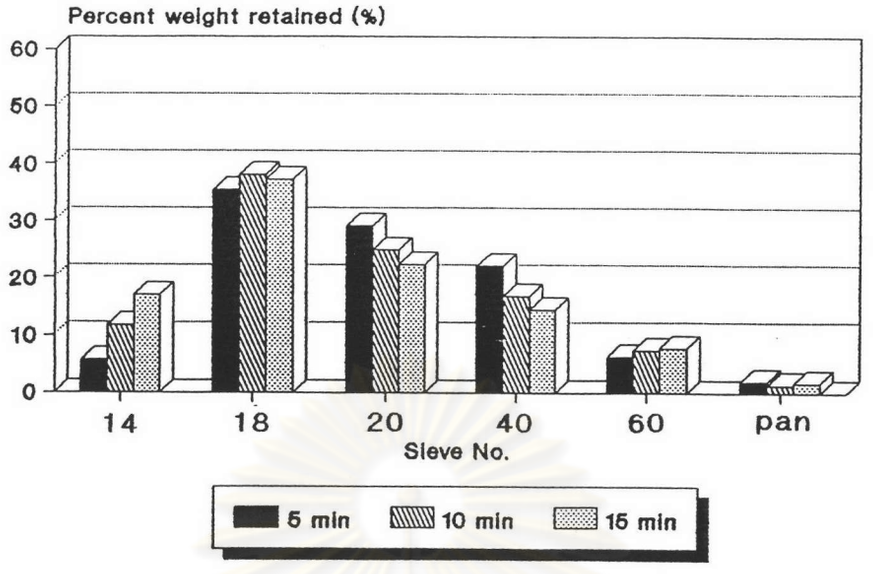

Figure 28 Percent retained on sieve of lactose-Avicel PH101^{R} pellets using 1.33 % w/w of HPC-M^{R} as a function of spheronization times

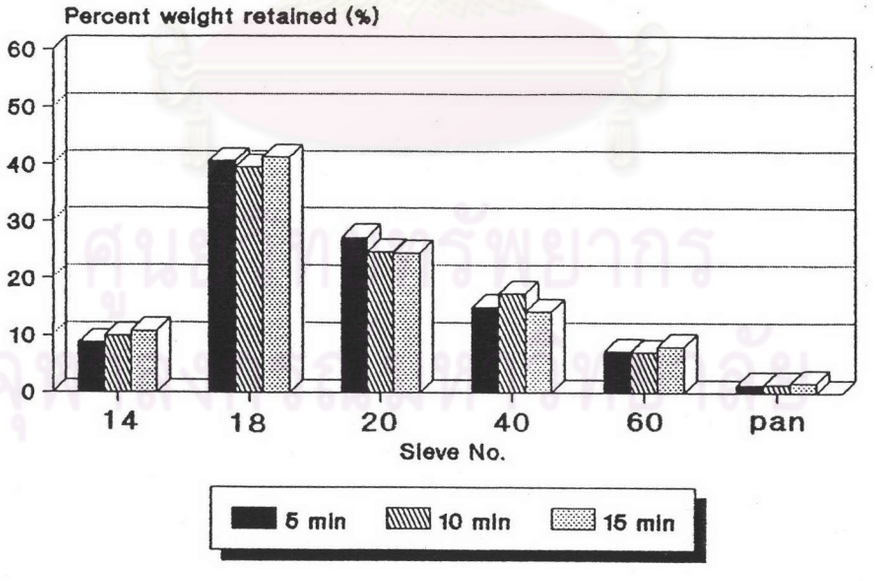

Figure 29 Percent retained on sieve of lactose-Avicel PH101^{R} pellets using 1.67 % w/w of HPC-M^{R} as a function of spheronization times

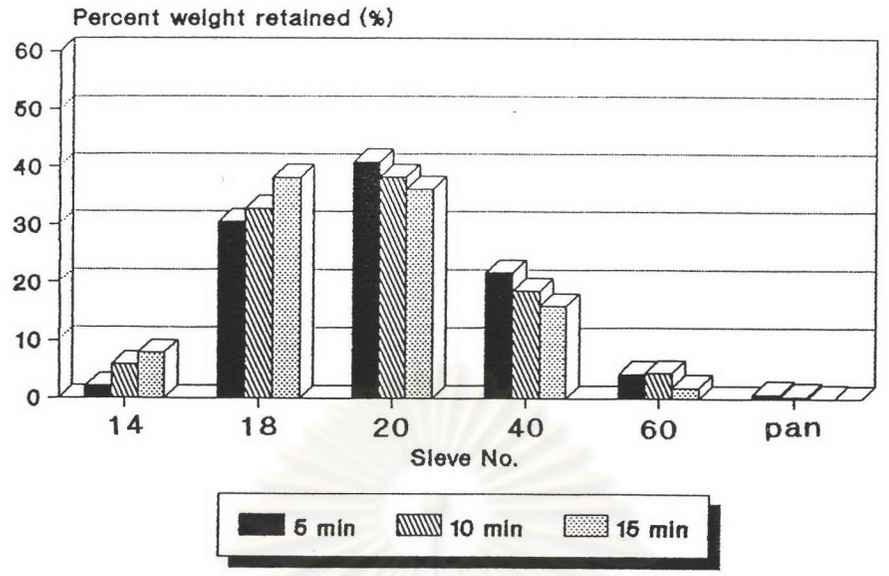

Figure 30 Percent retained on sieve of lactose-Avicel PH101^{R} pellets using 2.00 % w/w of HPC-M^{R} as a function of spheronization times

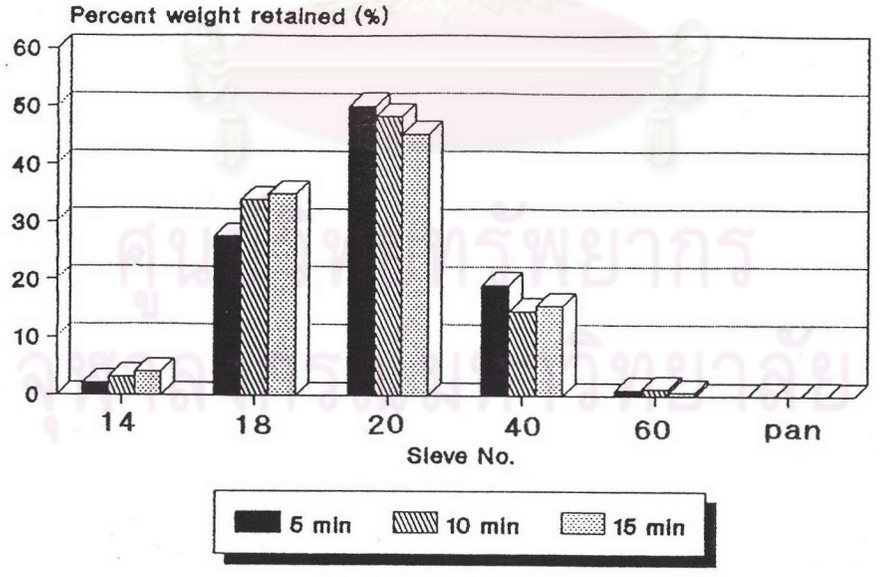

Figure 31 Percent retained on sieve of lactose-Avicel PH101^{R} pellets using 2.33 % w/w of HPC-M^{R} as a function of spheronization times

3 Mean Particle Size Determination

The effect of spheronization times, binder types and concentrations on the mean particle size of lactose-Avicel PH101^{R} pellets are given in Table 10 and Figures 32-38. The mean particle size was ranging from 0.800-1.784 mm.

3.1 Methocel E-15LV^{R}

Increasing spheronization time at 1.67% w/w and 2.00 % w/w of binder concentration were notsignificantly different in mean particle size at 95% confident level. But increasing of spheronization time at 1.33 % w/w resulted in increasing mean particle size . At each spheronization time, the orders of mean particle size of pellets were as followed : binder concentration 1.67 %w/w > 2.00 % w/w > 1.33 % w/w.

3.2 HPC-L^{R}

The mean particle size increased with increasing spheronization time at each binder concentration. At 10 and 15 min of spheronization time were observed that mean particle size at 1.67 % w/w of binder concentration was larger than 2.00 % w/w and 1.33 % w/w, respectively. In addition, increasing binder concentration at 5 min was not significantly different at 95% confident level.

3.3 Methocel A4M^{R}

Table 10 Granule size of lactose-Avicel PH101^{R} pellets prepared with various spheronization times, types and concentrations of binders

Binder	Concentration (% w/w)	Granule size (mm)(a) Spheronization Time (min)		
		5	10	15
Methocel E-15LV^{R}	1.33	0.885	0.934	0.952
	1.67	1.463	1.571	1.652
	2.00	1.138	1.202	1.115
HPC-L^{R}	1.33	0.878	0.970	1.120
	1.67	1.009	1.401	1.784
	2.00	0.928	1.125	1.315
Methocel A4M^{R}	0.33	0.928	0.985	0.989
	0.67	1.060	1.387	1.536
HPC-M^{R}	1.33	0.823	0.925	0.995
	1.67	0.904	0.910	0.926
	2.00	0.800	0.872	0.958
	2.33	0.859	0.902	0.927

(a) averaged from two determinations

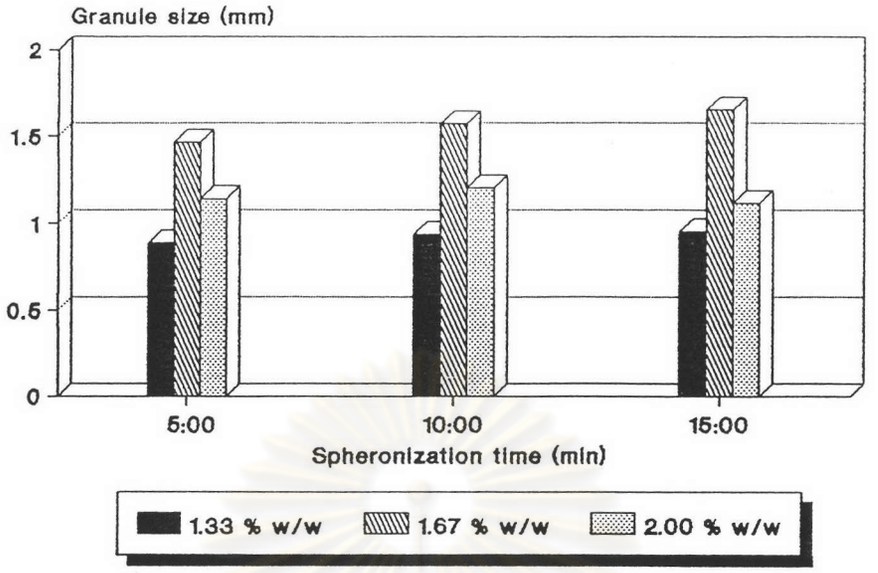

Figure 32 Granule size of lactose-Avicel PH101^{R} pellets using Methocel E-15LV^{R} as a function of Methocel E-15LV^{R} concentrations and spheronization times

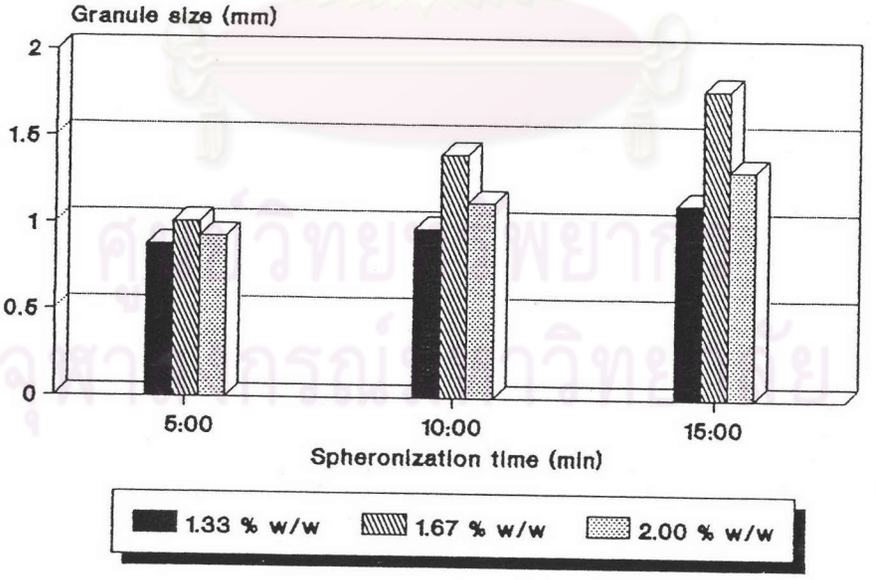

Figure 33 Granule size of lactose-Avicel PH101^{R} pellets using HPC-L^{R} as a function of HPC-L^{R} concentrations and spheronization times

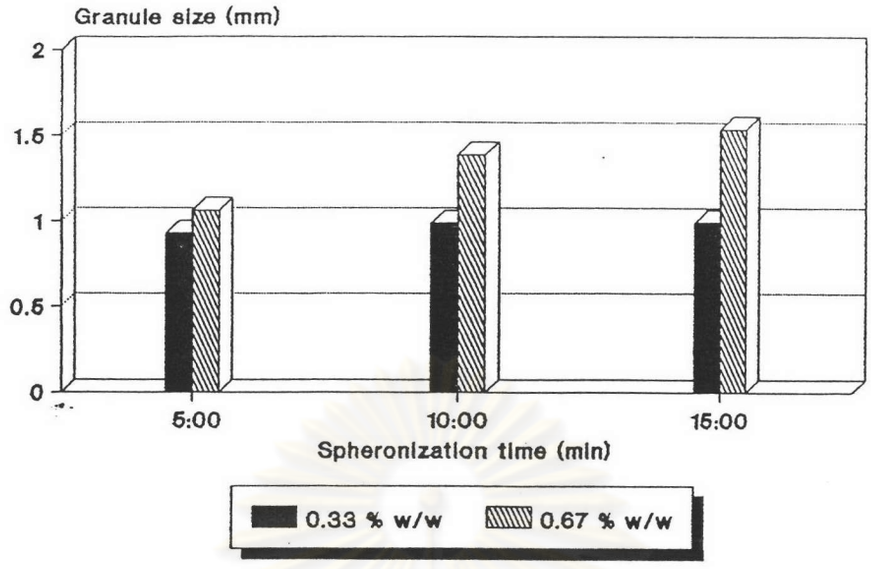

Figure 34 Granule size of lactose-Avicel PH101^{R} pellets using Methocel A4M^{R} as a function of Methocel A4M^{R} concentrations and spheronization times

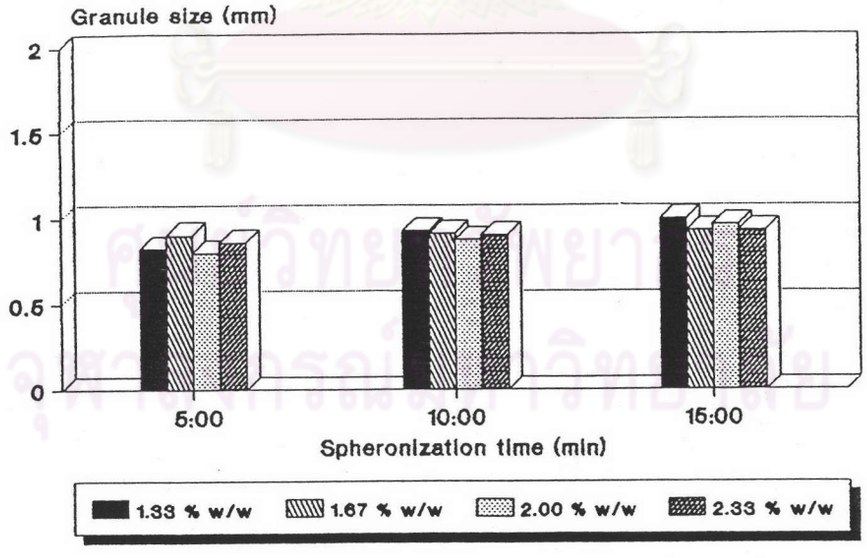

Figure 35 Granule size of lactose-Avicel PH101^{R} pellets using HPC-M^{R} as a function of HPC-M^{R} concentrations and spheronization times

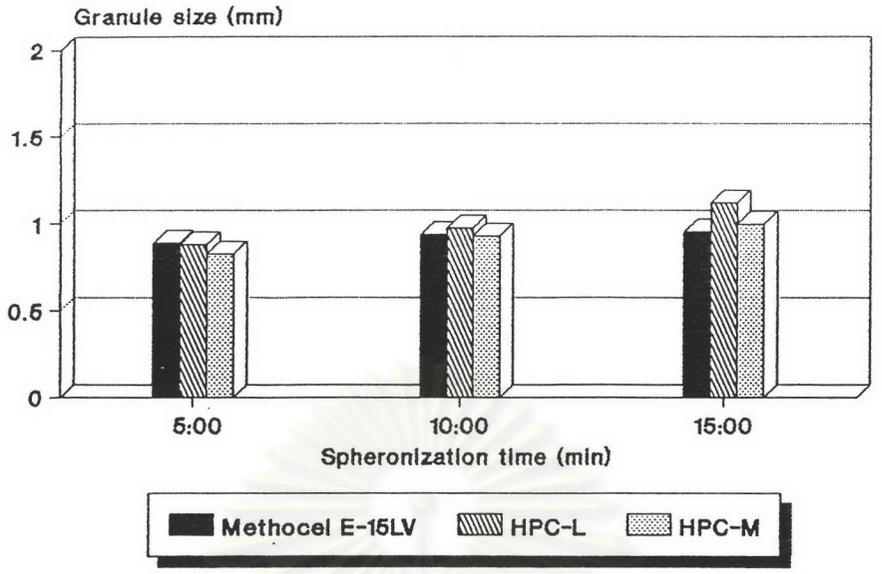

Figure 36 Granule size of lactose-Avicel PH101^{R} pellets using 1.33 % w/w of binder concentration as a function of binder types and spheronization times

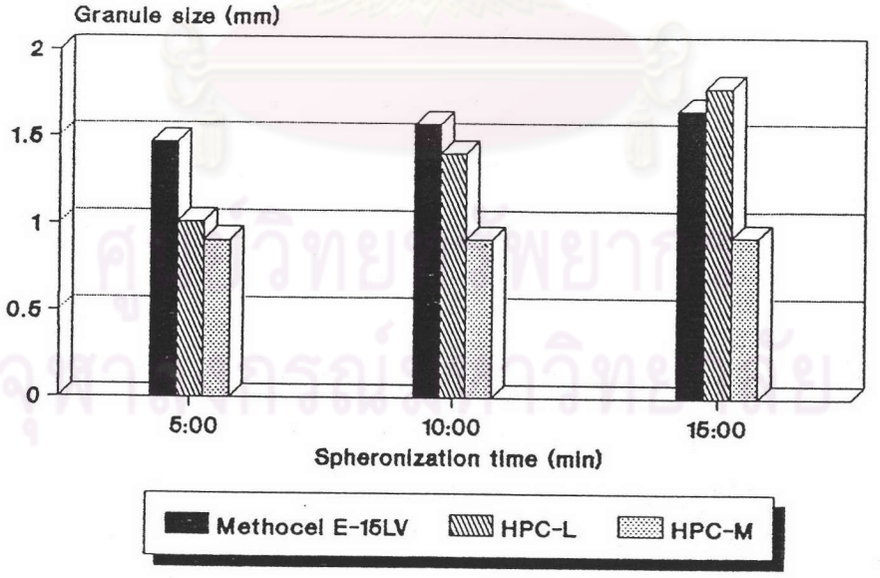

Figure 37 Granule size of lactose-Avicel PH101^{R} pellets using 1.67 % w/w of binder concentration as a function of binder types and spheronization times

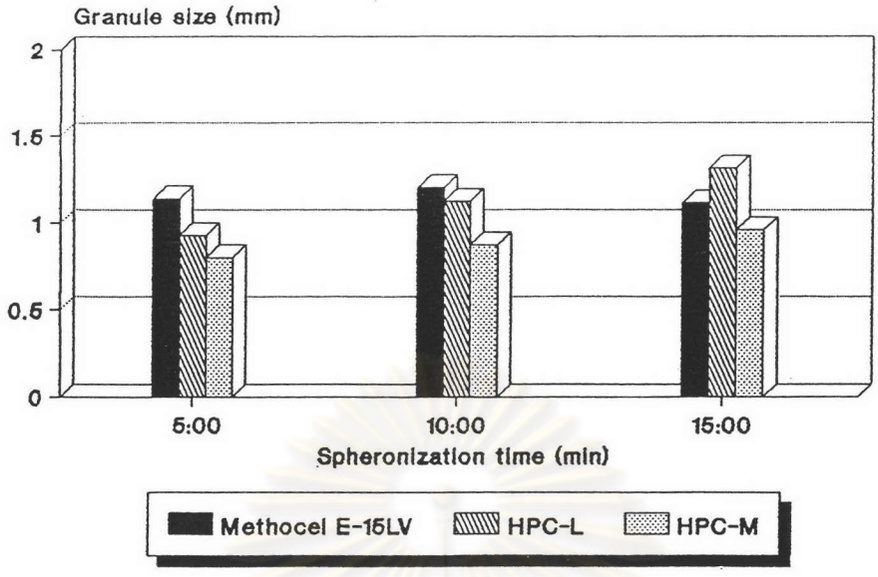

Figure 38 Granule size of lactose-Avicel PH101^{R} pellets using 2.00 % w/w of binder concentration as a function of binder types and spheronization times

Increasing spheronization time at 0.33 % w/w of binder concentration and increasing binder concentration a 5 min of spheronization time were not significantly different in mean particle size at 95% confident level. At 10 and 15 min, the orders of mean particle size of pellets were as followed : binder concentration 0.67 % w/w > 0.33 % w/w. However,the mean particle size increased with increasing spheronization time at 0.67 % w/w.

3.4 HPC-M^{R}

The mean particle size increased with increasing spheronization time at 1.33 % w/w and 2.00 % w/w of binder concentration. Increasing spheronization time at 1.67 % w/w, 2.33 % w/w and increasing binder concentration at each spheronization time were not significantly different at 95% confident level.

3.5 Compared Type of Binders at Different Concentrations and Spheronization Times on Mean Particle Size of Pellets

The mean particle size of pellets were varied in different binder types and concentrations, and spheronization times.

4 Percent Sieve Fraction on 14/20 Mesh Cut Determination

The effect of spheronization times, binder types and concentrations on percent sieve fraction on 14/20 mesh cut of lactose-Avicel PH101^{R} placebo pellets are shown in Table 11 and Figures 39-45.

Table 11 Percent sieve fraction on 14/20 mesh cut of lactose -Avicel PH101^{R} pellets prepared with various spheronization times, types and concentrations of binders

Binder	Concentration (% w/w)	Sieve fraction on 14/20 mesh cut(%)[a] Spheronization Time (min) 5	10	15
Methocel E-15LV^{R}	1.33	58.61	56.80	60.82
	1.67	43.23	40.45	38.43
	2.00	47.19	41.89	41.02
HPC-L^{R}	1.33	52.93	51.31	56.45
	1.67	50.44	43.65	39.19
	2.00	56.44	50.89	51.33
Methocel A4M^{R}	0.33	56.18	54.83	55.81
	0.67	53.50	48.55	47.14
HPC-M^{R}	1.33	64.28	62.85	59.36
	1.67	67.61	63.96	65.50
	2.00	71.18	70.91	74.18
	2.33	77.62	82.08	79.93

(a) averaged from two determinations

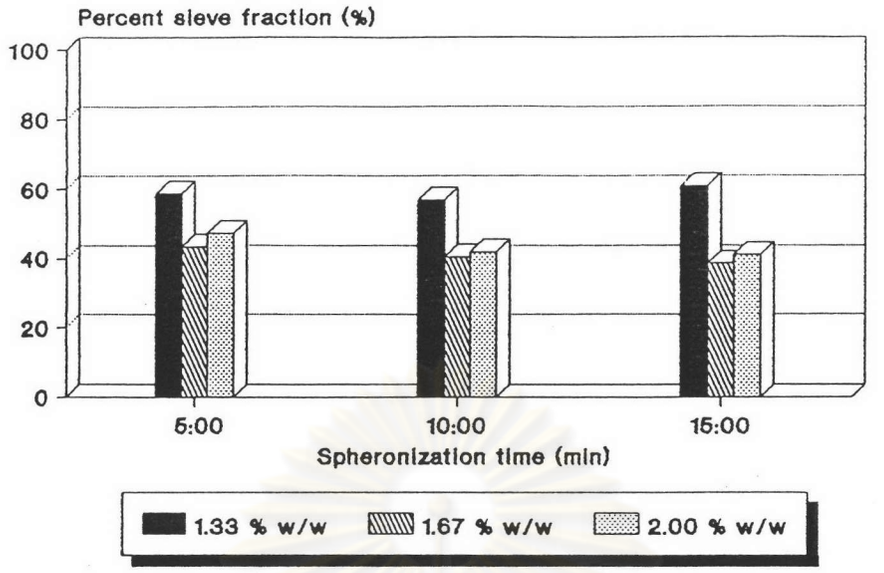

Figure 39 Percent sieve fraction on 14/20 mesh cut of lactose-Avicel PH101^{R} pellets using Methocel E-15LV^{R} as a function of Methocel E-15LV^{R} concentration and spheronization times

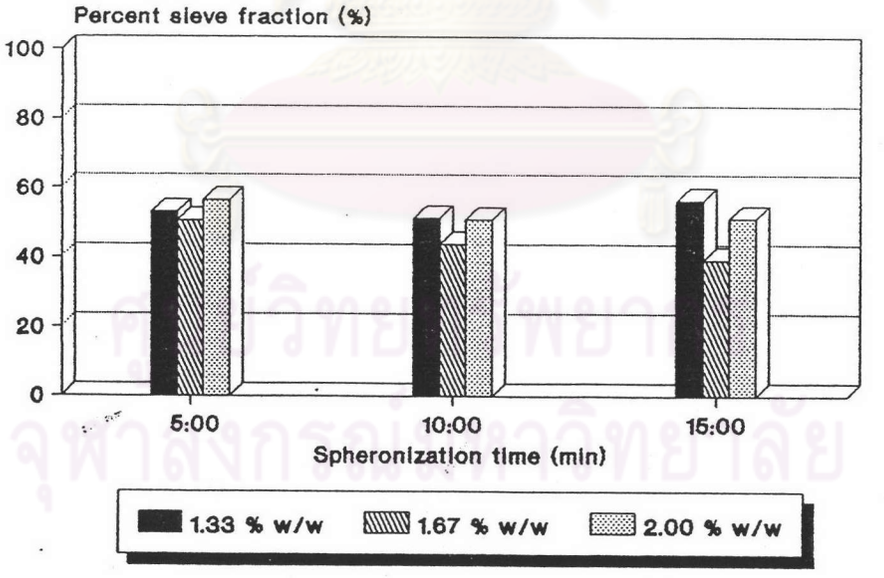

Figure 40 Percent sieve fraction on 14/20 mesh cut of lactose-Avicel PH101^{R} pellets using HPC-L^{R} as a function of HPC-L^{R} concentration and spheronization times

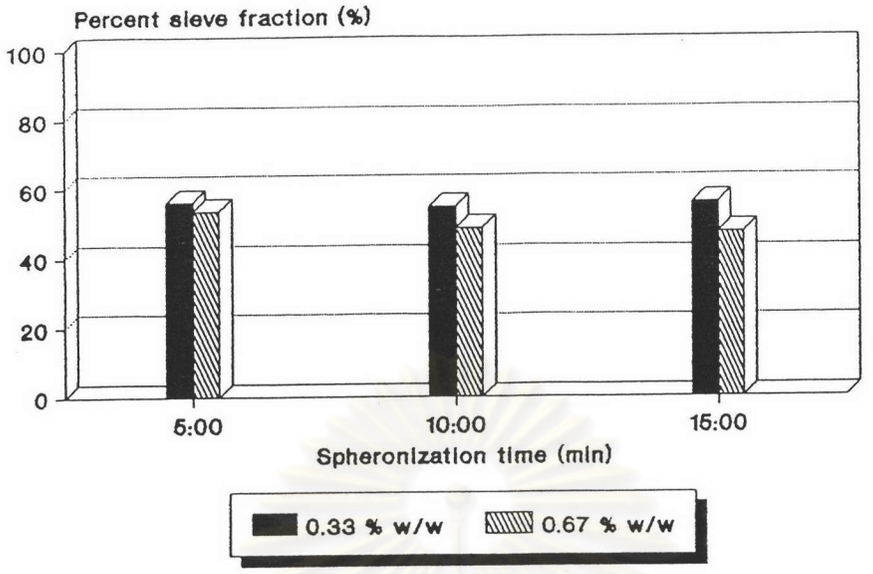

Figure 41 Percent sieve fraction on 14/20 mesh cut of lactose-Avicel PH101^{R} pellets using Methocel A4M^{R} as a function of Methocel A4M^{R} concentration and spheronization times

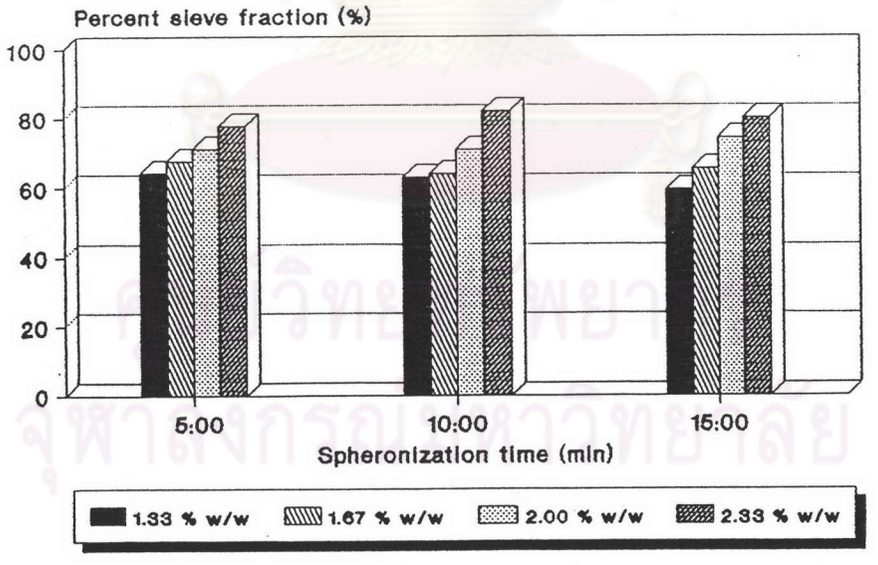

Figure 42 Percent sieve fraction on 14/20 mesh cut of lactose-Avicel PH101^{R} pellets using HPC-M^{R} as a function of HPC-M^{R} concentration and spheronization times

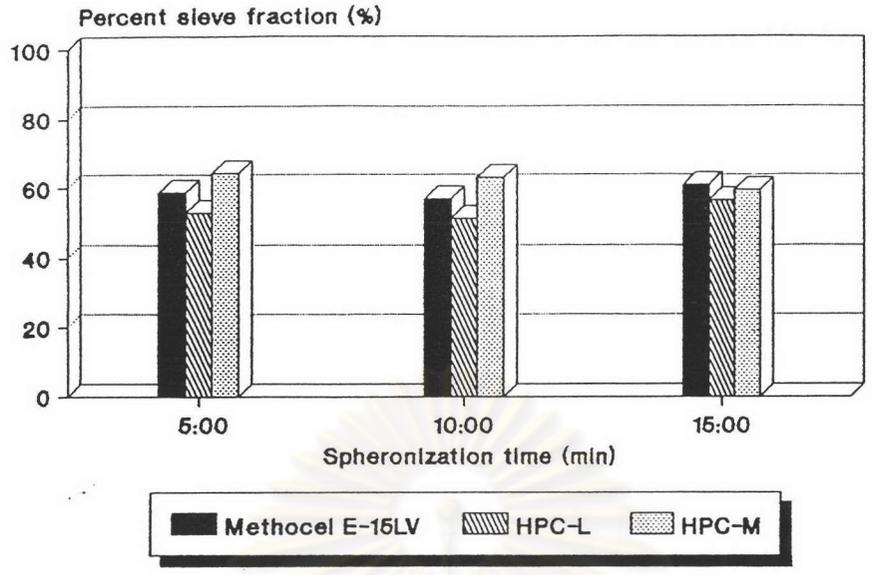

Figure 43 Percent sieve fraction on 14/20 mesh cut of lactose-Avicel PH101^{R} pellets using 1.33 % w/w of binder concentration as a function of binder types and spheronization times

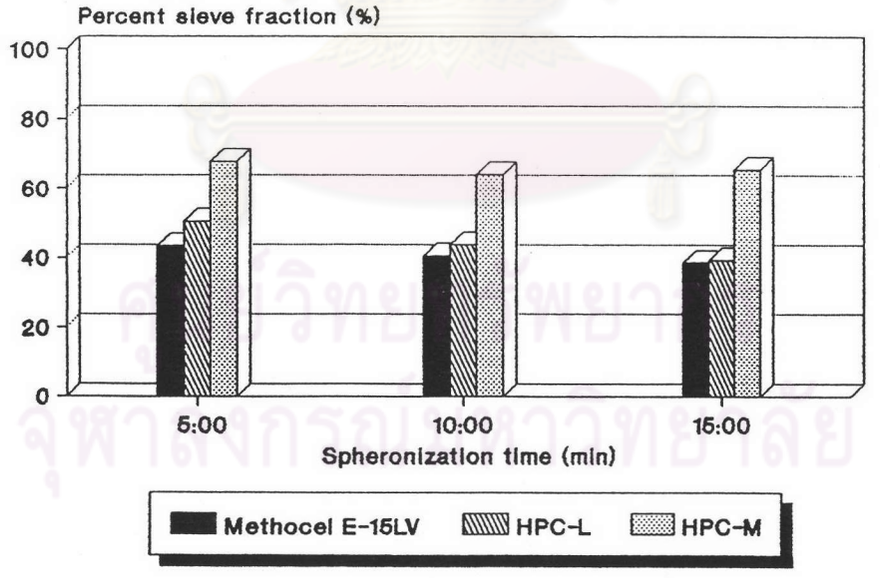

Figure 44 Percent sieve fraction on 14/20 mesh cut of lactose-Avicel PH101^{R} pellets using 1.67 % w/w of binder concentration as a function of binder types and spheronization times

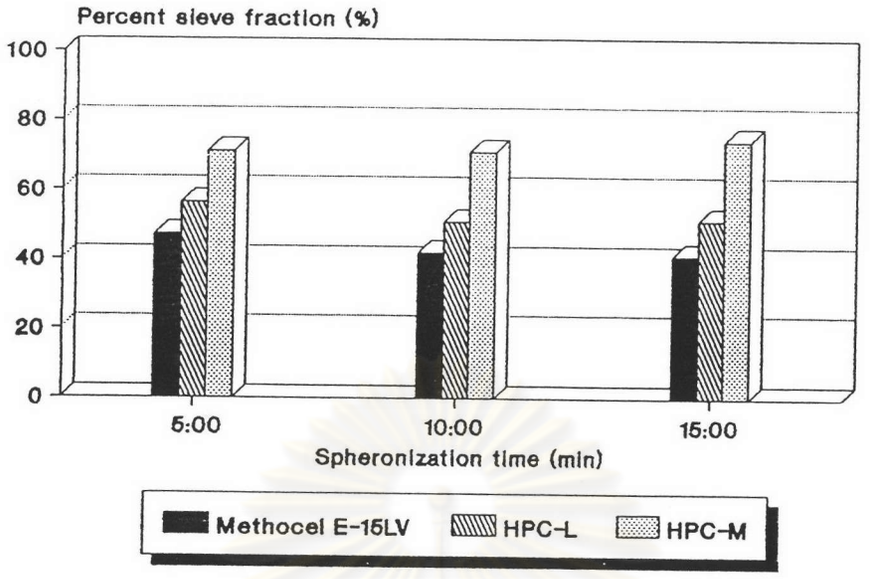

Figure 45 Percent sieve fraction on 14/20 mesh cut of lactose-Avicel PH101^{R} pellets using 2.00 % w/w of binder concentration as a function of binder types and spheronization times

The percent sieve fraction on 14/20 mesh cut was ranging from 38.43-82.08.

4.1 Methocel E-15LV^{R}

Increasing spheronization time at each of binder concentration was not significantly different in percent sieve fraction on 14/20 mesh cut at 95% confident level. At each spheronization time, percent sieve fraction on 14/20 mesh cut of 1.33 % w/w of binder concentration was higher than that of the others.

4.2 HPC-L^{R}

At 1.67 % w/w and 2.00 % w/w of binder concentration, percent sieve fraction on 14/20 mesh cut at 5 min of spheronization time was higher than that of the others. Increasing spheronization time at 1.33 % w/w and increasing binder concentration at 5 and 10 min were not significantly different at 95% confident level. But percent sieve fraction on 14/20 mesh cut of 1.33 % w/w at 15 min was higher than that of the others.

4.3 Methocel A4M^{R}

Increasing spheronization time at each binder concentration and increasing binder concentration at 5 min of spheronization time were not significantly different at 95% confident level. At 10 and 15 min of spheronization time, percent sieve fraction and 14/20 mesh cut of 0.33 % w/w was higher than that of 0.67 % w/w of

binder concentration.

4.4 HPC-M^R

Increasing spheronization time at each binder concentration was not significantly different in percent sieve fraction on 14/20 mesh cut at 95% confident level except at 1.33 % w/w of binder concentration. Percent sieve fraction on 14/20 mesh cut at 15 min of 1.33 % w/w was lower than that of the others. At each spheronization time,percent sieve fraction on 14/20 mesh cut of 2.33 % w/w was higher than that of the others.

4.5 Compared Type of Binders at Different Concentrations and Spheronization Times on Percent Sieve Fraction on 14/20 Meah Cut

The effect of spheronization times and binder concentrations were studied. The percent sieve fraction on 14/20 mesh cut of placebo pellets used HPC-M^R as a binder was higher than used the other binders. Except for the percent sieve fraction on 14/20 mesh cut of 1.33 % w/w of binder concentration at 15 min of spheronization time was not significantly different at 95% confident level.

5 Bulk Density and Tapped Density Determination

The effect of spheronization times, binder types and concentrations on bulk density, tapped density of lactose-Avicel PH101^R pellets are shown in Tables 12 and 13, respectively. For all case, the

Table 12 Bulk density of lactose-Avicel PH101^{R} pellets prepared with various spheronization times, types and concentrations of binders

Binder	Concentration (% w/w)	Bulk density (g/ml,+SD)[a] Spheronization Time (min) 5	10	15
Methocel E-15LV^{R}	1.33	0.82(0.01)	0.82(0.02)	0.82(0.01)
	1.67	0.83(0.01)	0.85(0.00)	0.83(0.01)
	2.00	0.87(0.01)	0.87(0.01)	0.86(0.00)
HPC-L^{R}	1.33	0.83(0.01)	0.85(0.00)	0.83(0.02)
	1.67	0.85(0.02)	0.84(0.01)	0.83(0.01)
	2.00	0.82(0.00)	0.82(0.01)	0.83(0.00)
Methocel A4M^{R}	0.33	0.84(0.01)	0.84(0.01)	0.83(0.01)
	0.67	0.84(0.02)	0.84(0.01)	0.84(0.01)
HPC-M^{R}	1.33	0.81(0.01)	0.83(0.01)	0.84(0.02)
	1.67	0.83(0.01)	0.85(0.01)	0.86(0.02)
	2.00	0.81(0.00)	0.83(0.01)	0.83(0.01)
	2.33	0.82(0.01)	0.84(0.00)	0.86(0.01)

(a) averaged from three determinations

Table 13 Tapped density of lactose-Avicel PH101^{R} pellets prepared with various spheronization times, types and concentrations of binders

Binder	Concentration (% w/w)	Tapped density (g/ml, +SD)[a] Spheronization Time (min)		
		5	10	15
Methocel E-15LV^{R}	1.33	0.86(0.01)	0.85(0.01)	0.86(0.01)
	1.67	0.87(0.01)	0.88(0.01)	0.86(0.01)
	2.00	0.90(0.02)	0.92(0.01)	0.89(0.00)
HPC-L^{R}	1.33	0.88(0.01)	0.90(0.01)	0.88(0.03)
	1.67	0.88(0.01)	0.86(0.01)	0.84(0.01)
	2.00	0.84(0.01)	0.83(0.01)	0.81(0.01)
Methocel A4M^{R}	0.33	0.89(0.00)	0.88(0.01)	0.88(0.01)
	0.67	0.88(0.01)	0.89(0.01)	0.88(0.02)
HPC-M^{R}	1.33	0.83(0.01)	0.86(0.01)	0.87(0.02)
	1.67	0.85(0.01)	0.87(0.00)	0.89(0.02)
	2.00	0.83(0.00)	0.86(0.01)	0.87(0.01)
	2.33	0.87(0.01)	0.87(0.00)	0.87(0.01)

(a) averaged from three determinations

bulk density and tapped density were ranging from 0.80-0.87 g/ml and 0.81-0.92 g/ml,respectively.Bulk density was not different from tapped density.

5.1 Methocel E-15LV^{R}

Increasing spheronization time had not effect on bulk density and tapped density. Bulk density and tapped density increased with increasing binder concentration.

5.2 HPC-L^{R}

At 15 min of spheronization time of each binder concentration, lower bulk density and tapped density were obtained.

5.3 Methocel A4M^{R}

Increasing binder concentration and spheronization time were not significantly different in bulk density and tapped density at 95% confident level.

5.4 HPC-M^{R}

At 15 min of spheronization time of each concentration, higher bulk density and tapped density were obtained except for 2.33 % w/w. Increasing spheronization time had not effect on bulk density and tapped density except for 5 min.

5.5 Compared Type of Binders at Different Concentrations and Spheronization Times on Bulk Density and Tapped Density of Pellets

The bulk density and tapped density of pellets were varied in different binder types concentrations and spheronization times.

6 Flow Rate Determination

From Table 14 and Figures 46-52, flow rate of lactose-Avicel PH101^{R} placebo pellets prepared with various spheronization times,binder types and concentrations are shown. The range of flow rate was between 224.72-296.14 g/min.

6.1 Methocel E-15LV^{R}

Ranging of flow rate as a function of spheronization time were followed as at 1.33 % w/w of binder concentration : 5 min $\tilde{}$ 10 min > 15 min and at 1.67 % w/w : 10 min > 5 min $\tilde{}$ 15 min. Increasing spheronization time at 2.00 % w/w and increasing binder concentration at 10 and 15 min were not effect on flow rate. The flow rate at 5 min as a function of binder concentration decreased inthe following order : 1.33 % w/w > 2.00 % w/w > 1.67 % w/w.

6.2 HPC-L^{R}

The orders of flow rate at 1.33 % w/w of binder concentration were followed as : spheronization time 10 min > 15 min >

Table 14 Flow rate of lactose-Avicel PH101^{R} pellets prepared with various spheronization times, types and concentrations of binders

Binder	Concentration (% w/w)	Flow rate (g/min,±SD)(a) Spheronization Time (min)		
		5	10	15
Methocel E-15LV^{R}	1.33	266.41(13.26)	283.99(11.35)	224.72(10.40)
	1.67	232.91(11.05)	266.11(3.59)	241.16(3.61)
	2.00	255.39(10.18)	269.69(7.23)	242.90(13.04)
HPC-L^{R}	1.33	251.43(3.38)	296.14(6.10)	264.81(6.31)
	1.67	265.08(8.57)	273.54(6.15)	252.13(13.45)
	2.00	252.36(15.37)	243.68(2.86)	238.15(8.82)
Methocel A4M^{R}	0.33	259.62(7.74)	266.47(1.46)	269.17(9.23)
	0.67	261.64(10.91)	236.06(4.88)	241.92(7.48)
HPC-M^{R}	1.33	241.14(10.99)	252.98(13.93)	278.16(10.83)
	1.67	251.89(14.57)	265.50(10.89)	282.55(9.13)
	2.00	249.12(14.90)	282.07(12.80)	282.42(5.48)
	2.33	247.55(3.83)	252.03(11.90)	258.18(8.87)

(a) averaged from three determinations

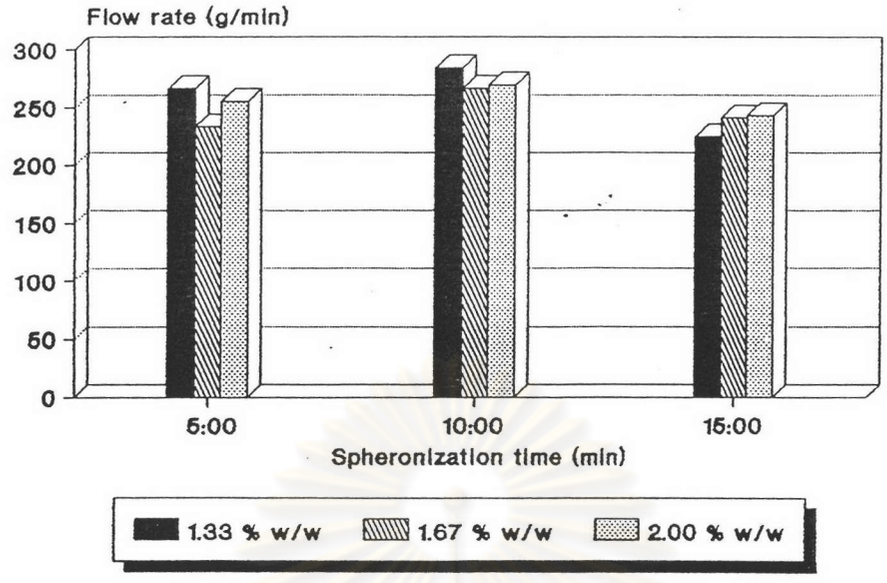

Figure 46 Flow rate of lactose-Avicel PH101^{R} pellets using Methocel E-15LV^{R} as a function of Methocel E-15LV^{R} concentration and spheronization times

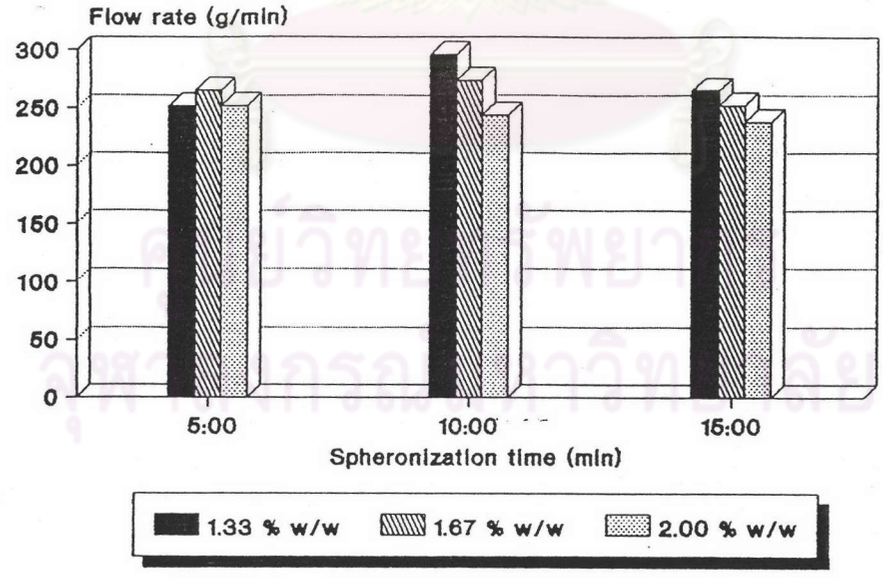

Figure 47 Flow rate of lactose-Avicel PH101^{R} pellets using HPC-L^{R} as a function of HPC-L^{R} concentration and spheronization times

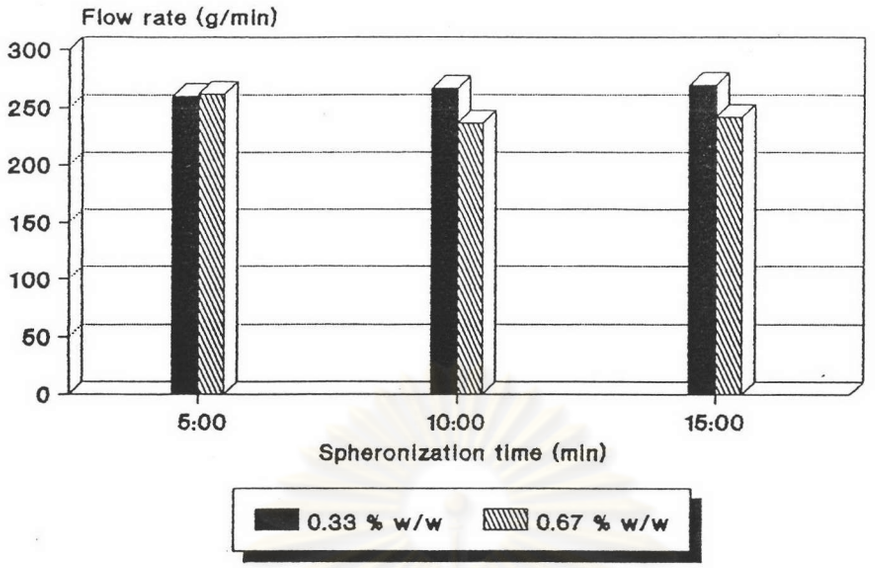

Figure 48 Flow rate of lactose-Avicel PH101^{R} pellets using Methocel A4M^{R} as a function of Methocel A4M^{R} concentration and spheronization times

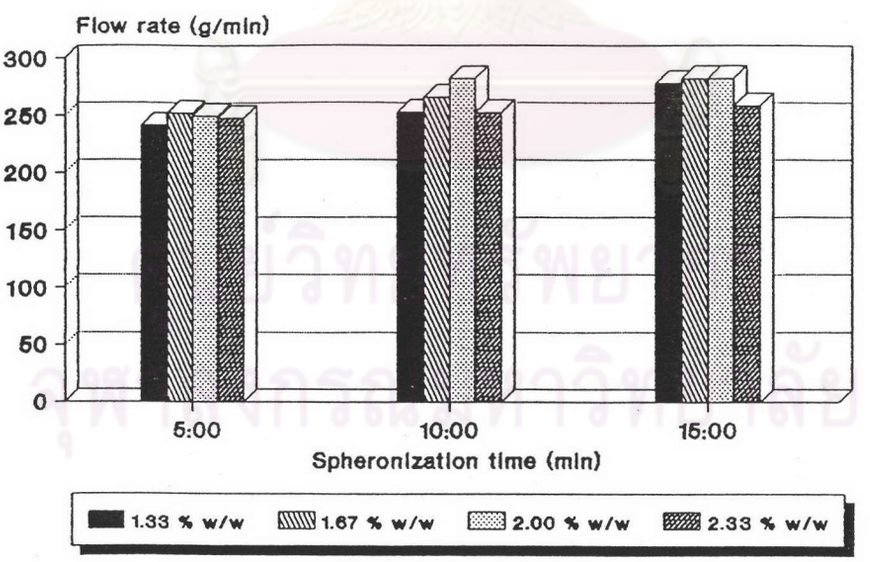

Figure 49 Flow rate of lactose-Avicel PH101^{R} pellets using HPC-M^{R} as a function of HPC-M^{R} concentration and spheronization times

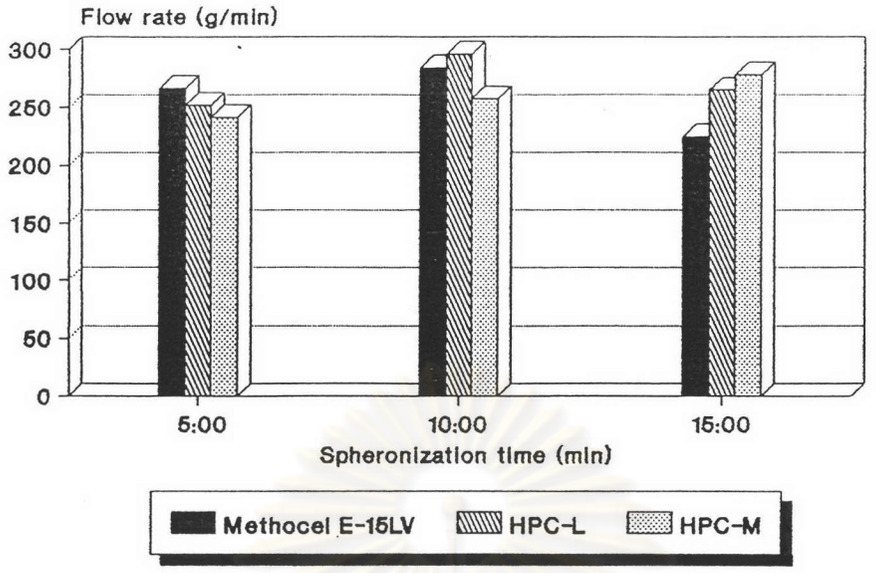

Figure 50 Flow rate of lactose-Avicel PH101^{R} pellets using 1.33 % w/w of binder concentration as a function of binder types and spheronization times

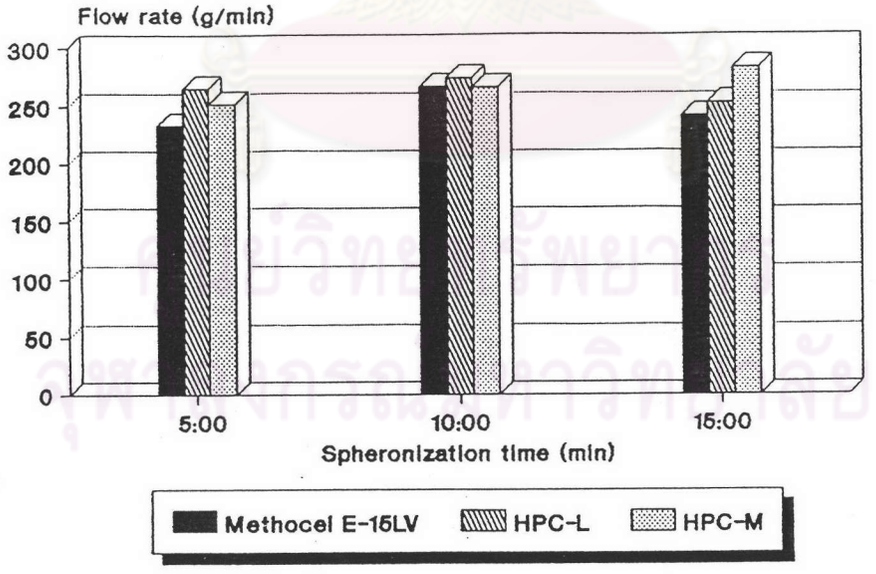

Figure 51 Flow rate of lactose-Avicel PH101^{R} pellets using 1.67 % w/w of binder concentration as a function of binder types and sphonization times

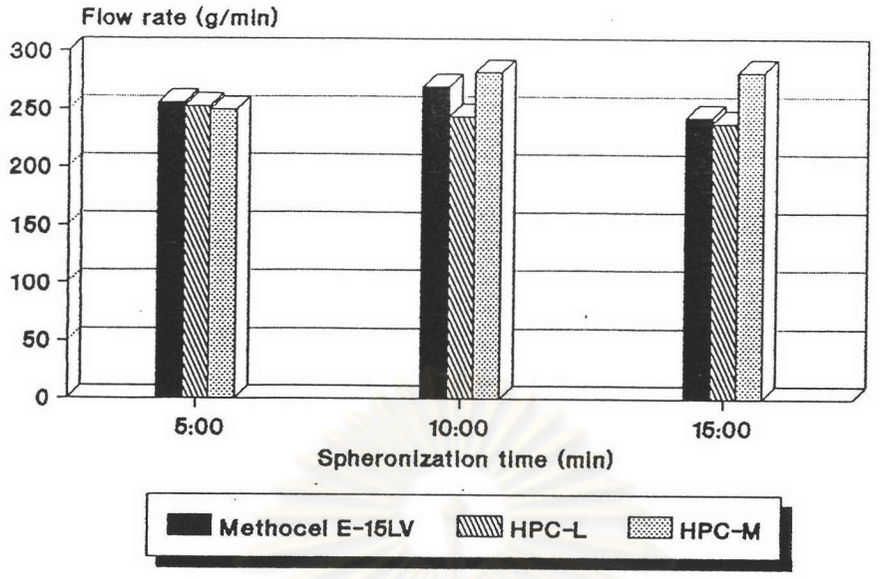

Figure 52 Flow rate of lactose-Avicel PH101^{R} pellets using 2.00 % w/w of binder concentration as a function of binder types and spheronization times

5 min.The flow rate reduced with increasing binder concentration at 10 and 15 min. But increasing spheronization time at 1.67 % w/w and 2.00 % w/w,and increasing binder concentration at 5 min were not significantly different (P> 0.05).

6.3 Methocel A4M^{R}

The orders of flow rate at 0.67 % w/w of binder concentration were followed as : spheronization time 5 min > 10 min $\tilde{}$ 15 min. The flow rate reduced with increasing binder concentration at 10 and 15 min. However,increasing spheronization time at 0.33 % w/w, and increasing binder concentration at 5 min were not significant different (P> 0.05).

6.4 HPC-M^{R}

The flow rate increased with increasing spheronization time at 1.33 % w/w and 2.00 % w/w of binder concentration. Increasing spheronization time at 1.67 % w/w and 2.33 % w/w; and increasing binder concentration at 5 min were not significant different at 95% confident level. At 10 and 15 min, the flow rate of 2.00 % w/w was higher than that of the others.

6.5 Compared Type of Binders at Different Concentrations and Spheronization Times on Flow Rate

At 1.33 % w/w and 2.00 % w/w of binder concentration

with 5 min of spheronization time ; and 1.67 % w/w of binder concentration with 10 min of spheronization time, the flow rate were not significantly different ($P > 0.05$). The other spheronization time and binder concentration were studied. High flow rate value was obtained from pellets using HPC-M^R as a binder except for 1.33 % w/w at 10 min. In addition, for 1.67 % w/w at 15 min; and 2.00 % w/w at 10 and 15 min, pellets using HPC-M^R as a binder gave the highest flow rate value.

7 Angle of Repose Determination

Angle of repose of lactose-Avicel PH101^R pellets prepared with various spheronization times, binder types and concentrations are shown in Table 15 and Figures 53-59. The range of angle of repose was between 20.64-30.83^o.

7.1 Methocel E-15LV^R

Almost of increasing binder concentration and spheronization time were not significantly different in angle of repose at 95% confident level. The angle of repose reduced with increasing spheronization time at 1.33 % w/w of binder concentration and increasing binder concentration at 5 min of spheronization time.

7.2 HPC-L^R

Increasing spheronization time at 1.33 % w/w and 1.67 % w/w of binder concentration were not significantly different in angle

Table 15 Angle of repose of lactose-Avicel PH101^{R} pellets prepared with various spheronization times, types and concentrations of binders

Binder	Concentration (% w/w)	Angle of repose (^{o},$^{+}$SD)(a) Spheronization Time (min.) 5	10	15
Methocel E-15LV^{R}	1.33	30.83(0.55)	28.49(0.27)	25.65(1.43)
	1.67	30.30(0.97)	27.93(1.36)	28.24(1.11)
	2.00	28.17(0.31)	28.09(1.44)	28.05(0.56)
HPC-L^{R}	1.33	23.98(1.74)	24.21(1.50)	20.64(1.38)
	1.67	23.81(1.40)	22.27(0.78)	23.79(1.34)
	2.00	29.35(1.47)	25.42(1.22)	25.35(0.82)
Methocel A4M^{R}	0.33	26.46(0.95)	23.85(0.51)	23.58(0.84)
	0.67	28.24(0.71)	22.32(1.38)	26.07(0.53)
HPC-M^{R}	1.33	26.03(1.67)	28.46(0.93)	27.24(0.15)
	1.67	29.57(1.23)	28.12(1.54)	29.08(1.20)
	2.00	28.05(1.63)	23.04(0.97)	27.32(0.88)
	2.33	27.02(1.66)	24.76(0.83)	24.28(1.71)

(a) averaged from three determinations

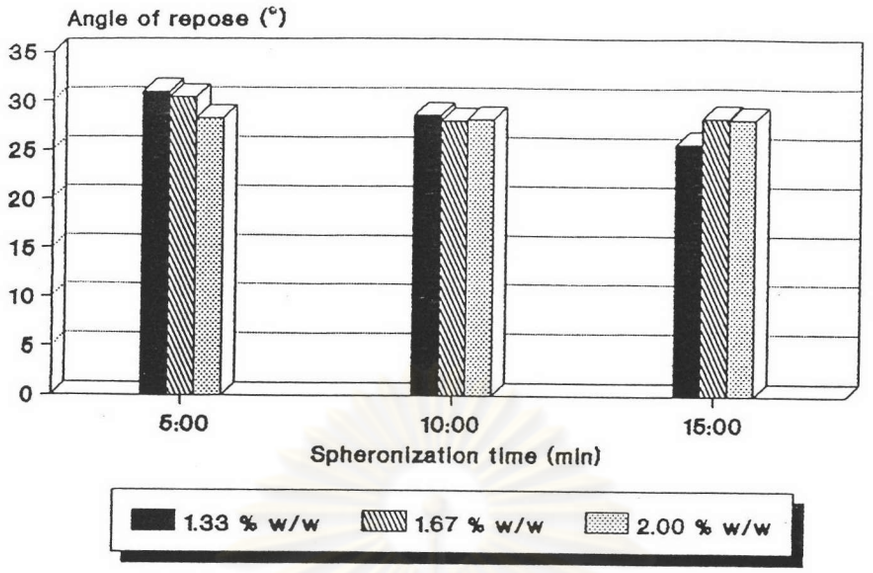

Figure 53 Angle of repose of lactose-Avicel PH101^{R} pellets using Methocel E-15LV^{R} as a function of Methocel E-15LV^{R} concentration and spheronization times

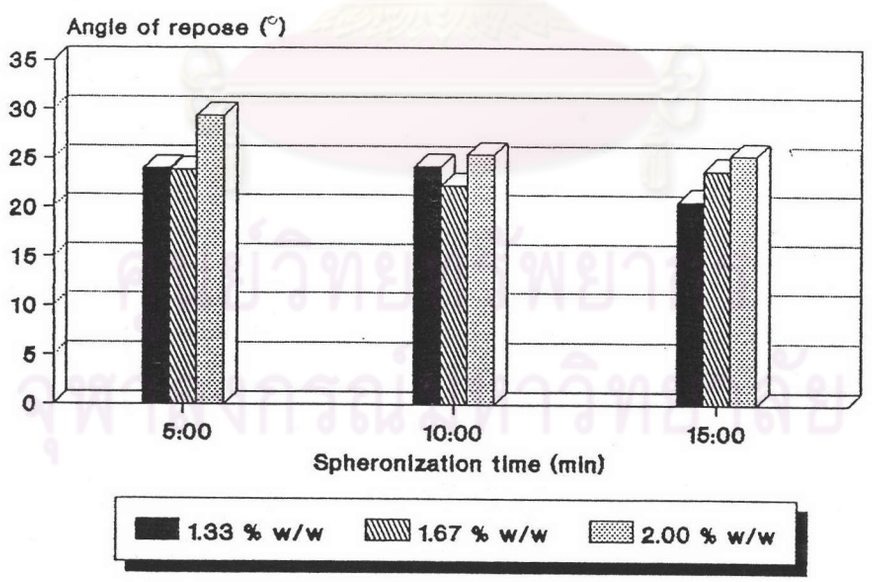

Figure 54 Angle of repose of lactose-Avicel PH101^{R} pellets using HPC-L^{R} as a function of HPC-L^{R} concentration and spheronization times

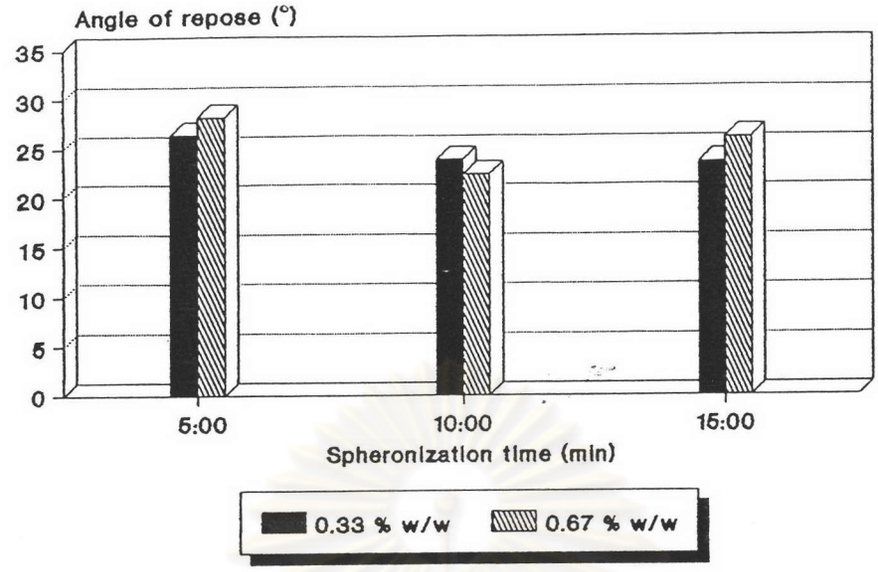

Figure 55 Angle of repose of lactose-Avicel PH101^{R} pellets using Methocel A4M^{R} as a function of Methocel A4M^{R} concentration and spheronization times

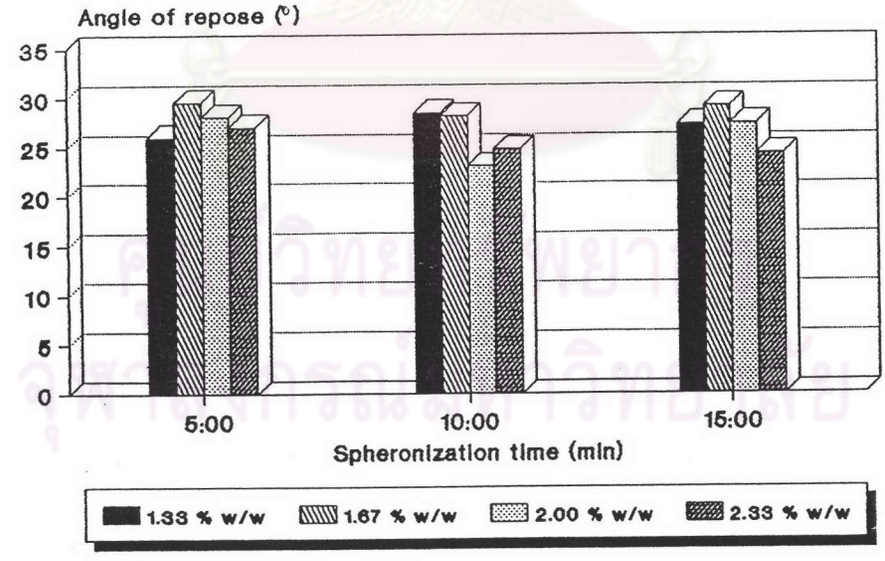

Figure 56 Angle of repose of lactose-Avicel PH101^{R} pellets using HPC-M^{R} as a function of HPC-M^{R} concentration and spheronization times

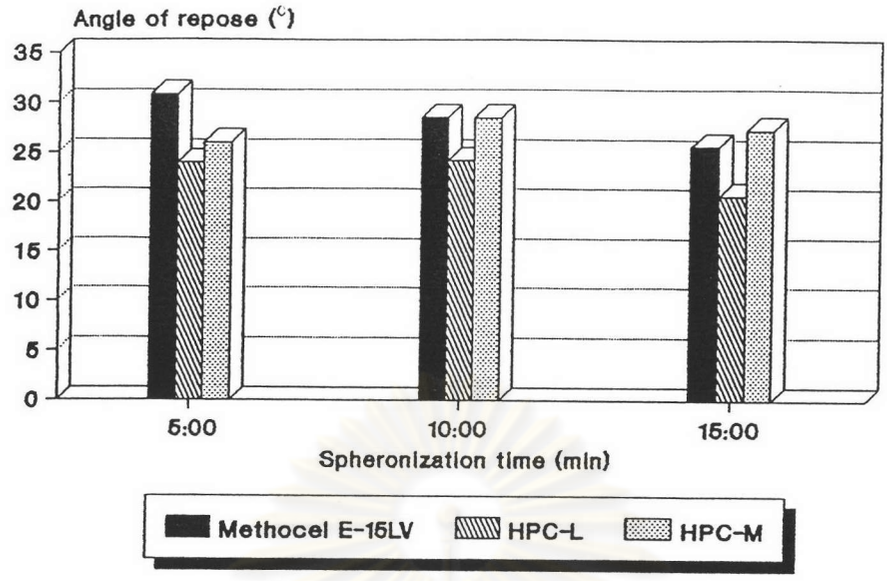

Figure 57 Angle of repose of lactose-Avicel PH101^{R} pellets using 1.33 % w/w of binder concentration as a function of binder types and spheronization time

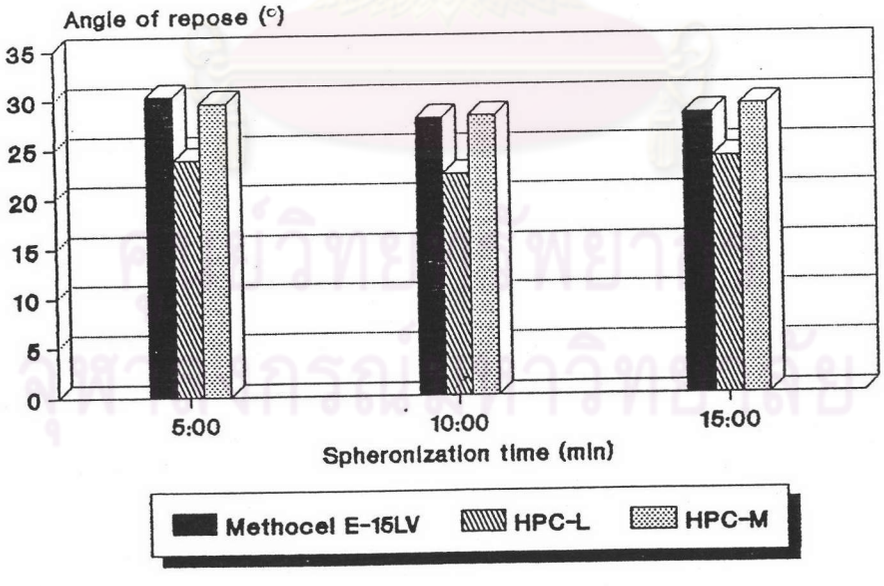

Figure 58 Angle of repose of lactose-Avicel PH101^{R} pellets using 1.67 % w/w of binder concentration as a function of binder types spheronization times

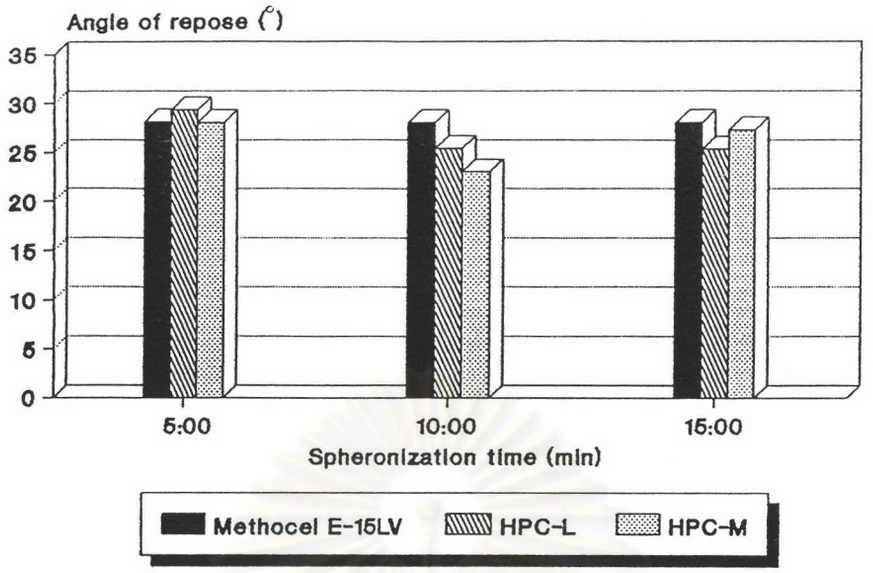

Figure 59 Angle of repose of lactose-Avicel PH101^{R} pellets using 2.00 % w/w of binder concentration as a function of binder types and spheronization times

of repose at 95% confident level. The orders were followed as, at 2.00 % w/w of binder concentration : spheronization time 5 min > 10 min $\tilde{}$ 15 min. At 2.00 % w/w of binder concentration at each spheronization time gave the highest angle of repose value.

7.3 Methocel A4M^{R}

Each binder concentration, angle of repose at 5 min was higher than that of 10 and 15 min of spheronization time. Increasing binder concentration at 5 and 10 min were not significantly different at 95% confident level. The angle of repose increased with increasing binder concentration at 15 min.

7.4 HPC-M^{R}

Almost of increasing binder concentration and spheronization time were not significantly different in angle of repose at 95% confident level.Except for the angle of repose of 2.00 % w/w of binder concentration at 10 min of spheronization time and 2.33% w/w of binder concentration at 10 and 15 min of spheronization time were lower than that of the other binder concentrations and spheronization times.

7.5 Compared Type of Binders at Different Concentrations and Spheronization Times on Angle of Repose

All spheronization times and binder concentrations were studied. The angle of repose of pellets used HPC-L^{R} as a binder was

lower than used the other binders. Except for the angle of repose of 2.00 % w/w of binder concentration at 5 min of spheronization time was not significantly different at 95% confident level. And in the case of 2.00 % w/w at 10 min, the angle of repose of pellets used HPC-M^{R} as a binder was lower than used the other binders.

8 Percent Friability Determination

The effect of spheronization times, binder types and concentrations on percent friability of lactose-Avicel PH101^{R} pellets are shown in Table 16 and Figures 60-66. For all case, the percent friability was ranging from 0.0560-0.6505.

8.1 Methocel E-15LV^{R}

Increasing binder concentrations and spheronization times were not significantly different in percent friability at 95% confident level.

8.2 HPC-L^{R}

Increasing binder concentrations and spheronization times were not significantly different in percent friability at 95% confident level except for 2.00 % w/w of binder concentration. The orders followed as, at 2.00 % w/w of binder concentration : spheronization time 5 min> 15 min> 10 min.

Table 16 Percent friability of lactose-Avicel PH101^{R} pellets prepared with various spheronization times, types and concentrations of binders

Binder	Concentration (% w/w)	Percent Friability (%)(a) Spheronization Time (min.)		
		5	10	15
Methocel E-15LV^{R}	1.33	0.3235	0.3120	0.3255
	1.67	0.1875	0.3125	0.4105
	2.00	0.3305	0.3810	0.4310
HPC-L^{R}	1.33	0.2180	0.1765	0.1922
	1.67	0.2980	0.0780	0.1475
	2.00	0.2545	0.0560	0.1635
Methocel A4M^{R}	0.33	0.0975	0.1045	0.1295
	0.67	0.0950	0.1160	0.1300
HPC-M^{R}	1.33	0.6505	0.5625	0.5280
	1.67	0.3335	0.4720	0.4620
	2.00	0.2155	0.4545	0.4630
	2.33	0.0660	0.1030	0.1810

(a) averaged from two determinations

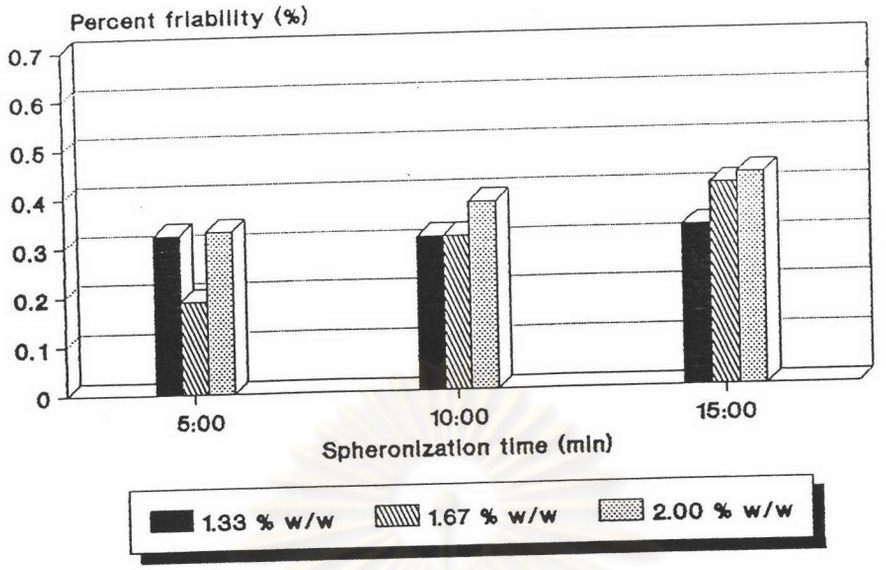

Figure 60 Percent friability of lactose-Avicel PH101^{R} pellets using Methocel E-15LV^{R} as a function of Methocel E-15LV^{R} concentration and spheronization times

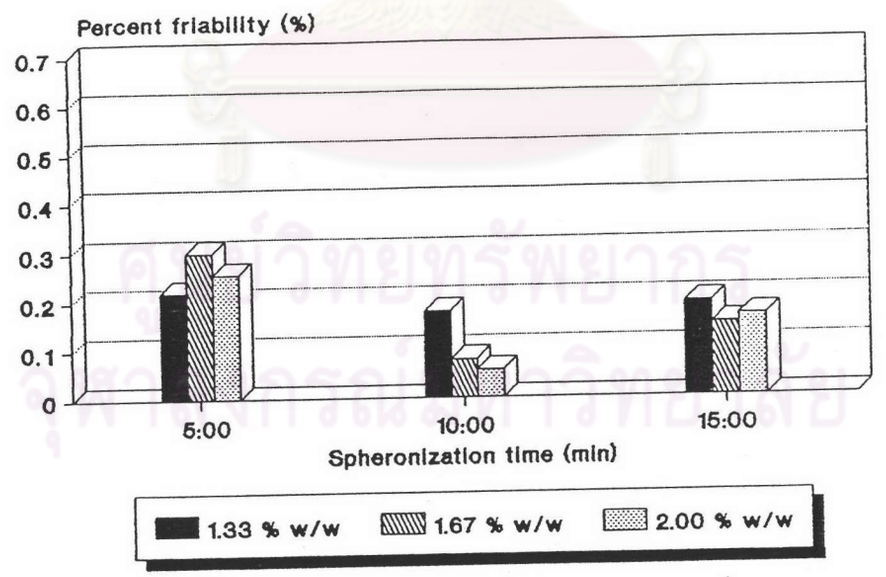

Figure 61 Percent friability of lactose-Avicel PH101^{R} pellets using HPC-L^{R} as a function of HPC-L^{R} concentration and spheronization times

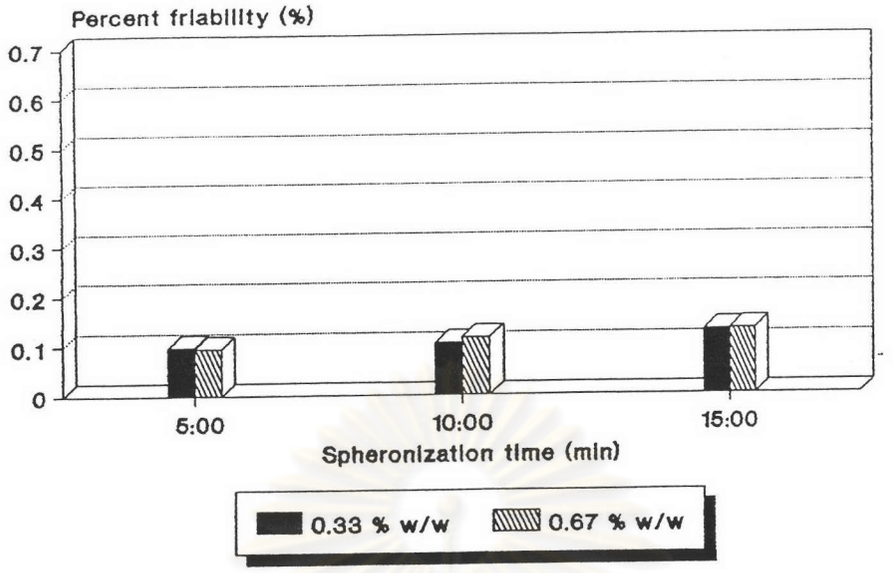

Figure 62 Percent friability of lactose-Avicel PH101^{R} pellets using Methocel A4M^{R} as a function of Methocel A4M^{R} concentration and spheronization times

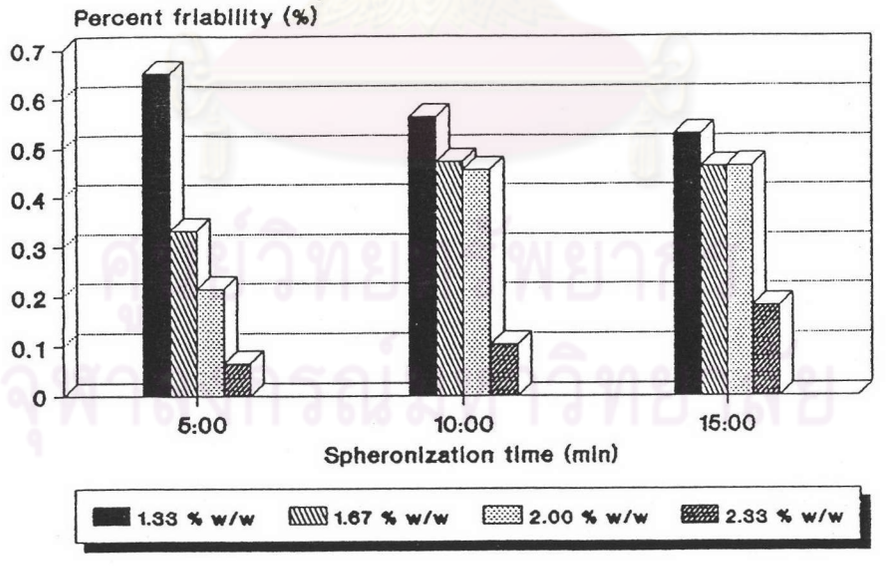

Figure 63 Percent friability of lactose-Avicel PH101^{R} pellets using HPC-M^{R} as a function of HPC-M^{R} concentration and spheronization times

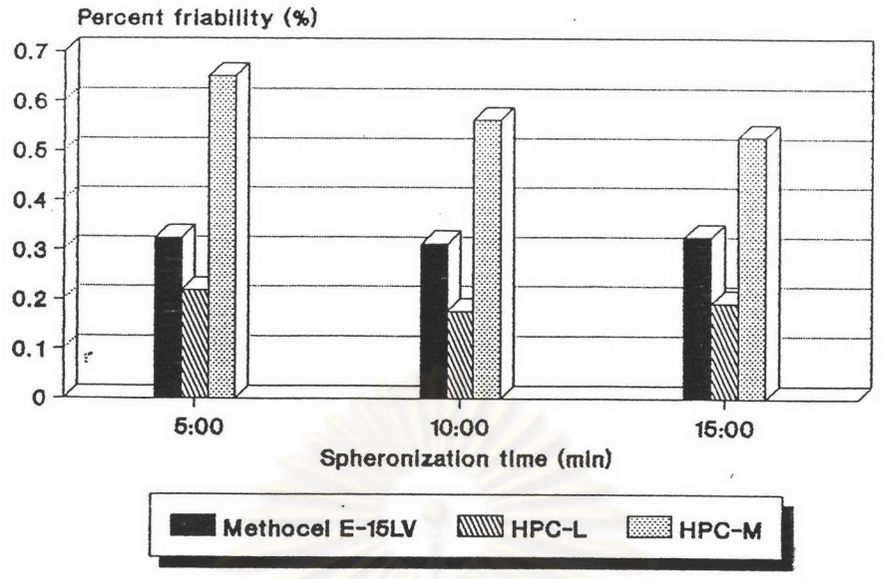

Figure 64 Percent friability of lactose-Avicel PH101^{R} pellets using 1.33 % w/w of binder concentration as a function of binder types and spheronization times

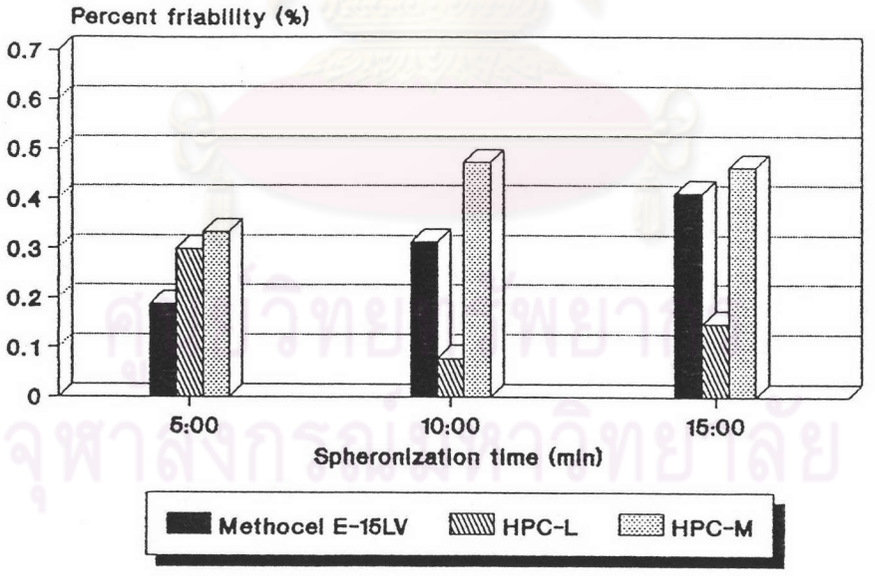

Figure 65 Percent friability of lactose-Avicel PH101^{R} pellets using 1.67 % w/w of binder concentration as a function of binder types and spheronization times

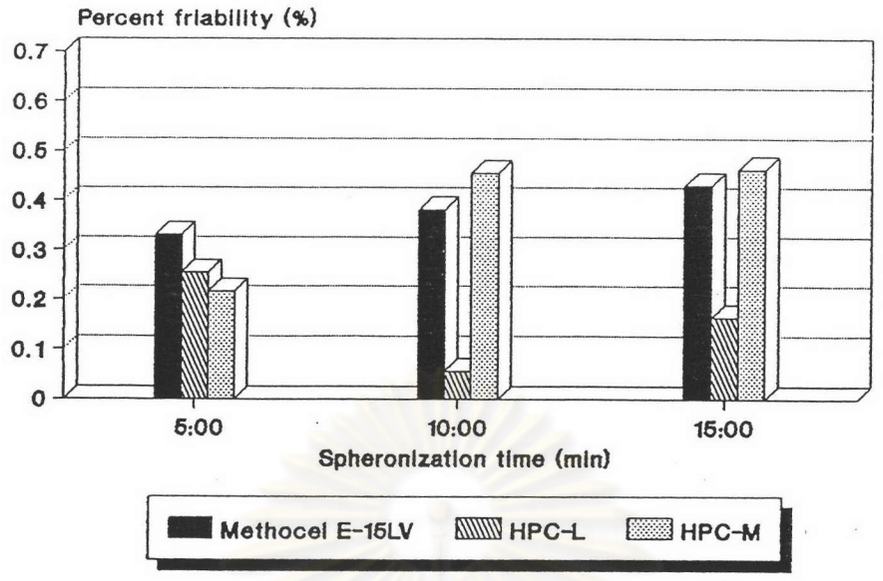

Figure 66 Percent friability of lactose-Avicel PH101^{R} pellets using 2.00 % w/w of binder concentration as a function of binder types and spheronization times

8.3 Methocel A4M^{R}

Increasing binder concentrations and spheronization times were not significantly different in percent friability at 95% confident level.

8.4 HPC-M^{R}

Increasing spheronization times were not significantly different in percent friability at 95% confident level. At 2.33 % w/w of binder concentration of each spheronization time gave the lowest percent friability.

8.5 Compared Type of Binders at Different Concentrations and Spheronization Times on Percent Friability

In the case of 1.33 % w/w of binder concentration at 5 and 10 min of spheronization time ; 1.67 % w/w at 10 and 15 min; and 2.00 % w/w at 10 min, the percent friability of pellets used HPC-L^{R} as a binder was lower than that the others. The percent friability of pellets prepared with the other binder concentrations and spheronization times were not significantly different at 95% confident level.

Physical Properties of Lactose-Avicel PH101^{R} Placebo Pellets Prepared with Various Water Contents

Physical properties of lactose-Avicel PH101^{R} pellets prepared

with various amount of water by using 2.00 % w/w of HPC-M^R as a binder and 15 min of spheronization time are presented in Table 17 and Figure 67.

1 Determination of the Pellets Appearance

At 35 % w/w of water content base on dry basis, pellets had long rod shape. At 40 %, 42 % and 44 % w/w of water content,respectively, pellets became sphere shape with rough surface. At 50 % w/w of water content very large size of pellets were obtained.

2 Particle Size Distribution Determination

The pellets using 40 %, 42 % and 44 % w/w of water content base on dry basis had narrow size distribution.

3 Mean Particle Size Determination

Mean particle size of the pellets using 40 %, 42 % and 44 % w/w of water content base on dry basis were not significantly different at 95% confident level. The mean particle size was ranging from 0.958 -1.013 mm.

4 Percent Sieve Fraction on 14/20 Mesh Cut Determination

Percent sieve fraction on 14/20 mesh cut was ranging from 74.18-77.99. The pellets using 40 % w/w of water content base on dry basis had lower percent sieve fraction on 14/20 much cut.

Table 17 Physical properties of lactose-Avicel PH101^{R} pellets prepared with various amounts of water by using 2 % w/w of HPC-M^{R} and 15 minutes of spheronization time

Physical Properties		Amount of water (% base on dry basis)		
		40	42	44
Sieve analysis[a]				
% weight retained on				
Sieve No.	14	7.84	8.27	4.47
	18	38.09	42.59	40.16
	20	36.09	34.61	37.83
	40	15.94	13.92	17.41
	60	1.88	0.61	0.12
	pan	0.03	0.00	0.00
Granule size (mm)[a] by sieve analysis		0.958	1.013	0.967
% sieve faction on 14/20 mesh cut pellets[a]		74.18	77.20	77.99
Bulk density (g/ml, $\pm$SD)[b]		0.83(0.01)	0.81(0.01)	0.80(0.01)
Tapped density (g/ml, $\pm$SD)[b]		0.87(0.01)	0.86(0.00)	0.84(0.01)
Flow rate (g/min, $\pm$SD)[b]		282.42(5.48)	255.86(8.31)	246.94(2.84)
Angle of repose (^{o}, $\pm$SD)[b]		27.32(0.88)	27.22(1.03)	27.27(1.15)
Percent friability(%)[a]		0.4630	0.3675	0.1935

(a) averaged from two determinations

(b) averaged from three determinations

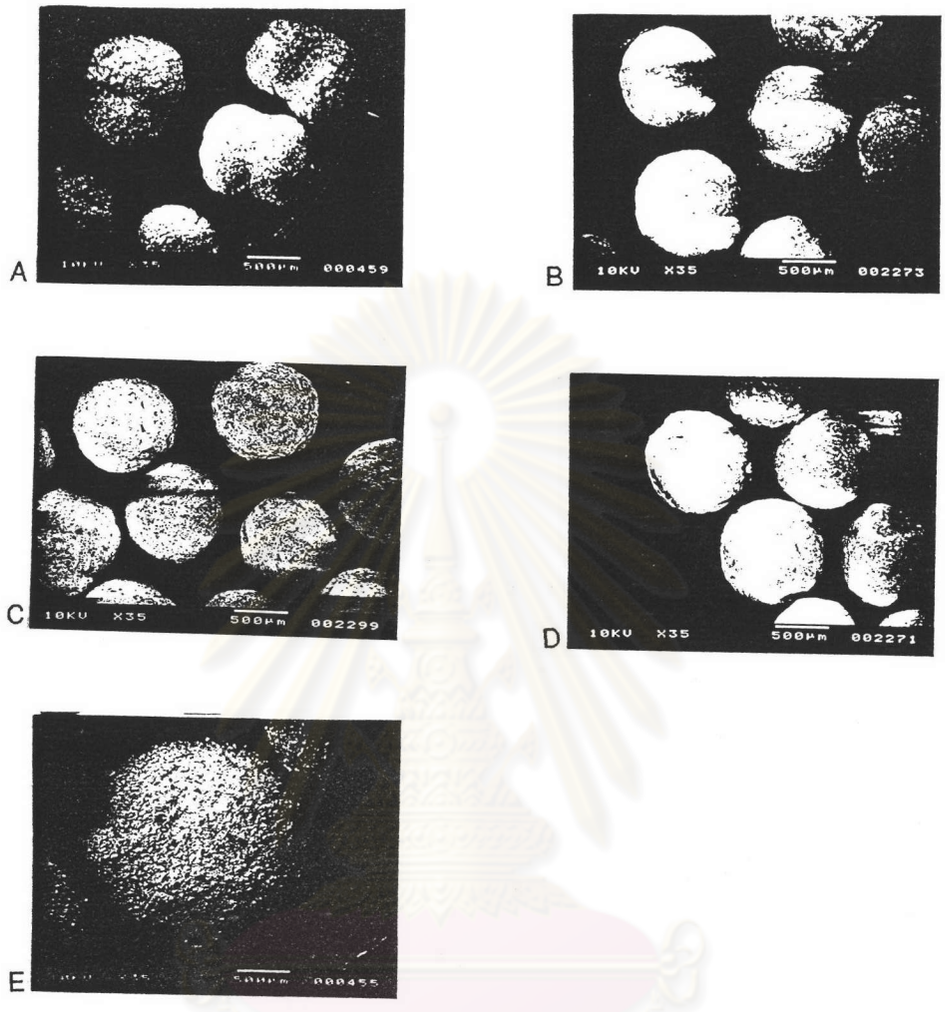

Figure 67 Photomicrographs of lactose-Avicel PH101^{R} pellets using various amount of water at 2.00 % w/w of HPC-M^{R}, 15 min of spheronization times and spheronizer speed of 951 rpm (x35) (A,B,C,D,E are 35 %,40 %,42 %,44 % and 50 % of water base on dry basis respectively)

5 Bulk Density and Tapped Density Determination

Bulk density and tapped density were ranging from 0.80-0.83 g/ml and 0.84-0.87 g/ml, respectively. Bulk density and tapped density of the pellets reduced with increasing amount of water.

6 Flow Rate Determination

Flow rate of pellets using 40 %, 42 % and 44 % w/w of water content was ranging from 246.94-282.42 g/min. Flow rate of the pellets decreased with increasing amount of water.

7 Angle of Repose Determination

Angle of repose was ranging from 27.22-27.32^{o}. Increasing amount of water was not significantly different at 95% confident level.

8 Percent Friability Determination

Percent friability was ranging from 0.1935-0.4630. Increasing amount of water was not significantly different at 95% confident level.

Physical Properties of Uncoated Terbutaline Sulphate Pellets

1 Determination of Uncoated Terbutaline Sulphate Pellets Appearance in Various Steps of Preparation

The microscopic appearance of product in each step in prepared the pellets is presented in Figure 68.

2 Physical Properties of Uncoated Terbutaline Sulphate Pellets

Physical properties of uncoated terbutaline sulphate pellets are presented in Table 18 and Figure 69. The pellets had narrow size distribution. The mean particle size was approximately about 0.962 mm and percent sieve fraction on 14/20 mesh cut was 77 %.Bulk density and tapped density were not different. The pellets had high flow rate but low angle of repose. The percent friability was very low.

3 Dissolution Profiles of Uncoated Terbutaline Sulphate Pellets

The dissolution data of uncoated terbutaline sulphate pellets is shown in Table 19. The released profile of uncoated terbutaline sulphate pellets which was plotted between the percentage amount of drug release as a function of time is presented in Figure 70.

Physical Properties of Film Coated Terbutaline Sulphate Pellets

1 Determination of Film Coated Terbutaline Sulphate Pellets Appearance

The microscopic appearance of film coated pellets both before and after dissolution test are given in Figures 71-78. Thickness of coated layer and smooth surface area were increased with increasing

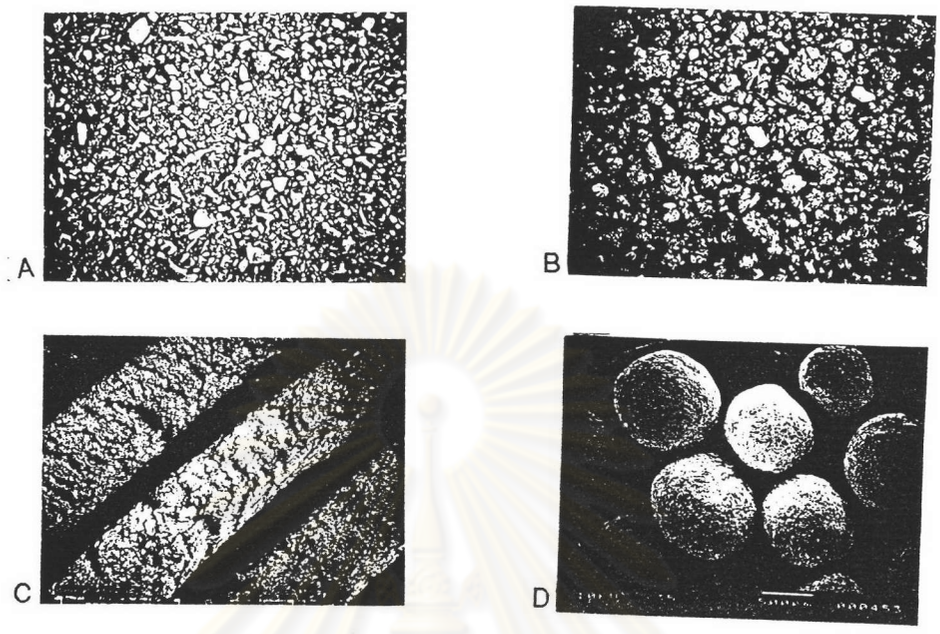

Figure 68 Photomicrographs of uncoated terbutaline sulphate pellets in various steps of preparation (x35)
(A = dry mixing; B = wetting; C = extrusion and D = spheronization)

Table 18 Physical properties of uncoated terbutaline sulphate pellets

Physical Properties	
Sieve analysis[a]	
% weight retained on	
Sieve No. 14	6.78
18	40.19
20	36.81
40	15.00
60	1.17
pan	0.05
Granule size (mm)[a]	0.962
by sieve analysis	
% sieve fraction on 14/20 mesh	77.00
cut pellets[a]	
Bulk density (g/ml, ±SD)[b]	0.83 (0.01)
Tapped density (g/ml, ±SD)[b]	0.86 (0.01)
Flow rate (g/min, ±SD)[b]	280.97 (6.31)
Angle of repose (°, ±SD)[b]	27.38 (1.54)
Percent friability (%)[a]	0.4270

(a) averaged from two determinations

(b) averaged from three determinations

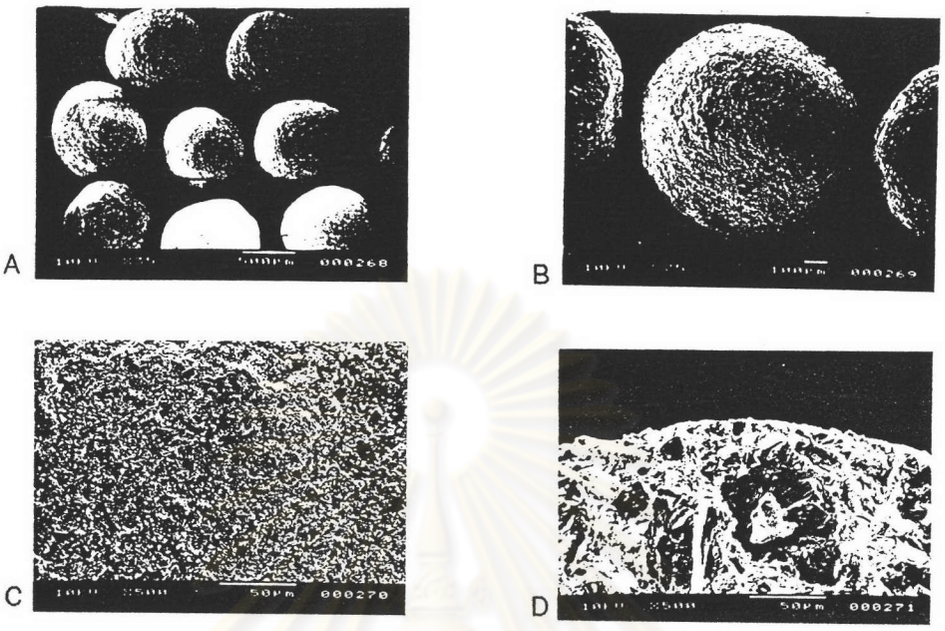

Figure 69 Photomicrographs of uncoated terbutaline sulphate pellets in various magnifications

(A = x35; B = x75; C = x500 and D = x500 (cross-section)

Table 19 Cumulative released of terbutaline sulphate from uncoated terbutaline sulphate pellets

Time (hr.)	Cumulative released of terbutaline sulphate(%)(n=3)			
	1	2	3	x±SD
0	0	0	0	0
0.5	45.72	41.93	38.68	42.11±3.52
0.10	62.29	63.89	65.19	63.79±1.45
0.25	93.95	87.47	89.28	90.23±3.34
0.50	96.67	93.35	90.27	93.43±3.20
1	95.79	95.14	91.16	94.03±2.51
2	95.22	95.02	96.14	95.46±0.60
4	97.45	98.24	96.25	97.31±1.00
8	98.82	98.95	97.10	98.29±1.03
12	98.66	97.66	98.54	98.29±0.55

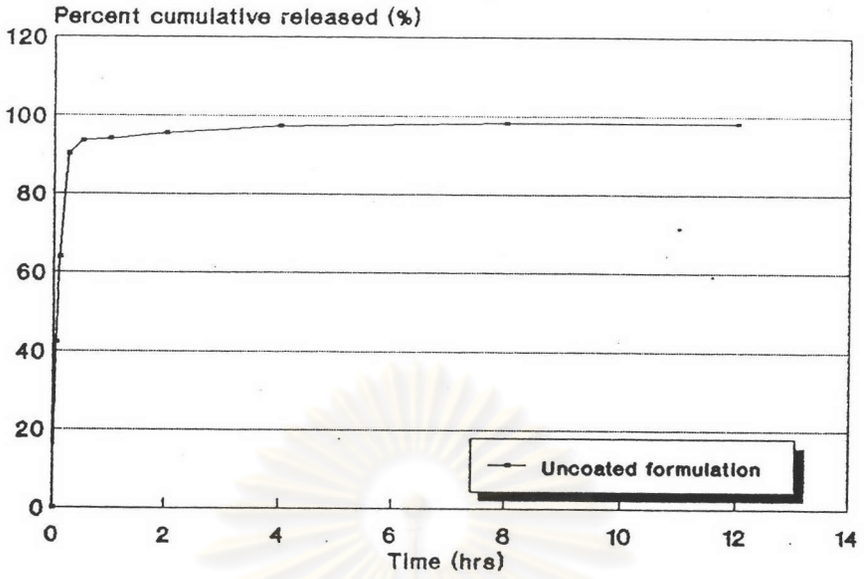

Figure 70 Dissolution profile of terbutaline sulphate from uncoated pellets

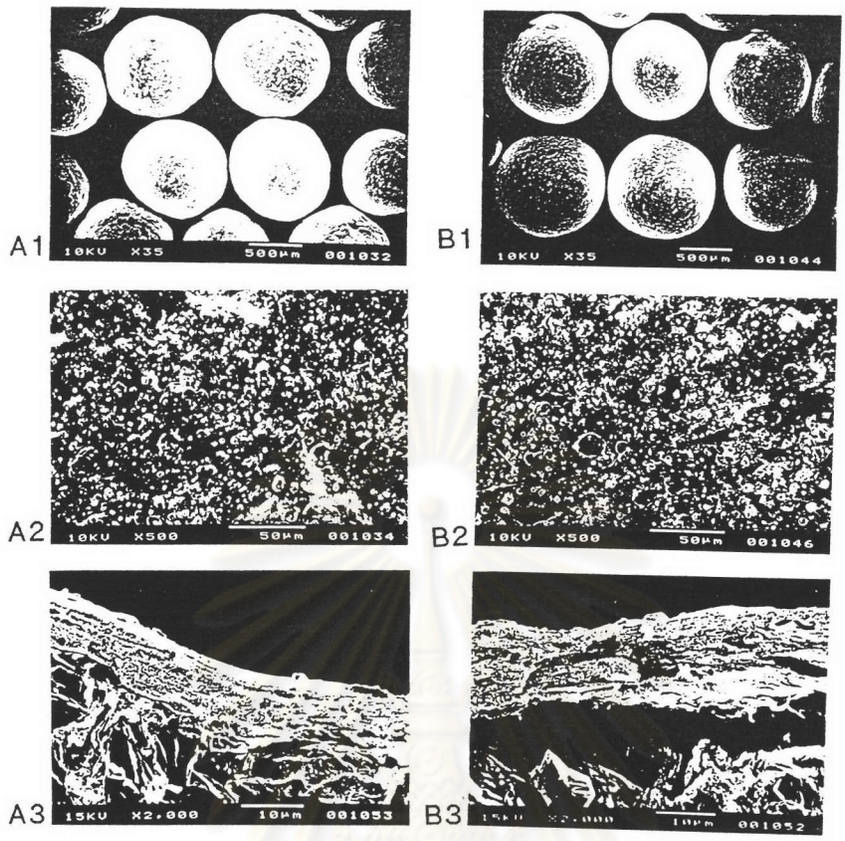

Figure 71 Photomicrographs of 5.4 % w/w film coated terbutaline sulphate pellets (formulation 2) at before and after test for dissolution

(A1,A2,A3 are before test for dissolution at x35, x500, x2000 (cross-section) of magnification; B1,B2,B3 are after test for dissolution at x35,x500,x2000 (cross-section) of magnification)

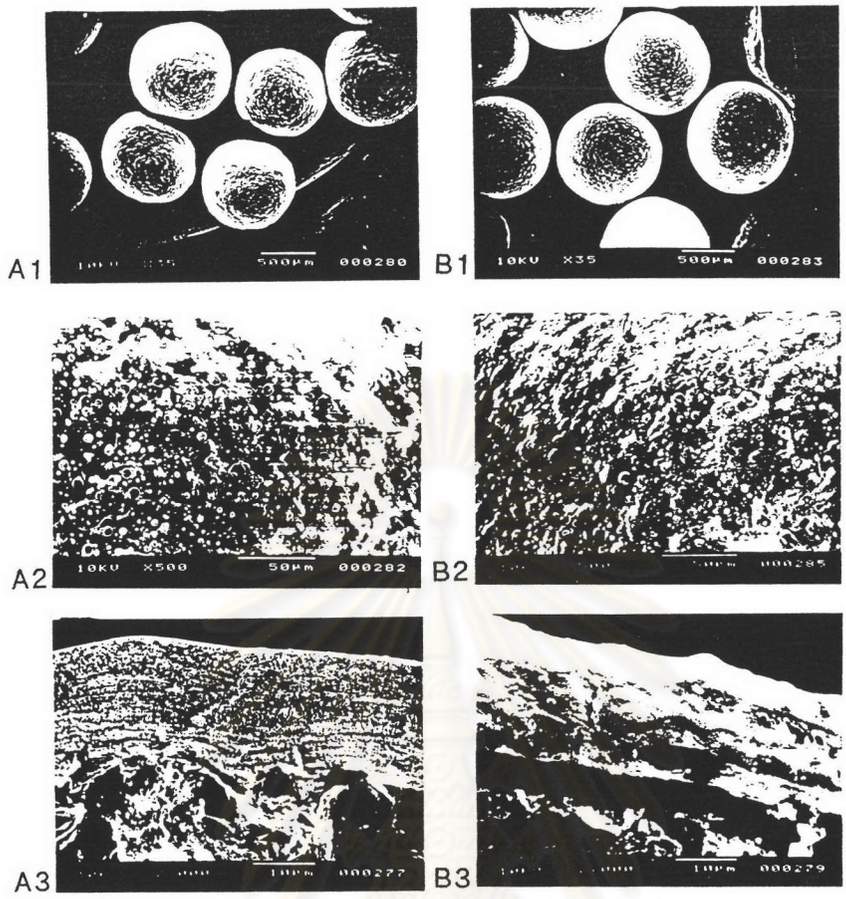

Figure 72 Photomicrographs of 5.4 % w/w film coated terbutaline sulphate pellets (formulation 1) at before and after test for dissolution

(A1,A2,A3 are before test for dissolution at x35, x500, x2000 (cross-section) of magnification; B1,B2,B3 are after test for dissolution at x35,x500,x2000 (cross-section) of magnification)

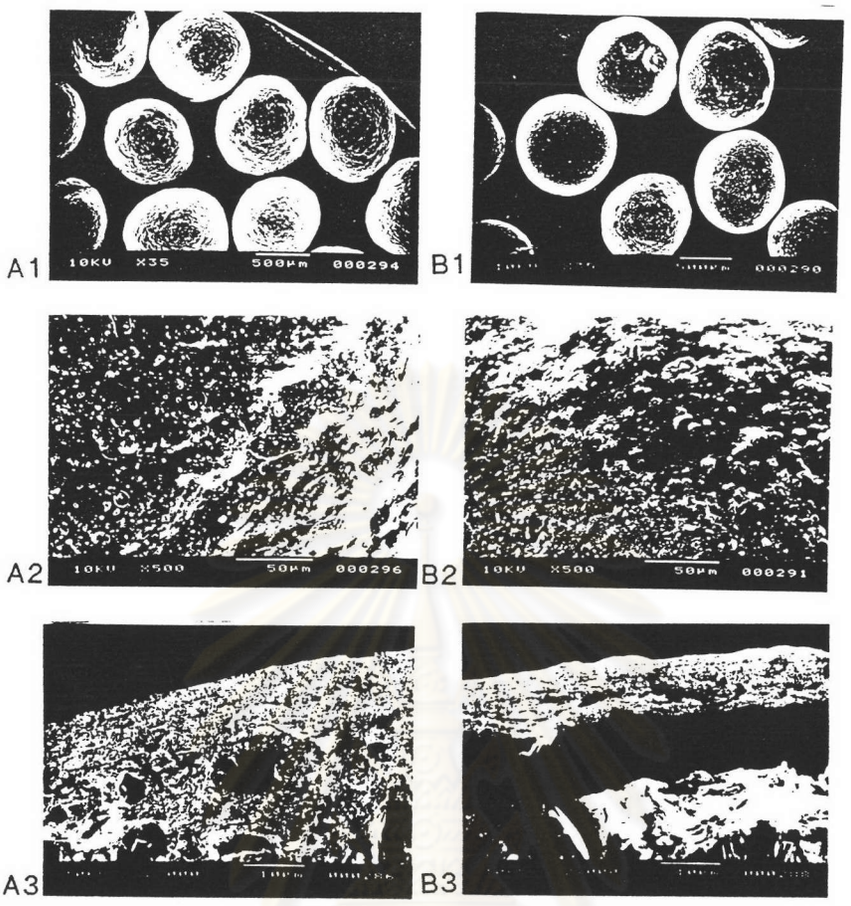

Figure 73 Photomicrographs of 3.2 % w/w film coated terbutaline sulphate pellets (formulation 1) at before and after test for dissolution

(A1,A2,A3 are before test for dissolution at x35, x500, x2000 (cross-section) of magnification; B1,B2,B3 are after test for dissolution at x35, x500, x2000 (cross-section) of magnification)

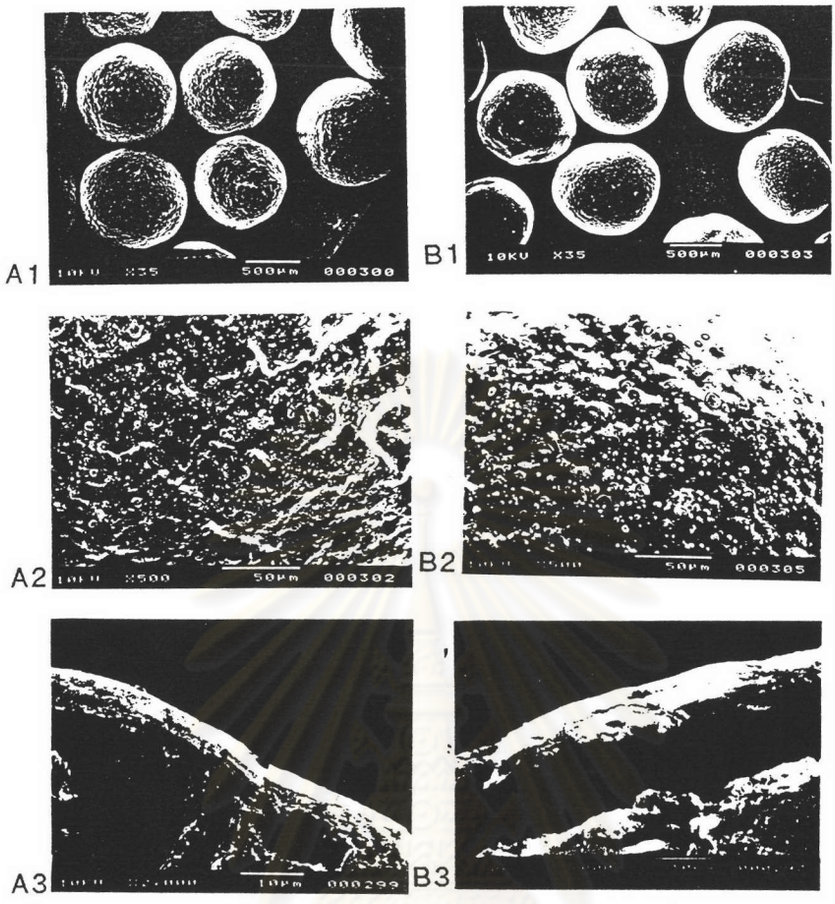

Figure 74 Photomicrographs of 1.5 % w/w film coated terbutaline sulphate pellets (formulation 1) at before and after test for dissolution

(A1,A2,A3 are before test for dissolution at x35, x500, x2000 (cross-section) of magnification; B1,B2,B3 are after test for dissolution at x35, x500, x2000 (cross-section) of magnification)

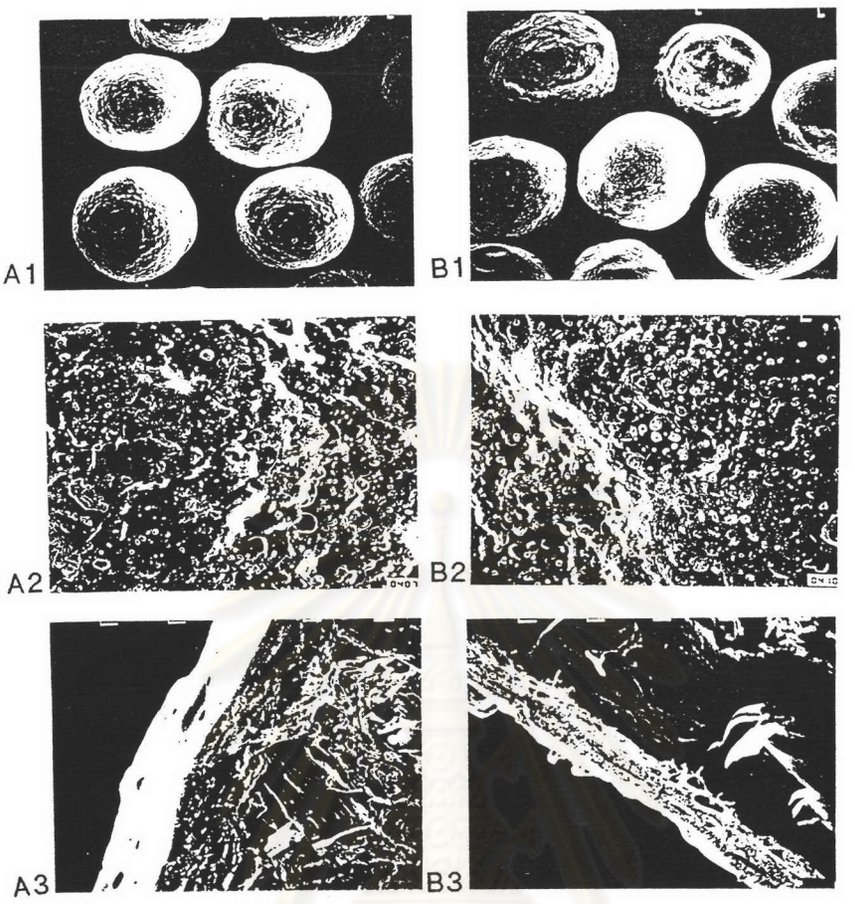

Figure 75 Photomicrographs of 1.1 % w/w film coated terbutaline sulphate pellets (formulation 1) at before and after test for dissolution

(A1,A2,A3 are before test for dissolution at x35, x500, x2000 (cross-section) of magnification ; B1,B2,B3 are after test for dissolution at x35,x500,x2000 (cross-section) of magnification)

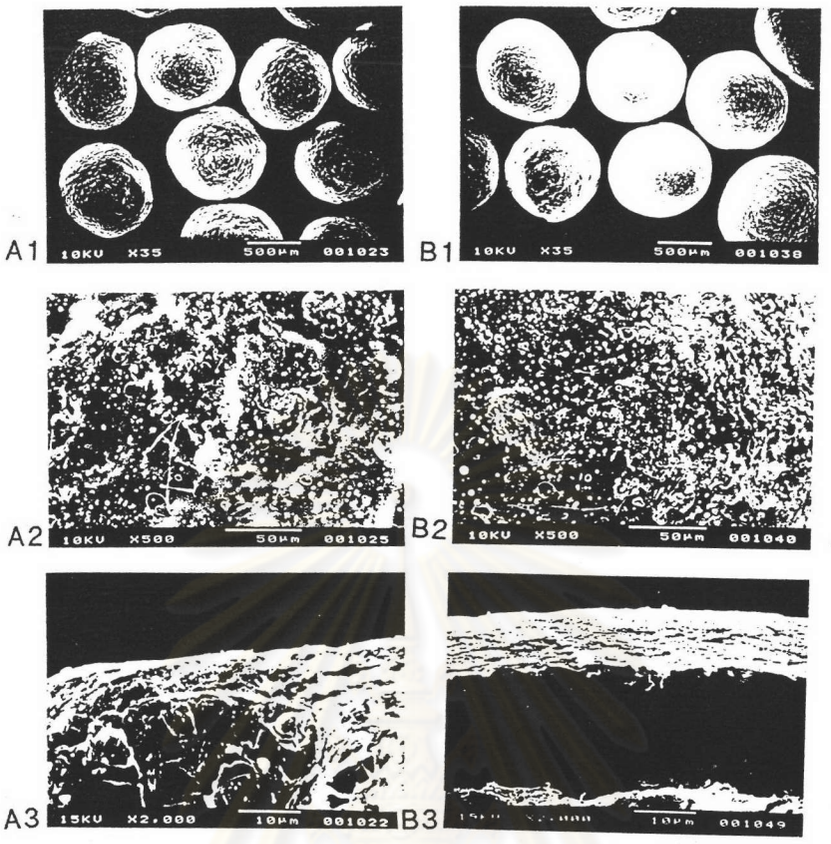

Figure 76 Photomicrographs of 3.2 % w/w film coated terbutaline sulphate pellets (formulation 3) at before and after test for dissolution

(A1,A2,A3 are before test for formulation at x35, x500, x2000 (cross-section) of magnification; B1,B2,B3 are after test for dissolution at x35, x500,x2000 (cross-section) of magnification)

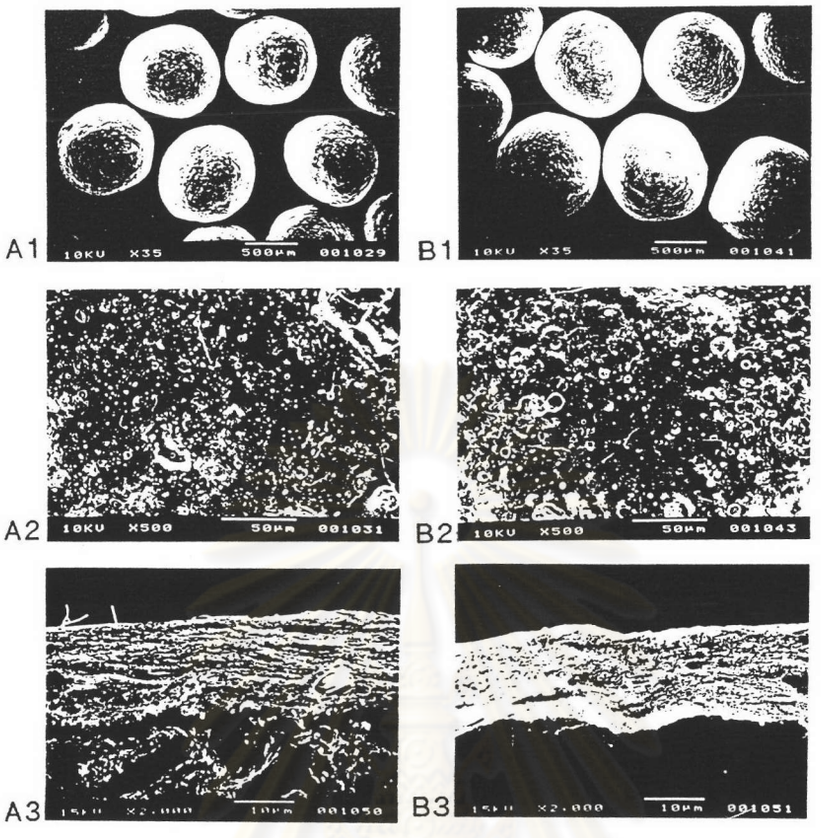

Figure 77 Photomicrographs of 3.2 % w/w film coated terbutaline sulphate pellets (formulation 4) at before and after test for dissolution

(A1,A2,A3 are before test for dissolution at x35, x500, x2000 (cross-section) of magnification; B1,B2,B3 are after test for dissolution at x35,x500,x2000 (cross-section) of magnification)

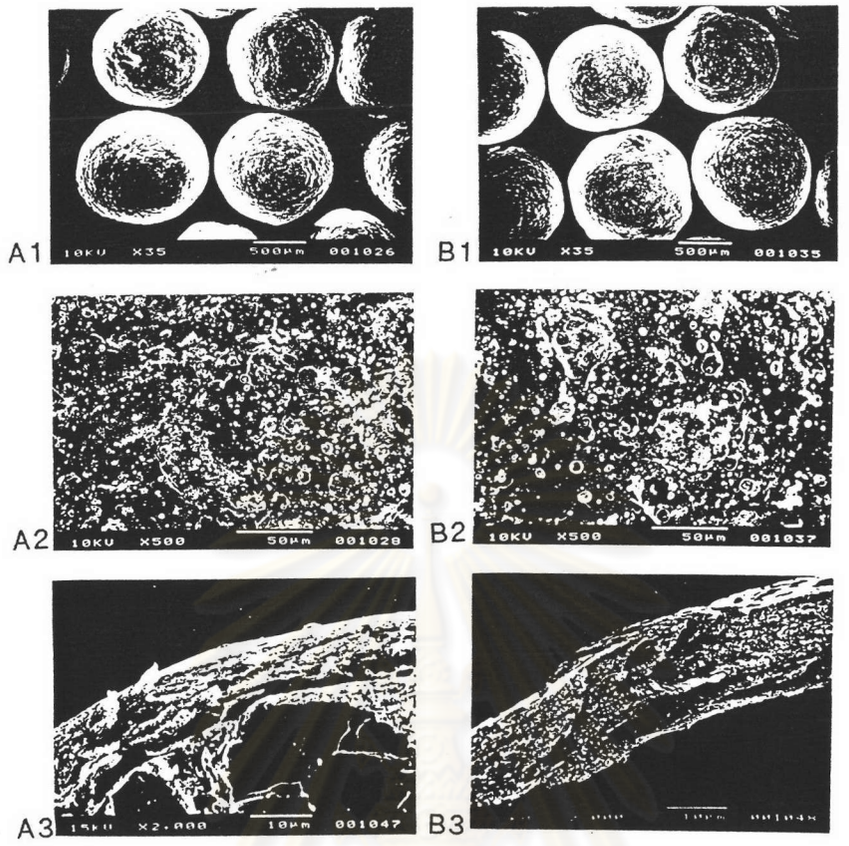

Figure 78 Photomicrographs of 3.2 % w/w film coated terbutaline sulphate pellets (formulation 5) at before and after test for dissolution

(A1,A2,A3 are before test for dissolution at x35, x500, x2000 (cross-section) of magnification; B1,B2,B3 are after test for dissolution at x35, x500,x2000 (cross-section) of magnification)

amount of ethylcellulose. After dissolution test, these pellets had channels in coated layer. Thickness of coated layer and surface area were not different with increasing amount of HPC-M^R in the film coating formulation. After dissolution test, these pellets had more number and size of channels in coated layer than pellets which had not contain HPC-M^R in the formulation.

2 Dissolution Profiles of Film Coated Terbutaline Sulphate Pellets

2.1 The Effect of Amount of Propylene Glycol on the Released Profile of Film Coated Terbutaline Sulphate Pellets

The dissolution data of each formulation are given in Tables 20 and 21. The released profile of each formulation which was plotted between the percentage amount of drug release as a function of time is presented in Figure 79. Amount of propylene glycol had no effect on drug released.

2.2 The Effect of Amount of Ethylcellulose on the Released Profile of Film Coated Terbutaline Sulphate Pellets

The dissolution data of each formulation are shown in Tables 21-24. The released profile of each formulation which was plotted between the percentage amount of drug released as a function of time is presented in Figure 80. The released profile of drug decreased with increasing amount of ethylcellulose.

Table 20 Cumulative released of terbutaline sulphate from 5.4 % w/w ethylcellulose film coated terbutaline sulphate pellets (Formulation 2)

Time (hr.)	Cumulative released of terbutaline sulphate (%)(n=3)			
	1	2	3	x±SD
0	0	0	0	0
0.5	0	0	0	0
1	0	0	0	0
2	0	0	1.64	0.55±0.95
3	0	0	2.72	0.91±1.57
4	6.10	4.14	3.84	4.69±1.23
5	8.53	7.04	6.02	7.20±1.26
6	9.62	8.56	6.43	8.20±1.62
8	17.89	14.48	15.14	15.84±1.81
10	21.97	19.85	19.41	20.41±1.37
12	30.21	33.65	35.40	33.09±2.64

Table 21 Cumulative released of terbutaline sulphate from 5.4 % w/w ethylcellulose film coated terbutaline sulphate pellets (Formulation 1)

Time (hr.)	Cumulative released of terbutaline sulphate (%)(n=3)			
	1	2	3	x±SD
0	0	0	0	0
0.5	0	0	0	0
1	0	0	0	0
2	0	0	4.83	1.61±2.79
3	5.11	4.81	5.34	5.09±0.27
4	6.00	6.89	6.91	6.60±0.52
5	8.18	8.74	9.00	8.64±0.42
6	9.50	10.96	10.44	10.30±0.74
8	13.90	17.26	13.85	15.00±1.95
10	17.49	19.75	17.18	18.14±1.40
12	20.75	25.65	20.48	22.29±2.91

Table 22 Cumulative released of terbutaline sulphate from 3.2 % w/w ethylcellulose film coated terbutaline sulphate pellets (Formulation 1)

Time (hr.)	Cumulative released of terbutaline sulphate (%)(n=3)			
	1	2	3	x±SD
0	0	0	0	0
0.5	0	0	0	0
1	4.97	4.43	4.63	4.68±0.27
2	8.42	7.30	7.80	7.84±0.56
3	13.33	12.97	11.93	12.74±0.73
4	19.26	17.49	18.21	18.32±0.89
5	28.39	22.21	24.27	24.96±3.15
6	31.43	28.01	28.96	29.47±1.77
8	39.07	36.19	40.94	38.73±2.39
10	45.88	47.28	50.12	47.76±2.16
12	54.51	56.50	60.31	57.11±2.95

Table 23 Cumulative released of terbutaline sulphate from 1.5 % w/w ethylcellulose film coated terbutaline sulphate pellets (Formulation 1)

Time (hr.)	Cumulative released of terbutaline sulphate (%)(n=3)			
	1	2	3	x±SD
0	0	0	0	0
0.5	0	1.97	0	0.66±1.14
1	3.67	5.98	3.56	4.40±1.37
2	21.94	23.74	24.32	23.33±1.24
3	41.72	38.19	41.41	40.44±1.95
4	47.72	49.36	52.17	49.75±2.25
5	59.08	64.61	64.80	62.83±3.25
6	68.20	68.71	66.49	67.80±1.16
8	82.21	84.52	79.79	82.17±2.37
10	85.53	84.90	89.16	86.53±2.30
12	90.94	86.58	89.52	89.01±2.22

Table 24 Cumulative released of terbutaline sulphate from 1.1 % w/w ethylcellulose film coated terbutaline sulphate pellets (Formulation 1)

Time (hr.)	Cumulative released of terbutaline sulphate (%)(n=3)			
	1	2	3	x±SD
0	0	0	0	0
0.5	1.64	0	0	0.55±0.95
1	11.61	9.76	9.54	10.30±1.14
2	37.40	39.22	38.47	38.36±0.91
3	53.65	57.45	57.05	56.05±2.09
4	62.63	65.18	67.45	65.09±2.41
5	72.16	75.99	75.69	73.98±2.10
6	80.97	82.45	81.25	81.56±0.79
8	80.96	84.05	85.79	83.60±2.45
10	88.13	95.43	88.78	90.78±4.04
12	94.59	98.63	99.81	97.68±2.74

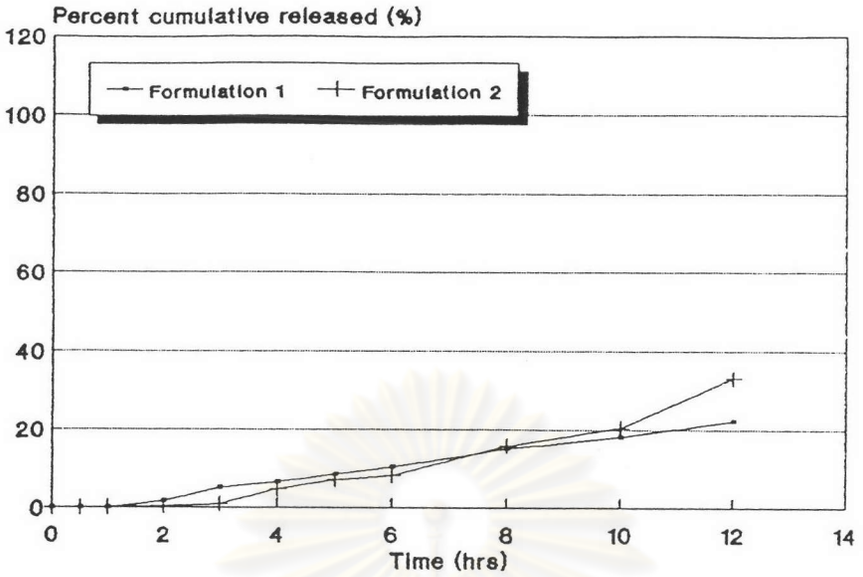

Figure 79 Dissolution profile of terbutaline sulphate from 5.4 % w/w of coating level of film coated terbutaline sulphate pellets formulation 1 and 2

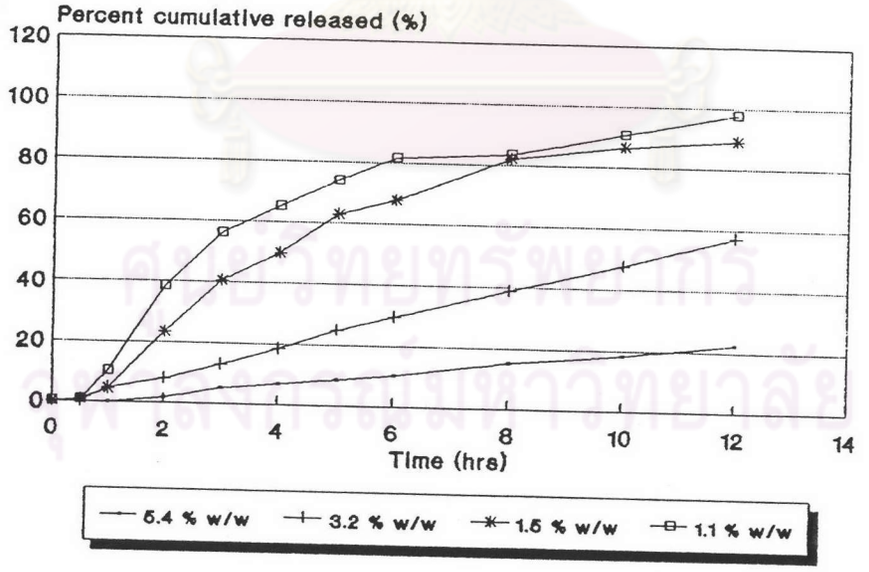

Figure 80 Dissolution profile of terbutaline sulphate from film coated terbutaline sulphate pellets formulation 1

2.3 The Effect of Ratio of HPC-M^R and Ethylcellulose on the Released Profile of Film Coated Terbutaline Sulphate Pellets

The dissolution data of each formulation are given in Tables 25-27.The released profile of each formulation which was plotted between the percentage amount of drug released as a function of time is presented in Figure 81. The released profile of drug increased with increasing ratio of HPC-M^R and ethylcellulose.

2.4 The Effect of Loading Dose on the Mixture of Uncoated Terbutaline Sulphate Pellets and Film Coated Terbutaline Sulphate Pellets

The dissolution data of each formulation are shown in Tables 28 and 29. The released profile of each formulation which was plotted between the percentage amount of drug released as a function of time is presented in Figure 82. During dissolution test, the released profile of drug increased in about first two hours when incorporate uncoated terbutaline sulphate pellets as loading dose.

2.5 Dissolution Profiles of Selected Formulation Compared with Commercial Product

The dissolution data of Bricanyl^R Durules and the selected formulation are shown in Tables 30 and 31, respectively. The released profiles of Bricanyl^R Durules and the selected formulation which were plotted between the percentage amount of drug released against time are presented in Figure 83. The released profile of drug

Table 25 Cumulative released of terbutaline sulphate from 3.2 % w/w ethylcellulose film coated terbutaline sulphate pellets (Formulation 3)

Time (hr.)	Cumulative released of terbutaline sulphate (%)(n=3)			
	1	2	3	x±SD
0	0	0	0	0
0.5	0	0	0	0
1	1.18	0	0.74	0.64±0.60
2	1.29	0.66	0.93	0.96±0.32
3	5.94	7.15	4.55	5.88±1.30
4	14.88	14.41	13.48	14.26±0.71
5	17.21	21.43	20.44	19.69±2.21
6	26.80	31.23	22.86	26.96±4.19
8	39.94	38.73	41.20	39.96±1.24
10	56.17	53.12	53.63	54.31±1.63
12	64.54	65.47	60.53	63.51±2.63

Table 26 Cumulative released of terbutaline sulphate from 3.2 % w/w ethylcellulose film coated terbutaline sulphate pellets (Formulation 4)

Time (hr.)	Cumulative released of terbutaline sulphate (%)(n=3)			
	1	2	3	x±SD
0	0	0	0	0
0.5	0	1.68	0	0.56±0.97
1	9.11	10.37	8.23	9.24±1.08
2	40.55	44.15	39.46	41.39±2.45
3	62.99	68.23	62.46	64.56±3.19
4	78.27	78.55	76.23	77.68±1.27
5	89.41	88.52	86.48	88.14±1.50
6	91.56	91.96	89.21	90.91±1.49
8	97.04	95.23	94.39	95.55±1.35
10	98.46	96.23	94.70	96.46±1.89
12	97.34	99.27	99.59	98.73±1.22

Table 27 Cumulative released of terbutaline sulphate from 3.2 % w/w ethylcellulose film coated terbutaline sulphate pellets (Formulation 5)

Time (hr.)	Cumulative released of terbutaline sulphate (%)(n=3)			
	1	2	3	x±SD
0	0	0	0	0
0.5	10.10	11.61	8.61	10.11±1.50
1	53.45	56.38	50.85	53.56±2.77
2	91.17	89.60	80.13	86.97±5.97
3	91.13	89.32	89.05	89.83±1.13
4	91.19	93.24	92.77	92.40±1.07
5	92.63	93.86	93.80	93.43±0.69
6	94.77	94.21	96.86	95.28±1.40
8	94.85	95.17	98.03	96.02±1.75
10	94.05	98.57	98.34	96.99±2.55
12	98.98	98.84	99.76	99.19±0.50

Table 28 Cumulative released of terbutaline sulphate from the mixture of 1.5 % w/w ethylcellulose film coated terbutaline sulphate pellets (Formulation 1) and uncoated terbutaline sulphate pellets ratio 7:1

Time (hr.)	Cumulative released of terbutaline sulphate (%)(n=3)			
	1	2	3	x±SD
0	0	0	0	0
0.5	23.15	18.49	18.54	20.06±2.68
1	23.67	21.32	20.11	21.70±1.81
2	38.52	34.95	34.26	35.91±2.29
3	58.97	54.15	48.47	53.86±5.26
4	66.34	60.17	66.90	64.47±3.73
5	70.81	70.23	67.69	69.58±1.66
6	76.50	73.86	73.81	74.72±1.54
8	80.58	78.33	80.71	79.87±1.34
10	86.12	85.52	87.38	86.34±0.95
12	87.36	90.05	92.82	90.08±2.73

Table 29 Cumulative released of terbutaline sulphate from the mixture of 1.1% w/w ethylcellulose film coated terbutaline sulphate pellets (Formulation 1) and uncoated terbutaline sulphate pellets ratio 7:1

Time (hr.)	Cumulative released of terbutaline sulphate (%)(n=3)			
	1	2	3	x±SD
0	0	0	0	0
0.5	12.54	11.09	9.67	11.10±1.44
1	21.25	20.79	18.70	20.25±1.36
2	42.38	50.42	43.51	45.44±4.35
3	59.98	56.10	60.02	58.70±2.25
4	70.18	74.39	72.31	72.29±2.11
5	74.41	78.02	72.91	75.11±2.63
6	75.94	82.42	78.73	79.03±3.25
8	83.06	83.92	82.65	83.21±0.65
10	87.19	90.52	86.80	88.17±2.04
12	94.59	97.55	96.38	96.17±1.49

Table 30 Cumulative released of terbutaline sulphate from Bricanyl Durules^{R}

Time (hr.)	Cumulative released of terbutaline sulphate (%)(n=3)			
	1	2	3	x±SD
0	0	0	0	0
0.5	14.89	19.03	23.04	18.99±4.08
1	25.02	28.78	26.42	26.74±1.90
2	38.64	39.87	40.54	39.68±0.96
3	50.25	52.77	51.98	51.67±1.29
4	61.12	66.23	67.25	64.87±3.28
5	75.59	73.50	74.85	74.65±1.06
6	79.63	78.47	80.50	79.53±1.02
8	93.74	84.47	89.79	89.33±4.65
10	94.83	87.54	96.08	92.82±4.61
12	101.99	99.52	98.47	99.99±1.81

Table 31 Cumulative released of terbutaline sulphate from sustained released pellets capsule (lot 1)

Time (hr.)	Cumulative released of terbutaline sulphate (%)(n=3)			
	1	2	3	x±SD
0	0	0	0	0
0.5	14.21	17.04	12.26	14.50±2.40
1	19.69	21.92	19.13	20.25±1.48
2	40.62	40.04	41.87	40.84±0.94
3	51.82	54.08	56.31	54.07±2.25
4	64.52	65.01	65.48	65.00±0.48
5	76.52	73.18	74.80	74.83±1.67
6	78.98	85.71	76.59	80.43±4.73
8	91.33	89.97	89.13	90.14±1.11
10	94.67	93.98	92.79	93.81±0.95
12	98.49	96.89	97.38	97.59±0.82

Table 32 Cumulative released of terbutaline sulphate from sustained released pellets capsule (lot 2)

Time (hr.)	Cumulative released of terbutaline sulphate (%)(n=3)			
	1	2	3	x±SD
0	0	0	0	0
0.5	12.48	15.44	15.12	14.35±1.62
1	25.97	25.32	32.65	27.98±4.06
2	47.06	48.09	46.52	47.22±0.80
3	61.12	56.96	50.12	56.07±5.55
4	77.05	73.28	71.76	74.03±2.72
5	83.90	81.50	75.56	80.32±4.29
6	84.54	86.01	81.84	84.13±2.12
8	90.91	89.49	84.35	88.25±3.45
10	96.49	92.95	90.59	93.34±2.97
12	98.39	101.12	96.41	98.64±2.36

Table 33 Cumulative released of terbutaline sulphate from sustained released pellets capsule (lot 3)

Time (hr.)	Cumulative released of terbutaline sulphate (%)(n=3)			
	1	2	3	x±SD
0	0	0	0	0
0.5	16.70	12.05	13.83	14.19±2.35
1	20.17	17.76	23.94	20.62±3.11
2	44.34	43.26	43.42	43.67±0.58
3	57.98	61.77	58.32	59.36±2.10
4	73.91	69.19	72.42	71.84±2.41
5	79.86	74.97	75.10	76.64±2.79
6	80.22	77.82	77.70	78.58±1.42
8	89.89	87.08	84.69	87.22±2.60
10	91.87	92.63	90.05	91.52±1.33
12	98.85	96.61	98.73	98.06±1.26

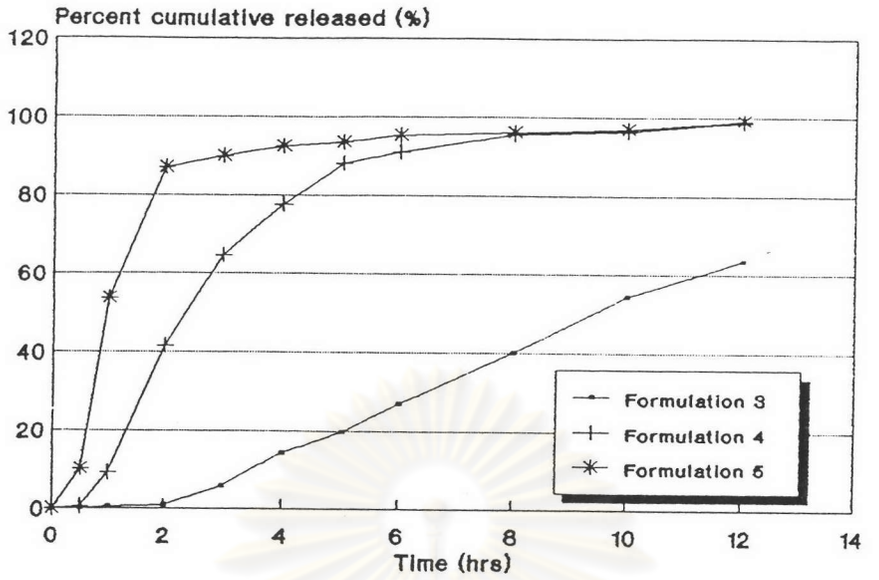

Figure 81 Dissolution profile of terbutaline sulphate from 3.2 % w/w of coating level of film coated terbutaline sulphate pellets formulation 3,4,5

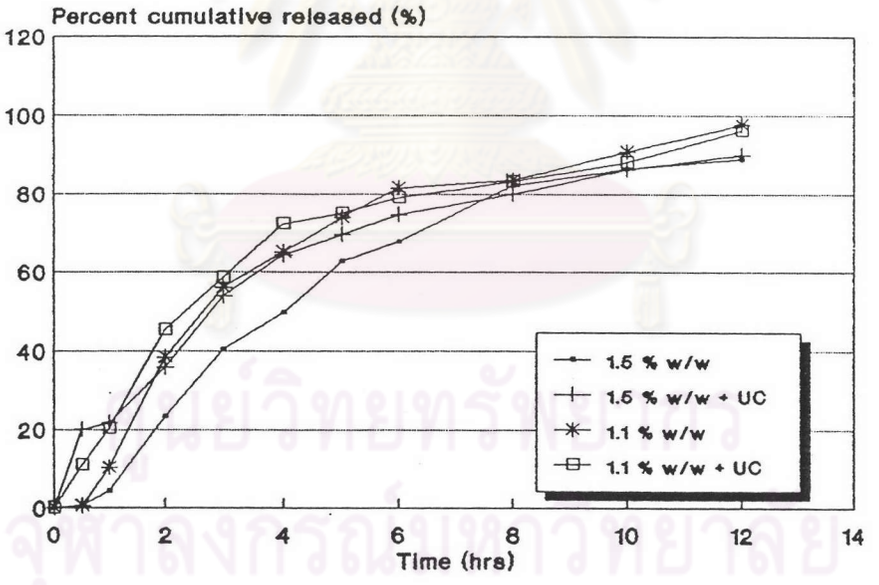

Figure 82 Dissolution profile of terbutaline sulphate from 1.1 %, 1.5 % w/w of coating level of film coated terbutaline sulphate pellets formulation 1 and mixture of 1.1 %, 1.5 % w/w of coating level of coated terbutaline sulphate pellets with uncoated terbutaline sulphate pellets ratio 7:1

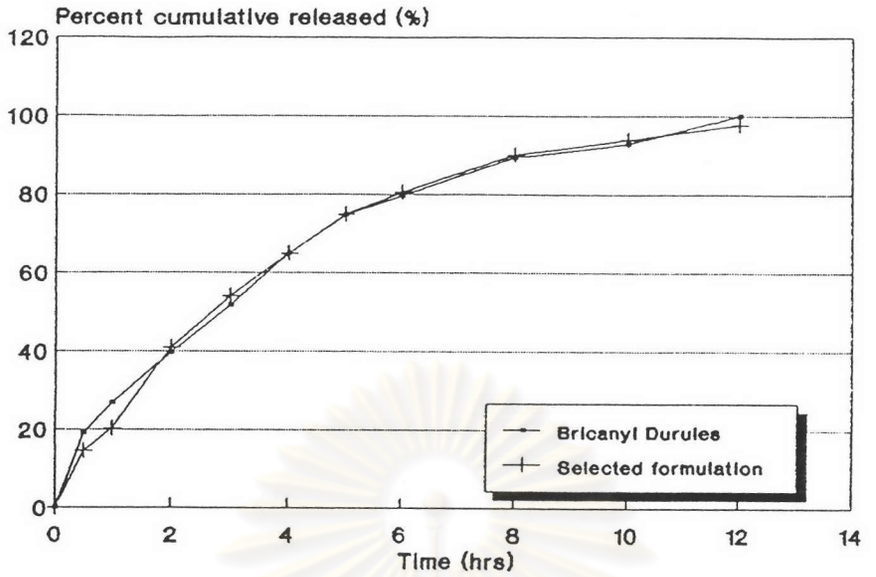

Figure 83 Dissolution profile of terbutaline sulphate from Bricanyl^{R} Durules and selected film coated terbutaline sulphate pellets formulation

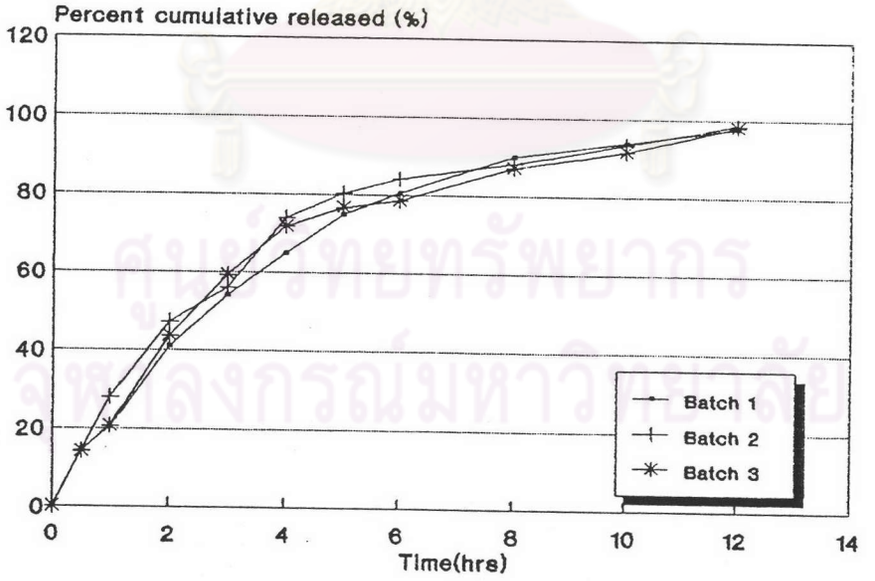

Figure 84 Dissolution profile of terbutaline sulphate from three batches of selected film coated terbutaline sulphate pellets capsule

from Bricanyl^{R} Durules and the selected formulation appear to be the same.

2.6 Reproducibility of Film Coated Terbutaline Sulphate Pellets

Three batches of the selected formulation were prepared to study the reproducibility of dissolution profiles of terbutaline sulphate from film coated terbutaline sulphate pellets. The dissolution data of three batches of the selected formulation are shown in Tables 31-33.The released profile of three batches of the selected formulation which were plotted between the percentage amount of drug released as a function of time is presented in Figure 84. The dissolution profiles of film coated terbutaline sulphate pellets which was selected were found to be reproducible.