

CHAPTER IV

RESULTS

1. Preparation of Nifedipine Solid Dispersion.

Nifedipine, in nature, is yellow crystalline powder and odourless. Two polyethylene glycols (PEG4000 and PEG6000) and three poloxamers (poloxamer188, poloxamer288, poloxamer407) are white-creamy colour with wax-liked surface. Cyclodextrins (β -cyclodextrin and 2-hydroxypropyl- β -cyclodextrin) are easily brittle, non-hygroscopic and free-flowing powder.

Most nifedipine solid dispersions are easily prepared except melting method for 2-hydroxypropyl- β -cyclodextrin and β -cyclodextrin and solvent method for 2-hydroxypropyl- β -cyclodextrin. For the solvent method, 2-hydroxypropyl- β -cyclodextrin could not dissolve in absolute ethanol as in PEGs and poloxamers systems. Methanol was therefore used to dissolve nifedipine and 2-hydroxypropyl- β -cyclodextrin in this method. The kneaded products of 2-hydroxypropyl- β -cyclodextrin and nifedipine at most ratio were wet more than kneaded mass of other carrier with nifedipine. These products then were dried in an incubator and pulverized to obtain brittle and free flowing powder.

The dispersions of PEGs and poloxamers were wax-like, therefore slightly hard to be pulverized. All dispersions were pale yellow powder.

2. The Calibration Curve.

Calibration curve of nifedipine in simulated gastric fluid without pepsin using linear regression plot is presented in appendix A. A high coefficient of determination (r^2) exhibited that the data were fit with this linear plot

3. Dissolution Study.

The summarized of dissolution results are shown as the T80% (Table 7), The dissolution profiles of nifedipine solid dispersions and treated pure drug by various methods namely physical mixing, kneading, solvent, and melting are presented in Figure 16-41. For the aim of fast release behavior of nifedipine system, the initial dissolution rate constant at the first 30 min. were examined. The rate constant was calculated by the Sigma-minus method (Martin, 1993) since it was found that the dissolution profiles fit the first order plot (Appendix F). The dissolution rate constants of all systems were given in Appendix E. The two way analysis of variance ($\alpha = 0.05$) of the rate constants are presented in Appendix D. All detailed experimental data were given in Appendix B and C.

From two way analysis of variance of dissolution rate constants at initial 30 min, it was found that method, ratio and method-ratio interaction were significantly different in PEGs, and poloxamers system but in cyclodextrin system, the statistically significant difference were found in only method and ratio.

The results from dissolution profiles and dissolution rates constant revealed that poloxamers, in general, gave the fastest dissolution followed by PEGs and cyclodextrins respectively.

3.1 Dissolution studies of nontreated pure drug and treated pure drug.

The dissolution profiles of pure drug treated by various methods was found that nontreated nifedipine showed better dissolution profile than that of other carrier systems (Figure 16). The reason was possibly the agglomerate of nifedipine particles in treated drug caused a lower specific surface area, hence, poorer dissolution profiles. Additionally, the dissolution rate constants between treated drug and nontreated drug were similar except nifedipine treated by solvent method was negligible higher than that of nontreated drug (Appendix E).

3.2 Dissolution studies of nifedipine-PEG4000 solid dispersions.

The maximum initial dissolution rate constant at 30 min was obtained at ratio 1:10 by melting method followed by 1:10 solvent method and 1:5 melting method, respectively. However these three values of dissolution rate constant were not statistically significant difference ($p > 0.05$). The summary of two way analysis of variance is shown in Appendix D.

Comparing within the individual methods, the ratio of 1:10 mostly showed the highest dissolution rate constants whereas the ratio 1:1 usually gave the lowest rates. Among the same ratio, melting method was the most favorable preparation procedure for the system with PEG4000.

From the dissolution profiles (Figure 17-21), it was found that physical mixtures showed lower dissolution profile than nontreated pure nifedipine in every ratio. The other methods, behaved differently, gave the better profiles than nontreated pure nifedipine at every ratio. Consistency with the dissolution rate constants, the ratio of 1:10 exhibited the best dissolution profiles.

3.3 Dissolution studies of nifedipine-PEG6000 solid dispersions.

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Similarly to the system of PEG4000, the solid dispersions of nifedipine-PEG6000 gave the highest dissolution rate constants at the ratio of 1:10 for solvent, melting and kneading methods respectively. All three values were not statistically different ($p > 0.05$). It should be pointed out that for the maximum dissolution rate constants of nifedipine-PEG4000 was the melting method whereas for the nifedipine-PEG6000 the maximum rate was the solvent method both at the same ratio of 1:10 (Figures 21-24).

The solid dispersions of nifedipine-PEG4000 and nifedipine-PEG6000 had the dissolution profile in common. From the dissolution profiles, the ratio 1:10 in all methods gave the highest dissolution rate constant except kneading method. For the kneading method, the ratio of 1:5 was the best profile because it gave the higher percent dissolved than that of the ratio of 1:10 after 200 minutes. In the physical mixtures, it was found that the profile of ratio 1:3 was higher than the profile of nontreated pure nifedipine whereas the other ratios showed poor dissolution profiles. However these poor profiles still show that nifedipine dissolve rapidly in the initial period of dissolution profiles.

3.4 Dissolution studies of nifedipine-poloxamer188 solid dispersions.

In poloxamer188 system (Figure 25-28), the ratio of 1:3 melting method give the highest dissolution rate constant among all treatments of poloxamer188 and all carriers. The following ranks were the ratios and methods of 1:5 melting, 1:10 kneading, and 1:10 solvent respectively. The ratio of 1:10 solvent method was not statistically different from kneading 1:10 ($p > 0.05$) and melting method at the ratio of 1:5 but it was different from 1:3 melting method ($p < 0.05$) (Figure 27).

From the dissolution profile point of view, the ratios of 1:10 solid dispersion prepared by every methods showed good profile and superior to physical mixtures (Figure 27). For the melting method, the profile of 1:3, 1:5 and 1:10 seemed to superimposed on one another. For the physical mixtures, the best profile was found at the ratio of 1:5, which the other ratios initially higher than non treated pure nifedipine but showed lower in percent dissolved when they reached equilibrium.

3.5 Dissolution studies of nifedipine-poloxamer288 solid dispersions.

From two way ANOVA, it revealed that melting 1:10 gave the highest dissolution rate constant at 30 min followed by melting 1:5, solvent 1:10 and kneading 1:10. Melting method 1:10 was not significant different with melting 1:5 ($p>0.05$) but different from solvent 1:10 and kneading 1:10 ($p<0.05$). Solvent 1:10 ratio was not significantly different from kneading 1:10 ($p>0.05$). The results were shown in (Appendix D).

The dissolution profiles shown in Figure 29-32 of physical mixture depicted that all ratios of them were close to one another but a little higher than nontreated pure nifedipine. The kneading method, 1:10 ratio was obviously higher than the group of the other ratios and nontreated drug. In solvent method all ratios gave superimposed profiles except 1:1 ratio which was close to nontreated drug. Focus on the melting method, the higher group composed of 1:10 and 1:5 ratio had superior design to that of 1:3, 1:1 and nontreated pure nifedipine.

3.6 Dissolution studies of nifedipine-poloxamer407 solid dispersions.

The highest dissolution rate constant was found in 1:10 ratio melting method followed by 1:10 ratio of kneading method, 1:10 of solvent and 1:5 ratio by melting method, respectively. All of them that mentioned above were not statistically different ($p>0.05$).

From the dissolution profiles (Figures 33-36), physical mixtures were not different in each ratio and initially higher than nontreated pure nifedipine. The profile of melting method, 1:10, 1:5 and kneading method 1:10 were close to one another and obviously higher than melting method 1:3 and nontreated pure nifedipine. In solvent method, 1:10 and 1:5 ratio were superimposed but higher than group of other ratios and nontreated pure nifedipine. For kneading method, 1:10 ratio showed highest dissolution in the initial dissolution profile followed by 1:3 ratio. The ratio of 1:1 and 1:5 were almost superimposed, and higher than nontreated pure nifedipine but lower than 1:3 ratio.

3.7 Dissolution studies of nifedipine- β -cyclodextrin solid dispersion.

From two way ANOVA showed that interaction between method and ratio was not statistically different ($p>0.05$) but the difference was found within group of ratios and methods ($p<0.05$).

In testing the difference among methods, it was found that physical mixture was significantly different from kneading method. Similarly, among the ratio testing when methods were negligible, the result showed that ratio 1:5 was not significantly different from 1:10 ratio but the rest of them were significantly different. The best dissolution rate constant was kneading 1:5 ratio followed by kneading 1:10 and kneading 1:3 ratio, respectively.

From dissolution profile, Figures 37-38, all ratios in physical mixtures seemed to be lower than nontreated nifedipine, except 1:10 ratio that was initially higher than the others. The dissolution profiles of kneading method were close to one another and a little higher than nontreated pure nifedipine. However 1:10 ratio was higher than the others.

3.8 Dissolution studies of nifedipine-2-hydroxypropyl- β -cyclodextrin solid dispersion.

From two way ANOVA, only group of ratios and group of methods were significantly different ($p < 0.05$)

Within method testing, it was found that kneading method gave significant different rate constant from solvent method and physical mixture ($p < 0.05$). The testing within ratio, only 1:3 was not significantly different from 1:1 and 1:5 ratio ($p > 0.05$), but the rest of the ratios were significantly different.

The best dissolution rate constant in the group of 2-hydroxypropyl- β -cyclodextrin was ratio 1:10 of kneading method followed by 1:10 ratio of solvent method and 1:3 or 1:5 ratio of kneading method.

The dissolution profiles of physical mixture were the same as β -cyclodextrin physical mixtures that all ratios were so closely and almost superimposed to nontreated nifedipine except 1:1 ratio that seems to be the lowest profile (Figures 39-41).

In solvent method the 1:10 ratio obviously higher than the other ratios and nontreated pure nifedipine. All ratios of kneading method were closely to

one another but 1:10 seemed to be the highest and all of them were a little higher than nontreated nifedipine.

3.9 The time of 80% dissolution.

The time for 80% nifedipine dissolved ($T_{80\%}$) was chosen to be additive comparative parameter other than initial dissolution rate constant. The USP XXIII states not less than 80% of the labeled amount of nifedipine dissolved in 20 min.

As shown in Table 7, the time at 80% of nifedipine dissolved, obtained from the dissolution profiles (Figure 16-41) were presented. The $T_{80\%}$ of all systems varied from the shortest time at 15 min to as high as 1185 min. Certain systems, e.g. 1:3, 1:5, and 1:10 PEG physical mixtures, 1:10 PEG6000 physical mixture could not reach the 80% level of dissolution despite of their plateau levels.

It was interesting that solid dispersions prepared by melting method of poloxamer188 and poloxamer407 gave the shortest $T_{80\%}$ at the ratio of 1:3, 1:5 and 1:10. Moreover, poloxamer407 solid dispersions prepared by all methods, that were melting, solvent and kneading methods.as 15 min at the ratio of 1:10, gave the shortest $T_{80\%}$.

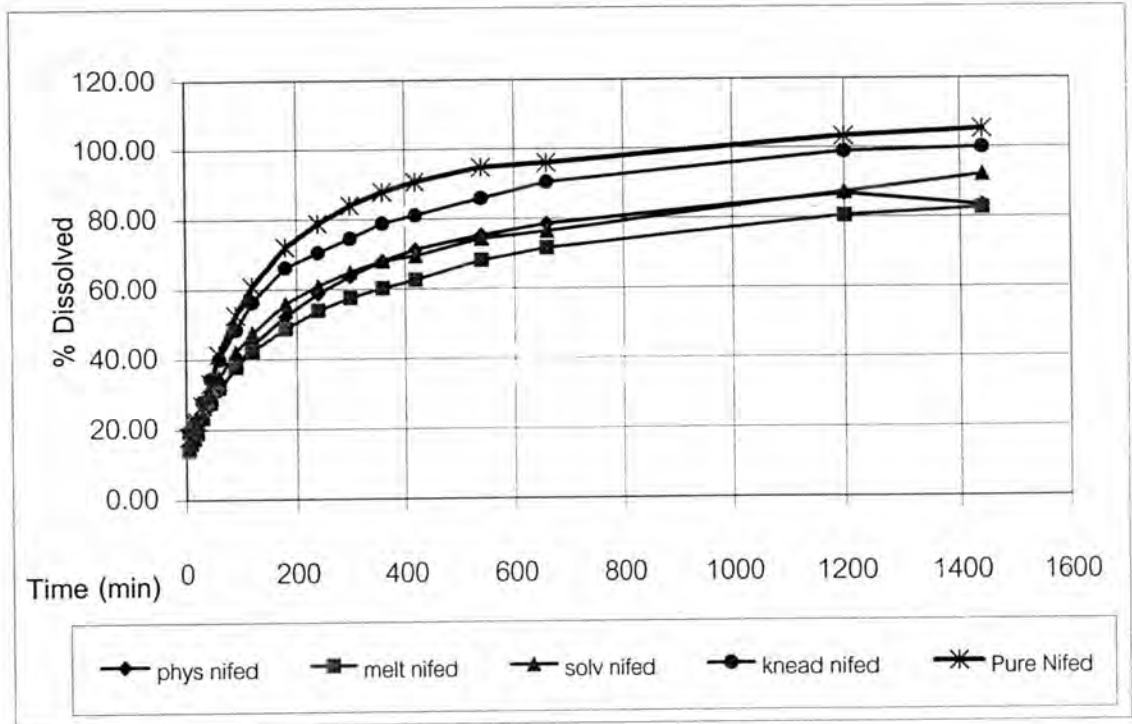


Figure 16 Dissolution profiles of treated and nontreated nifedipine

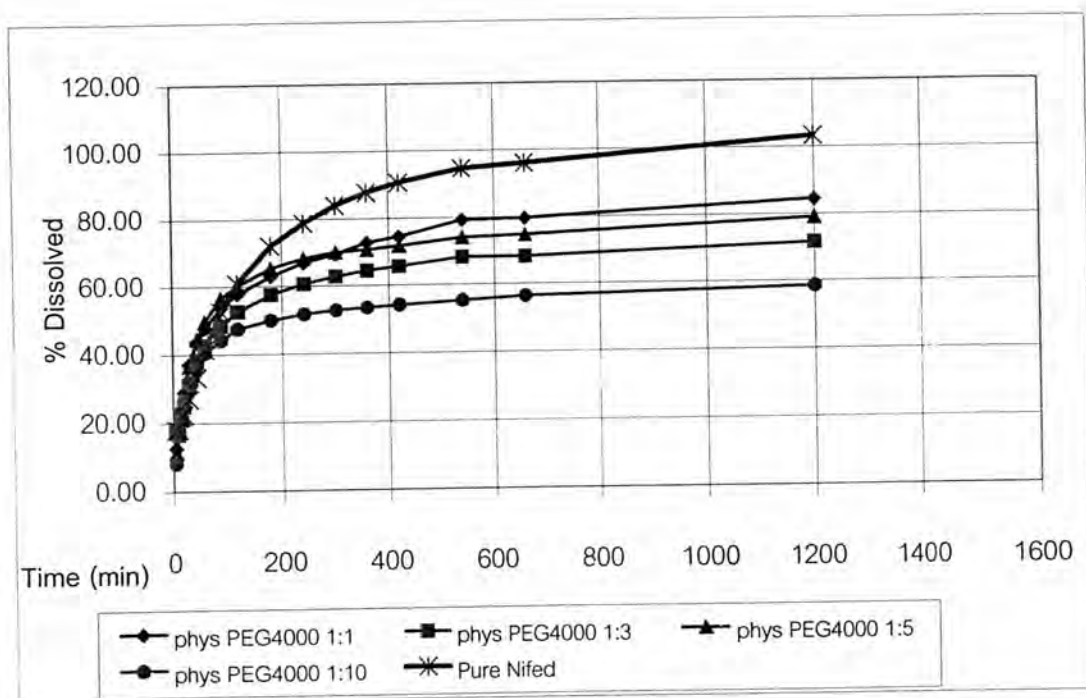


Figure 17 Dissolution profile of nifedipine from nifedipine-PEG4000 physical mixtures.

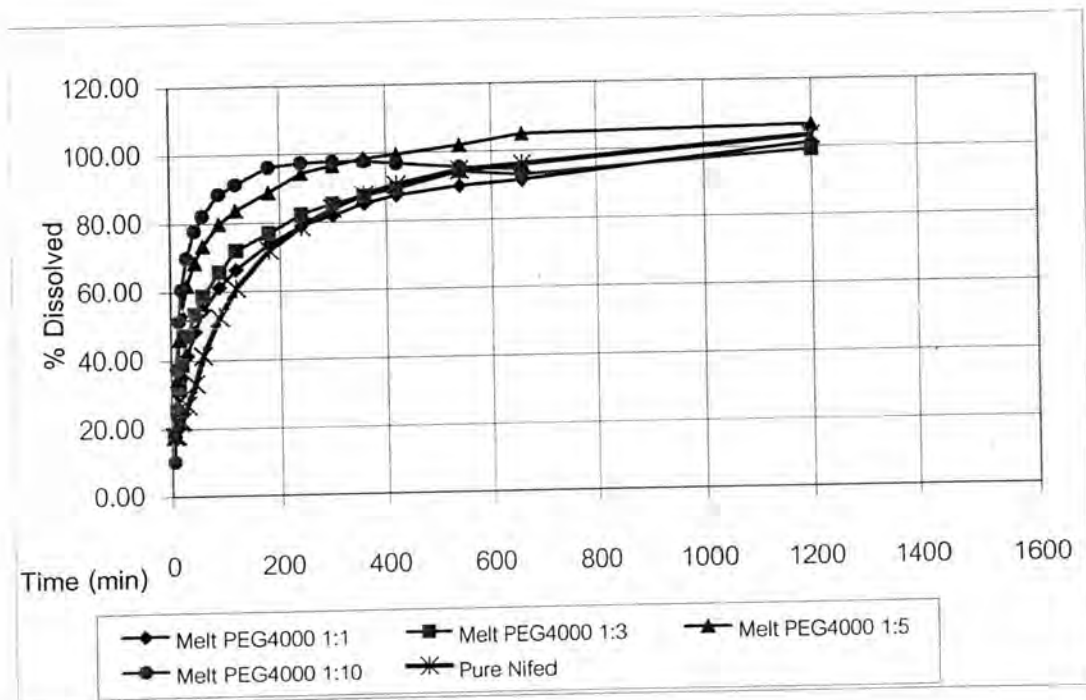


Figure 18 Dissolution profile of nifedipine from nifedipine-PEG4000 melting method.

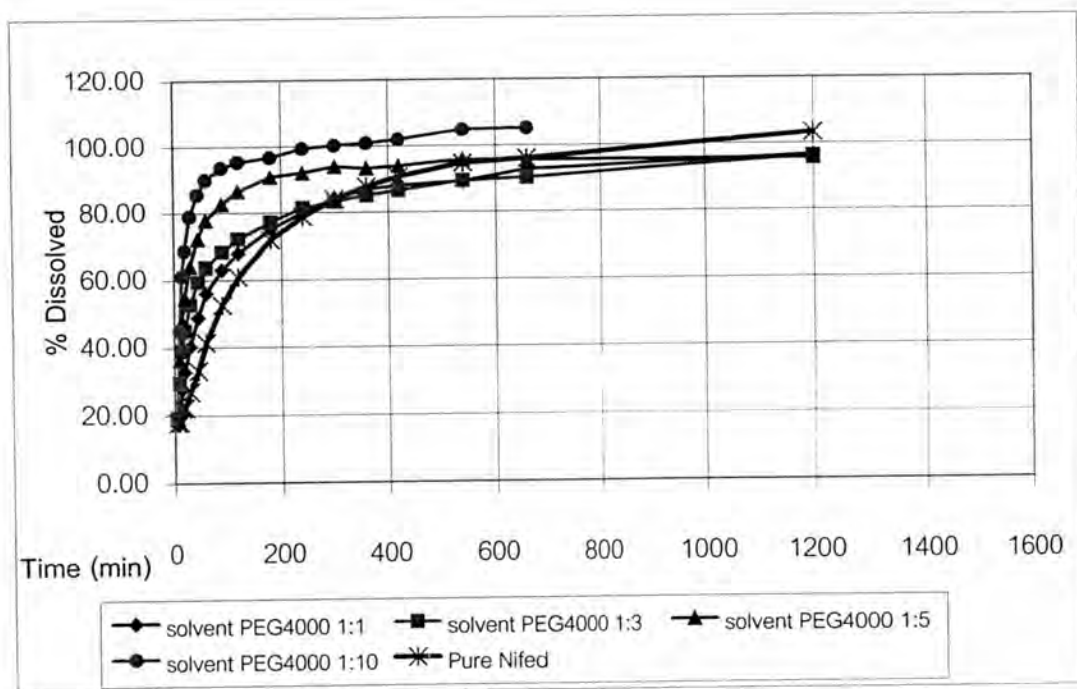


Figure 19 Dissolution profile of nifedipine from nifedipine-PEG4000 solvent method.

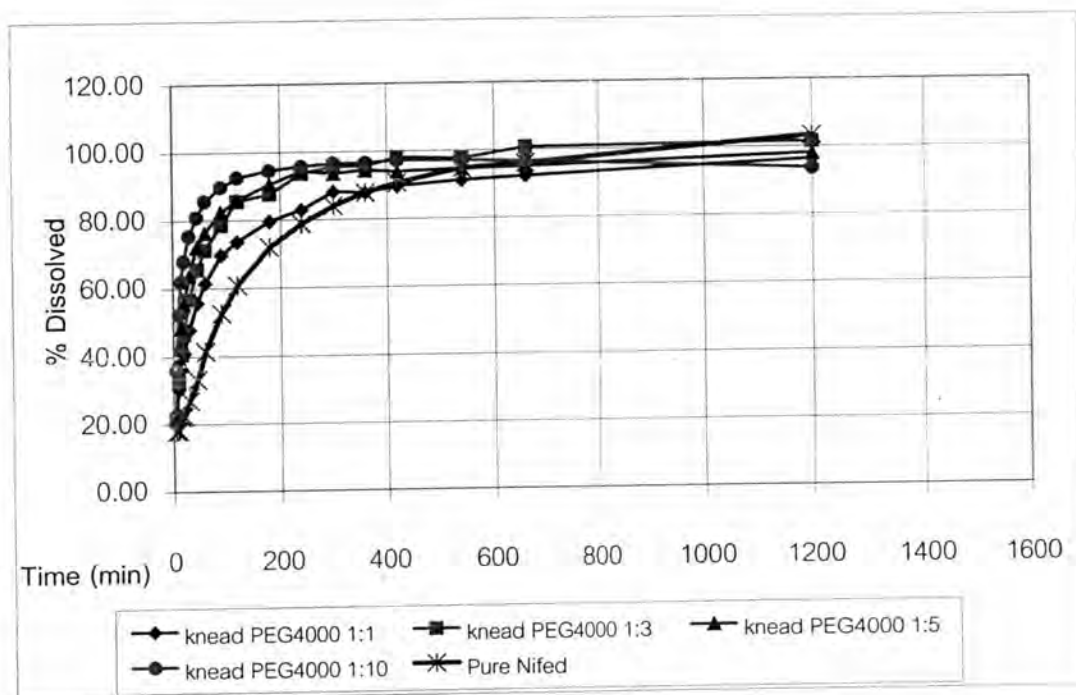


Figure 20 Dissolution profile of nifedipine from nifedipine-PEG4000 kneading method.

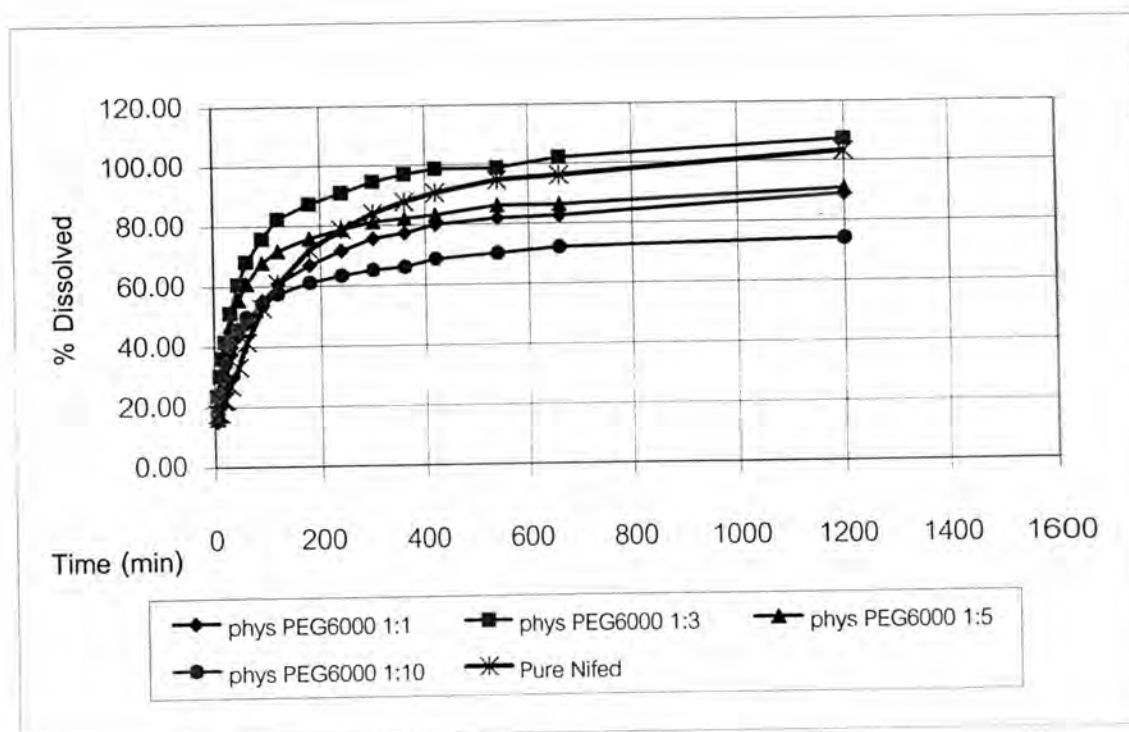


Figure 21 Dissolution profiles of nifedipine from nifedipine-PEG6000 physical mixtures.

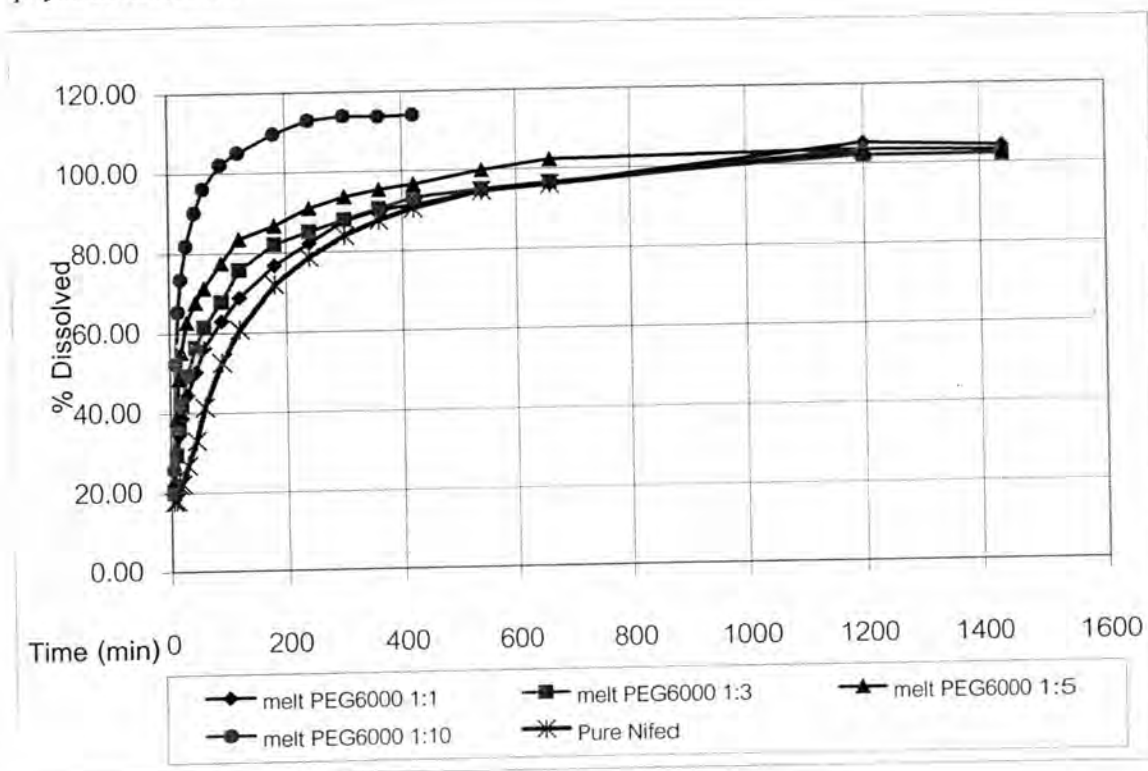


Figure 22 Dissolution profiles of nifedipine from nifedipine-PEG6000 solid dispersions prepared by melting method.

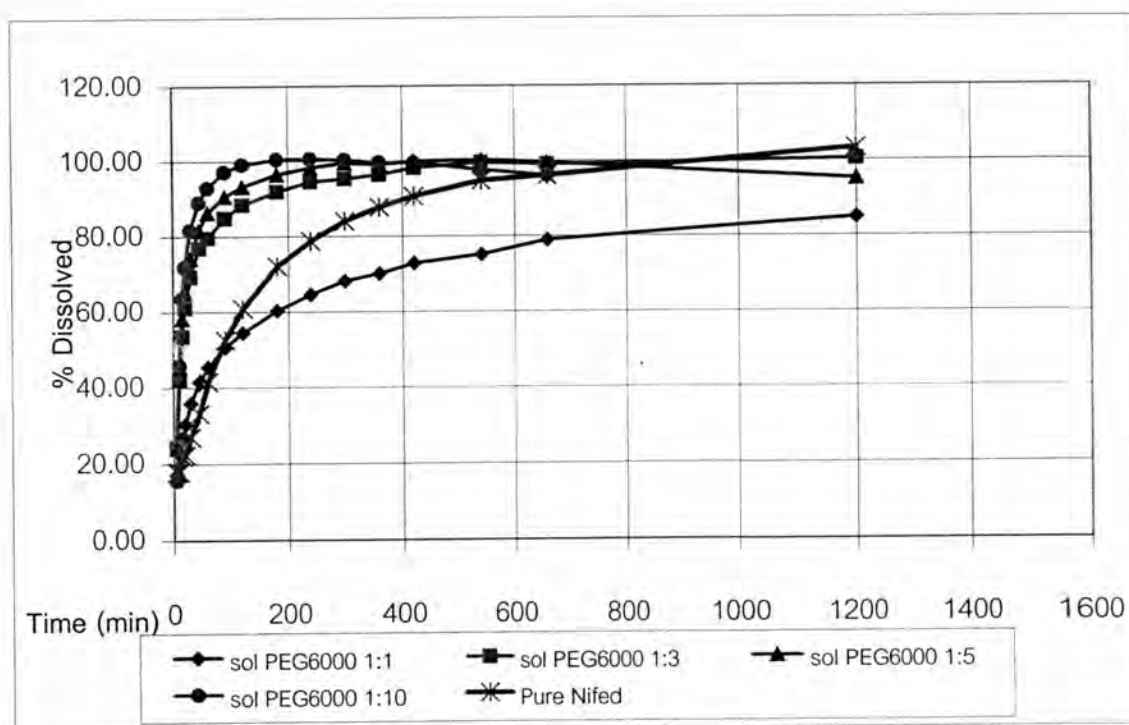


Figure 23 Dissolution profiles of nifedipine from nifedipine-PEG6000 solid dispersions prepared by solvent method.

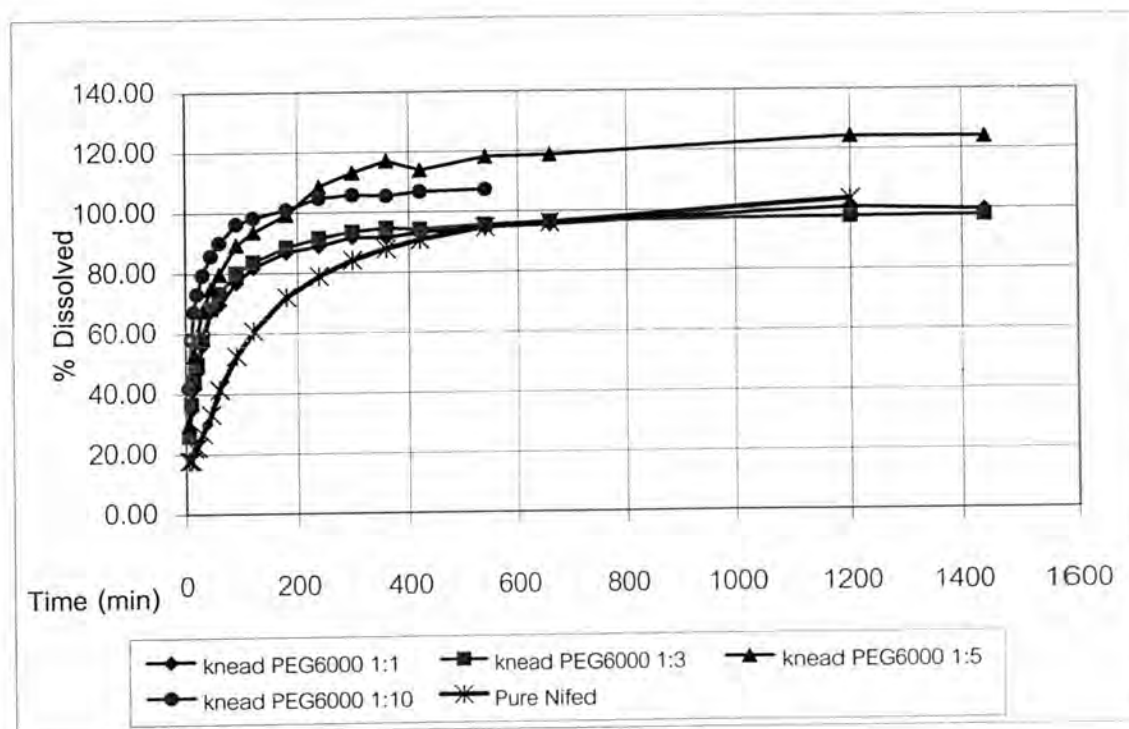


Figure 24 Dissolution profiles of nifedipine from nifedipine-PEG6000 solid dispersions prepared by kneading method.

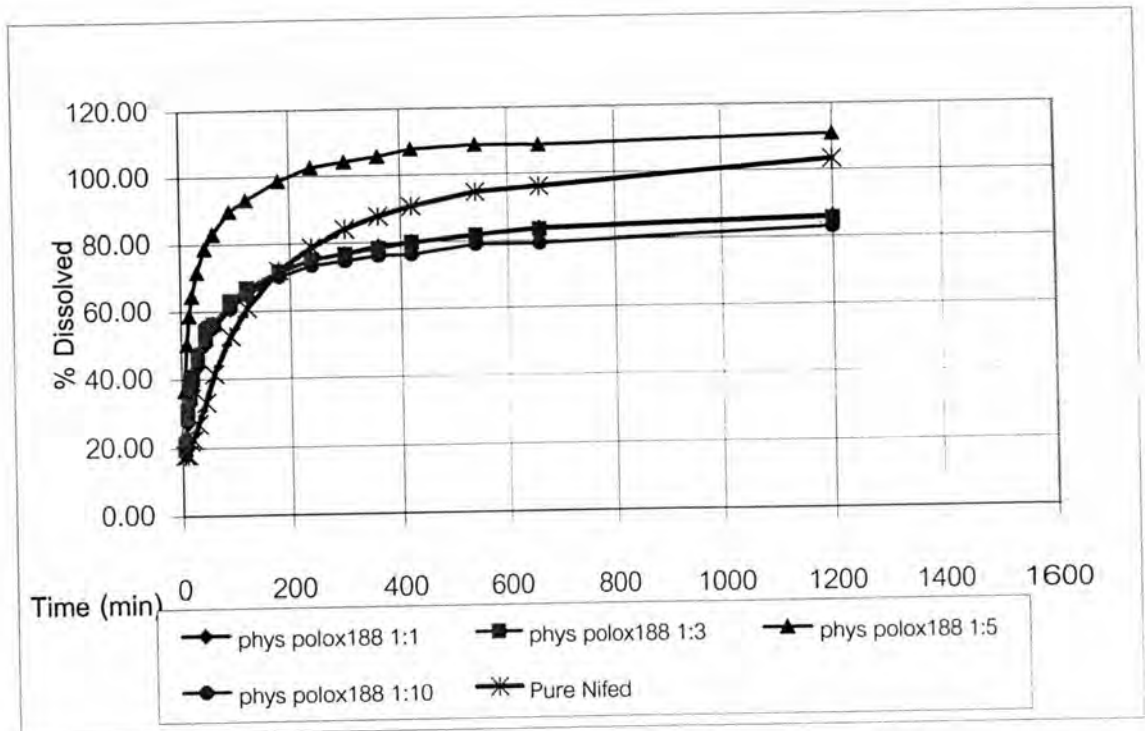


Figure 25 Dissolution profiles of nifedipine from nifedipine-poloxamer188 physical mixtures.

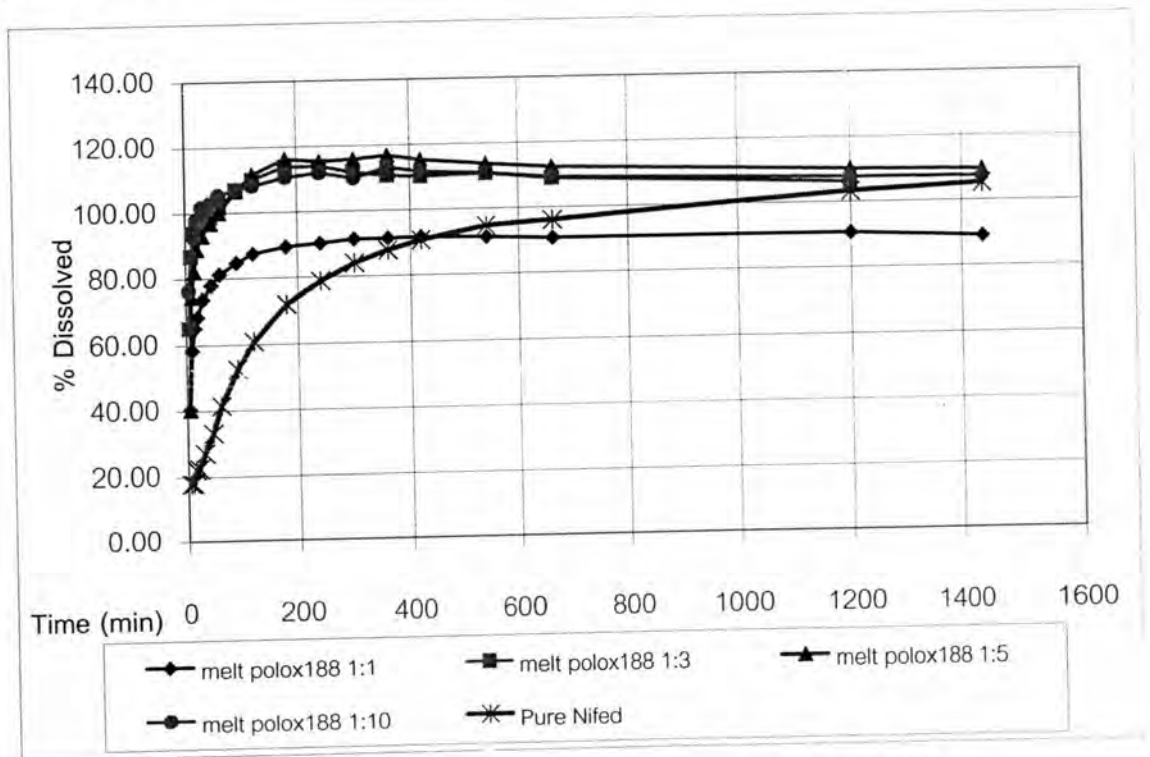


Figure 26 Dissolution profiles of nifedipine from nifedipine-poloxamer188 solid dispersions prepared by melting method.

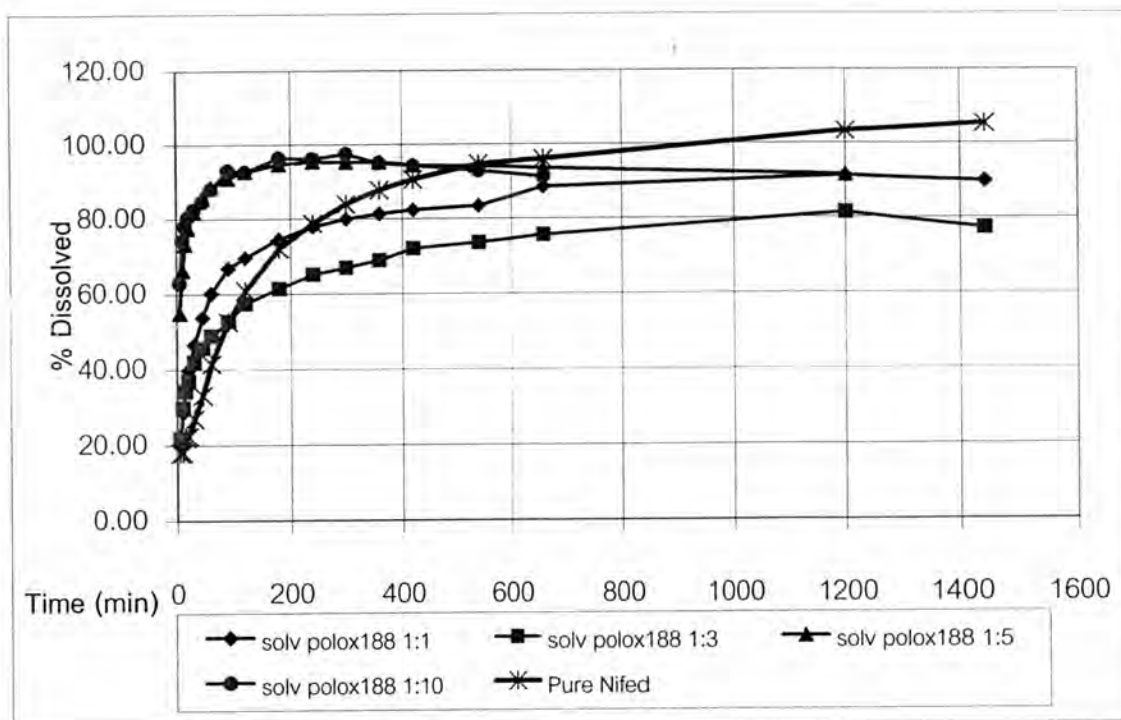


Figure 27 Dissolution profiles of nifedipine from nifedipine-poloxamer188 solid dispersions prepared by solvent method.

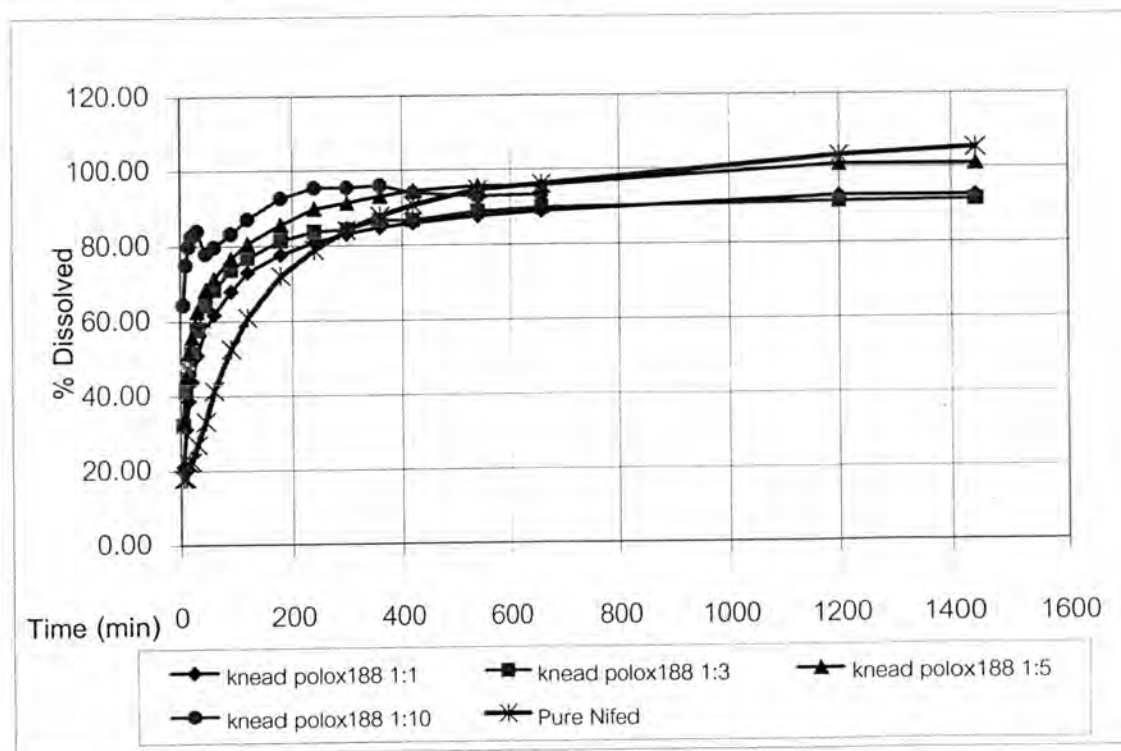


Figure 28 Dissolution profiles of nifedipine from nifedipine-poloxamer188 solid dispersions prepared by kneading method.

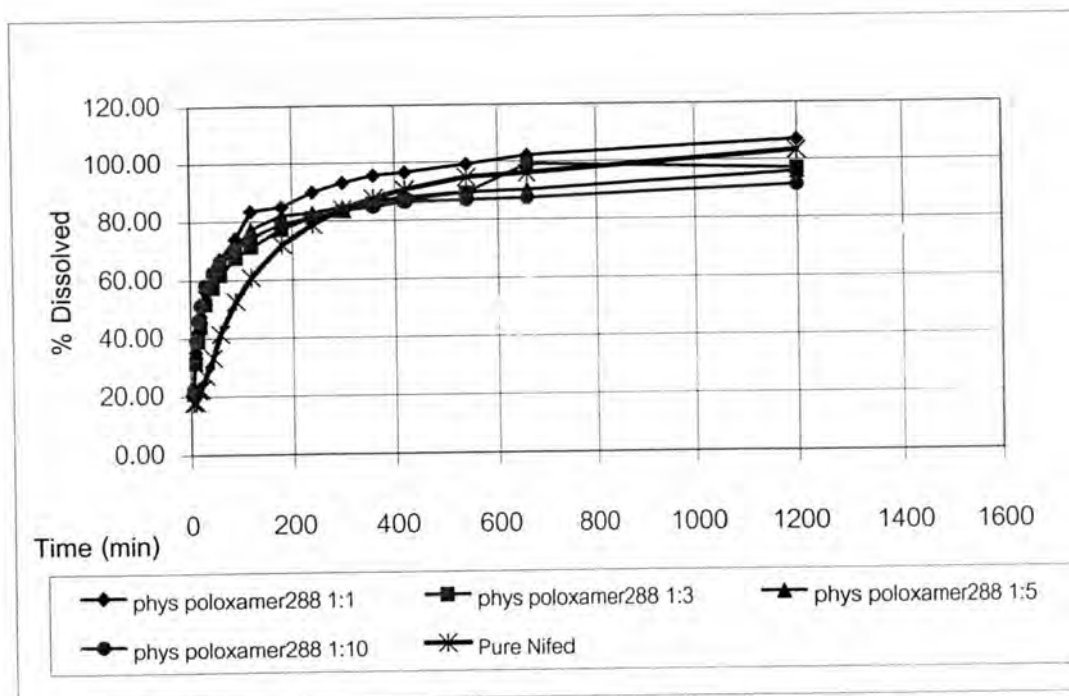


Figure 29 Dissolution profiles of nifedipine from nifedipine-poloxamer288 physical mixtures.

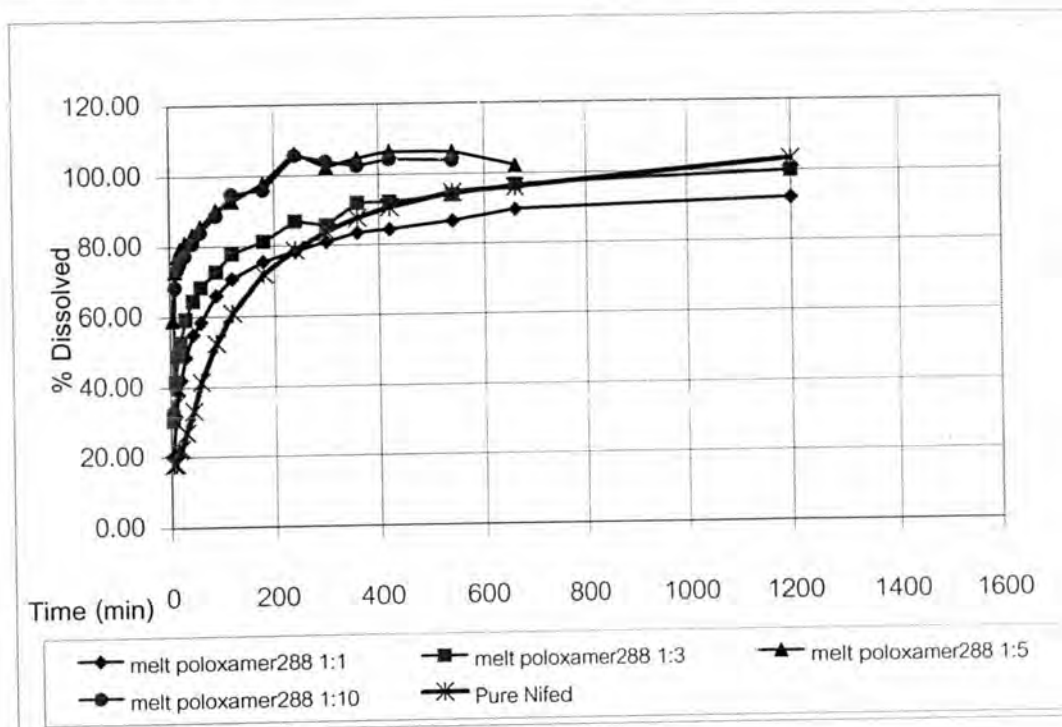


Figure 30 Dissolution profiles of nifedipine from nifedipine-poloxamer288 solid dispersions prepared by melting method.

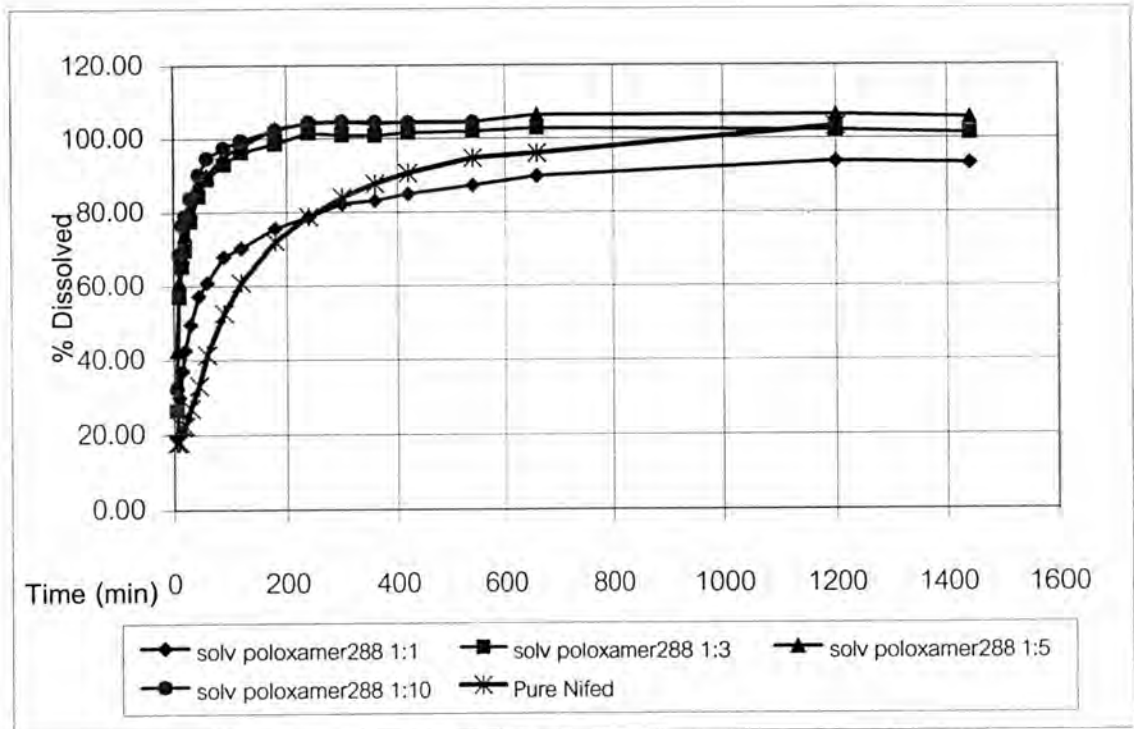


Figure 31 Dissolution profiles of nifedipine from nifedipine-poloxamer288 solid dispersions prepared by solvent method.

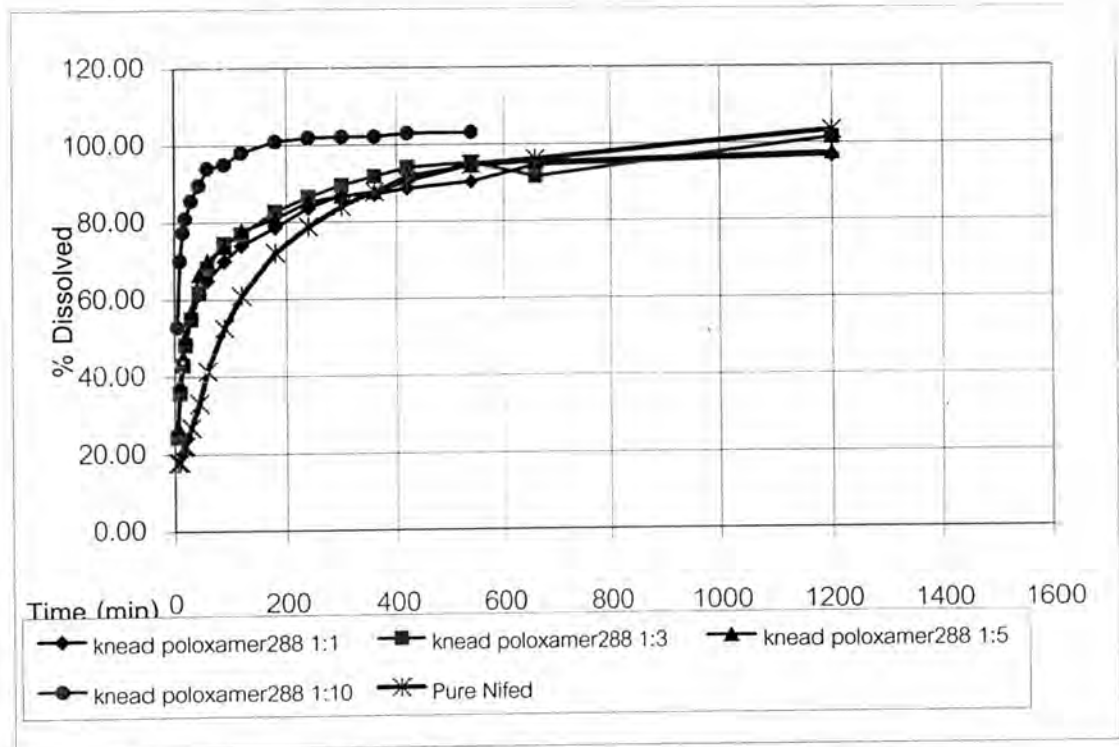


Figure 32 Dissolution profiles of nifedipine from nifedipine-poloxamer288 solid dispersions prepared by kneading method.

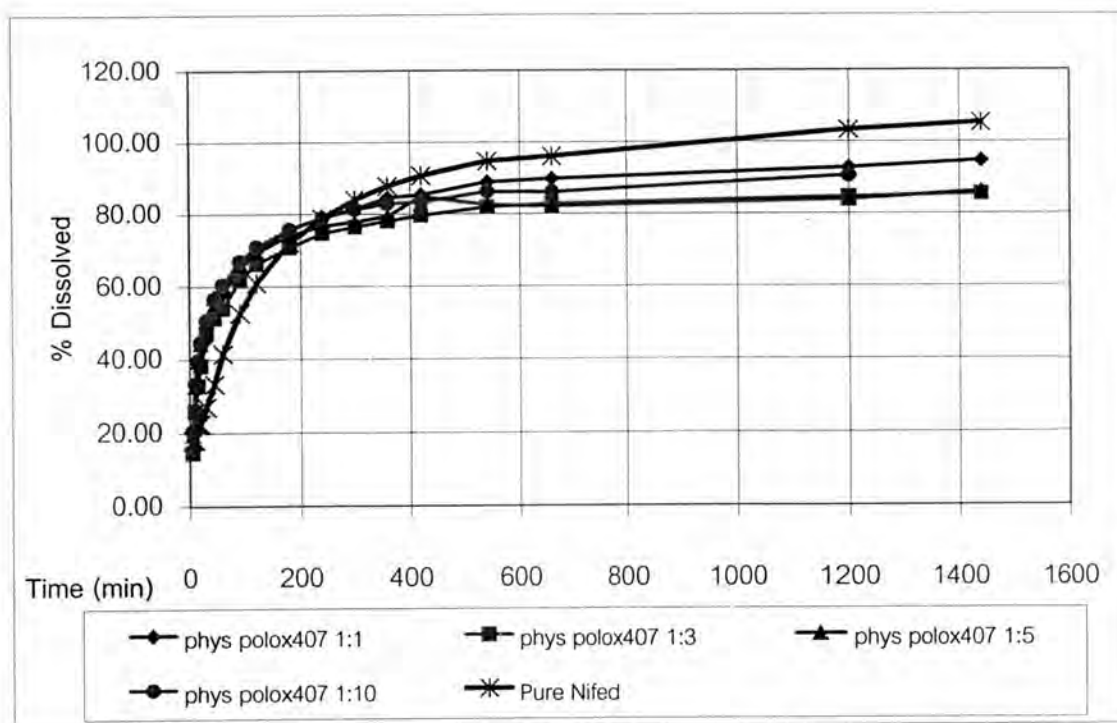


Figure 33 Dissolution profiles of nifedipine from nifedipine-poloxamer407 physical mixtures.

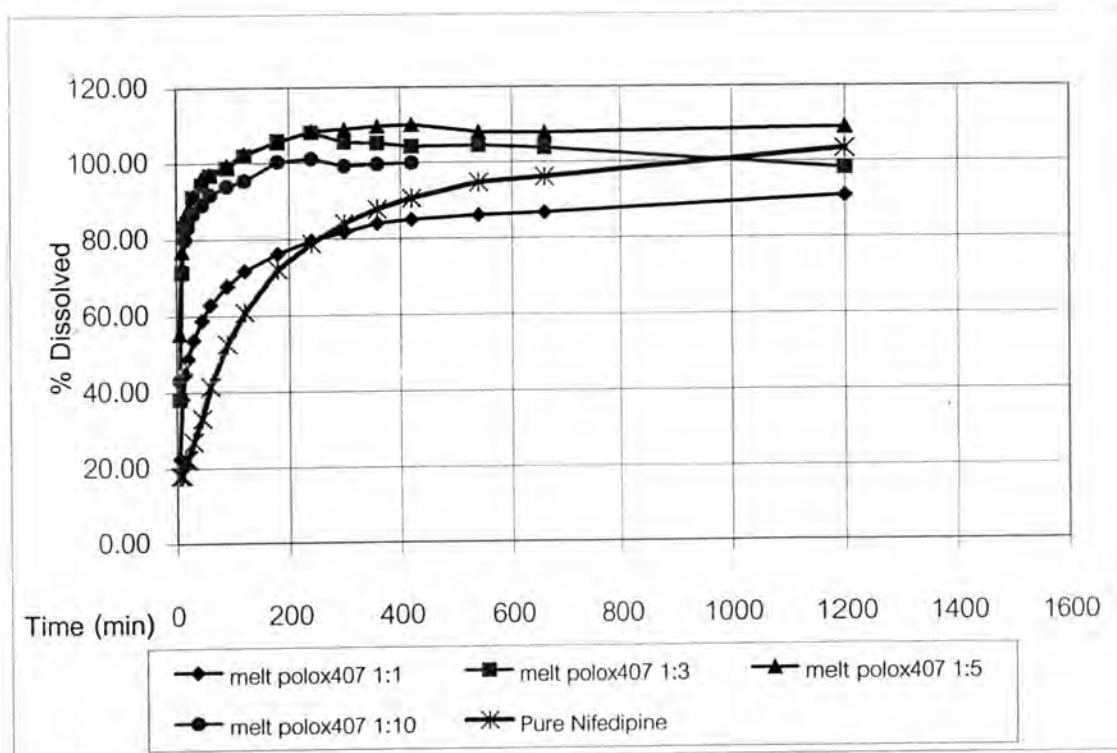


Figure 34 Dissolution profiles of nifedipine from nifedipine-poloxamer407 solid dispersions prepared by melting method.

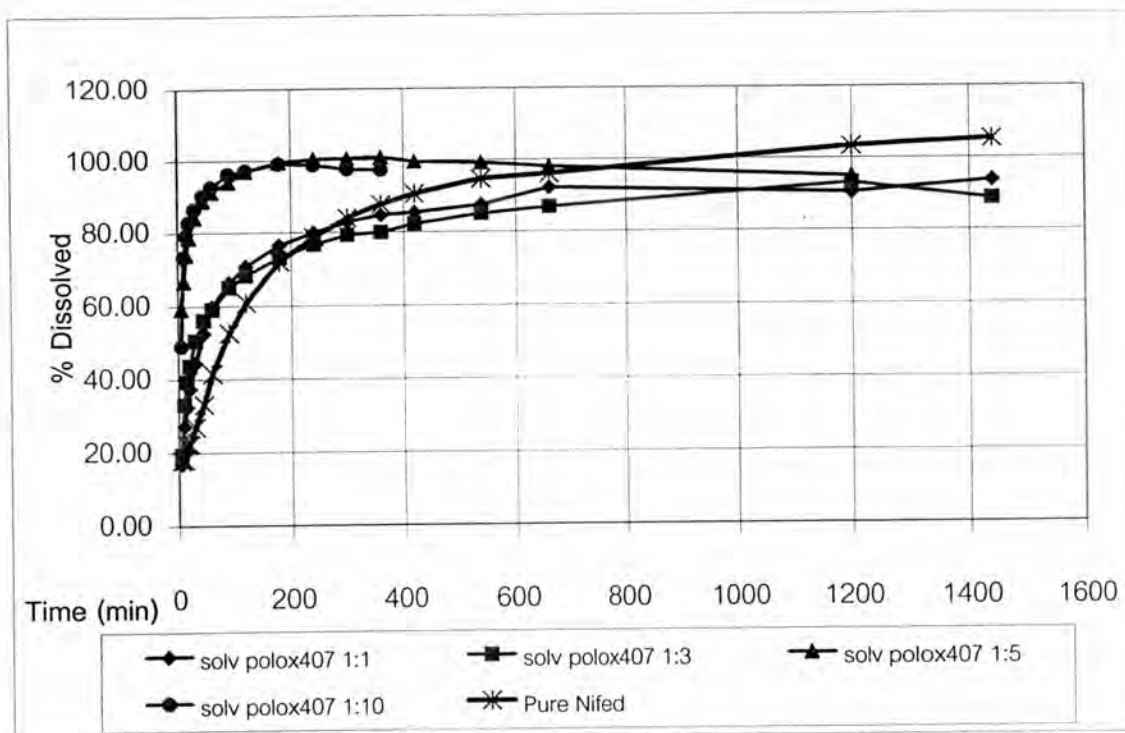


Figure 35 Dissolution profiles of nifedipine from nifedipine-poloxamer407 solid dispersions prepared by solvent method.

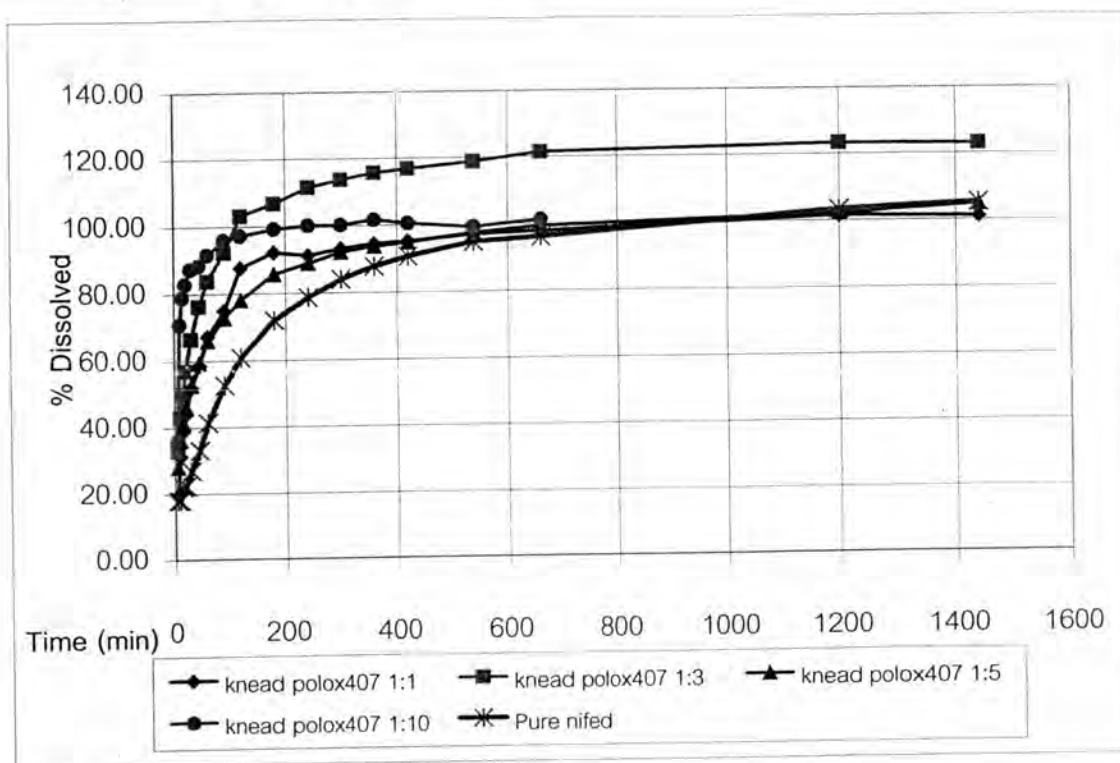


Figure 36 Dissolution profiles of nifedipine from nifedipine-poloxamer407 solid dispersions prepared by kneading method.

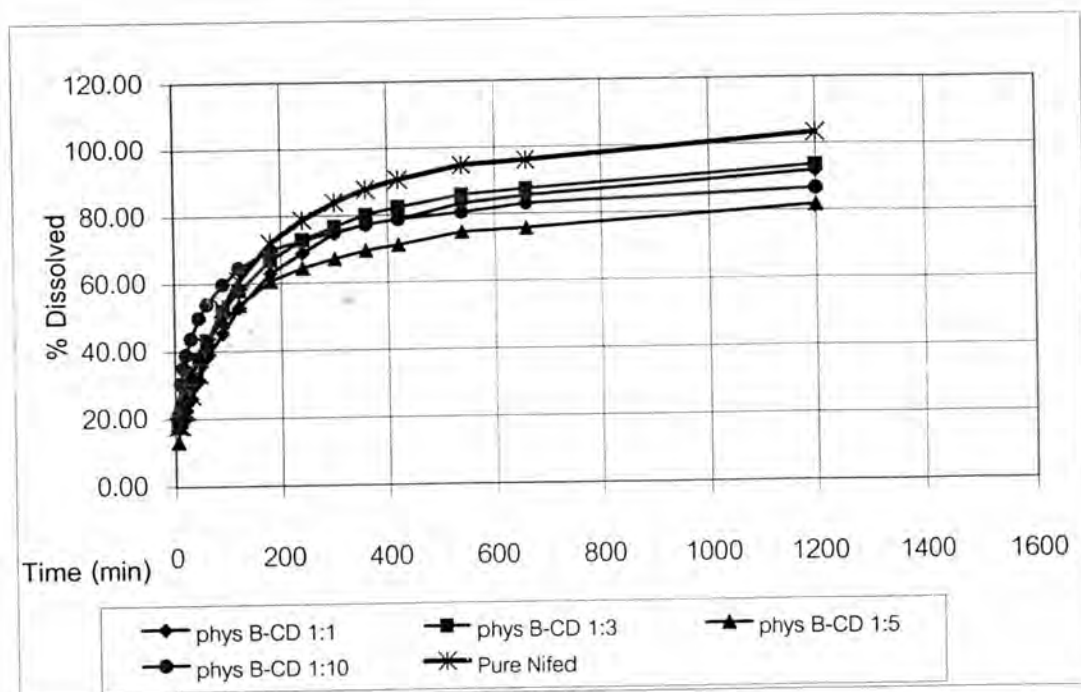


Figure 37 Dissolution profiles of nifedipine from nifedipine- β -cyclodextrin physical mixtures.

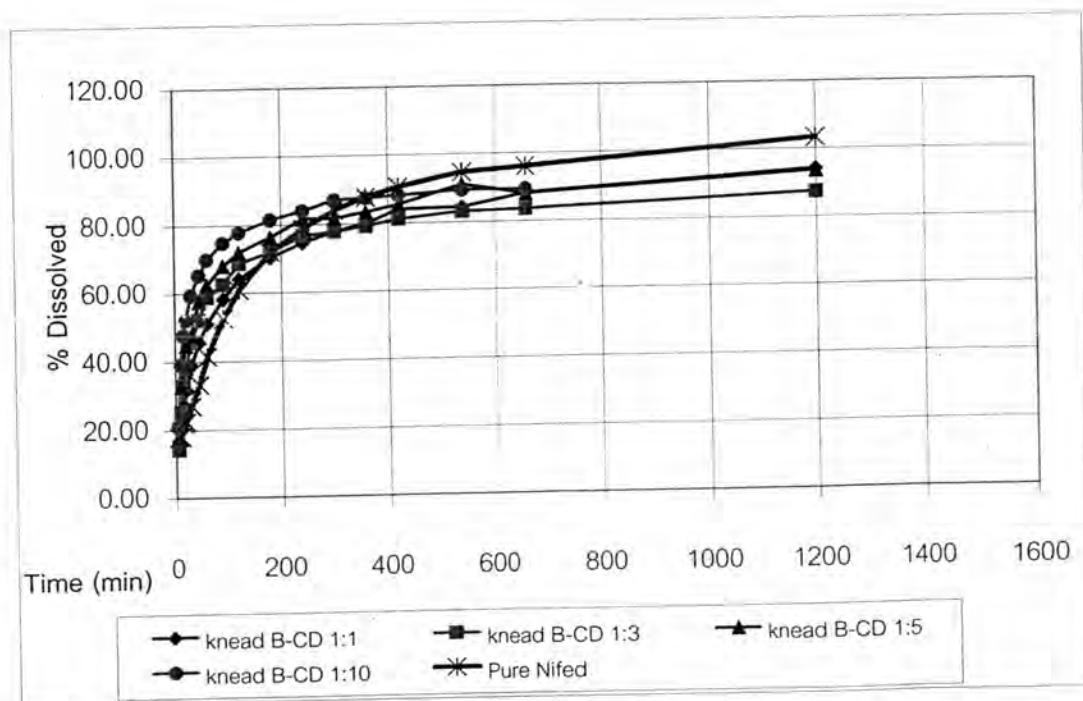


Figure 38 Dissolution profiles of nifedipine from nifedipine- β -cyclodextrin solid dispersions prepared by kneading method.

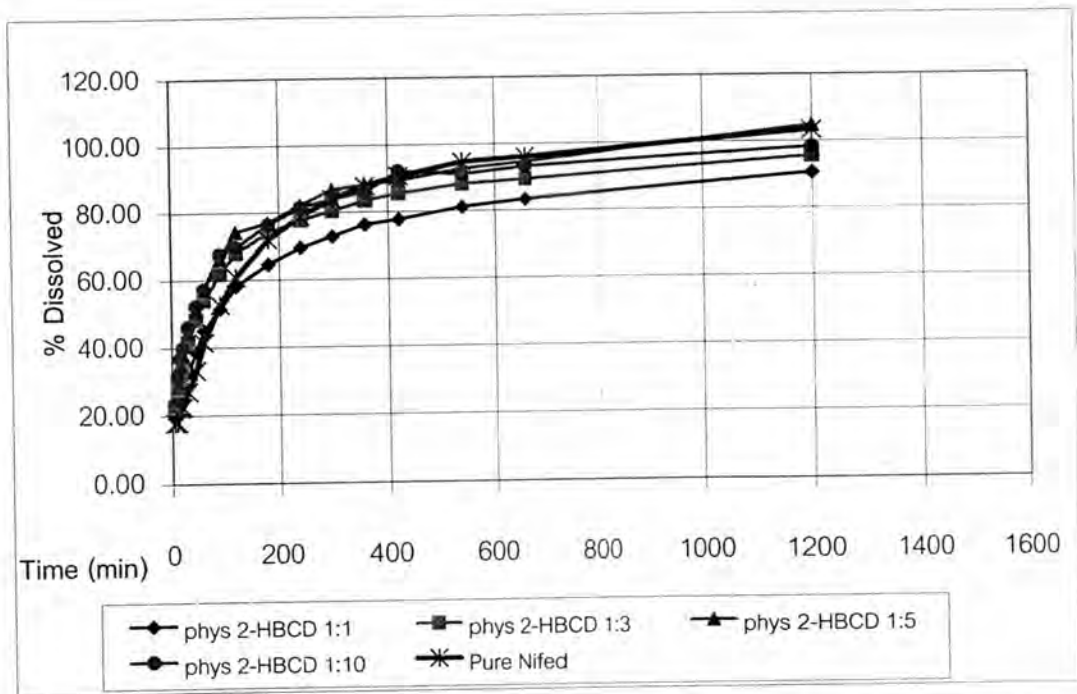


Figure 39 Dissolution profiles of nifedipine from nifedipine-2-hydroxypropyl- β -cyclodextrin physical mixtures.

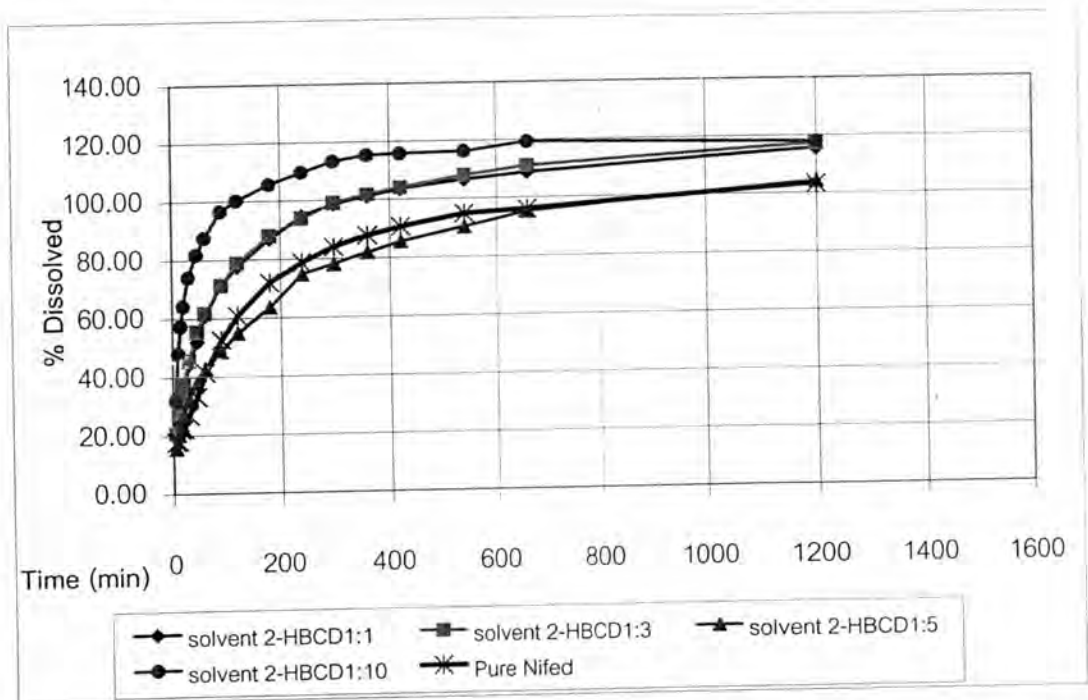


Figure 40 Dissolution profiles of nifedipine from nifedipine-2-hydroxypropyl- β -cyclodextrin solid dispersions prepared by solvent method.

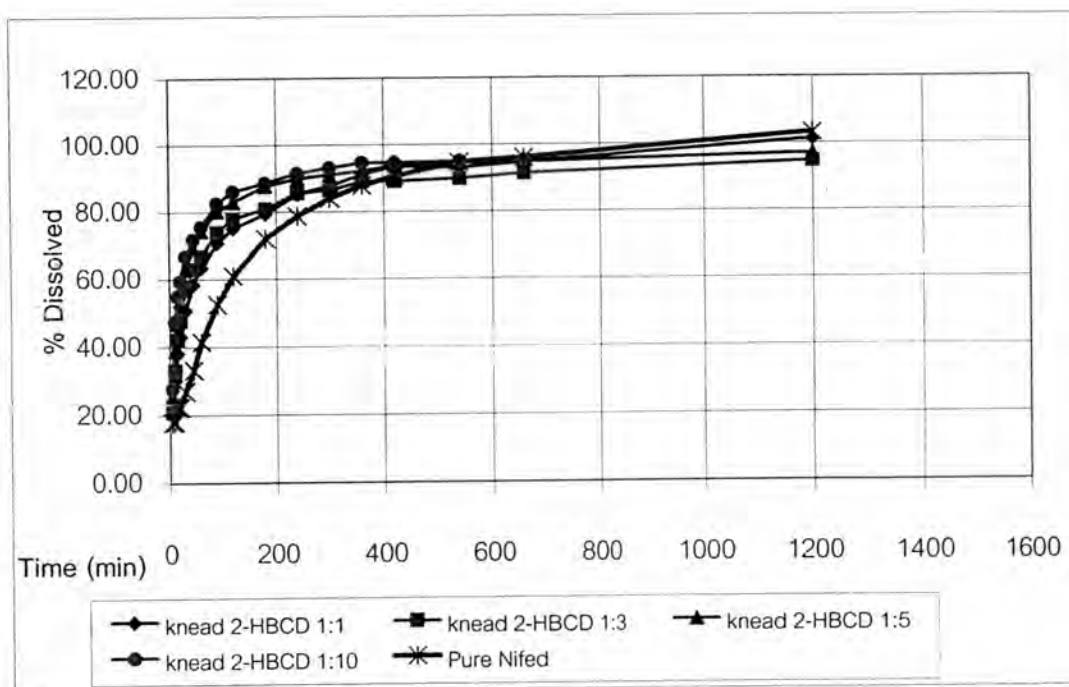


Figure 41 Dissolution profiles of nifedipine from nifedipine-2-hydroxypropyl- β -cyclodextrin solid dispersions prepared by kneading method.

Table 7 Time at 80% of nifedipine dissolved.

Carrier	Ratio (drug: carrier)	The time of 80% dissolution (min)				
		Method				
		Physical	Melting	Solvent	Kneading	Nontreated
(Pure drug)	1:0	770	1185	840	395	255
PEG4000	1:1	660	270	245	195	-
	1:3	*	215	230	90	-
	1:5	*	90	75	80	-
	1:10	*	55	45	45	-
PEG6000	1:1	420	225	765	105	-
	1:3	105	160	60	90	-
	1:5	270	110	45	60	-
	1:10	*	30	30	30	-
polox188	1:1	420	55	300	200	-
	1:3	420	15	1080	155	-
	1:5	55	15	33	120	-
	1:10	780	15	30	20	-
polox288	1:1	110	270	260	200	-
	1:3	225	155	33	150	-
	1:5	160	30	30	165	-
	1:10	110	35	25	15	-
polox407	1:1	270	260	240	100	-
	1:3	455	15	350	55	-
	1:5	375	15	20	130	-
	1:10	255	15	15	15	-
β -cyclo	1:1	450	-	-	380	-
	1:3	360	-	-	355	-
	1:5	990	-	-	220	-
	1:10	510	-	-	150	-
2-HBCD	1:1	495	-	330	180	-
	1:3	295	-	135	165	-
	1:5	220	-	135	90	-
	1:10	220	-	40	75	-

* The ratio that did not reach 80% dissolution

- No dissolution profiles

4. Physicochemical Properties Study.

4.1 Scanning electron micrograph (SEM)

Scanning electron micrographs of nifedipine solid dispersions prepared by various methods and ratios are illustrated in Figures 42-72 with different magnification factors, x100 or x200 for the low level and x800 for the high level.

4.1.1 SEM of pure drug and non treated pure drug.

The nontreated nifedipine which directly withdrawn from the reagent bottle had smooth surface crystals. Corner and sides of the crystals were clearly noticed under the microscope. The treated drug with melting and solvent methods were very similar in terms of the roughness of the surfaces except more porous surface was found in the pure drug treated with solvent method. A slightly smooth surface was found in the drug prepared by kneading and physical mixing methods (Figures 42-43).

From the comparison of crystal size of nifedipine and the carriers, it was clearly seen that the size of nifedipine particles in the solid dispersion were smaller than carrier particles. This has an advantage in differentiation of drug to carriers once they present in the solid dispersion pattern.

The microscopic appearance of PEG4000, PEG6000, poloxamer188, poloxamer288, poloxamer407, β -cyclodextrin and 2-hydroxypropyl- β -cyclodextrin are illustrated in Figures 44-47, respectively.

Photomicrographs of pure PEG4000 and PEG6000 (Figure 44) were very identical and showed spherical in shape with smooth surface. The diameters are range of 100-200 μm . However PEG4000 seems to be bigger than that of PEG6000.

The microscopic appearance of poloxamers (Figure 45-46) were similar to PEGs, rounded shape, smooth surface, but the range of diameter was wider at about or less than 100 μm for small ones and more than 200 μm for big ones. Some small particles (less than 100 μm) attached to the surface of the big ones.

For β -cyclodextrin (Figure 47), it appeared as rod shaped crystals at irregular sizes. In contrast, 2-hydroxypropyl- β -cyclodextrin was fine porous particles.

4.1.2 SEM of nifedipine-PEGs solid dispersion.

The SEM results of PEG4000 (Figure 48-51) and PEG6000 (Figure 52-55) showed very similar outcomes. Descriptions of most treatments were applicable to both carriers. In the melting method, nifedipine was found to be dispersed on the surface of carrier crystals. This result was found similar to solid dispersion prepared by solvent method whose amount of drug particles spread onto the carrier surface were lower. Some drug particles have even implanted on the surface of PEGs particles whereas majority were just physically deposited on the surface.

For physical mixed dispersions, drug particles found spreading on the PEGs surface were lower than those of melting and solvent method. Kneaded products were somewhere in between melting or solvent method and physical mixture.

The surfaces in most methods were rougher than pure carrier. However corners and sides still could be noticed. This suggested that carriers were in crystalline state.

Different drug-carrier ratios seemed not to influence the way particles presented in the system. However it affected the degree of roughness of drug particles. This was possible due to the amount of drug was lower at the higher ratio i.e. drug-carrier ratio at 1:10 contained fewer drug particles than the ratio of 1:3.

4.1.3 SEM of nifedipine-poloxamers solid dispersion.

The non treated poloxamer188 and 407, like PEGs, were spherical in shape with very smooth surface. The poloxamer288 system was small in size, about 10-50 μm , the surface was smooth like melted wax and the particles were irregular shape.

From Figure 56-59, 60-63 and 64-67, melting method of nifedipine-poloxamers gave very interesting observation. It was found that the drug particles have embedded into the surface of the carriers, not just deposited on it, resulting in jagged particles from inside but smooth surface from outside. Poloxamer188 was the smoothest with a lot of drug implantation, especially at the ratio of 1:3, followed by poloxamer288 and poloxamer407 respectively. Few drug crystals were found in this treatment.

For nifedipine-poloxamer188 prepared by kneading, the photo micrographs showed (Figure 59) that poloxamer188 particles had the most smooth surface among the three poloxamers. In contrast, the surface of

poloxamer288 (Figure 67) were still rough whereas poloxamer407 (Figure 63) the surface was slightly smoother than that of poloxamer228 but not as smooth as poloxamer188. The drug particles spread on the surface of carrier were higher than that of the melting method. This phenomenon became dominant when compared with physical mixture.

The system of nifedipine-poloxamers from solvent method were depicted in Figure 58 . Some drug particles were embedded into the surface of the carriers whereas some other part of the drug spread out between the carrier particles. In general, the surface of the particles were still rough and most of them were smaller compared with physical mixture at the same ratio.

Drug particle implantation was rarely found in the physical mixtures. Most drug particles spread between the carrier particles. The carrier particles also showed the most rough surface.

4.1.4 SEM of nifedipine-cyclodextrins solid dispersion.

It should be noted here again that β -cyclodextrin could not be prepared by melting and solvent methods and 2-hydroxypropyl- β -cyclodextrin could not be prepared by melting method. β -Cyclodextrin was found presenting in crystalline forms. 2-Hydroxypropyl- β -cyclodextrin was fine particles.

As pure β -cyclodextrin presented as smooth surfaced and rod shaped crystal, physical mixtures of β -cyclodextrin (Figure 68), nifedipine spread both on the surface and between the carrier particles. Carriers, as well as the drug, were existed in the crystalline form because its corner and sides were still clearly found. Both drug and carrier showed smooth surfaced particles. The drug distribution was high as the drug to carrier ratio increased. However, 2-

hydroxypropyl- β -cyclodextrin physical mixtures (Figure 70) showed nifedipine particles adsorbed on the carrier surface.

Kneaded products of both carriers still (Figure 69 and 70) showed drug and carriers crystals. However, carrier particles were distorted slightly resulting in rougher surface when compared to the physical mixtures. This was possibly the result of compression force during kneading. Drug particles were found deposit on the surface of the carrier.

For the solvent method, only 2-hydroxypropyl- β -cyclodextrin could be prepared, the surface of 2-hydroxypropyl- β -cyclodextrin particle was smooth. Drug particles were found on the surface of the carrier as porous particles.

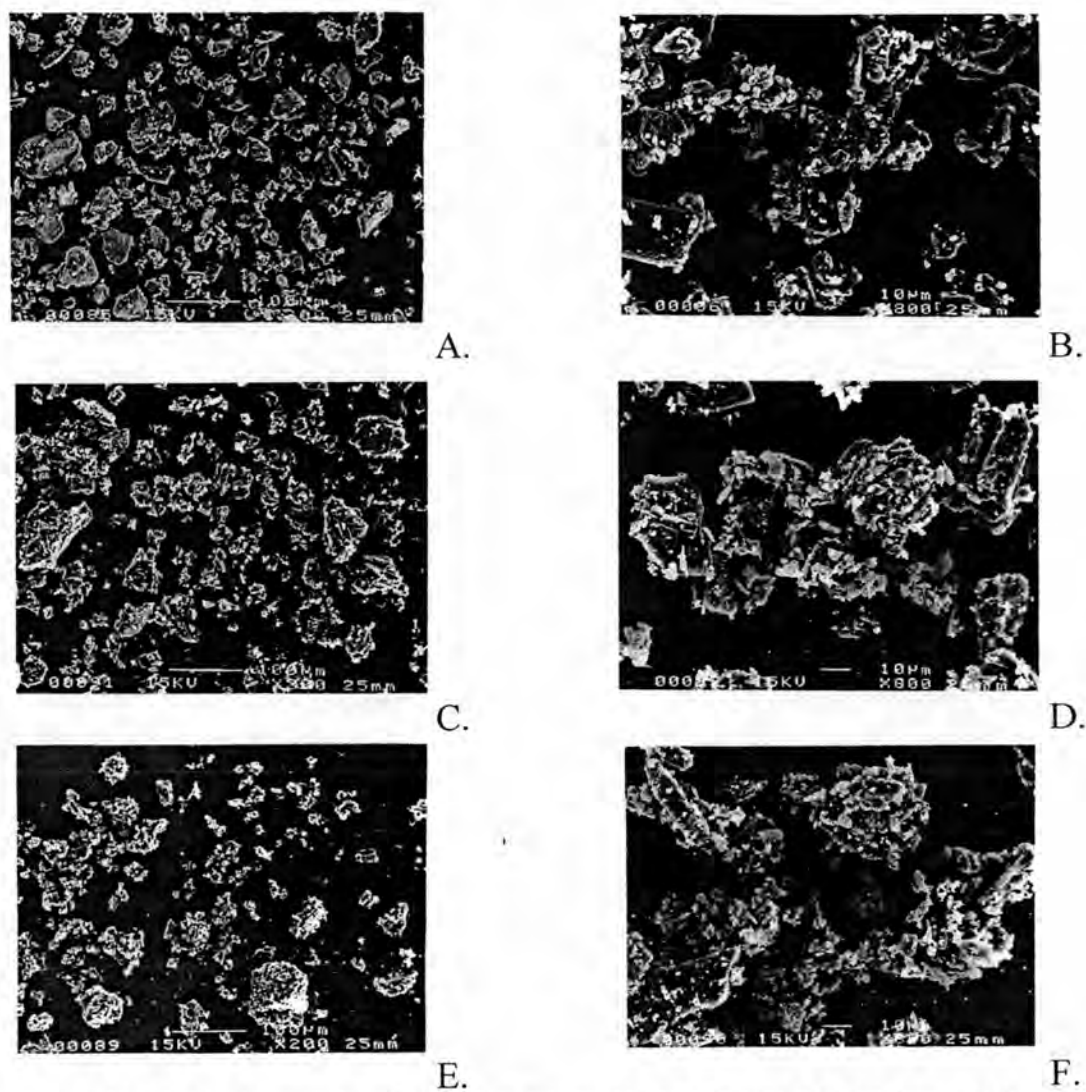


Figure 42 Photomicrographs of nifedipine nontreated and treated with various methods.

A and B: Non treated,

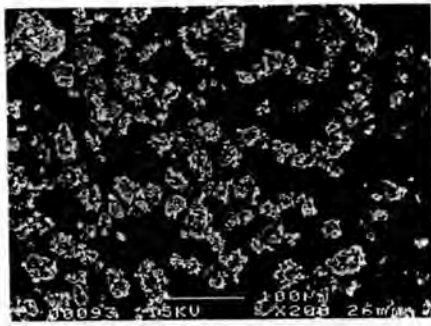
A. x200, B. x800

C and D: Treated by solvent method,

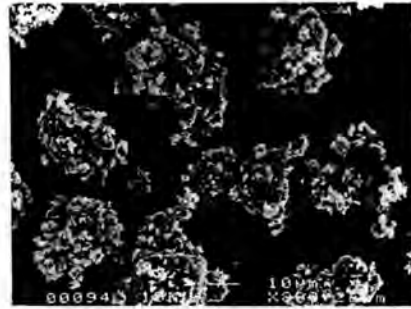
C. x200, D. x800

E and F: Treated by melting method,

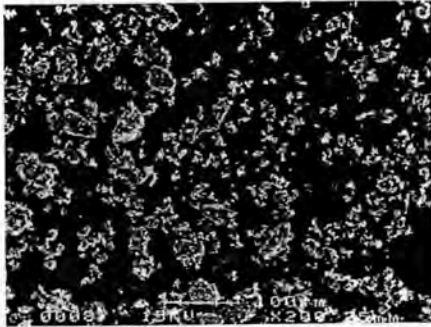
E. x200, F. x800



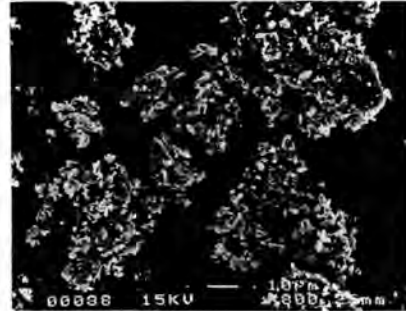
A.



B.



C.



D.

Figure 43 Photomicrographs of nifedipine treated with various methods.

A and B: Treated by kneading method,

A. x200, B. x800

C and D: Treated by physical mixing

C. x200, D. x800

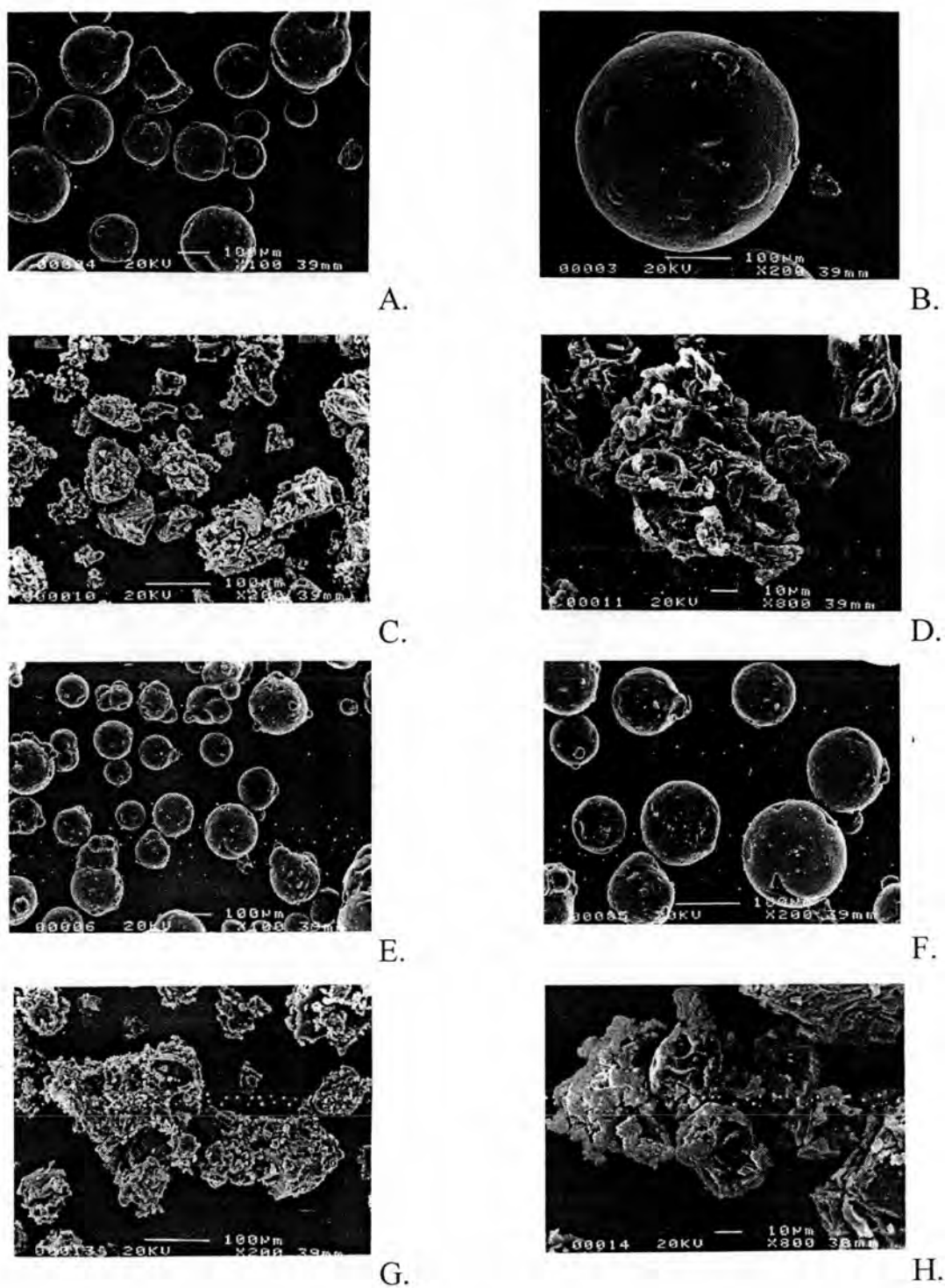


Figure 44 Photomicrographs of pure PEG4000 and PEG6000.

A and B: PEG4000 non pulverized and sieved,	A. x100, B. x200
C and D: PEG4000 pulverized and sieved,	C. x200, D. x800
E and F: PEG6000 non pulverized and sieved,	E. x100, F. x200
G and H: PEG6000 pulverized and sieved,	G. x200, H. x800

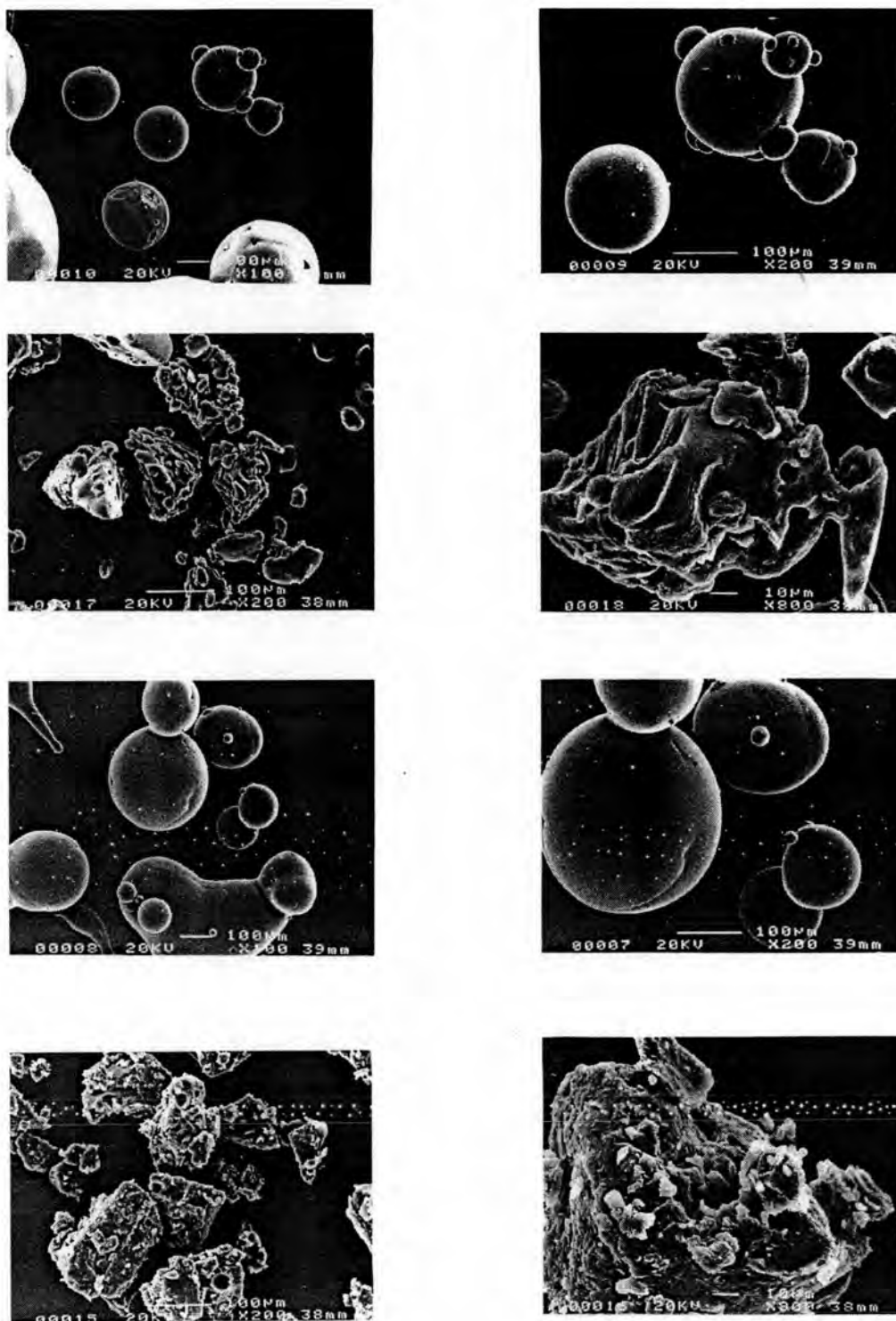


Figure 45 Photomicrographs of pure poloxamer 188 and poloxamer 407.

A and B: poloxamer 188 non pulverized and sieved,

A. x100, B. x200

C and D: poloxamer 188 pulverized and sieved,

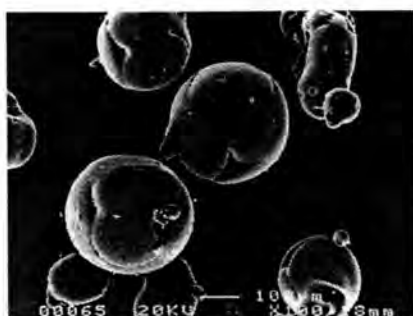
C. x200, D. x800

E and F: poloxamer 407 non pulverized and sieved,

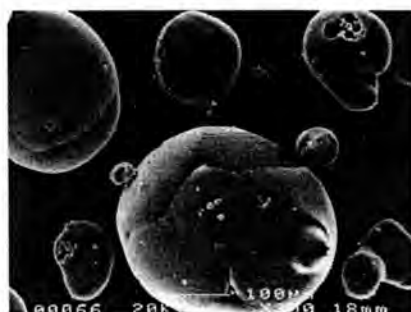
E. x100, F. x200

G and H: poloxamer 407 pulverized and sieved,

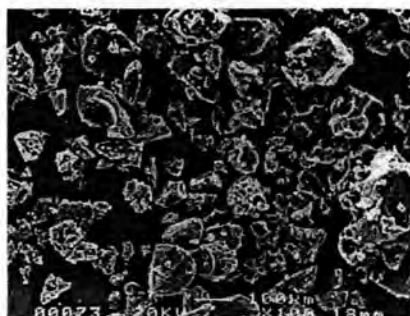
G. x200, H. x800



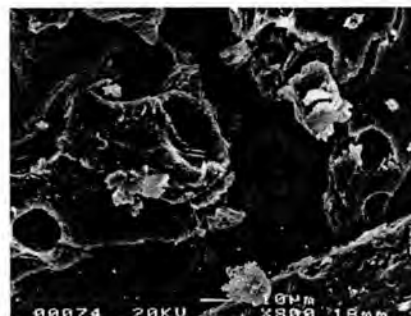
A.



B.



C.



D.

Figure 46 Photomicrographs of pure poloxamer288.

A and B: poloxamer288 non pulverized and sieved,

A. x100, B. x200

C and D: poloxamer288 pulverized and sieved,

C. x200, D. x800

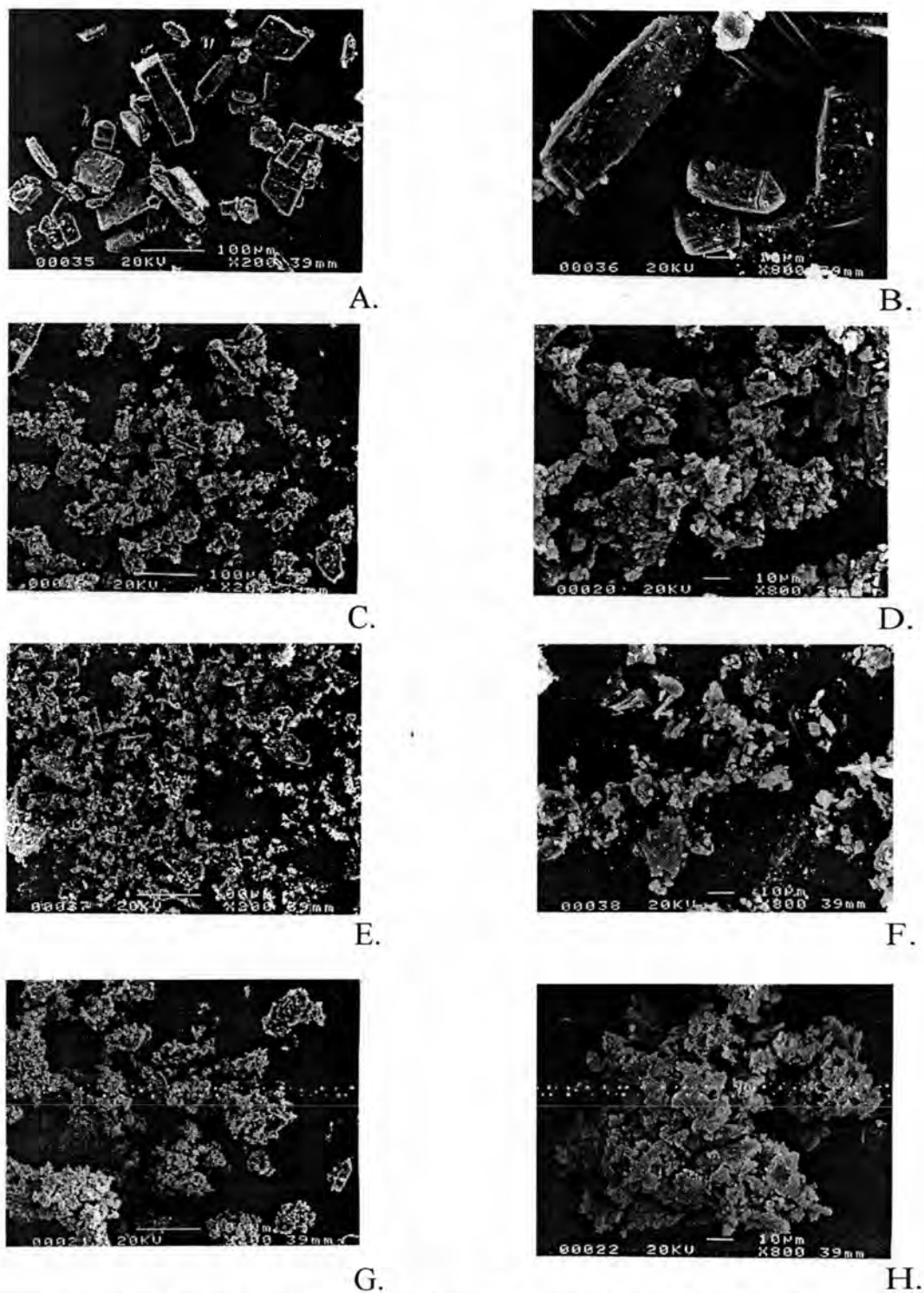


Figure 47 Photomicrographs of β -cyclodextrin and 2-hydroxypropyl- β -cyclodextrin.

A and B: β -cyclodextrin non pulverized and sieved,

A. x200, B. x800

C and D: β -cyclodextrin pulverized and sieved,

C. x200, D. x800

E and F: 2-hydroxypropyl- β -cyclodextrin non pulverized and sieved,

E. x200, F. x800

G and H: 2-hydroxypropyl- β -cyclodextrin pulverized and sieved,

G. x200, H. x800

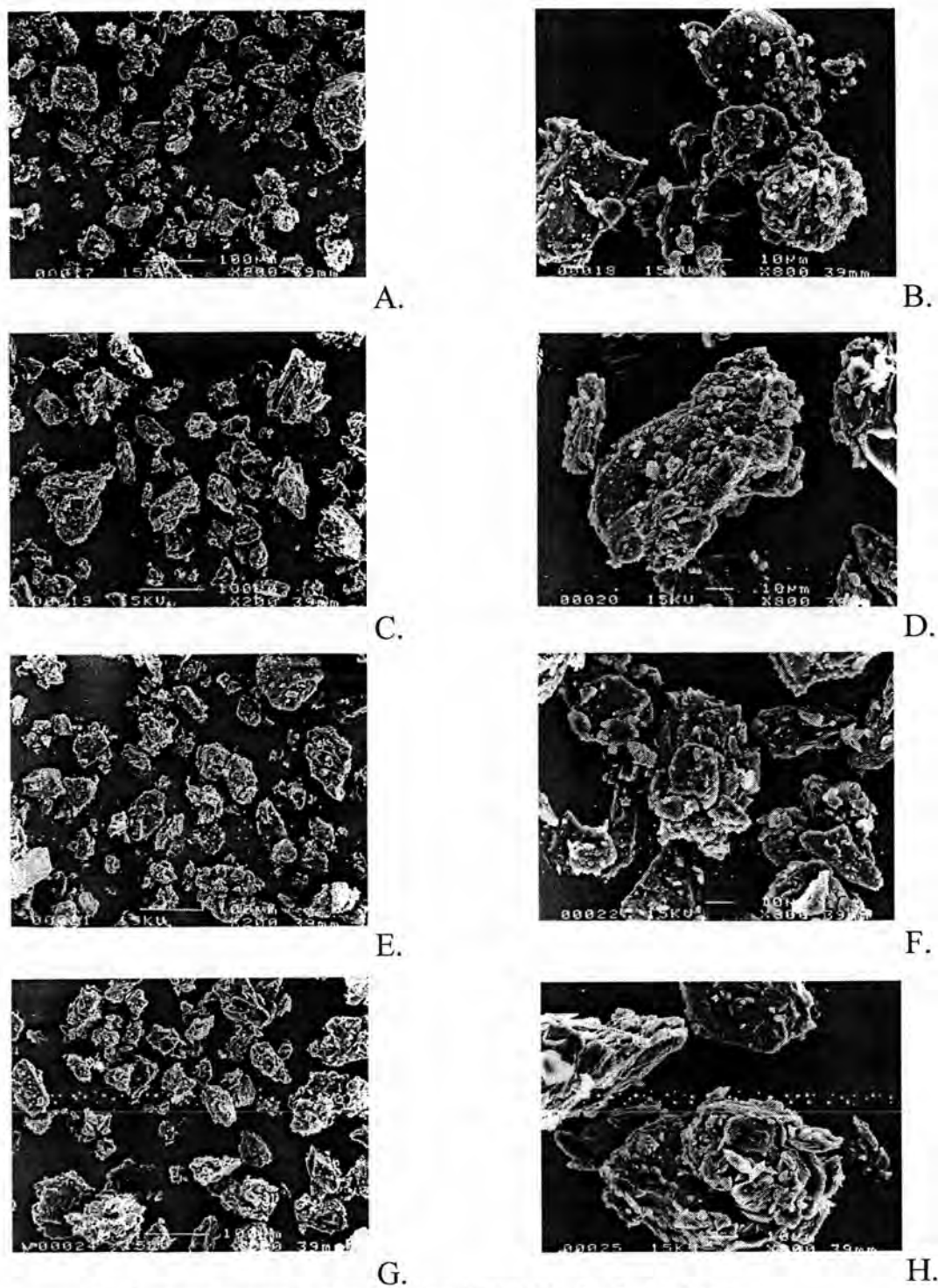


Figure 48 Photomicrographs of nifedipine-PEG4000, physical mixture

A and B: Drug-carrier ratio at 1:1,

A. x200, B. x800

C and D: Drug-carrier ratio at 1:3,

C. x200, D. x800

E and F: Drug-carrier ratio at 1:5,

E. x200, F. x800

G and H: Drug-carrier ratio at 1:10,

G. x200, H. x800

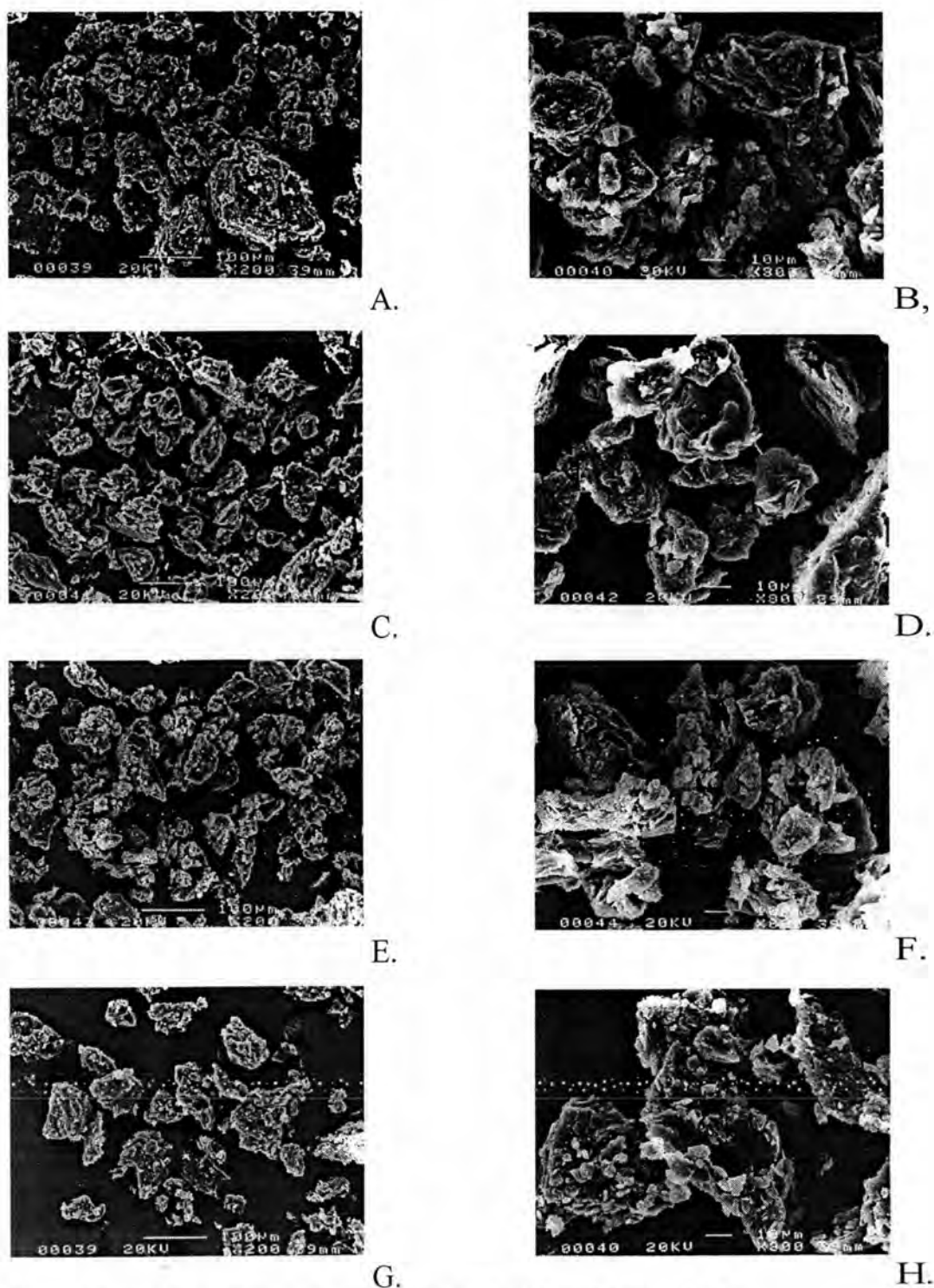


Figure 49 Photomicrographs of nifedipine-PEG4000, melting method.

A and B: Drug-carrier ratio at 1:1, A. x200, B. x800

C and D: Drug-carrier ratio at 1:3, C. x200, D. x800

E and F: Drug-carrier ratio at 1:5, E. x200, F. x800

G and H: Drug-carrier ratio at 1:10, G. x200, H. x800

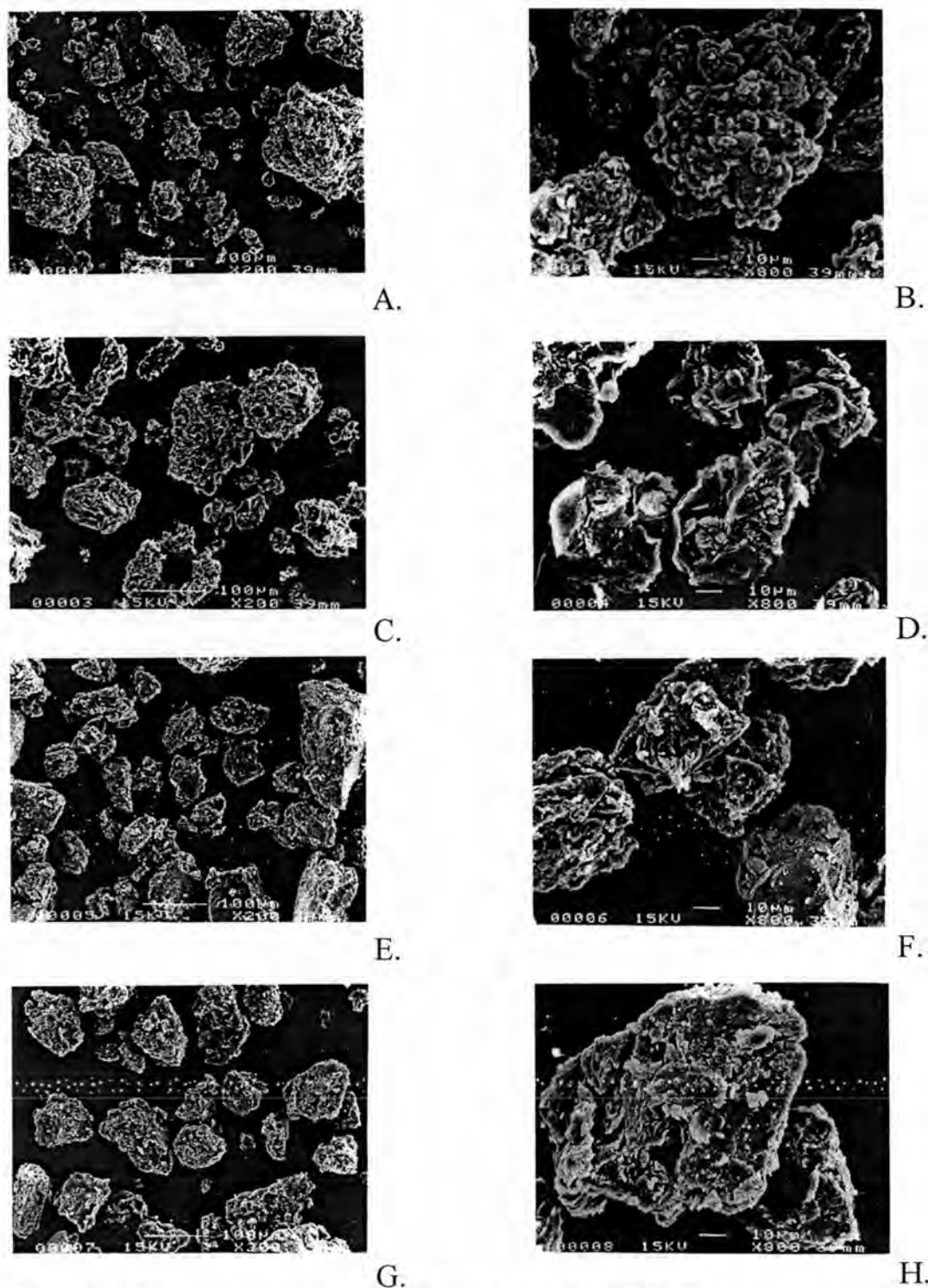


Figure 50 Photomicrographs of nifedipine-PEG4000, solvent method.

A and B: Drug-carrier ratio at 1:1, A. x200, B. x800

C and D: Drug-carrier ratio at 1:3, C. x200, D. x800

E and F: Drug-carrier ratio at 1:5, E. x200, F. x800

G and H: Drug-carrier ratio at 1:10, G. x200, H. x800

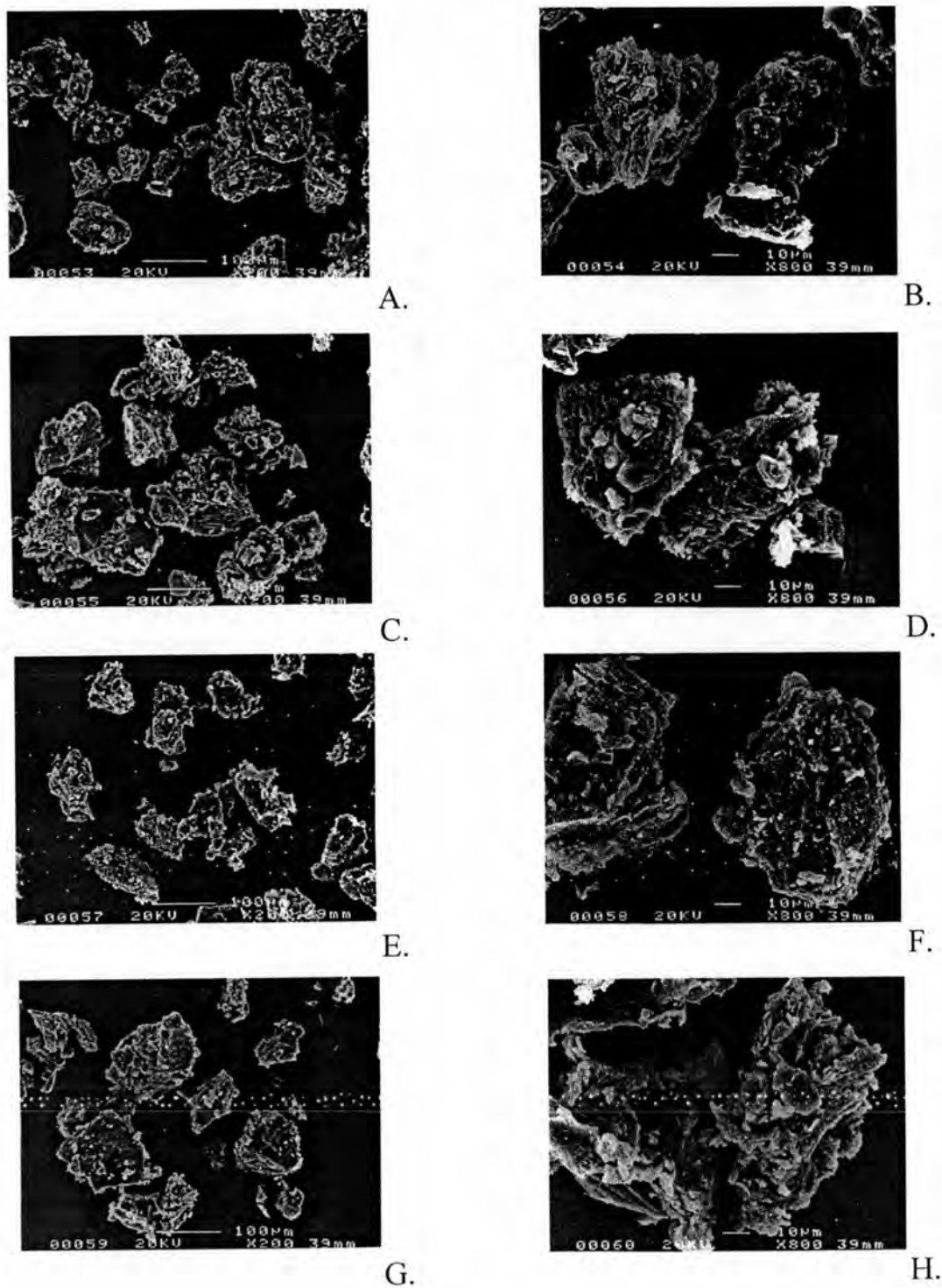


Figure 51 Photomicrographs of nifedipine-PEG4000, kneading method.

A and B: Drug-carrier ratio at 1:1,	A. x200, B. x800
C and D: Drug-carrier ratio at 1:3,	C. x200, D. x800
E and F: Drug-carrier ratio at 1:5,	E. x200, F. x800
G and H: Drug-carrier ratio at 1:10,	G. x200, H. x800

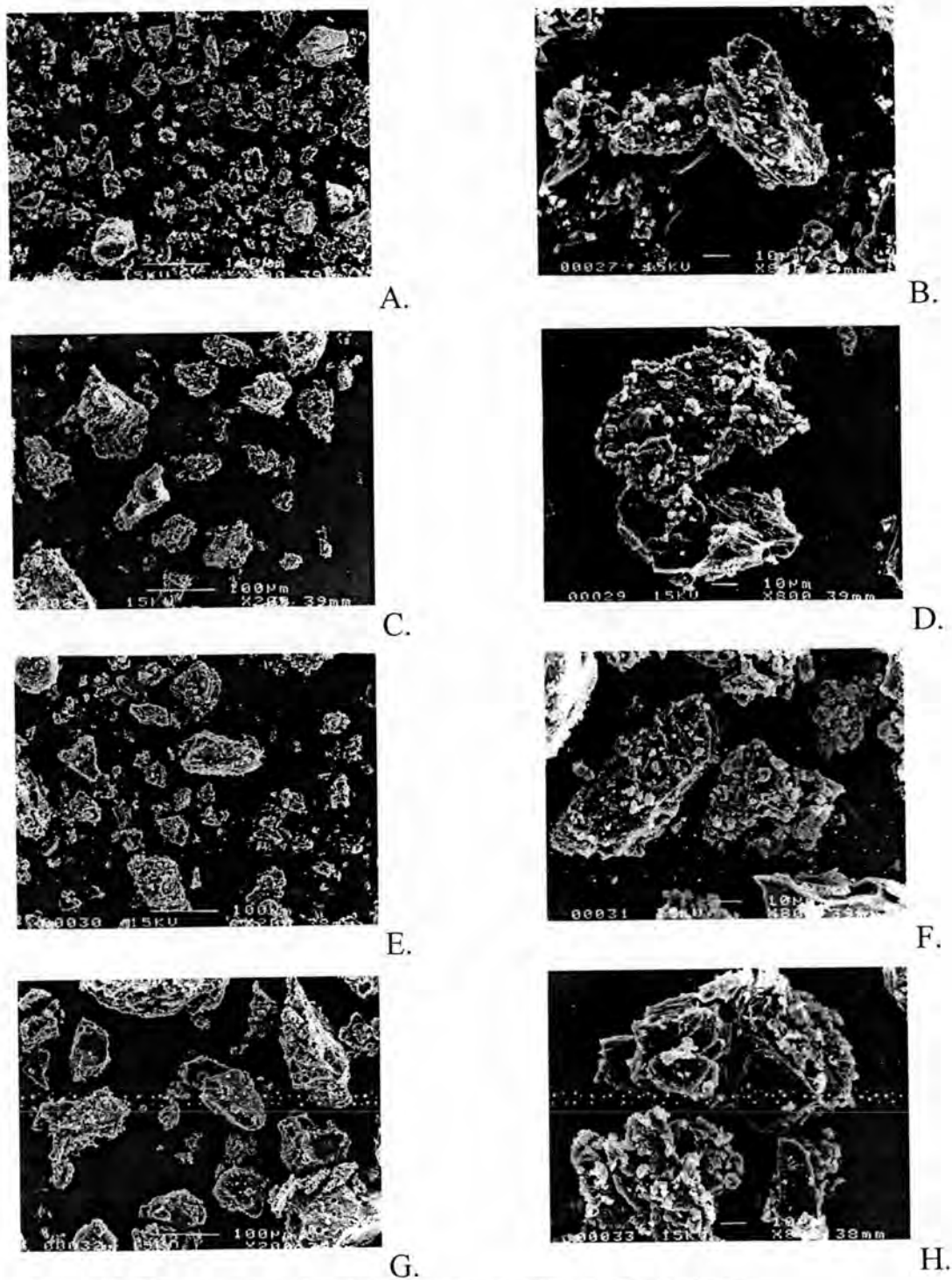


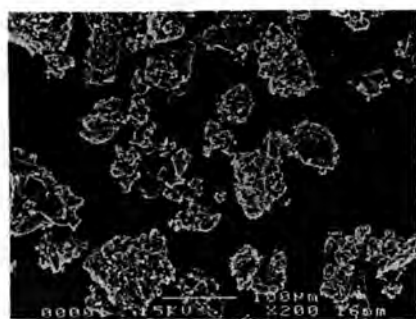
Figure 52 Photomicrographs of nifedipine-PEG6000, physical mixture.

A and B: Drug-carrier ratio at 1:1, A. x200, B. x800

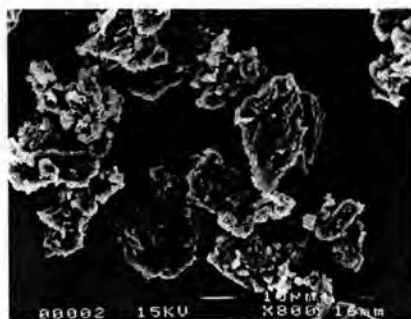
C and D: Drug-carrier ratio at 1:3, C. x200, D. x800

E and F: Drug-carrier ratio at 1:5, E. x200, F. x800

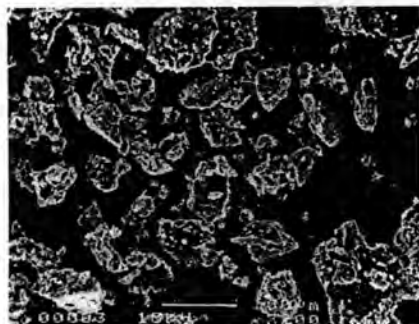
G and H: Drug-carrier ratio at 1:10, G. x200, H. x800



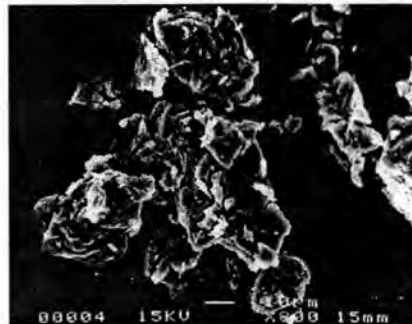
A.



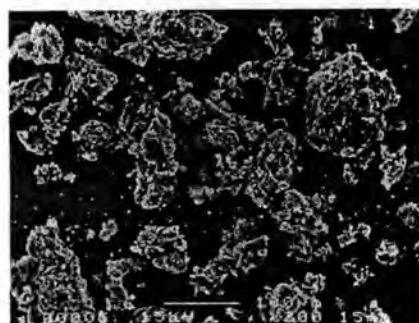
B.



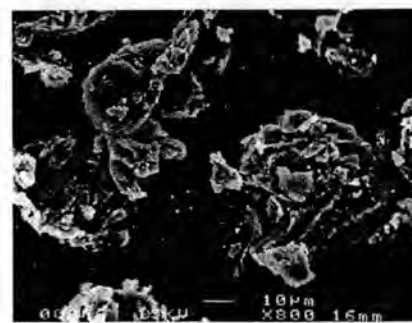
C.



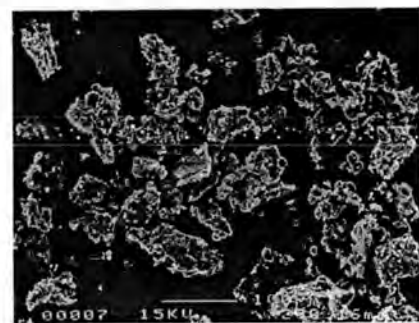
D.



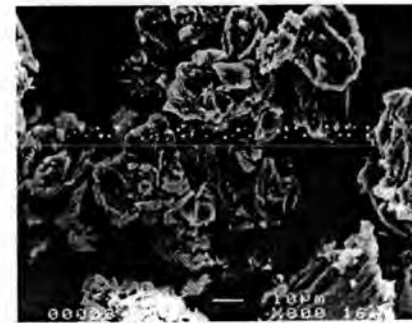
E.



F.



G.



H.

Figure 53 Photomicrographs of nifedipine-PEG6000, melting method.

A and B: Drug-carrier ratio at 1:1,

A. x200, B. x800

C and D: Drug-carrier ratio at 1:3,

C. x200, D. x800

E and F: Drug-carrier ratio at 1:5,

E. x200, F. x800

G and H: Drug-carrier ratio at 1:10,

G. x200, H. x800

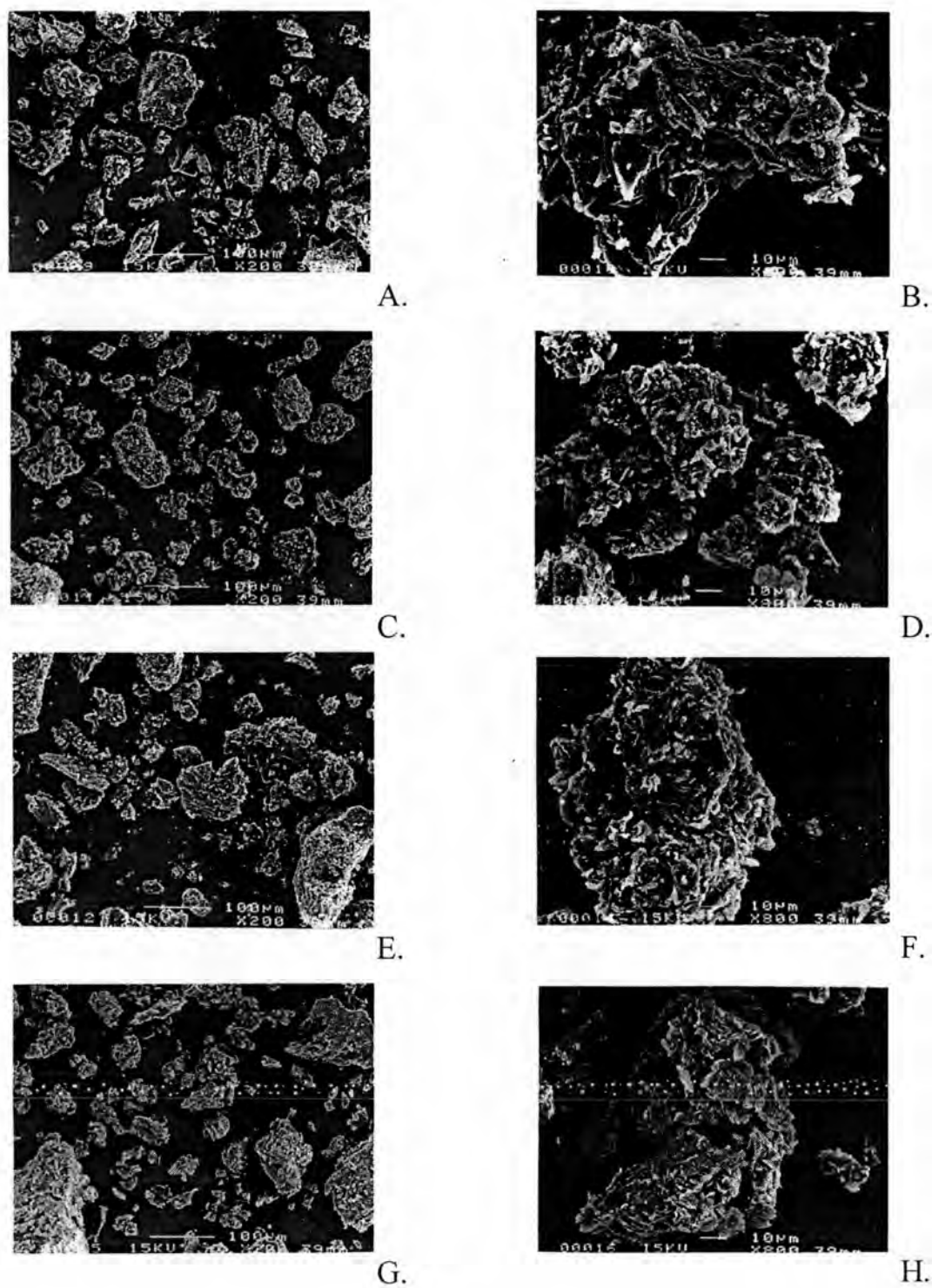


Figure 54 Photomicrographs of nifedipine-PEG6000, solvent method.

A and B: Drug-carrier ratio at 1:1,	A. x200, B. x800
C and D: Drug-carrier ratio at 1:3,	C. x200, D. x800
E and F: Drug-carrier ratio at 1:5,	E. x200, F. x800
G and H: Drug-carrier ratio at 1:10,	G. x200, H. x800

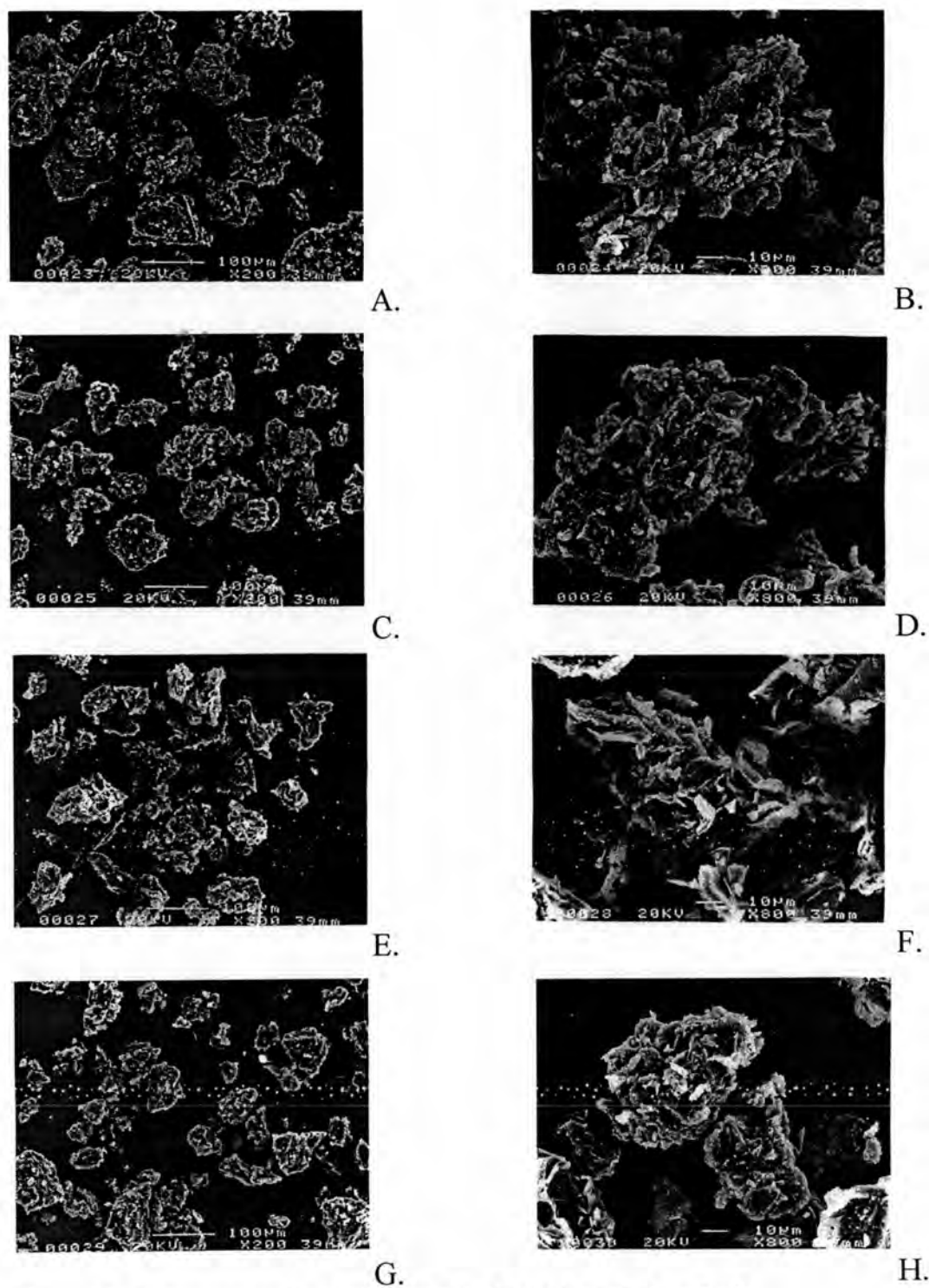


Figure 55 Photomicrographs of nifedipine-PEG6000, kneading method.

- | | |
|--------------------------------------|------------------|
| A and B: Drug-carrier ratio at 1:1, | A. x200, B. x800 |
| C and D: Drug-carrier ratio at 1:3, | C. x200, D. x800 |
| E and F: Drug-carrier ratio at 1:5, | E. x200, F. x800 |
| G and H: Drug-carrier ratio at 1:10, | G. x200, H. x800 |

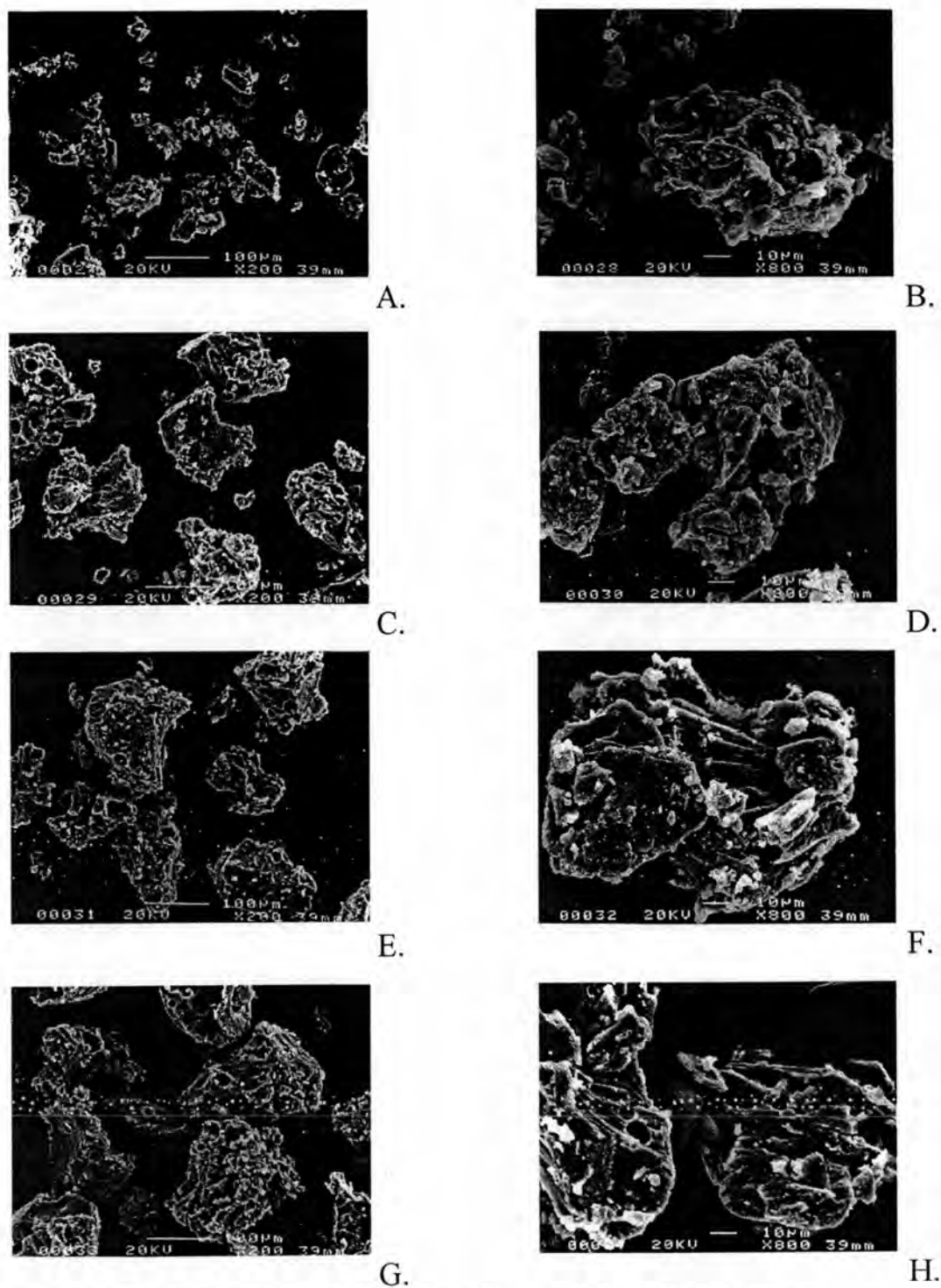


Figure 56 Photomicrographs of nifedipine-poloxamer 188, physical mixture

A and B: Drug-carrier ratio at 1:1, A. x200, B. x800

C and D: Drug-carrier ratio at 1:3, C. x200, D. x800

E and F: Drug-carrier ratio at 1:5, E. x200, F. x800

G and H: Drug-carrier ratio at 1:10, G. x200, H. x800

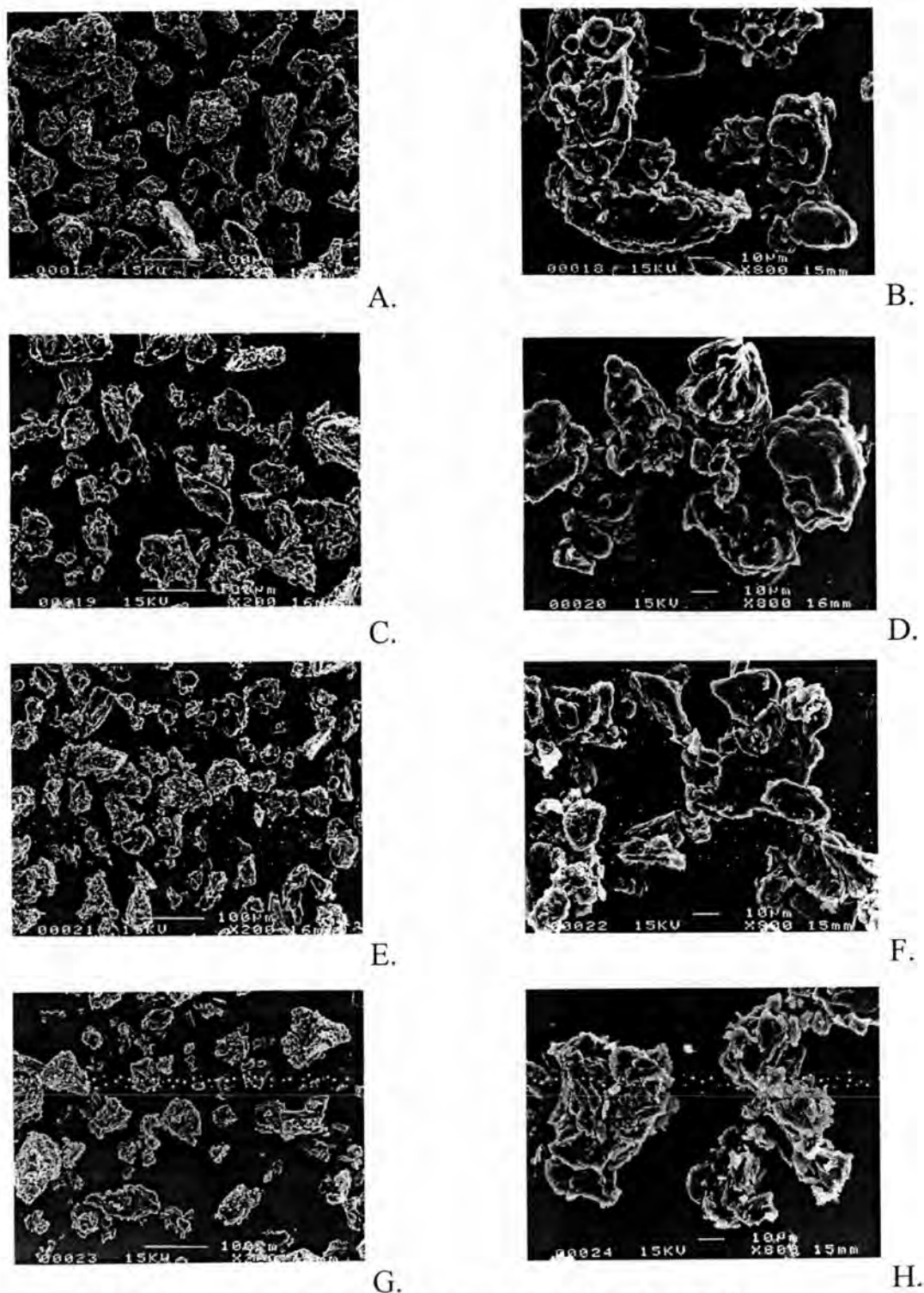
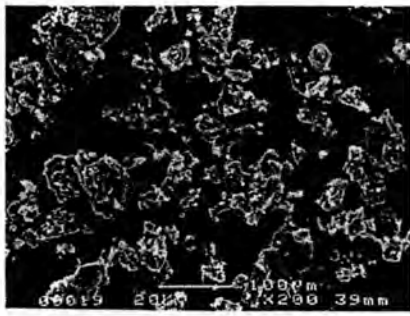
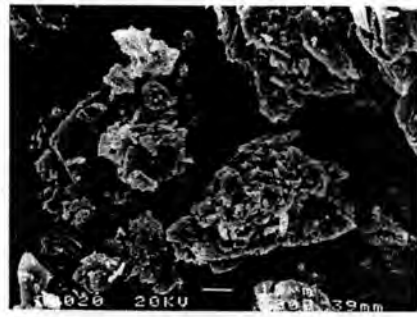


Figure 57 Photomicrographs of nifedipine-poloxamer 188, melt method.

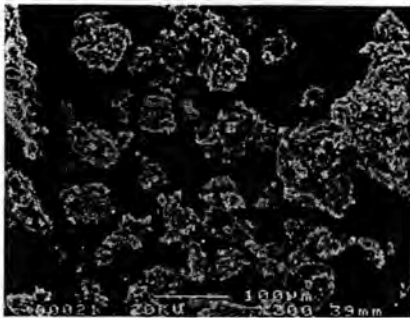
A and B: Drug-carrier ratio at 1:1,	A. x200, B. x800
C and D: Drug-carrier ratio at 1:3,	C. x200, D. x800
E and F: Drug-carrier ratio at 1:5,	E. x200, F. x800
G and H: Drug-carrier ratio at 1:10,	G. x200, H. x800



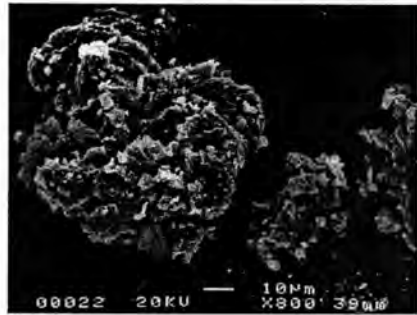
A.



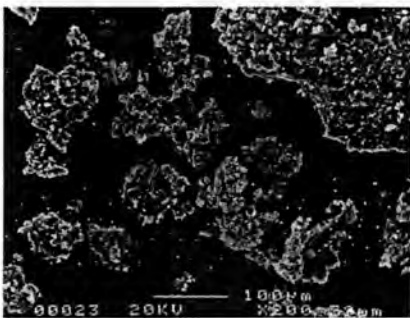
B.



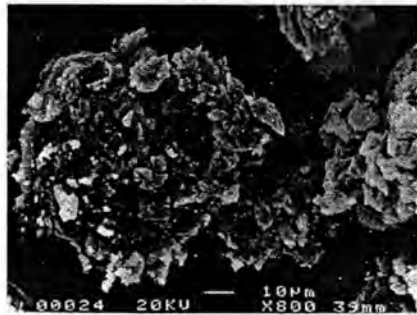
C.



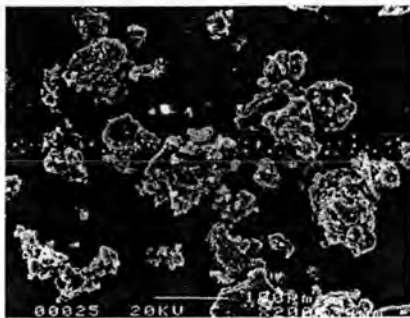
D.



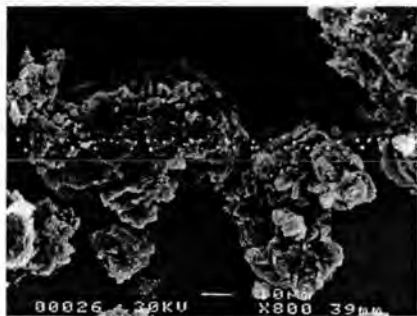
E.



F.



G.



H.

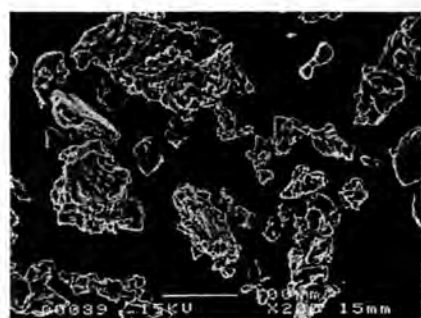
Figure 58 Photomicrographs of nifedipine-poloxamer 188, solvent method.

A and B: Drug-carrier ratio at 1:1, A. x200, B. x800

C and D: Drug-carrier ratio at 1:3, C. x200, D. x800

E and F: Drug-carrier ratio at 1:5, E. x200, F. x800

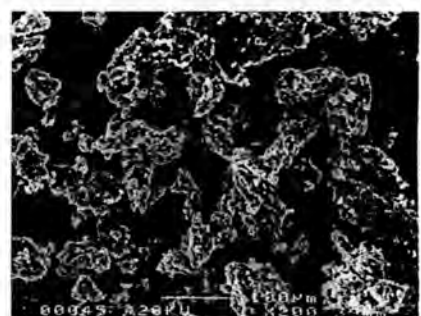
G and H: Drug-carrier ratio at 1:10, G. x200, H. x800



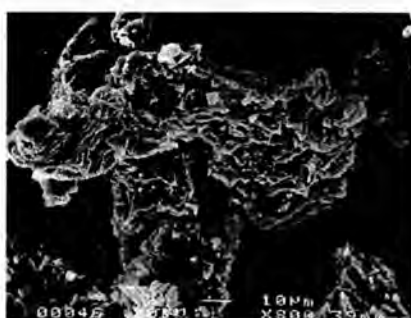
A.



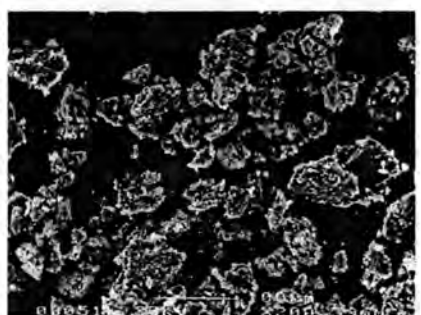
B.



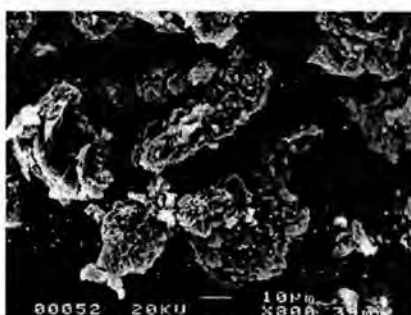
C.



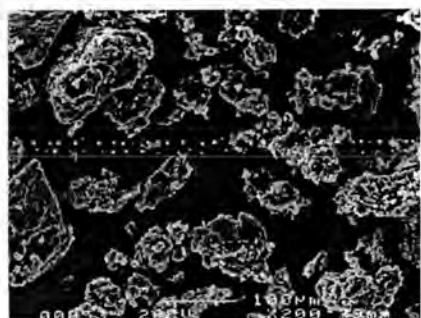
D.



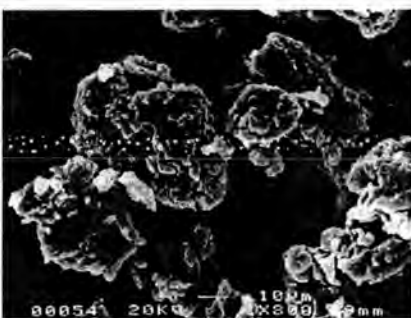
E.



F.



G.



H.

Figure 59 Photomicrographs of nifedipine-poloxamer 188, kneading method.

A and B: Drug-carrier ratio at 1:1,

A. x200, B. x800

C and D: Drug-carrier ratio at 1:3,

C. x200, D. x800

E and F: Drug-carrier ratio at 1:5,

E. x200, F. x800

G and H: Drug-carrier ratio at 1:10,

G. x200, H. x800

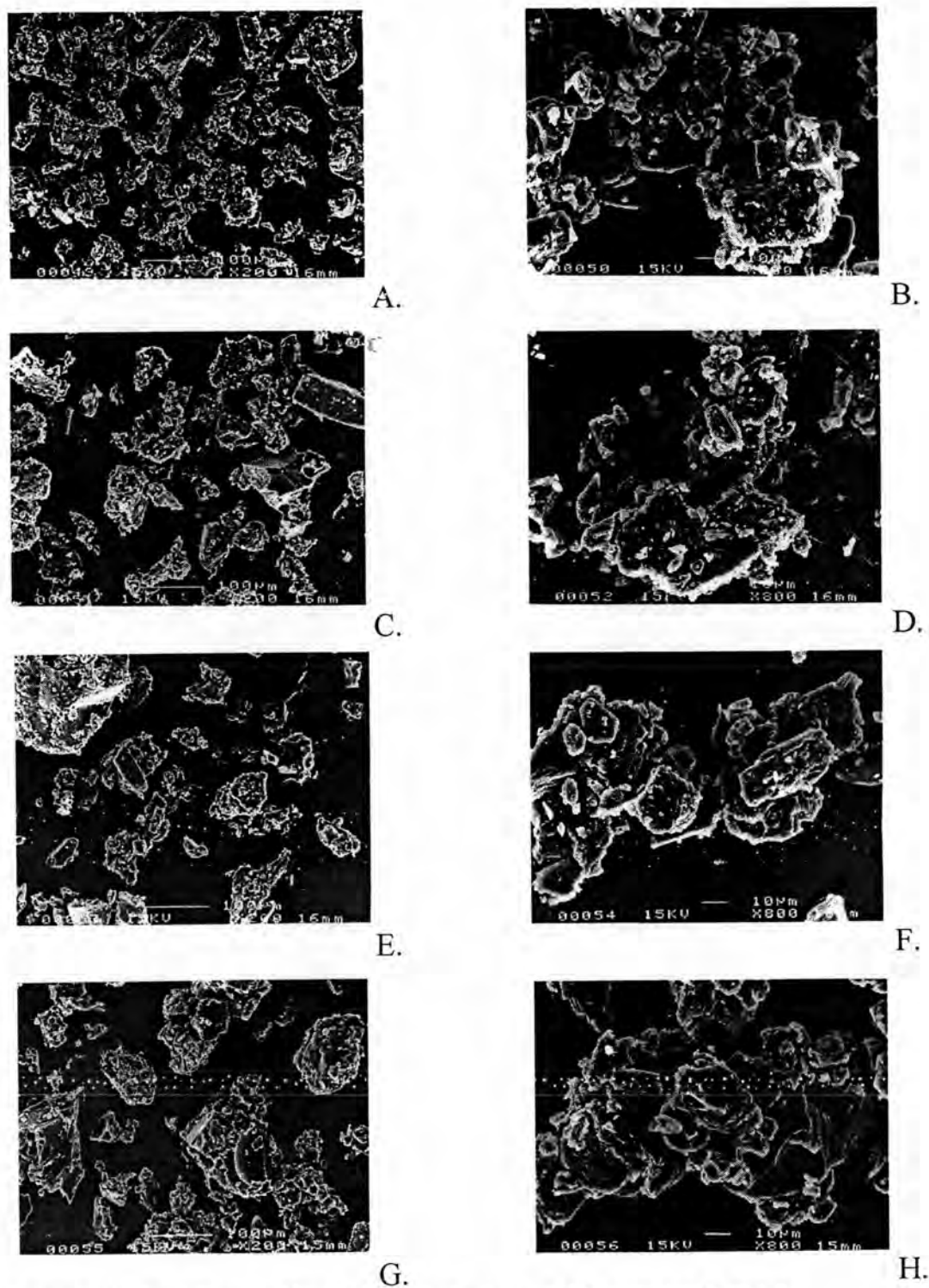


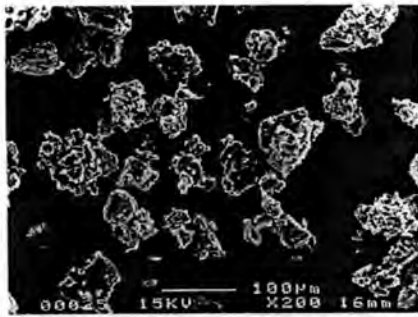
Figure 60 Photomicrographs of nifedipine-poloxamer288, physical mixture

A and B: Drug-carrier ratio at 1:1, A. x200, B. x800

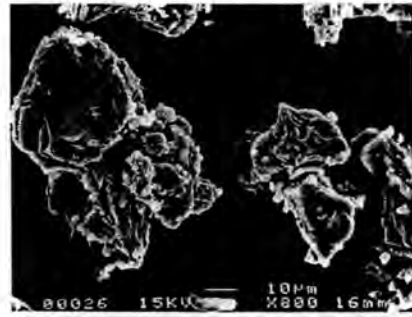
C and D: Drug-carrier ratio at 1:3, C. x200, D. x800

E and F: Drug-carrier ratio at 1:5, E. x200, F. x800

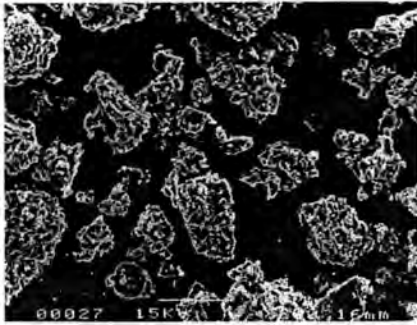
G and H: Drug-carrier ratio at 1:10, G. x200, H. x800



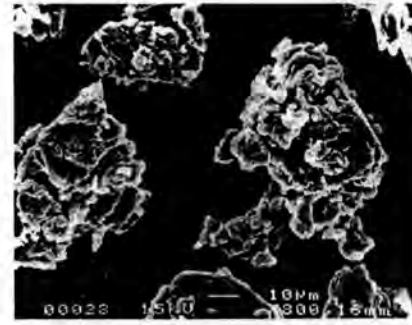
A.



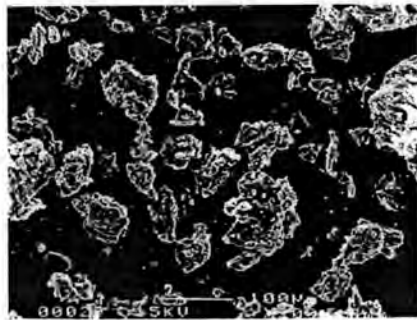
B.



C.



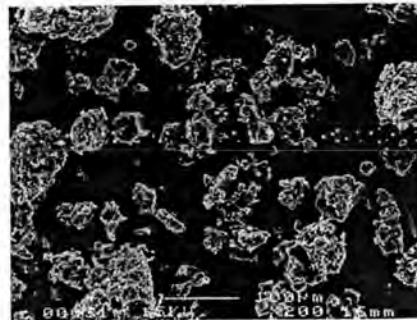
D.



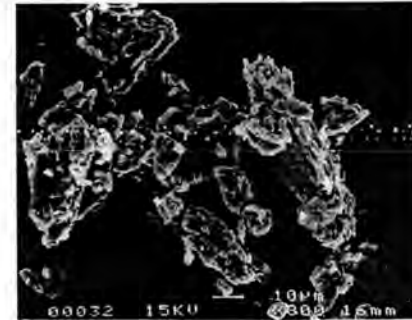
E.



F.



G.



H.

Figure 61 Photomicrographs of nifedipine-poloxamer288, melting method.

A and B: Drug-carrier ratio at 1:1, A. x200, B. x800

C and D: Drug-carrier ratio at 1:3, C. x200, D. x800

E and F: Drug-carrier ratio at 1:5, E. x200, F. x800

G and H: Drug-carrier ratio at 1:10, G. x200, H. x800

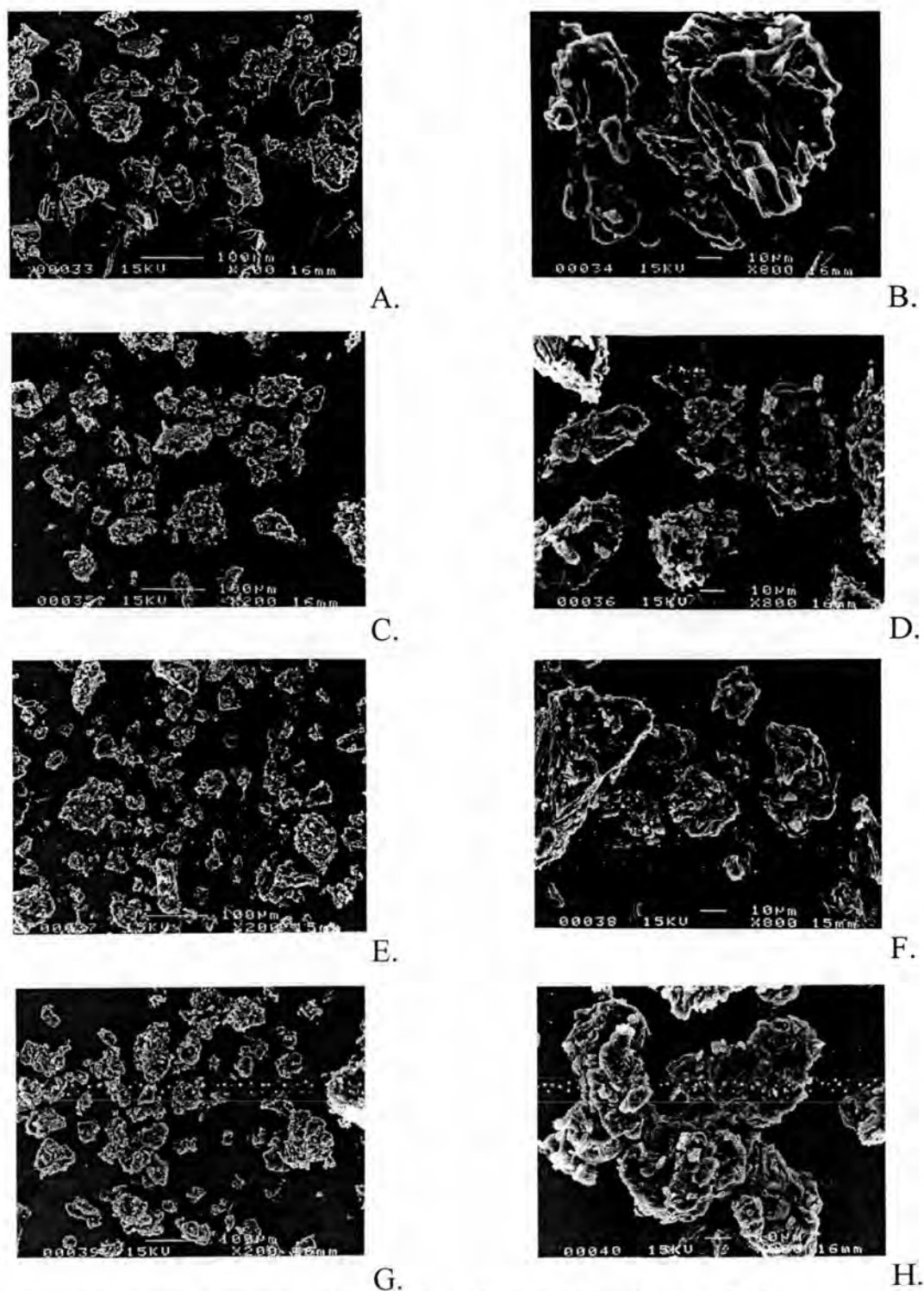


Figure 62 Photomicrographs of nifedipine-polyoxamer288, solvent method.

A and B: Drug-carrier ratio at 1:1,	A. x200, B. x800
C and D: Drug-carrier ratio at 1:3,	C. x200, D. x800
E and F: Drug-carrier ratio at 1:5,	E. x200, F. x800
G and H: Drug-carrier ratio at 1:10,	G. x200, H. x800

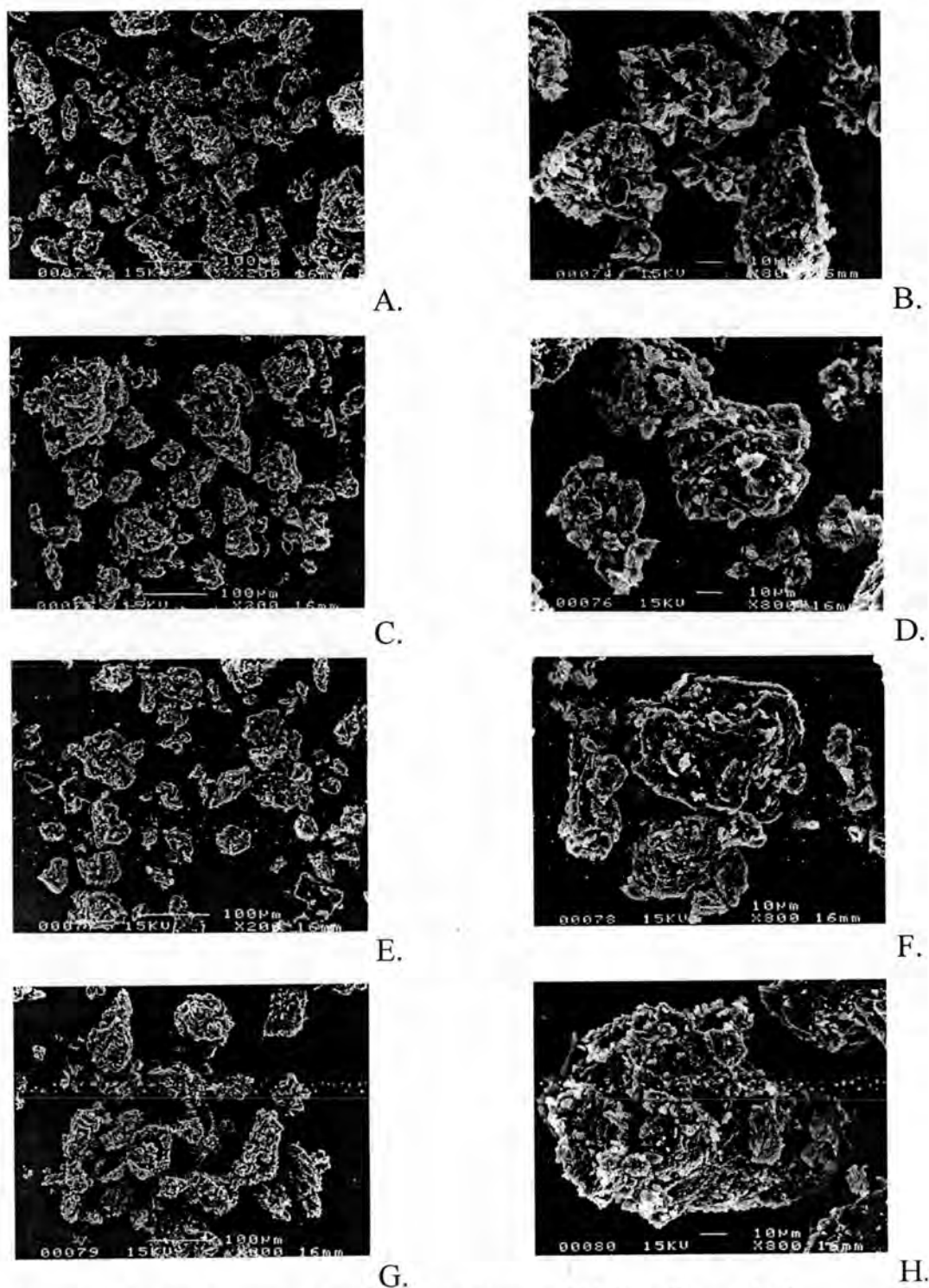


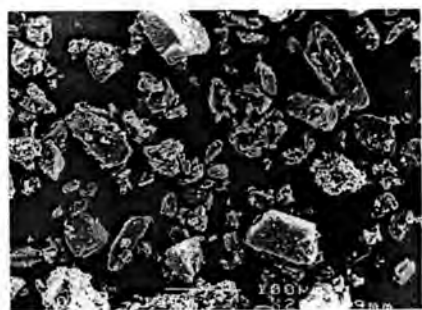
Figure 63 Photomicrographs of nifedipine-poloxamer288, kneading method.

A and B: Drug-carrier ratio at 1:1, A. x200, B. x800

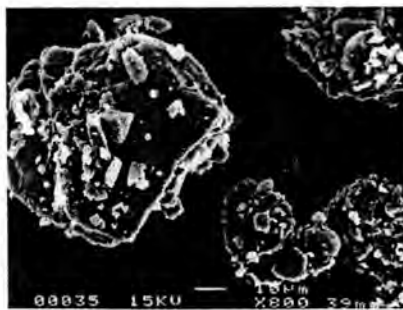
C and D: Drug-carrier ratio at 1:3, C. x200, D. x800

E and F: Drug-carrier ratio at 1:5, E. x200, F. x800

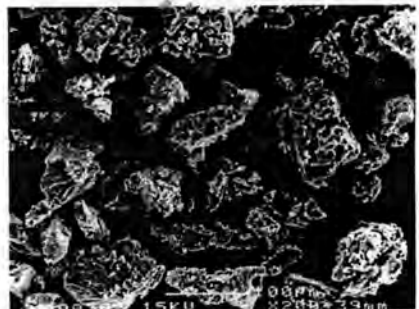
G and H: Drug-carrier ratio at 1:10, G. x200, H. x800



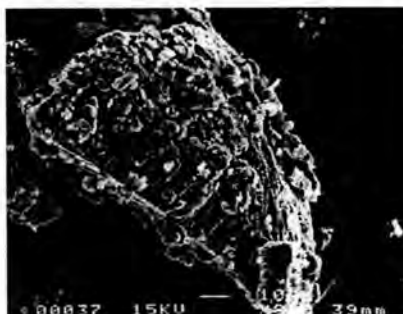
A.



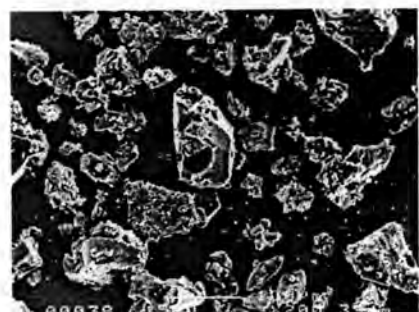
B.



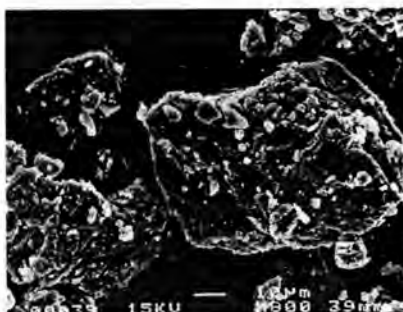
C.



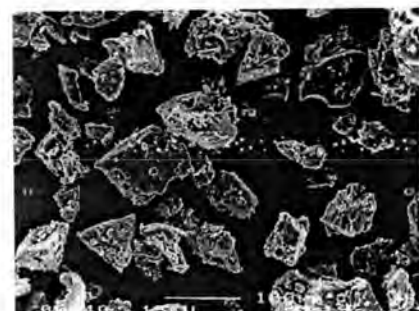
D.



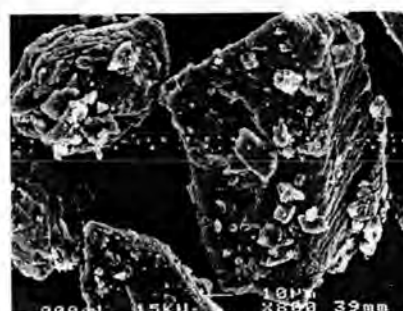
E.



F.



G.



H.

Figure 64 Photomicrographs of nifedipine-poloxamer 407, physical mixture

A and B: Drug-carrier ratio at 1:1,

A. x200, B. x800

C and D: Drug-carrier ratio at 1:3,

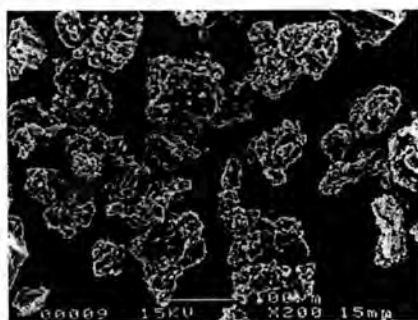
C. x200, D. x800

E and F: Drug-carrier ratio at 1:5,

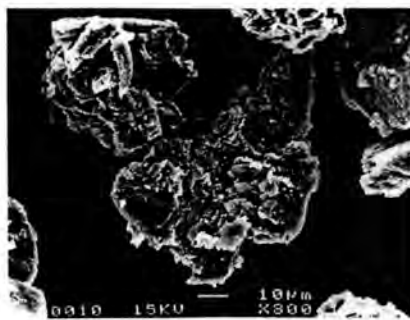
E. x200, F. x800

G and H: Drug-carrier ratio at 1:10,

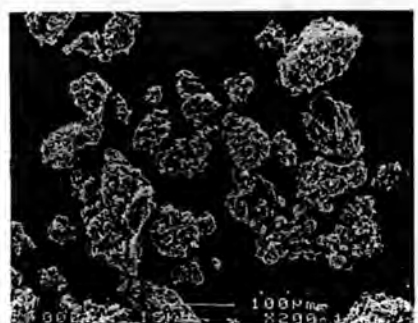
G. x200, H. x800



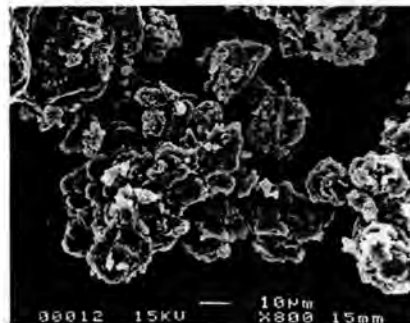
A.



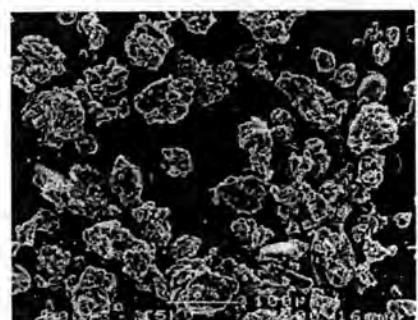
B.



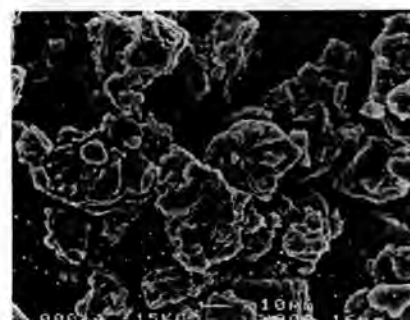
C.



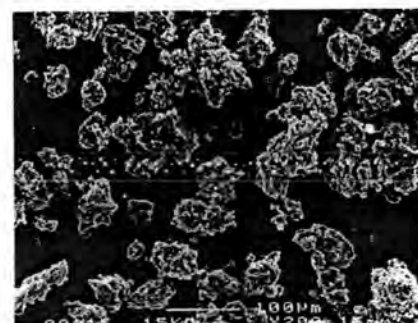
D.



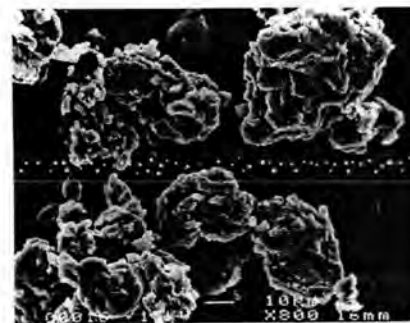
E.



F.



G.



H.

Figure 65 Photomicrographs of nifedipine-poloxamer 407, melting method.

A and B: Drug-carrier ratio at 1:1,	A. x200, B. x800
C and D: Drug-carrier ratio at 1:3,	C. x200, D. x800
E and F: Drug-carrier ratio at 1:5,	E. x200, F. x800
G and H: Drug-carrier ratio at 1:10,	G. x200, H. x800

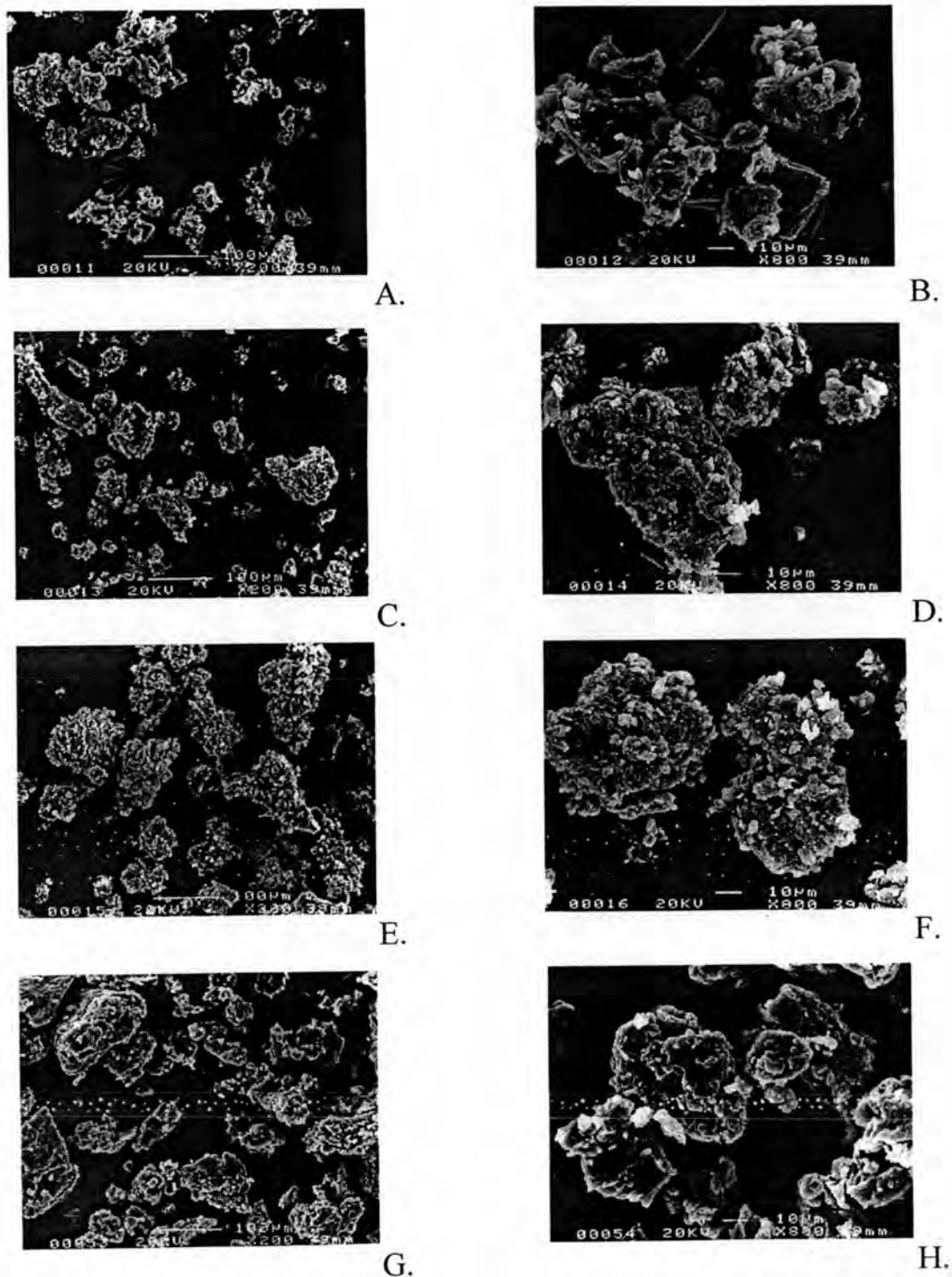


Figure 66 Photomicrographs of nifedipine-poloxamer 407, solvent method.

A and B: Drug-carrier ratio at 1:1, A. x200, B. x800
 C and D: Drug-carrier ratio at 1:3, C. x200, D. x800
 E and F: Drug-carrier ratio at 1:5, E. x200, F. x800
 G and H: Drug-carrier ratio at 1:10, G. x200, H. x800

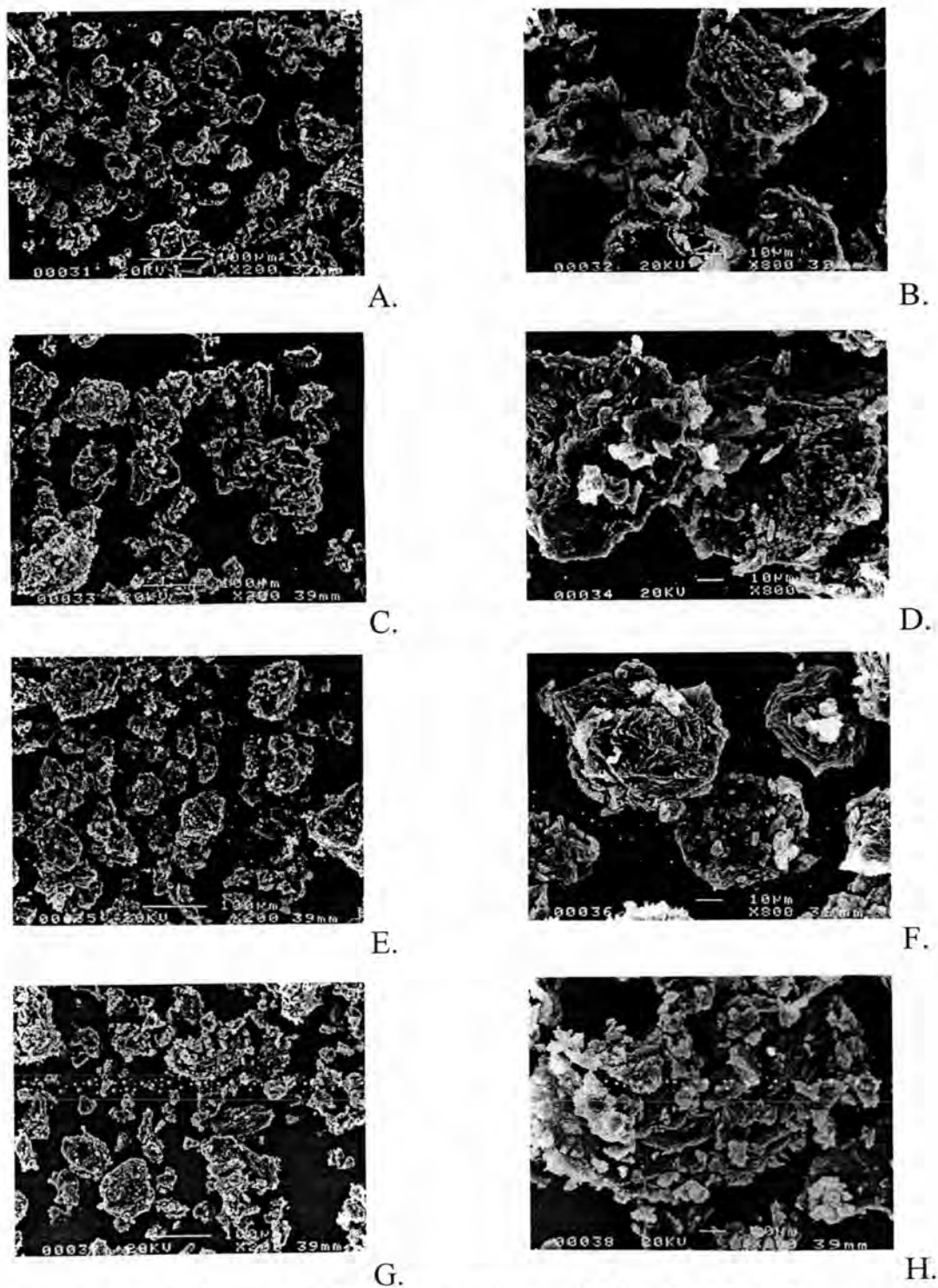


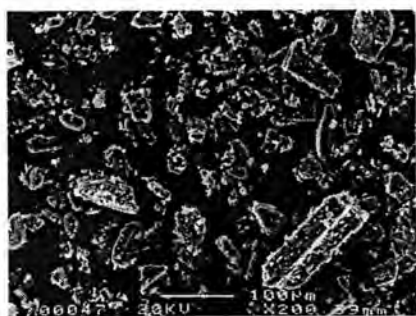
Figure 67 Photomicrographs of nifedipine-poloxamer 407, kneading method.

A and B: Drug-carrier ratio at 1:1, A. x200, B. x800

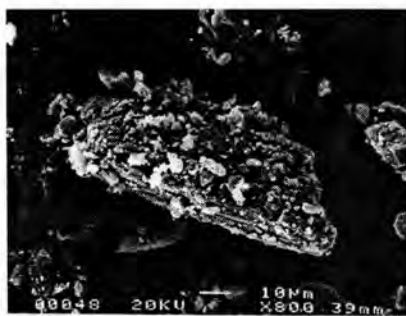
C and D: Drug-carrier ratio at 1:3, C. x200, D. x800

E and F: Drug-carrier ratio at 1:5, E. x200, F. x800

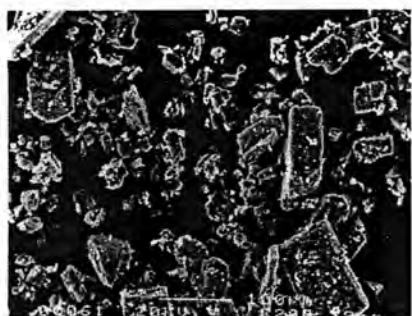
G and H: Drug-carrier ratio at 1:10, G. x200, H. x800



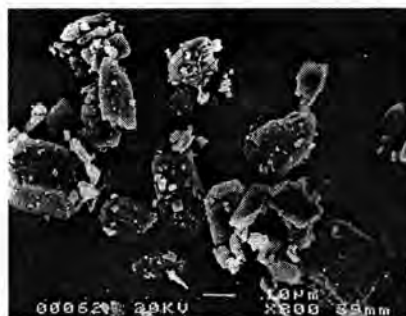
A.



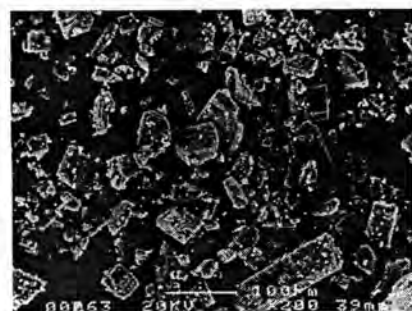
B.



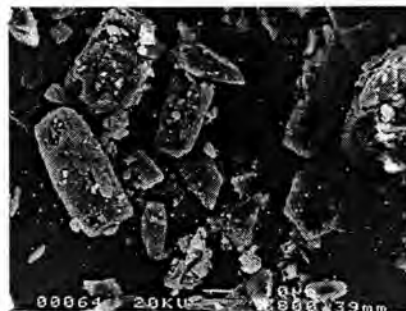
C.



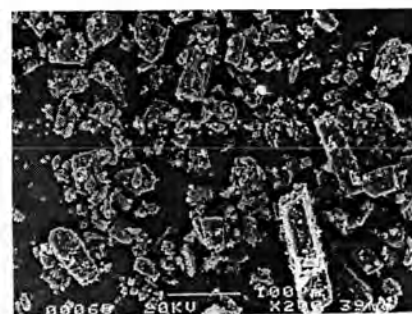
D.



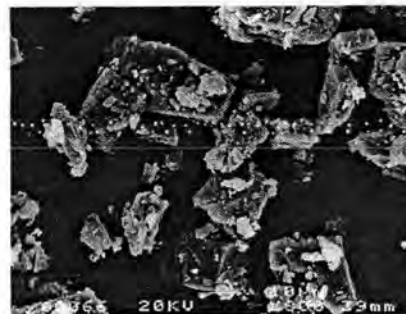
E.



F.



G.



H.

Figure 68 photomicrographs of nifedipine- β -cyclodextrin, physical mixture

A and B: Drug-carrier ratio at 1:1,	A. x200, B. x800
C and D: Drug-carrier ratio at 1:3,	C. x200, D. x800
E and F: Drug-carrier ratio at 1:5,	E. x200, F. x800
G and H: Drug-carrier ratio at 1:10,	G. x200, H. x800

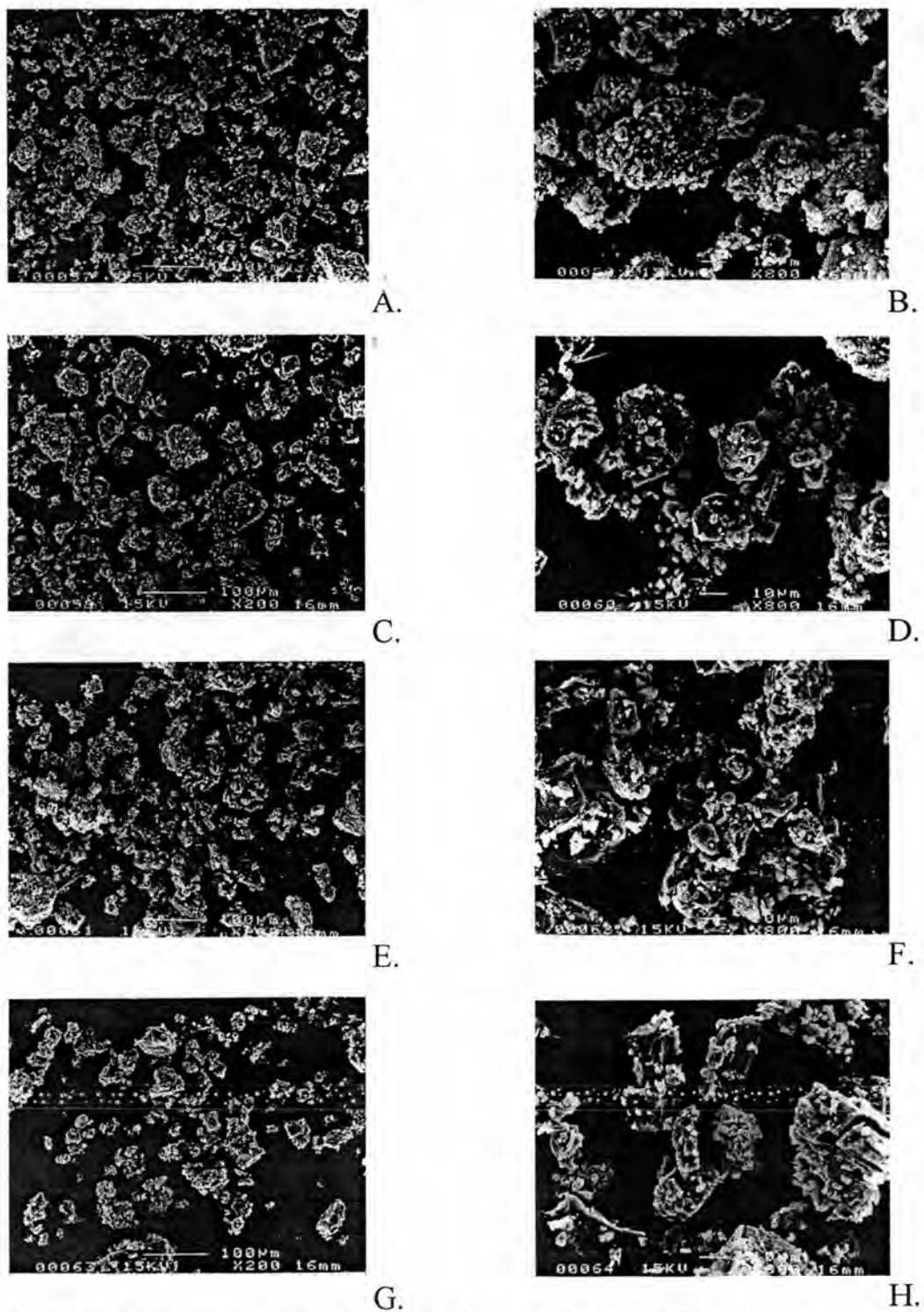


Figure 69 Photomicrographs of nifedipine- β -cyclodextrin, kneading method.

A and B: Drug-carrier ratio at 1:1,	A. x200, B. x800
C and D: Drug-carrier ratio at 1:3,	C. x200, D. x800
E and F: Drug-carrier ratio at 1:5,	E. x200, F. x800
G and H: Drug-carrier ratio at 1:10,	G. x200, H. x800

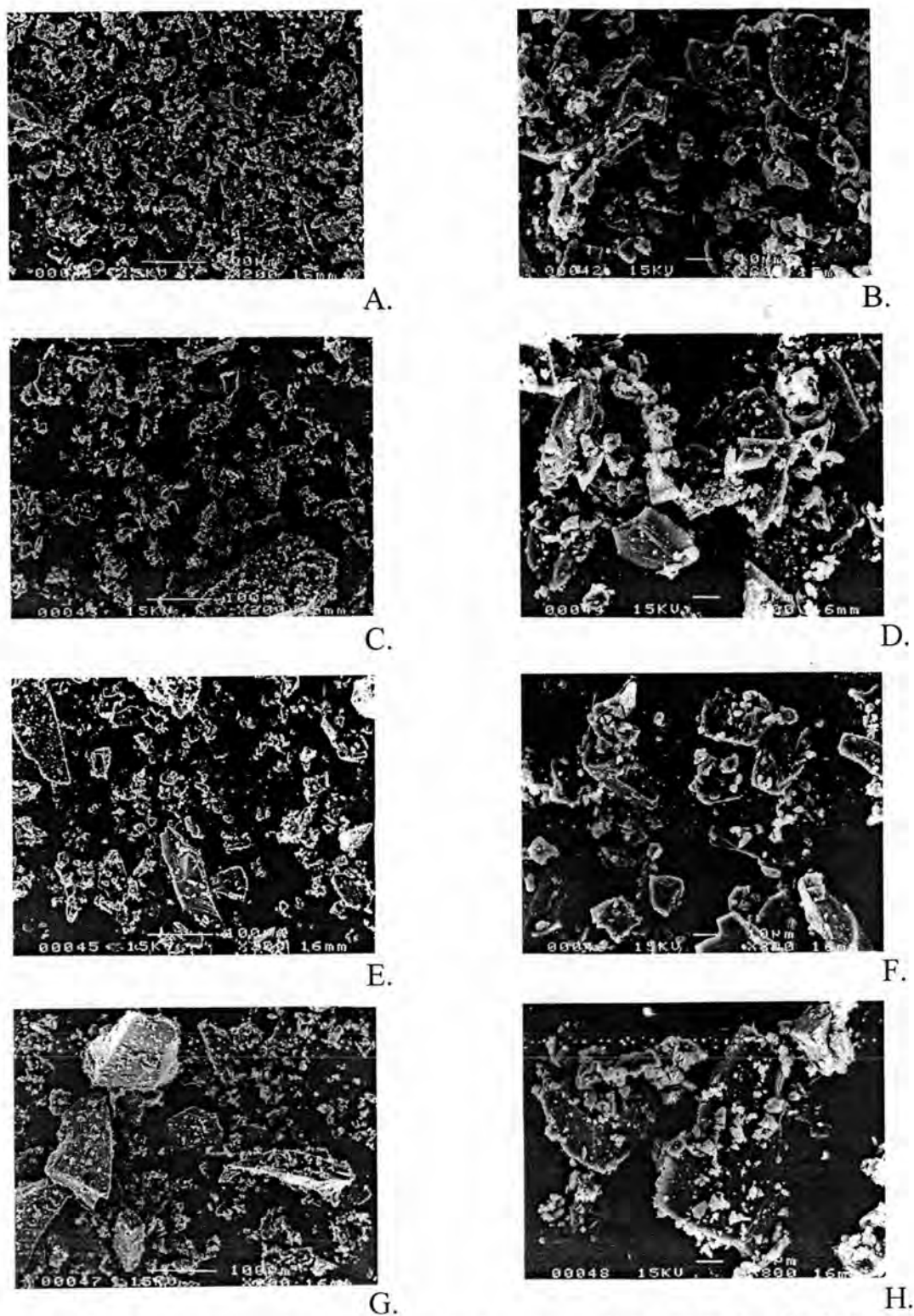
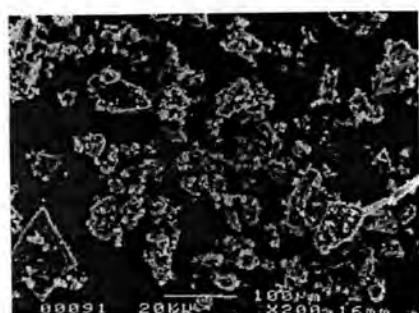
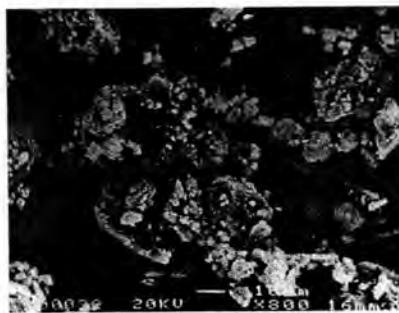


Figure 70 Photomicrographs of nifedine-2-hydroxypropyl- β -cyclodextrin , physical mixture

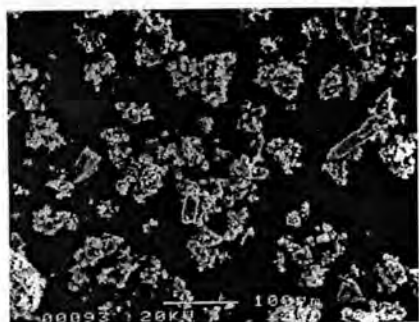
A and B: Drug-carrier ratio at 1:1,	A. x200, B. x800
C and D: Drug-carrier ratio at 1:3,	C. x200, D. x800
E and F: Drug-carrier ratio at 1:5,	E. x200, F. x800
G and H: Drug-carrier ratio at 1:10,	G. x200, H. x800



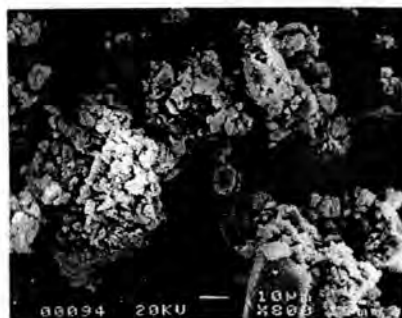
A.



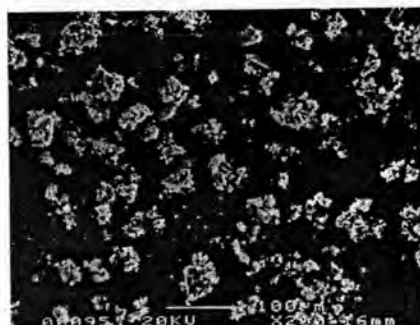
B.



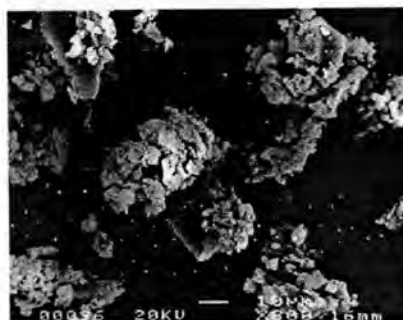
C.



D.



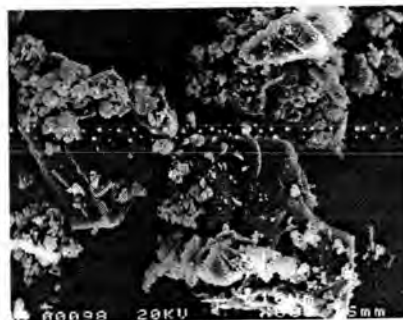
E.



F.



G.



H.

Figure 71 Photomicrographs of nifedipine-2-hydroxypropyl- β -cyclodextrin, solvent method.

A and B: Drug-carrier ratio at 1:1, A. x200, B. x800

C and D: Drug-carrier ratio at 1:3, C. x200, D. x800

E and F: Drug-carrier ratio at 1:5, E. x200, F. x800

G and H: Drug-carrier ratio at 1:10, G. x200, H. x800

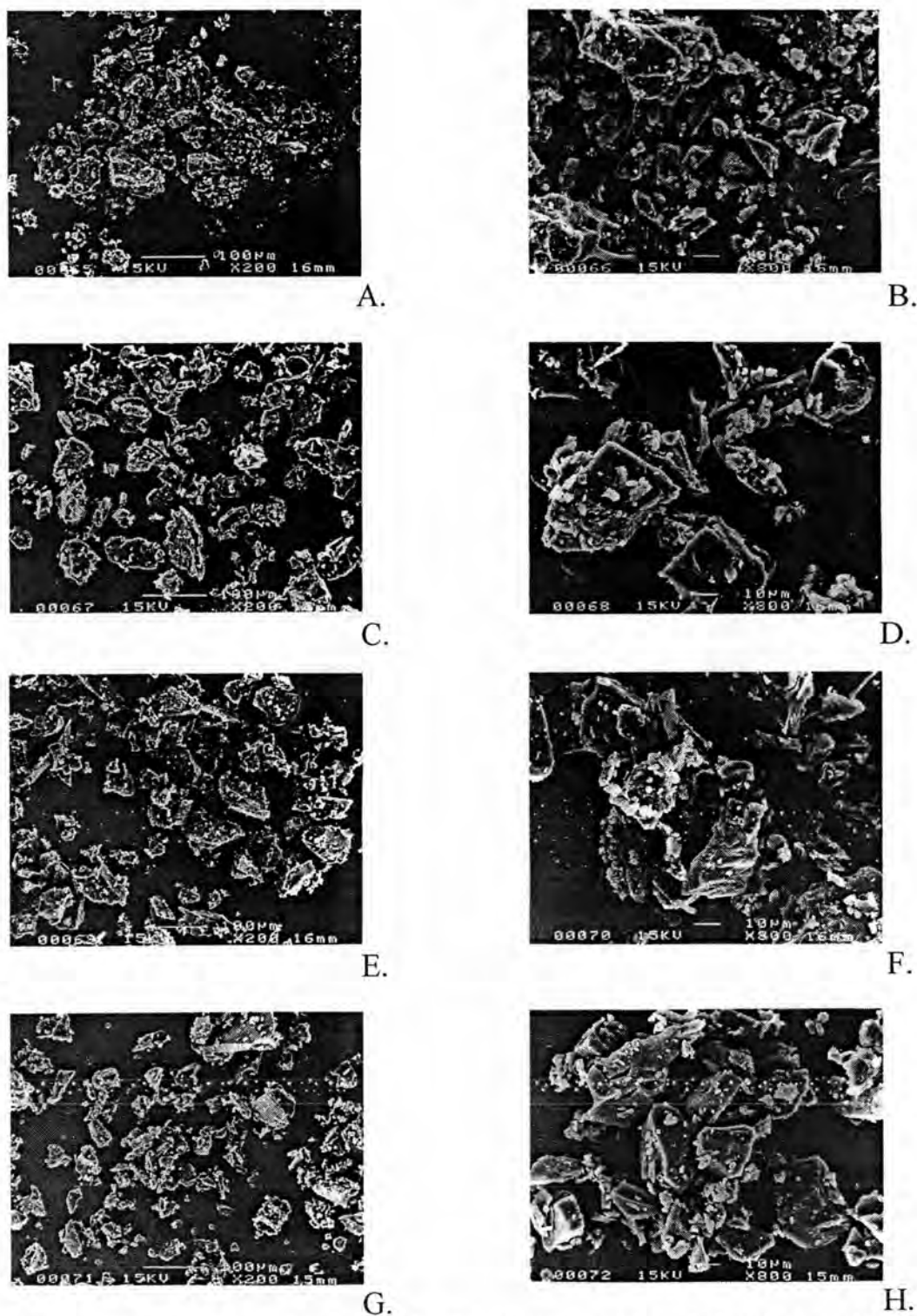


Figure 72 Photomicrographs of nifedipine-2-hydroxypropyl- β -cyclodextrin, kneading method.

A and B: Drug-carrier ratio at 1:1, A. x200, B. x800

C and D: Drug-carrier ratio at 1:3, C. x200, D. x800

E and F: Drug-carrier ratio at 1:5, E. x200, F. x800

G and H: Drug-carrier ratio at 1:10, G. x200, H. x800

4.2 The X-ray Diffractograms

4.2.1 X-ray diffractogram of pure drug and nontreated pure drug.

Major X-ray diffraction peaks of nifedipine were particularly observed at five diffraction angle of 8.0, 11.9, 16.2, 19.5 and 24 at 2θ (Figure 73). PEG4000, PEG6000 were in crystalline form. Their peaks were particularly observed at 19.5° and 23.5° respectively (Figures 74-81). Poloxamers were also in crystalline form with the peaks of 19° and 23.5° (Figures 82-93). A crystalline β -cyclodextrin, in Figures 94-95, a distinguished peaks were at 8.5° and 12.5° . In contrast of 2-hydroxypropyl- β -cyclodextrin in Figure 96-98, it was in amorphous form.

4.2.2 X-ray diffractogram of nifedipine-PEGs solid dispersion.

The X-ray diffraction pattern of nifedipine-PEGs systems are illustrated in Figures 74-81. PEG4000 and PEG6000, in all systems were in a similar manner. The observed major peaks of nifedipine presented at 8° , 11.9° , 15.9° and 16.8° , however at higher ratio of carriers their peak intensity were markedly decreased. At the ratio of 1:10, the distinguished peak of nifedipine could not be detected, it can be assumed that amorphous of nifedipine may be taken placed in the system. For the dispersion of PEG6000 physical mixtures, it was found that the distinguished peaks of nifedipine could rarely be detected since 1:3 to 1:5 ratio. In each system, two major peaks of PEG4000 or PEG6000 can be observed about 19.2° and 23.4° . When compared between method of preparations at 1:10 ratio, it revealed that PEG4000 dispersion by melting method seemed similar to the melt of PEG6000 at 1:10 ratio.

4.2.3 X-ray diffractogram of nifedipine-poloxamers solid dispersion.

The X-ray diffractogram of poloxamer system are demonstrated in Figures 82-93. In the case of poloxamer, the result in the system was similar to PEG systems that when ratio of carrier was increased, the major peaks of nifedipine were gradually disappeared. However, it can be seen a little peak even in the 1:10 ratio. Poloxamer407 system prepared by solvent method at 1:3 ratio, the peak at 11.7° was 2 times higher than 1:1 ratio. The crystalline peak of poloxamer407 were found at 19.3° and 23.42° throughout the dispersion system. Similarly, poloxamer188 showed distinguished peaks of at 19.3° and 23.4° in all dispersion system.

4.2.4 X-ray diffractogram of nifedipine-cyclodextrins solid dispersion.

It was revealed that each ratio in physical mixture and kneading of β -cyclodextrin, the diffraction pattern of nifedipine was still found but 2-3 times less intensity than nifedipine. Moreover the crystallinity in all systems resulted from the crystallinity of β -cyclodextrin itself, at 8.9° , 10.6° , and 12.5° were the major peaks of β -cyclodextrin (Figures 94-95). In contrast, 2-hydroxypropyl- β -cyclodextrin itself was in amorphous form as seen as the halo pattern in Figures 96-98. From the dispersion of solvent method, when the ratio of 2-hydroxypropyl- β -cyclodextrin was increased, the major peaks of nifedipine decreased. At the ratio of 1:5 and 1:10, the halo pattern similar to 2-hydroxypropyl- β -cyclodextrin curve itself were found but at the lower intensity. For the kneading method, the major peaks of nifedipine also showed a decrease mostly to be a halo pattern. However, a little diffraction could still be observed. The most detectable peaks of nifedipine were found in all physical mixtures.

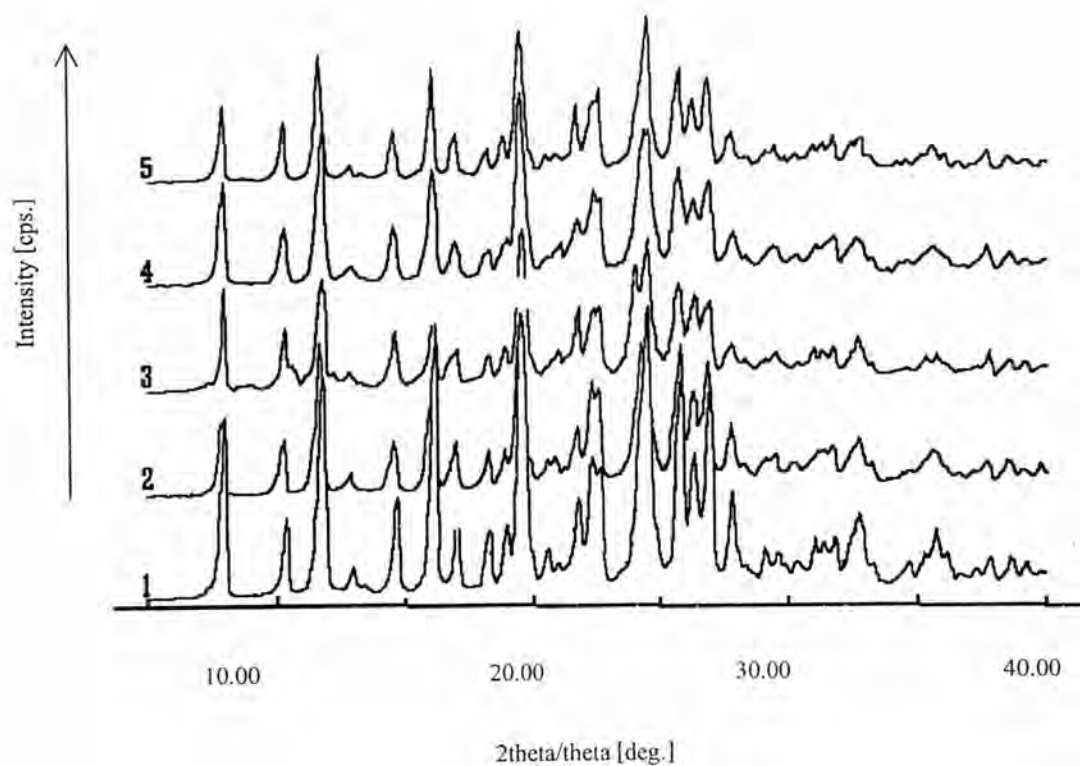


Figure 73 Powder X-ray diffraction patterns of nontreated nifedipine (1) and treated nifedipine by (2) physical mixing, (3) melting method, (4) solvent method and (5) kneading method

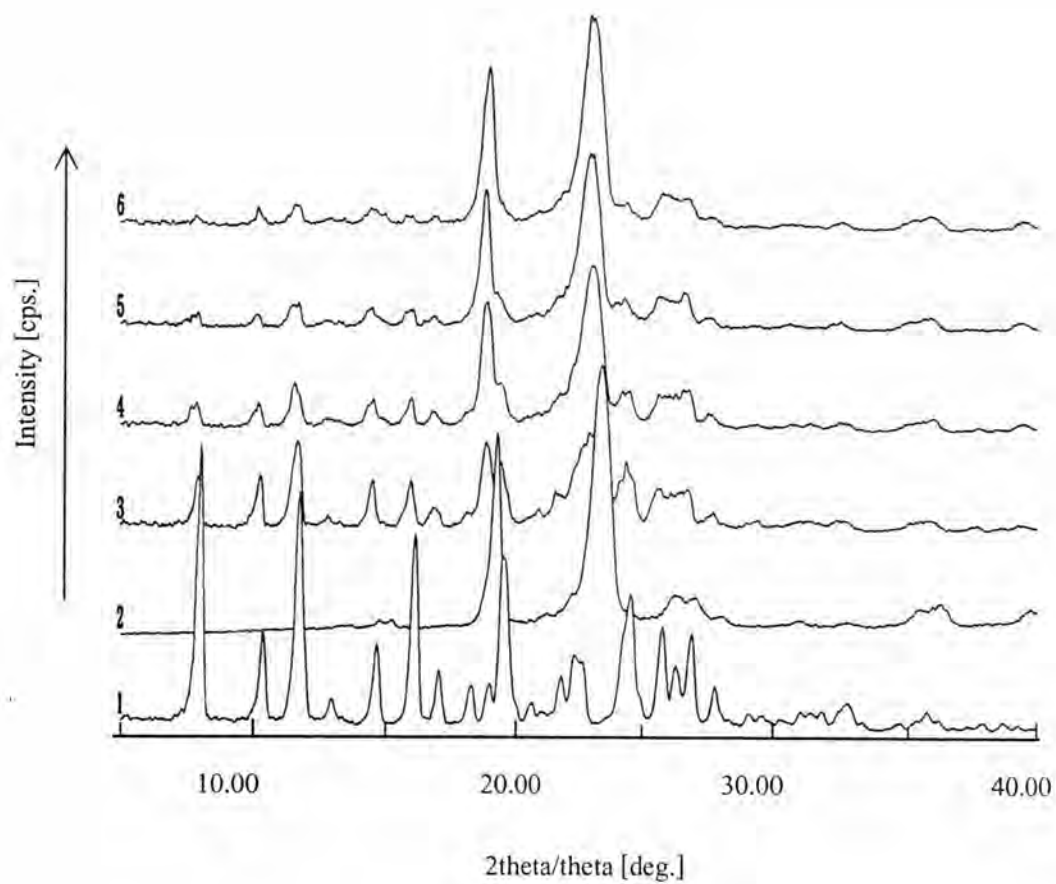


Figure 74 Powder X-ray diffraction patterns of nifedipine-PEG4000 system prepared by physical mixing (1) nifedipine, (2) PEG4000, (3) - (6) 1:1, 1:3, 1:5 and 1:10 drug: carrier ratios

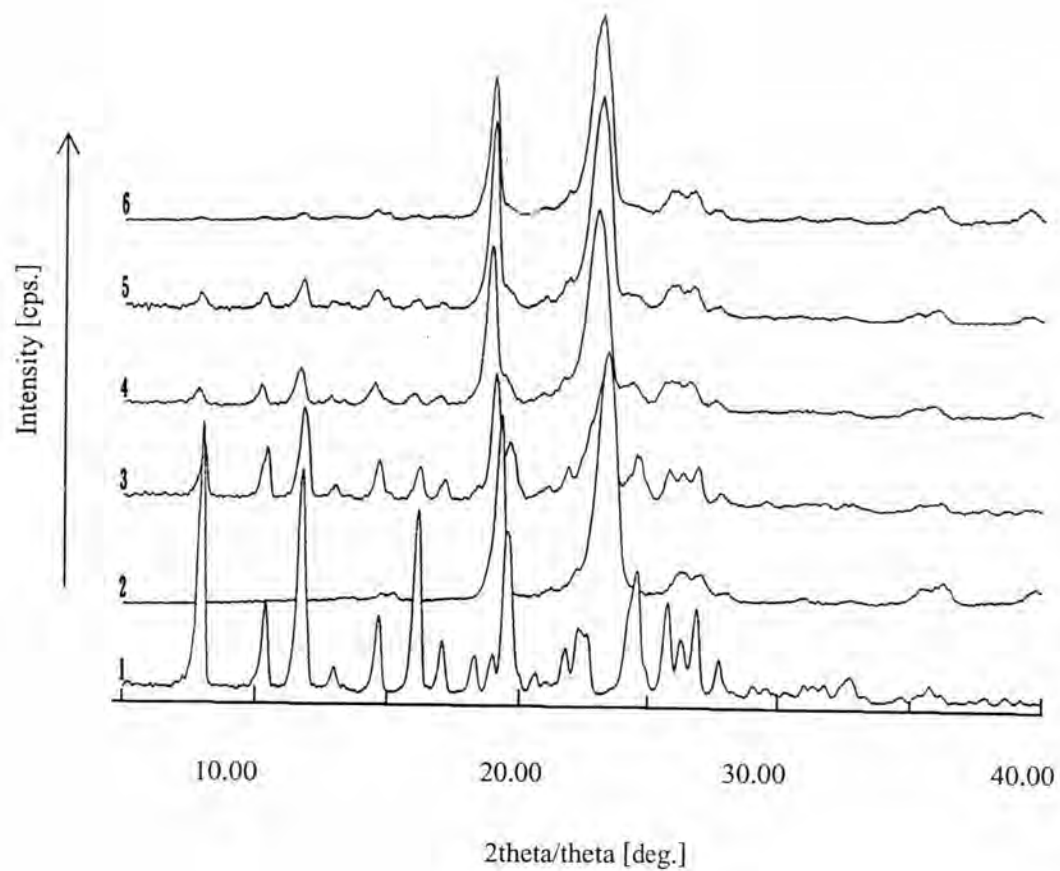


Figure 75 Powder X-ray diffraction patterns of nifedipine-PEG4000 system prepared by melting method (1) nifedipine, (2) PEG4000, (3) - (6) 1:1, 1:3, 1:5 and 1:10 drug: carrier ratios

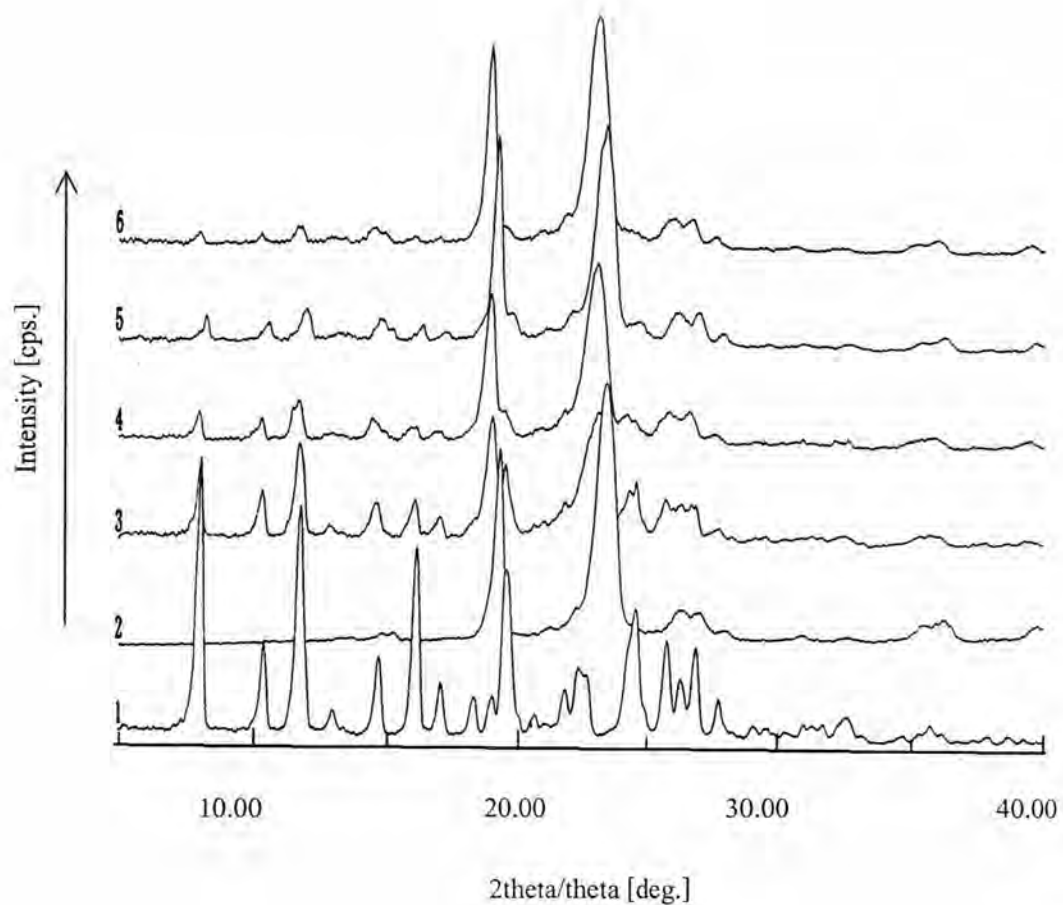


Figure 76 Powder X-ray diffraction patterns of nifedipine-PEG4000 system prepared by solvent method (1) nifedipine, (2) PEG4000, (3) - (6) 1:1, 1:3, 1:5 and 1:10 drug: carrier ratios

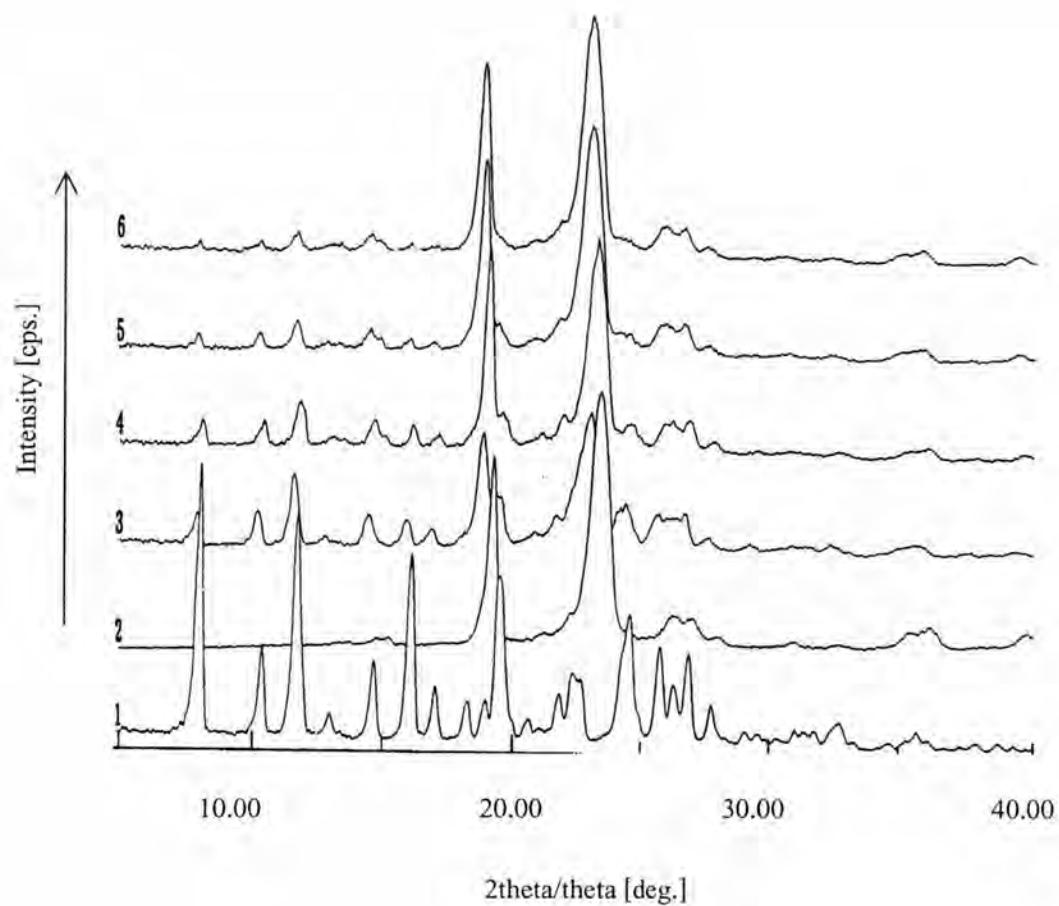


Figure 77 Powder X-ray diffraction patterns of nifedipine-PEG4000 system prepared by kneading method (1) nifedipine, (2) PEG4000, (3) - (6) 1:1, 1:3, 1:5 and 1:10 drug: carrier ratios

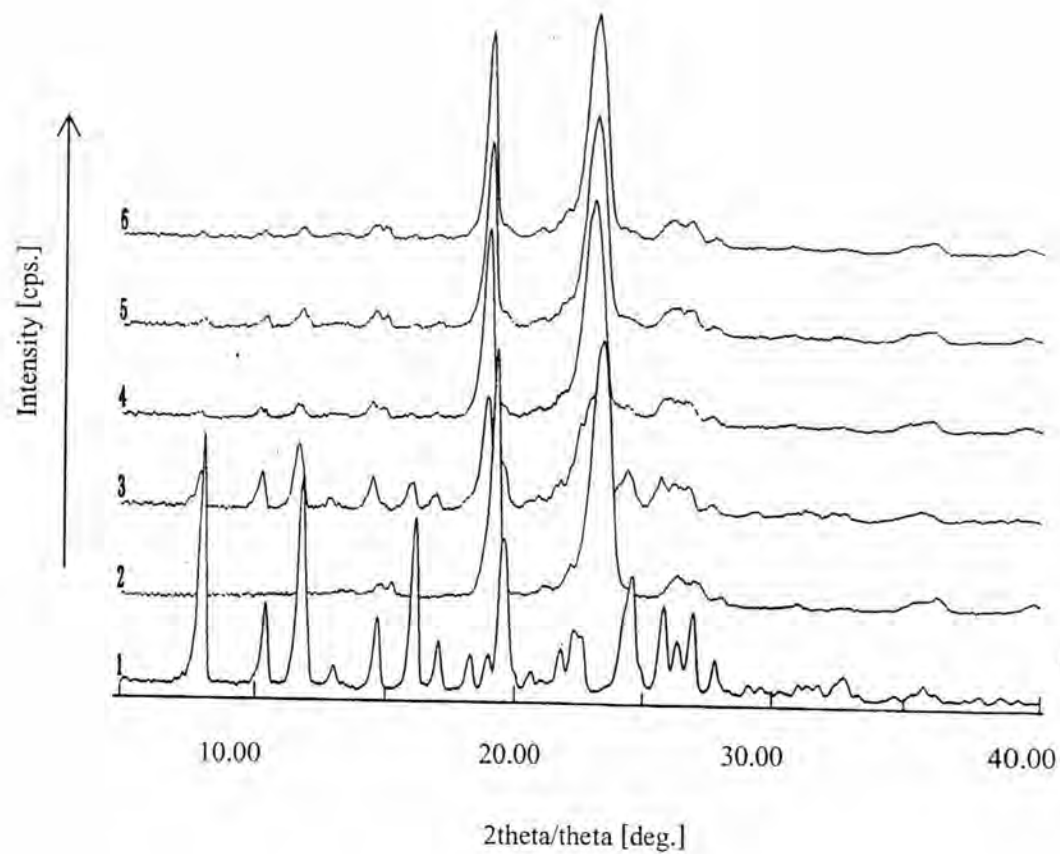


Figure 78 Powder X-ray diffraction patterns of nifedipine-PEG6000 system prepared by physical mixing (1) nifedipine, (2) PEG6000, (3) - (6) 1:1, 1:3, 1:5 and 1:10 drug: carrier ratios

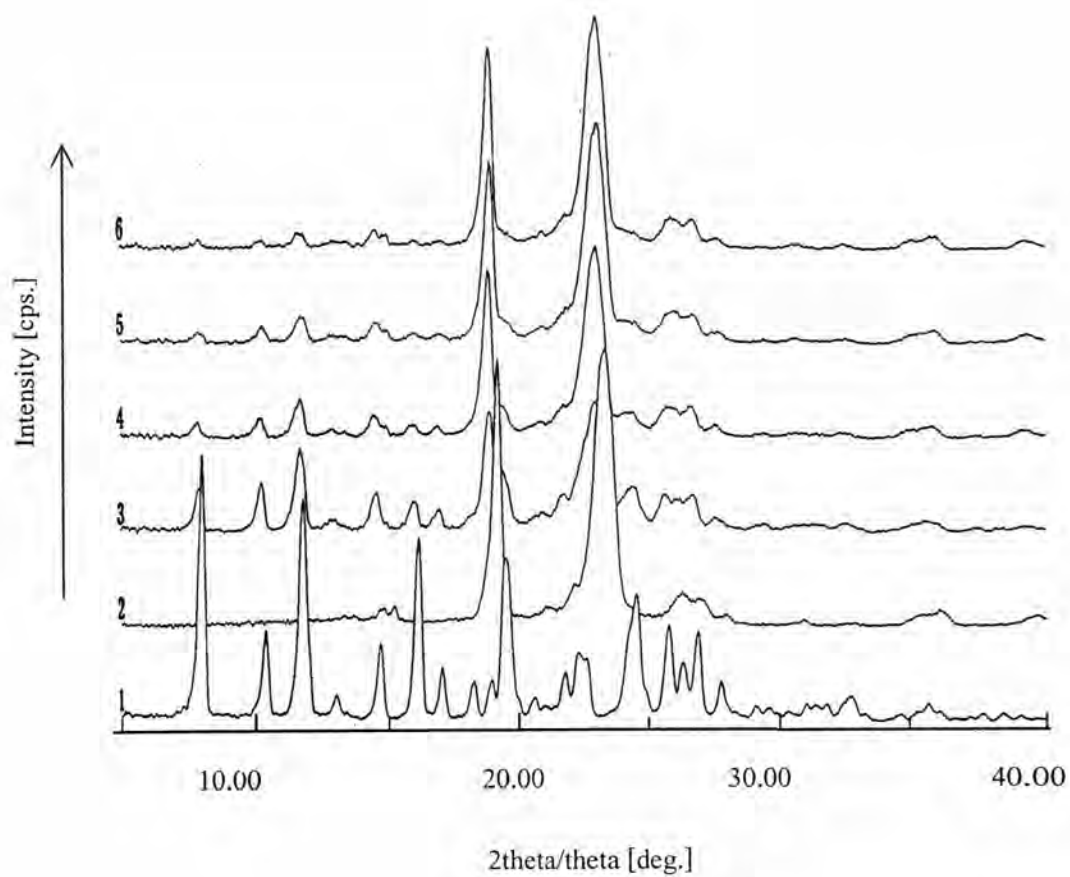


Figure 79 Powder X-ray diffraction patterns of nifedipine-PEG6000 system prepared by melting method (1) nifedipine, (2) PEG6000, (3) - (6) 1:1, 1:3, 1:5 and 1:10 drug: carrier ratios

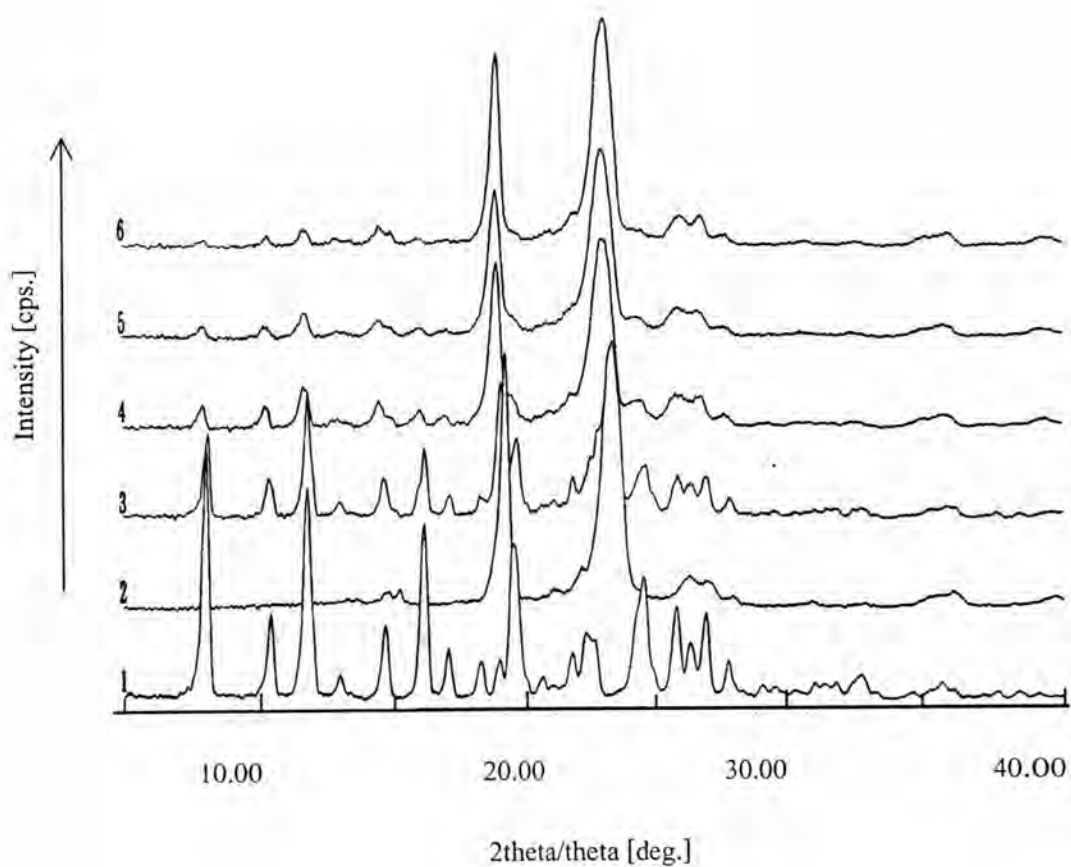


Figure 80 Powder X-ray diffraction patterns of nifedipine-PEG6000 system prepared by solvent method (1) nifedipine, (2) PEG6000, (3) - (6) 1:1, 1:3, 1:5 and 1:10 drug: carrier ratios

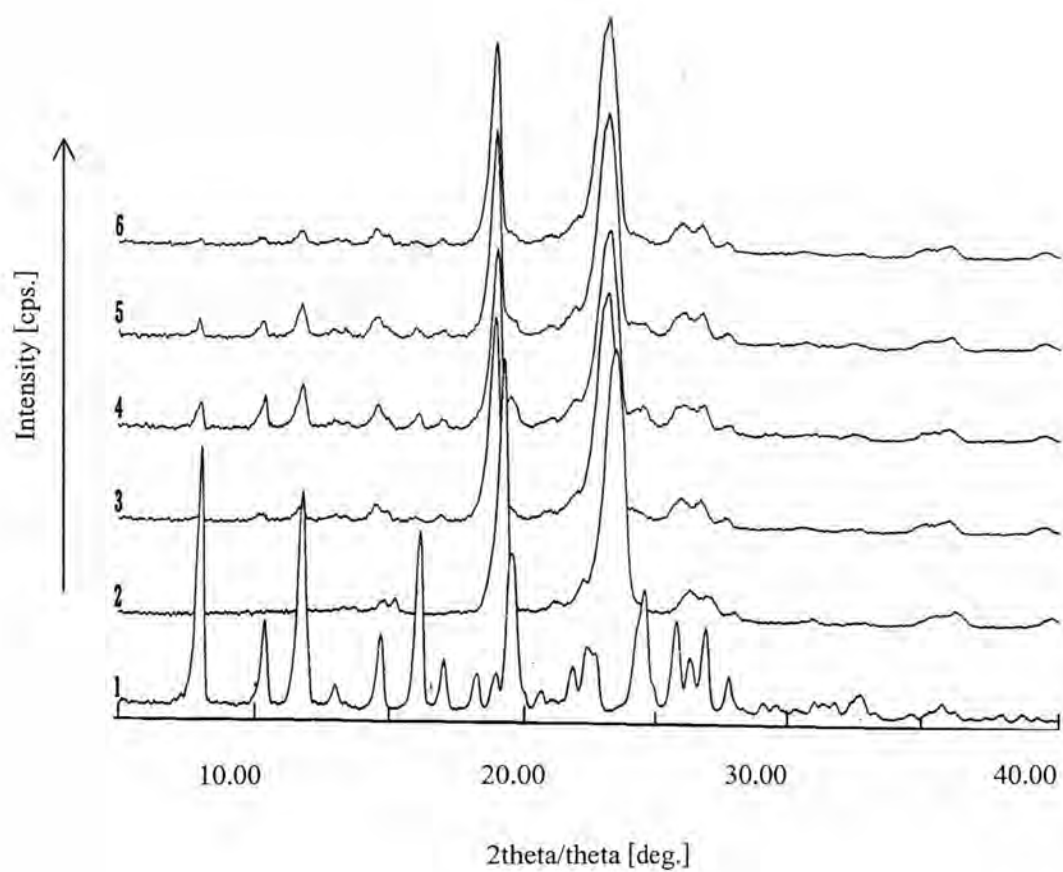


Figure 81 Powder X-ray diffraction patterns of nifedipine-PEG6000 system prepared by kneading method (1) nifedipine, (2) PEG6000, (3) - (6) 1:1, 1:3, 1:5 and 1:10 drug: carrier ratios

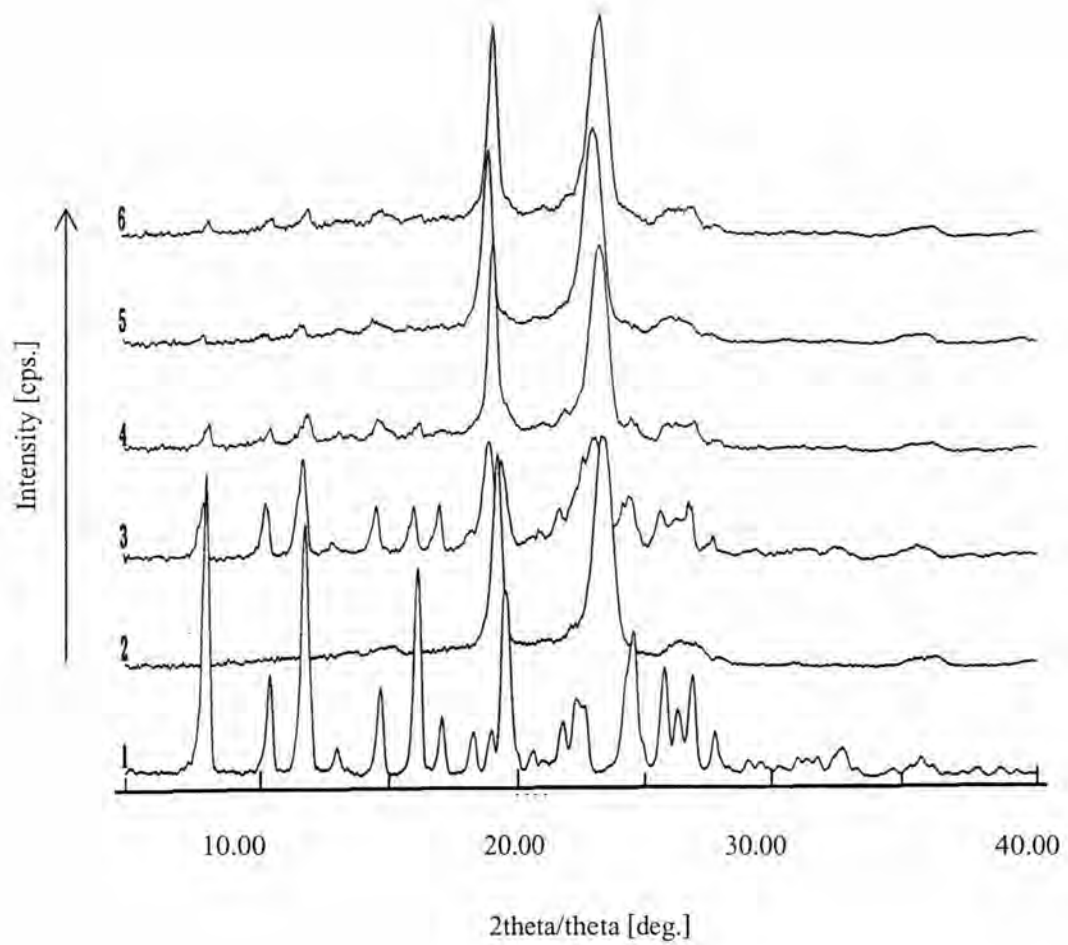


Figure 82 Powder X-ray diffraction patterns of nifedipine-poloxamer 188 system prepared by physical mixing (1) nifedipine, (2) poloxamer 188, (3) - (6) 1:1, 1:3, 1:5 and 1:10 drug: carrier ratios

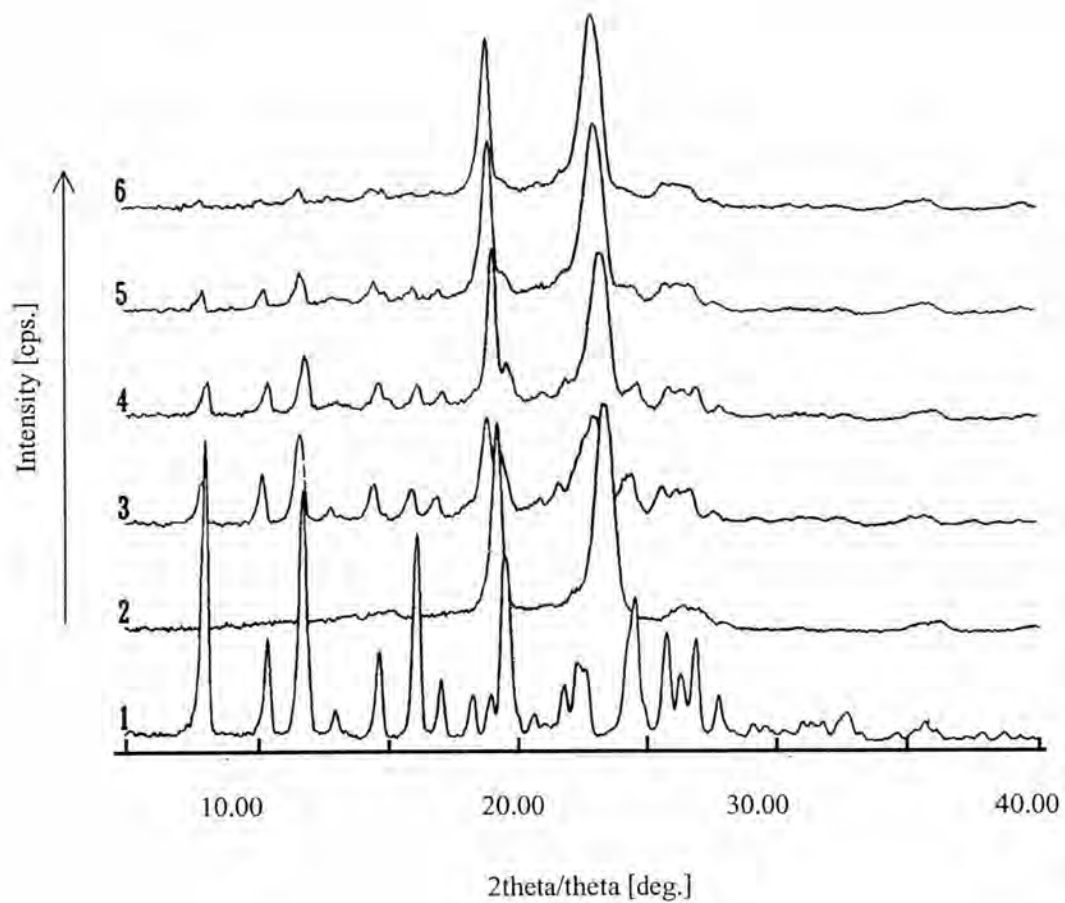


Figure 83 Powder X-ray diffraction patterns of nifedipine-poloxamer 188 system prepared by melting method (1) nifedipine, (2) poloxamer 188, (3) - (6) 1:1, 1:3, 1:5 and 1:10 drug: carrier ratios

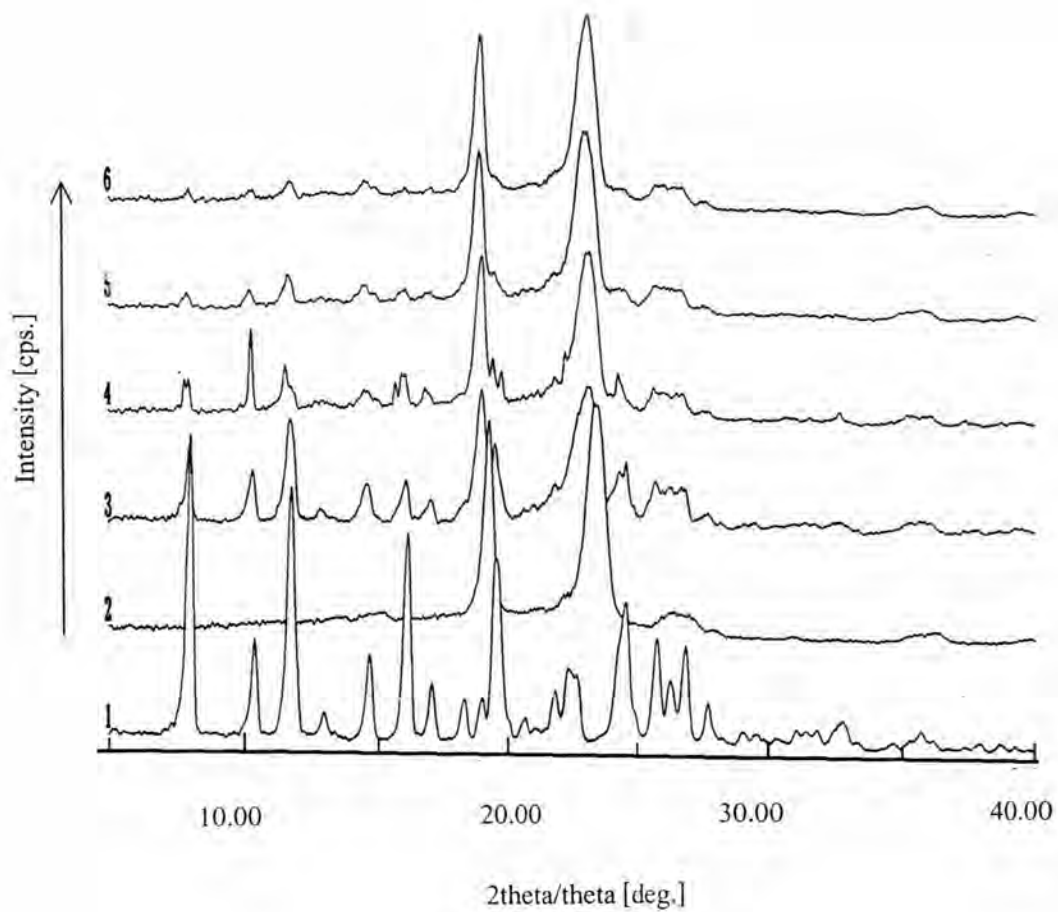


Figure 84 Powder X-ray diffraction patterns of nifedipine-poloxamer 188 system prepared by solvent method (1) nifedipine, (2) poloxamer 188, (3) - (6) 1:1, 1:3, 1:5 and 1:10 drug: carrier ratios

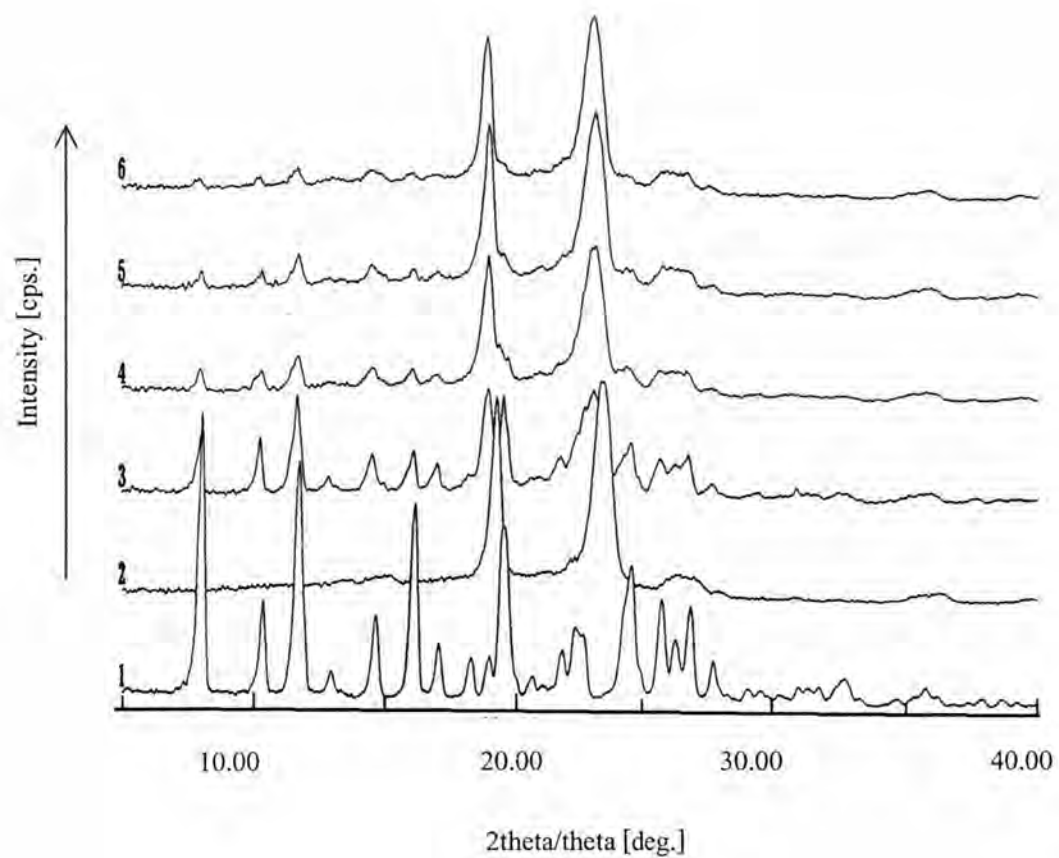


Figure 85 Powder X-ray diffraction patterns of nifedipine-poloxamer 188 system prepared by kneading method (1) nifedipine, (2) poloxamer 188, (3) - (6) 1:1, 1:3, 1:5 and 1:10 drug: carrier ratios

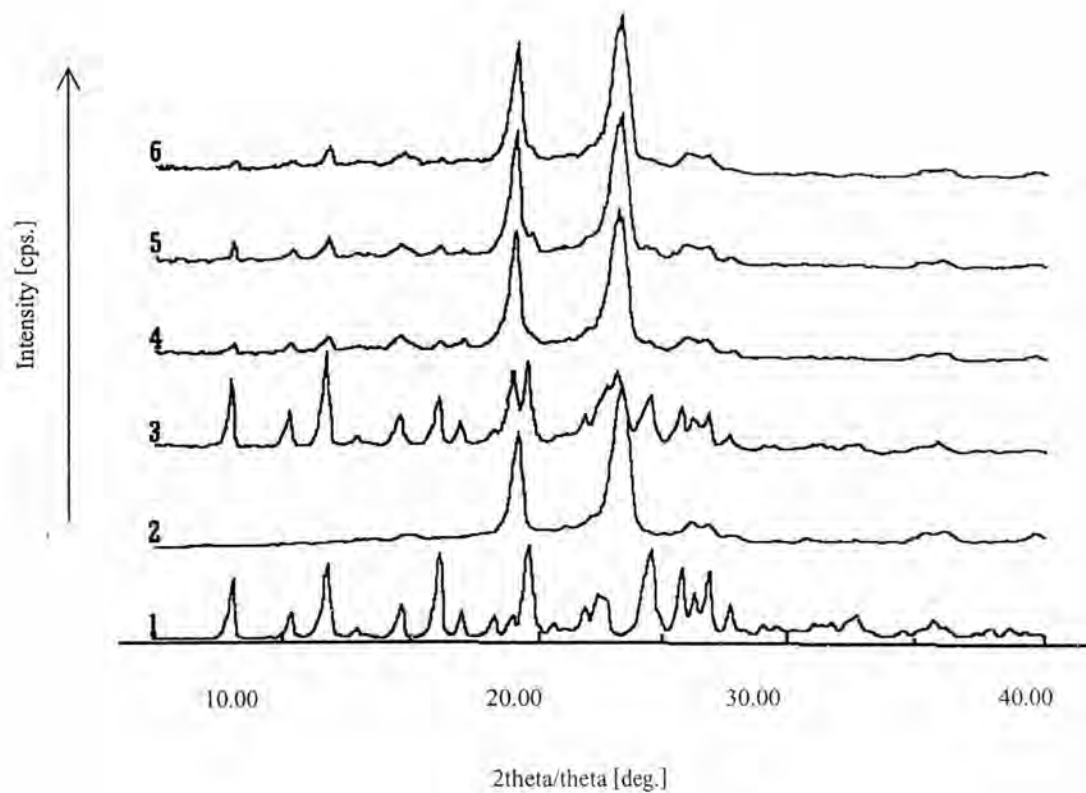


Figure 86 Powder X-ray diffraction patterns of nifedipine- poloxamer288 system prepared by physical mixing (1) nifedipine, (2) poloxamer288, (3) - (6) 1:1, 1:3, 1:5 and 1:10 drug: carrier ratios

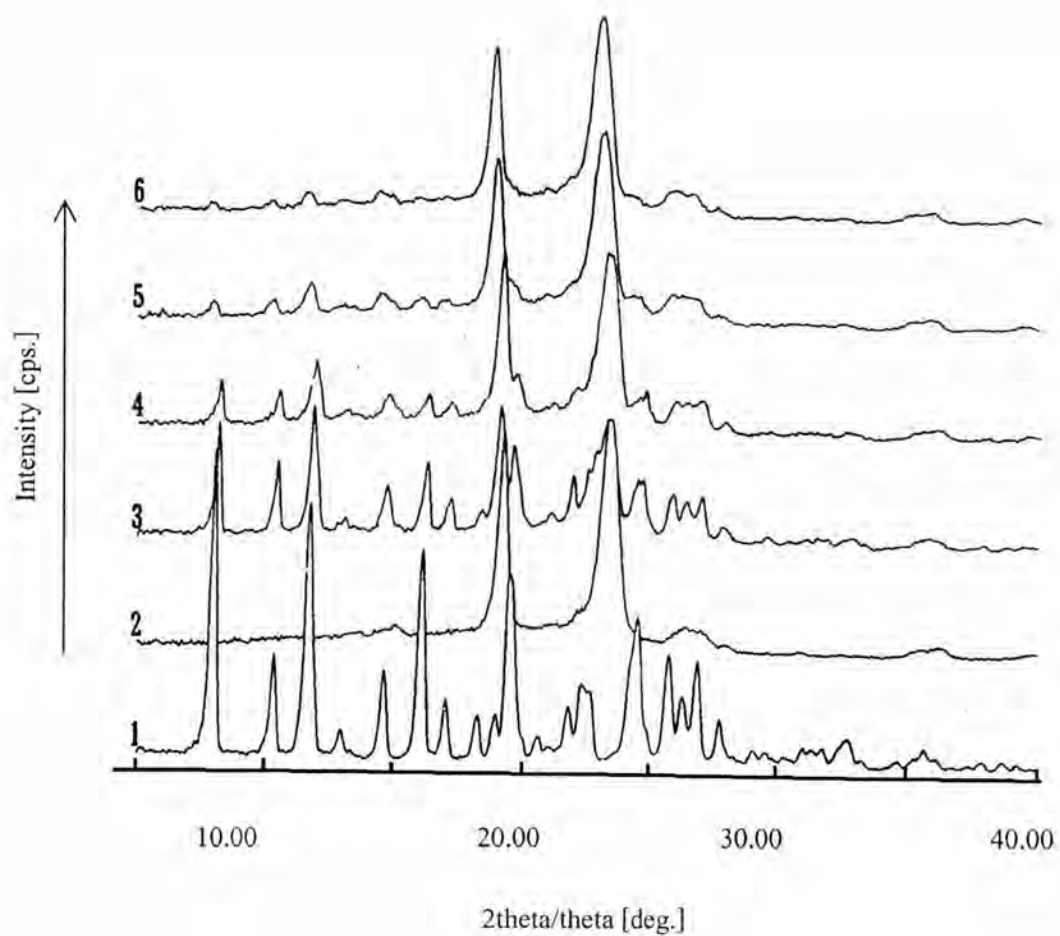


Figure 87 Powder X-ray diffraction patterns of nifedipine-poloxamer 288 system prepared by melting method (1) nifedipine, (2) poloxamer 288, (3) - (6) 1:1, 1:3, 1:5 and 1:10 drug: carrier ratios

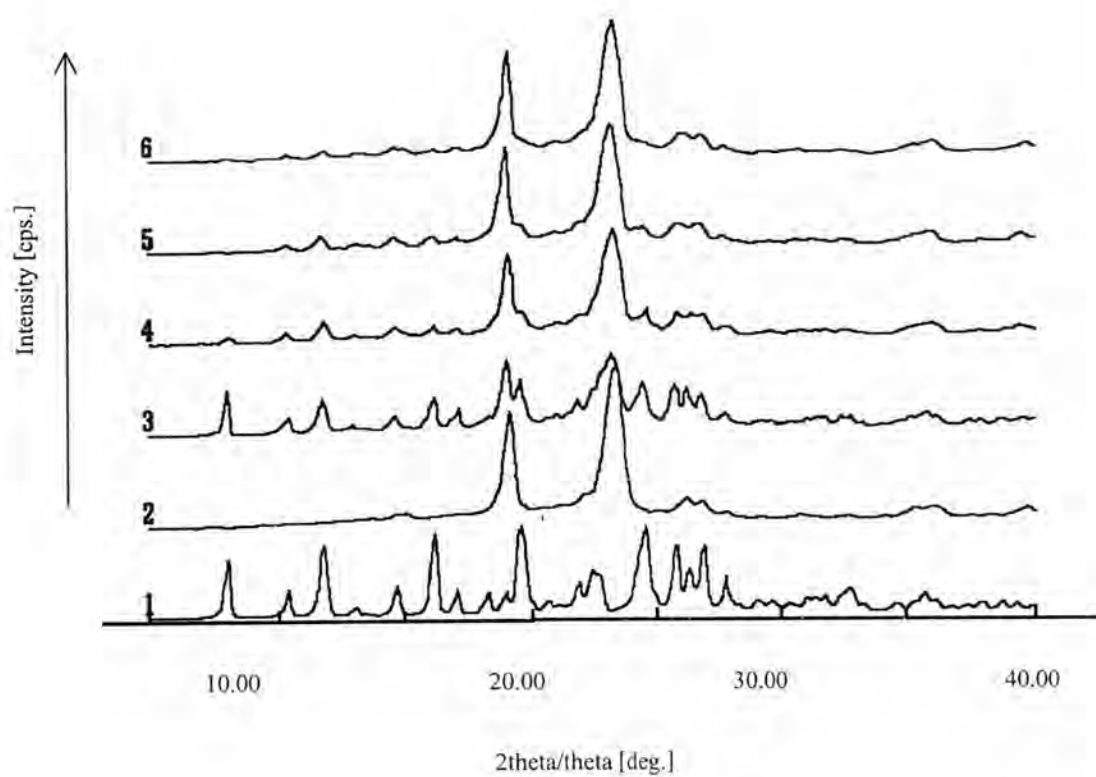


Figure 88 Powder X-ray diffraction patterns of nifedipine-poloxamer288 system prepared by solvent method (1) nifedipine, (2) poloxamer288,(3) - (6) 1:1, 1:3, 1:5 and 1:10 drug: carrier ratios

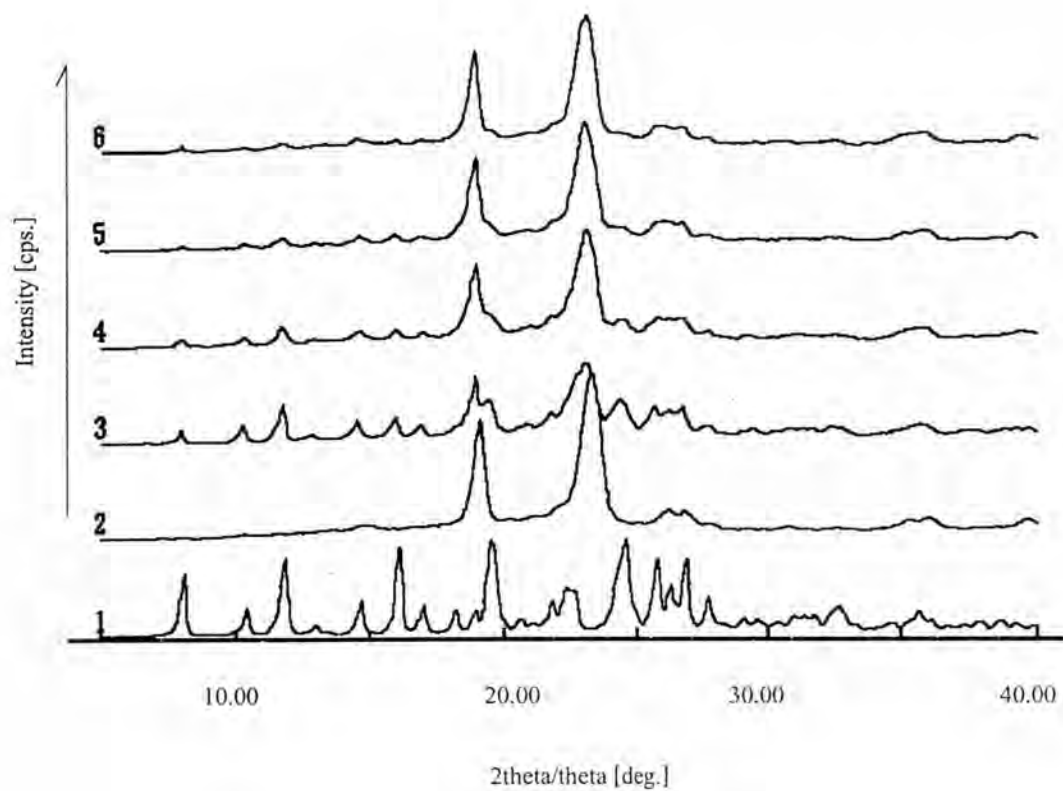


Figure 89 Powder X-ray diffraction patterns of nifedipine-poloxamer288 system prepared by kneading method (1) nifedipine, (2) poloxamer288, (3) - (6) 1:1, 1:3, 1:5 and 1:10 drug: carrier ratios

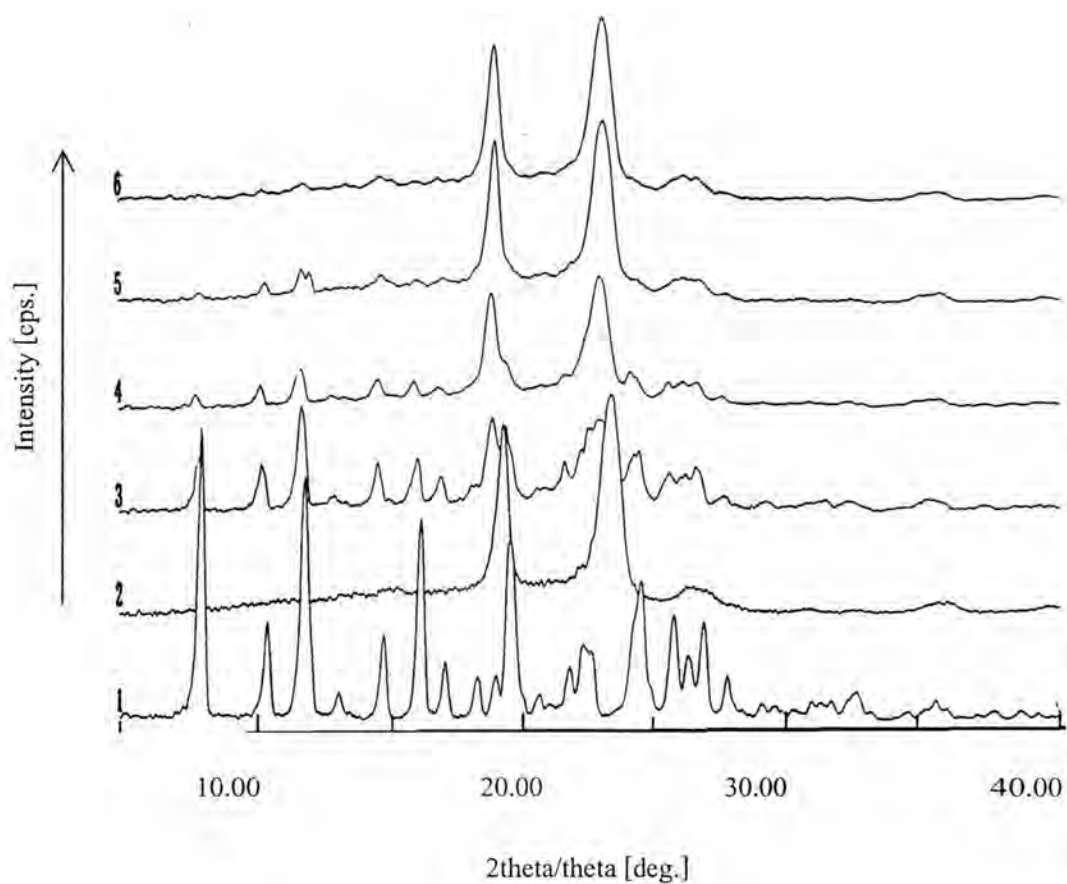


Figure 90 Powder X-ray diffraction patterns of nifedipine-poloxamer 407 system prepared by physical mixing (1) nifedipine, (2) poloxamer 407, (3) - (6) 1:1, 1:3, 1:5 and 1:10 drug: carrier ratios

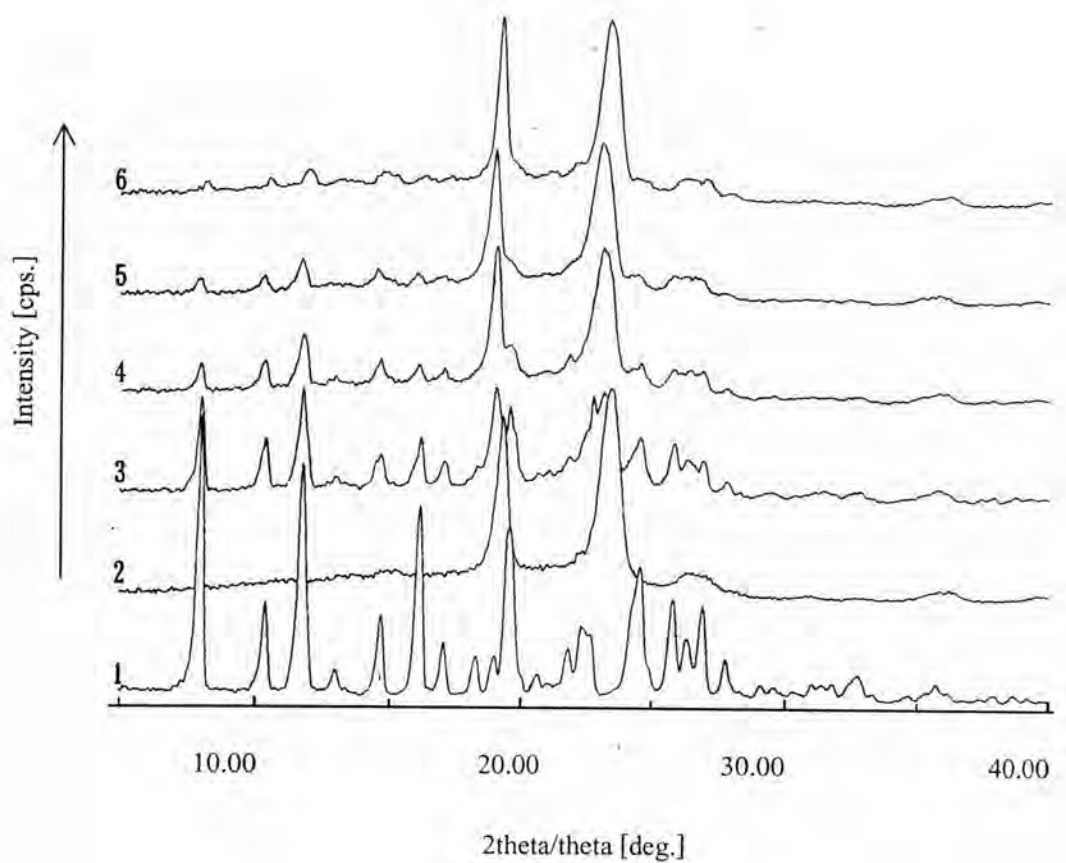


Figure 91 Powder X-ray diffraction patterns of nifedipine-poloxamer 407 system prepared by melting method (1) nifedipine, (2) poloxamer 407, (3) - (6) 1:1, 1:3, 1:5 and 1:10 drug: carrier ratios

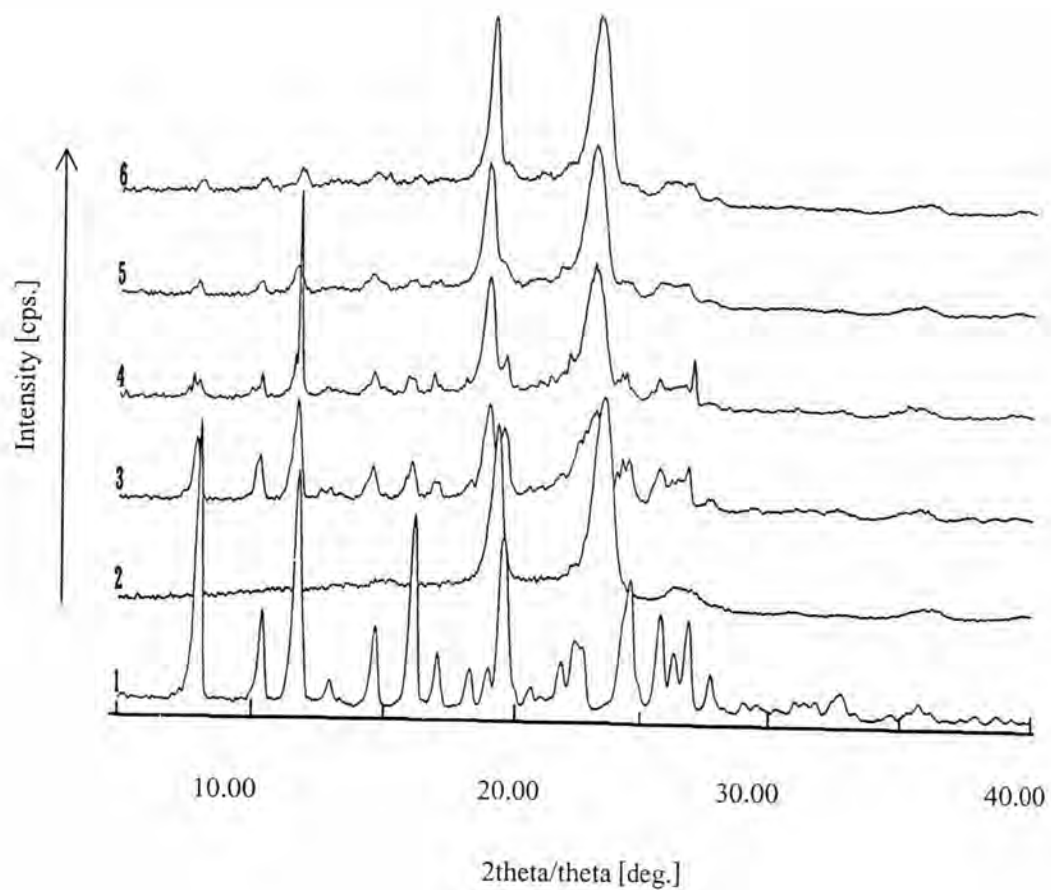


Figure 92 Powder X-ray diffraction patterns of nifedipine-poloxamer 407 system prepared by solvent method (1) nifedipine, (2) poloxamer 407, (3) - (6) 1:1, 1:3, 1:5 and 1:10 drug: carrier ratios

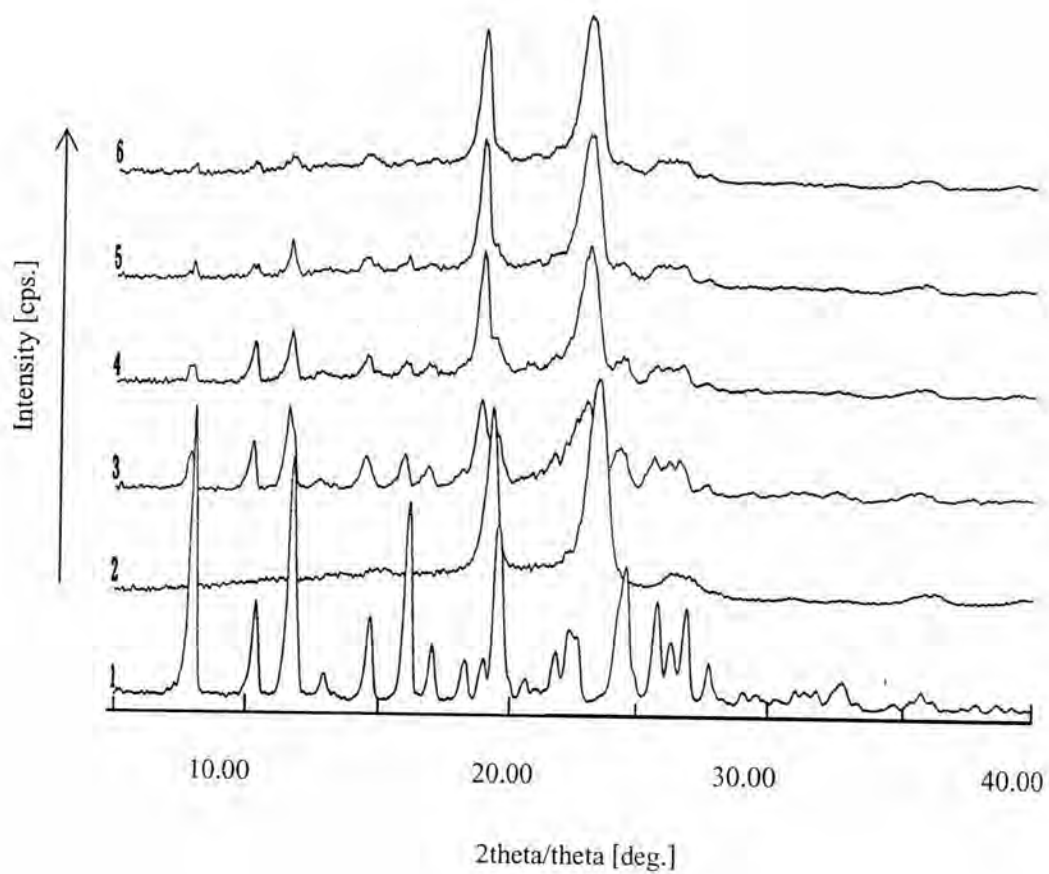


Figure 93 Powder X-ray diffraction patterns of nifedipine-poloxamer 407 system prepared by kneading method (1) nifedipine, (2) poloxamer 407, (3) - (6) 1:1, 1:3, 1:5 and 1:10 drug: carrier ratios

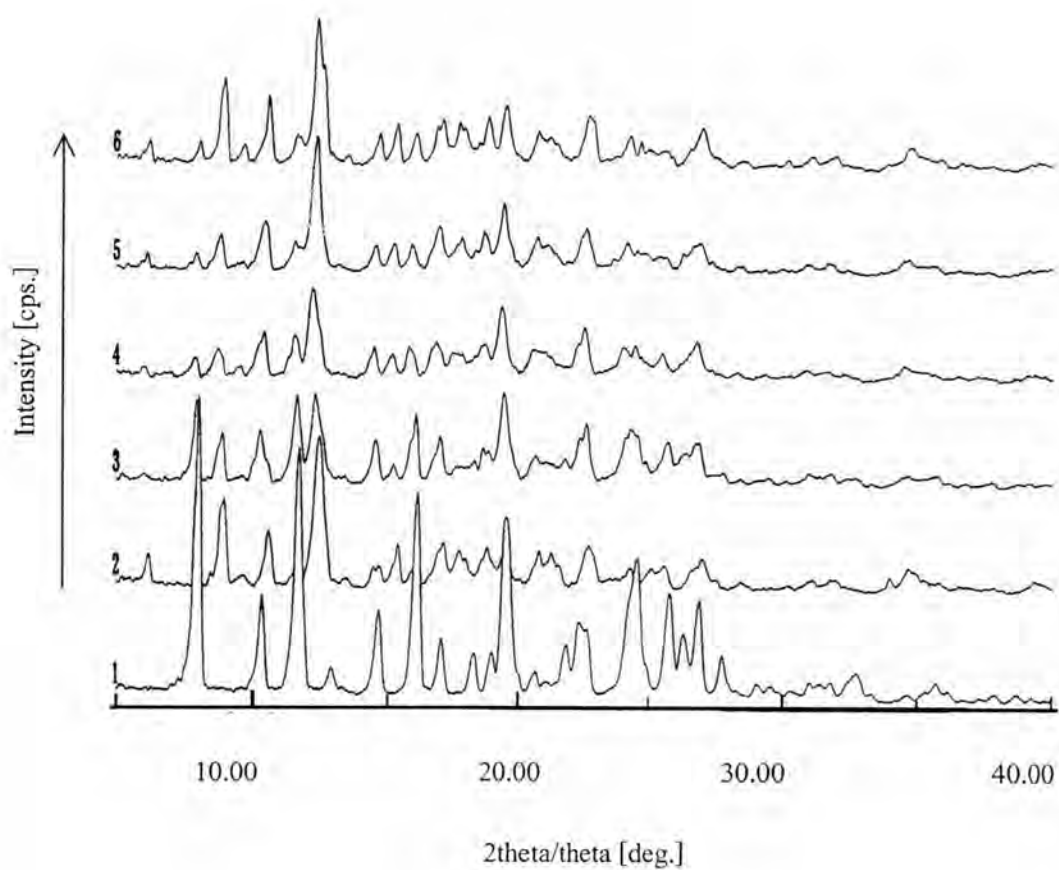


Figure 94 Powder X-ray diffraction patterns of nifedipine- β -cyclodextrin(BCD) system prepared by physical mixing (1) nifedipine, (2) BCD, (3) - (6) 1:1, 1:3, 1:5 and 1:10 drug: carrier ratios

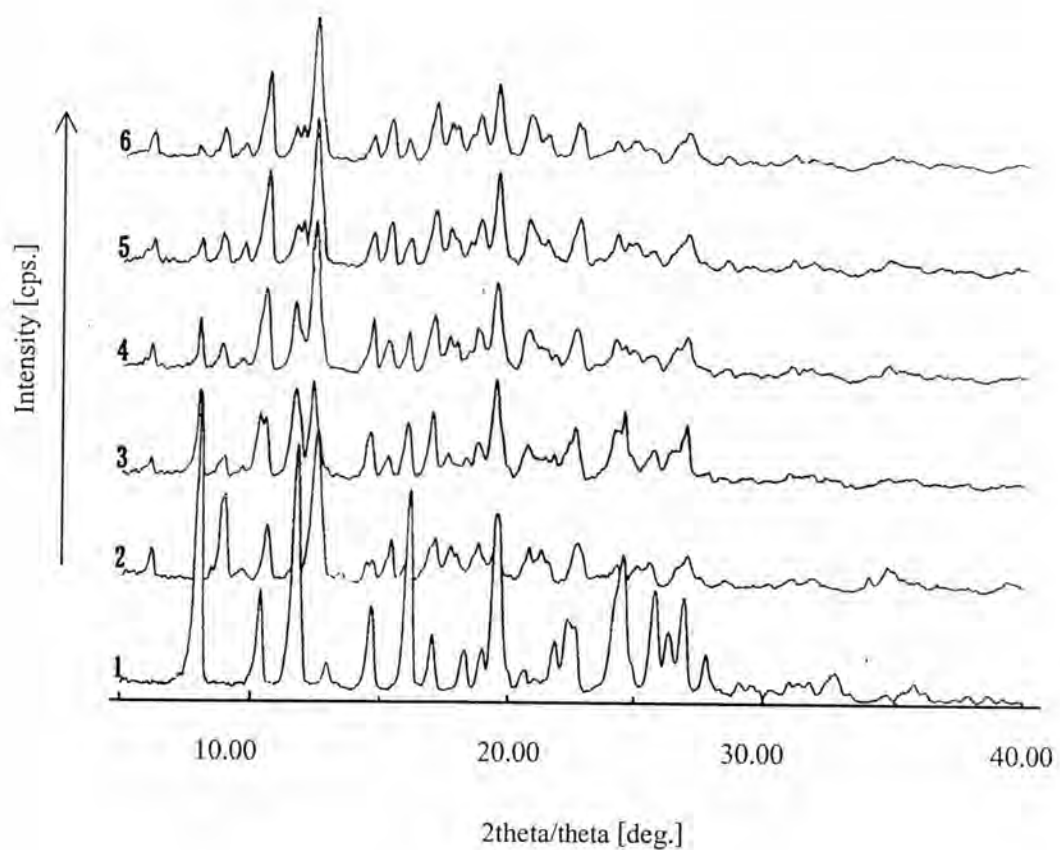


Figure 95 Powder X-ray diffraction patterns of nifedipine- β -cyclodextrin(BCD) system prepared by kneading method (1) nifedipine, (2) BCD,(3) - (6) 1:1, 1:3, 1:5 and 1:10 drug: carrier ratios

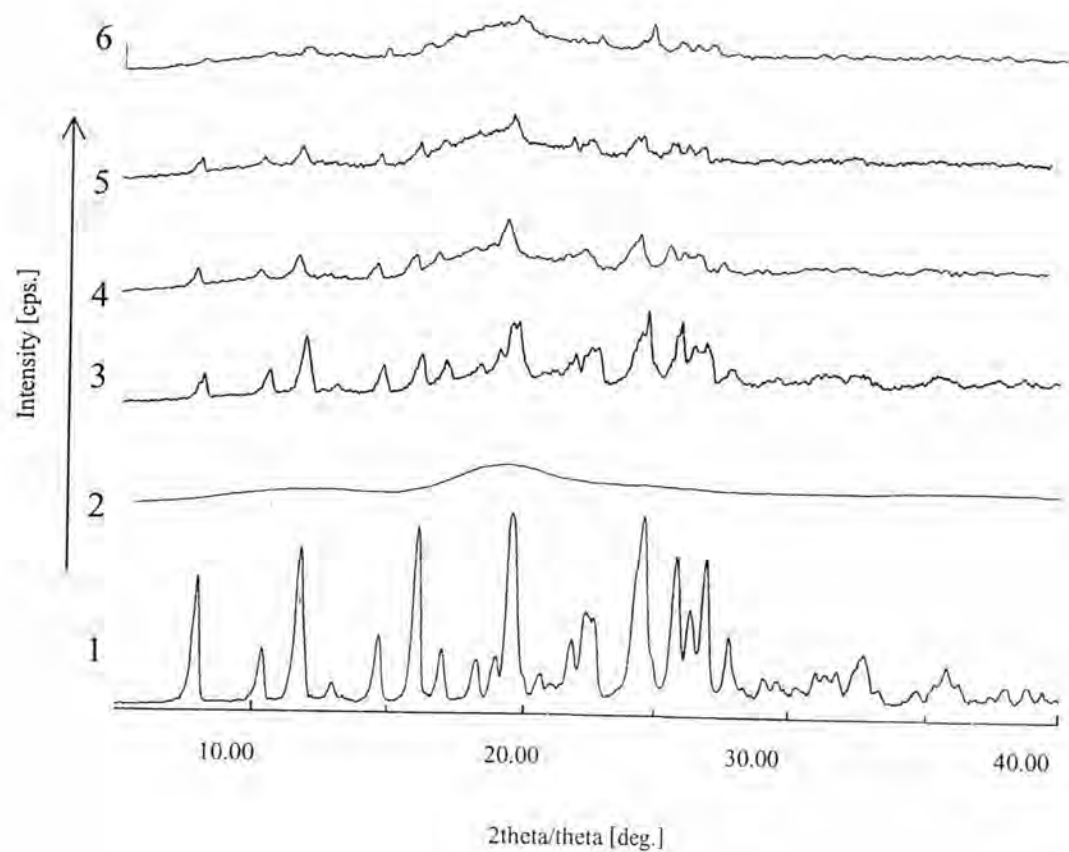


Figure96 Powder X-ray diffraction patterns of nifedipine-2-hydroxypropyl β -cyclodextrin system prepared by physical mixing (1) nifedipine, (2) 2-HBCD, (3) - (6) 1:1, 1:3, 1:5 and 1:10 drug: carrier ratios

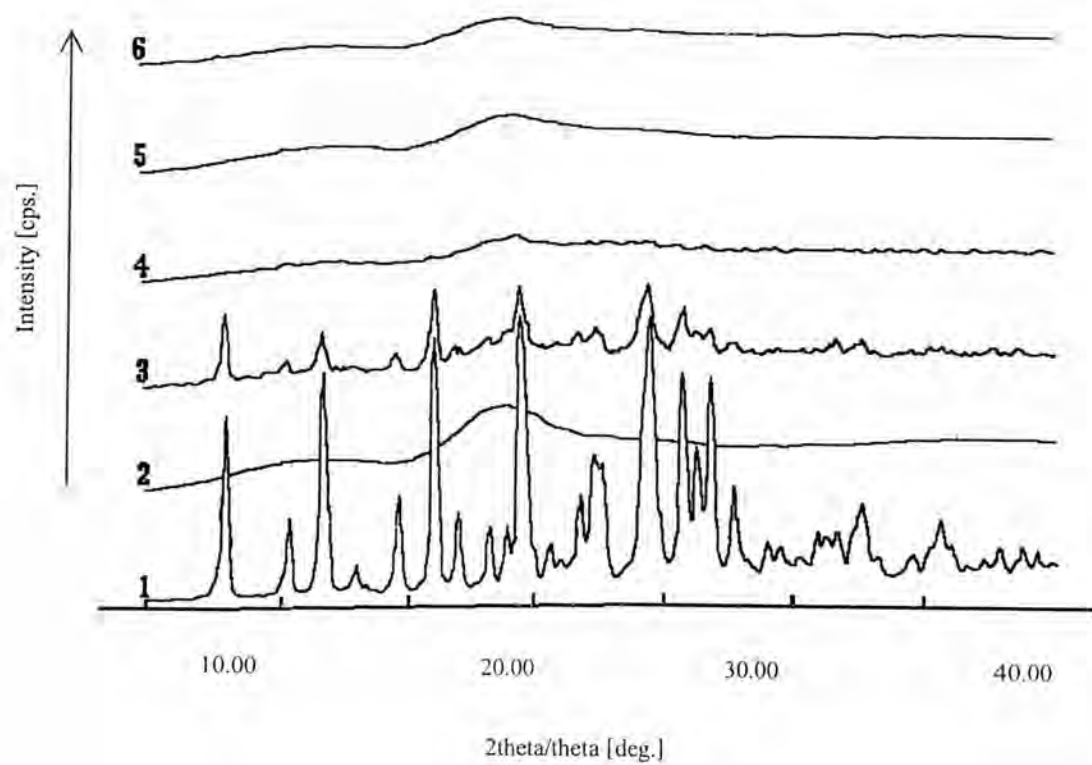


Figure 97 Powder X-ray diffraction patterns of nifedipine-2-hydroxypropyl β -cyclodextrin system prepared by solvent method (1) nifedipine, (2) 2-HBCD, (3) - (6) 1:1, 1:3, 1:5 and 1:10 drug: carrier ratios

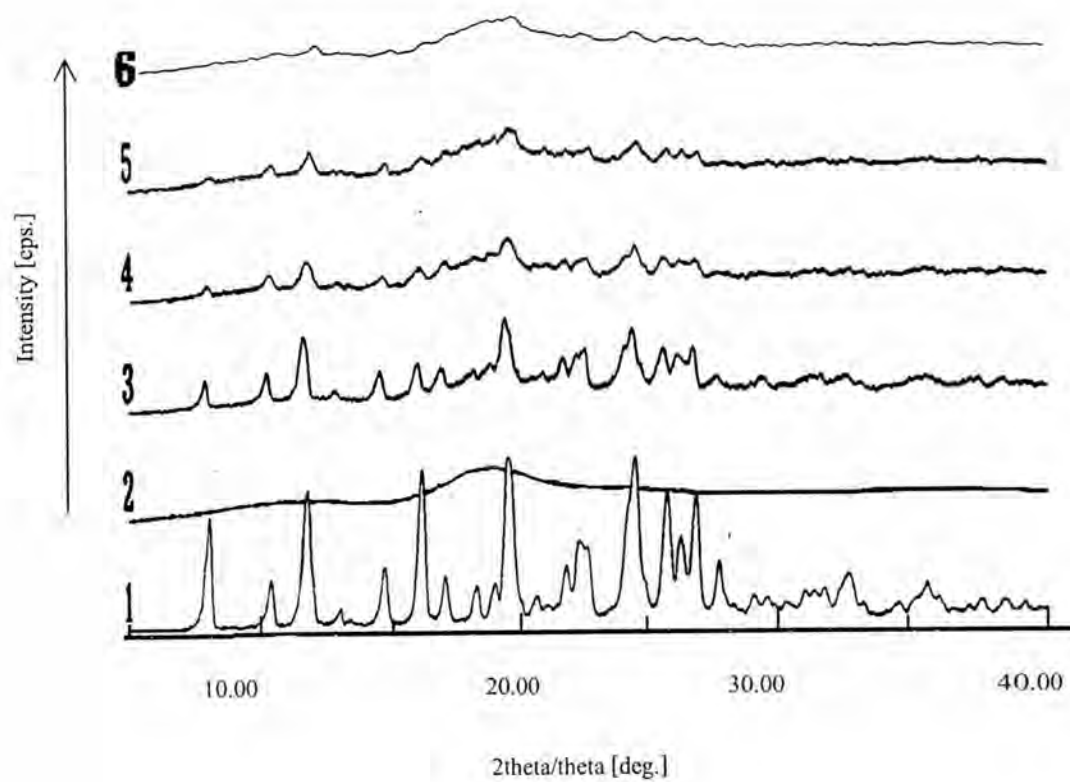


Figure98 Powder X-ray diffraction patterns of nifedipine-2-hydroxypropyl β -cyclodextrin system prepared by kneading method (1) nifedipine, (2) 2-HBCD, (3) - (6) 1:1, 1:3, 1:5 and 1:10 drug: carrier ratios

4.3 The Differential Scanning Calorimetry (DSC)

The DSC curves of pure nifedipine, treated nifedipine, carriers, physical mixtures and solid dispersions of nifedipine with various ratio of carriers are illustrated in Figures 99-124.

4.3.1 DSC thermograms of nifedipine and carriers.

The DSC curves of pure nontreated nifedipine (Figure 99) showed the characteristic melting endotherm at 174.8 °C. Nifedipine treated by physical mixing, melting, solvent and kneading method showed the similar melting endotherms at 174.6, 174.6, 174.4 and 174.6 °C respectively.

The thermogram of PEGs displayed endothermic peak approximately at 62.0 °C for PEG4000 and 62.2 °C for PEG6000 (Figures 100-107).

For poloxamers, the endothermic peaks showed melting point at 54.6 °C for poloxamer188, 60.5 °C for poloxamer288 and 57.5 °C for poloxamer407 (Figure 108-119).

β -Cyclodextrin (Figure 120-121) showed a broad endothermic peak of dehydration at 155.7 °C while 2-hydroxypropyl- β -cyclodextrin, (Figures 122-124) showed no endothermic peak in the experimental temperature range.

4.3.2 DSC thermograms of nifedipine-PEGs solid dispersions.

The thermogram of nifedipine-PEG4000 systems were illustrated in Figure 99-107.

The nifedipine-PEG4000 physical mixtures (Figure 100) at all mixing ratios displayed melting endotherm of PEG 4000 at 57.1-57.7°C. Only at the 1:1 mixing ratio, the thermogram showed a broad endothermic peak at 162°C. As the proportion of PEG4000 increased (at 1:3, 1:5 and 1:10 ratios), this broad peak could not be observed.

The similar DSC thermograms could also be observed in the solid dispersions prepared by melting, solvent and kneading methods.

The melts showed sharp melting endotherms of PEG4000 at 58.1-59.3°C (Figure 101). The broad melting endotherm of nifedipine could be observed only in the melt of 1:1 ratio at 151°C. In addition, a small endothermic peak was observed at 230°C.

The coevaporates showed sharp melting endotherms of PEG4000 at 56.8-59.2°C (Figure 102). The broad nifedipine melting endotherm was detected at 1:1 ratio at 145°C. Lastly, the kneaded mixtures showed sharp melting peaks of PEG4000 at 59.0-60.0°C. The broad endothermic peak of nifedipine were found at 153°C (Figure 103).

The DSC thermograms of nifedipine-PEG6000 systems were presented in Figure 104-107.

The PEG6000 physical mixtures (Figure 104) showed two endothermic peaks. One was a sharp melting endotherm of PEG6000 at the temperature slightly lower than that of pure carrier. The melting point of PEG6000 were lowered at 61.5-62.0°C. The other was a broad melting endotherm of nifedipine at 156, 140, 140 and 138°C for 1:1, 1:3, 1:5 and 1:10 ratios, respectively.

The solid dispersions prepared by melting method showed PEG6000 melting points in the range of 58.7-59.0°C (Figure 105). Melting endotherm of nifedipine was found only at the 1:1 ratio at 154°C.

The coevaporates of PEG6000 displayed PEG6000 melting endothermic peaks at 60.9-62.2°C (Figure 106). Nifedipine melting could be observed in the 1:1 and 1:3 ratios at 148° and 138°C, respectively.

For the kneaded solid dispersions, PEG6000 melting appeared at 58.5-59.8°C. Broadened peaks of nifedipine melting were found in the kneaded mixtures at 1:1, 1:5 and 1:3 ratios at 148°, 140° and 140°C, respectively (Figure 107).

4.3.3 DSC thermogram of nifedipine-poloxamers solid dispersion.

The DSC thermograms of nifedipine-poloxamers system were illustrated in Figure 108-119.

In all poloxamer188 system (Figure108-111), displayed poloxamer188 sharp melting endothermic peaks at the temperatures ranges lower than that of pure poloxamer188 itself of 54.6°C. Physical mixtures, showed poloxamer188 melting points in the range of 53.7-54.6°C, the melt mixtures at 52.5-52.9°C, the coevaporates at 52.9-53.2°C and the kneaded mixtures at 53.7-54.0°C.

Broadened endotherms of nifedipine could be detected only at 1:1 ratio of physical mixtures, melts, coevaporates and kneaded mixtures at 161, 156, 141 and 151°C, respectively.

Similarly, in all systems of poloxamer288 (Figure 122-115), showed poloxamer288 melting endotherms at the temperature ranges slightly lower than that of pure poloxamer288 at 60.5°C. Physical mixtures displayed poloxamer288 melting points at 58.6-59.0°C, the melts as much lower at 54.8-56.4°C, coevaporates at 57.7-59.0°C and the kneaded mixtures at 57.4-58.7°C.

Only at 1:1 ratio of poloxamer288 systems that nifedipine melting could be observed at broadened peaks at 164, 158, 157, and 156°C in physical mixtures, melts, coevaporates and kneaded mixtures, respectively.

For all nifedipine-poloxamer407 systems (Figure116-119), similar observations to the other two poloxamers were found. Poloxamer407 melting endotherms could be observed at the temperature ranges slightly lower than that of its pure poloxamer407 at 57.5°C. Physical mixtures showed poloxamer407 melting point at 55.3-56.0°C, the melts as much lower range at 52.4-53.1°C, the coevaporates at 54.2-55.8°C and the kneaded mixtures at 54.0-55.7°C.

Only the 1:1 ratio that nifedipine melting could be observed as broadened peaks at 160, 159, 158, and 162°C in physical mixtures, melts, coevaporates and kneaded mixtures. However, a small broadened peak of nifedipine melting could be detected also in the 1:3 ratio of kneaded mixture at 161°C.

4.3.4 DSC thermogram of nifedipine-cyclodextrins solid dispersion.

The thermograms of β -cyclodextrin systems were illustrated in Figure 120-121. The physical mixtures exhibited two characterized endotherms which referred to that of water and nifedipine (Figure 120). Nifedipine melting

could be observed in all ratios of physical mixture at the slightly lower temperature than that of pure nifedipine at 167-174°C

Similarly results were obtained in the kneaded mixture of β -cyclodextrin systems that two melting endotherms could be detected (Figure 121). It was noticed that at the ratios of 1:5 and 1:10 that two endotherms became more closely and partially fused. However, nifedipine melting could be detected at the temperatures at 167-168°C.

The thermograms of 2-hydroxypropyl- β -cyclodextrin systems were shown in Figure 122-124. As 2-hydroxypropyl- β -cyclodextrin exhibited peak of nifedipine were detected in all ratios of physical mixtures at the temperatures slightly lower than that of pure nifedipine, at 171-174°C.

However, nifedipine melting disappeared in the coevaporates of 2-hydroxypropyl- β -cyclodextrin, at the ratio of 1:5 and 1:10. While the kneaded mixtures exhibited similar thermograms to those of their physical mixtures. Nifedipine melting exhibited at the temperature range 167-173°C as small endothermic peak.

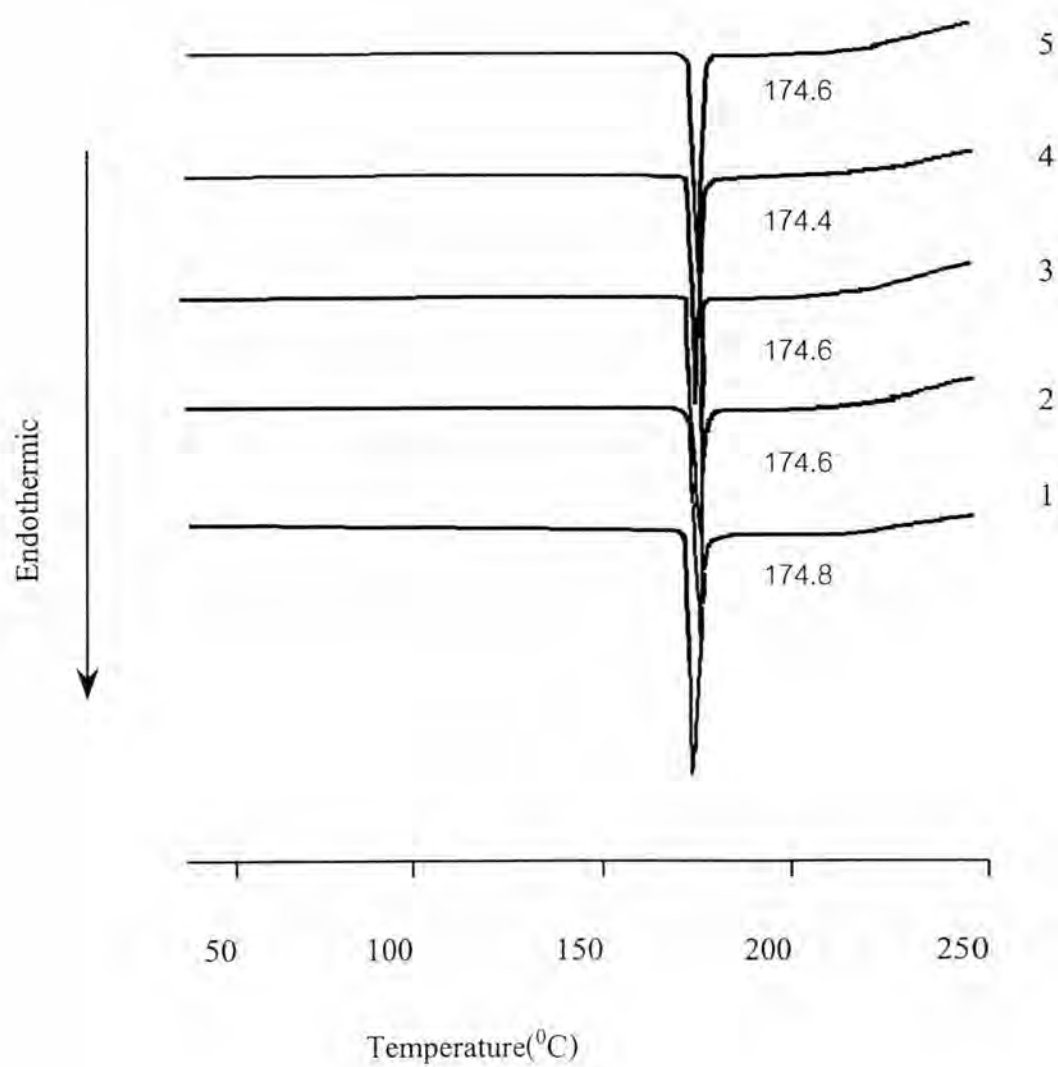


Figure 99: DSC curves of nontreated nifedipine (1) and treated nifedipine by (2) physical mixing , (3) melting method , (4) solvent method and (5) kneading method.

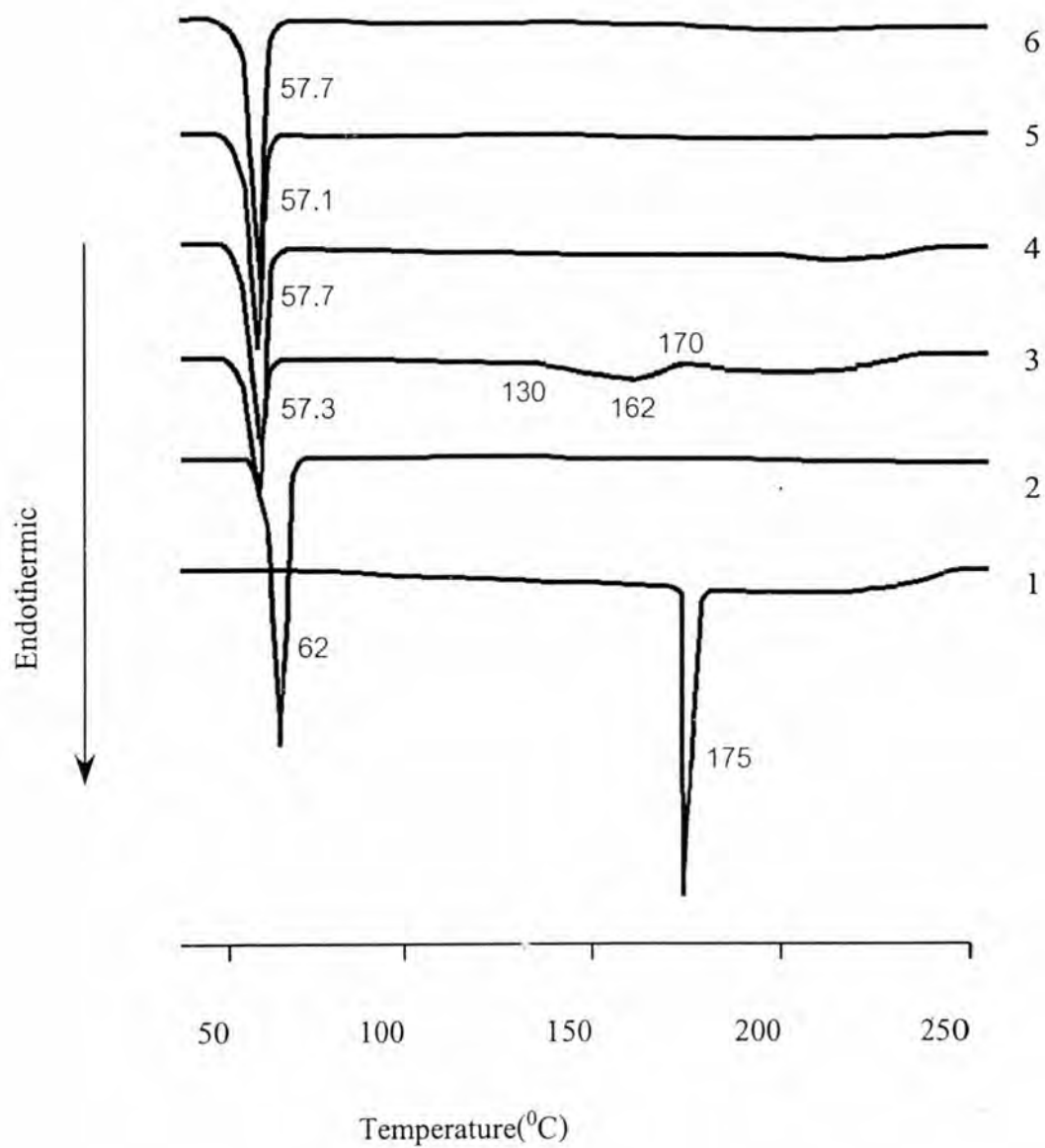


Figure 100: DSC curves of nifedipine - PEG 4000 physical mixtures containing nifedipine (1), PEG4000(2), and systems containing with ratios of 1:1(3), 1:3 (4), 1:5 (5) and 1:10 (6)

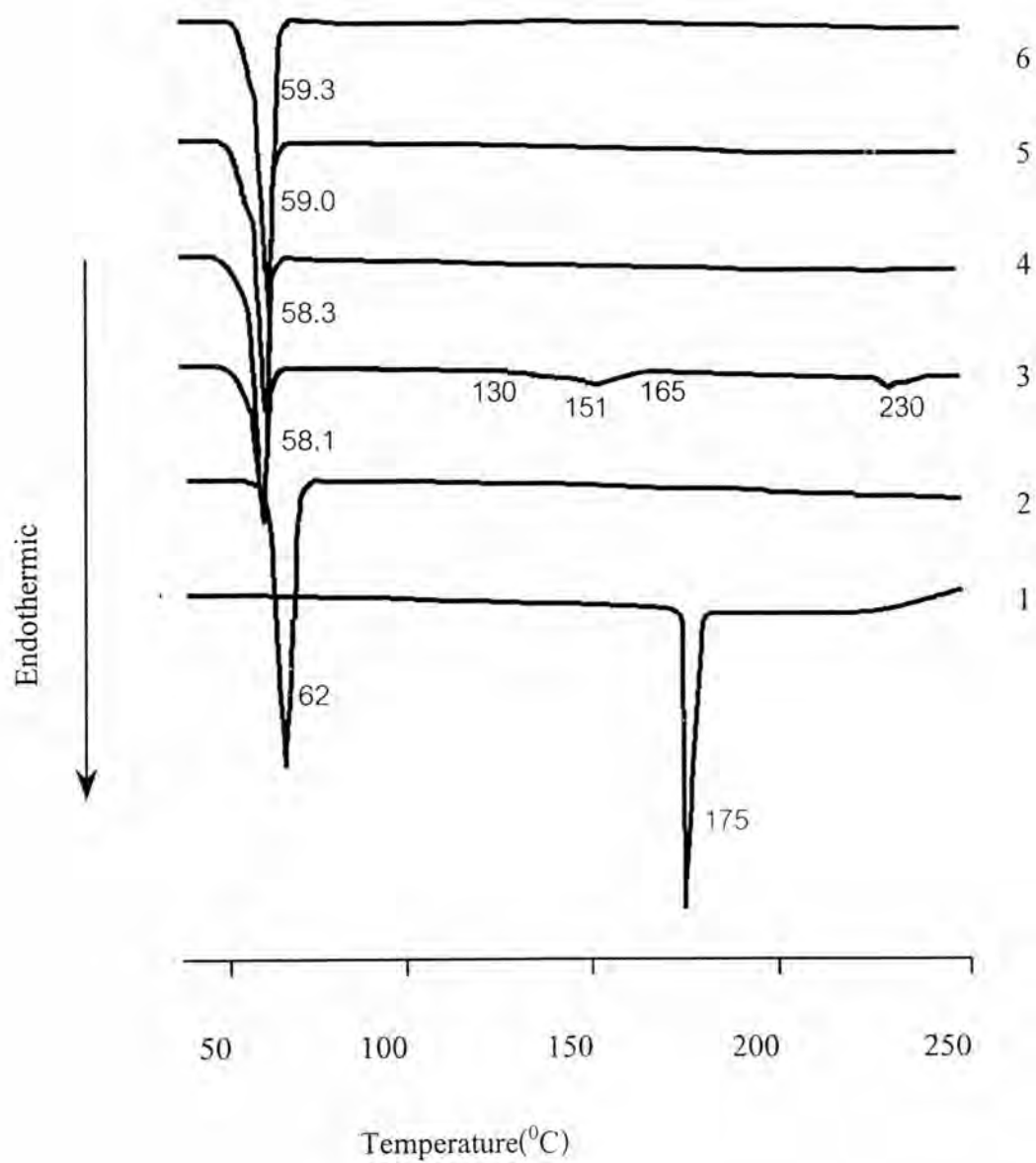


Figure 101: DSC curves of nifedipine - PEG 4000 solid dispersions prepared by melting method containing nifedipine (1), PEG 4000(2), and systems containing with ratios of 1:1(3), 1:3 (4), 1:5 (5) and 1:10 (6)

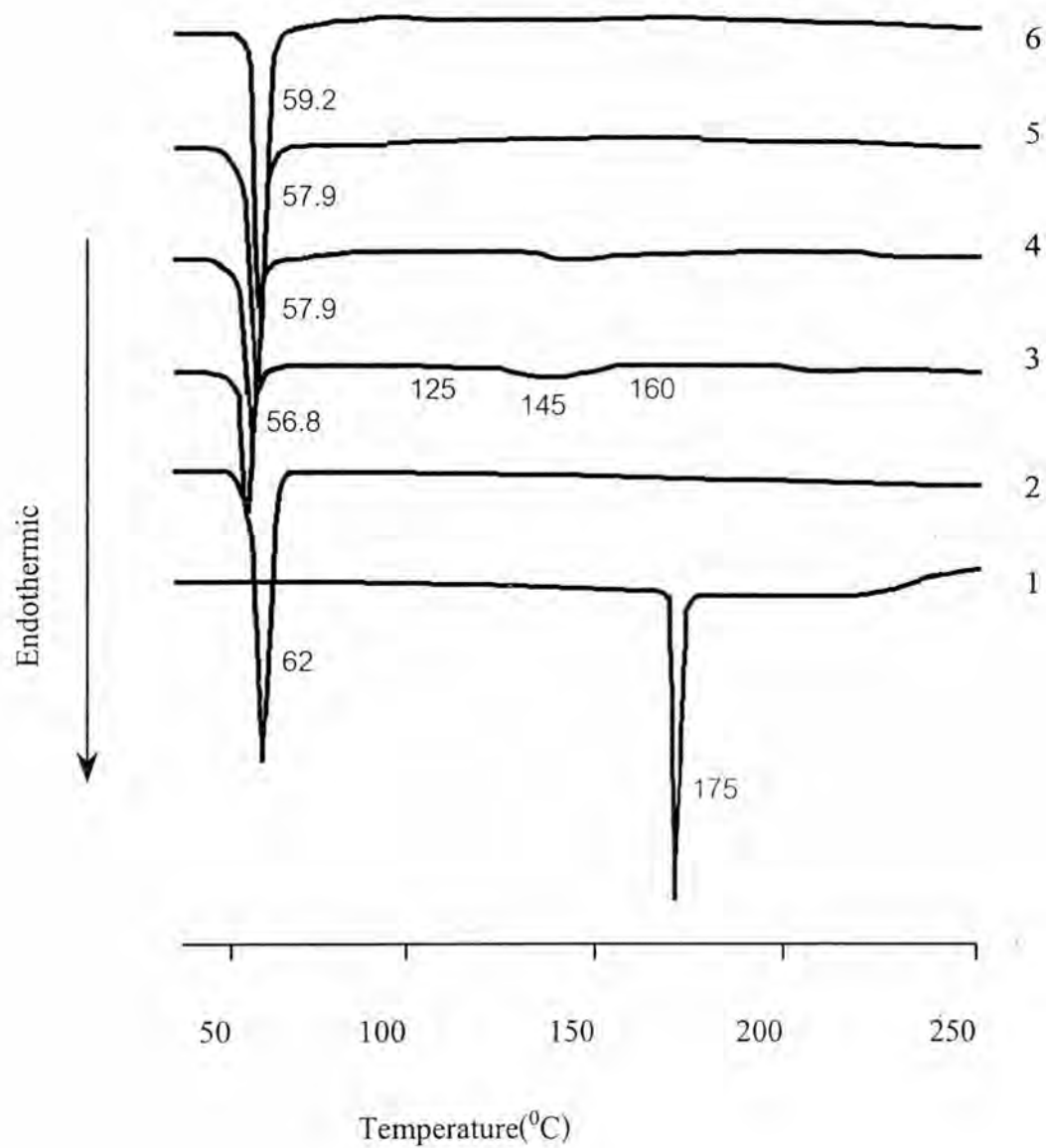


Figure 102: DSC curves of nifedipine - PEG 4000 solid dispersions prepared by solvent method containing nifedipine (1), PEG4000(2), and systems containing with ratios of 1:1(3), 1:3 (4), 1:5 (5) and 1:10 (6)

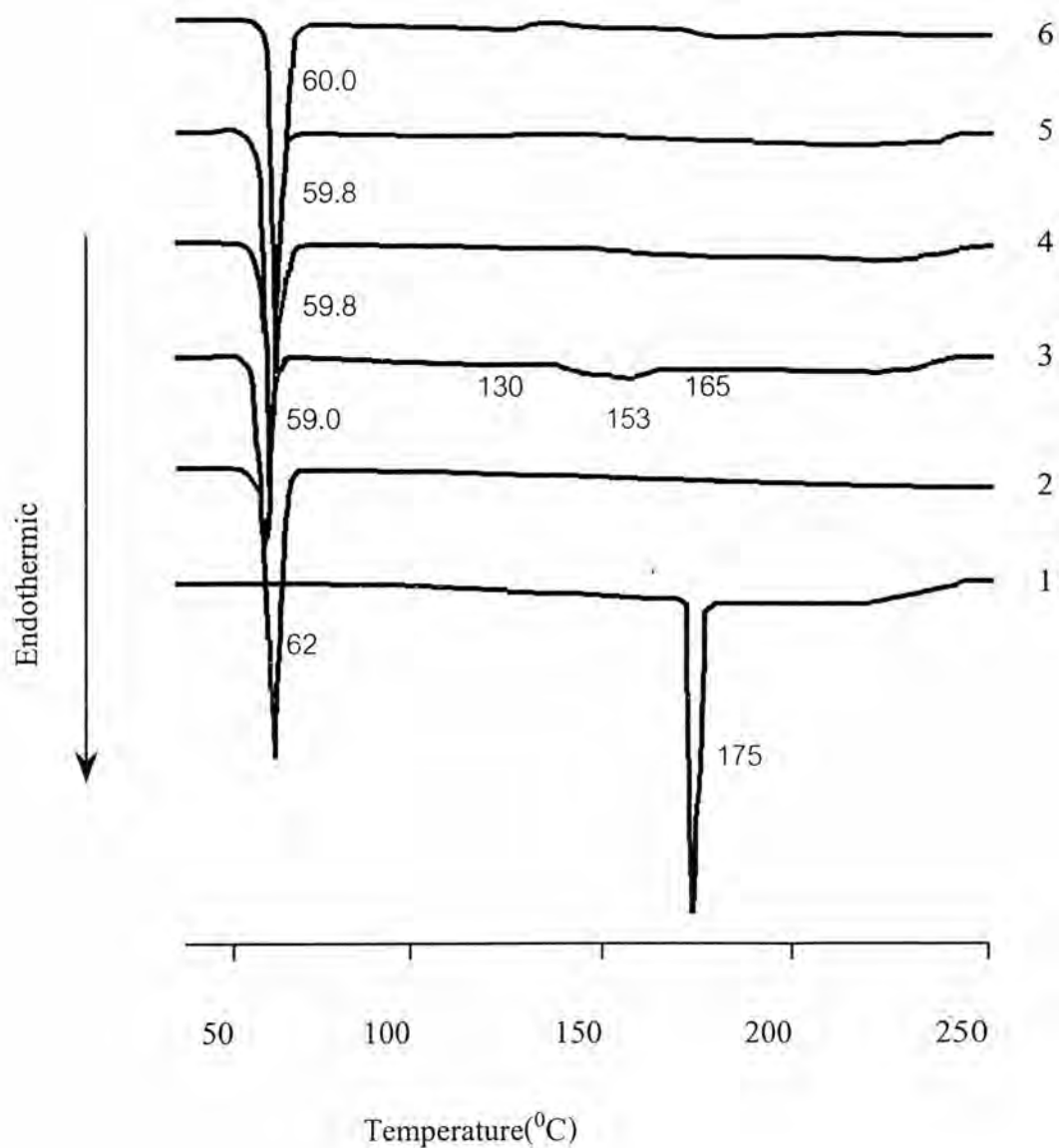


Figure 103: DSC curves of nifedipine - PEG 4000 solid dispersions prepared by kneading method containing nifedipine (1), PEG4000(2), and systems containing with ratios of 1:1(3), 1:3 (4), 1:5 (5) and 1:10 (6)

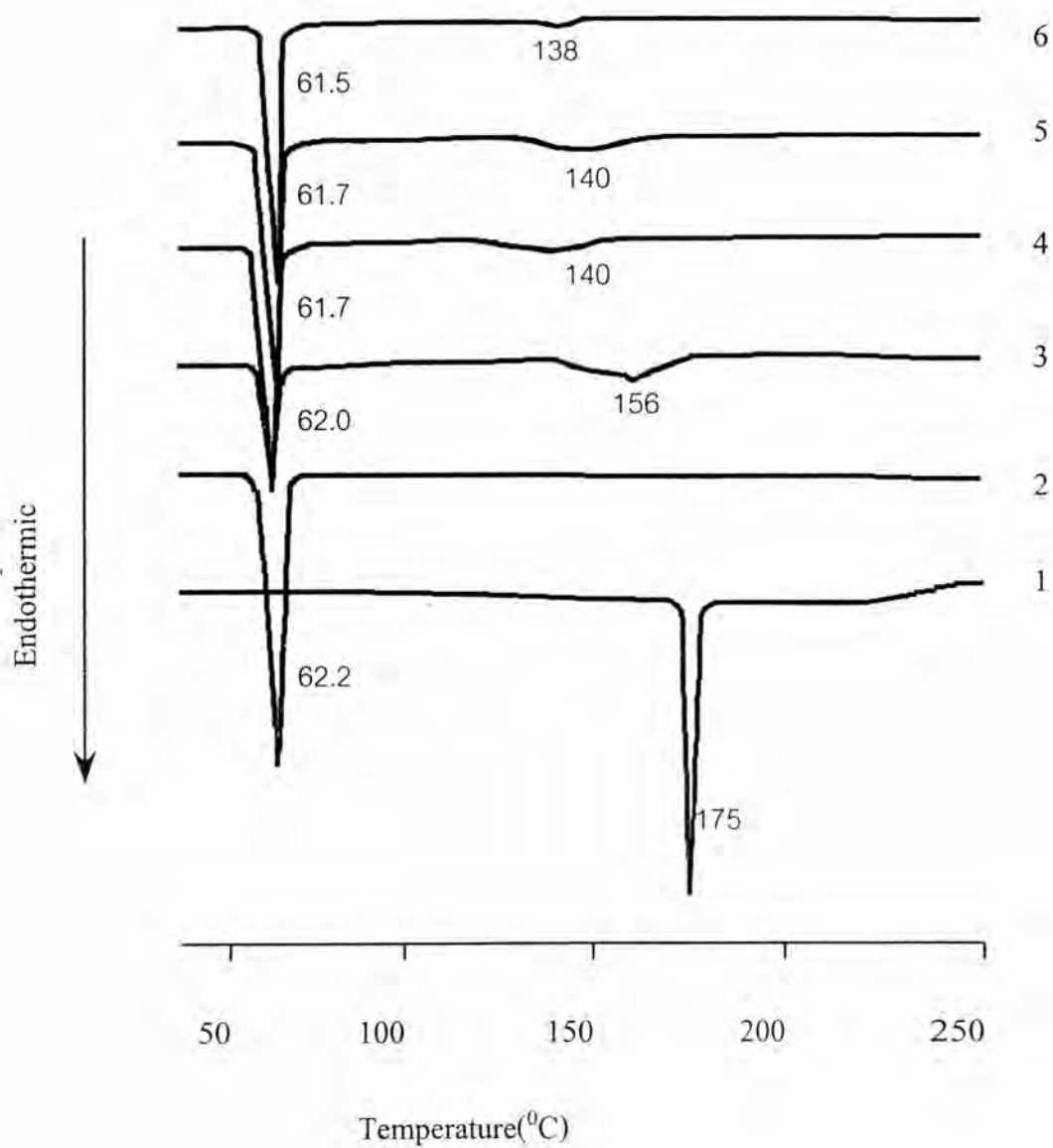


Figure 104: DSC curves of nifedipine - PEG 6000 physical mixtures containing nifedipine (1), PEG6000(2), and systems containing with ratios of 1:1(3), 1:3 (4), 1:5 (5) and 1:10 (6)

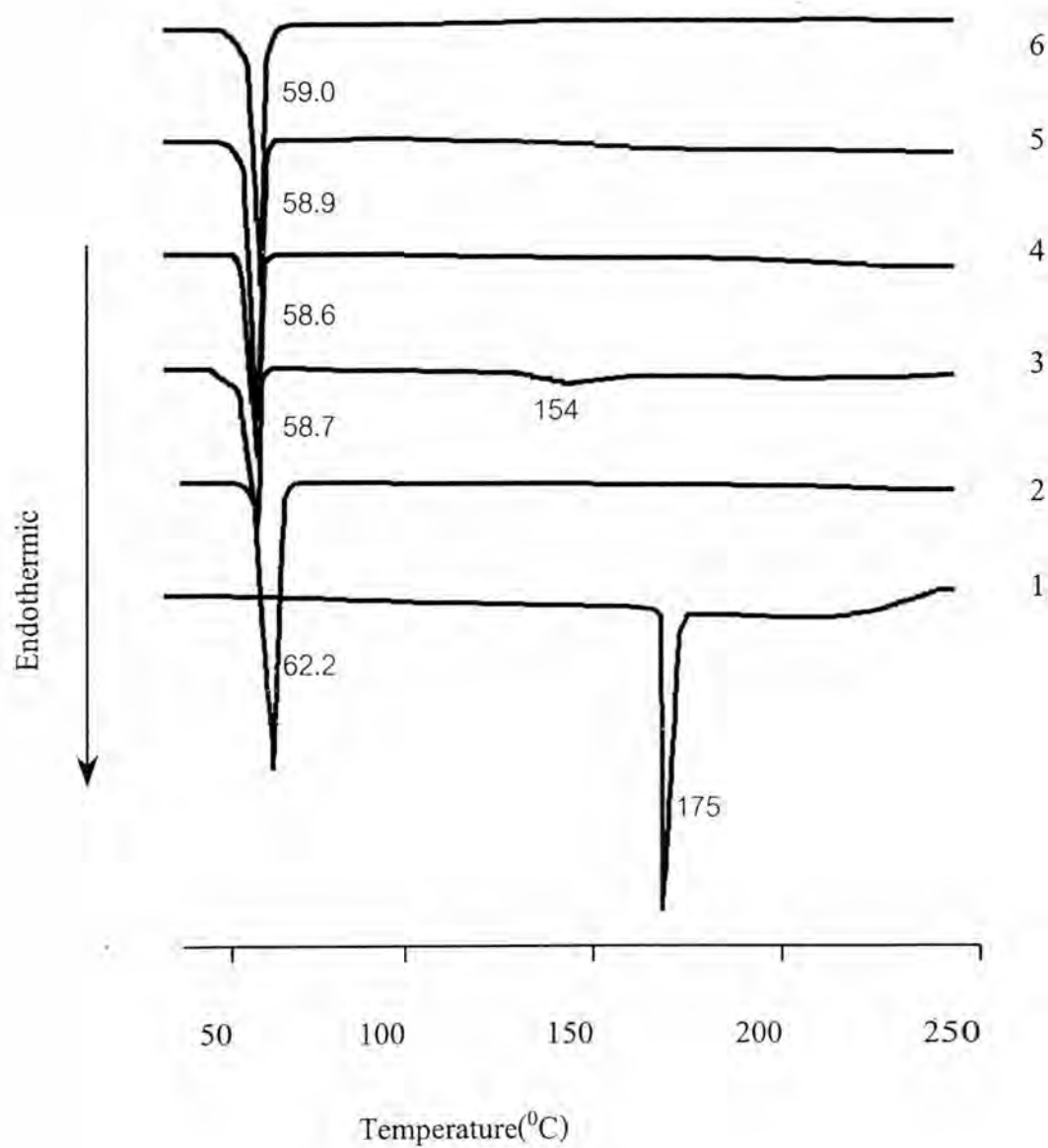


Figure 105: DSC curves of nifedipine - PEG 6000 solid dispersions prepared by melting method containing nifedipine (1), PEG6000(2), and systems containing with ratios of 1:1(3), 1:3 (4), 1:5 (5) and 1:10 (6)

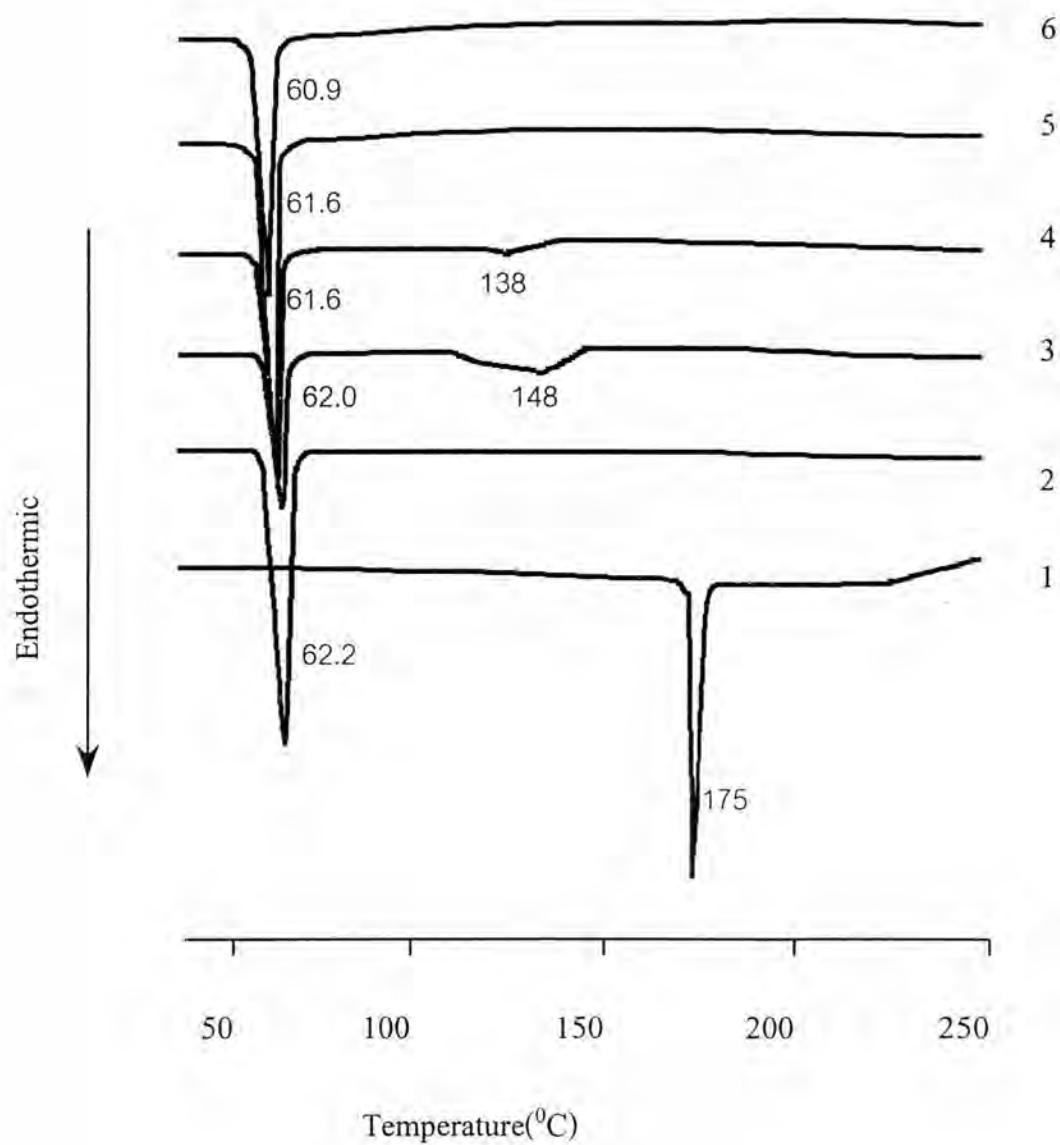


Figure 106: DSC curves of nifedipine - PEG 6000 solid dispersions prepared by solvent method containing nifedipine (1), PEG6000(2), and systems containing with ratios of 1:1(3), 1:3 (4), 1:5 (5) and 1:10 (6)

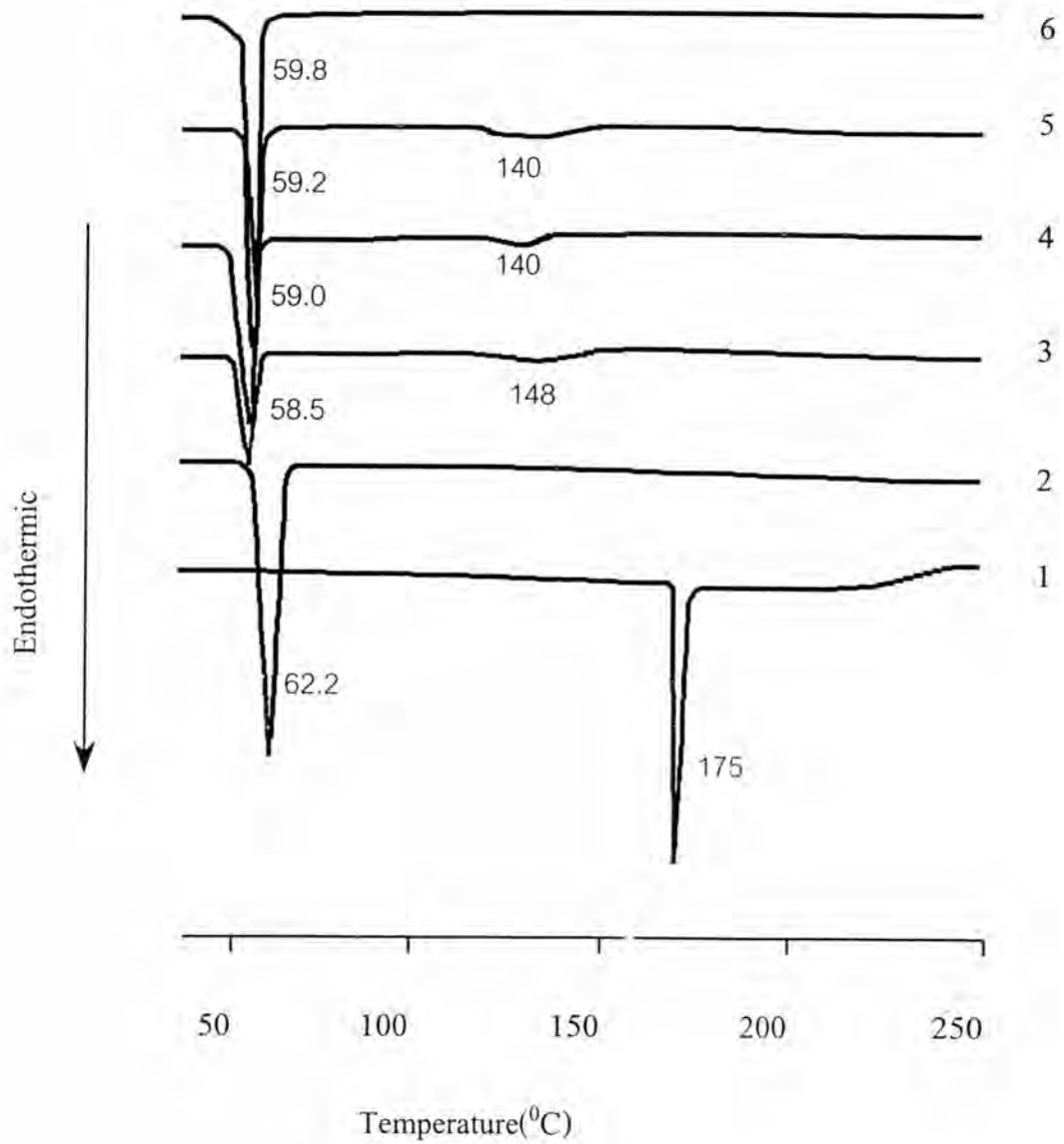


Figure 107: DSC curves of nifedipine - PEG 6000 solid dispersions prepared by kneading method containing nifedipine (1), PEG6000(2), and systems containing with ratios of 1:1(3), 1:3 (4), 1:5 (5) and 1:10 (6)

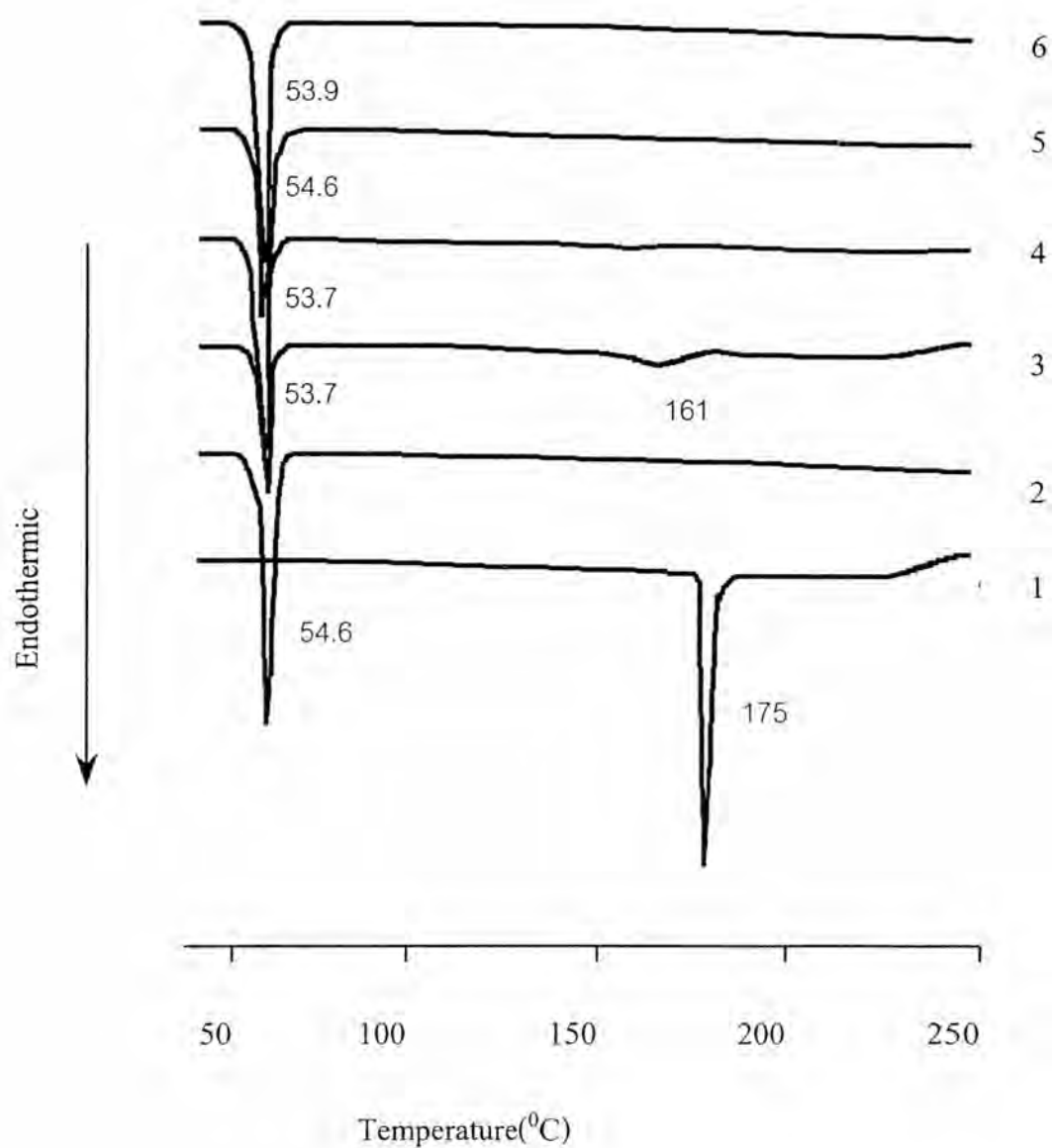


Figure 108: DSC curves of nifedipine - poloxamer 188 physical mixtures containing nifedipine (1), poloxamer 188(2), and systems containing with ratios of 1:1(3), 1:3 (4), 1:5 (5) and 1:10 (6)

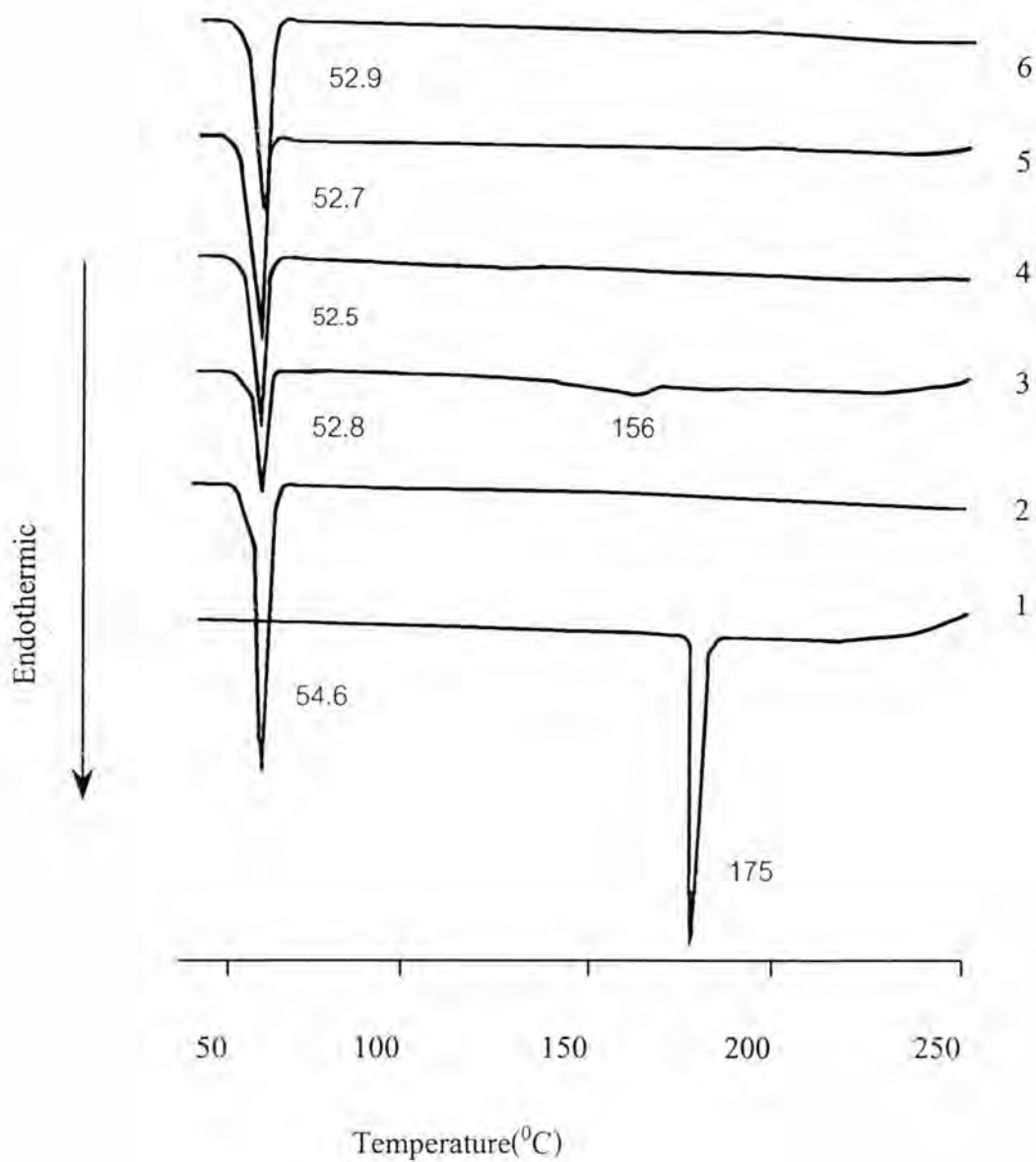


Figure 109 : DSC curves of nifedipine - poloxamer 188 solid dispersions prepared by melting method containing nifedipine (1), poloxamer 188(2), and systems containing with ratios of 1:1(3), 1:3 (4), 1:5 (5) and 1:10 (6)

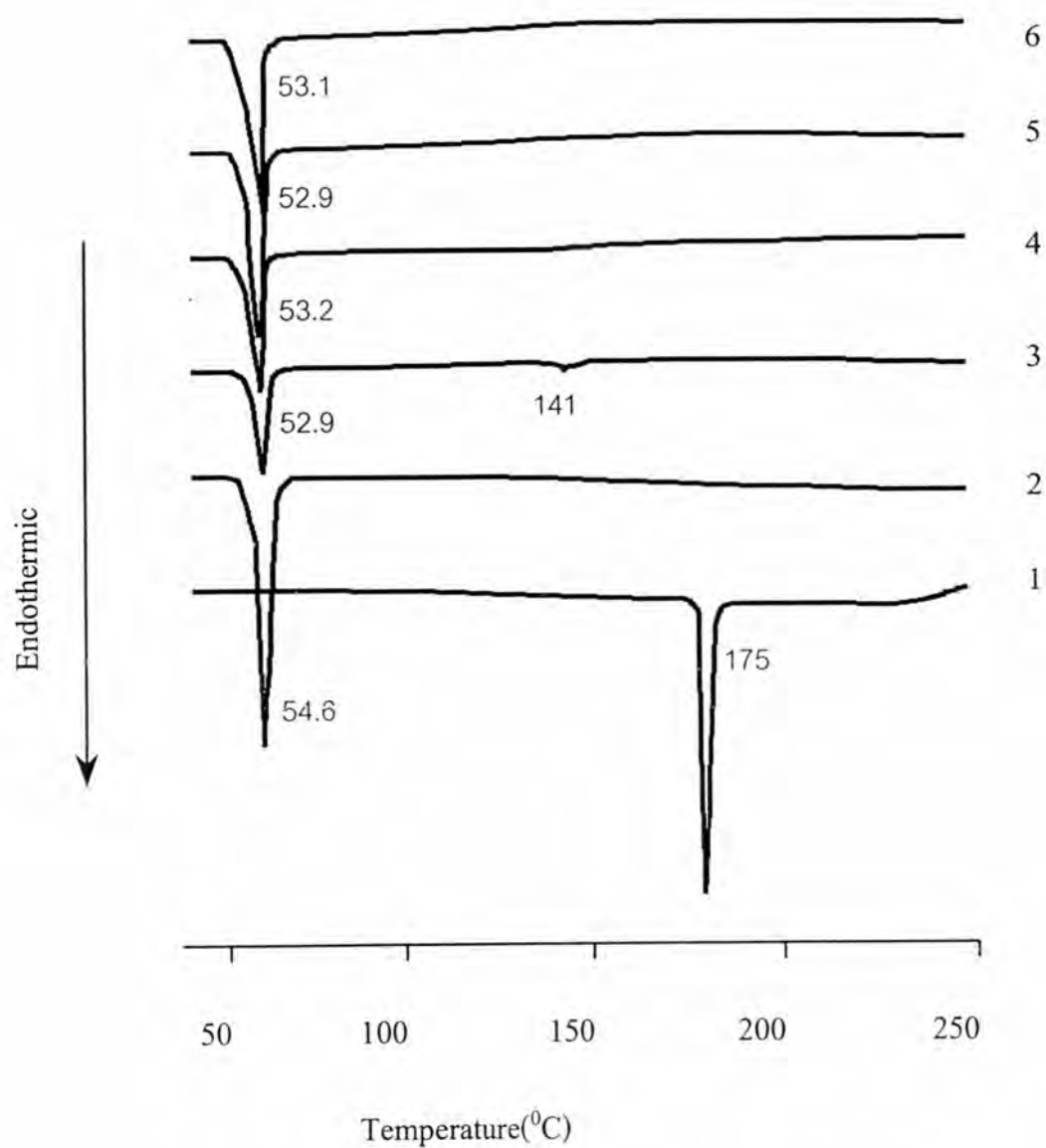


Figure 110: DSC curves of nifedipine - poloxamer 188 solid dispersions prepared by solvent method containing nifedipine (1), poloxamer 188(2), and systems containing with ratios of 1:1(3), 1:3 (4), 1:5 (5) and 1:10 (6)

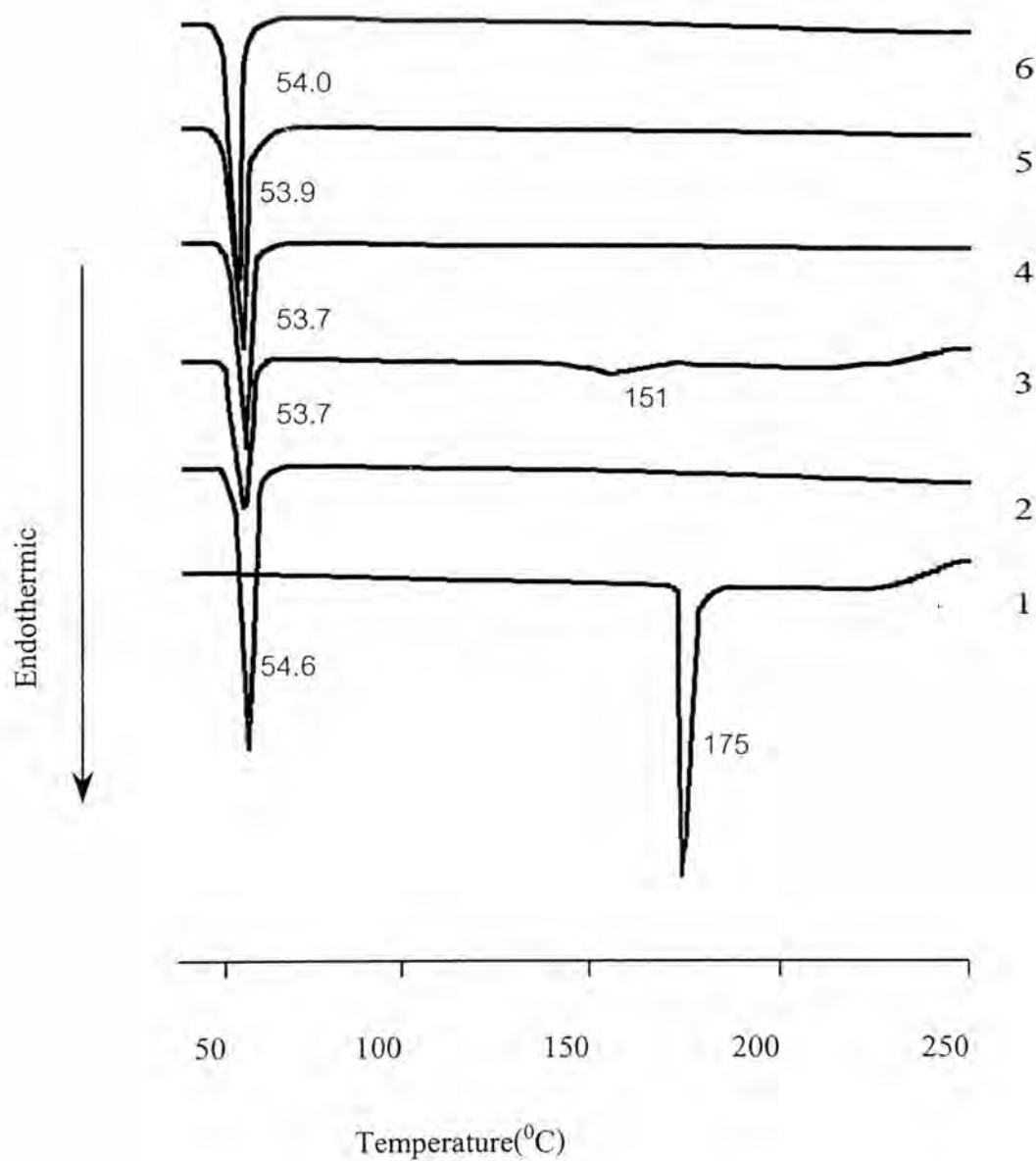


Figure 111: DSC curves of nifedipine - poloxamer 188 solid dispersions prepared by kneading method containing nifedipine (1), poloxamer 108(2), and systems containing with ratios of 1:1(3), 1:3 (4), 1:5 (5) and 1:10 (6)

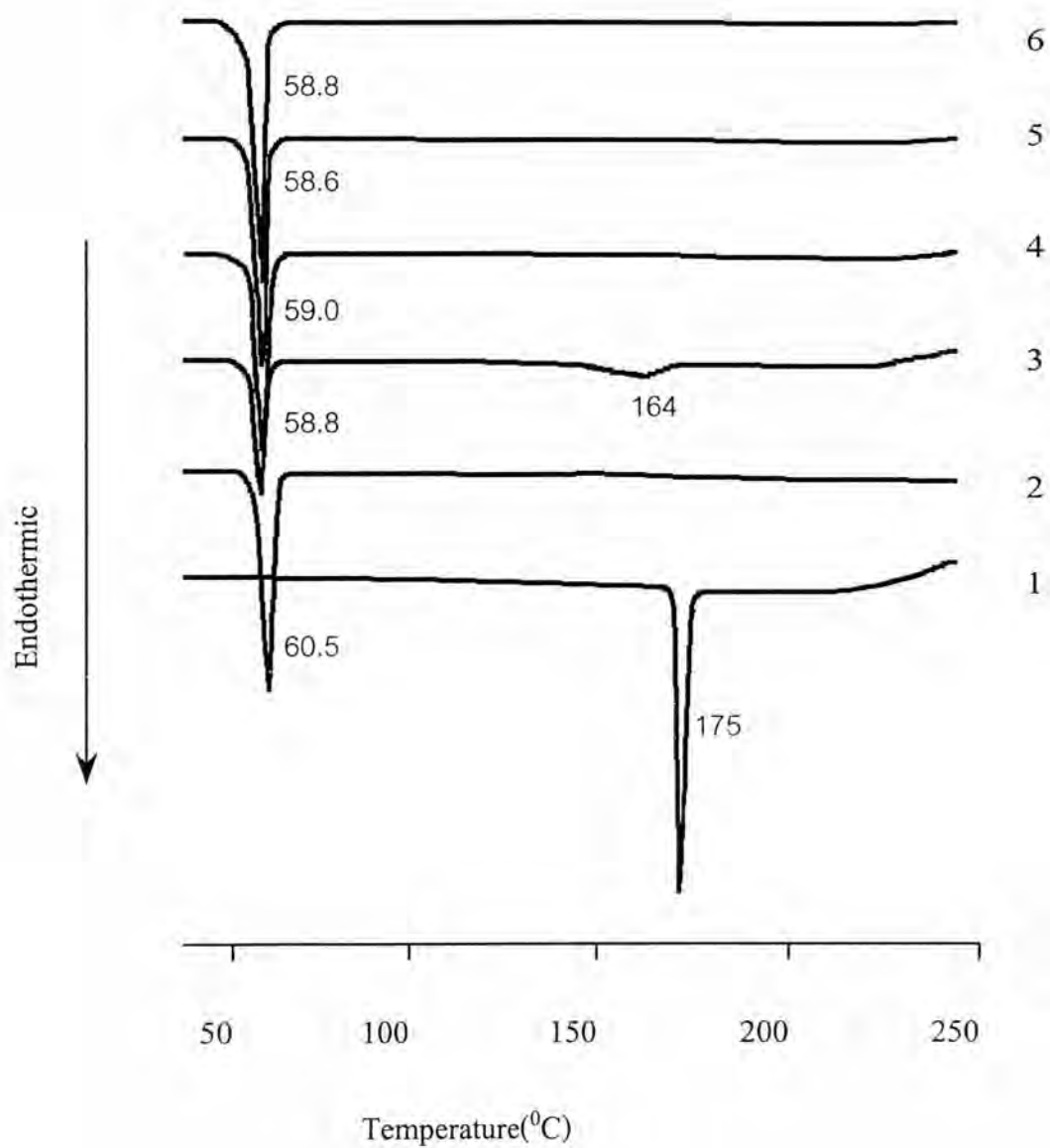


Figure 112 : DSC curves of nifedipine - poloxamer288 physical mixtures containing nifedipine (1), poloxamer288(2), and systems containing with ratios of 1:1(3), 1:3 (4), 1:5 (5) and 1:10 (6)

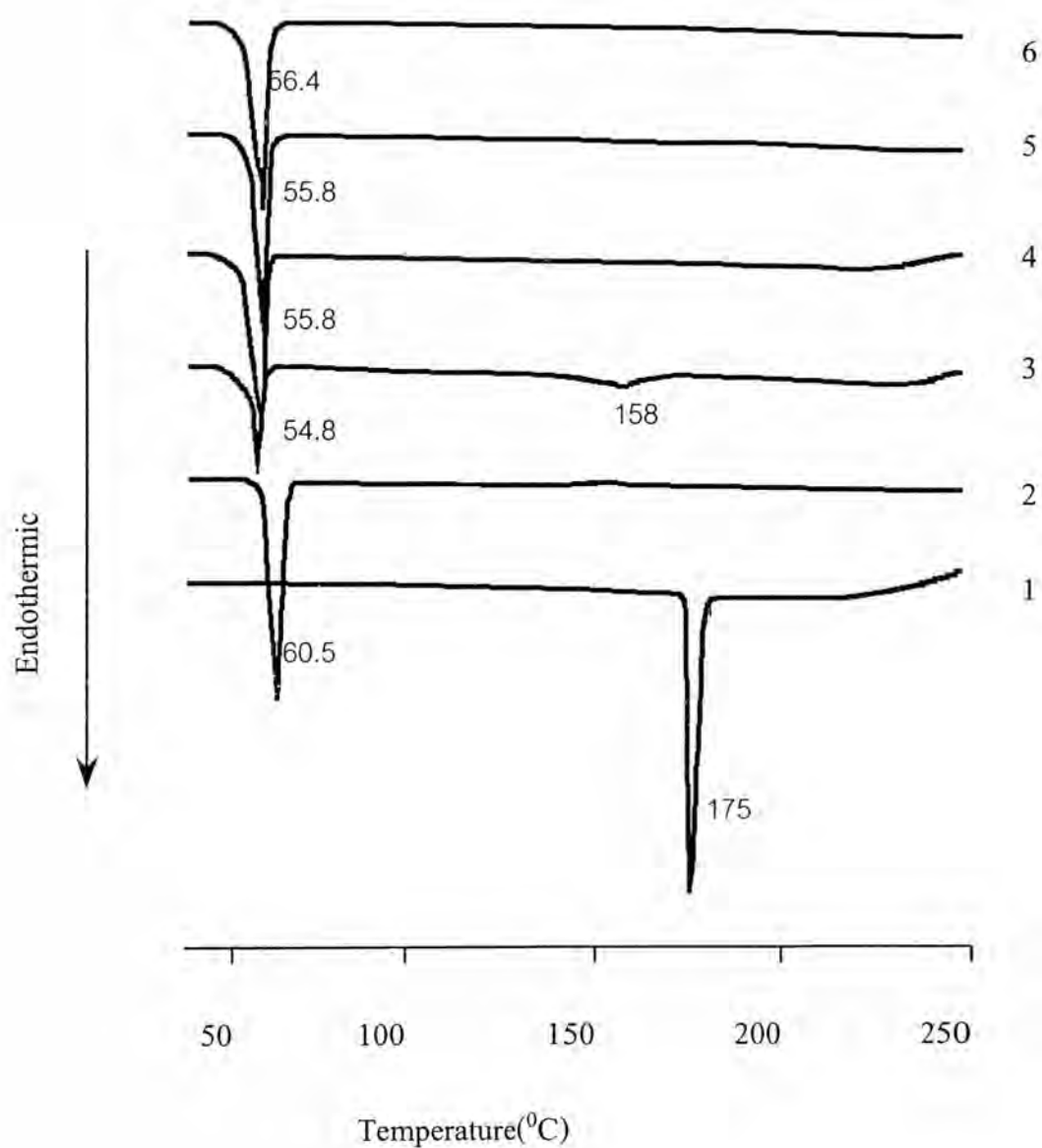


Figure 113: DSC curves of nifedipine - poloxamer288 solid dispersions prepared by melting method containing nifedipine (1), poloxamer288(2), and systems containing with ratios of 1:1(3), 1:3 (4), 1:5 (5) and 1:10 (6)

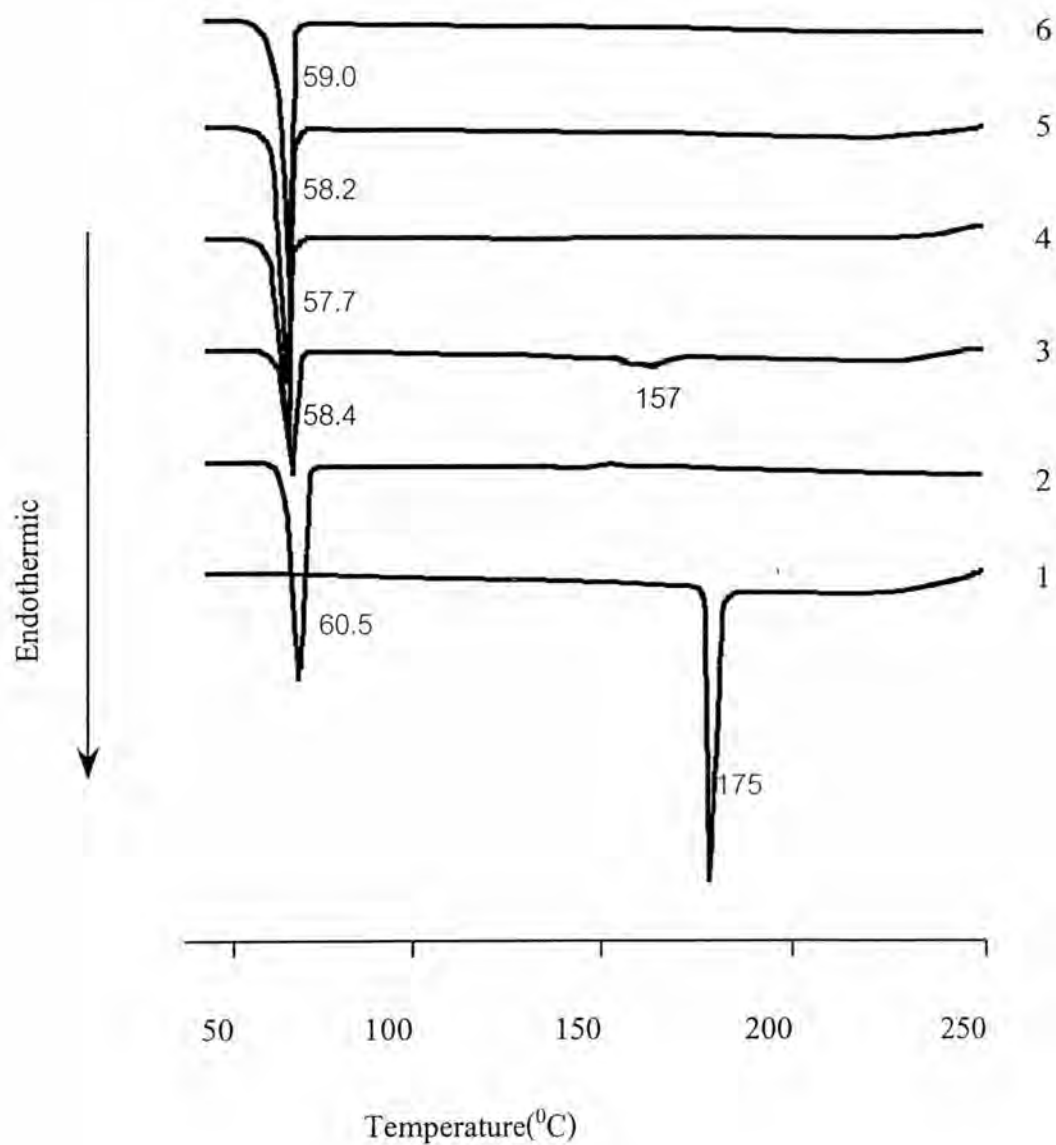


Figure 114: DSC curves of nifedipine - poloxamer288 solid dispersions prepared by solvent method containing nifedipine (1), poloxamer288(2), and systems containing with ratios of 1:1(3), 1:3 (4), 1:5 (5) and 1:10 (6)

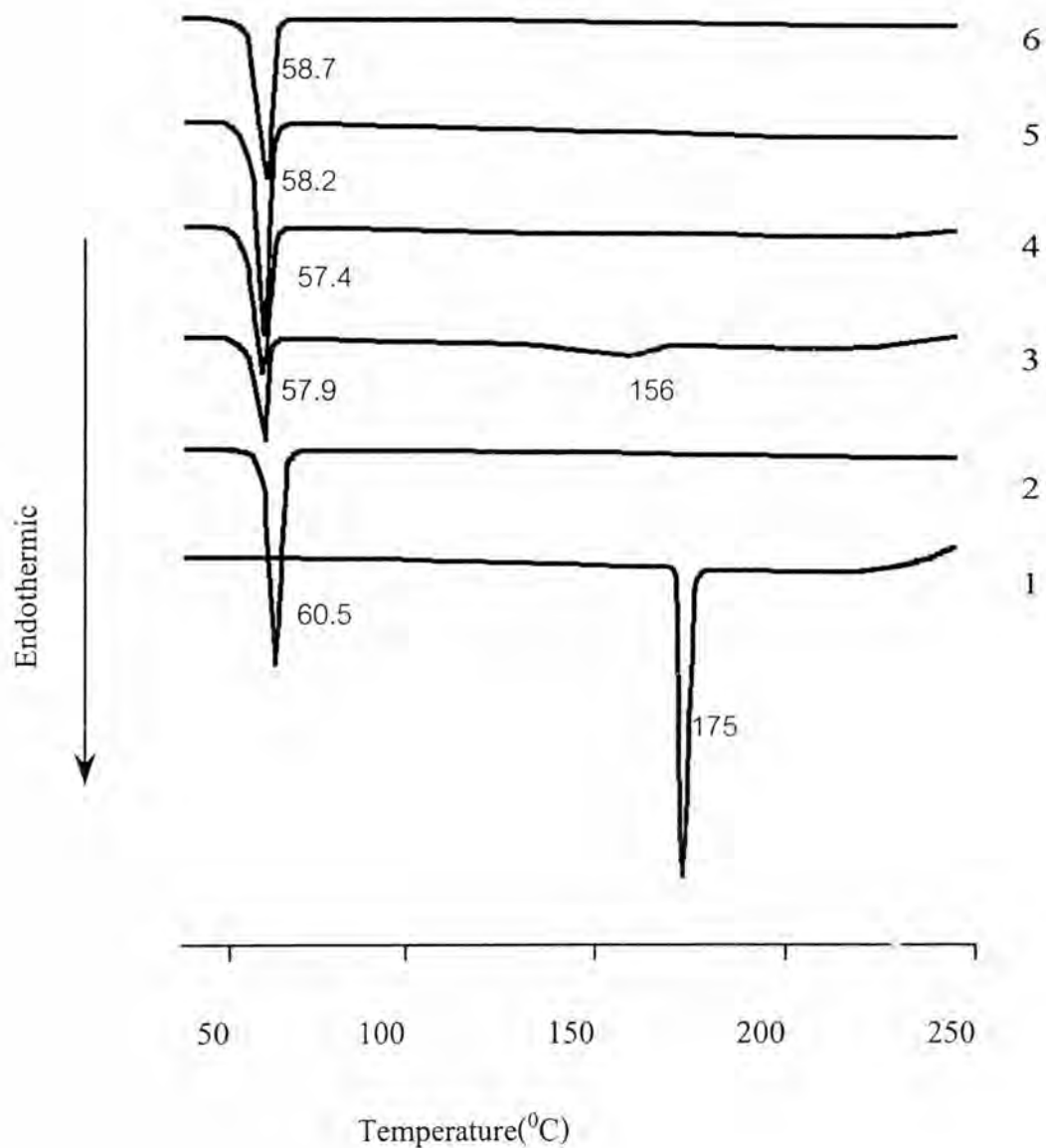


Figure 115: DSC curves of nifedipine - poloxamer288 solid dispersions prepared by kneading method containing nifedipine (1), poloxamer288(2), and systems containing with ratios of 1:1(3), 1:3 (4), 1:5 (5) and 1:10 (6)

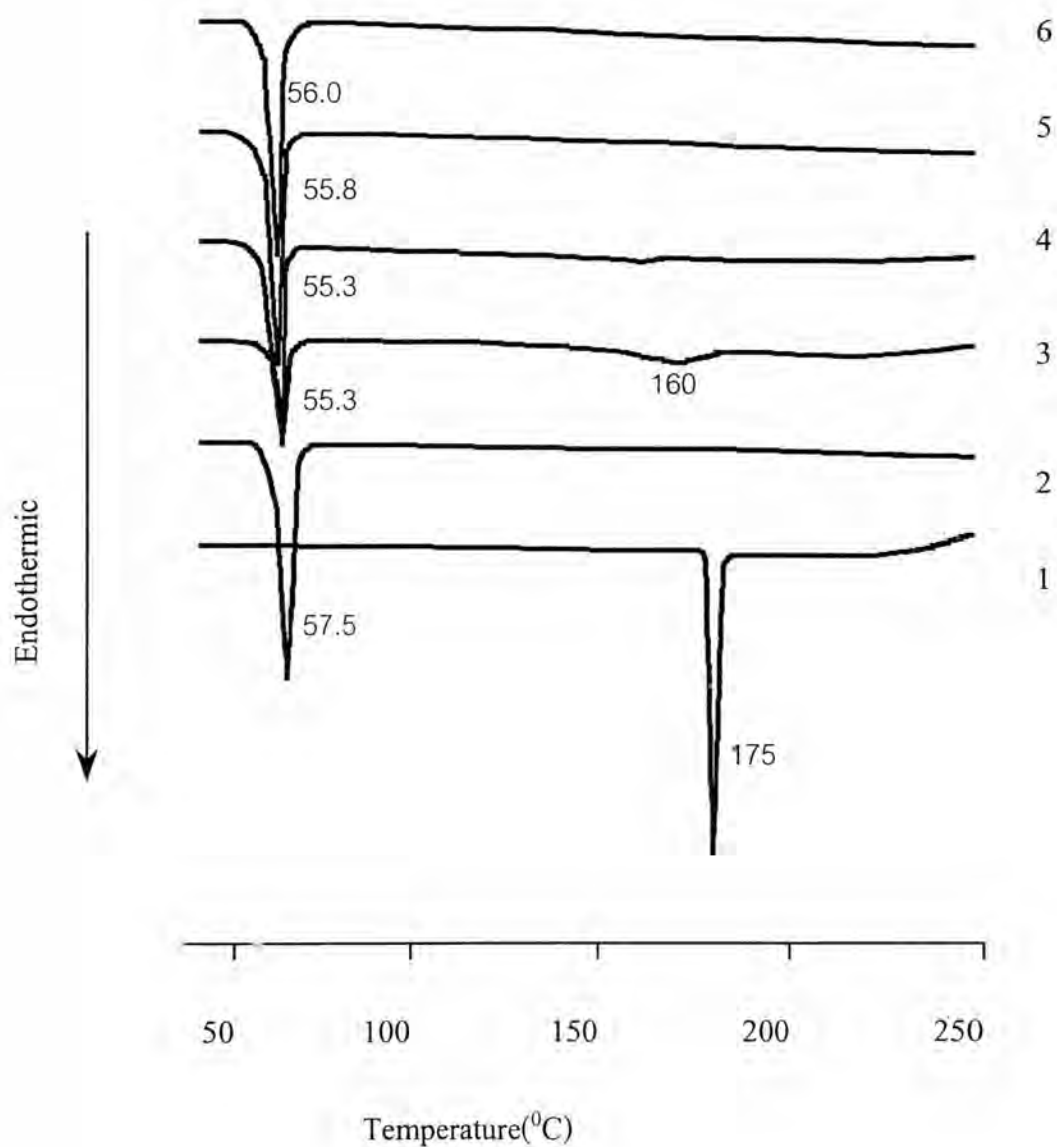


Figure 116: DSC curves of nifedipine - poloxamer 407 physical mixtures containing nifedipine (1), poloxamer 407(2), and systems containing with ratios of 1:1(3), 1:3 (4), 1:5 (5) and 1:10 (6)

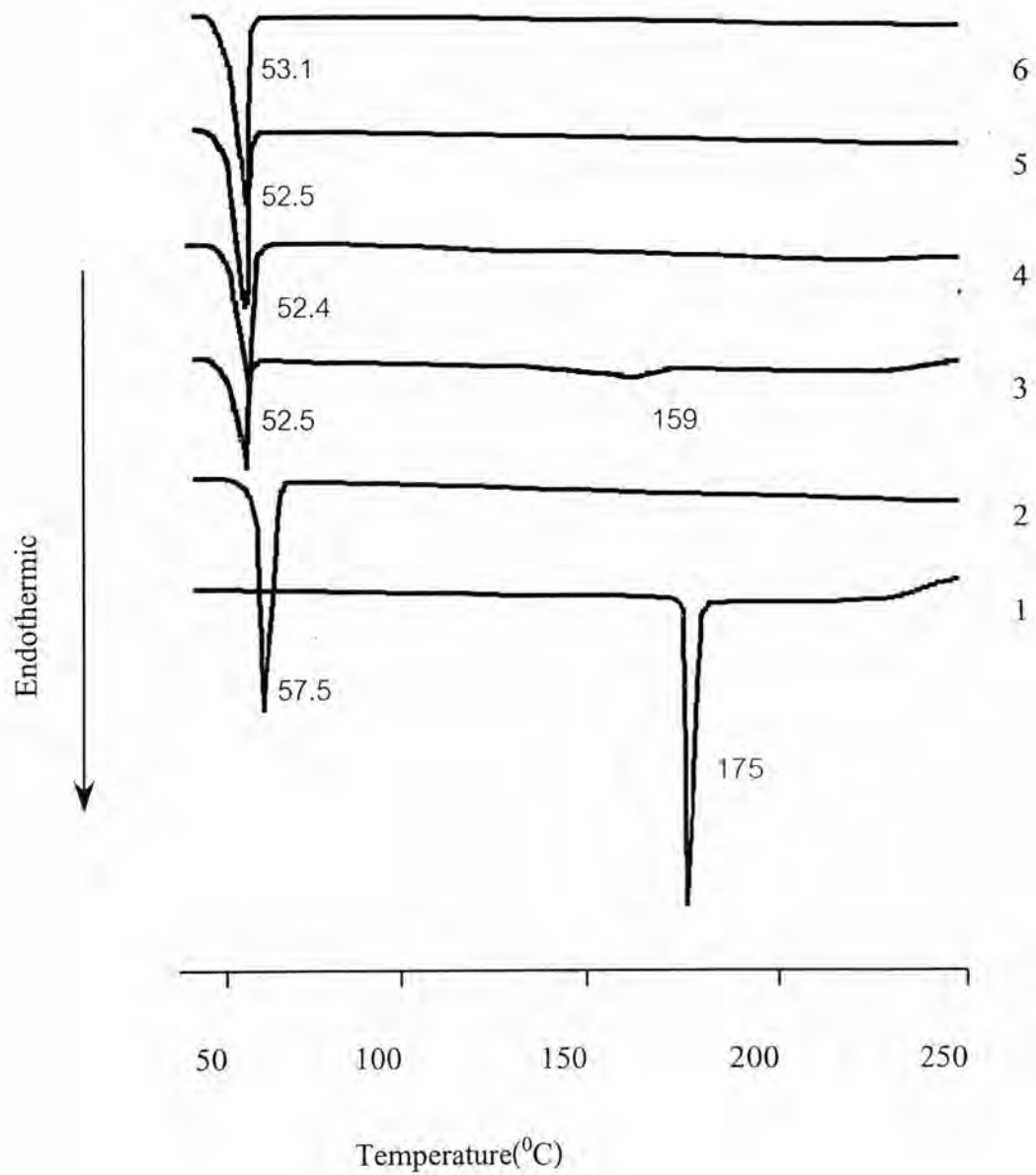


Figure 117: DSC curves of nifedipine - poloxamer 407 solid dispersions prepared by melting method containing nifedipine (1), poloxamer 407(2), and systems containing with ratios of 1:1(3), 1:3 (4), 1:5 (5) and 1:10 (6)

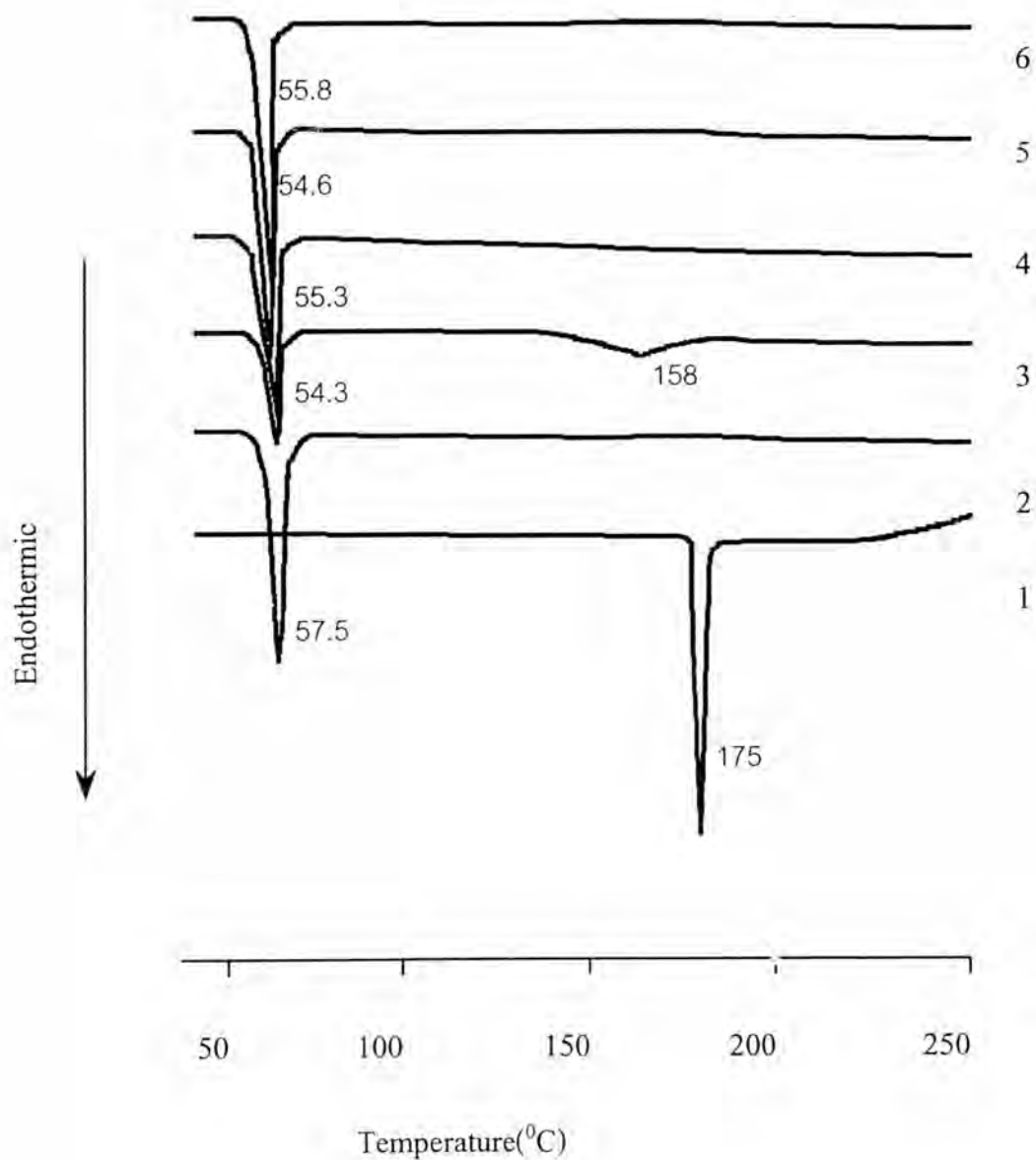


Figure 118: DSC curves of nifedipine - poloxamer 407 solid dispersions prepared by solvent method containing nifedipine (1), poloxamer 407(2), and systems containing with ratios of 1:1(3), 1:3 (4), 1:5 (5) and 1:10 (6)

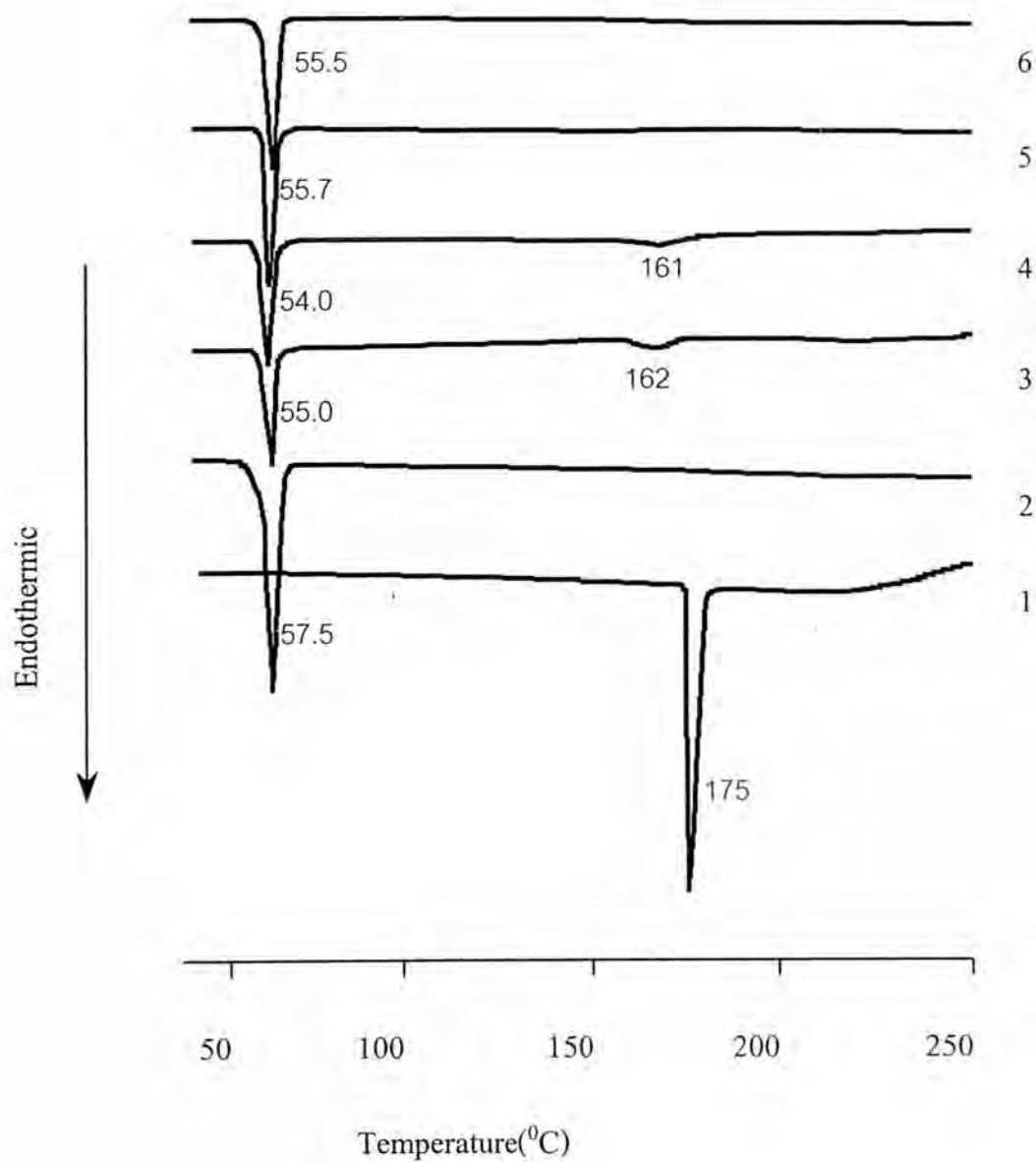


Figure 119: DSC curves of nifedipine - poloxamer 407 solid dispersions prepared by kneading method containing nifedipine (1), poloxamer 407(2), and systems containing with ratios of 1:1(3), 1:3 (4), 1:5 (5) and 1:10 (6)

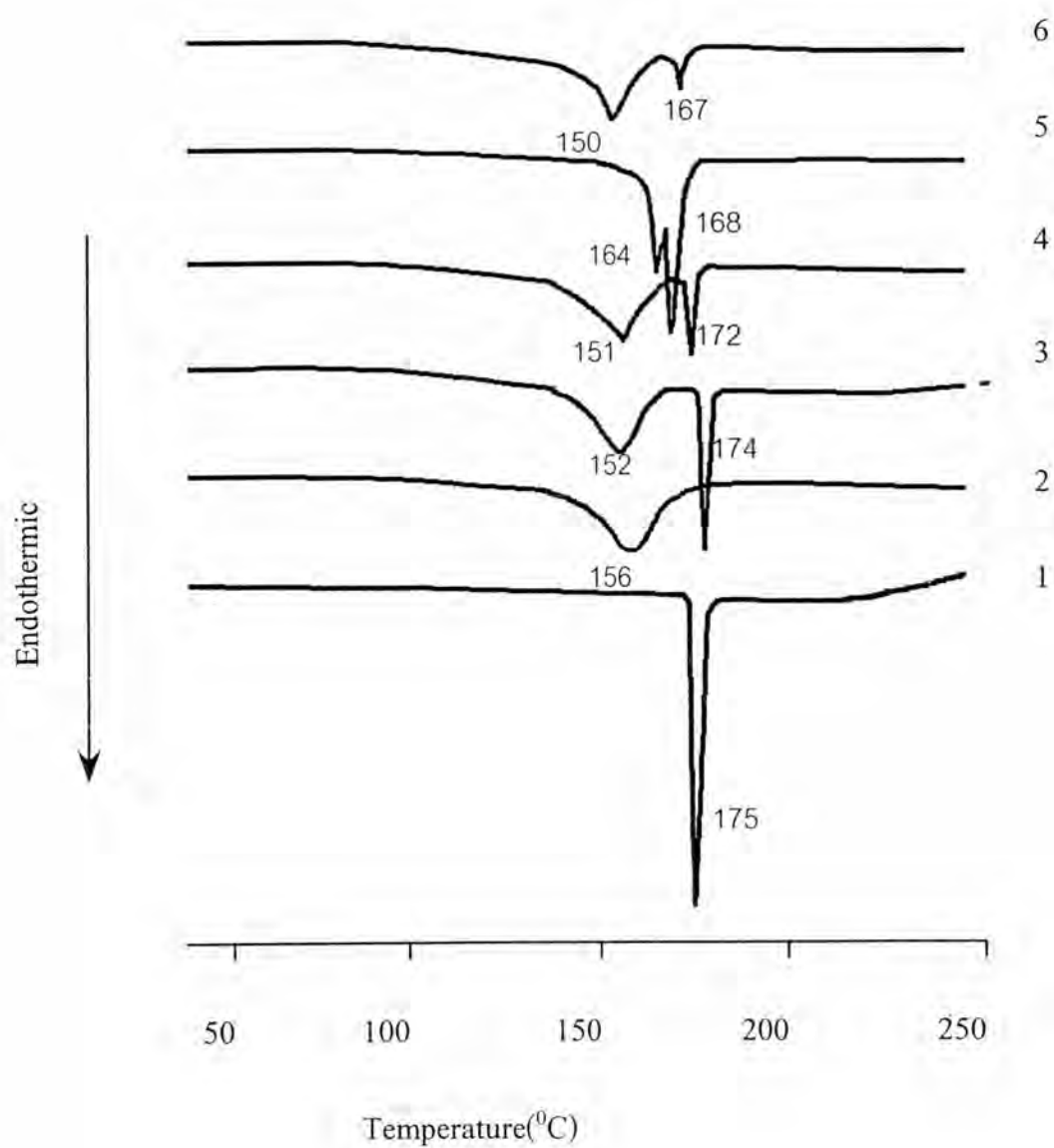


Figure 120: DSC curves of nifedipine- β -cyclodextrin physical mixtures containing nifedipine (1), BCD(2), and systems containing with ratios of 1:1(3), 1:3 (4), 1:5 (5) and 1:10 (6)

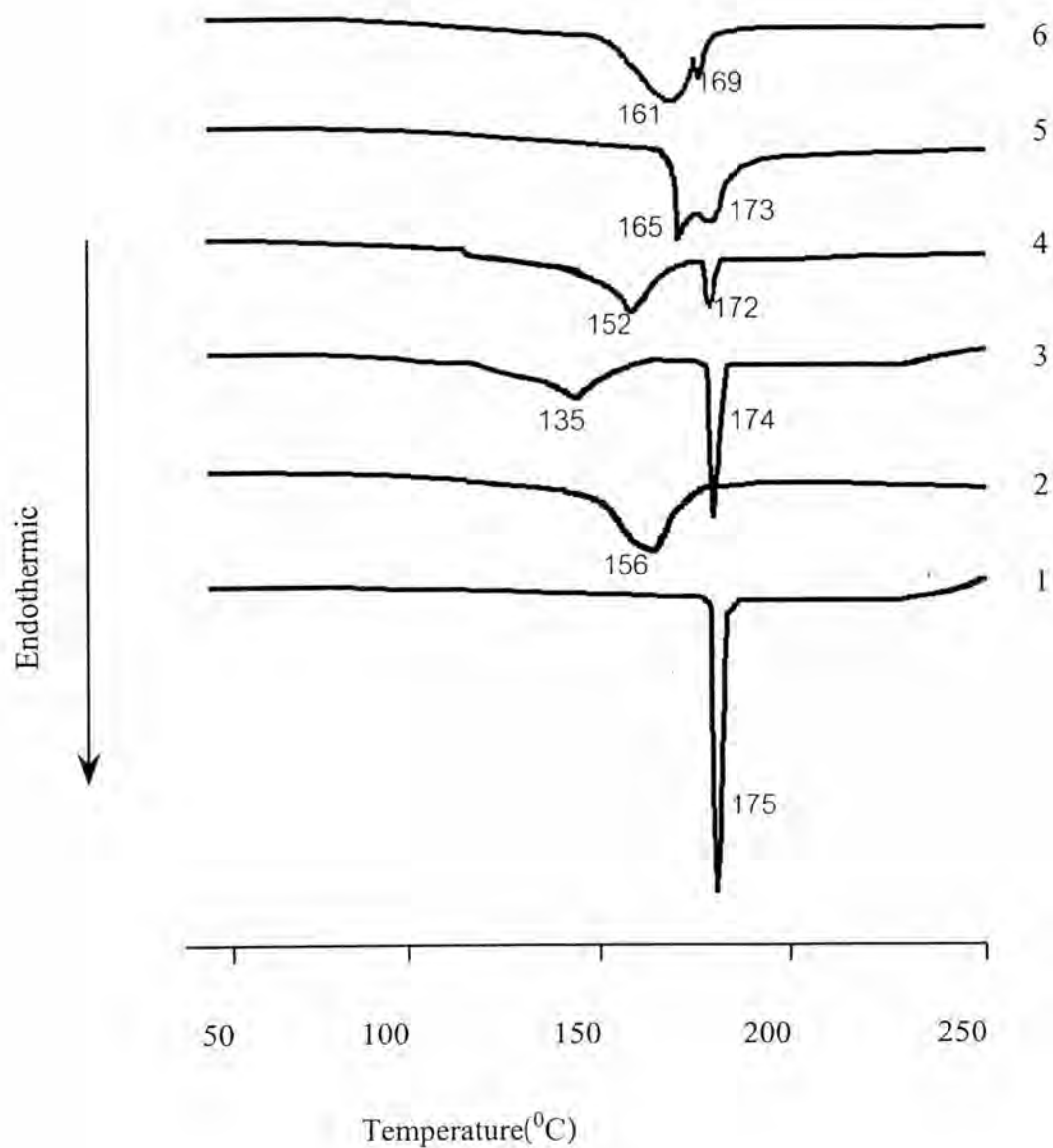


Figure 121: DSC curves of nifedipine- β -cyclodextrin solid dispersions prepared by kneading method containing nifedipine (1), BCD(2), and systems containing with ratios of 1:1(3), 1:3 (4), 1:5 (5) and 1:10 (6)

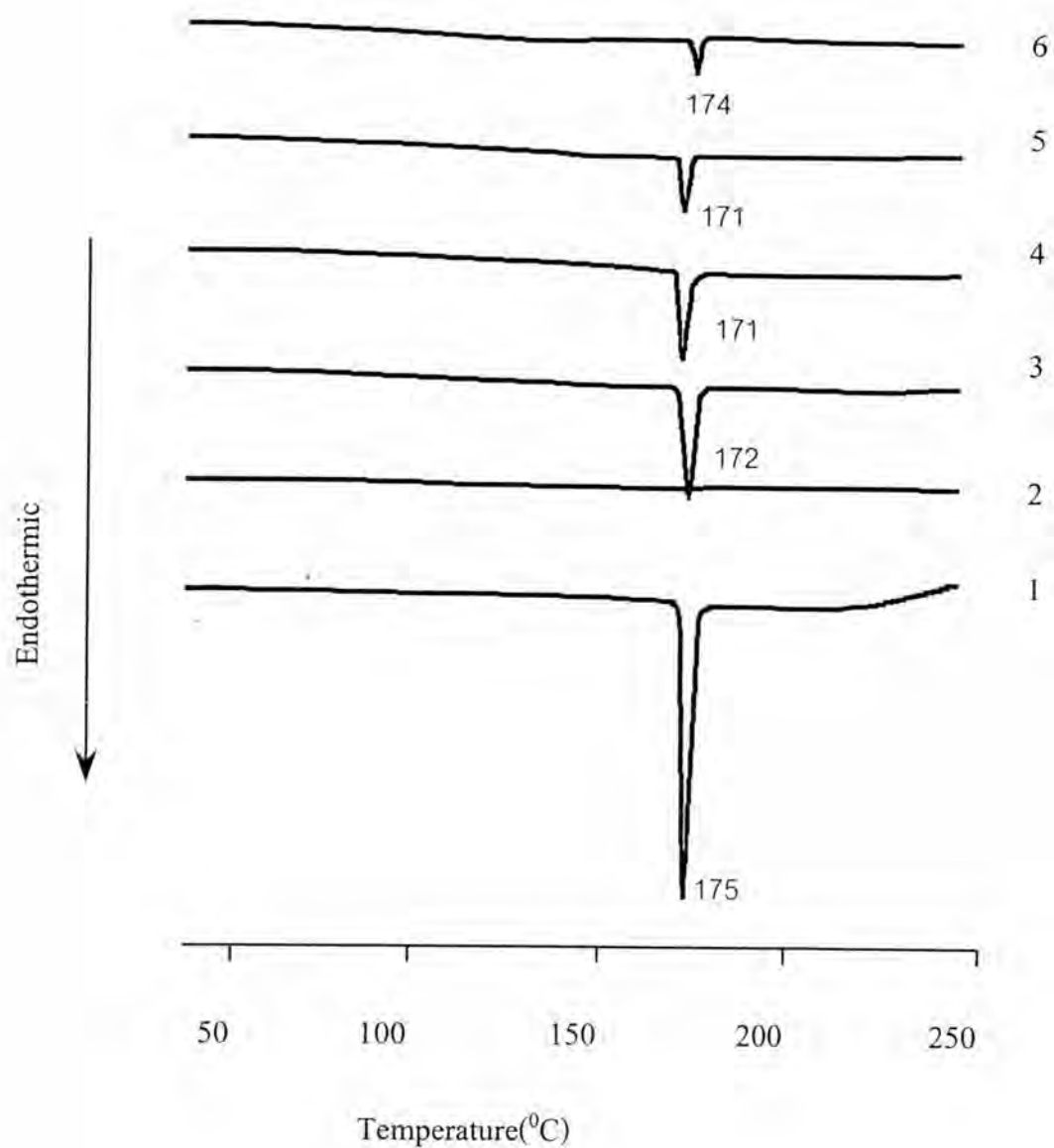


Figure 122: DSC curves of nifedipine-2-hydroxypropyl- β -cyclodextrin physical mixtures containing nifedipine (1), 2-HBCD(2), and systems containing with ratios of 1:1(3), 1:3 (4), 1:5 (5) and 1:10 (6)

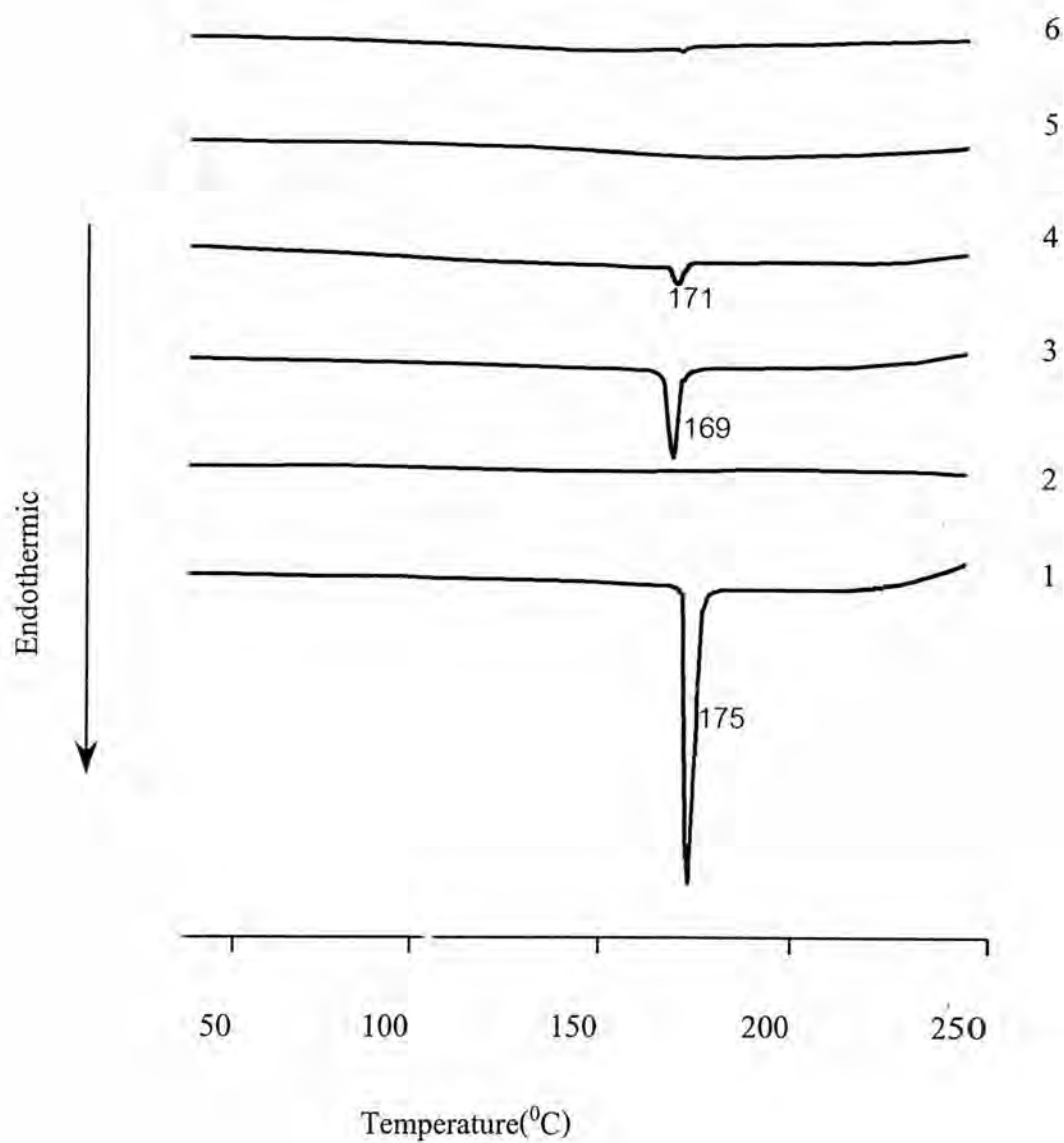


Figure 123: DSC curves of nifedipine-2-hydroxypropyl- β -cyclodextrin solid dispersions prepared by solvent method containing nifedipine (1), 2-HBCD(2), and systems containing with ratios of 1:1(3), 1:3 (4), 1:5 (5) and 1:10 (6)

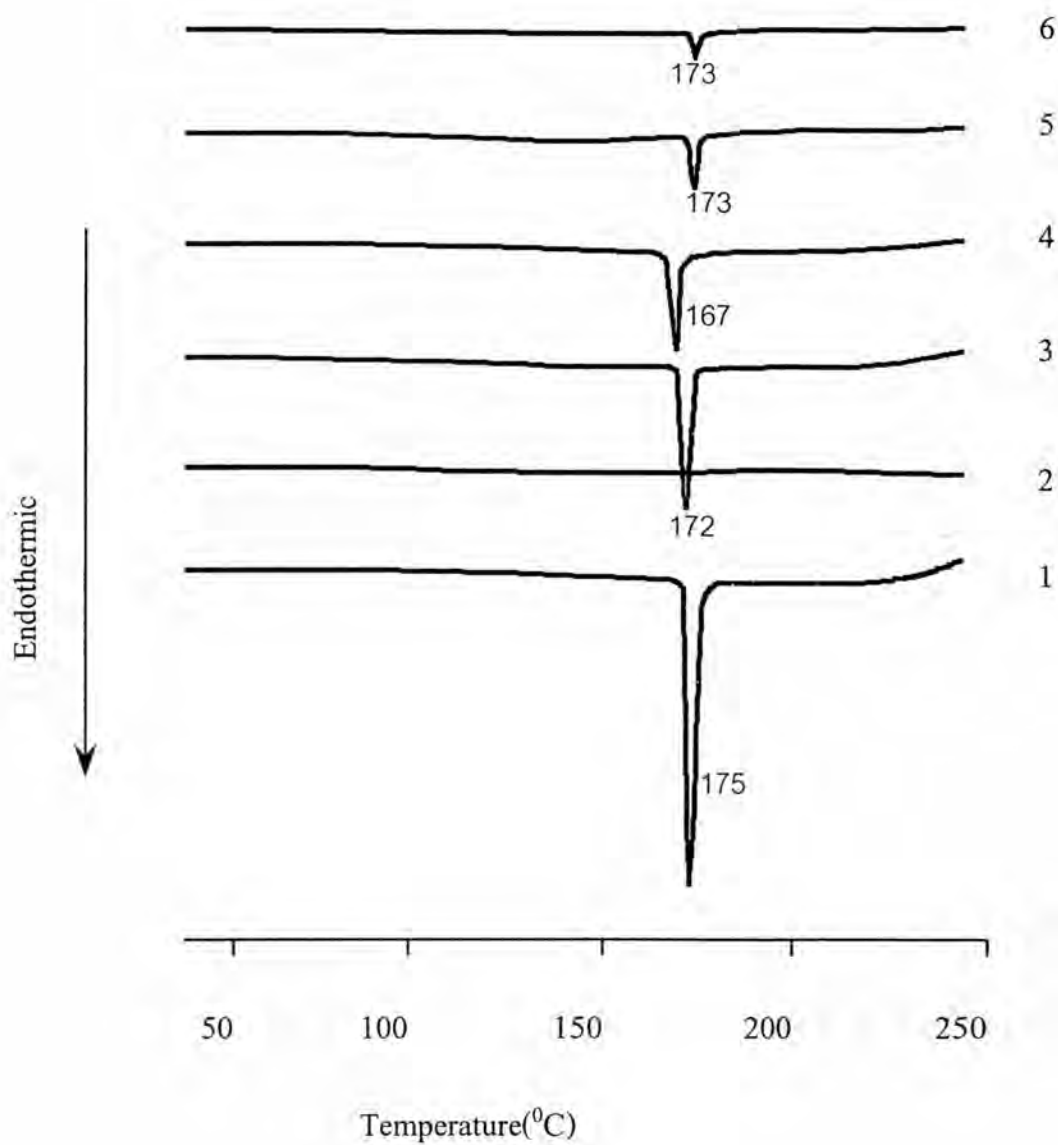


Figure 124: DSC curves of nifedipine-2-hydroxypropyl- β -cyclodextrin solid dispersions prepared by kneading method containing nifedipine (1), 2-HBCD(2), and systems containing with ratios of 1:1(3), 1:3 (4), 1:5 (5) and 1:10 (6)

4.4 The IR Spectra.

4.4.1 The IR spectra of pure drug and nontreated pure drug.

The IR spectra of nontreated and treated nifedipine by physical mixing, melting, solvent and kneading method were shown in Figure 125. The IR spectra of all nifedipine samples showed characteristic absorption bands of N-H stretching vibrations at $3331-3332\text{ cm}^{-1}$. The peak at 3102 cm^{-1} indicated C-H aromatic vibration and at 2954 cm^{-1} referred to C-H-aliphatic stretching. The major peaks of carbonyl C=O stretching showed at 1689 and 1680 cm^{-1} and C-O ester stretching at 1228 and 1122 cm^{-1} . The sharp peaks of NO_2 stretching was noticed at 1530 cm^{-1} .

After being treated by different methods nifedipine showed the IR spectra pattern including the fingerprint region below 1300 cm^{-1} which were quite similar to the untreated drug.

4.4.2 The IR spectra of nifedipine-PEG4000 solid dispersions

The IR spectra of PEG4000, as shown in Figure 126B-129B, showed characteristic broad peaks of O-H stretching vibration from 3300 to 3600 cm^{-1} , C-H stretching of OC_2H_5 groups from 2800 to 2990 cm^{-1} and C-O stretching band of other from 1000 to 1200 cm^{-1} . The noticeable peak also showed at 1960 cm^{-1} .

The nifedipine-PEG4000 physical mixtures, especially at the 1:1 mixing ratio showed the superimposed spectra of both compounds (Figure 126C). At higher drug : carrier mixing ratios, according to the dilution effect, the intensity of some vibration bands of nifedipine markedly reduced.

The solid dispersions of nifedipine-PEG4000 prepared by melting, solvent and kneading method (Figure 127-129) showed similar IR spectra patterns to their corresponding physical mixture (Figure 126). The IR spectra of both nifedipine and PEG4000 superimposed. However, the IR spectra of the solid dispersion prepared by melting method at 1:5 and 1:10 ratios (Figure 127E,F) showed noticeable changes of C=O stretching bands at 1690 and 1680 cm^{-1} . The C=O ester peaks of nifedipine at 1690 cm^{-1} shifted to the lowering frequency at 1686 cm^{-1} and at 1680 cm^{-1} could not be detected. In addition, the spectra of PEG4000 at 1960 cm^{-1} in all solid dispersions showed certain changes in their peak intensity.

4.4.3 The IR spectra of nifedipine-PEG6000 solid dispersions.

The IR spectra of PEG6000 as shown from Figure 130B-133B showed similar patterns to PEG4000, due to their similarity in their molecular structure. The characteristic broad peaks of O-H stretching bands showed from 3300 to 3600 cm^{-1} , C-H stretching from 2800 to 2990 cm^{-1} and C-O stretching from 1000 to 1200 cm^{-1} . The medium intensity peak at 1960 cm^{-1} were also detected.

The IR spectra of nifedipine-PEG6000 solid dispersion (Figure 130-133) showed no differences from their corresponding physical mixtures. The spectra showed the superimposition of characteristic peaks of both nifedipine and PEG6000. Certainly, at the higher mixing ratios, the intensity of nifedipine peaks reduced due to the dilution by PEG6000.

4.4.4 The IR spectra of nifedipine-poloxamer188 solid dispersion

The IR spectra of poloxamer188 (Figure134B-137B) showed the characteristics broad peaks of O-H stretching from 3300 to 3600 cm^{-1} , C-H stretching from 2800 to 2990 cm^{-1} and C-O stretching of ether linkage from 1000-1200 cm^{-1} .

The physical mixtures of nifedipine and poloxamer188 showed superimposed characteristic peaks of both compounds. However, the intensity of nifedipine peaks were reduced at higher mixing ratios.

The solid dispersions of nifedipine-poloxamer188 prepared by melting, solvent and kneading method showed similar IR spectral patterns to their corresponding physical mixtures (Figure135-137). It was interesting that all solid dispersions showed some changes of the O-H stretching band of poloxamer188. The intensity of the broad O-H stretching band of intermolecular hydrogen bonding was more than poloxamer itself and also shift to lower frequency.

4.4.5 The IR spectra of nifedipine-poloxamer288 solid dispersions

The IR spectra of poloxamer288 were very similar to those of the other two poloxamers (Figure138B-141B). The broad peak of O-H stretching were detected from 3300 to 3600 cm^{-1} , C-H stretching from 2800 to 2990 cm^{-1} and C-O stretching from 1000-1200 cm^{-1} .

The physical mixtures of nifedipine and poloxamer288 showed superimposed IR spectra of both compounds (Figure138). However, at the higher mixing ratio, many peaks of nifedipine showed reduced intensity.

The solid dispersions prepared by melting, solvent and kneading method showed IR spectra non different from their corresponding physical mixtures (Figure139-141). The shift of O-H stretching to lowering frequency that observed in the poloxamer188 and 407 could not be clearly detected in poloxamer288 systems.

4.4.6 The IR spectra of nifedipine-poloxamer407 solid dispersions.

The IR spectra of poloxamer407 (Figure142-145) showed no differencee from those of poloxamer188, due to their similarity in the molecular structure. They showed broad O-H stretching from 3300 to 3600 cm^{-1} , C-H stretching from 2800 to 2990 cm^{-1} and C-O stretching of ether linkage from 1000 to 1200 cm^{-1} , however this latter bond was more intense than that of poloxamer188.

The IR spectra of nifedipine-poloxamer407 physical mixtures (Figure142) showed the superimposition of those of nifedipine and poloxamer407.

The solid dispersions prepared by melting method and kneading method at 1:5 and 1:10 mixing ratios (Figure143 and 145) showed some changes of C=O stretching at 1690 cm^{-1} that lowered to 1686 cm^{-1} .

All solid dispersions showed the slight shift to lower frequency of O-H stretching of poloxamer407 and changes in C-O stretching band appearances at 1000-1200 cm^{-1} of poloxamer407.

4.4.7 The IR spectra of nifedipine- β -cyclodextrin solid dispersion.

β -cyclodextrin in Figure 146B-147B showed characteristic broad O-H stretching peak from 3000 to 3600 cm^{-1} . The C-H stretching could be detected at 2927 cm^{-1} . The C-O stretching of primary O-H groups and secondary O-H groups could be observed at 1029 and 1158 cm^{-1} , respectively.

The physical mixtures showed superimposed IR spectral patterns of nifedipine and β -cyclodextrin.

The solid dispersions prepared from kneading method showed similar IR spectra to their corresponding physical mixtures. However, both systems at higher mixing ratios at 1:5 and 1:10 showed slight changes of aromatic C-H stretching of nifedipine at 3102 cm^{-1} and aliphatic C-H stretching at 2954 cm^{-1} . The aromatic C=C stretching of phenyl nucleus at 1600 cm^{-1} showed some changes in their patterns.

4.4.8 The IR spectra of nifedipine -2-hydroxypropyl- β -cyclodextrin solid dispersions.

The IR spectra of 2-hydroxypropyl- β -cyclodextrin showed very intense O-H stretching vibration from 3000 to 3600 cm^{-1} . The C-H stretching vibration showed at 2930 cm^{-1} . The primary O-H stretching and secondary O-H stretching could be detected at 1033 and 1156 cm^{-1} , respectively (Figures 148-150).

The IR spectra of physical mixtures showed superimposition of those of nifedipine and 2-hydroxypropyl- β -cyclodextrin. Certainly many peaks of nifedipine disappeared due to the dilution by the carrier. However, at higher

mixing ratios, some changes could be observed at the C-H stretching of nifedipine at 3102 and 2954 cm^{-1} .

The solid dispersions prepared by kneading methods showed similar IR spectra to their corresponding physical mixtures (Figure150).

It was interesting that the IR spectra of the solid dispersions prepared by solvent method (Figure149) showed remarkable changes at the mixing ratio 1:1 to 1:10. Besides the change of C-H stretching of nifedipine at 3102 and 2954 cm^{-1} , the change to C=O stretching of nifedipine at 1689 cm^{-1} could be observed. In addition the aromatic C=C stretching of phenyl nucleus at 1600 cm^{-1} showed noticeable changes in their patterns.

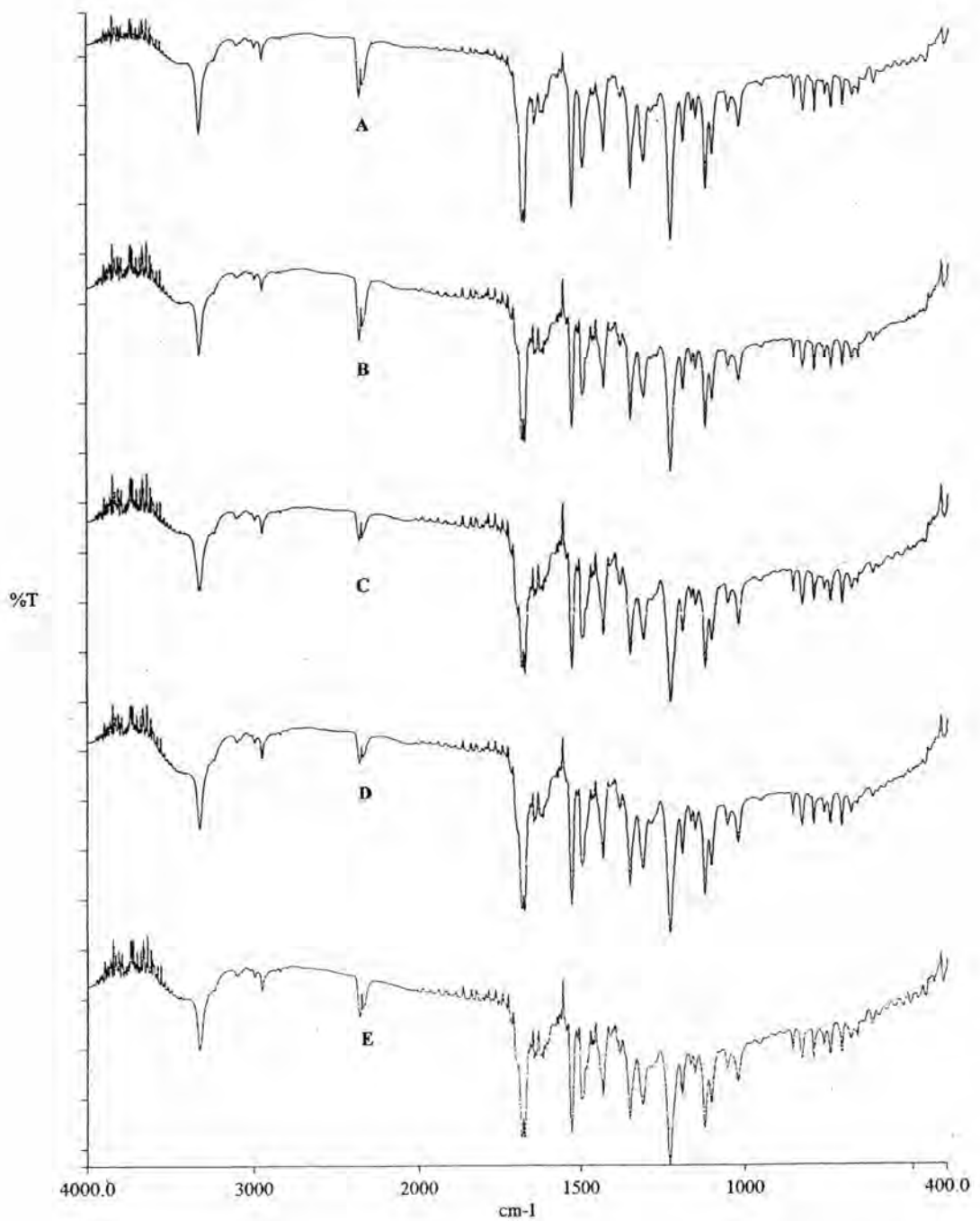


Figure 125 IR spectra of nontreated and treated nifedipine with various methods.

A: Nontreated nifedipine

B: Treated by physical mixing

C: Treated by melting method

D: Treated by solvent method

E: Treated by kneading method

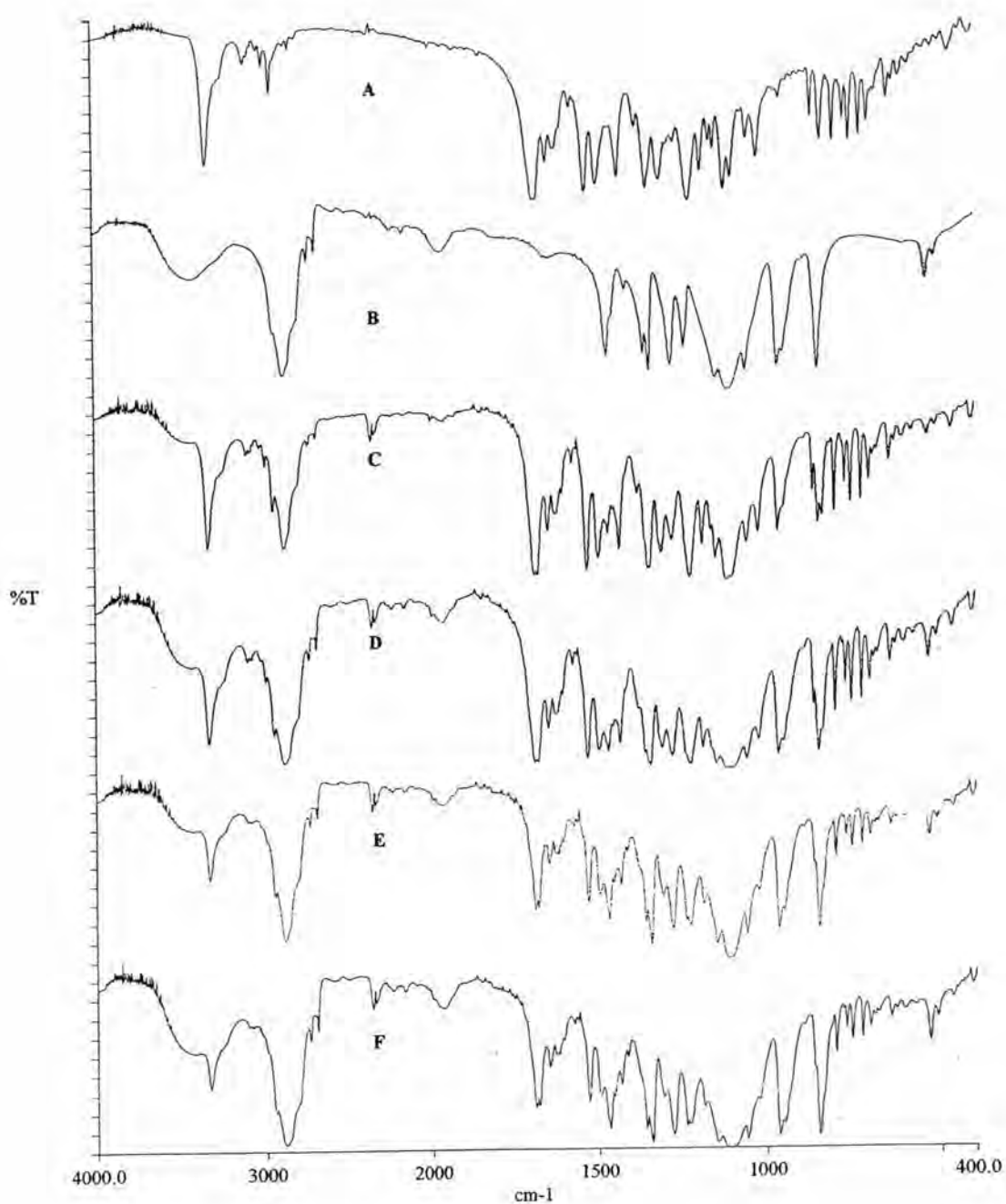


Figure 126 IR spectra of nifedipine-PEG4000 prepared by physical mixing

A: nifedipine

B: carrier

C: drug to carrier ratio of 1:1

D: drug to carrier ratio of 1:3

E: drug to carrier ratio of 1:5

F: drug to carrier ratio of 1:10

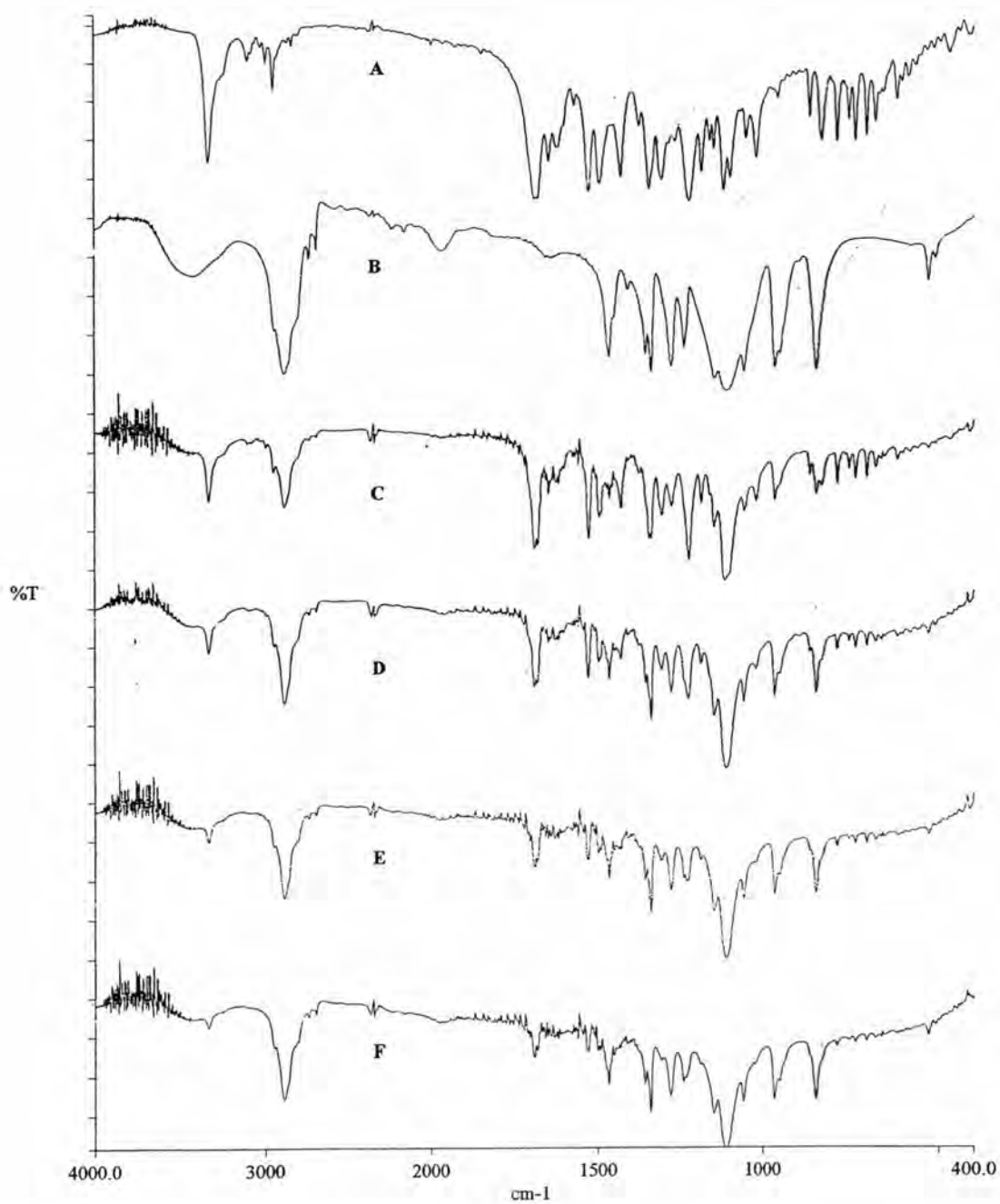


Figure 127 IR spectra of nifedipine-PEG4000 prepared by melting method.

A: nifedipine

B: carrier

C: drug to carrier ratio of 1:1

D: drug to carrier ratio of 1:3

E: drug to carrier ratio of 1:5

F: drug to carrier ratio of 1:10

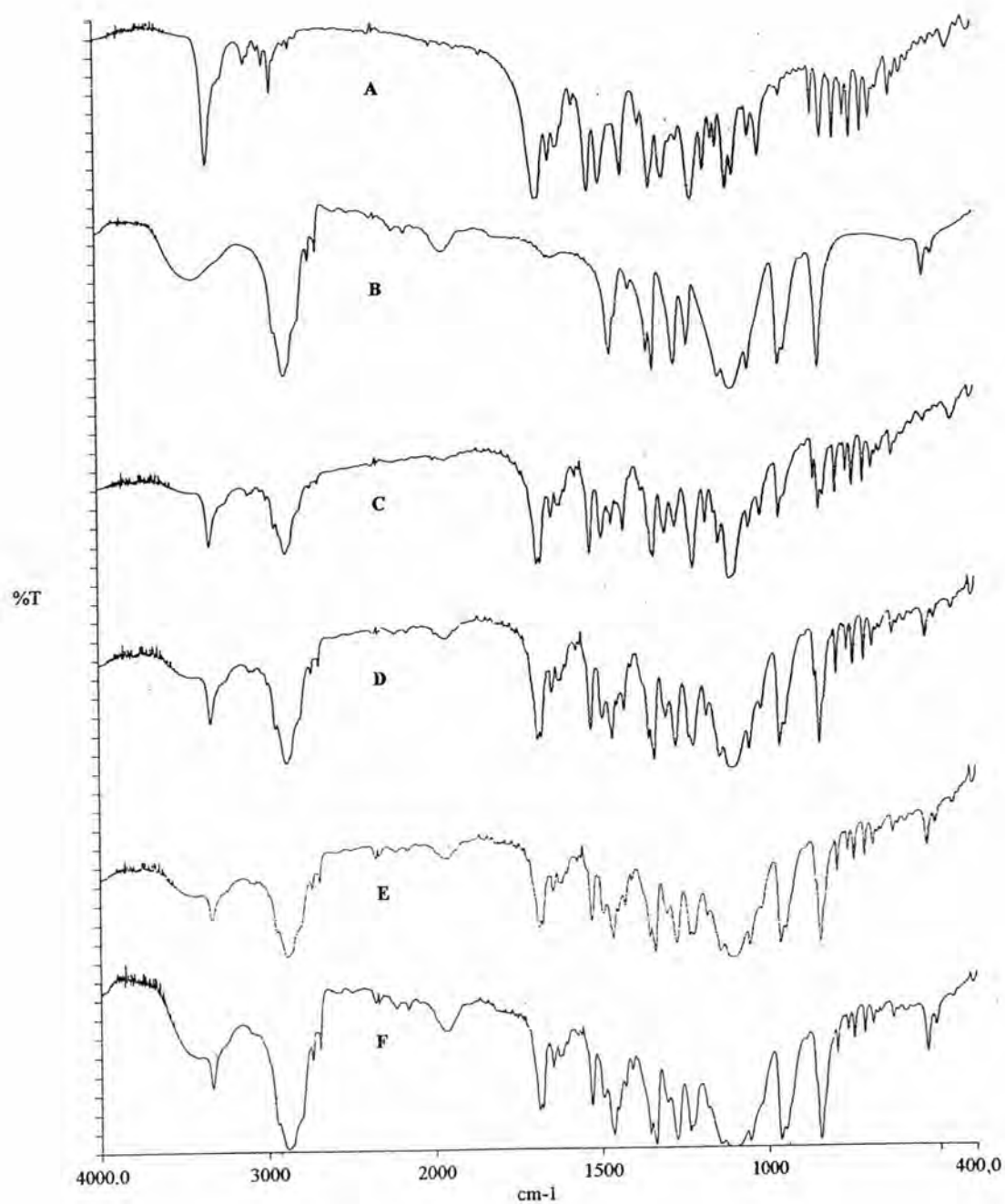


Figure 128 IR spectra of nifedipine-PEG4000 prepared by solvent method.

A: nifedipine

B: carrier

C: drug to carrier ratio of 1:1

D: drug to carrier ratio of 1:3

E: drug to carrier ratio of 1:5

F: drug to carrier ratio of 1:10

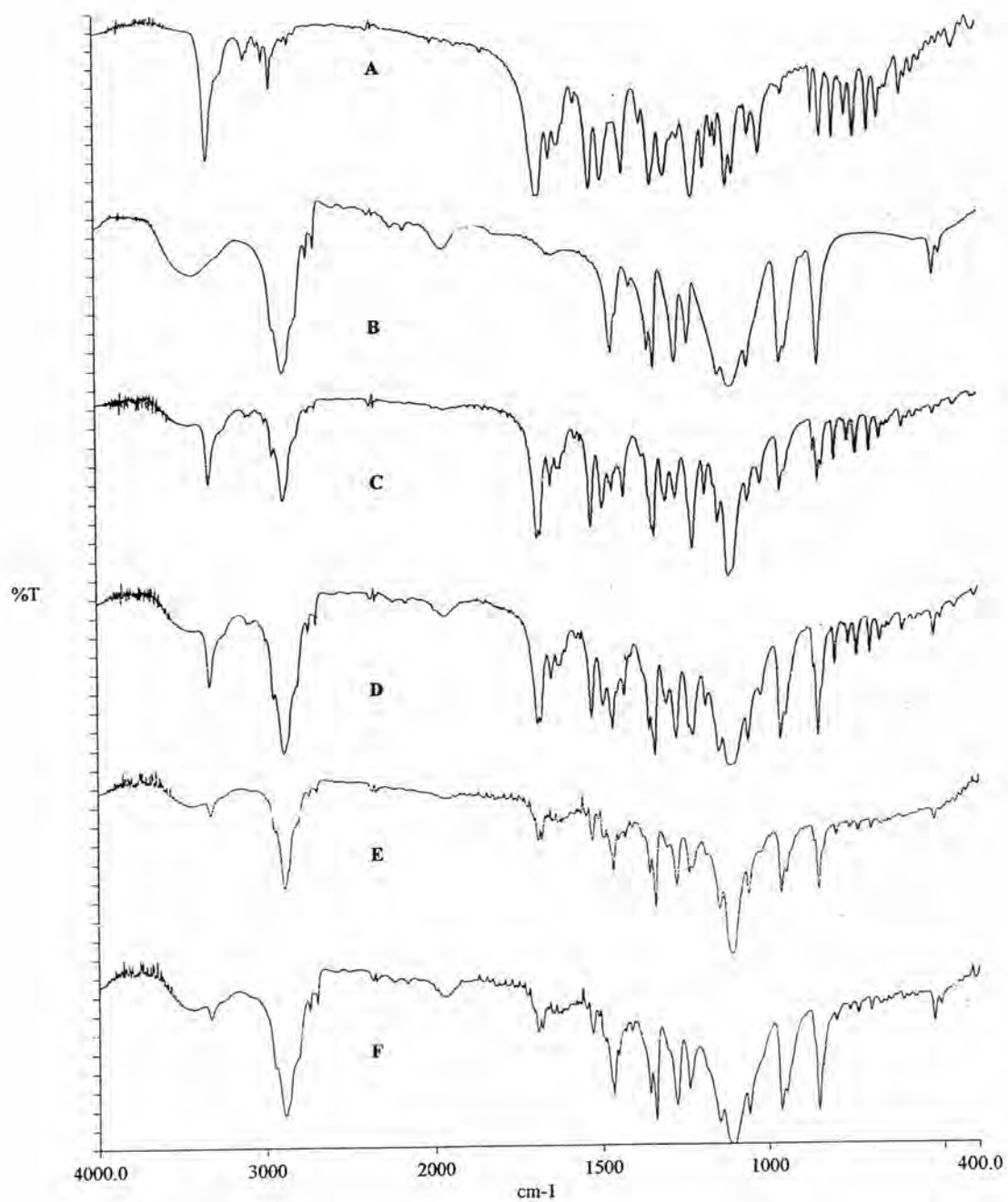


Figure 129 IR spectra of nifedipine-PEG4000 prepared by kneading method.

A: nifedipine

B: carrier

C: drug to carrier ratio of 1:1

D: drug to carrier ratio of 1:3

E: drug to carrier ratio of 1:5

F: drug to carrier ratio of 1:10

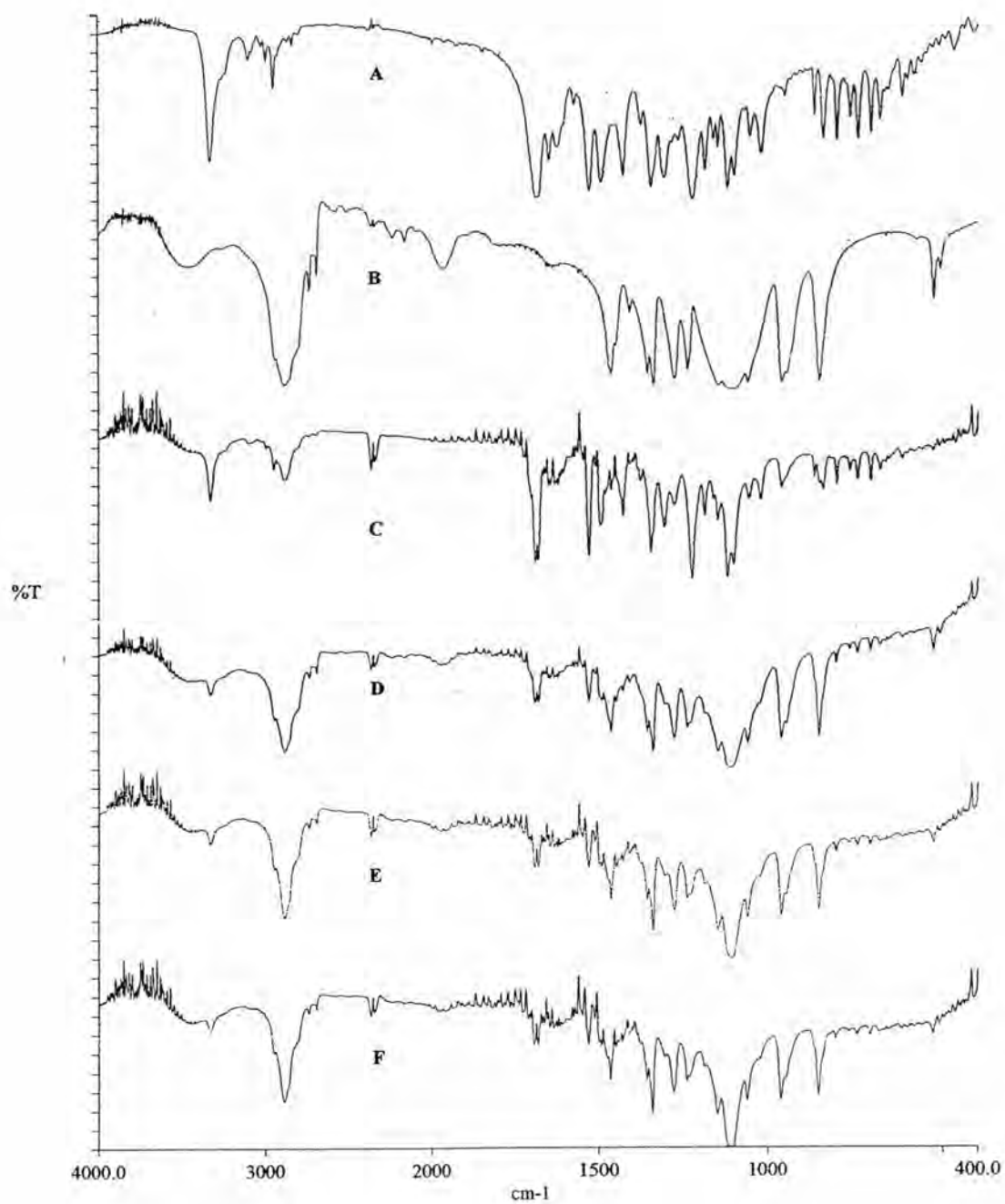


Figure 130 IR spectra of nifedipine-PEG6000 prepared by physical mixing.

A: nifedipine

B: carrier

C: drug to carrier ratio of 1:1

D: drug to carrier ratio of 1:3

E: drug to carrier ratio of 1:5

F: drug to carrier ratio of 1:10

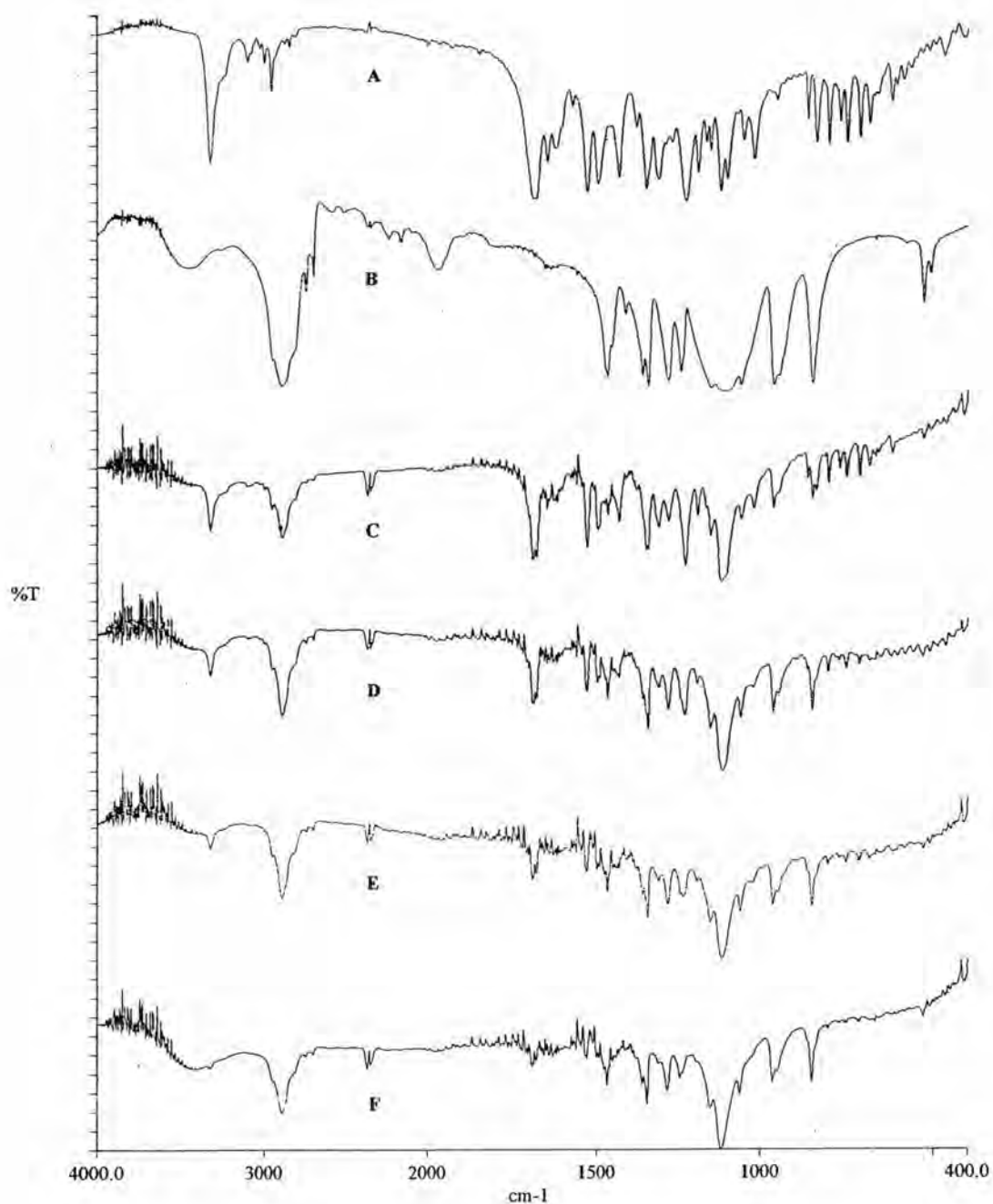


Figure 131 IR spectra of nifedipine-PEG6000 prepared by melting method.

A: nifedipine

B: carrier

C: drug to carrier ratio of 1:1

D: drug to carrier ratio of 1:3

E: drug to carrier ratio of 1:5

F: drug to carrier ratio of 1:10

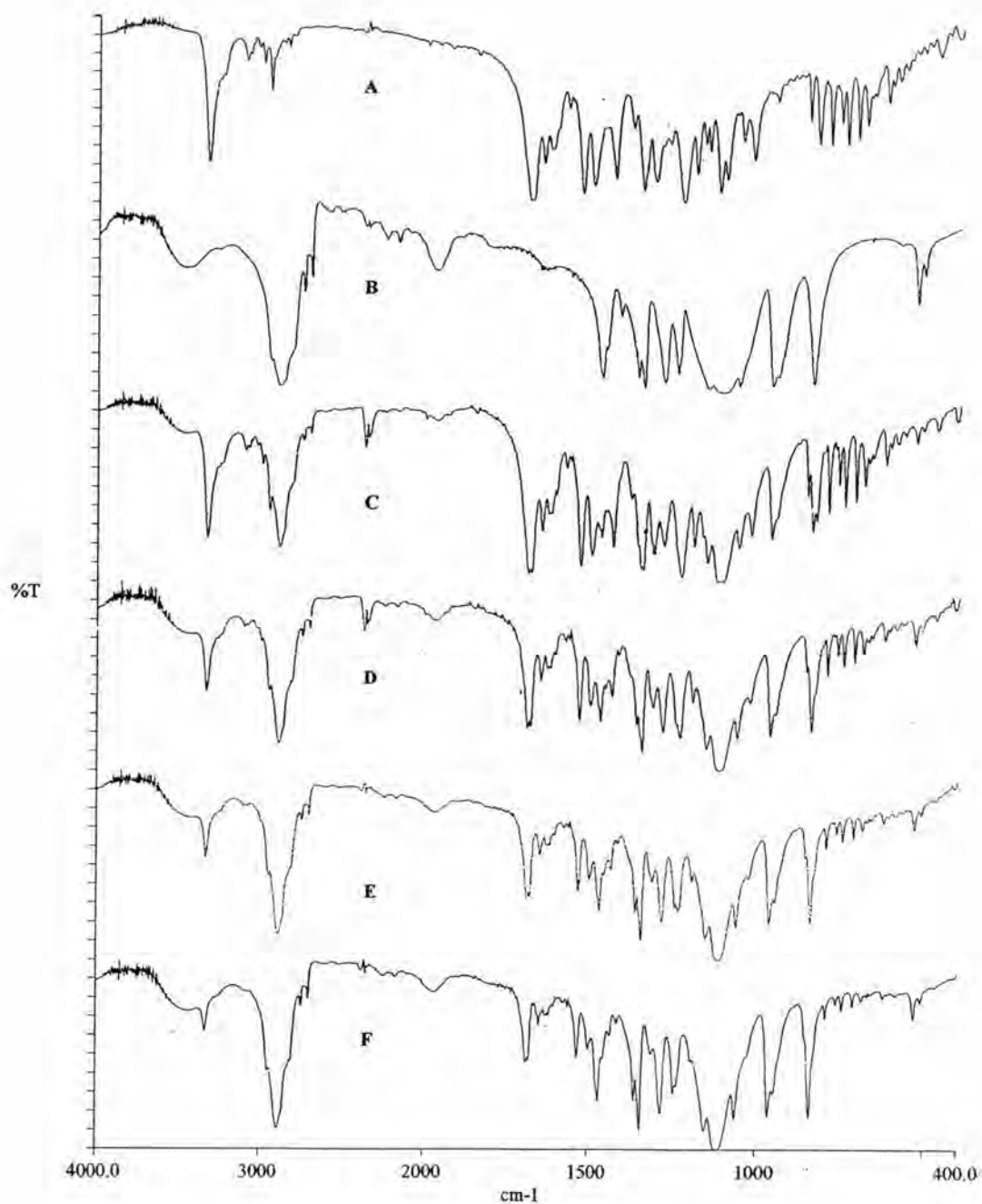


Figure 132 IR spectra of nifedipine-PEG6000 prepared by solvent method.

A: nifedipine

B: carrier

C: drug to carrier ratio of 1:1

D: drug to carrier ratio of 1:3

E: drug to carrier ratio of 1:5

F: drug to carrier ratio of 1:10

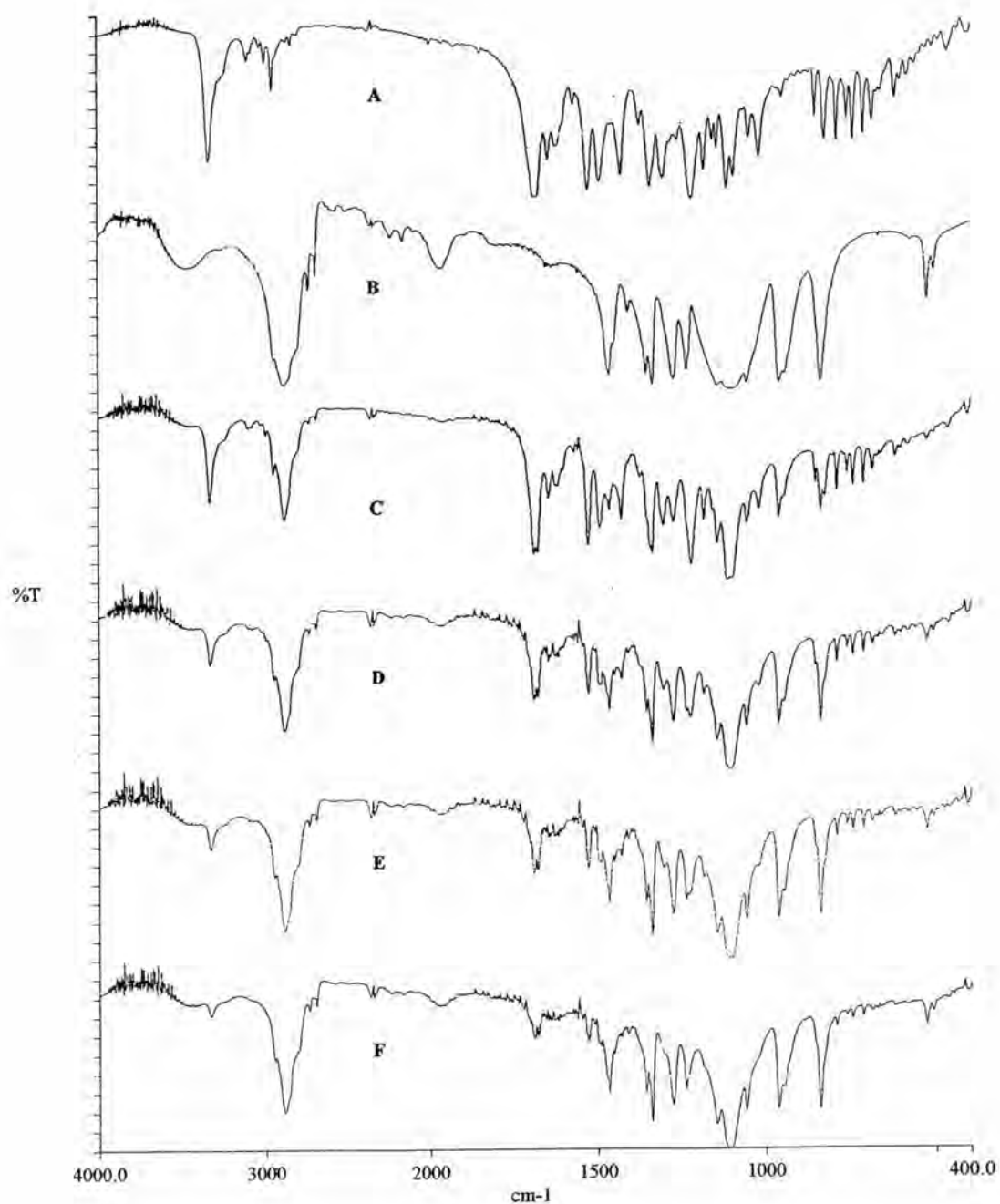


Figure 133 IR spectra of nifedipine-PEG6000 prepared by kneading method.

A: nifedipine

B: carrier

C: drug to carrier ratio of 1:1

D: drug to carrier ratio of 1:3

E: drug to carrier ratio of 1:5

F: drug to carrier ratio of 1:10

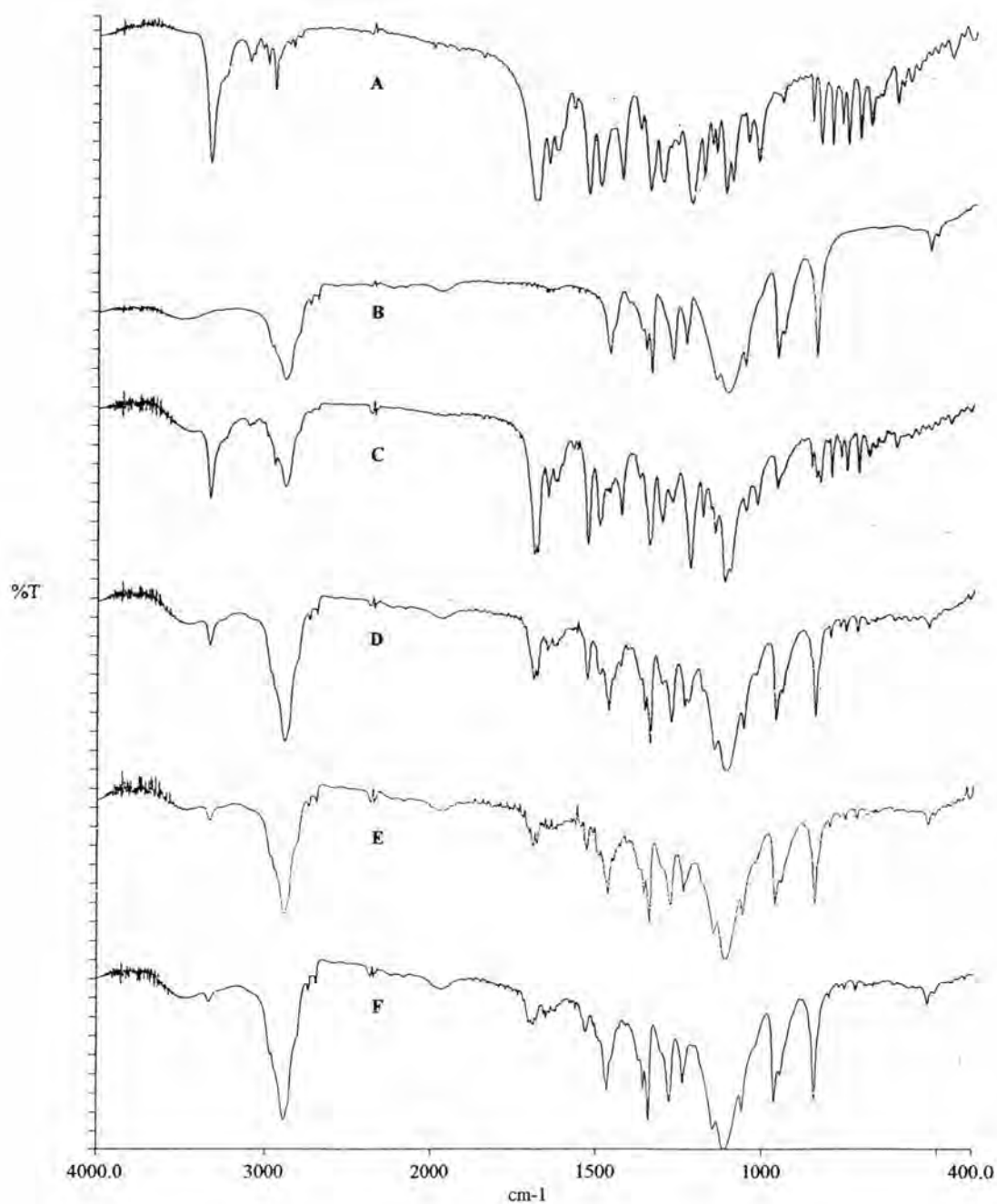


Figure 134 IR spectra of nifedipine-poloxamer188 prepared by physical mixture

A: nifedipine

B: carrier

C: drug to carrier ratio of 1:1

D: drug to carrier ratio of 1:3

E: drug to carrier ratio of 1:5

F: drug to carrier ratio of 1:10

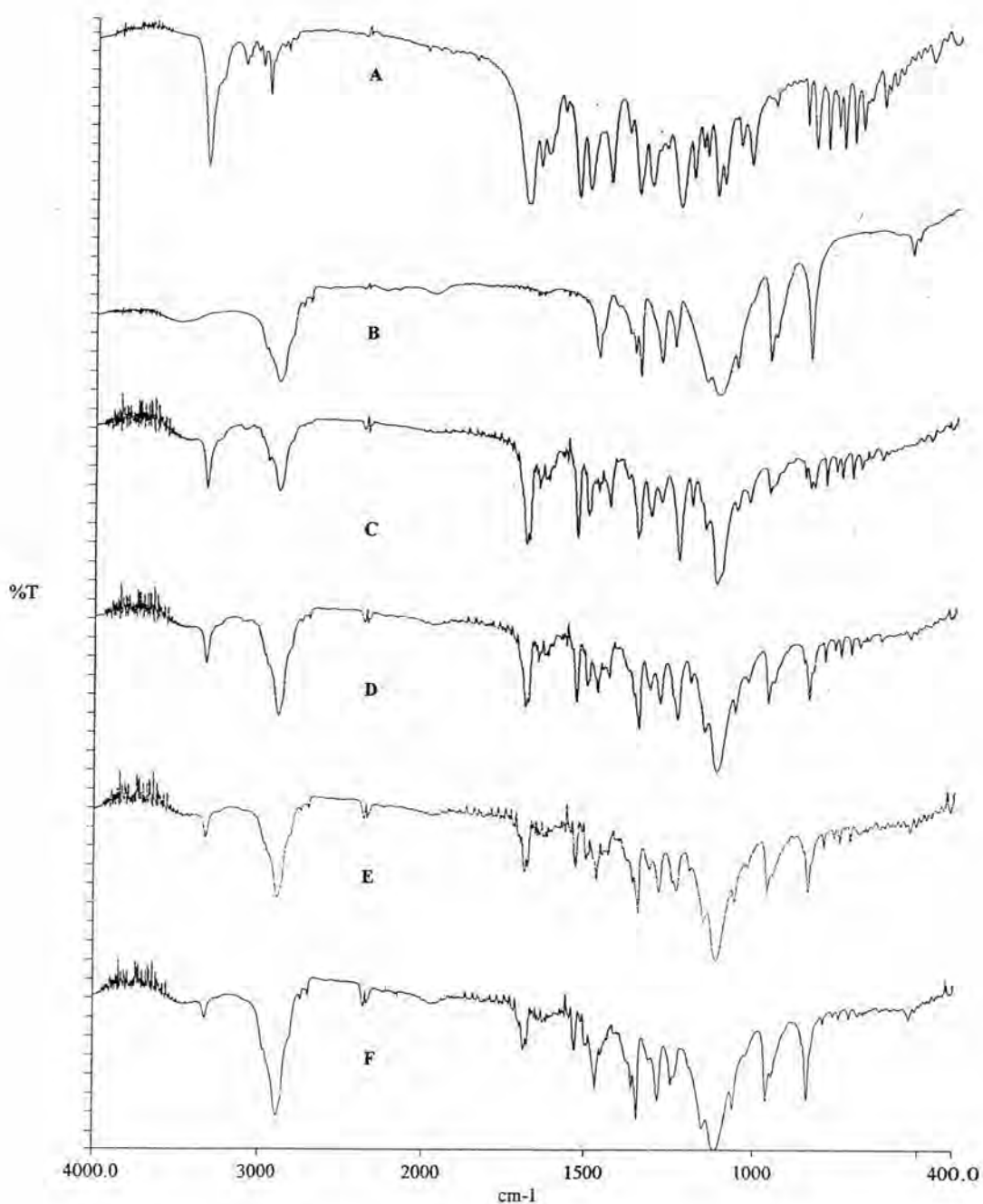


Figure 135 IR spectra of nifedipine-poloxamer188 prepared by melting method.

A: nifedipine

B: carrier

C: drug to carrier ratio of 1:1

D: drug to carrier ratio of 1:3

E: drug to carrier ratio of 1:5

F: drug to carrier ratio of 1:10

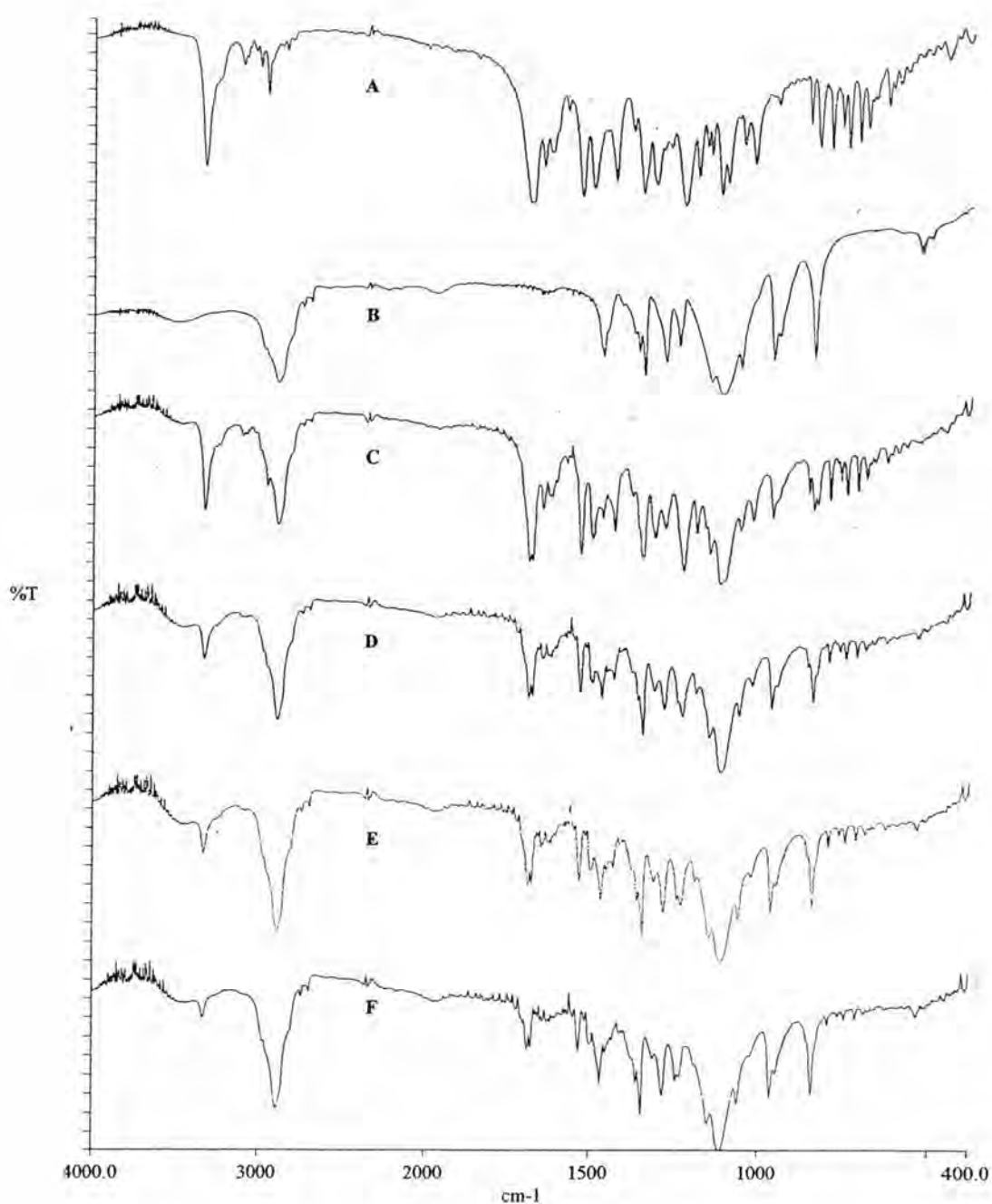


Figure 136 IR spectra of nifedipine-poloxamer188 prepared by solvent method.

A: nifedipine

B: carrier

C: drug to carrier ratio of 1:1

D: drug to carrier ratio of 1:3

E: drug to carrier ratio of 1:5

F: drug to carrier ratio of 1:10

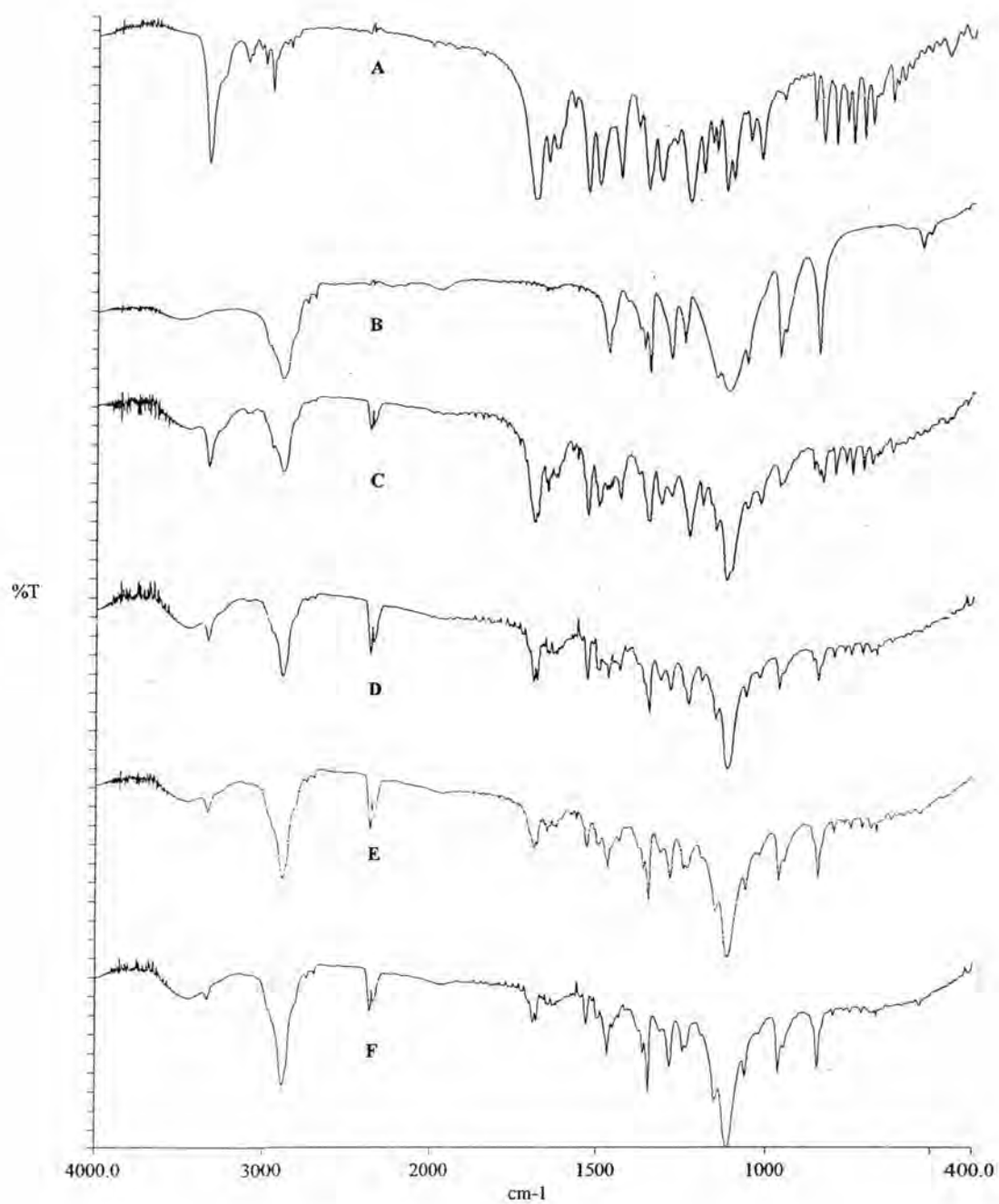


Figure 137 IR spectra of nifedipine-poloxamer188 prepared by kneading method.

A: nifedipine

B: carrier

C: drug to carrier ratio of 1:1

D: drug to carrier ratio of 1:3

E: drug to carrier ratio of 1:5

F: drug to carrier ratio of 1:10

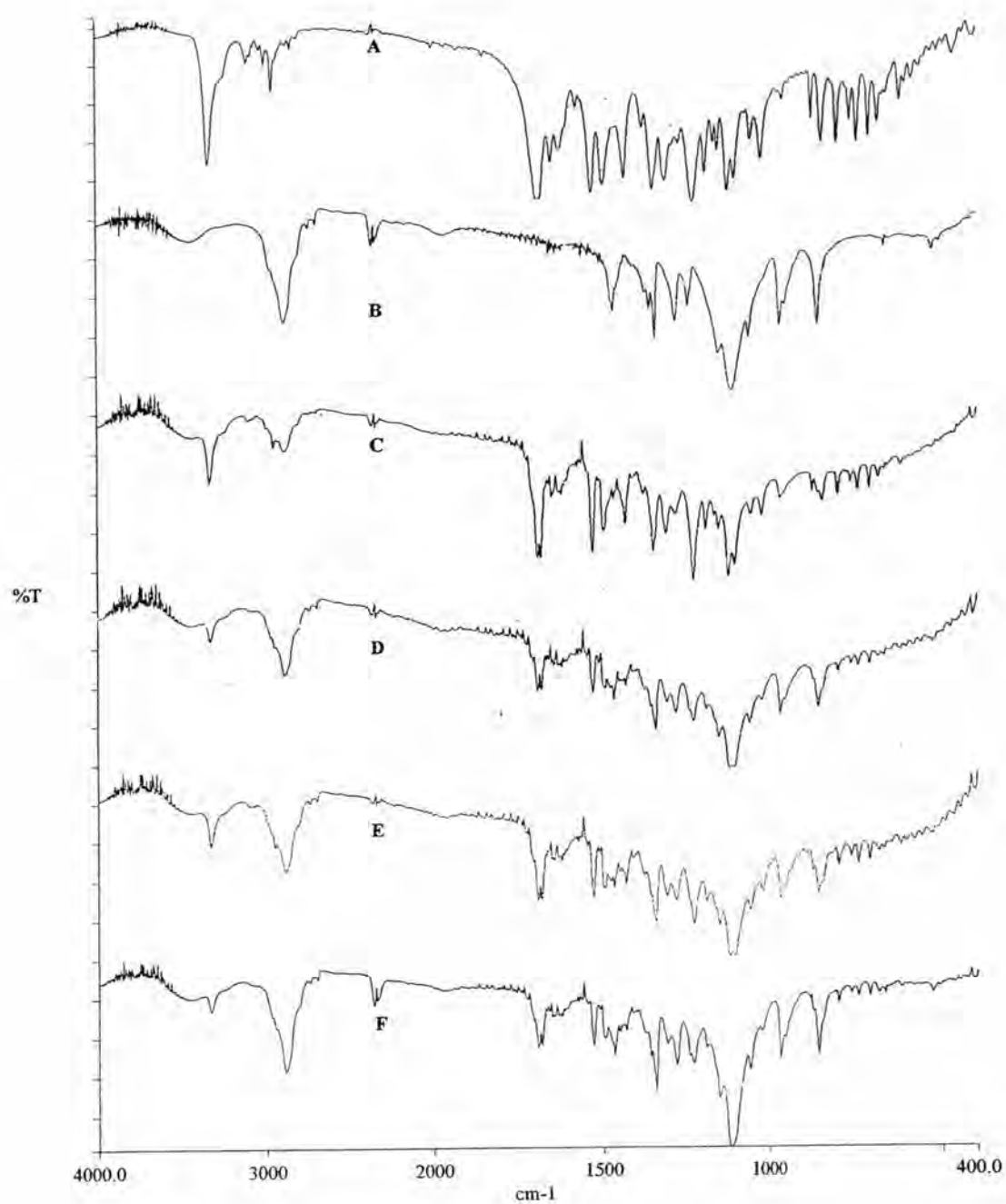


Figure 138 IR spectra of nifedipine-poloxamer288 prepared by physical mixture.

A: nifedipine

B: carrier

C: drug to carrier ratio of 1:1

D: drug to carrier ratio of 1:3

E: drug to carrier ratio of 1:5

F: drug to carrier ratio of 1:10

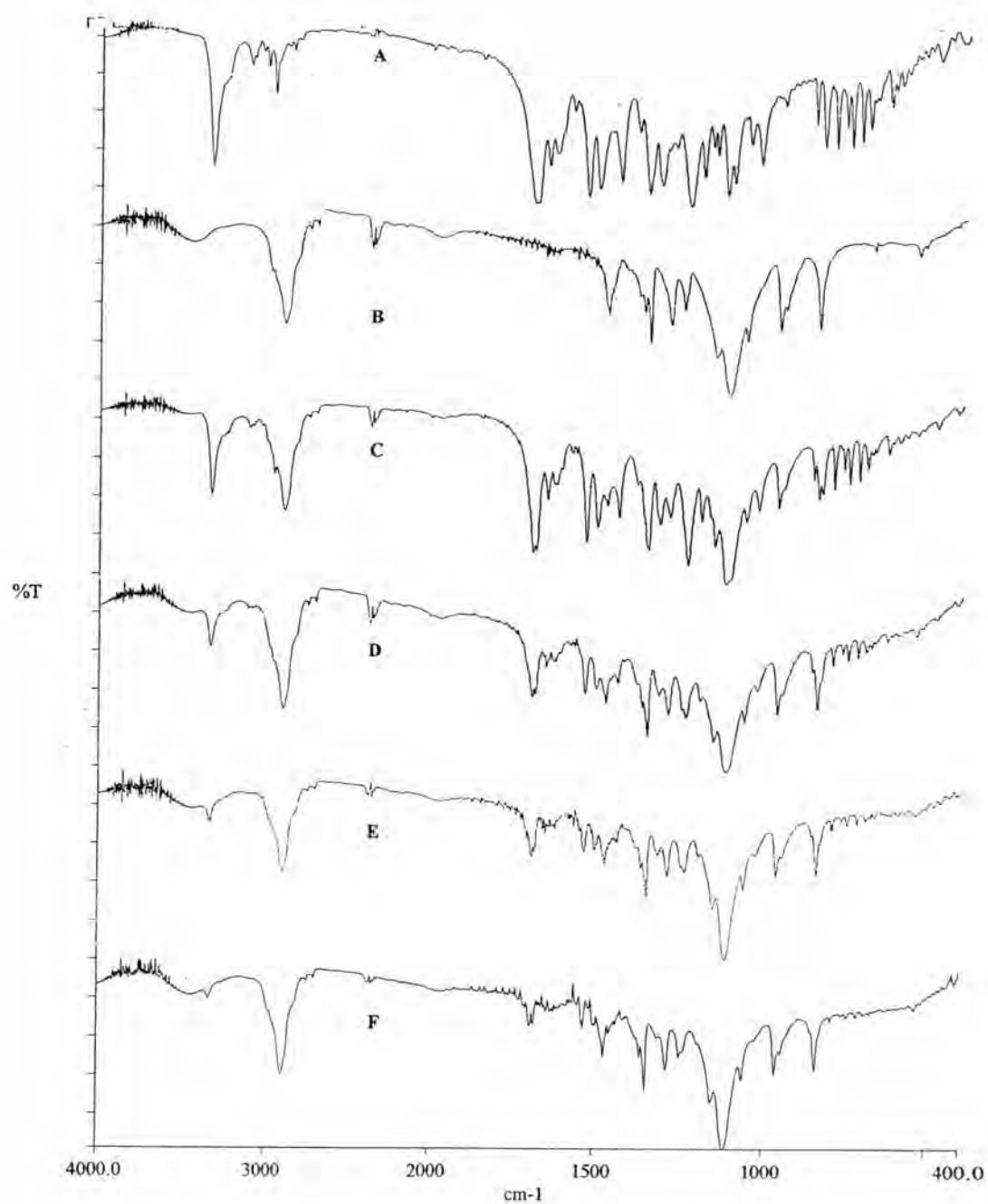


Figure 139 IR spectra of nifedipine-poloxamer288 prepared by melting method.

A: nifedipine

B: carrier

C: drug to carrier ratio of 1:1

D: drug to carrier ratio of 1:3

E: drug to carrier ratio of 1:5

F: drug to carrier ratio of 1:10

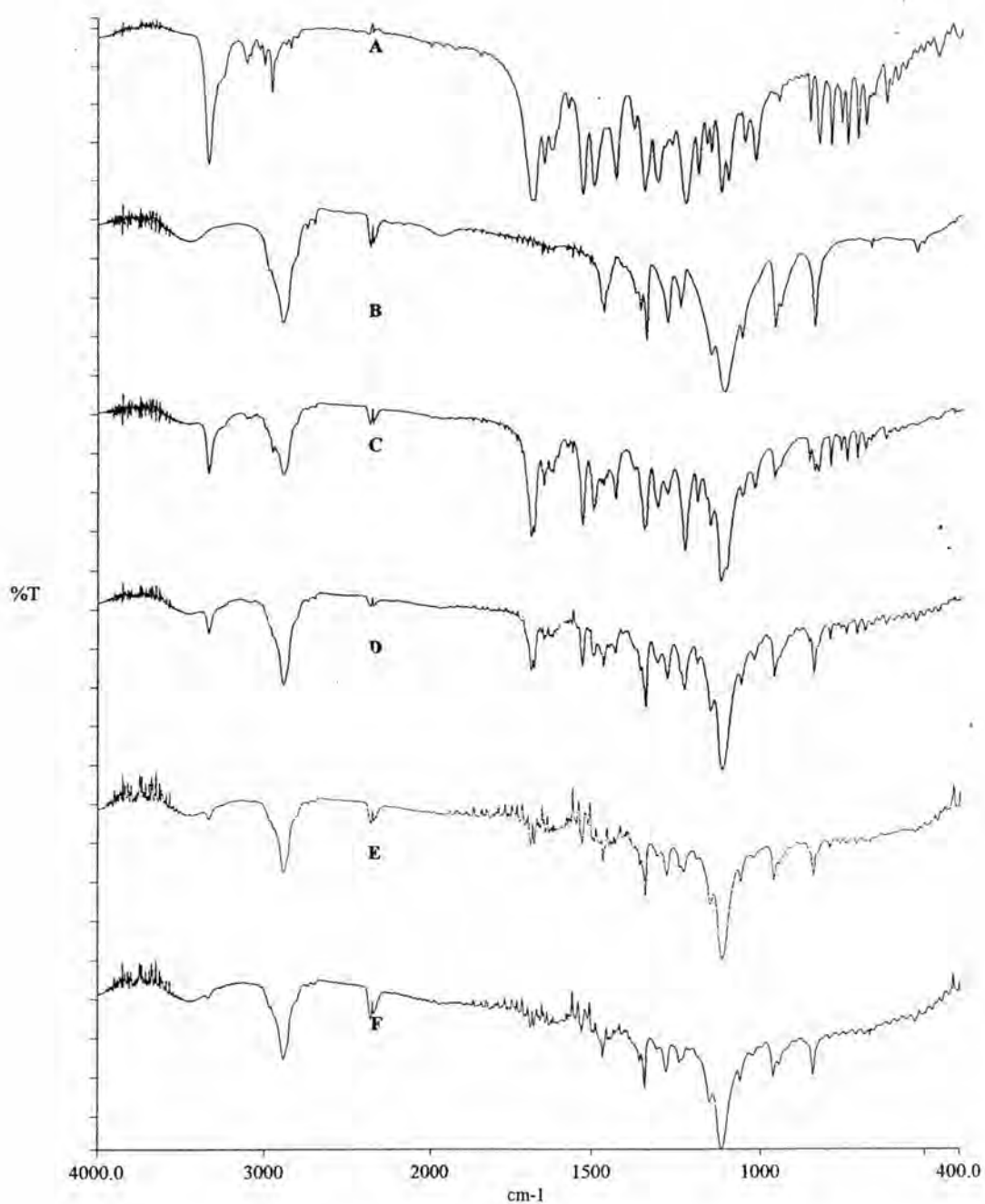


Figure 140 IR spectra of nifedipine-poloxamer288 prepared by solvent method.

A: nifedipine

B: carrier

C: drug to carrier ratio of 1:1

D: drug to carrier ratio of 1:3

E: drug to carrier ratio of 1:5

F: drug to carrier ratio of 1:10

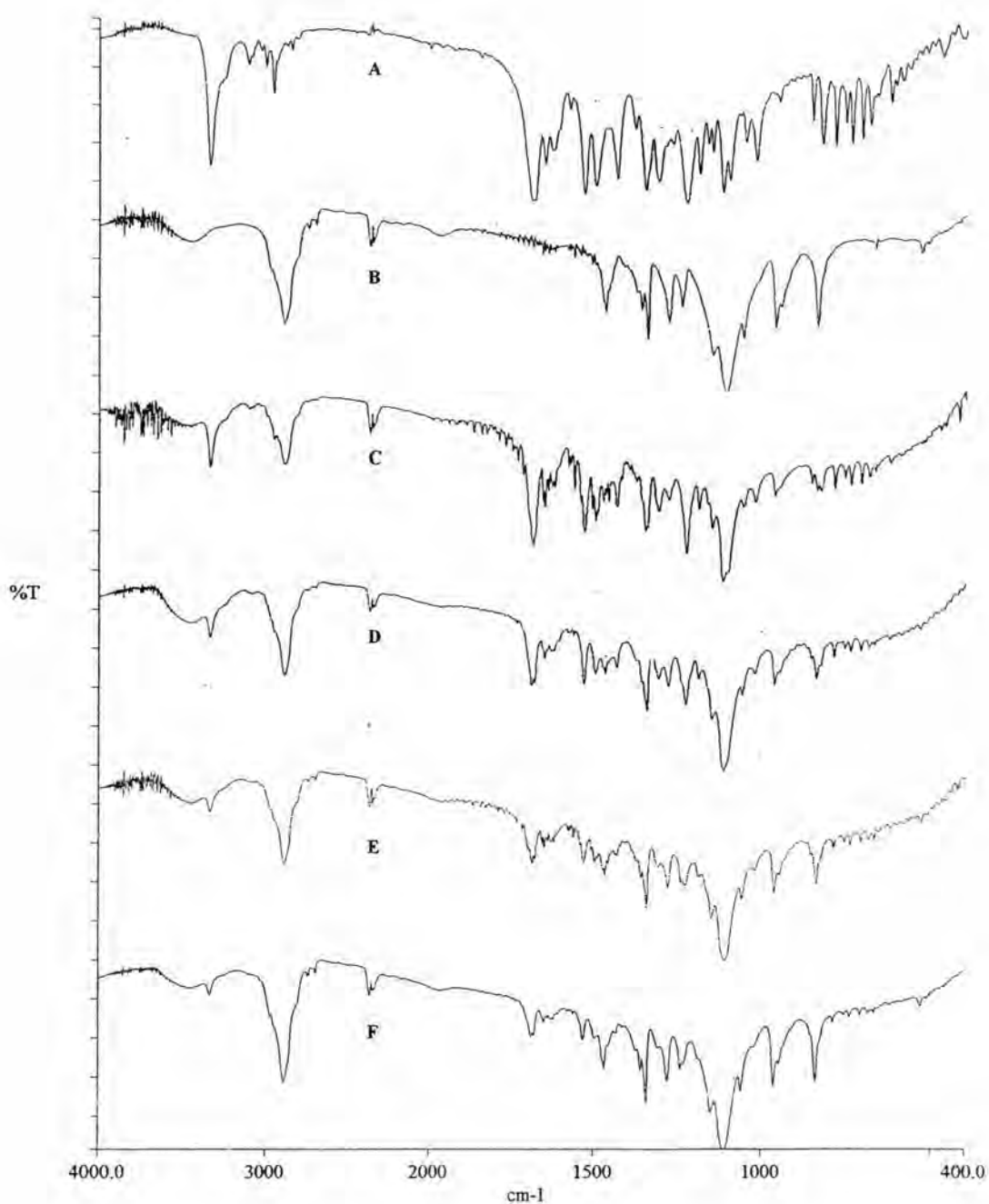


Figure 141 IR spectra of nifedipine-poloxamer288 prepared by kneading method.

A: nifedipine

B: carrier

C: drug to carrier ratio of 1:1

D: drug to carrier ratio of 1:3

E: drug to carrier ratio of 1:5

F: drug to carrier ratio of 1:10

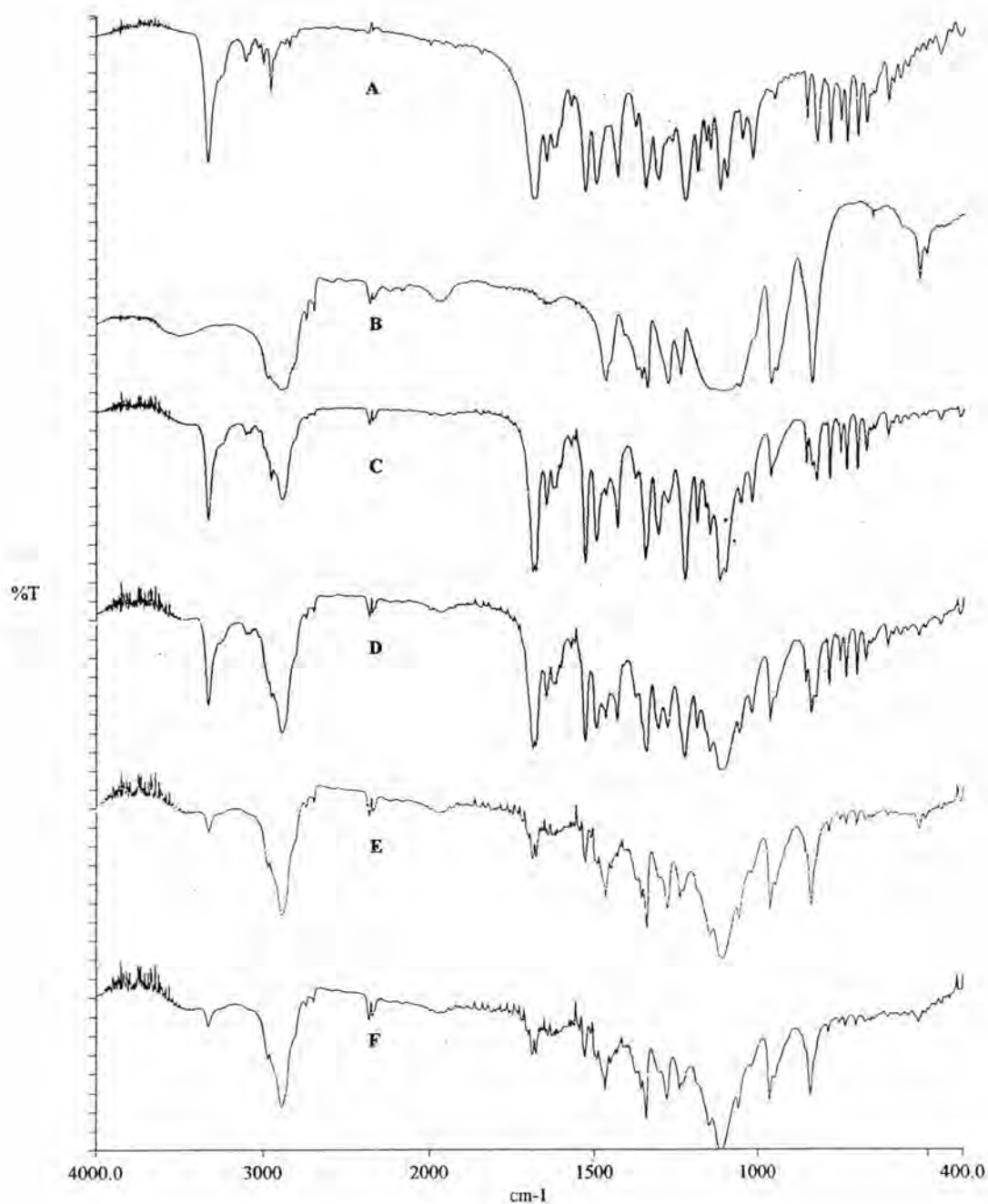


Figure 142 IR spectra of nifedipine-poloxamer407 prepared by physical mixture.

A: nifedipine

B: carrier

C: drug to carrier ratio of 1:1

D: drug to carrier ratio of 1:3

E: drug to carrier ratio of 1:5

F: drug to carrier ratio of 1:10

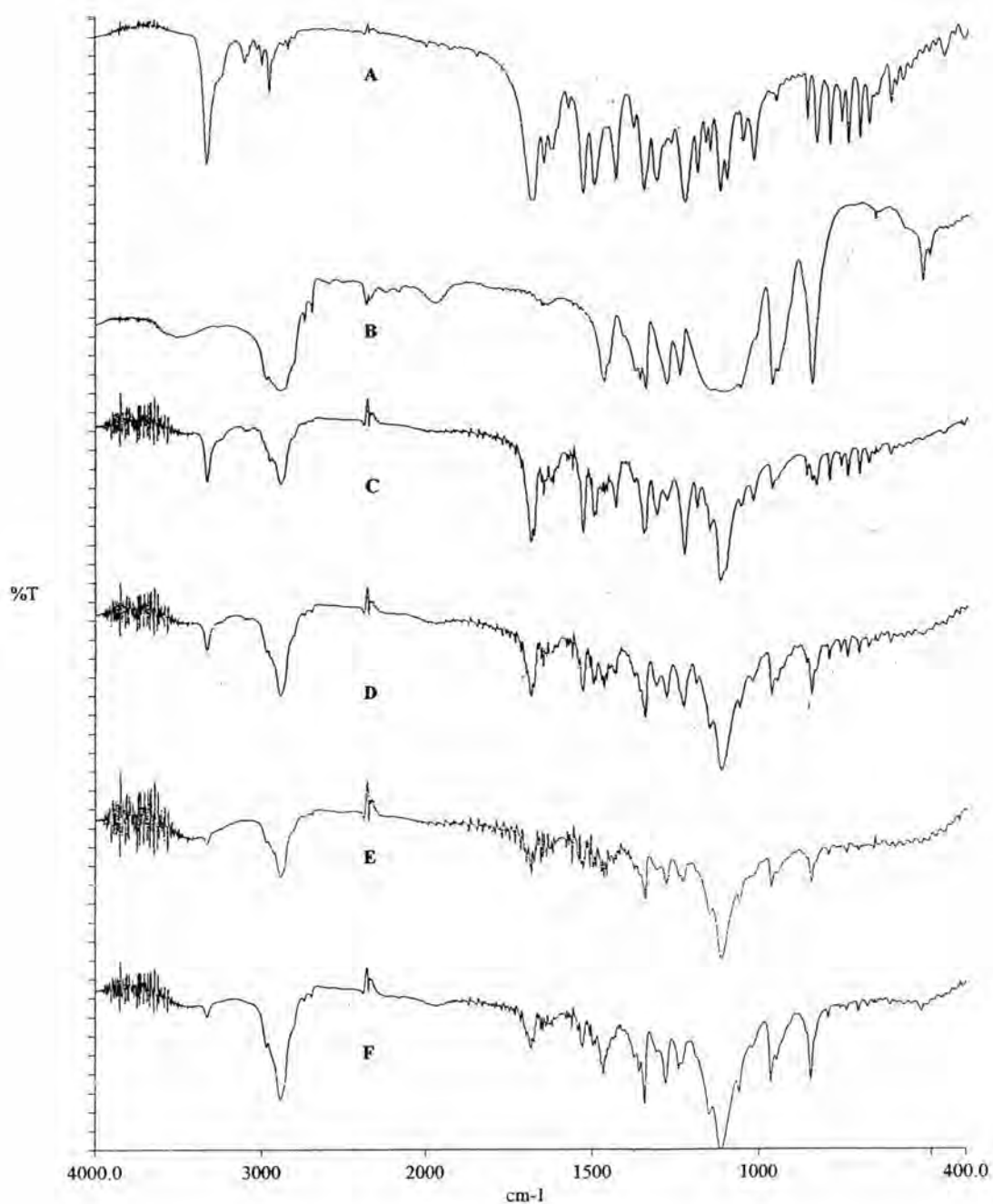


Figure 143 IR spectra of nifedipine-poloxamer407 prepared by melting method.

A: nifedipine

B: carrier

C: drug to carrier ratio of 1:1

D: drug to carrier ratio of 1:3

E: drug to carrier ratio of 1:5

F: drug to carrier ratio of 1:10

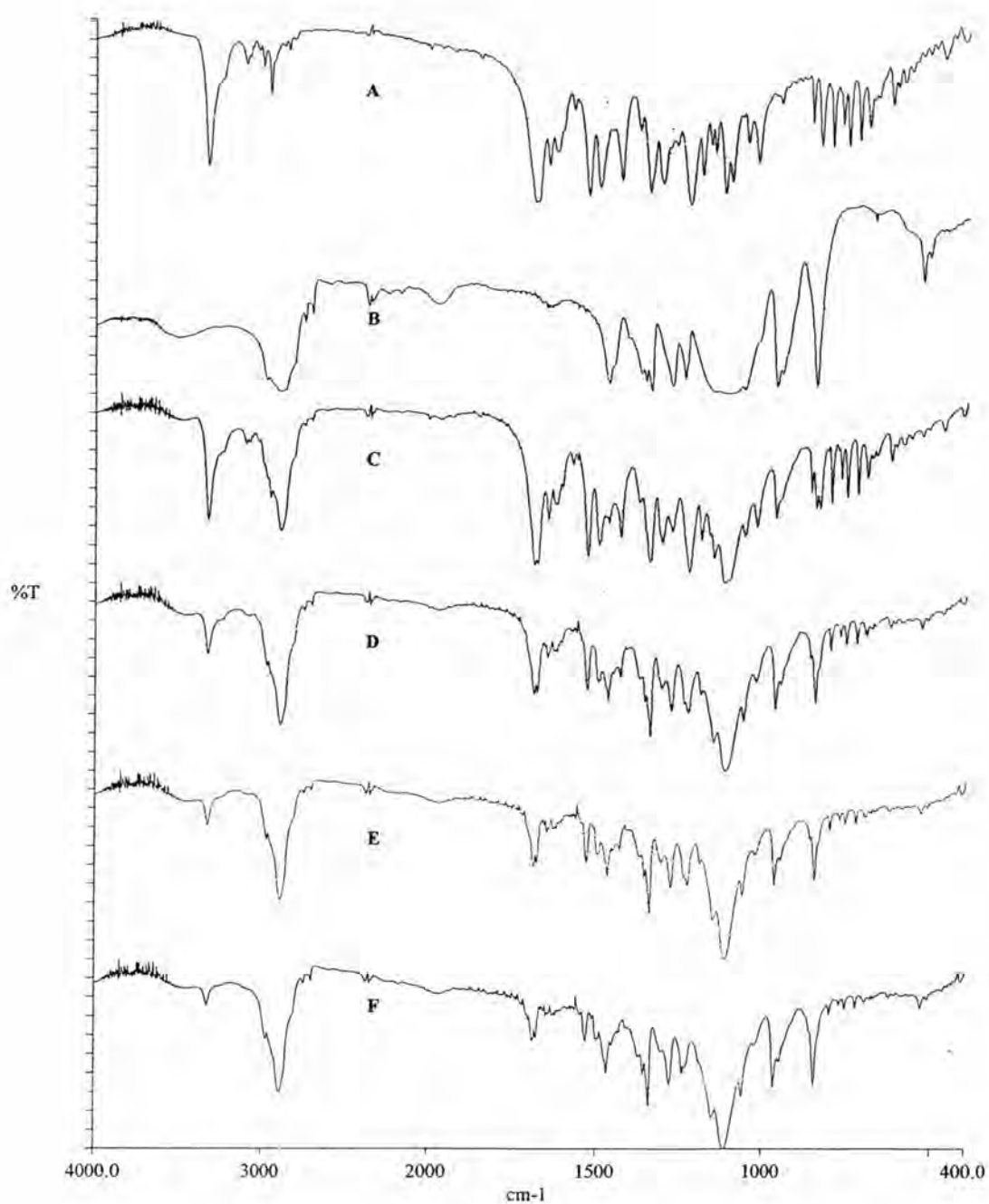


Figure 144 IR spectra of nifedipine-poloxamer407 prepared by solvent method.

A: nifedipine

B: carrier

C: drug to carrier ratio of 1:1

D: drug to carrier ratio of 1:3

E: drug to carrier ratio of 1:5

F: drug to carrier ratio of 1:10

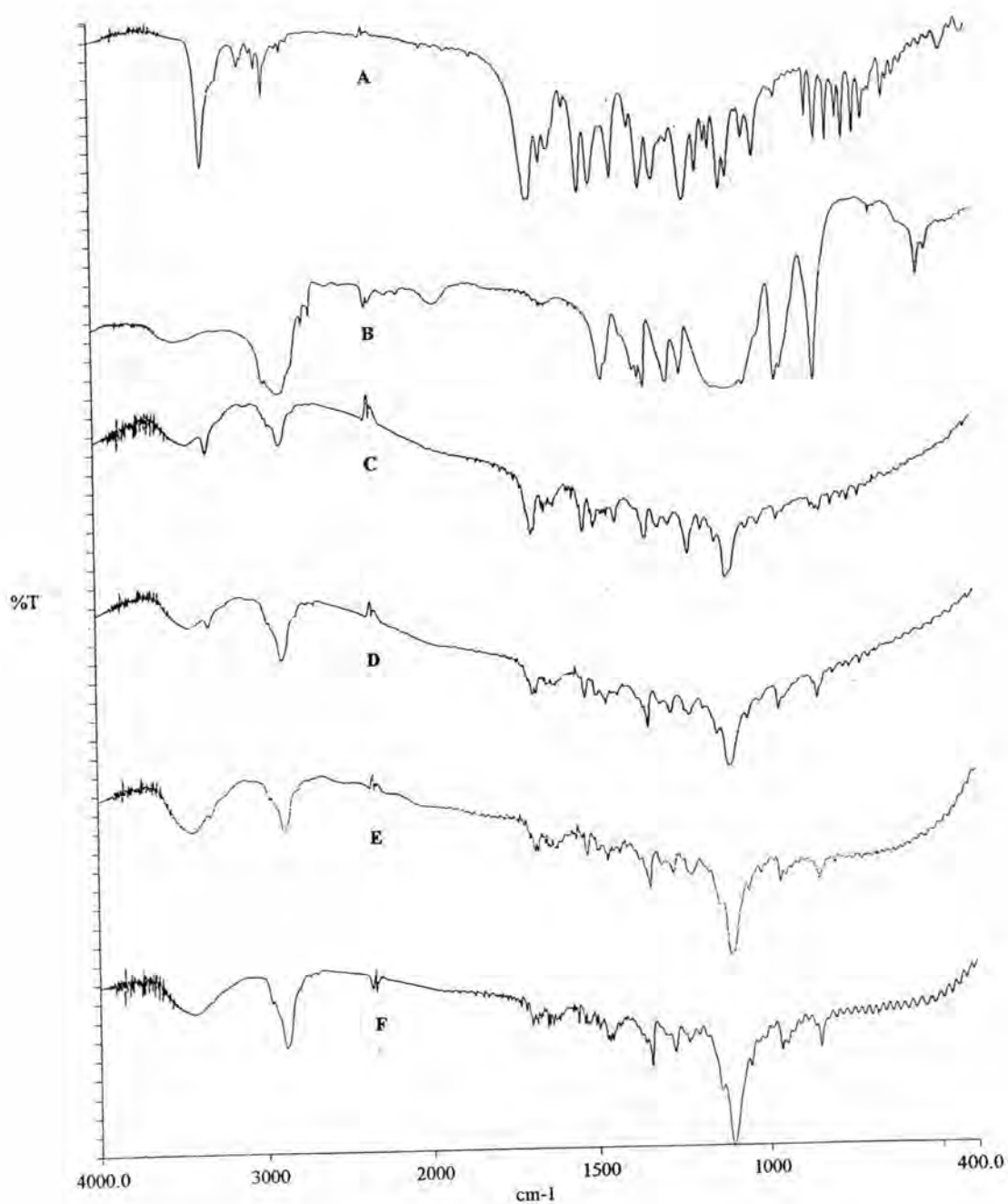


Figure 145 IR spectra of nifedipine-poloxamer407 prepared by kneading method.

A: nifedipine

B: carrier

C: drug to carrier ratio of 1:1

D: drug to carrier ratio of 1:3

E: drug to carrier ratio of 1:5

F: drug to carrier ratio of 1:10

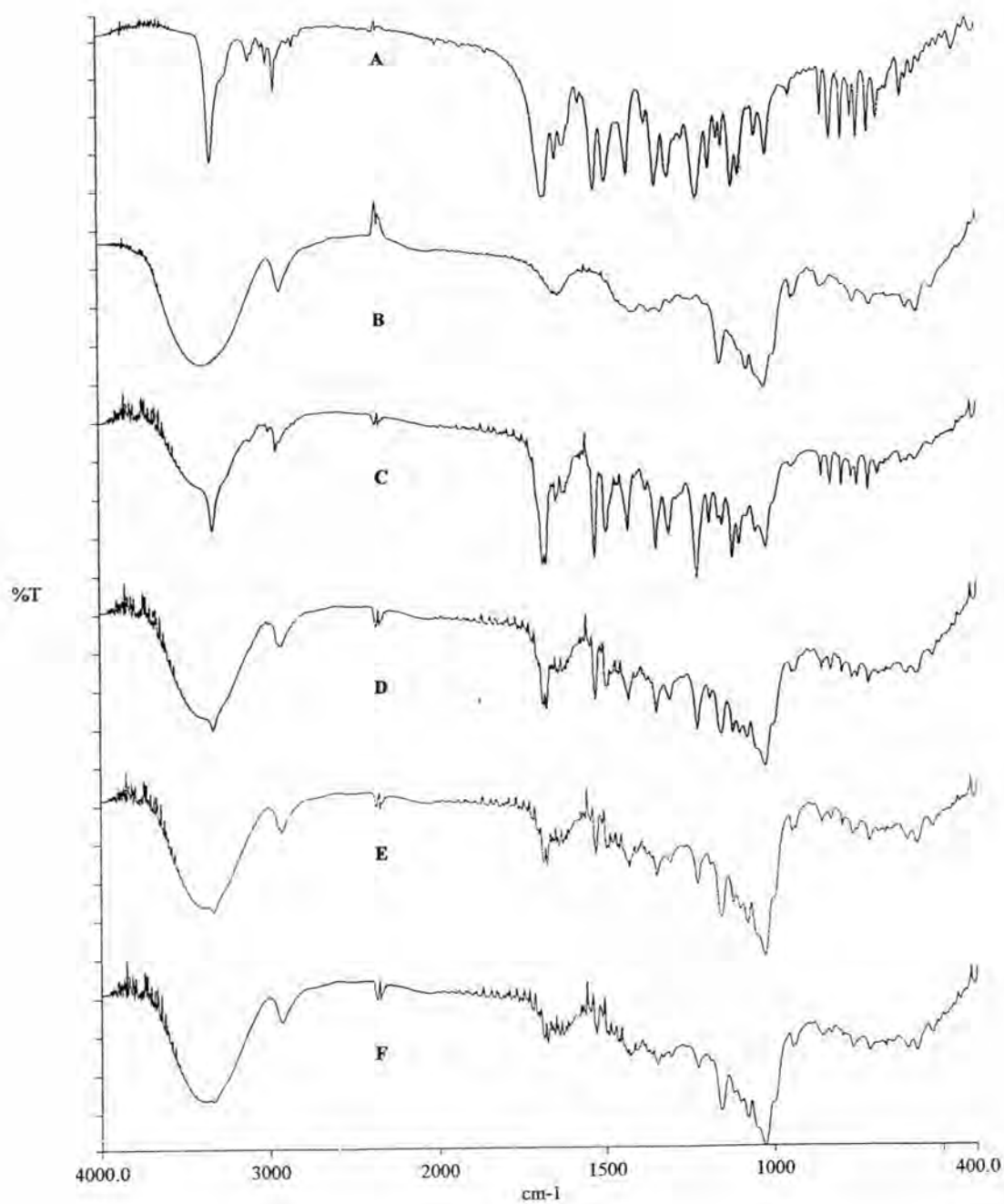


Figure 146 IR spectra of nifedipine- β -cyclodextrin prepared by physical mixture.

A: nifedipine

B: carrier

C: drug to carrier ratio of 1:1

D: drug to carrier ratio of 1:3

E: drug to carrier ratio of 1:5

F: drug to carrier ratio of 1:10

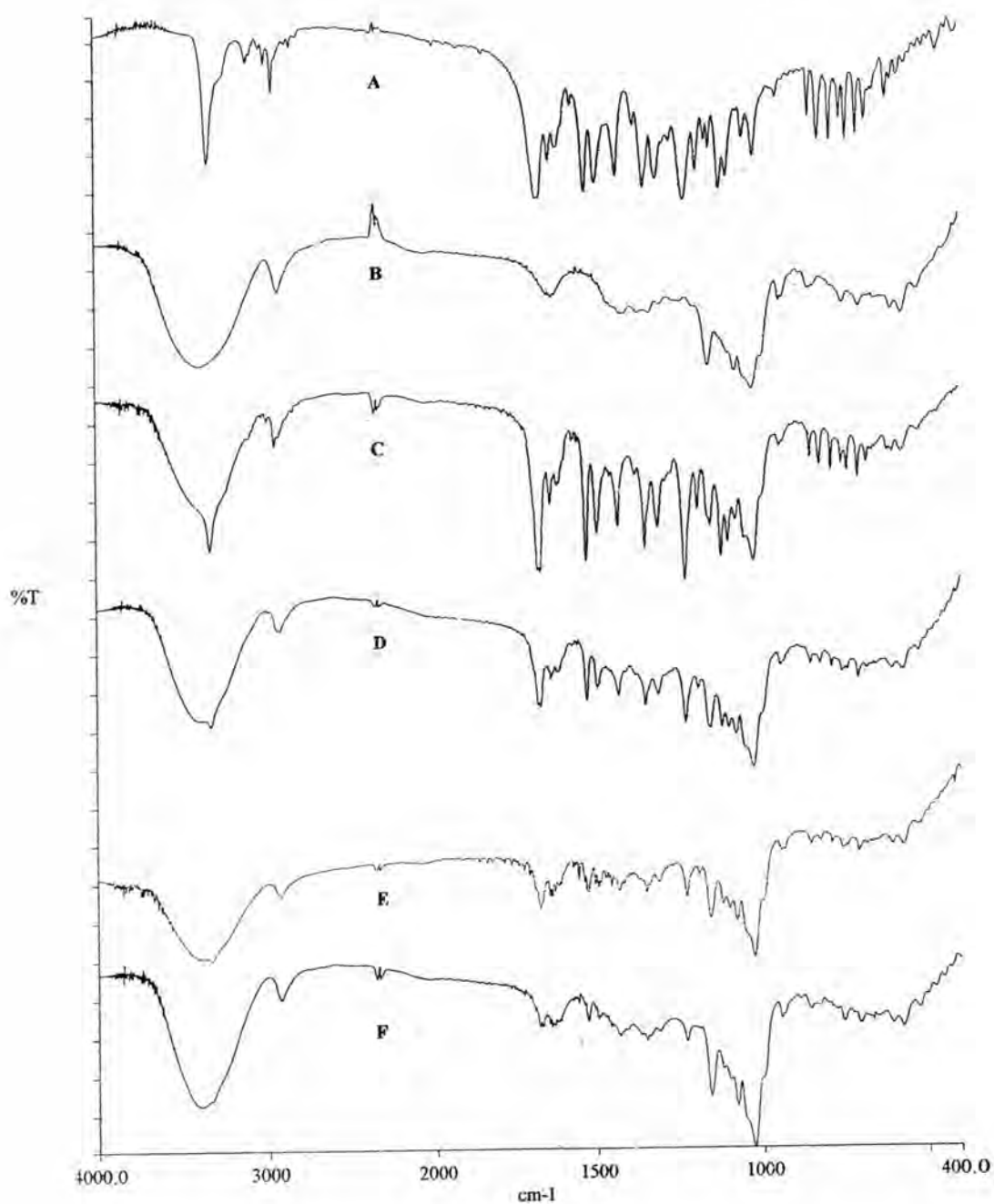


Figure 147 IR spectra of nifedipine- β -cyclodextrin prepared by kneading method.

A: nifedipine

B: carrier

C: drug to carrier ratio of 1:1

D: drug to carrier ratio of 1:3

E: drug to carrier ratio of 1:5

F: drug to carrier ratio of 1:10

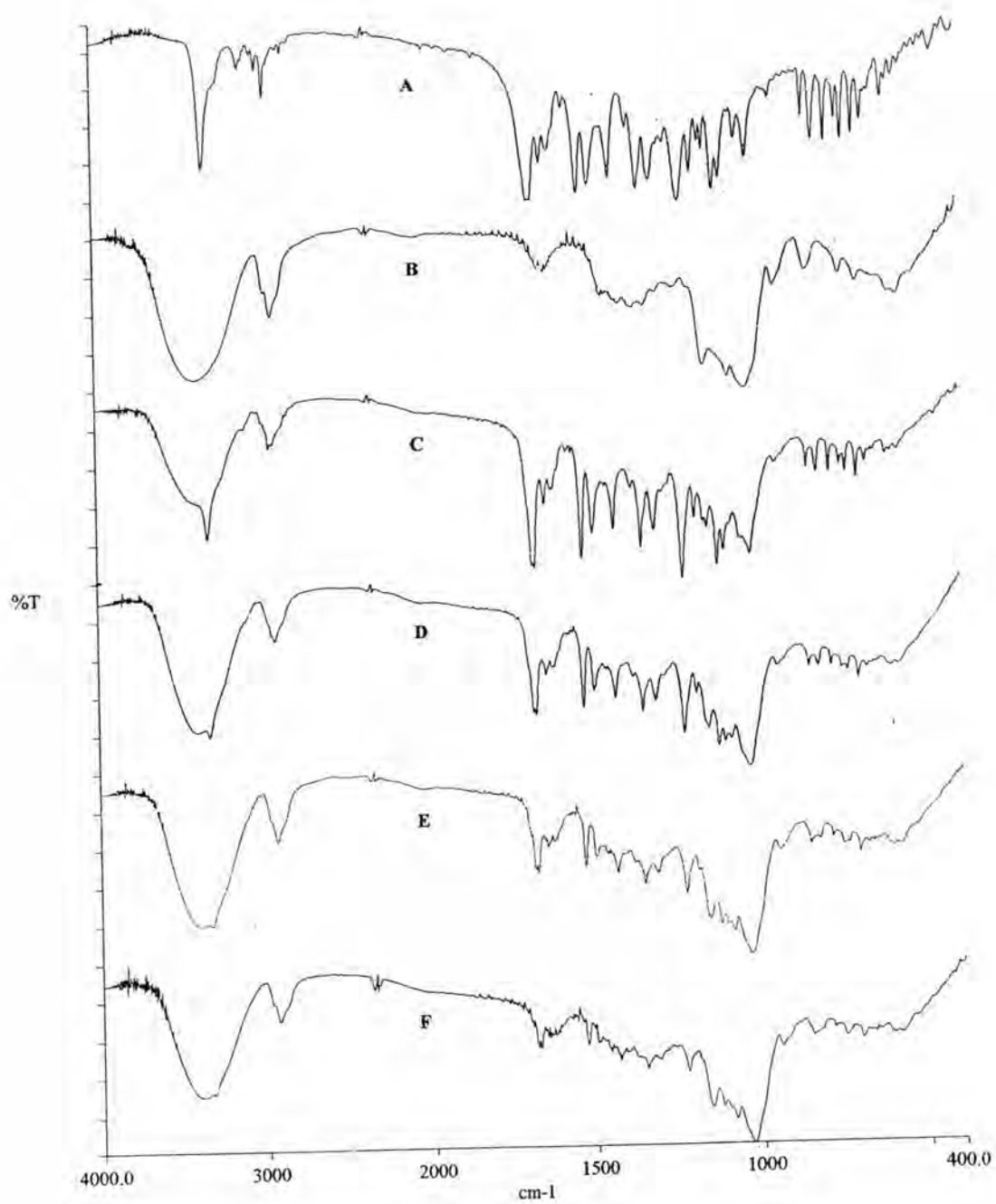


Figure 148 IR spectra of nifedipine-2-hydroxypropyl- β -cyclodextrin prepared by physical mixture .

A: nifedipine

B: carrier

C: drug to carrier ratio of 1:1

D: drug to carrier ratio of 1:3

E: drug to carrier ratio of 1:5

F: drug to carrier ratio of 1:10

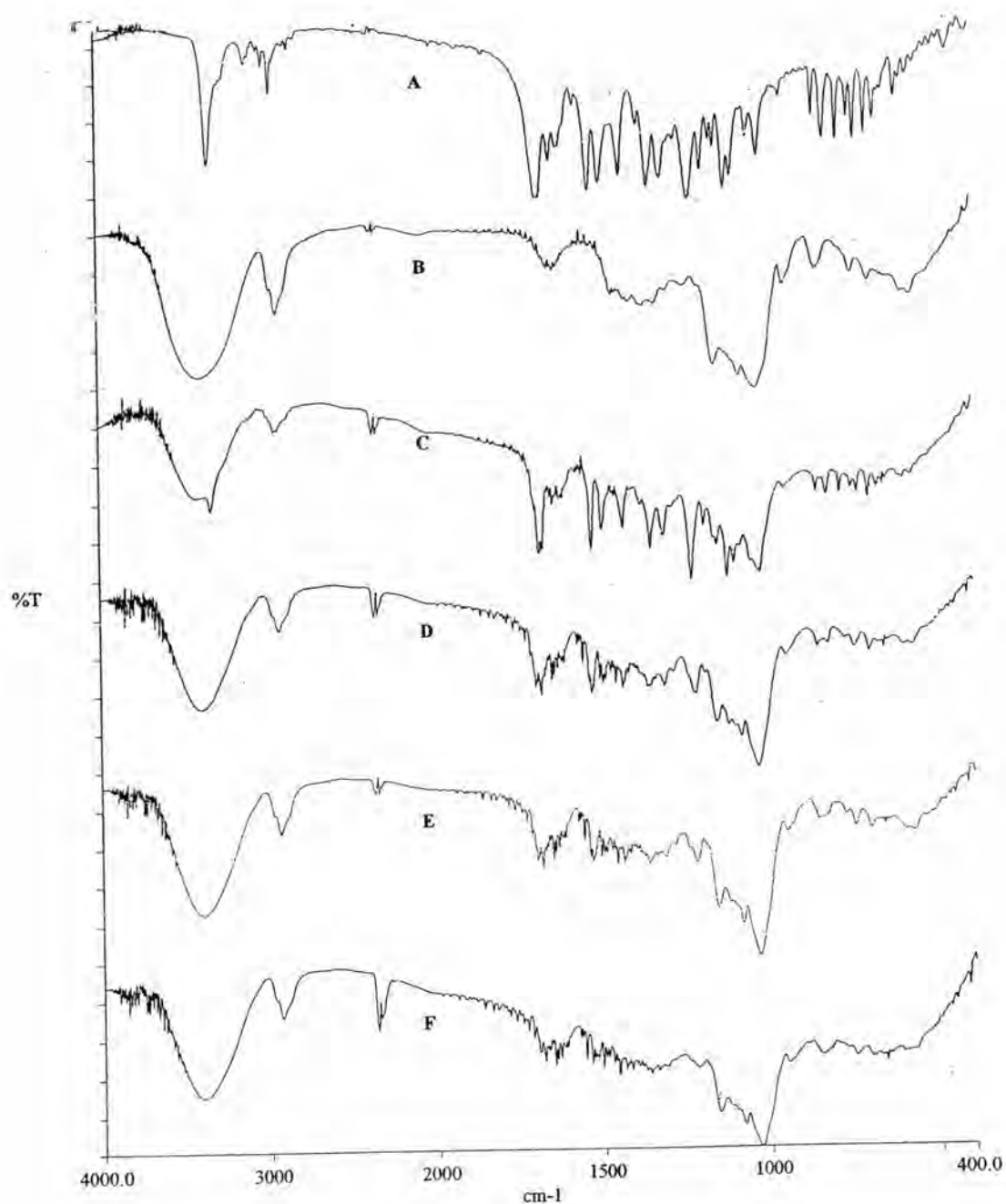


Figure 149 IR spectra of nifedipine-2-hydroxypropyl- β -cyclodextrin prepared by solvent method.

A: nifedipine

B: carrier

C: drug to carrier ratio of 1:1

D: drug to carrier ratio of 1:3

E: drug to carrier ratio of 1:5

F: drug to carrier ratio of 1:10

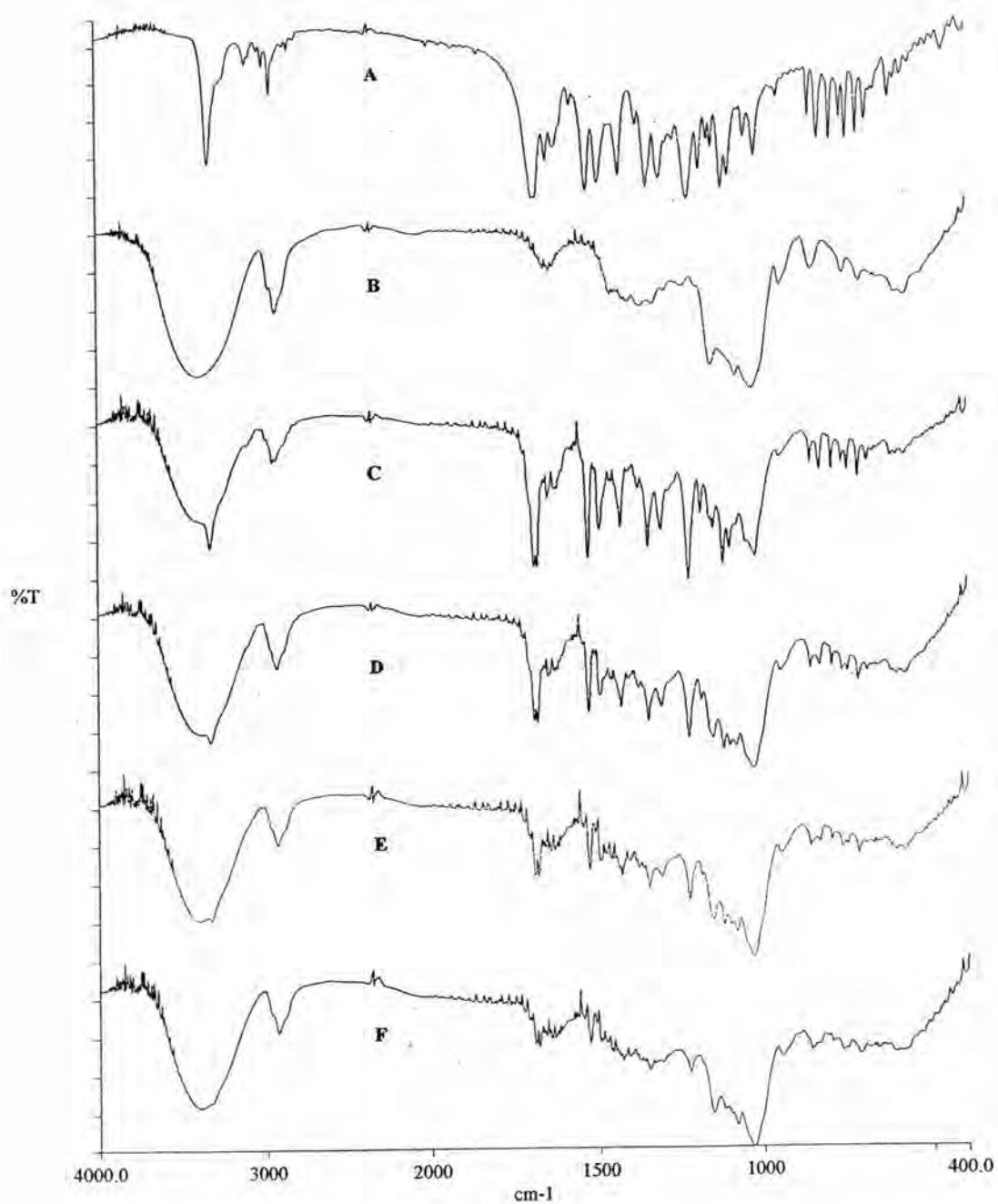


Figure 150 IR spectra of nifedipine-2-hydroxypropyl- β -cyclodextrin prepared by kneading method.

A: nifedipine

B: carrier

C: drug to carrier ratio of 1:1

D: drug to carrier ratio of 1:3

E: drug to carrier ratio of 1:5

F: drug to carrier ratio of 1:10

4.5 Solubility study.

The solubility phase diagram of nifedipine in PEGs were illustrated in Table 8 and Figure 151. The solubility of nifedipine in deionized water at 24 hours was about 8.0 $\mu\text{g/ml}$. From solubility study of the 1-4% of carrier system, it was revealed that PEG4000 had solubilizing effect in the range of 9.3-14.8 $\mu\text{g/ml}$ which almost the same solubilizing effect as PEG6000 which gave the range of 9.0-14.3 $\mu\text{g/ml}$.

From the Table 9 and Figure 152 in the group of poloxamers, poloxamer407 obviously affected solubility of nifedipine more than the other two of poloxamers which have solubilizing effect of 9.5-19.3 $\mu\text{g/ml}$ for poloxamer188 and 11.25-29.31 $\mu\text{g/ml}$ for poloxamer288 respectively. The solubility effect of poloxamer407 was 32.5-214.4 $\mu\text{g/ml}$ which was about 4 to 27-fold of the pure drug solubility.

From the Table 10 and Figure 153, β -cyclodextrin, differently, studied in the range of 0.1-0.8%. The range studied was limited by the limited solubility of the carrier. It showed good solubility as in its range. 2-Hydroxypropyl- β -cyclodextrin had the solubilizing effect of 9.5-17.8 $\mu\text{g/ml}$.

Overall, the solubility of most carrier are in the range of 9-14 $\mu\text{g/ml}$ which means that they are identical in solubility point of view. Poloxamer407 is an exceptional which gave the highest solubilizing effect.

Table 8 Solubility of nifedipine at various concentration of PEG400 and PEG6000

Carrier conc.	Drug solubility ug/ml	Drug solubility ug/ml
% carrier	PEG4000	PEG6000
0	7.974	7.974
1	9.366	9.066
2	11.194	11.111
3	12.507	13.089
4	14.801	14.311

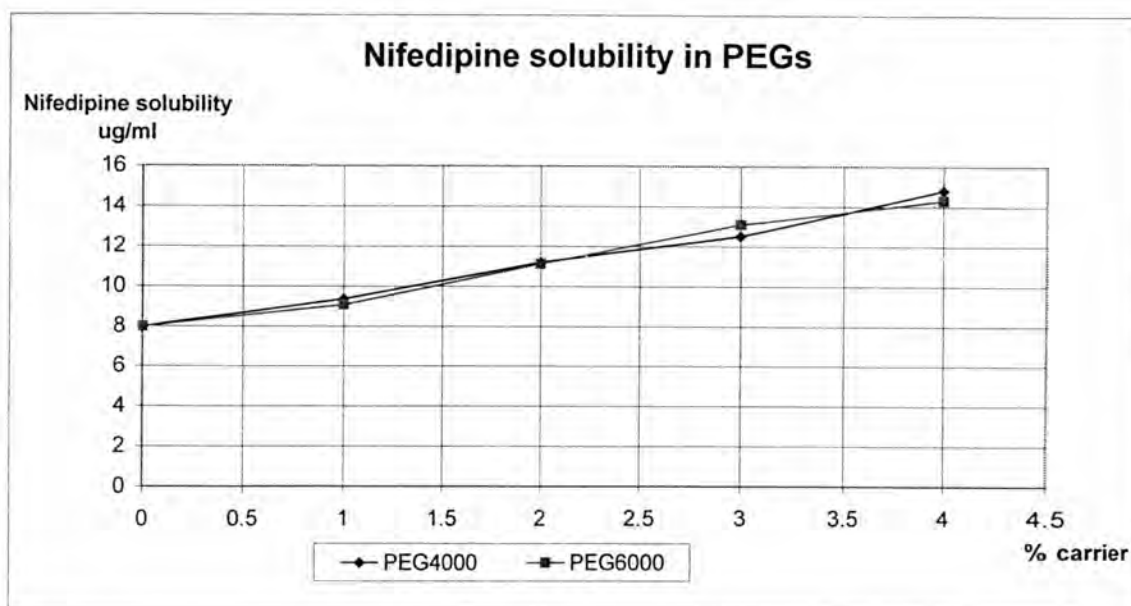


Figure 151 Solubility of nifedipine at various concentration of PEG400 and PEG6000

Table 9 Solubility of nifedipine at various concentration of poloxamer188 and 407 and poloxamer288

Carrier conc. % carrier	Drug solubility ug/ml Poloxamer188	Drug solubility ug/ml Poloxamer407	Drug solubility ug/ml Poloxamer288
0	7.974	7.974	7.974
1	9.587	32.538	11.251
2	12.689	88.069	17.422
3	15.849	149.711	25.351
4	19.324	214.475	29.318

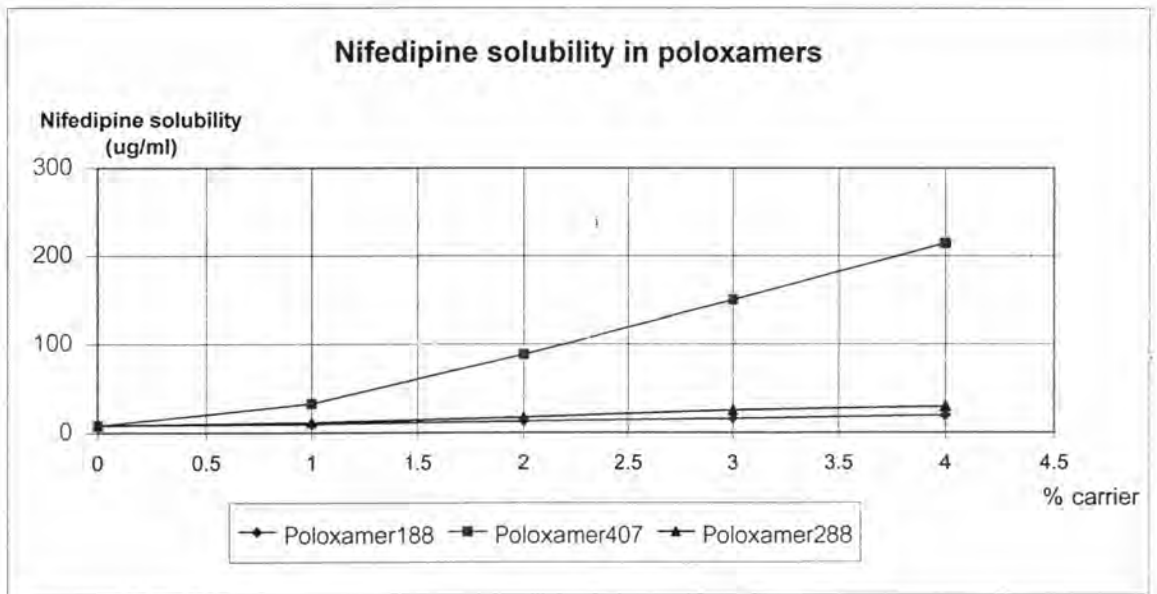


Figure 152 Solubility of nifedipine at various concentration of poloxamer188 and 407 and poloxamer288.

Table 10 Solubility of nifedipine at various concentration of β -cyclodextrin and 2-hydroxypropyl- β -cyclodextrin.

Carrier conc. % carrier	Drug solubility ug/ml β -cyclodextrin
0	7.974
0.1	7.067
0.2	7.288
0.3	7.885
0.4	8.164
0.6	8.147
0.8	9.212

Carrier conc. % carrier	Drug solubility ug/ml 2-HBCD
0	7.974
1	9.590
2	12.488
4	17.850

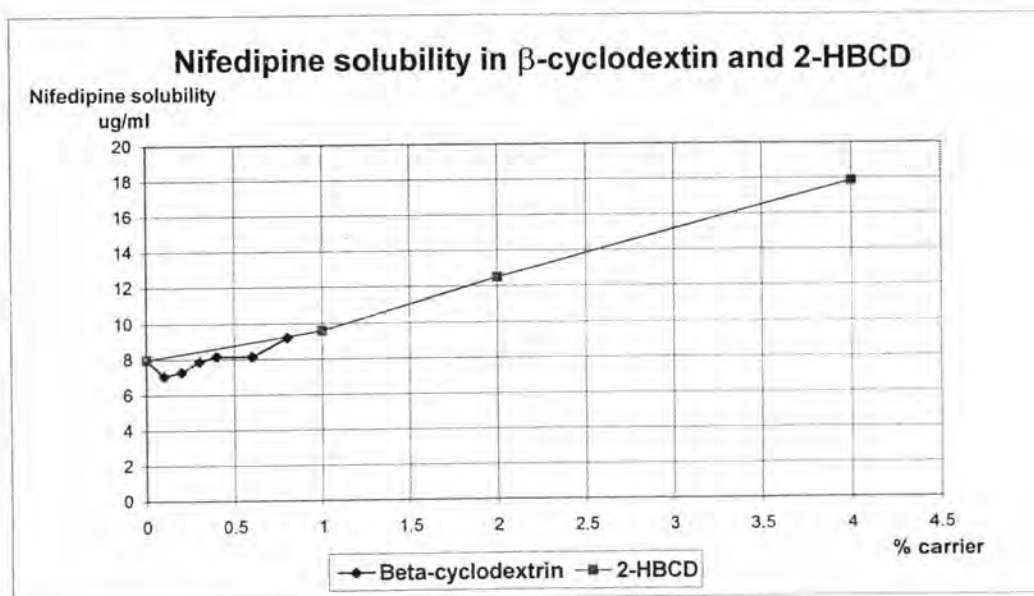


Figure 153 Solubility of nifedipine at various concentration of β -cyclodextrin and 2-hydroxypropyl- β -cyclodextrin.

4.6 Wettability study.

From Table 11 and Figure 154, it showed that pure drug gave very high contact angle of 85° . Treated drug by various methods showed a decrease in contact angles at about 52° - 60° . The nifedipine-carrier solid dispersions gave lower contact angle than pure drug and higher than the pure carriers used in each treatments. The contact angles of all carriers in the study were shown in Table 12 and Figure 155.

For PEGs system in general, the contact angle was decreased with the amount of carrier increased. This indicated that the higher amount of carrier, the better wettability obtained.

For the system of PEG4000, comparing between different methods, at the ratio of 1:10, melting method exhibited the lowest contact angle. The contact angle ranked within the ratio of 1:10 was melting < solvent < kneading < physical mixture. Very interestingly, at the ratio of 1:10 the contact angle is almost as good as PEG4000 itself.

Differently from PEG4000, the lowest contact angle was found in PEG6000 at the ratio of 1:10 prepared by kneading methods. Obvious difference was not found between solvent, melting and physical mixing methods.

Most poloxamers exhibited high contact angles compared to those of PEGs. Unlike the PEGs system, the contact angles were not dramatically decreased with an increment of the poloxamers. It was found that the typical range of contact angles of poloxamer407 poloxamer288 and poloxamer188 were at about 50° , 40° and 30° respectively .

For β -cyclodextrin, the contact angle was decreased dramatically when amount of carrier increased. At the ratio 1:10, the contact angle, surprisingly, became 0° giving the best wettability among all carriers. 2-hydroxypropyl- β -cyclodextrin gave the contact angle between $30-40^\circ$ which found very similar to those of poloxamers group.

Table 11 Contact angle of nifedipine measured by compressed disc method

Contact angle				
	Mean	1	2	S.D.
Melting method	52	54	50	2.8
Solvent method	59	58	60	1.4
Kneading method	59.5	59	60	0.7
Physical mixture	59.5	60	59	0.7
Nontreated	85	86	84	1.4

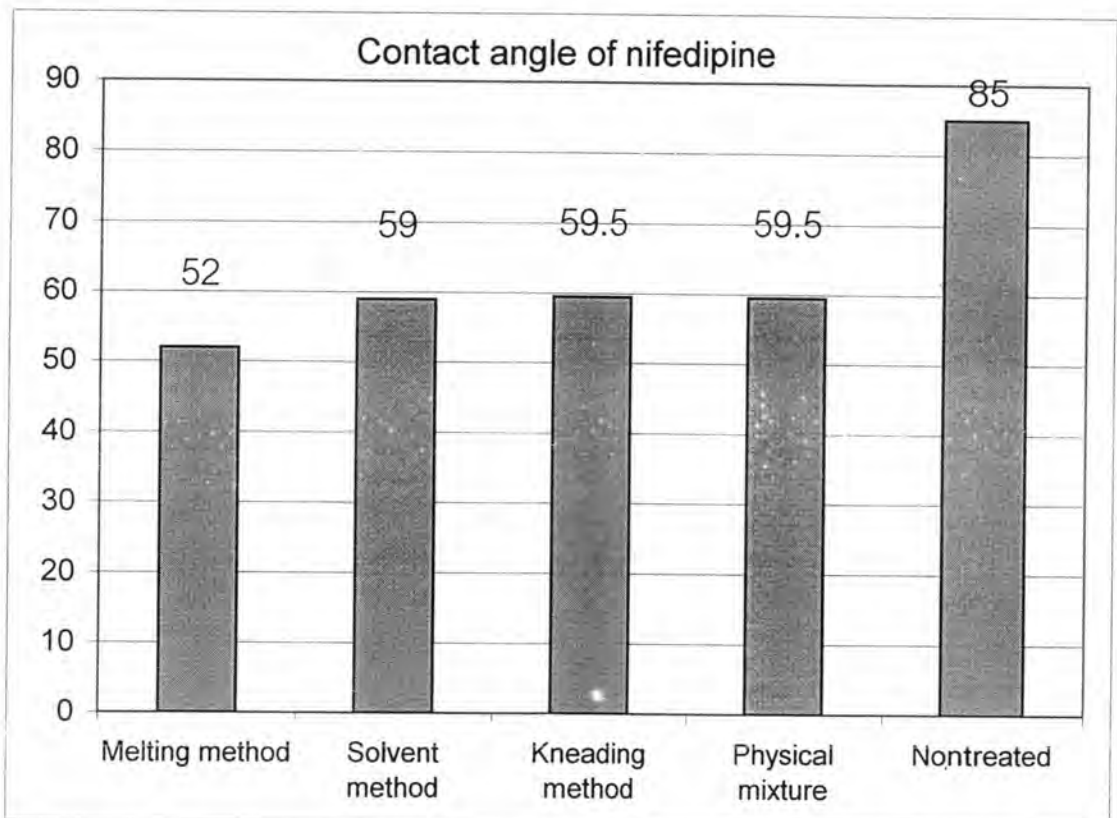


Figure 154 Contact angle of nifedipine system measured by compressed disc method

Table 12 Contact angle of various carriers measured by compressed disc method

Carriers	Mean	Measure1	Measure2	S.D.
PEG4000	14.5	15	14	0.71
PEG6000	13.0	12	14	1.41
Poloxamer407	37.5	37	38	0.71
Poloxamer188	23.5	25	22	2.12
Poloxamer288	32.5	32	33	0.71
BCD	0.0	0	0	0.00
HBCD	24.0	24	24	0.00

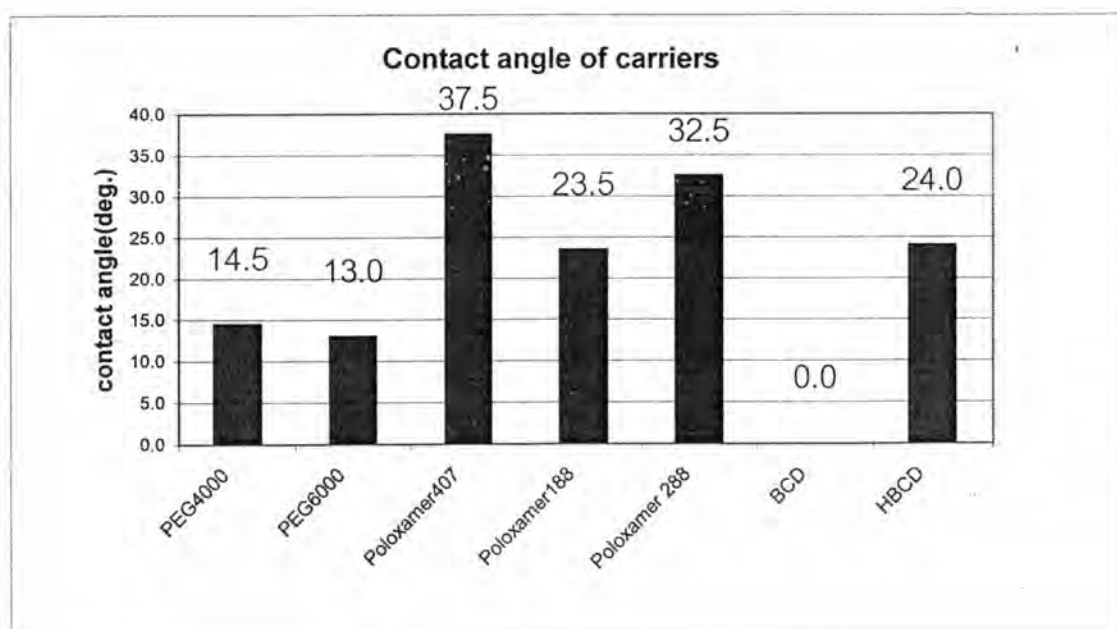


Figure 155 Contact angle of carriers measured by compressed disc method.

Table 13 Contact angle of nifedipine-PEG4000 system at various drug:carrier ratios measured by compressed disc method

Ratio	Duplication	Melting method	Solvent method	Kneading method	Physical mixture
1:1	1	25	21	28	32
	2	27	21	32	30
	Mean	26	21	30	31
	S.D.	1.4	0.0	2.8	1.4
1:3	1	21	19	26	22
	2	21	21	24	27
	Mean	21	20	25	24.5
	S.D.	0.0	1.4	1.4	3.5
1:5	1	17	17	20	22
	2	18	20	22	24
	Mean	17.5	18.5	21	23
	S.D.	0.7	2.1	1.4	1.4
1:10	1	16	14	16	25
	2	13	16	21	21
	Mean	14.5	15	18.5	23
	S.D.	2.1	1.4	3.5	2.8

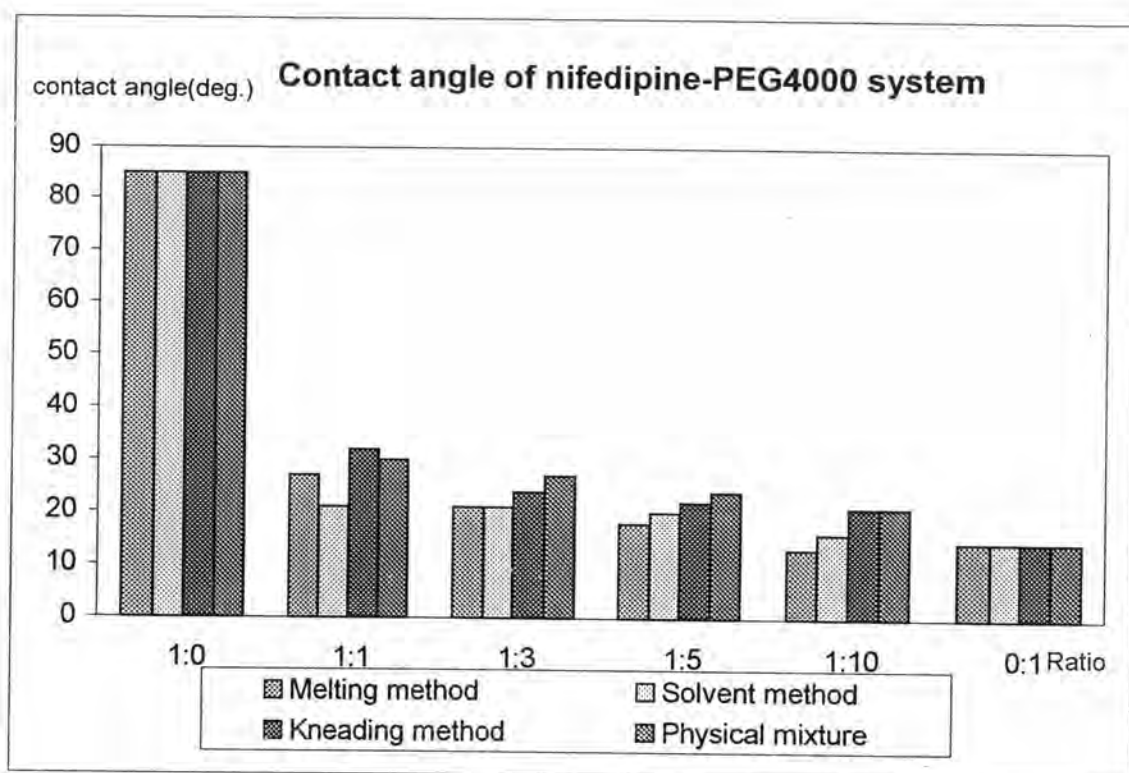


Figure 156 Contact angle of nifedipine-PEG4000 system measured by compressed disc method

Table 14 Contact angle of nifedipine-PEG6000 system at various drug:carrier ratios measured by compressed disc method

Ratio		Melting method	Solvent method	Kneading method	Physical mixture
1:1	1	27	29	24	35
	2	27	29	25	33
	Mean	27	29	24.5	34
	S.D.	0.0	0.0	0.7	1.4
1:3	1	21	24	21	26
	2	24	22	19	29
	Mean	22.5	23	20	27.5
	S.D.	2.1	1.4	1.4	2.1
1:5	1	20	19	19	23
	2	22	17	19	21
	Mean	21	18	19	22
	S.D.	1.4	1.4	0.0	1.4
1:10	1	17	16	16	20
	2	16	16	14	19
	Mean	16.5	16	15	19.5
	S.D.	0.7	0.0	1.4	0.7

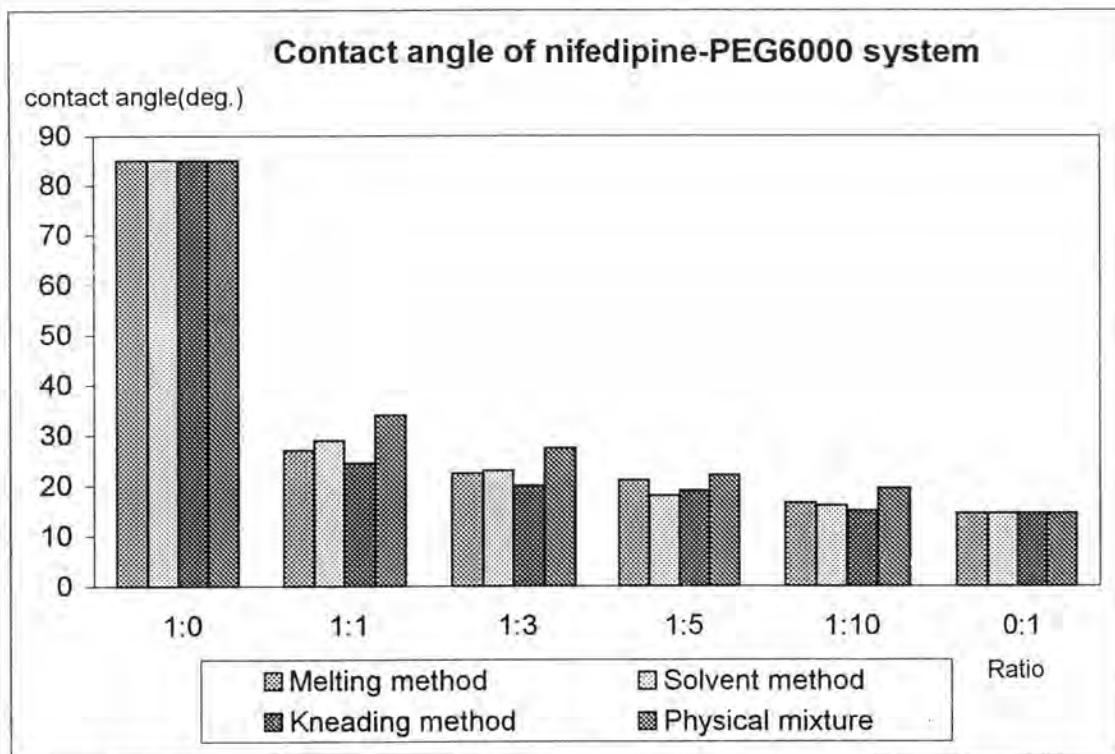


Figure 157 Contact angle of nifedipine-PEG6000 system measured by compressed disc method.

Table 15 Contact angle of nifedipine-poloxamer 188 system at various drug:carrier ratios measured by compressed disc method

Ratio		Melting method	Solvent method	Kneading method	Physical mixture
1:1	1	34	29	28	29
	2	29	31	27	31
	Mean	31.5	30	27.5	30
	S.D.	3.5	1.4	0.7	1.4
1:3	1	32	32	28	30
	2	33	29	27	30
	Mean	32.5	30.5	27.5	30
	S.D.	0.7	2.1	0.7	0.0
1:5	1	30	30	26	33
	2	30	32	28	30
	Mean	30	31	27	31.5
	S.D.	0.0	1.4	1.4	2.1
1:10	1	30	30	27	32
	2	29	30	28	31
	Mean	29.5	30	27.5	31.5
	S.D.	0.7	0.0	0.7	0.7

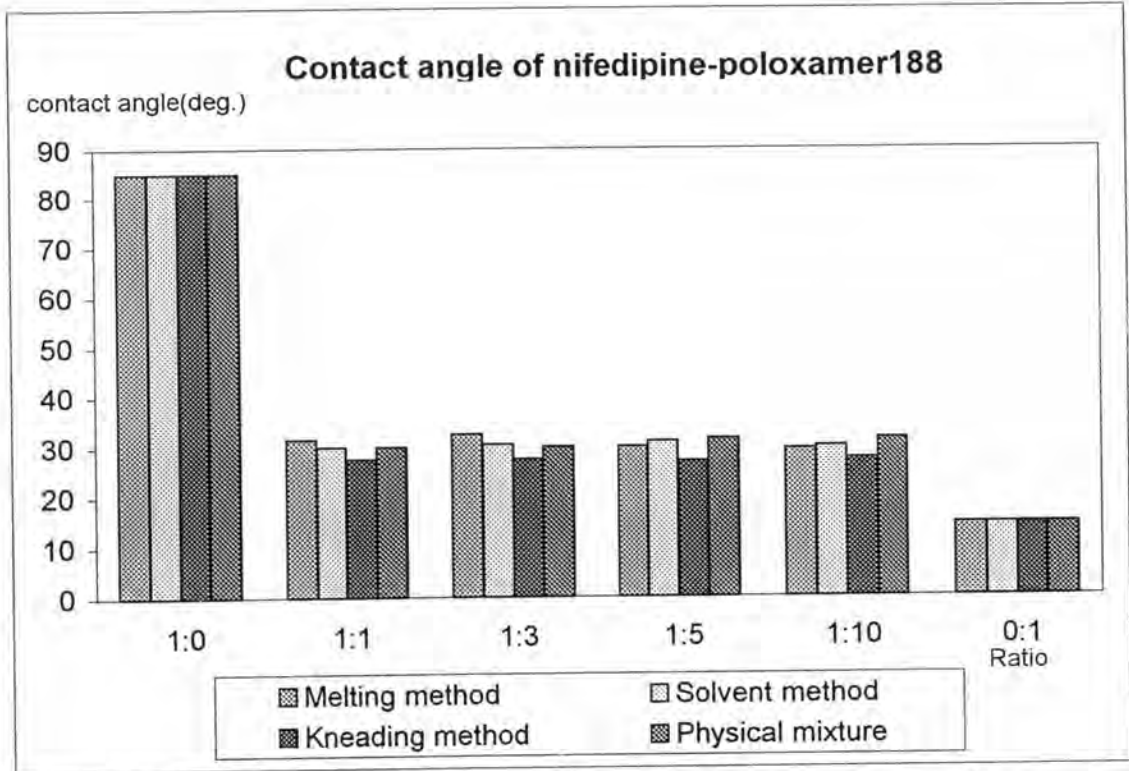


Figure 158 Contact angle of nifedipine-poloxamer188 system measured by compressed disc method

Table 16 Contact angle of nifedipine-poloxamer288 system at various drug:carrier ratios measured by compressed disc method

Ratio		Melting method	Solvent method	Kneading method	Physical mixture
1:1	1	36	44	40	46
	2	36	36	42	48
	Mean	36	40	41	47
	S.D.	0	5.7	1.4	1.4
1:3	1	35	38	36	47
	2	36	41	44	45
	Mean	35.5	39.5	40	46
	S.D.	0.7	2.1	5.7	1.4
1:5	1	35	38	42	44
	2	36	40	40	43
	Mean	35.5	39	41	43.5
	S.D.	0.7	1.4	1.4	0.7
1:10	1	35	31	40	40
	2	35	32	40	38
	Mean	35	31.5	40	39
	S.D.	0.0	0.7	0.0	1.4

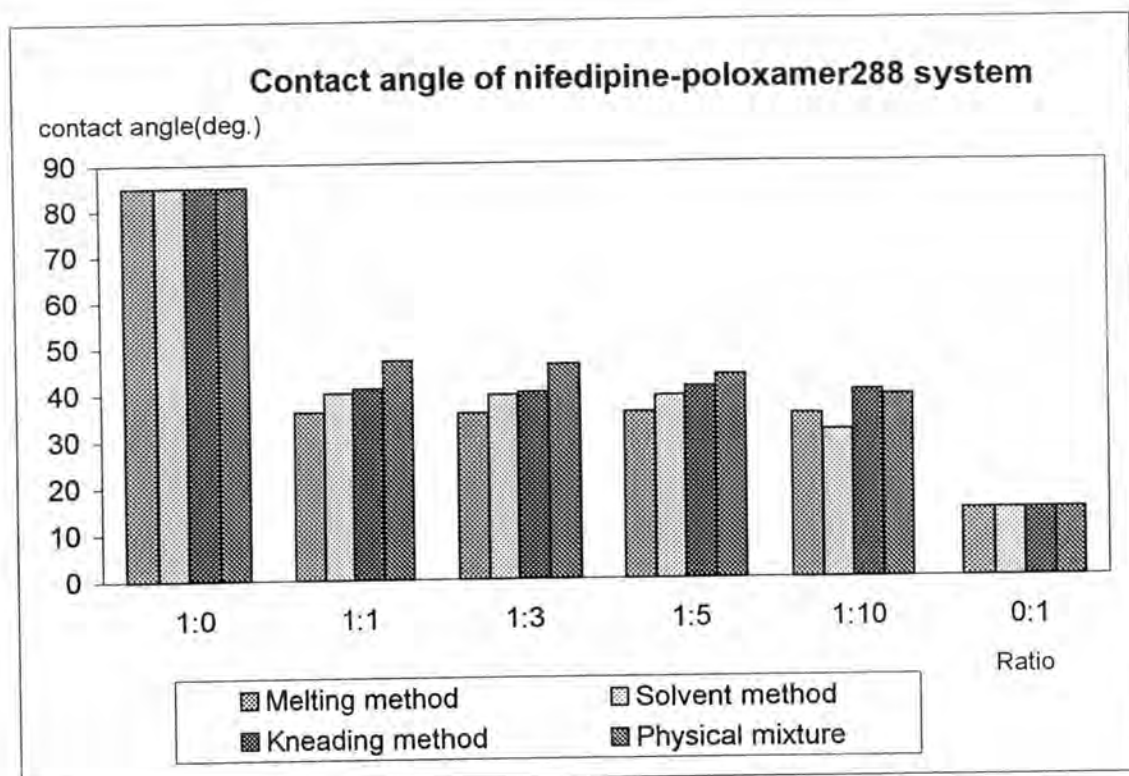


Table 17 Contact angle of nifedipine- poloxamer 407 system at various drug:carrier ratios measured by compressed disc method

Ratio		Melting method	Solvent method	Kneading method	Physical mixture
1:1	1	55	55	39	38
	2	55	51	40	42
	Mean	55	53	39.5	40
	S.D.	0.0	2.8	0.7	2.8
1:3	1	50	53	38	44
	2	54	48	40	50
	Mean	52	50.5	39	47
	S.D.	2.8	3.5	1.4	4.2
1:5	1	40	50	37	45
	2	48	43	40	46
	Mean	44	46.5	38.5	45.5
	S.D.	5.7	4.9	2.1	0.7
1:10	1	44	42	40	42
	2	47	50	41	41
	Mean	45.5	46	40.5	41.5
	S.D.	2.1	5.7	0.7	0.7

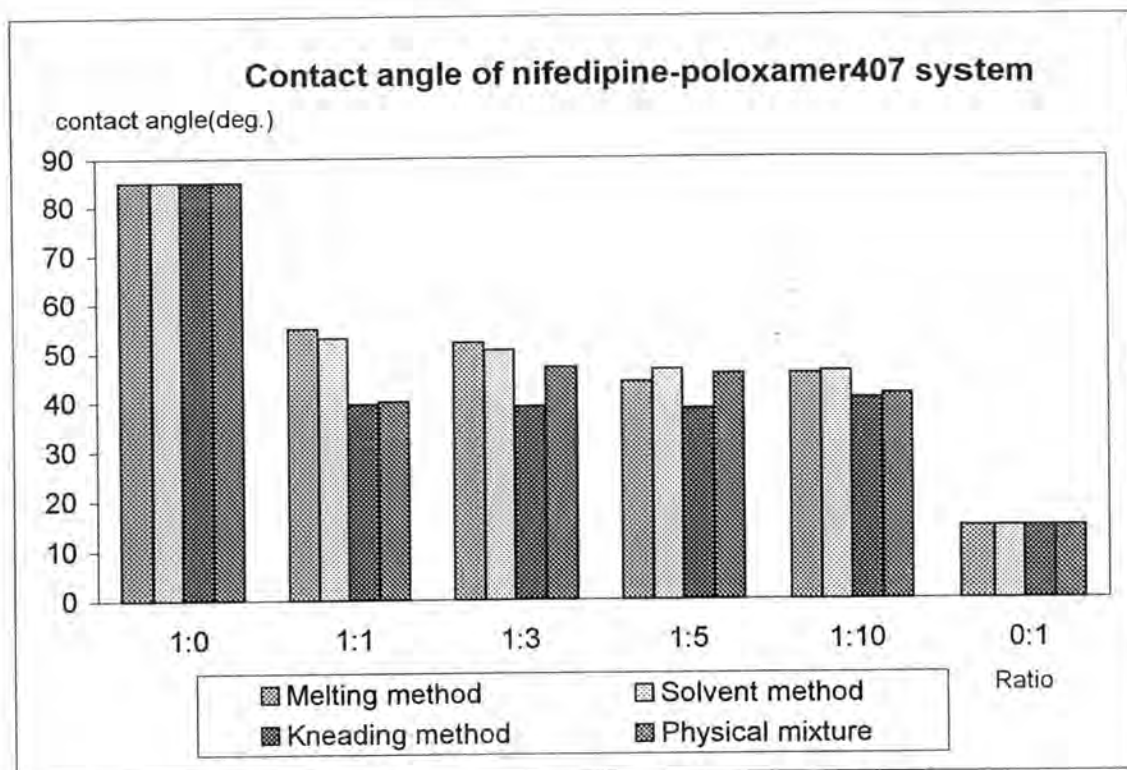


Figure 160 Contact angle of nifedipine-poloxamer407 system measured by compressed disc method

Table 18 Contact angle of nifedipine-beta cyclodextrin system at various drug:carrier ratios measured by compressed disc method

Ratio		Kneading method	Physical mixture
1:1	1	35	47
	2	38	48
	Mean	36.5	47.5
	S.D.	2.1	0.7
1:3	1	20	24
	2	20	25
	Mean	20	24.5
	S.D.	0.0	0.7
1:5	1	10	15
	2	8	9
	Mean	9	12
	S.D.	1.4	4.2
1:10	1	0	0
	2	0	0
	Mean	0	0
	S.D.	0.0	0.0

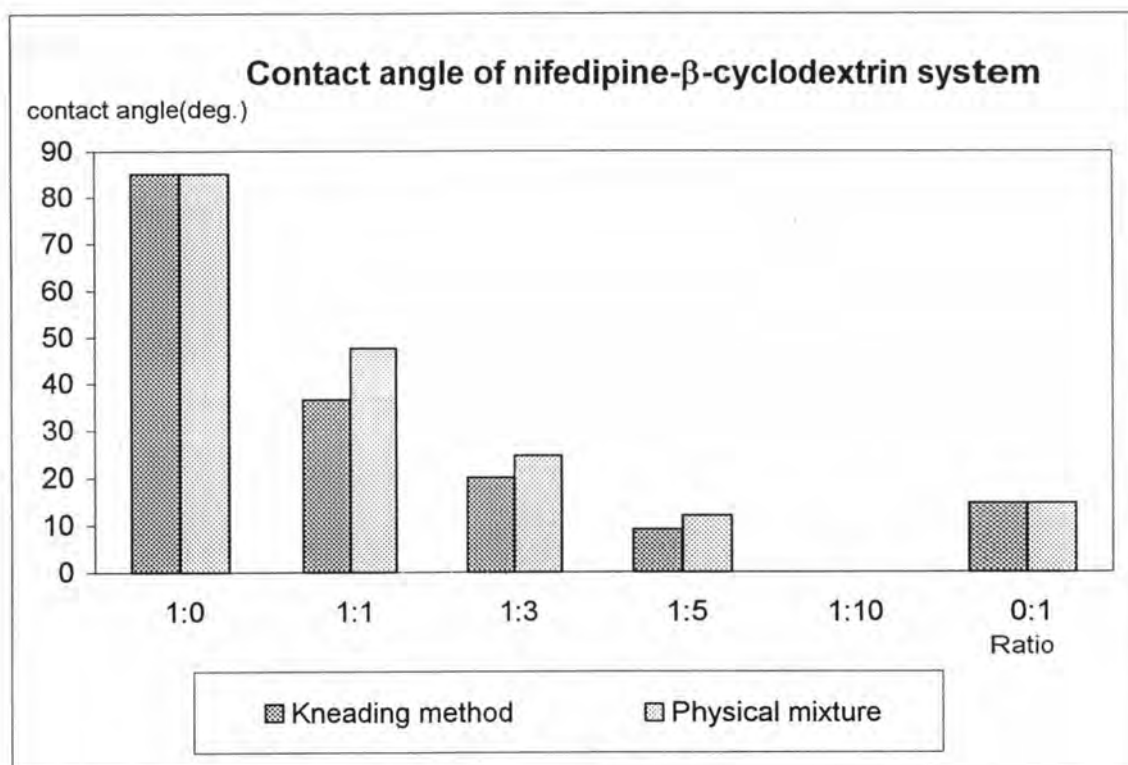


Figure 161 Contact angle of nifedipine- β -cyclodextrin system measured by compressed disc method

Table 19 Contact angle of nifedipine-2-hydroxypropyl- β -cyclodextrin system at various drug:carrier ratios measured by compressed disc method

Ratio		Solvent method	Kneading method	Physical mixture
1:1	1	33	40	37
	2	27	40	37
	Mean	30	40	37
	S.D.	4.2	0.0	0.0
1:3	1	30	34	34
	2	27	32	35
	Mean	28.5	33	34.5
	S.D.	2.1	1.4	0.7
1:5	1	27	26	31
	2	27	25	29
	Mean	27	25.5	30
	S.D.	0.0	0.7	1.4
1:10	1	26	24	29
	2	24	25	30
	Mean	25	24.5	29.5
	S.D.	1.4	0.7	0.7

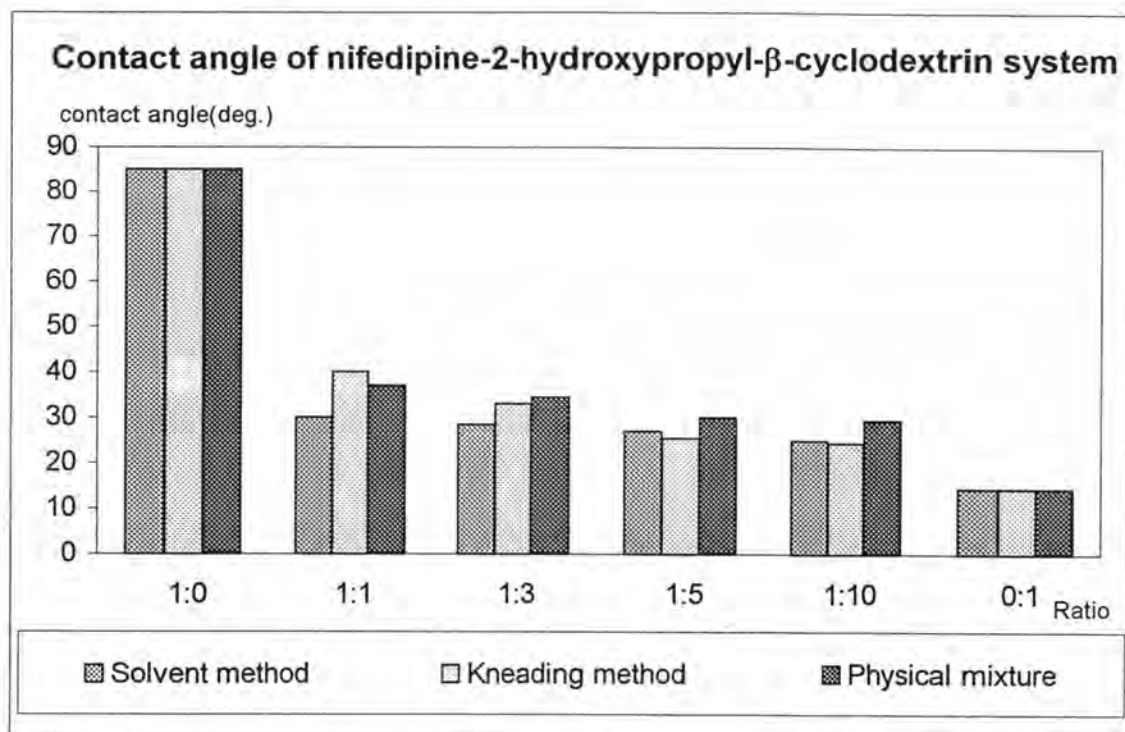


Figure 162 Contact angle of nifedipine-2-hydroxypropyl- β -cyclodextrin system measured by compressed disc method