CHAPTER IV

RESULTS AND DISCUSSION

1. Preparation of nifedipine spray dried microspheres

Nifedipine microspheres could be attained by the spray drying techniques. The nifedipine-combined carrier microspheres were obtained as yellowish, discrete, dried powder in the Eudragit RS100 system. In the Eudragit RL100 system, however, a small agglomerated particles could be observed by naked eyes.

1. Percentage yield (% yield)

Table 1 shows the percentage yield of nifedipine spray dried products prepared from 5 and 10% spray solutions at 55, 65 and 75°C inlet temperatures. Inlet temperature and concentration of spray solution were shown to affect the total percentage yield. The highest yield was obtained from the systems prepared at 55°C inlet temperature. The total yield were 85.25-87.36 % in Eudragit RS100 system and 80.73-84.41% in Eudragit RL 100 system. As the inlet temperature increased, the total yield decreased.

As expected, the yield from the collector was found higher than from the chamber. To consider the percentage yield from the collector, it was found that inlet temperature at 55°C also resulted higher values than at higher temperatures. The highest yield was obtained from the system with higher proportion of PVP K30 to be 65.23% yield. Products obtained from the collector were remarkably

Table 1 The percentage yield (%yield) of spray dried products obtained from 5 and 10 % spray solutions at various inlet temperatures

Nifedipine : Eudragit RS or RL100 : PVP K30	%Yield								
	55°C			65°C			75°C		
	**a	***b	total	a	b	total	a	b	total
1:10:0									
5% (w/v)	55.23	30.02	85.25	49.23	29.34	78.57	37.89	34.73	72.62
	*53.62	27.95	81.57						
10%(w/v)	52.16	27.86	80.02	48.62	27.34	75.96	34.56	34.87	69.43
1:8:2									
5%(w/v)	59.35	27.55	86.90	48.76	30.21	78.97	42.52	33.95	76.47
	*57.43	25.87	83.30						
10%(w/v)	54.75	28.62	83.37	46.79	30.41	77.20	39.85	34.56	74.41
1:5:5									
5%(w/v)	57.64	28.22	85.86	47.26	30.58	77.84	39.47	35.52	74.99
	*54.32	26.41	80.73						
10%(w/v)	51.38	30.02	81.40	45.23	29.85	75.08	34.15	35.12	69.27
1:2:8									
5%(w/v)	65.23	22.13	87.36	50.56	28.26	78.82	48.36	27.58	75.94
	*61.85	22.56	84.41						
10%(w/v)	62.11	20.68	82.79	47.89	27.51	75.40	43.17	29.63	72.80
1:0:10									
5%(w/v)	63.37	23.67	87.04	54.21	25.67	79.88	50.14	25.32	75.46
	*59.71	24.63	84.34						
10%(w/v)	56.23	27.65	83.88	50.67	25.34	76.01	46.64	26.98	73.62

* % Yield of nifedipine : Eudragit RL100 : PVP K30

** a is defined as % yield in collector

*** b is defined as % yield in chamber

affected by different spray concentrations. As the concentration increased from 5% to 10%, the yield decreased. This might be resulted from the increased viscosity of the spray solution. For the Eudragit RL100 system, slightly lower yield values of spray dried products were obtained.

2. Nifedipine content of the microspheres

The percentage content of nifedipine microspheres are shown in Table 9 and 10 (in Appendix A). Percent content of nifedipine of spray dried product in the range 82.37-98.56% and 84.17-96.76% of 5 and 10% spray solution respectively. The inlet temperature, mixing ratio and concentration of spray solution did not affect the percent content of nifedipine microspheres.

II. Physicochemical characteristics of nifedipine spray dried microspheres.

1. Morphology of spray dried microspheres

Figure 5 shows the scanning electron photomicrographs of intact nifedipine and spray dried products of nifedipine, Eudragit RS100, Eudragit RL100 and PVP K30. Nifedipine crystals were rod shaped of various sizes. The shape and surface topography of spray dried nifedipine and carriers are shown in Figures 5 C-J. The products obtained were spherical with slightly shrunken surface. The surface of spray dried nifedipine was rough, whereas those of Eudragit RS100, Eudragit RL100 and PVP K30 were smooth.

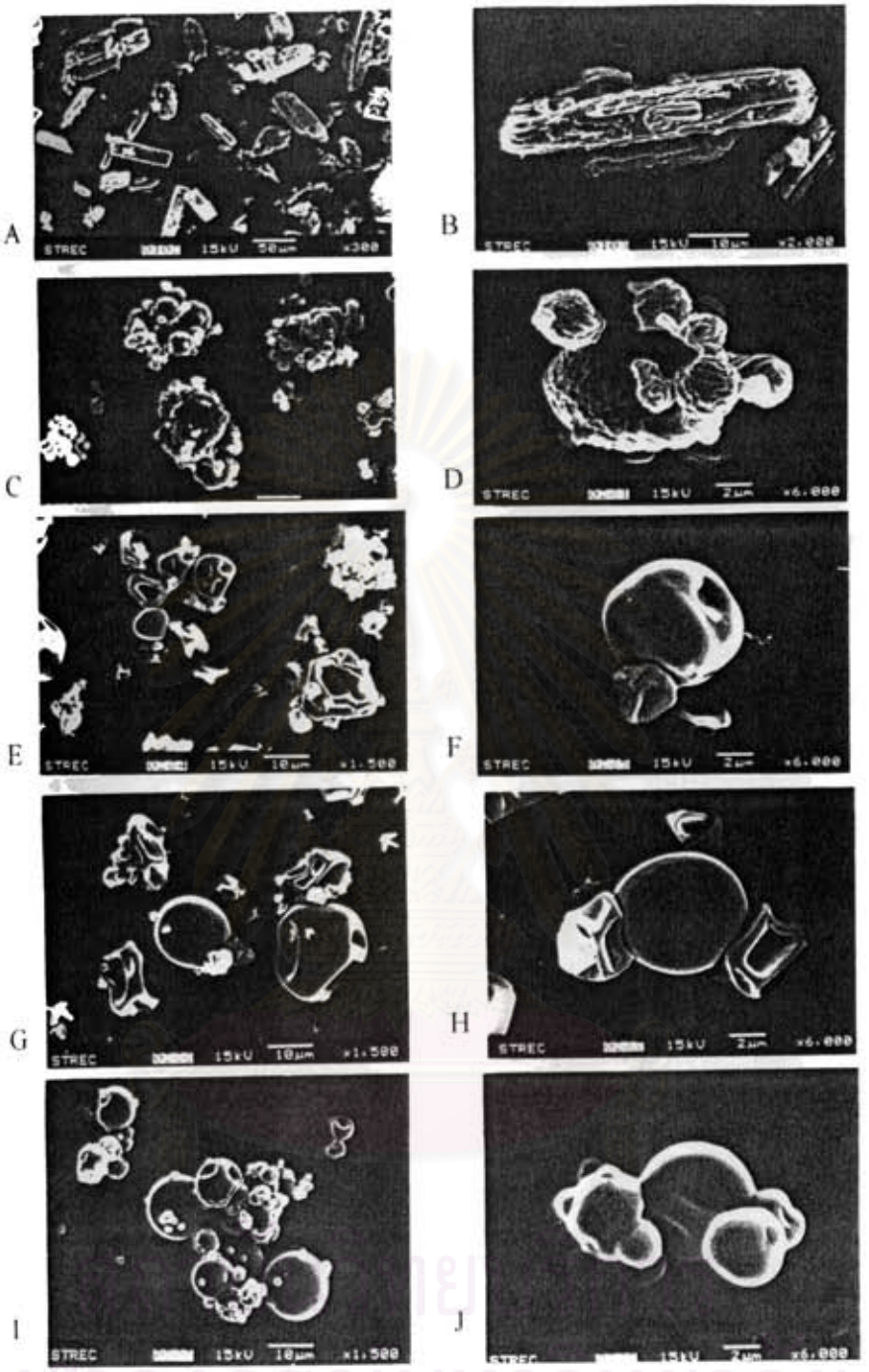


Figure 5 Photomicrographs of nifedipine and carriers prepared by spray drying at 55°C of 5% spray solution

A and B Nontreated nifedipine	A x 300, B x 2000
C and D Nifedipine spray dried	C x 1500, D x 6000
E and F Eudragit RS100 spray dried	E x 1500, F x 6000
G and H Eudragit RL100 spray dried	G x 1500, H x 6000
I and J PVP K30 spray dried	I x 1500, J x 6000

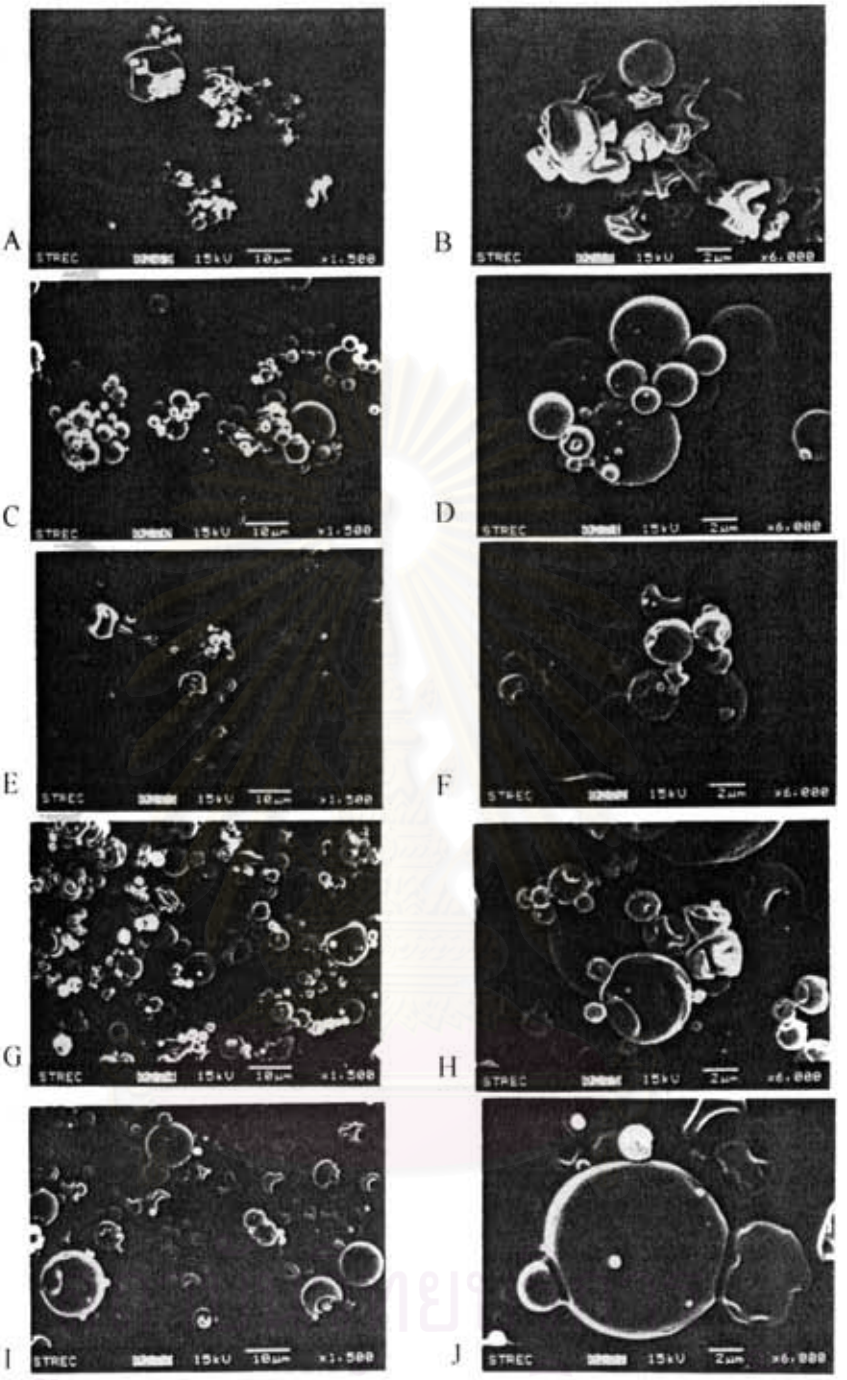


Figure 6 Photomicrographs of nifedipine-Eudragit RS100-PVP K30 microspheres at various ratios prepared by spray drying at 55°C of 5% spray solution

A and B at 1:10:0	A x 1500, B x 6000
C and D at 1:8:2	C x 1500, D x 6000
E and F at 1:5:5	E x 1500, F x 6000
G and H at 1:2:8	G x 1500, H x 6000
I and J at 1:0:10	I x 1500, J x 6000

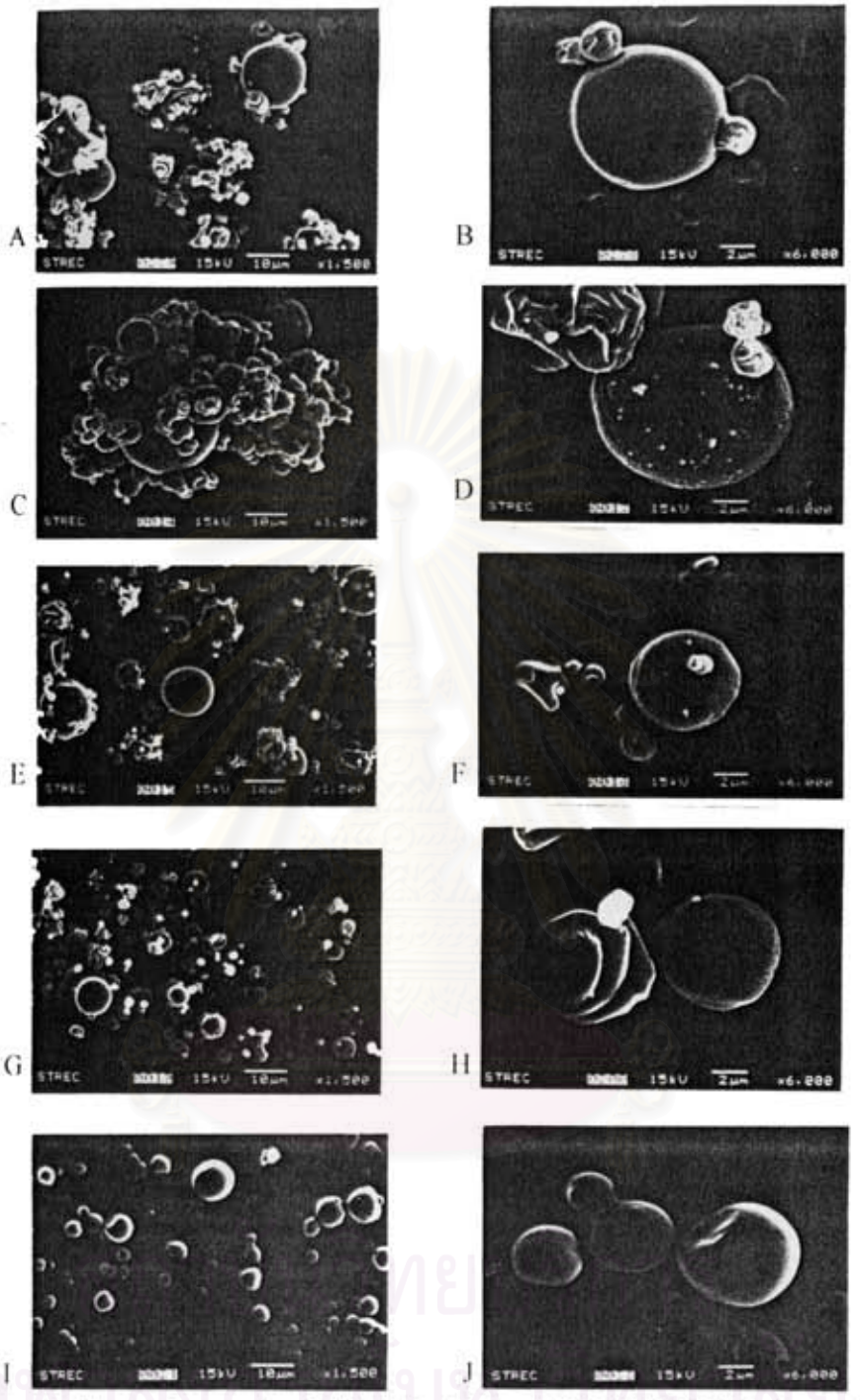


Figure 7 Photomicrographs of nifedipine-Eudragit RS100-PVP K30 microspheres at various ratios prepared by spray drying at 55°C of 10% spray solution

A and B at 1:10:0 — A x 1500, B x 6000

C and D at 1:8:2 — C x 1500, D x 6000

E and F at 1:5:5 — E x 1500, F x 6000

G and H at 1:2:8 — G x 1500, H x 6000

I and J at 1:0:10 — I x 1500, J x 6000

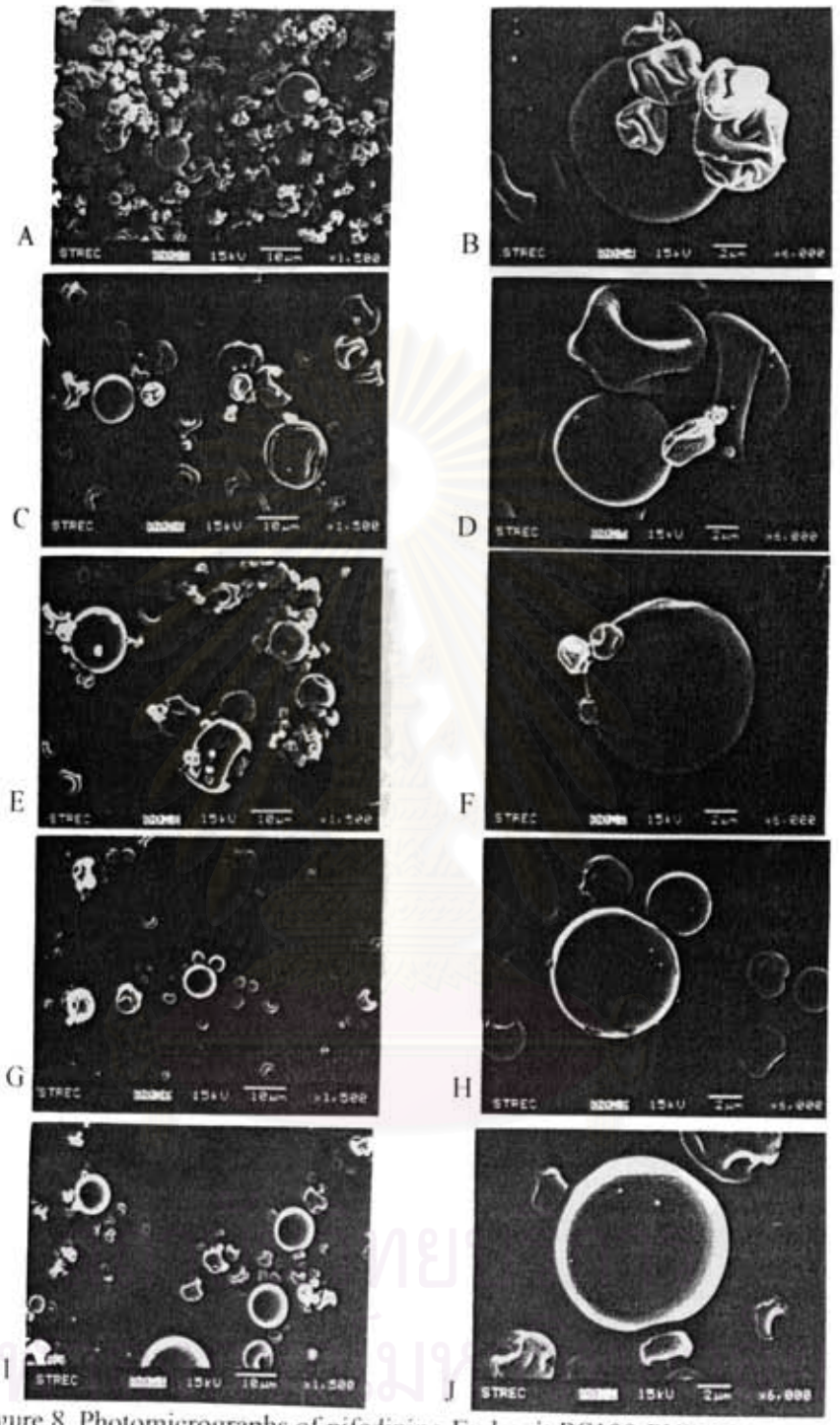


Figure 8 Photomicrographs of nifedipine-Eudragit RS100-PVP K30 microspheres at various ratios prepared by spray drying at 65°C of 5% spray solution

A and B at 1:10:0 — A x 1500, B x 6000

C and D at 1:8:2 — C x 1500, D x 6000

E and F at 1:5:5 — E x 1500, F x 6000

G and H at 1:2:8 — G x 1500, H x 6000

I and J at 1:0:10 — I x 1500, J x 6000

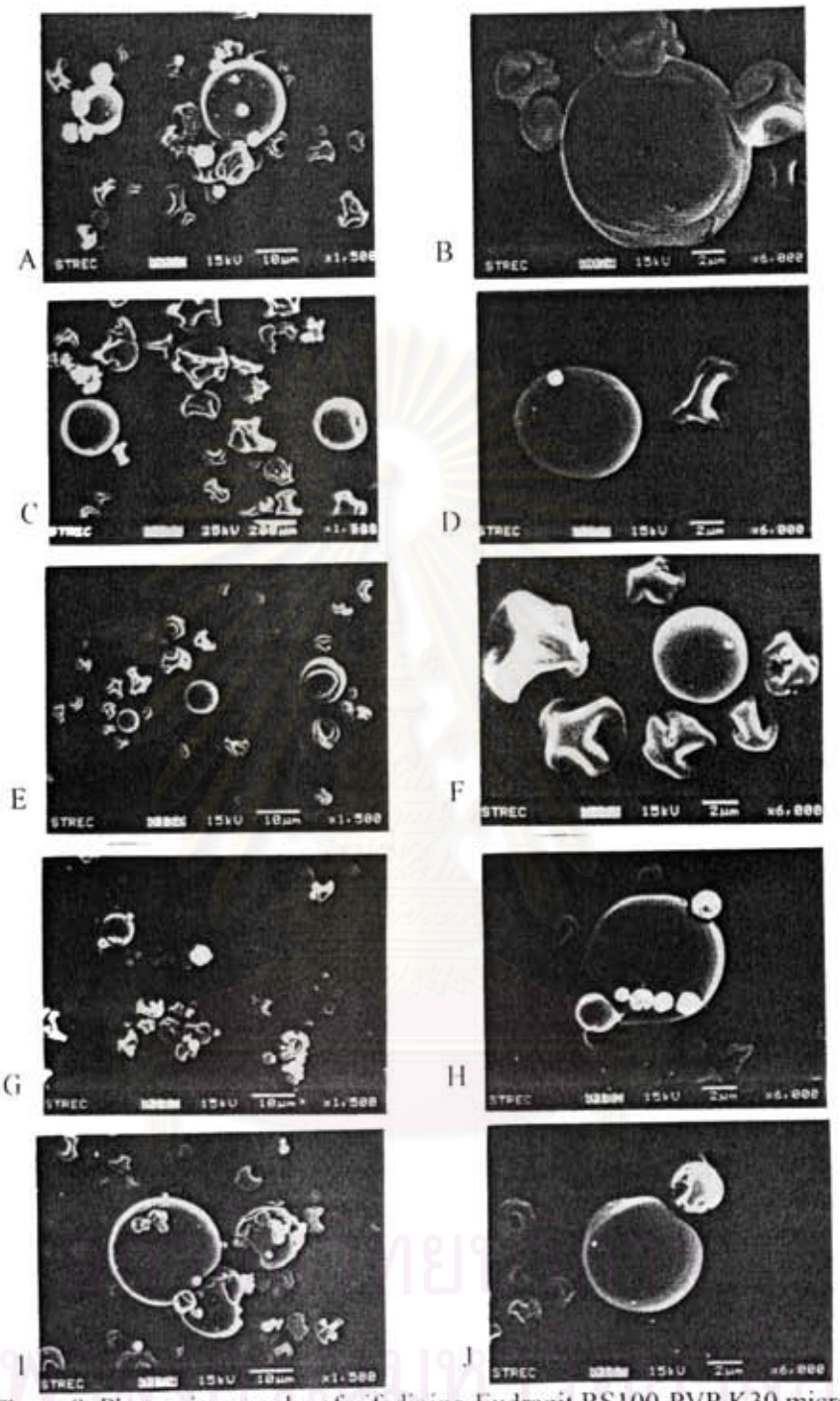


Figure 9 Photomicrographs of nifedipine-Eudragit RS100-PVP K30 microspheres at various ratios prepared by spray drying at 65°C of 10% spray solution

A and B at 1:10:0	A x 1500, B x 6000
C and D at 1:8:2	C x 1500, D x 6000
E and F at 1:5:5	E x 1500, F x 6000
G and H at 1:2:8	G x 1500, H x 6000
I and J at 1:0:10	I x 1500, J x 6000

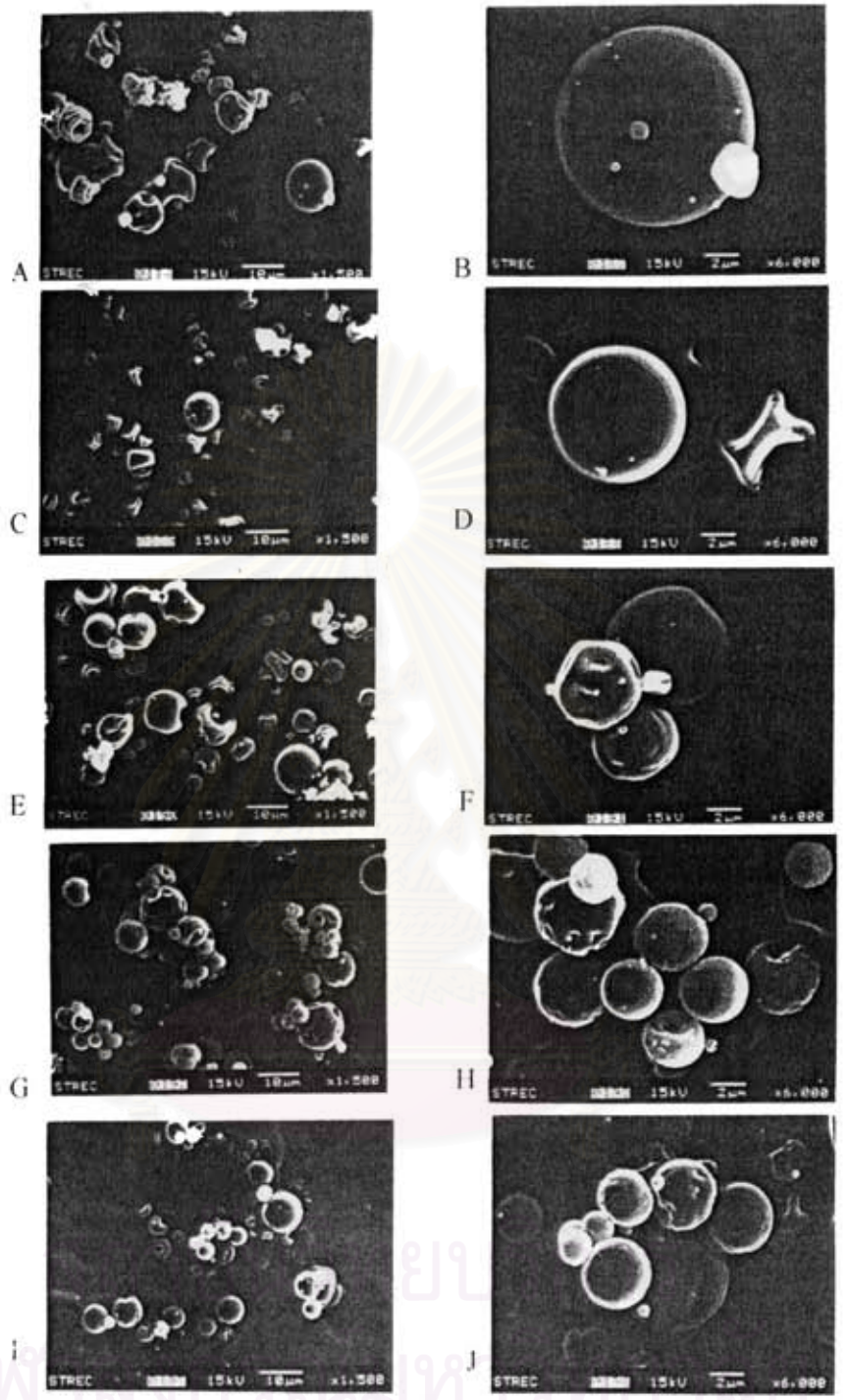


Figure 10 Photomicrographs of nifedipine-Eudragit RS100-PVP K30 microspheres at various ratios prepared by spray drying at 75°C of 5% spray solution

A and B at 1:10:0	A x 1500, B x 6000
C and D at 1:8:2	C x 1500, D x 6000
E and F at 1:5:5	E x 1500, F x 6000
G and H at 1:2:8	G x 1500, H x 6000
I and J at 1:0:10	I x 1500, J x 6000

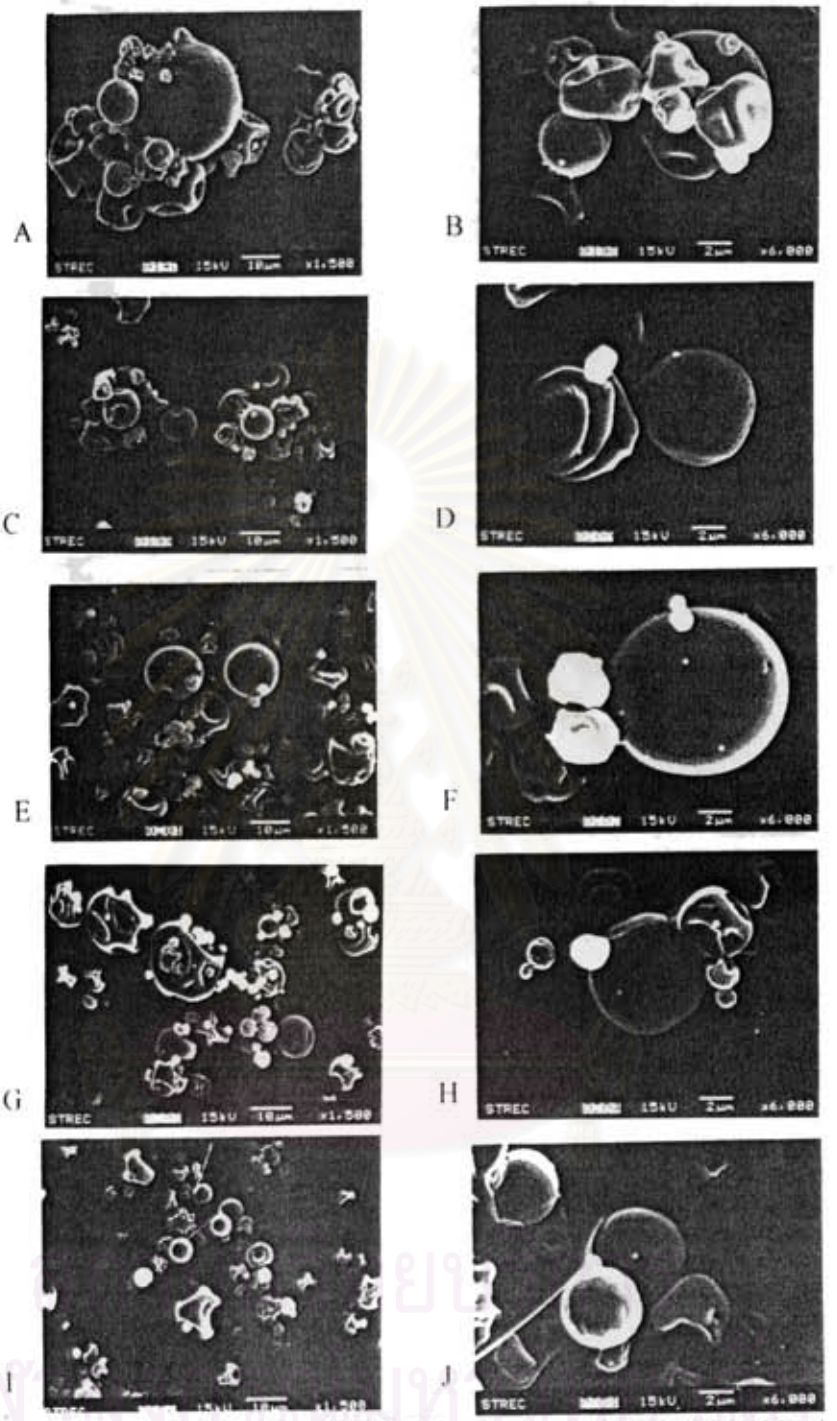


Figure 11 Photomicrographs of nifedipine-Eudragit RS100-PVP K30 microspheres at various ratios prepared by spray drying at 75°C of 10% spray solution

A and B at 1:10:0 A x 1500, B x 6000

C and D at 1:8:2 C x 1500, D x 6000

E and F at 1:5:5 E x 1500, F x 6000

G and H at 1:2:8 G x 1500, H x 6000

I and J at 1:0:10 I x 1500, J x 6000

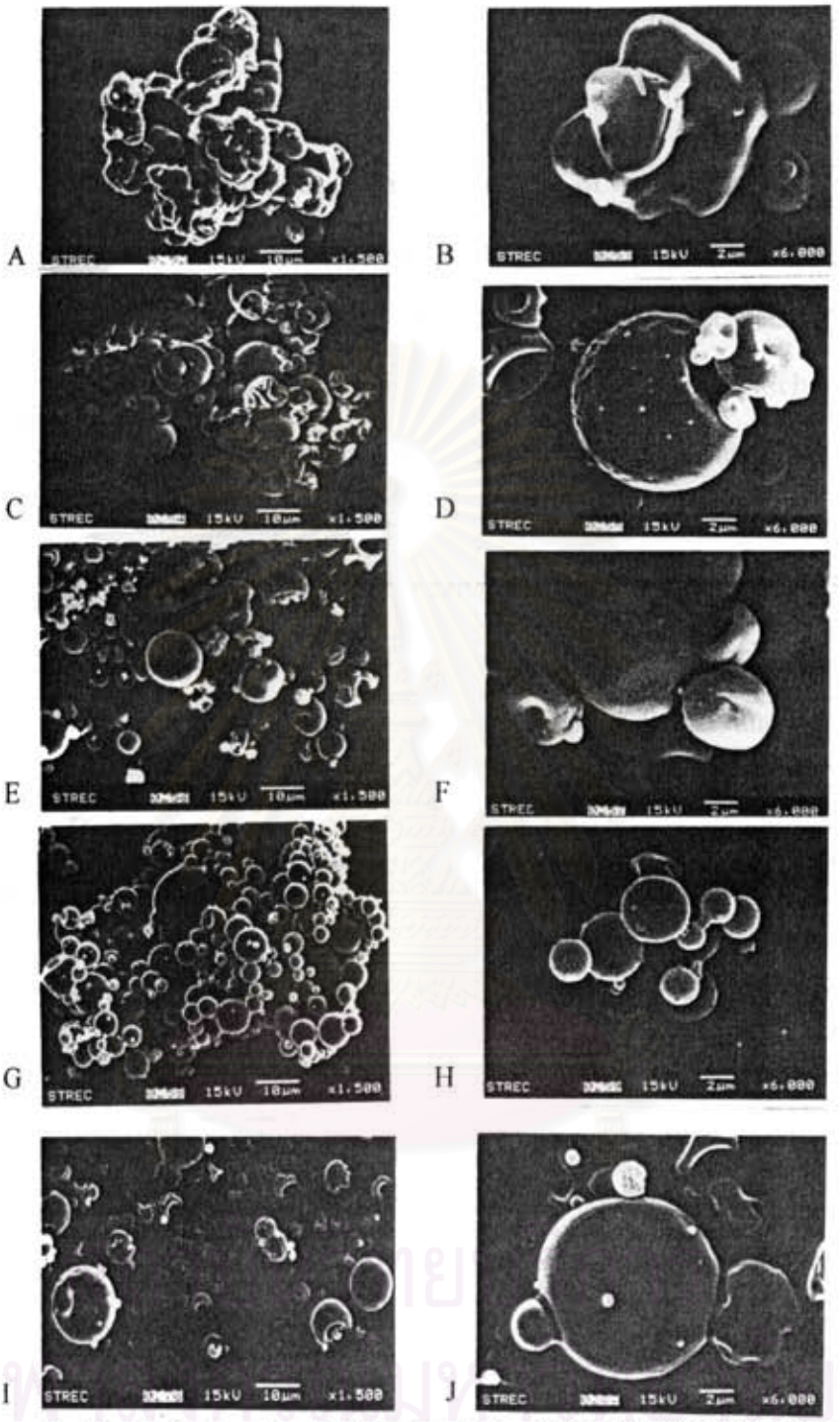


Figure 12 Photomicrographs of nifedipine-Eudragit RL100-PVP K30 microspheres at various ratios prepared by spray drying at 55°C of 5% spray solution

A and B at 1:10:0	A x 1500, B x 6000
C and D at 1:8:2	C x 1500, D x 6000
E and F at 1:5:5	E x 1500, F x 6000
G and H at 1:2:8	G x 1500, H x 6000
I and J at 1:0:10	I x 1500, J x 6000

The photomicrographs of microspheres of nifedipine-Eudragit RS100-PVP K30 produced at different conditions were shown in Figures 6-11. The surface of nifedipine microspheres was smooth and the shape was spherical with different degrees of shrinkage. Some particles were collapsed, which might be due to the complexity of the atomization mechanism and distortions of droplets during drying. Nevertheless during the gold coating process, the nifedipine microspheres which might comprise internal void volumes and probably became deflated by the vacuums required to carry out the coating process or rehydration of the microspheres regenerated their spherical shape (Barkai, Pathak and Benita, 1990).

The microspheres produced at inlet air temperatures of 55°C (Figure 6, 7) gave larger microspheres than those produced at 65° and 75°C (Figure 8-11). Higher extent of agglomerates were formed when inlet air temperature of 65° and 75°C were employed. The product prepared at 75°C formed looser agglomerates than that prepared at 65°C. It was noticed that at higher proportions of PVP K30 resulted in a decrease in number of collapsed particles as shown in Figures 6-12. Higher concentration of spray solution yielded larger microspheres and more agglomerated particles.

The photomicrographs of nifedipine-Eudragit RL100-PVP K30 microspheres are shown in Figure 12. The microscopic images of particle showed similar results to nifedipine–Eudragit RS100-PVP K30 microspheres but remarkably more agglomerated and larger particles. It was clearly shown in all photographs that there were no free nifedipine crystals adhering on the surfaces.

This might be expected that nifedipine was uniformly distributed or dissolved in the polymer matrix.

2. Residual solvent content

The residual solvent contents of spray dried products are presented in Table 2. The moisture contents of all products were very low between 1.83-2.86%. As the inlet temperature increased, the moisture content also lowered. The moisture also reduced when the proportion of PVP K30 in combined carrier decreased and the concentration of spray solution decreased.

The inlet temperature is the temperature of the heated drying air, whereas the outlet temperature is the temperature of the air with solid particles before entering cyclone. In contrast to the inlet temperature, the outlet temperature cannot be set with a temperature regulator. It is the result of many parameters : inlet temperature, aspirator, flow rate, peristaltic pump setting and concentration of the spray solution. Usually a small residual moisture content can be obtained when inlet temperature is as high as possible and inlet-outlet temperature difference is as small as possible (Table 3).

The marked results could be observed from Table 2 and 3. At the high inlet temperature, 75^{o}C, which also occupied relatively smaller inlet-outlet temperature differences, showed lower moisture contents than those at 55^{o} and 65^{o}C. The increase of inlet temperature led to decreased residual moisture contents (Bitz and Doelker 1996).

Table 2 The percentage moisture content of spray dried products obtained from 5 and 10 % spray solutions at various inlet temperatures

Nifedipine : Eudragit RS or RL100 : PVP K30	% Residual solvent content***		
	55°C	65°C	75°C
1:10:0			
5% (w/v)	2.12(0.10)* **2.53(0.09)	2.21(0.06)	1.83(0.07)
10%(w/v)	2.58(0.10)	2.36(0.13)	1.87(0.11)
1:8:2			
5%(w/v)	2.54(0.11) 2.56(0.14)	2.27(0.06)	2.02(0.06)
10%(w/v)	2.56(0.18)	2.31(0.09)	2.04(0.07)
1:5:5			
5%(w/v)	2.43(0.16) 2.59(0.15)	2.31(0.12)	2.16(0.07)
10%(w/v)	2.66(0.19)	2.48(0.08)	2.19(0.13)
1:2:8			
5%(w/v)	2.56(0.11) 2.68(0.12)	2.39(0.09)	2.18(0.07)
10%(w/v)	2.72(0.07)	2.51(0.10)	2.21(0.14)
1:0:10			
5%(w/v)	2.86(0.17) 2.73(0.12)	2.58(0.08)	2.23(0.07)
10%(w/v)	2.83(0.07)	2.66(0.09)	2.28(0.11)

* Standard deviation

** % Moisture Content of nifedipine : Eudragit RL100 : PVP K30

*** Average from three determinations

Table 3 The inlet–outlet temperature differences of spray dried products obtained from 5 and 10 % spray solutions at various inlet temperatures

Nifedipine : Eudragit RS or RL100 : PVP K30	Inlet –outlet temperature difference(°C)		
	55°C	65°C	75°C
1:10:0			
5% (w/v)	32 * 38	30	27
10%(w/v)	35	32	30
1:8:2			
5%(w/v)	35 40	33	30
10%(w/v)	38	35	32
1:5:5			
5%(w/v)	36 41	35	33
10%(w/v)	43	39	35
1:2:8			
5%(w/v)	37 43	38	35
10%(w/v)	45	41	38
1:0:10			
5%(w/v)	40 45	39	37
10%(w/v)	42	40	39

* Inlet – Outlet temperature difference of nifedipine : Eudragit RL100 : PVP K30

3. Particle size and size distribution

The geometric mean diameter (D_{50}), the size at 50% cumulative frequency plotted on probability scale, was determined and compared between different formulations of microspheres (Table 4). Frequency distribution plot of some microspheres were selected to be shown in Appendix F.

The increasing proportion of PVP K 30 in the nifedipine-Eudragit RS100 microspheres resulted in smaller particle sizes. This effect could be observed in all inlet temperatures used. This might be attributed to the effect of viscosity of spray solution. In preliminary study, it was found that the solution with higher proportion of Eudragit has higher viscosity than that with high content of PVP K30. This explanation might be also applied to the results that 10% spray concentrations gave larger microspheres as compared to 5% spray concentration. An increase in particle size was the result of an increase in the concentration and viscosity of spray drying solution (Master, 1985).

The type of Eudragits used obviously affected the size of microspheres. Larger microspheres were obtained from Eudragit RL100 system. This could be confirmed with SEM images (Figure12). The Eudragit RL100 microspheres showed aggregates or agglomerates. It is possible that the optimal processing conditions for Eudragit RS100 might be inappropriate for Eudragit RL100.

Table 4 The geometric mean diameter of spray dried products obtained from 5 and 10 % spray solutions at various inlet temperatures

Nifedipine : Eudragit RS or RL100 : PVP K30	Geometric mean diameter (D_{50}) ; μm***		
	55°C	65°C	75°C
1:10:0 5% (w/v)	9.17(0.35)* **12.38(0.35)	8.88(0.74)	7.45(0.23)
10%(w/v)	12.39(0.72)	12.82(0.70)	14.77(0.62)
1:8:2 5%(w/v)	4.83(0.13) 11.34(0.71)	9.39(0.10)	6.59(0.07)
10%(w/v)	18.75(0.51)	10.77(0.02)	8.16(0.06)
1:5:5 5%(w/v)	8.85(0.28) 8.17(0.21)	6.99(0.19)	4.94(0.04)
10%(w/v)	6.12(0.01)	7.57(0.12)	6.69(0.06)
1:2:8 5%(w/v)	1.77(0.01) 9.85(0.80)	8.23(0.06)	3.20(0.03)
10%(w/v)	2.79(2.41)	7.20(0.09)	8.68(0.17)
1:0:10 5%(w/v)	2.17(0.02) 1.74(0.28)	1.96(0.04)	3.70(0.26)
10%(w/v)	3.40(0.05)	2.16(0.07)	1.12(0.03)

* Standard deviation

** Geometric mean diameter of nifedipine : Eudragit RL100 : PVP K30

*** Average from three determinations

4. Powder X-ray diffractometry

4.1 Powder X-ray diffractograms of spray dried nifedipine, Eudragit RS 100, Eudragit RL100 and PVP K30

The diffraction pattern of intact nifedipine showed that the drug was highly crystalline in nature as indicated by numerous distinctive diffraction peaks. Major diffraction peaks of spray dried nifedipine were also similarly observed at diffraction angle of 8.0, 11.9, 16.2, 19.5 and 24.0°(Figure 13). The diffraction patterns of spray dried Eudragit RL100, Eudragit RS100 and PVP K30 showed halo patterns, thus revealed that they were in amorphous state.

Spray drying has been reported to obtain the amorphous state of many poorly soluble drugs and resulted in enhancement of dissolution rate e.g. ursodeoxycholic acid (Ueno et al., 1998) and clarithromycin (Yonemichi et al., 1999). In this study, amorphization of nifedipine could not be obtained by this technique. This might be attributed to some processing parameters, e.g. heating rate and inlet temperatures. Spray dried tolbutamide without any excipient was also found to be crystallized without amorphism (Takeuchi, Handa and Kawashima, 1987).

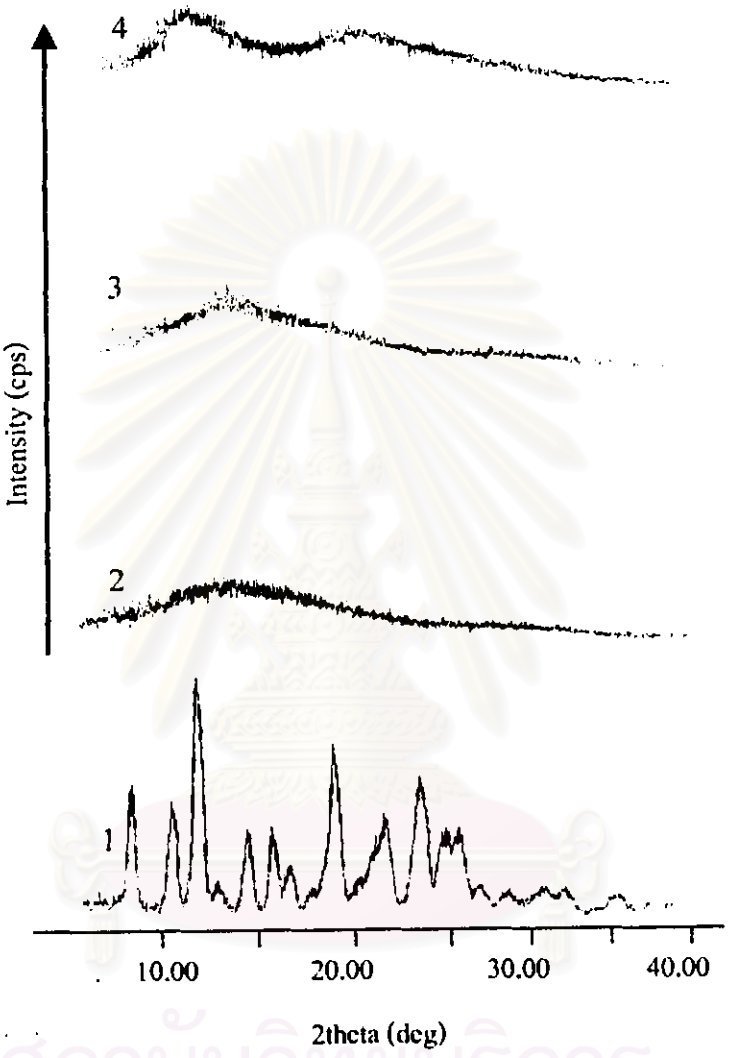


Figure 13 Powder X-ray diffraction patterns of spray dried samples prepared at 55°C of 5% spray solution (1) nifedipine (2) Eudragit RL100 (3) Eudragit RS100 and (4)PVP K30

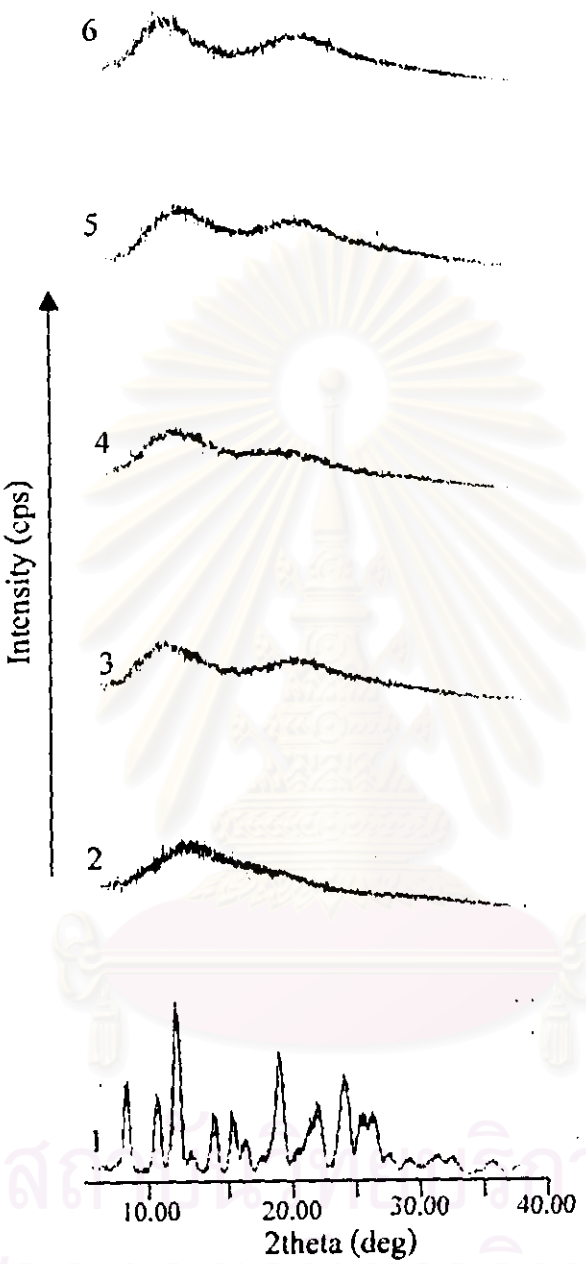


Figure14 Powder X-ray diffraction patterns of spray dried samples prepared at 55°C of 5% spray solution of nifedipine : Eudragit RS 100 : PVP K30 at various ratios : (1) nifedipine (2) 1:10:0 (3) 1:8:2 (4) 1:5:5 (5) 1:2:8 and (6) 1:0:10

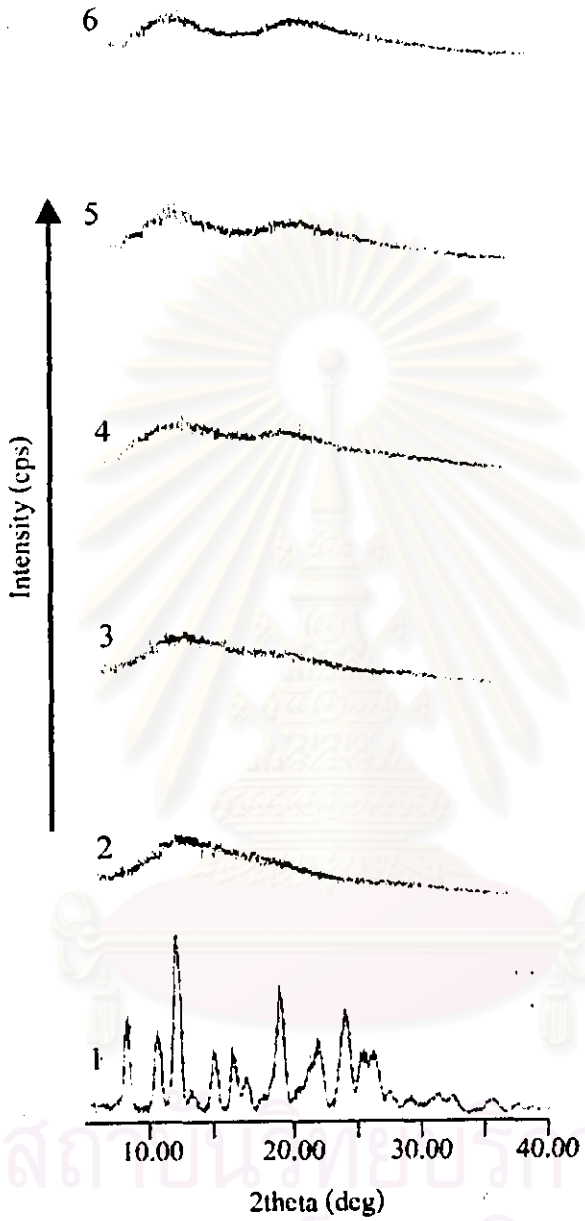


Figure15 Powder X-ray diffraction patterns of spray dried samples prepared at 55°C of 10% spray solution of nifedipine : Eudragit RS100 : PVP K30 at various ratios : (1) nifedipine (2) 1:10:0 (3) 1:8:2 (4) 1:5:5 (5) 1:2:8 and(6) 1:0:10

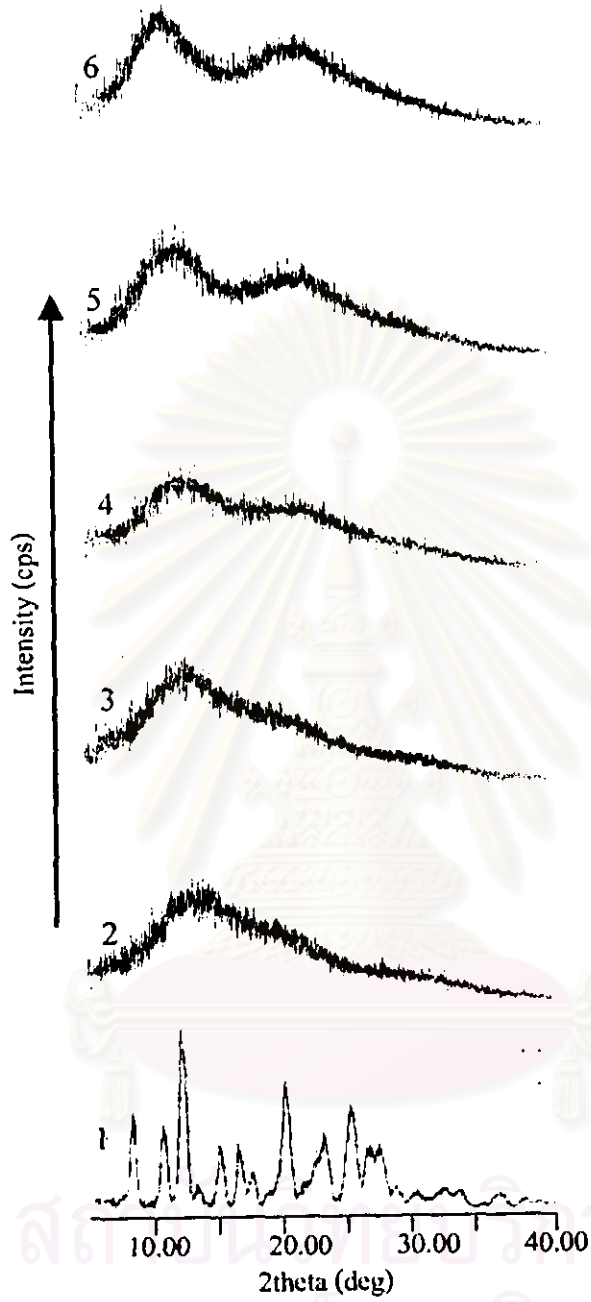


Figure16 Powder X-ray diffraction patterns of spray dried samples prepared at 65°C of 5% spray solution of nifedipine : Eudragit RS100 : PVP K30 at various ratios : (1) nifedipine (2) 1:10:0 (3) 1:8:2 (4) 1:5:5 (5) 1:2:8 and (6) 1:0:10

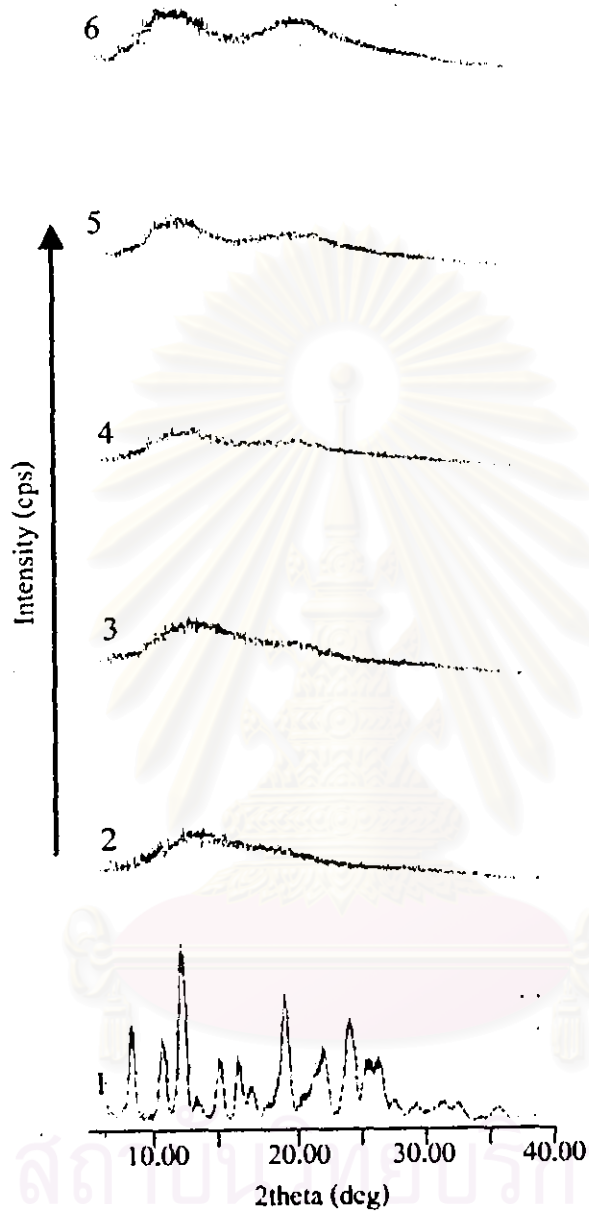


Figure 17 Powder X-ray diffraction patterns of spray dried samples prepared at 65°C of 10% spray solution of nifedipine : Eudragit RS100 : PVP K30 at various ratios : (1) nifedipine (2) 1:10:0 (3) 1:8:2 (4) 1:5:5 (5) 1:2:8 and (6) 1:0:10

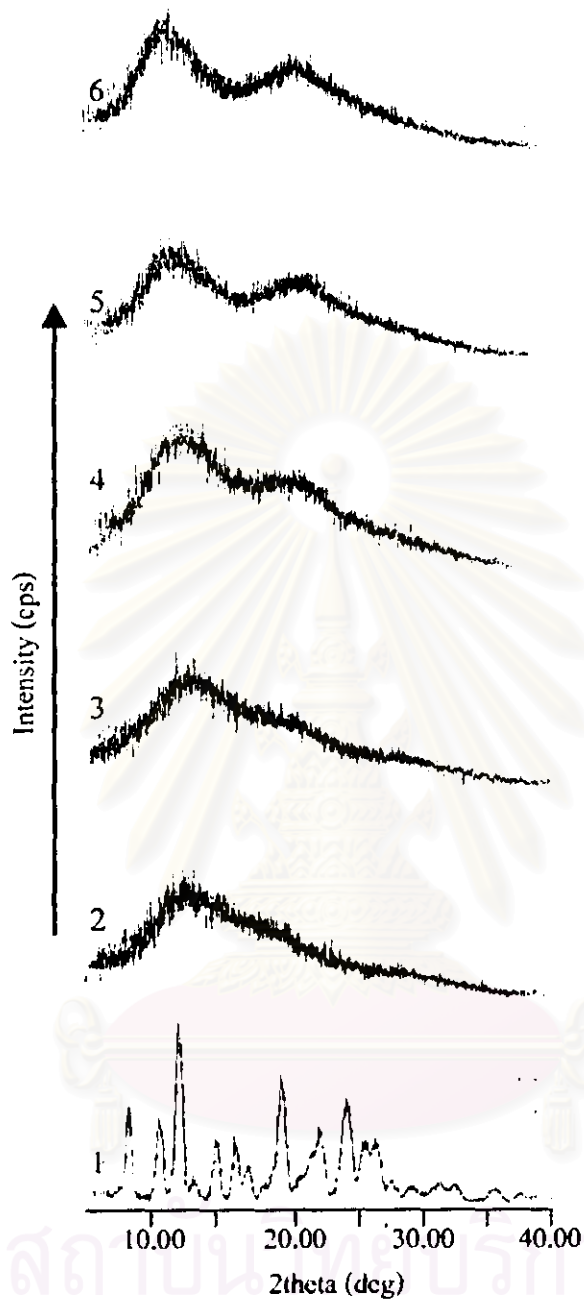


Figure 18 Powder X-ray diffraction patterns of spray dried samples prepared at 75°C of 5% spray solution of nifedipine : Eudragit RS100 : PVP K30 at various ratios : (1) nifedipine (2) 1:10:0 (3) 1:8:2 (4) 1:5:5 (5) 1:2:8 and (6) 1:0:10

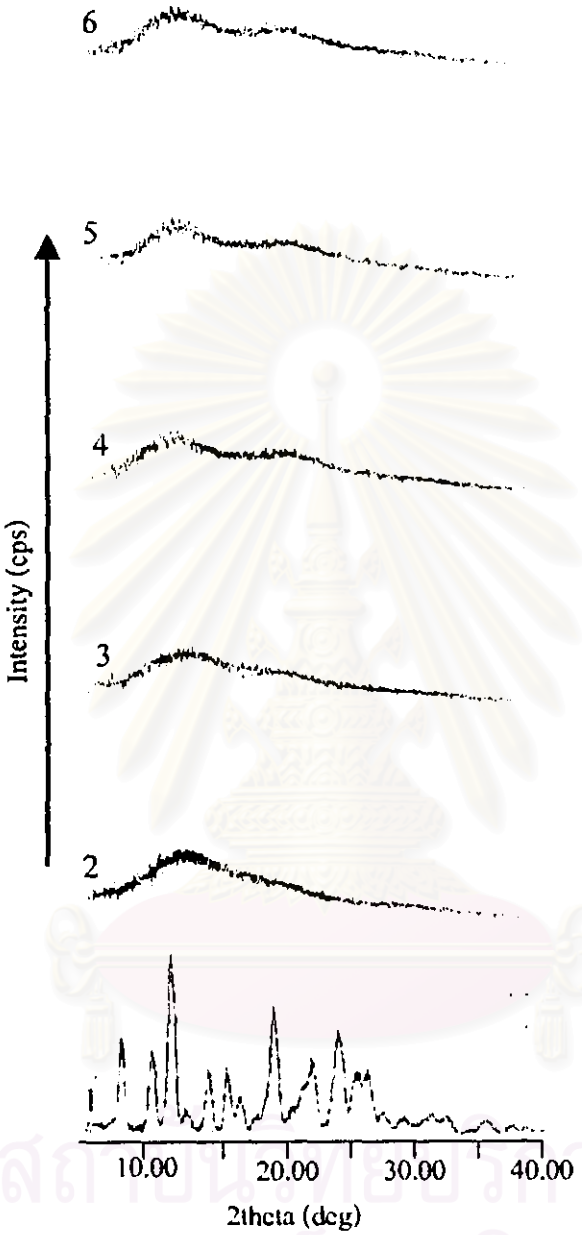


Figure 19 Powder X-ray diffraction patterns of spray dried samples prepared at 75°C of 10% spray solution of nifedipine : Eudragit RS100 : PVP K30 at various ratios : (1) nifedipine (2) 1:10:0 (3) 1:8:2 (4) 1:5:5 (5) 1:2:8 and (6) 1:0:10

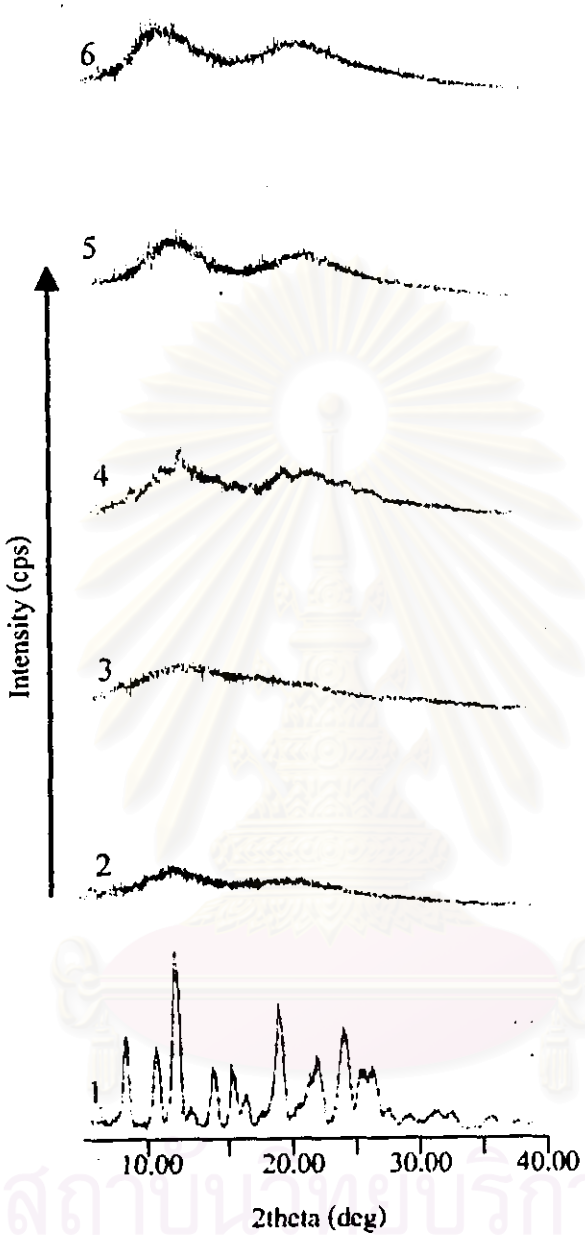


Figure 20 Powder X-ray diffraction patternsof spray dried samples prepared at 55°C of 5% spray solution of nifedipine : Eudragit RL 100 : PVP K30 at various ratios : (1) nifedipine (2) 1:10:0 (3) 1:8:2 (4) 1:5:5 (5) 1:2:8 and (6) 1:0:10

4.2 Powder X-ray diffractograms of nifedipine-Eudragit RS100-PVP K30 microspheres

Figures 14-19 compared the diffraction patterns between the microspheres prepared from the 5% and 10% concentrations of spray solution. Although they demonstrated similar halo patterns at all inlet temperatures, remarkably higher areas under the diffraction patterns were found in those of 5% concentration. There was no difference between the diffraction patterns of spray dried samples prepared at different inlet temperatures. The powder X-ray diffractograms thus confirmed that nifedipine in all preparations was in the amorphous state. Similar results have been reported from Eudragit microspheres containing nicardipine hydrochloride (Yuksel et al., 1996) and Eudragit microcapsules of nifedipine (Chowdary and Sankar, 1997).

In this study, the concentration of nifedipine in microspheres was 1:10 (approximately 10%), which was within the detection limit of the powder X-ray diffraction. As reported in many investigations the drug concentration, which was reported to show diffraction peaks was as low as 5%. Owusu-Ababio et al. (1998) investigated the powder X-ray diffraction of mefenamic acid in solid dispersion at the drug-carrier ratio 1:1, 1:2, 1:10 and 1:20 and show clear diffraction peaks of mefenamic acid even in the ratio of 1:20. The similar results also reported for nifedipine in solid dispersion by Save and Venkitachalam (1992); Farag Badawy et al. (1992) and Law et al. (1992)

The powder X-ray diffractograms of Nifedipine-Eudragit RL100-PVP K30 system are demonstrated in Figure 20. The diffraction patterns of all mixing ratios showed halo patterns quite similar to those of Eudragit RS 100 system. This revealed that the major peaks of nifedipine were gradually disappeared. However, it was noticeable that at the 1:5:5 mixing ratio, small diffraction peaks corresponding to nifedipine crystalline peaks could be observed. This revealed that the major part of the drug transformed to the amorphous state, whereas a small part was in crystalline or microcrystalline form. The dispersion of the drug in the polymer matrix as well as the drug-polymer ratio was an important factor for the drug transformation to the amorphous state. In the Eudragit RS100 system, regardless of the mixing ratio, all microspheres showed the amorphization of nifedipine. In contrary, in the Eudragit RL100 system, only some mixing ratios resulted in the drug amorphization (Takeuchi, Handa and Kawashima, 1987).

5. The Differential scanning calorimetry (DSC)

The DSC curves of spray dried nifedipine, Eudragit RL100, Eudragit RS100 and PVP K30 are illustrated in Figure 21. And DSC curves for nifedipine microspheres of various mixing ratios and concentrations of spray solutions at different inlet temperatures are shown in Figures 22-28.

5.1 DSC thermograms of spray dried nifedipine and carriers

The DSC curve of spray dried nifedipine showed the characteristic sharp endothermic peak at 174.39°C, corresponding exactly to the melting point of nifedipine, and thus indicating that the drug after spray drying was still in crystalline form. This was consistent to the result of powder XRD pattern of spray dried nifedipine.

The thermograms of Eudragit RL100 and Eudragit RS100 had similar thermal events. Eudragit RL100 and Eudragit RS100 showed a thermal transition that was attributed to the glass transition temperature, Tg, at the 51.94°C and 46.71°C, respectively that slightly lower than reported by Kristmundsdottir, Gudmundson, and Ingvarsdottir (1996). A little broad curvature could also be observed in both thermograms at 179.28 or 191.20°C, which might be due to melting of the polymer. PVP K30 demonstrated a broad endotherm corresponding to its melting point at 72.05°C.

5.2 DSC thermograms of nifedipine-Eudragit RS100-PVP K30 microspheres

The DSC curves of nifedipine-Eudragit RS100-PVP K30 microspheres are illustrated in Figures 22-27. The microspheres prepared from 5% spray solution at 55°C inlet temperature of all mixing ratios (Figure 22) demonstrated the disappearance of endothermic peak of nifedipine. This could therefore be deduced

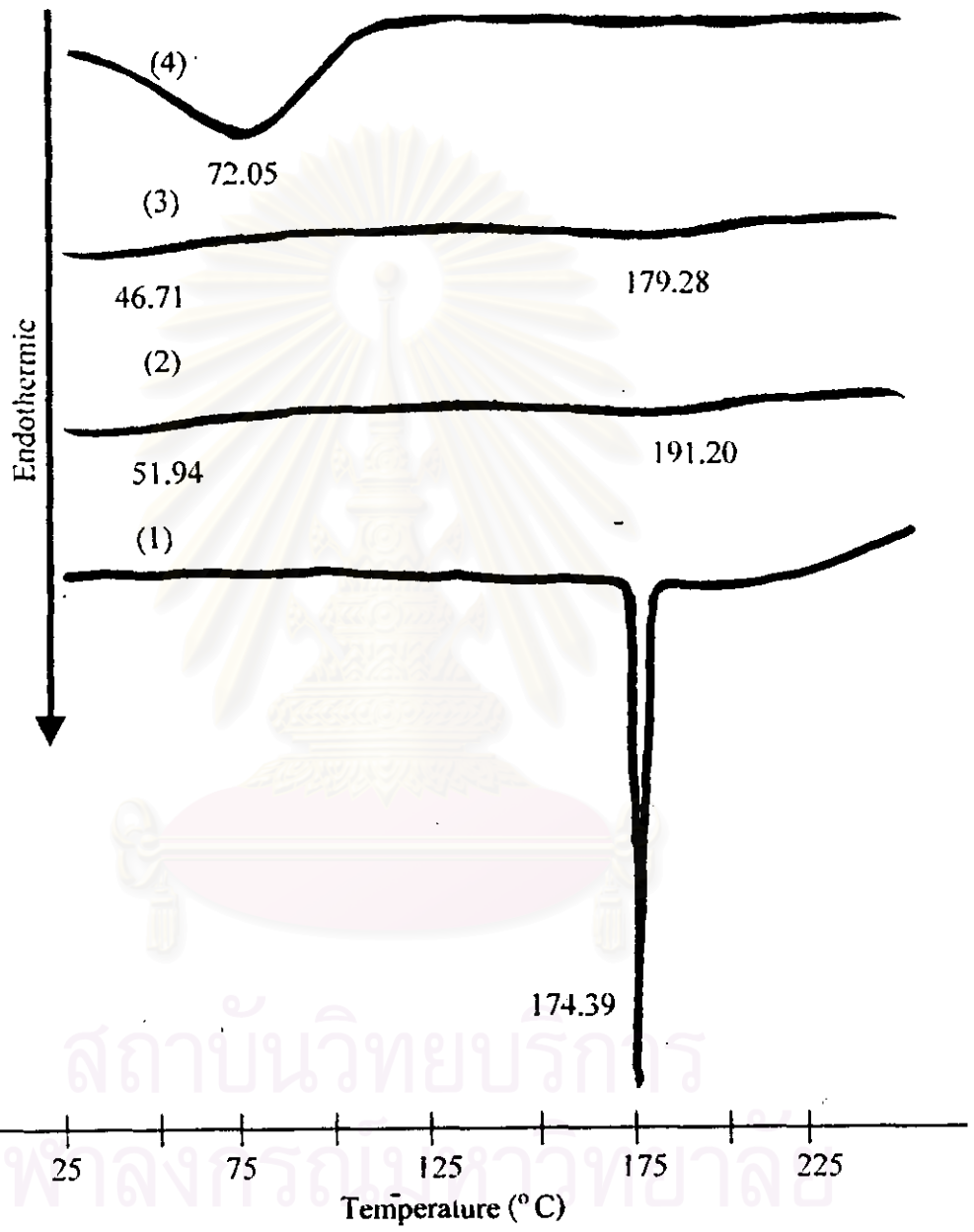


Figure 21 DSC curves of spray dried microspheres prepared at 55° C of 5% spray solution of : (1) nifedipine (2) Eudragit RL 100 (3) Eudragit RS 100 (4) PVP K30

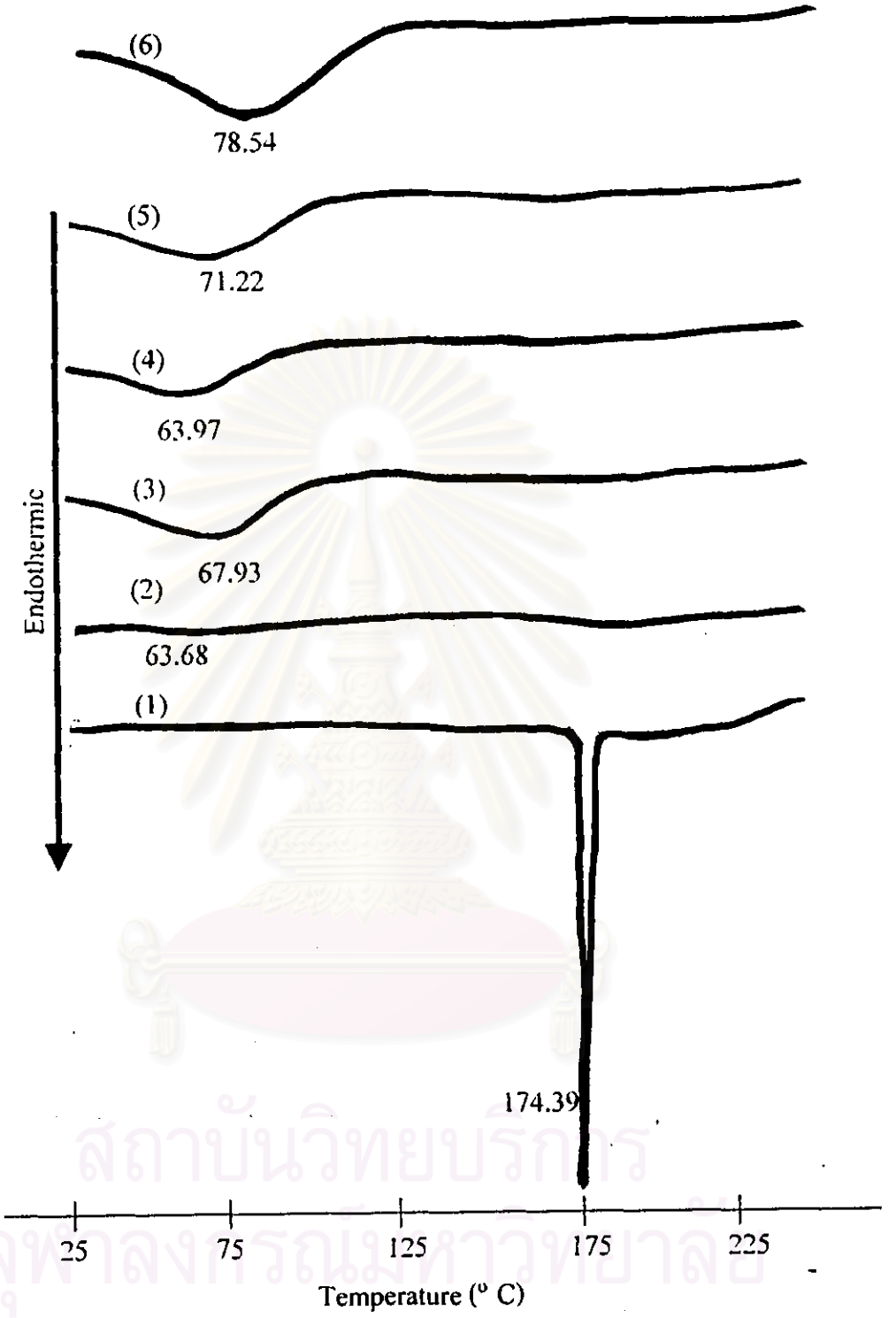


Figure 22 DSC curve of spray dried microspheres prepared at 55°C of 5% spray solution of nifedipine : Eudragit RS 100 : PVP K30 at various ratios : (1) nifedipine (2) 1:10:0 (3) 1:8:2 (4) 1:5:5 (5) 1:2:8 (6) 1:0:10

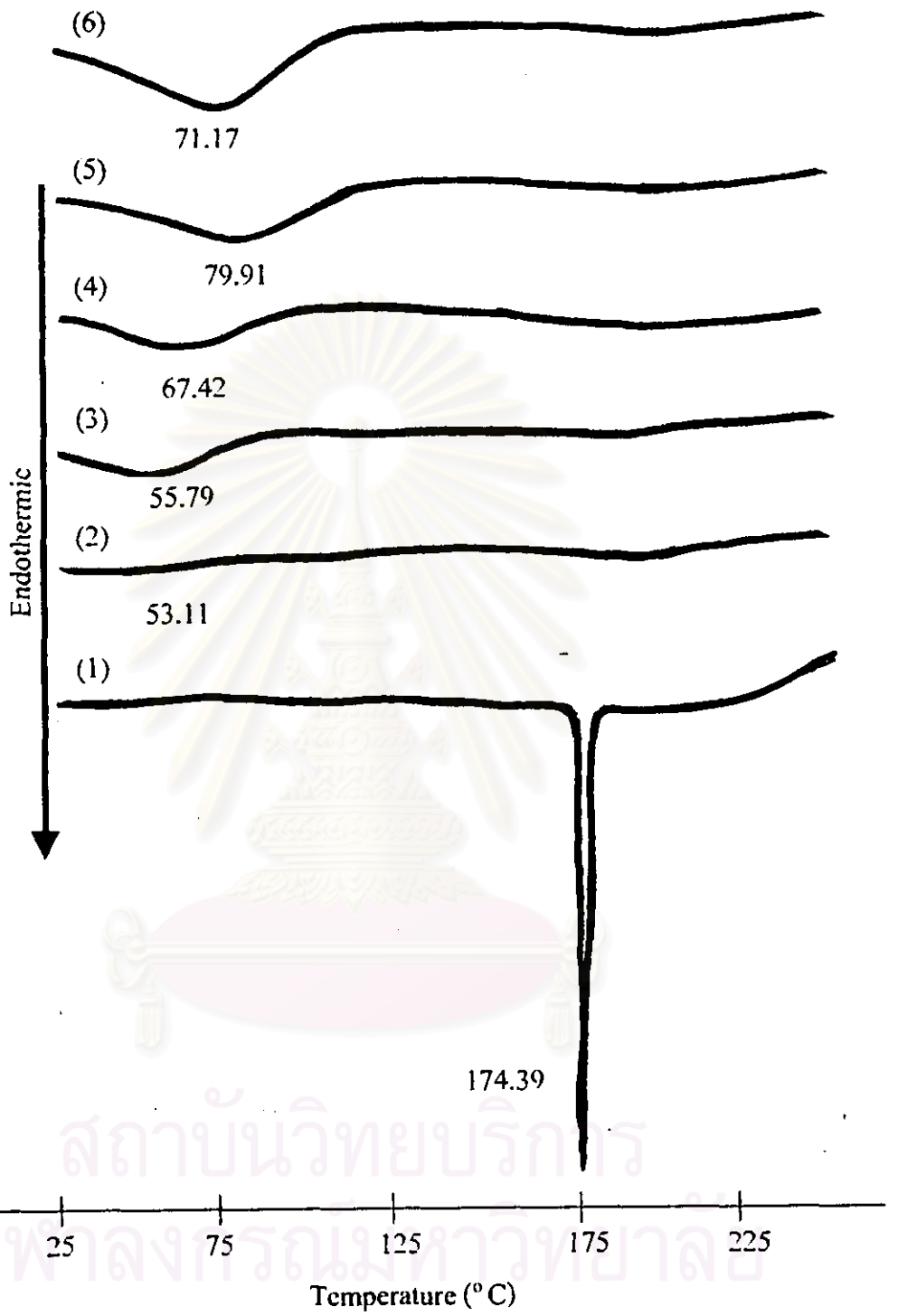


Figure 23 DSC curves of spray dried microspheres prepared at 55° C of 10% spray solution of nifedipine : Eudragit RS100 : PVP K30 at various ratios : (1) nifedipine (2) 1:10:0 (3) 1:8:2 (4) 1:5:5 (5) 1:2:8 (6) 1:0:10

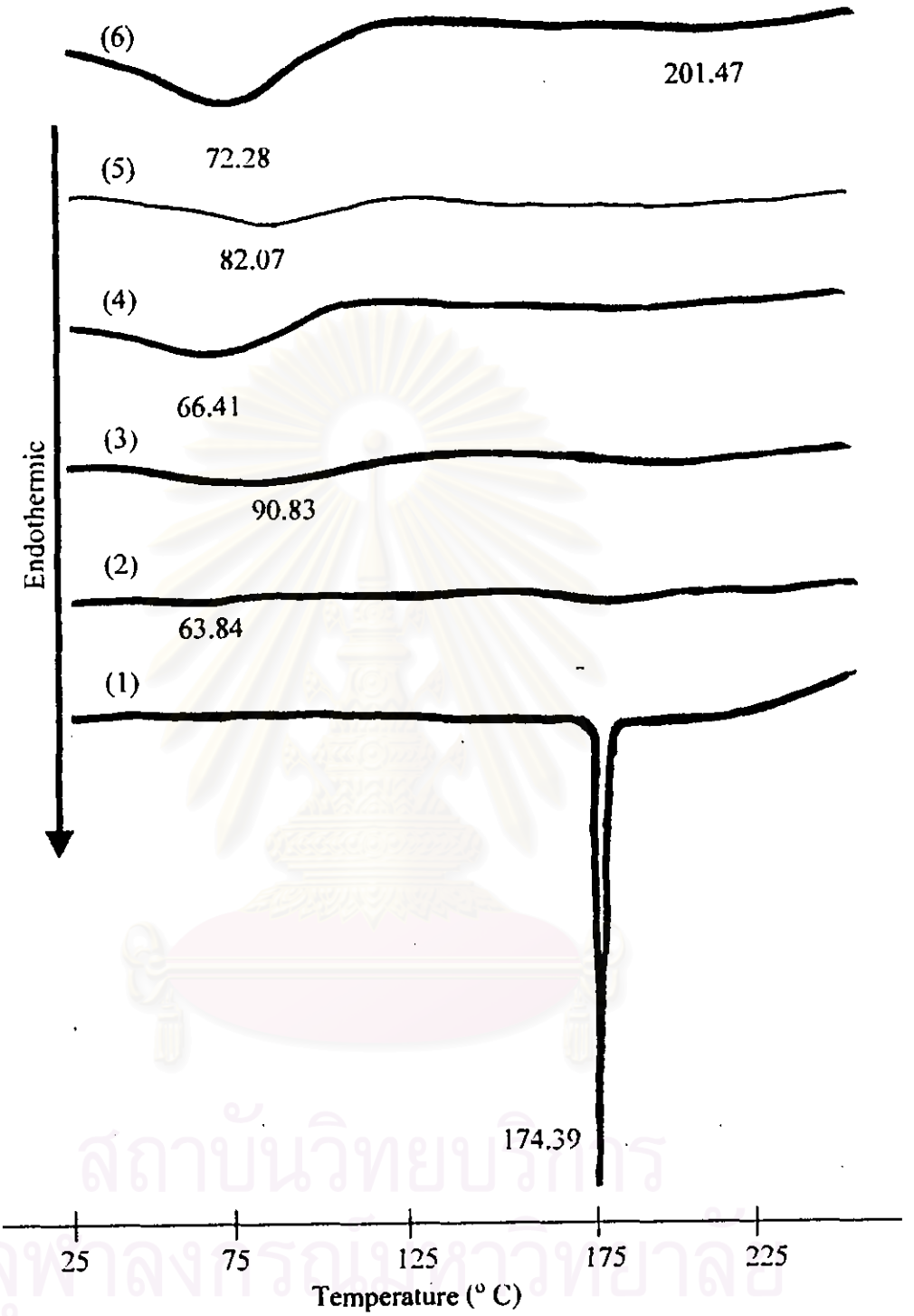


Figure 24 DSC curves of spray dried microspheres prepared at 65° C of 5% spray solution of nifedipine : Eudragit RS 100 : PVP K30 at various ratios : (1) nifedipine (2) 1:10:0 (3) 1:8:2 (4) 1:5:5 (5) 1:2:8 (6) 1:0:10

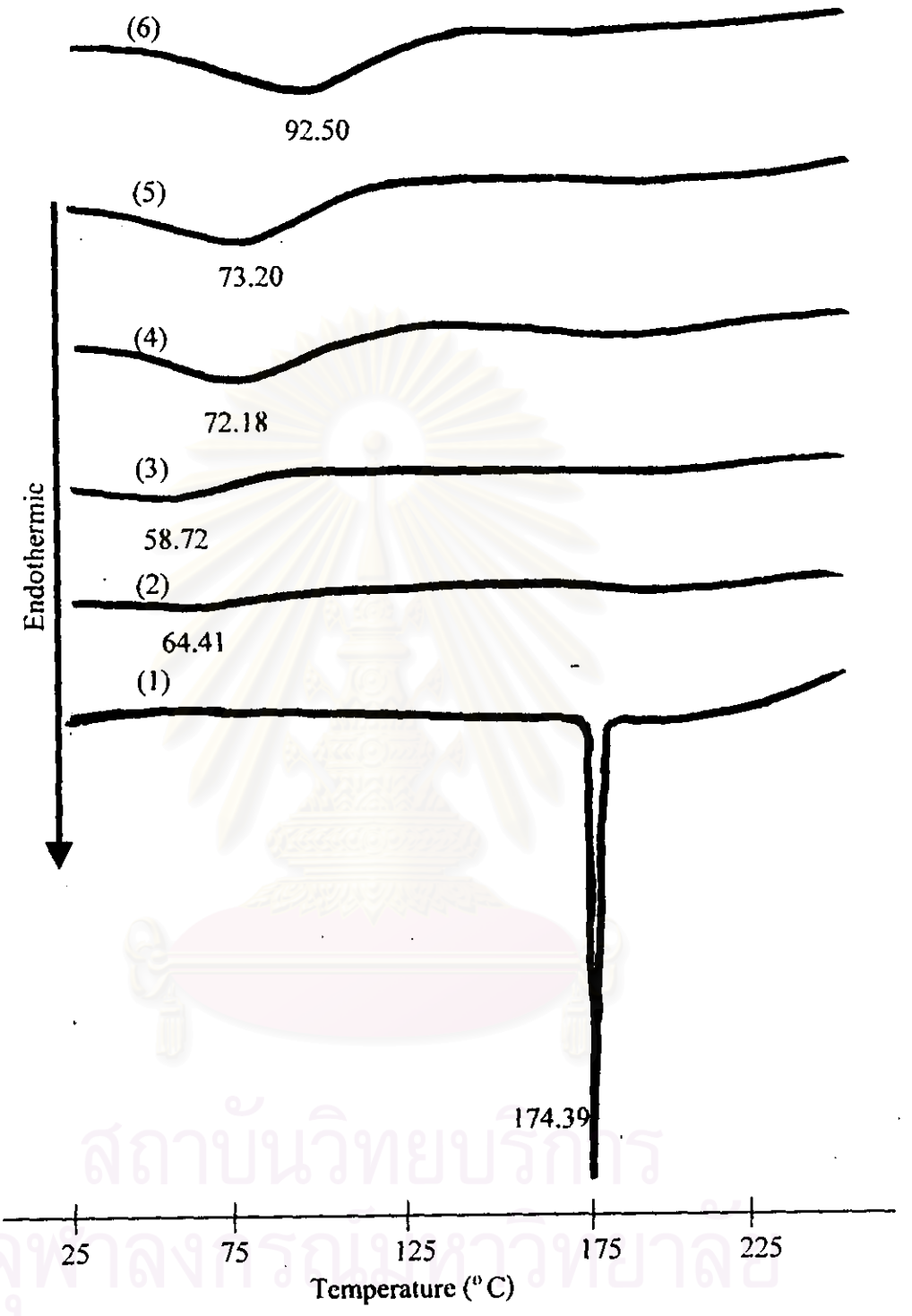


Figure 25 DSC curves of spray dried microspheres prepared at 65°C of 10% spray solution of nifedipine : Eudragit RS100 : PVP K30 at various ratios : (1) nifedipine (2) 1:10:0 (3) 1:8:2 (4) 1:5:5 (5) 1:2:8 (6) 1:0:10

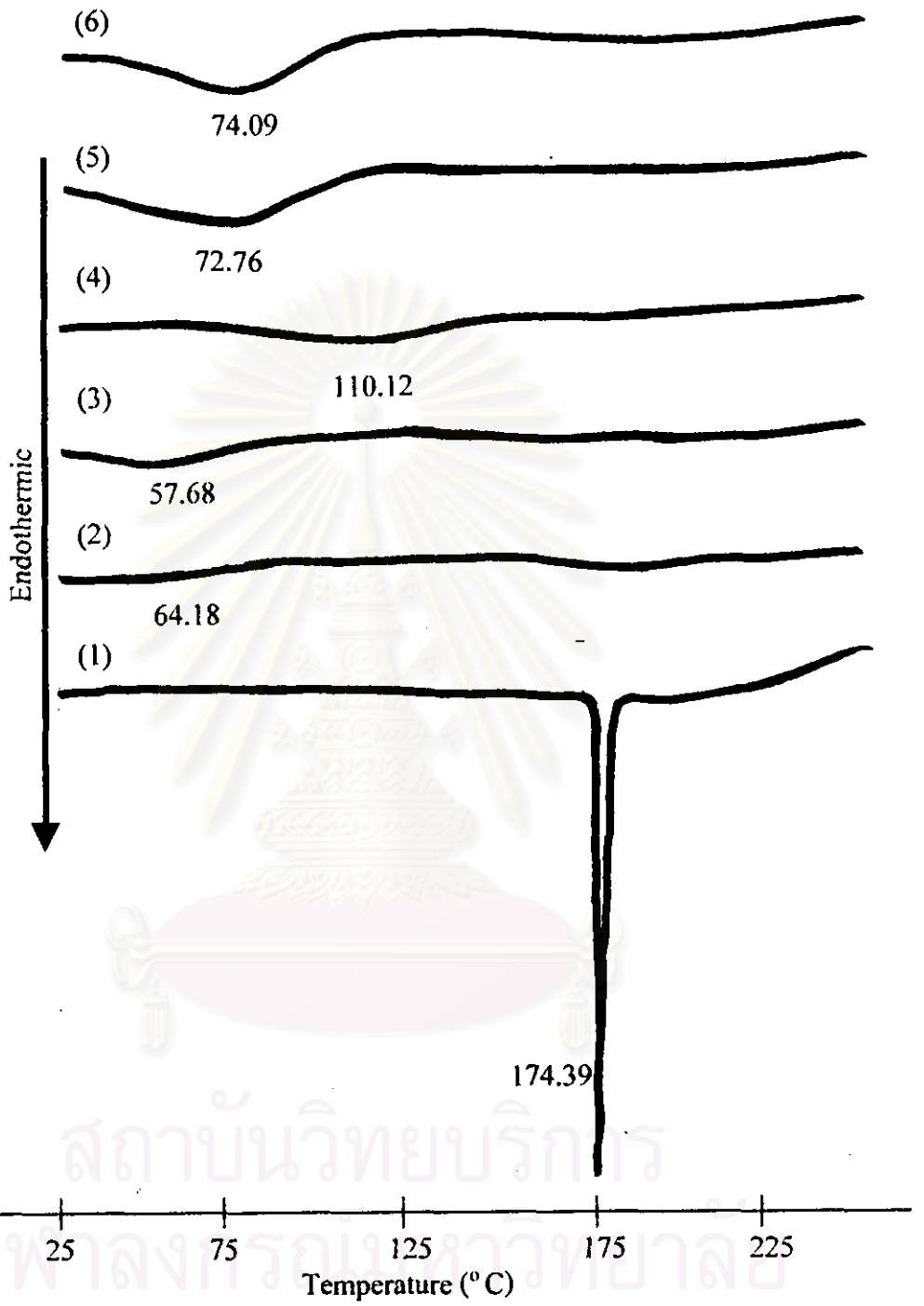


Figure 26 DSC curves of spray dried microspheres prepared at 75° C of 5% spray solution of nifedipine : Eudragit RS100 : PVP K30 at various ratios : (1) nifedipine (2) 1:10:0 (3) 1:8:2 (4) 1:5:5 (5) 1:2:8 (6) 1:0:10

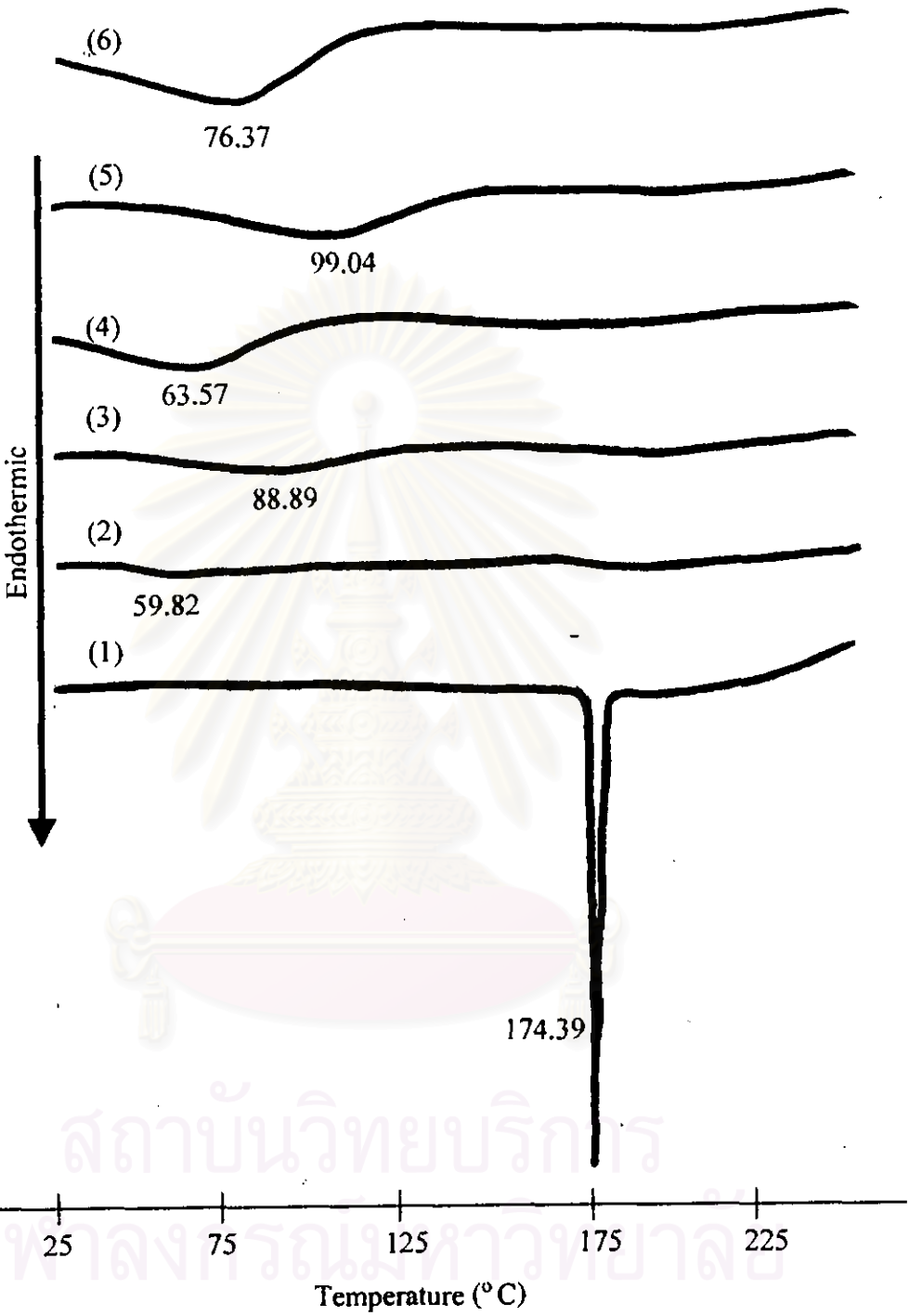


Figure 27 DSC curves of spray dried microspheres prepared at 75° C of 10% spray solution of nifedipine : Eudragit RS100 : PVP K30 at various ratios : (1) nifedipine (2) 1:10:0 (3) 1:8:2 (4) 1:5:5 (5) 1:2:8 (6) 1:0:10

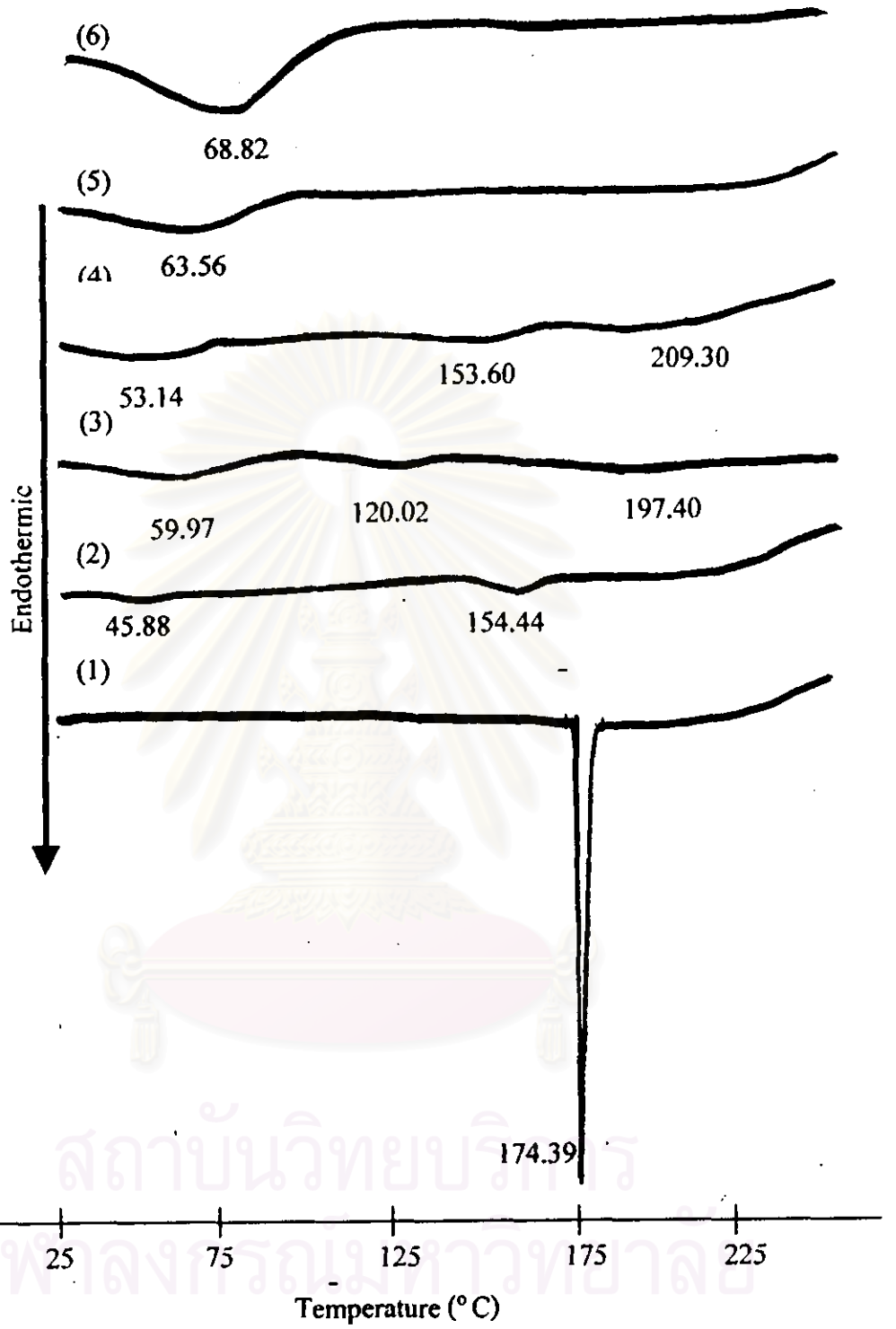


Figure 28 DSC curves of spray dried microspheres prepared at 55° C of 5% spray solution of nifedipine : Eudragit RL100 : PVP K30 at various ratios : (1) nifedipine (2) 1:10:0 (3) 1:8:2 (4) 1:5:5 (5) 1:2:8 (6) 1:0:10

that nifedipine in the microspheres was in amorphous form and was either in a molecular dispersion or a solid solution state.

This result was consistent to the powder XRD diffraction patterns (Figure 14) that nifedipine diffraction peaks disappeared and also was confirmed by the SEM images (Figure 6) that no free nifedipine crystals could be observed depositing on the microsphere surface. The combination of the two polymers in the microspheres showed the fusion of transition endotherm of Eudragit RS 100 and melting endotherm of PVP K30 into only one broad endotherm ranged from 63.68-78.54°C. It was noticeable that the increase of PVP K30 proportion resulted in the increase of this melting temperature.

In the system using 10% spray solution, similar DSC thermograms could be observed (Figure 23). No melting endotherm of nifedipine could be observed. The result was also consistent to the powder XRD patterns in Figure 15 and the SEM analysis in Figure 7. There was a little lower of melting endotherms of combined polymers than in the 5% system. The endotherms of the systems of various mixing ratios ranged between 53.11-79.91°C. It seemed that the concentration of spray solution showed negligible effect to the thermal behavior of the spray dried microspheres.

The DSC thermograms of nifedipine-Eudragit RS100-PVP K30 microspheres prepared by spray drying at 65° and 75°C inlet temperatures from 5% spray solution of all mixing ratios (Figure 24, 26) demonstrated the disappearance

of endothemic peak of nifedipine. The combination of Eudragit RS100 and PVP K30 in the microspheres showed the fusion of transition endotherm of the two polymers into only one broad endotherm range from 63.84-90.83°C for 65°C inlet temperature and 57.68-110.12°C for 75°C inlet temperature. This result was consistent to the powder XRD diffraction patterns (Figure 16, 18) showing the disappearance of nifedipine diffraction peaks and also was confirmed by the SEM images (Figure 8, 10) that no free nifedipine crystals could be observed on the microsphere surface.

In the system using 10% spray solution similar DSC thermograms could be observed (Figure 25,27). The result was also consistent to the powder XRD patterns in Figures 17, 19 and the SEM analysis in Figures 9 and 11. No melting endotherm of nifedipine could be observed. There was a little higher melting endotherms of combined polymers than in the 5% system. The endotherms of the systems of various mixing ratios ranged between 58.72-92.50°C for 65°C inlet temperature and 59.82-99.04°C for 75°C inlet temperature. The results of DSC thermograms indicated that the increase of PVP K30 proportion in combined carrier resulted in the increase of melting temperature closed to pure PVP K30 melting. It seemed that the concentration and temperature showed clear effect to the thermal behavior of the spray dried microspheres. The presence of nifedipine in the microspheres cause Tg of combined polymers to change. This change was presumably caused by nifedipine being soluble in the polymer (Kristmundsdottir, Gudmundsson and Ingravsdottir, 1996). This should also result in the disapperance of the melting point peak for nifedipine, which indicated that the polymer and most likely the nifedipine were amorphous in the microspheres.

5.3 DSC thermograms of nifedipine-Eduragit RL 100-PVP K30 microspheres

The DSC curves of nifedipine-Eudragit RL100-PVP K30 microspheres are illustrated in Figure 28. Broad endotherms of the combination of the two polymers in the microspheres showed the fusion of transition endotherm of Eudragit RL100 and melting endotherm of PVP K30 into one broad endotherm range from 45.88-68.82°C. The broad melting endotherm of nifedipine could be observed in the ratios of 1:10:0, 1:8:2 and 1:5:5 at 154.44°C, 120.02°C and 153.60°C respectively. This result was consistent to the powder XRD patterns that nifedipine diffraction peaks could be observed in some powder XRD patterns, e.g., the microspheres of 1:5:5 ratio (Figure 20). The results might indicate that at ratio 1:10:0, 1:8:2 and 1:5:5, the polymers and the drug were partially amorphous in the microspheres. This could also result in the lowering and broadening of the melting peak of nifedipine from 174.39 °C to 120.02-154.44 °C.

The broad endothermic peaks as observe in the microspheres in the ratio of 1:2:8 and 1:5:5 to be 197.40 and 209.30°C, respectively might be due to the melting of Eudragit RL. As observe in the DSC thermogram of spray dried Eudragit RL and PVP K30 (1:1) with no nifedipine the melting endothermic of PVP was observed at 70.86 °C and Eudragit RL at 179.69 °C.

6. The FTIR spectra

6.1 The FTIR spectra of spray dried nifedipine and combined carriers

The FTIR spectra of spray dried nifedipine, Eudragit RS100, Eudragit RL100 and PVP K30 are illustrated in Figure 29. The FTIR spectra of nifedipine samples showed characteristic absorption bands of N-H stretching vibration at 3329cm^{-1}. The peak at 3099 cm^{-1} indicated C-H aromatic vibration and at 2996 cm^{-1}and 2952 cm^{-1} referred to C-H aliphatic stretching. The major peaks of carbonyl C=O stretching showed at 1689 cm^{-1} and C-O ester stretching at 1226 cm^{-1} and 1120 cm^{-1}. The sharp peak of NO_2 stretching was noticed at 1528 cm^{-1}.

The FTIR spectra of spray dried Eudragits RS100 showed characteristic peaks of N-H stretching at 3445 cm^{-1}, C-H aliphatic stretching vibration at 2995 cm^{-1} and 2951 cm^{-1}. The peak at 1734-1740 cm^{-1} indicated carbonyl C=O stretching and C-O ester streching at 1238-1270 cm^{-1}, 1148-1190 cm^{-1}. The FTIR spectra of Eudragit RL100 showed very similar characteristic absorption spectra to Eudragit RS100, due to the similarity in their molecular structures. The characteristic peaks of C-H aliphatic stretching at 2987 cm^{-1}and 2953 cm^{-1}, C=O streching at 1729-1740 cm^{-1}. The peak at 1247-1270 cm^{-1} and 1186-1150 cm^{-1} referred to C-O ester stretching and 3445 cm^{-1} referred to N-H stretching vibration.

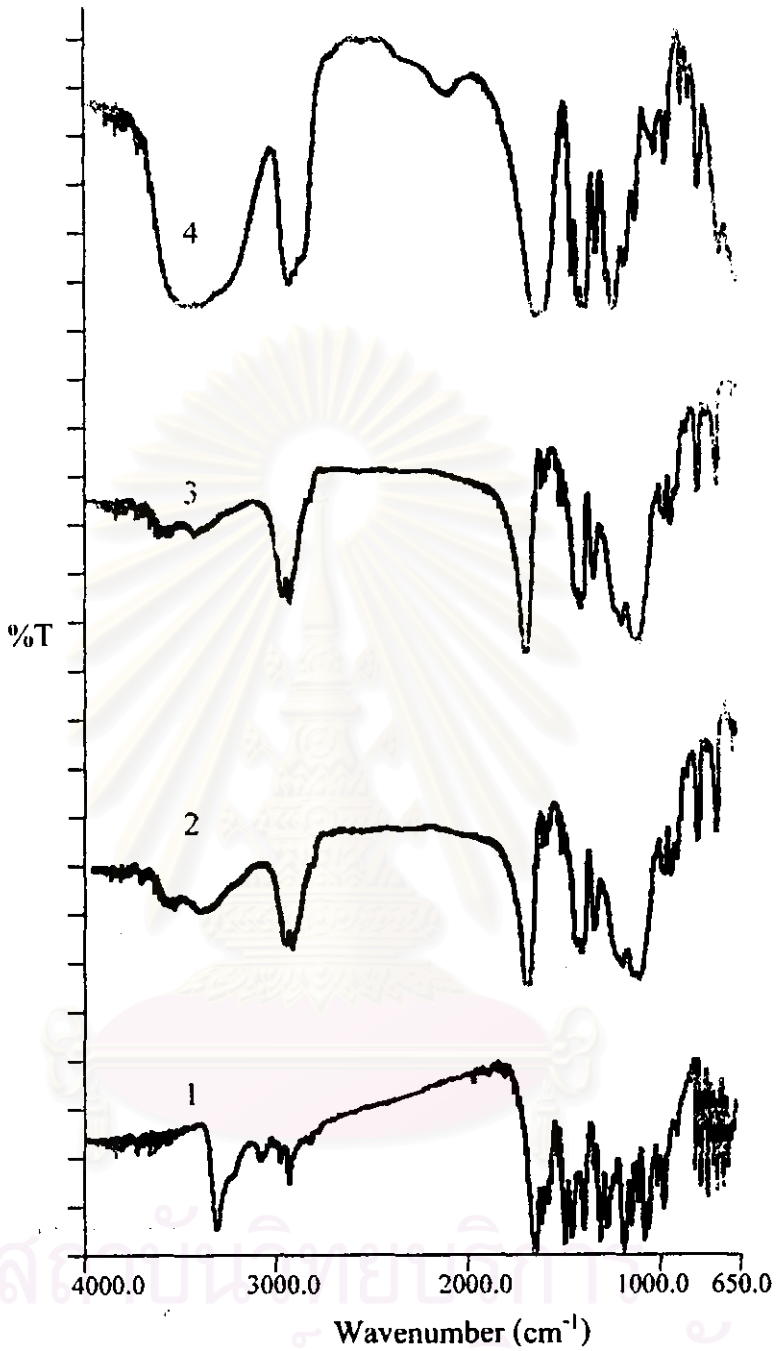


Figure 29 FTIR spectra of spray dried samples prepared at 55°C of 5% spray solution of :(1) nifedipine (2) Eudragit RL100 (3) Eudragit RS100 and (4) PVP K30

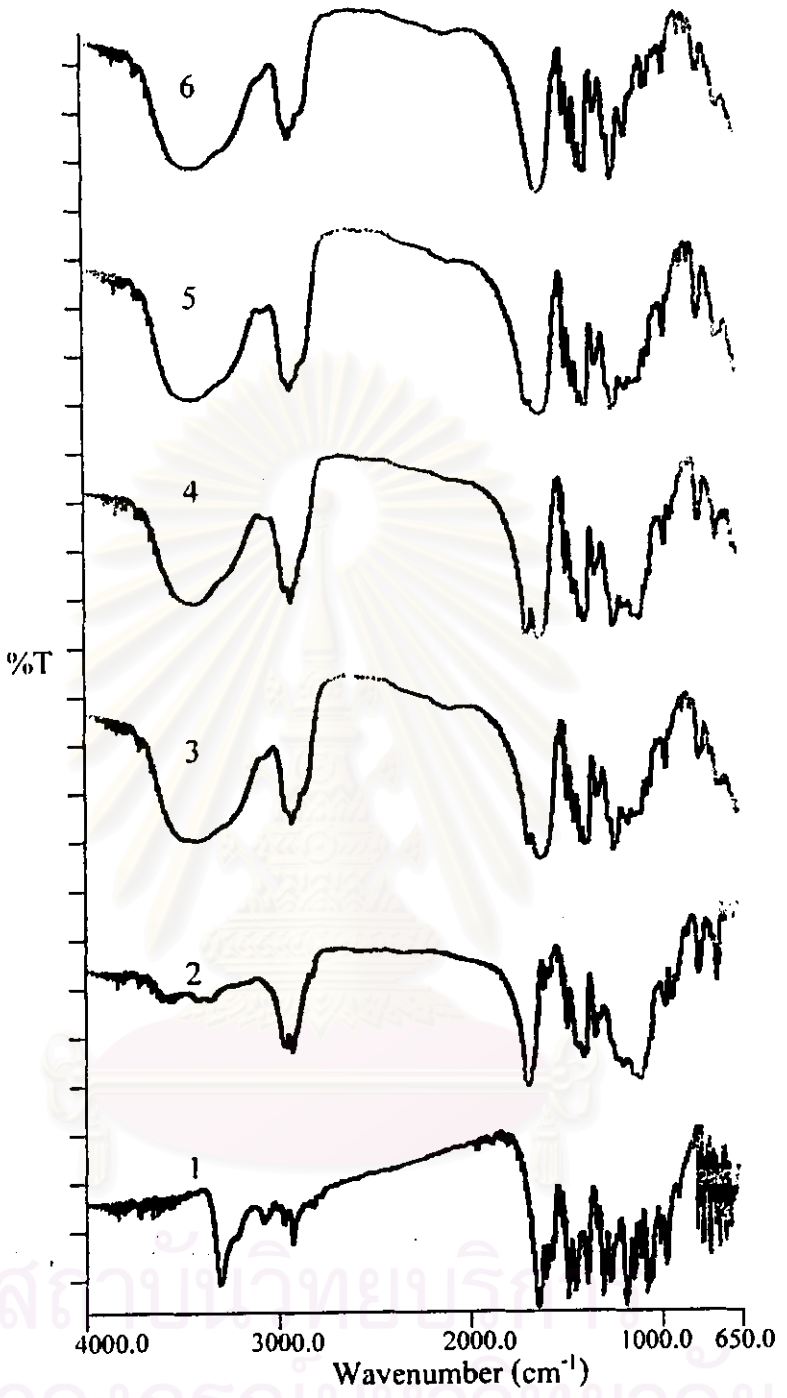


Figure 30 FTIR spectra of spray dried samples prepared at 55°C of 5% spray solution of nifedipine : Eudragit RS 100 : PVP K30 at various ratios:(1) nifedipine (2)1:10:0 (3) 1:8:2 (4) 1:5:5 (5) 1:2:8 and (6) 1:0:10

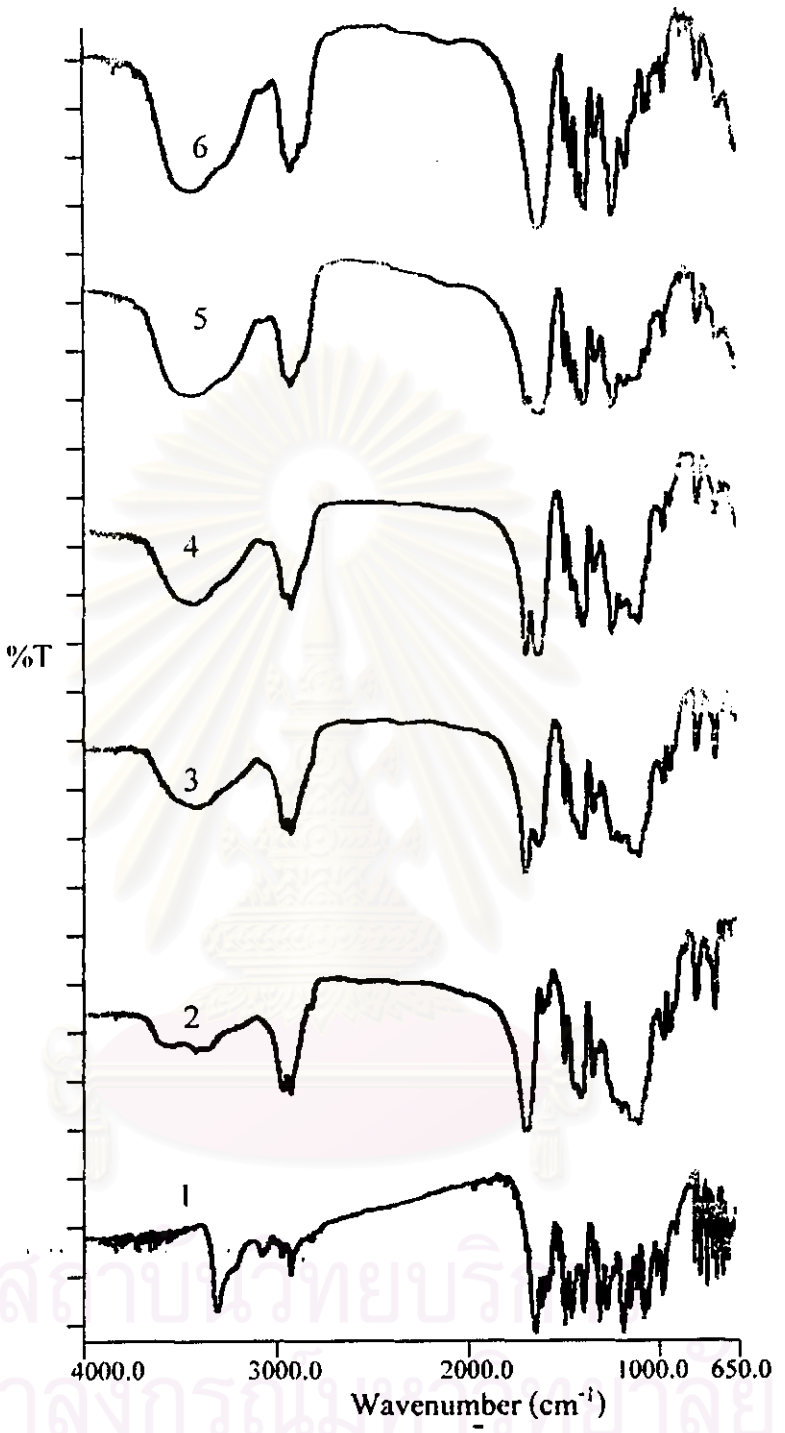


Figure 31 FTIR spectra of spray dried samples prepared at 55°C of 10% spray solution of nifedipine : Eudragit RS100 : PVP K30 at various ratios: (1) nifedipine (2) 1:10:0 (3) 1:8:2 (4) 1:5:5 (5) 1:2:8 and (6) 1:0:10

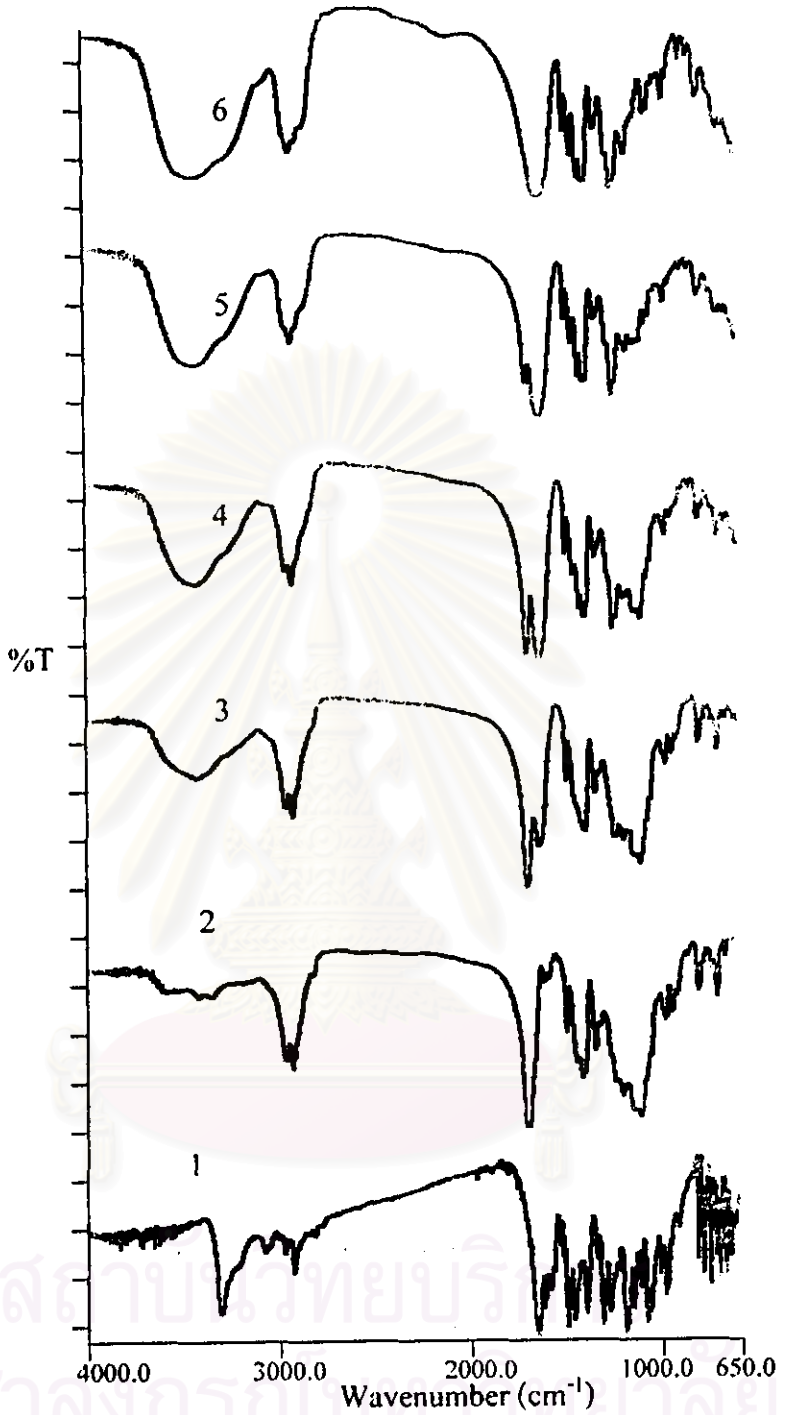


Figure 32 FTIR spectra of spray dried samples prepared at 65°C of 5% spray solution of nifedipine : Eudragit RS 100 : PVP K30 at various ratios: (1) nifedipine (2) 1:10:0 (3) 1:8:2 (4) 1:5:5 (5) 1:2:8 and (6) 1:0:10

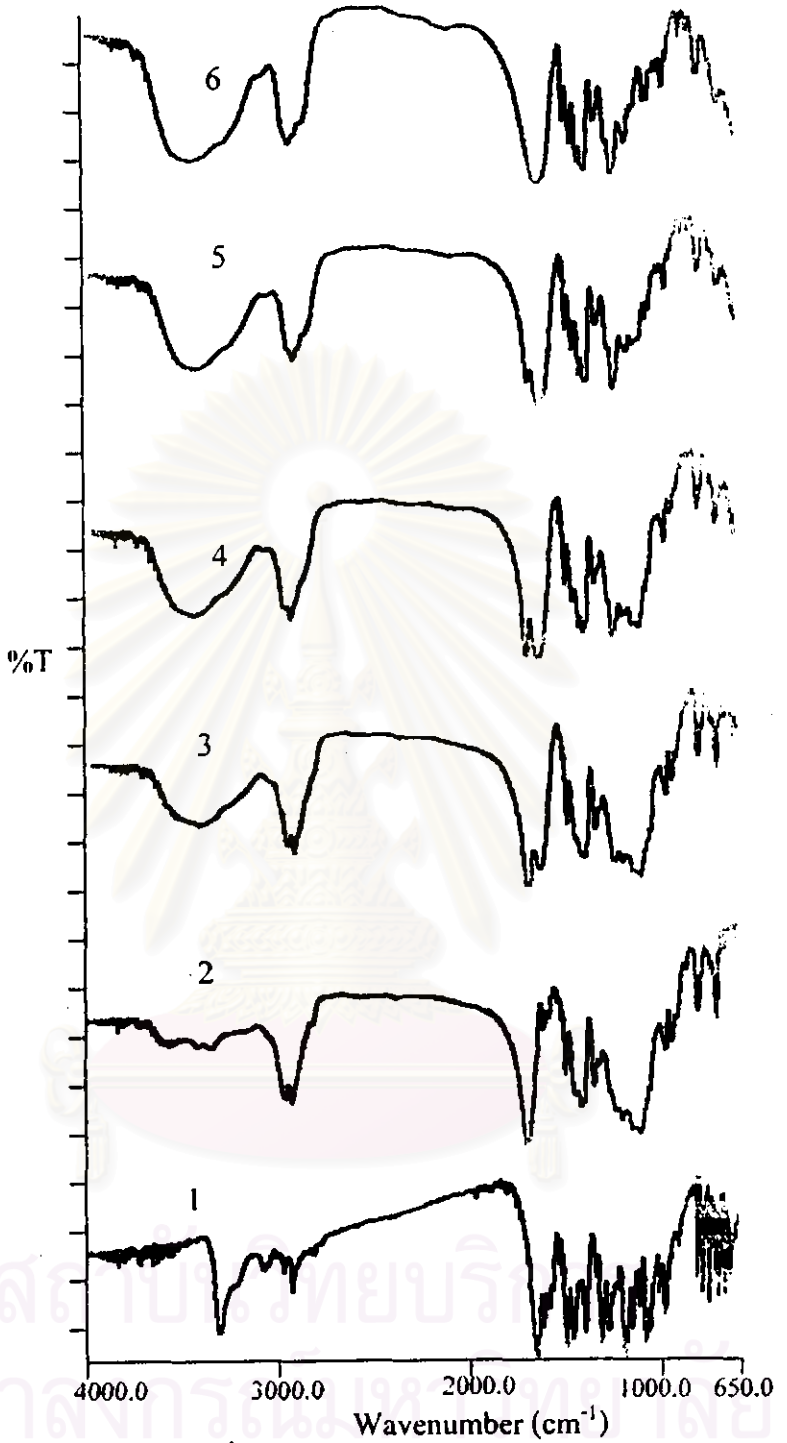


Figure 33 FTIR spectra of spray dried samples prepared at 65°C of 10% spray solution of nifedipine : Eudragit RS100 : PVP K30 at various ratios: (1) nifedipine (2) 1:10:0 (3) 1:8:2 (4) 1:5:5 (5) 1:2:8 and (6) 1:0:10

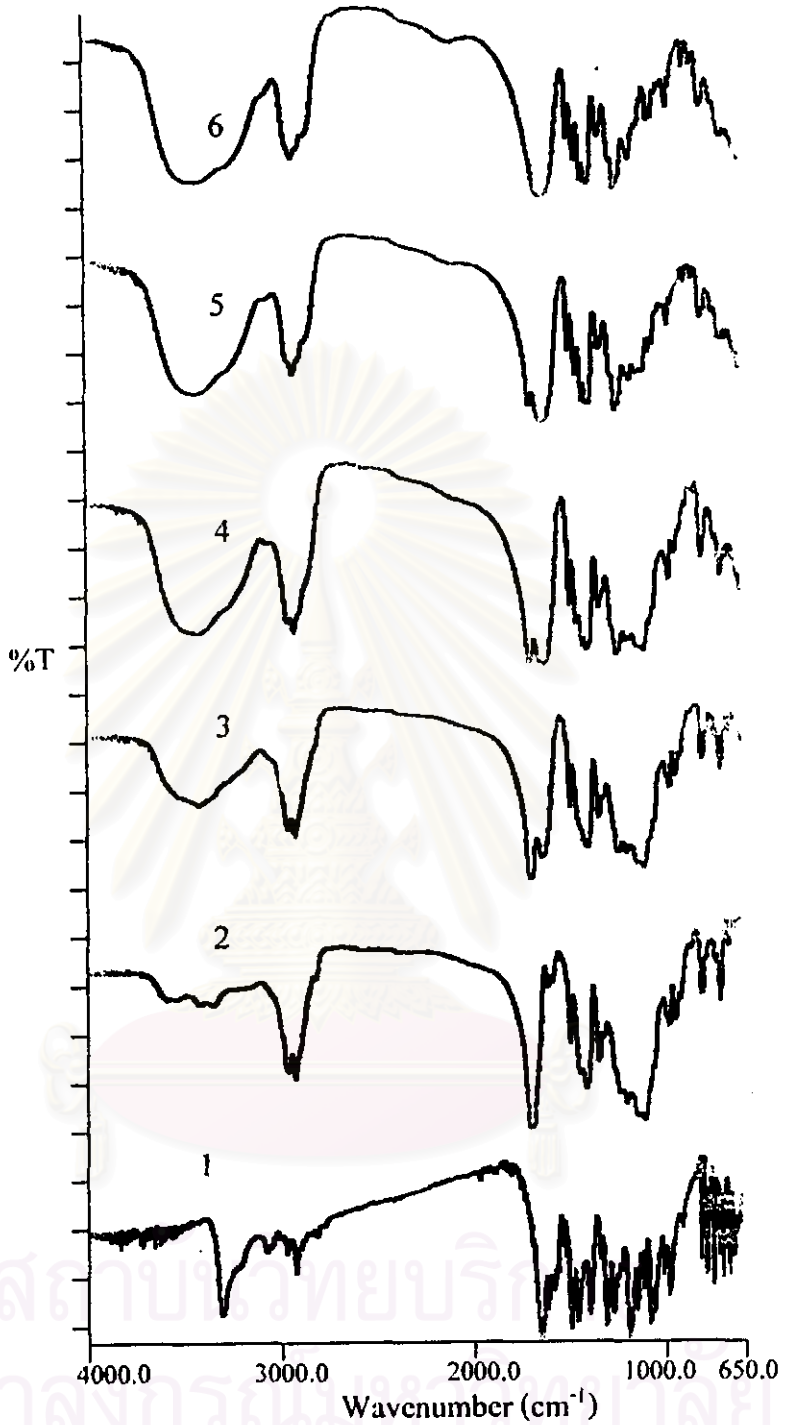


Figure 34 FTIR spectra of spray dried samples prepared at 75°C of 5% spray solution of nifedipine : Eudragit RS100 : PVP K30 at various ratios : (1) nifedipine (2) 1:10:0 (3) 1:8:2 (4) 1:5:5 (5) 1:2:8 and (6) 1:0:10

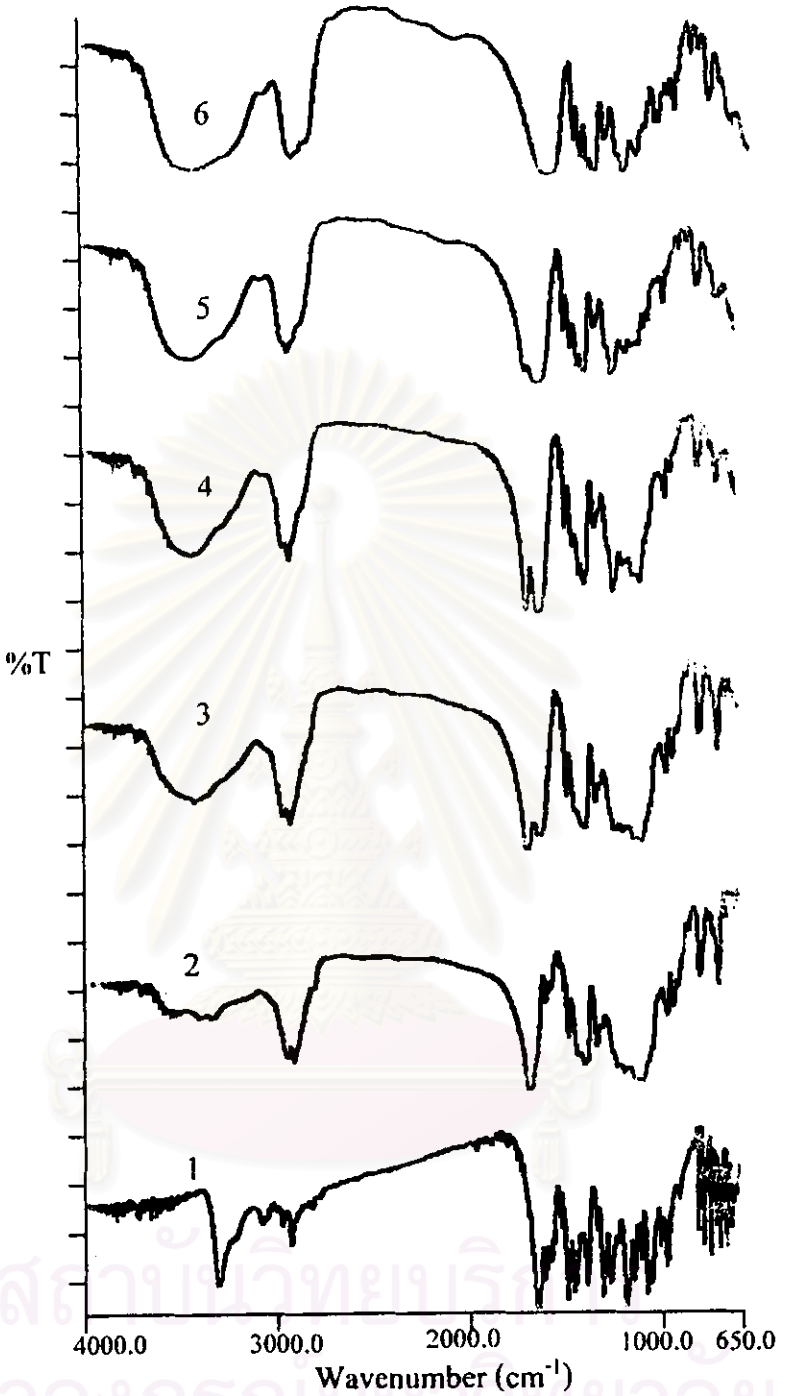


Figure 35 FTIR spectra of spray dried samples prepared at 75°C of 10% spray solution of nifedipine : Eudragit RS100 : PVP K30 at various ratios : (1) nifedipine (2) 1:10:0 (3) 1:8:2 (4) 1:5:5 (5) 1:2:8 and (6) 1:0:10

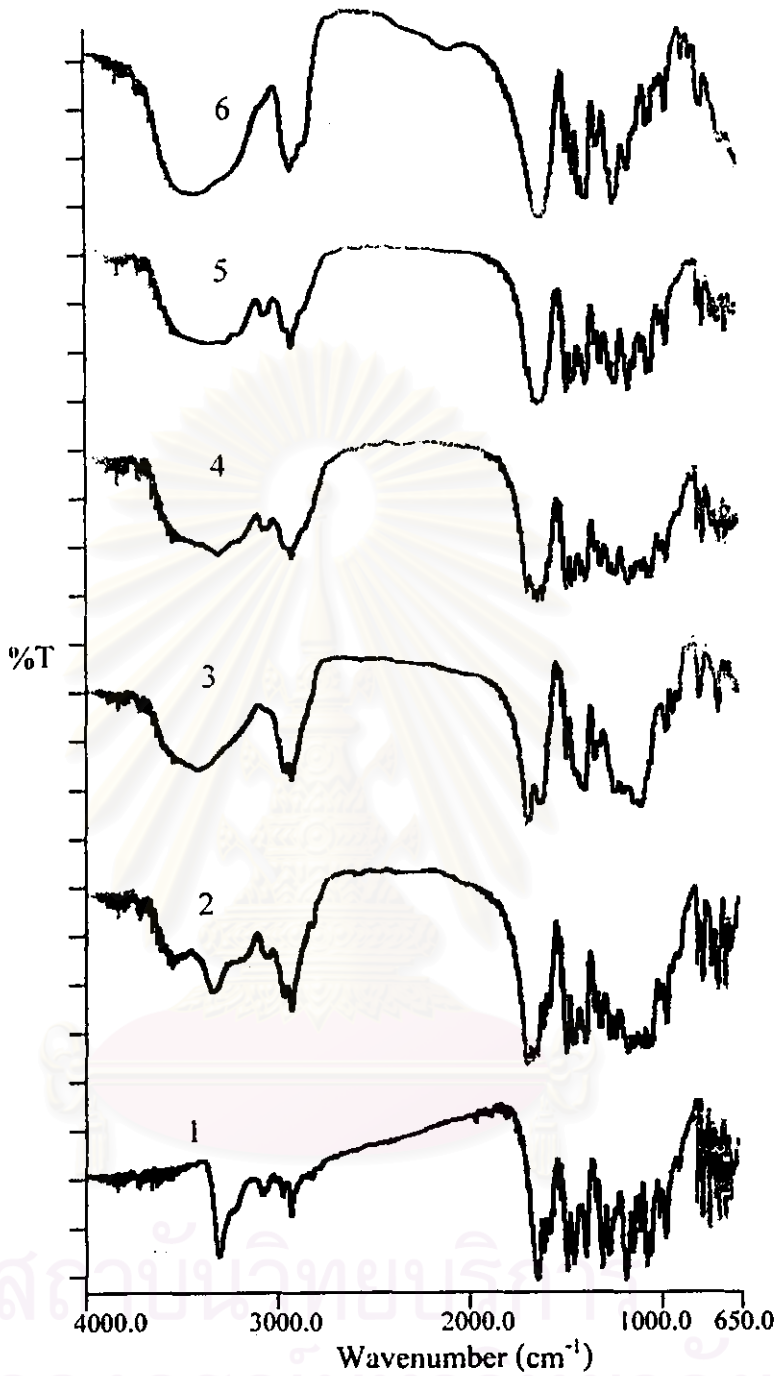


Figure 36 FTIR spectra of spray dried samples prepared at 55°C of 5% spray solution of nifedipine : Eudragit RL100 : PVP K30 at various ratios : (1) nifedipine (2) 1:10:0 (3) 1:8:2 (4) 1:5:5 (5) 1:2:8 and (6) 1:0:10

The FTIR spectra of spray dried PVP K30 showed the charateristic peak of O-H streching vibration from 3380 cm^{-1} to 3550 cm^{-1}. The peak of C-H aliphatic stretching at 2958 cm^{-1} and 2874 cm^{-1} and carbonyl C=O stretching at 1680-1630 cm^{-1} and 1636-1630 cm^{-1}. Thc charactcristic vibration bands of C-O strctching at 1289-1280 cm^{-1}, 1229-1200 cm^{-1} and 1169-1165 cm^{-1}. Thc FTIR spectra of nifedipine-Eudragit RS100-PVP K30 microspheres that were prepared from various spray drying conditions are shown in Figures 30-36. The absorption spectra corresponding to nifedipine could not bc clearly observed in all nifedipine-carrier microspheres. The microspheres at 1:10:0 ratio showed the IR spectra corresponding to Eudragit RS100 while the 1:0:10 ratio showed the FTIR spectra corresponding to PVP K30. The microspheres of 1:8:2, 1:5:5 and 1:2:8 ratios showed the superimposed spectra of only Eudragit RS100 and PVP K30.

The microspheres prepared at 55°C (Figure 30 and 31) showed the disapperance of N-H stretching vibration band of nifedipine at 3329 cm^{-1} and also thc C=O stretching at 1683 cm^{-1}. Thc 1:10:0 ratio showcd small changes of N-H streching bands of Eudragit RS100 at 3445 cm^{-1} that shifted to the lower frequency at 3438 cm^{-1}. The increasing proportion of PVP K30 content showed the superimposed spectra of Eudragit RS100 and PVP K30. The disappearance of nifedipine absorption spectra and the C=O streching of all ratios shifting to the lower frequency showed an evidence that the interaction between the three components existed, which might be hydrogen bonding.

In the systems using 5% and 10% spray solution similar FTIR spectra could be observed. The FTIR spectra of nifedipine-Eudragit RS100-PVP K30

microspheres at 65°C and 75°C at all mixing ratios and concentrations of spray solution showed similar FTIR spectral patterns to their corresponding spectra at 55°C (Figures 32-35). The increasing of inlet temperature resulted in the shift of N-H stretching to lower frequency from 3445 to 3437 cm^{-1}. The FTIR spectra showed noticeable change of C=O stretching band from 1729 to 1734 cm^{-1}. The increase of PVP content in the microspheres, the C-H stretching band became more intense.

The FTIR spectra of nifedipine-Eudragit RL100-PVP K30 microspheres illultrated in Figure 36 showed the characteristic peaks differently from the nifedipine-Eudragit RS100-PVP K30 system. The N-H stretching peak was shifted from 3445 cm^{-1} to 3367 cm^{-1}. The higher PVP K30 content markedly reduced some vibration bands. Nifedipine characteristic absorption spectra could be observed in the microspheres at all various ratios, except at 1:0:10 ratio. The IR spectra of 1:0:10 ratio showed some evidence of hydrogen bonding formation between the components. The existence of N-H stretching vibration of nifedipine in the ratio 1:10:0, 1:8:2, 1:5:5 and 1:2:8 consisted to the results from powder XRD patterns and DSC thermograms that diffraction peaks corresponding to nifedipine crystalline, broad melting endotherm referring to nifedipine crystalline.

The results of FTIR spectra suggested that the presence of intermolecular hydrogen bonds between nifedipine-Eudragit RS100-PVP K30. Different ratios of drug to combined carriers showed different FTIR spectra except the ratio 1:2:8, 1:5:5 and 1:8:2 showed similar FTIR spectra. The spray solution concentration

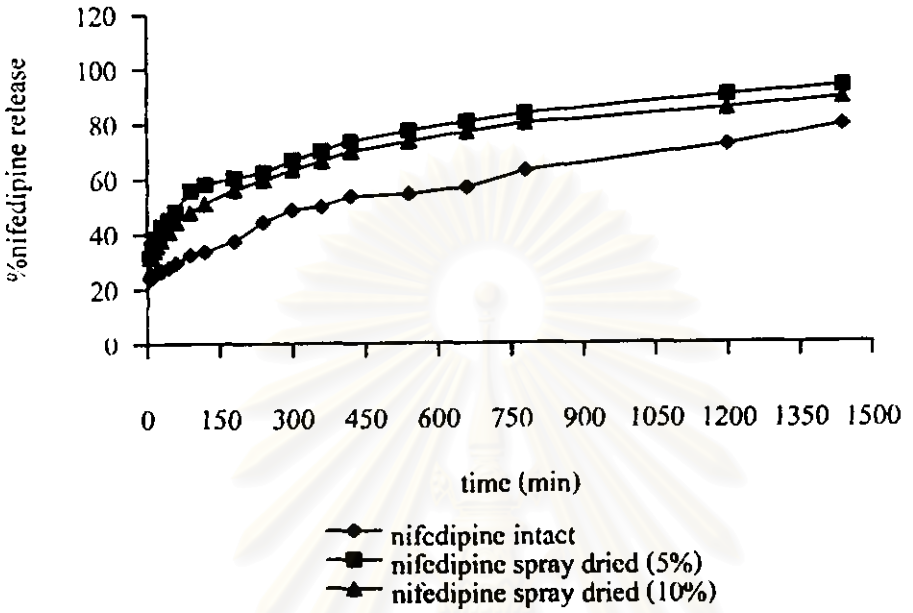
and inlet temperature did not affect FTIR spectra. In the case of nifedipine Eudragit RL100-PVP K30, the result suggested that there was weak interaction between nifedipine and combined carriers. In the ratio of 1:10:0, it showed that no interaction between nifedipine and Eudragit RL100 occurred, whereas the ratio 1:0:10, the intermolecular hydrogen bonds between nifedipine and PVP K30 might exist. The FTIR spectra results thus agreed with the DSC thermogram and powder XRD patterns.

7. Dissolution Study

The dissolution profiles of nifedipine microspheres prepared from spray drying with various mixing ratios of combined carriers are shown in Figures 37-50. The profiles were plotted between the percentage drug release versus time as presented in Appendix B.

7.1 Dissolution Efficiency

In this study, a parameter suitable for the evaluation of *in vitro* dissolution, the dissolution efficiency (DE) was applied. It was defined as the area under the dissolution curve up to a certain time, t, expressed as a percentage of the area of the rectangle described by 100% dissolution in the same time (Khan, 1975). Therefore, the parameter DE calculated from the dissolution of the drug from a particular formulation after 24 hours was used to compare between formulations. The concept of DE has certain advantages, for example, it is the summation of



Figur 37 Dissolution profile of nifedipine and nifedipine spray dried at 55° C of 5 and 10% spray solutions in simulated intestinal fluid without enzyme (pH 7.5)

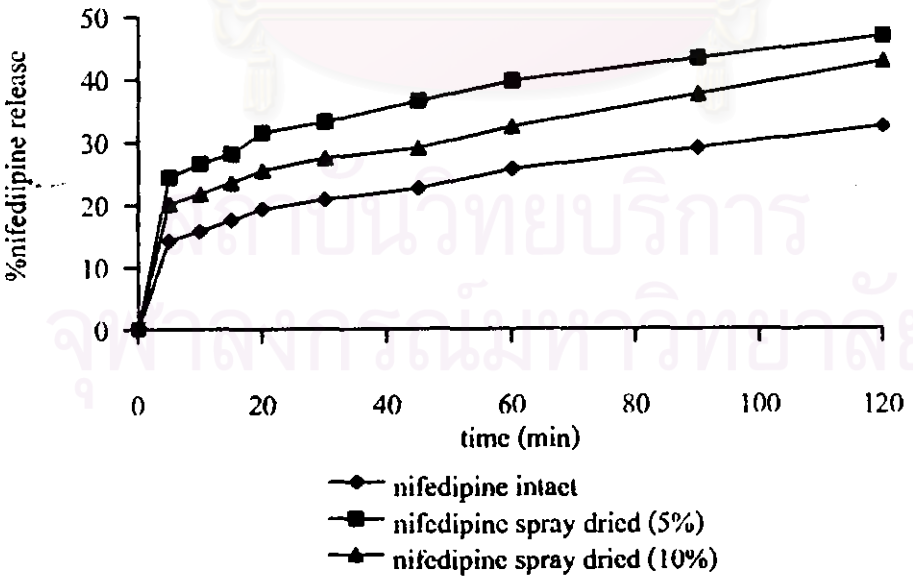


Figure 38 Dissolution profile of nifedipine and nifedipine spray dried at 55° C of 5 and 10% spray solutions in simulated gastic fluid without enzyme (pH 1.2)

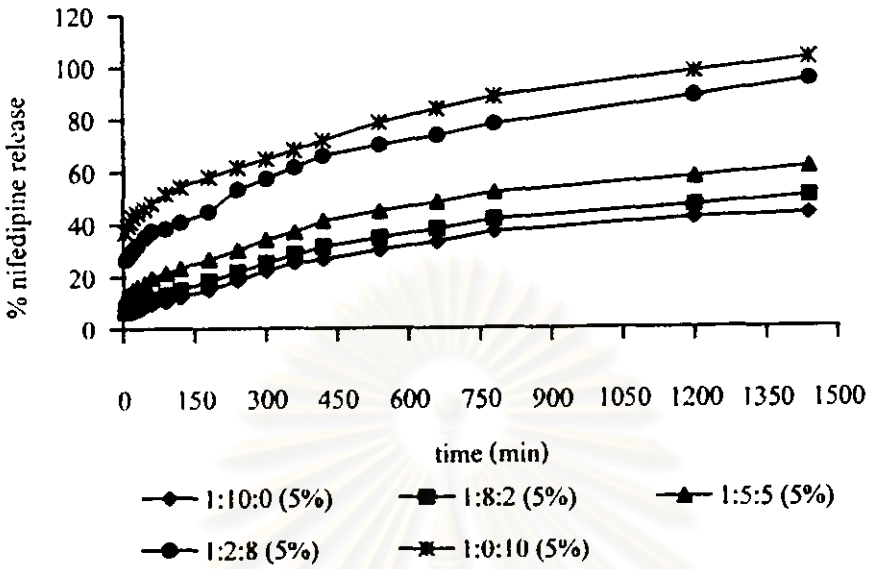


Figure 39 Effect of Eudragit RS100:PVP K30 ratios on the percentage of nifedipine release in simulated intestinal fluid without enzyme (pH 7.5) as a function of time at 55°C of 5% spray solution for various nifedipine:Eudragit RS100:PVP K30 ratios

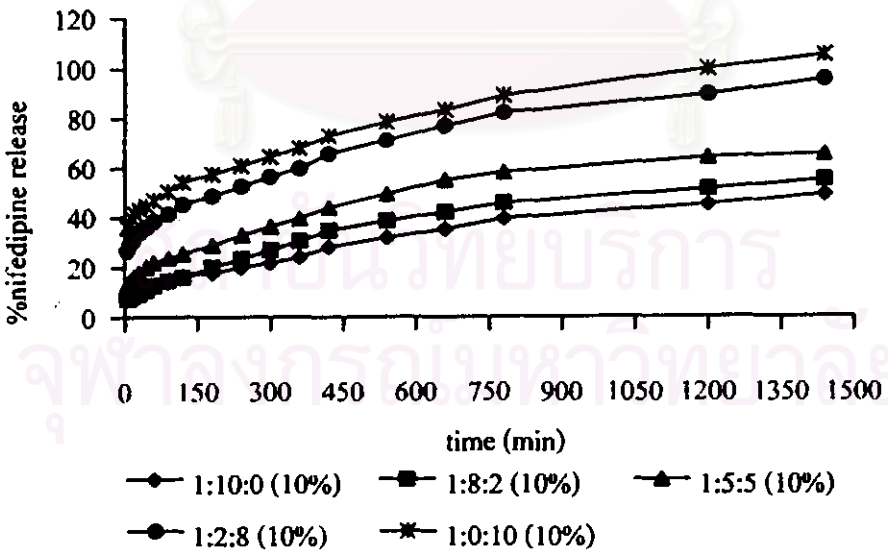


Figure 40 Effect of Eudragit RS100:PVP K30 ratios on the percentage of nifedipine released in simulated intestinal fluid without enzyme (pH 7.5) as a function of time at 55°C of 10% spray solution for various nifedipine:Eudragit RS100:PVP K30 ratios

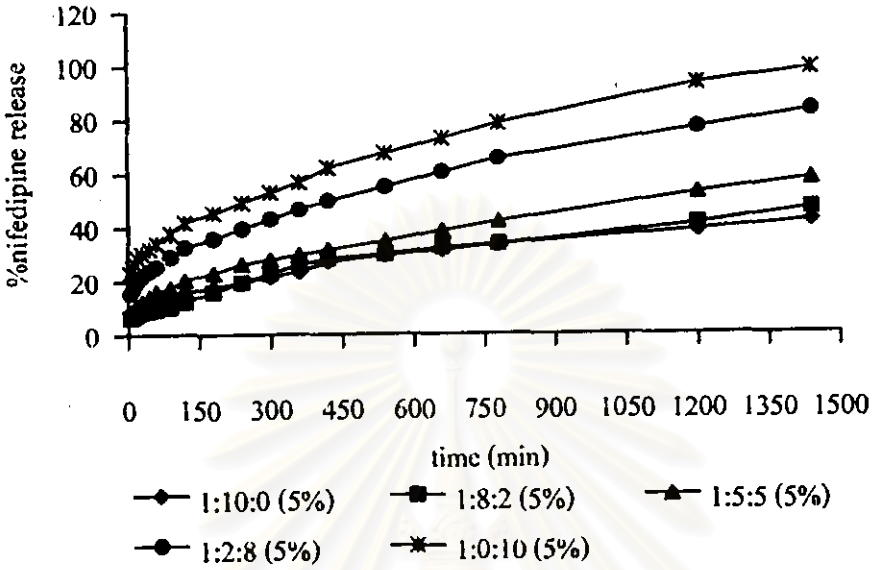


Figure 41 Effect of Eudragit RS100:PVP K30 ratios on the percentage of nifedipine released in simulated intestinal fluid without enzyme (pH 7.5) as a function of time at 65° C of 5% spray solution for various nifedipine:Eudragit RS100:PVP K30 ratios

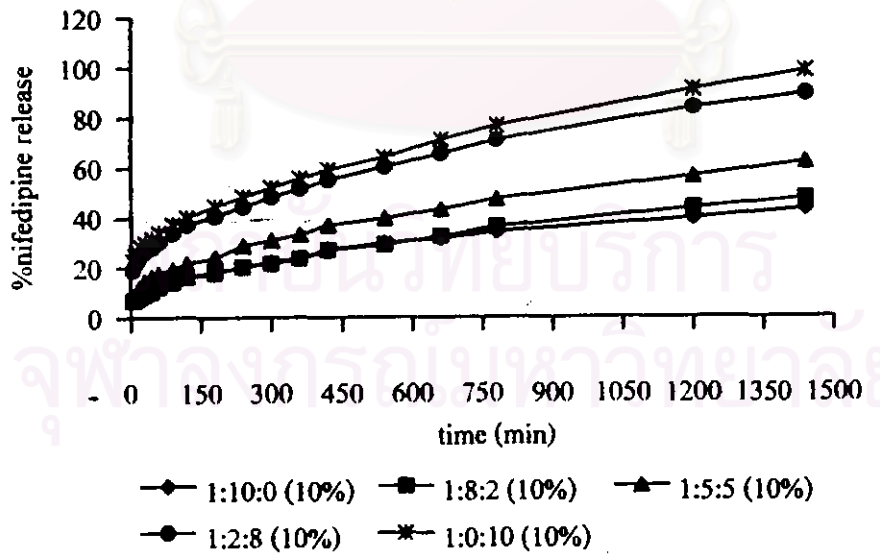


Figure 42 Effect of Eudragit RS100:PVP K30 ratios on the percentage of nifedipine released in simulated intestinal fluid without enzyme (pH 7.5) as a function of time at 65 C of 10% spray solition for various nifedipine :Eudragit RS100:PVP K30 ratios

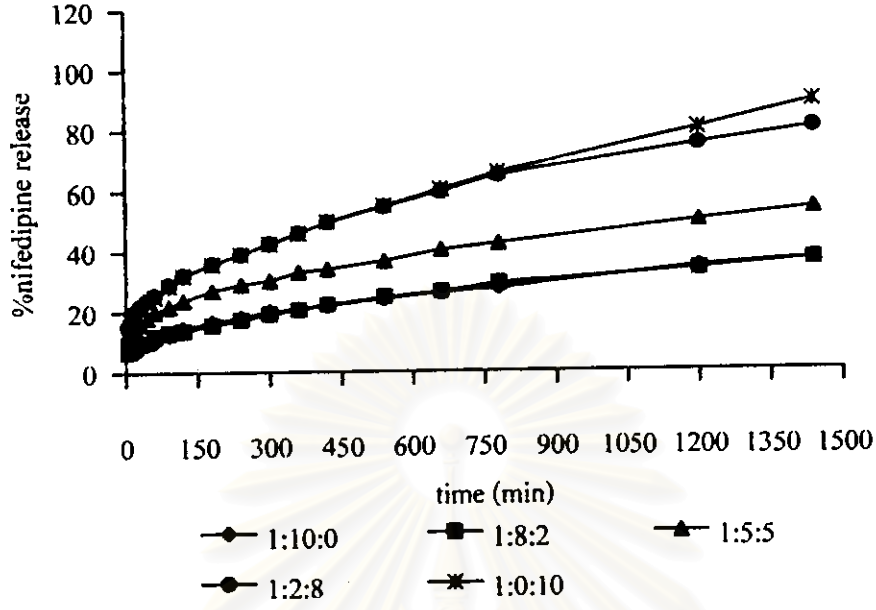


Figure 43 Effect of Eudragit RS100:PVP K30 ratios onthe percentage of nifedipine released in simulated intestinal fluid without enzyme (pH 7.5) as a function of time at 75°C of 5% spray solution for various nifedipine:Eudragit RS100:PVP K30 ratios

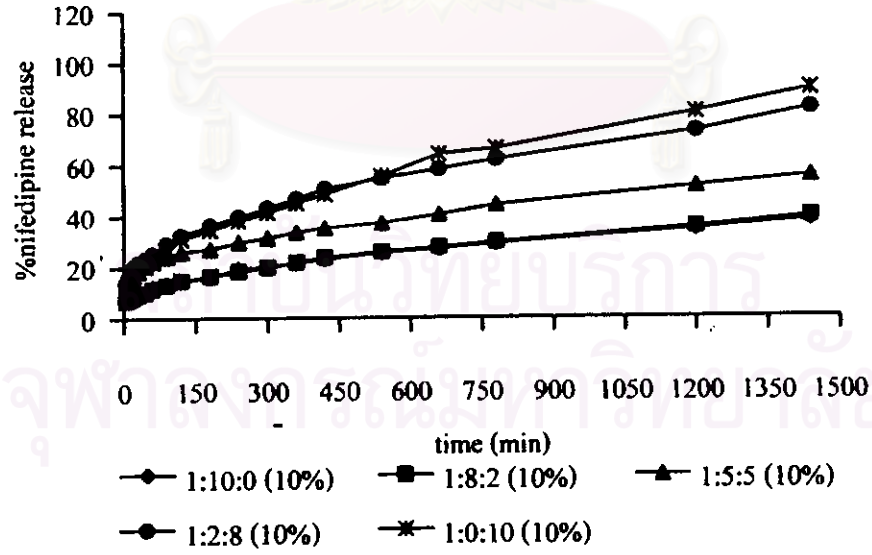


Figure 44 Effect of Eudragit RS100:PVP K30 ratios on the percentage of nifedipine release in simulated intestinal fluid without enzyme (pH 7.5) as a function of time at 75°C of 10% spray solution for various nifedipine:Eudragit RS100:PVP K30 ratios

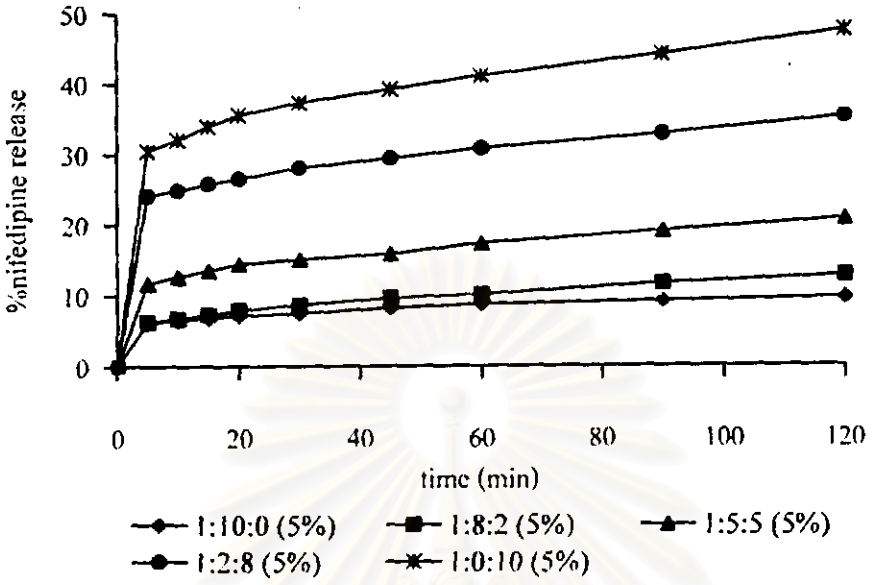


Figure 45 Effect of Eudragit RS100:PVP K30 ratios on the percentage of nifedipine released in simulated gastic fluid without enzyme (pH 1.2) as a function of time at 55° C of 5% spray solution for various nifedipine:Eudragit RS100:PVP K30 ratios

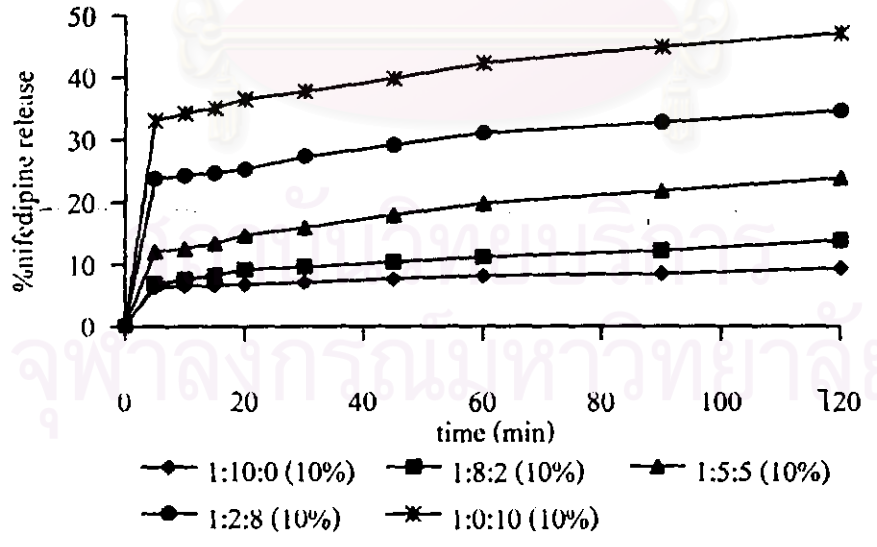


Figure 46 Effect of Eudragit RS100:PVP K30 ratios on the percentage of nifedipine released in simulated gastic fluid without enzyme (pH 1.2) as a function of time at 55° C of 10% spray solution for various nifedipine:Eudragit RS100:PVP K30 ratios

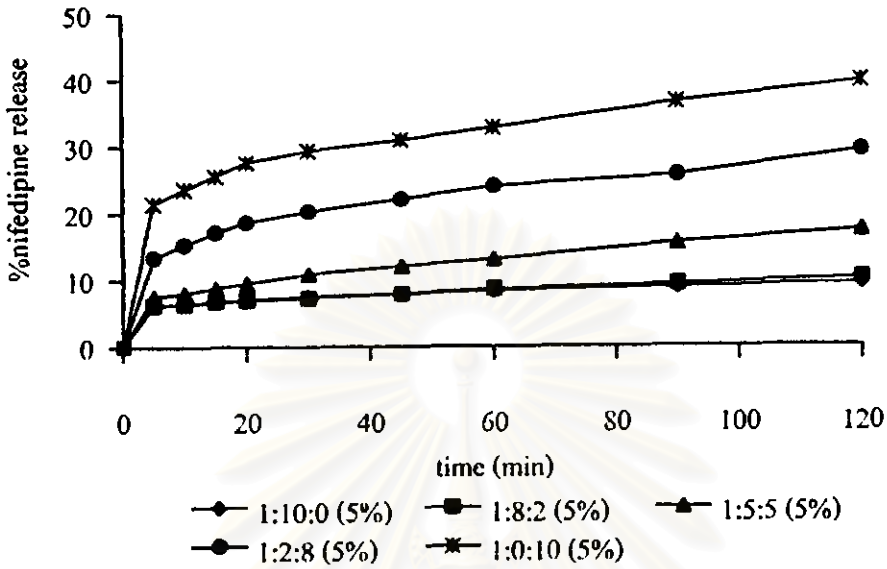


Figure 47 Effect of Eudragit RS100:PVP K30 ratios on the percentage of nifedipine released in simulated gastic fluid without enzyme (pH 1.2) as a function of time at 65°C of 5% spray solution for various nifedipine:Eudragit RS100:PVP K30 ratios

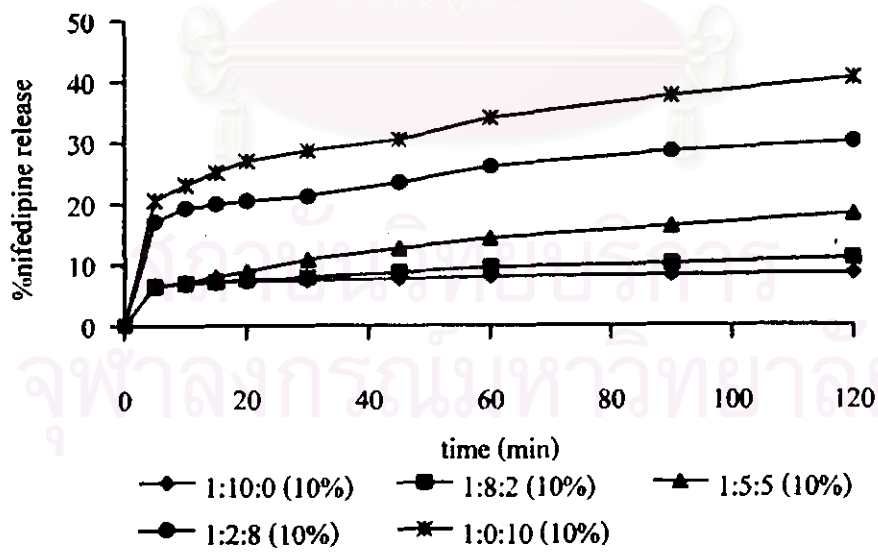


Figure 48 Effect of Eudragit RS100:PVP K30 ratios on the percentage of nifedipine released in simulated gastic fluid without enzyme (pH 1.2) as a function of time at 65°C of 10% spray solution for various nifedipine:Eudragit RS100:PVP K30 ratios

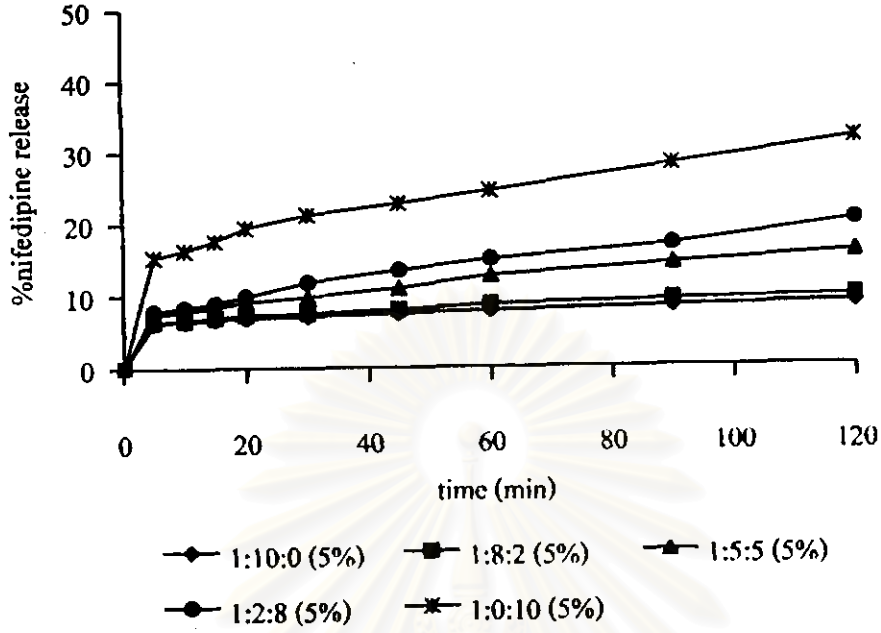


Figure 49 Effect of Eudragit RS100:PVP K30 ratios on the percentage of nifedipine released in simulated gastic fluid without enzyme (pH 1.2) as a function of time at 75° C of 5% spray solution for various nifedipine:Eudragit RS100:PVP K30 ratios

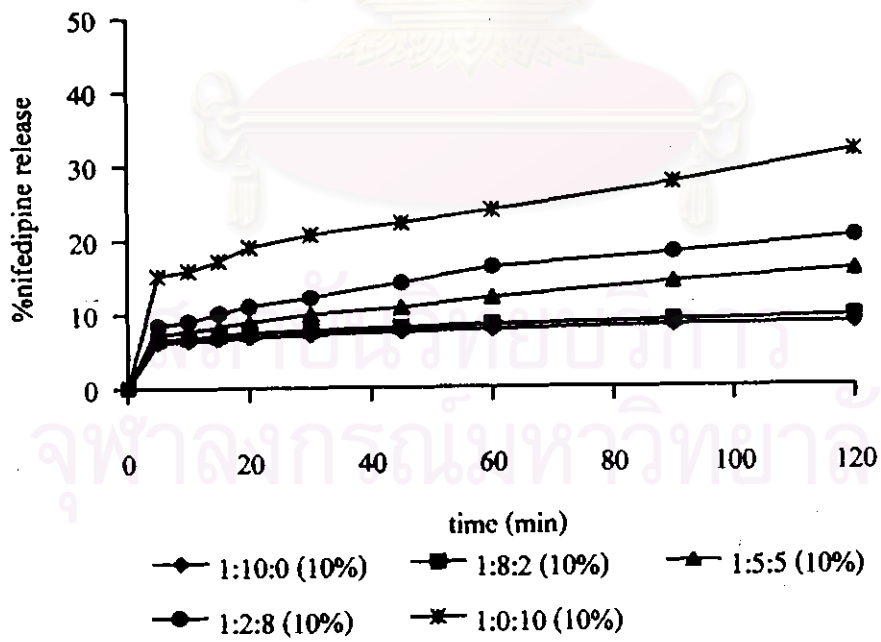


Figure 50 Effect of Eudragit RS100:PVP K30 ratios on the percentage of nifedipine released in simulated gastic fluid without enzyme (pH 1.2) as a function of time at 75° C of 10% spray solution for various nifedipine:Eudragit RS100:PVP K30 ratios

Table 5 Dissolution efficiency (DE) over 24 h release in simulated intestinal fluid without enzyme (pH 7.5) from different types of microspheres

Temperature (°C)	Nifedipine intact	Nifedipine spray-dried	DE (%) Nifedipine:Eudragit RS or RL100:PVP K30 1:10:0	1:8:2	1:5:5	1:2:8	1:0:10
55°C 5%(w/v)	58.00	77.67	31.37 *41.07	35.74 49.72	45.55 56.91	71.40 74.38	80.88 80.88
10%(w/v)	-	73.54	33.83	39.17	50.27	73.10	81.50
65°C 5%(w/v)	-	-	29.98	31.04	38.84	58.91	71.78
10%(w/v)	-	-	30.69	32.18	42.71	64.58	70.13
75°C 5%(w/v)	-	-	25.95	26.00	39.30	58.16	60.25
10%(w/v)	-	-	26.74	27.26	40.70	57.24	60.35

DE is defined as the area under the dissolution curve up to the certain time (here 24 h) expressed as the percentage of the rectangle described by 100% in the same time (Khan , 1975)

*DE of nifedipine : Eudragit RL100 : PVP K30 microspheres

Table 6 Dissolution efficiency (DE) over 2 h release in simulated gastic fluid without enzyme (pH 1.2) from different types of microspheres

Temperature (°C)	Nifedipine intact	Nifedipine spray-dried	DE (%) Nifedipine:Eudragit RS or RL100:PVP K30				
			1:10:0	1:8:2	1:5:5	1:2:8	1:0:10
55°C 5%(w/v)	24.28	37.34	8.01 *10.64	9.66 34.66	16.37 22.89	29.18 14.68	38.97 38.97
10%(w/v)	-	31.57	7.66	10.56	18.26	28.91	39.76
65°C 5%(w/v)	-	-	7.77	8.03	12.54	22.22	31.36
10%(w/v)	-	-	7.49	8.76	13.03	24.12	31.69
75°C 5%(w/v)	-	-	7.40	8.08	11.70	13.94	23.55
10%(w/v)	-	-	7.35	8.02	11.54	14.78	23.15

DE is defined as the area under the dissolution curve up to the certain time (here 2 h) expressed as the percentage of the rectangle described by 100% in the same time (Khan ,1975)

*DE. of nifedipine : Eudragit RL100 : PVP K30 microspheres

Table 7 Release rate constant (k) of nifedipine microspheres over 24 h in simulated intestinal fluid without enzyme (pH 7.5)

Temperature (°C)	Nifedipine intact	Nifedipine spray-dried	k ($min^{-1/2}$) Nifedipine:Eudragit RS or RL100:PVP K30 1:10:0	1:8:2	1:5:5	1:2:8	1:0:10
55°C 5%(w/v)	1.5641	1.7443	1.1540	1.3367	1.4646	1.9800	1.8636
			*1.5349	1.7904	1.7628	2.0770	1.8636
10%(w/v)	-	1.7502	1.2111	1.4576	1.6116	1.9721	1.9533
65°C 5%(w/v)	-	-	1.0225	1.1578	1.3480	1.8882	2.1128
10%(w/v)	-	-	1.0384	1.1496	1.4867	1.9575	2.0712
75°C 5%(w/v)	-	-	0.8211	0.8386	1.1601	1.8403	2.0274
10%(w/v)	-	-	0.8548	0.9054	1.1218	1.8373	2.1363

*Release rate constant (k) of nifedipine:Eudragit RL100:PVP K30 microspheres

Table 8 Release rate constant (k) of nifedipine microspheres over 2 h in simulated gastic fluid without enzyme (pH 1.2)

			k ($min^{-1/2}$)				
			Nifedipine:Eudragit RS or RL100:PVP K30				
Temperature (°C)	Nifedipine intact	Nifedipine spray-dried	1:10:0	1:8:2	1:5:5	1:2:8	1:0:10
55°C 5%(w/v)	2.0568	2.5777	0.4128 *0.7304	0.7491 1.4982	1.0085 1.6777	1.2613 2.3334	1.8841 1.8841
10%(w/v)	-	2.5040	0.3506	0.7530	1.4032	1.3351	1.6397
65°C 5%(w/v)	-	-	0.3541	0.4507	1.1308	1.7152	1.9921
10%(w/v)	-	-	0.2124	0.5181	1.4055	1.4821	2.2328
75°C 5%(w/v)	-	-	0.2845	0.3880	0.9864	1.4149	1.8448
10%(w/v)	-	-	0.2774	0.3279	0.9910	1.3934	1.8492

*Release rate constant (k) of nifedipine:Eudragit RL100:PVP K30 microspheres

drug release data into a single figure which enables a ready comparison to be made between a large number of formulations. Additionally, it can be theoretically related to *in vivo* data. There were many investigations using the DE values to evaluate the sustained release solid dispersions of paracetamol and rifampicin (Ammar and Khalil, 1997), controlled release microspheres of nifedipine (Chowdary and Ramesh, 1995).

The area under dissolution curve was calculated by the trapezoidal rule. The DE over 24 hour dissolution in simulated intestinal fluid and simulated gastic fluid without enzyme in all systems were determined and summarized in Tables 5-6. The two way analysis of variance (ANOVA, $\alpha = 0.05$) of the DE are presented in Tables 58-62 (in Appendix E). From the two way ANOVA of DE, it was found that the inlet temperature, the mixing ratio and the temperature-ratio interaction were significantly affected the DE in all systems of nifedipine microspheres.

7.2 Kinetics and release rate constants

As depicted in Figures 39-50 all dissolution profiles demonstrated that Eudragit RS and Eudragit RL, zwitterionic polymers with quaternary ammonium groups had remarkable retardant properties. They both show low solublility in water, but are capable of swelling without disintegration at pH 1.2-7.4 (Ammar and Khalil, 1997). To investigate the kinetics of nifedipine release from microspheres, drug release data were plotted according to zero-order kinetics, first-order kinetics and the Higuchi equation. The data were analyzed according to

different models to obtain release rate constant (k) and the regression coefficient or coefficient of determination (R^2) was determined to demonstrate the linearity as shown in Tables 51-54 and 55-58. (in Appendix D).

Among all the models tested, the model for diffusion-controlled release given by Higuchi (1963) appeared to provide the best fits for all the investigated formulations (Tables 51-54 in Appendix D and Figure 53-55 in Appendix C).

The release rate constants according to the Higuchi diffusion-controlled models were summarized and shown in Tables 7-8. These results confirmed that the process of dissolution of nifedipine from these systems was a diffusion-controlled process. The dissolution rate constants of all systems were analysed by the two way ANOVA (α = 0.05) of the k are presented in Tables 63-66 (in Appendix E). It was found that inlet temperature, mixing ratio and temperature-ratio interaction were significantly affected the release rate constant in all systems.

7.3 Dissolution study of spray dried nifedipine

The dissolution profile of spray dried nifedipine was demonstrated to show an improvement as compared to intact drug both in simulated intestinal fluid without enzyme (pH 7.5) and in simulated gastic fluid without enzyme (pH 1.2) and as depicted in Figures 37 –38. This might be possibly attributed to smaller particle sizes resulting from spray drying process and hence larger surface area.

From powder XRD patterns (Figure 13), spray dried nifedipine still existed in crystalline form. In contrast to some spray dried drugs, i.e., clarithromycin (Yonemoshi.et al, 1999) and ursodeoxycholic acid (Ueno et al, 1998) which changed into an amorphous state giving an enhanced dissolution rate.

7.4 Effect of nifedipine-Eudragit RS100-PVP K30 mixing ratios

From Tables 5-6, the maximal dissolution efficiency was obtained from the 1:0:10 mixing ratio, which referred to the microspheres containing no Eudragit RS100 content as 80.88% and 81.50% for 5 and 10% spray concentration systems at 55°C ($p < 0.05$). As the content of PVP K30 in combined carriers increased from 0, 20, 50, 80 and 100% the DE parameters clearly increased from 31.37 to 80.88% and from 33.83 to 81.50% in 5 and 10% spray concentration systems, respectively. Many efforts focused on polymeric blend in the formulation of delay or sustained release, using an insoluble matrix and a water-soluble component. In this case the drug was released through pores presumably created by the dissolution of the water-soluble phase ; the morphology and interactions in the blend were of primary importance to the drug release (Chowdary and Sankar, 1997, Chowdary and Ramesh, 1995)

Eudragit RS100 is a zwitterionic copolymer that was reported to sustain the drug release most efficiently over a certain period (Kislalioglu et al, 1991). Eudragit RS is capable of swelling in aqueous media at pH 1.2-7.4, and due to its

permeability, diffusion occurred (Ammar and Khalil, 1997). PVP K30, a water-soluble polymer, improved nifedipine dissolution via solid dispersions as reported by Sugimoto et al. (1980). Addition of PVP K30 into nifedipine-Eudragit RS100 microspheres increased nifedipine release via channel formation. As PVP K30 dissolved in the dissolution medium, nifedipine in the Eudragit matrix was diffused and dissolved into the dissolution medium via the channels. It was thought that the channels formed by the dissolving of PVP K30 corresponding to openings, cracks, and intergranular spaces in the matrix granules (Yuasa et al., 1991 and 1993). As shown in Table 4, the particle size of microspheres also showed an influence to a certain extent to drug dissolution. The finer particle sizes were obtained when the PVP K30 content increased, thus synergistically increase the release.

The release rate constants in Table 7 and 8 also showed that the highest rate constant was obtained from the microspheres containing no Eudragit RS100 as 2.136 min^{-1} at 75°C from 10% spray concentration in simulated intestinal fluid without enzyme (pH 7.5) ($p < 0.05$). The release rate constants in simulated gastic fluid without enzyme (pH 1.2) were found obviously lower than those in simulated intestinal fluid.

7.5 Effect of inlet temperature in spray drying process

From Table 5 and 6 it was obvious that DE values decreased as the inlet temperature in spray drying process increased both in 5 and 10% spray concentrations ($p < 0.05$). At the nifedipine:Eudragit RS100:PVP K30 of 1:0:10 ratio, the DE reduced from 80.88% (55°C) to 71.78% (65°C) and 60.25% (75°C). The release rate constants in Table 7 and 8 also showed similar results that the release rate constants decreased as the inlet temperature increased. Since from Table 4, it was shown that the microspheres prepared at high inlet temperatures had rather smaller particle sizes as compared to those at lower inlet temperature, it could be said that in this study, particle size of microspheres showed no enhancing effect on the dissolution rate of nifedipine from microspheres. As reported by Master (1985), high inlet temperature and high feed spray rate produced particles with a slower dissolution rate due to ineffective atomization.

7.6 Effect of concentration of spray solution

In simulated intestinal fluid without enzyme, the higher spray concentration (10% spray solution) in the spray drying process resulted in nifedipine microspheres with higher DE and k values ($p < 0.05$). At the same inlet temperature (55°C) the DE values of the 5% solution system ranged between 31.37-80.88%, whereas they ranged between 33.83-81.50% in the 10% solution.

The release rate constants in the 5% solution ranged between 1.1540-1.8636 min^{-1} while they ranged between 1.2111-1.9533 min^{-1} in the 10% solution. The similar results were also obtained in the dissolution in simulated gastic fluid without enzyme from Table 4. The 10% solution produced larger microspheres which showed higher DE and higher release rate constants. This discrepancy could be explained that larger particles produced from high concentration possessed higher porosity than particles prepared from lower spray concentration.

7.7 Dissolution study of nifedipine-Eudragit RL100-PVP K30 microspheres

To investigate the effect of type of Eudragit polymers, Eudragit RL100 was used to prepare nifedipine microspheres with the same instrumental and process settings; 55°C inlet temperature and 5% spray concentration, Eudragit RL100 and RS100 are similar zwitterionic copolymers having ammonium neutral methacrylic acid ester ratios of 1:20 in Eudragit RL100 and 1:40 in Eudragit RS100. This difference rendered Eudragit RL100 more hydroplitic and more permeable, thus showed less retardant effect than Eudragit RS100 (Rafice-Tehrani and Sadegh-Shobeiri, 1995).

As expected, nifedipine release from Eudragit RL microspheres were higher than Eudragit RS100. This was demonstrated by both DE and Higuchi rate constants ($P < 0.05$). From Table 5 and 6, the DE in Eudragit RL microspheres ranged between 41.07-80.88% (pH 7.5) and 10.64-38.97% (pH 1.2),

whereas the Eudragit RS microspheres had the DE ranged 31.37-80.88% (pH 7.5) and 8.01-38.97% (pH 1.2). The release rate constant of Eudragit RL microspheres were 1.5349-1.8636 min^{-1} (pH 7.5) and 0.7304-1.8841 min^{-1} (pH 1.2), whereas Eudragit RS100 had the release rate constants ranged between 1.1540-1.8636 min^{-1} (pH 7.5) and 0.7304-1.8841 min^{-1} (pH 1.2). This less retarding effect of Eudragit RL100 could be obtained in this study inspite of the increase in numbers of larger microspheres obtained in the system of Eudragit RL100 (Table 4). This results were much noticeable in the microspheres with higher content of Eudragit RL100 than those with high PVP K30 content.