CHAPTER III

RESULTS

I. Spray Dried Powder

1. Physicochemical Properties of Spray Dried Powders

1.1 Morphology of Spray Dried Powders

The observation of size, shape and surface topography was done by scanning electron microscopy. The results were separated into groups by the amount and type of the polymer and the ratio of chitosan to diclofenac sodium.

Some microcapsules produced in this experiment were exploded in the scanning electron photomicrographic process, especially the microcapsules from formulations using glycerin as the plasticizers. The exploded microcapsules were broken in the two-capped characters.

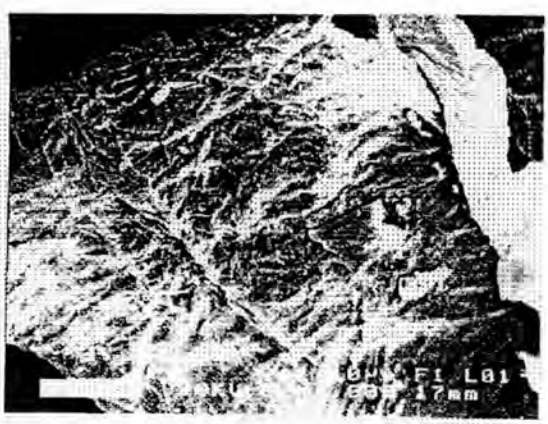
Figure 7 shows the scanning electron photomicrographs of pure diclofenac sodium powder and two grades of pure chitosan in different magnifications. Diclofenac sodium powder was of irregular crystal shapes, rough surface in various sizes adhering together. Seacure® 243 and 343 were irregular flakes of different sizes with rough surface. They did not display any different morphology between the two grades of chitosan.

The photomicrographs of spray dried powder obtained from Seacure® 243 at different ratios (1:5, 1:10, 1:15, 1:20 and 1:30, respectively) are shown in Figure 8. The amount of Seacure® 243 in the formulation had an important effect to the shape and surface topography of the microcapsules.

A x 800

A x 3,000

B x 100

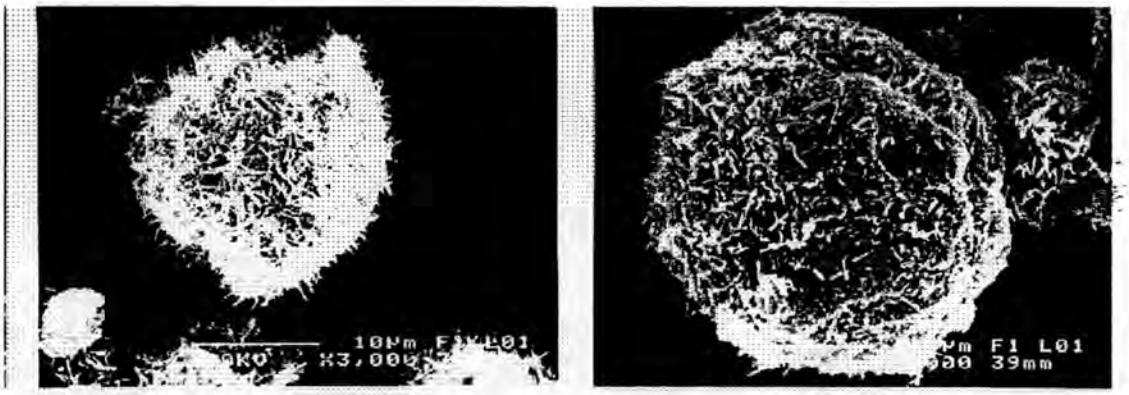


B x 1,000

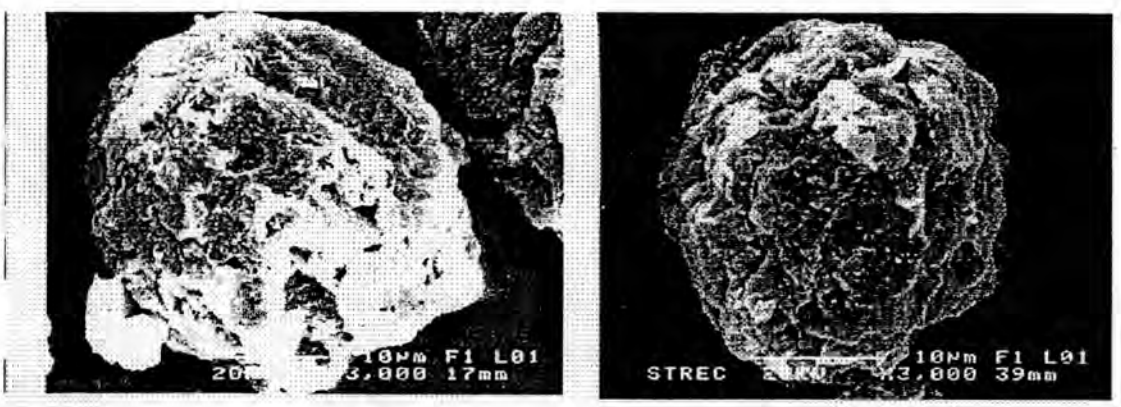
C x 100

C x 1,000

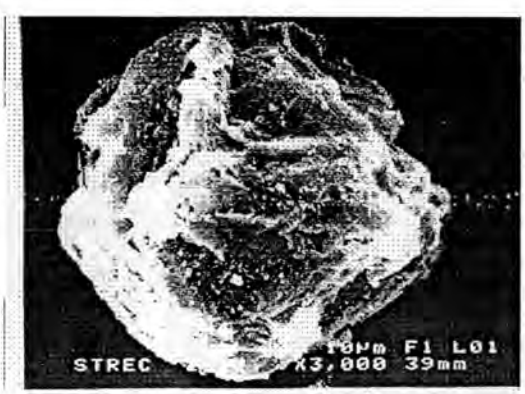
Figure 7 Scanning electron photomicrographs of pure diclofenac sodium powder (A), Seacure® 243 (B) and 343 (C) at different magnifications.



A1 A2



A3 A4



A5

Figure 8 Scanning electron photomicrographs of spray-dried diclofenac sodium powders produced from Seacure® 243 at various drug to polymer ratios (A1 = 1:5, A2 = 1:10, A3 = 1:15, A4 = 1:20 and A5 = 1:30), (x3,000).

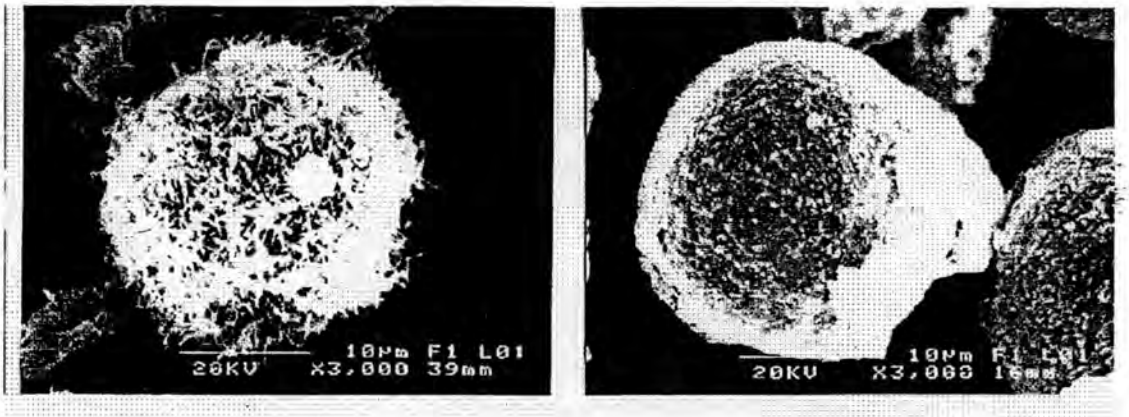
All microcapsules obtained by Seacure® 243 were incomplete because they had irregular shapes and rough surfaces filled with pores. The smoother surface with fewer pores appeared in the formulations which contained lower amount of Seacure® 243. At the polymer to drug ratio of 1:5, the surface of the particles was covered with a number of long and narrow needle-like microcrystals that resulted in irregular shaped microcapsules. The amount of spikes was lowered when the amount of polymer used in the formulation was lowered to the ratio of 1:10. These needles were not found in the ratios of 1:15, 1:20 and 1:30.

The photomicrographs of the spray dried powders using Seacure® 343 at the polymer to drug ratios of 1:5, 1:10, 1:15, 1:20 and 1:30 are shown in Figure 9. The same morphology of microcapsules was obtained in the formulations using both grades of polymer at the ratio of 1:5. As those needles were not longer found in the ratio of 1:10 of Seacure® 343 which presented rough, spherical microcapsules with fewer pores.

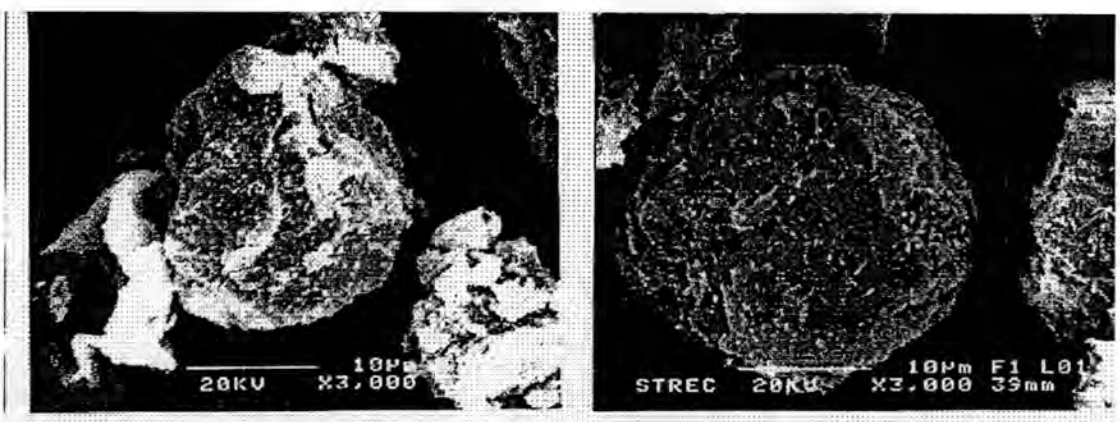
The microcapsules of other ratios of Seacure® 343 had rough surfaces with number of pores but the smoother surface with a fewer pores was found when the proportion of the polymer in the formulation was decreased.

The photomicrographs of the spray dried powder produced by Seacure® 243 at the ratio of 1:5 with two different plasticizers, propylene glycol or glycerin, are shown in Figure 10. The microcapsules of formulations with these two plasticizers had irregular shape with rough surface. Numbers of pores appeared in every formulation.

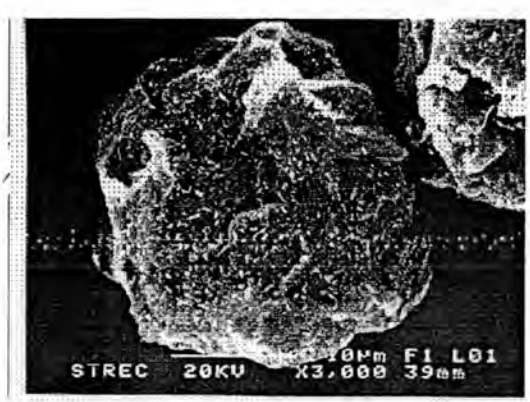
The types of plasticizers presented the same results on size and shape of the microcapsules except the surface characteristics. Propylene glycol-plasticized microcapsules showed rosette aggregates in various shapes and sizes covered with microcrystals, whereas glycerine-plasticized microcapsules showed irregular shape with rough, fish scale-like surface.



B1 B2

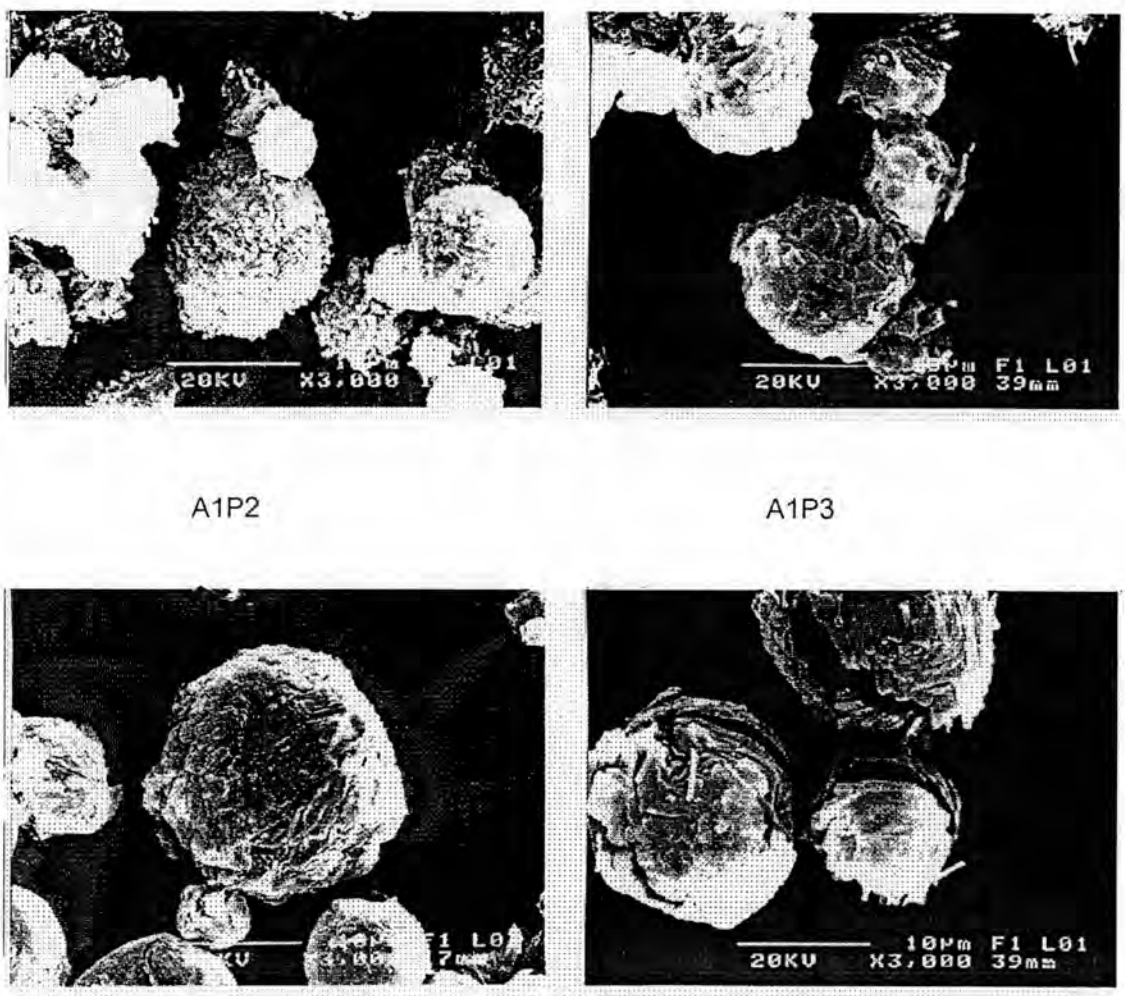


B3 B4



B5

Figure 9 Scanning electron photomicrographs of spray-dried diclofenac sodium powders produced from Seacure® 343 at various drug to polymer ratios (B1 = 1:5, B2 = 1:10, B3 = 1:15, B4 = 1:20 and B5 = 1:30), (x3,000).



A1P2 A1P3

A1G2 A1G3

Figure 10 Scanning electron photomicrographs of spray-dried diclofenac sodium powders produced from Seacure® 243 at the ratio of 1:5 with 20% (A1P2) and 33% propylene glycol (A1P3) and 20% (A1G2) and 33% glycerin (A1G3), (x3,000).

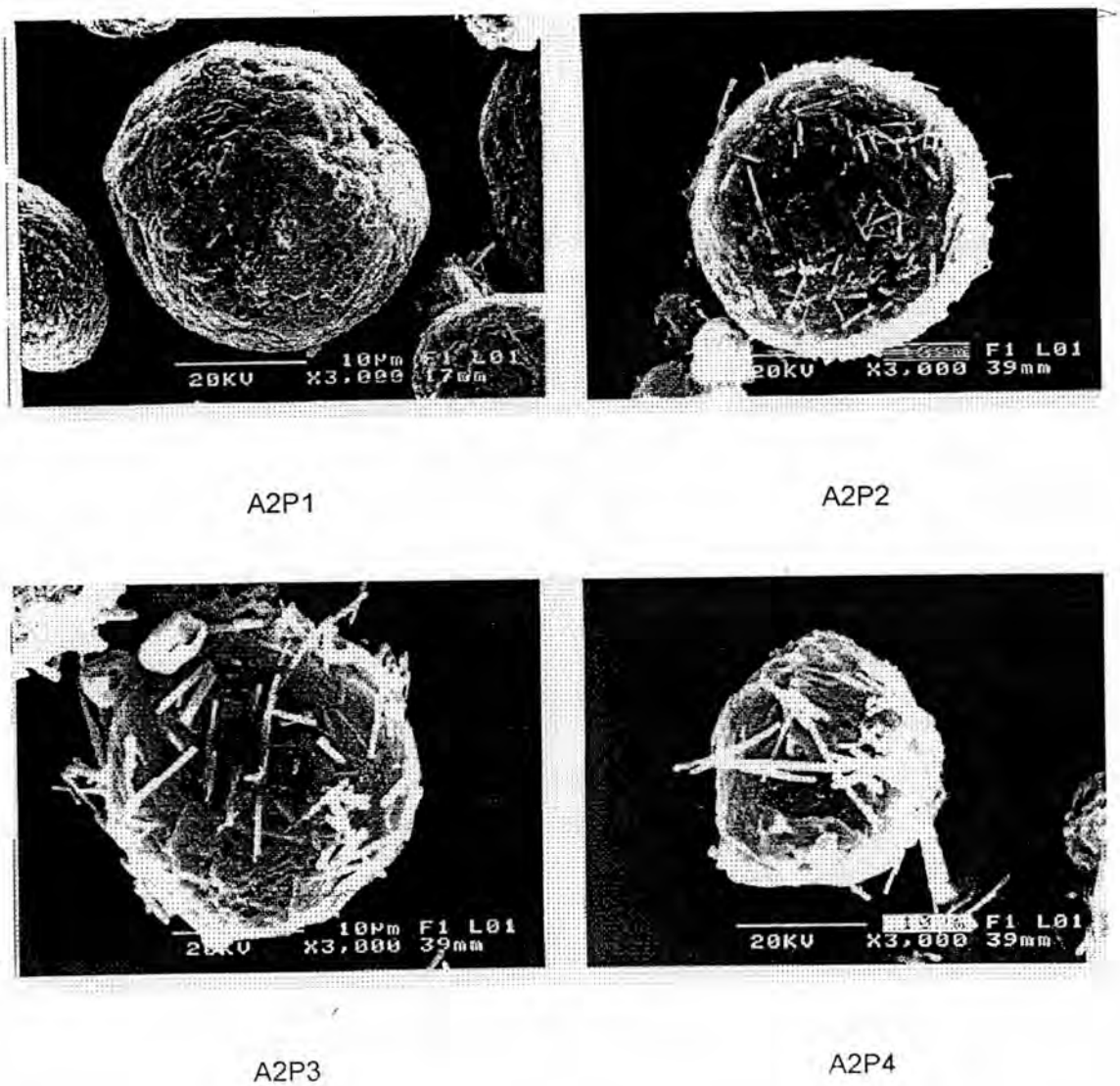
The microscopic images of spray dried diclofenac sodium with Seacure® 243 at the polymer to drug ratio of 1:10 with the aid of propylene glycol or glycerin are shown in Figures 11 and 12, respectively. When the amount of Seacure® 243 was decreased to the ratio of 1:10 with the aid of plasticizer, all spray dried particles exhibited good characters of rounded microcapsules, smooth surfaces with a hollow spherical shape. At low percentage of plasticizers in the formulations (10%), the number of pores are also found on the surface.

Propylene glycol improved the properties of diclofenac sodium spray dried microcapsules, especially at 20% of propylene glycol. However, the surface was covered with long and rectangular-shaped microcrystals. When percentage of propylene glycol increased, the amount and size of the microcrystals decreased and caused rougher surface of the microcapsules. Nevertheless, the size of the microcapsules was partly shrunken and the particles were more agglomerated, particularly when the quantity of propylene glycol was increased to 40% of the polymer and drug content.

Glycerin-plasticized formulations produced irregular shaped microcapsules with fish scale-like surfaces and few pores. Like propylene glycol-plasticized microcapsules, the size of these microcapsules was smaller and more agglomerated when the amount of glycerin was increased. When 33% of glycerin was used in the formulations, the fish scale-like surface was clearly seen (Figure 12).

The shapes and surface topographies of the spray dried powder prepared by Seacure® 343 at the polymer to drug ratio of 1:10 with glycerin and propylene glycol are shown in Figures 12 and 13, respectively. All particles were remarkably different but still showed good characters of microcapsules.

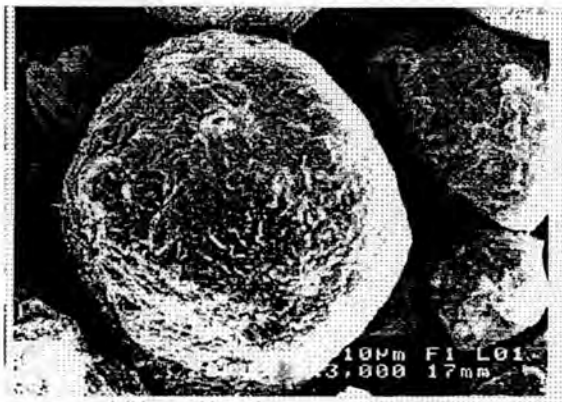
Microcapsules with pores were made by the aid of propylene glycol except when at 40% of plasticizer, irregular shaped microcapsules filled with microcrystals on the surface were produced. On the contrary, the round and smooth



A2P1 A2P2

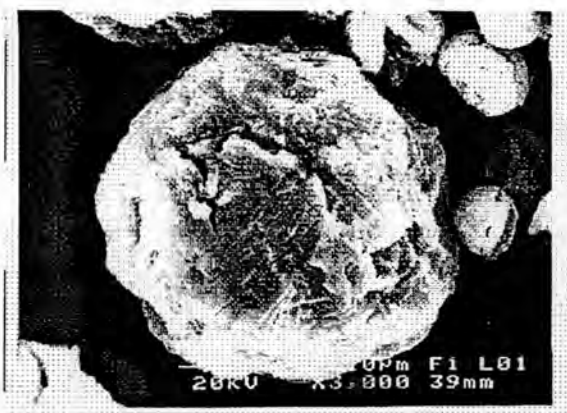
A2P3 A2P4

Figure 11 Scanning electron photomicrographs of spray-dried diclofenac sodium powders produced from Seacure® 243 at the ratio of 1:10 with the aid of 10% (A2P1), 20% (A2P2), 33% (A2P3) and 40% propylene glycol (A2P4), (x3,000).

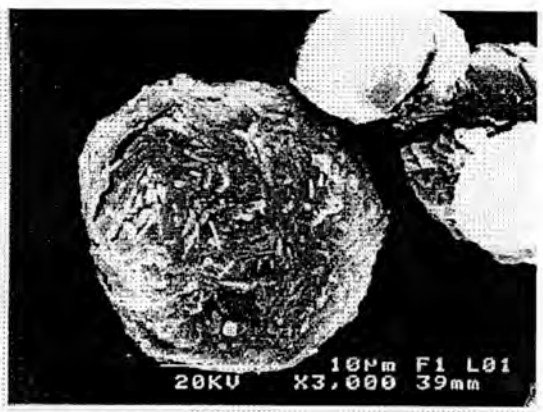


A2G1

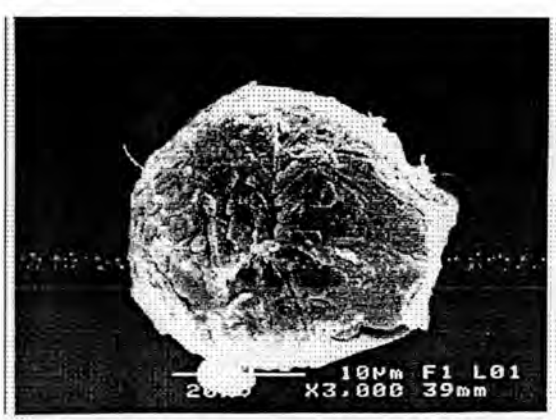
B2G1



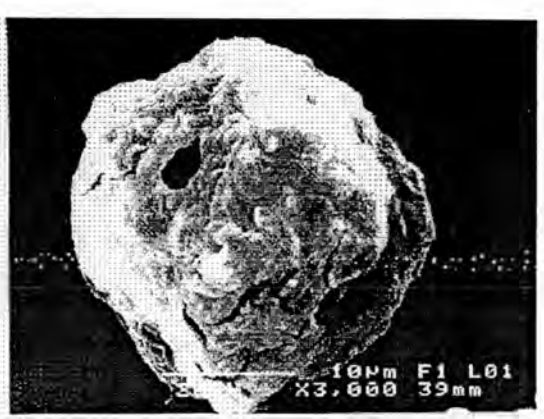
A2G2



B2G2



A2G3



B2G3

Figure 12 Scanning electron photomicrographs of spray-dried diclofenac sodium powders produced from Seacure® 243 and 343 at the ratio of 1:10 with the aid of 10% (A2G1/B2G1), 20% (A2G2/B2G2) and 33% glycerin (A2G3/B2G3), (x3,000).

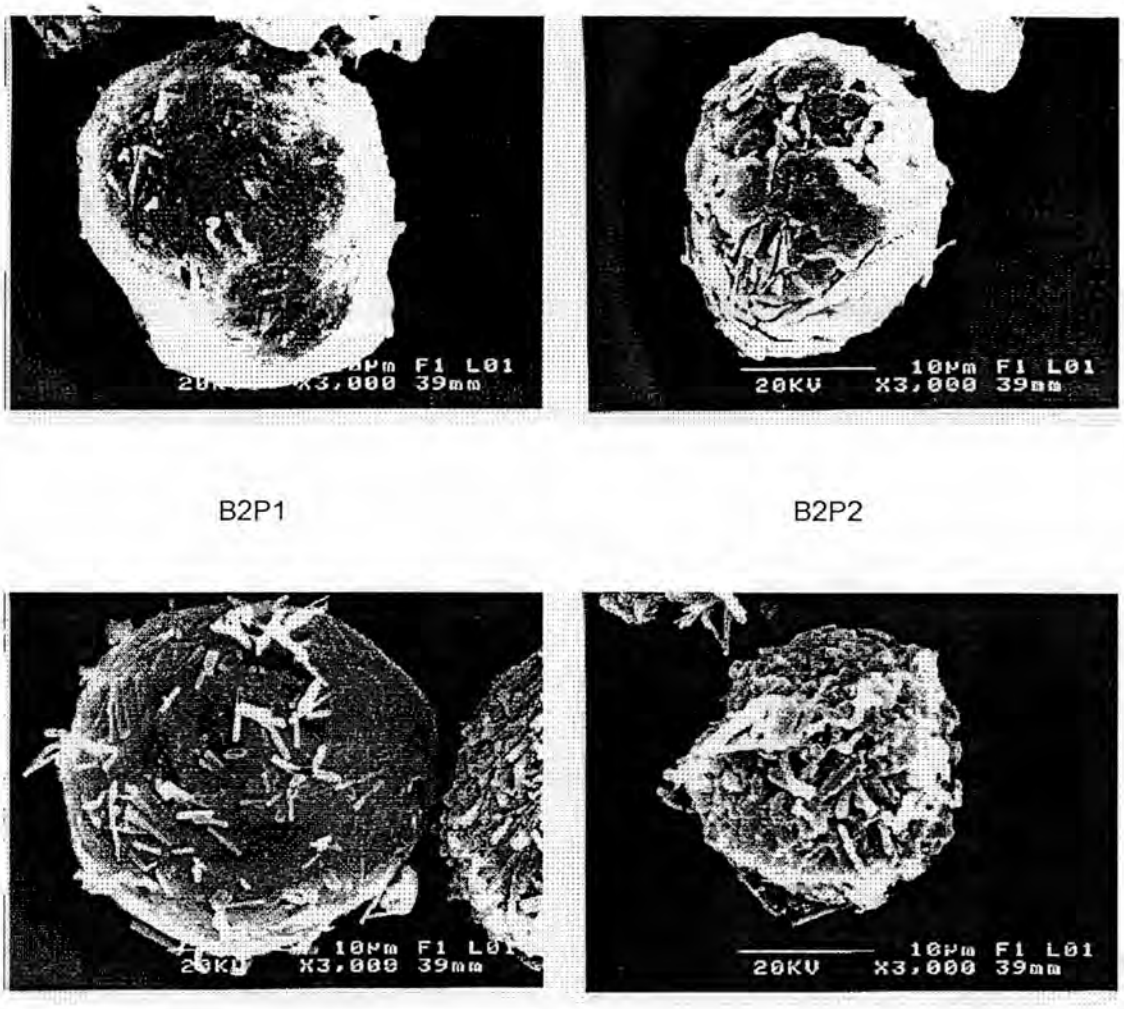


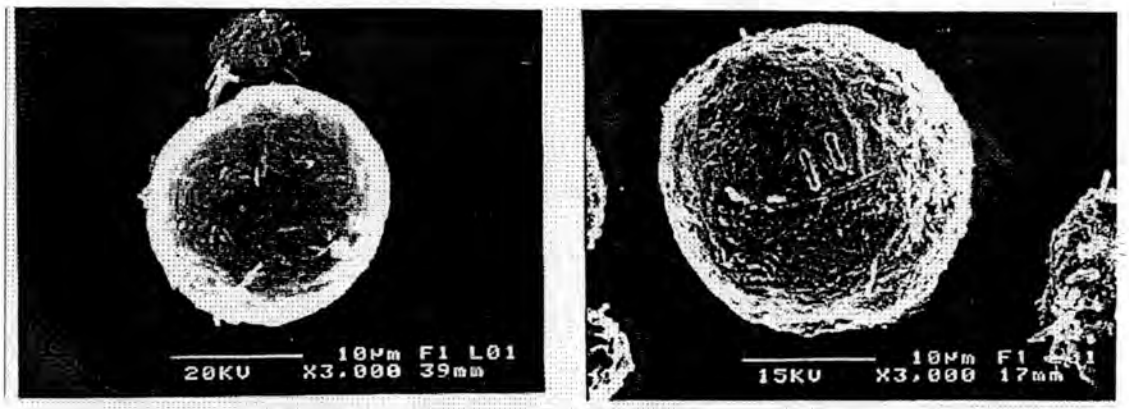
Figure 13 Scanning electron photomicrographs of spray-dried diclofenac sodium powders produced from Seacure® 343 at the ratio of 1:10 with the aid of 10% (B2P1), 20% (B2P2), 33% (B2P3) and 40% propylene glycol (B2P4), (x3,000).

surfaced microcapsules were obtained from the formulations that used proper amount of propylene glycol, which were 10% to 33% of the polymer and drug content. Even though the long and rectangular shaped microcrystals were deposited all around the surface and increased in amount and size when percent of propylene glycol used was increased higher than 10%. Agglomeration of microcapsules found when percent of propylene glycol was up to 40%.

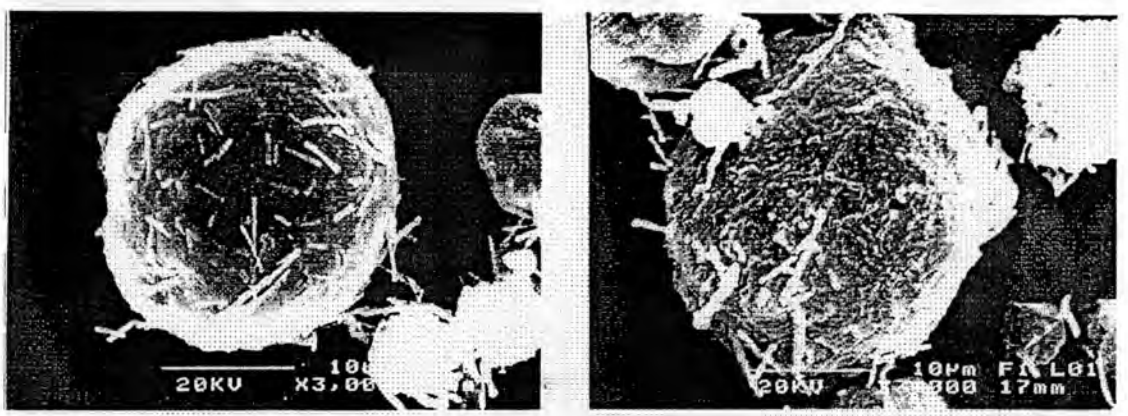
The photomicrographs of the formulations used Seacure® 343 with glycerin at the polymer to drug ratio of 1:10 showed a little smoother surface of the microcapsules compared with those from the formulations used Seacure® 243 at the same ratio. The smoothest surface of microcapsules was produced when 33% of glycerin was used, but no difference in size of the microcapsules were detectable in these set of formulations.

The microscopic views of spray dried diclofenac sodium with Seacure® 243 in the polymer to drug ratio of 1:15 with the addition of propylene glycol are shown in Figure 14. The overall shape of microcapsules was nearly spherical with different sizes. The proper amount of 20% propylene glycol presented complete microcapsules with smooth surface and spherical shape. The amount of microcrystals on the surface of the microcapsules depended on the amount of propylene glycol used and the agglomeration of the microcapsules started when 33% of propylene glycol was used.

When the photomicrographs of Figure 14 that used the same formulations except the polymer grade was changed from Seacure® 243 to Seacure® 343 were compared, only the formulation that used 33% of propylene glycol produced spherical shaped microcapsules with smooth surface. Whereas the two lower levels of percent plasticizers (10 and 20%) showed the microcapsules with rough surface like orange peel texture. All propylene glycol-plasticized microcapsules had a number of long, rectangular shaped microcrystals adhered on the surface.



A3P1 B3P1



A3P2 B3P2

A3P3 B3P3

Figure 14 Scanning electron photomicrographs of spray-dried diclofenac sodium powders produced from Seacure® 243 and 343 at the ratio of 1:15 with the aid of 10% (A3P1/B3P1), 20% (A3P2/B3P2) and 33% propylene glycol (A3P3/B3P3), (x3,000).

From Figure 15, the formulations which used glycerin instead of propylene glycol showed good characteristic microcapsules. When 10% of glycerin was used, complete microcapsules with smooth surface were produced while the 20% glycerin-plasticized microcapsules had spherical shape but the surface were mostly cracked. When the amount of glycerin was increased to 33%, the microcapsules with fish scale-like surface were found.

1.2 Angle of Repose, Bulk Density, Tapped Density and Percent Compressibility

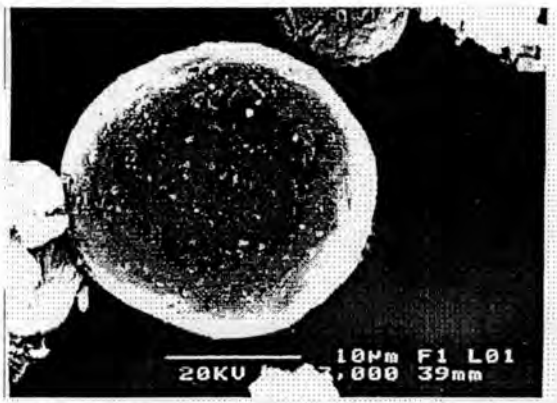
Angle of repose, bulk density, tapped density and percent compressibility of the spray dried powder prepared from different formulations are shown in Table 16.

Angle of reposes from the spray dried powders produced by the polymer to drug ratio of 1:20 and 1:30 were lower than 20 degree and no remarkable difference was detected, when different grade of Seacure® was used.

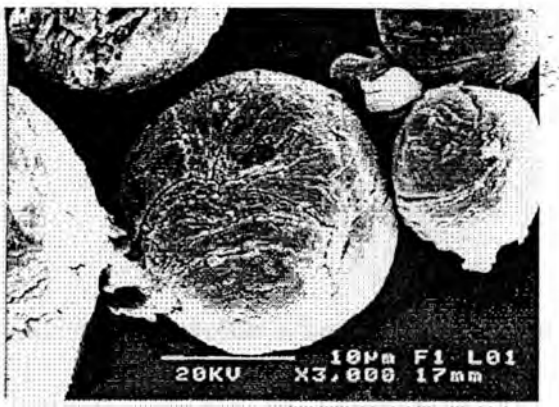
The bulk and tapped densities of all preparations could not be clearly concluded, because the determined values varied. However, when these densities were calculated to percent compressibility, the new results could be interpreted and showed the effects of formulation modifications.

Percent compressibility values of the spray dried powders prepared from different amount of Seacure® 243 and 343 without plasticizer were presented in the same pattern. When the polymer to drug ratios were 1:5, 1:10 and 1:15, percent compressibility showed no significant difference but this value was obviously increased in the ratio of 1:20 and 1:30.

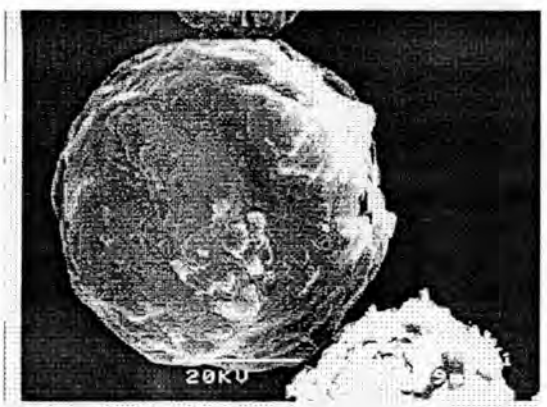
Two type of plasticizers, propylene glycol and glycerin, showed the parallel effect on the percent compressibility. The powders produced from Seacure®



B3G1



B3G2



B3G3

Figure 15 Scanning electron photomicrographs of spray-dried diclofenac sodium powders produced from Seacure® 343 at the ratio of 1:15 with the aid of 10% (B3G1), 20% (B3G2) and 33% glycerin (B3G3), (x3,000).

Table 16 The angle of repose, the bulk density, tapped density and percent compressibility of the spray-dried products prepared from different formulations.

Formulation	Angle of repose* (degree)	Bulk Density * (g/ml)	Tapped Density * (g/ml)	% Compreesibility (%)
A1	25.9	0.2990	0.5091	41.3
A2	25.1	0.2804	0.4365	35.8
A3	26.3	0.2560	0.4095	37.5
A4	18.3	0.2488	0.4708	47.1
A5	19.4	0.2591	0.4741	45.4
B1	24.7	0.2605	0.4240	38.6
B2	26.0	0.3507	0.5309	35.4
B3	28.0	0.2776	0.4302	35.4
B4	20.2	0.2119	0.4717	55.0
B5	17.6	0.2449	0.4644	47.3
A1 P2	30.3	0.3770	0.6003	37.2
A1 P3	28.2	0.3114	0.5079	38.7
A1 G2	30.7	0.3793	0.5935	36.1
A1 G3	35.2	0.3450	0.5773	40.2
A2 P1	31.5	0.3671	0.5824	36.9
A2 P2	29.2	0.3977	0.6449	38.4
A2 P3	35.1	0.3157	0.5363	41.1
A2 P4	30.1	0.2542	0.5276	51.8
A2 G1	30.5	0.3807	0.6058	37.1
A2 G2	32.3	0.2963	0.5764	48.5
A2 G3	31.1	0.3246	0.5560	41.6
B2 P1	29.3	0.3411	0.5563	39.2
B2 P2	29.2	0.3167	0.5533	42.7
B2 P3	31.7	0.3494	0.6055	42.3
B2 P4	30.3	0.2535	0.5515	53.9
B2 G1	28.2	0.3724	0.6187	39.8
B2 G2	32.9	0.3376	0.5846	42.2
B2 G3	28.8	0.3502	0.5825	39.9
A3 P1	28.5	0.3135	0.5815	46.1
A3 P2	29.7	0.3584	0.6269	43.2
A3 P3	32.5	0.3266	0.5908	43.9
B3 P1	30.1	0.3296	0.5202	36.7
B3 P2	35.4	0.3336	0.5435	38.6
B3 P3	31.5	0.3921	0.6801	42.3
B3 G1	28.4	0.3654	0.5904	38.1
B3 G2	30.3	0.3675	0.6140	40.1
B3 G3	30.7	0.3543	0.5969	40.6

* Average from 3 determinations.

243 at the polymer to drug ratio of 1:5 with plasticizer gave 36 - 40 percent compressibility value in all formulations which were lower than the percent compressibility of the unplasticized formulations. Whereas the other ratios displayed the opposite results. All percent compressibility values of the spray dried powders with the aid of plasticizers at the polymer to drug ratio of 1:10 and 1:15 of both Seacure® 243 and 343 were higher than the values of their unplasticized formulations. There was a tendency to increase in the percent compressibility, when the percent of the plasticizer in the formulation increased.

1.3 The Yield of Production

The yield of spray dried powder is expressed as the weight in percent of the final product harvested with respected to the initial amount of all components in each formulation. In spray drying process, the suspension was fed through the atomizing head nozzles into droplets, then the droplets were dried immediately. The product was collected from the collector and chamber and the amount of the products from two sources was calculated as the percent yield. The yields of production are shown in Table 17.

The results displayed that the percent yield from the collector was higher than that from the chamber in every formulation. No difference in percent yield was detected in the formulations produced by both Seacure® 243 and 343 without plasticizer. The percent yields of unplasticized spray dried powders were in the range of 80 - 90% of the initial amount, while almost all of the plasticized formulations gave only 60 - 80%. Four plasticized formulations had percent yield higher than 80% and all of them used the lowest level of plasticizers in the spray dried formulations (10% of drug and polymer content). Thus it could be concluded that the percent yield of the product was significantly decreased when the percent of the plasticizer used in the formulation was increased.

Table 17 The percent yield and the loss on drying values of spray-dried products .

Formulation	Percent Yield of Production			Loss on Drying* (%)
	Collector	Chamber	Total	
A1	78.15	8.22	86.37	5.56
A2	76.59	8.30	84.89	4.23
A3	80.45	10.30	90.75	4.54
A4	80.78	8.17	88.95	4.11
A5	82.13	8.05	90.18	4.26
B1	77.56	9.33	86.89	4.56
B2	71.08	9.64	80.72	3.70
B3	75.22	7.07	82.29	4.20
B4	85.38	4.67	90.05	4.92
B5	85.63	5.26	90.89	3.23
A1 P2	66.42	6.50	72.92	6.14
A1 P3	62.38	5.42	67.80	6.76
A1 G2	59.46	9.82	69.28	10.16
A1 G3	55.37	12.74	68.11	12.02
A2 P1	67.70	8.78	76.48	4.33
A2 P2	53.34	15.30	68.64	3.03
A2 P3	54.54	8.39	62.93	3.17
A2 P4	61.88	3.68	64.86	9.31
A2 G1	69.43	13.80	83.23	7.64
A2 G2	67.25	9.38	76.63	11.57
A2 G3	46.89	16.85	63.74	12.45
B2 P1	66.16	4.62	70.78	5.08
B2 P2	69.14	4.41	73.55	5.31
B2 P3	49.49	13.85	63.34	3.46
B2 P4	57.03	8.75	65.78	10.24
B2 G1	68.80	12.88	81.68	8.37
B2 G2	64.16	14.33	78.49	11.65
B2 G3	49.98	15.18	65.16	9.65
A3 P1	73.63	3.87	77.50	3.94
A3 P2	56.44	5.62	62.06	4.05
A3 P3	58.28	6.66	64.94	3.76
B3 P1	75.44	7.64	83.08	4.39
B3 P2	69.52	5.22	74.74	4.98
B3 P3	58.44	10.40	68.84	4.62
B3 G1	73.54	8.37	81.91	5.75
B3 G2	57.69	12.99	70.68	8.42
B3 G3	44.80	21.86	66.66	9.36

* Average from 3 determinations

1.4 Loss on Drying

The loss on drying values of the spray dried powders prepared from various formulations are presented in Table 17. The polymer to drug ratio and grade of polymer in the unplasticized formulations had insignificant effect on the loss on drying value of the powder. Propylene glycol exhibited strongly water absorbing property compared to the spray dried powder only when the highest amount of the plasticizer (40%) was used. No remarkable difference in the formulations used propylene glycol in the range of 10 - 33%, when compared with the unplasticized formulations.

On the contrary, glycerin used in the formulation as the plasticizer remarkably affected the loss on drying value of the spray dried powder. The higher amount of glycerin used, the higher loss on drying value detected.

1.5 Drug Content

The percent drug contents of the spray dried powders from various formulations are shown in the Table 18. The percent drug content in this study was examined from the collector only. The standard deviation indicated the uniformity of drug in the spray dried products.

From the table, the difference between theoretical drug content and experimental drug content was presented as percent difference that showed the important effects of the components in the formulation.

Percent difference in the range of ± 5% was acceptable that there were no significant difference between percent theoretical and percent experimental drug content. All percent experimental drug content of the unplasticized formulation were lower than their theoretical drug content. Most values of the unplasticized formulations conformed to this criteria except those of the polymer to drug ratio of 1:5 produced by both types of Seacure® and 1:20 of Seacure® 343.

Table 18 The percentage of drug content in spray-dried products.

Formulation	% Theoretical Drug Content	% Experimental Drug content [SD] *	% Difference
A1	79.36	70.76 [0.9103]	-8.60
A2	86.58	84.56 [0.3819]	-2.02
A3	89.28	86.28 [0.5777]	-3.00
A4	90.74	86.04 [0.3204]	-4.70
A5	92.16	89.61 [1.5280]	-2.55
B1	79.36	74.35 [0.1877]	-5.01
B2	90.91	87.92 [0.1061]	-2.99
B3	93.81	90.94 [1.1650]	-2.87
B4	90.74	85.27 [0.5008]	-5.47
B5	92.16	89.12 [0.2828]	-3.04
A1 P2	66.67	74.70 [0.2207]	8.03
A1 P3	60.24	73.89 [0.6048]	13.65
A1 G2	66.67	70.40 [0.4801]	3.73
A1 G3	60.24	64.89 [0.2363]	4.65
A2 P1	78.74	85.14 [0.2758]	6.40
A2 P2	72.67	86.71 [0.6010]	14.04
A2 P3	65.88	83.92 [0.5186]	18.04
A2 P4	62.11	80.99 [0.1637]	18.88
A2 G1	78.74	77.34 [3.2739]	-1.40
A2 G2	72.67	70.67 [0.2060]	-2.00
A2 G3	65.88	69.75 [0.3387]	3.87
B2 P1	78.86	83.02 [0.5091]	4.16
B2 P2	72.67	82.48 [0.8974]	9.81
B2 P3	65.88	83.90 [0.8656]	18.02
B2 P4	62.11	78.60 [0.9832]	16.49
B2 G1	78.93	78.45 [0.3686]	-0.48
B2 G2	72.67	72.56 [0.5496]	-0.11
B2 G3	65.88	69.64 [0.5798]	3.76
A3 P1	80.64	89.35 [1.0336]	8.71
A3 P2	74.07	87.04 [0.3150]	12.97
A3 P3	67.57	87.86 [0.1792]	20.29
B3 P1	81.50	85.78 [0.5503]	4.28
B3 P2	74.96	87.36 [0.0354]	12.40
B3 P3	67.93	82.46 [0.6006]	14.53
B3 G1	81.50	84.71 [0.4636]	3.21
B3 G2	75.19	80.67 [0.1838]	5.48
B3 G3	67.93	70.50 [0.6435]	2.57

* Calculated from the Collector only and standard deviation from 3 determinations

The formulations used propylene glycol as plasticizer had percent difference out of this range (± 5%) except some formulations that used the lowest amount of propylene glycol (10% of drug and polymer content). Whereas the use of glycerin gave a narrow range of percent difference. Only one formulation produced by Seacure® 343 at polymer to drug ratio of 1:15 with 20% of glycerine showed the value of +5.48%.

1.6 Infrared Spectra

The IR spectra of diclofenac sodium alone , Seacure® and spray dried powders prepared from various formulations are separated into related groups and shown in Figures 16 - 22. The principle peaks of diclofenac sodium were observed at the wavenumbers of 747, 765, 1281, 1303, 1506 and 1573 cm^{-1}. The peaks at 747 and 765 cm^{-1} were resulted from C-H out of plane bending. The IR absorption bands at 1281 and 1303 cm^{-1} were resulted from C-N stretching and the peaks at 1506 and 1573 cm^{-1} were resulted from C=C stretching.

The IR spectra of Seacure® showed the broad bands of N-H stretching and O-H stretching at the wavenumber of 3400 cm^{-1}. The C-H stretching peak was represented at 2870 cm^{-1} but could not be clearly seen. The most important peak at 1653 cm^{-1} was resulted from the characteristic N-H Bending of the chitosan structure. The broad peaks of -C-O-C- bond in the hexagonal ring was located at 1092 cm^{-1}.

The IR spectra of spray dried diclofenac sodium with Seacure® 243 at the different polymer to drug ratios without plasticizers are illustrated in Figure 18. The IR spectra of spray dried powders showed the combination of diclofenac sodium peaks with those of Seacure®, whereas the characteristic peaks of both diclofenac sodium and Seacure® were also revealed. The N-H bending peaks of polymer was shifted to the higher wavenumber in all spray dried formulations. The positions after shifting of characteristic peaks of the spray dried powders are presented in Table 19.

The IR spectra of the spray dried powders of the formulations produced by the different grade of Seacure® are shown in Figure 19. There was no difference between the principle spectra of the formulation using Seacure® 243 and 343. These results indicated that the interaction between drug and polymer was hardly seen and grade of polymer had no effect on the IR spectra in this study.

Figure 20 depicts the spectra of spray dried powders using Seacure® 243 as a polymer with and without plasticizers. The observation indicated no difference in the positions of the spectra and still revealed the eminent peaks of both drug and polymer.

The IR spectra of the formulations used Seacure® 243 with the addition of propylene glycol and glycerin are depicted in Figures 21 and 22, respectively. The IR characteristic bands of the mix powder was not shown any interaction between drug, polymer and plasticizers after the spray drying process.

The amount of plasticizers used in the formulations did not affect the IR spectra of the spray dried powders. The characteristic peaks of the plasticized formulations were not shifted from their positions compared to the IR spectra of the unplasticized formulations.

1.7 Powder X-ray Diffraction

The X-ray diffraction patterns of diclofenac sodium, Seacure® and spray dried powders from various formulations are separated into related groups and illustrated in Figures 23 - 26. These diffraction patterns were run by Jeol JDX-3530.

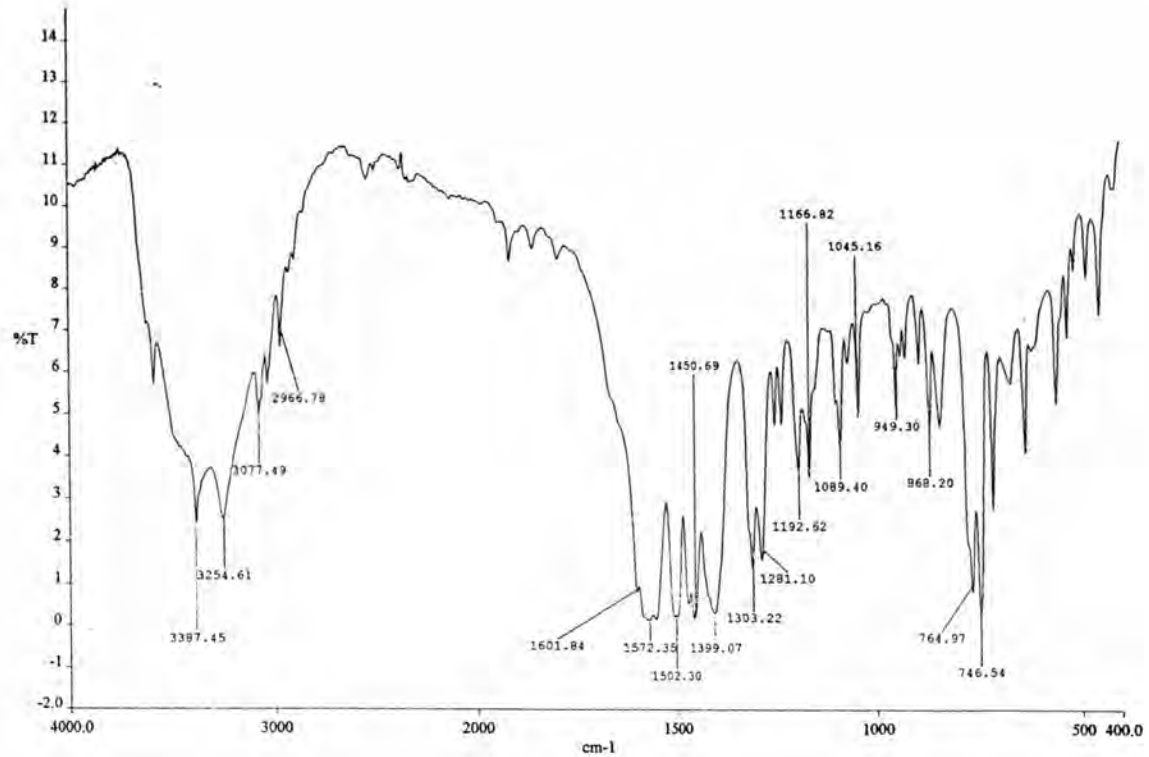


Figure 16 IR spectra of diclofenac sodium (DS).

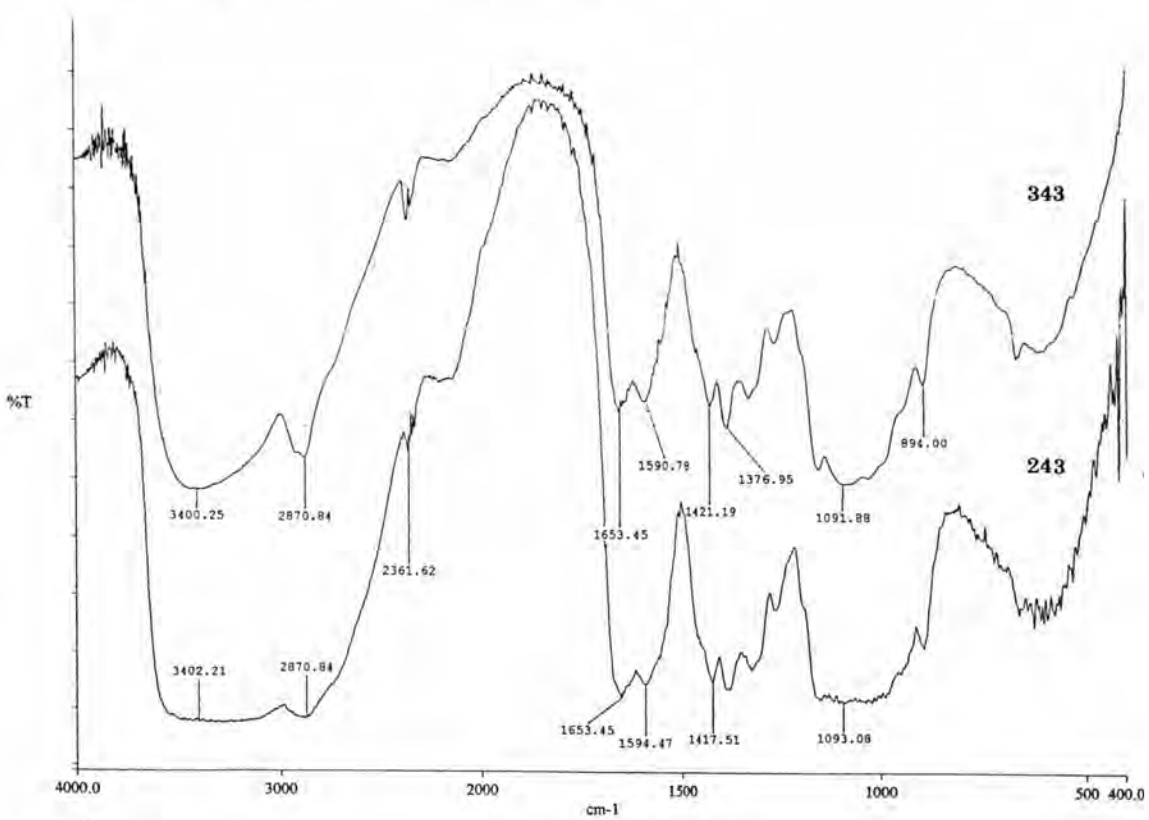


Figure 17 IR spectra of Seacure® 243 (243) and 343 (343).

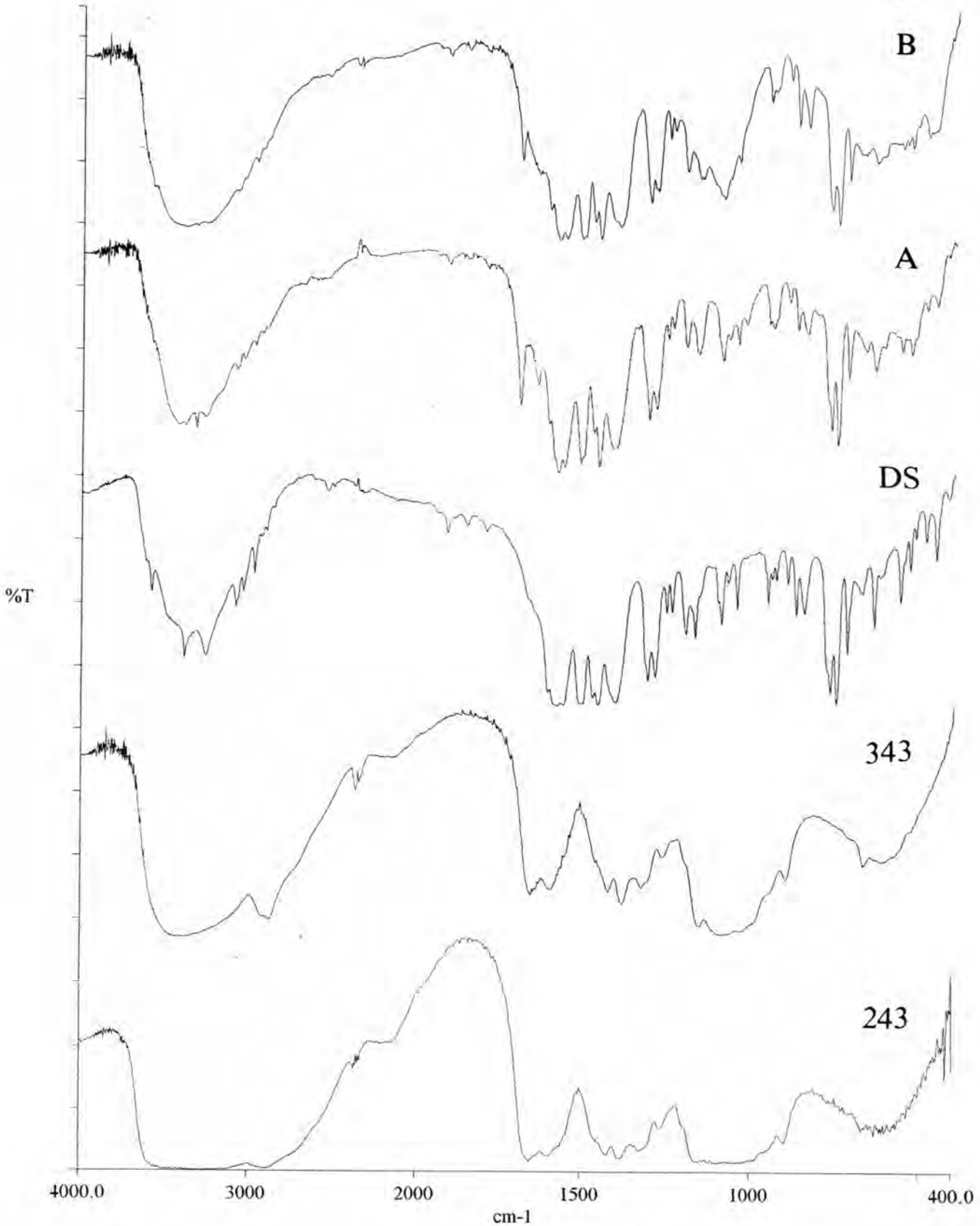


Figure 18 IR spectra of diclofenac sodium (DS), Seacure® 243 (243) and 343 (343) and spray dried powders produced from two grades of Seacure® at the ratio of 1:15 without plasticizer (A and B).

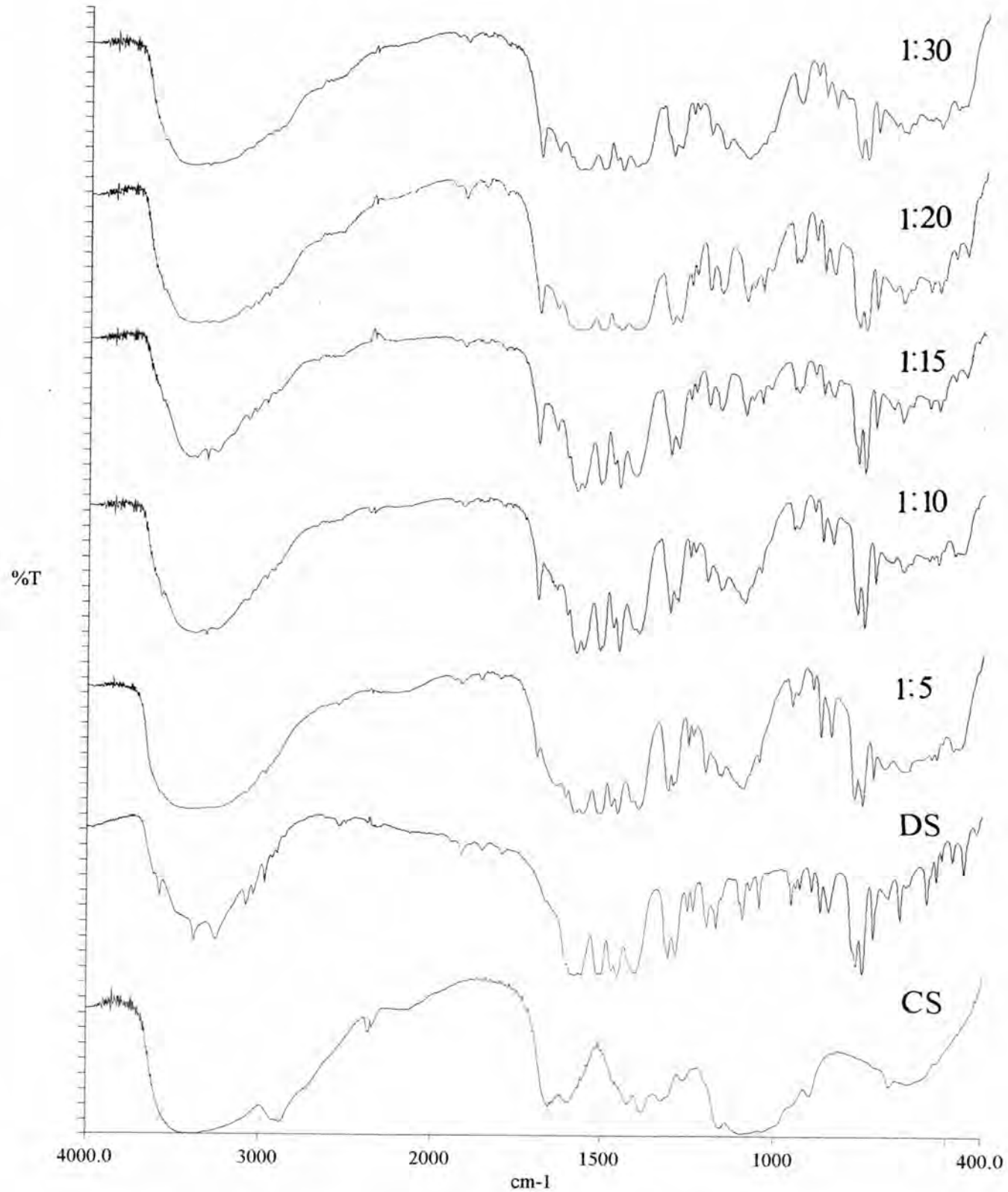


Figure 19 IR spectra of diclofenac sodium (DS), Seacure® 243 (CS) and spray dried powders produced from Seacure® 243 at the various ratios without plasticizer (1:5, 1:10, 1:15, 1:20 and 1:30).

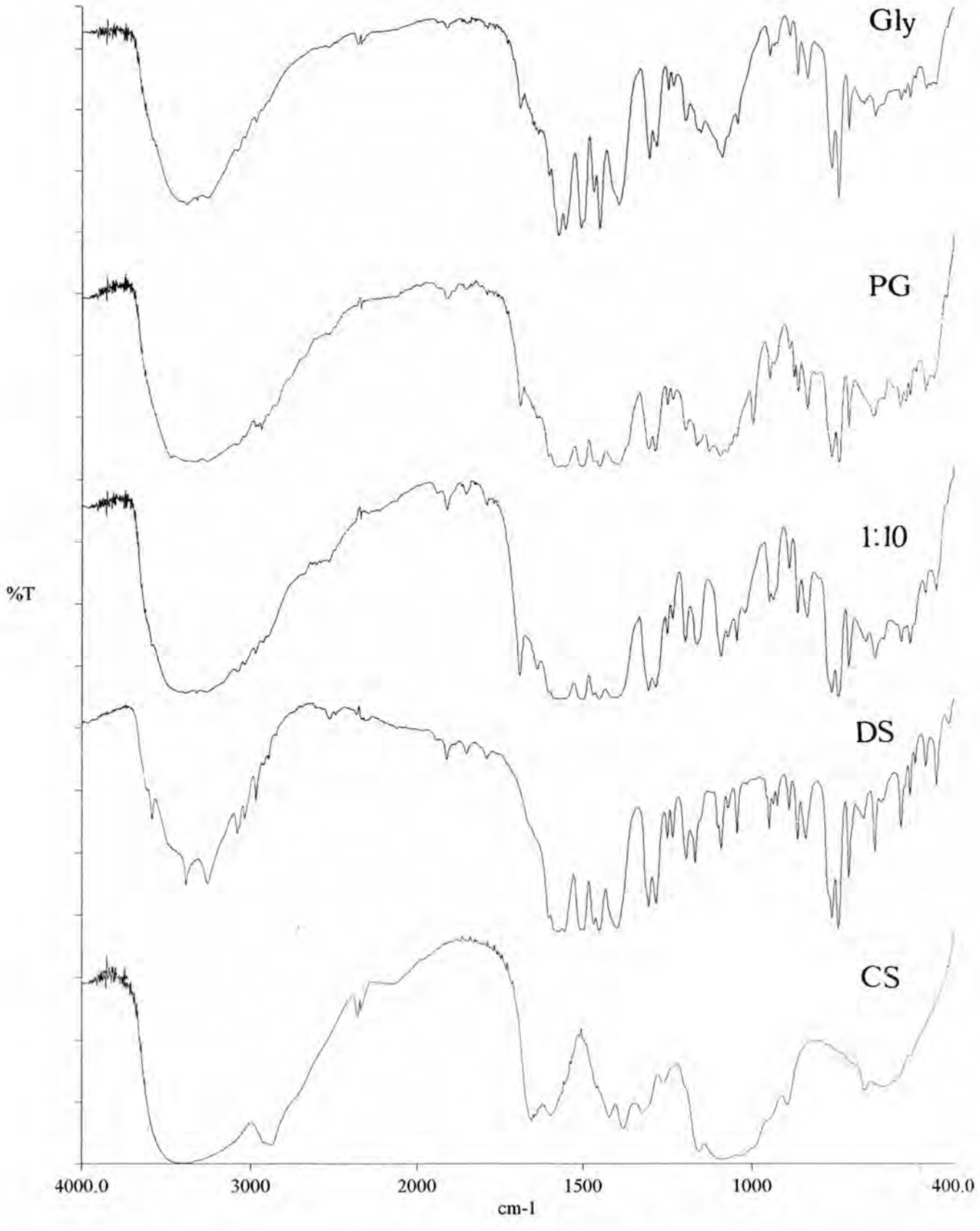


Figure 20 IR spectra of diclofenac sodium (DS), Seacure® 243 (CS) and spray dried powders produced from Seacure® 243 at the ratio of 1:10 without plasticizer (1:10) and with 10% of propylene glycol (PG) and glycerin (Gly).

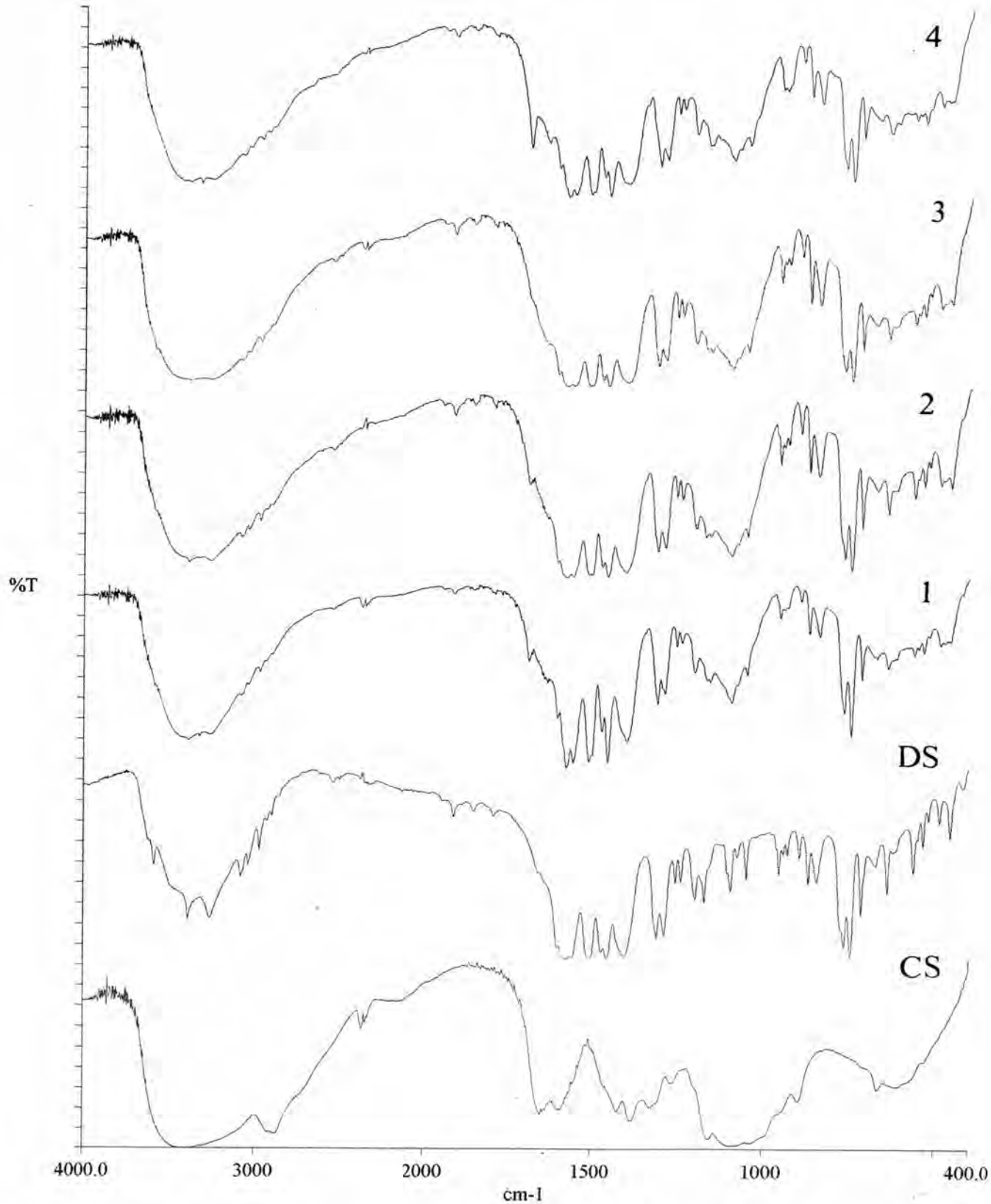


Figure 21 IR spectra of diclofenac sodium (DS), Seacure® 243 (CS) and spray dried powders produced from Seacure® 243 at the ratio of 1:10 with various amount of propylene glycol (10%PG = 1, 20%PG = 2, 33%PG = 3 and 40%PG = 4).

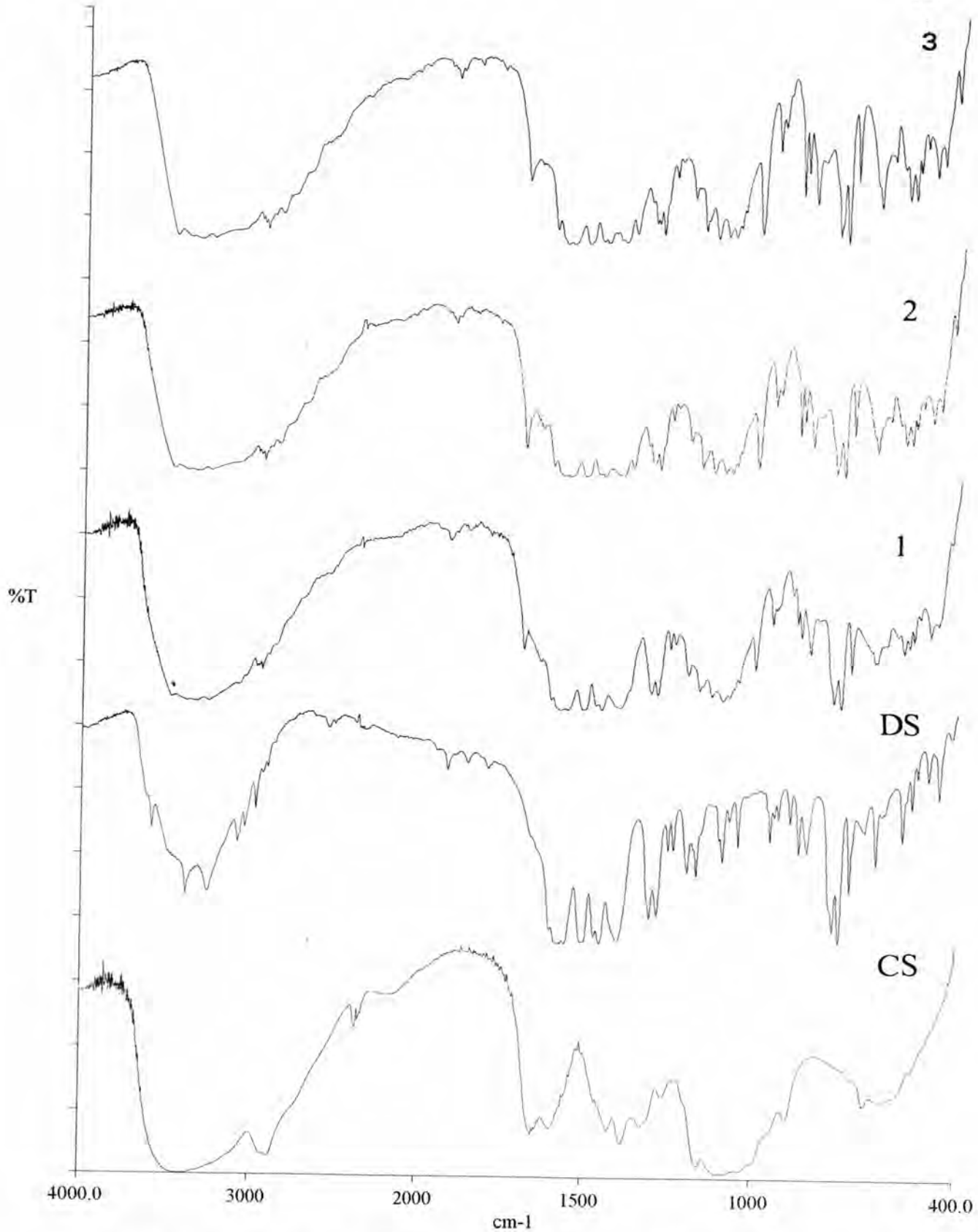


Figure 22 IR spectra of diclofenac sodium (DS), Seacure® 243 (CS) and spray dried powders produced from Seacure® 243 at the ratio of 1:10 with various amount of glycerin (10%Gly = 1, 20%Gly = 2 and 33%Gly = 3).

Table 19 Characteristic peaks of the IR spectra of spray dried products produced by different types and proportions of polymers and plasticizers.

Formulation	Characteristic Peaks (cm-1)								
Diclofenac sodium	747	765	.	1281	1303	1506	1573	.	.
Seacure 243	.	.	1093	.	.	.	.	1653	3402
Seacure 343	.	.	1092	.	.	.	.	1653	3400
A1	748	765	1089	1281	1303	1506	1577	1694	3325
A2	746	765	1089	1281	1303	1506	1571	1694	3324
A3	747	765	1089	1281	1303	1505	1576	1694	3324
A4	748	765	1089	1281	1303	1506	1577	1694	3324
A5	748	769	1089	1281	1303	1508	1576	1694	3401
B3	748	765	1089	1281	1303	1506	1577	1694	3391
A2 P1	747	765	1089	1281	1303	1506	1577	1694	3388
A2 P2	747	765	1089	1281	1303	1506	1575	1694	3388
A2 P3	747	765	1089	1281	1303	1506	1574	x	3390
A2 P4	747	765	1089	1281	1303	1506	1577	1694	3324
A2 G1	743	765	1093	1285	1303	1506	1575	1694	3325
A2 G2	743	765	1093	1285	1303	1506	1576	1694	3325
A2 G3	744	765	1093	1285	1303	1506	1572	1694	3339

x = no absorption peak.

The X-ray diffraction patterns of diclofeanc sodium alone showed characteristic peaks at 6.5°, 8.5°, 15.2°, 17.1°, 19.8°, 23.4°, 27.8° and small peaks at the diffraction angle between 15 - 30°. The intensities of the diffraction peaks of the spray dried powders of every formulations were weaker than those of diclofenac sodium alone, especially the small peaks. Slightly higher baseline was detected but the eminent peaks were still found. The characteristic halo of amorphous of Seacure® 243 was shown at 10.6° and 20.1°. Whereas those of Seacure® 343 was slightly shifted to 10.9° and 20.2°, respectively.

No difference between the X-ray diffraction patterns of diclofenac sodium alone and diclofenac sodium spray dried powders prepared by both grades of Seacure®. Therefore, diclofenac sodium was still in crystalline form but different degree of crystallinity in all formulations. The difference in the X-ray diffraction patterns of diclofenac sodium with various amount of polymer were not detectable except the diffraction pattern of the formulation of polymer to drug ratio of Seacure® 243 at 1:5. Some characteristic peaks of all formulations were shifted from that of diclofenac sodium. The shifts of the X-ray diffraction peaks of spray dried formulation are shown in Table 20.

The X-ray diffraction patterns of some formulations were run by two equipment those are Joel JDX-3530 and Rigaku Denki. The X-ray diffraction patterns and characteristic peaks positions of Rigaku Denki are shown in the Figure 27 and Table 20, respectively.

The characteristic peak of diclofenac sodium at 17.1° was disappeared in all glycerin-plasticized formulations done by both equipment except 10% glycerin-plasticized formulation produced by Jeol JDX-3530 that still shows this peak but shift to 17.7°. The other peaks of the spray dried powders of 20 and 33% glycerin-plasticized formulations done by Rikagu Denki are similar to those of unplasticized and propylene glycol-plasticized formulations. Whereas the characteristic peaks produced by Joel JDX-3530 at 6.5, 8.5, 17.1 and 19.8° disappeared with the higher baseline.

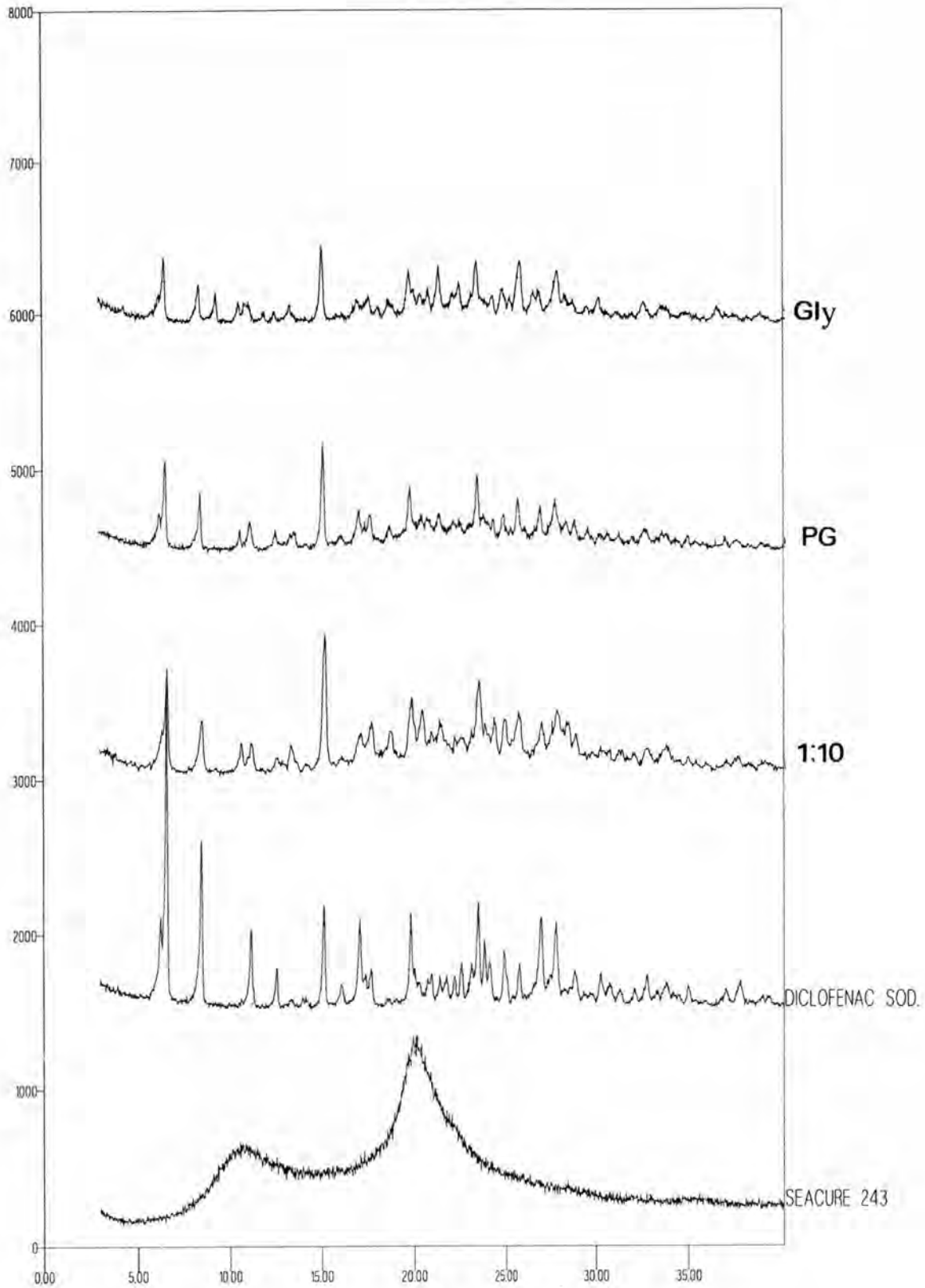


Figure 23 X-ray diffractograms of diclofenac sodium, Seacure® 243 and spray dried powder produced from Seacure® 243 at the ratio of 1:10 without plasticizer (1:10) and with 10% of propylene glycol (PG) and glycerin (Gly) by using Jeol JDX-3530.

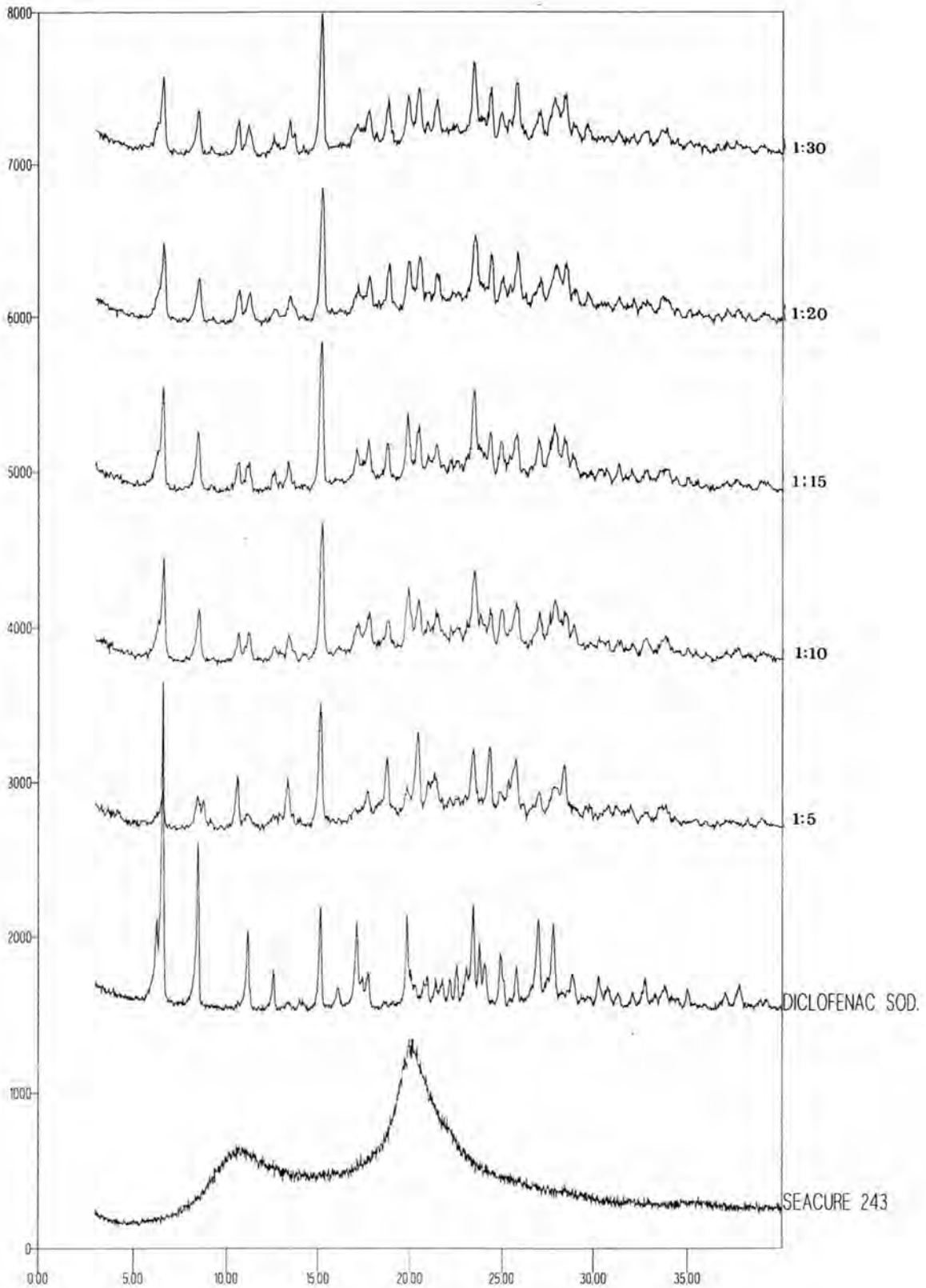


Figure 24 X-ray diffractograms of diclofenac sodium, Seacure® 243 and spray dried powder produced from Seacure® 243 at the various ratios without plasticizer (1:5, 1:10, 1:15, 1:20 and 1:30) by using Jeol JDX-3530.

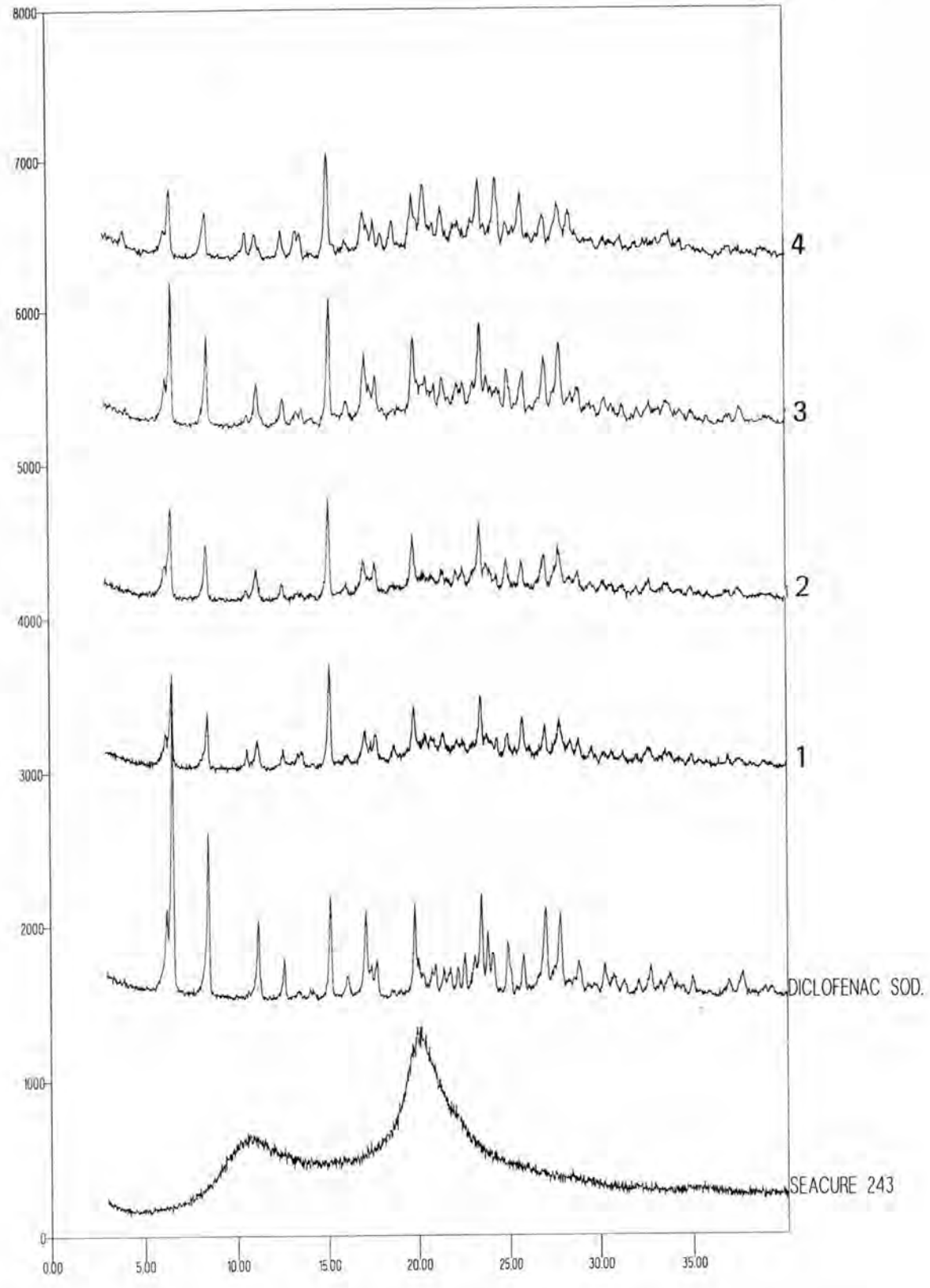


Figure 25 X-ray diffractograms of diclofenac sodium, Seacure® 243 and spray dried powder produced from Seacure® 243 at the ratio of 1:10 with various amount of propylene glycol (10%PG = 1, 20%PG = 2, 33%PG = 3 and 40%PG = 4) by using Jeol JDX-3530.

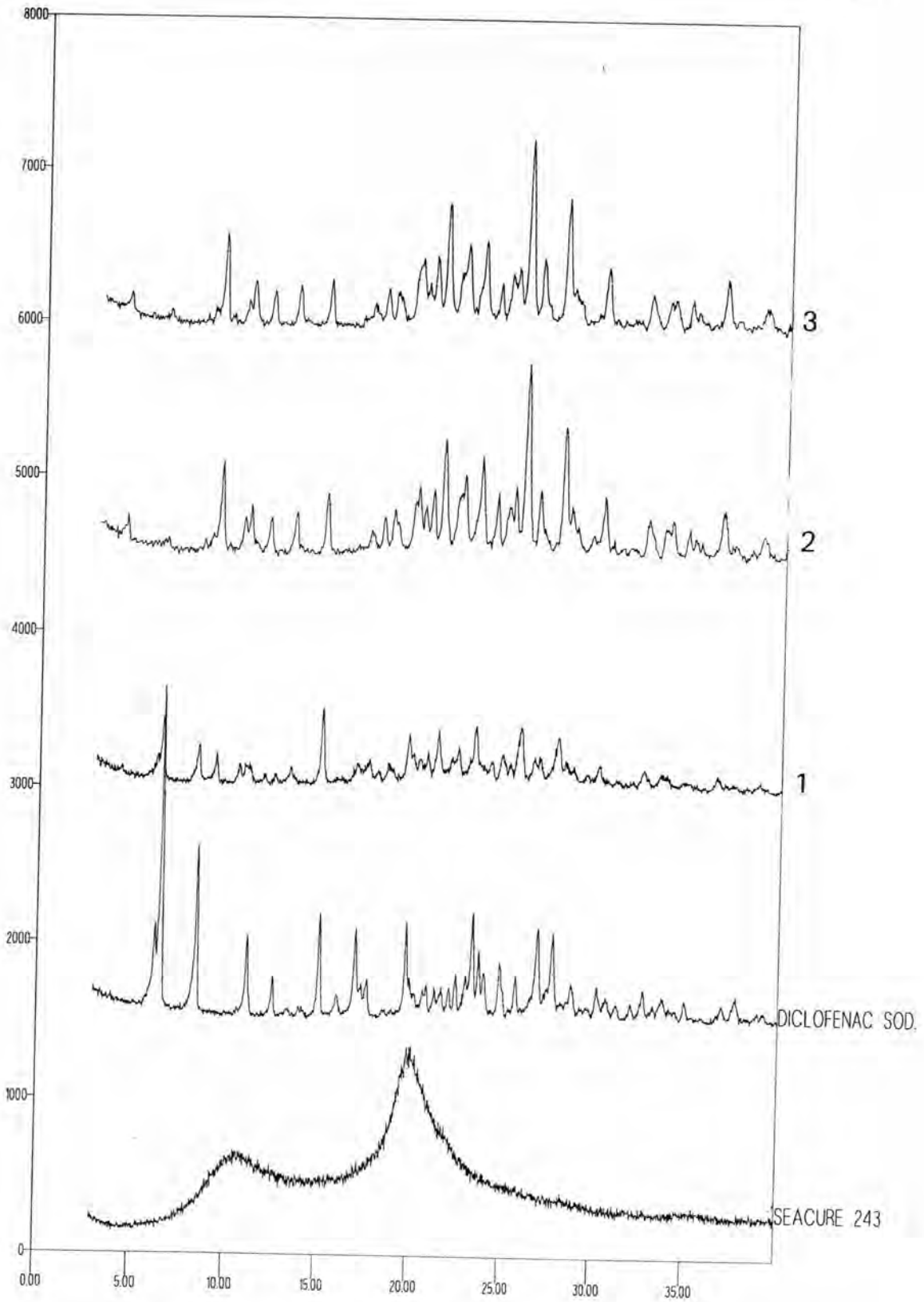


Figure 26 X-ray diffractograms of diclofenac sodium, Seacure® 243 and spray dried powder produced from Seacure® 243 at the ratio of 1:10 with various amount of glycerin. (10%Gly = 1, 20%Gly = 2, and 33%Gly = 3) by using Jeol JDX-3530.

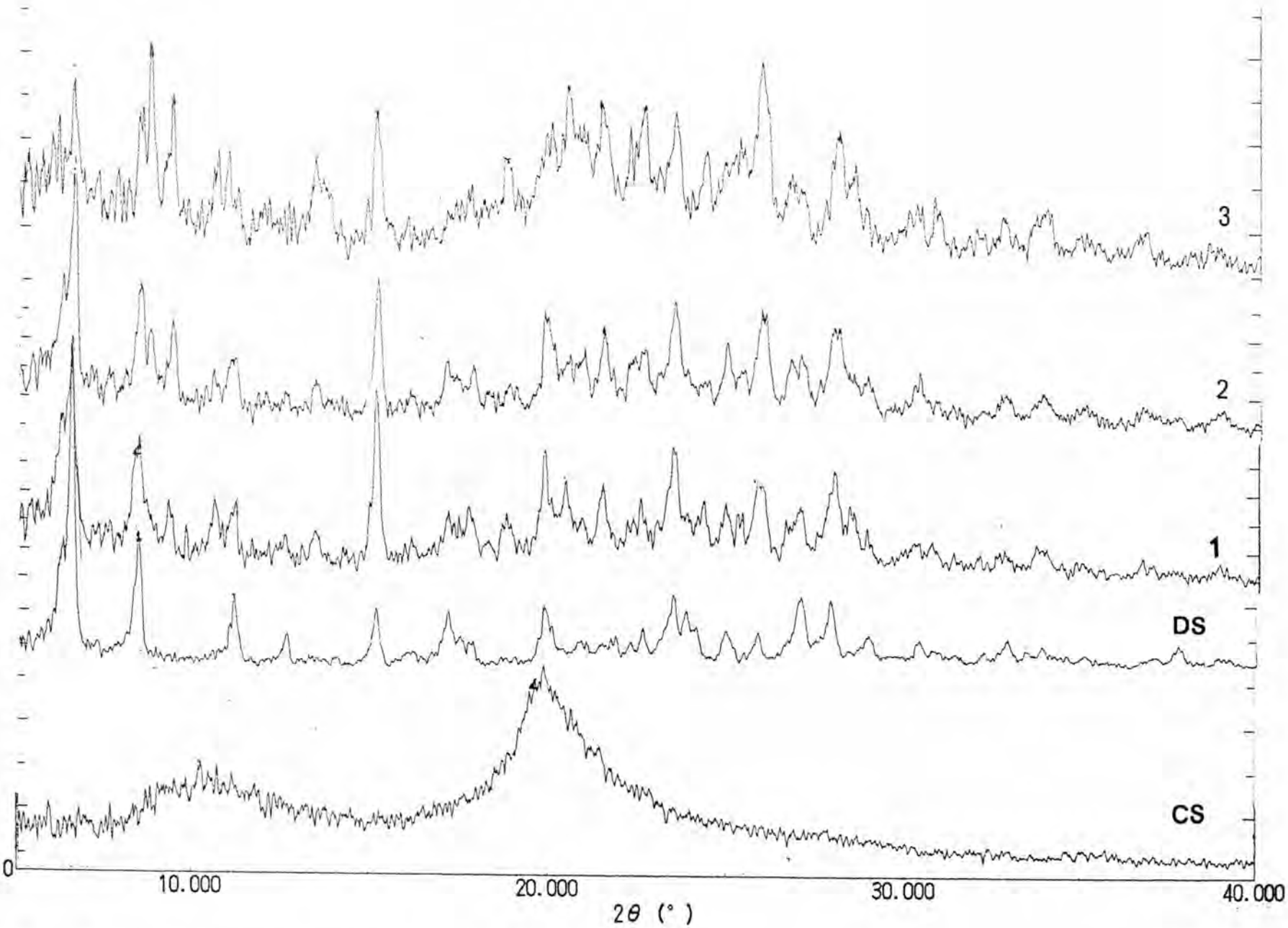


Figure 27 X-ray diffractograms of diclofenac sodium (DS), Seacure 243 (CS) and spray dried powders produced from Seacure 243 at the ratio of 1:10 with various amount of glycerin (10%Gly = 1, 20%Gly = 2, and 33%Gly = 3) by using Rigaku Denki (Miniflex)

Table 20 Characteristic peaks of the X-ray diffraction patterns of spray dried products produced by different types and proportions of polymers and plasticizers.

Formulation	Characteristic Peaks (degree)								
Diclofenac sodium	6.5	8.5	.	15.2	17.1	19.8	.	23.4	27.8
Seacure 243	.	.	10.6	.	.	.	20.1	.	.
Seacure 343	.	.	10.9	.	.	.	20.2	.	.
A1	6.5	8.8	10.6	15.1	17.7	19.8	20.4	23.4	28.4
A2	6.6	8.5	10.7	15.2	17.8	19.9	20.5	23.5	28.0
A3	6.6	8.5	10.7	15.2	17.7	19.8	20.4	23.5	27.9
A4	6.6	8.5	10.7	15.2	17.8	20.0	20.6	23.6	28.4
A5	6.6	8.5	10.7	15.2	17.8	19.9	20.5	23.5	28.5
A2 P1	6.5	8.4	11.1	15.1	17.7	19.8	x	23.4	27.8
A2 P2	6.5	8.4	11.2	15.1	17.7	19.8	x	23.4	27.8
A2 P3	6.6	8.5	11.2	15.2	17.2	19.9	x	23.5	27.9
A2 P4	6.6	8.5	10.6	15.1	17.1	19.8	20.4	23.4	27.8
A2 G1*	6.5	8.4	10.9	15.1	17.7	19.8	x	23.4	28.0
A2 G2*	x	9.4	11.0	15.1	x	x	20.1	23.5	28.1
A2 G3*	x	9.4	10.9	15.2	x	x	20.1	23.5	28.0
A2 G1**	6.6	8.4	10.7	15.2	x	19.8	20.4	23.5	28.0
A2 G2**	6.6	8.5	10.7	15.2	x	19.9	20.5	23.5	28.0
A2 G3**	6.6	8.9	10.7	15.2	x	19.9	20.5	23.5	28.1

* Model JDX-3530, Jeol Ltd.,Japan

** Rigaku Denki (Miniflex), Japan

x = no absorption peak.

1.8 Thermal Analysis

1.8.1 Differential Scanning Calorimetry

The DSC thermograms of pure diclofenac sodium, Seacure®, propylene glycol, glycerin and spray dried powders prepared from different formulations are shown in Figures 28-30. The exotherm and endotherm of all components and spray dried products are indicated in Table 21.

The thermogram of pure diclofenac sodium presented the characteristic exotherm at 292.7°C, then followed by the endotherm at 311.5°C. Seacure® 243 and 343 had the same patterns of DSC thermograms and presented the exotherm at 108.0°C and 108.4°C, followed by the endotherm at 319.5°C and 322.4°C, respectively. The DSC thermograms of propylene glycol revealed only endotherm at 193.4°C, whereas glycerin showed two endotherm peaks at 259.8°C and 302.5°C.

From Figure 28, there was no difference between the DSC thermogram patterns of diclofenac sodium alone and those of the formulations prepared by spray drying process but the different in DSC peak temperatures were detected. The exotherm and endotherm of the formulation produced by polymer to drug ratio of 1:10 of Seacure® 243 without plasticizer were shifted to the lower temperature at 285.3°C and 305.2°C, respectively. The slightly lower of the thermograms detected in the range of 40 - 200°C was detected.

The spray drying formulations used various levels of propylene glycol exhibited similar patterns in the DSC thermograms as diclofenac sodium but different in DSC peak positions (Figure 29). The exotherm and endotherm of all propylene glycol-plasticized formulations were shifted to the lower temperature. When glycerin was used instead of propylene glycol, an important difference was detected. The broad endotherm peak was observed in the range of 50 - 150°C and this peak was broaden as the amount of glycerin in the formulation increased.

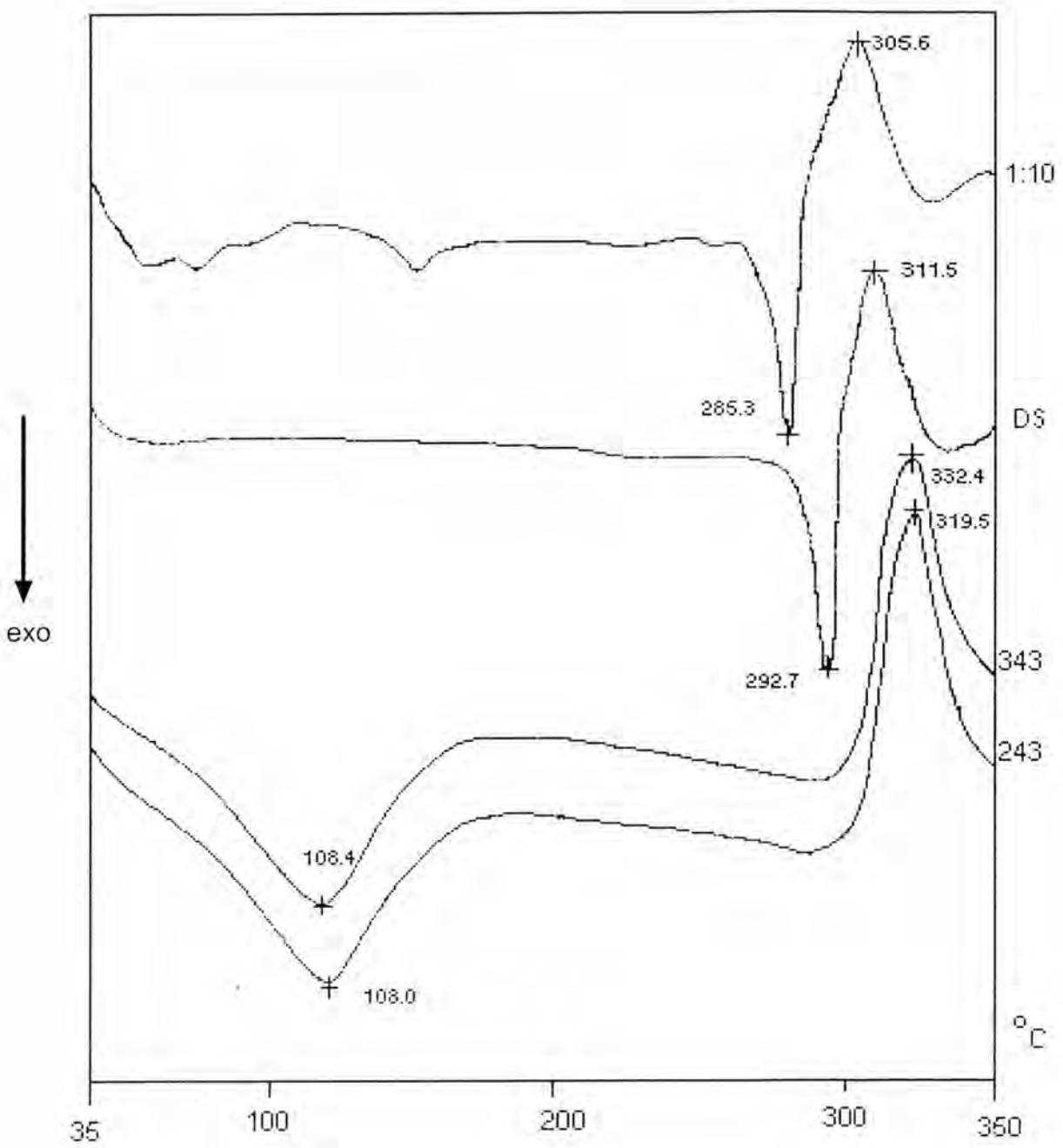


Figure 28 DSC thermograms of diclofenac sodium (DS), Seacure® 243 (243) and 343 (343) and spray dried powder at the ratio of 1:10 without plasticizer (1:10).

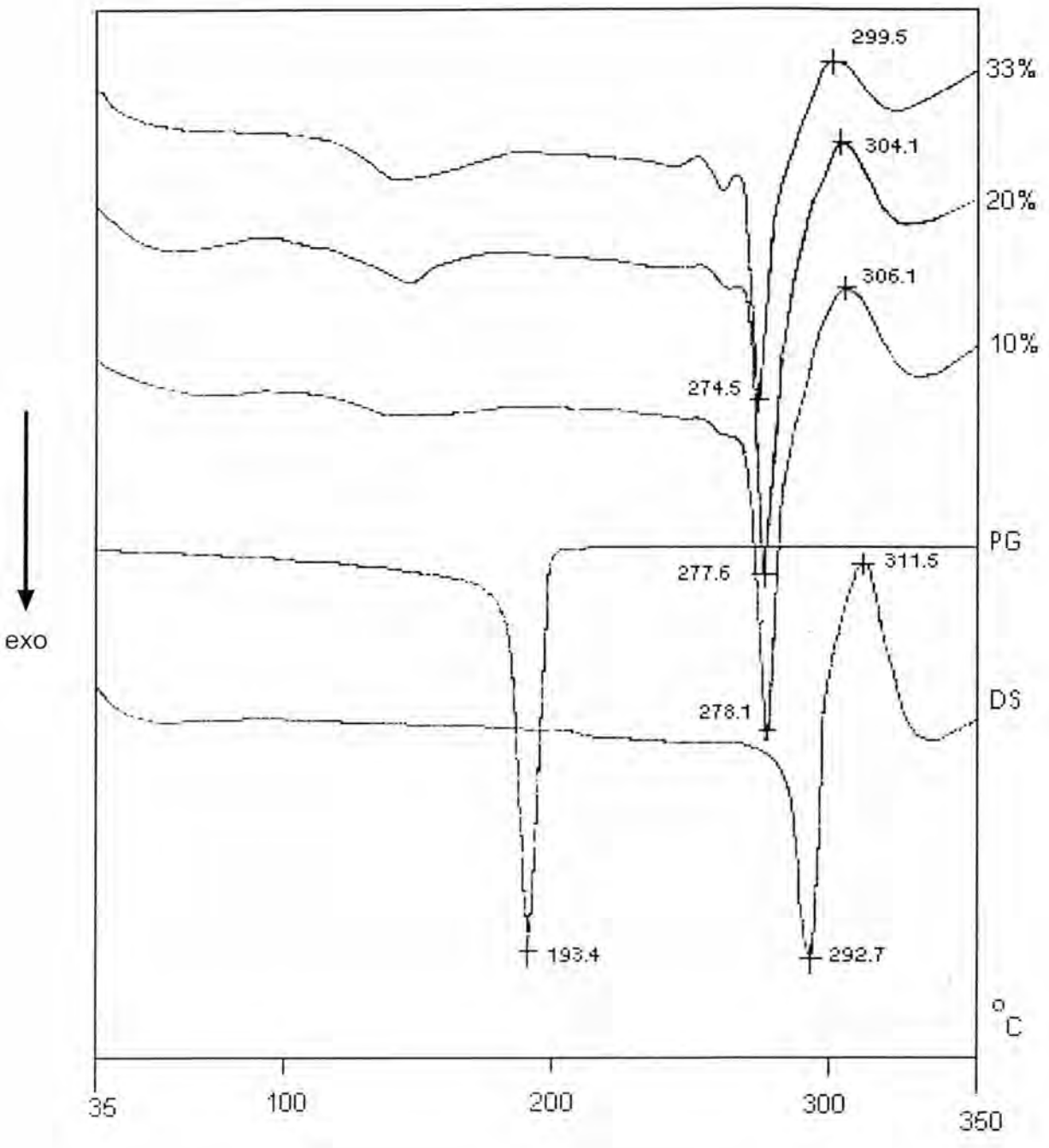


Figure 29 DSC thermograms of diclofenac sodium (DS), propylene glycol (PG) and spray dried powders at the ratio of 1:10 with propylene glycol 10, 20 and 33%.

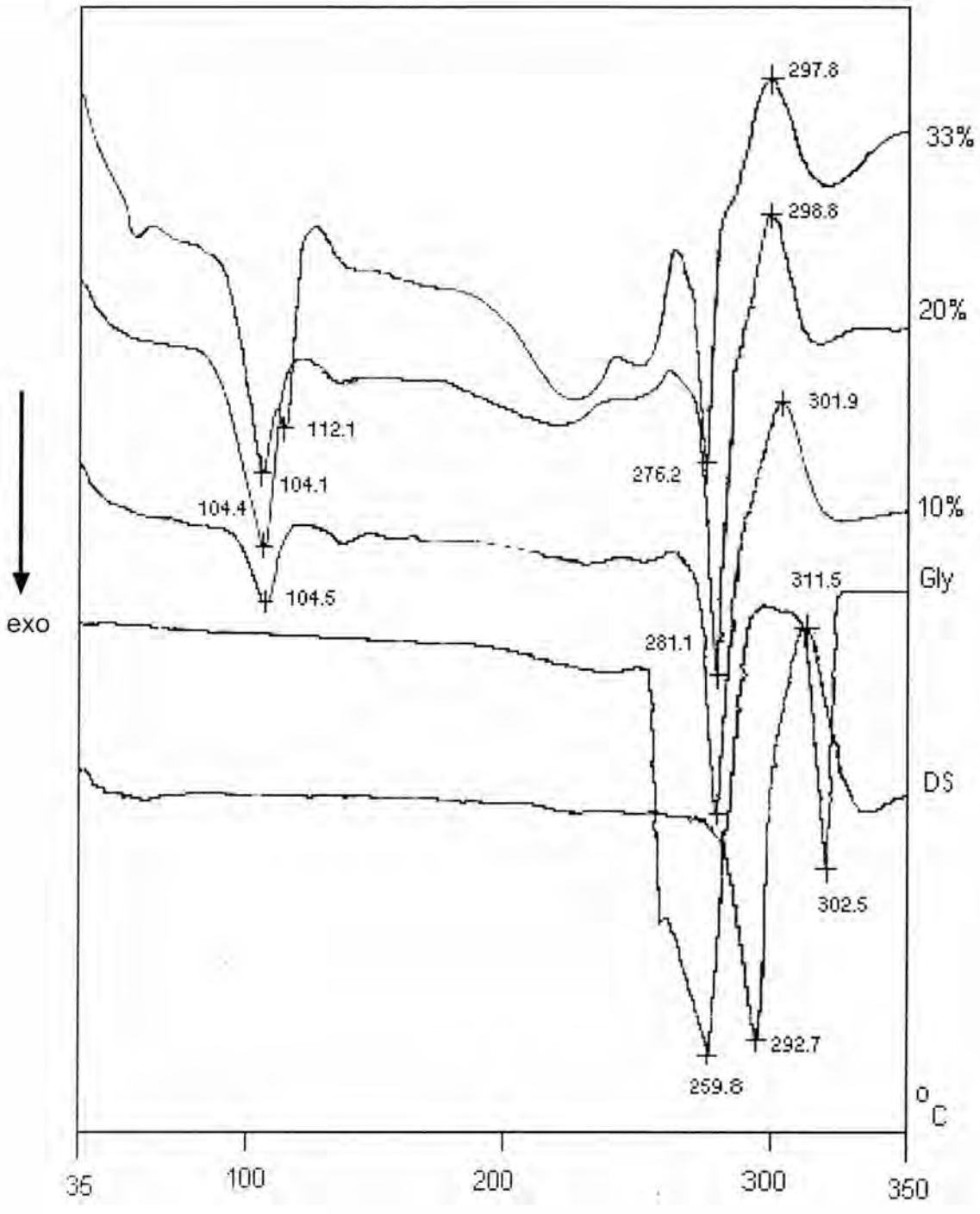


Figure 30 DSC thermograms of diclofenac sodium (DS), glycerin (Gly) and spray dried powders at the ratio of 1:10 with glycerin 10, 20 and 33%.

Formulation	DSC Peaks (degree celcious)		DTA Peaks (degree celcious)		Percent weight loss
	Exotherm	Endotherm	Exotherm	Endotherm	(%)
Diclofenac sodium	292.7	311.5	283.3	293.0	28.75
Seacure 243	108.0	319.5	/	/	/
Seacure 343	108.4	322.4	59.8 and 257.1	306.6	46.97
Propylene glycol	193.4	x	106.5 and 129.7	x	98.66
Glycerine	259.8 and 302.5	x	229.6	x	99.95
A2	285.3	305.6	274.9	290.5	30.44
A2 P1	278.1	306.1	269.2	255.7 and 284.5	36.13
A2 P2	277.6	304.1	/	/	/
A2 P3	274.5	299.5	269.6	258.3 and 288.0	39.36
A2 G1	104.5 and 281.3	301.9	268.3	287.1	42.30
A2 G2	104.4 and 281.1	298.8	/	/	/
A2 G3	104.1, 112.1 and 276.2	297.8	273.3	285.0	40.98

X = no absorption peak

/ = not evaluated

Table 21 The exotherm, endotherm and percent weight loss of thermal analysis of spray dried products produced by different types and proportions of polymers and plasticizers.

1.8.2 Thermal Gravimetry and Differential Thermal Analysis

TG and DTA thermograms of pure diclofenac sodium, polymer , plasticizers and spray dried products prepared from different formulations are shown in Figures 31 - 33 and 34 - 36, respectively. Percent weight loss from TG thermograms and the temperature peaks from DTA thermograms of all components and spray dried products are presented in Table 21.

The results from TG and DTA could be used to confirm the results of DSC by checking the temperature peaks and percent weight loss of the substances compared to that of pure drug, polymer and plasticizers. The melting of pure diclofenac sodium started at 283.3°C, then followed by the degradation after 293.0°C, whereas the loss weight was 28.75%. Seacure® showed broad peaks from 59.8°C and finished by degradation at the point of 306.6°C with 46.97% weight loss. The thermograms of propylene glycol revealed a broad peak with two lowest temperature points at 106.5°C and 129.7°C, whereas glycerin showed the broader peak and had a lowest point at 229.6°C. Both of propylene glycol and glycerin loss almost all of their weight after their degradation points.

The thermogram patterns between diclofenac sodium alone and the formulations prepared by polymer to drug ratio of 1:10 of Seacure® 243 without plasticizer were different and the peaks of spray dried products were shifted to the lower temperature. The spray drying formulations using various amounts of plasticizers exhibited the irregular patterns in the TG/DTA thermograms. The exotherm and endotherm of those plasticized formulations were not clearly identified compared to those of pure diclofenac sodium. The characteristic peaks of active ingredients in all plasticized formulation were shifted to the lower temperature. On the contrary, those peaks were shifted to the higher temperature, when amount of the plasticizer in the formulation was increased.

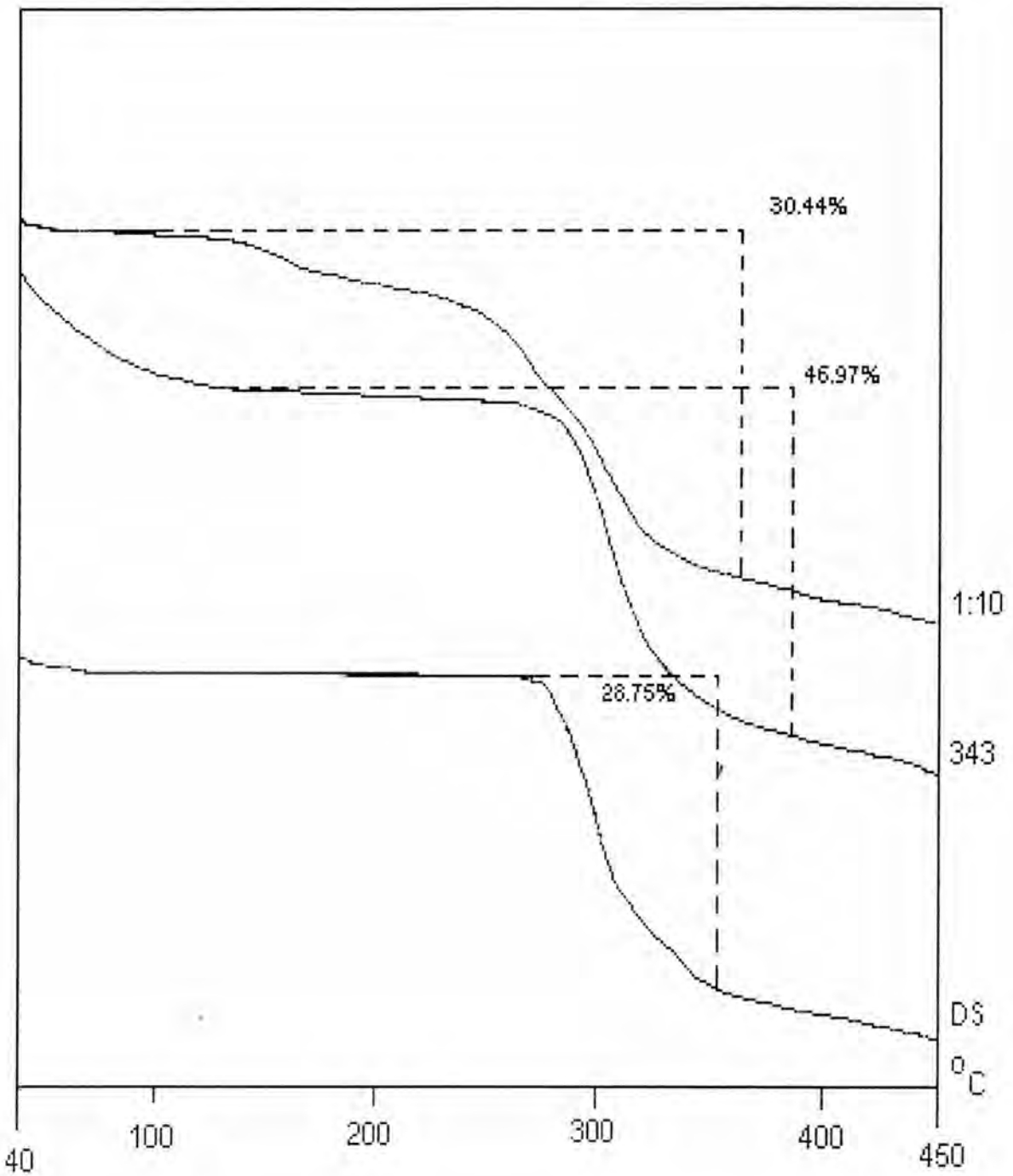


Figure 31 TG thermograms of diclofenac sodium (DS), Seacure® 343 (343) and spray dried powder at the ratio of 1:10 without plasticizer (1:10).

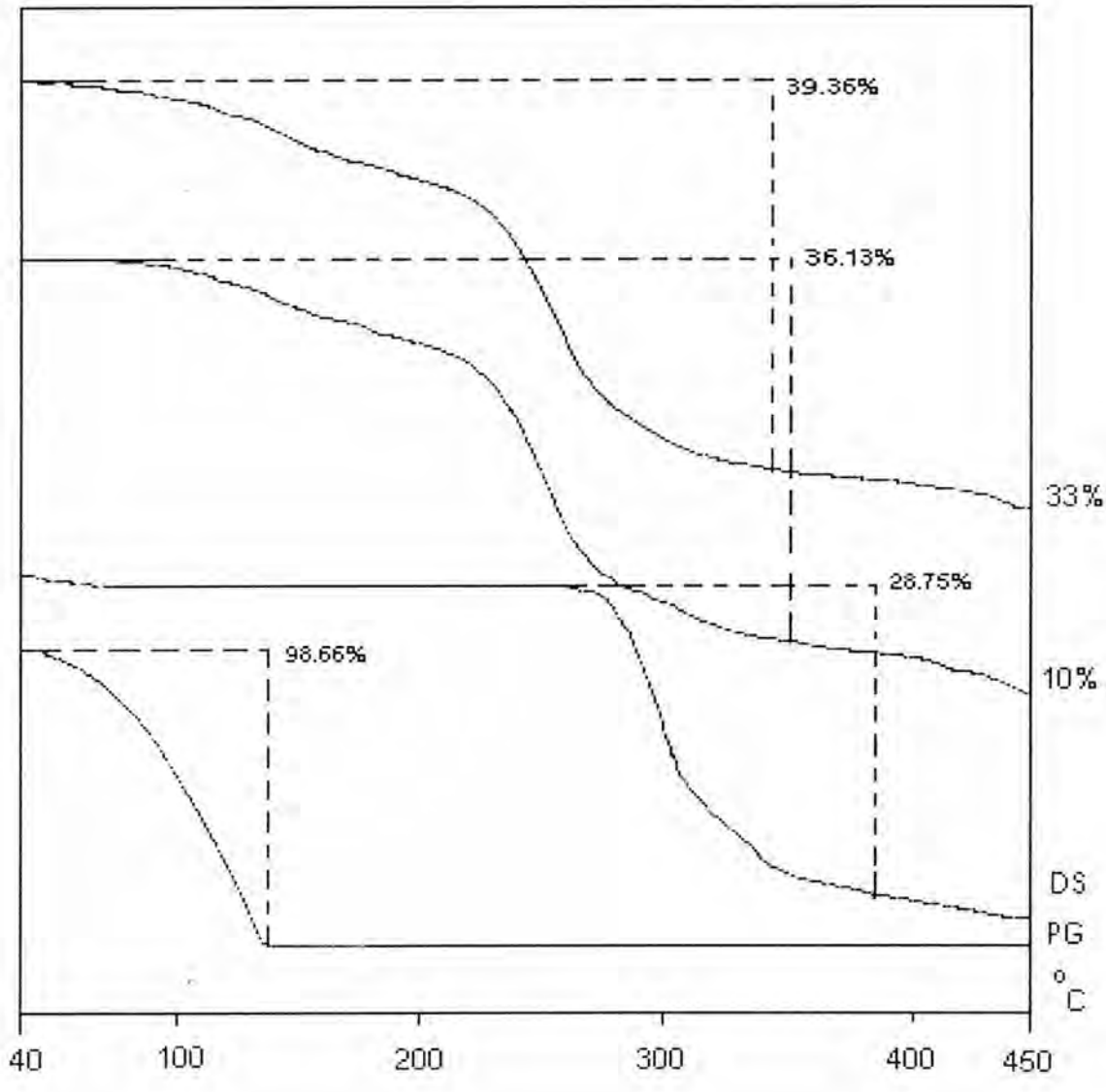


Figure 32 TG thermograms of diclofenac sodium (DS), propylene glycol (PG) and spray dried powders at the ratio of 1:10 with propylene glycol 10 and 33%.

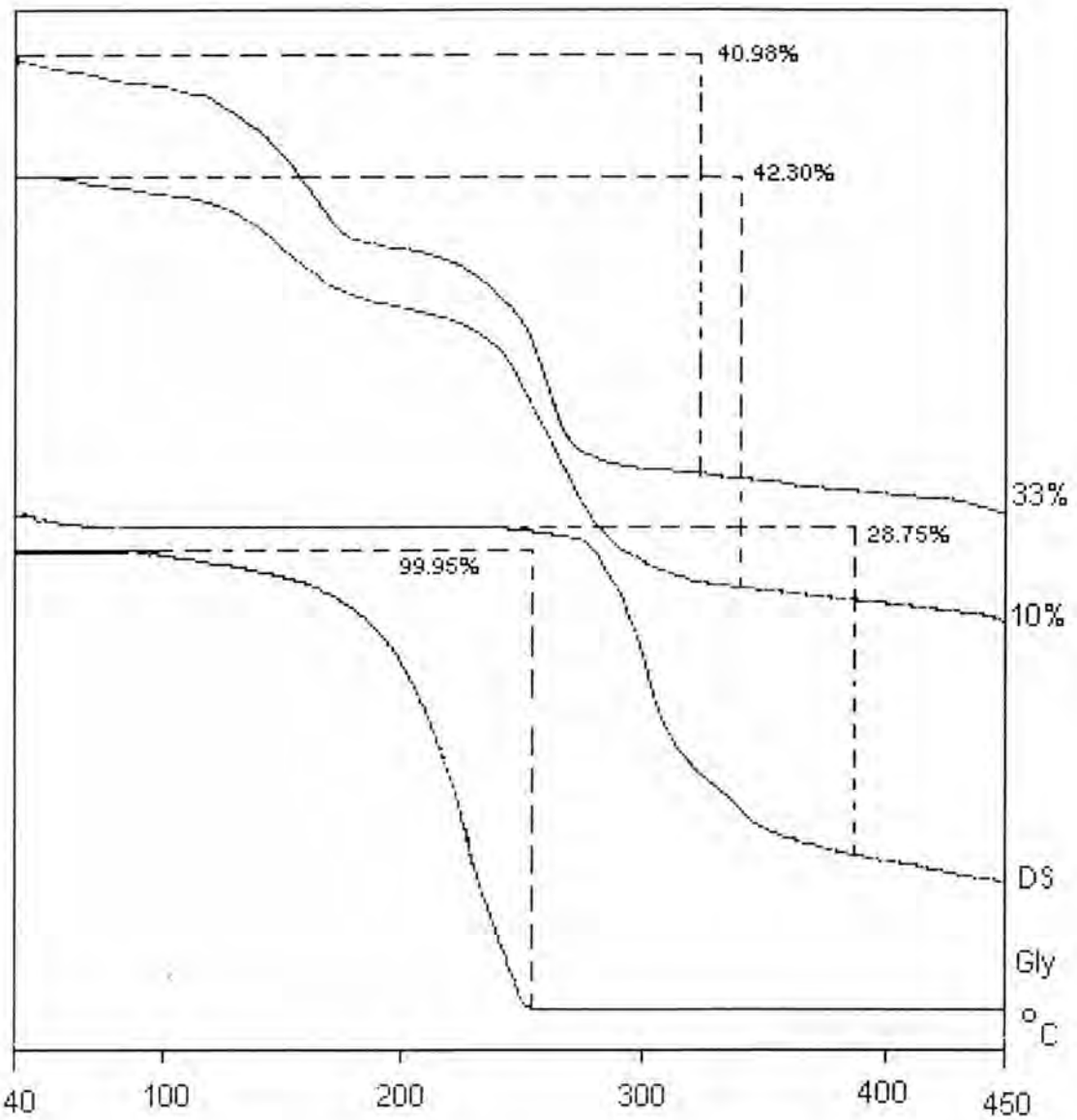


Figure 33 TG thermograms of diclofenac sodium (DS), glycerin (Gly) and spray dried powders at the ratio of 1:10 with glycerin 10 and 33%.

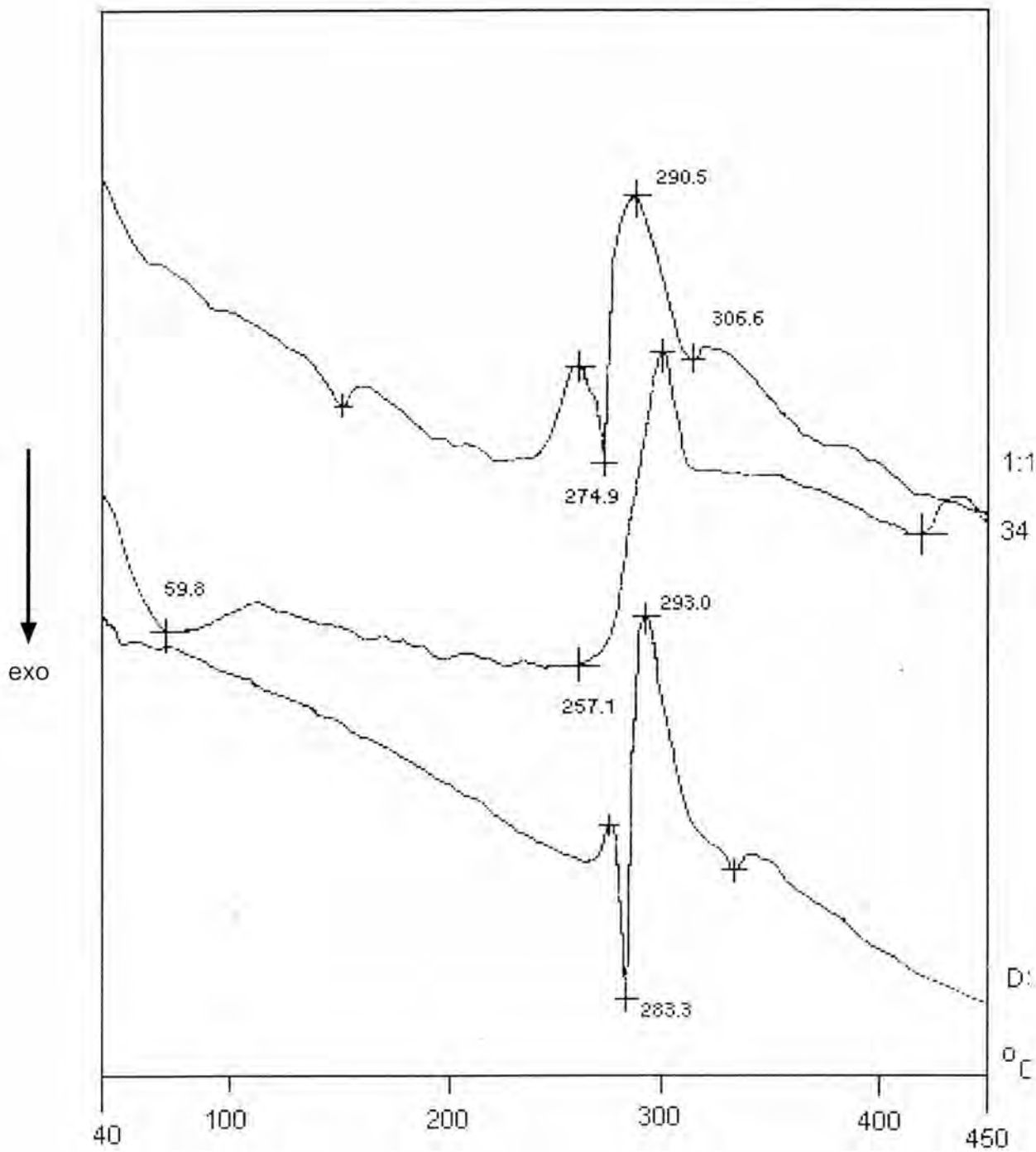


Figure 34 DTA thermograms of diclofenac sodium (DS), Seacure® 343 (343) and spray dried powder at the ratio of 1:10 without plasticizer (1:10).

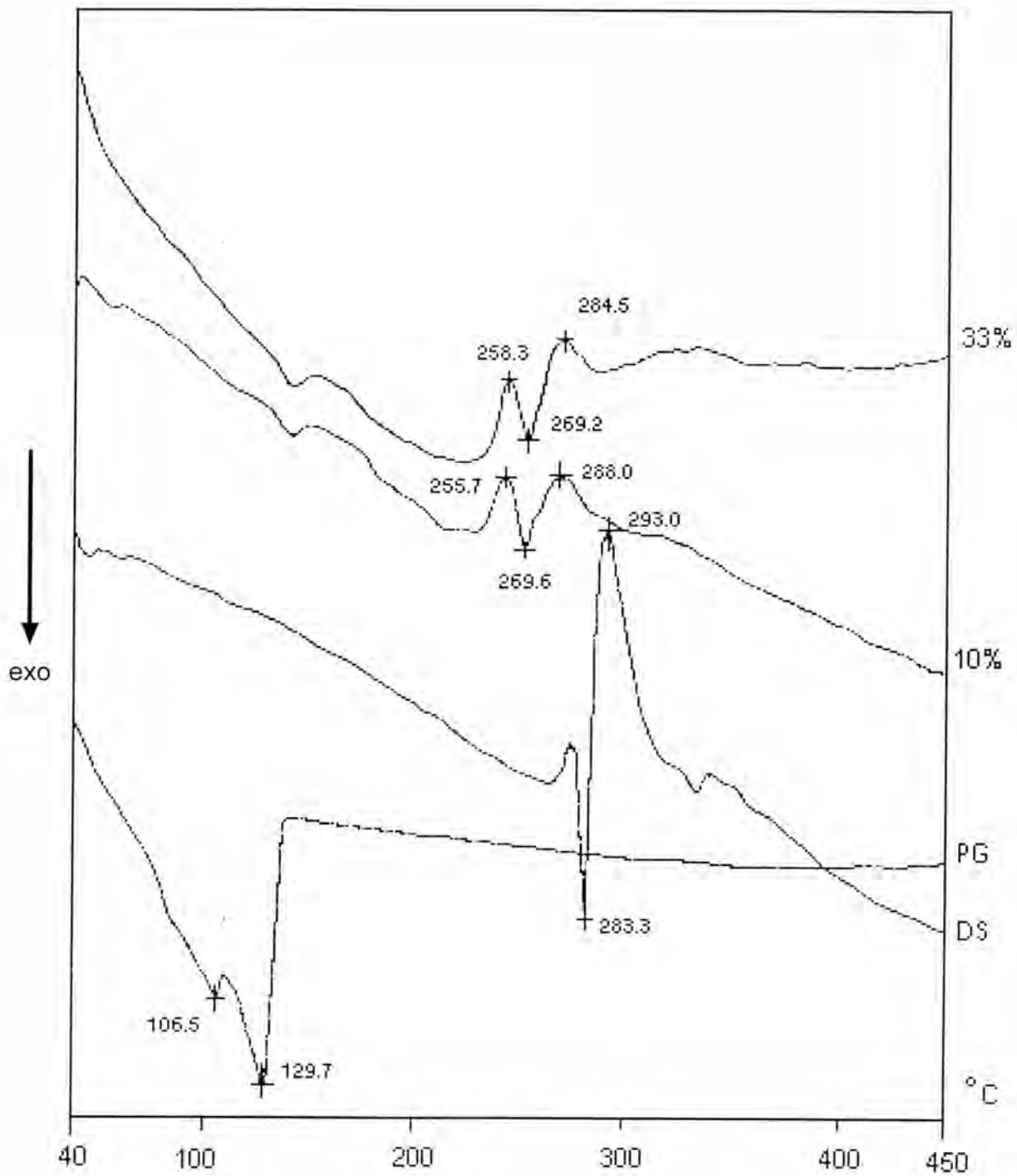


Figure 35 DTA thermograms of diclofenac sodium (DS), propylene glycol (PG) and spray dried powders at the ratio of 1:10 with propylene glycol 10 and 33%.

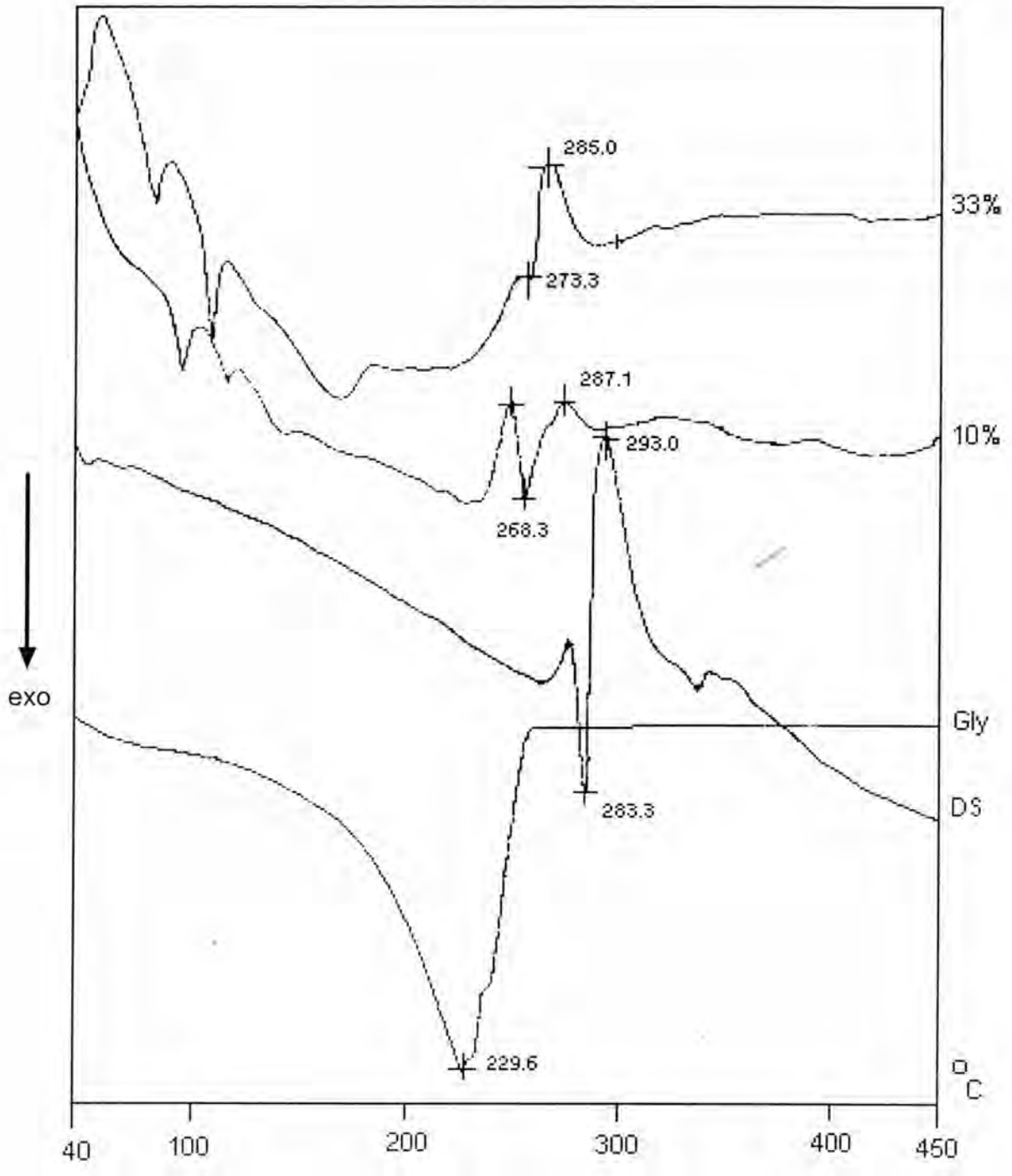


Figure 36 DTA thermograms of diclofenac sodium (DS), glycerin (Gly) and spray dried powders at the ratio of 1:10 with glycerin 10 and 33%.

II. Matrix Tablets

1. Preliminary Study of Matrix Tablets

In the preliminary study, the formulation of polymer to drug ratio of 1:5 using Seacure® 243 as a polymer with 20% of glycerin was used as a model for tabletting process. Aerosil®, 1% of table weight, was added to the spray dried powder as lubricant, although 5% of Aerosil® had already been used in the spray drying suspension. Five levels of compressional forces were varied from 100 to 500 pound. Thickness, diameter, hardness and weight per tablet of this investigation are shown in Table 22.

From the table, it could be concluded that the compressional force had important effects on the thickness and hardness of the matrix tablets. When higher compressional force was given, the hardness of matrix tablets was higher but the thickness was lower.

Table 22 Results of the preliminary test of matrix tabletting at different compressional force and preferred values of those parameters.

Parameter	Determination values					Preferred values
Compressional force (pound	100	200	300	400	500	-
Thickness (mm)	4.52	4.26	4.22	3.80	3.56	-
Diameter (mm)	6.42	6.42	6.44	6.43	6.46	6.50
Weight / tablet (mg)	154.0	156.1	152.0	150.3	154.2	151.5
Hardness (kp)	11.4 [0.7071]*	12.2 [0.6364]	13.4 [0.4950]	19.3 [0.3568]	24.5 [0.4509]	11.0 -18.0

* Standard deviation of hardness.

At 100 and 200 pound of compressional forces, the hydraulic punch machine was very difficult to control. Whereas, 400 and 500 pound force gave the over preferred range of hardness. Thus 300 pound force was used as compressional forces for tabletting process for all spray dried matrix tablet preparations. The acceptable range of hardness value in this study was 11.0 - 18.0 kp (about 5.0 - 8.0 kg).

2. Physical Properties of Matrix Tablets Prepared from Spray Dried Powders

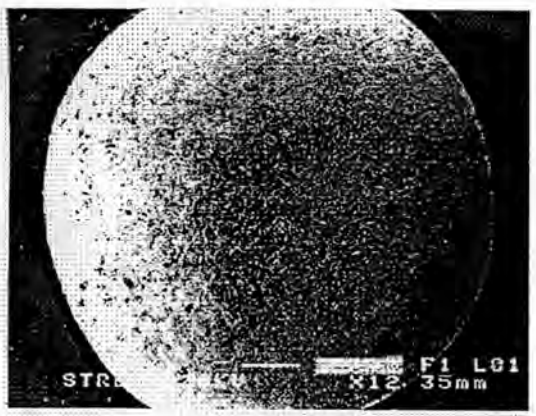
2.1 Morphology of Matrix Tablets

Scanning electron photographic process was used to observe the surface topographies of the spray dried diclofenac sodium matrix tablets in different situations both before and after dissolution test. The photomicrographs were compared to those of commercial product, Voltaren® SR 100 mg.

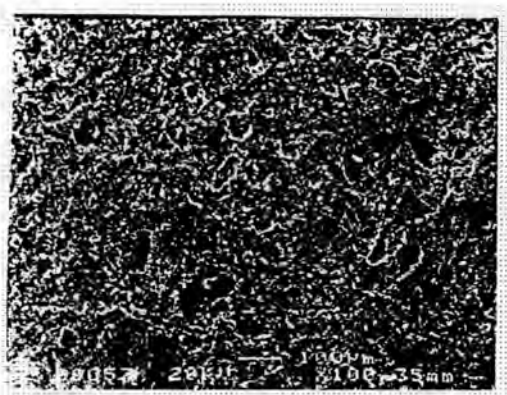
The scanning electron photomicrographs of Voltaren® SR are shown in Figure 37. The Voltaren® SR, film-coated preparation, was soaked in 0.1 N HCl for 2 hours as in the acidic stage of dissolution test and washed the film off. After drying, the photomicrographs of the tablet were taken in different magnifications. The surface of the acid-treated tablet was rough with various sizes of pores. Rougher surface caused by attached small flakes were shown by higher magnifications.

The microscopic views of Voltaren® SR after 24 hours dissolution test were significantly different from those before the test. The irregular surface filled with large pores was observed.

The microscopic images of spray dried diclofenac sodium matrix tablets using Seacure® 343 without plasticizer at different drug to polymer ratios of 1:30 and 1:15 are illustrated on Figures 38 and 39, respectively. The upper and lower surfaces of the matrix tablets of these formulations before dissolution test had

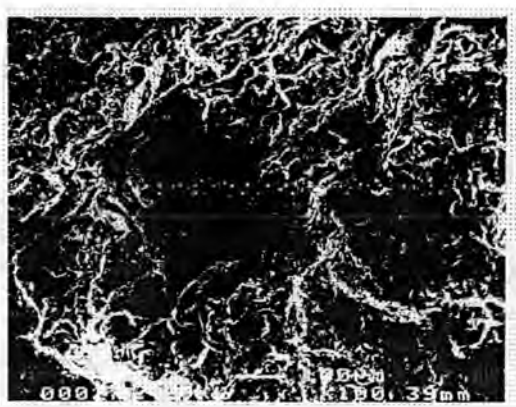


I X 12

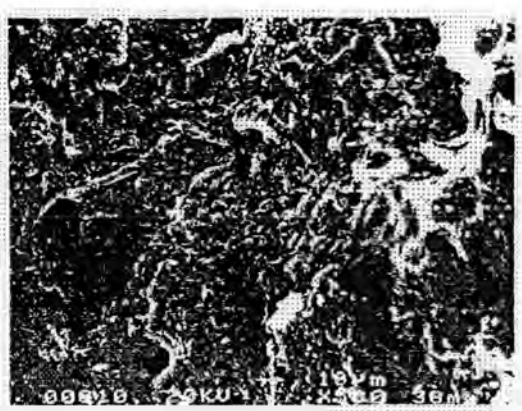


I X 100

I X 1,000

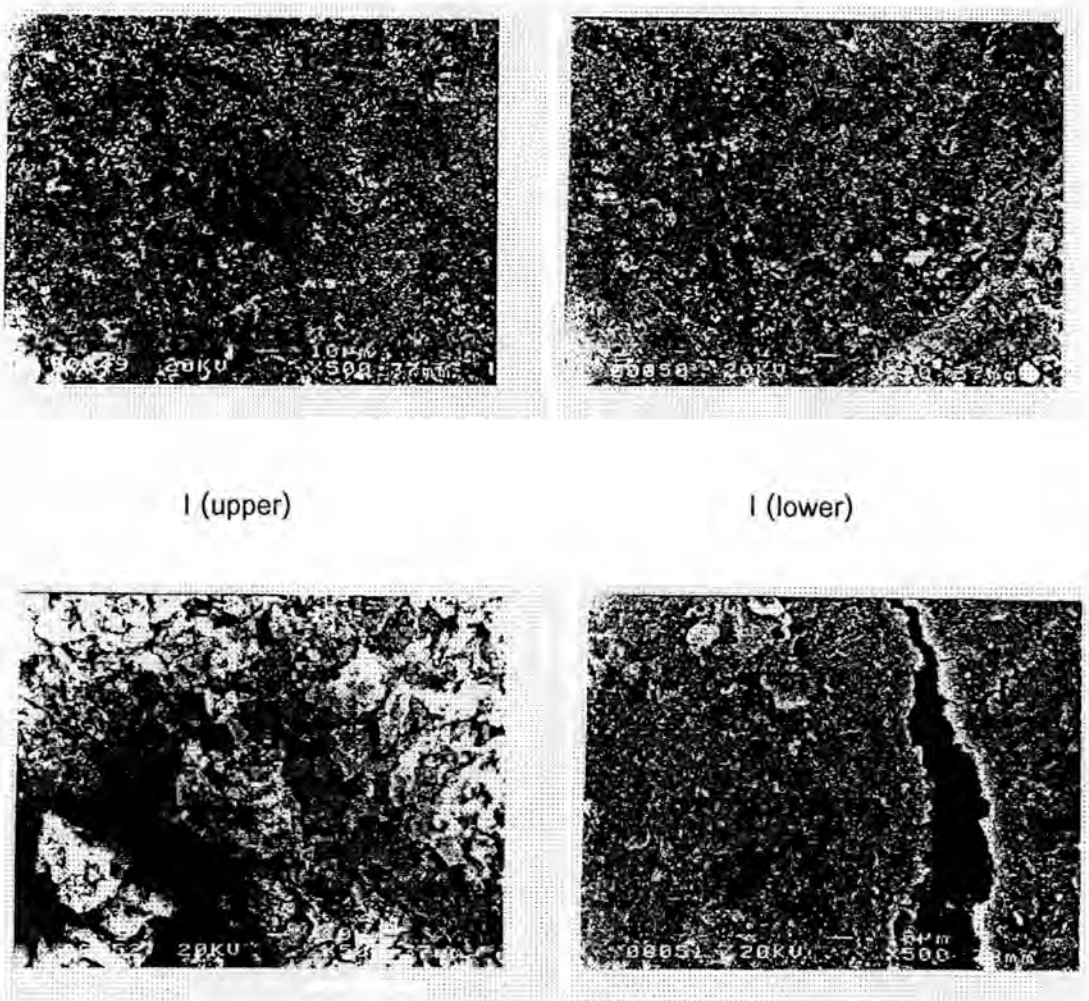


II X 100



II X 500

Figure 37 Scanning electron photomicrographs of Voltaren® SR at different magnifications both before (I) and after (II) dissolution test.



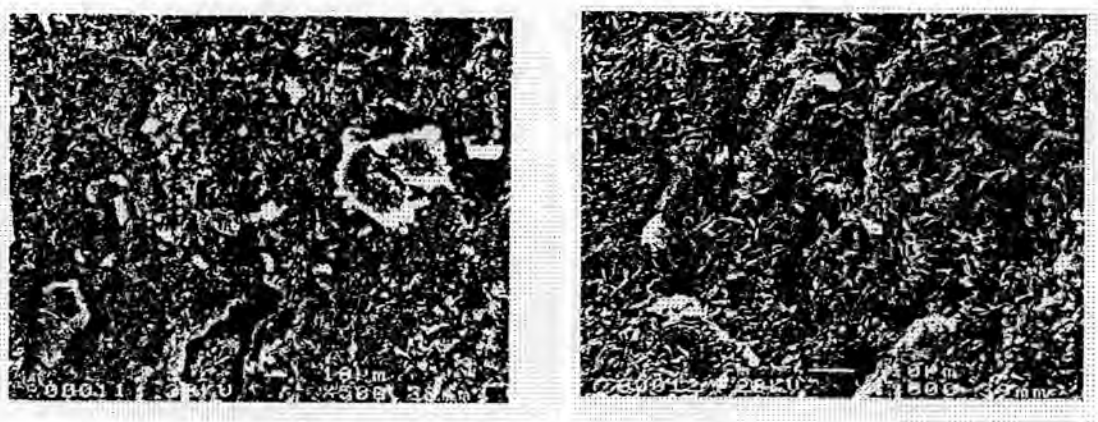
I (upper)

I (lower)

II (inner)

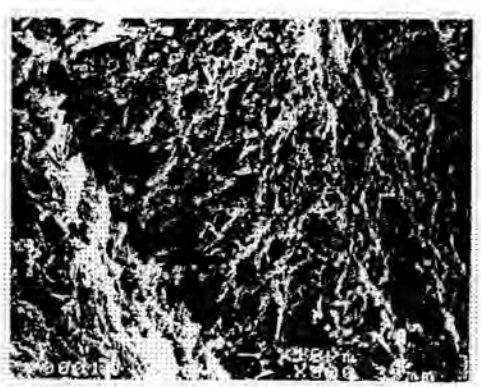
II (outer)

Figure 38 Scanning electron photomicrographs of tablets containing spray-dried diclofenac sodium powders produced from Seacure® 343 at the ratio of 1:30 without plasticizer at different sides both before (I, upper and lower) and after dissolution test (II, inner and outer), (x 500).



II (inner)

II (outer)



II (side)

Figure 39 Scanning electron photomicrographs of tablets containing spray-dried diclofenac sodium powders produced from Seacure® 343 at the ratio of 1:15 without plasticizer at different sides after dissolution test (II, inner, outer and side of the tablet), (x 500).

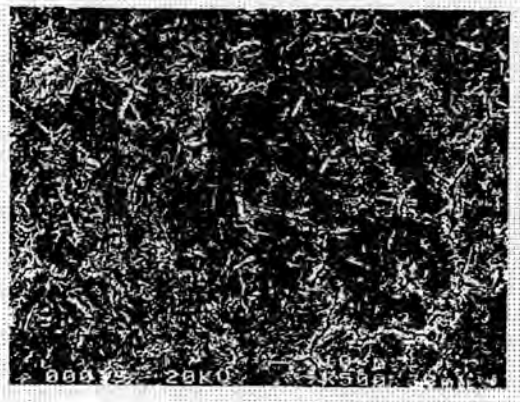
similar smooth texture with small holes attached with some white particles. There were no detectable differences in surface topographies of the matrix tablets obtained from different amount of drug and polymer.

After dissolution test, the surfaces of the tablets were rougher than those before the test. The large and deep pores on the upper and lower surfaces of the matrix tablets occurred after 24 hours of dissolution test, whereas the side of the tablets were swollen until broken into two capped characters in some formulations especially at high percentage of polymer.

The rougher texture on the upper and lower surfaces caused by the flakes of the matrix tablets were seen clearly by the higher magnifications. The swollen side of the tablet was eroded and shown net-like structure of the polymer after the dissoluble part of the tablet was released in the dissolution process.

Figures 40 and 41 show the microscopic appearances of the spray dried matrix tablets prepared from the formulation containing Secure® 343 to diclofenac sodium at the ratio of 1:15 with the aid of 33% and 40% propylene glycol, respectively. Two flat surfaces of the matrix tablets had similar characteristic texture with small pores connected in canal-like structure. The needle-like microparticles were attached on the surfaces all around the tablets.

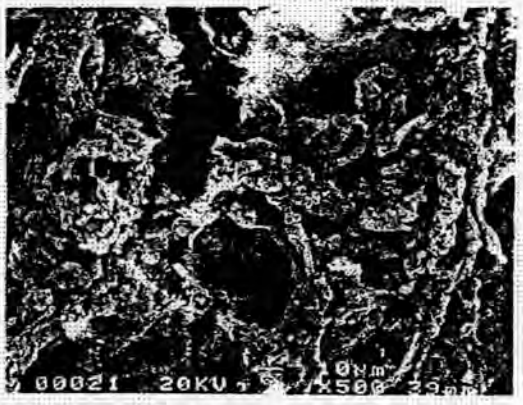
After dissolution test, whole plasticized matrix tablets were dissolved more than those of unplasticized formulations. The larger sized pores on the rough surface were produced. The pores found on the side of the tablets were bigger than those on the upper and lower surfaces. The inner part of the matrix tablet after breaking presented rod-like microcrystals in various sizes stuck together in different directions.



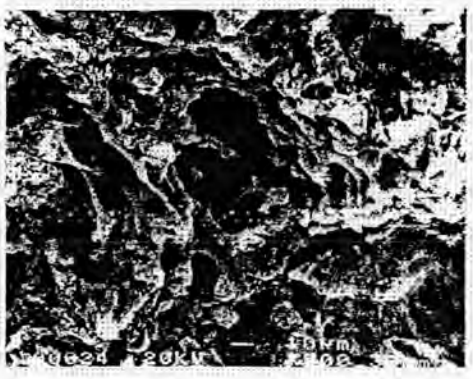
I (upper)

I (lower)

II (inner)



II (outer)

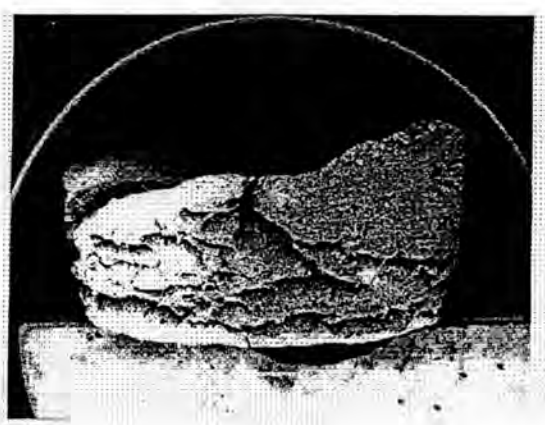


II (side)

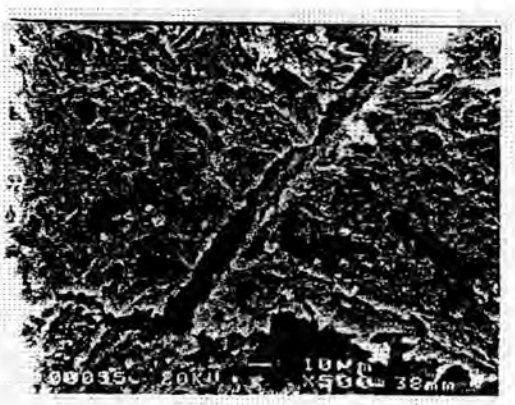
Figure 40 Scanning electron photomicrographs of tablets containing spray-dried diclofenac sodium powders produced from Seacure® 343 at the ratio of 1:15 with 33% propylene glycol at different sides both before (I, upper and lower) and after dissolution test (II, inner, outer and side of the tablet),(x 500).

II (inner)

II (outer)



II (side x 14)



II (side)

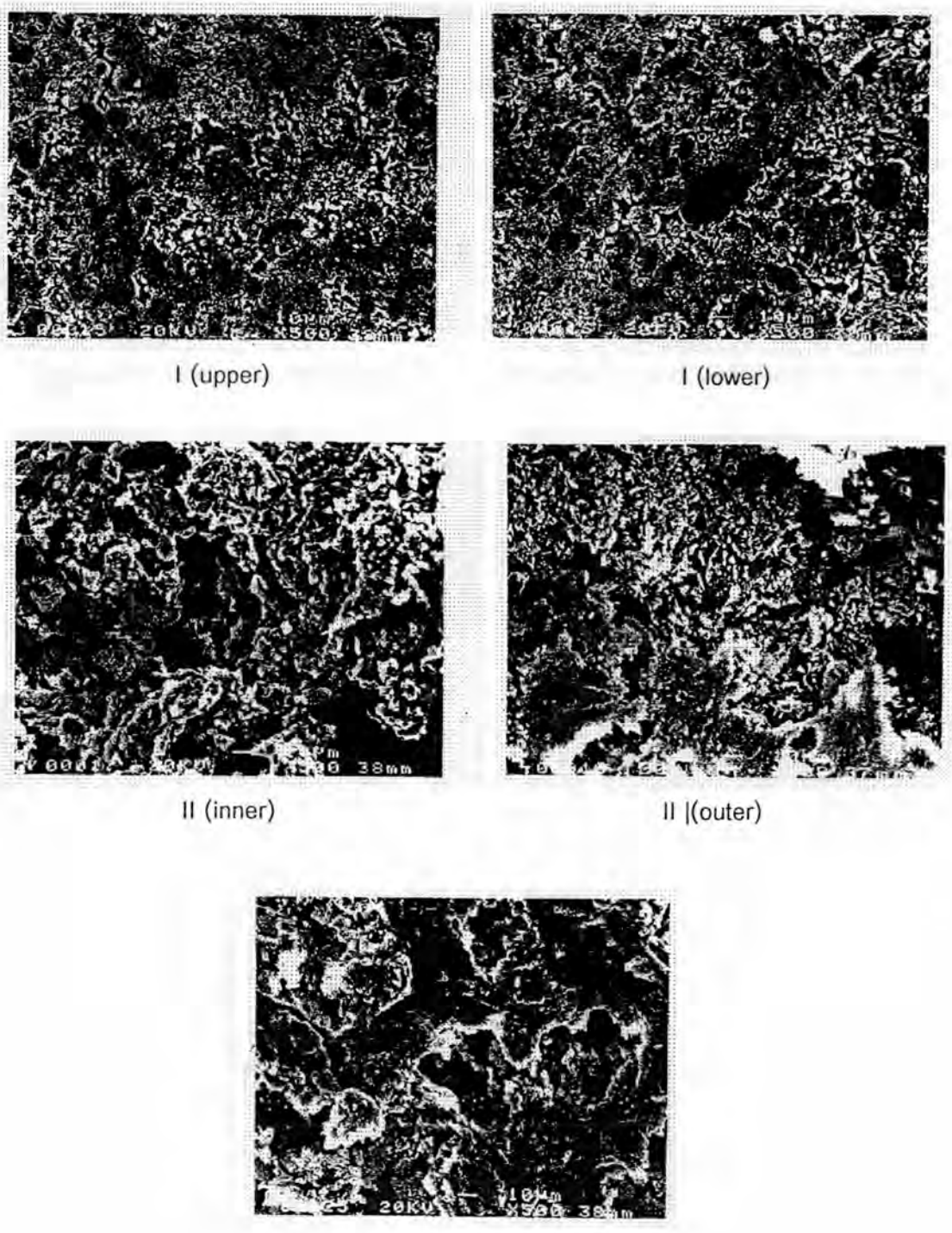
Figure 41 Scanning electron photomicrographs of tablets containing spray-dried diclofenac sodium powders produced from Seacure® 243 at the ratio of 1:10 with 40% propylene glycol at different sides after dissolution test (II, inner, outer and side of the tablet), (x 500).

The photomicrographs of the spray dried matrix tablets obtained from the formulation that used Seacure® 243 to drug ratio of 1:15 with glycerin are shown in Figure 42. Before dissolution test, two flat sides of the tablet showed different sizes of pores on the surfaces which were bigger than those of propylene glycol-plasticized formulations. No needle-like microparticles on the surface was found in the formulation used glycerin.

All surfaces of the matrix tablets used glycerin in the formulations were dissimilar to those used propylene glycol after 24 hours dissolution test. The rough texture occupied with the number of large and deep pores was blanketed by the smooth outer surface. When the matrix tablets was broken especially at the side of the tablet in the dissolution process, the rougher surfaces with various size of pores were shown.

The microscopic views of the spray dried matrix tablets produced from Seacure ® 243 to drug ratio of 1:5 with and without plasticizers are shown in Figure 43. The matrix tablets from these formulations displayed different results in scanning electron photomicrography compared to those used the lower amount of the polymer (1:15). The largest pores on the matrix tablets were presented from the unplasticized formulations.

After dissolution test, the matrix tablets of the propylene glycol-plasticized formulations were diminished in size. The higher magnifications presented the less erosion of the matrix tablets produced by the addition of propylene glycol compared to those of unplasticized formulations. On the contrary, the matrix tablets prepared from the glycerin-plasticized formulations were enlarged because of the swelling more than eroding. The microscopic images of the formulations used glycerin showed the cracking of the matrix tablets particularly at their side.



I (upper)

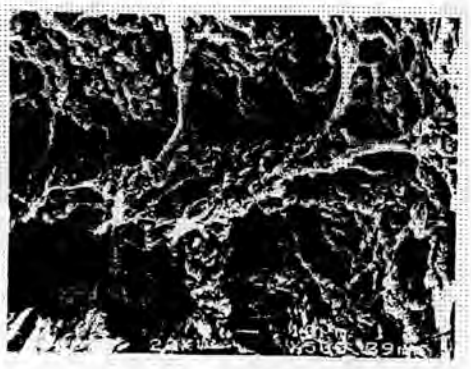
I (lower)

II (inner)

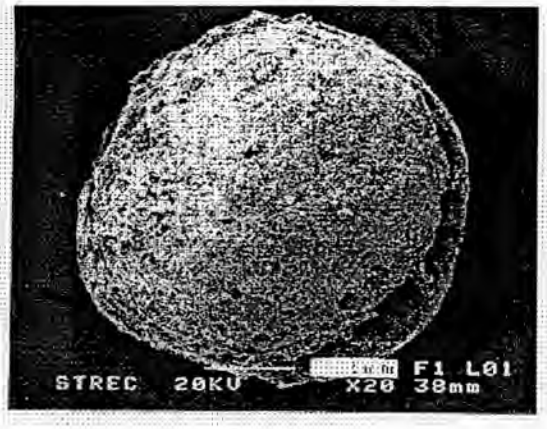
II |(outer)

II (side)

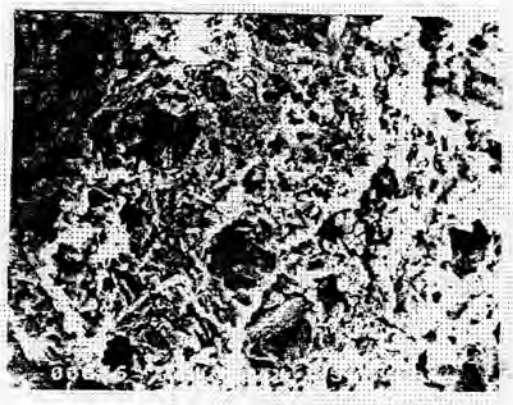
Figure 42 Scanning electron photomicrographs of tablets containing spray-dried diclofenac sodium powders produced from Seacure® 343 at the ratio of 1:15 with 33% glycerin at different sides both before (I, upper and lower) and after dissolution test (II, inner, outer and side of the tablet),(x 500).



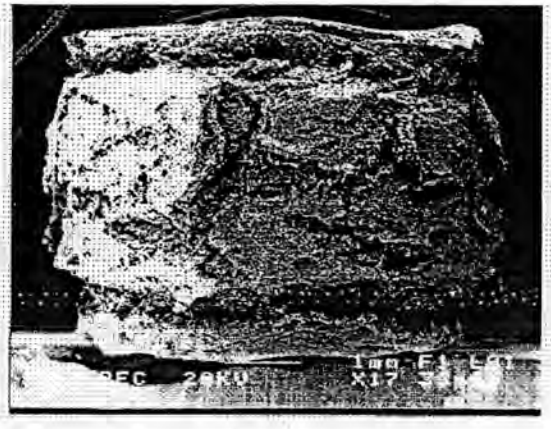
A X 500



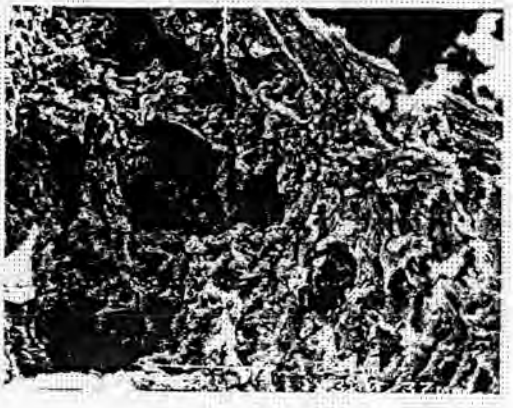
B x 20



B x 500



C x 17



C x 300

Figure 43 Scanning electron photomicrographs of tablets containing spray-dried diclofenac sodium powders produced from Seacure® 243 at the ratio of 1:5 with and without plasticizers at the tablet sides after dissolution test using different magnifications (A = without plasticizer, B = with 33% propylene glycol and C = with 33% glycerin).

2.2 Thickness, Diameter and Hardness of Matrix Tablets

Thickness, diameter and hardness of matrix tablets are presented in Table 23. The mean thickness was mostly in the range of 2.80 - 3.60 mm that directly depended on the total amount of the components in the spray dried formulations. The thickness value was still corresponded with the hardness of the matrix tablets, when compared between the formulations that had the same weight per tablet values. The lowest thickness value of the matrix tablets at 2.63 mm was produced by the formulations using polymer to drug ratio of 1:30 of Seacure® 243. Whereas, the highest thickness value at 4.22 mm was produced by the formulation that used the same polymer grade at the ratio of 1:5 with 30% of glycerin.

The diameter of the spray dried matrix tablets was in the narrow range of 6.42 - 6.70, because the diameter of all spray dried matrix tablets was strongly controlled by the die of the hydraulic punch for tabletting.

The mean hardness was mostly ranged from 11.0 - 16.0 kp. The lowest hardness value at 8.1 kp was obtained from spray dried powders prepared by the formulation used the ratio of 1:15 of Seacure® 343 with 33% of glycerin. However, five formulations with highest amounts of plasticizers showed the hardness values more than 20.0 kp. Only one formulations in these groups used 33% of glycerine whereas the other used propylene glycol.

The hardness of all unplasticized matrix tablets was lower than 16.0 kp except the formulation that used Seacure® 343 at the ratios of 1:10 and 1:15 which were 8.9 and 8.6 kp, respectively.

Weight per tablet values were directly depended on the total amount of the components in the spray dried formulations and equivalent to 100 mg of diclofenac sodium as the commercial dose. The results show that twenty-six of thirty-seven formulations had standard deviation of the weight per tablet value higher than 1.0.

Table 23 Thickness, diameter, hardness and weight per tablet values of matrix tablets from various spray dried formulations.

Formulation	Thickness (mm)	Diameter (mm)	Hardness (kp)	Weight / tablet* (mg)
A1	3.31	6.43	16.6 (2.2426)**	129.8 (2.7124)***
A2	2.98	6.46	11.8 (0.7320)	116.1 (2.2321)
A3	2.74	6.42	12.3 (0.5686)	114.4 (2.1492)
A4	2.75	6.42	13.7 (2.5007)	107.9 (0.8182)
A5	2.63	6.59	12.6 (2.2008)	107.0 (1.1221)
B1	3.36	6.48	15.1 (0.9500)	130.3 (2.2147)
B2	2.99	6.62	8.9 (0.9673)	107.1 (0.8345)
B3	2.78	6.52	8.6 (0.3109)	106.0 (4.5356)
B4	2.68	6.56	11.8 (1.2741)	106.4 (0.7882)
B5	2.68	6.43	12.1 (0.5508)	103.6 (0.7944)
A1 P2	3.68	6.42	17.7 (0.0816)	149.3 (0.5774)
A1 P3	4.00	6.46	25.3 (2.6069)	174.4 (2.5036)
A1 G2	4.22	6.44	13.4 (0.4950)	151.5 (1.7320)
A1 G3	4.01	6.59	20.9 (1.8583)	173.6 (0.7440)
A2 P1	2.93	6.53	13.1 (1.3638)	130.2 (1.3887)
A2 P2	3.10	6.55	15.3 (0.8083)	136.3 (0.4880)
A2 P3	3.43	6.57	14.4 (1.1150)	150.3 (1.6036)
A2 P4	3.56	6.60	22.8 (0.2646)	161.6 (1.9955)
A2 G1	3.13	6.63	12.0 (2.9466)	131.0 (0.7559)
A2 G2	3.38	6.44	14.2 (0.8544)	138.0 (1.5118)
A2 G3	3.60	6.57	13.3 (0.5560)	154.3 (1.1127)
B2 P1	2.96	6.48	13.3 (1.3450)	125.5 (0.7559)
B2 P2	3.15	6.54	14.5 (1.3454)	137.3 (1.9760)
B2 P3	3.51	6.58	14.6 (0.3214)	153.3 (1.2536)
B2 P4	3.56	6.60	23.5 (2.1079)	161.6 (1.9955)
B2 G1	3.05	6.42	12.9 (0.9845)	134.9 (1.2464)
B2 G2	3.38	6.57	18.9 (1.9296)	142.0 (1.0690)
B2 G3	3.72	6.70	10.2 (3.8578)	153.1 (1.0690)
A3 P1	2.81	6.50	14.4 (10.693)	126.8 (2.1339)
A3 P2	3.05	6.52	15.8 (1.2702)	135.4 (1.4079)
A3 P3	3.30	6.60	16.8 (3.3788)	151.0 (3.0237)
B3 P1	2.86	6.50	12.8 (2.9614)	126.8 (2.8860)
B3 P2	3.03	6.50	12.8 (0.4933)	136.6 (3.1594)
B3 P3	3.42	6.46	20.1 (3.9686)	150.8 (1.3887)
B3 G1	3.35	6.66	6.9 (0.7572)	121.6 (0.5345)
B3 G2	3.28	6.49	12.2 (2.1992)	137.4 (1.4079)
B3 G3	3.61	6.45	8.1 (0.8485)	148.4 (0.9161)

* Used Aerosil 1% of the total weight of one tablet as a lubricant.

** Standard deviation of hardness value calculated from three determinations.

*** Standard deviation of weight / tablet value calculated from eight determinations.

III. Pellets

1. Preliminary Study of Pelletization

The important parameters as amount and type of diluents and polymer, spheronization speed and spheronization time were evaluated. The effect of these parameters could be interpreted clearly from the morphology and sieve analysis of the pellets.

From the preliminary study, the extruded mass load was tested in the range of 250 - 300 g. The results showed that the suitable mass load had to be more than 300 g, because some portions was loss in the process that yielded inadequate amount of pellets especially in the step of extrusion. The extruded damp mass had to be enough for spheronization process. In addition, the spheronization speed at 500 rpm and the spheronization time at 15 min were used as standard condition. The results of the pelletization are shown in Table 24.

2. Physical Properties of Pellets

2.1 Morphology of Pellets

Scanning electron photomicrographs of pellets were taken to investigate the surface topography and completeness of the particles. The microscopic images were taken in three magnifications for each formulation.

Figure 44 shows the photomicrographs of pellets obtained from different ratio of diclofenac sodium to Avicel® that used Seacure® 343 as a binder. The overall shape of the pellets was spherical but the surface was rough and covered with some small white particles. The amount of the white particles was lower in the formulation that used the lower amount of Avicel®. At diclofenac sodium to Avicel®

Table 24 Amount of the components in percent used in the pellet formulations and results of the pelletization.

Formulation	Percent of all components*					Results
	DS	AV	LC	243	343	**
L1	cc	.	cc	cc	cc	C
L2	cc	.	cc	cc	cc	C
L3	cc	.	cc	cc	cc	C
AA1	48.92	48.92	.	2.16	.	IP
AA2	cc	cc	.	cc	cc	C
AA3	cc	cc	.	cc	cc	C
AA4	32.27	64.54	.	3.19	.	P
AA5	36.27	60.45	.	3.28	.	P
BA1	48.81	48.81	.	.	2.38	P
BA2	39.00	58.50	.	.	2.50	P
BA3	32.47	64.94	.	.	2.59	P
BA4	27.74	69.34	.	.	2.92	P
BA5	24.18	72.53	.	.	3.29	P
AAL1	27.87	34.90	34.90	2.33	.	P
BAL1	28.06	35.15	35.15		1.64	P
BAL2	32.76	32.76	32.76	.	1.72	P

* Percent of all components calculated from the total components of the formulations.

** C = pellets could not be produced at any amount of polymer.

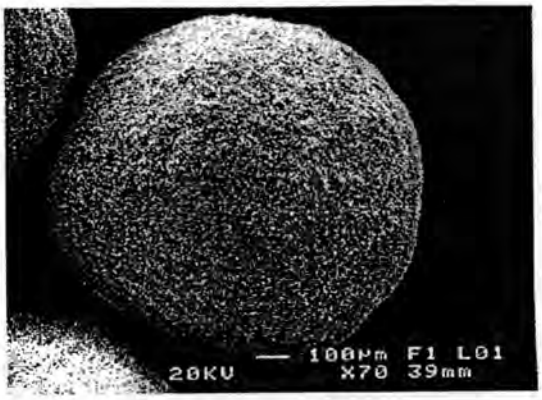
P = pellets could be occured.

IP = incompleted pellets occured.

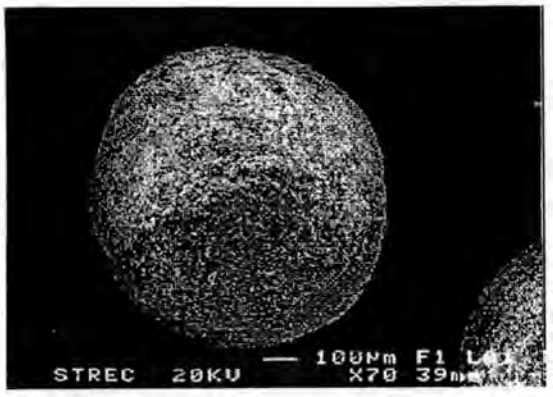
cc = cannot be calculated

DS = Diclofenac sodium, AV = Avicel PH 101, LC = Lactose,

S243 = Seacure 243 and S343 = Seacure 343.



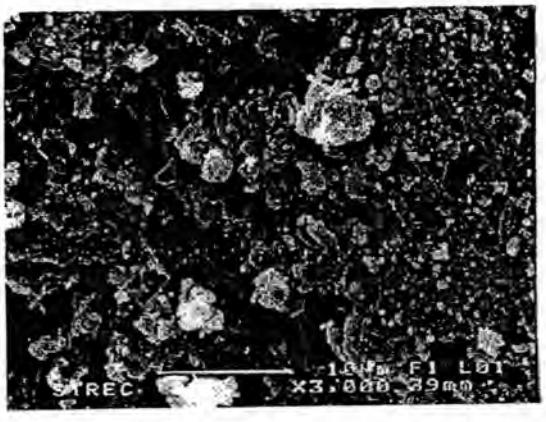
BA1 X 70



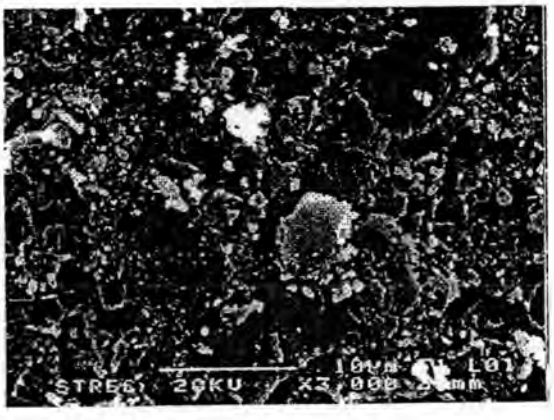
BA3 X 70

BA1 X 500

BA3 X 500

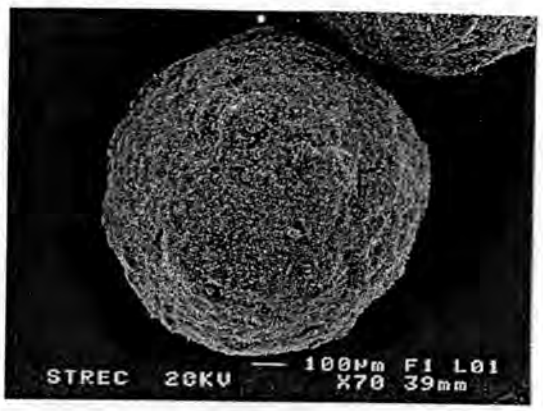


BA1 X 5,000

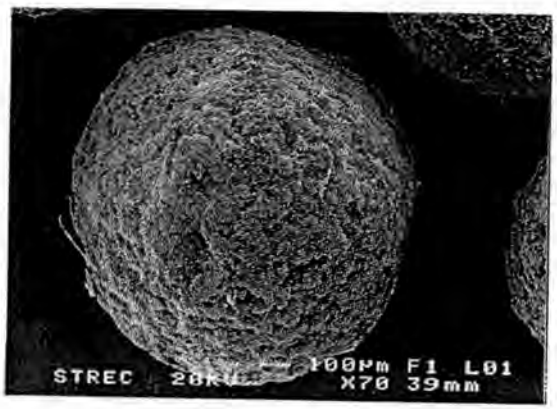


BA3 X 5,000

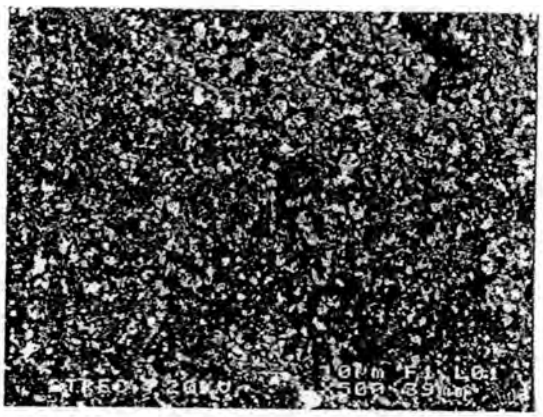
Figure 44 Scanning electron photomicrographs of matrix pellet from the formulations using various diclofenac sodium to Avicel® ratios (BA1 = 1:1, BA3 = 1:2) containing Seacure® 343 at different magnifications.



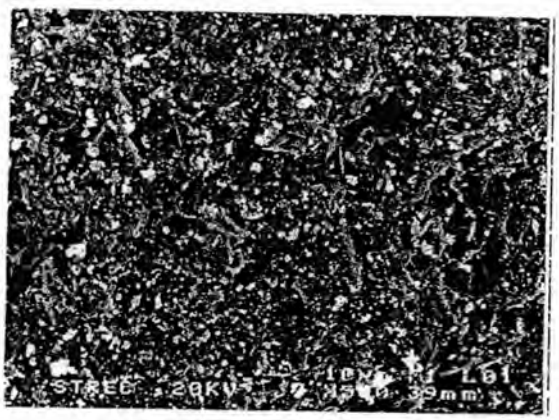
BA5 X 70



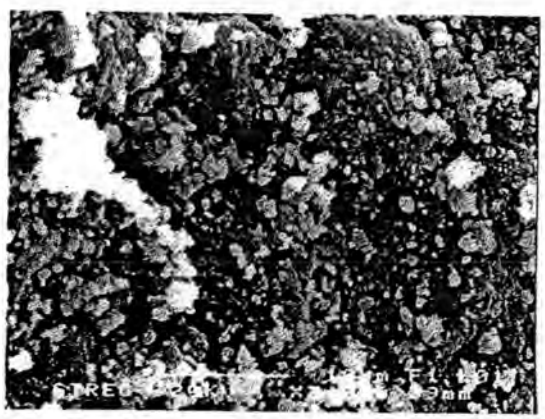
BAL2 X 70



BA5 X 300



BAL2 X 500



BA5 X 3,000

BAL2 X 3,000

Figure 44 (cont.) Scanning electron photomicrographs of matrix pellet from the formulations using various diclofenac sodium to Avicel® ratios (BA1 = 1:1, BA3 = 1:2 and BA5 = 1:3) and diclofenac sodium to Avicel® to lactose ratio (BAL2 = 1:1:1) containing Seacure® 343 at different magnifications.

ratio of 1:3,the moon-like surface with small white particles attached on the surface of the pellets was clearly seen, when the higher magnifications were used.

The photomicrographs of the pellets produced by two diluent systems at the ratio of diclofenac sodium to Avicel® to lactose of 1:1:1 were similar to those of one diluent system at the ratio of diclofenac sodium to Avicel® of 1:3, except that the surface of the pellets from two diluents system was rougher and the amount of white particles was lower.

There was no difference in size, shape and surface topography of the pellets obtained by different type of Seacure® in the formulations used Avicel® alone. The pellets made from Seacure® 343 presented little smoother surfaces compared to those used Seacure® 243. The photomicrographs of the formulations using different grade of Seacure® are shown in Figure 45.

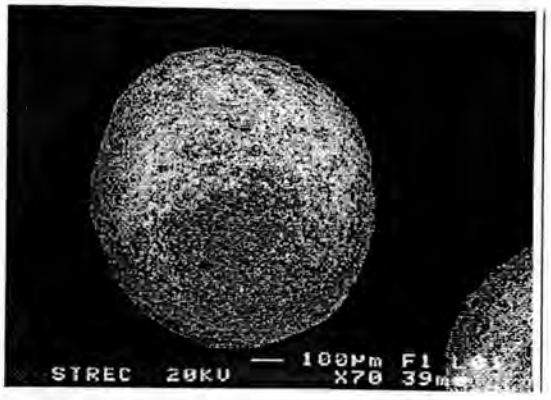
The shape and surface topographies of the pellets produced by the same formulations at different spheronization speed are shown in Figure 46. The rounder pellets were obtained from the higher spheronization speed, but the dryness of the surface was found. The outer skins of the pellets were stripped off when the spheronization speed of 900 rpm was used.

The effects of the spheronization time are shown in Figure 47. No difference in size, shape and surface topography of the pellets produced by the same formulation at different spheronization time of 15 and 30 min was detectable in every magnifications.

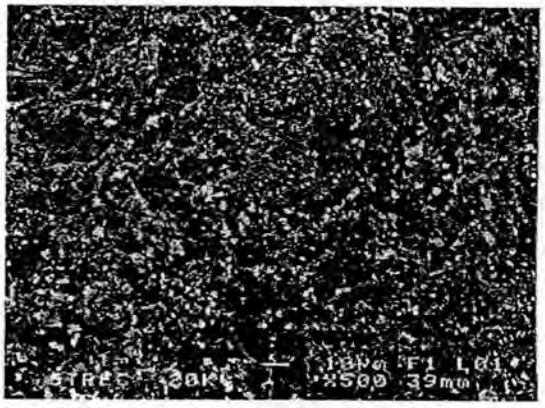
2.2 Size Distributions

The size distributions of the pellets are shown in Tables 25 and 26. They indicated the factors affected pelletization process as illustrated in Figures 48 - 51. The parameters of the pelletization process were as follow :

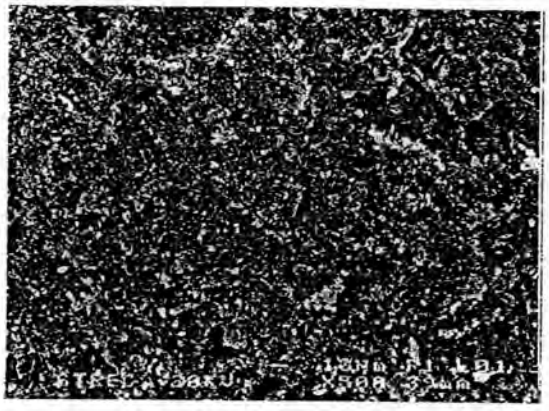
AA4 X 70



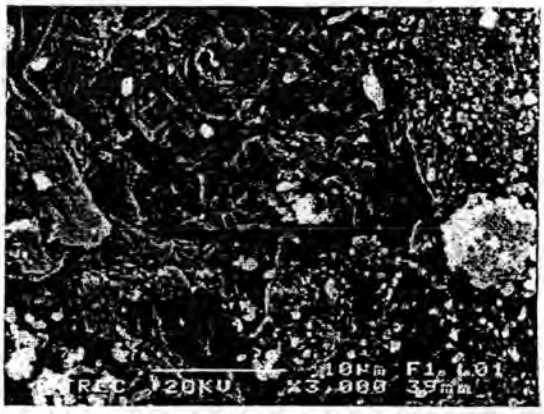
BA3 X 70



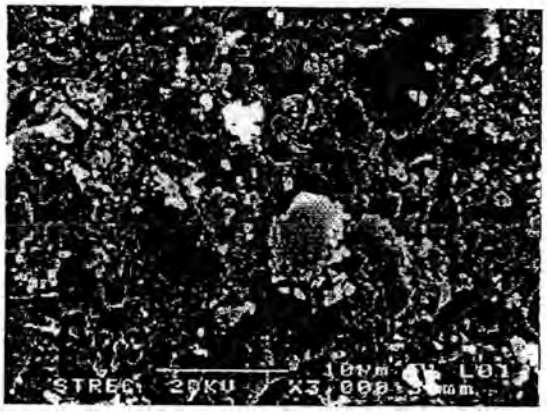
AA4 X 500



BA3 X 500

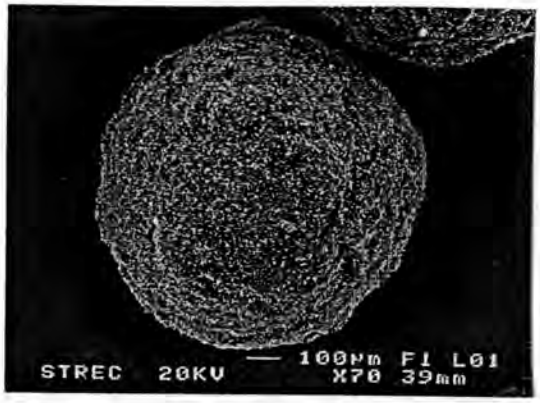


AA4 X 3,000

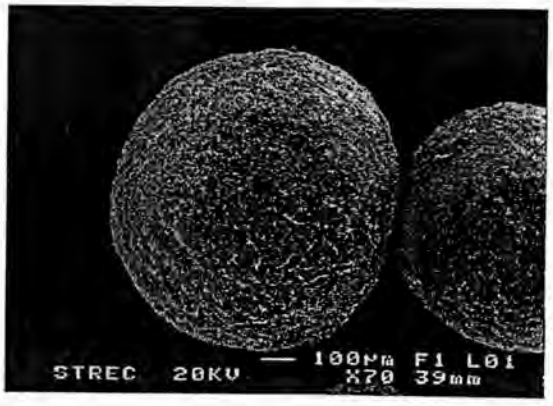


BA3 X 3,000

Figure 45 Scanning electron photomicrographs of matrix pellets with the same diclofenac sodium to Avicel® ratio containing different grade of Seacure® (Seacure® 243; AA4 = 1:2 and Seacure® 343; BA3 = 1: 2) at different magnifications.

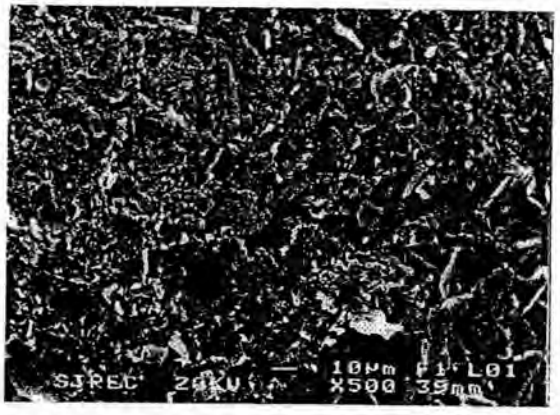


(500) X 70

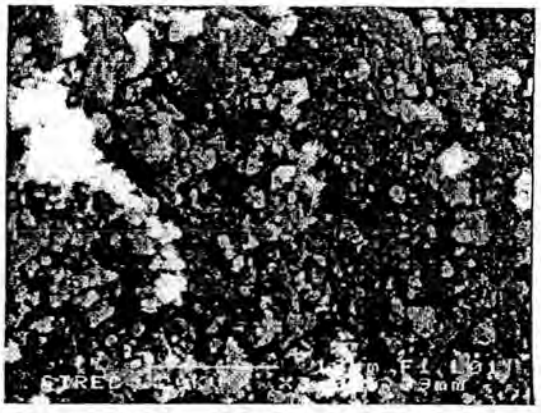


(900) X 70

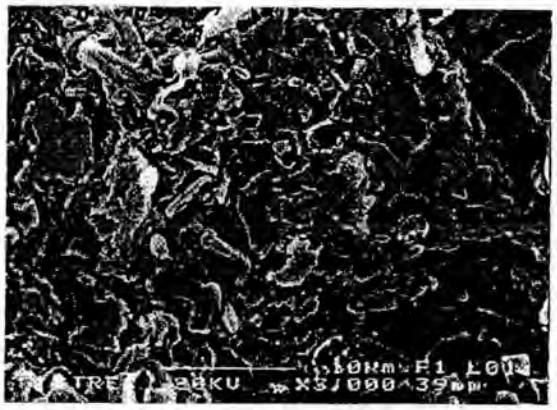
(500) X 500



(900) X 500

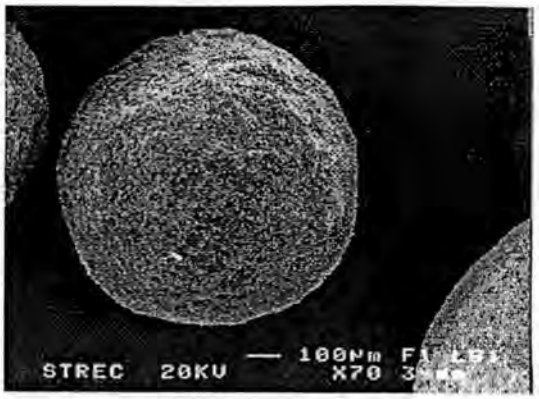


(500) X 3,000

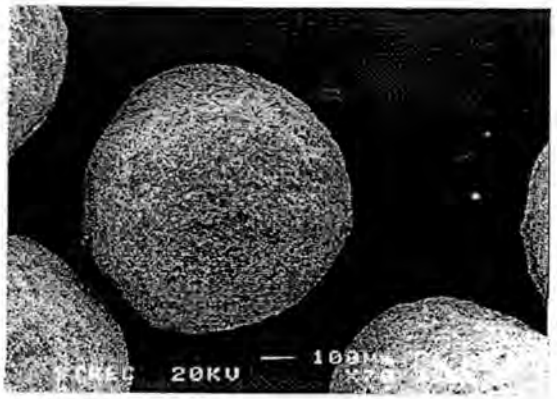


(900) X 3,000

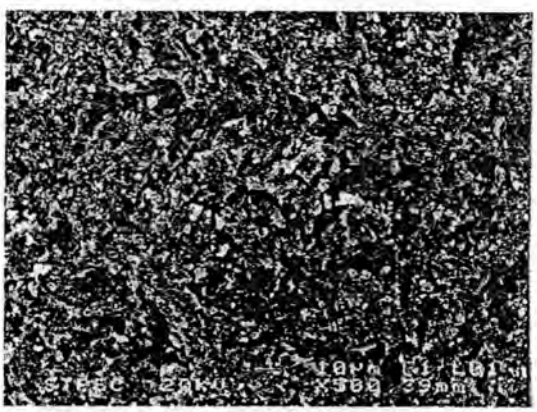
Figure 46 Scanning electron photomicrographs of matrix pellets with diclofenac sodium to Avicel® ratio of 1: 3 containing Seacure® 343 (BA5) prepared from different spheronization speeds (500 and 900 rpm) at different magnifications.



(15 min) X 70

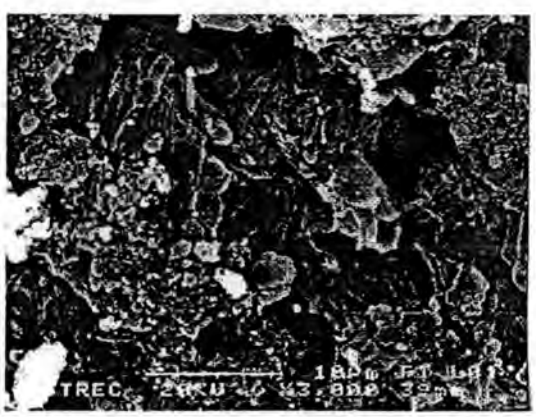


(30 min) X 70

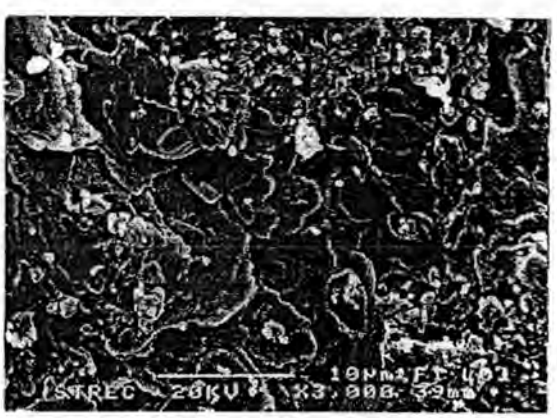


(15 min) X 500

(30 min) X 500



(15 min) X3,000



(30 min) X 3,000

Figure 47 Scanning electron photomicrograph of matrix pellets with diclofenac sodium to Avicel® ratio of 6: 10 containing Secure® 243 (AA5) prepared by different spheronization times (15 and 30 minutes) at different magnifications.

2.2.1 Amount and Type of Diluents

The formulations produced by one diluent could be obtained by Avicel® but not lactose. The pellets also could not be produced from the formulations that used more amount of diclofenac sodium than that of Avicel®. When Seacure® 243 was used at the drug to diluent ratio of 1:1, irregular shaped and rough surfaced pellets were presented, whereas Seacure® 343 could produce the good pellets. The same as the formulation using one diluent, those of two diluents could be produced by using drug to diluent ratio more than 1:1.

There was no noticeable in size distributions of the pellets when different amount of Avicel® alone was used in the formulation using Seacure® 343, except at drug to diluents ratio 1:1 (Figure 48, Table 25). Most pellets (78.9%) of this formulation was retained on the sieve size No. 18, whereas the other formulations had this size of the pellets about 50.0% and the smaller size (sieve size No.20) about 30.0 - 40.0%.

The size of distributions of the formulations containing two diluents are shown in Figure 49 (table 25). Percentage of the smaller size of the pellets was increased and wider size distributions was detected from these formulations. There was no difference in size distribution between the formulations containing one and two diluents.

2.2.2 Amount and Type of Polymer.

The amount of the polymer used in the pelletization process was in the range of 1.60 - 3.30%. The amount of Seacure® 243 was higher than that of Seacure® 343 when compared with the formulations that used the same amount and type of the diluents. The size distributions of pellets prepared from different grade of Seacure® are presented in Tables 25-26.

Table 25 Sieve analysis of each pellet formulation from the spheronization time of 15 min at different spheronization speed.

Formulation	Speed (rpm)	Percent retained on each sieve sizes*				
		14	18	20	25	Pan
AA4	500	.	6.0	12.1	55.2	26.7
AA5	500	.	3.9	18.0	57.0	21.1
BA1	500	8.6	78.9	11.3	1.1	.
BA2	500	0.6	51.0	40.0	8.3	.
BA3	500	6.9	58.1	34.1	0.7	.
BA4	500	1.4	55.6	27.5	14.6	0.7
BA5	500	6.3	48.6	30.8	13.7	0.4
BA5	900	18.8	77.6	3.2	0.3	0.1
AAL1	500	3.6	43.2	28.4	23.9	0.9
BAL1	500	5.6	67.3	17.1	9.6	0.4
BAL2	500	28.4	66.0	4.0	1.4	0.2

* Underlined the highest percent yield of sieve analysis.

Table 26 Sieve analysis of each pellet formulation from the spheronization speed of 500 rpm at different spheronization time.

Formulation	Time (min)	Percent retained on each sieve sizes*				
		14	18	20	25	Pan
AA4	5	IP**	IP	IP	IP	IP
	10	.	9.5	33.4	46.4	10.7
	15	.	6.0	12.1	55.2	26.7
	20	.	4.9	24.3	59.7	11.1
	25	.	4.9	25.3	59.0	10.8
	30	.	4.6	23.3	60.7	11.4
AA5	5	IP	IP	IP	IP	IP
	10	IP	IP	IP	IP	IP
	15	.	3.9	18.0	57.0	21.1
	20	.	3.6	15.0	62.7	18.7
	25	.	3.6	13.8	65.3	17.3
	30	.	3.0	14.7	64.9	17.4

* Underlined the highest percent yield of sieve analysis.

** IP = incompleted pellets occurred.

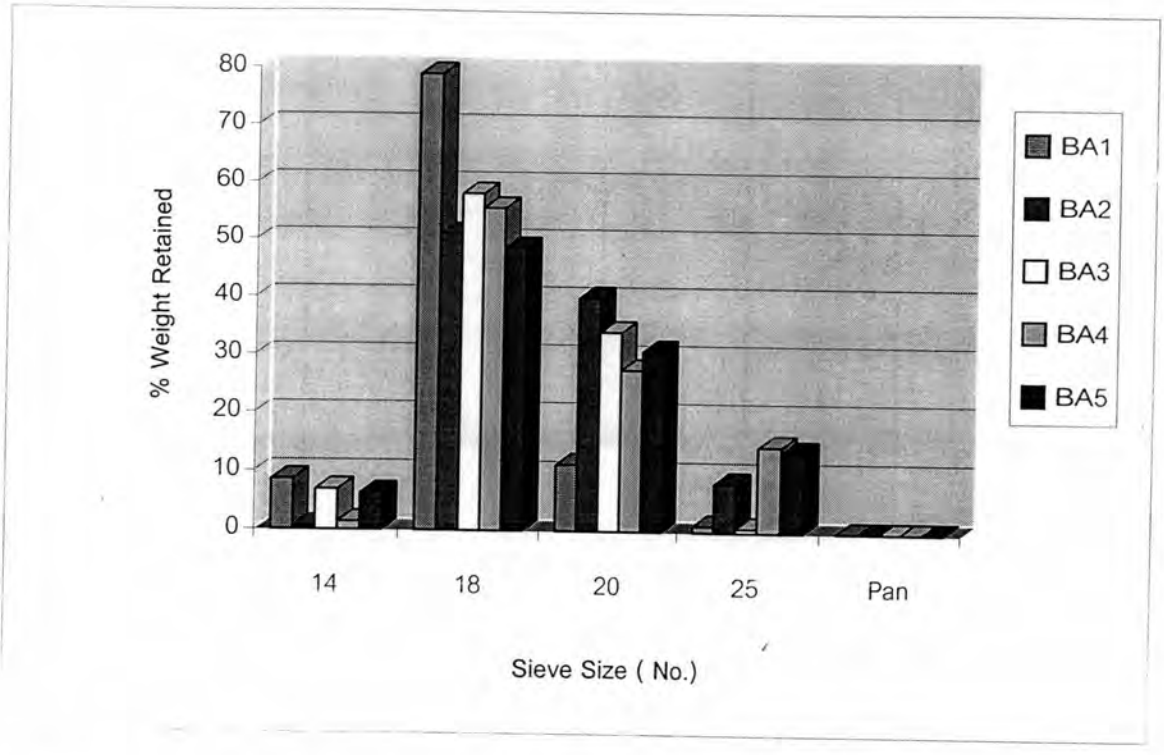


Figure 48 Size distributions of diclofenac sodium pellets with various drug and diluent ratios produced by Seacure 343 at the same pelletization conditions.

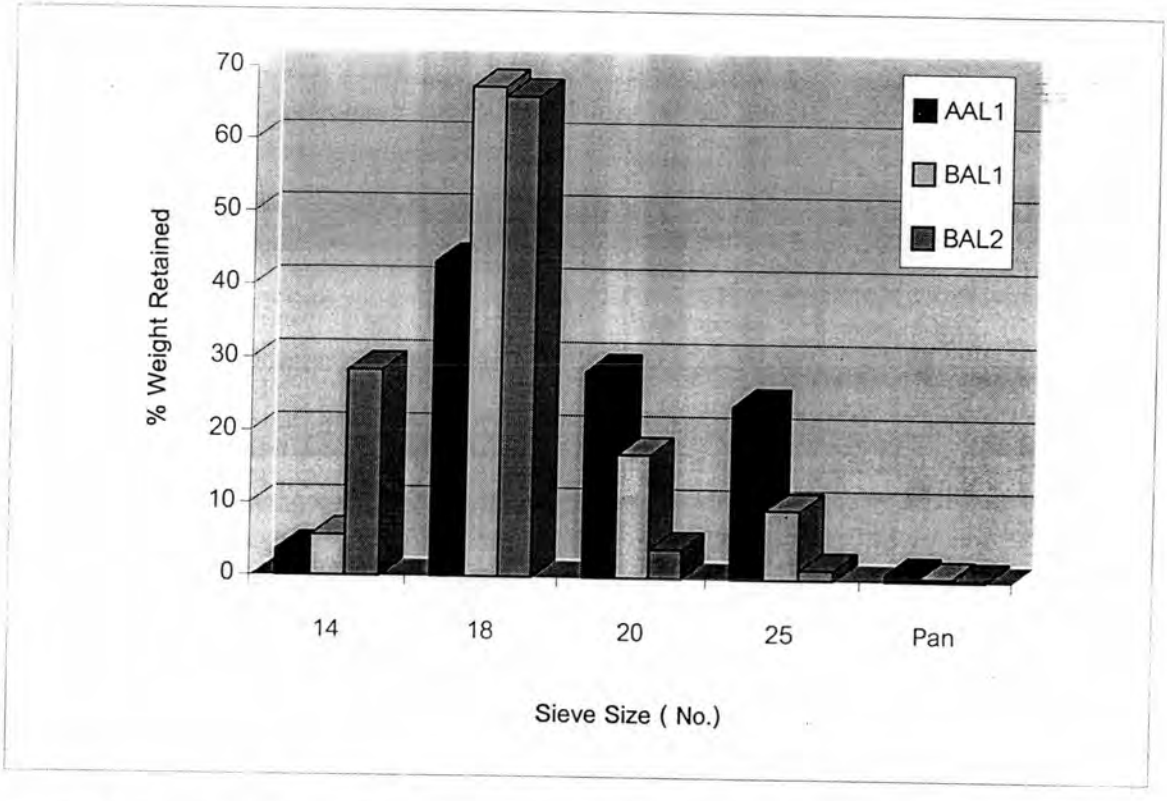


Figure 49 Size distributions of diclofenac sodium pellets with two diluent system at various ratios produced by same pelletization conditions.

The pellets size of the formulations that used Avicel® alone with Seacure® 243 was smaller than those used Seacure® 343. The results are shown in Table 25. More than 80% of the pellets produced by Seacure® 243 were smaller than 700 μm (sieve size No.25). The highest amount of the pellets was retained on sieve size No.25, whereas the highest amount of pellets that produced by Seacure® 343 was retained on sieve size No.18.

When two diluents system was used, the highest amount of the pellets was retained on sieve size No.18. This result was obtained by the formulations used both Seacure® 243 and 343 (Figure 49, Table 25). The pellets produced from Seacure® 243 had wider size distribution than those from Seacure® 343.

2.2.3 Spheronization Speed

The size distributions of the pellets produced by different spheronization speed are shown in Figure 50, Table 25. The narrow size distributions and the bigger pellets were presented, when the spheronization speed was increased. Although 900 rpm of spheronization speed gave better results in pelletization process, but 500 rpm was selected in order to prevent the overload of the machine.

2.2.4 Spheronization Time

The size distributions of the pellets produced by different spheronization time are presented in Figure 51, Table 26. The suitable spheronization time in this study was 15 min in all formulations. The incomplete pellets were produced, when the spheronization time was lower than 15 min. Using the spheronization time of more than 15 min did not display any significant difference in the size distributions of the pellets. Thus 15 min was used to save the time and energy in the process.

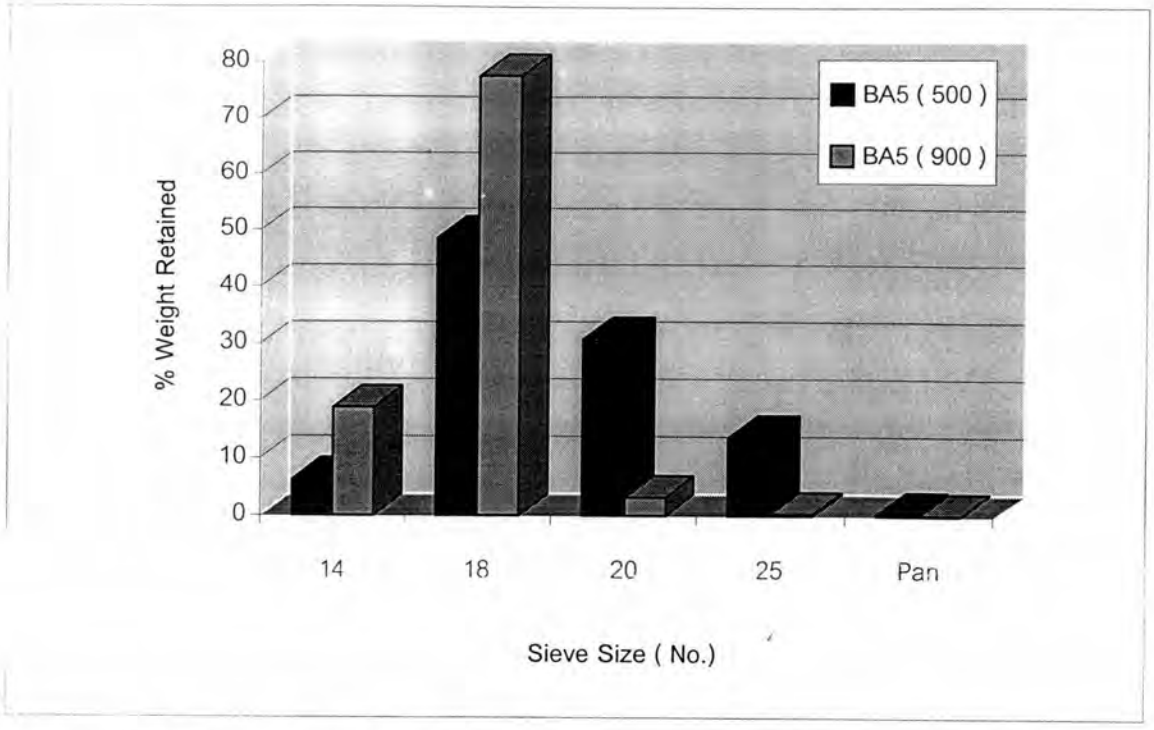


Figure 50 Size distributions of diclofenac sodium pellets at the ratio of 1:1 of Seacure 343 (BA5) produced by different spheronization speed.

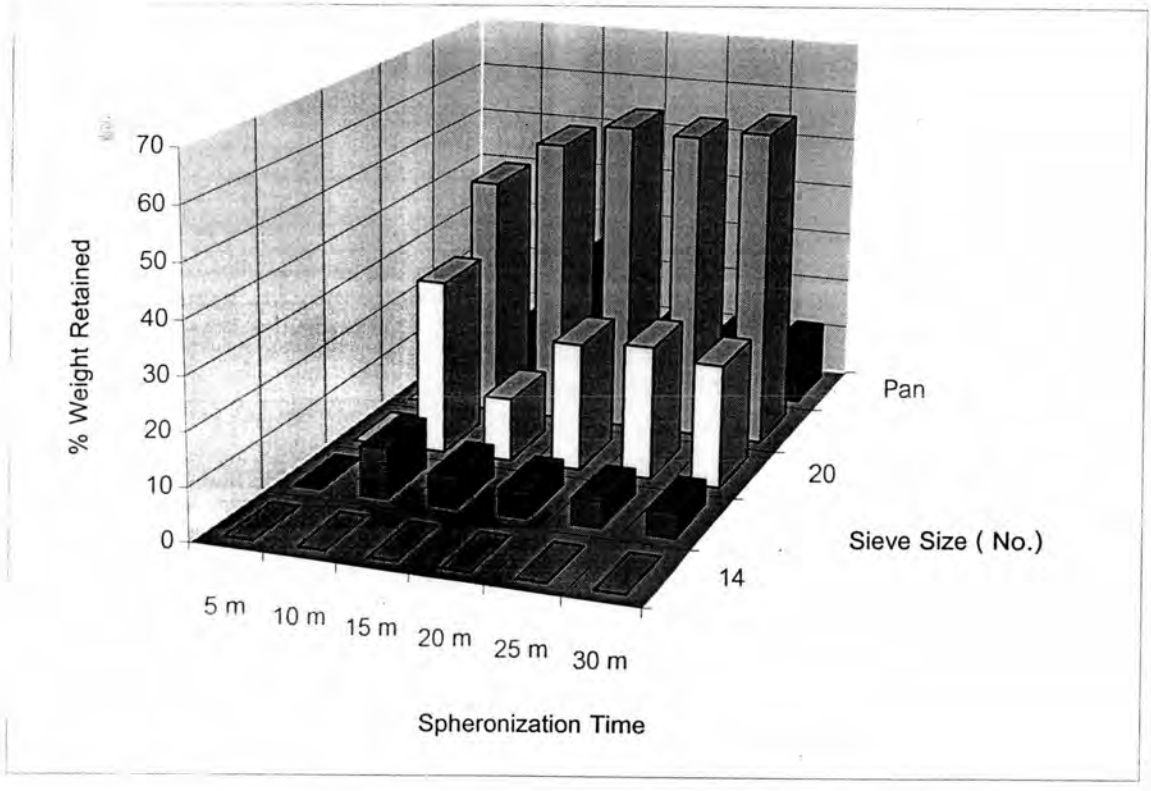


Figure 51 Size distributions of diclofenac sodium pellets at the ratio of 1:2 (AA4) at different spheronization time.

IV. Dissolution Study

1. Dissolution Profiles

The dissolution or the release profiles could be plotted between percent of drug released against time. The dissolution data of each formulation and blank diclofenac sodium capsules, reference tablets and Voltaren® SR tablets were described in Tables 32 - 42. (Appendix B)

Three preparations of diclofenac sodium were produced by filling into capsules or compressed into tablets equivalent to 100.0 mg of drug. All preparations were evaluated in pH-change systems by testing those preparations in the acidic stage (0.1 N HCl, pH 1.2) for 2 hours and followed by phosphate buffer pH 6.8 until 24 hours.

The percentages of drug released in the acidic stage from all formulations were less than 4.0%. After 24 hours dissolution test, more than 75.0% of diclofenac sodium released from Voltaren® SR tablets was observed. This released level passed the criteria of percent drug released from sustained release preparations in USP XXIII. Thus it was used as a standard for this study.

1.1 The Reference Diclofenac Sodium Capsules and Tablets

The drug release data of pure diclofenac sodium in capsule and tablet preparations are listed in Table 32 (Appendix B) and drug release profiles are shown in Figure 52.

The percentages of drug released in the acidic stage of diclofenac sodium capsules and tablets were 3.6% and 0.7%, respectively. In phosphate buffer pH 6.8, 80.0% of drug was released after 3 hours for capsule preparations and 4 hours for tablet preparations. The results indicated that diclofenac sodium was more soluble in phosphate buffer pH 6.8 than in 0.1 N HCl.

1.2 The Commercial Product

The dissolution data and drug released profile of commercial product, Voltaren® SR 100.0 mg tablets, are presented in Table 32 (Appendix B) and Figure 52, respectively. The release of diclofenac sodium from Voltaren® SR was affected by dissolution medium. The percentage of the drug released at the first 2 hours was less than 1.0%, whereas the percent released in basic stage was gradually increased until reached 79.0% of drug content at the 24th hour. The release rate of this tablet decreased as the time increased. After the test, the polymer was still in the original shape of undissolved tablet except the upper surface was broken because of swelling of the polymer.

1.3 The Spray Dried Powder

The dissolution profiles of spray dried diclofenac sodium powder prepared by Seacure® 243 and 343 at various ratios without plasticizer in the pH-change system are shown in Figures 53 - 54 (Tables 33 - 34, Appendix B), respectively. Each point represents the average value obtained from three determinations at a given sampling time.

In acidic stage, the percent drug released from all samples containing Seacure® 243 were lower than 3.0%. Those containing Seacure® 343 released about 3.0%. When the pH of medium was raised to 6.8, the amount of drug released went up very fast. More than 50% of drug was released at the 3rd hour and more than 85% was at the 24th hour. However, the formulation containing Seacure® 243 at drug to polymer ratio of 1:5 released only 18.4% after 3 hours and gradually increased to 62.7% at the 24th hours. This formulation showed significant difference in release patterns from the other ratios produced by Seacure® 243 only.

Although the formulation containing Seacure® 243 at the ratio of 1:5 exhibited satisfactory controlled release profile of the capsules preparations, the

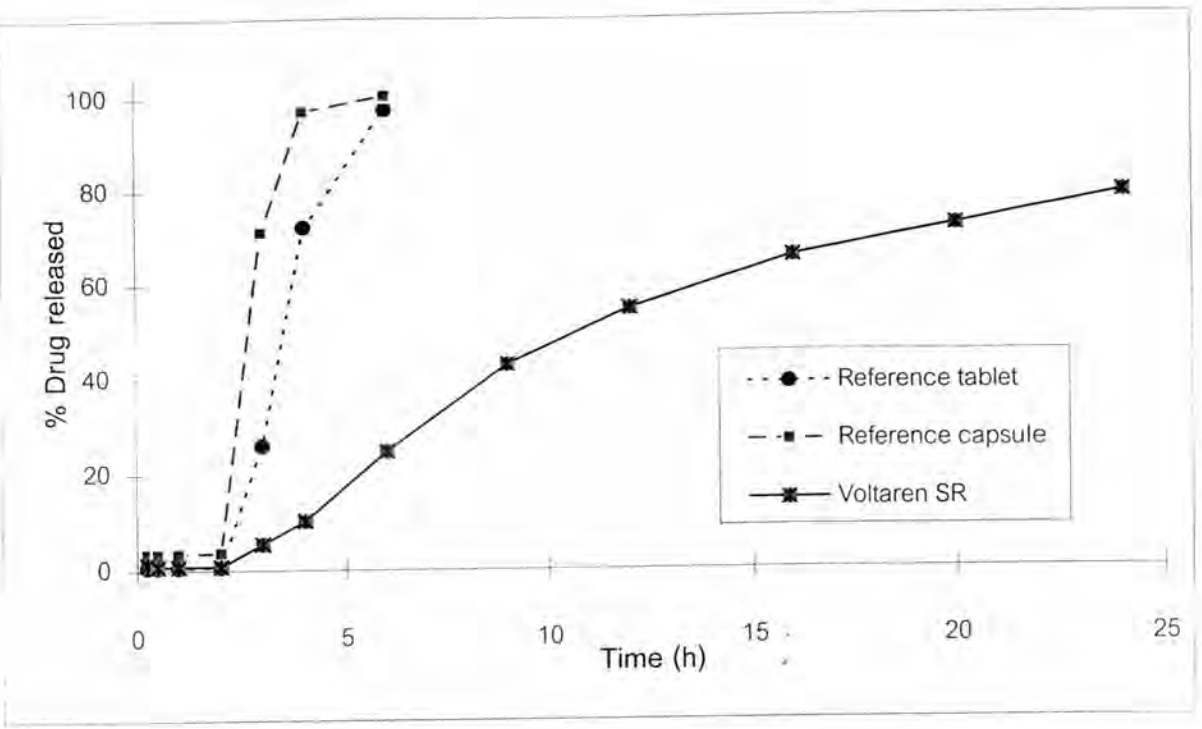


Figure 52 The release profiles of reference diclofenac sodium capsules, reference tablets and Voltaren SR tablets in pH-change media.

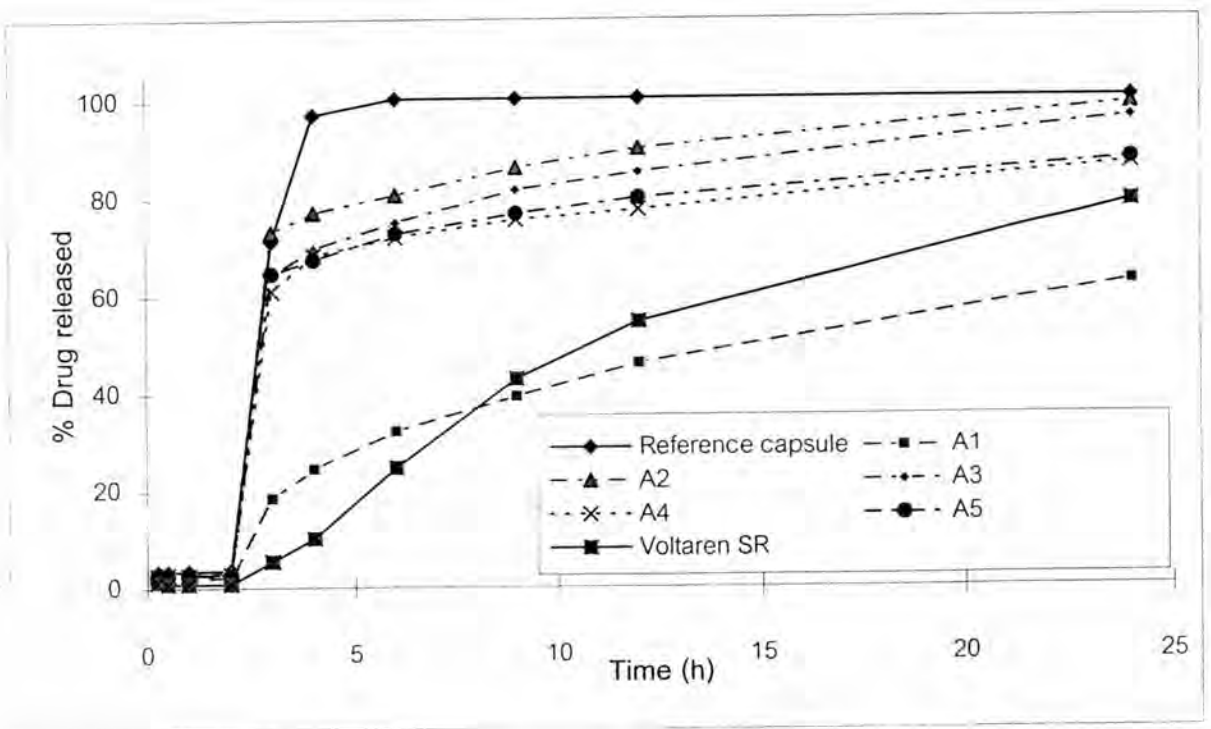


Figure 53 The release profiles of spray dried powders of Formulations A1 - A5 in pH-change media (Seacure 243; A1 = 1:5, A2 = 1:10, A3 = 1:15, A4 = 1:20 and A5 = 1:30).

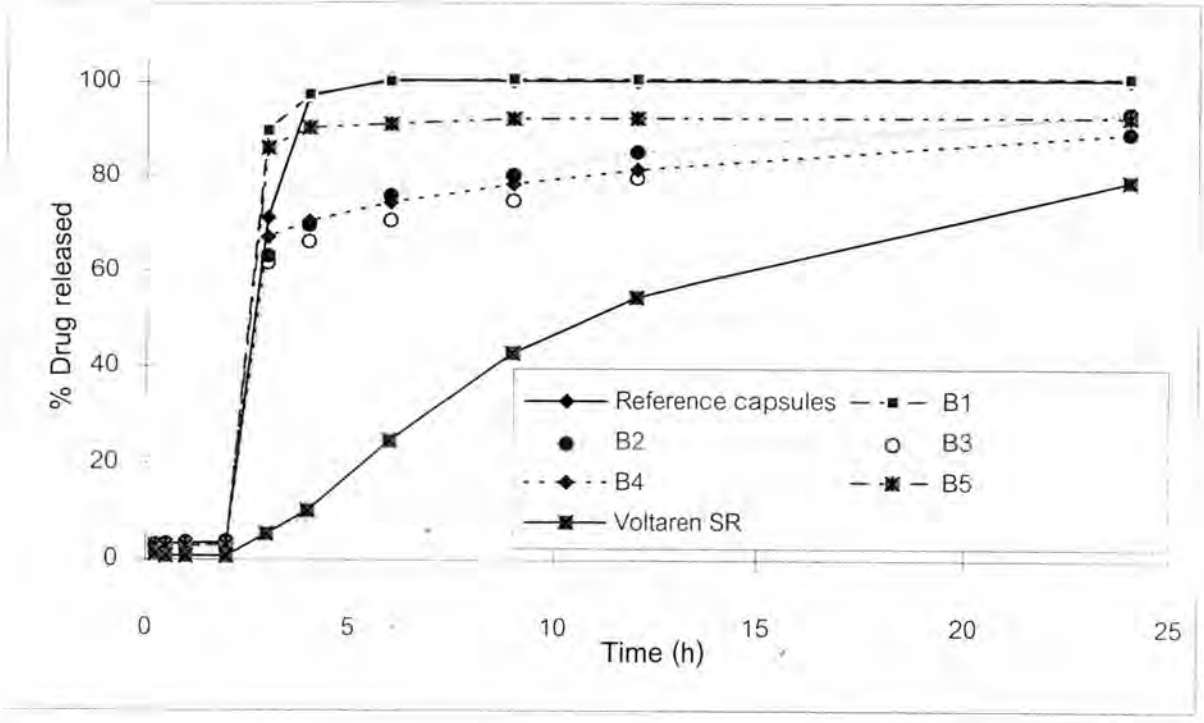


Figure 54 The release profiles of spray dried powders of Formulations B1 - B5 in pH-change media (Seacure 343; B1 = 1:5, B2 = 1:10, B3 = 1:15, B4 = 1:20 and B5 = 1:30).

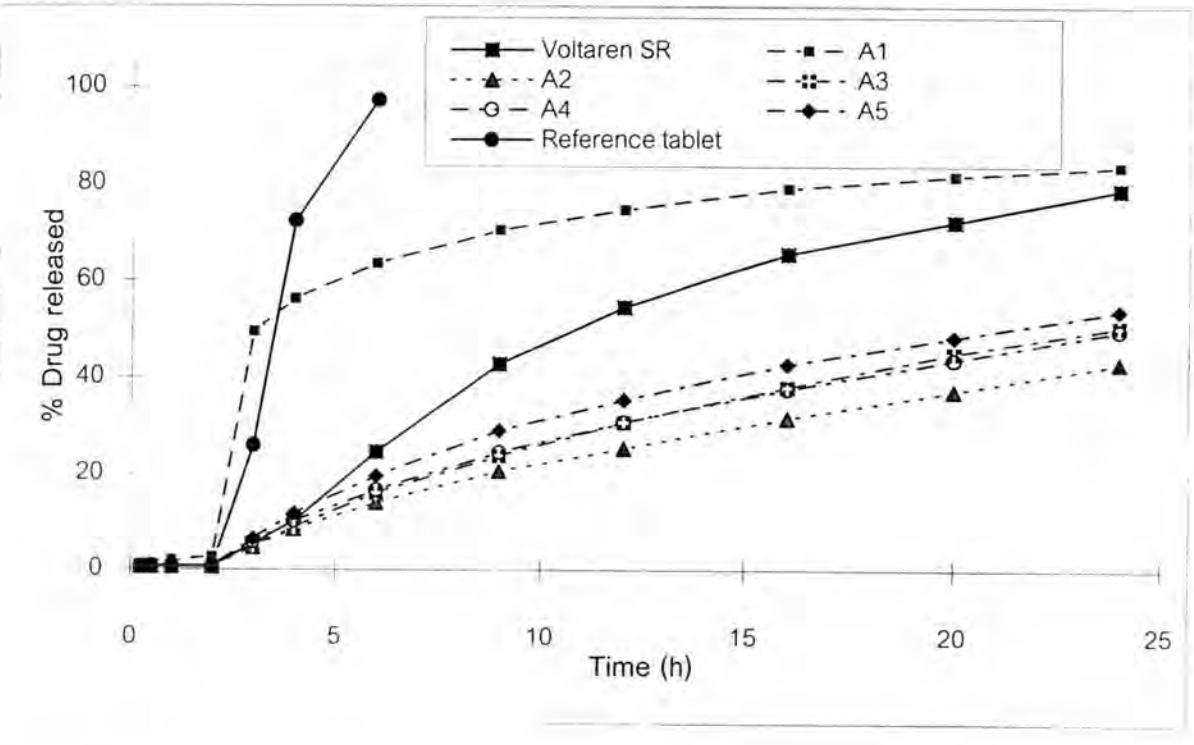


Figure 55 The release profiles of tablets containing spray dried powders of Formulations A1 - A5 in pH-change media (Seacure 243; A1 = 1:5, A2 = 1:10, A3 = 1:15, A4 = 1:20 and A5 = 1:30).

formulation containing Seacure® 343 at the same ratio showed faster drug release. About 89% of drug was released at the 3rd hour and reached 100% at the 6th hour. No significantly different release pattern was detected from formulations containing other ratios of this polymer grade.

1.4 The Matrix Tablets

The dissolution data and release profiles of the matrix tablets were divided into many groups depended on the type and amount of polymer and plasticizer used in the formulations. The matrix tablet formulations were classified as the following :

a) The Formulations A1 - A5 and B1 - B5

The release data of spray dried diclofenac sodium matrix tablet from the formulations containing Seacure® 243 with various ratios are listed in Table 35, Appendix B and release profiles of these preparations are illustrated in Figure 55.

The percentage of drug release at the 24th hour was increased when the proportion of polymer in the formulation was decreased, unless that of 1:5 ratio that percent release in basic stage increased very fast and came to the plateau state. Whereas the dissolution profiles of the matrix tablets prepared from the ratio 1:15 and 1:20 seemed to be similar.

The dissolution patterns of spray dried matrix tablets prepared form various amount Seacure® 343 were similar to those containing Seacure® 243. Those results are depicted in Figure 56 (Table 36, Appendix B).

The formulation using ratio of 1:5 showed the fastest percent release after the 3rd hour of dissolution test compared to the other formulations in this group. The percent releases of the formulations prepared form the other ratios at the 24th hour was increased from 25.3% to 34.3% to 45.2% and 56.0% when polymer to drug

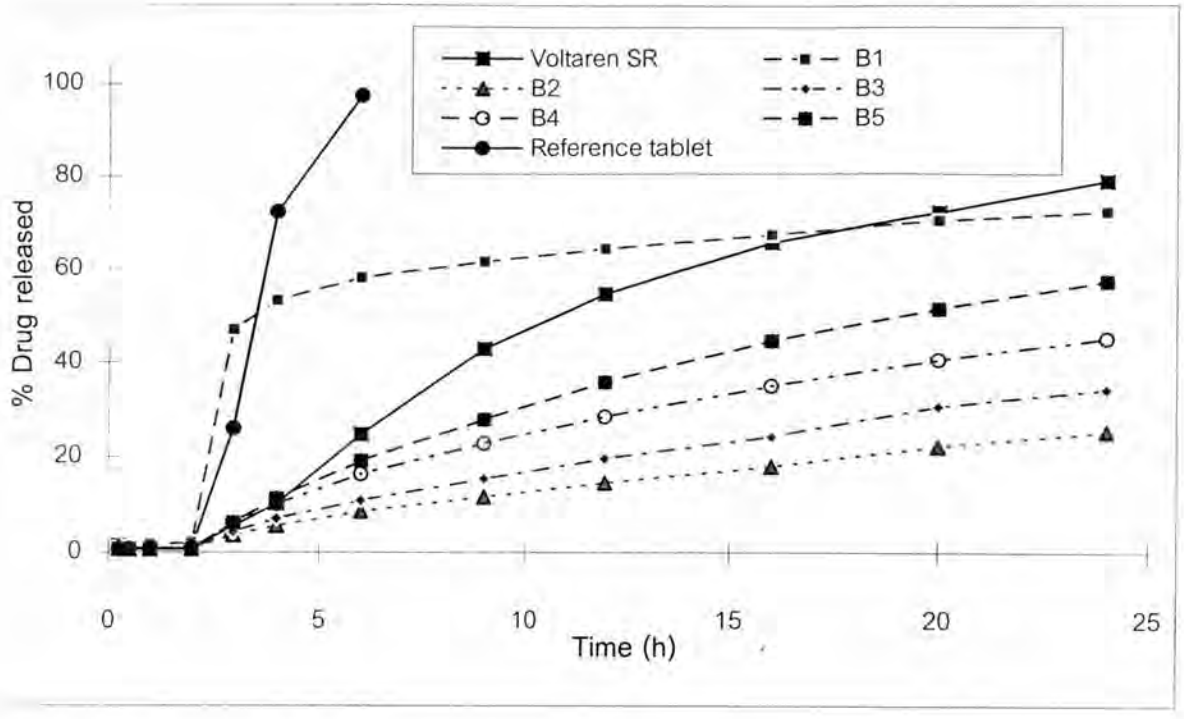


Figure 56 The release profiles of tablets containing spray dried powders of Formulations B1 - B5 in pH-change media (Seacure 343; B1 = 1:5, B2 = 1:10, B3 = 1:15, B4 = 1:20 and B5 = 1:30).

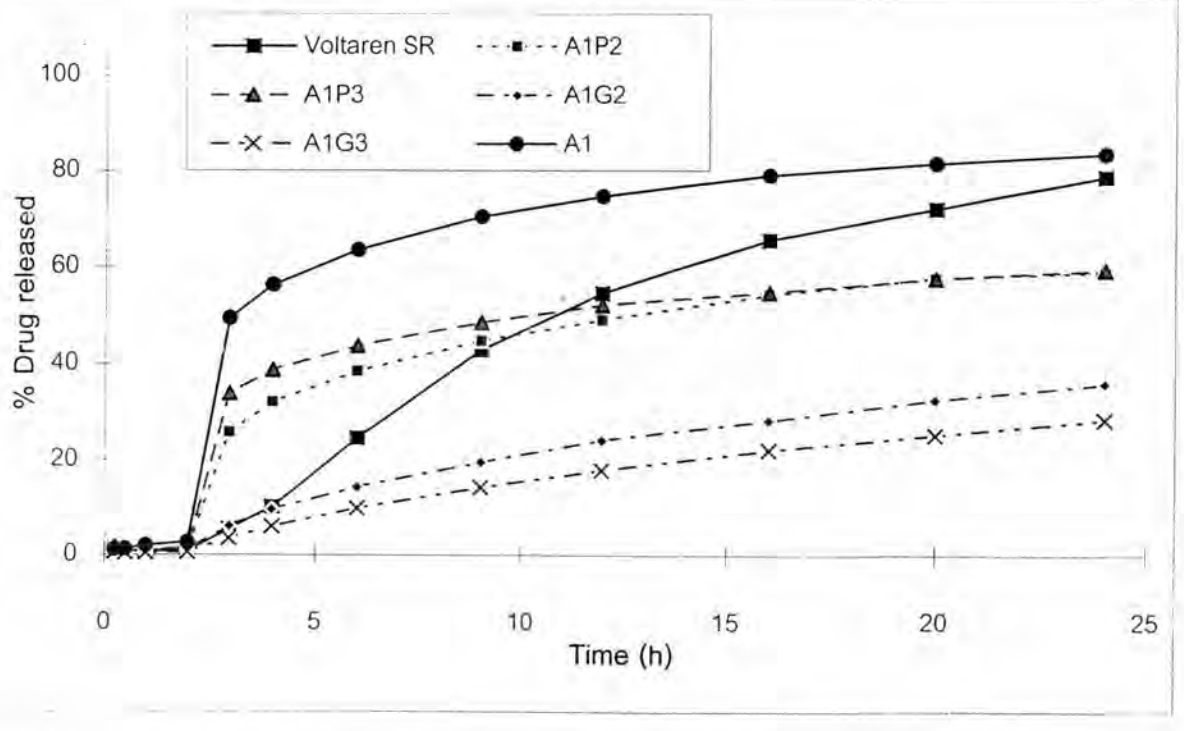


Figure 57 The release profiles of tablets containing spray dried powders of Formulations A1P2, A1P3, A1G2 and A1G3 in pH-change media (Seacure 243; 1:5 + PG 20, 33% and + Gly 20, 33%).

ratios was changed from 1:10, 1:15, 1:20 to 1:30, respectively. As expected, the percent drug releases were increased with decreasing amount of the polymer in the formulations.

The significant difference in release patterns was found between the matrix tablet formulations produced by the ratio of 1:5 and those from the other ratios. No difference in release patterns was detected from the formulations produced by each grade of polymer in the formulations using both grades of Seacure®.

The matrix tablet preparations of unplasticized spray dried powders of the highest amount of Seacure® (ratio of 1:5) dissolved very rapidly and presented the release percentages of 86.6% and 72.4% form the formulations using Seacure®243 and 343, respectively.

Comparison of the dissolution profiles of spray dried powders and spray dried matrix tables, all preparations of the former showed higher released percentages than that of the commercial product, except the formulation using Seacure® 243 to drug ratio of 1:5. On the contrary, the percent released of most matrix tablets preparations were lower than that of Voltaren®SR tablets.

b) The Formulations A1P2, A1P3, A1G2 and A1G3

From Figure 55, the release profiles of the matrix tablet formulations prepared from Seacure® 243 to drug ratio of 1:5 without plasticizers was compared to the same formulation with plasticizer. Those release profiles are illustrated in Figure 57 (Table 37, Appendix B).

Plasticizer could decrease the percent released of the unplasticized formulation, especially when glycerin was used. Two types of plasticizers presented the significant different release profiles from each other and from that of unplasticized formulations using the same polymer to drug ratio. When amount of glycerin was increased, the drug release was decreased, whereas the increased amount

of propylene glycol showed no significant difference in the percent released after the 12th hour of dissolution test. The faster release rates were observed from the unplasticized matrix tablets followed by propylene glycol-plasticized and glycerin-plasticized matrix tablets, respectively.

c) The Formulations A2P1 - A2P4 and B2P1 - B2P4

The dissolution profiles of the formulations containing Seacure® 243 at drug to polymer ratio of 1:10 with various amount of propylene glycol are presented in Figure 58 (Table 38, Appendix B).

The profiles were almost superimposed and lower than that of Voltaren® SR. The amount of propylene glycol from 10 to 33% had no effect on drug release. However, when increasing the amount of propylene glycol to 40%, the drug release was decreased to 36.6%. The formulations used propylene glycol in the range of 10 - 33% exhibited 10 - 15% drug released higher than those without plasticizer. The formulation containing 33% propylene glycol showed the highest drug release of 56.9%.

When Seacure® 243 was replaced by Seacure® 343, their percent released were different. The percent released of these formulations were lower when the same amount of propylene glycol was used. All dissolution profiles of this group are presented in Figure 59 (Table 39, Appendix B). At the 24th hour of the dissolution test, the formulation that used 40% propylene glycol still exhibited the lowest percent released of 26.6% whereas that used 33% propylene glycol showed the highest percent released of 47.6%. There was only a slight difference between the formulations that used 10% and 20% of propylene glycol.

It was interesting that the comparison between each matrix tablets formulations produced from different grade of Seacure® at the ratio of 1:10 with various amount of propylene glycol showed no significant difference in release patterns. Except when 40% of propylene glycol was used, the delayed release was detected.

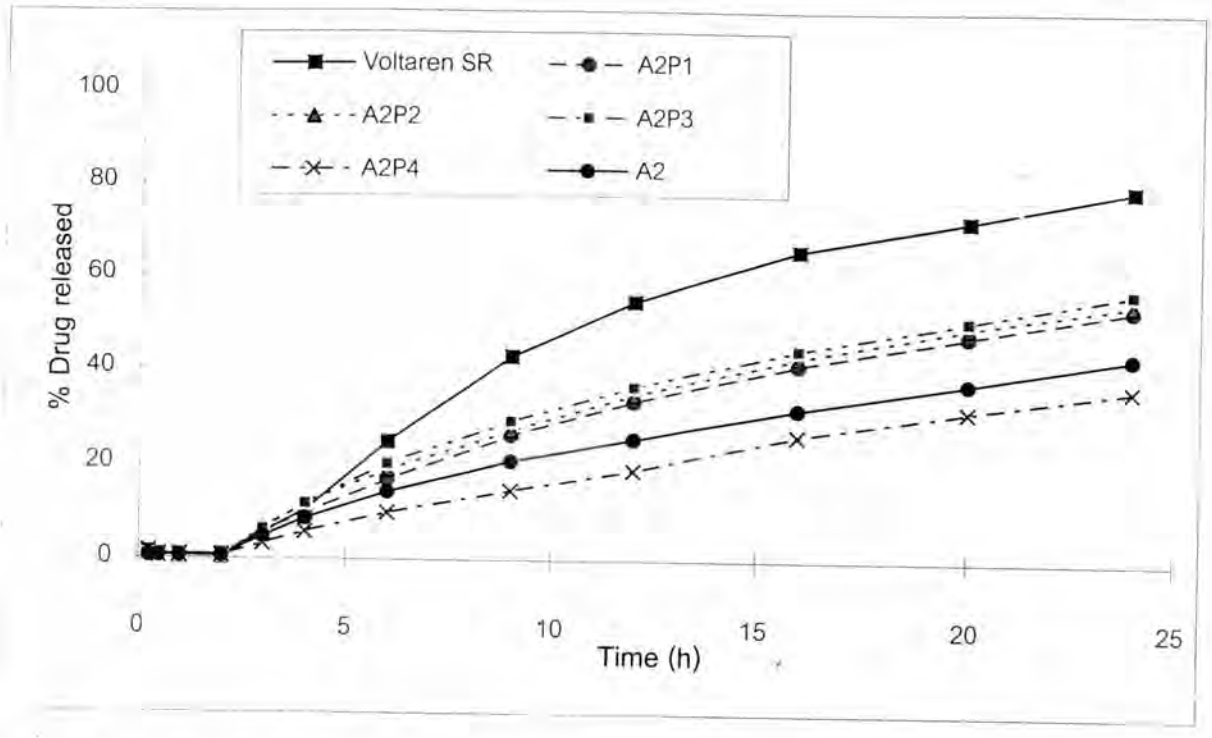


Figure 58 The release profiles of tablets containing spray dried powders of Formulations A2P1 - A2P4 in pH-change media (Seacure 243; 1:10 + PG 10, 20, 33 and 40%).

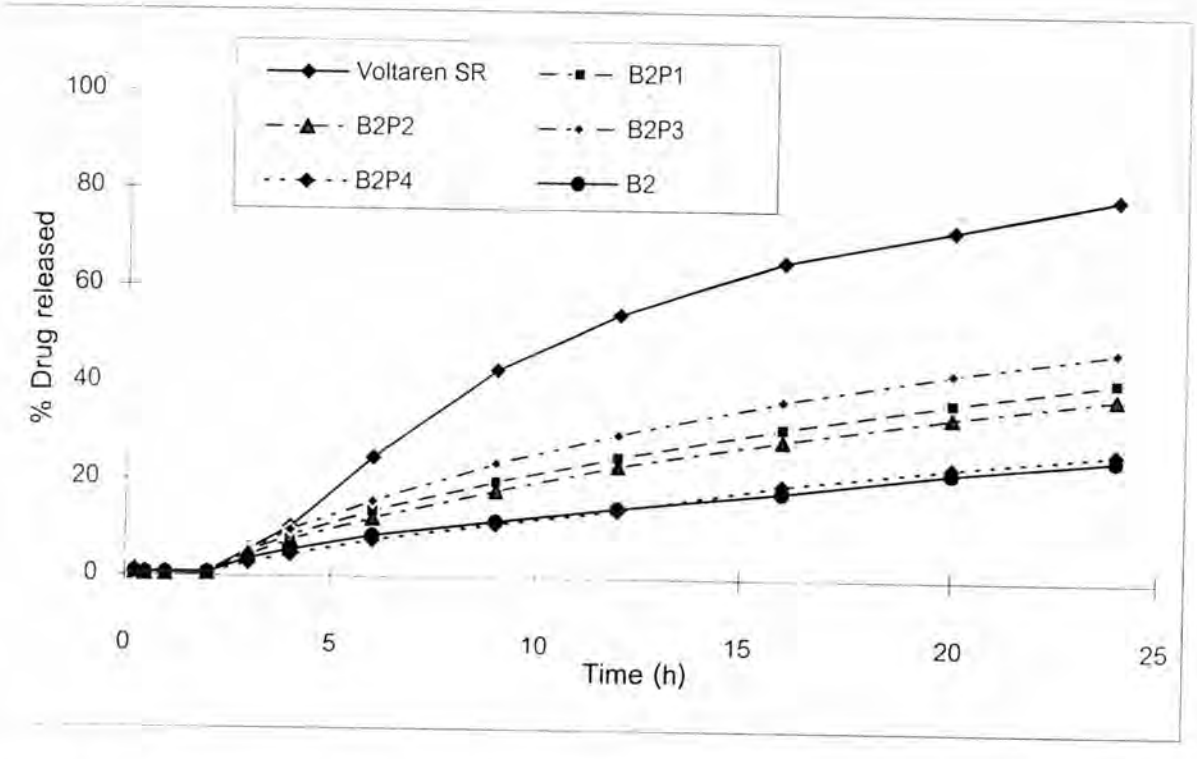


Figure 59 The release profiles of tablets containing spray dried powders of Formulations B2P2 - B2P4 in pH-change media (Seacure 343; 1:10 + PG 10, 20, 33 and 40%).

d) The Formulations A2G1 - A2G3 and B2G1 - B2G3

The dissolution results of the controlled release formulations of Seacure® 243 and diclofenac sodium at the ratio of 1:10 with glycerin are depicted in Figure 60 (Table 40, Appendix B). The formulation with 10% glycerin showed slightly higher percent released than that without plasticizer, but those with 20 and 33% glycerin gave the lower percent released of 36.6% and 30.9%, respectively.

In Figure 61 (Table 40, Appendix B), the percentage of drug released from all formulations using Seacure® 343 with glycerin were higher than unplasticized formulations prepared form the same amount of components. The highest percent released was obtained from the formulations used 20% glycerin. No statistically significant difference in percent drug released between the formulations with 10% and 33% of glycerin was detected. As in the formulations using propylene glycol, there was no significant difference in release patterns form the formulations produced from the same grade and amount of polymer at any amount of glycerin used.

e) The Formulations A3P1 - A3P3

The drug release profiles of diclofenac sodium from spray dried matrix tablets of Seacure® 243 to diclofenac sodium of 1:15 with propylene glycol are shown in Figure 62 (Table 41, Appendix B).

The percent released of plasticized formulations were higher than unplasticized preparations, except formulation using 20% propylene glycol. About 10% of propylene glycol in the formulations using Seacure® 243 at the ratio of 1:15 gave a better dissolution results after 24 hours when compared to the unplasticized formulations. It had almost the same percent released and release profiles as the formulations containing Seacure® 243 at the ratio of 1:10 with 33% of propylene glycol. In the opposite way, the higher amount of propylene glycol in these formulations exhibited the lower percent released.

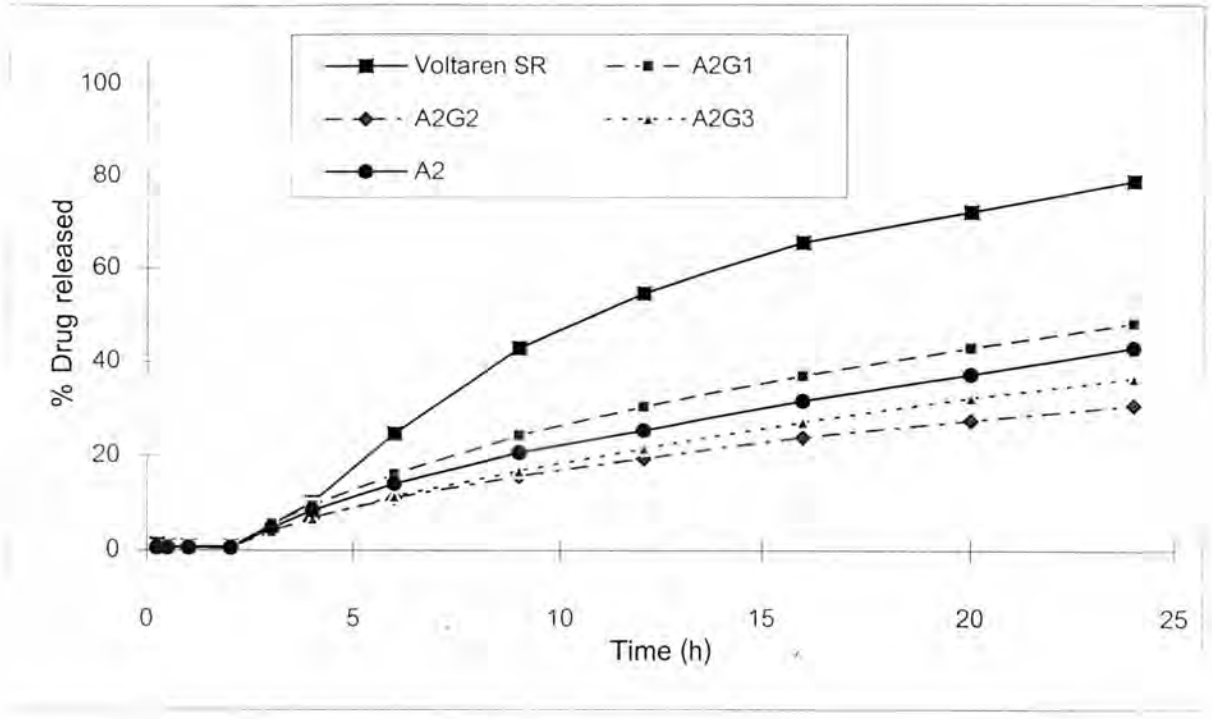


Figure 60 The release profiles of tablets containing spray dried powders of Formulations A2G1 - A2G3 in pH-change media (Seacure 243; 1:10 + Gly 10, 20 and 33%).

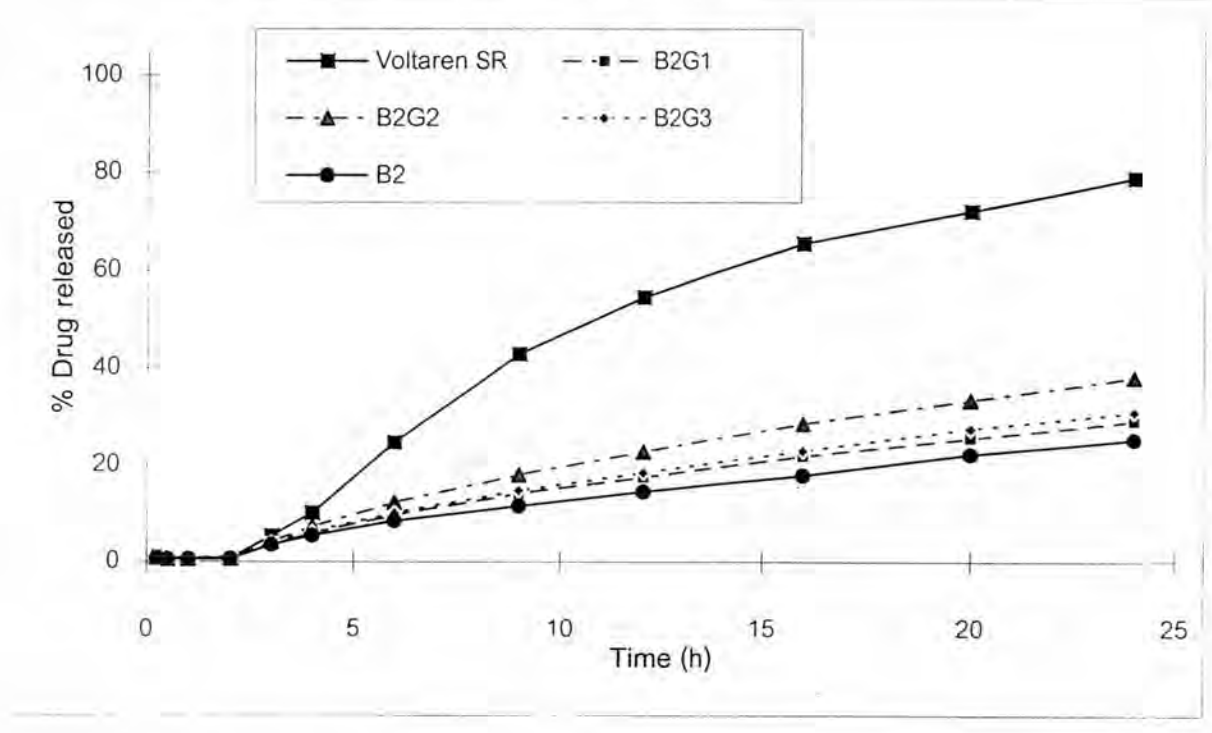


Figure 61 The release profiles of tablets containing spray dried powders of Formulations B2G1 - B2G3 in pH-change media (Seacure 343; 1:10 + Gly 10, 20 and 33%).

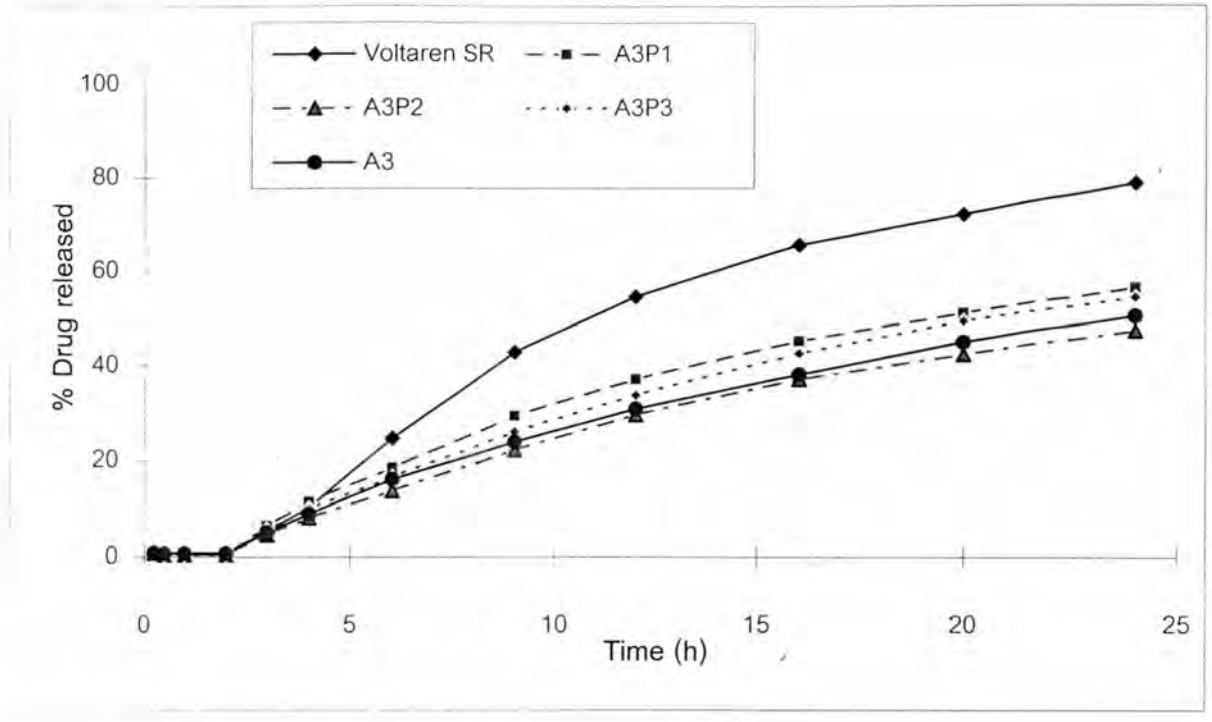


Figure 62 The release profiles of tablets containing spray dried powders of Formulations A3P1 - A3P3 in pH-change media (Seacure 243; 1:15 + PG 10, 20 and 33%).

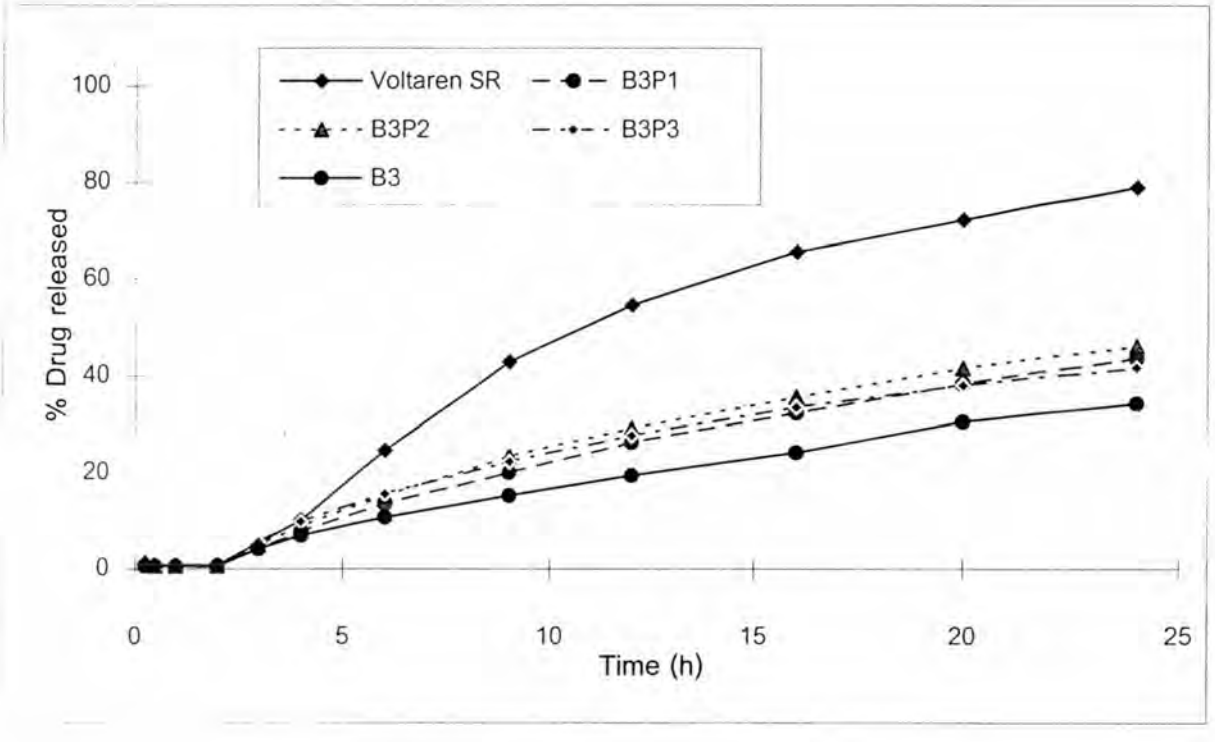


Figure 63 The release profiles of tablets containing spray dried powders of Formulations B3P1 - B3P3 in pH-change media (Seacure 343; 1:15 + PG 10, 20 and 33%).

f) The Formulations B3P1 - B3P3 and B3G1 - B3G3

The release profiles of the formulations containing Seacure® 343 to diclofenac sodium at the ratio of 1:15 with propylene glycol are exhibited in Figure 63 (Table 42, Appendix B). It was evident that no significant difference in percent released and release profiles of every formulation in this group. Percent released of all formulations were higher than those of unplasticized formulation. At 10%, 20% and 33% of propylene glycol added to the formulation, the percentages of drug released from the matrix tablets were 43.7%, 46.2% and 41.7%, respectively.

When glycerin was used instead of propylene glycol, the percent released tended to decrease, especially in the formulation with 33% glycerin. These release profiles are shown in Figure 64 (Table 42, Appendix B). The higher amount of glycerin showed the lesser percent drug release. At 10%, 20% and 33% of glycerin in the formulations, the percent released were 45.4%, 41.0% and 31.8%, respectively. The percent released of formulation using 33% glycerin was slightly lower than that of unplasticized formulations.

The patterns of dissolution profiles of the matrix tablet formulations produced from both grades of Seacure® at the ratio of 1:15 with both types of plasticizers indicated no significantly different.

1.5 The Matrix Pellets

The dissolution data and release profiles of the pellets were separated into groups to explain the important effects of formulation modifications and spheronization process used in the formulations. The pellets formulations were classified as the following :

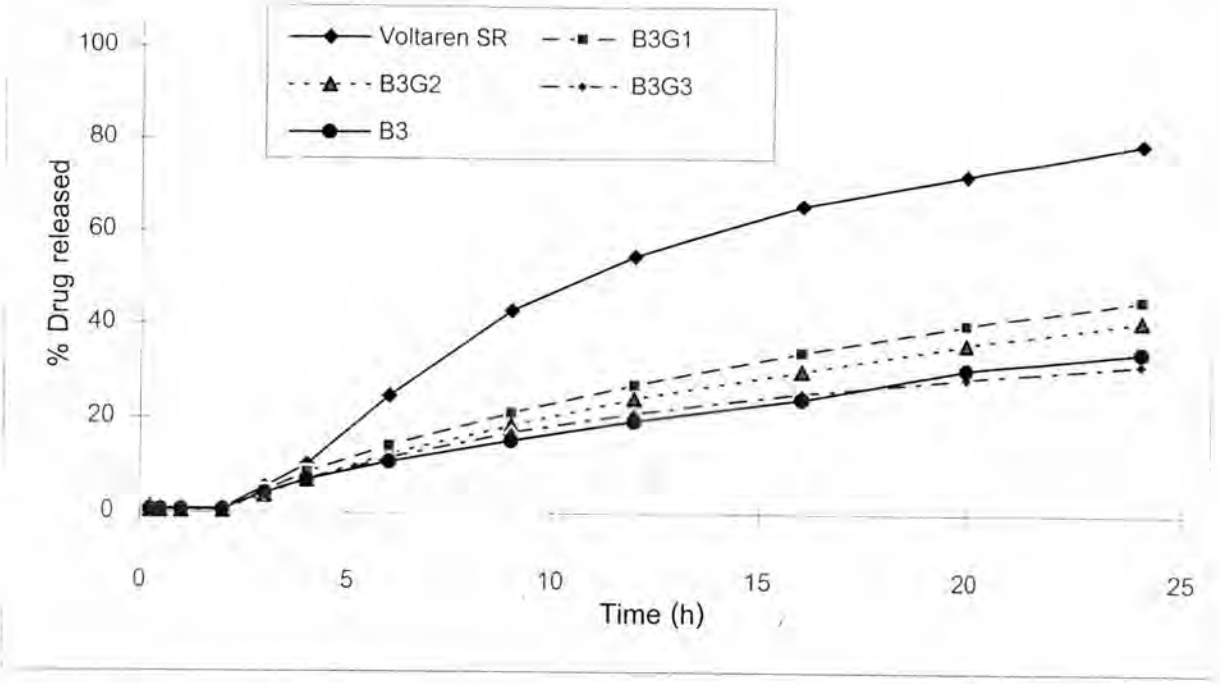


Figure 64 The release profiles of tablets containing spray dried powders of Formulations B3G1 - B3G3 in pH-change media (Seacure 343; 1:15 + Gly 10, 20 and 33%).

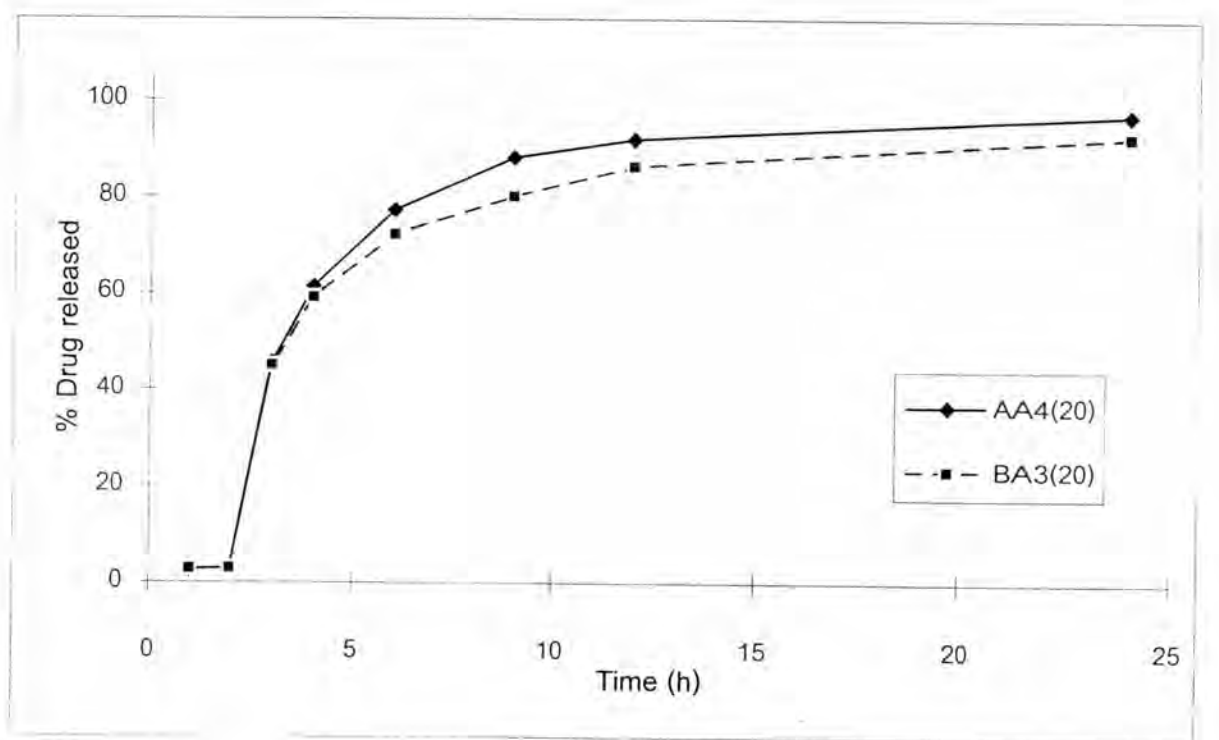


Figure 65 The release profiles of diclofenac sodium pellets(size No.20) prepared from Formulations AA4 and BA3 using the same drug to Avicel PH101 ratio at the same spheronization process (Seacure243; AA4 =1:2 and 343; BA3 = 1:2).

a) Effect of formulation modifications

The dissolution profiles of the pellet formulations produced from different grade of Seacure® are presented in Figure 65. Whereas the dissolution profiles of diclofenac sodium pellets produced by Avicel® PH101 using Seacure® 243 and 343 as binder with different drug to diluent ratio are shown in Figures 66 - 68 (Tables 43 and 44 - 46, Appendix B), respectively.

Both grade of Seacure® exhibited fast released of diclofenac sodium pellets. After the medium was changed from acid to base, the drug dissolved rapidly and release rate was constant after the 9th hour. There was no difference in release patterns of the formulations used different grade of polymer at the same drug to diluent ratio. Slightly higher in percent drug released was detected in the formulations of Seacure®243 compared to those of Seacure®343.

The higher amount of Avicel® in the formulation significantly resulted in the higher release of drug from the pellets. In the formulations that used Seacure®343 as binder, percent released of diclofenac sodium at the 3rd hour of the test were 69.7%, 44.0%, 44.4%, 43.3% and 30.6% and at the 24th hour were 98.4%, 98.2%, 94.4%, 92.1% and 89.2%, when the proportions of Avicel® were decreased from the drug to diluent ratios of 1:3.0, 1:2.5, 1:2.0, 1:1.5 and 1:1.0, respectively. Although the difference could be detected from the formulations using the ratio of 1:1.0, 1:2.0 and 1:3.0, no significant difference was found in the formulations of 1:1.5, 1:2.0 and 1:2.5.

Percent released of the formulations used Seacure®243 at the drug to diluent ratio of 6:10 was 37.2% at the 3rd hour, whereas percent released of the formulation used 1:2 ratio was 46.0%. At the end of the test, percent released of the former and latter were 94.5% and 98.3%, respectively.

In the formulations used Seacure®343, the lowest percent released of 34.7% was presented from the formulation of drug sodium to Avicel® at ratio

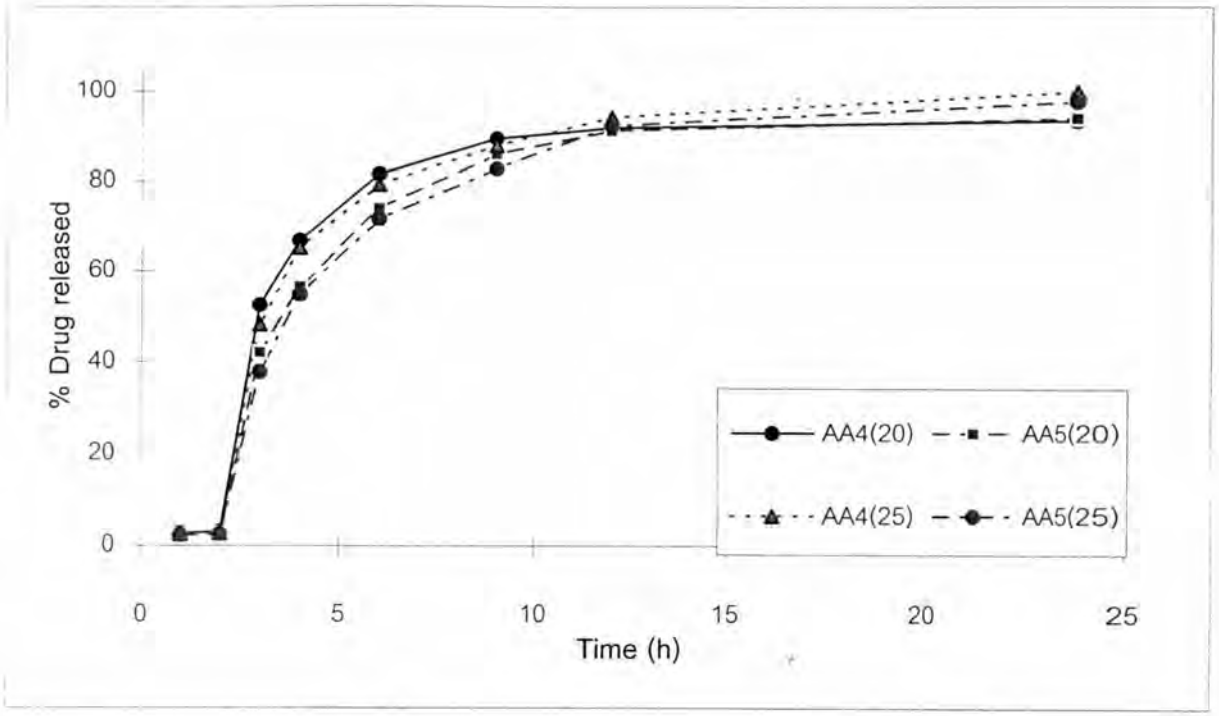


Figure 66 The release profiles of diclofenac sodium pellets (size No.20 and 25) prepared from Formulations AA4 and AA5 using different drug to Avicel PH101 ratios at the same spheronization process (Seacure 243; AA4 = 1:2 and AA5 = 6:10).

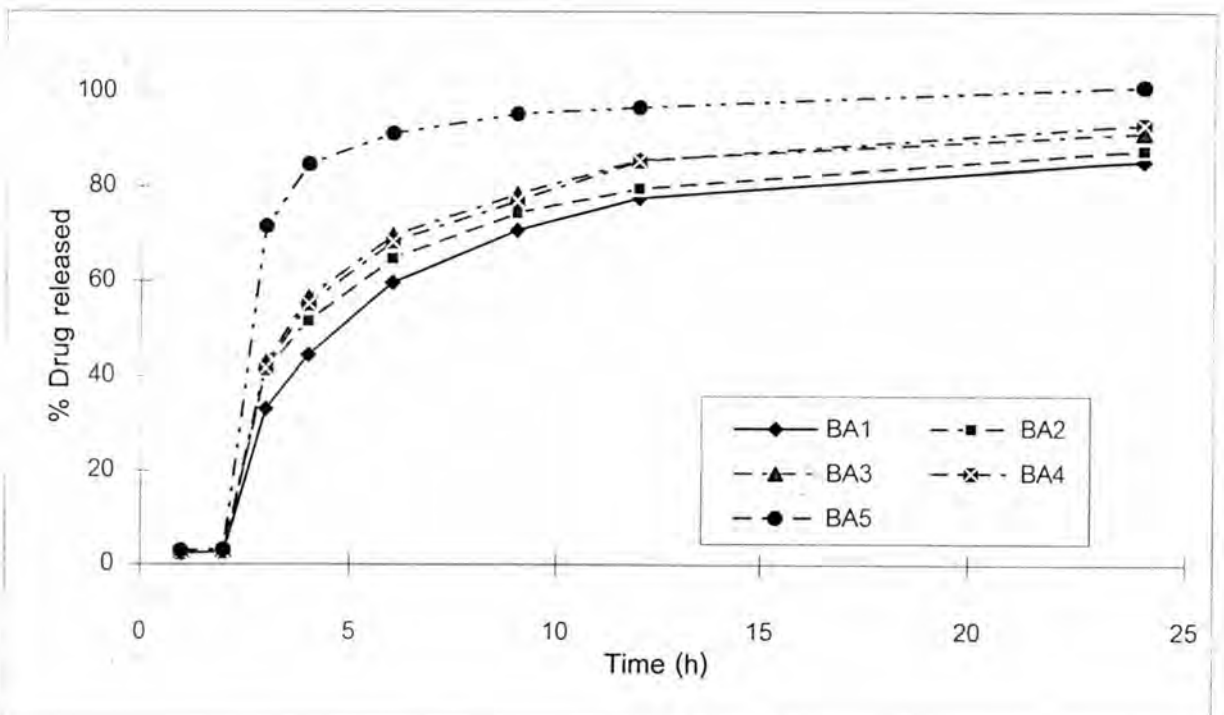


Figure 67 The release profiles of diclofenac sodium pellets (size No.18) prepared from Formulations Ba1 - BA5 using various drug to Avicel PH101 ratio at the same spheronization process (Seacure 343; BA1 = 1:1.0, BA2 = 1:1.5,BA3 = 1:2.0, BA4 = 1:2.5 and BA5 = 1:3.0).

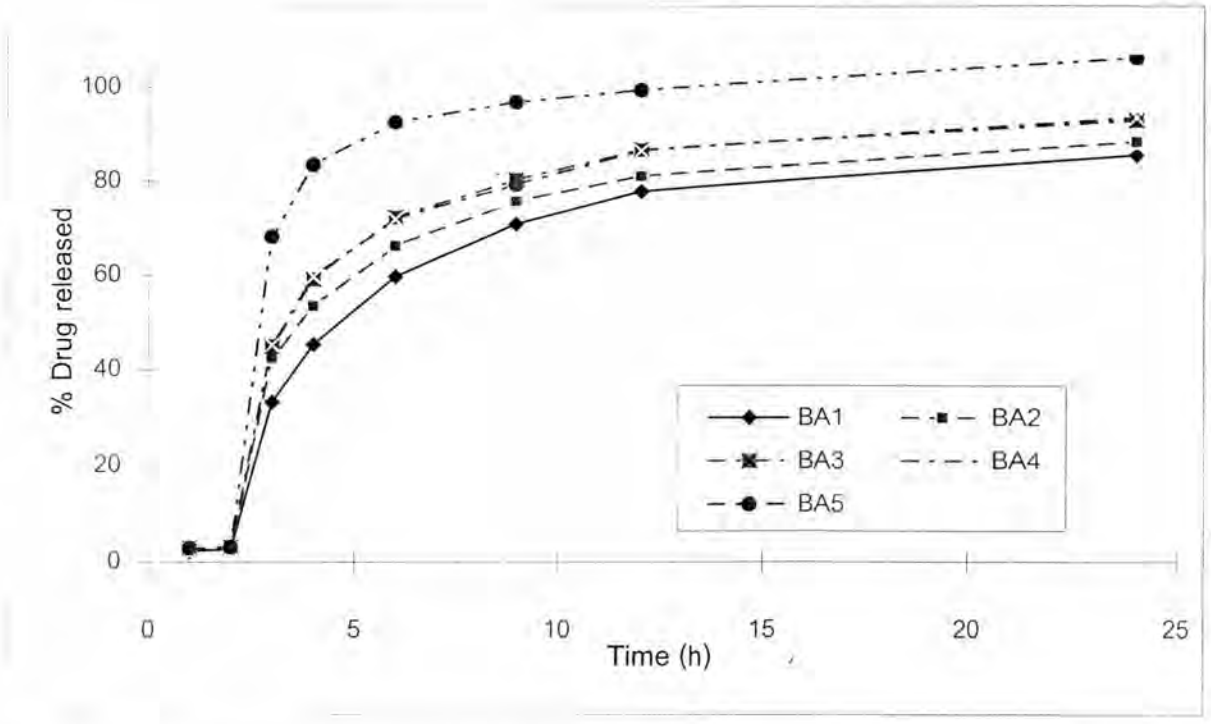


Figure 68 The release profiles of diclofenac sodium pellets (size No.20) prepared from Formulations Ba1 - BA5 using various drug to Avicel PH101 ratio at the same spheronization process (Seacure 343; BA1 = 1:1.0, BA2 = 1:1.5,BA3 = 1:2.0, BA4 = 1:2.5 and BA5 = 1:3.0).

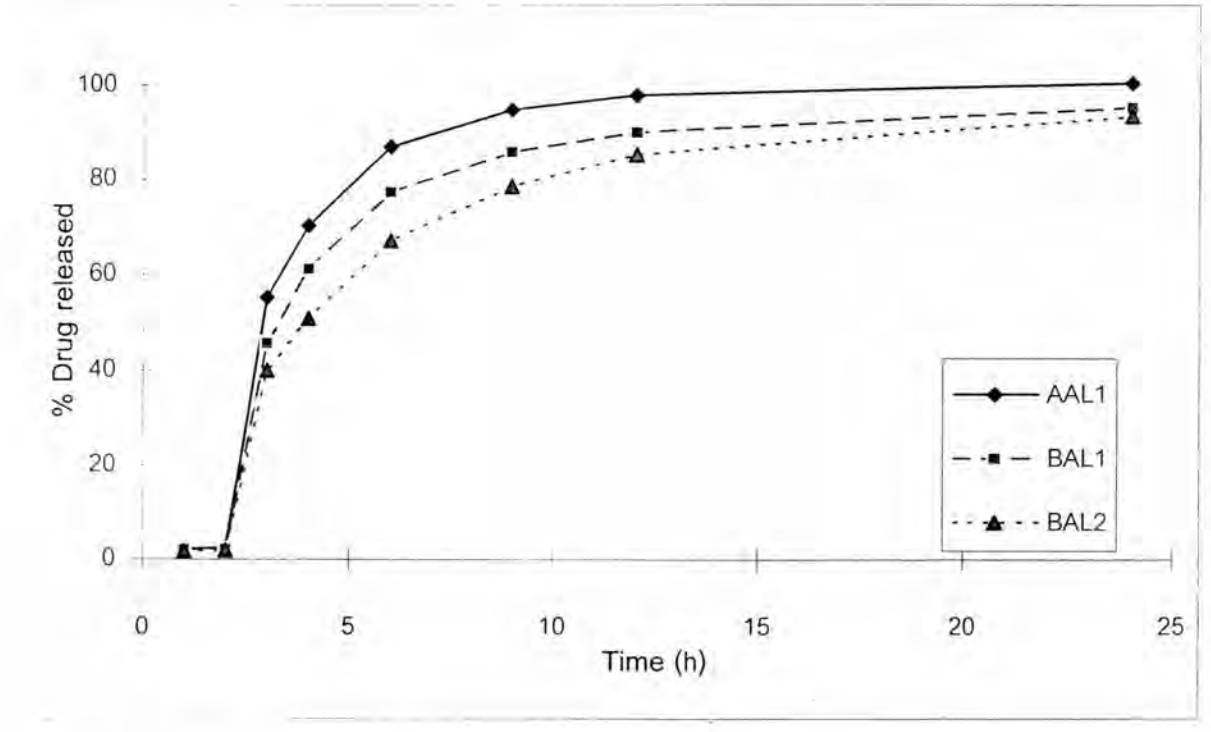


Figure 69 The release profiles of diclofenac sodium pellets (size No.18) prepared from Formulations AAL1, BAL1 and BAL2 using different drug to Avicel PH101 to lactose ratios (Seacure 243; AAL1 = 1:1:1 and 343; BAL1 = 1:1:1 and BAL2 = 1:1.25:1.25).

of 1:1 at the 3rd hour of the dissolution test and the highest percent released of 69.7% was from the formulation using the highest amount of Avicel® at ratio of drug to diluent of 1:3.

The formulation using Avicel® and lactose exhibited the same results compared to those of Avicel® alone. The release profiles of diclofenac sodium pellets of the formulations using two diluents are depicted in Figure 69 (Table 44, Appendix B). The higher in percent released of diclofenac sodium was occurred with increasing the amount of both diluents. Different percent release could be observed from the formulations of 1:2.0 and 1:2.5 ratio. It was shown that Seacure® 243 produced the faster drug release form the pellets than Seacure® 343.

b) Effect of pellets size

The dissolution profiles of drug from the same pellets formulations that used different size of pellets are presented in Figures 66 - 68 (Tables 45 - 46, Appendix B). Slightly difference in the percent release was found, when three sizes of pellets which gave the highest amount retained on the sieve were chosen for dissolution test. The bigger pellets exhibited the slightly lower percent released when compared to the smaller pellets produced from both grade Seacure® 243.

c) Effect of spheronization speed

The release profiles of the pellets containing drug and Avicel® at the ratio of 1:3 with two levels of spheronization speeds, 500 and 900 rpm, are illustrated in Figure 69 (Table 45, Appendix B). Slightly faster release of the pellets was obtained from the formulation that used the faster speed, except at some time intervals. The results were insignificant, even if the size of the pellets was changed from pellet size No.18 to No.20.

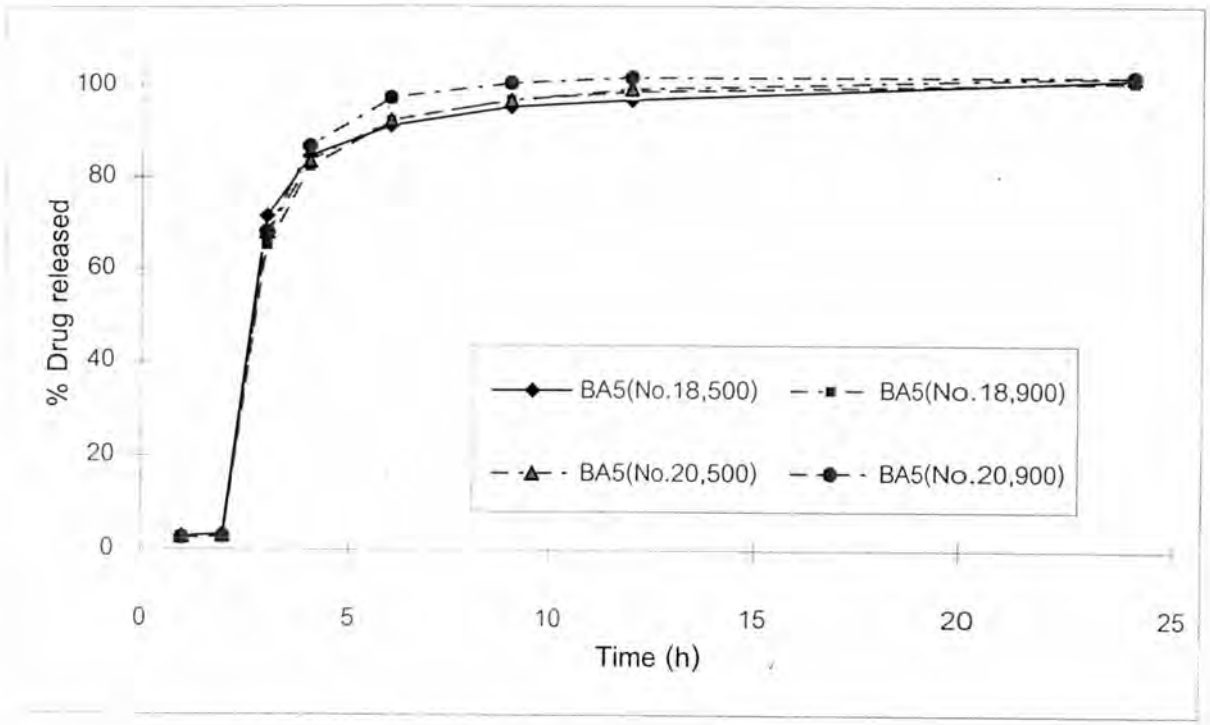


Figure 70 The release profiles of diclofenac sodium pellets (size No. 18 and 20) prepared from Formulation BA5 using Seacure 343 at different spheronization speed of 500 and 900 rpm (BA5 = 1:3.0).

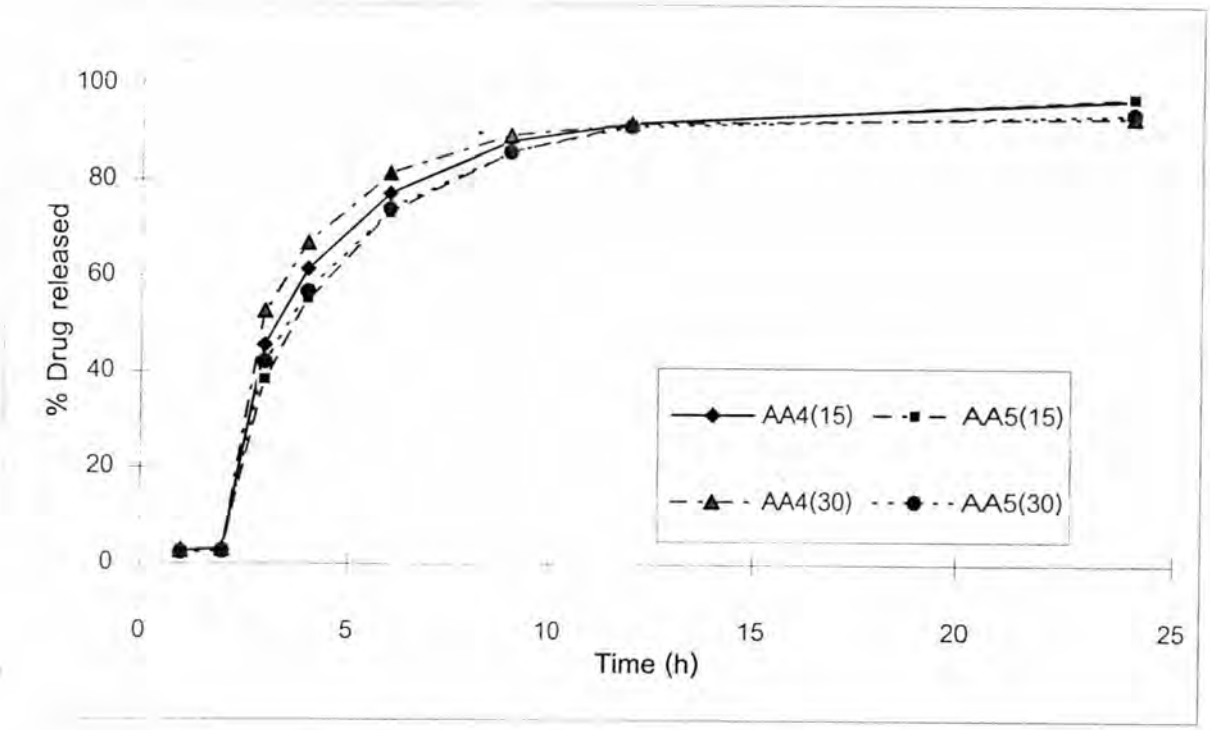


Figure 71 The release profiles of diclofenac sodium pellets (size No.20) prepared from Formulations AA4 and AA5 using Seacure 243 at different spheronization time; 15 and 30 minutes (AA4 = 1:2 and AA5 = 6:10).

d) Effect of spheronization time

The percent drug released from the formulation of diclofenac sodium and Avicel® at the different ratios using Seacure® 243 are illustrated in Figure 71 (Table 46, Appendix B). At spheronization time of 15 min, the release rate of diclofenac sodium pellets was slightly lower than that at 30 min.

2. The Elucidation of Drug Released Model

In general, the release kinetics of controlled-release preparations can be described by using three kinetic models : zero-order, first-order and Higuchi square root equation. The analysis of all dissolution data was carried out to elucidate the suitable model. Therefore, the plots of these kinetic models were constructed. The best correlation value was accepted as a model of drug release.

The coefficients of Higuchi and first-order relationships did not allow unambiguous distinction between the two release kinetics. Therefore, the other two release kinetics proposed by Benita and Donbrow (1982) were applied to distinct the determination of coefficient of these two model relationships. The plots of rate of release versus 1/Q were linear when the release was fitted with Higuchi model. If the plots of rate of release versus Q were linear, the first-order model was operated. The correlation coefficients of the rate of release against reciprocal amount (1/Q) and amount (Q) of diclofenac sodium spray dried powders released are shown in Table 27, whereas values for rate, amount released and the corresponding reciprocal for the release are shown in Tables 47 - 57, Appendix B.

Because most matrix tablets preparations had less than 60% release after the test. It was unnecessary to elucidate for kinetic model. So, only two release kinetics of Benita and Donbrow was used in this study to predict the suitable drug release model.

Table 27 Comparison of linearity between plots of rate of release against reciprocal amount (1/Q) and amount (Q) of diclofenac sodium released from reference, standard (Voltaren SR) and all spray dried powder and matrix tablet preparations.

Formulation	pH change system		Formulation	pH change system	
	Q	1/Q		Q	1/Q
Reference capsules	0.8740	0.8009	A1G2**	0.9501	0.4058
Reference tablets	0.9119	0.8192	A1G3**	0.9672	0.4624
Voltaren SR	0.9469	0.4437	A2P1**	0.9702	0.4346
A1*	0.8509	0.3928	A2P2**	0.9653	0.4391
A2*	0.5148	0.3679	A2P3**	0.9611	0.4391
A3*	0.5583	0.3694	A2P4**	0.9898	0.4051
A4*	0.5197	0.3661	A2G1**	0.9662	0.4495
A5*	0.5141	0.3674	A2G2**	0.9637	0.4608
B1*	0.7195	0.6932	A2G3**	0.9791	0.4692
B2*	0.5442	0.3701	B2G1**	0.8408	0.4377
B3*	0.5457	0.3695	B2G2**	0.9760	0.4574
B4*	0.5033	0.3277	B2G3**	0.9817	0.5022
B5*	0.3465	0.3268	B2P1**	0.9743	0.4565
A1**	0.6703	0.3865	B2P2**	0.9755	0.4526
A2**	0.9749	0.4636	B2P3**	0.9679	0.4354
A3**	0.9750	0.4599	B2P4**	0.9890	0.4515
A4**	0.9696	0.4568	A3P1**	0.9602	0.3936
A5**	0.9538	0.4520	A3P2**	0.9732	0.4319
B1**	0.6248	0.3709	A3P3**	0.9721	0.3977
B2**	0.9813	0.4789	B3P1**	0.9773	0.4596
B3**	0.9839	0.4733	B3P2**	0.9661	0.4075
B4**	0.9648	0.4630	B3P3**	0.9524	0.4545
B5**	0.9694	0.4519	B3G1**	0.9769	0.4595
A1P2**	0.7764	0.4172	B3G2**	0.9799	0.4668
A1P3**	0.6885	0.4058	B3G3**	0.9550	0.4759

* Spray dried powder filled in capsules

** Spray dried powder compressed into tablets

Reference capsules, tablets and Voltaren® SR showed that the correlation coefficient of the rate of release versus Q was higher than those of rate versus 1/Q. Therefore, the first order model would possibly be operated by these preparations.

For spray dried powder preparations, only formulations produced from both grades of Seacure® at the ratio of 1:5 presented the correlation coefficients of rate of release versus Q higher than 0.7. The results indicated that these two preparations might have followed the first-order model while the models of others could not be specified.

Almost all of the matrix tablet preparations showed the correlation coefficient values of the rate of release versus Q higher than those of rate versus 1/Q. The first-order plots of these formulations were linear with the correlation coefficient values greater than 0.95. Opposite to the spray dried powder preparations, the matrix tablet formulations produced from both grades of Seacure® at the ratio of 1:5 presented the lowest correlation coefficient values and could not specify the release model for these preparations. Nevertheless, the matrix tablets of the formulations prepared from Seacure® 243 at the ratio of 1:5 with 20 and 33% propylene glycol exhibited the correlation coefficient values of 0.7764 and 0.6885, respectively that could be interpreted like those without plasticizers.

The correlation coefficient of rate of release against reciprocal amount (1/Q) and amount (Q) of diclofenac sodium pellets released are presented in Table 28 and values for rate, amount released and the corresponding reciprocal for the release as shown in Table 58 - 59, Appendix B. All pellet preparations had the correlation coefficient values of rate against Q higher than those against 1/Q. However, all values of pellet preparations were in the range of 0.37 - 0.68 that meant the model of these preparations could not be clearly specified.

Table 28 Comparison of linearity between plots of rate of release against reciprocal amount (1/Q) and amount (Q) of diclofenac sodium released from all matrix pellet preparations.

Formulation	pH-change system	
	Q	1/Q
BA1	0.6814	0.2679
BA2	0.5868	0.2604
BA3	0.5636	0.2596
BA4	0.5719	0.2588
AAL1	0.4811	0.2536
BAL1	0.6194	0.2579
BAL2	0.5378	0.2561
AA4(15 min/No.20)	0.5478	0.2601
AA4(30 min/No.20)	0.4705	0.2549
AA4(30 min/No.25)	0.5461	0.2578
AA5(15 min/No.20)	0.5978	0.2646
AA5(30 min/No.20)	0.5576	0.2595
AA5(30 min/No.25)	0.6133	0.2619
BA5(500rpm/No.18)	0.3920	0.2508
BA5(900rpm/No.18)	0.4073	0.2509
BA5(500rpm/No.20)	0.3713	0.2494
BA5(900rpm/No.20)	0.3905	0.2505