CHAPTER III

RESULTS

1. Preliminary Study

From the preliminary study, the amount of polymer should not be more than 20 %w/w because a large amount of the feed suspension retained and dried in the atomizing wheel, so the path of feed suspension was obstructed. In addition, most spray dried powders adhered to the walls of drying chambers and cyclone collector, which was hardly harvested.

The addition of colloidal silica (Aerosil®) was recommened to reduce the tendency to stick during spray drying process. Furthermore, aerosil was also added to improve the flow of small particles. By visual observation, the flow property of the formulation contained aerosil was better than that without aerosil. With increasing amount of aerosil in the formulation, the quantity of spray-dried powder adhered to the wall of drying chamber decreased. The optimal amount of aerosil used was 30 %w/w of polymer.

The spray drying conditions were drying inlet air temperature of 170° C, the feed rate of 20 ml/min, and the atomizing air pressure of 3 bars. These conditions produced unsatisfactory physical properties of the products. The spray dried particles were agglomerated, irregularly shaped with rough surfaces.

2. The Yield of Production

The yield of production is expressed as the weight percentage of the final product harvested with respect to the initial amount of polymer and drug sprayed. The spray dried porducts were collected from the collector and chamber. The percent yield in collector and chamber are shown in Table 6. It was found that the percent yield of powder products from the collector was higher than that from the chamber, except in Formulation 4. The total percent yield was good, particularly in the low quantity of polymer used for preparation. With increasing concentration of polymer in the formulation, the percent yield decreased especially that from the collector. Large amount of powder adhered to the wall of drying chamber and could not be harvested from the chamber. The change of inlet air temperature did not affect the percent yield.

Table 6 The percent yield of spray-dried products.

Formulation	Percent Yield of Production		
	Collector	Chamber	Total
1	75.60	16.99	92.59
2	70.25	17.30	87.55
3	79.82	12.08	91.90
4	25.94	45.29	71.23
5	66.54	21.41	87.95
6	73.36	14.18	87.54
7	77.58	12.66	90.24
8	68.13	20.08	88.21
9	74.52	14.56	89.11
10	73.58	11.64	85.22
11	78.16	13.30	91.46
12	56.86	29.20	86.06
13	71.00	16.26	87.26
14	74.24	13.63	87.87
15	73.57	12.03	85.60
16	76.72	13.27	89.99
17	77.58	10.15	87.73

3. Drug Content

The percent drug content of spray dried product prepared from various formulations are displayed in Table 7. The standard deviation shown implied the uniformity of drug distribution in spray dried product. The data showed slightly different drug content between the products collected from the collector and chamber.

Table 7 The percentage of drug content in spray-dried products.

Formulation	% Theoretical Drug Content	% Drug Content (SD)*	
		Collector	Chamber
1	87.37	90.06 (0.15)	92.12 (0.62)
2	89.43	92.17 (1.38)	93.84 (0.84)
3	92.02	94.70 (0.06)	96.14 (0.58)
4	75.42	77.92 (0.53)	76.24 (1.15)
5	83.28	85.62 (0.39)	84.17 (2.20)
6	87.37	88.56 (0.39)	91.03 (0.90)
7	89.43	93.08 (0.27)	93.53 (2.20)
8	92.02	94.31 (1.15)	94.27 (0.62)
9	87.37	88.55 (0.86)	89.76 (0.30)
10	89.43	90.72 (0.53)	93.07 (0.56)
11	92.02	95.87 (0.24)	97.49 (0.26)
12	87.37	90.71 (0.30)	91.99 (0.73)
13	89.43	92.14 (0.91)	91.53 (0.30)
14	92.02	93.99 (0.04)	97.14 (0.86)
15	88.71	82.97 (0.32)	93.02 (0.10)
16	88.71	85.40 (0.56)	93.29 (0.55)
17	88.71	90.81 (0.98)	91.43 (0.35)

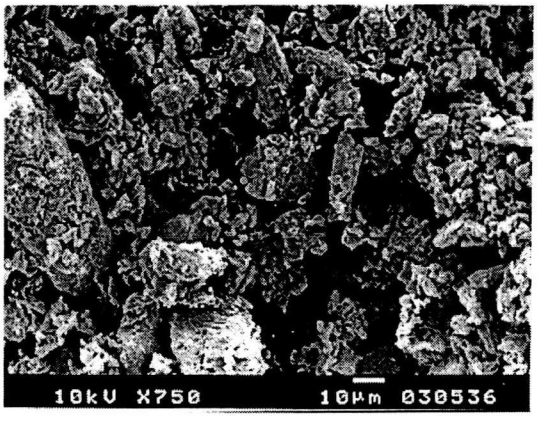
* Standard deviation from three determinations.

4. Physical Properties of Spray Dried Powders

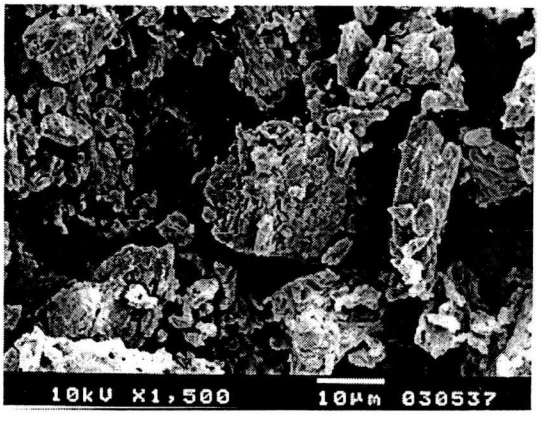
4.1 Morphology of Powders

Scanning electron photomicrographs of the spray dried products were taken to investigate the surface topography and shape of the spray dried particles. The scanning electron photomicrographs of pure diclofenac sodium powder in different magnifications are revealed in Figure 6. The powder composed of irregular thick crystal shapes in various sizes. The surface of powder was rough.

The scanning electron photomicrographs of spray dried diclofenac sodium with Eudragit® NE 30D at drying inlet air temperature of 150°C (Formulations 1-3) are shown in Figure 7. The spray dried particles were irregular shape with different sizes and partly shrunken. The surface of spray dried particle was rough. The agglomeration of particle was observed. No remarkable morphological difference was evident in the case of the particles prepared with the different polymer to drug ratio.

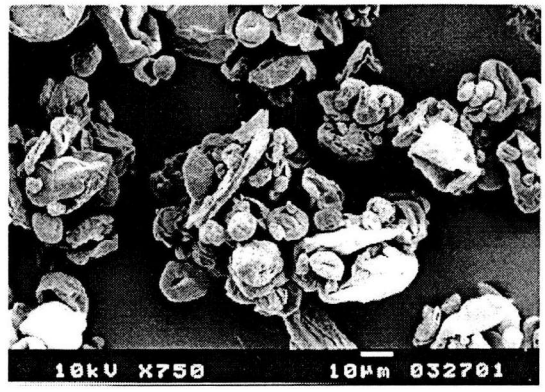


A x 750



B x 1,500

Figure 6 Scanning electron photomicrographs of pure diclofenac sodium powder.



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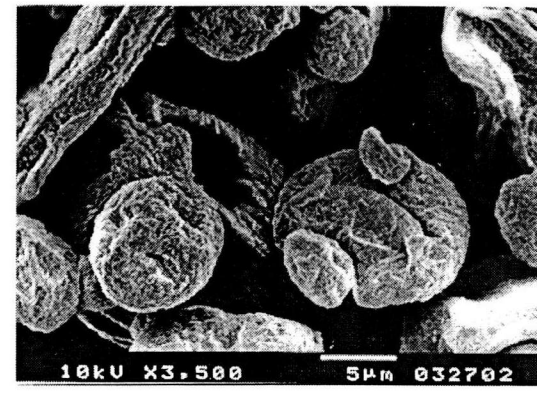

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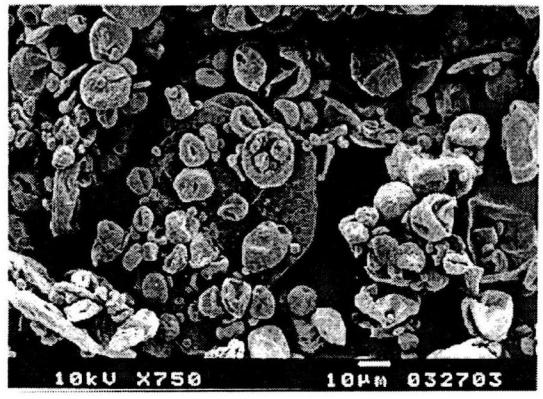

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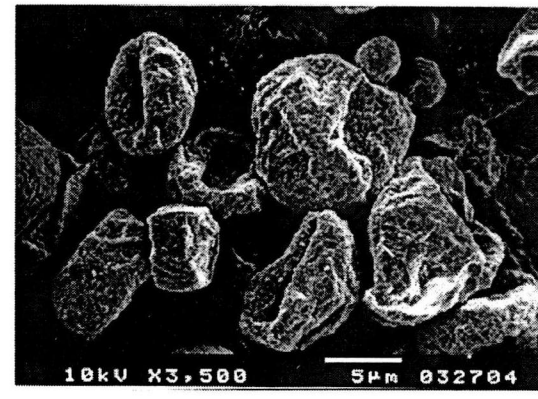

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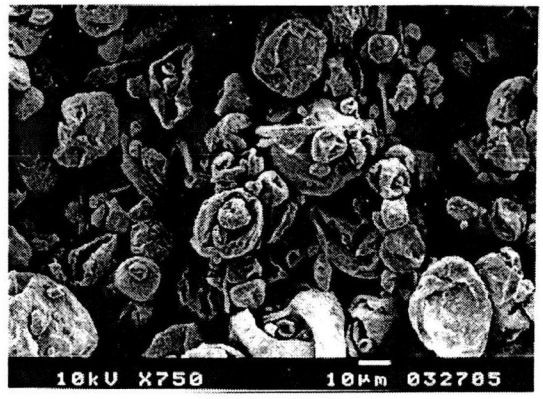

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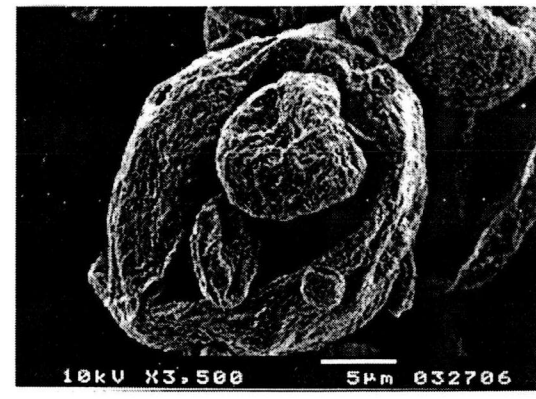
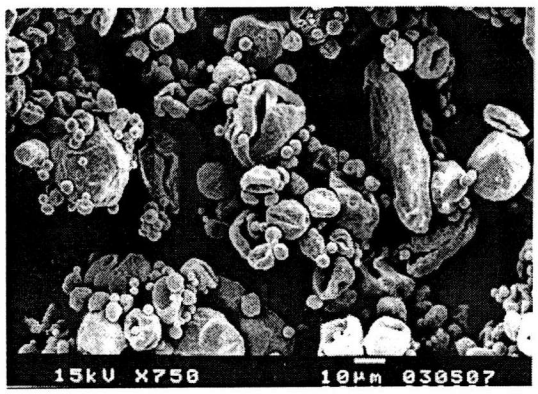


7.3 (B)

Figure 7 Scanning electron photomicrographs of spray-dried diclofenac sodium with Eudragit® NE 30D at inlet air temperature of 150°C (Formulations 1-3).
(7.1) NE 1:9, (7.2) NE 1:11, (7.3) NE 1:15
(A x 750, B x 3,500)



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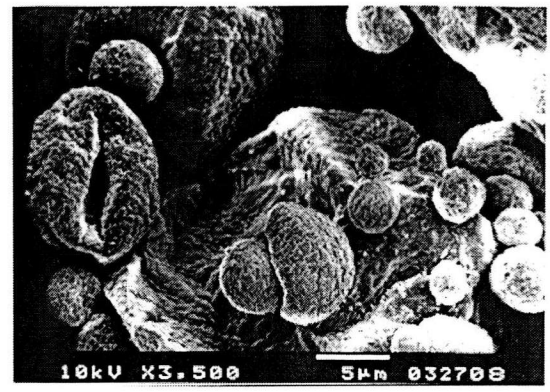

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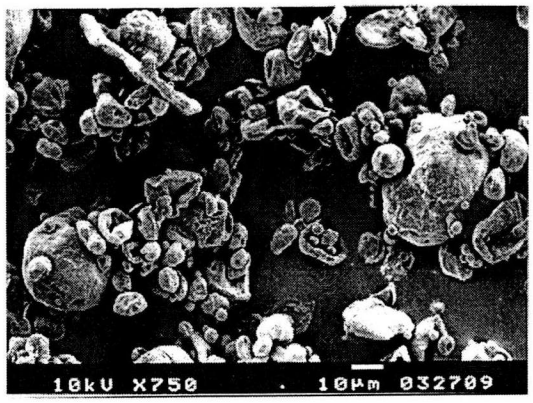

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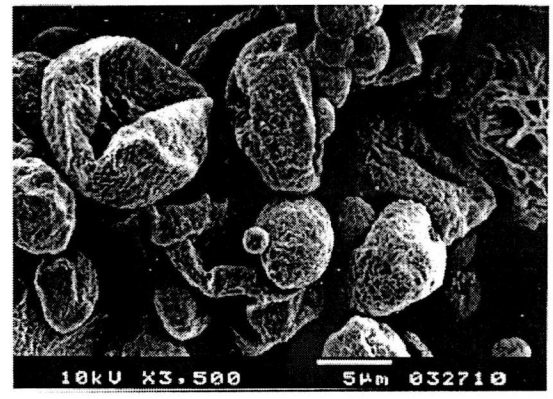

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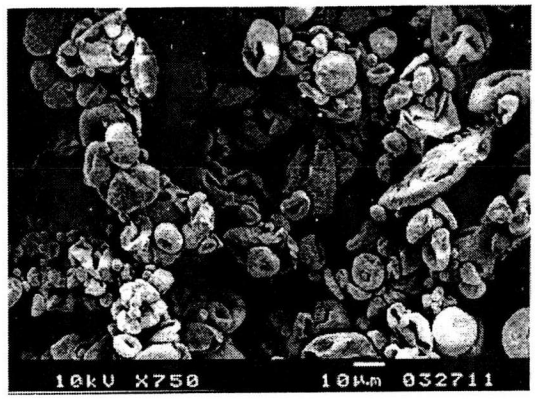

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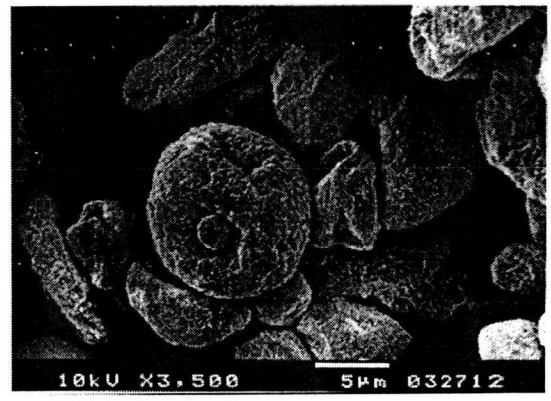
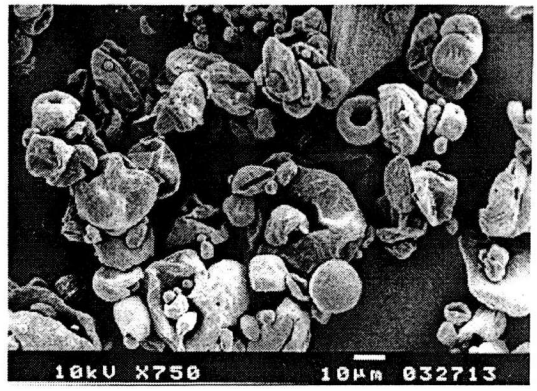


8.3 (B)

Figure 8 Scanning electron photomicrographs of spray-dried diclofenac sodium with Eudragit® NE 30D at inlet air temperature of 170°C (Formulations 4-6).
(8.1) NE 1:4, (8.2) NE 1:6, (8.3) NE 1:9
(A x 750, B x 3,500)



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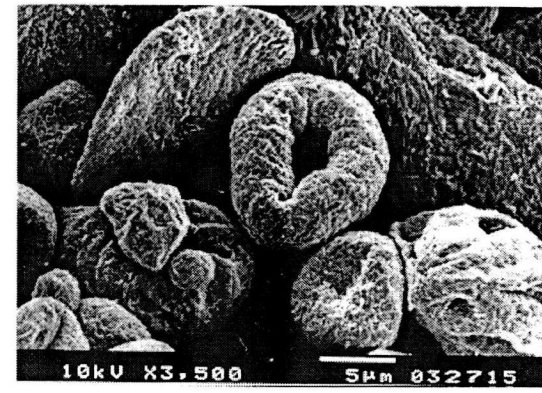

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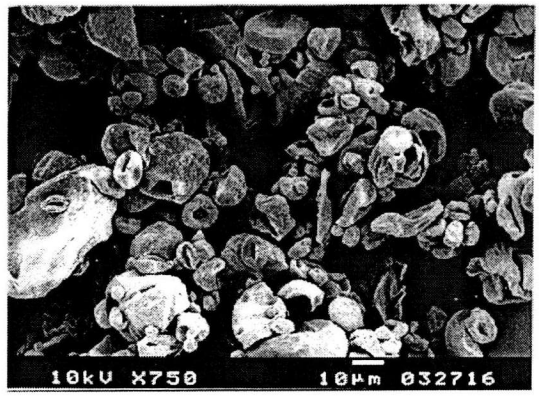

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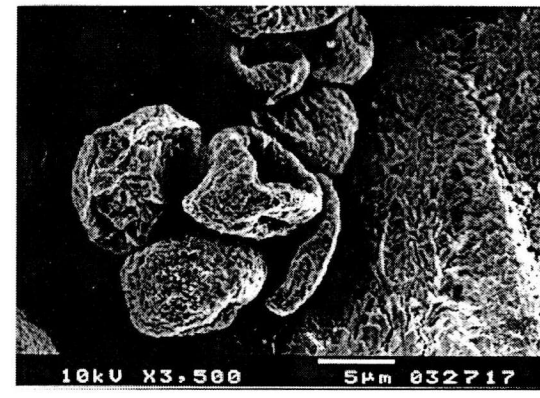


8.5 (B)

Figure 8 (cont.) Scanning electron photomicrographs of spray-dried diclofenac sodium with Eudragit® NE 30D at inlet air temperature of 170°C (Formulations 7-8).
(8.4) NE 1:11, (8.5) NE 1:15
(A x 750, B x 3,500)

The microscopic appearance of spray dried diclofenac sodium with Eudragit® NE 30D at drying inlet air temperature of 170°C (Formulations 4-8) are displayed in Figure 8. A mixture of rings and tiny spherical particle and also irregular particles were obtained. The surface had an orange peel texture. Some of the small particles were attached to each other and/or attached to the large particles. No difference was detectable when changing the polymer to drug ratio.

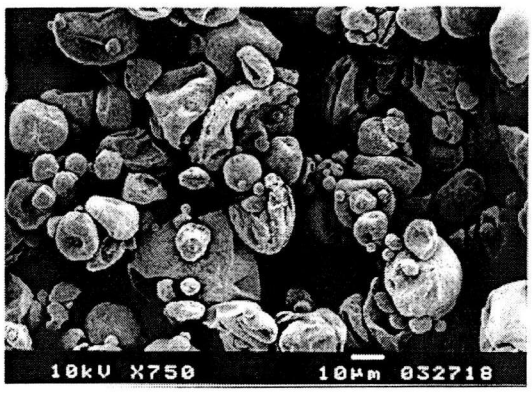
The microscopic images of spray dried diclofenac sodium with Eudragit® NE 30D at inlet air temperature of 190°C (Formulations 9-11) are illustrated on Figure 9. The agglomerated particles were consist of bigger, irregularly shaped particles and smaller microspheres. The particles were relatively more spherical shaped than those obtained from inlet air temperatures of 150°C and 170°C. The surface of the particles were rough.

The scanning electron photomicrographs of spray dried diclofenac sodium with Eudragit® NE 30D at inlet air temperature of 210°C (Formulations 12-14) are presented in Figure 10. The shape of particles was spherical with different sizes. Some of the very small spheres were found attached to the large particles. The particles showed hollow but rough surfaces.

The scanning electron photomicrographs of spray dried diclofenac sodium with Eudragit® RS 30D in the polymer to drug ratio of 1:11 at inlet air temperature of 210°C (Formulation 15) are shown in Figure 11. The agglomerated particles include bigger irregularly shaped particles and smaller microspheres. The surface of some particles was shrunken with an orange peel texture and some of them were cracked.

The microscopic images of spray dried diclofenac sodium with Eudragit® RL 30D in the polymer to drug ratio of 1:11 at inlet air temperature of 210°C (Formulation 16) are represented in Figure 12. The particles were ball shaped with relatively small sizes. The surface of microballs were rough.

The microscopic views of spray dried diclofenac sodium with Eudragit® RS and RL 30D in the polymer to drug ratio of 0.5:0.5:11 at inlet air temperature of 210°C (Formulation 17) are shown in Figure 13. The overall shape of agglomerated particles were nearly spherical shape with different sizes. The surface had an orange peel texture.



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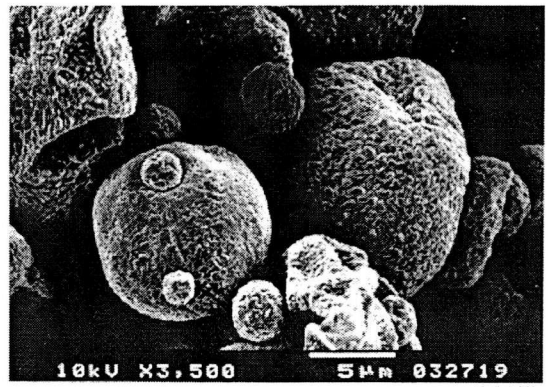
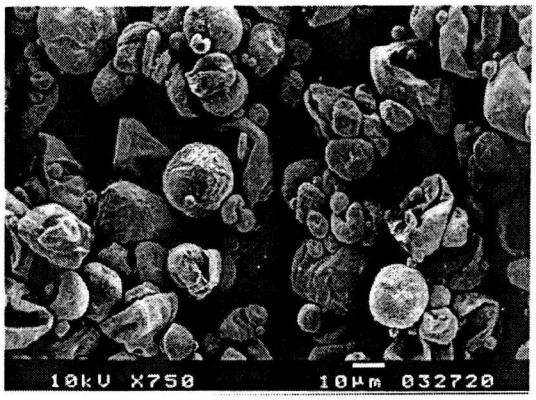
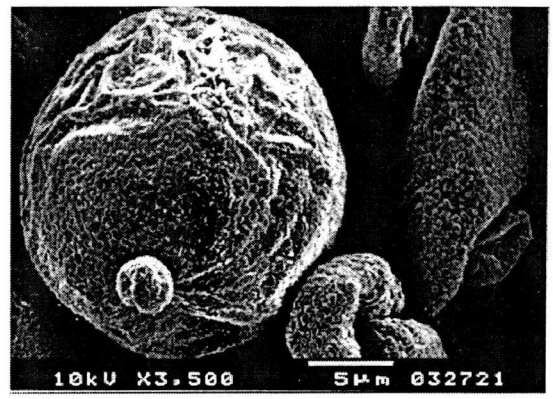


9.1 (B)



9.2 (A)



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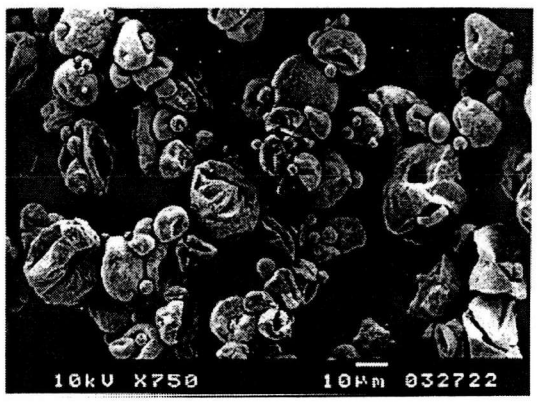

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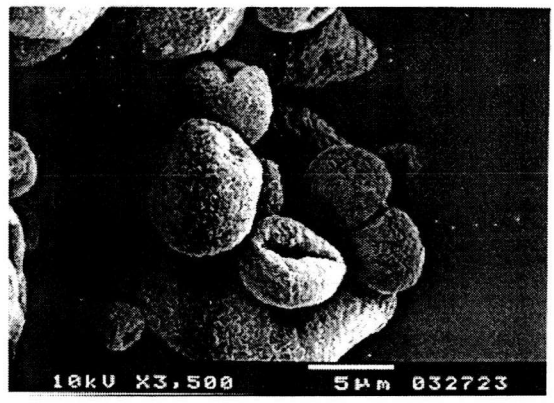
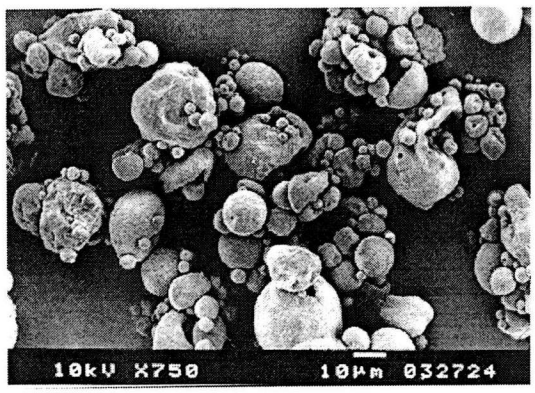


9.3 (B)

Figure 9 Scanning electron photomicrographs of spray-dried diclofenac sodium with Eudragit® NE 30D at inlet air temperature of 190°C (Formulations 9-11).
(9.1) NE 1:9, (9.2) NE 1:11, (9.3) NE 1:15
(A x 750, B x 3,500)



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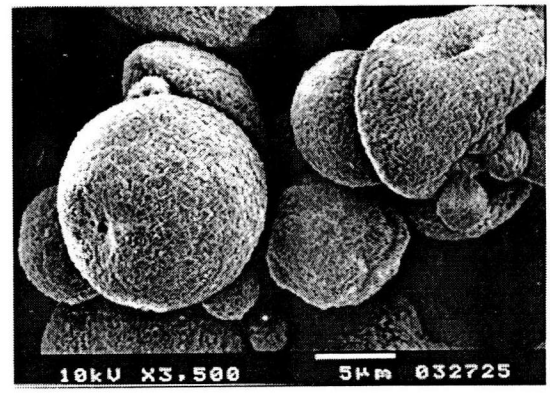

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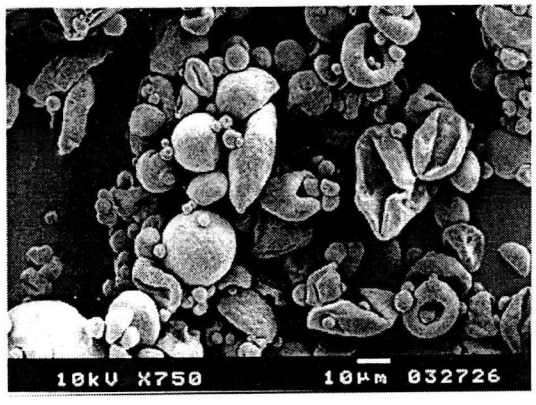

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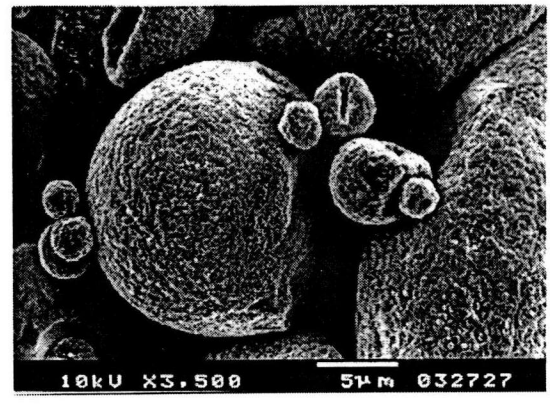

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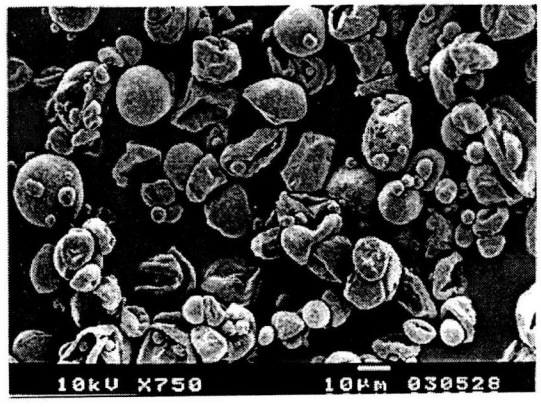

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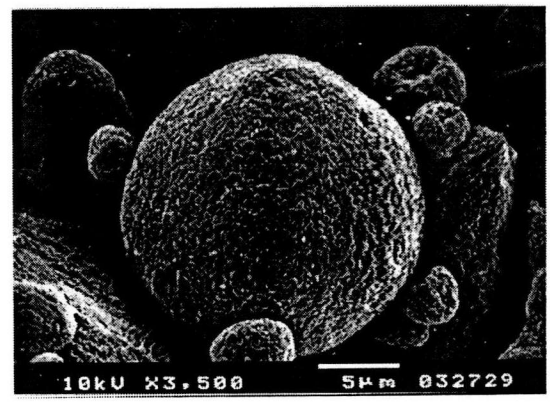

10.3 (B)

Figure 10 Scanning electron photomicrographs of spray-dried diclofenac sodium with Eudragit® NE 30D at inlet air temperature of 210°C (Formulations 12-14).
(10.1) NE 1:9, (10.2) NE 1:11, (10.3) NE 1:15
(A x 750, B x 3,500)

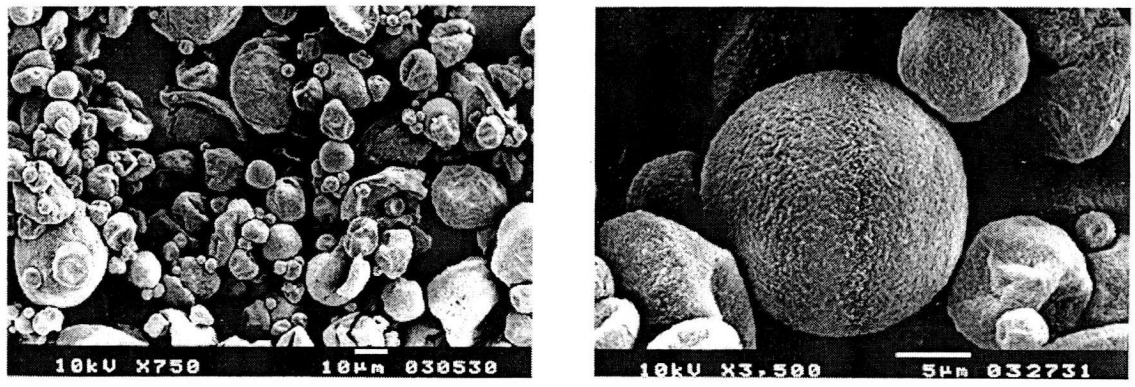

Figure 11 Scanning electron photomicrographs of spray-dried diclofenac sodium with Eudragit® RS 30D at inlet air temperature of 210°C (Formulation 15). (A x 750, B x 3,500)

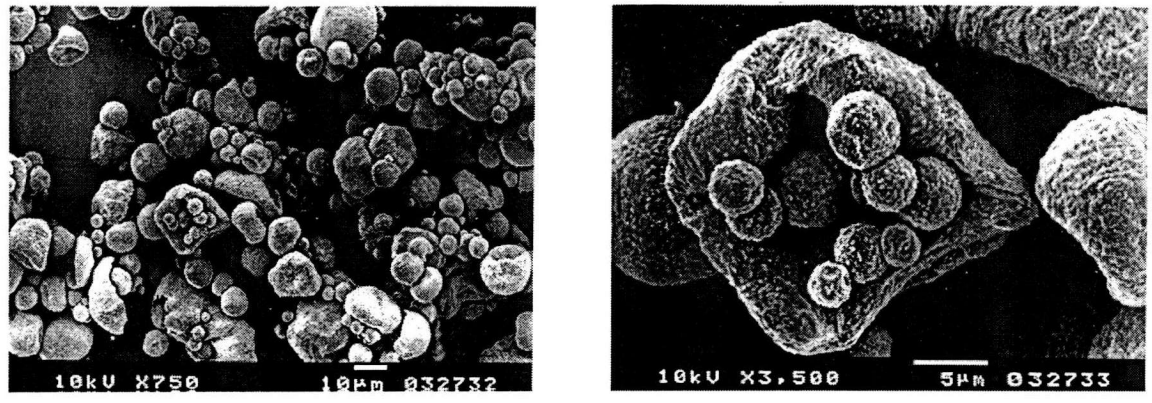

Figure 12 Scanning electron photomicrographs of spray-dried diclofenac sodium with Eudragit® RL 30D at inlet air temperature of 210°C (Formulation 16). (A x 750, B x 3,500)

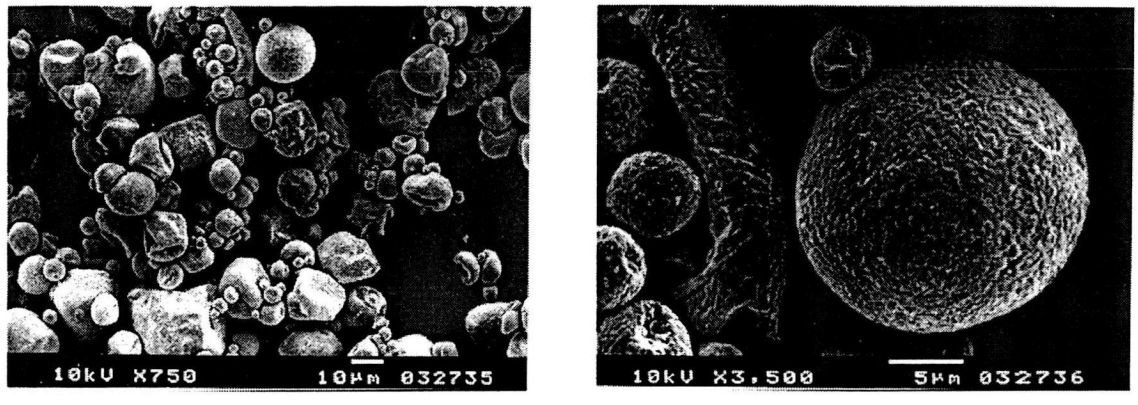

Figure 13 Scanning electron photomicrographs of spray-dried diclofenac sodium with Eudragit® RS and RL 30D at inlet air temperature of 210°C (Formulation 17). (A x 750, B x 3,500)

4.2 Angle of Repose

The angle of repose of spray-dried powder could not be determined. When the powder was filled to the top of the cylinder and then the cylinder was slowly lifted in a vertical direction, it was found that the powder did not flow out to form a conical heap on the base. The height and the radius of the cone could not be measured.

4.3 Particle Size Distribution

The particle size distributions of the spray dried powders are shown in Table 8. The particle size distributions were affected by process conditions such as inlet air temperature as illustrated in Figures 14-16. The size of particle appeared to increase when the inlet air temperature increased. At lower inlet air tempertures, the polymer to drug ratio had little effect to the particle size. The increment of polymer content gave higher percent of small particles as displayed in Figures 17-21.

Table 8 Particle size distribution of spray dried powders.

Formulation	Inlet Air Temperature (°C)	Polymer to Drug ratio	% Weight Retained on Sieve Size*					
			pan	106μm	150μm	180μm	250μm	425μm
1	150	NE 1: 9	1.38	18.31	71.13	4.41	2.43	1.57
2	150	NE 1: 11	0.84	1.42	3.64	86.42	5.71	1.96
3	150	NE 1: 15	1.00	1.30	3.48	82.12	10.52	1.58
4	170	NE 1: 4	0.96	5.06	81.14	8.39	2.30	2.15
5	170	NE 1: 6	0.70	1.04	5.56	77.35	12.67	2.67
6	170	NE 1: 9	0.60	1.40	2.34	69.38	23.96	2.30
7	170	NE 1: 11	0.98	0.42	1.48	67.69	26.02	3.14
8	170	NE 1: 15	1.20	0.87	2.27	51.55	41.48	2.61
9	190	NE 1: 9	0.86	0.52	1.69	39.15	55.21	2.58
10	190	NE 1: 11	0.99	0.73	2.48	50.15	42.85	2.79
11	190	NE 1: 15	0.88	0.88	2.18	55.88	33.32	6.86
12	210	NE 1: 9	1.80	0.92	1.20	16.22	57.11	23.64
13	210	NE 1: 11	0.76	0.76	1.42	11.86	60.99	24.22
14	210	NE 1: 15	1.12	1.04	1.58	13.25	64.29	18.13
15	210	RS 1: 11	0.85	0.32	1.17	9.24	56.44	31.98
16	210	RL 1: 11	0.90	0.42	1.28	9.66	36.78	50.95
17	210	RS:RL: DS 0.5 : 0.5 : 11	1.25	0.54	0.90	5.12	36.12	56.07

* Average from two determinations.

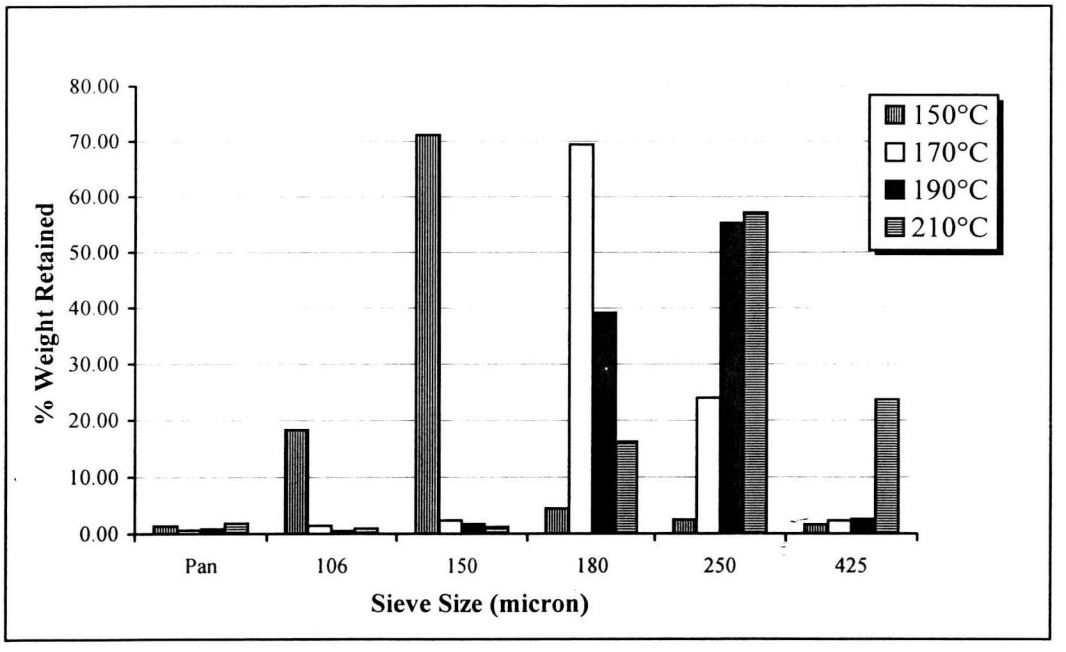

Figure 14 Particle size distributions of spray-dried diclofenac sodium with Eudragit® NE 30D (NE 1:9) at various inlet air temperatures.

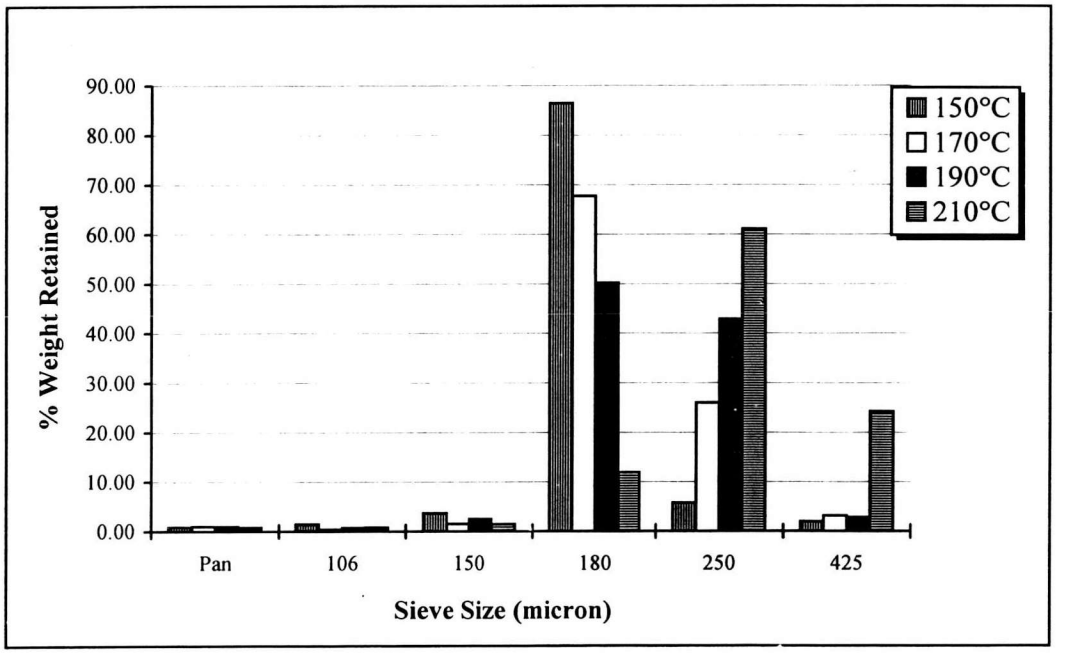

Figure 15 Particle size distributions of spray-dried diclofenac sodium with Eudragit® NE 30D (NE 1:11) at various inlet air temperatures.

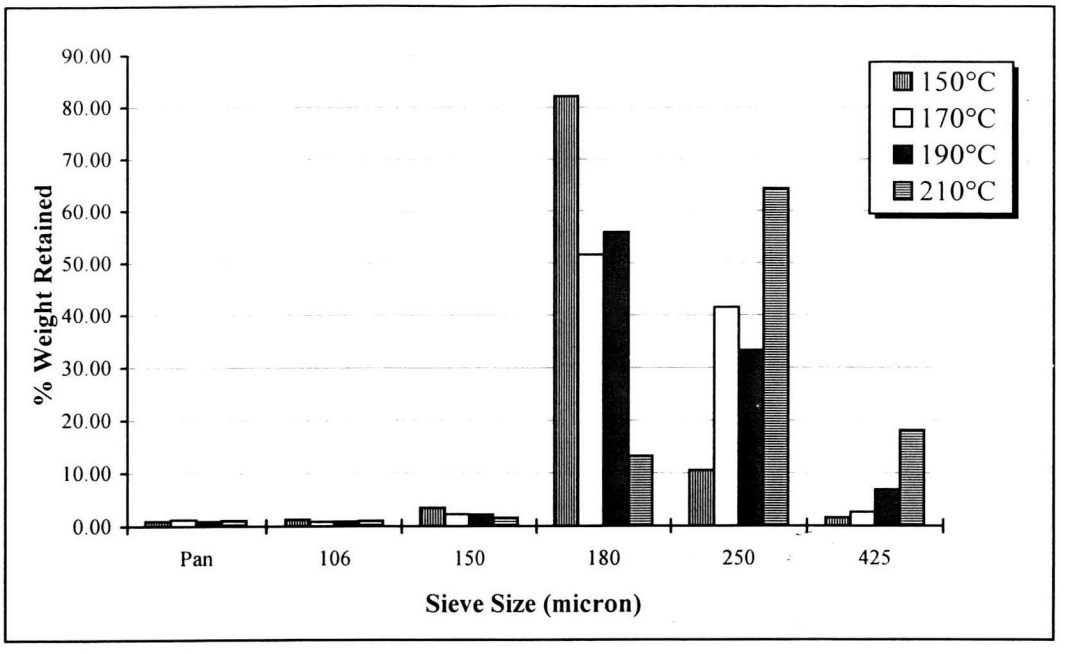

Figure 16 Particle size distributions of spray-dried diclofenac sodium with Eudragit® NE 30D (NE 1:15) at various inlet air temperatures.

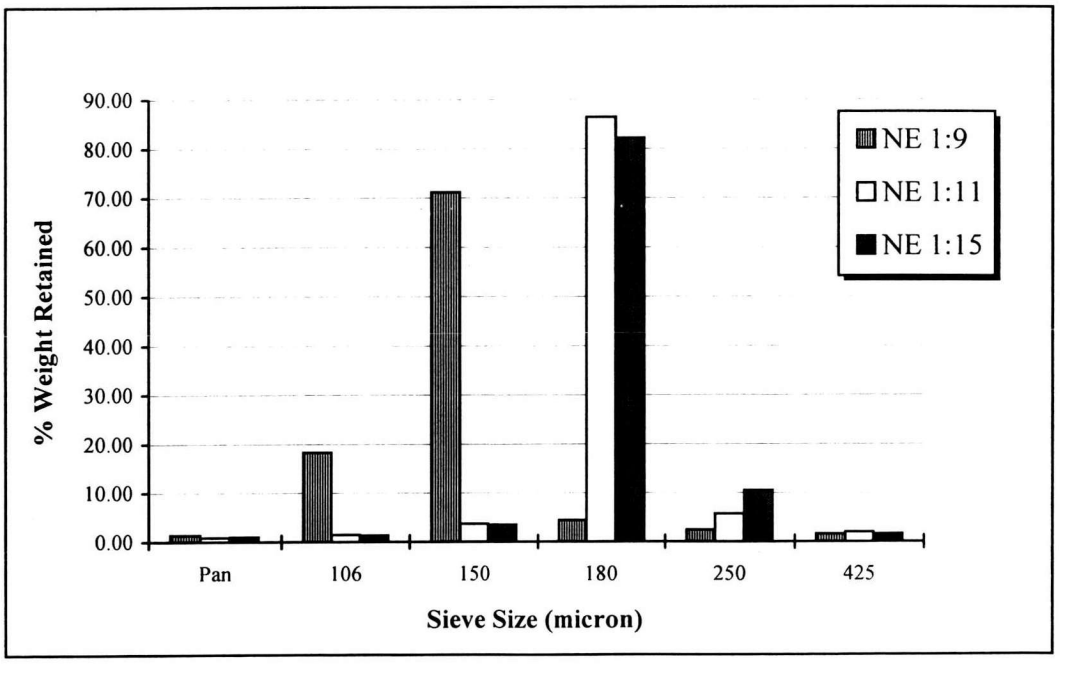

Figure 17 Particle size distributions of spray-dried diclofenac sodium with Eudragit® NE 30D at various polymer to drug ratios (inlet air temperature of 150°C).

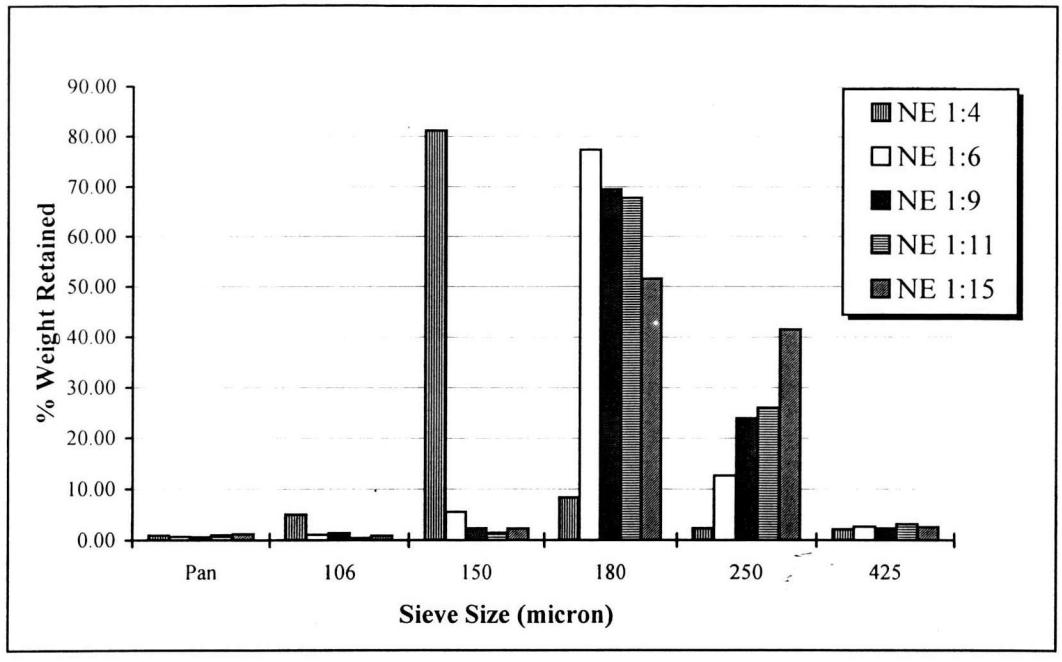

Figure 18 Particle size distributions of spray-dried diclofenac sodium with Eudragit® NE 30D at various polymer to drug ratios (inlet air temperature of 170°C).

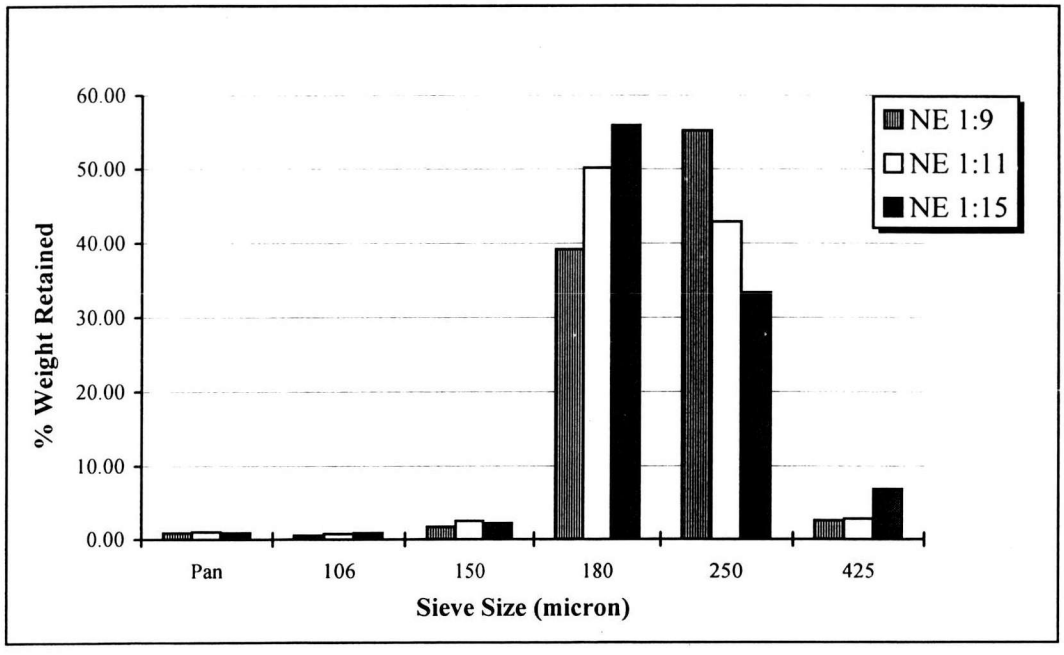

Figure 19 Particle size distributions of spray-dried diclofenac sodium with Eudragit® NE 30D at various polymer to drug ratios (inlet air temperature of 190°C).

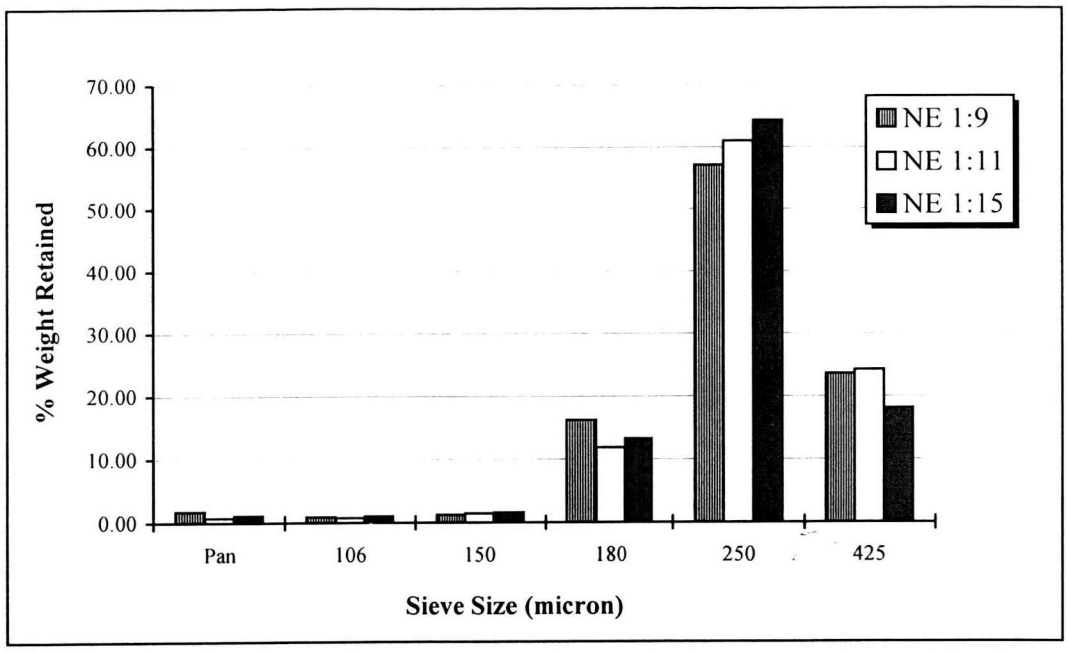

Figure 20 Particle size distributions of spray-dried diclofenac sodium with Eudragit® NE 30D at various polymer to drug ratios (inlet air temperature of 210°C).

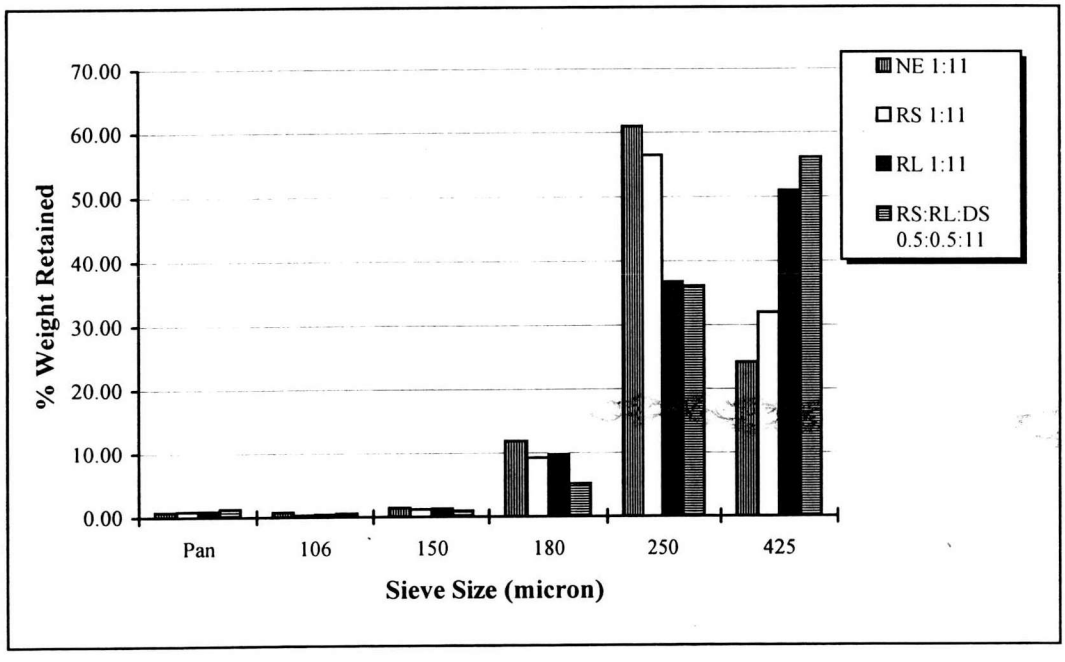

Figure 21 Particle size distributions of spray-dried diclofenac sodium with various polymers (inlet air temperature of 210°C).

4.4 Moisture Content

The moisture content of spray-dried powders prepared from various formulations are shown in Table 9. The product obtained from a higher drying temperature had a lower moisture content. The polymer to drug ratio had an insignificant effect on the moisture content of the powder.

Table 9 The moisture content of spray-dried powders prepared from various formulations.

Inlet Air Temperature (°C)	Formulation	% Moisture Content (SD)*
150	1	1.00 (0.05)
	2	1.06 (0.25)
	3	0.98 (0.28)
170	4	0.61 (0.06)
	5	0.67 (0.06)
	6	0.65 (0.07)
	7	0.49 (0.06)
	8	0.66 (0.16)
190	9	0.45 (0.14)
	10	0.36 (0.02)
	11	0.38 (0.02)
210	12	0.46 (0.06)
	13	0.43 (0.10)
	14	0.38 (0.10)
	15	0.40 (0.40)
	16	0.47 (0.01)
	17	0.41 (0.04)

* Standard deviation from three determinations.

4.5 Porosity Determination

The surface area and the total pore volume of spray-dried particles were measured by BET method. The specific surface area and the total pore volume of spray-dried diclofenac sodium with polymer in different drug to polymer ratios and different inlet air temperature are displayed in Table 10.

Table 10 The specific surface area and the total pore volume of spray-dried powders.

Formulation	Inlet Air Temperature (°C)	Polymer to Drug Ratio	Specific Surface Area (m^2/g)	Total Pore Volume (cm^3/g)
1	150	NE 1: 9	2.69 ± 0.02	0.62
6	170	NE 1: 9	1.83 ± 0.02	0.42
9	190	NE 1: 9	1.64 ± 0.04	0.38
12	210	NE 1: 9	1.52 ± 0.01	0.35
13	210	NE 1: 11	1.51 ± 0.01	0.35
14	210	NE 1: 15	1.78 ± 0.01	0.41
15	210	RS 1: 11	1.88 ± 0.03	0.43
17	210	RS: RL: DS 0.5 : 0.5 : 11	1.32 ± 0.02	0.30

The formulation that contained the same polymer to drug ratio and prepared at higher inlet air temperature had a lower specific surface area and also lower total pore volume (Formulations 1, 6, 9, and 12). No difference of the specific surface area and the total pore volume between the formulation that contained the polymer to drug ratio of 1:9 and 1:11 and prepared at inlet air temperature of 210°C (Formulations 12 and 13), while at the same inlet air temperature, the ratio of 1:15 (Formulation 14) gave the higher specific surface area and also total pore volume than those of two formulations.

The spray-dried powders that contained Eudragit® RS had the specific surface area and total pore volume higher than that contained Eudragit® NE at the same polymer to drug ratio.

4.6 IR Spectra

The IR spectra of diclofenac sodium are shown in Figure 22. The principal peaks were observed at wavenumbers 756, 775, 1286, 1308, 1504 and 1572 cm^{-1} (Moffat et al., 1986). The peaks at 756 and 775 cm^{-1} were resulted from C-H out of

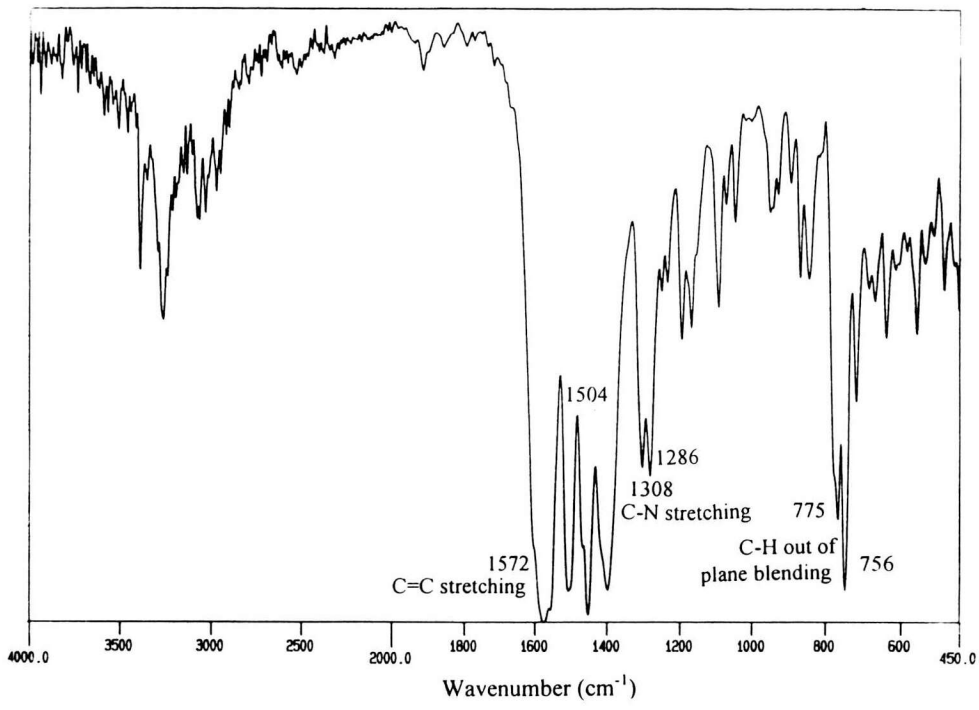

Figure 22 IR spectra of diclofenac sodium.

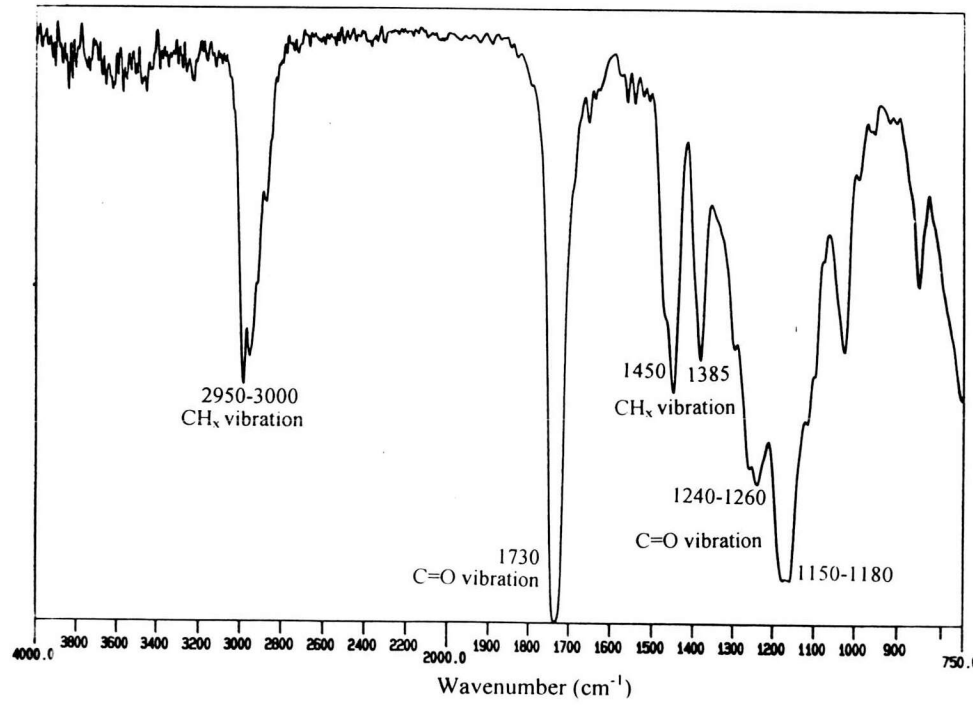

Figure 23 IR spectra of Eudragit® NE 30D.

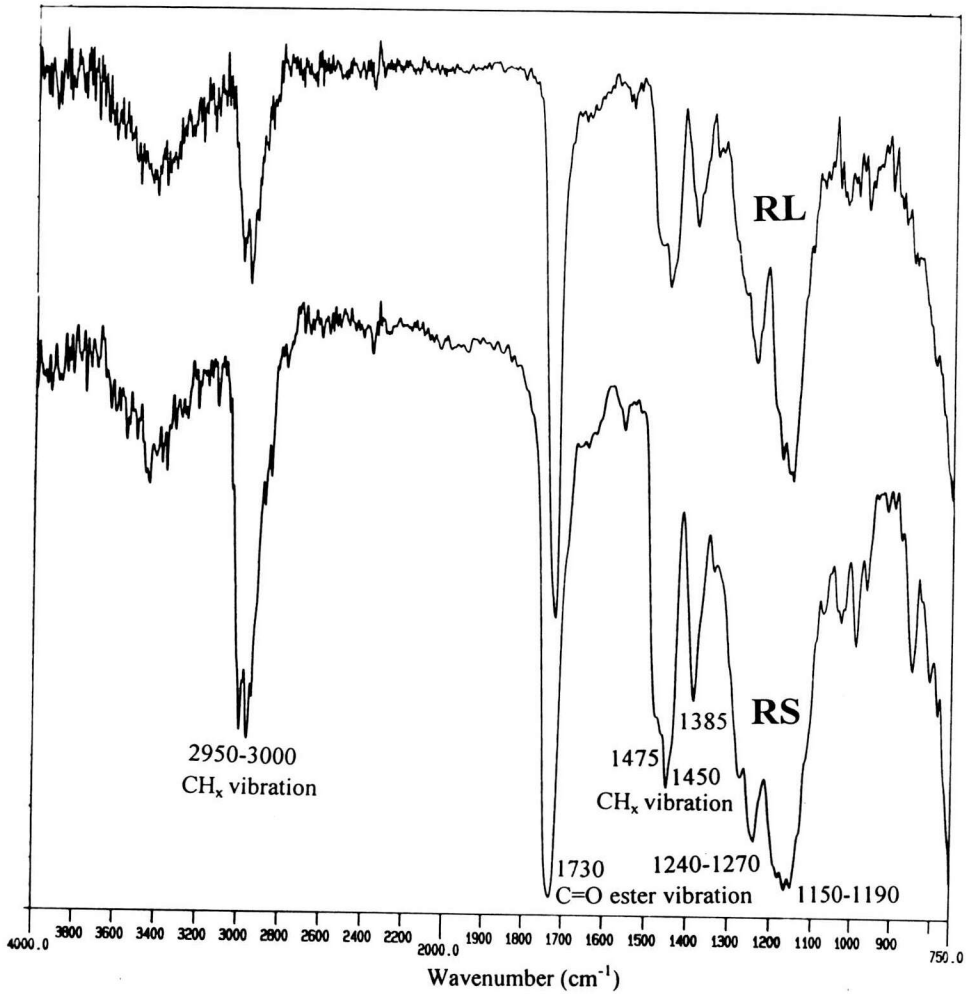

Figure 24 IR spectra of Eudragit® RS and RL 30D.

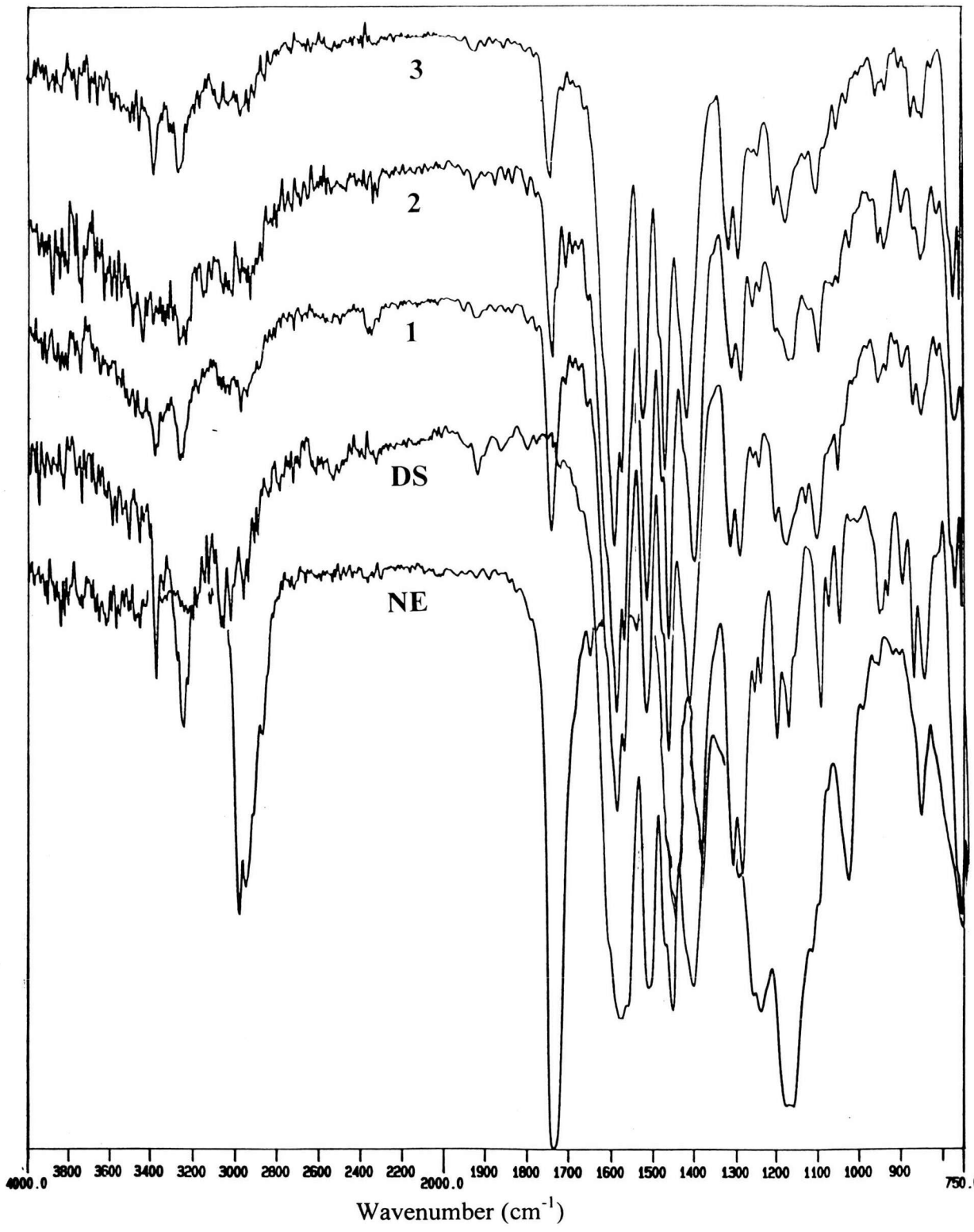

Figure 25 IR spectra of spray-dried diclofenac sodium with Eudragit® NE 30D at inlet air temperature of 150°C (Formulations 1-3).
(1 = NE 1:9, 2 = NE 1:11, 3 = NE 1:15)

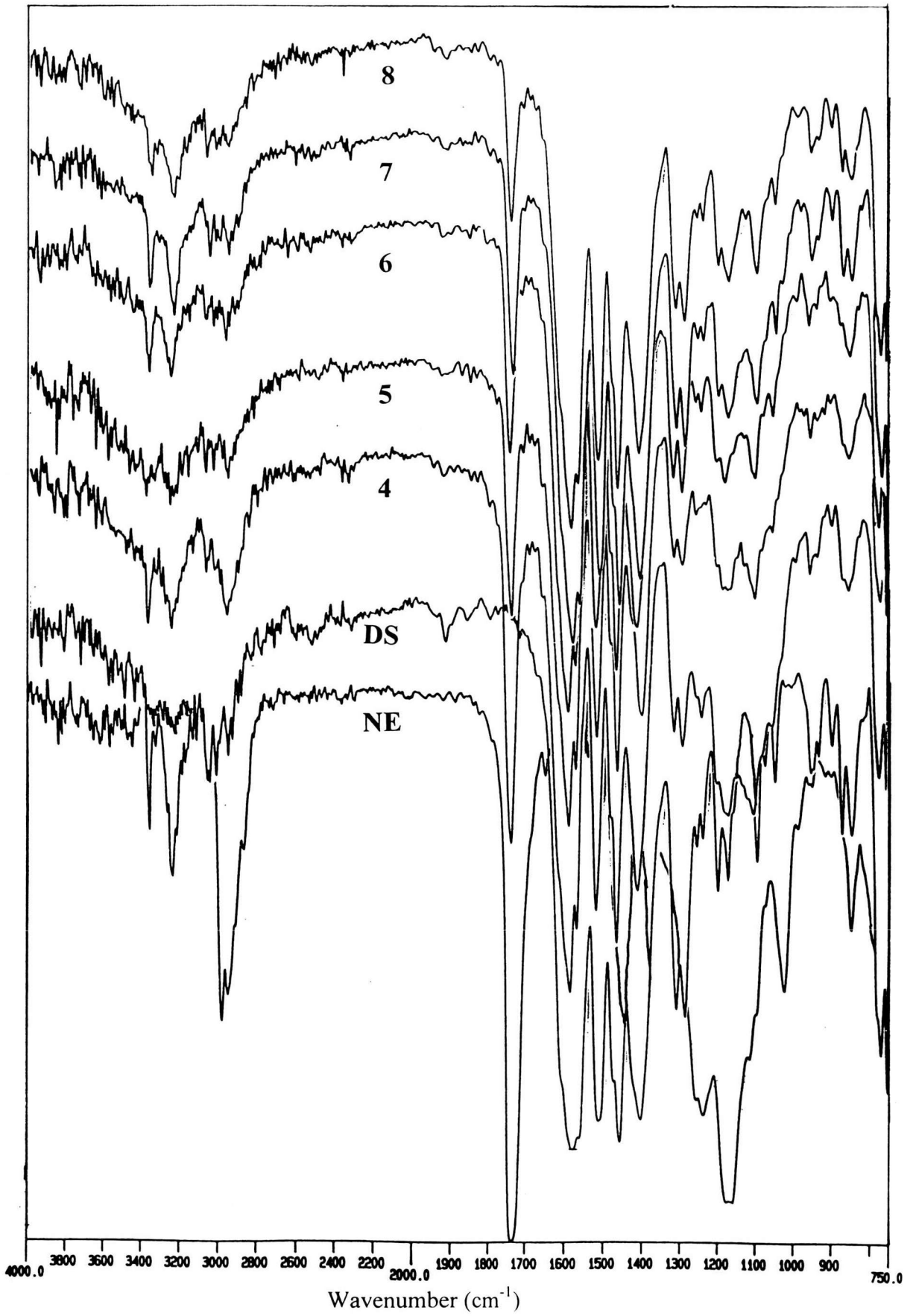

Figure 26 IR spectra of spray-dried diclofenac sodium with Eudragit® NE 30D at inlet air temperature of 170°C (Formulations 4-8).
(4 = NE 1:4, 5 = NE 1:6, 6 = NE 1:9, 7 = NE 1:11, 8 = NE 1:15)

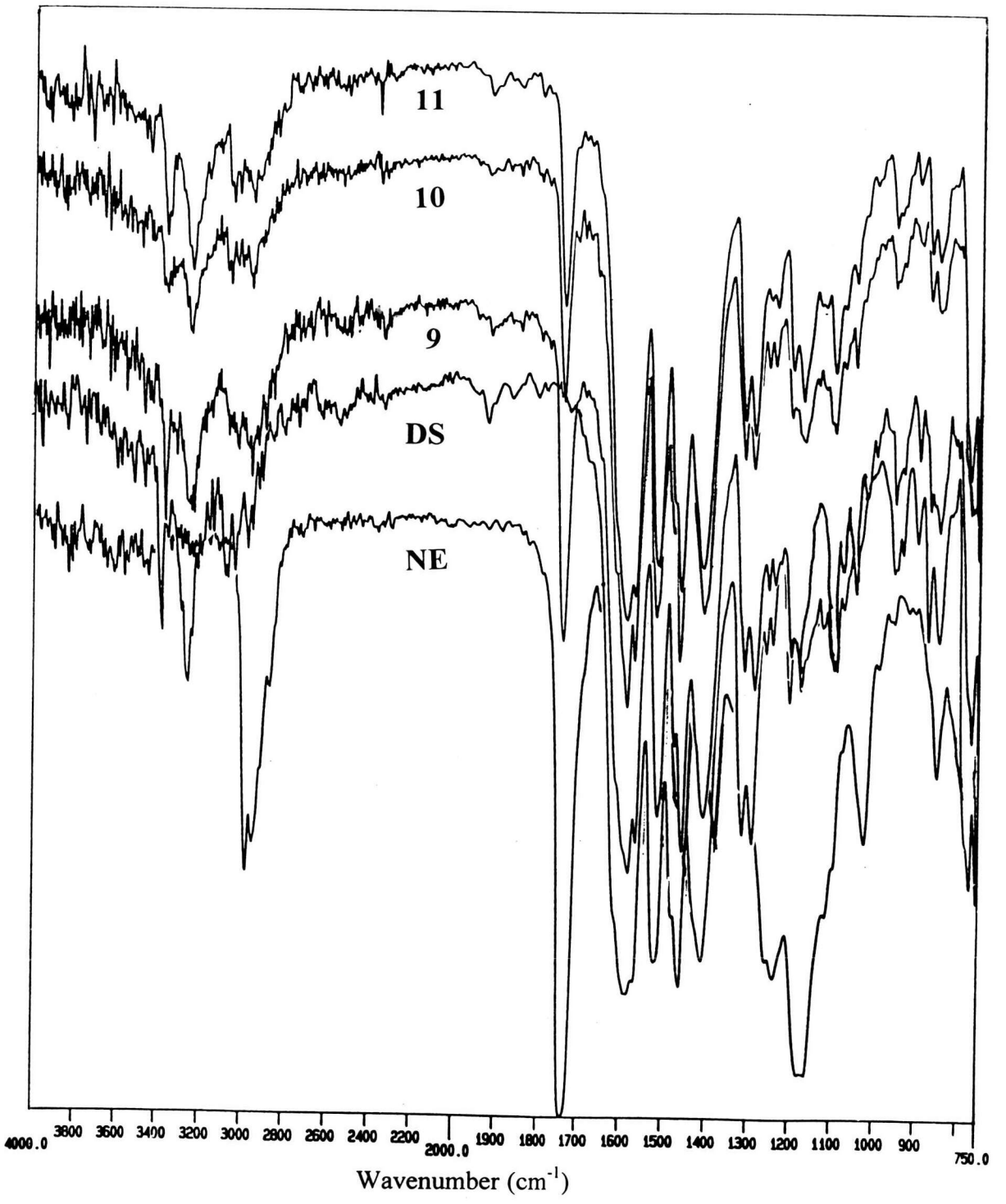

Figure 27 IR spectra of spray-dried diclofenac sodium with Eudragit® NE 30D at inlet air temperature of 190°C (Formulations 9-11).

(9 = NE 1:9, 10 = NE 1:11, 11 = NE 1:15)

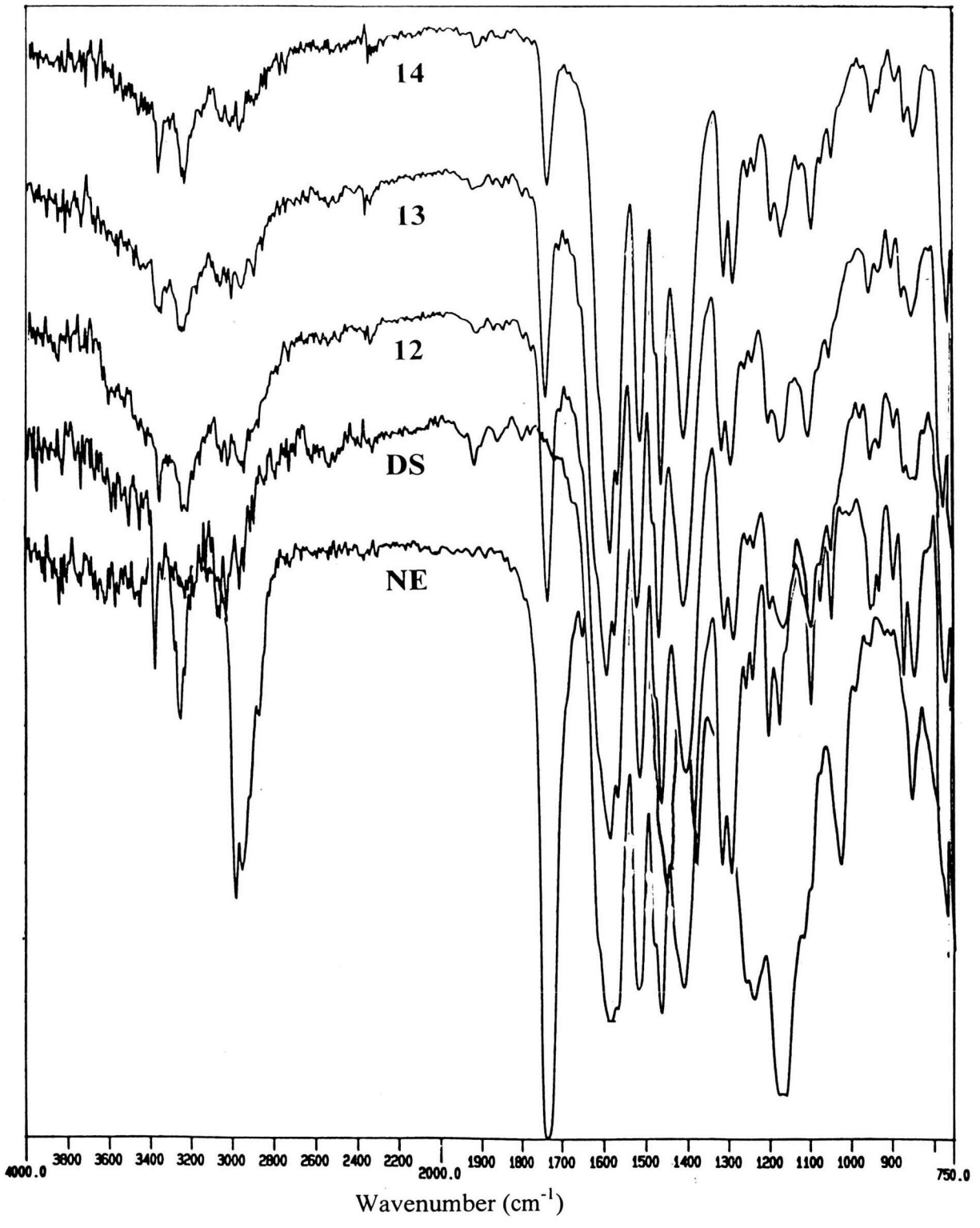

Figure 28 IR spectra of spray-dried diclofenac sodium with Eudragit® NE 30D at inlet air temperature of 210°C (Formulations 12-14).
(12 = NE 1:9, 13 = NE 1:11, 14 = NE 1:15)

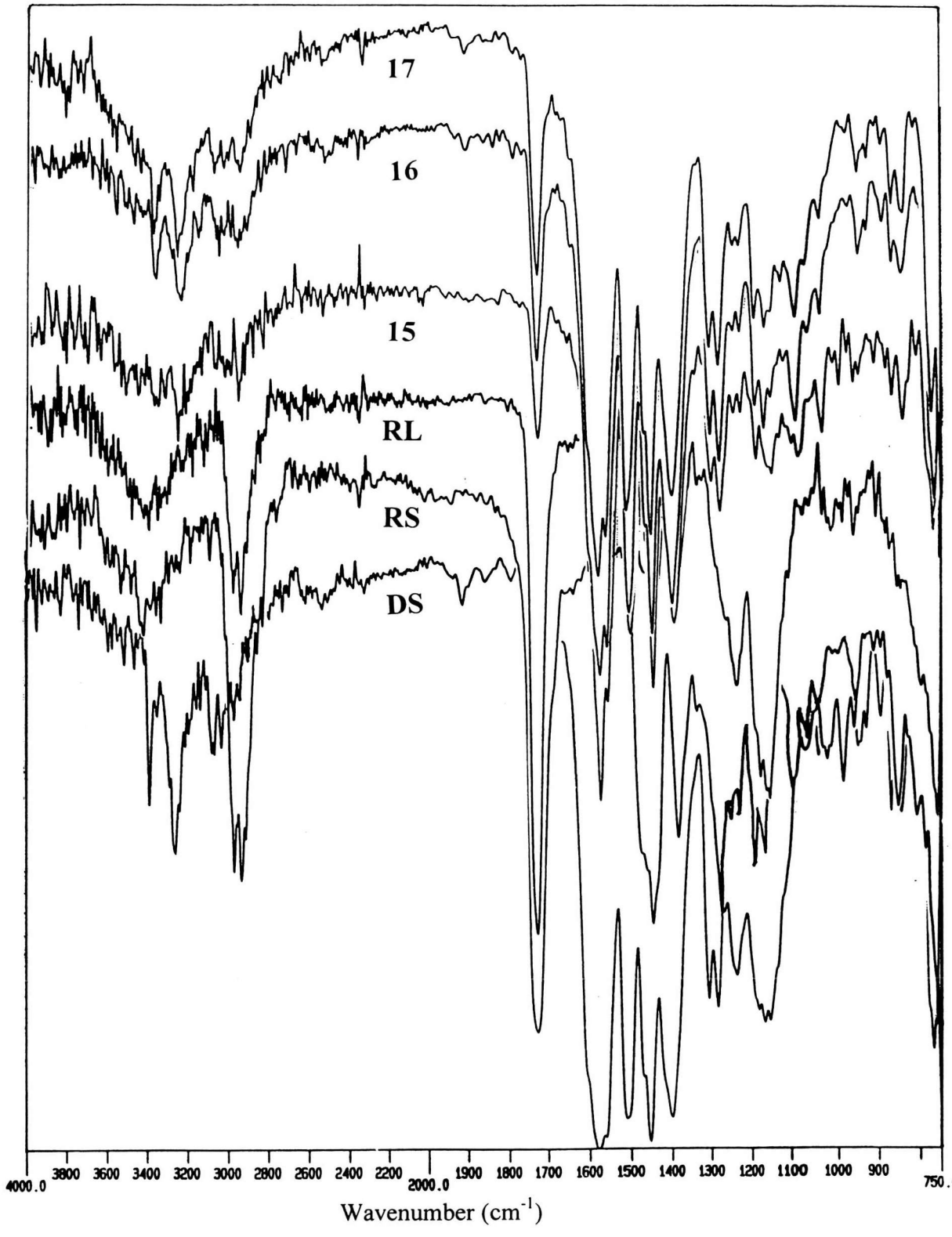

Figure 29 IR spectra of spray-dried diclofenac sodium with Eudragit® RS 30D and RL 30D at inlet air temperature of 210°C (Formulations 15-17).

(15 = RS 1:11, 16 = RL 1:11, 17 = RS:RL:DS, 0.5:0.5:11)

plane blending. The IR absorption bands at 1286 and 1308 cm^{-1} were resulted from C-N stretching. The peaks at 1504 and 1572 cm^{-1} were resulted from C=C stretching.

The IR spectra of Eudragit® NE 30D are depicted in Figure 23. This figure shows the characteristic bands for the C=O vibration of the ester groups at 1730 cm^{-1}, further ester vibrations at 1150-1180 and 1240-1260 cm^{-1} and various CH_x vibrations at 1385, 1450 and 2950-3000 cm^{-1} could also be seen.

Figure 24 exhibits the IR spectra of Eudragit® RS 30D and RL 30D. The characteristic bands of the ester groups are shown at 1150-1190 and 1240-1270 cm^{-1} and the C=O ester vibration at 1730 cm^{-1}. The IR absorption spectra at 1385, 1450, 1475 and 2950-3000 cm^{-1} resulted from CH_x vibrations.

The IR spectra of spray-dried diclofenac sodium with Eudragit® NE 30D at the different polymer to drug ratio that prepared from various inlet air temperatures are illustrated in Figures 25-28. The spray-dried powders showed the spectra of diclofenac sodium and Eudragit® NE 30D, and also revealed that the eminent peaks of spectra of both diclofenac sodium and Eudragit® NE 30D did not shift. These indicated that the interaction between diclofenac sodium and Eudragit® NE 30D was scarce.

Figure 29 depicts the IR spectra of spray-dried diclofenac sodium with Eudragit® RS and RL 30D and with combination of these polymers. The characteristic bands of both diclofenac sodium and polymers (Eudragit® RS 30D or Eudragit® RL 30D or Eudragit® RS and RL 30D) are shown. These reveal that no interaction between drug and polymer occurred.

4.7 X-ray Powder Diffraction

The X-ray diffraction patterns of diclofenac sodium and spray-dried diclofenac sodium with Eudragit® NE 30D at the ratio of 1:9 polymer to drug in various inlet air

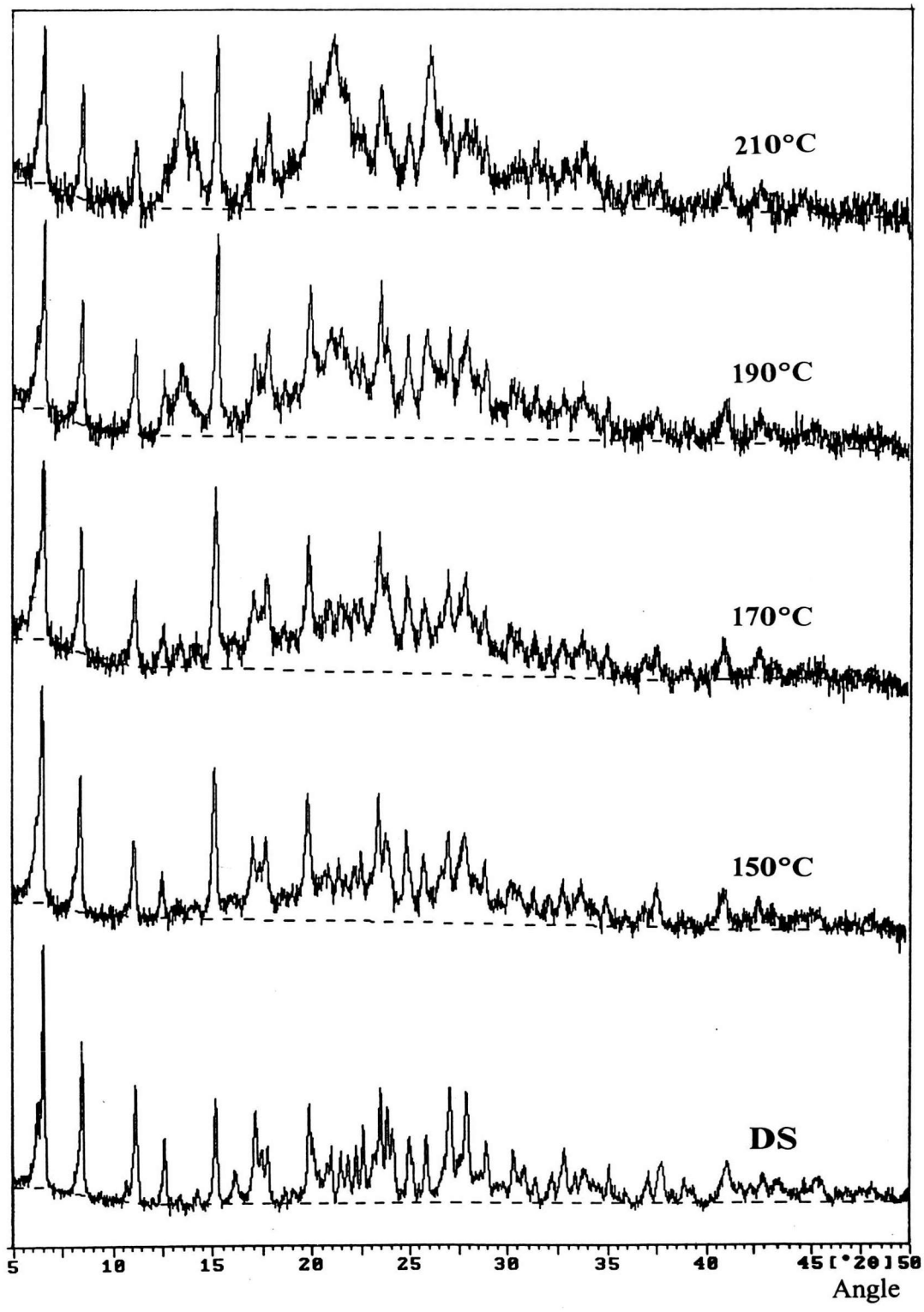

Figure 30 X-ray diffractograms of diclofenac sodium and of spray-dried diclofenac sodium with Eudragit®NE 30D (NE 1:9) prepared at various inlet air temperatures.

temperatures are shown in Figure 30. The diffraction of pure diclofenac sodium showed sharp peaks at 6.7°, 8.6° and 11.2° and also showed the heap of small peaks at the diffraction angle between 20-30°. It was observed that the intensities of the diffraction peaks of spray-dried diclofenac sodium and Eudragit® NE 30D were weaker than that of diclofenac sodium, particularly, the peaks at the diffraction angle between 20-30°. However, the characteristic peaks of diclofenac sodium at the diffraction angle of 6.7°, 8.6° and 11.2° were detected. The reduced intensities of the spray-dried product peaks indicated that some crystals in the product converted to an amorphous form. With increasing inlet air temperature, the amorphous form of diclofenac sodium increased.

4.8 Differential Scanning Calorimetry

The DSC thermograms of pure diclofenac sodium and spray-dried diclofenac sodium with Eudragit® NE 30D at the ratio of 1:9 polymer to drug in various inlet air temperatures are revealed in Figure 31. The DSC thermogram of pure diclofenac sodium gave an exotherm at 270°C, followed by an endotherm at 297°C, while spray-dried diclofenac sodium with Eudragit® NE 30D also had an exothermic and endothermic peak. The DSC peak temperatures of spray-dried products are shown in Table 11. In addition, a broad endothermic peak at 100-150°C was observed in spray-dried powder prepared at lower inlet air temperature. However, this peak seemed to be broader as the inlet air temperature increased.

Table 11 DSC peak temperatures of diclofenac sodium and spray-dried diclofenac sodium with Eudragit® NE 30D at various inlet air temperatures.

Formulation	Polymer to Drug Ratio	Inlet Air Temperature (°C)	Temperature of Exothermic Peak (°C)	Temperature of Endothermic Peak (°C)
DS	-	-	270	297
1	NE 1: 9	150	250	274
6	NE 1: 9	170	248	273.5
9	NE 1: 9	190	248	273.9
12	NE 1: 9	210	248	274.6

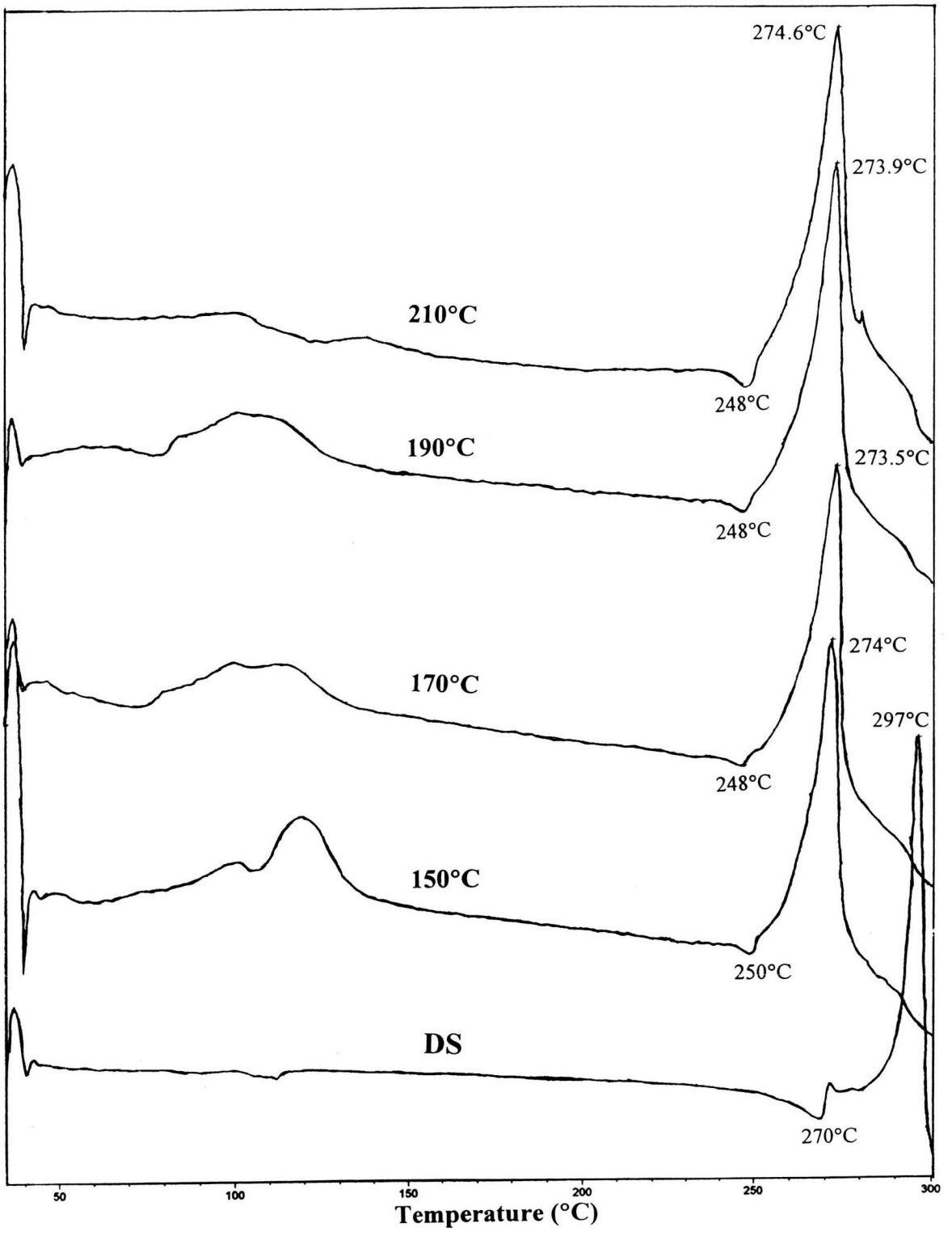

Figure 31 DSC thermograms of diclofenac sodium and of spray-dried diclofenac sodium with Eudragit® NE 30D (NE 1:9) prepared at various inlet air temperatures.

5. Dissolution Study

5.1 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 the microparticles. The dissolution and release rate data of each formulation are described in Tables 17-23 (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 the drug (see data in Tables 24-30, Appendix B). The rate, then was plotted with the average time interval. It was shown that the rate of release decreased with time.

Pure diclofenac sodium and spray-dried diclofenac sodium with polymer from every formulation that filled into capsules were evaluated in 2 dissolution systems, pH-change and phosphate buffer pH 6.8 systems. In pH-change system, these capsules were tested in acid stage (0.1 N HCl, pH 1.2) for 2 hours, the percentage of drug release from all formulations were less than 3.5 %. Then the pH of dissolution medium was adjusted to 6.8, the capsules were continuously tested until 24 hours. For phosphate buffer pH 6.8 system, pH of dissolution medium was 6.8 throughout the dissolution test, 24 hours. More than 70 % of drug released from the capsules in the first 2 hours.

5.1.1 The Blank Diclofenac Sodium Capsules

The drug release data of pure diclofenac sodium in 2 dissolution systems are listed in Table 17 (Appendix B) and the drug release profiles are shown in Figures 32 and 34. The release of diclofenac sodium was affected by the dissolution medium.

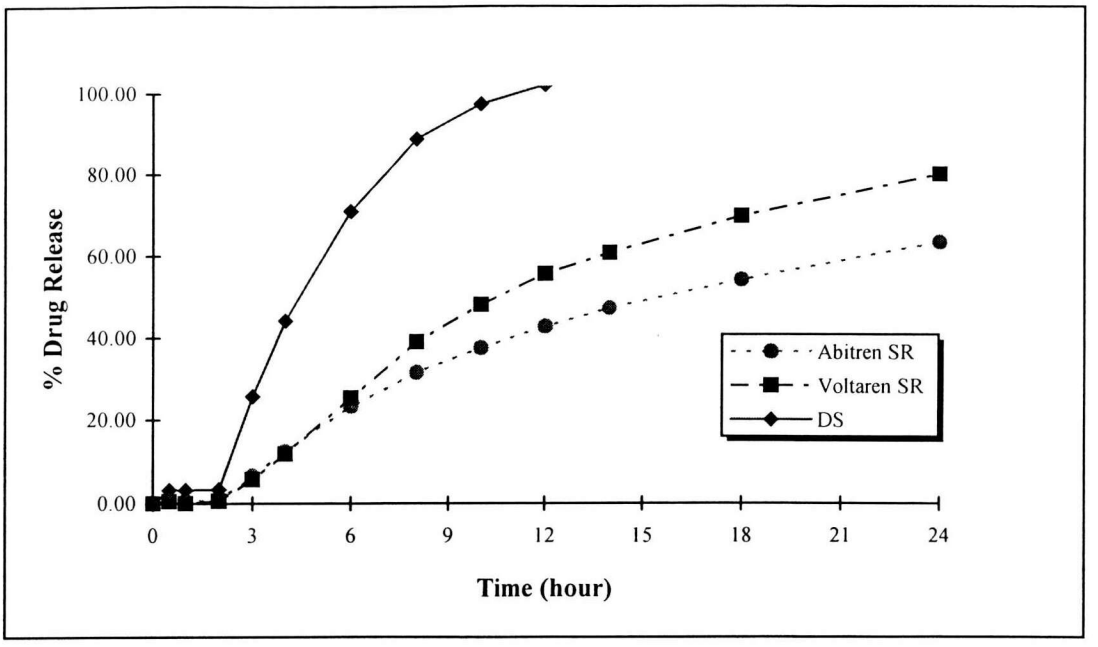

Figure 32 The release profiles of diclofenac sodium in pH-change system.

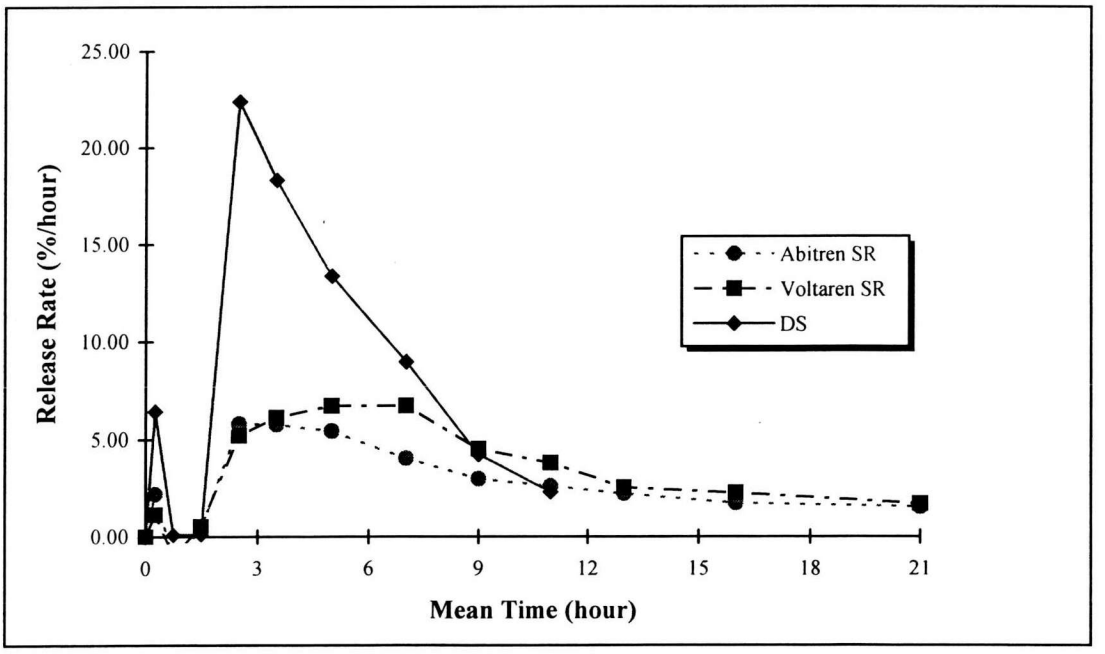

Figure 33 The release rate profiles of diclofenac sodium in pH-change system.

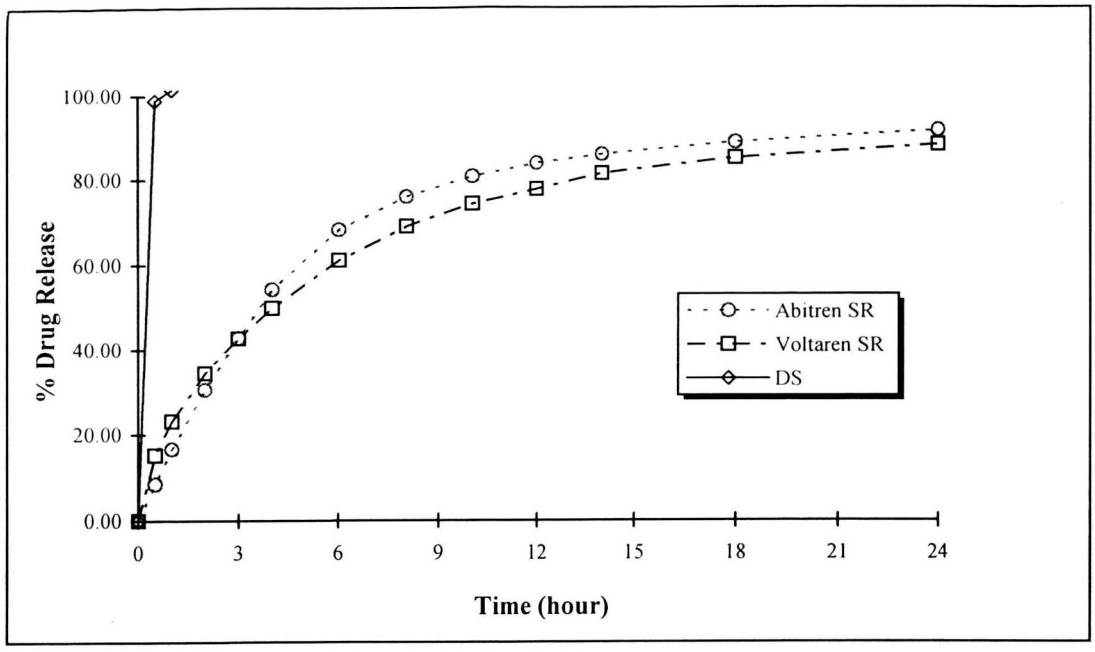

Figure 34 The release profiles of diclofenac sodium in phosphate buffer pH 6.8 system.

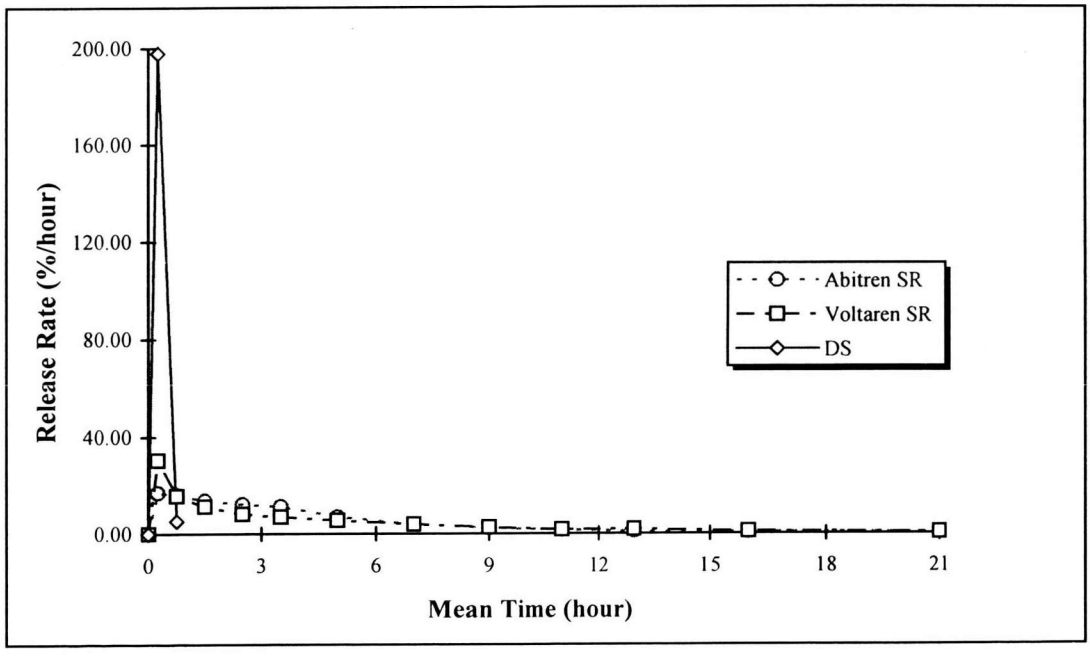

Figure 35 The release rate profiles of diclofenac sodium in phosphate buffer pH 6.8 system.

In pH-change system, the percentage of diclofenac sodium release in the first 2 hours (0.1 N HCl) was 3% and it was completely dissolved within 12 hours. Whereas, in phosphate buffer pH 6.8 system, it was completely dissolved within the first hour. The release rate profiles of diclofenac sodium in 2 dissolution systems are illustrated in Figures 33 and 35. The release rate of diclofenac sodium in phosphate buffer pH 6.8 was faster than in pH-change system. This result indicated that diclofenac sodium was more soluble in phosphate buffer pH 6.8 than in 0.1 N HCl.

5.1.2 The Commercial Products

The commercial products used were Abitren®SR and Voltaren®SR (as 100 mg. tablet). The dissolution data are also shown in Table 17 (Appendix B) and the difference of drug release profiles in both pH-change and phosphate buffer pH 6.8 system were detected. The release of diclofenac sodium from Abitren®SR and Voltaren®SR were affected by dissolution medium as illustrated in Figures 32 and 34. In pH-change system, the percentage of drug release from both Abitren®SR and Voltaren®SR at the first 2 hours (acid stage) were less than 1%. Whereas, the percentage of drug release at the first 2 hours were more than 30% in phosphate buffer pH 6.8 system. Faster dissolution was obtained in phosphate buffer pH 6.8 system. However, the controlled release action of these commercial products were obtained from both dissolution systems. The release rate of these tablets decreased as the time increased as shown in Figures 35 and 35. After the drug was released for 24 hours, the polymer keeping the original shape of tablet remained undissolved.

5.1.3 Effect of Formulation Modification

a) The Formulations 1-3 microparticles prepared at inlet temperature of 150°C

The dissolution profiles of diclofenac sodium from spray-dried microparticles with various Eudragit®NE 30D ratios in pH-change and in phosphate buffer pH 6.8

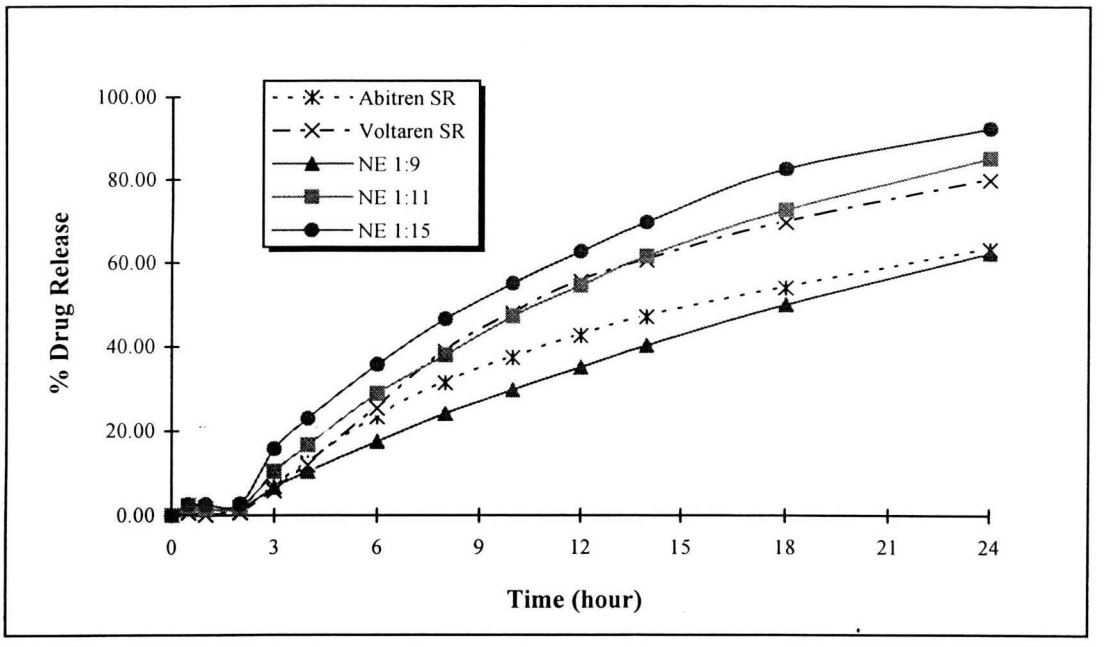

Figure 36 The release profiles of spray-dried diclofenac sodium with Eudragit® NE 30D prepared at inlet air temperature of 150°C in pH-change systems.

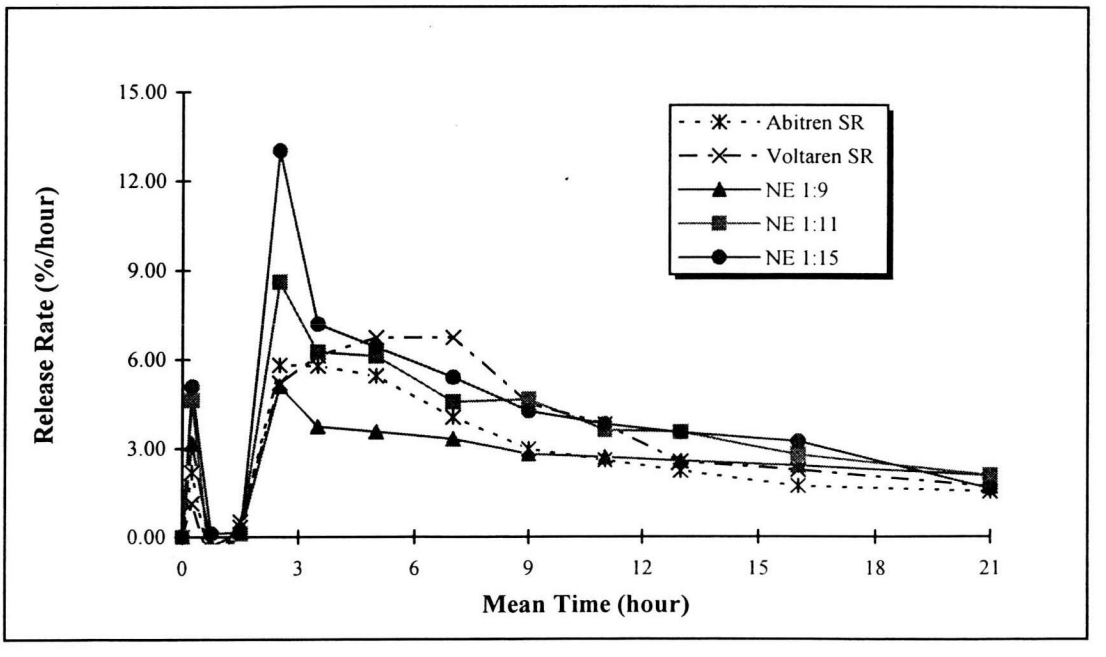

Figure 37 The release rate profiles of spray-dried diclofenac sodium with Eudragit®NE 30D prepared at inlet air temperature of 150°C in pH-change system.

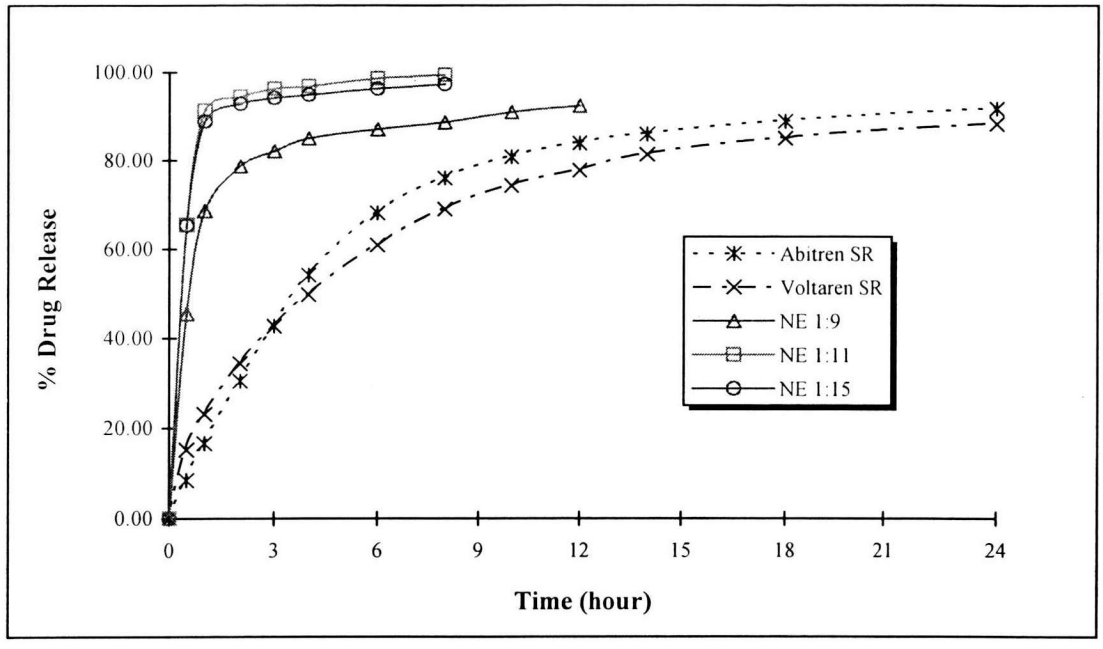

Figure 38 The release profiles of spray-dried diclofenac sodium with Eudragit® NE 30D prepared at inlet air temperature of 150°C in buffer pH 6.8 systems.

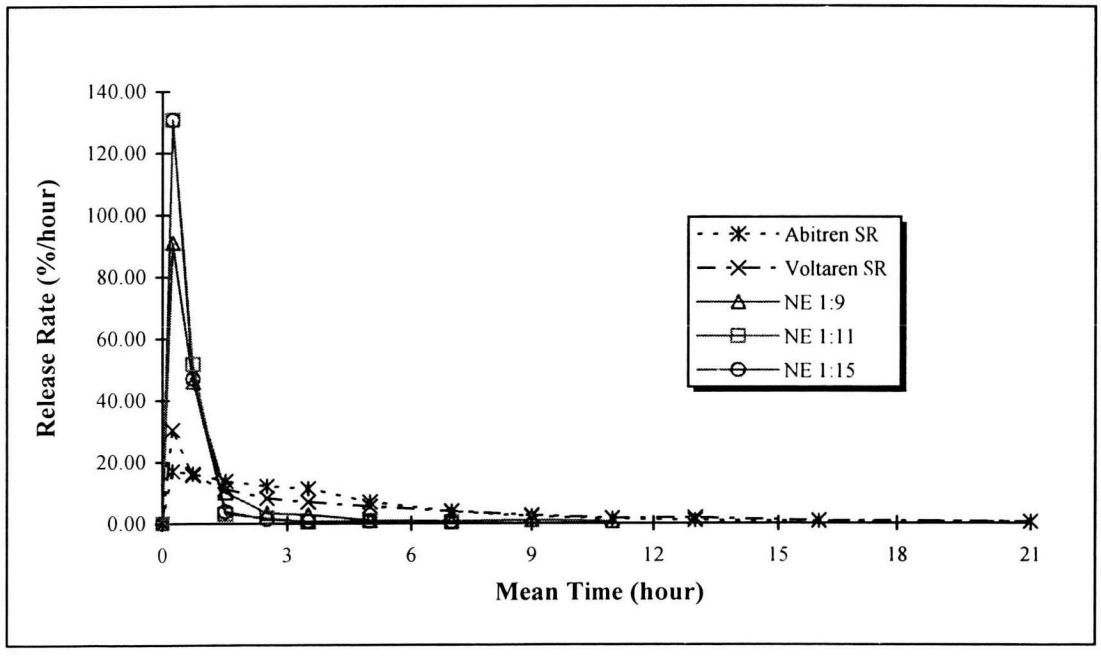

Figure 39 The release rate profiles of spray-dried diclofenac sodium with Eudragit®NE 30D prepared at inlet air temperature of 150°C in buffer pH 6.8 system.

systems are shown in Figures 36 and 37, respectively (Table 18, Appendix B). Each point represents the average value obtained from three determinations at the given sampling time. The release rate was decreased with time as shown in Figures 37 and 39. The release pattern was strongly dependent of pH of the dissolution medium.

In pH-change system, at the first 2 hours (acid stage), the percentage of drug release from these formulations was less than 3%. When the pH was raised to 6.8, by the addition of the phosphate buffer, the amount of drug release was increased. Increasing the amount of polymer, resulted in a corresponding decrease of the dissolution rate. The percentage of diclofenac sodium release at 24 hours were increased from 62.37% to 85.20% and 92.44% when the proportions of polymer in the formulations were decreased from the polymer to drug ratio of 1:9 to 1:11 and 1:15, respectively. After the drug was released in 24 hours, the polymer matrix remained undissolved. The release of drug was controlled until 24 hours.

In phosphate buffer pH 6.8 system, the initial rapid release of drug was observed. More than 70% of drug in these formulations released within the first 2 hours. No capability to control the release of drug from microparticles in this system.

b) The Formulations 4-8 microparticles prepared at inlet temperature of 170°C

The drug release profiles of diclofenac sodium from spray-dried microparticles of diclofenac sodium with various Eudragit®NE 30D ratios in both pH-change and phosphate buffer pH 6.8 systems were shown in Figures 40 and 42, respectively (Tables 19-20, Appendix B). The release rate in phosphate buffer pH 6.8 was higher than in pH-change system as shown in Figures 41 and 43. The release patterns of these products and of the commercial products, Abitren®SR and Voltaren®SR, seemed to be similar.

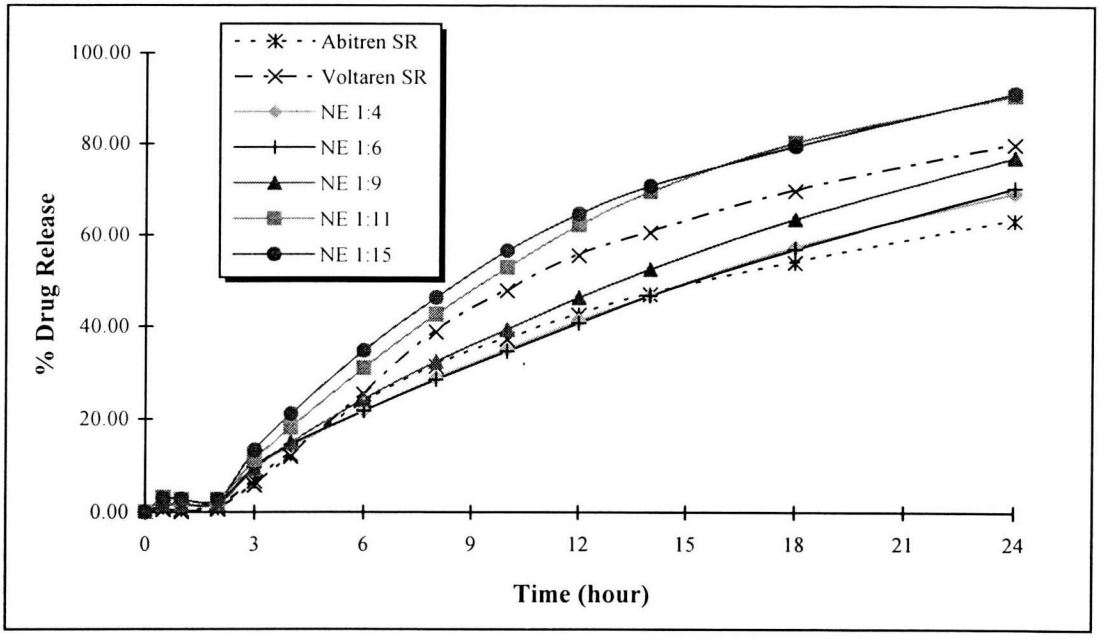

Figure 40 The release profiles of spray-dried diclofenac sodium with Eudragit® NE 30D prepared at inlet air temperature of 170°C in pH-change system.

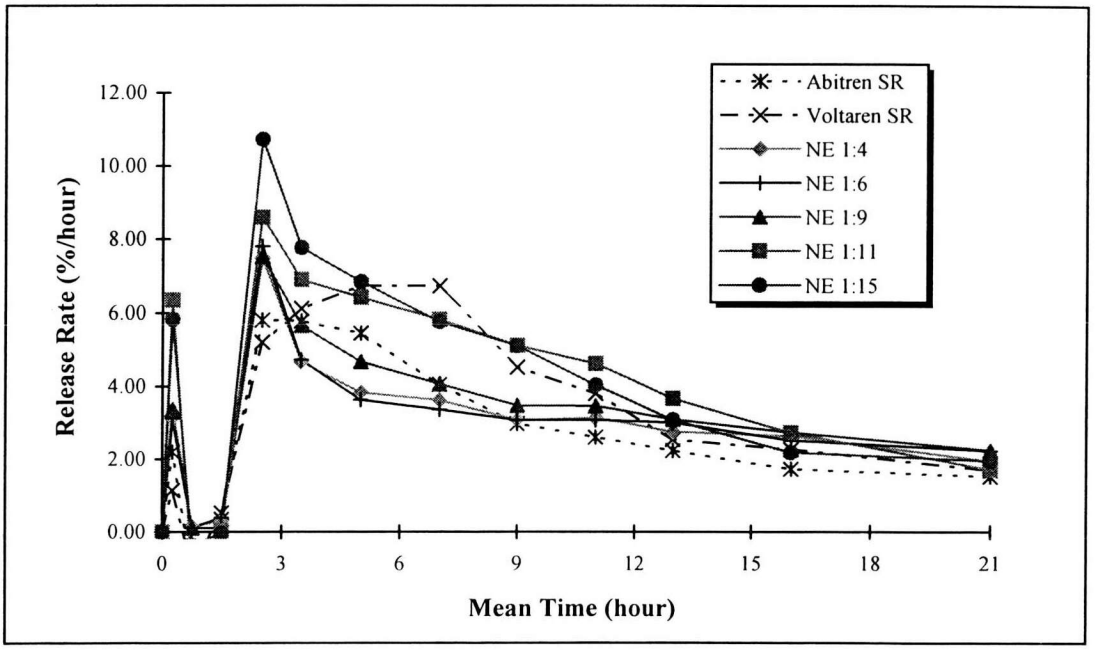

Figure 41 The release rate profiles of spray-dried diclofenac sodium with Eudragit®NE 30D prepared at inlet air temperature of 170°C in pH-change system.

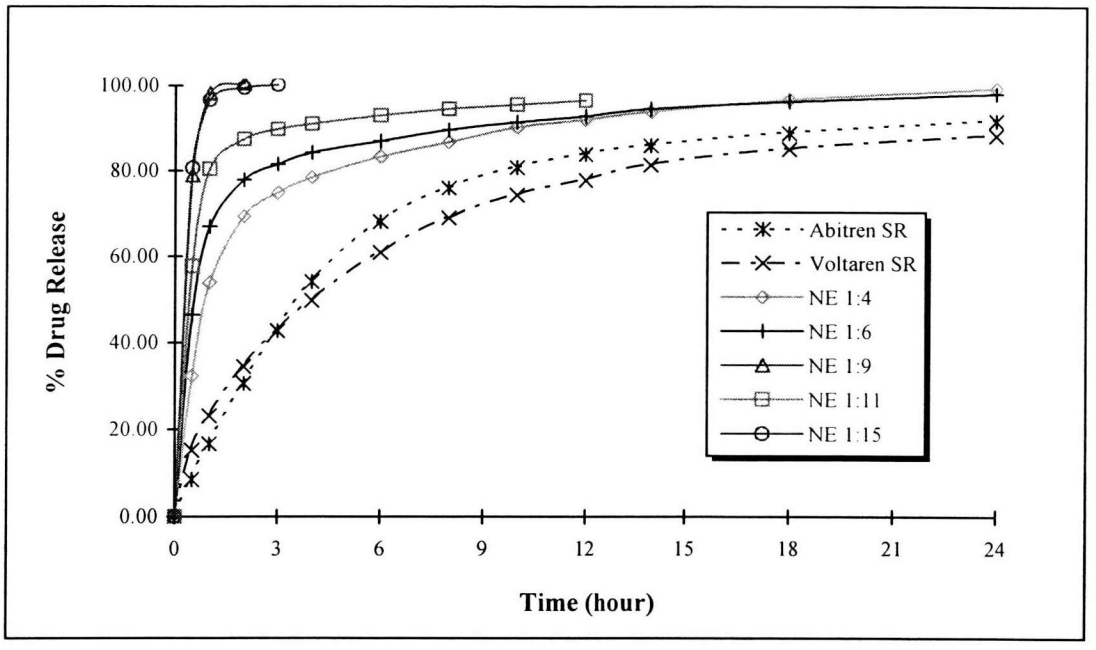

Figure 42 The release profiles of spray-dried diclofenac sodium with Eudragit® NE 30D prepared at inlet air temperature of 170°C in buffer pH 6.8 system.

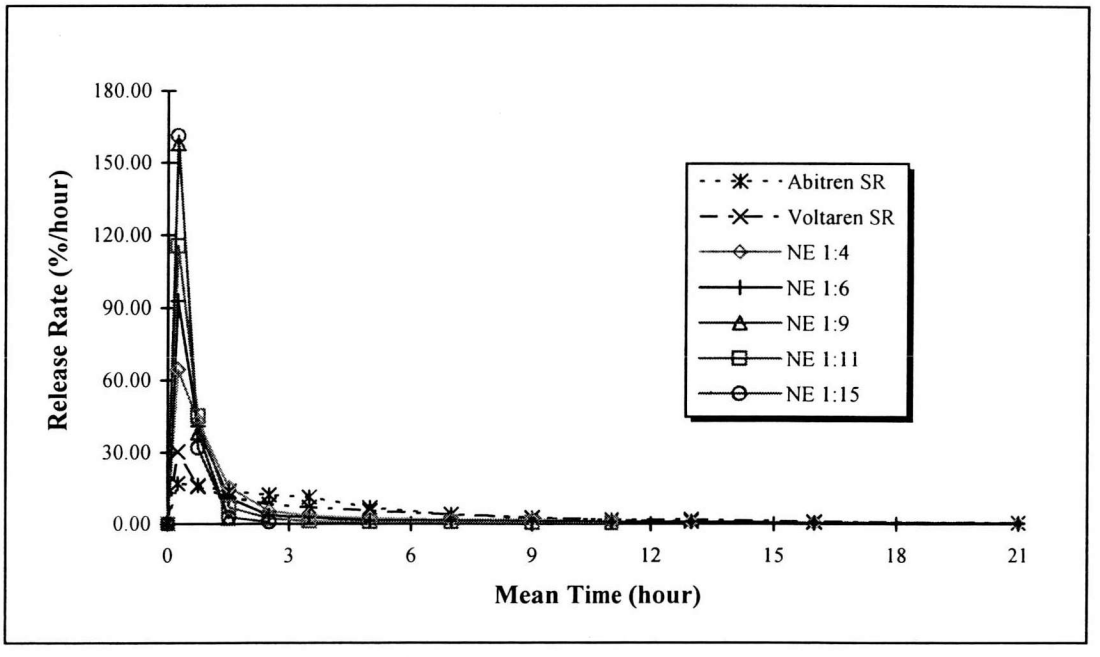

Figure 43 The release rate profiles of spray-dried diclofenac sodium with Eudragit®NE 30D prepared at inlet air temperature of 170°C in buffer pH 6.8 system.

In pH-change system, the polymer to drug ratio of 1:4 and 1:6 and also 1:11 and 1:15 showed no statistically significant difference ($p>0.05$) on the drug release pattern (Table 39, Appendix C). As expected, the release of diclofenac sodium decreased with the increasing of the amount of polymer in the formulation.

In phosphate buffer pH 6.8 system, the polymer to drug ratio of 1:4 and 1:6 released the drug immediately on the first hour of the experiment followed by slightly increased released up to 24 hours. Whereas, the ratio of 1:9, 1:11 and 1:15 gave the drug release of more than 80% of total capacity in the first hour of the experiment.

c) The Formulations 9-11 microparticles prepared at inlet temperature of 190°C

The drug release patterns of spray-dried powders containing diclofenac sodium with Eudragit® NE 30D at various polymer to drug ratios in pH-change and in phosphate buffer pH 6.8 system are demonstrated in Figures 44 and 46, respectively (Table 21, Appendix B). The release rate in phosphate buffer pH 6.8 was faster than in pH-change system and both also decreased with time as shown in Figures 45 and 47, respectively.

Controlled release of drug was observed in the pH-change system. A very low percentage of drug release was remarked in the first 2 hours (acid stage). The polymer to drug ratio of 1:9 showed lower dissolution rate than the ratio of 1:11 and 1:15, while the polymer to drug ratio of 1:11 and 1:15 showed no statistically significant difference ($p>0.05$) on the drug release pattern (Table 39, Appendix C).

A rapid drug release from microparticles was noted in phosphate buffer pH 6.8. The percentage of drug release in the first 2 hours was increased from 89.26% to 90.73% and 95.72% when the proportions of polymer in the formulation were decreased from the polymer to drug ratio of 1:9 to 1:11 and 1:15 respectively. These formulations failed to controlling release the drug for 24 hours in this system.

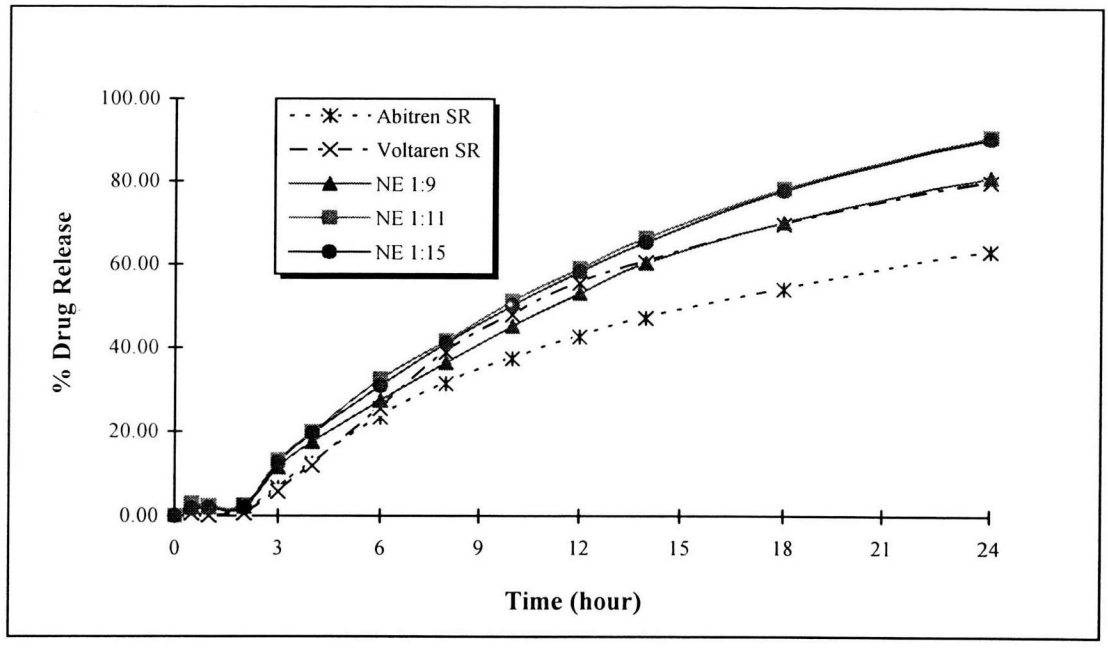

Figure 44 The release profiles of spray-dried diclofenac sodium with Eudragit®NE 30D prepared at inlet air temperature of 190°C in pH-change system.

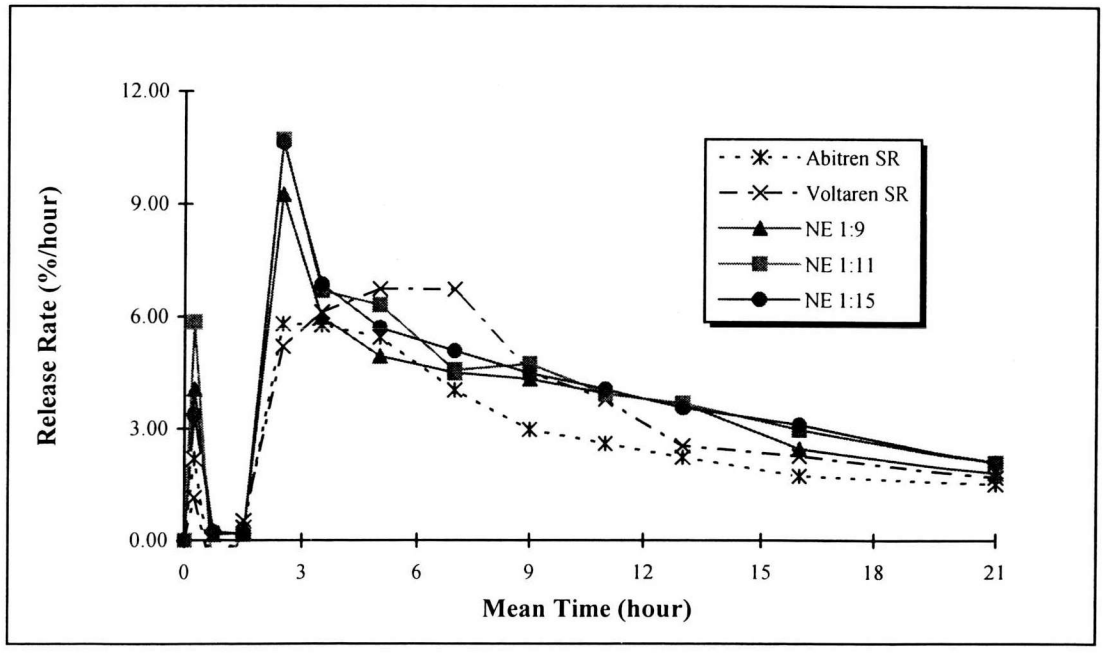

Figure 45 The release rate profiles of spray-dried diclofenac sodium with Eudragit®NE 30D prepared at inlet air temperature of 190°C in pH-change system.

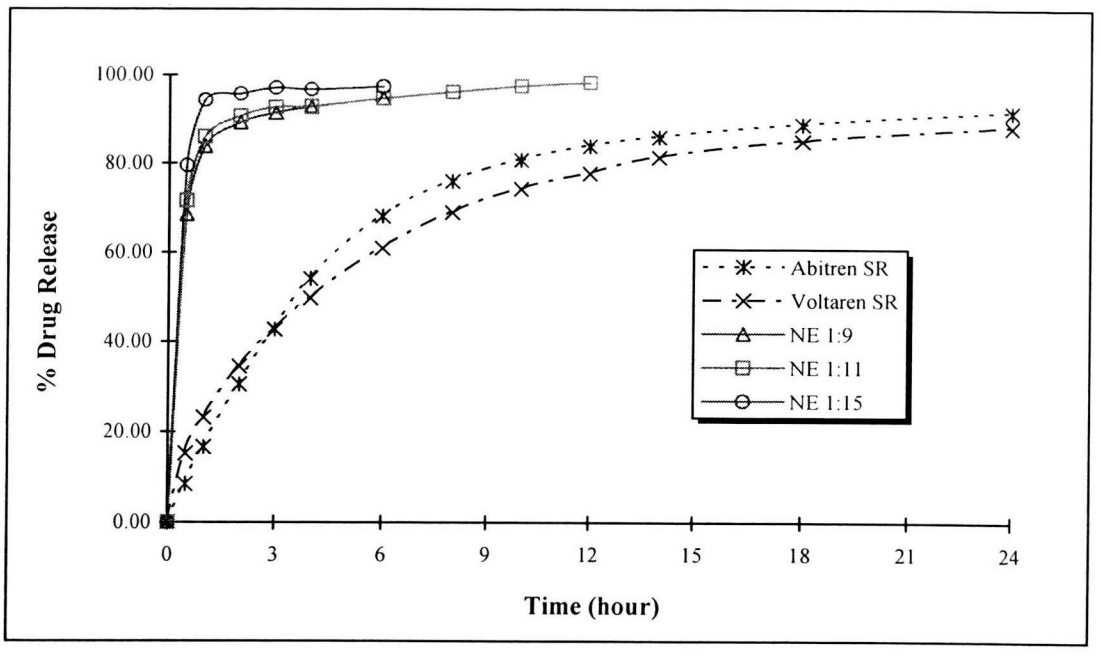

Figure 46 The release profiles of spray-dried diclofenac sodium with Eudragit®NE 30D prepared at inlet air temperature of 190°C in pH 6.8 system.

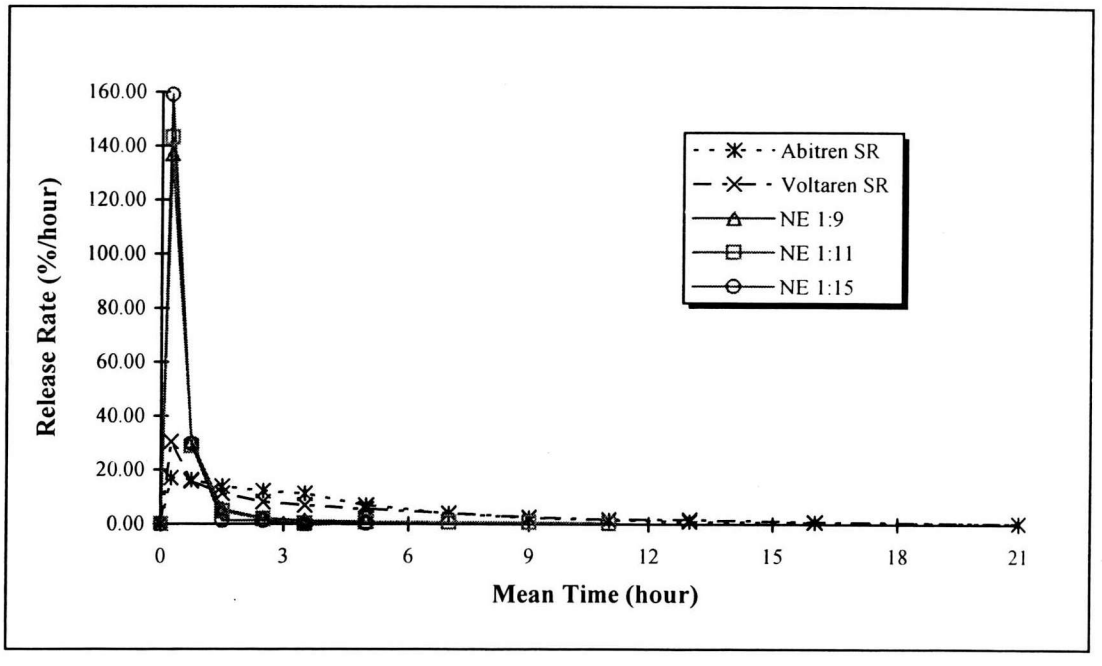

Figure 47 The release rate profiles of spray-dried diclofenac sodium with Eudragit®NE 30D prepared at inlet air temperature of 190°C in pH 6.8 system.

d) The Formulations 12-14 microparticles prepared at inlet temperature of 210°C

The release profiles of diclofenac sodium from spray-dried powders of diclofenac sodium with Eudragit® NE 30D prepared from various polymer to drug ratios in pH-change and in phosphate buffer pH 6.8 system are exhibited in Figures 48 and 50, respectively (Table 22, Appendix B). It was evident that the dissolution rate of spray-dried products in phosphate buffer pH 6.8 system was much faster than that in pH-change system, as shown in Figures 49 and 51.

In pH-change system, the highest amount of diclofenac sodium release in 24 hours obtained from Formulation 14 that had polymer to drug ratio of 1:15. The release rate of this formulation was also faster than the others. Nevertheless, the polymer to drug ratio of 1:9 and 1:11 showed no statistically significant difference ($p>0.05$) on the drug release pattern (Table 39, Appendix C).

In phosphate buffer pH 6.8 system, every formulation showed fast drug release. These formulations had no capability to control the drug release for 24 hours.

e) The Formulations 15-17 microparticles prepared at inlet temperature of 210°C

Figure 52 displays the dissolution profiles of spray-dried diclofenac sodium with various types of polymer matrix in pH-change system (see data in Table 23, Appendix B). Less than 3.5% of drug released from every formulation at the first 2 hours (acid stage). The release of drug increased when the pH was raised to 6.8. The Formulation 16, containing diclofenac sodium with Eudragit® RL 30D, showed the highest amount of drug release throughout 24 hours of the test. While the formulation contained diclofenac sodium with Eudragit® RS 30D and with Eudragit® NE 30D showed no statistically significant difference ($p>0.05$) on the drug release pattern

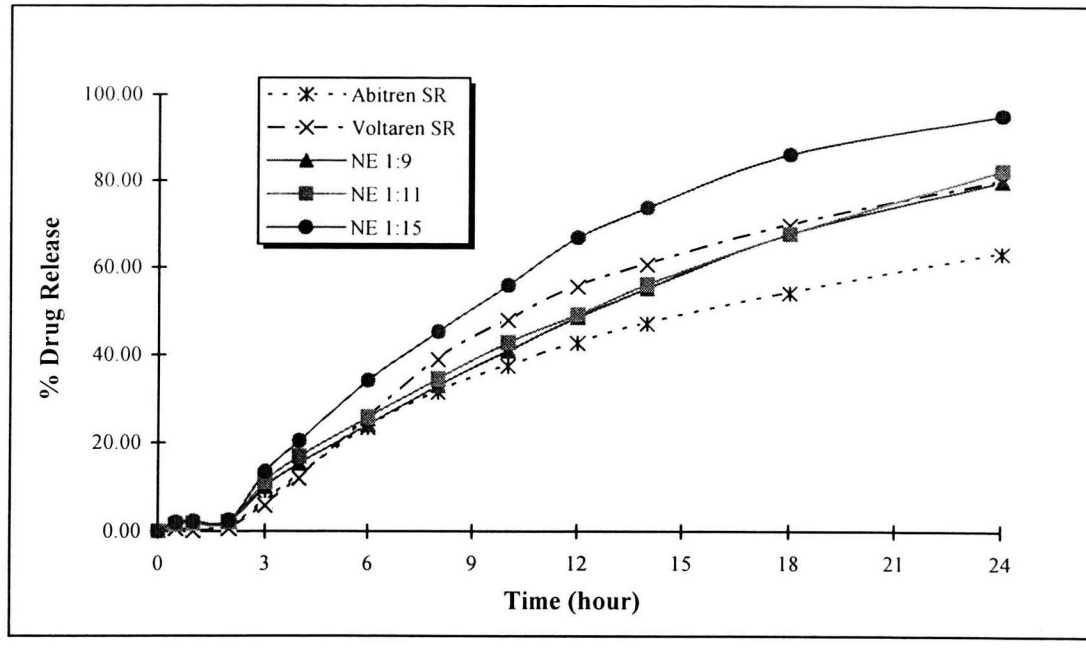

Figure 48 The release profiles of spray-dried diclofenac sodium with Eudragit®NE 30D prepared at inlet air temperature of 210°C in pH-change system.

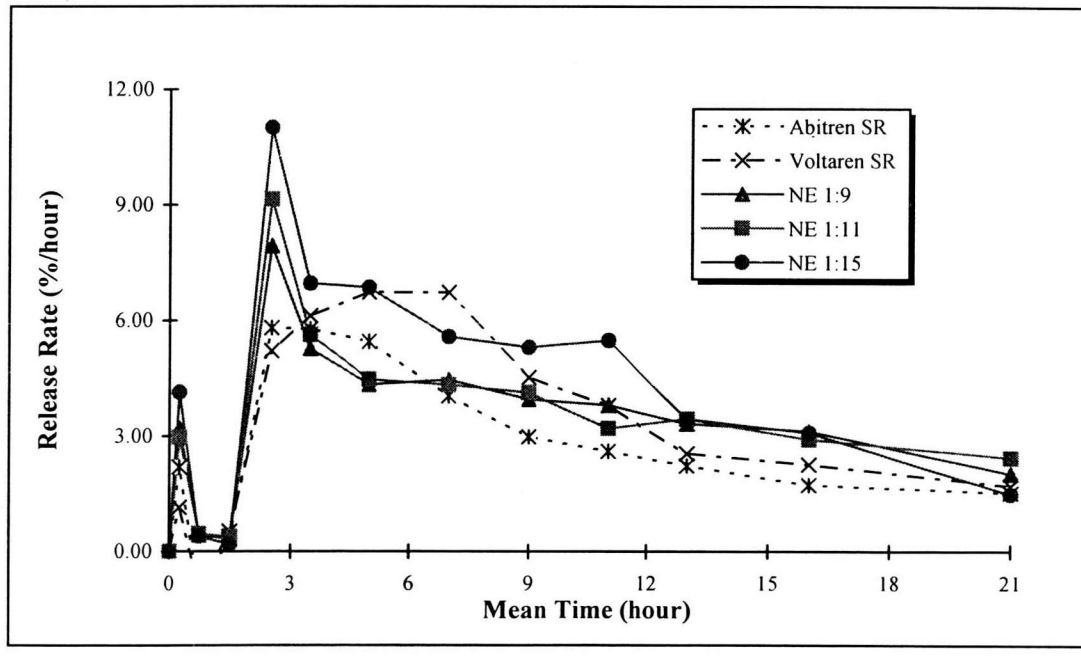

Figure 49 The release rate profiles of spray-dried diclofenac sodium with Eudragit®NE 30D prepared at inlet air temperature of 210°C in pH-change system.

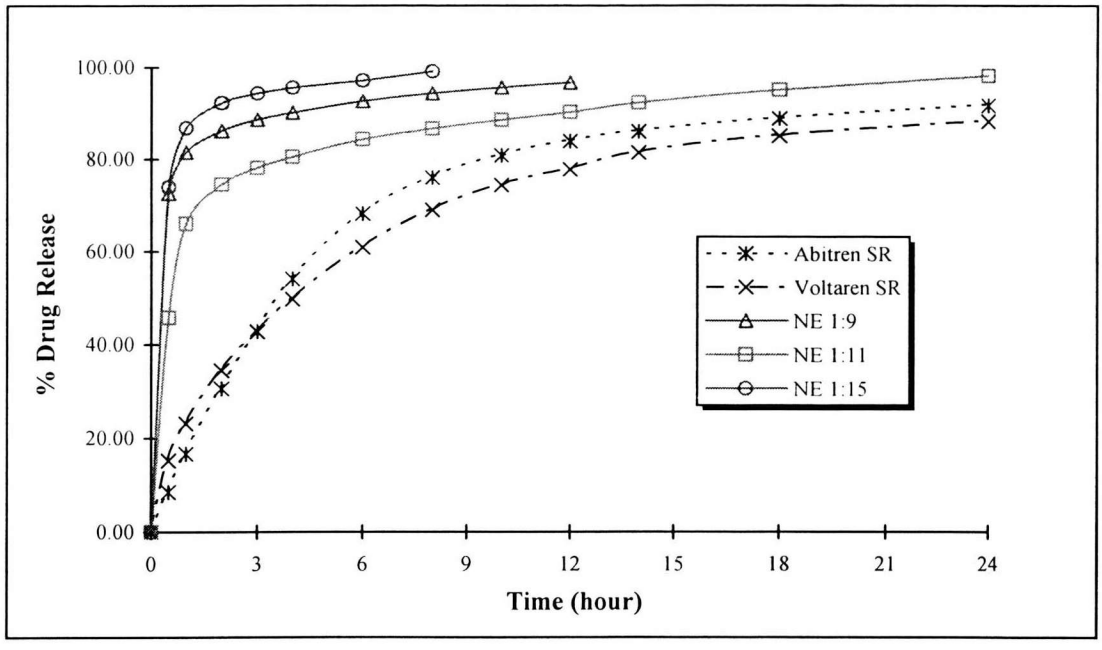

Figure 50 The release profiles of spray-dried diclofenac sodium with Eudragit®NE 30D prepared at inlet air temperature of 210°C in buffer pH 6.8 system.

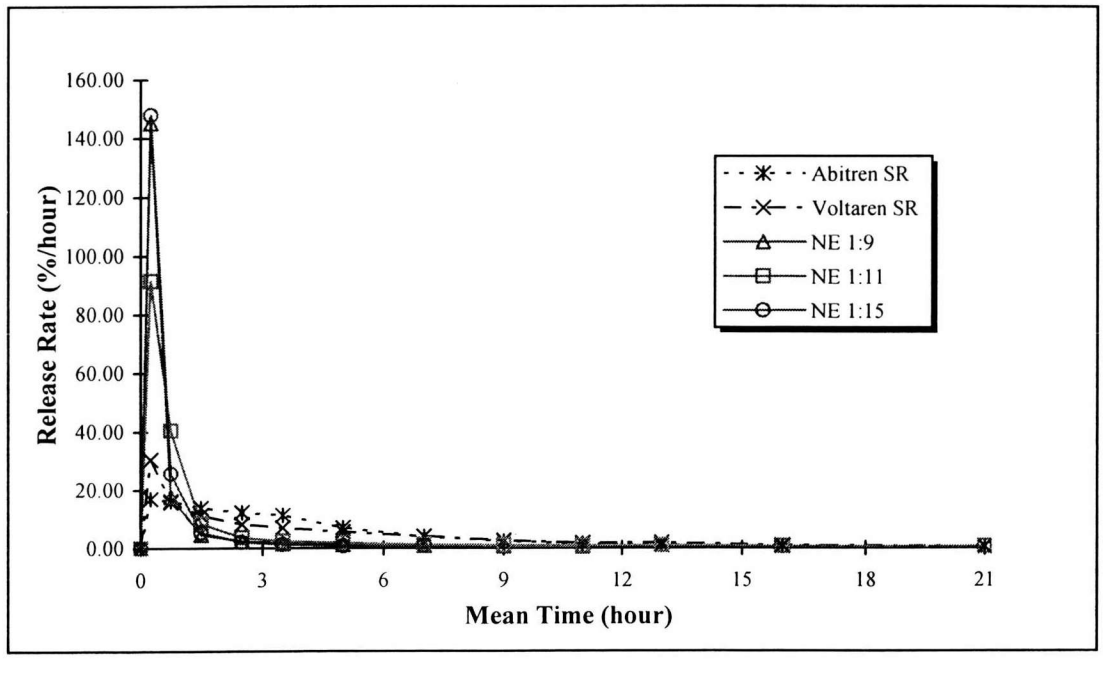

Figure 51 The release rate profiles of spray-dried diclofenac sodium with Eudragit®NE 30D prepared at inlet air temperature of 210°C in buffer pH 6.8 system.

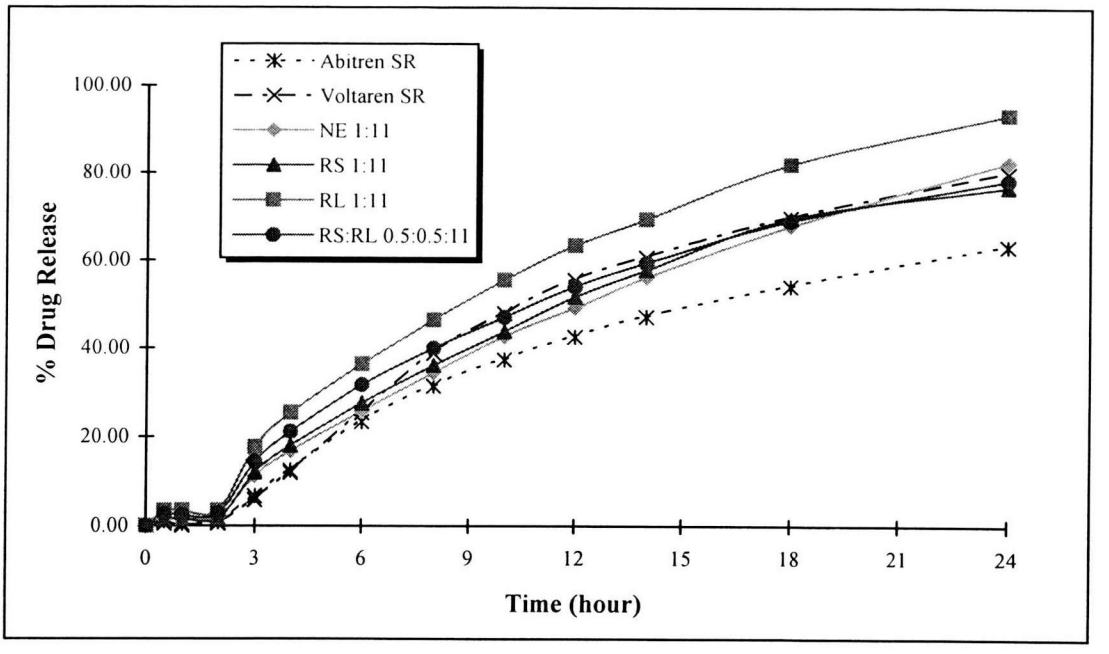

Figure 52 The release profiles of spray-dried diclofenac sodium with various polymers prepared at inlet air temperature of 210°C in pH-change system.

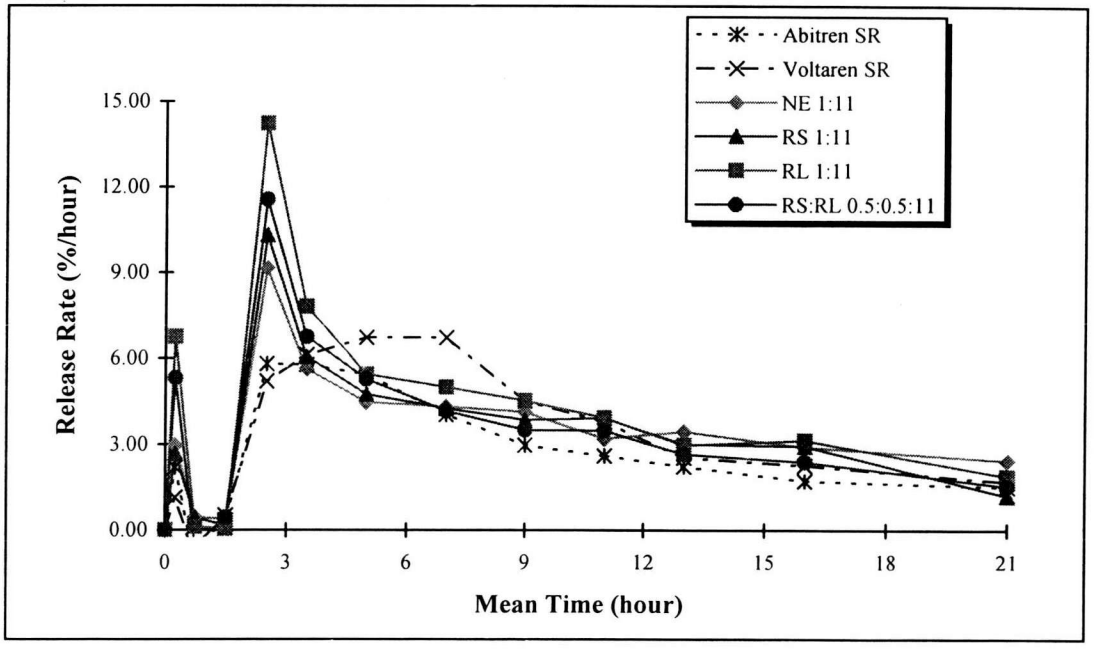

Figure 53 The release rate profiles of spray-dried diclofenac sodium with various polymers prepared at inlet air temperature of 210°C in pH-change system.

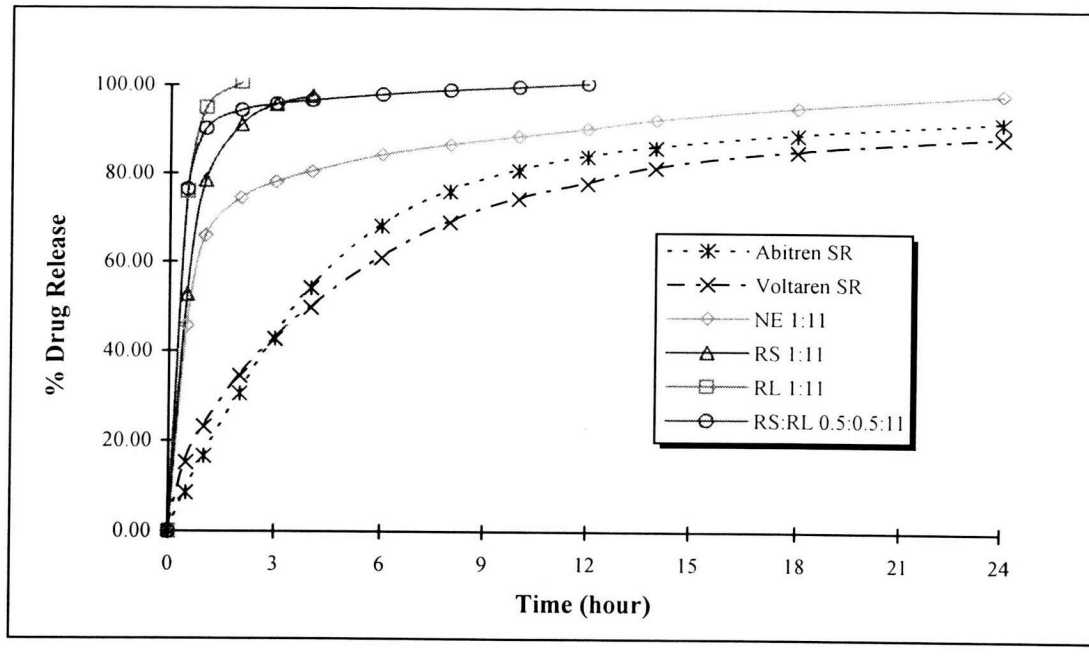

Figure 54 The release profiles of spray-dried diclofenac sodium with various polymers prepared at inlet air temperature of 210°C in buffer pH 6.8 system.

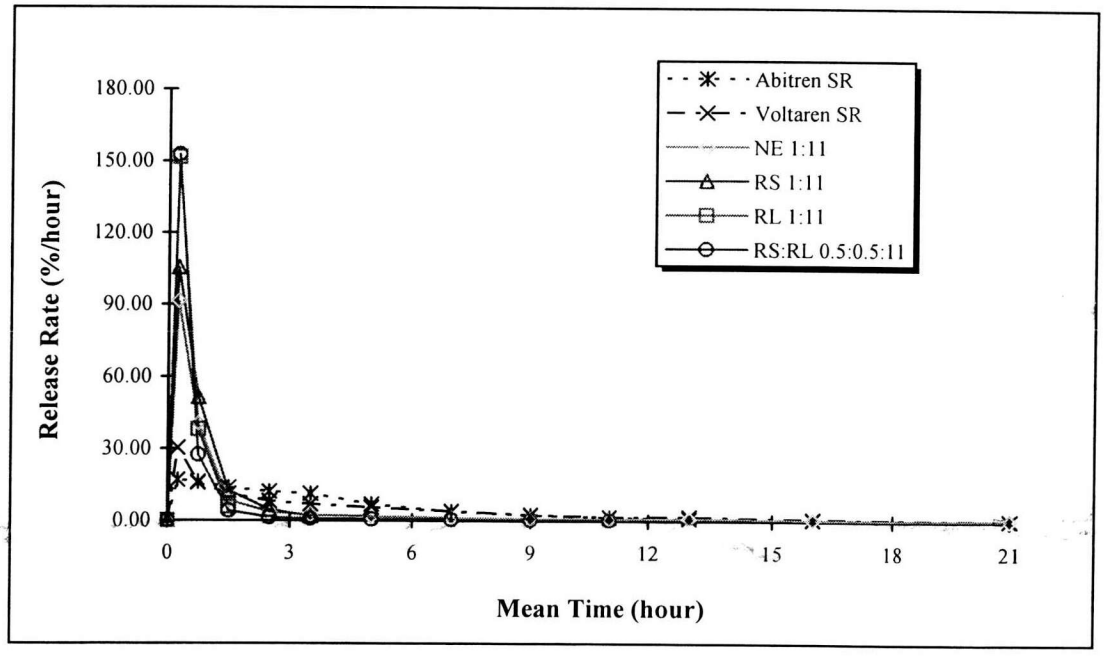

Figure 55 The release rate profiles of spray-dried diclofenac sodium with various polymers prepared at inlet air temperature of 210°C in buffer pH 6.8 system.

(Table 39, Appendix C). The release profiles of Formulation 17, containing diclofenac sodium with combination of Eudragit®RS 30D and Eudragit®RL 30D at the polymer to drug ratio of 0.5:0.5:11, presented between the release profiles of formulating with both polymers but it was inclined to the formulation containing Eudragit®RS 30D.

Figure 54 shows the dissolution profiles of these formulations in phosphate buffer pH 6.8 system. The complete ineffectiveness in controlling drug release was obtained from every formulation. The amount of drug released from these formulations was more than 90% in the first 2 hours.

The release rate of these formulations in both pH-change and in phosphate buffer pH 6.8 system are depicted in Figures 53 and 55, respectively. The release rate decreased with the time increased was revealed from these figures. The release rate in phosphate buffer pH 6.8 was much higher than the release rate in pH-change system.

5.1.4 Effect of Inlet Air Temperature

a) The polymer to drug ratio of 1:9

The release profiles and the release rate profiles of spray-dried diclofenac sodium with Eudragit® NE 30D at the polymer to drug ratio of 1:9 prepared from 4 levels of inlet air temperature in 2 dissolution systems are shown in Figures 56-59. The formulation prepared at inlet air temperature of 150°C showed lower dissolution rate in both pH-change and phosphate buffer pH 6.8 system than the other formulations that prepared at inlet air temperature of 170°C, 190°C and 210°C. However, the results of statistic test showed no statistically significant difference ($p>0.05$) between all of these formulations, as illustrated in Table 40 (Appendix C).

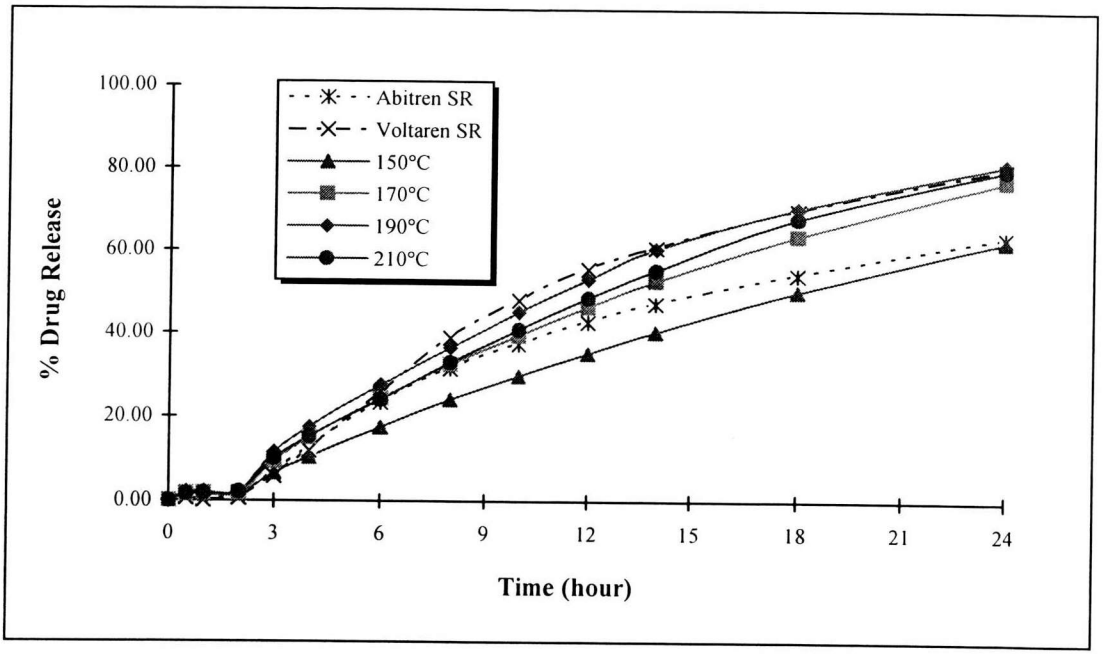

Figure 56 The release profiles of spray-dried diclofenac sodium with Eudragit®NE 30D (NE 1:9) prepared at different inlet air temperature in pH-change system.

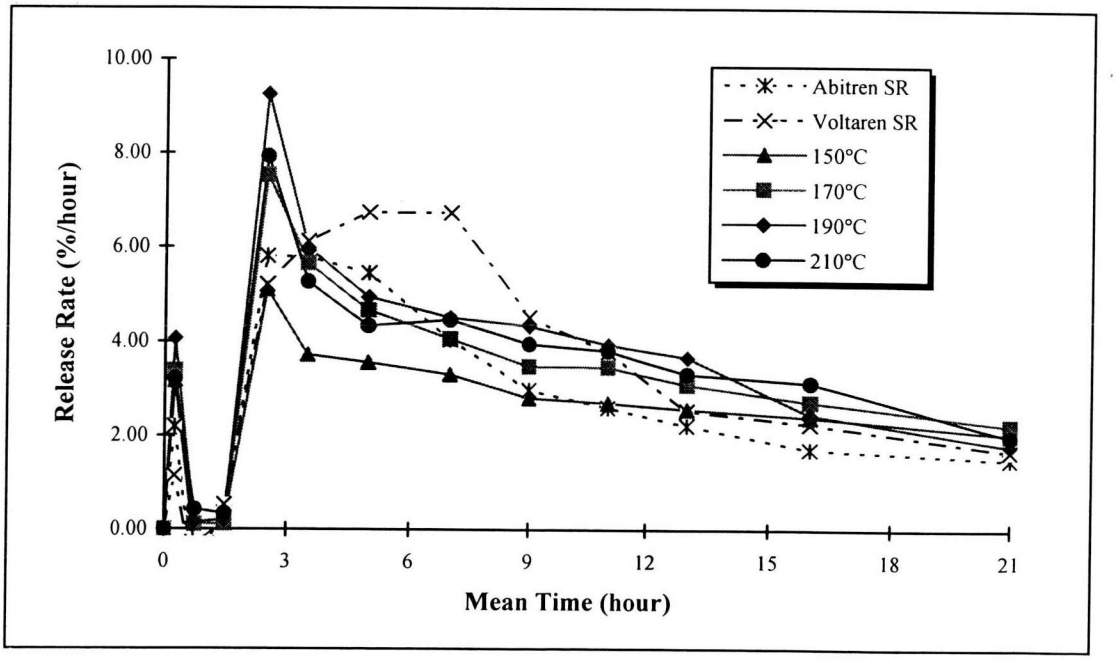

Figure 57 The release rate profiles of spray-dried diclofenac sodium with Eudragit®NE 30D (NE 1:9) prepared at different inlet air temperature in pH-change system.

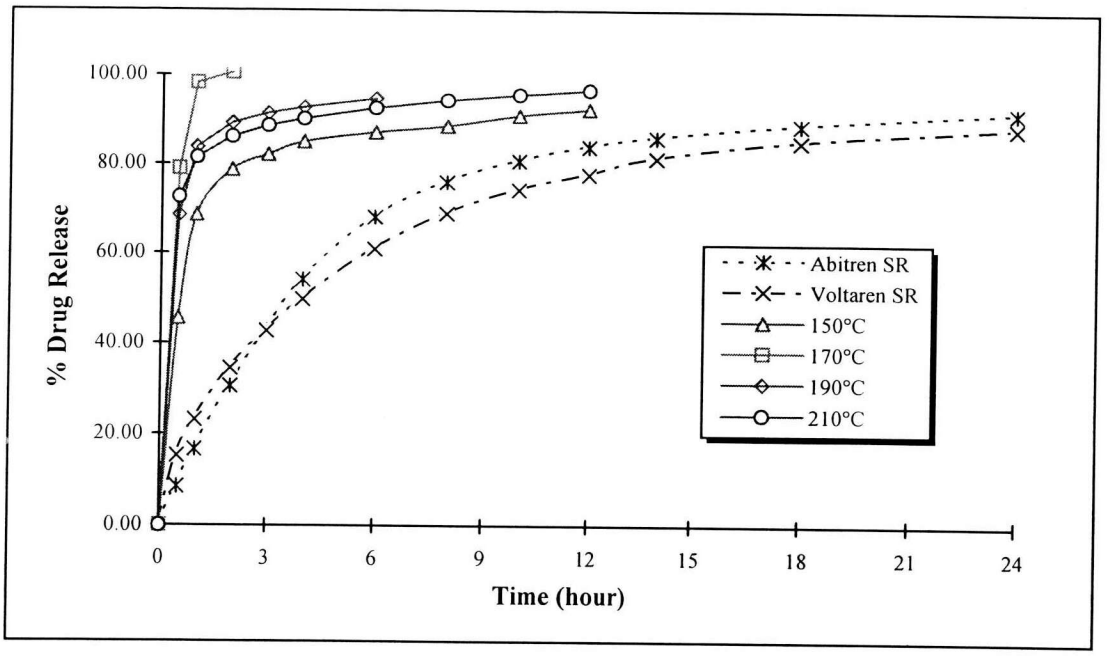

Figure 58 The release profiles of spray-dried diclofenac sodium with Eudragit®NE 30D (NE 1:9) prepared at different inlet air temperature in buffer pH 6.8 system.

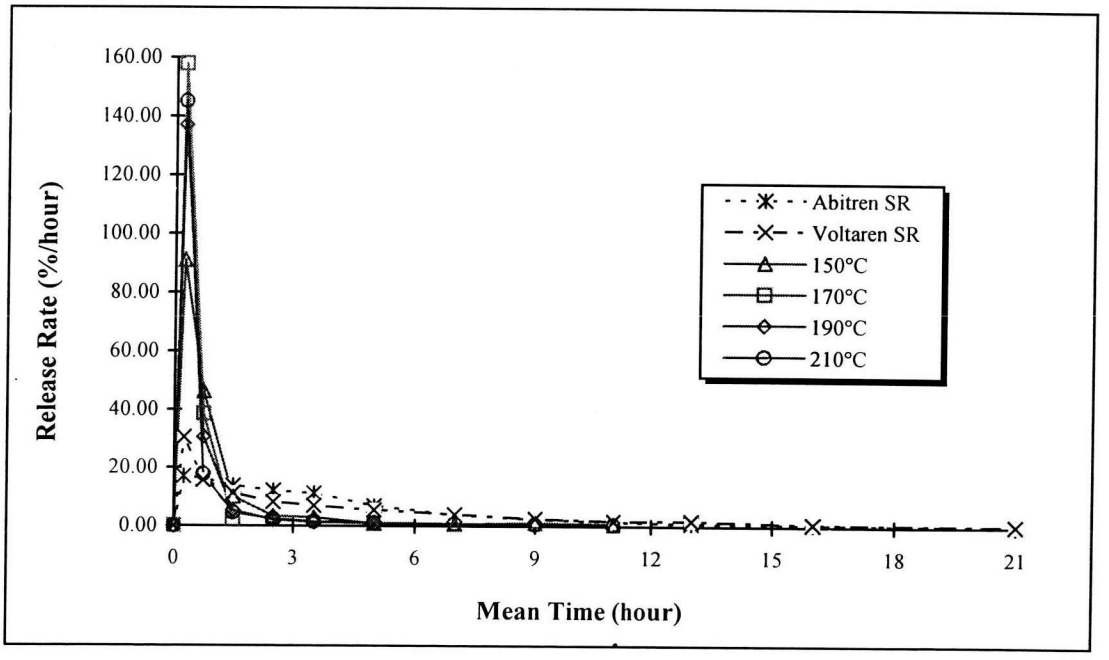

Figure 59 The release rate profiles of spray-dried diclofenac sodium with Eudragit®NE 30D (NE 1:9) prepared at different inlet air temperature in buffer pH 6.8 system.

b) The polymer to drug ratio of 1:11

The release of diclofenac sodium from spray-dried diclofenac sodium with Eudragit® NE 30D prepared at 4 levels of inlet air temperature were affected by dissolution medium as displayed in Figures 60 and 62. The release rate in phosphate buffer pH 6.8 was much faster than in pH-change system as shown in Figures 61 and 63.

The amount of drug released from the formulation prepared at inlet air temperature of 210°C was slightly lower than other formulation in pH-change system. Nevertheless, no statistically significant difference ($p>0.05$) between these formulations was observed from the statistic test (Table 40 Appendix C).

In phosphate buffer pH 6.8 system, the release profiles and the release rate profiles of these formulations seemed to be equivalent.

c) The polymer to drug ratio of 1:15

The dissolution profiles and the dissolution rate profiles of spray-dried diclofenac sodium with Eudragit® NE 30D prepared at various levels of inlet air temperature in pH-change and in phosphate buffer pH 6.8 system are depicted in Figures 64-67. The closeness of these release profiles in each dissolution system was revealed from these figures. The statistic test also showed no statistically significant difference ($p>0.05$) on these release profiles (Table 40, Appendix C).

5.2 The Elucidation of Drug Release Model

In general, the release kinetics of controlled-release preparations can be described by the use of one or more of three kinetic models comprising the zero-order equation, the first-order equation and the Higuchi square root equation. The analysis

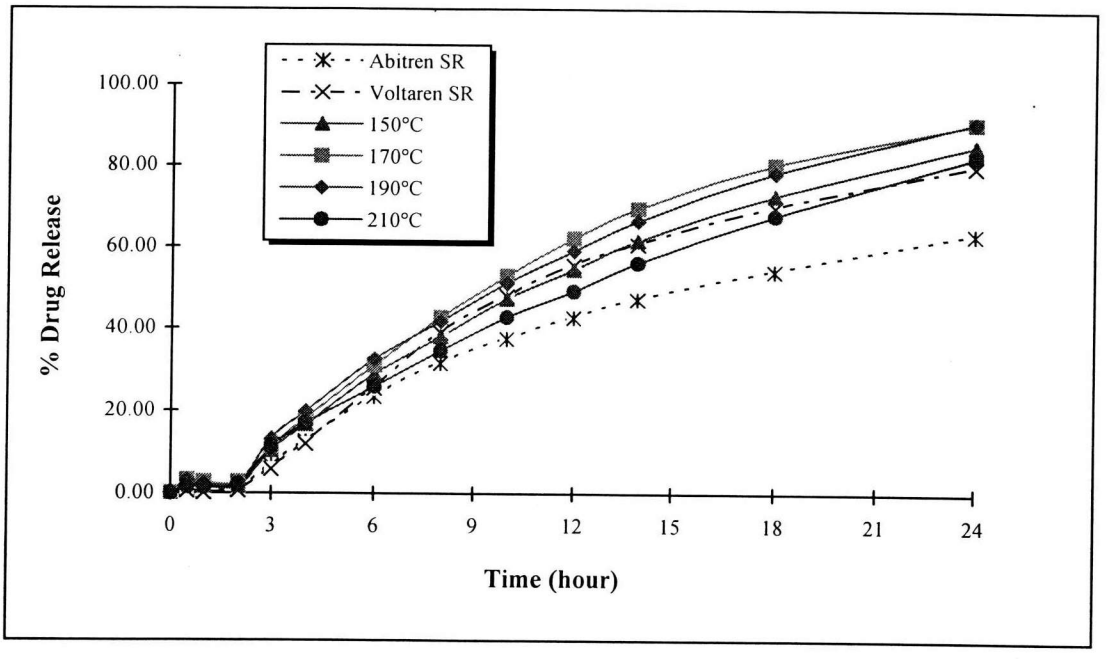

Figure 60 The release profiles of spray-dried diclofenac sodium with Eudragit®NE 30D (NE 1:11) prepared at different inlet air temperature in pH-change system.

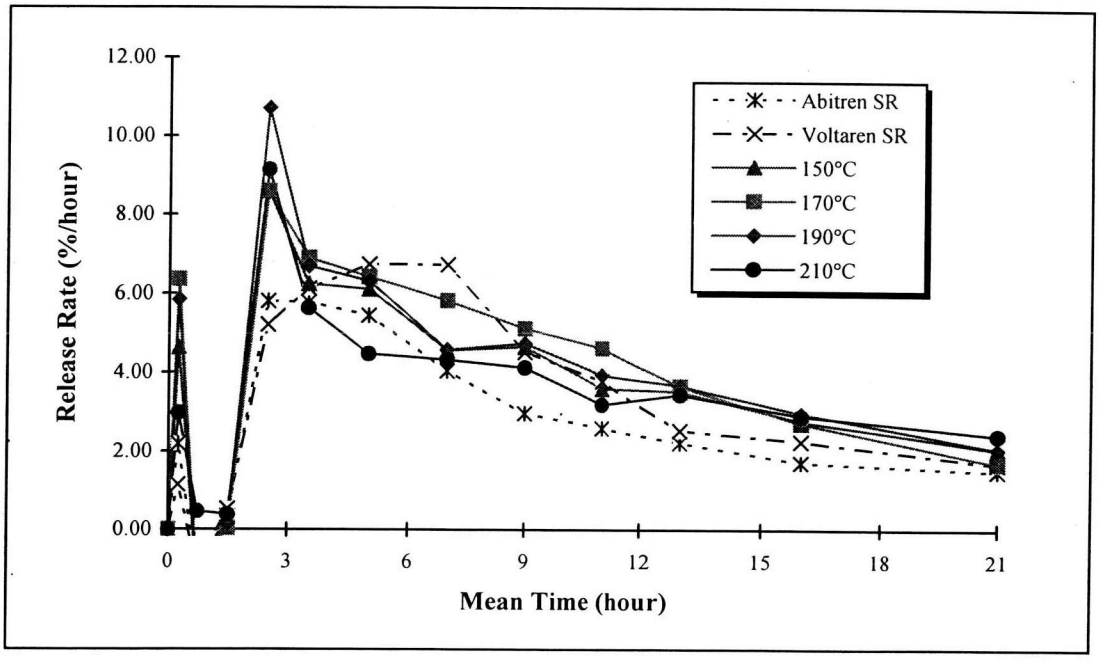

Figure 61 The release rate profiles of spray-dried diclofenac sodium with Eudragit®NE 30D (NE 1:11) prepared at different inlet air temperature in pH-change system.

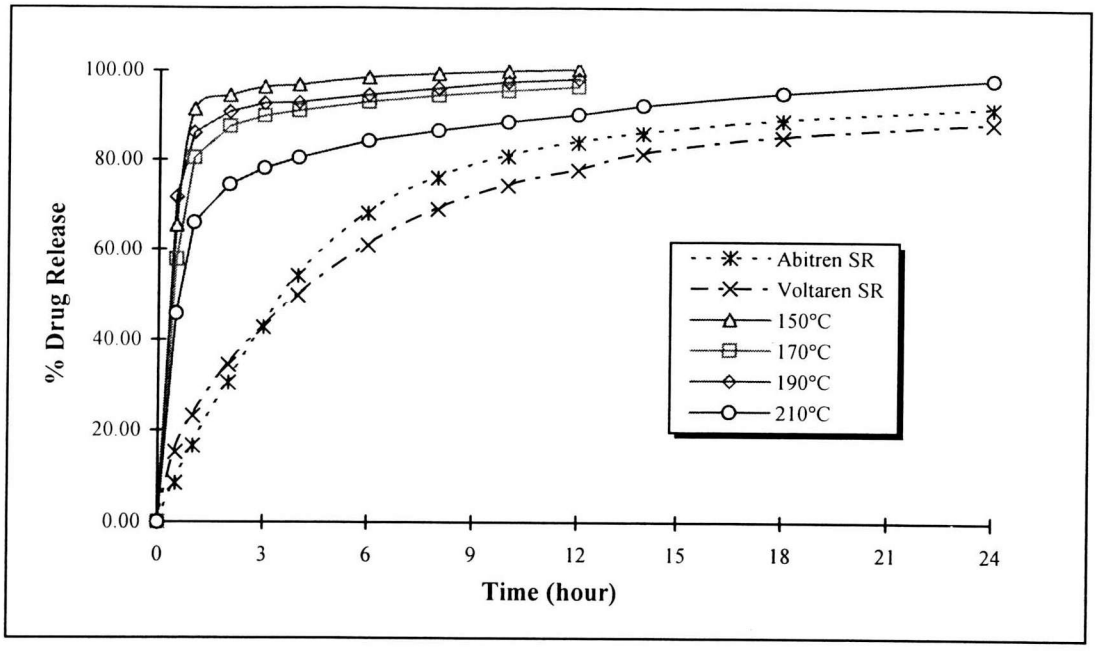

Figure 62 The release profiles of spray-dried diclofenac sodium with Eudragit®NE 30D (NE 1:11) prepared at different inlet air temperature in buffer pH 6.8 system.

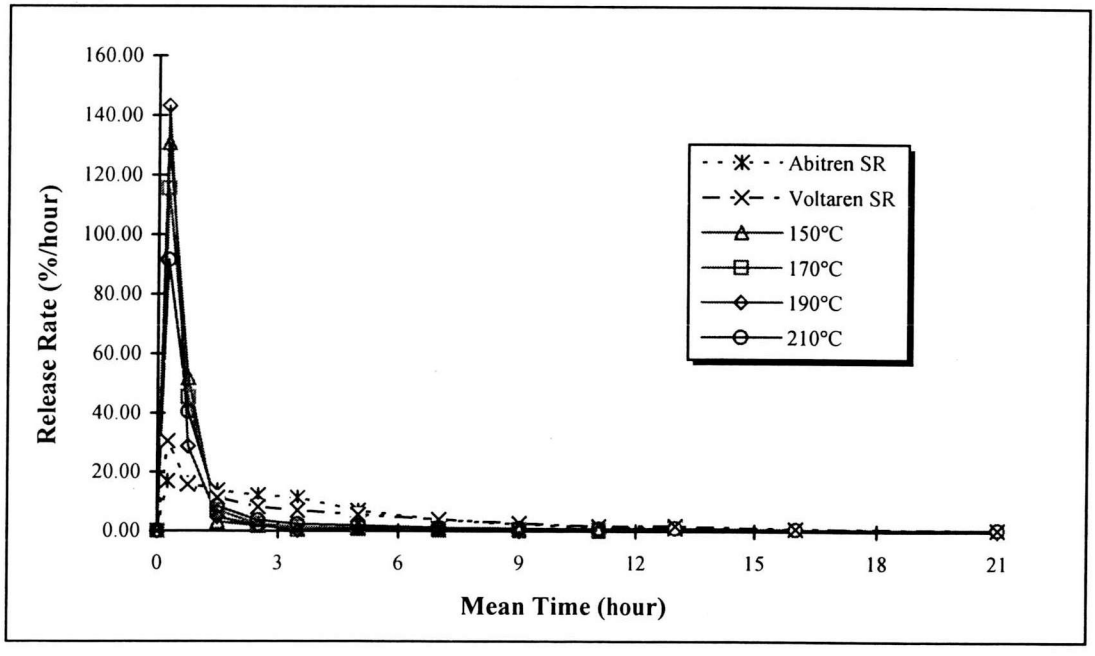

Figure 63 The release rate profiles of spray-dried diclofenac sodium with Eudragit®NE 30D (NE 1:11) prepared at different inlet air temperature in buffer pH 6.8 system.

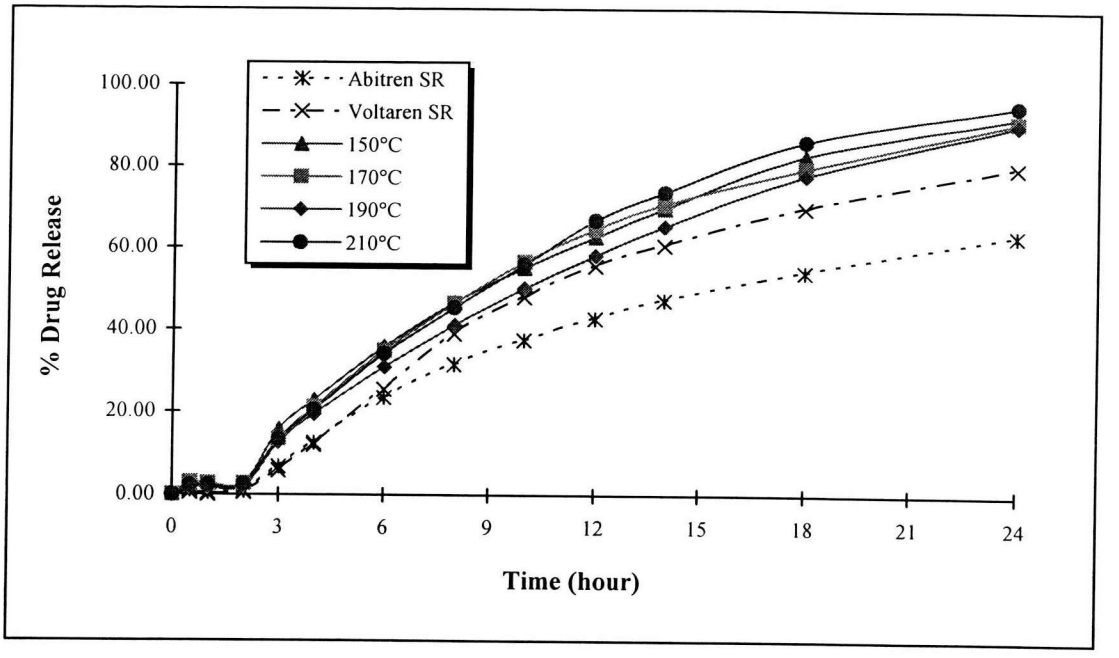

Figure 64 The release profiles of spray-dried diclofenac sodium with Eudragit®NE 30D (NE 1:15) prepared at different inlet air temperature in pH-change system.

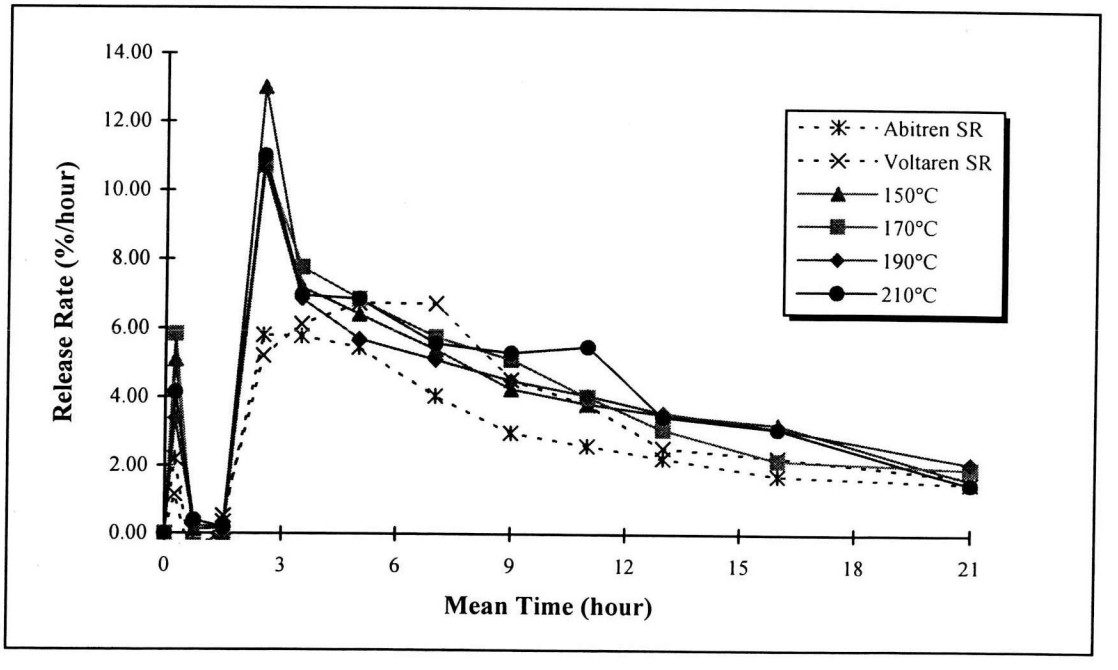

Figure 65 The release rate profiles of spray-dried diclofenac sodium with Eudragit®NE 30D (NE 1:15) prepared at different inlet air temperature in pH-change system.

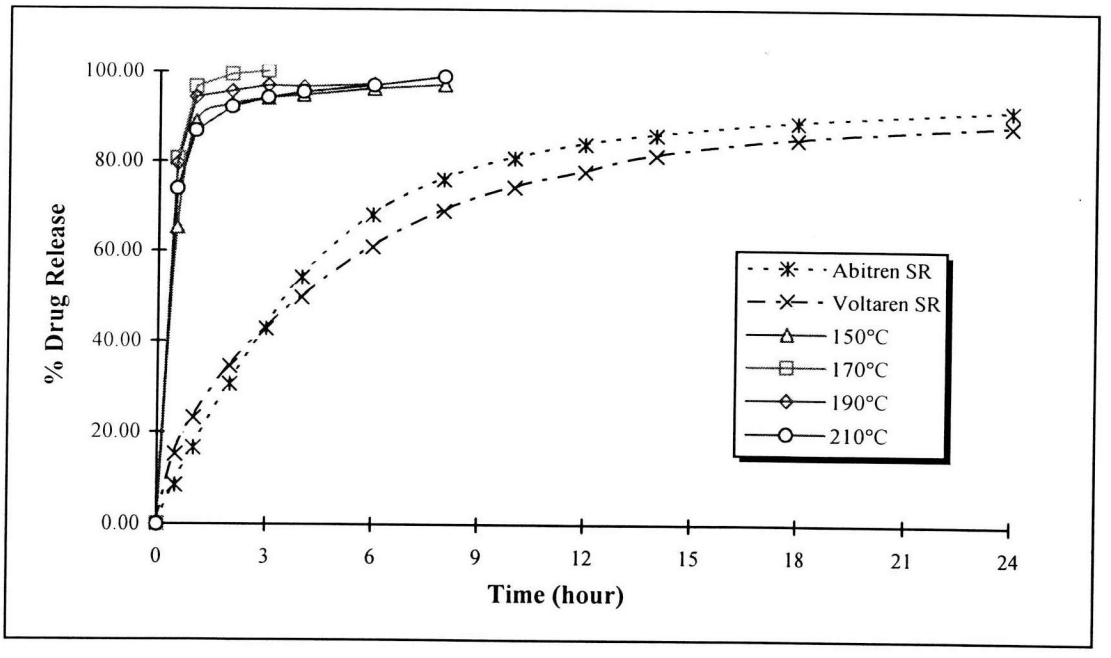

Figure 66 The release profiles of spray-dried diclofenac sodium with Eudragit®NE 30D (NE 1:15) prepared at different inlet air temperature in buffer pH 6.8 system.

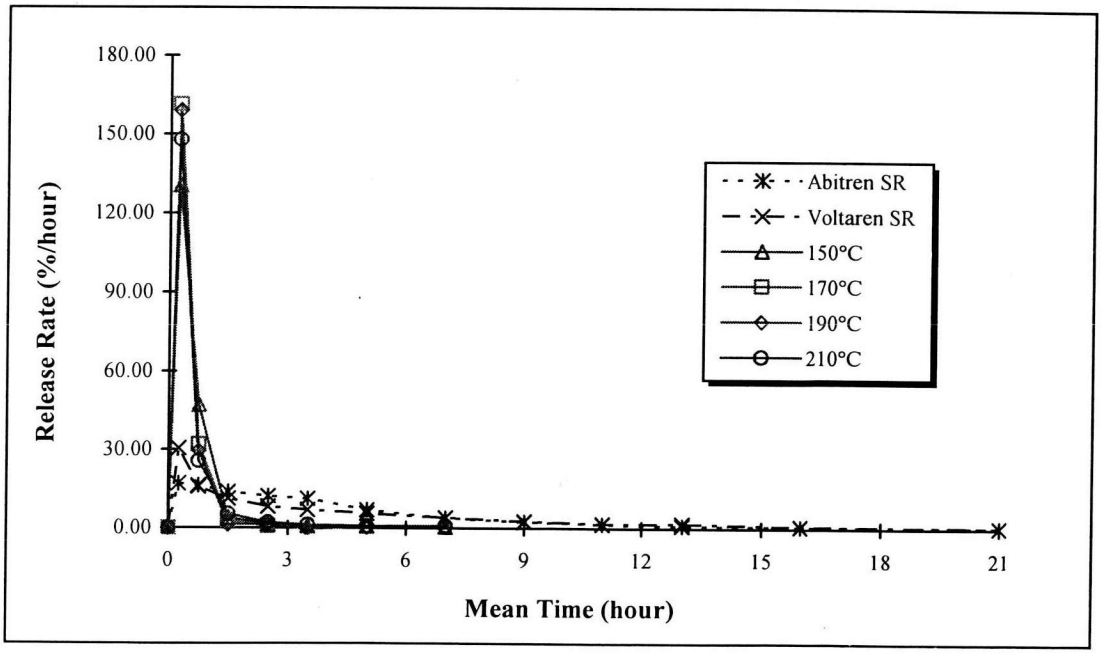

Figure 67 The release rate profiles of spray-dried diclofenac sodium with Eudragit®NE 30D (NE 1:15) prepared at different inlet air temperature in buffer pH 6.8 system.

of all dissolution data was performed to elucidate what model could be fitted by the data. The plots between percentage of drug against time (zero-order), log percent of drug remained versus time (first-order), and percentage of drug versus square root of time (Higuchi model) were, therefore, constructed and determined the one which was the most linear as the accepted model of drug release. Whenever, the determination coefficient of the Higuchi and first-order relationships did not allow unambiguous distinction to made between the two release kinetics. Therefore, the more stringent mathematical treatment proposed by Benita and Donbrow (1982) was applied. 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 12.

5.2.1 The Blank Diclofenac Sodium Capsules

The correlation coefficients were obtained as tabulated in Table 13. In pH-change system, the highest correlation coefficient was 0.9495 that obtained from zero-order plot. Whereas, in phosphate buffer pH 6.8, diclofenac sodium dissolved completely within the first hour. It was a fast release.

5.2.2 The Commercial Products

In pH-change system, the highest correlation coefficient of Voltaren®SR and Abitren®SR were 0.9915 and 0.9880, respectively, obtained from the first-order plot. Whereas, in phosphate buffer pH 6.8, both the Higuchi model and the first-order model were interested. In further treatment, Voltaren®SR showed the correlation coefficient of rate of release versus 1/Q higher than those of rate versus Q as shown in Table 12. The Higuchi model would probably be operative. But Abitren®SR showed opposite result, the correlation coefficient of rate of release against Q was higher than those against 1/Q, therefore, the first-order model would probably be operative.

Table 12 Comparison of linearity between plots of rate of release against reciprocal amount (1/Q) and amount (Q) of diclofenac sodium released from the microparticles.

Formulaiton	Dissolution System			
	pH-change System		Phosphate Buffer pH 6.8 System	
	Versus Q	Versus 1/Q	Versus Q	Versus 1/Q
Blank (DS)	0.0010	0.2867	1.0000	1.0000
Voltaren® SR	0.0094	0.3752	0.8137	0.9848
Abitren® SR	0.0005	0.4670	0.9690	0.5662
1	0.0036	0.3575	0.9530	0.9557
2	0.0018	0.3546	0.9444	0.9340
3	0.0273	0.1450	0.9678	0.9556
4	0.0027	0.2286	0.8980	0.9293
5	0.0013	0.2229	0.8857	0.9681
6	0.0010	0.2937	0.9846	0.9792
7	0.0116	0.2246	0.9615	0.9711
8	0.0290	0.1709	0.9989	0.9970
9	0.0104	0.2212	0.9553	0.9812
10	0.0112	0.2273	0.8966	0.9433
11	0.0054	0.2709	0.9917	0.9912
12	0.0006	0.2737	0.6995	0.7749
13	0.0015	0.2509	0.9714	0.9604
14	0.0118	0.2251	0.8931	0.9366
15	0.0098	0.2251	0.9937	0.9606
16	0.0444	0.0760	0.9999	0.9986
17	0.0092	0.1124	0.9116	0.9483

Table 13 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 System					
	pH-change System			Phosphate Buffer pH 6.8 System		
	A	B	C	A	B	C
Blank (DS)	0.9495	0.9008	0.9123	0.7693	0.9308	1.0000
Voltaren® SR	0.9470	0.9302	0.9915	0.7783	0.9541	0.9446
Abitren® SR	0.9496	0.9448	0.9880	0.7414	0.9233	0.9256
1	0.9899	0.9341	0.9941	0.4644	0.7215	0.7675
2	0.9680	0.9464	0.9885	0.3135	0.5635	0.8899
3	0.9509	0.9574	0.9818	0.3646	0.6440	0.7017
4	0.9821	0.9475	0.9959	0.5359	0.7849	0.9601
5	0.9856	0.9467	0.9932	0.4173	0.6688	0.8843
6	0.9804	0.9456	0.9910	0.6252	0.8859	0.9833
7	0.9570	0.9450	0.9848	0.3753	0.6318	0.7562
8	0.9432	0.9519	0.9881	0.5027	0.7902	0.9738
9	0.9664	0.9505	0.9946	0.4241	0.7109	0.7396
10	0.9651	0.9525	0.9763	0.3120	0.5565	0.7844
11	0.9674	0.9511	0.9761	0.3354	0.6207	0.5915
12	0.9811	0.9434	0.9885	0.3339	0.5767	0.7778
13	0.9808	0.9483	0.9834	0.3252	0.5784	0.7326
14	0.9524	0.9476	0.9700	0.3539	0.6345	0.8601
15	0.9582	0.9524	0.9943	0.6645	0.8981	0.9677
16	0.9519	0.9623	0.9741	0.6599	0.9079	0.9994
17	0.9460	0.9611	0.9969	0.2862	0.5271	0.8732

5.2.3 The Formulations 1-3 Microparticles

These formulations showed similar release model in pH-change system. The first-order plots were linear with the correlation coefficient values greater than 0.98. In phosphate buffer pH 6.8, Formulations 2 and 3, the highest correlation coefficients were 0.8899 and 0.7017, respectively, obtained from first-order plots. Whereas, Formulation 1, both the Higuchi plot and the first-order plot were rather linear, it was necessary to discriminate between the models. The correlation coefficient of rate of release versus 1/Q was slightly higher than those of rate versus Q as exhibited in Table 12, but the t-value did not show statistically significant difference ($p>0.05$), as shown in Table 42 (Appendix C). The release profiles of Formulations 2 and 3 would probably follow the first-order model, while Formulation 1 could not be specified.

5.2.4 The Formulations 4-8 Microparticles

All these formulations showed similar release model in both dissolution systems. The first-order plot was linearity with the correlation coefficient values greater than 0.98 in pH-change. In phosphate buffer pH 6.8, the highest correlation coefficients of these formulations were also obtained from the first-order plot.

5.2.5 The Formulations 9-11 Microparticles

In pH-change system, Formulations 9-11, the highest correlation coefficient, as presented in Table 13, obtained from the first-order plot. In phosphate buffer pH 6.8, Formulations 9 and 11, both the Higuchi plot and the first-order plot were interested. In further treatment, Formulation 9, the correlation coefficient of rate of release against 1/Q was higher than those against Q. This indicated that the Higuchi model would possibly be better followed. Whereas, Formulation 11, the correlation coefficient of rate of release against Q and against 1/Q showed no statistically significant difference (Table 42, Appendix C). Therefore, the model of this

formulation was not cleared. Formulation 10, the highest correlation coefficient was obtained from the first-order plot.

5.2.6 The Formulations 12-14 Microparticles

In pH-change system, the highest correlation coefficient of these formulations was obtained from the first-order plot, therefore, this model could be specified.

In phosphate buffer pH 6.8, all these formulations showed similar release model. The highest correlation coefficients were obtained from the first-order plot, therefore, the first-order model could be specified for these formulations.

5.2.7 The Formulations 15-17 Microparticles

All these formulations gave similar release model in both dissolution systems. In pH-change system, the highest correlation coefficient values of Formulations 15-17 were 0.9943, 0.9741 and 0.9969, respectively, obtained from the first-order plot. In phosphate buffer pH 6.8, the correlation coefficient of the first-order plot was higher than other models. Therefore, the release profiles of these formulations might follow the first-order model.