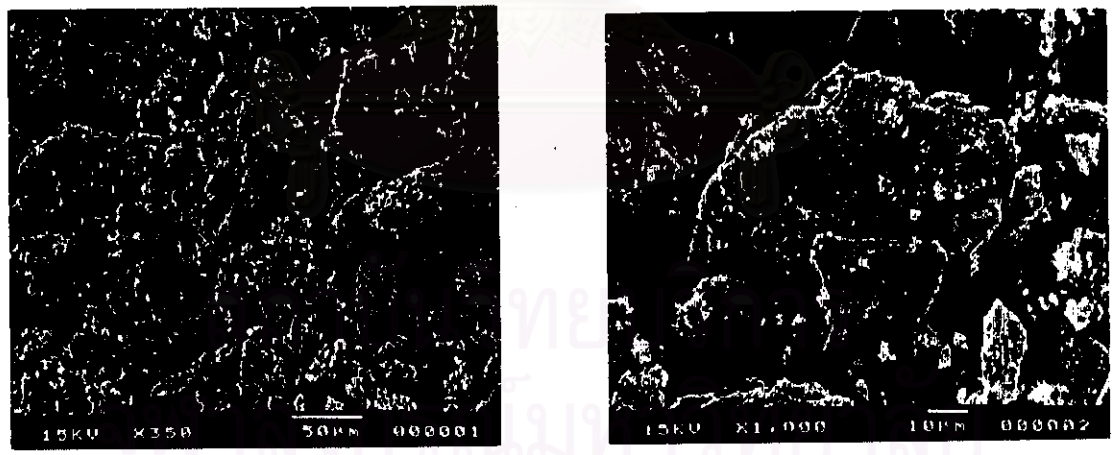
CHAPTER III

RESULTS

Effects of Spray Drying Conditions on the Physical Properties of Spray Dried Powder

The spray drying conditions were investigated in the preparation of diclofenac sodium spray dried powder using HPMC. The following conditions : the polymer to drug ratio of solution, the inlet air temperature, the feed rate and the atomizing air pressure were varied at various levels; then the physical properties of the obtained powder were evaluated.

1. Morphology of Spray Dried Powder



(A) x 350 (B) x 1,000

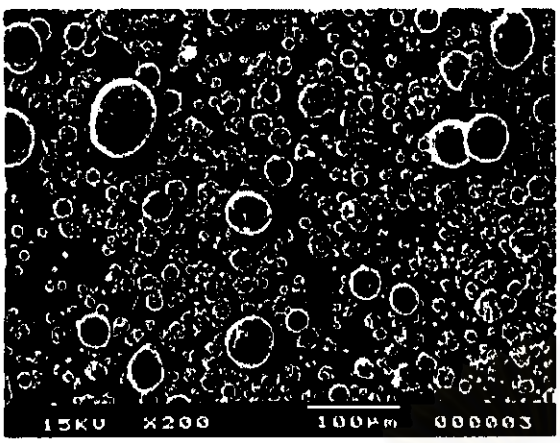
Figure 11 Photomicrographs of original diclofenac sodium powder.

Figure 11 shows the scanning electron photomicrographs of diclofenac sodium drug powder at different magnifications. Diclofenac sodium powder was composed of irregular thick crystal shapes in various sizes. The surface of the powder was rough.

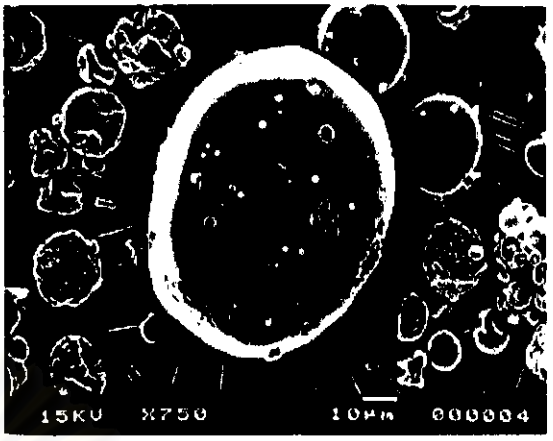
The photomicrographs of the spray dried particles prepared from different polymer to drug ratios of solution are shown in Figure 12. When HPMC was formulated with the polymer to drug ratios of 1:4 and 1:6, microballs with a lot of pores on the surface was observed, but with the ratio of 1:2, most particles were microcapsules with smooth surface. When the proportion of polymer in the formulation was decreased, the number of pores on the surface of the microballs were increased.

The shape and surface topography of the spray dried powder prepared at different inlet air temperatures are shown in Figure 13. When varying the inlet air temperature, every temperature levels used (130, 150 and 170 °C) were successful in the spray drying process of diclofenac sodium suspension. Most products obtained were microcapsules with smooth surface. As the temperature was increased from 130 to 150 and 170 °C, the surface of the powder were smoother. The powder produced at the inlet air temperature of 170 °C was slightly larger than those produced at 130 and 150 °C.

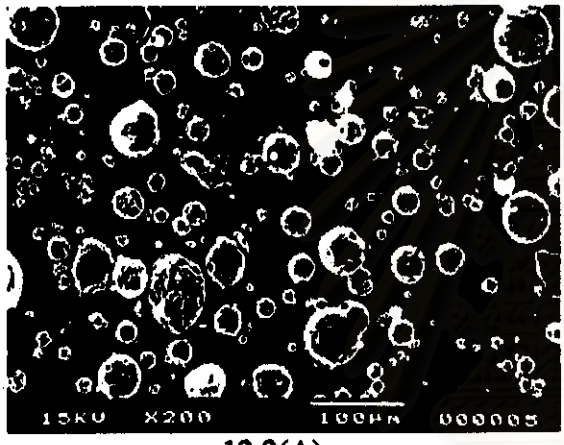
The photomicrographs of the spray dried powder produced at different feed rates are shown in Figure 14; most products obtained were microcapsules with smooth surface. As the feed rate was increased from, 14 to 20 and 26 ml./min., the size of the powder increased respectively. The powder produced at the feed rate of 26 ml./min. were the largest, followed by those at 20 and 14 ml./min., respectively.



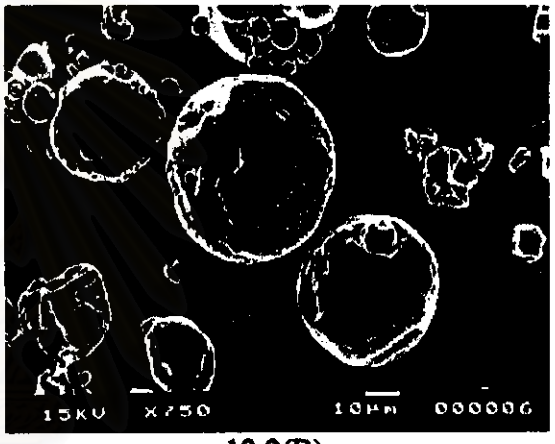
12.1(A)



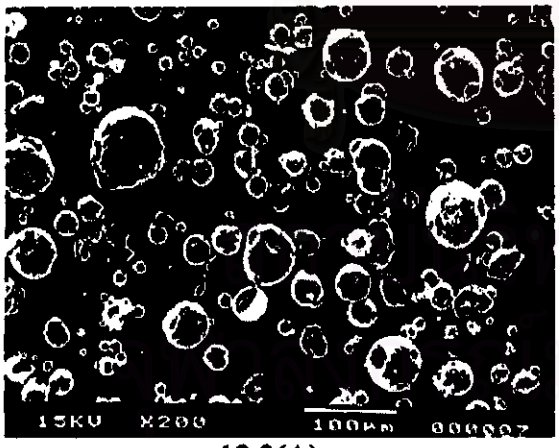
12.1(B)



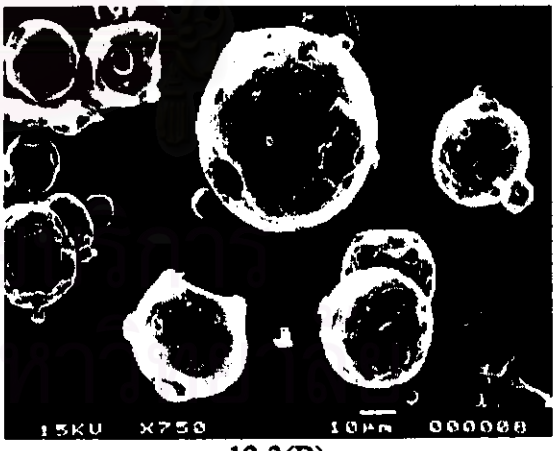
12.2(A)



12.2(B)

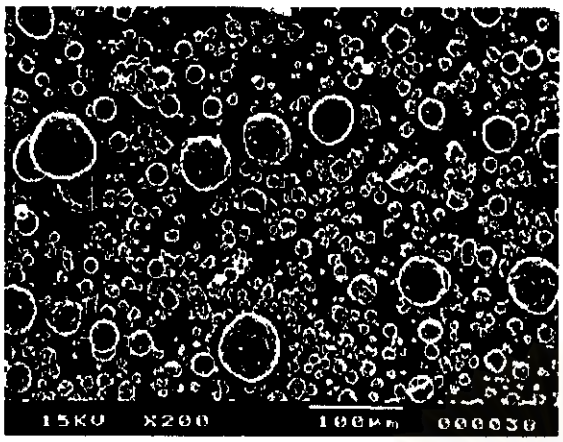


12.3(A)

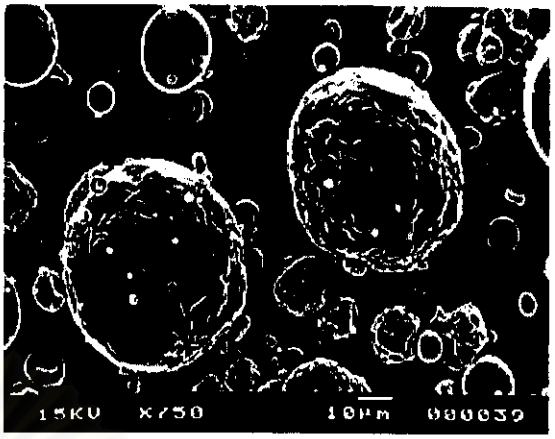


12.3(B)

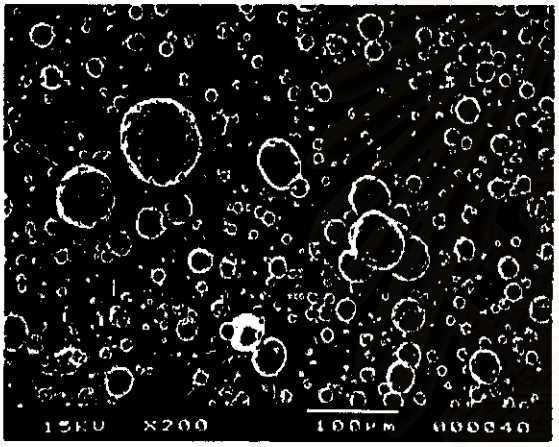
Figure 12 Photomicrographs of spray dried particles prepared at various polymer to drug ratios in the formulations.
(12.1) 1:2, (12.2) 1:4, (12.3) 1:6
(A x200, B x750)



13.1(A)



13.1(B)



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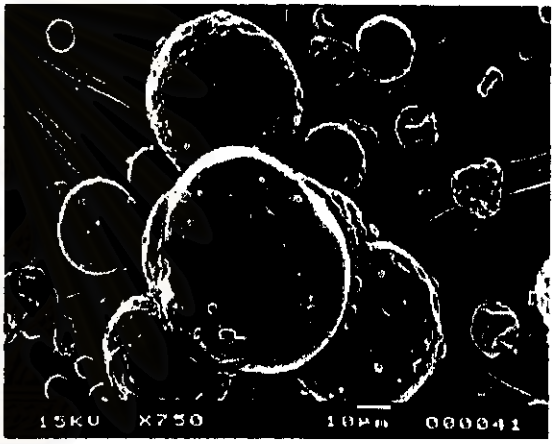
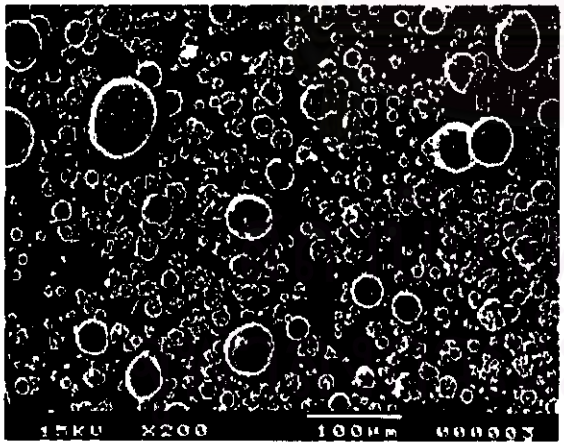
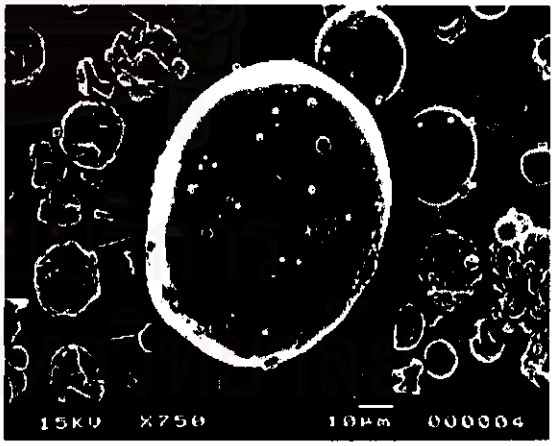


13.2(B)

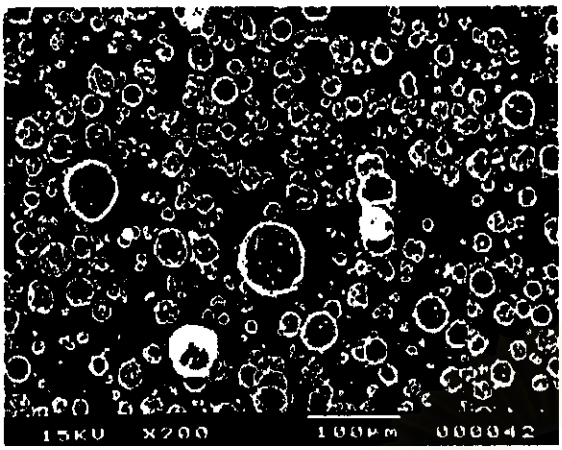


13.3(A)

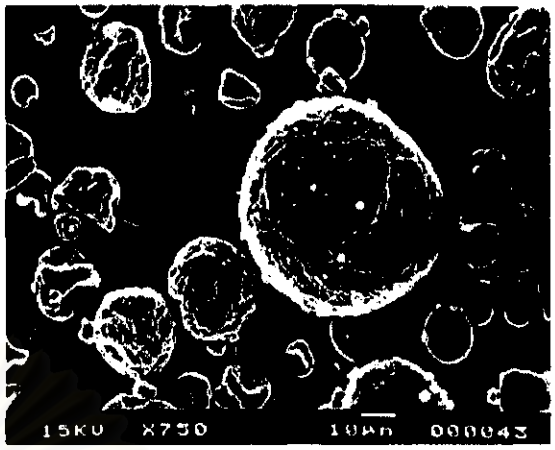


13.3(B)

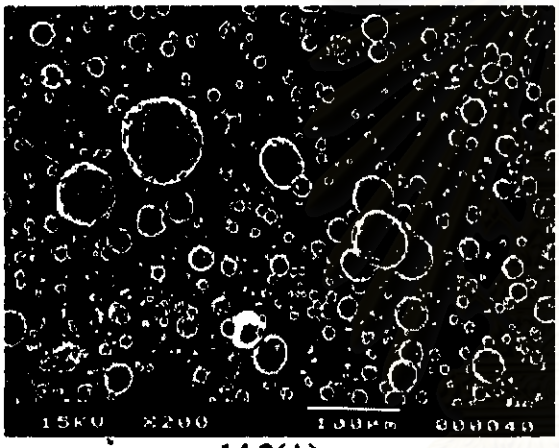
Figure 13 Photomicrographs of spray dried particles prepared at various inlet air temperatures.
(13.1) 130 °C, (13.2) 150 °C, (13.3) 170 °C
(A x200, B x750)



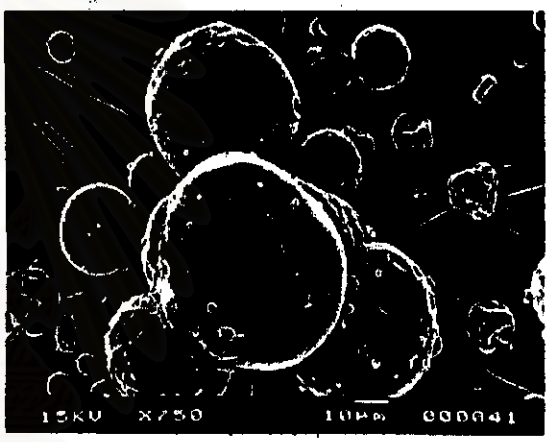
14.1(A)



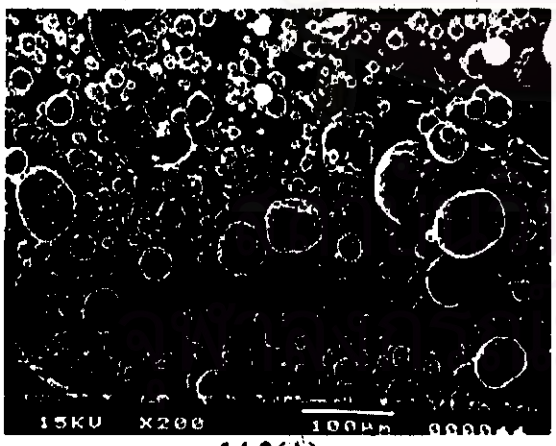
14.1(B)



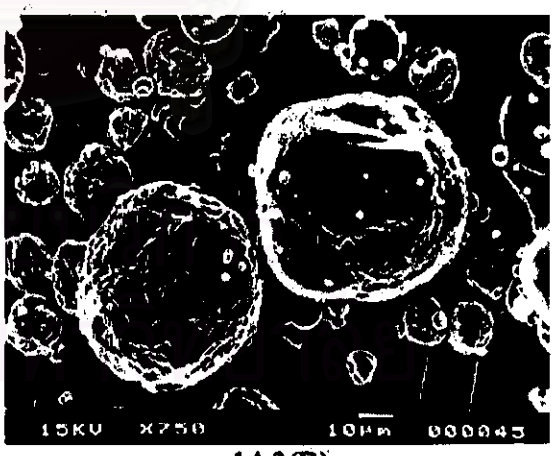
14.2(A)



14.2(B)



14.3(A)



14.3(B)

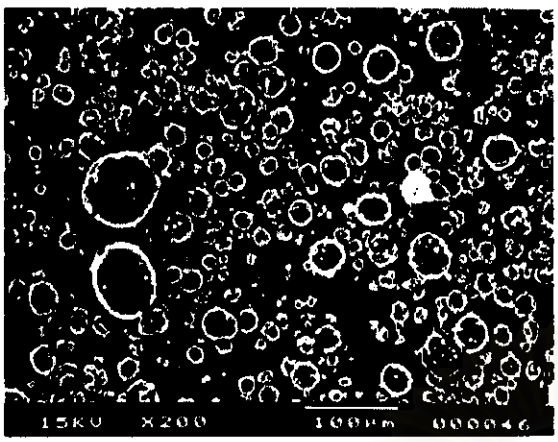
Figure 14 Photomicrographs of spray dried particles prepared at various feed rates. (14.1) 14 ml./min., (14.2) 20 ml./min., (14.3) 26 ml./min. (A x200, B x750)

The microscopic images of the spray dried particles prepared at various atomizing air pressure are shown in Figure 15. Most products obtained were microcapsules with smooth surface. It was found that higher atomizing air pressure produced smaller microcapsules. The powder produced at the pressure of 2 bars were larger microcapsules than those produced at 3 and 4 bars. The higher number of the agglomerates was formed when the pressure of 4 bars was employed. The powder produced at 4 bars showed more small microcapsules attached to the surface of big microcapsules. It appeared that the agglomerates of the spray dried powder prepared at 4 bars was composed mostly of small microcapsules.

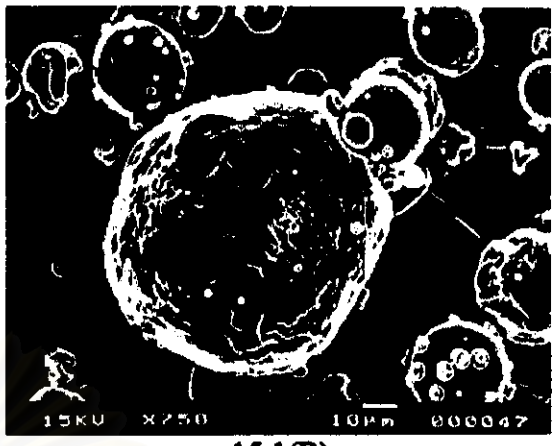
2. Drug Content

The percentage drug contents of the spray dried powder prepared from various processing variables are shown in Table 13. The processing variables were the inlet air temperature, the feed rate, the atomizing air pressure, and the polymer to drug ratio of solution. The theoretical drug content in the product with the polymer to drug ratio of 1:2 was 66.67%. In the case of the formulations with the polymer to drug ratios of 1:4 and 1:6, the theoretical drug contents in the products were 80.00 and 85.71% , respectively. The standard deviation shown implied the uniformity of the drug distribution in the spray dried powder.

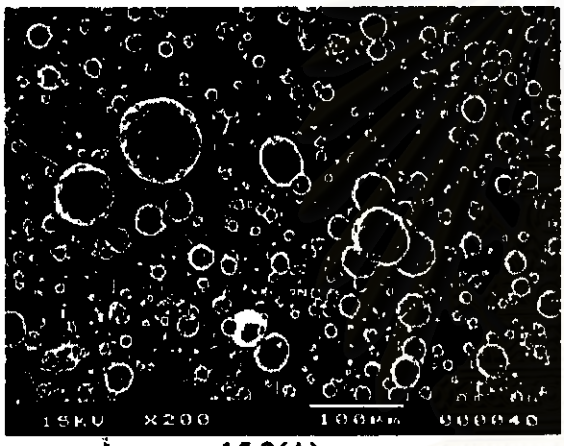
The data revealed that the spray drying conditions did not influence the drug distribution. The feed rate at 26 ml/min. produced slightly higher drug content of the powder in the chamber (67.08%).



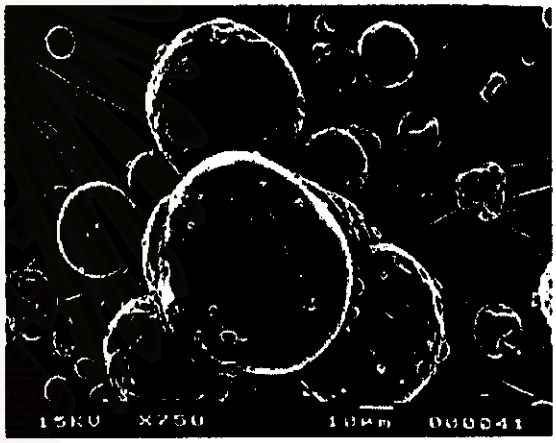
15.1(A)



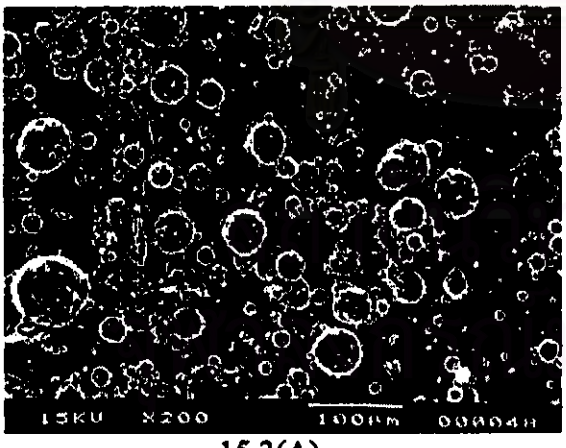
15.1(B)



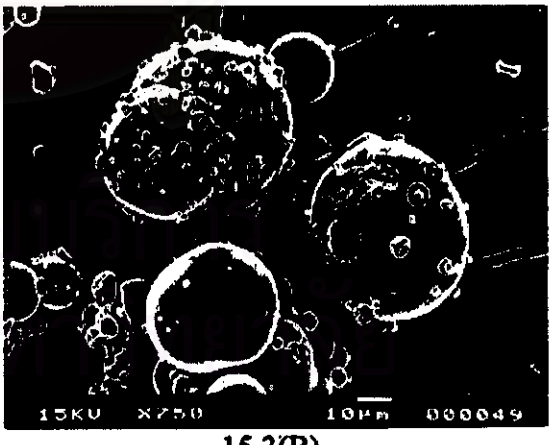
15.2(A)



15.2(B)



15.3(A)



15.3(B)

Figure 15 Photomicrographs of spray dried particles prepared at various atomizing air pressures.
(15.1) 2 bars, (15.2) 3 bars, (15.3) 4 bars
(A x200, B x750)

3. Moisture Content

The moisture content of the spray dried powder are also presented in Table 13 . Increasing the inlet air temperature and the atomizing air pressure obtained the products with lower moisture contents. Higher feed rate was likely to produce higher moisture content in the powder . Apparently , the polymer to drug ratio of solution had an insignificant effect on the moisture content of the powder.

Table 13 The percentages of the drug content and the moisture content of the spray dried products at various the spray drying conditions.

Process Variable /Level	%Drug Content*		%Moisture Content*
	Collector	Chamber	
Polymer : Drug Ratio			
1:2	66.61 (0.295)**	66.11 (0.317)	2.43 (0.051)
1:4	80.25 (0.144)	80.70 (0.439)	2.57 (0.025)
1:6	86.02(0.317)	86.13 (0.189)	2.41 (0.021)
Inlet Temperature (°C)			
130	66.10 (0.289)	66.19 (0.075)	3.29 (0.031)
150	66.37 (0.144)	66.21 (0.069)	2.92 (0.06)
170	66.61 (0.295)	66.11 (0.317)	2.43 (0.051)
Feed Rate (ml/min.)			
14	66.36 (0.194)	66.24 (0.150)	2.46 (0.108)
20	66.37 (0.144)	66.21 (0.069)	2.92 (0.061)
26	66.08 (0.189)	66.83 (0.193)	3.18 (0.021)
Atomization Pressure (bar)			
2	66.75 (0.795)	66.16 (0.125)	3.17 (0.139)
3	66.37 (0.144)	66.21 (0.069)	2.92 (0.061)
4	66.90 (0.125)	67.08 (0.189)	2.53 (0.038)

* Average from three determinations

** Standard deviation

4. Angle of Repose, Bulk Density and True Density

The angle of repose , the bulk density and the true density of the products prepared from different conditions are shown in Table 14. The angle of repose indicates the flowability of the powder. Lower angle of repose is obtained from the powder with better flowability (Lantz and Schwartz, 1990).

The angles of repose of the spray dried powder prepared from various processing variables were indeterminable because the powder could not flow from the cylinder.

The products prepared at the polymer to drug ratios of 1:4 and 1:6 showed no significant difference on the bulk densities but the density obviously increased at the ratio of 1:2. The highest bulk density of powder was obtained when it was prepared at 130° C and it was decreased when higher inlet air temperature was used. The feed rates at 14, 20 and 26 ml./min. produced powder with comparable bulk densities. In the case of the atomizing air pressure, the highest bulk density was obtained from the product prepared at the air pressure of 4 bars, followed by at the atomizing pressures of 3 and 2 bars, respectively.

The true densities of the spray dried powders prepared at various aforementioned processing variables could not be determined by pycnometer method. The powders floated over the surface of solvents; water, hexane, acetone and petroleum benzin (specific gravities of the solvents were 0.99, 0.81, 0.79 and 0.66, respectively). Therefore, the true densities of the obtained products were less than 0.66 g./ml..

Table 14 The angle of repose, the bulk density and the true density of the products prepared from different conditions.

Process Variable /Level	Angle of Repose (degree)	Bulk Density** (g/ml)	True Density (g/ml)			
			Water	Hexane	Acetone	Petroleum Benzin
Polymer: Drug Ratio						
1:2	*	0.1333	*	*	*	*
1:4	*	0.0520	*	*	*	*
1:6	*	0.0511	*	*	*	*
Inlet Temperature(°C)						
130	*	0.1551	*	*	*	*
150	*	0.1428	*	*	*	*
170	*	0.1333	*	*	*	*
Feed Rate (ml/min.)						
14	*	0.1460	*	*	*	*
20	*	0.1428	*	*	*	*
26	*	0.1439	*	*	*	*
Atomization Pressure (bar)						
2	*	0.1118	*	*	*	*
3	*	0.1428	*	*	*	*
4	*	0.1551	*	*	*	*

* Cannot be determined

** Average from three determinations

5. Particle Size Distribution

The particle size distributions of the powders are shown in Table 15. The powder produced from the polymer to drug ratio of solution of 1:2 provided the largest particles. The powders prepared from the ratios of 1:4 and 1:6 exhibited rather different particle size distributions. However, most particles were under the size of 425 μm..

The particle size of the powder prepared at the inlet temperatures of 130,150 and 170°C, appeared to be increased when the inlet temperature increased. When higher atomizing air pressure was used, smaller particle size was obtained.

Table 15 The particle size distributions of the spray dried powders.

Process Variable /Level	% Weight Retained on Sieve Size*					
	Pan	106μm	150μm	180μm	250μm	425μm
Polymer : Drug Ratio						
1:2	0.00	0.00	0.00	3.20	86.20	10.40
1:4	0.00	0.00	0.40	6.20	82.84	0.80
1:6	0.00	0.00	1.76	9.16	86.84	0.00
Inlet Temperature(°C)						
130	0.00	0.00	0.80	8.42	88.22	1.60
150	0.00	0.00	0.60	3.22	89.36	6.80
170	0.00	0.00	0.00	3.20	86.20	10.40
Feed Rate(ml/min.)						
14	0.00	0.00	0.20	2.00	76.82	19.40
20	0.00	0.00	0.60	3.22	89.36	6.80
26	0.00	0.00	1.80	4.22	69.42	24.24
Atomization Pressure (bar)						
2	0.00	0.00	0.20	1.44	59.60	38.00
3	0.00	0.00	0.60	3.22	89.36	6.80
4	0.00	0.40	0.80	77.22	22.00	0.80

* Average from two determinations

6. Percentage Recovery

In spray drying process the liquid was atomized into droplets and the droplets were transformed into the dried partcles. The products were collected from the collector and the chamber. The percentage recovery from the collector and the chamber are displayed in Table 16. It clearly shows that the polymer to drug ratio, the inlet air temperature, the feed rate and the atomizing air pressure did not affected the total percentage recovery of the spray dried product.

Generally the percentage recovery of powder from the collector was higher than that in the chamber. When higher air pressure was used higher percentage recovery of powder in the collector was found. The total percentage recovery of powder obtained from both the chamber and the collector were not different at different polymer to drug ratios of 1:2, 1:4 and 1:6, the inlet air temperatures of 130, 150 °C and the feed rates of 20, 26 ml./min.. But the percent recovery of powder in the collector slightly increased at the inlet temperature of 170°C and the feed rate of 14 ml./min..

Table 16 The percentage recovery of the spray dried product at various spray drying conditions.

Process Variable /Level	Percentage Recovery		
	Collector	Chamber	Total
Polymer : Drug Ratio			
1:2	72.21	8.79	81.00
1:4	76.28	6.73	83.01
1:6	73.33	7.44	80.77
Inlet Temperature(°C)			
130	66.50	10.46	76.96
150	68.56	10.33	78.89
170	72.21	5.79	78.00
Feed Rate (ml/min)			
14	75.65	4.61	80.26
20	68.56	10.33	78.89
26	69.65	10.03	79.68
Atomization Pressure (bar)			
2	53.33	23.36	76.69
3	68.59	10.33	78.89
4	72.78	5.83	78.61

7. Infrared Spectrometry

The IR spectra of diclofenac sodium alone and diclofenac sodium with HPMC spray dried powders prepared from different conditions are shown in Figures 16 - 19. The principle peaks of diclofenac sodium were at the wavenumbers of 756, 775, 1286, 1308, 1504 and 1572 $cm.^{-1}$. (Moffat et al., 1986). The peaks of diclofenac sodium at 756 and 775 $cm.^{-1}$ were resulted from C-H out of plane bending. The IR absorption bands at 1286 and 1308 $cm.^{-1}$ were resulted from C-N stretching. The peaks at 1504

and 1572 $cm.^{-1}$ were resulted from C=C stretching. The interaction between diclofenac sodium and HPMC was scarce and the prominent peaks of the spectra did not shifted as shown in Table 17.

According to the preceeding results, the drying inlet air temperature of 170°C, the feed rate of 20 ml/min. and the atomizing air pressure of 3 bar, which gave the most satisfactory physical properties of the spray dried powder, were selected to be the optimum spray drying conditions for further studies. The polymer to drug ratio of solution depended on the type of polymer in each formulation.

Table 17 IR peaks of spectra of diclofenac sodium and of diclofenac sodium spray dried products at various the spray drying conditions.

Process Variable (/Level)	Principle Peak (cm^{-1}.)					
Diclofenac Sodium	756	775	1286	1308	1504	1572
Polymer : Drug Ratio						
1:2	747	769	1286	1311	1506	1578
1:4	747	765	1285	1308	1505	1570
1:6	746	768	1283	1306	1506	1577
Inlet Temperature (°C)						
130	745	773	1285	1306	1507	1579
150	746	771	1286	1307	1507	1579
170	747	769	1286	1311	1506	1578
Feed Rate (ml/min.)						
14	746	770	1284	1306	1506	1580
20	746	771	1286	1307	1507	1579
26	746	769	1284	1308	1507	1579
Atomization Pressure (bar)						
2	746	770	1285	1310	1507	1579
3	746	771	1286	1307	1507	1579
4	746	769	1284	1307	1507	1578

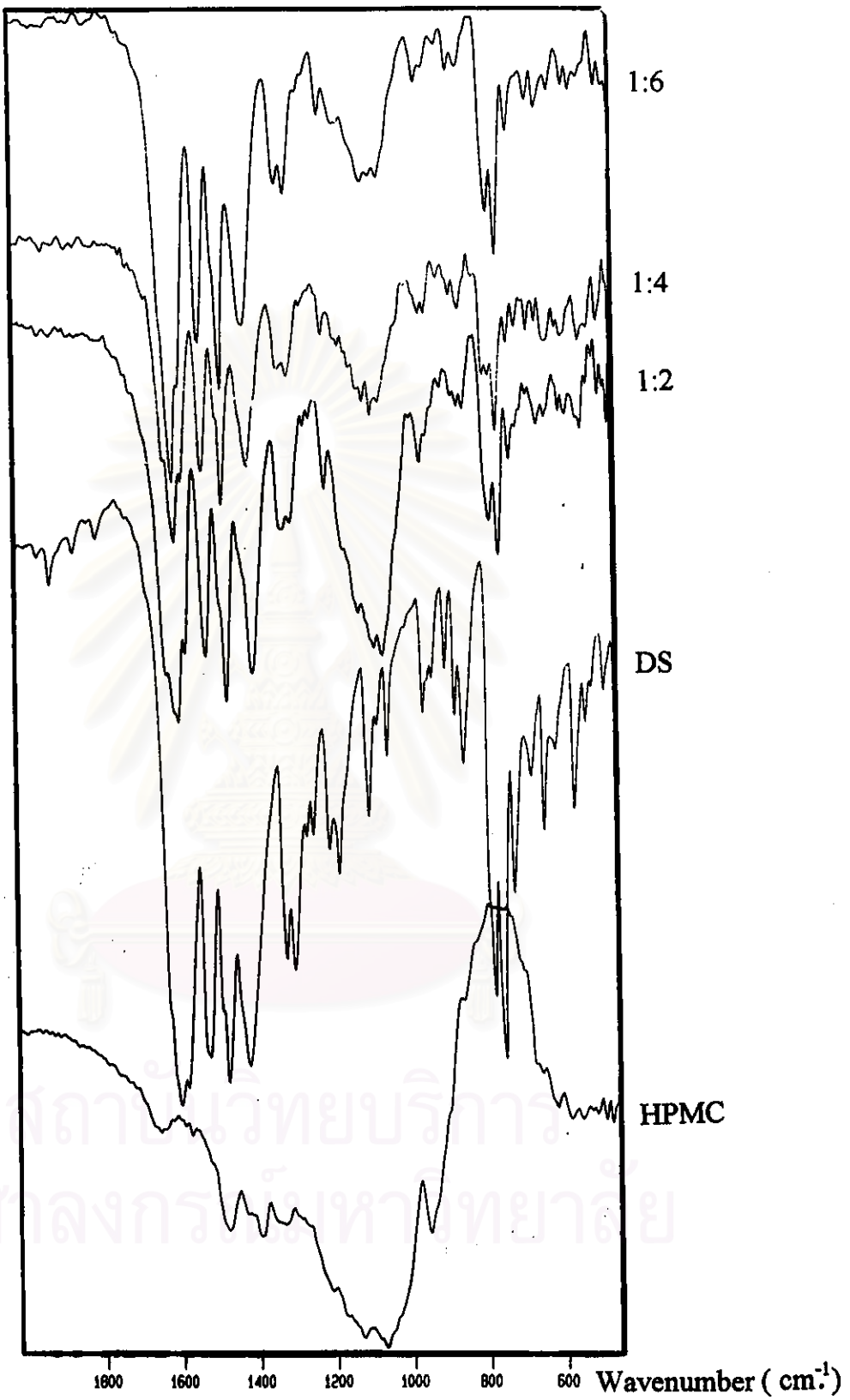


Figure 16 IR spectra of diclofenac sodium with HPMC spray dried powders prepared from different polymer to drug ratios of solution.

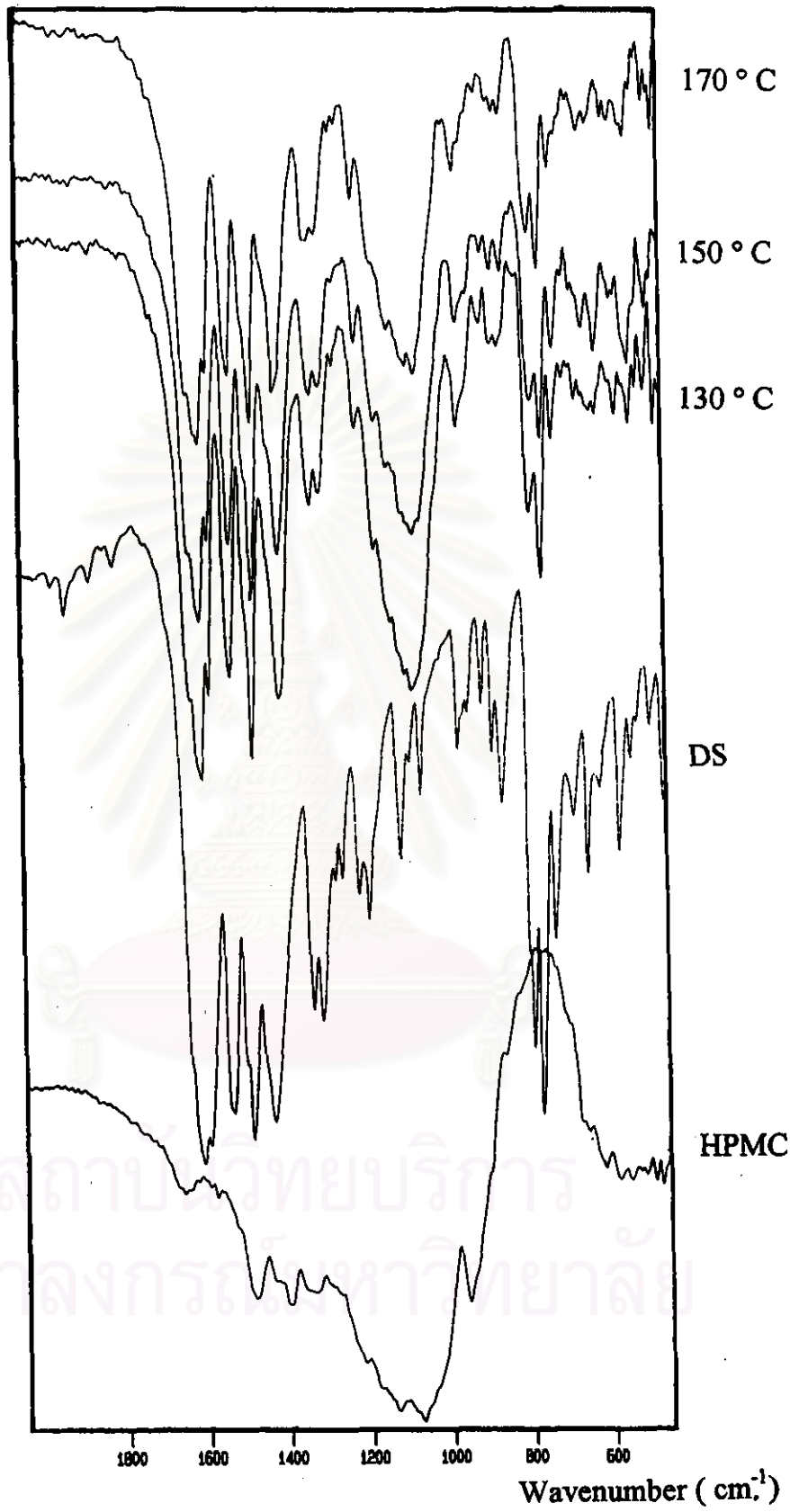


Figure 17 IR spectra of diclofenac sodium with HPMC spray dried powders prepared from different inlet air temperatures.

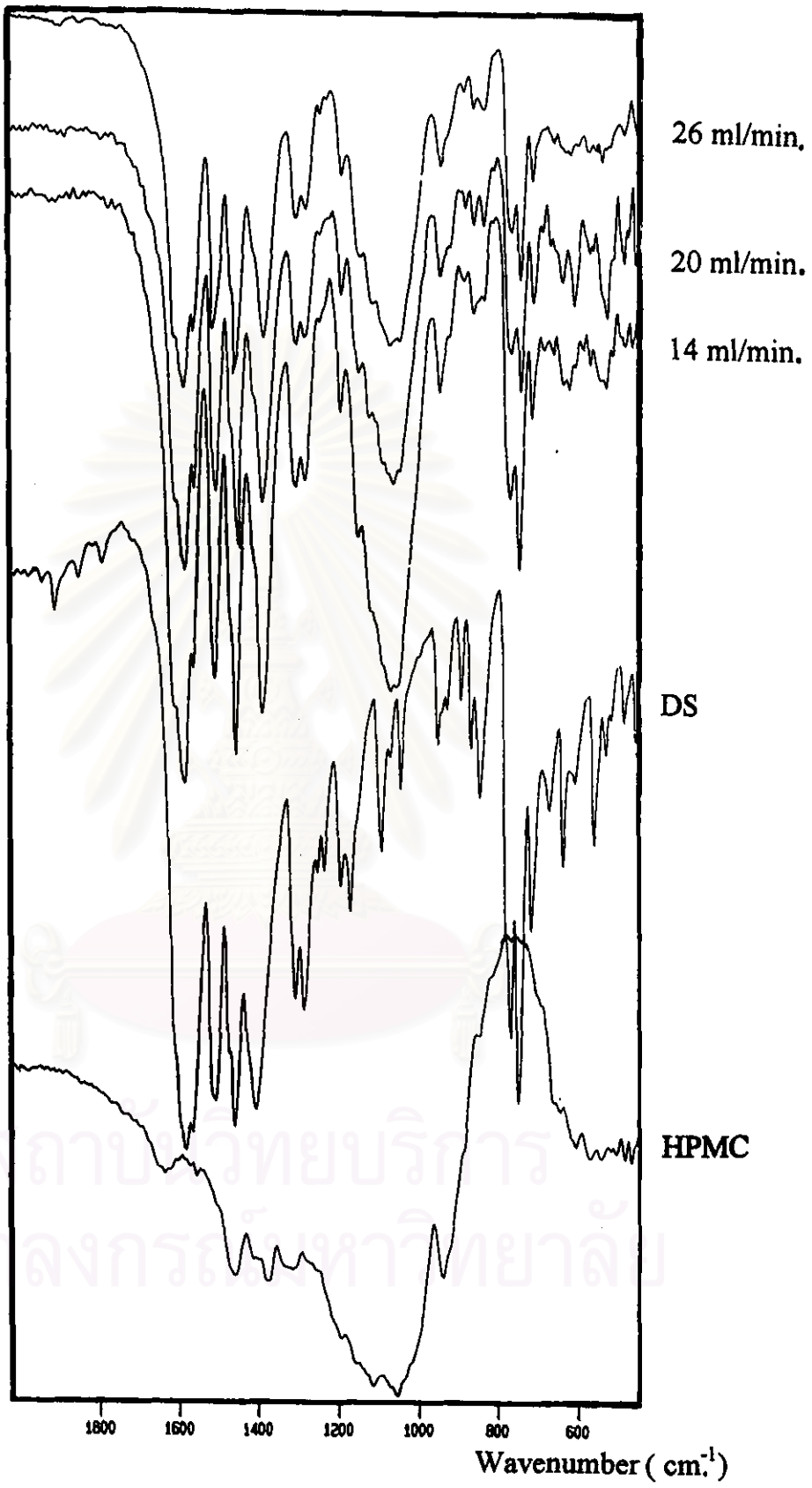


Figure 18 IR spectra of diclofenac sodium with HPMC spray dried powders prepared from different feed rates.

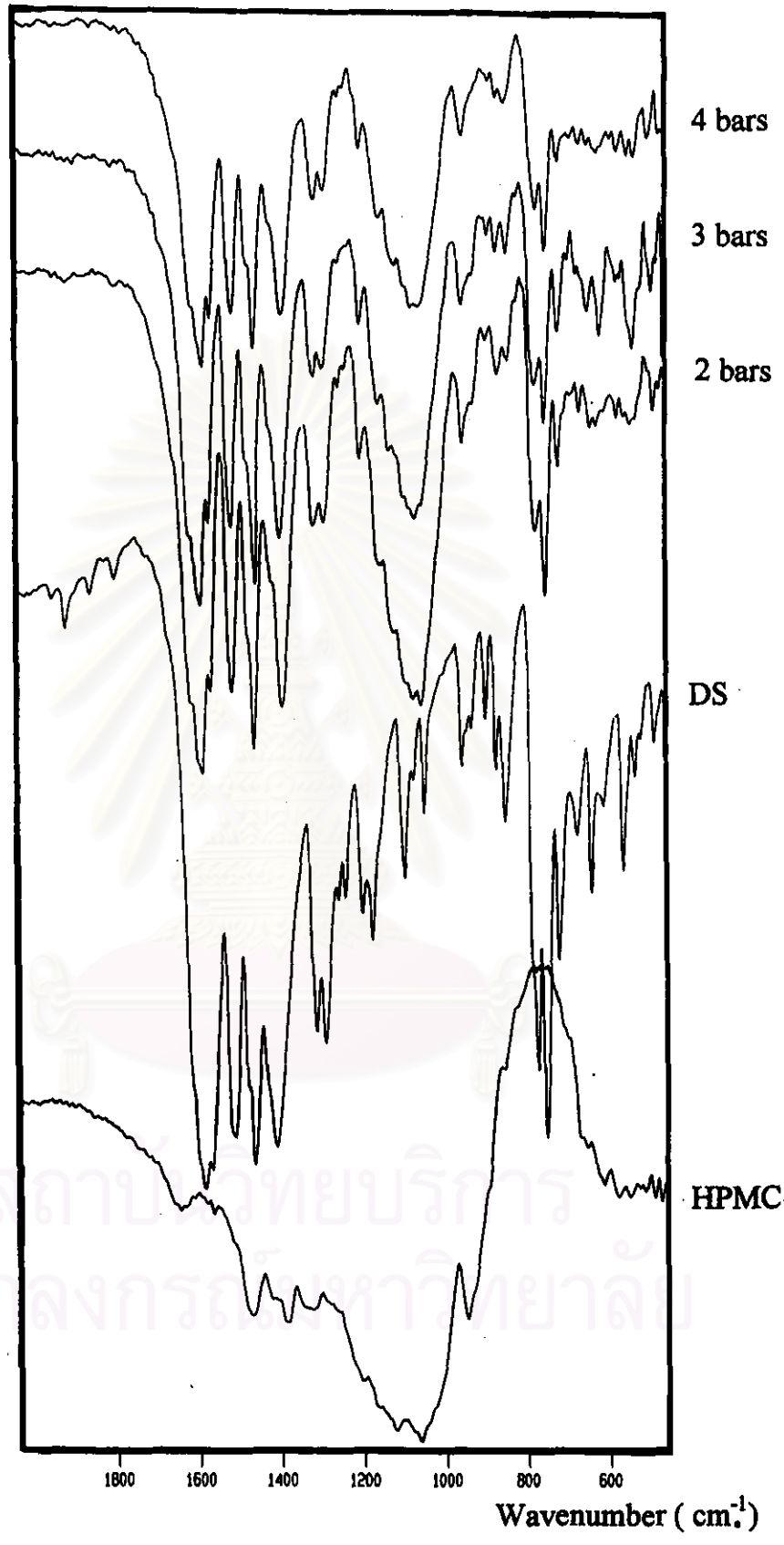


Figure 19 IR spectra of diclofenac sodium with HPMC spray dried powders prepared from different atomizing air pressures.

Effects of Types and Proportions of Polymers on the Physicochemical Properties of Spray Dried Powder

Before proceeding with the preparations of spray dried powder, the preliminary investigation of the spray drying process was carried out to determine the optimum condition.

Table 18 summarizes the conditions which are varied to determine the optimum condition for diclofenac sodium with polymer spray dried powder.

Table 18 Summary of spray drying conditions used in the preparation of spray dried powders.

Condition	Formulation				
	1-3	4-7	8-10	11-16*	17-21*
Inlet Temperature (°C)	170	170	170	170	170
Feed Rate (ml/min.)	20	60	20	20	20
Atomization Pressure (bar)	3	3	3	3	3
Dilution Medium	Water	Water	2% Citric Acid Solution	Water	2% Citric Acid Solution

* Combined formulations are presented in Table 9.

In Formulations 1-3, the inlet air temperature of 170°C was used to avoid melting of diclofenac sodium. The liquid feed rate of 20 ml/min. was used and the atomizing air pressure of 3 bars was chosen.

In Formulations 4-7, the inlet air temperature and the atomizing air pressure were maintained at 170°C and 3 bars, but the feed rate was increased. The maximum liquid feed rate at 60 ml/min. was used to produce larger microcapsules than those produced at 20ml/min. It was found that formulation containing Aquacoat(R) had lower viscosity than that containing HPMC. Aquacoat(R) was low in viscosity (8 cps.) , while Methocel E 15 LV available then was 15 cps. (viscosity of a 2% solution at 20°C).

In Formulations 8-21, the same condition as Formulations 1-3 were used, except Formulations 8-10 and 17-21 which used 2% citric acid solution as the dilution medium because chitosan dissolved in diluted acid solution.

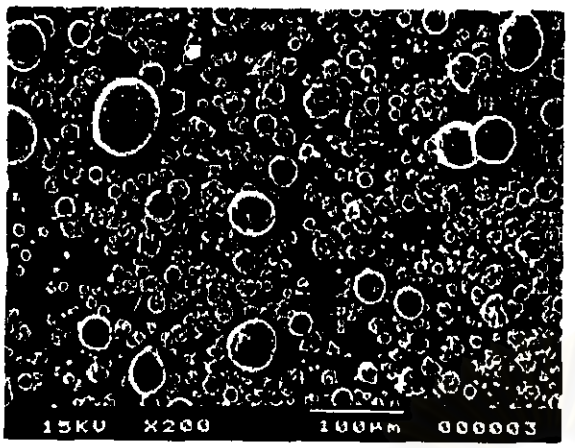
In the experiments with the formulations containing HPMC and chitosan, large amount of the obtained products adhered to the wall of drying chamber, and could not be recovered from the chamber.

1. Morphology of Diclofenac Sodium with Polymer Spray Dried Powder

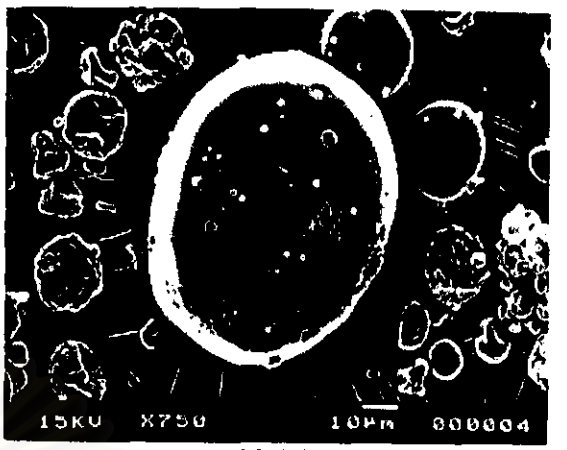
The shape and surface topography of the spray dried particles were found to be affected by the formulation of the drug mixture preparation.

When chitosan was used as the polymer (Formulations 8-10 and 17-21), a high quantity of irregular shaped particles was observed in the spray dried products. On the contrary, most spray dried powders prepared by using HPMC and Aquacoat(R) (Formulations 1-7 and 11-16) were in the form of microcapsules.

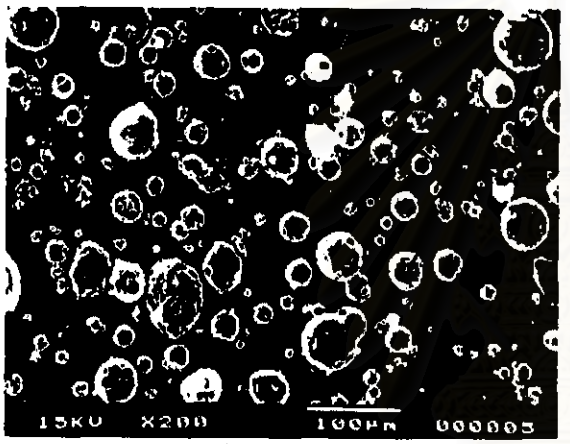
The photomicrographs of diclofenac sodium with HPMC spray dried powders (Formulations 1 - 3) are shown in Figure 20. The shape of particles



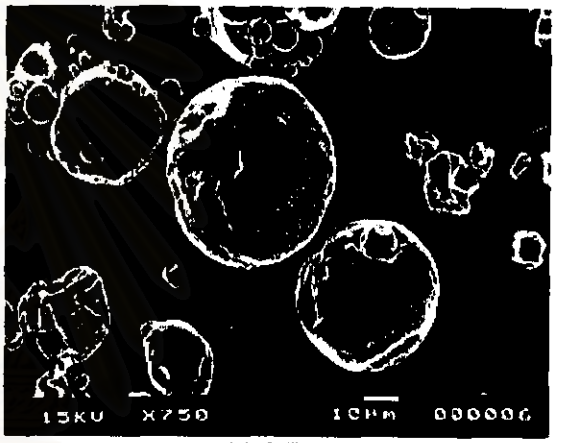
20.1(A)



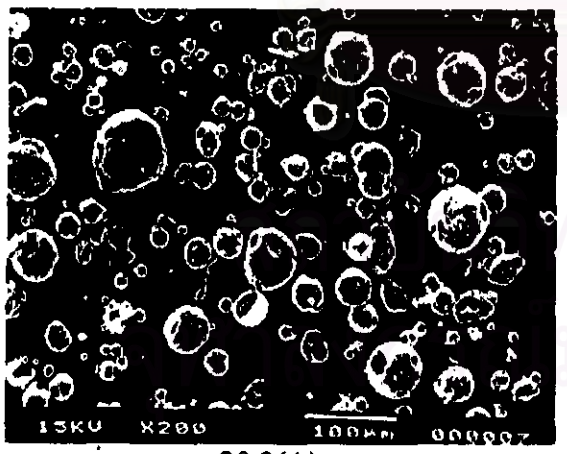
20.1(B)



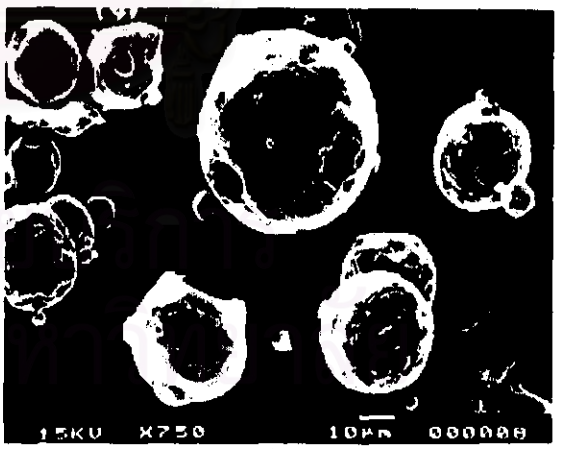
20.2(A)



20.2(B)



20.3(A)



20.3(B)

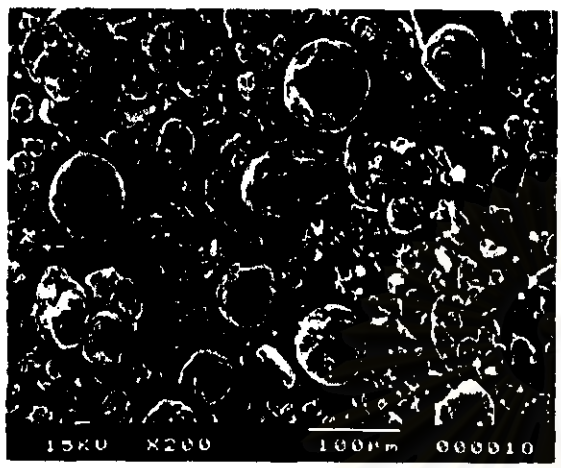
Figure 20 Photomicrographs of diclofenac sodium with HPMC spray dried particles prepared at various polymer to drug ratios in the formulations.
(20.1) 1:2, (20.2) 1:4, (20.3) 1:6
(A x200, B x750)

was that of microcapsules with different sizes. The surface of microcapsules were smooth. When the proportion of polymer in the formulation was decreased, the number of pores on the surface of particles were increased.

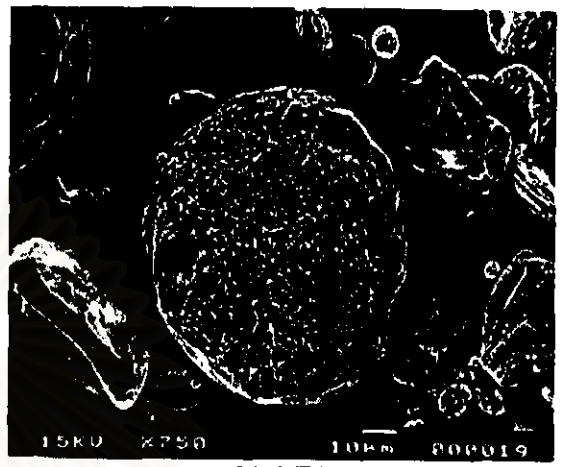
The photomicrographs of diclofenac sodium with Aquacoat$^{(R)}$ spray dried powder (Formulations 5 and 6) in different magnifications are shown in Figure 21. Most products obtained were microcapsules with different sizes. The surface of microcapsules were not smooth with some deposition of diclofenac sodium microcrystals. However, some of them had rather smooth surface.

The microscopic images of diclofenac sodium with chitosan spray dried powder (Formulations 9 and 10) in different magnifications are shown in Figure 22. The microparticles were more irregular shaped rough particles than microcapsules.

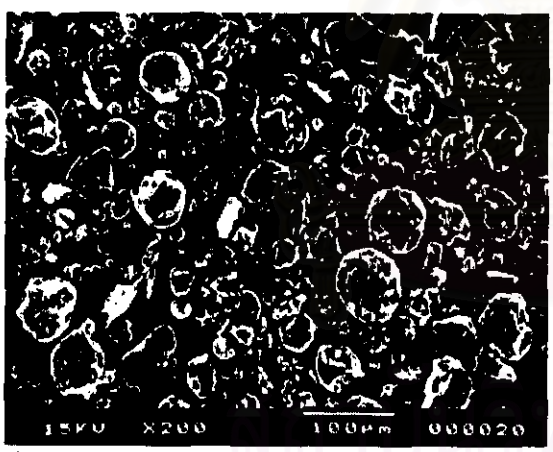
The photomicrographs of diclofenac sodium with HPMC and Aquacoat$^{(R)}$ spray dried powder (Formulations 12, 13, 15 and 16) are shown in Figures 23 and 24. Most products obtained were microcapsules with smooth surface. The microcapsules were relatively larger than those of the other polymer formulations. When the proportion of polymer in the ratio of polymer to drug was decreased, the number of pores on the surface of the particles were increased (Figure 23). When the amounts of HPMC and Aquacoat$^{(R)}$ in the proportion of polymer were varied from the ratio of (1:1) : 12 to the ratios of (2:1) : 12 and (1:2) : 12, the surface of the powder were smoother respectively. The powder formulated with the polymer to drug ratio of (1:2) : 12 had the smoothest surface (Figure 24).



21.1(A)



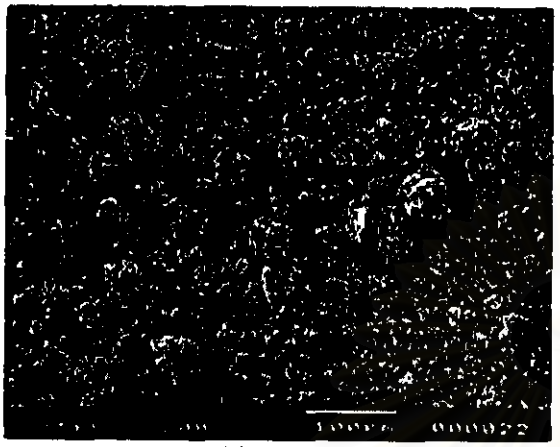
21.1(B)



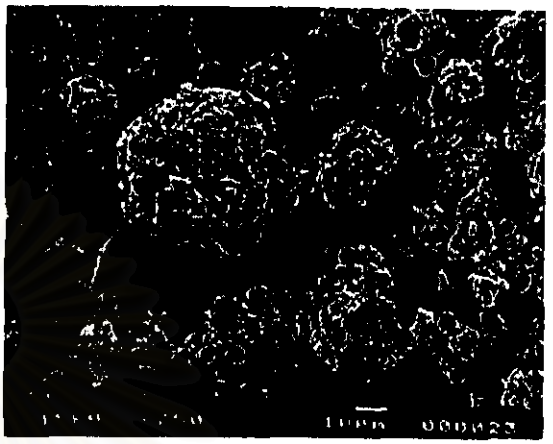
21.2(A)

21.2(B)

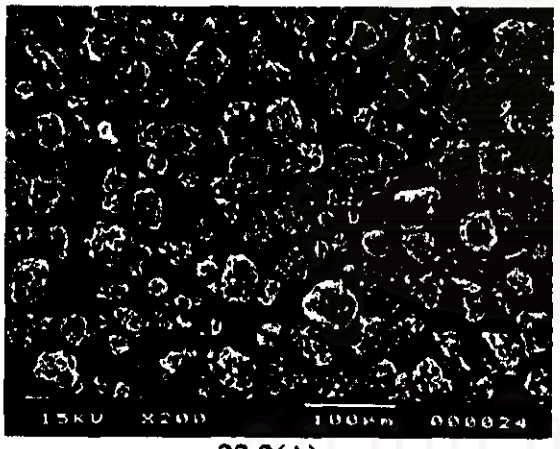
Figure 21 Photomicrographs of diclofenac sodium with Aquacoat$^{(R)}$ spray dried particles prepared at various polymer to drug ratios in the formulations.
(21.1) 1:2, (21.2) 1:4
(A x200, B x750)



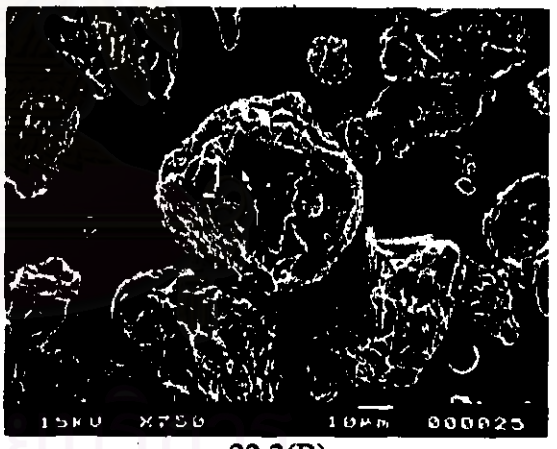
22.1(A)



22.1(B)

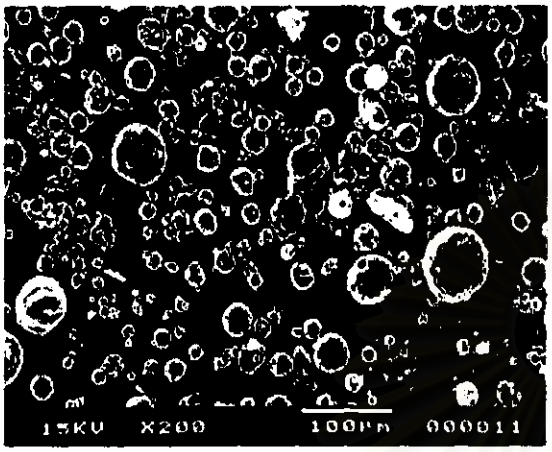


22.2(A)

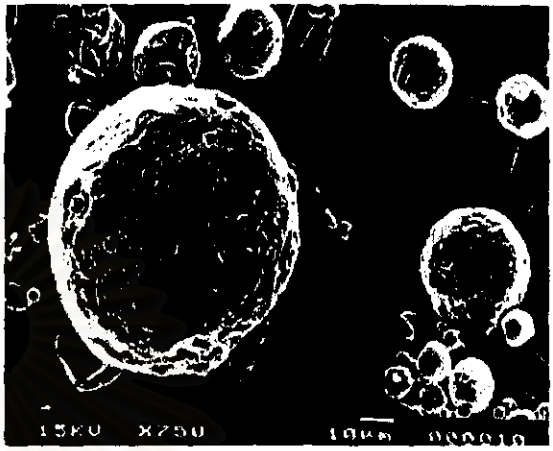


22.2(B)

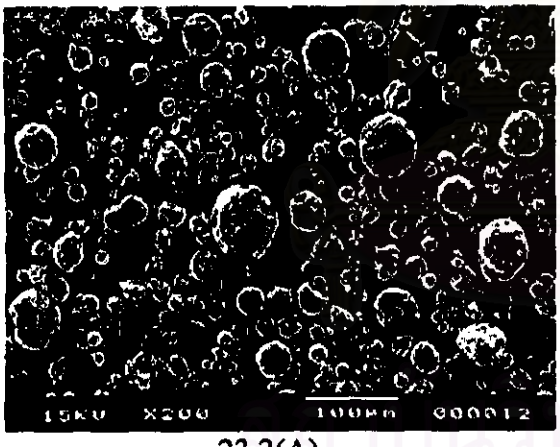
Figure 22 Photomicrographs of diclofenac sodium with chitosan spray dried particles prepared at various polymer to drug ratios in the formulations. (22.1) 1:4, (22.2) 1:6
(A x200, B x750)



23.1(A)



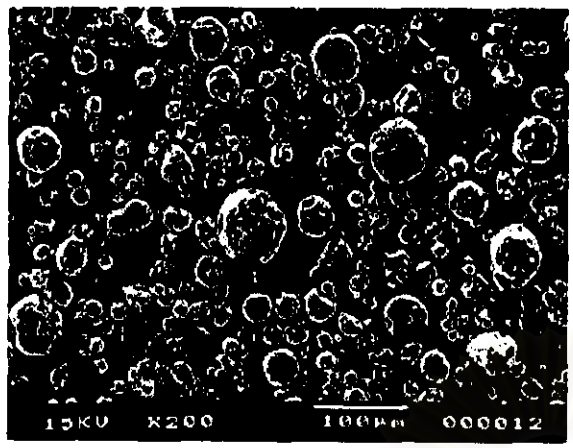
23.1(B)



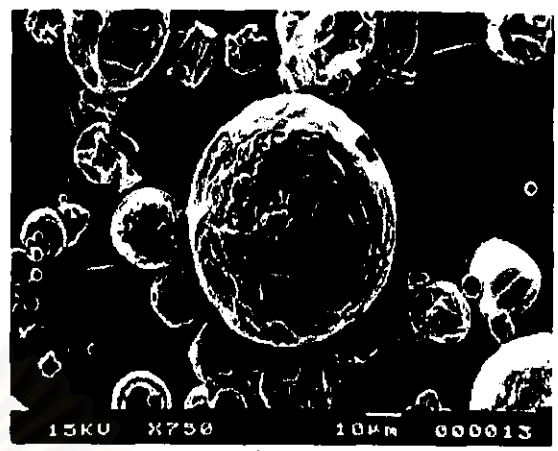
23.2(A)

23.2(B)

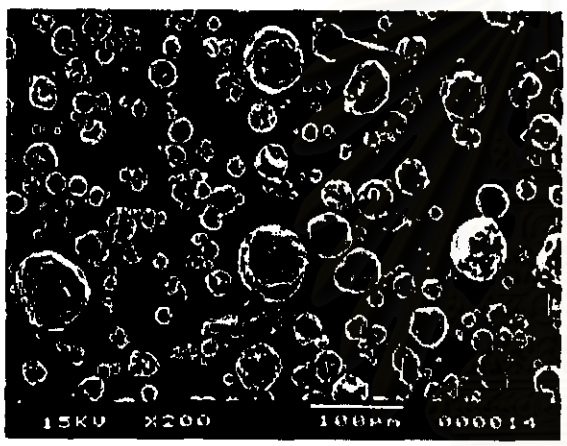
Figure 23 Photomicrographs of diclofenac sodium with HPMC and Aquacoat$^{(R)}$ spray dried particles prepared at various polymer to drug ratios in the formulations (Formulations 12 and 13).
(23.1) (1:1):8, (23.2) (1:1):12
(A x200, B x750)



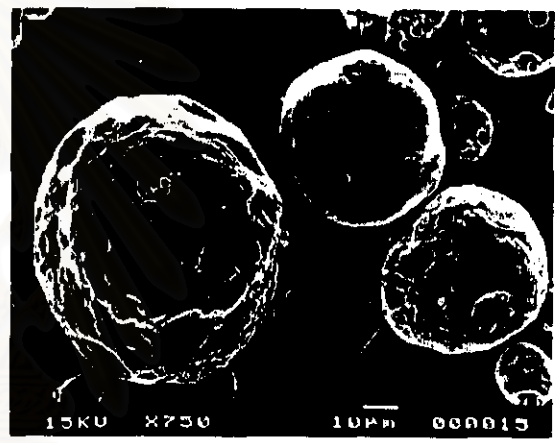
24.1(A)



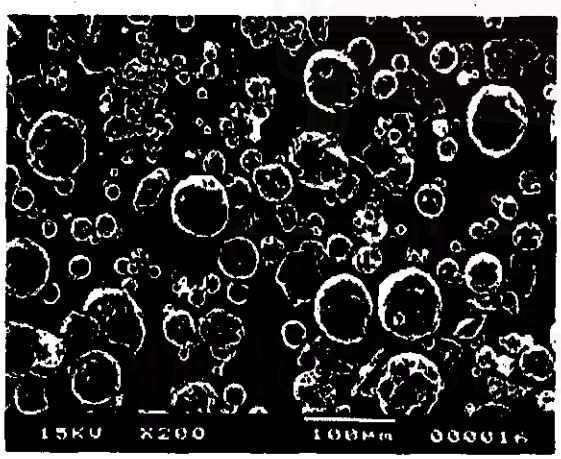
24.1(B)



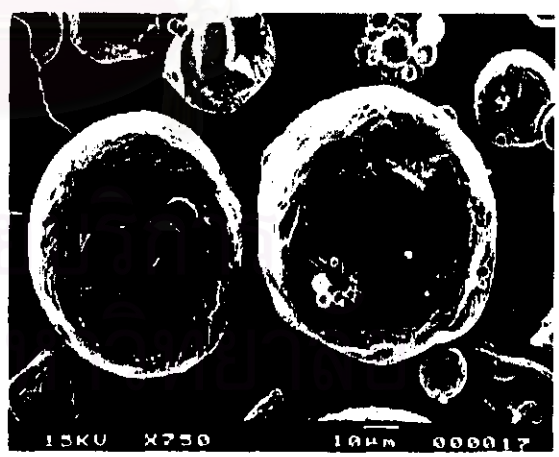
24.2(A)



24.2(B)



24.3(A)



24.3(B)

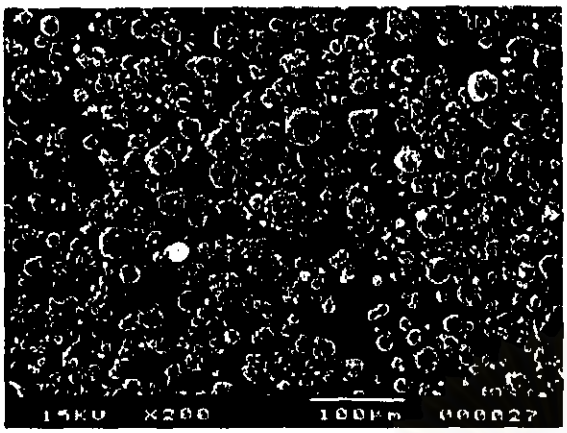
Figure 24 Photomicrographs of diclofenac sodium with HPMC and Aquacoat$^{(R)}$ spray dried particles prepared at various polymer to drug ratios in the formulations (Formulations 13, 15 and 16).
(24.1) (1:1):12, (24.2) (2:1):12, (24.3) (1:2):12
(A x200, B x750)

The photomicrographs of diclofenac sodium with HPMC and chitosan spray dried powder (Formulations 17-21) are shown in Figures 25 and 26. The shape of the particle was that of a microball with different sizes. The surface of the microballs was rough (Figure 25). When the amount of HPMC in the proportion of polymer was increased from the ratio of (1:1) :12 to (2:1) : 12, the surface of the powder became smoother. On the contrary, when the amount of chitosan in the proportion of polymer was increased from the ratio of (1:1) : 12 to (1:2) : 12, the microparticles looked like irregular shaped and rough particles rather than microcapsules (Figure 26).

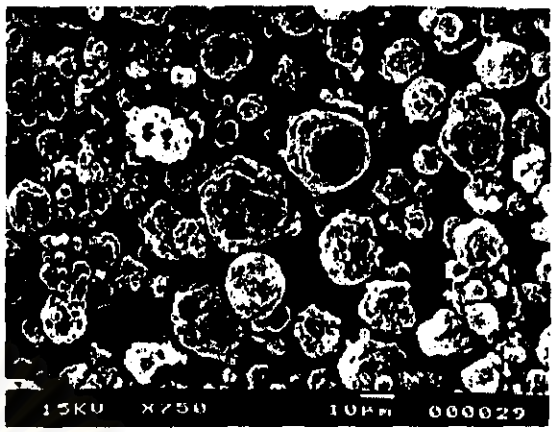
2. Drug Content

The theoretical drug content and the percentage drug content of the spray dried powder prepared from different types and proportions of polymers are shown in Table 19. The standard deviation shown implied the uniformity of drug distribution in the spray dried powder.

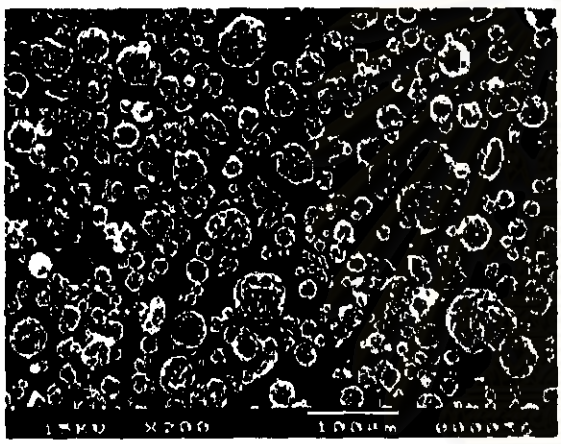
Formulations 4-10 had different drug contents between the products collected from the collector and the chamber. The drug contents from Formulations 4-7 from the collector were less than those collected from the chamber, but opposite results were obtained from Formulations 8-10. The drug contents of the powder prepared according to Formulations 1-3 , 11-16 and 17-21 were relatively similar.



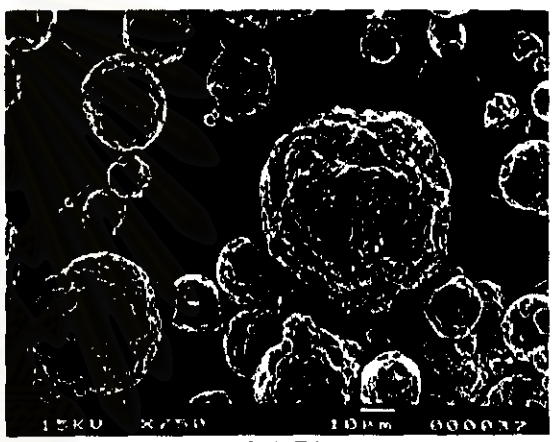
25.1(A)



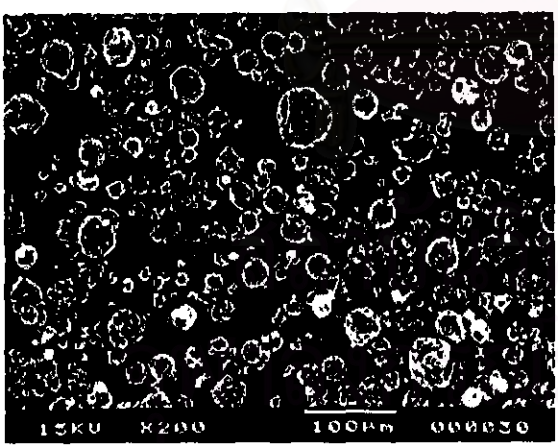
25.1(B)



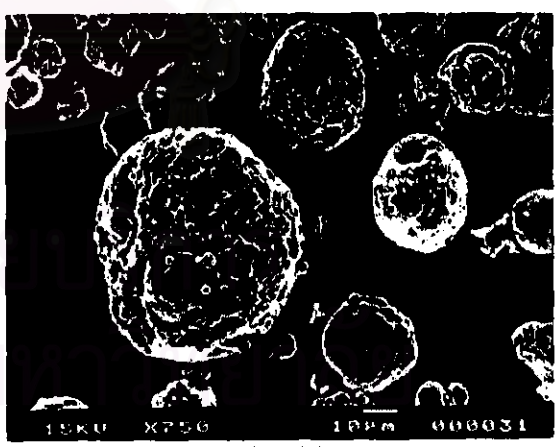
25.2(A)



25.2(B)

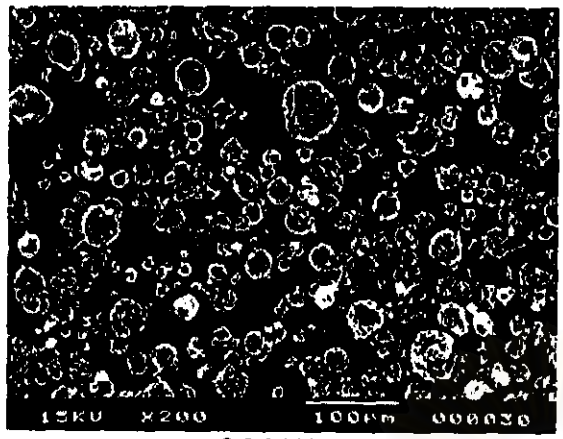


25.3(A)

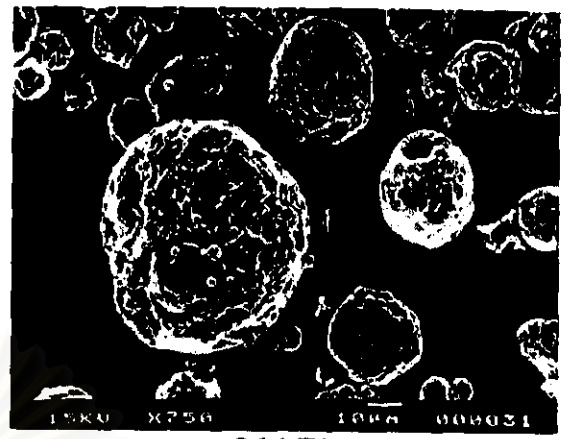


25.3(B)

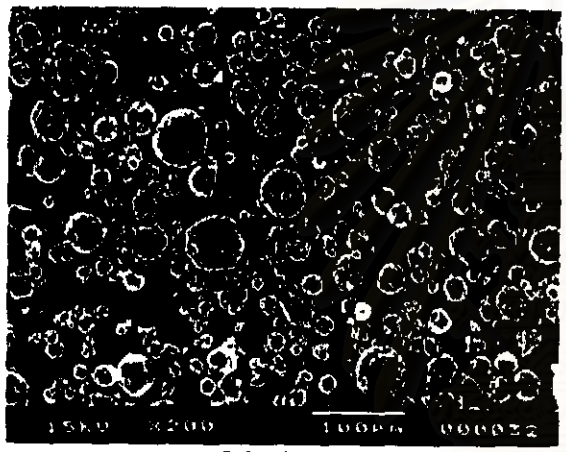
Figure 25 Photomicrographs of diclofenac sodium with HPMC and chitosan spray dried particles prepared at various polymer to drug ratios in the formulations (Formulations 17-19).
(25.1) (1:1):4, (25.2) (1:1):8, (25.3) (1:1):12
(A x200, B x750)



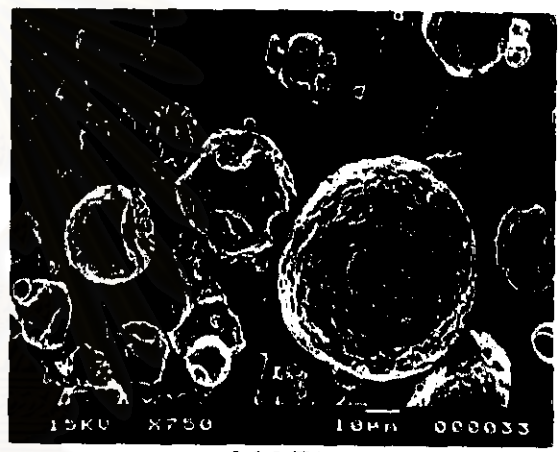
26.1(A)



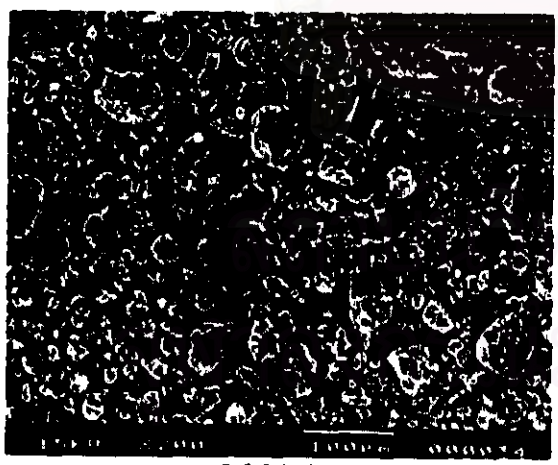
26.1(B)



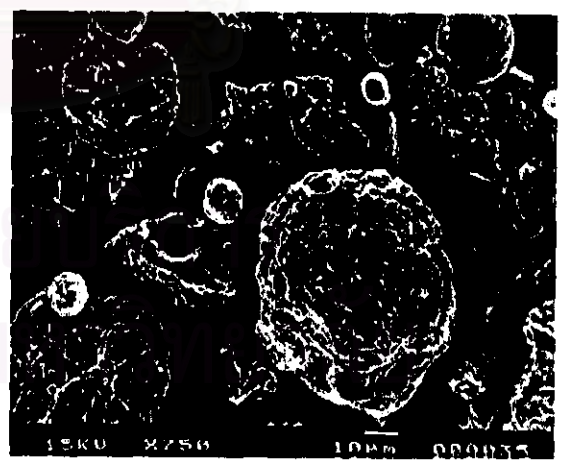
26.2(A)



26.2(B)



26.3(A)



26.3(B)

Figure 26 Photomicrographs of diclofenac sodium with HPMC and chitosan spray dried particles prepared at various polymer to drug ratios in the formulations (Formulations 19-21).
(26.1) (1:1):12, (26.2) (2:1):12, (26.3) (1:2):12
(A x200, B x750)

Table 19 The percentage of the drug content of the spray dried products prepared from different types and proportions of polymers.

Formulation	% Drug Content*		
	Theory	Collector	Chamber
1	66.67	66.61 (0.295)**	66.11 (0.317)
2	80.00	80.25 (0.144)	80.70 (0.439)
3	85.71	86.02 (0.317)	86.13 (0.189)
4	50.00	47.40 (0.259)	50.54 (0.193)
5	66.67	64.30 (0.193)	69.78 (0.125)
6	80.00	79.57 (0.250)	84.51 (0.144)
7	85.71	84.36 (0.261)	91.16 (0.193)
8	66.67	58.40 (0.387)	55.14 (0.144)
9	80.00	79.44 (0.333)	70.00 (0.193)
10	85.71	83.00 (0.193)	79.78 (0.259)
11	66.67	66.07(0.265)	65.60 (0.144)
12	80.00	79.49 (0.520)	80.36 (0.329)
13	85.71	85.76 (0.125)	86.97 (0.189)
14	82.76	81.91 (0.312)	82.25 (0.433)
15	80.00	79.85 (0.335)	79.48 (0.250)
16	80.00	78.15 (0.317)	78.39 (0.193)
17	66.67	60.90 (0.214)	60.39 (0.250)
18	80.00	75.68 (0.193)	75.59 (0.250)
19	85.71	81.87 (0.255)	81.62 (0.375)
20	80.00	76.40 (0.403)	76.77 (0.189)
21	80.00	84.60 (0.075)	84.02 (0.333)

* Average from three determinations

** Standard deviation

3. Moisture Content

The moisture contents of the spray dried powder are presented in Table 20. The polymer to drug ratio of solution had an insignificant effect on the moisture content of the powder in each polymer.

The Formulations 4-7 and 11-16 gave the products with the lowest moisture content, while Formulations 17-21 gave the products with the highest moisture content. The Formulations 1-3 and 8-10 gave the products with similar moisture content. The formulations that contained Aquacoat$^{(R)}$ had lower moisture content than other formulations. Using HPMC and chitosan as polymers in the formulations showed too much moisture in the obtained products.

The controlled release diclofenac sodium capsules were kept in open containers and stored at 45°C and 75% RH for 30 days for the moisture content study. The moisture contents of the powder after test are also shown in Table 20. The moisture contents of the spray dried powder were found to be increased. Lower moisture contents were obtained from the powder prepared with Aquacoat$^{(R)}$ (Formulations 4-7) and with chitosan (Formulations 8-10). The moisture contents of the powder prepared according to Formulations 1-3, 11-16 and 17-21 were relatively similar. The formulations containing HPMC had higher moisture content than other formulations.

Table 20 The moisture content of spray dried products prepared from different types and proportions of polymers.

Formulation	% Moisture Content*	
	Initial	30 Days
1	2.43	19.00
2	2.57	20.54
3	2.41	20.31
4	0.91	10.74
5	0.95	10.38
6	0.97	11.49
7	0.91	10.96
8	2.34	10.10
9	2.12	11.07
10	2.14	12.31
11	0.89	17.03
12	0.83	16.82
13	0.81	18.48
14	0.79	16.89
15	0.81	17.66
16	0.85	16.63
17	3.15	19.67
18	3.05	20.73
19	3.35	19.98
20	3.32	19.06
21	3.27	20.11

* Average from three determinations

4. Angle of Repose, Bulk Density and True Density

The angle of repose, the bulk density and the true density of the products prepared from different types and proportions of polymers are shown in Table 21.

Table 21 The angle of repose ,the bulk density and the true density of products prepared from different types and proportions of polymers.

Formulation	Angle of Repose** (degree)	Bulk Density ** (g/ml)	True Density (g/ml)			
			Water	Hexane	Acetone	Petroleum Benzin
1	*	0.0933	*	*	*	*
2	*	0.0520	*	*	*	*
3	*	0.0511	*	*	*	*
4	11.98	0.2745	*	*	*	*
5	21.82	0.2413	*	*	*	*
6	20.93	0.2248	*	*	*	*
7	18.95	0.2201	*	*	*	*
8	*	0.5573	*	*	*	*
9	*	0.4348	*	*	*	*
10	*	0.2991	*	*	*	*
11	*	0.0964	*	*	*	*
12	*	0.1048	*	*	*	*
13	*	0.1005	*	*	*	*
14	*	0.0949	*	*	*	*
15	*	0.0970	*	*	*	*
16	*	0.1099	*	*	*	*
17	*	0.1944	*	*	*	*
18	*	0.1419	*	*	*	*
19	*	0.1419	*	*	*	*
20	*	0.1640	*	*	*	*
21	*	0.1752	*	*	*	*

* Cannot be determined

** Average from three determinations

The angles of repose of the spray dried powder from Formulations 1-3 and 8-12 were indeterminable because the powders could not flow from the cylinder. The angles of repose of the powders from Formulations 4-7 could be determined. The lowest angle of repose was obtained from the polymer to drug ratio of 1:1. The products prepared at the ratios of 1:2, 1:4 and 1:6 showed no significant difference in the angle of repose.

Among Formulations 1-3 which used HPMC, the highest bulk density was obtained from the product of formulation 1. While Formulations 2 and 3 obtained the products of similar bulk densities. The products of Formulations 4-7 showed no significant difference on the bulk density. In the case of Formulations 8-10, the highest bulk density was obtained from the product prepared at the polymer to drug ratio of 1:2. The bulk densities were lower for the powder produced at the ratios of 1:4 and 1:6. From Formulations 11-16 and 17-21, the bulk densities were not remarkably affected by different amount of HPMC, Aquacoat$^{(R)}$ or chitosan in the proportion of polymer in the formulations. Apparently, the formulations that contained chitosan (Formulations 8-10) had higher bulk densities than of the formulations with Aquacoat$^{(R)}$ powder (Formulations 4-7). The bulk densities of the formulations with HPMC powder (Formulations 1-3) were relatively lower than those of the other formulations. Higher bulk densities of the spray dried powder were obtained from the formulations with HPMC and Aquacoat$^{(R)}$ powder (Formulations 11-16) and with HPMC and chitosan powder (Formulations 17-21) respectively.

The true density of the spray dried powder could not be determined by pycnometer method. All powders floated over the surface of solvents.

5. Porosity Measurement

The total pore volume of the spray dried powders prepared from solutions of different polymer to drug ratios are shown in Table 22. Decreasing the proportion of polymer in the formulation increased the total pore volume (Formulations 1-3). It could be seen that the polymer to drug ratio might affect the total pore volume of the spray dried powder. In the case of different polymers, the highest total pore volume was obtained from the products prepared from HPMC (Formulations 1-3). The products prepared from Aquacoat(R) (Formulation 7) and from chitosan (Formulation 10) did not show significant different on the total pore volume. The products from the formulations that contained HPMC exhibited higher total pore volume than those from the other formulations.

Table 22 The total pore volume values of spray dried powders of diclofenac sodium with different polymers.

Formulation	Polymer : Drug	Total Pore Volume (m^2/g)
1	HPMC : DS (1:2)	0.00356
2	HPMC : DS (1:4)	0.00537
3	HPMC : DS (1:6)	0.00614
7	EC : DS (1:6)	0.00161
10	CT : DS (1:6)	0.00156
13	(HPMC : EC) :DS (1:1) : 12	0.00303
19	(HPMC : CT) : DS (1:1) : 12	0.00261

6. Particle Size Distribution

The particle size distributions of the powders are shown in Table 23. The particle size of diclofenac sodium with HPMC and Aquacoat(R) spray dried powder (Formulations 11-16) was the largest, mostly over 250 μm. The products from the formulations that contained HPMC exhibited larger particle size than those from other formulations (Formulations 1-3 and 11-21). Higher percentages of fine powder were attained from the formulations with Aquacoat(R) (Formulations 4-7) and with chitosan (Formulations 8-10).

Table 23 The particle size distributions of spray dried powders prepared from different types and proportions of polymers.

Formulation	% Weight Retained on Sieve Size*					
	Pan	106 μm.	150 μm.	180 μm.	250μm.	425 μm.
1	0.00	0.00	0.00	3.20	86.20	10.40
2	0.00	0.00	0.40	6.20	82.84	0.80
3	0.00	0.00	1.76	9.16	86.84	0.00
4	78.60	4.80	4.40	7.60	3.20	1.60
5	81.84	4.84	6.40	4.44	2.80	1.60
6	83.62	4.60	4.00	4.22	3.00	1.60
7	84.20	7.22	3.20	2.82	1.60	1.40
8	91.60	6.00	3.10	0.80	0.00	0.00
9	88.24	7.40	4.00	0.40	0.00	0.00
10	80.20	11.43	8.20	1.50	0.00	0.00
11	0.00	0.00	0.80	17.80	47.10	34.20
12	0.00	0.00	0.40	24.82	46.20	28.80
13	0.00	0.00	0.40	17.50	50.20	32.20
14	0.00	0.00	0.00	17.80	53.20	29.40
15	0.00	0.00	0.20	24.00	51.60	34.70
16	0.00	0.00	0.40	16.32	49.60	33.80
17	0.00	0.00	0.00	12.02	88.22	3.00
18	0.00	0.00	0.40	18.22	76.02	6.00
19	0.00	0.00	0.40	11.40	83.00	7.20
20	0.00	0.00	0.00	12.00	81.00	7.20
21	0.00	0.00	0.00	11.18	83.69	6.21

* Average from two determinations

7. Percentage Recovery

The percentage recovery of powder in the collector and the chamber are represented in Table 24. The percentage recovery of powder obtained from both the chamber and the collector were not remarkably affected by the amounts and the proportions of polymers in the formulations. Formulations 1-3 , using HPMC, showed higher percentage recovery in the chamber than the other formulations, because a lot of powder adhered to the chamber wall. Each formulation had good percentage recovery of above 80 %.

Table 24 The percentage recovery of spray dried product prepared from different types and proportions of polymers.

Formulation	Percentage Recovery		
	Collector	Chamber	Total
1	72.21	8.79	81.00
2	76.28	6.73	83.01
3	73.33	7.44	80.77
4	87.13	2.62	89.25
5	36.73	2.55	89.28
6	82.93	3.31	86.24
7	86.58	2.85	89.43
8	77.42	3.11	80.53
9	81.43	4.01	85.44
10	79.08	3.44	82.52
11	82.16	2.27	84.43
12	82.22	2.72	84.94
13	84.53	3.33	87.86
14	86.75	2.69	89.44
15	86.05	2.07	88.12
16	84.20	2.44	86.64
17	76.94	5.20	82.14
18	75.11	5.13	80.24
19	78.64	4.28	82.92
20	76.38	5.95	82.33
21	77.20	4.67	81.87

8. Infrared Spectrometry

The IR spectra of the spray dried powder of diclofenac sodium with HPMC, of diclofenac sodium with ethylcellulose, and of diclofenac sodium with chitosan are depicted in Figure 27. The interaction between drug and polymers were scarce and the prominent peaks of spectra did not shift as shown in Table 25.

The IR spectra of the spray dried powder of diclofenac sodium with HPMC and ethylcellulose and of diclofenac sodium with HPMC and chitosan are depicted in Figure 28. These also reveal that no interaction or slight interaction occurred.

Table 25 IR peaks of spectra of spray dried powders of diclofenac sodium with different types and proportions of polymers.

Formulation	Principle Peak (cm^{-1})					
Diclofenac Sodium	756	775	1286	1308	1504	1572
1	747	769	1286	1311	1506	1578
2	747	765	1285	1308	1505	1570
3	746	768	1283	1306	1506	1577
5	747	766	1284	1307	1508	1576
6	747	766	1283	1306	1507	1576
9	742	767	1282	1304	1507	1577
10	744	767	1283	1304	1507	1577
12	747	767	1284	1305	1507	1577
13	747	766	1284	1305	1507	1576
15	746	766	1282	1306	1506	1577
16	746	768	1284	1308	1508	1577
17	743	768	1282	1303	1508	1588
18	746	768	1195	1303	1505	1588
19	746	767	1282	1304	1506	1577
20	745	769	1284	1303	1506	1578
21	745	767	1282	1304	1506	1577

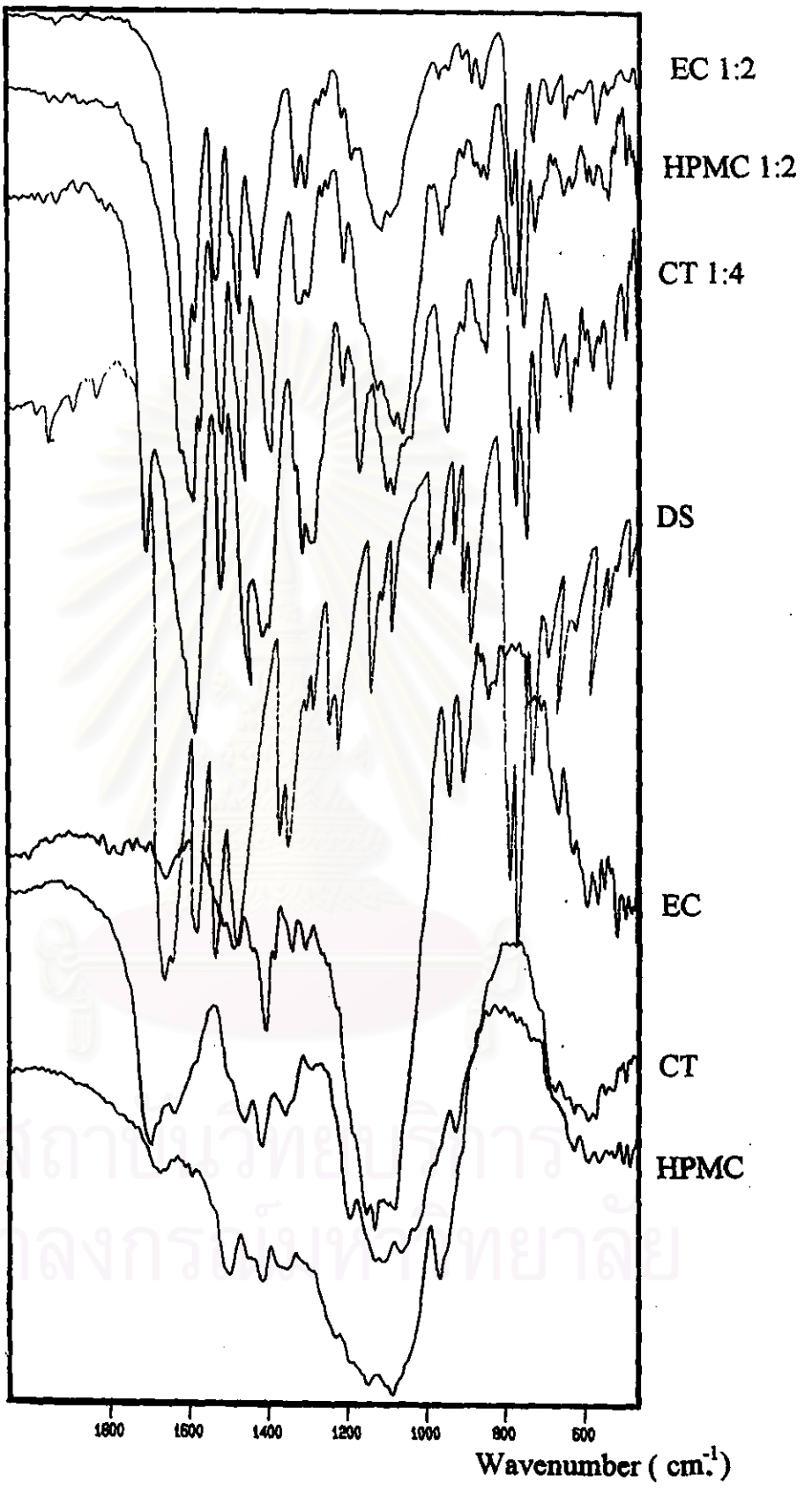


Figure 27 IR spectra of diclofenac sodium with single polymer systems.

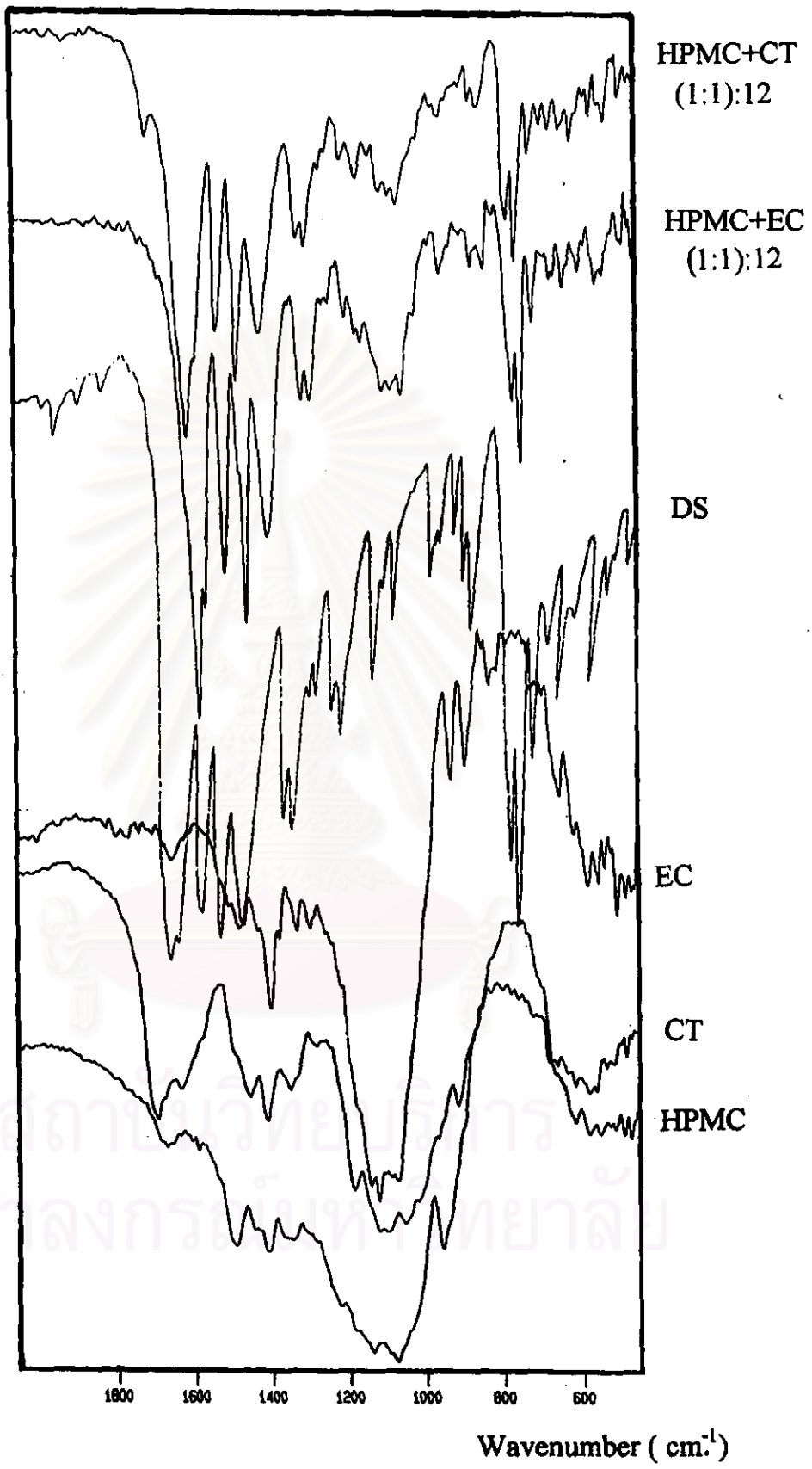


Figure 28 IR spectra of diclofenac sodium with combined polymer systems.

9. X-ray Diffraction

The X-ray diffraction patterns of diclofenac sodium and diclofenac sodium spray dried with different polymers are illustrated in Figures 29. The X-ray diffractogram of diclofenac sodium was particularly observed at 6.5°, 8.5° and 11°.

The X-ray diffraction pattern of diclofenac sodium with HPMC powder (Formulation 1) exhibited absence of crystalline diclofenac sodium peaks. Diclofenac sodium was changed to amorphous form.

No difference was observed between the X-ray diffraction patterns of diclofenac sodium alone and diclofenac sodium with ethylcellulose powder (Formulation 5). Therefore, diclofenac sodium was still in crystalline form.

The X-ray diffraction pattern of diclofenac sodium with HPMC and ethylcellulose powder (Formulation 13) showed the same pattern as diclofenac sodium but remarkably fewer intense peaks, and a slightly higher baseline was detected.

The X-ray diffraction patterns of diclofenac sodium with chitosan powder (Formulation 10) and of diclofenac sodium with HPMC and chitosan powder (Formulation 21) compared with diclofenac sodium alone showed different peaks and intensities. The sharp diffraction peaks attributed to diclofenac sodium crystal were disappeared, some of diclofenac sodium wchanged to amorphous form.

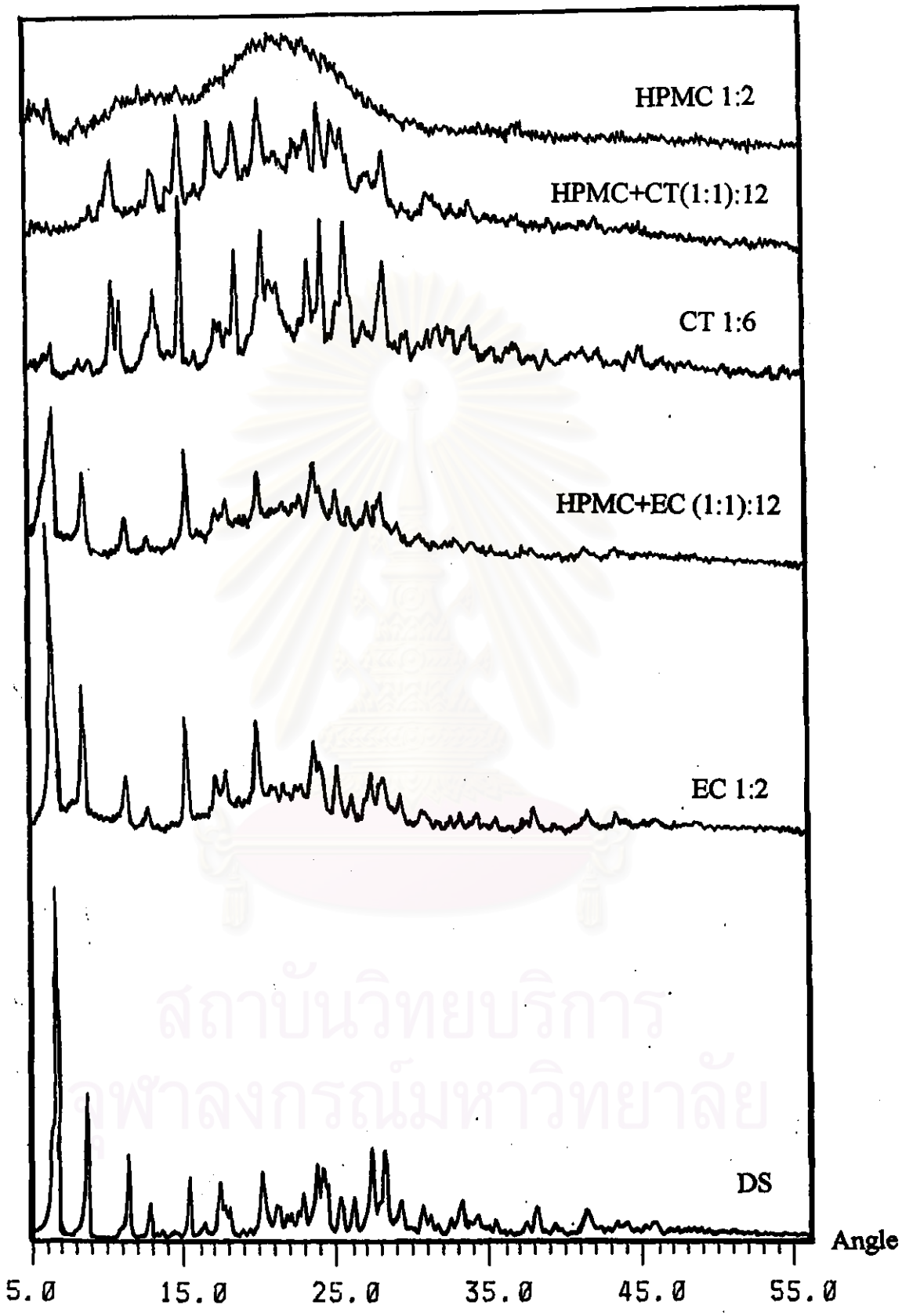


Figure 29 X-ray diffractograms of diclofenac sodium and of diclofenac sodium with different polymers spray dried powders.

10. Differential Scanning Calorimetry

The DSC thermograms of diclofenac sodium and of diclofenac sodium with different polymers spray dried powders are shown in Figure 30. The thermogram of pure diclofenac sodium exhibited the characteristic melting exotherm at 280°C, followed by an endotherm. The DSC peak temperatures of diclofenac sodium with different polymers spray dried powders are shown in Table 26.

Diclofenac sodium with different polymers spray dried powders also exhibited the similar pattern of DSC curves as diclofenac sodium but different in DSC peak temperatures.

Table 26 DSC peak temperatures of diclofenac sodium and of diclofenac sodium with the diclofenac sodium with different polymers spray dried powder.

Formulation	Polymer : Drug	DSC Peak Temperature (°C)
Diclofenac Sodium	-	280
3	HPMC : DS 1:6	260
7	EC : DS 1:6	267
10	CT : DS 1:6	256
13	(HPMC : EC) : DS (1:1) : 12	275
19	(HPMC : CT) : DS (1:1) : 12	276

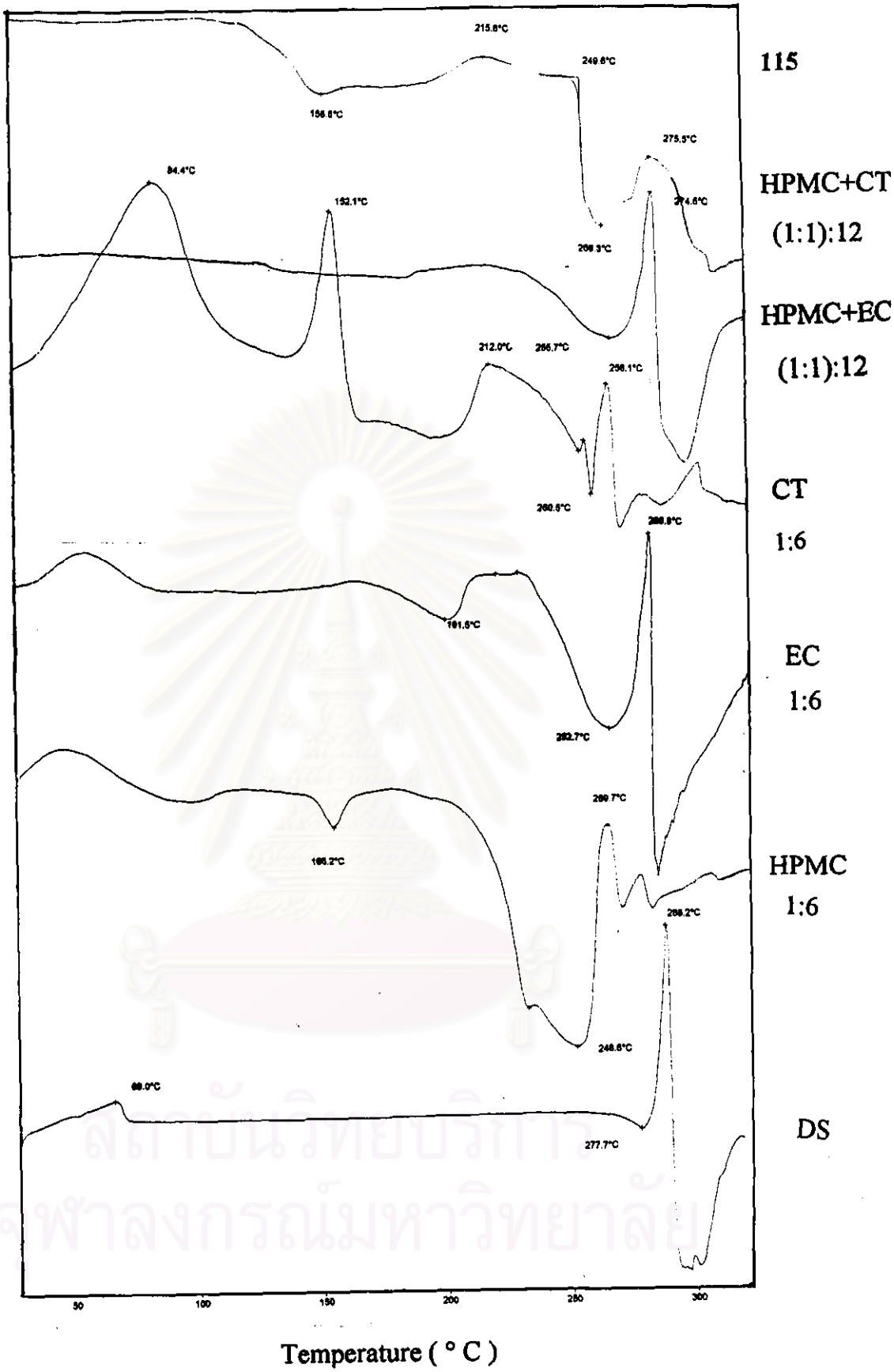


Figure 30 DSC Thermograms of diclofenac sodium and of diclofenac sodium with different polymers spray dried powders.

Dissolution Study

1. Dissolution Profiles and Release Rate Profiles

From the experimental data, the dissolution or the release profiles could be plotted between the amount of drug release against time. Then, the change of release rate profile was constructed from the dissolution profile to elucidate the release rate at various time interval during the course of drug dissolution from microparticles. The dissolution and release rate profiles of each formulation are described in Tables 31-42 (Appendix B).

The release rate was calculated by dividing the difference of percent drug release at various time interval with the time utilized to release that certain amount of the drug. The rate, then, was plotted with the mid point of the time interval. It was shown that the rate of release decreased with the time.

For the capsules that contained diclofenac sodium only and diclofenac sodium with various polymers spray dried powders tested in acid stage (0.1 N. HCl) for 2 hours, the percentages of drug release from all samples were less than 3 % . Then the capsules were subjected to the dissolution test in phosphate buffer pH 6.8.

1.1 The Control Diclofenac Sodium Capsule

The dissolution profile of capsule containing only diclofenac sodium 100 mg. is shown in Figure 31. The capsule tested in acid stage for 2 hours, the percentage of drug release from the sample was less than 1%. In buffer stage, the average percentage of drug release was more than 80% within the first 2 hours. This result indicated that diclofenac sodium was more

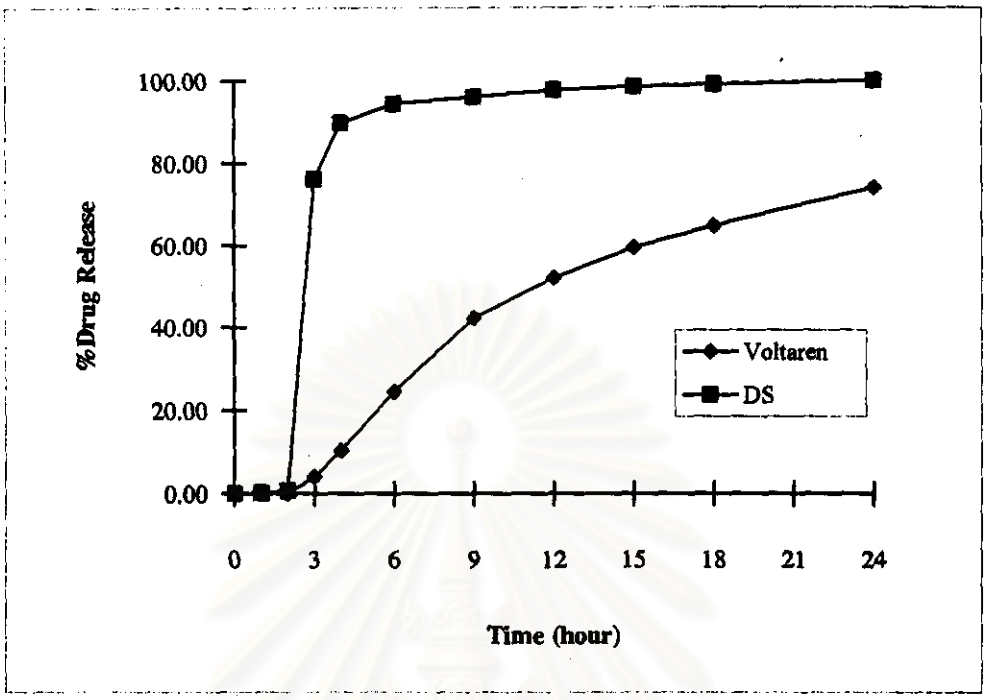


Figure 31 The release profiles of diclofenac sodium capsule and commercial product by pH changing system.

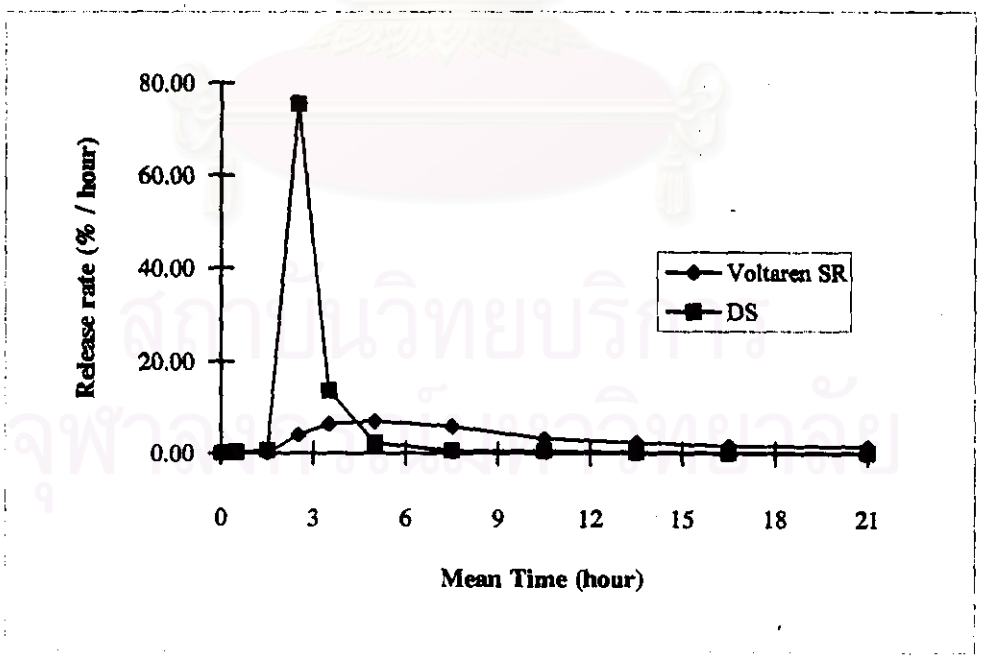


Figure 32 The release rate profiles of diclofenac sodium capsule and commercial product by pH changing system.

soluble in phosphate buffer pH 6.8 than in 0.1 N.HCl. The release rate profile is shown in Figure 32.

1.2 The Voltaren SR Tablet

The commercial product used was Voltaren SR 100 mg. tablet. The amount of drug release at any time interval are presented in Table 31 (Appendix B). The release of diclofenac sodium from Voltaren SR tablet was affected by dissolution medium as illustrated in Figure 31. The observed wave-like appearance was in agreement with previously reported data (Sheu et al., 1992). The release rate of this tablet decreased as the time increased as shown in Figure 32. The amount of drug that released in 24 hours was 73.88%.

1.3 The Formulations 1-3 Microparticles

The dissolution profiles of diclofenac sodium from diclofenac sodium with HPMC spray dried powders with various HPMC ratios in 0.1 N. HCl and phosphate buffer pH 6.8 by pH change method are shown in Figure 33 (Table 32, Appendix B). The release rate of these formulations decreased as the time increased as shown in Figure 34.

In acid stage for 2 hours, the percentages of drug release from all samples were less than 3%. The polymer to drug ratio of 1:2 gave the drug release of more than 80% of total capacity at the 18th hour and the ratio of 1:4 and 1:6 yielded the same level at the 15th hour. The initial rapid release of drug in the first 9 hours followed by slower release until 24 hours was observed. The dissolution profiles of microcapsules prepared at the polymer to drug ratios of 1:2, 1:4 and 1:6 seemed to be similar. The t-values showed no statistically significant difference ($p > 0.05$) in the release pattern (Table 51, Appendix C).

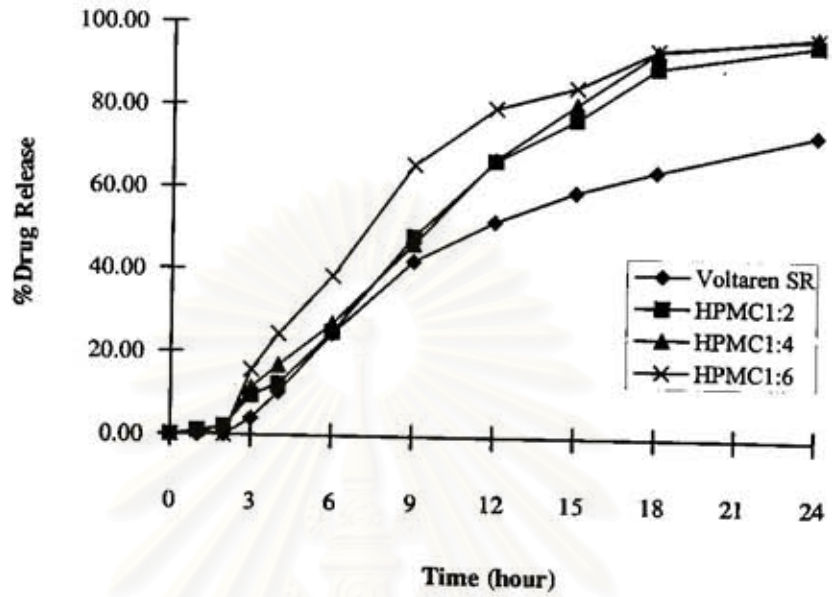


Figure 33 The release profiles of diclofenac sodium with HPMC spray dried powders by pH changing system.

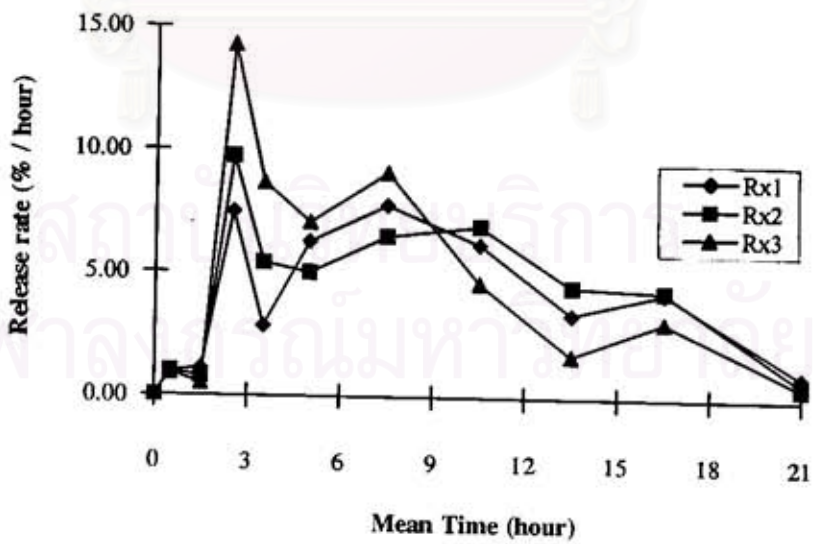


Figure 34 The release rate profiles of diclofenac sodium with HPMC spray dried powders by pH changing system.

Nevertheless, microcapsules prepared at the ratio of 1:6 produced faster dissolution rate. In addition, every formulation gave the same release profile with a maximum drug release of more than 95%. Complete drug release was seen on the 24th hour of experiment.

1.4 The Formulations 4-7 Microparticles

The dissolution profiles of diclofenac sodium from diclofenac sodium with ethylcellulose spray dried powder with various ethylcellulose ratios into pH changing system are shown in Figure 35 (Table 33, Appendix B). The release rate was decreased with time as shown in Figure 36. After the drug was released in 24 hours, the polymer matrix remained undissolved.

The percentages of diclofenac sodium release at 24 hours were increased from 43.59% to 63.48% and 94.72% when the proportions of polymer in the formulations were decreased from the polymer to drug ratios of 1:1 to 1:2 and 1:4 respectively. The percentage of diclofenac sodium release at 24 hours of the ratio of 1:6 was 94.87% . When the proportion of polymer was decreased from the ratios of 1:4 to 1:6, the dissolution rate was not increased. The t-value showed no statistically significant difference ($p>0.05$) in the drug release pattern (Table 51, Appendix C). Provided that each series of matrix microcapsule was prepared from ethylcellulose, the release of diclofenac sodium decreased with the increasing of the amount of polymer in the formulation as expected. The concentration of ethylcellulose in the formulation was the determining factor in controlling release rate of drug.

It is interesting that the comparison between the microcapsules produced with ethylcellulose at the polymer to drug ratio of 1:2 (Formulation 5) and a commercial sustained release tablet of diclofenac sodium (Voltaren SR)

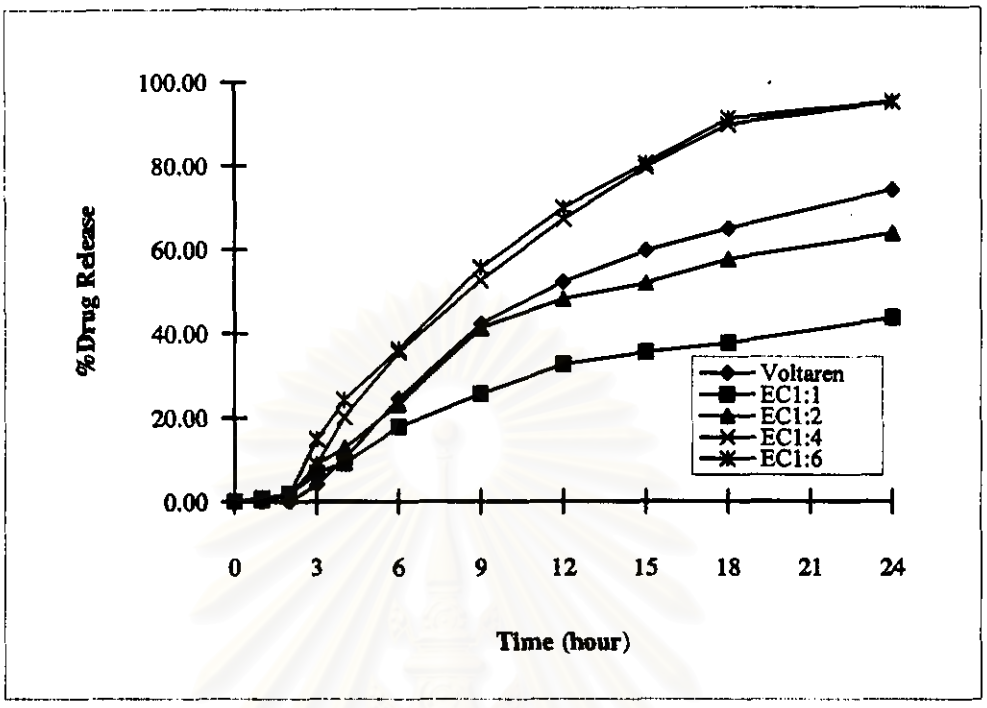


Figure 35 The release profiles of diclofenac sodium with ethylcellulose spray dried powders by pH changing system.

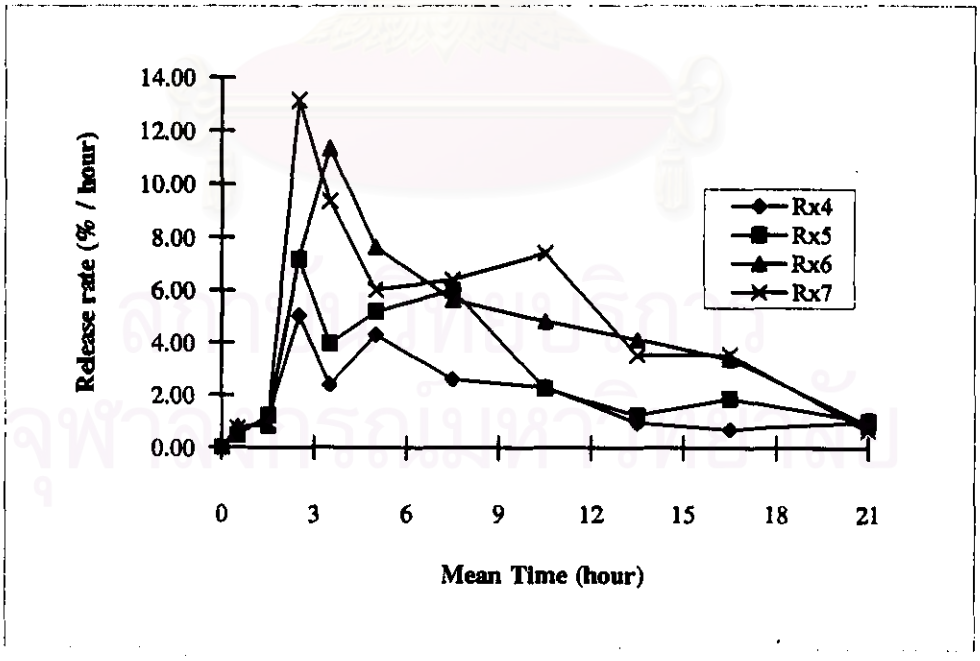


Figure 36 The release rate profiles of diclofenac sodium with ethylcellulose spray dried powders by pH changing system.

showed no statistically significant difference ($p>0.05$) on the drug release pattern (Table 51, Appendix C). The dissolution rate within first 9 hours of Formulation 5 microcapsule and Voltaren SR tablet seemed to be similar. The amount of drug that released in 24 hours were 63.48% and 73.88% for Formulation 5 microcapsule and Voltaren SR tablet, respectively.

1.5 The Formulations 8-10 Microparticles

The dissolution profiles of diclofenac sodium from diclofenac sodium with chitosan spray dried powder with various chitosan ratios into a pH changing system are shown in Figure 37 (Table 34, Appendix B). The release rate was decreased with time as shown in Figure 38.

The controlled release capsules of diclofenac sodium with chitosan spray dried powders at the polymer to drug ratios of 1:2, 1:4 and 1:6, showed no capability to control the drug release. Every formulations released the drug immediately on the 3rd hour of experiment followed by slightly increased release up to 24 hours, even when the polymer to drug ratio was 1:2. The release rates of these formulations were also faster than the formulations prepared from other polymers.

1.6 The Formulations 11-16 Microparticles

These formulations contained diclofenac sodium with HPMC and ethylcellulose but the ratio of both polymers in each formulation was adjusted differently in order to modify the release rate (Table 9). The controlled release function was obtained by formulating HPMC and ethylcellulose at different ratios. After the drug was released in 24 hours, the polymer matrix remained undissolved. Figure 39 and 41 (Table 35, Appendix B) show the release of

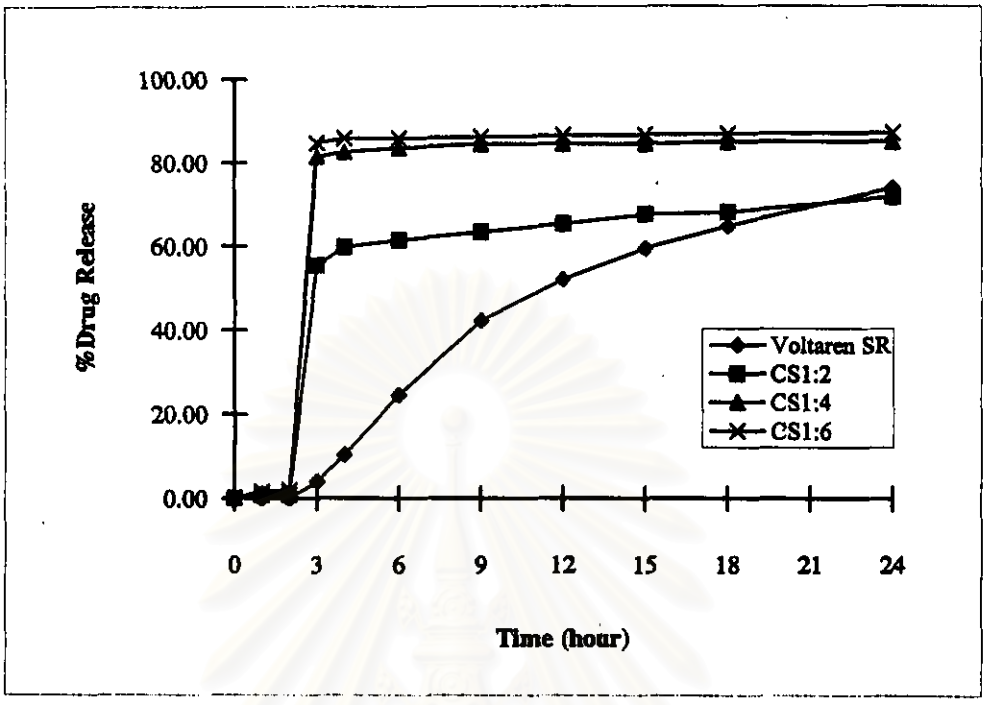


Figure 37 The release profiles of diclofenac sodium with chitosan spray dried powders by pH changing system.

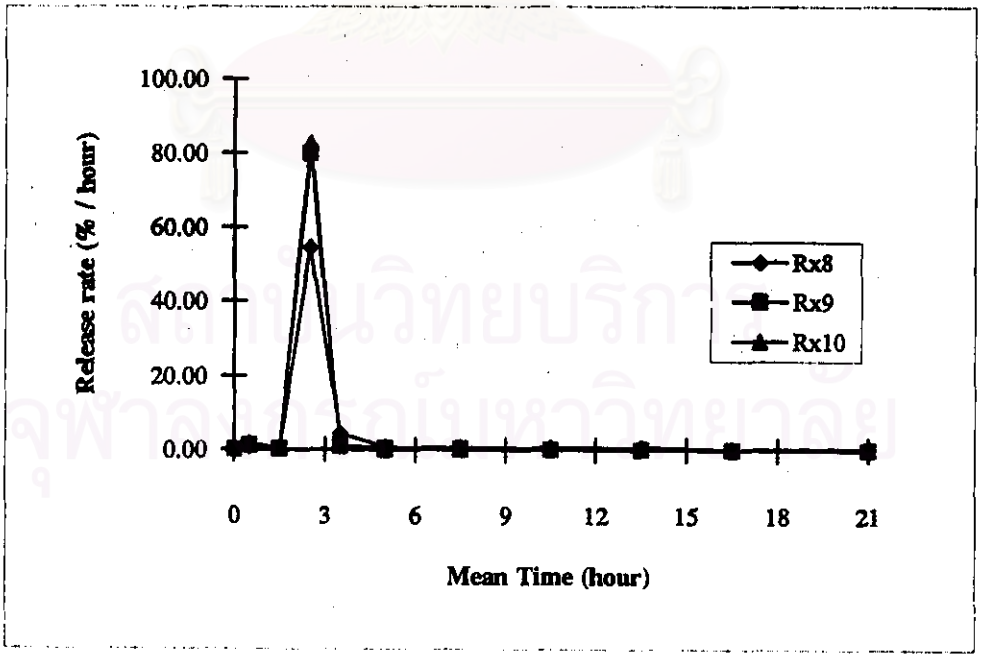


Figure 38 The release rate profiles of diclofenac sodium with chitosan spray dried powders by pH changing system.

diclofenac sodium from Formulations 11-16 microcapsules affected by dissolution medium. The release rates of these formulations decreased as the time increased as displayed in Figures 40 and 42.

In Figure 39, the percentage of diclofenac sodium release at 24 hours was increased from 54.08% to 60.75% and 78.60% when the proportion of polymer in the formulations was decreased from the polymer to drug ratios of (1:1): 4 to (1:1): 8 and (1:1): 12, respectively. The dissolution profiles of microcapsule prepared at the ratios of (1:1) : 4 and (1:1) : 8 seem to be similar. The t-value showed no statistically significant difference ($p>0.05$) in the release pattern (Table 51, Appendix C). Nevertheless, microcapsules prepared at the ratio of (1:1) : 12 produced fastest dissolution rate. As expected, the release of diclofenac sodium decreased with increasing amount of polymer in the formulation.

In Figure 41, when the amount of HPMC in the proportion of polymer was increased from the ratios of (1:1): 12 to (1.5:1): 12 and (2:1): 12, the dissolution rate of matrix microcapsules increased. The initial rapid release of drug in the first 9 hours followed by a slower release up to 24 hours was observed. In the case of ethylcellulose, the amount of ethylcellulose in the proportion of polymer was increased from the ratio of (1:1): 12 to (1:2): 12, and the matrix microcapsules showed good durability. The lowest dissolution rate was obtained from the polymer to drug ratio of (1:2): 12; the curve was practically linear after the first portion, this means that, excluding the first 2 hours.

Formulated with the polymer to drug ratio of (1:1) : 12, the release pattern of Formulation 13 was very similar to that of a commercial sustained

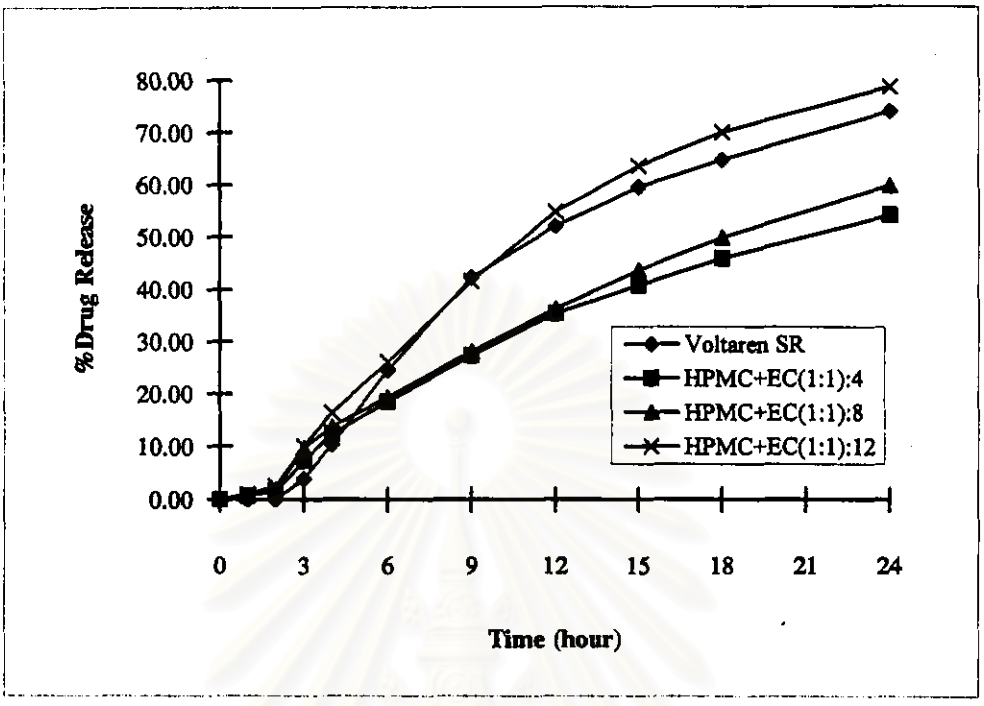


Figure 39 The release profiles of diclofenac sodium with HPMC and ethylcellulose spray dried powders at various proportions of drug by pH changing system.

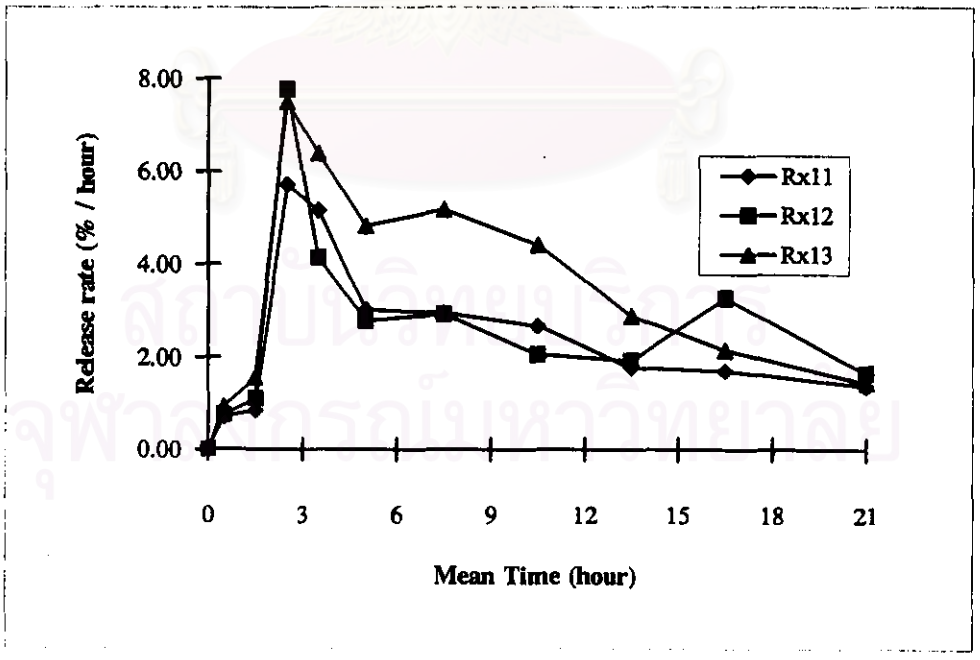


Figure 40 The release rate profiles of diclofenac sodium with HPMC and ethylcellulose spray dried powders at various proportions of drug by pH changing system .

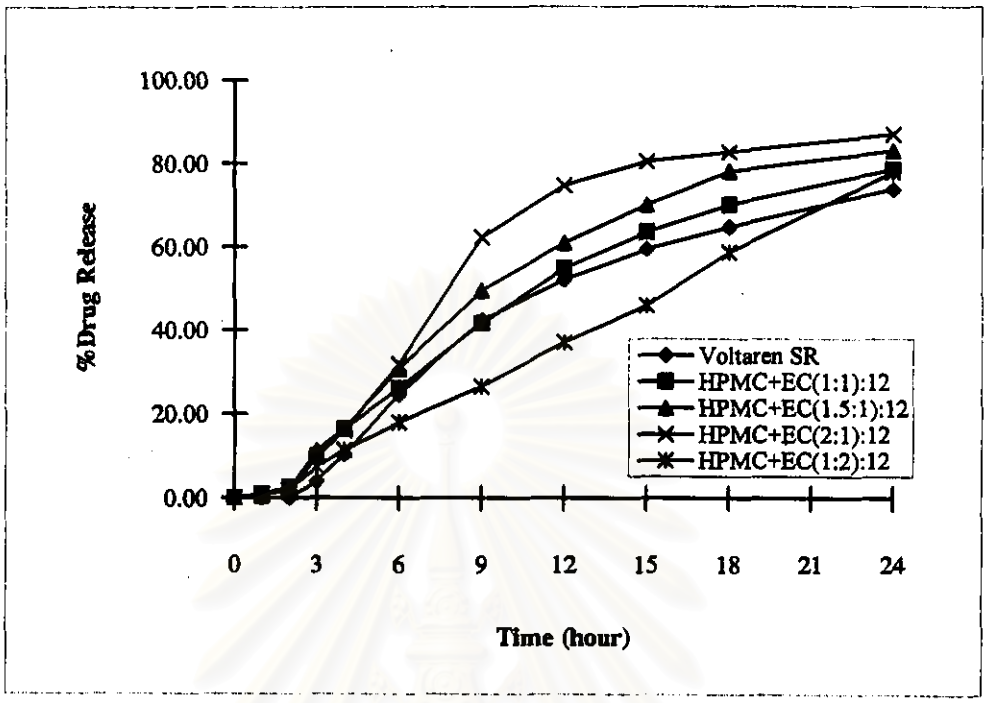


Figure 41 The release profiles of diclofenac sodium with HPMC and ethylcellulose spray dried powders at various types and proportions of polymer by pH changing system.

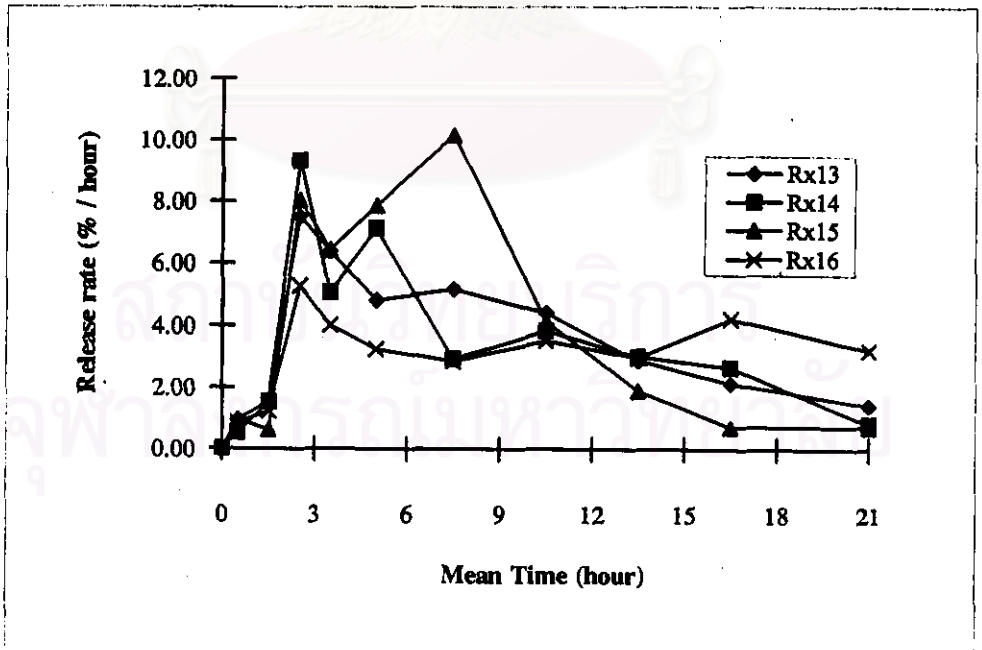


Figure 42 The release rate profiles of diclofenac sodium with HPMC and ethylcellulose spray dried powders at various types and proportions of polymer by pH changing system.

release tablet of diclofenac sodium (Voltaren SR) tested under the same dissolution conditions. The amounts of drug released in 24 hours were 78.60% and 73.88% for Formulation 13 microcapsule and Voltaren SR tablet, respectively. The release rate of Voltaren SR tablet was lower during the first 3 hours comparing with Formulation 13 microcapsule and the same rate was observed thereafter. The results of statistic tests are shown in Table 51, Appendix C. They indicate that patterns of dissolution profile of Formulation 13 microcapsule and Voltaren SR tablet were not significantly different ($p>0.05$).

1.7 The Formulations 17-21 Microparticles

These formulations contained diclofenac sodium with HPMC and chitosan but the ratio of both polymers in each formulation was adjusted differently in order to modify the release rate (Table 9). The pictures of the releases of diclofenac sodium from Formulations 17-21 particles affected by dissolution medium are shown in Figure 43. The release rate of these formulations decreased with time as shown in Figure 44.

The controlled release capsules of diclofenac sodium with HPMC and chitosan spray dried powders with various the polymer to drug ratios of solution showed no capability to control the drug release. Every formulation released the drug immediately followed by slightly increased release until 24 hours. The effect of concentration was the same as the, results obtained from the aforementioned polymers. Increasing the amount of polymers in the formulation decreased the amount of drug released from particles. Patterns of dissolution profile of diclofenac sodium with chitosan particles (Formulations 8-10) and of diclofenac sodium with HPMC and chitosan particles (Formulations 17-21) were similar.

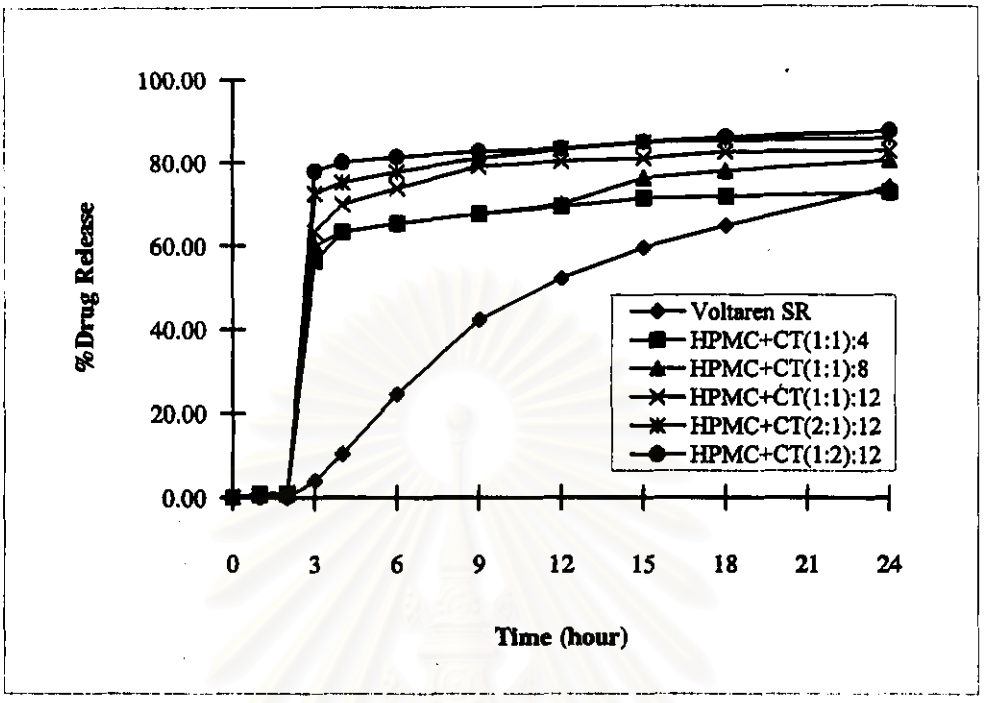


Figure 43 The release profiles of diclofenac sodium with HPMC and chitosan spray dried powders by pH changing system.

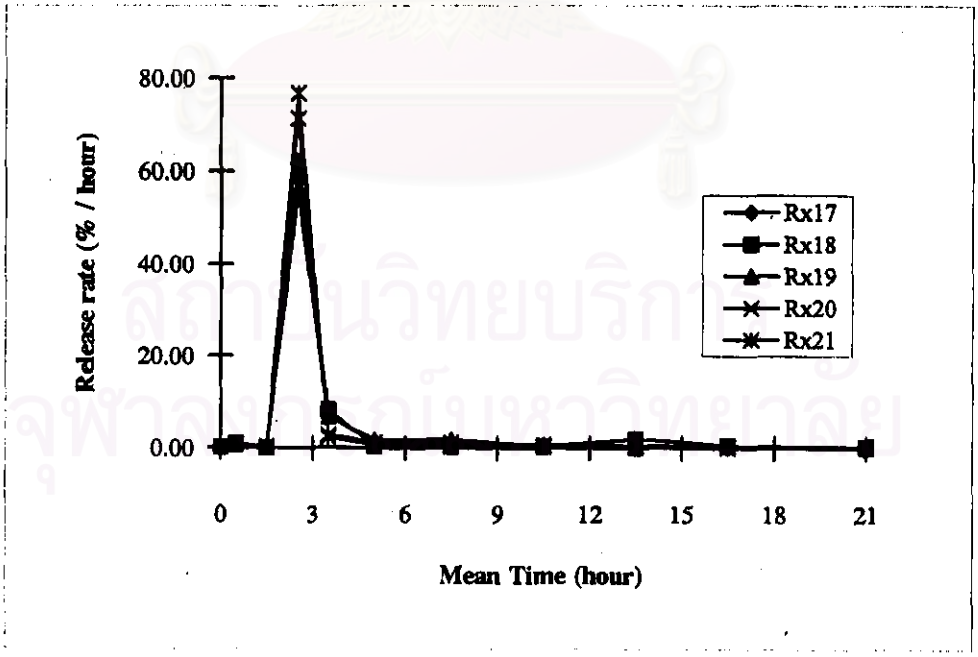


Figure 44 The release rate profiles of diclofenac sodium with HPMC and chitosan spray dried powders by pH changing system.

2. Elucidation of Drug Release Model

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

For the test in phosphate buffer pH 6.8, the values of correlation coefficient of the relationship pointed out that the first-order model and the Higuchi model were of interest. The further treatment was based upon the use of the different forms of the first-order and Higuchi equations. The plots of rate of release versus 1/Q were linear when the release was fitted with the Higuchi model. If the plots of rate of release versus Q were linear, they indicated that the first-order model was operative. The correlation coefficients of rate of release against reciprocal amount (1/Q) and amount (Q) of diclofenac sodium released from the microparticles are shown in Table 27.

2.1 The Control Diclofenac Sodium Capsule

The correlation coefficients were obtained as tabulated in Table 28. The highest correlation coefficient was 0.9313 obtained from the first-order plot in phosphate buffer pH 6.8.

Table 27 Comparison of linearity between plots of rate of release against reciprocal amount (1/Q) and amount (Q) of diclofenac sodium released from the microparticles in phosphate buffer pH 6.8.

Formulation	Correlation coefficient of rate dQ/dt	
	Versus Q	Versus 1/Q
Blank	0.9271	0.8967
Voltaren SR	0.5584	0.0482
1	0.2499	0.0768
2	0.4859	0.4601
3	0.7823	0.7483
4	0.6843	0.5412
5	0.6488	0.5110
6	0.7766	0.2841
7	0.8002	0.7845
8	0.4957	0.5531
11	0.8727	0.8810
12	0.4746	0.8273
13	0.9217	0.7459
14	0.7687	0.7231
15	0.5049	0.2492
17	0.7314	0.8152
18	0.5619	0.6901
19	0.6827	0.7072
20	0.4723	0.6682
21	0.4412	0.4522

Table 28 Correlation coefficient of the relationships between percentage drug released versus time (A), percentage drug released versus square root time (B), and log percentage drug remained versus time (C).

Formulation	Dissolution Study					
	pH Change Method			Phosphate Buffer pH 6.8		
	A	B	C	A	B	C
Blank	0.4892	0.6706	0.8744	0.5541	0.6596	0.9313
Voltaren SR	0.9415	0.9200	0.9861	0.9123	0.9729	0.9840
1	0.9555	0.9170	0.9639	0.9311	0.9751	0.9804
2	0.9574	0.9218	0.9421	0.9360	0.9740	0.9595
3	0.9030	0.9287	0.9834	0.8658	0.9415	0.9888
4	0.9343	0.9452	0.961	0.9142	0.9726	0.9475
5	0.9242	0.9336	0.9667	0.8929	0.9585	0.9513
6	0.9428	0.9341	0.9799	0.9191	0.9758	0.9888
7	0.9346	0.9418	0.9809	0.9191	0.9744	0.9849
8	0.5211	0.6940	0.6199	0.9269	0.9650	0.9550
9	0.4050	0.5886	0.4420	0.6807	0.7918	0.7007
10	0.3971	0.5808	0.4246	0.7962	0.8601	0.8178
11	0.9681	0.9494	0.9923	0.9669	0.9974	0.9929
12	0.9821	0.9480	0.9946	0.9910	0.9932	0.9945
13	0.9568	0.9418	0.9945	0.9421	0.9866	0.9956
14	0.9358	0.9362	0.9877	0.9104	0.9704	0.9858
15	0.8843	0.9044	0.9559	0.8188	0.9069	0.9340
16	0.9976	0.9045	0.9449	0.9986	0.9745	0.9483
17	0.5057	0.6846	0.5956	0.7539	0.8464	0.8092
18	0.5268	0.6981	0.6607	0.8426	0.8744	0.8919
19	0.5150	0.6945	0.6475	0.7189	0.8272	0.7870
20	0.4825	0.6623	0.6211	0.8344	0.9223	0.8783
21	0.4483	0.6281	0.5624	0.9361	0.9748	0.9681

2.2 The Voltaren SR Tablet

In the pH change method, the highest correlation coefficient was 0.9861 obtained from the first-order plot. In buffer pH 6.8, the correlation coefficients of rate of release versus Q were higher than those of rate versus 1/Q. The first-order model might possibly be operative.

2.3 The Formulations 1-3 Microparticles

In the pH change method, Formulations 1 and 2, both the zero-order plots and the first-order plots were linear with the correlation coefficient values greater than 0.94. However, the highest correlation coefficients of Formulations 1 and 3 were 0.9639 and 0.9834, respectively. The results indicated that the release data might have followed the first-order model. In the case of Formulation 2, the highest correlation coefficient was 0.9574 that obtained from the zero-order plot.

For the test in buffer pH 6.8, Formulations 2 and 3, the correlation coefficient of rate of release against Q was higher than those against 1/Q, but the t-values did not show statistically significant difference ($p > 0.05$) between them, shown in Table 50 in Appendix C. The release profile of Formulation 1 might have followed the first-order model while the models of Formulations 2 and 3 could not be specified.

2.4 The Formulations 4-7 Microparticles

In pH change system, these formulations showed similar release model. The first-order plot was linear with the correlation coefficient values of greater than 0.96.

In phosphate buffer pH 6.8, the correlation coefficient of rate of release against Q was higher than those against 1/Q. This was true for all the microparticles having different ratios of polymer to drug. For the Formulation 7, the t-value did not show statistically significant difference ($p > 0.05$) of the correlation coefficient of rates of release against Q and those of 1/Q, shown in Table 50 in Appendix C. Therefore, the release profiles of Formulations 4-6 might have followed the first-order model while the model of Formulation 7 could not be specified.

2.5 The Formulations 8-10 Microparticles

All these formulations showed similar release model. The highest correlation coefficient, as presented in Table 27, was obtained from the Higuchi plot of dissolution medium pH 6.8. For Formulation 8, the correlation coefficients of rate of release against 1/Q were higher than those against Q. In conclusion, the Formulations 8-10 might have followed the Higuchi model.

2.6 The Formulations 11-16 Microparticles

For the test of the pH changing system, Formulations 11-13, the first-order plots were linear ith the correlation coefficient values greater than 0.99. For Formulations 14 and 15, the highest correlation coefficients were 0.9877 and 0.9559 from the first-order plot. In the case of Formulation 16, the amount of ethylcellulose in the proportion of polymer was increased from the polymer to drug ratio of (1:1): 12 to (1:2): 12. The highest correlation coefficient was 0.9976 from zero-order plot.

In buffer pH 6.8, Formulations 11-15 showed similar release model. The correlation coefficients of rate of release versus 1/Q were higher

than those against Q. This was true for Formulations 11 and 12, but Formulations 13-15 showed opposite results as shown in Table 28. For Formulations 11 and 14, the t-value of Formulation 11 did not show statistically significant difference (Table 50, Appendix C). The release profiles of Formulations 13-15 might show the first-order model, the Formulation 12 might have exhibited the Higuchi model and the model of Formulation 11 could not be specified. In the case of Formulation 16, the highest correlation coefficient was 0.9986 obtained from the zero-order plot.

2.7 The Formulations 17-21 Microparticles

The correlation coefficients of rate of release against 1/Q were higher than those of rate against Q. But the t-values of Formulations 19 and 21 showed no statistically significant difference ($p > 0.05$) (Table 50 in Appendix C). In conclusion, the release profiles of Formulations 17, 18 and 20 might have come after the Higuchi model while the models of Formulations 19 and 21 could not be specified.