CHAPTER III

RESULTS

Preparation of grounded mixtures, kneaded mixtures, solvent mixtures of indomethacin and corresponding indomethacin powder

The appearance of indomethacin is pale, yellow-tan, odourless, crystalline powder. Four cyclodextrins (α-, β-, δ- CD and DIMEB) are white crystalline powder except DIMEB is white creamy wax-like. They are easily brittle when pulverized, non-hygroscopic and free-flowing powder.

Both grounded mixtures and kneaded mixtures were relatively easy to prepare. During preparation of kneaded mixture of α-, β- and δ-CD, the kneaded products were smooth, white homogeneous paste, except for δ-CD, kneaded mixture was pale yellow paste. They were easily screened through a 30 mesh, easily pulverized to obtained brittle and free-flowing granule when dried and passed through a 40 mesh. For DIMEB kneaded mixture, the yellow sticky viscous mass product was obtained. Then, the product was dried without screening. After drying, it was yellow stable mass and very brittle when pulverized which could be manipulated to granule form.

During preparation of the solvent mixture of α-, β- and δ-CD, the products were yellow masses and similar to kneaded products, however after drying process the products were white, white and very

pale yellow in α-, β- and δ-CD, respectively. They were more brittle when the amount of cyclodextrin increased in the preparation. The products were free-flowing granules when sieved through a 40 mesh. For DIMEB solvent mixture, the product was yellow glass-like, transparent and brittle, easily grounded and free-flowing powder except in ratio of 1:1, the product was somewhat sticky mass. The products were melt at high temperature. Then the products were dried in desiccator to remove the residual solvent.

Assay for content of indomethacin in dispersed systems

The calibration curve of indomethacin in the mixture of phosphate buffer of pH 7.2 : deionized water (1:4) as determined using linear regression is presented in Appendix 1 and 2.

The percentage content of indomethacin in each dispersed systems obtained are shown in Appendix 5. The indomethacin contents were between 95.30 - 102.85% and meet the requirement of USP XXII.

Dissolution studied of indomethacin in dispersed systems

The dissolution profiles of grounded mixtures, kneaded mixtures, solvent mixtures, pure drug, grounded drug, kneaded drug and treated drug powders are presented in Figures 7-30, experimental data are given in Appendices 6-18, respectively. The results from grounded mixtures, kneaded mixtures and solvent mixtures dissolution

determinations revealed that DIMEB gave the fastest dissolution profile, followed by δ-, β- and α-CD.

1. Pure drug, grounded drug, kneaded drug and treated drug

The dissolution profiles and data of pure drug, grounded drug, kneaded drug and treated drug are demonstrated in Figure 7 and Appendix 6, respectively. The grounded drug exhibited the fastest dissolution profile, followed by pure drug, treated drug and kneaded drug, respectively.

2. Grounded mixture systems

The dissolution profiles and data of grounded mixture systems are shown in Figures 8–15 and Appendices 7-10, respectively. The grounded mixtures gave the highest dissolution profile followed by grounded drug and pure drug. The grounded mixtures of four cyclodextrins (α-, β-, δ-CD and DIMEB) gave the highest dissolution when the amount of cyclodextrins in the preparations were the highest too. And the dissolution of indomethacin increased as the content of cyclodextrins increased in the grounded mixture systems.

There were slightly increased in dissolution profiles of α-CD in the ratios between 1:0.5 to 1:2, β-CD in the ratios 1:0.5 to 1:2 and δ-CD in 1:0.5 to 1:1. In the case of indomethacin : DIMEB grounded mixture systems in the ratios of 1:0.5 to 1:3 the slightly different results in theirs dissolution profiles were observed. As

the weight fraction of DIMEB increased, the dissolution rate also slightly increased. In addition, it was observed that the DIMEB systems gave markedly faster dissolution rates than grounded drug and pure drug systems.

All grounded mixture systems, the release of indomethacin were approximately 100% within 60 minutes, while the grounded drug and pure drug the dissolutions of indomethacin were approximately 93 and 92%, respectively.

By comparing dissolution data, the best cyclodextrin for improving indomethacin dissolution was ranked as follow : DIMEB > δ-CD ≃ α-CD > β-CD. There were slightly different in theirs dissolution profiles of α- and δ-CD in the ratio 1:0.5 and 1:3, while in the ratio 1:1 they yielded similar dissolution rate and obtained the enhancement in dissolution profiles with increasing the amount of cyclodextrins. In addition, nearly gave the same dissolution rate of DIMEB system in the ratio 1:3.

3. **Kneaded mixture systems**

The dissolution data and dissolution profiles of kneaded mixture systems are respectively presented in Appendices 11-14 and Figures16–23 .

Among these ratios of kneaded mixture systems, the fastest indomethacin dissolution rate was obtained from 1:3, 1:10,

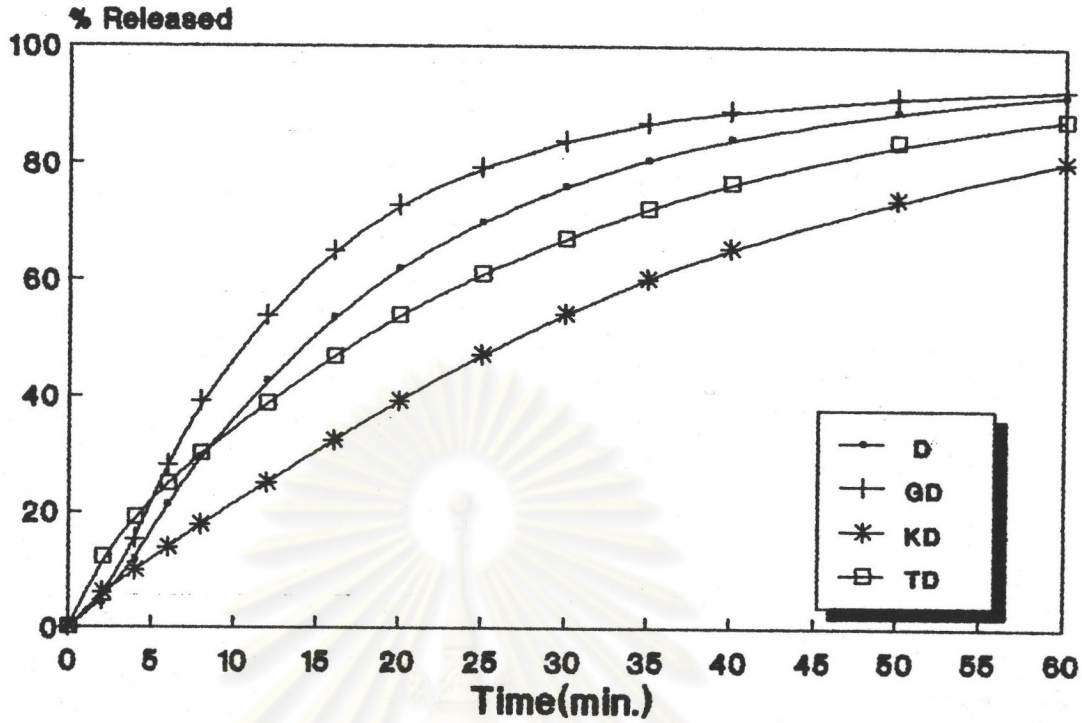


Figure 7 Dissolution profiles of IDM from pure drug(D), grounded drug (GD), kneaded drug (KD) and treated drug(TD) powders.

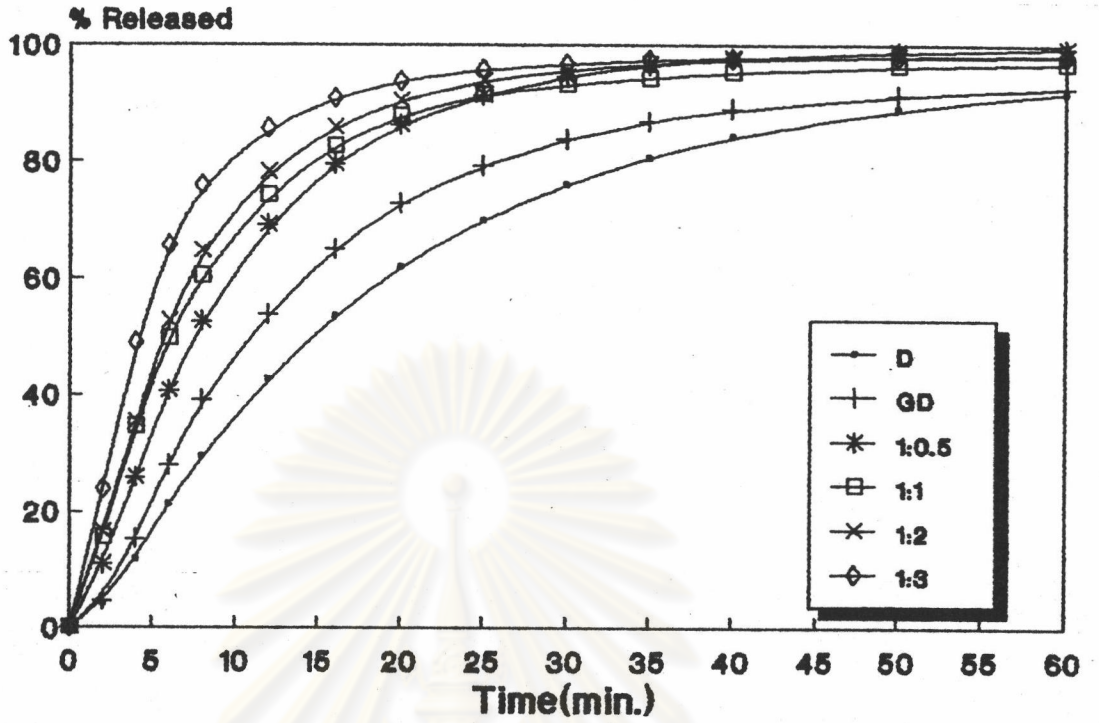


Figure 8 Dissolution profiles of IDM from IDM : ALPHA-CD grounded mixtures at various ratios as compared with pure drug(D) and grounded drug(GD).

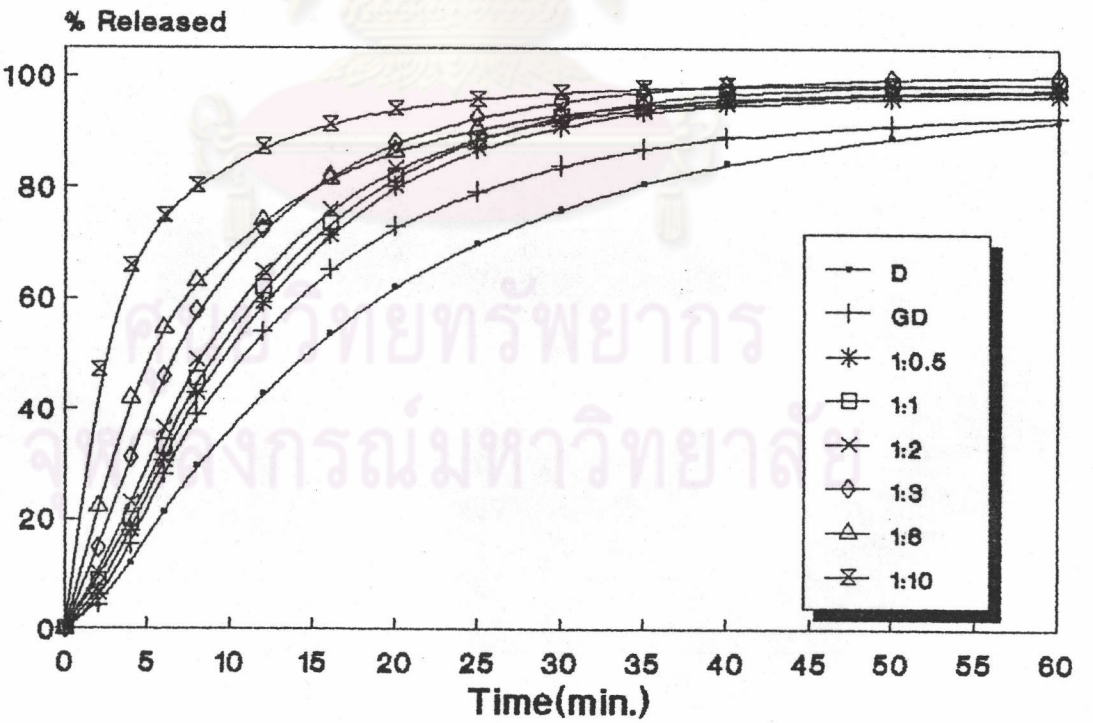


Figure 9 Dissolution profiles of IDM from IDM : BETA-CD grounded mixtures at various ratios as compared with pure drug(D) and grounded drug(GD).

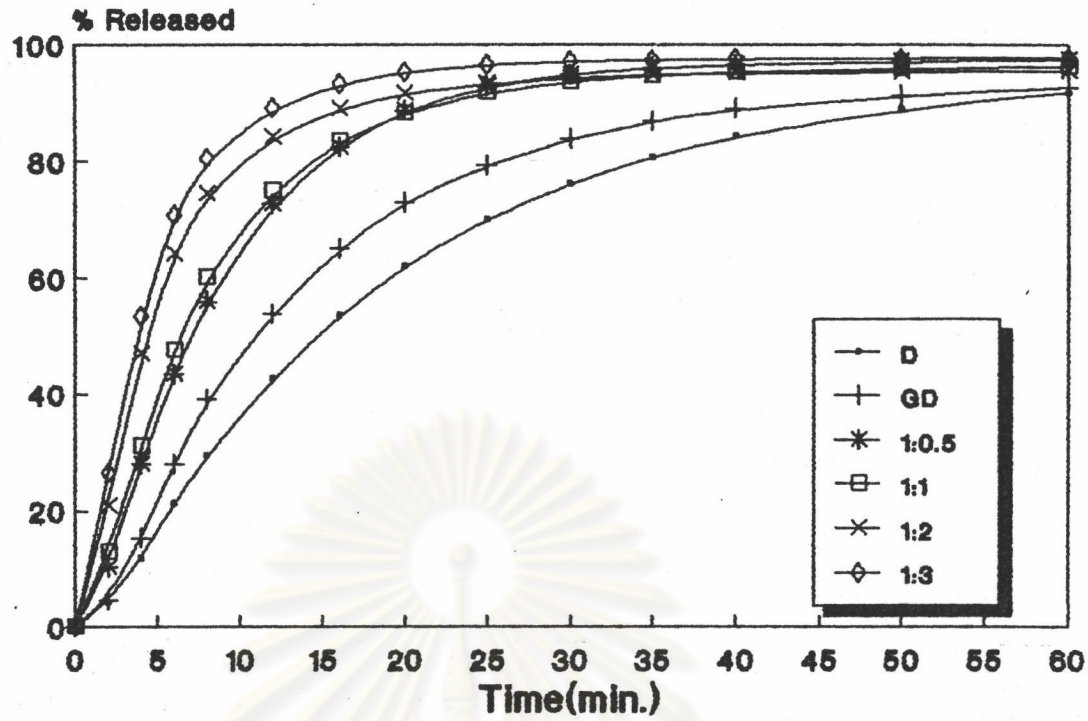


Figure 10 Dissolution profiles of IDM from IDM : GAMMA-CD grounded mixtures at various ratios as compared with pure drug(D) and grounded drug(GD).

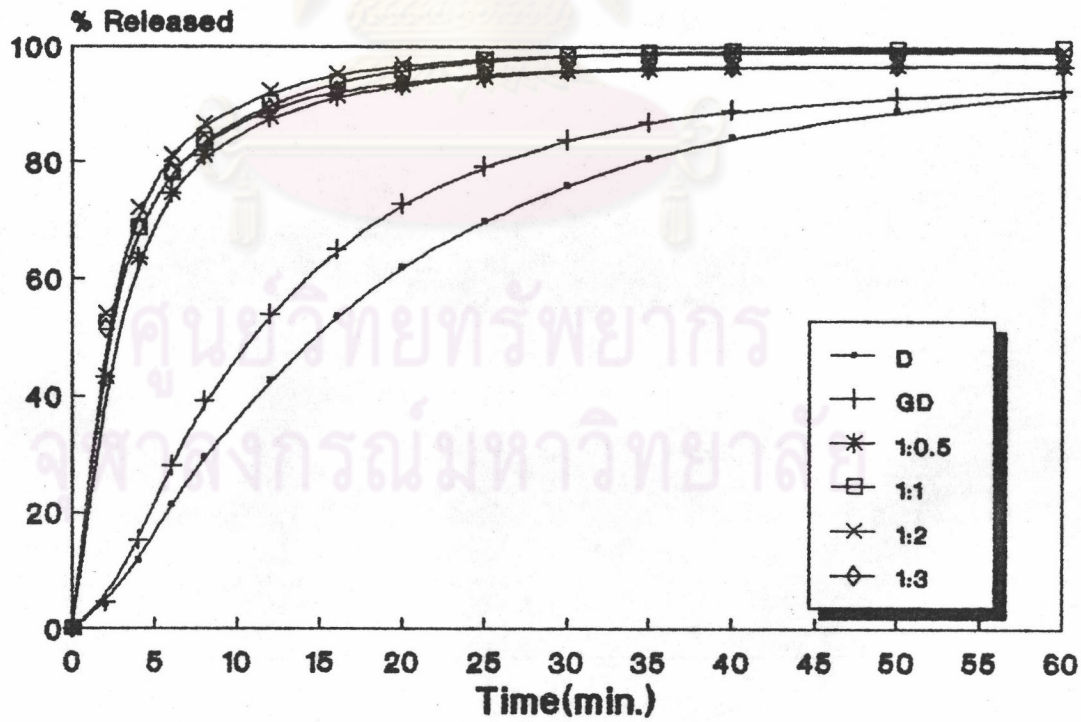


Figure 11 Dissolution profiles of IDM from IDM : DIMEB grounded mixtures at various ratios as compared with pure drug(D) and grounded drug(GD).

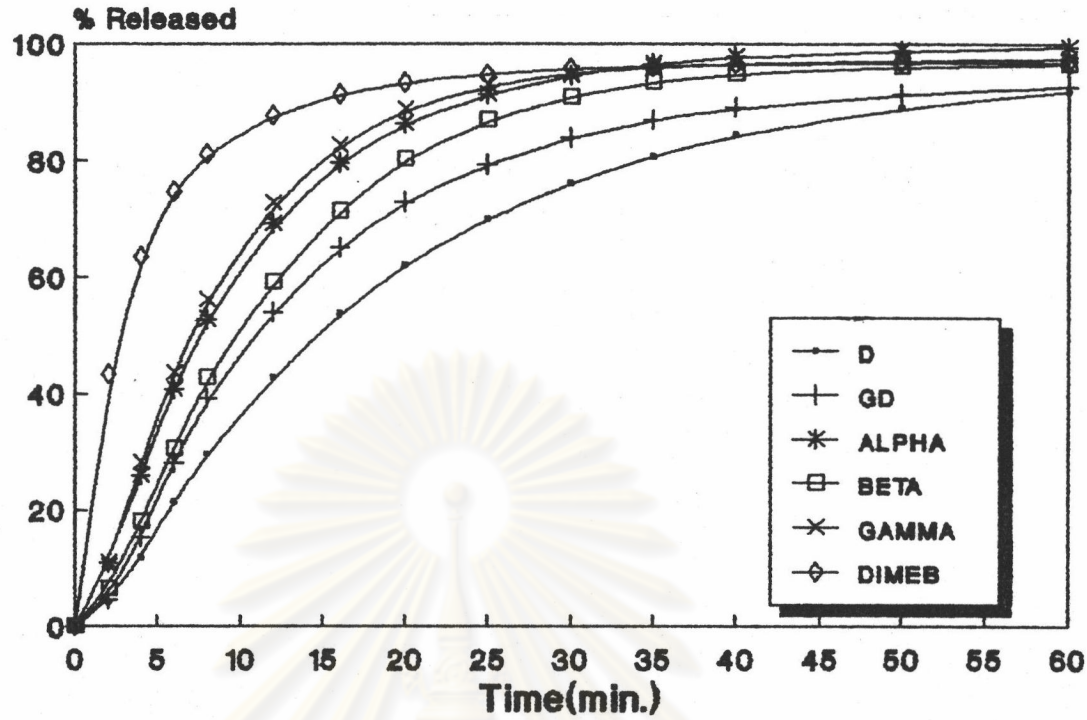


Figure 12 Dissolution profiles of IDM from 1:0.5(IDM : CD) grounded mixtures by using different cyclodextrins as compared with pure drug(D) and grounded drug(GD).

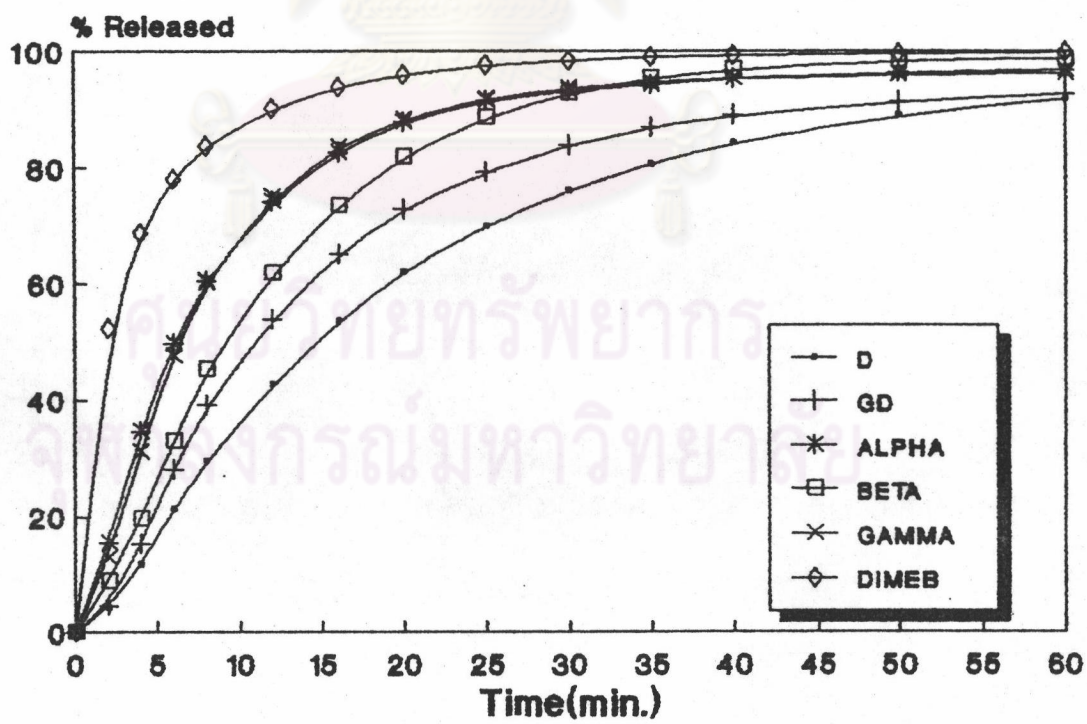


Figure 13 Dissolution profiles of IDM from 1:1 (IDM : CD) grounded mixtures by using different cyclodextrins as compared with pure drug(D) and grounded drug(GD).

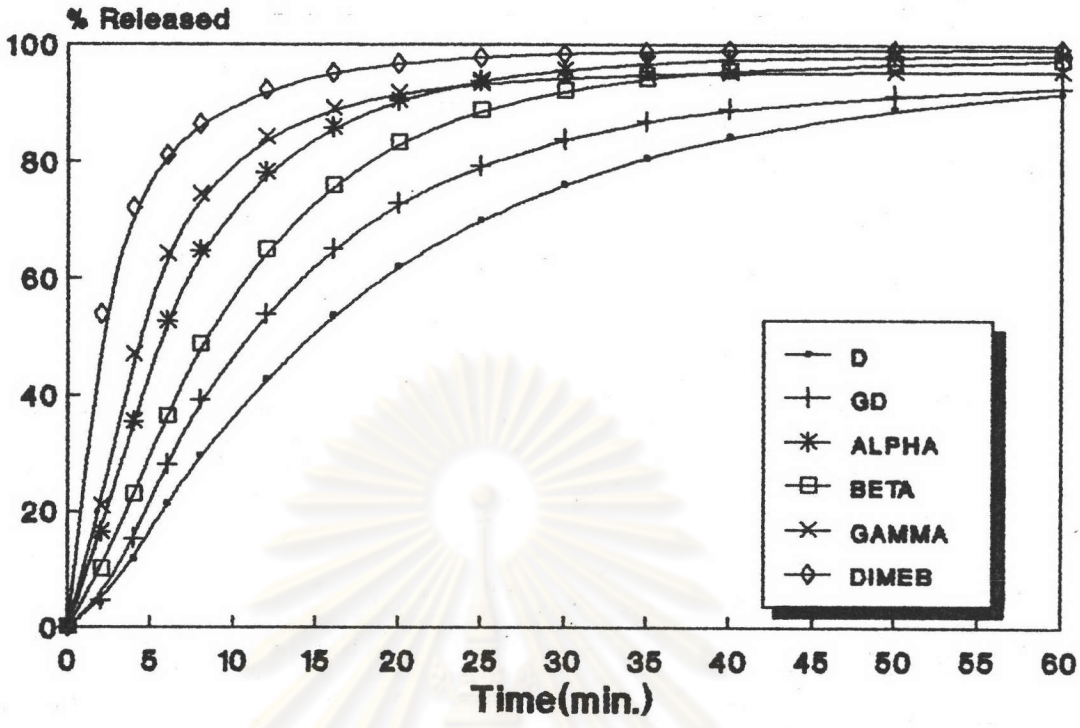


Figure 14 Dissolution profiles of IDM from 1:2 (IDM : CD) grounded mixtures by using different cyclodextrins as compared with pure drug(D) and grounded drug(GD).

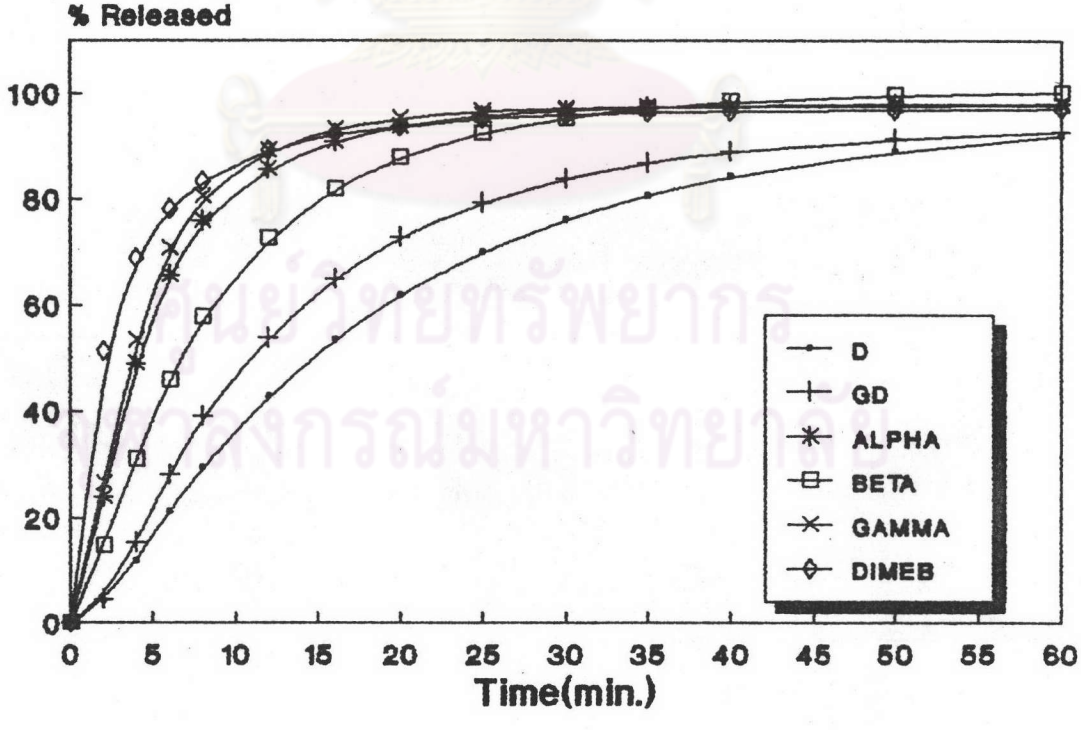


Figure 15 Dissolution profiles of IDM from 1:3 (IDM : CD) grounded mixtures by using different cyclodextrins as compared with pure drug(D) and grounded drug(GD).

1:2 and 1:2 in indomethacin : α-, β-, δ-CD and DIMEB kneaded mixture systems, respectively. The dissolution rate of the raios 1:0.5 and 1:1 indomethacin : α-CD gave the similar dissolution rate in the initial profile, but at 5 minutes later 1:1 ratio yielded higher dissolution rate than 1:0.5. For 1:0.5 indomethacin : β-CD system had the same dissolution profile as found in pure drug, but the dissolution markedly increased with increasing weight fraction of β-CD. There were slightly increased in their dissolution profiles in the ratios between 1:2 to 1:10 for β-CD, 1:1 to 1:3 for δ-cd and 1:0.5 to 1:3 for DIMEB but gave markedly higher dissolution rates than kneaded drug and pure drug.

It was shown that, at all cases of indomethacin kneaded mixtures resulted in faster dissolution profiles than pure drug and kneaded drug, while kneaded drug gave the slowest dissolution profile. Moreover, the dissolution of indomethacin increased as the content of cyclodextrins increased.

From dissolution data, the high indomethacin dissolution rate was in the following order : DIMEB > δ-CD > α-CD > β-CD in the ratio 1:0.5 but in the ratio between 1:1 to 1:3 the order was ranked as follow : DIMEB > δ-CD > β-CD > α-CD. The dissolution of 1:0.5 indomethacin : α-CD gave the same profile as pure drug,but 1:1 ratio α-CD shown slightly increase in the initial dissolution profile, after 8 minutes the dissolution rate decreased as compared to β-CD. It was obvious that the dissolution of 1:1 to 1:3 indomethacin : δ-CD gave high dissolution rate and nearly equal to DIMEB. When

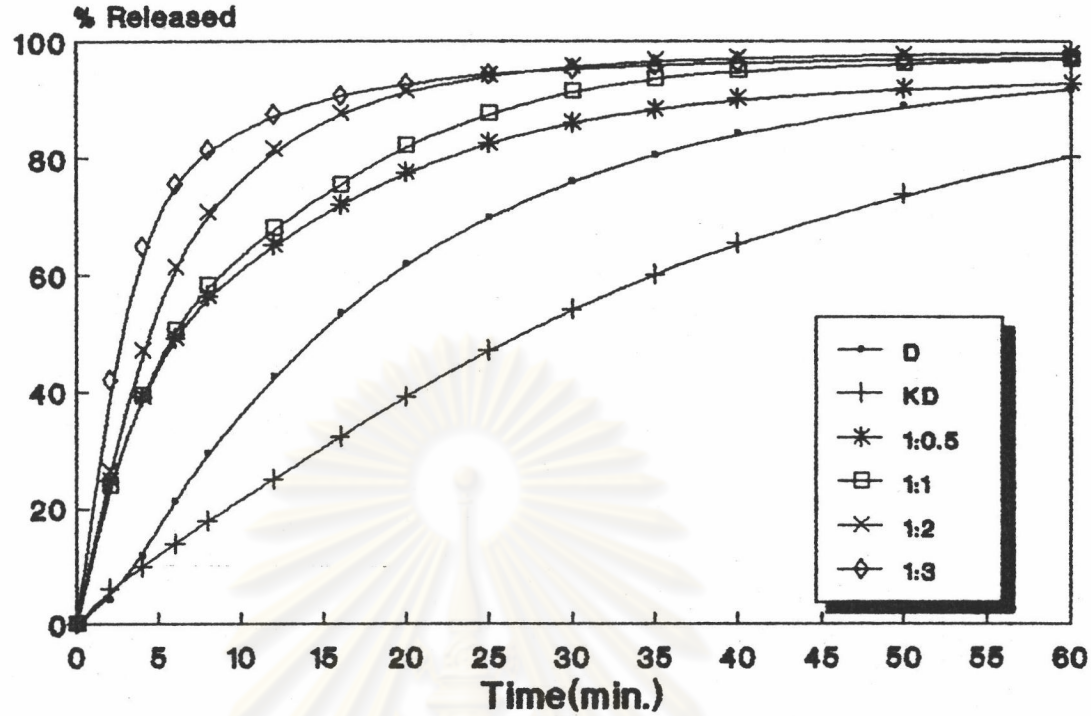


Figure 16 Dissolution profiles of IDM from IDM : ALPHA-CD kneaded mixtures at various ratios as compared with pure drug(D) and kneaded drug(KD).

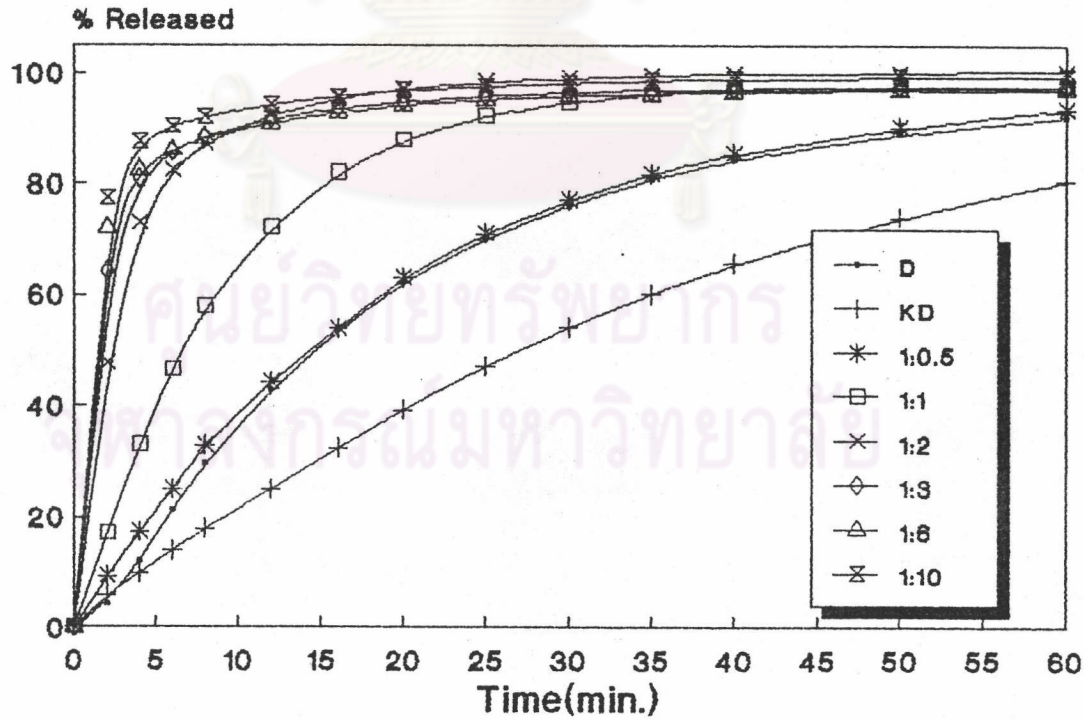


Figure 17 Dissolution profiles of IDM from IDM : BETA-CD kneaded mixtures at various ratios as compared with pure drug(D) and kneaded drug(KD).

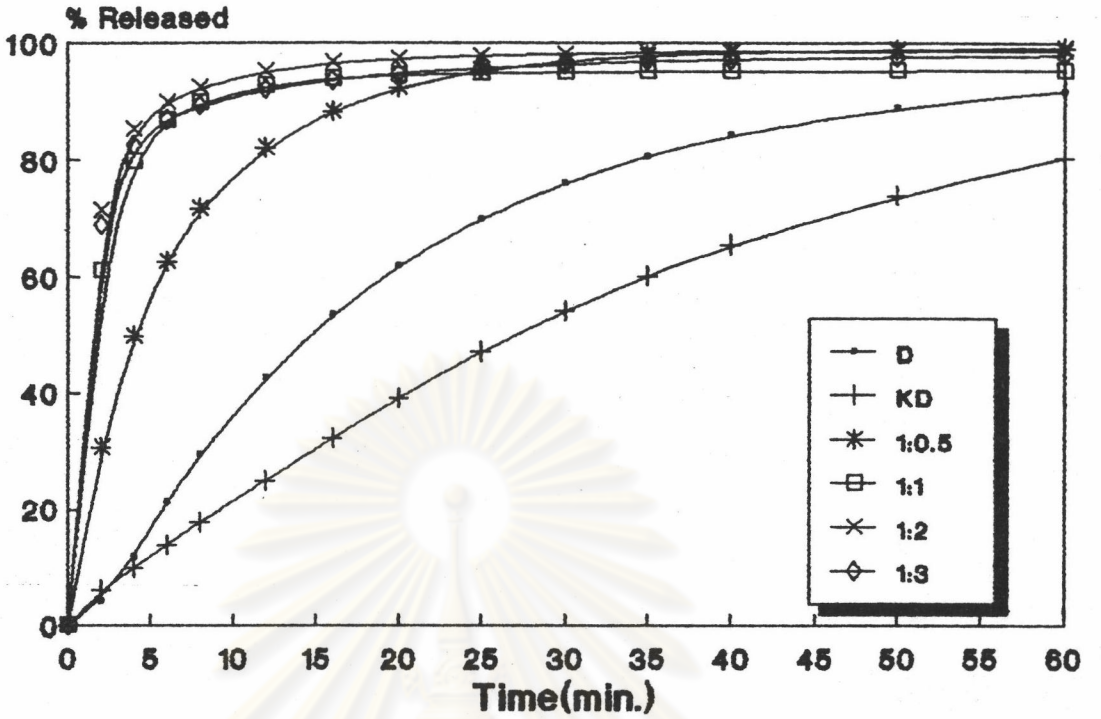


Figure 18 Dissolution profiles of IDM from IDM : GAMMA-CD kneaded mixtures at various ratios as compared with pure drug(D) and kneaded drug(KD).

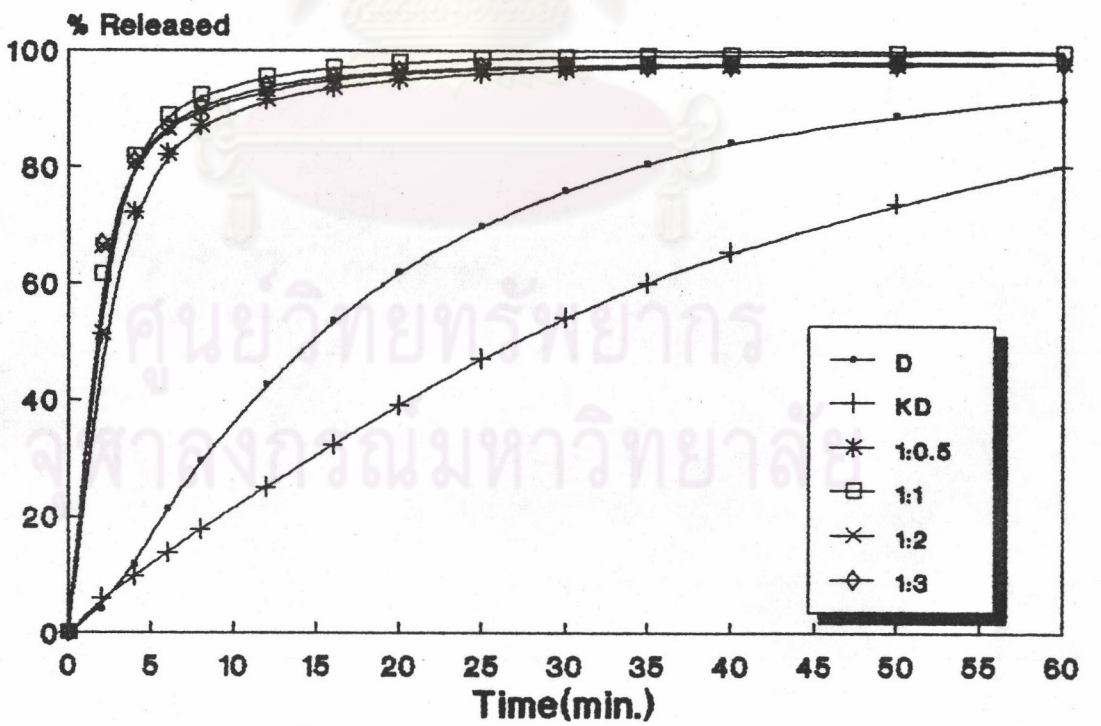


Figure 19 Dissolution profiles of IDM from IDM : DIMEB kneaded mixtures at various ratios as compared with pure drug(D) and kneaded drug(KD).

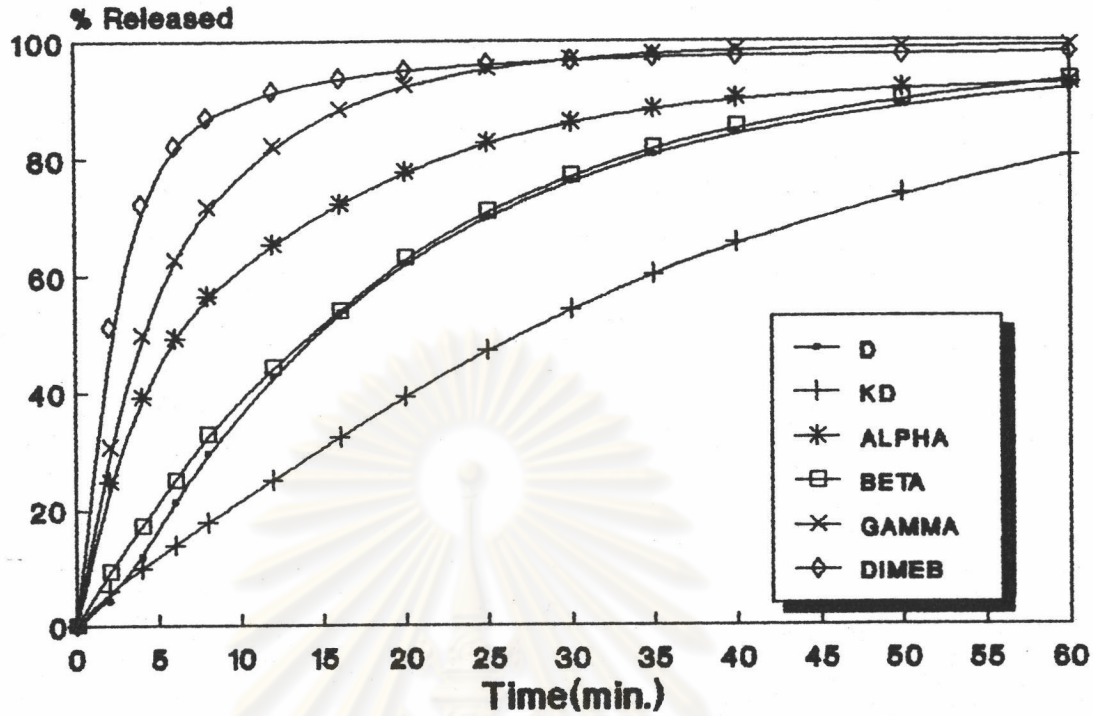


Figure 20 Dissolution profiles of IDM from 1:0.5 (IDM : CD) kneaded mixtures by using different cyclodextrins as compared with pure drug(D) and kneaded drug(KD).

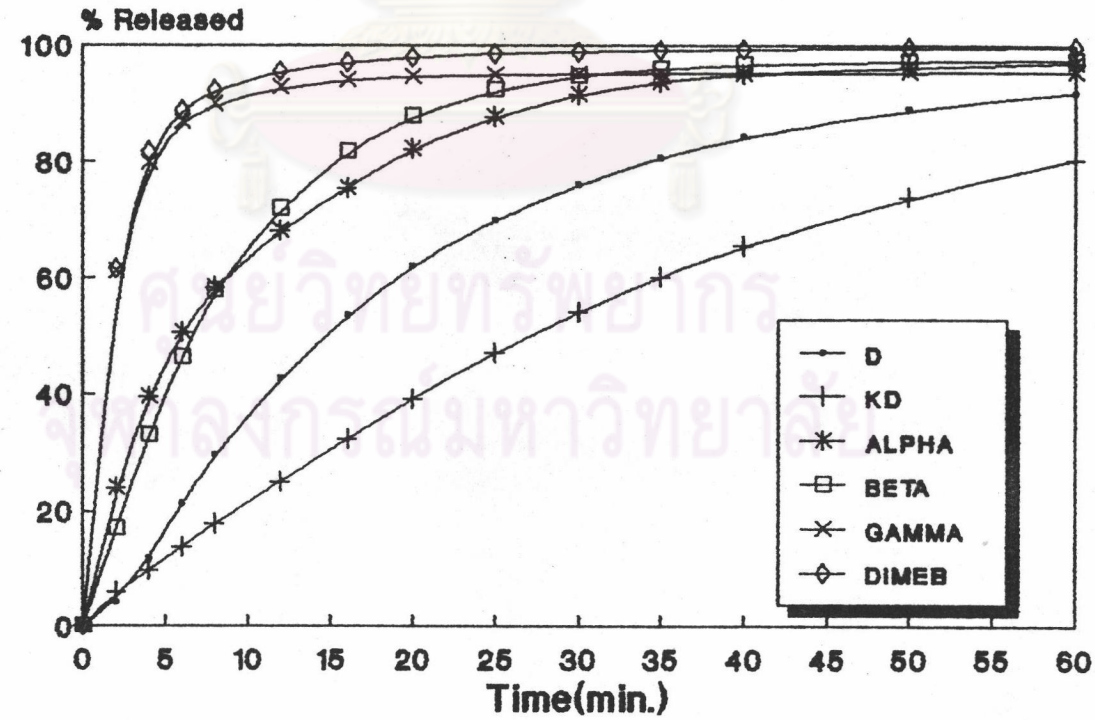


Figure 21 Dissolution profiles of IDM from 1:1 (IDM : CD) kneaded mixtures by using different cyclodextrins as compared with pure drug(D) and kneaded drug(KD).

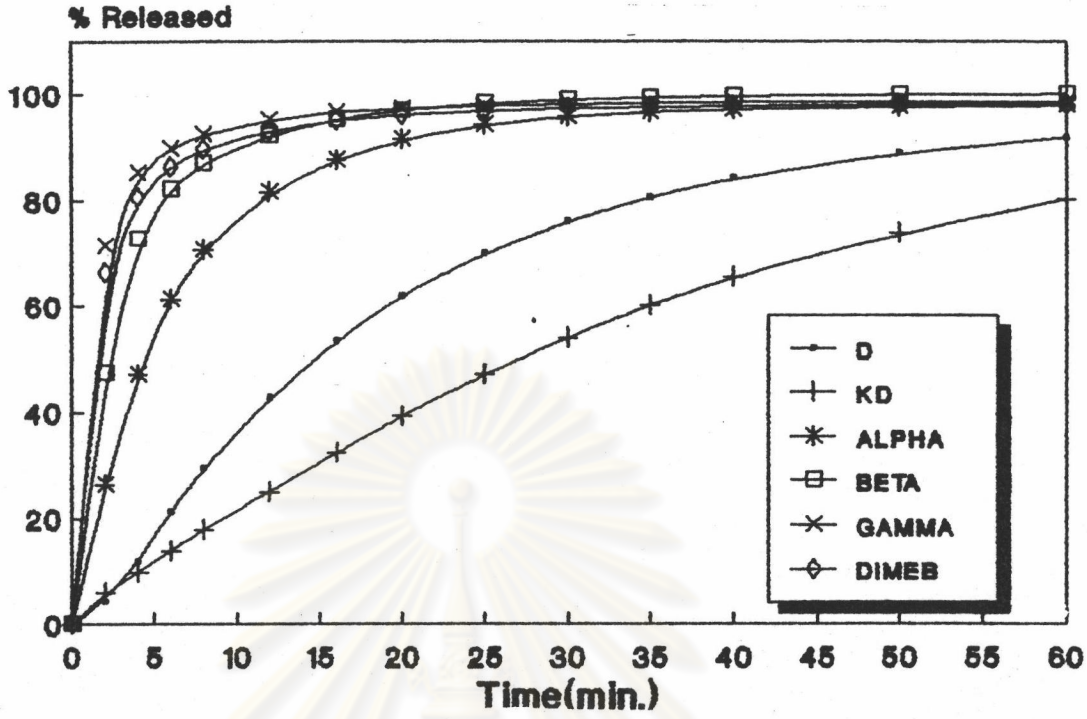


Figure 22 Dissolution profiles of IDM from 1:2 (IDM : CD) kneaded mixtures by using different cyclodextrins as compared with pure drug(D) and kneaded drug(KD).

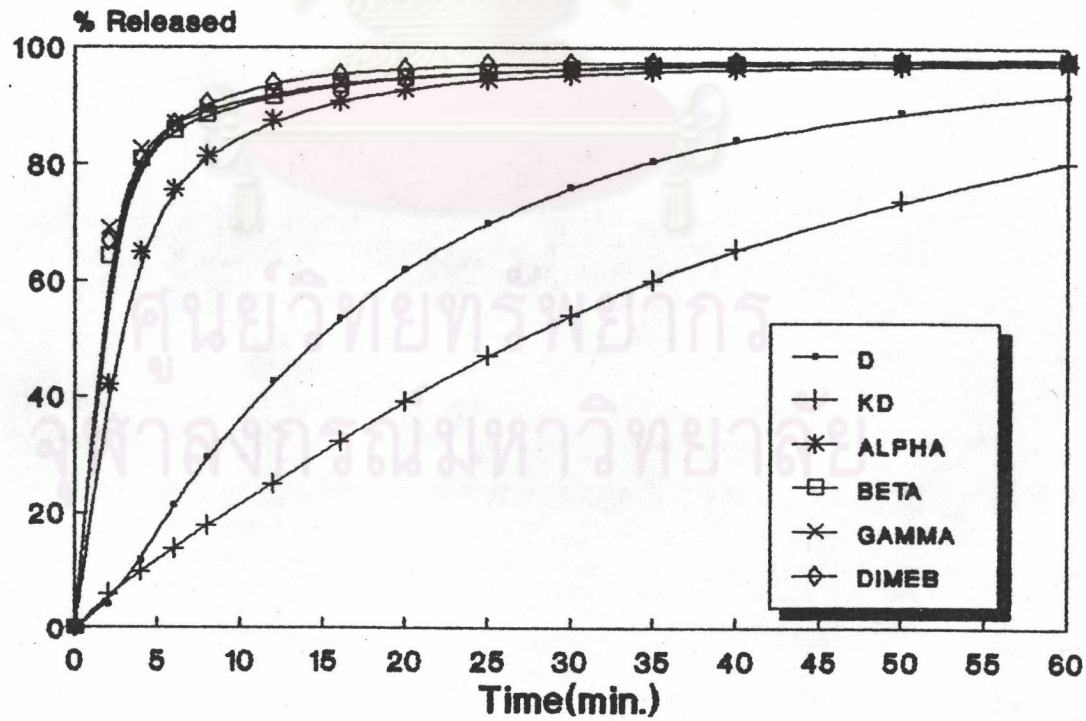


Figure 23 Dissolution profiles of IDM from 1:3 (IDM : CD) kneaded mixtures by using different cyclodextrins as compared with pure drug(D) and kneaded drug(KD).

increased the content of cyclodextrin,the dissolution profiles of β-CD and δ-CD were markedly increased and nearly obtained an equal dissolution of DIMEB. For 1:3 indomethacin : β-CD, δ-CD and DIMEB kneaded mixtures gave the same dissolution profiles and they were the highest dissolution rate.

4. Solvent mixture Systems

The dissolution profiles and experimental data are presented in Figures 24–30 and Appendices 15-18. The dissolution of 1:3 indomethocin : cyclodextrin resulted the fastest dissolution rate, followed by 1:2, 1:1, pure drug and treated drug, respectively. However, the dissolution rate of pure drug was higher than the dissolution rate of treated drug, except before 8 minutes the slower dissolution rate than treated drug had been seen. For 1:1 indomethacin : DIMEB coevaporated system obtained high dissolution at the initial stage and slightly increased in dissolution after 25 minutes and it gave 83.24% release of indomethacin within 60 minutes. The reason may be attributed to the contact of IDM powder with the dissolution medium, it would gather together to become a large sticky plate and still remained in dissolution medium within 60 minutes especially in 1:1 ratio, while in the ratios of 1:2 and 1:3, they dissolved very quickly and completely soluble within 60 minutes. For 1:2 and 1:3 indomethacin : DIMEB solvent mixtures, the similar dissolution profiles were observed and resulted the highest dissolution rate.

By comparing dissolution data, cyclodextrins that gave the highest dissolution was ranked as follow : DIMEB > δ-CD > β-CD > α-CD. There was no different in dissolution profiles of 1:1 indomethacin : α-CD and β-CD but the tendency of dissolution rate increased with increasing the amount of cyclodextrin in the preparations had been seen.

From three dispersion methods : grinding, kneading and solvent deposition or coevaporation were studied. It was observed that the dispersion methods that gave the higher dissolution profiles depended on type of cyclodextrins used in the preparations. They were ordered as follow :

Kneading > Grinding > Solvent deposition	for α-CD
Kneading > Solvent deposition > Grinding	for β- and δ-CD
Coevaporation > Kneading > Grinding	for DIMEB

except for the ratio of 1:1 indomethacin : β-, δ-CD and DIMEB, theirs orders were similar to α-CD. Furthermore, the DIMEB systems obtained the highest dissolution profiles when compared with these three dispersion methods.

Time required for 80 percent of indomethacin dissolved in dispersion systems

Time required for 80 percent of drug dissolved (T80%) was read from the dissolution profile and it could be measured by

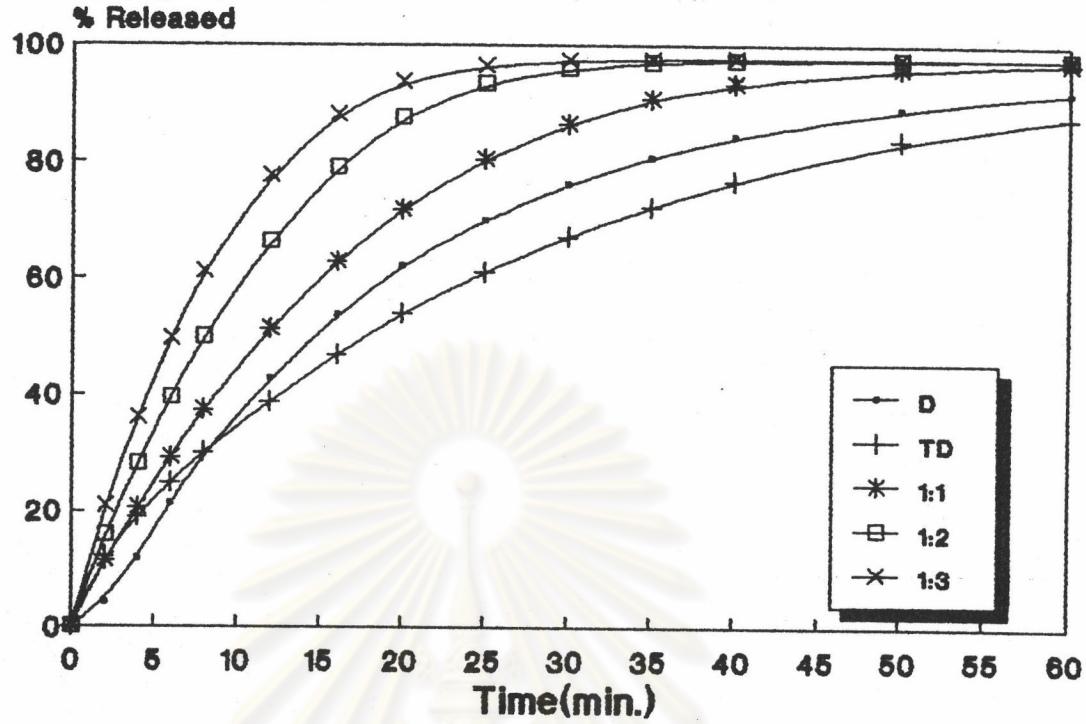


Figure 24 Dissolution profiles of IDM from IDM : ALPHA-CD solvent mixtures at various ratios as compared with pure drug(D) and treated drug(TD).

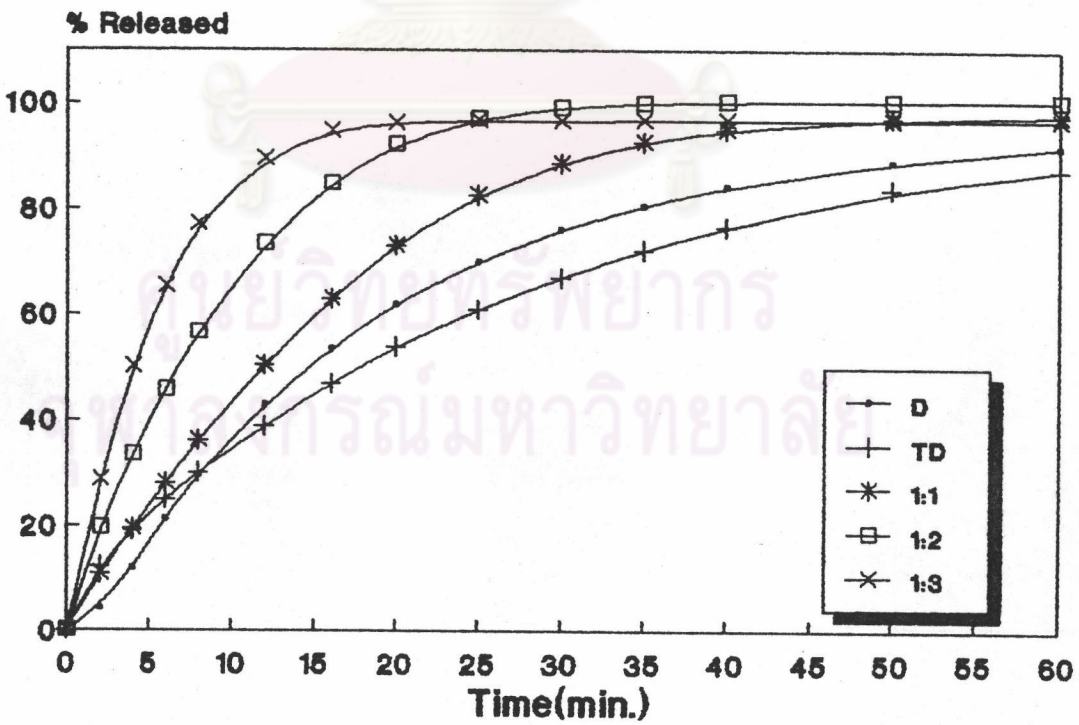


Figure 25 Dissolution profiles of IDM from IDM : BETA-CD solvent mixtures at various ratios as compared with pure drug(D) and treated drug(TD).

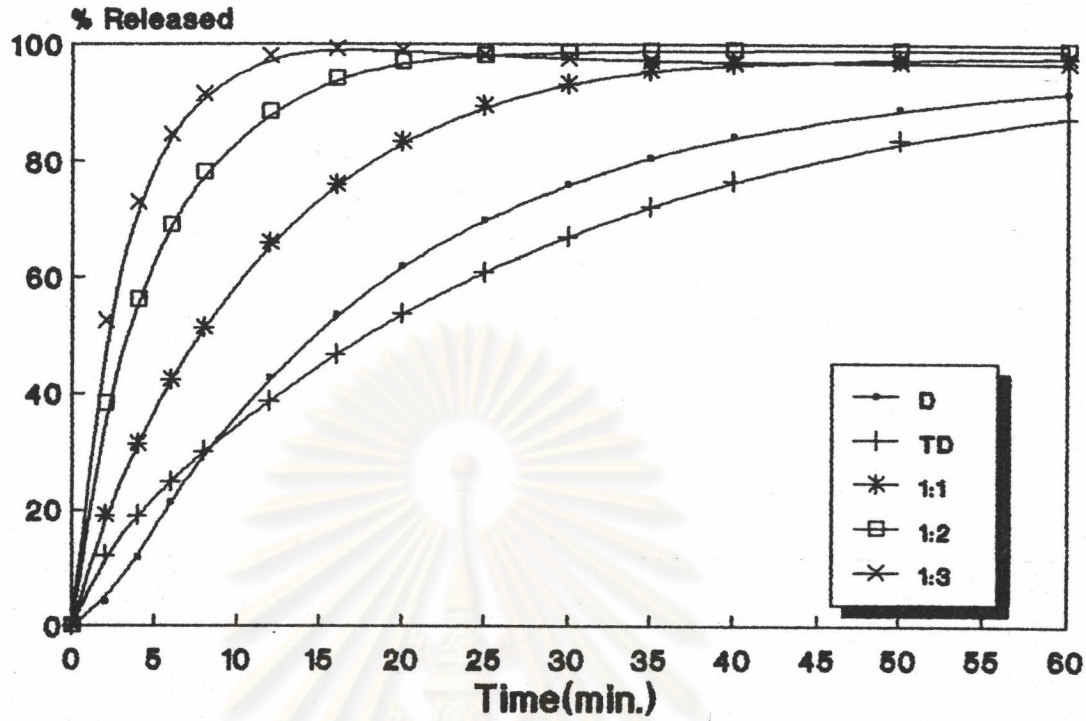


Figure 26 Dissolution profiles of IDM from IDM : GAMMA-CD solvent mixtures at various ratios as compared with pure drug(D) and treated drug(TD).

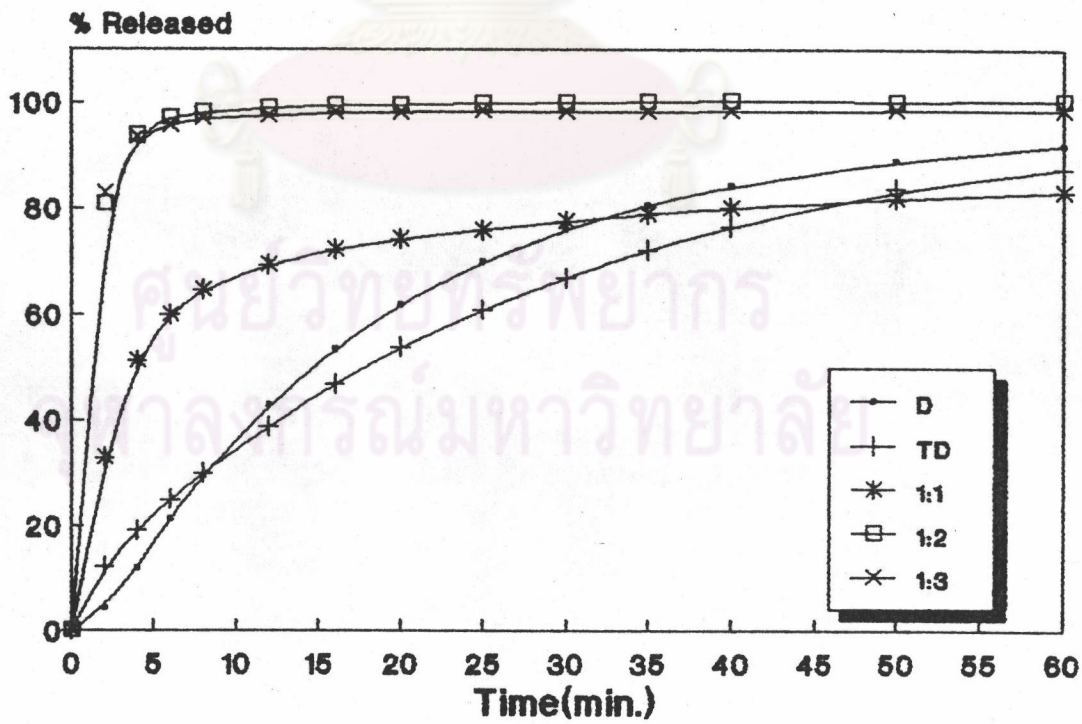


Figure 27 Dissolution profiles of IDM from IDM : DIMEB solvent mixtures at various ratios as compared with pure drug(D) and treated drug(TD).

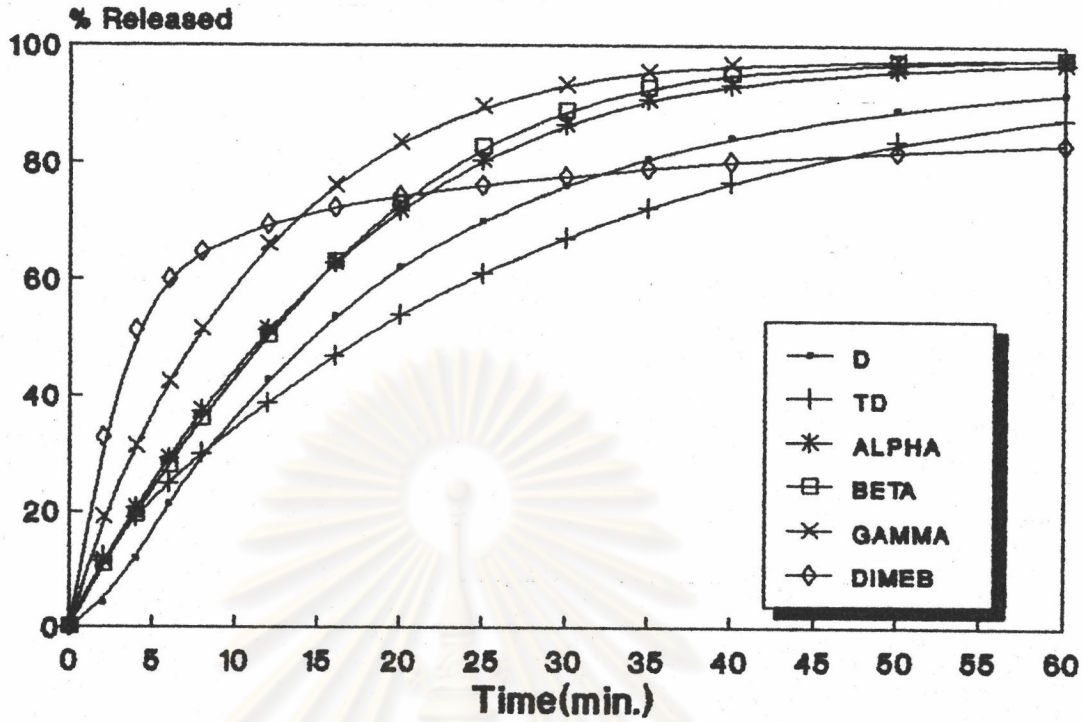


Figure 28 Dissolution profiles of IDM from 1:1 (IDM : CD) solvent mixtures by using different cyclodextrins as compared with pure drug(D) and treated drug(TD).

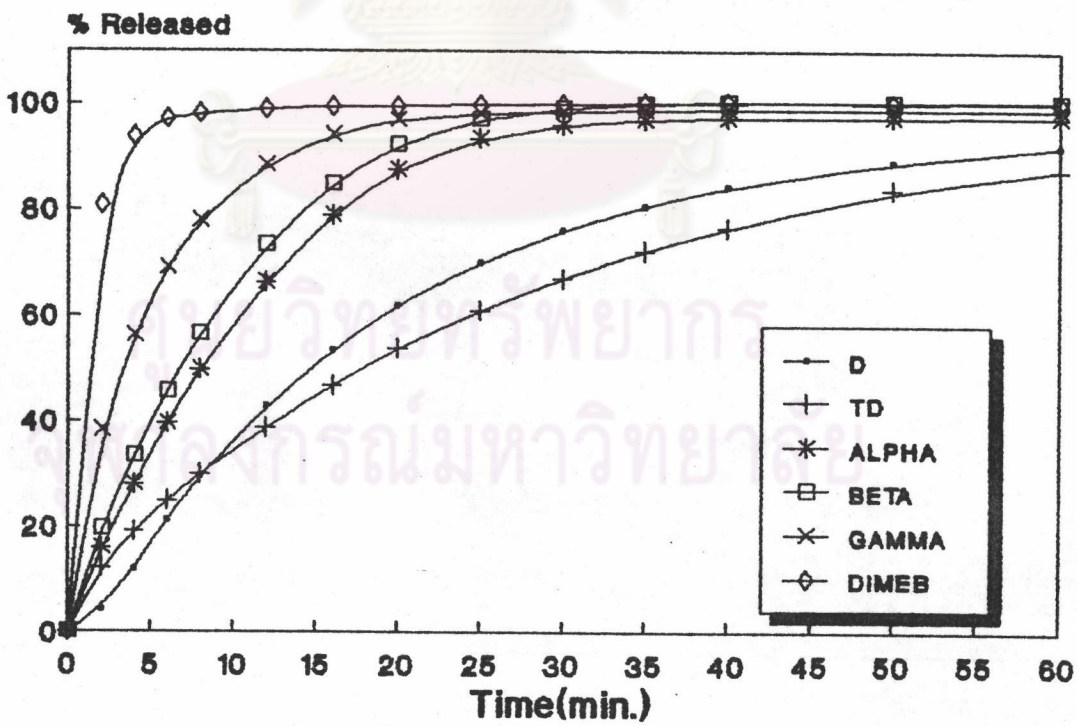


Figure 29 Dissolution profiles of IDM from 1:2 (IDM : CD) solvent mixtures by using different cyclodextrins as compared with pure drug(D) and treated drug(TD).

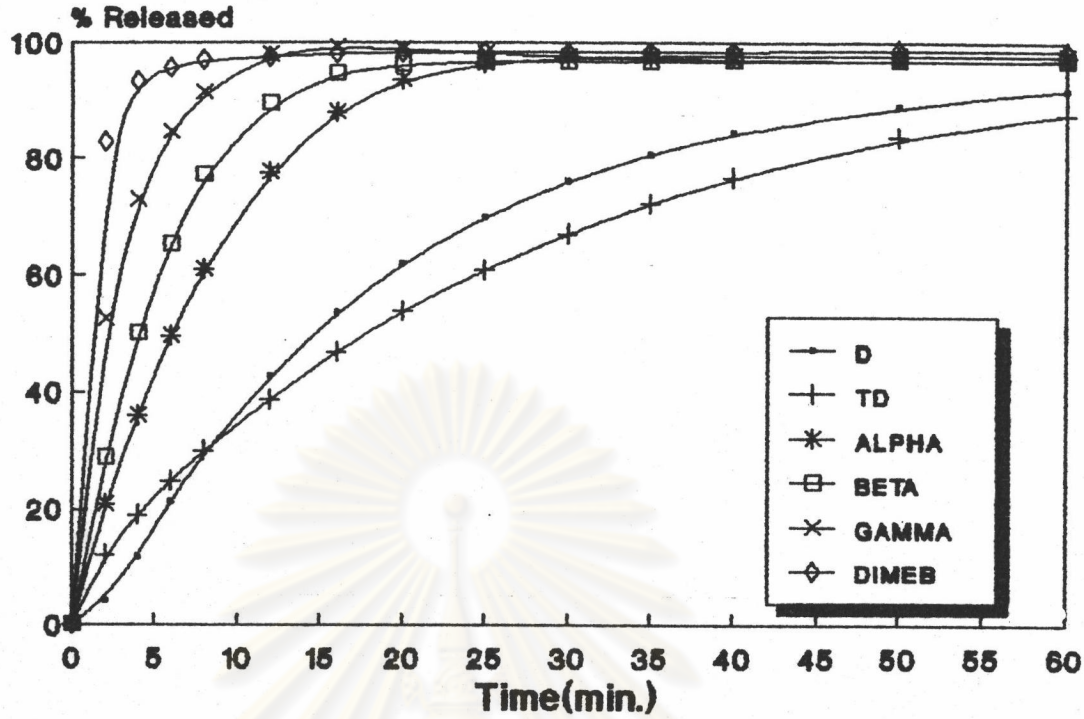


Figure 30 Dissolution profiles of IDM from 1:3 (IDM : CD) solvent mixtures by using different cyclodextrins as compared with pure drug(D) and treated drug(TD).

extraporating the 80 percent of drug to the dissolution time scale. It is recommended that the limit of T80% should be not more than 20 minutes as suggested by USPXXII.

1. Pure drug, grounded drug, kneaded drug and treated drug

The time required for 80 percent of indomethacin to dissolve of pure drug, grounded drug, kneaded drug and treated drug are present in Table 9 and Figure 31. There were found that the T80% was more than 20 minutes and did not meet the requirement according to dissolution test of indomethacin. The T80% of kneaded drug gave the highest time followed by treated drug, pure drug and grounded drug.

2. Grounded mixture systems

The time required for 80 percent of drug to dissolve of grounded mixture systems are shown in Table 10 and Figure 32. The grounded mixtures of four cyclodextrins gave the shortest time of T80% when the quantity of cyclodextrins in the preparations were the highest and the T80% decreased as the content of cyclodextrins increased in the grounded mixture systems.

The T80% of grounded mixture was less than 20 minutes and meet the requirement of the dissolution test except for 1:0.5 indomethacin : β-CD.

Table 9 Effect of type of preparations as a function of time for 80% released of indomethacin.

Type of preparations	T 80 % Released (min.)
Drug	34.23
Grounded Drug	25.58
Kneaded Drug	60.15
Treated Drug	45.38

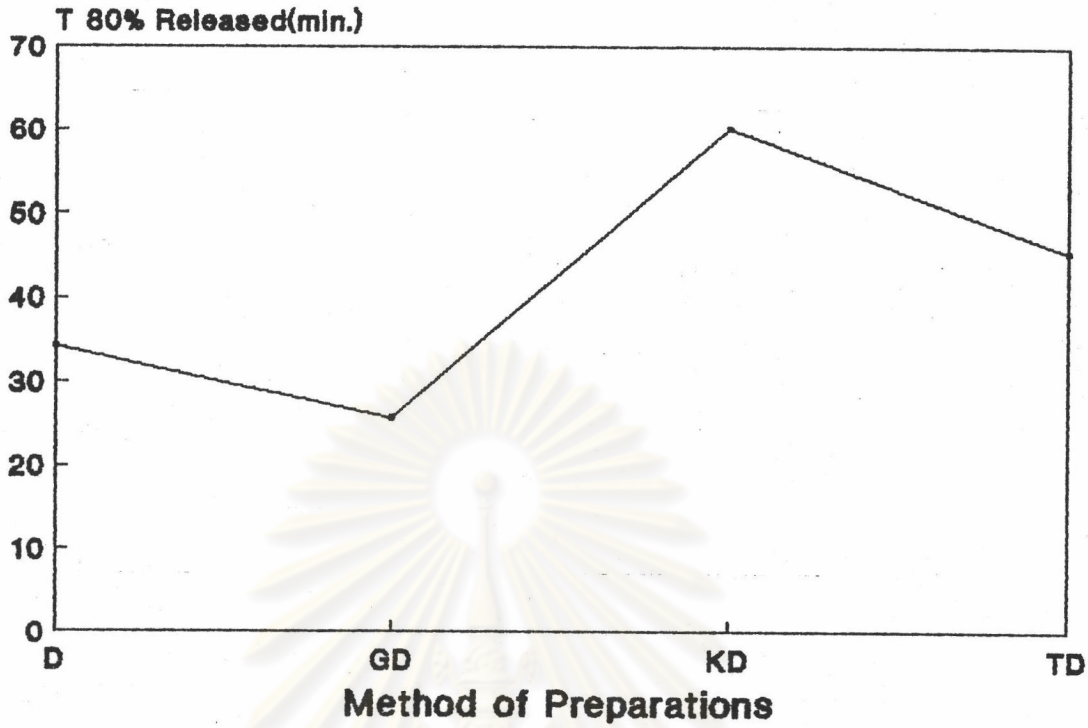


Figure 31 Time of 80% released of IDM from pure drug (D), grounded drug(GD), kneaded drug(KD) and treated drug(TD).

Table 10 Effect of cyclodextrins at various ratios as a function of time for 80% released of IDM in grounded mixtures.

Type of cyclodextrins	T 80 % released at various ratios (min.)					
	1:0.5	1:1	1:2	1:3	1:6	1:10
alpha-CD	16.69	15.00	13.08	9.62	-	-
beta-CD	23.85	19.62	18.46	15.38	15.38	8.27
gamma-CD	15.31	14.62	10.19	8.08	-	-
DIMEB	8.00	6.73	5.77	6.73	-	-

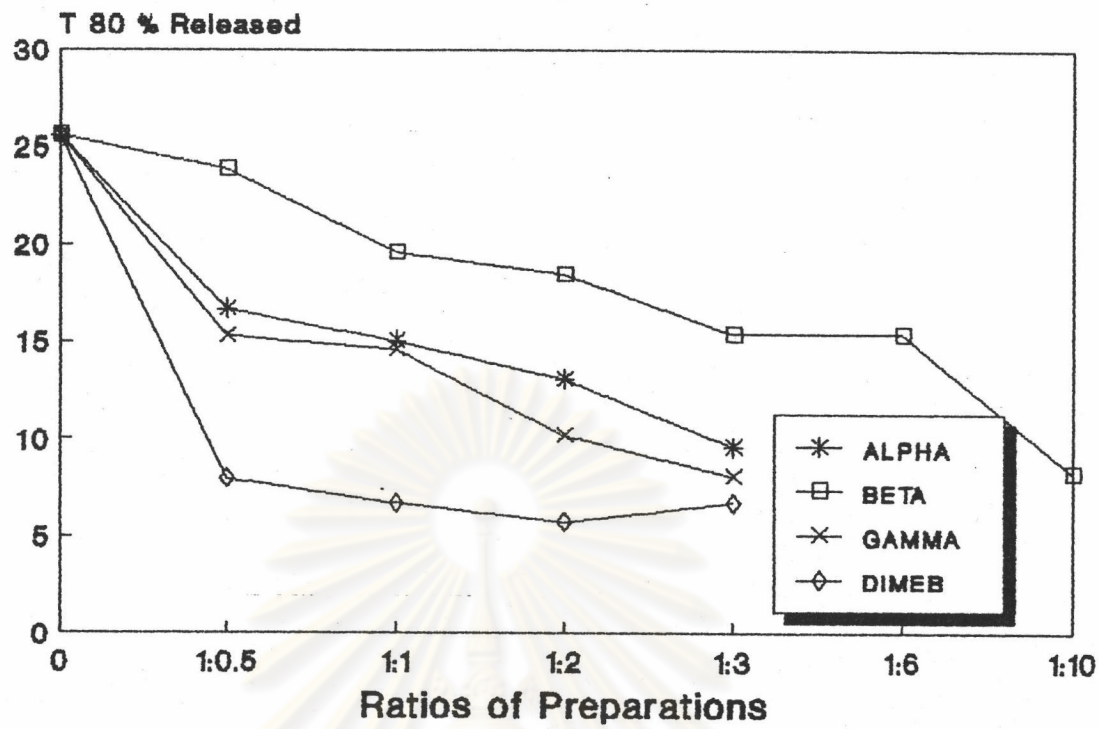


Figure 32 Time of 80% released of IDM from grounded mixtures at various ratios by using different type of cyclodextrins.

By comparing the T80% at the same ratio of preparations, it was found that DIMEB gave the shortest time of T80%, followed by ɣ-, α-, and β-CD, respectively.

3. Kneaded mixture systems

The time required for 80% percent of drug to dissolve of kneaded mixture systems are demonstrated in Table 11 and Figure 33 .

The T80% of kneaded mixture meet the requirement of the dissolution test and the time was less than 20 minutes except for 1:0.5 indomethacin : α- and β-CD. The T80% decreased with increasing the amount of cyclodextrins and gave the shortest time when the amount of cyclodextrin was the highest in the preparation except for 1:3 ratio of IDM : ɣ-CD, the slightly increased was found as to 1:2 ratio. However, was no different in T80% between 1:1 to 1:3 indomethacin : DIMEB ratios.

Among these four cyclodextrins, the T80% was ranked as follow : DIMEB < ɣ-CD < α-CD < β-CD at 1:0.5 ratio. However at 1:1 to 1:3 ratios the following order of T80% was DIMEB < ɣ-CD < β-CD < α-CD.

4. Solvent mixture systems

The time required for 80 percent of indomethacin to dissolve in solvent mixture systems are presented in Table 12 and Figure 34 .

The T80% of 1:1 indomethacin : DIMEB gave the highest time but at the ratios of 1:2 and 1:3, the shortest time of T80% was found. It was observed that the amount of cyclodextrin increased with decreasing T80%

At the same ratio, there was found that T80% was ranked as follow : DIMEB < ɣ-CD < β-CD < α-CD.

By comparing between three dispersion methods, the following order of T80% was :

Grinding < Kneading < solvent deposition for α-CD at 1:1 ratio

Kneading < Grinding < solvent deposition for 1:2 and 1:3 in α-CD, 1:1 in β-CD, ɣ-CD and DIMEB

Kneading < solvent deposition < Grinding for β-CD and ɣ-CD at 1:2 and 1:3 ratios

Coevaporate < Kneading < Grinding for DIMEB in 1:2 and 1:3 ratios.

From the dissolution studied of all type of cyclodextrins in different dispersion methods, there were appeared that two cyclodextrins ɣ-CD and DIMEB, seemed to be more advantageous than other CDS to give the high dissolution profile and the short time of T80% when compared with the others at the same ratio.

Table 11 Effect of cyclodextrins at various ratios as a function of time for 80% released of IDM in kneaded mixtures.

Type of cyclodextrins	T 80 % released at various ratios (min.)					
	1:0.5	1:1	1:2	1:3	1:6	1:10
alpha-CD	23.08	19.23	11.54	7.69	-	-
beta-CD	33.85	15.38	5.77	4.23	3.85	3.00
gamma-CD	11.54	4.38	3.46	3.85	-	-
DIMEB	5.77	4.04	4.04	4.04	-	-

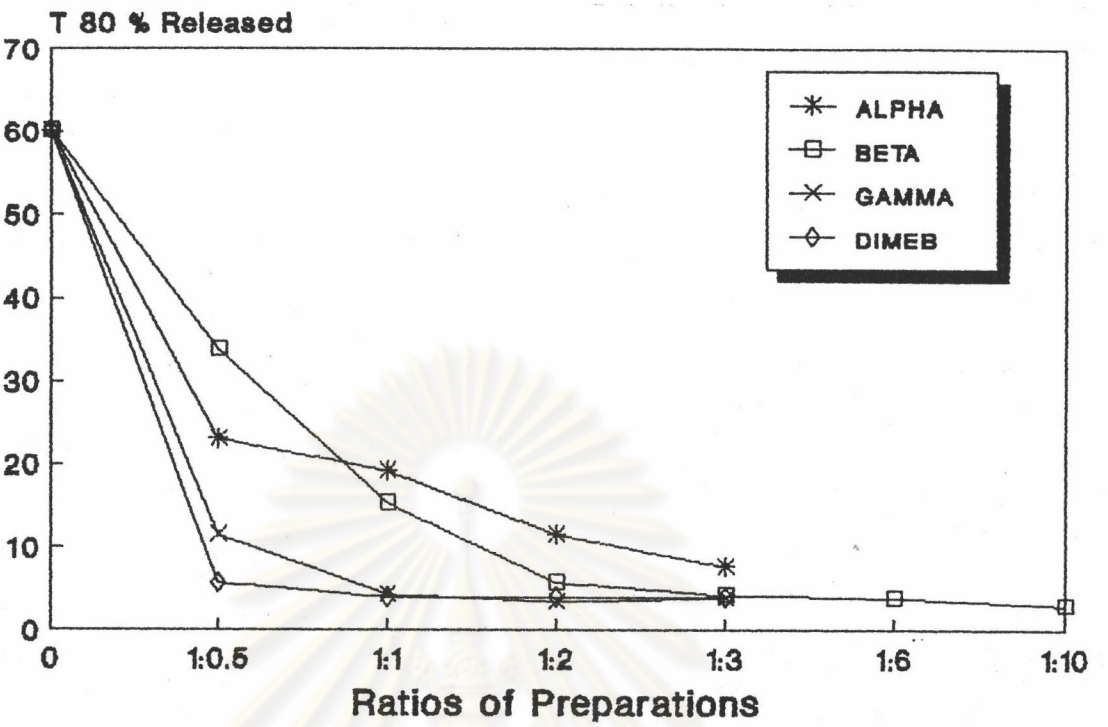


Figure 33 Time of 80% released of IDM from kneaded mixtures at various ratios by using different type of cyclodextrins.

Table 12 Effect of cyclodextrins at various ratios as a function of time for 80% released of IDM in solvent mixtures.

Type of cyclodextrins	T 80 % released at various ratios (min.)		
	1:1	1:2	1:3
alpha-CD	24.81	16.73	12.69
beta-CD	23.85	14.38	8.85
gamma-CD	18.64	8.85	5.38
DIMEB	39.62	2.50	2.50

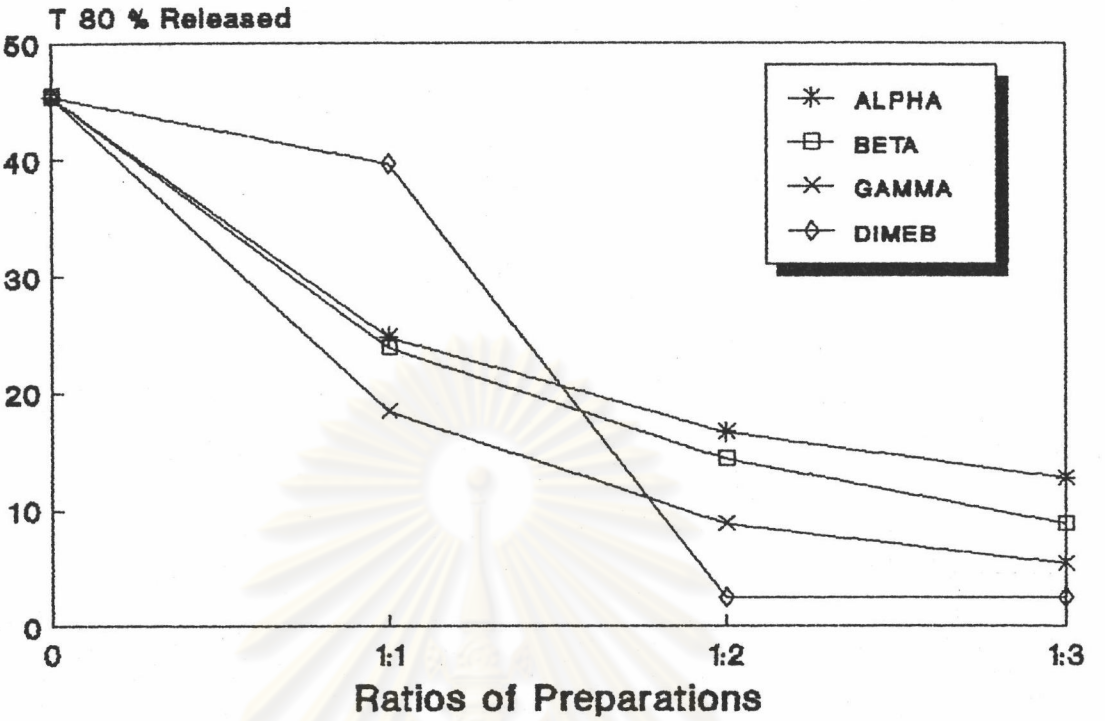


Figure 34 Time of 80% released of IDM from solvent mixtures at various ratios by using different type of cyclodextrins.

Due to DIMEB gave the highest dissolution profile with the smallest amount to be employed in the preparation. It was selected for further investigations on preparation of capsule products.

Physicochemical properties of indomethacin pure drug and mixed powders

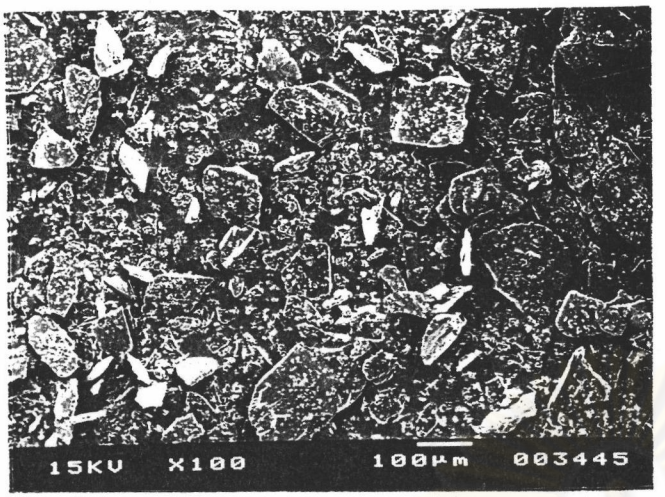
1. Morphology of pure drug and mixed powders

Photomicrographs of pure drug, grounded drug, kneaded drug, treated drug, carriers and all type of 1:3 dispersion systems (i.e., grounded mixture, kneaded mixture and solvent mixture) are presented in Figures 35-46 with different magnifications. The general shape and surface topography could be observed.

1.1 Pure drug, grounded drug, kneaded drug and treated drug

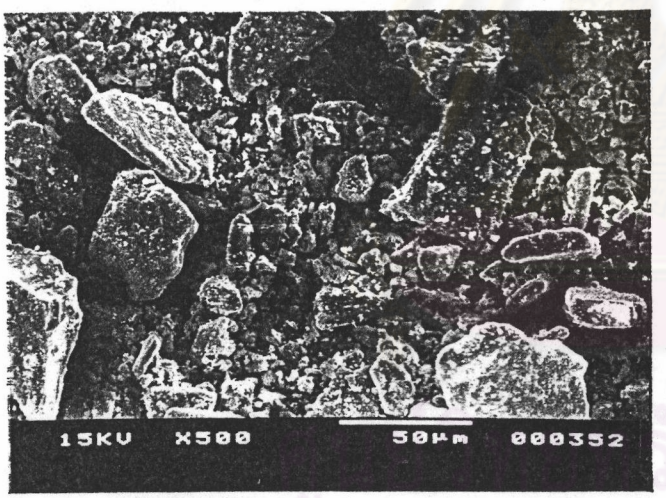
IDM compose of irregular plate with different size, and the surface of the powder was smooth. The appearance of grounded drug was similar to pure IDM but smaller in size. They are illustrated in Figure 35 (A-D).

For kneaded drug, the size of granule was about 400-500 μm with irregular shape and with rough surface. The surface of granule was observed to compose of small and large plates of IDM that held together. Treated IDM granule was larger than kneaded drug in size. It composed of long needle crystal to form the bundle and the surface was smooth. The SEM are shown in Figure 36 (A-D).

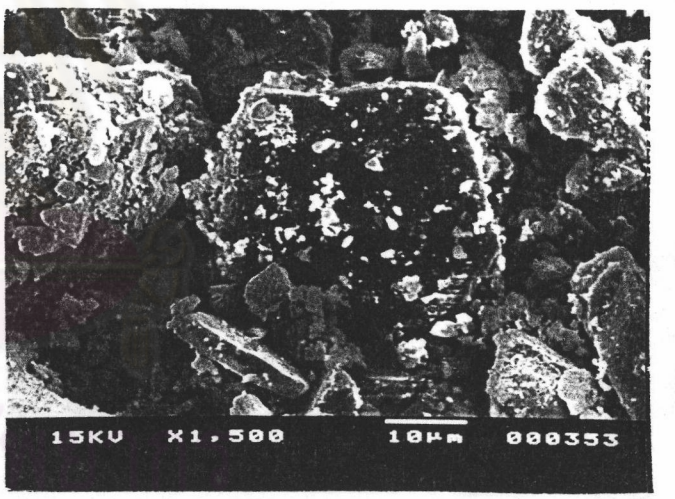


A

B

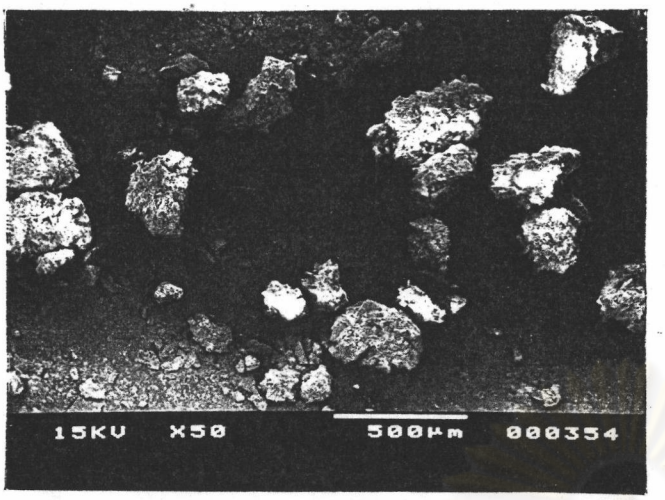


C

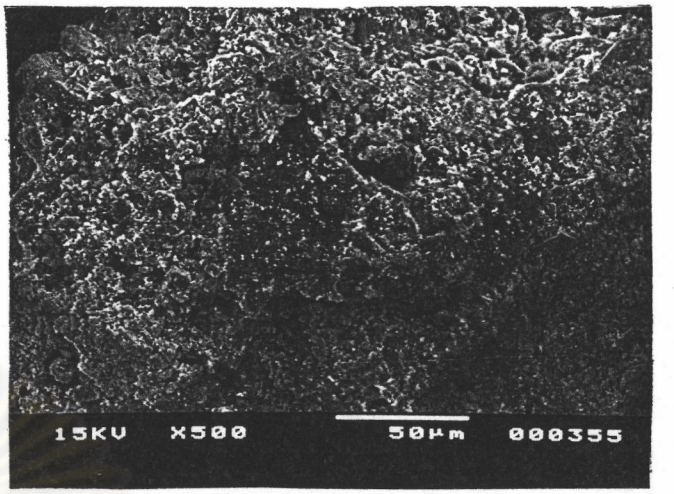


D

Figure 35 The photomicrographs of indomethacin powder and grounded indomethacin (key : A and B are indomethacin powder, AX100, BX500, C and D are grounded indomethacin powder, CX500, DX1500).

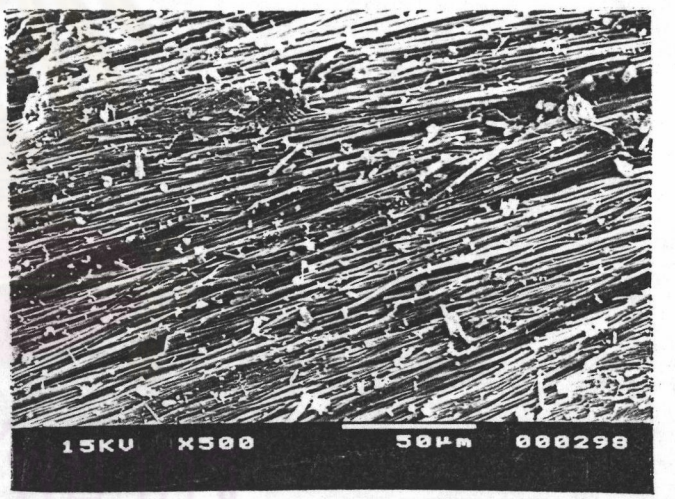


A



B

C



D

Figure 36 The photomicrographs of kneaded indomethacin and treated indomethacin (key : A and B are kneaded indomethacin, AX50, BX500, C and D are treated indomethacin, CX50, DX500).

1.2 α-CD, β-CD, δ-CD and DIMEB

The microscopic appearance of α-CD, β-CD, δ-CD and DIMEB are illustrated in Figures 37 - 40 , respectively. Photomicrograph of α-CD was rod shape crystal and some prism forms with different size. For β-CD and δ-CD were irregular crystal with rough surface but the size of δ-CD was smaller than β-CD. In the case of DIMEB, it was composed of needle shape with various lengths and some needles agglomerated together.

1.3 α-CD systems

The SEM photomicrographs of 1:3 drug : α-CD ratio of grounded mixture, kneaded mixture and solvent deposition are displayed in Figure 41 . In grounded mixture, most small plate particles of IDM adhered on the surface of α-CD particles. While the kneaded mixture and solvent deposition, the shape of particle was irregular with different size. The surface of them were not smooth.

1.4 β-CD systems

Grounded mixture of β-CD shown the small particles of IDM separated from β-CD particles and some drug particles adhered on the surface (Figure 42). For kneaded mixture, the granule broken when observe under the Scanning Electron Microscope. There was a split on the surface and it was not smooth. The size of granule from

solvent deposition process was larger than kneaded mixture. It was irregular shape and size, with rough surface.

1.5 ŏ-CD systems

The SEM appearance of ŏ-CD systems are depicted in Figure 43 . In grounded mixture, the surface of ŏ-CD was covered with IDM particles. Kneaded mixture particles constituted of very small particles held together to be granule form. For solvent deposition, the shape of the particles were irregular with different size and there was rough with a groove on the surface.

1.6 DIMEB and DIMEB systems

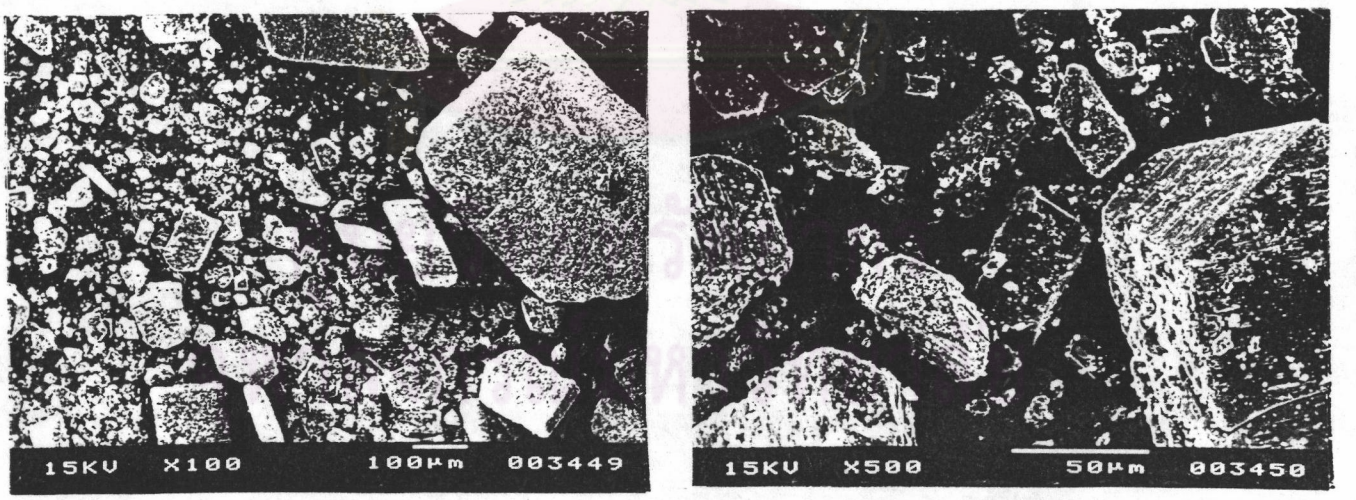
Photomicrograph of grounded mixture and kneaded mixture are illustrated in Figure 44 , treated DIMEB in Figure 45 and for 1:1 to 1:3 indomethacin : DIMEB coevaporate systems in Figure 46 .

In grounded mixture of DIMEB, the surface of DIMEB was covered with IDM particles and some separated from DIMEB particles. For kneaded mixture, the granule was irregular shape with rough surface. The size of granule was approximately 400-600 μm.

DIMEB changed from needle shape to irregular shape and size with rough surface after treated with absolute ethanol. For evaporation of indomethacin and DIMEB, the particles were similar to

A B

Figure 37 The photomicrographs of α-cyclodextrin (key : AX100, Bx500).

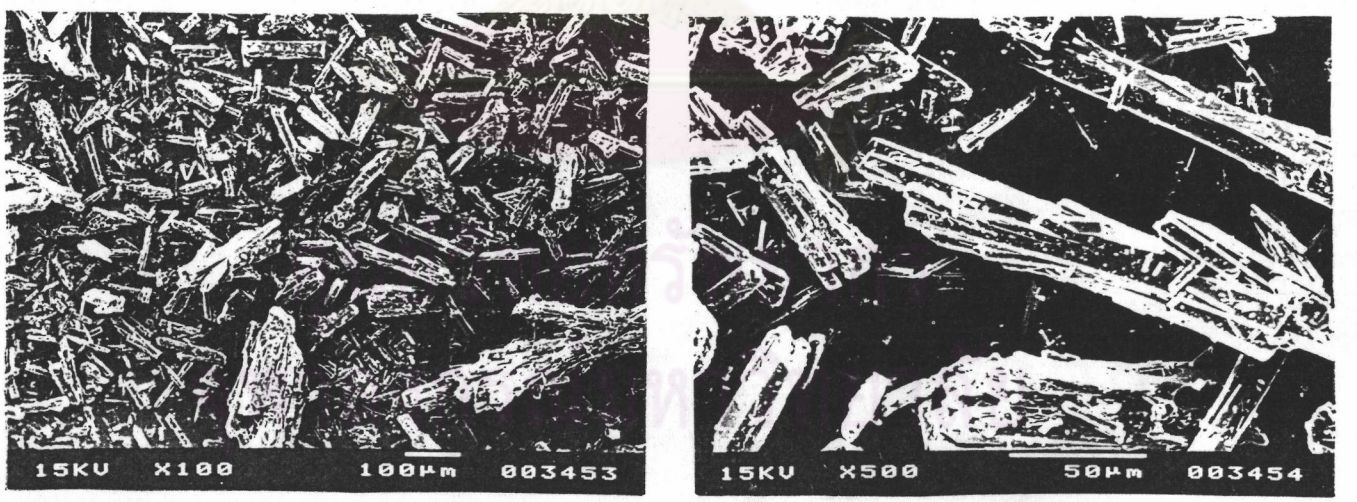


A B

Figure 38 The photomicrographs of β-cyclodextrin (key : AX100, BX500).

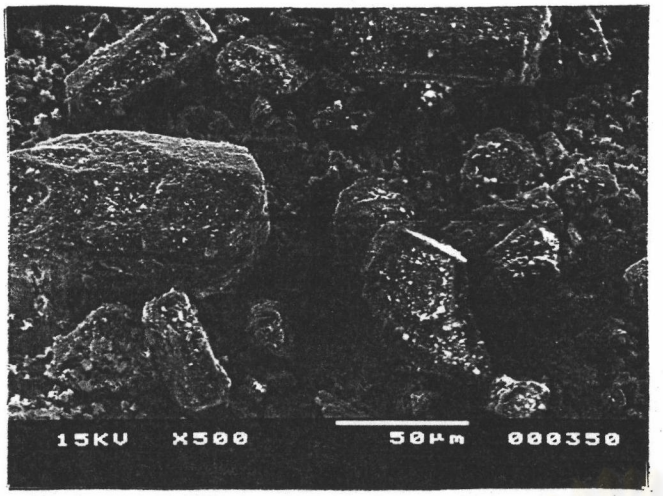
A B

Figure 39 The photomicrographs of ϑ-cyclodextrin (key : AX100, BX500).

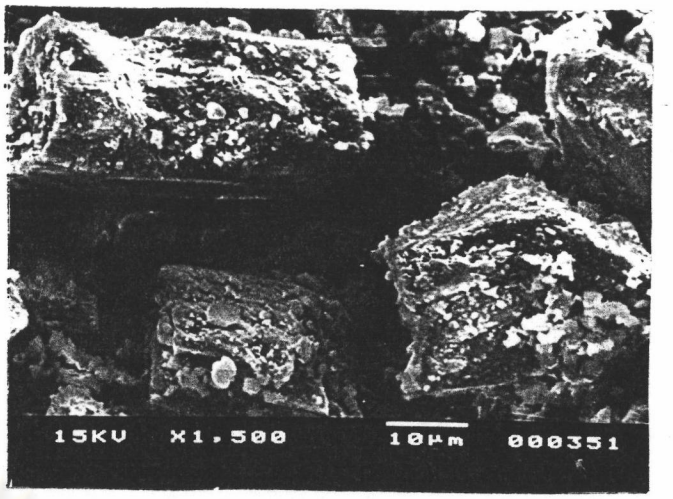


A B

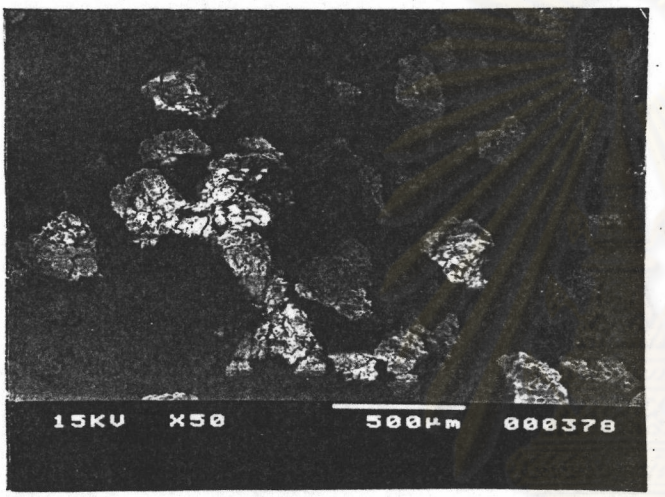
Figure 40 The photomicrographs of dimethyl-β-cyclodextrin (key : AX100, BX500).



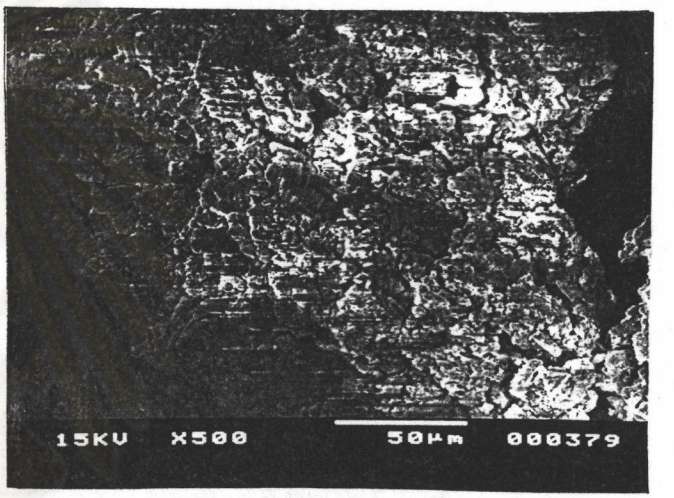
A



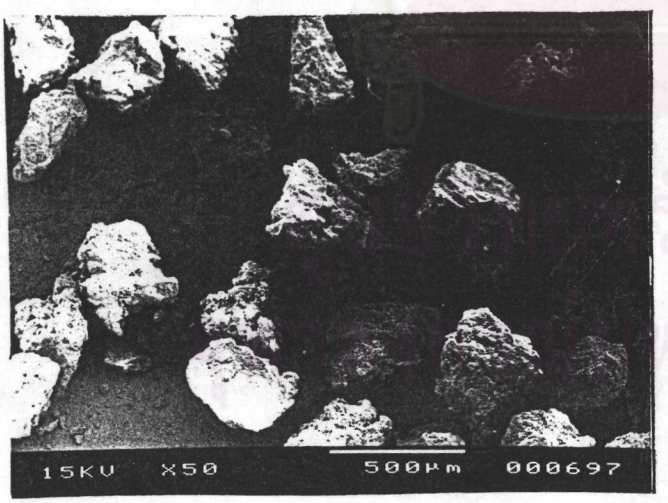
B



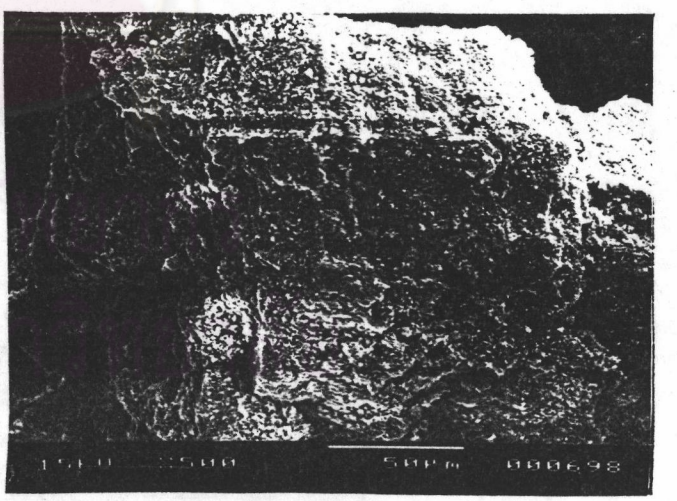
C



D

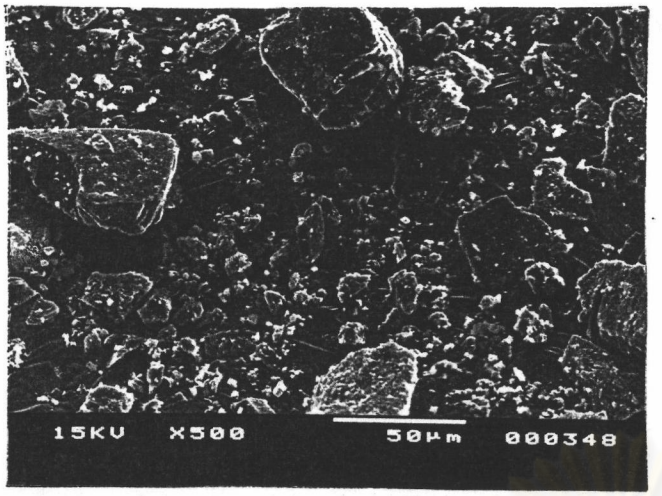


E

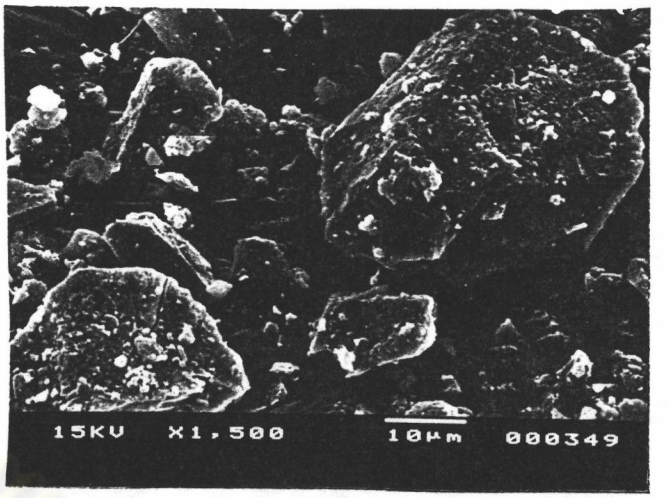


F

Figure 41 The photomicrographs of indomethacin-α-cyclodextrins systems ratio 1:3 (key : A and B are grounded mixture, AX500, BX1500; C and D are kneaded mixture, CX50, DX500; E and F are solvent deposition, EX50, FX500).

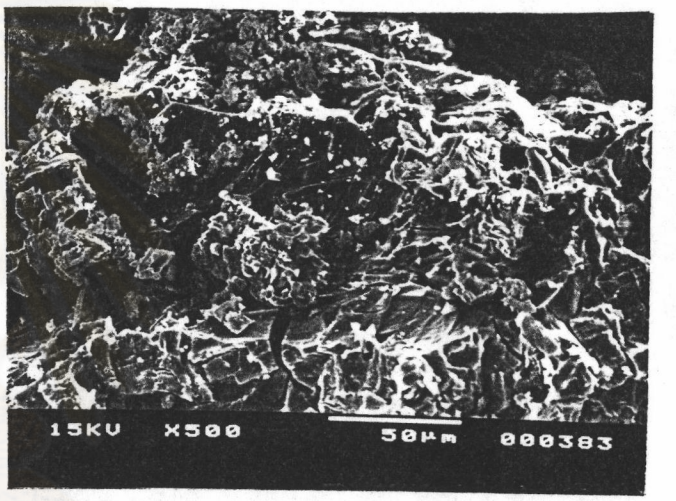


A

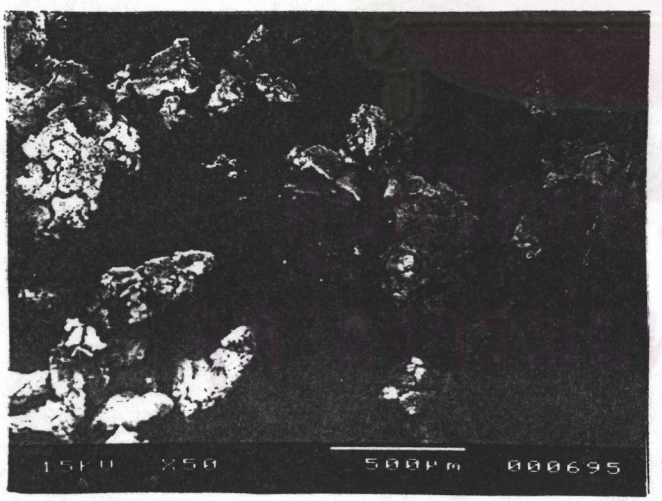


B

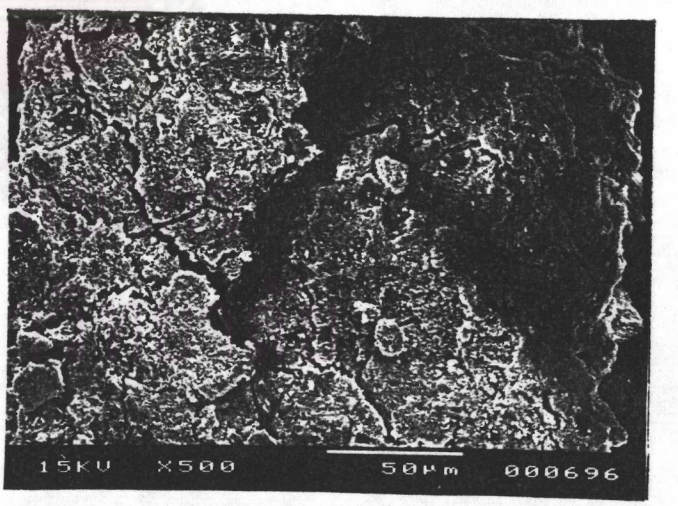
C



D

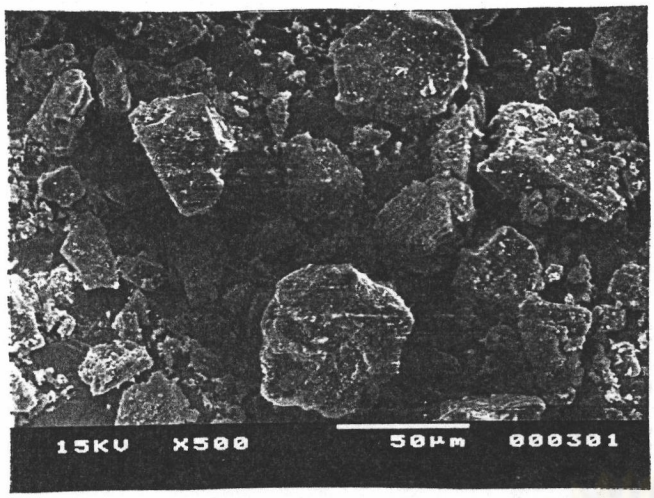


E

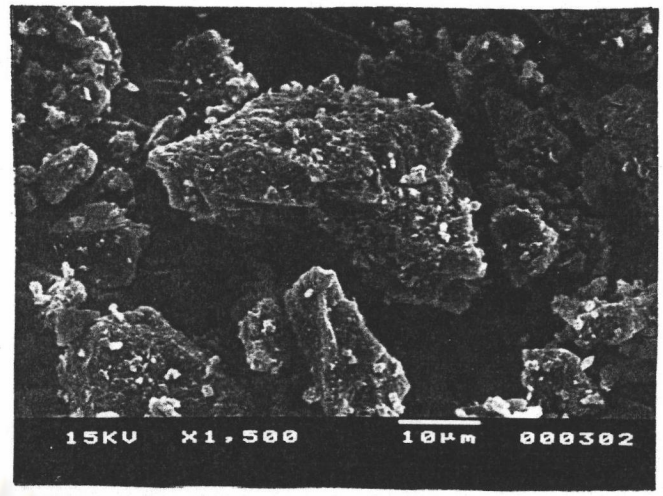


F

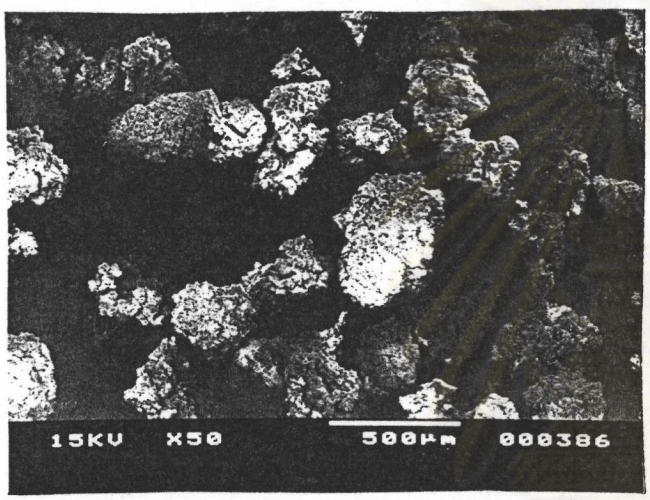
Figure 42 The photomicrographs of indomethacin-β-cyclodextrin systems ratio 1:3 (key : A and B are grounded mixture, AX500, BX1500; C and D are kneaded mixture, CX50, DX500; E and F are solvent deposition, EX50, FX500).



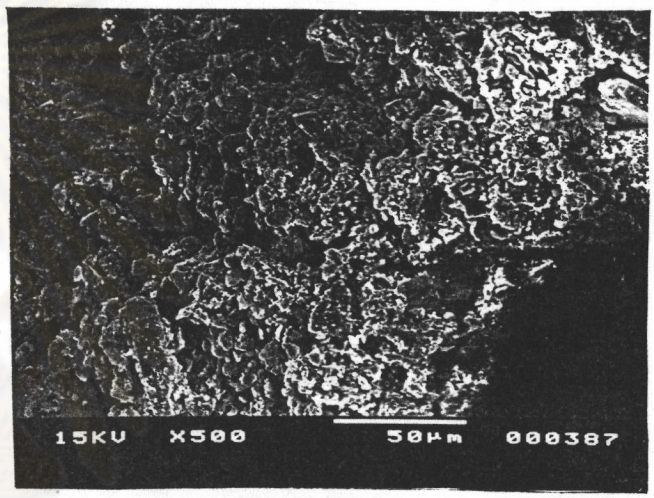
A



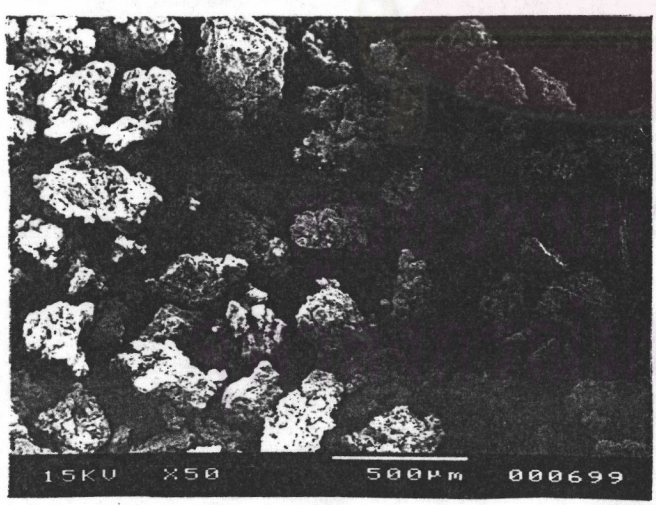
B



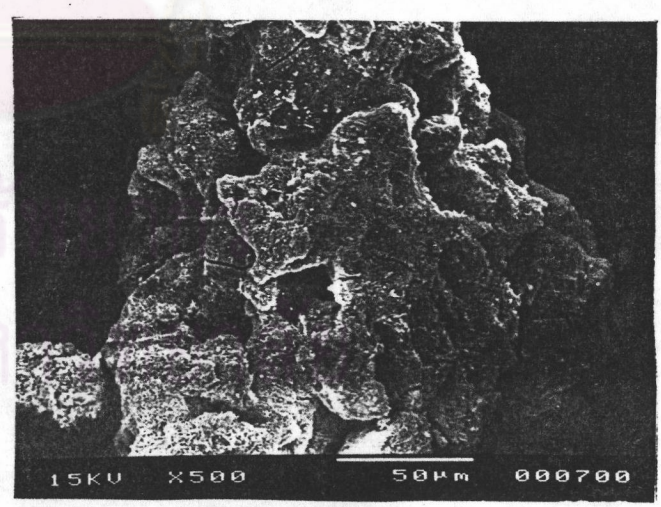
C



D

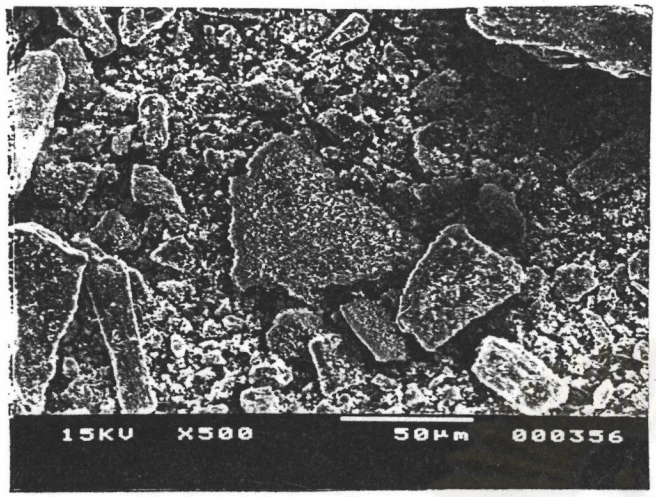


E

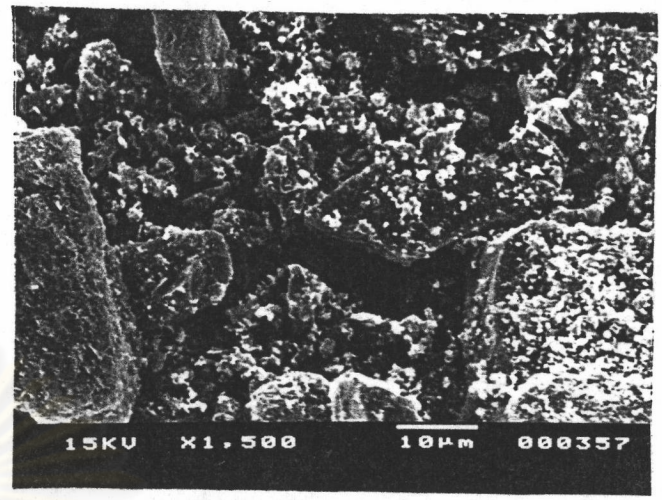


F

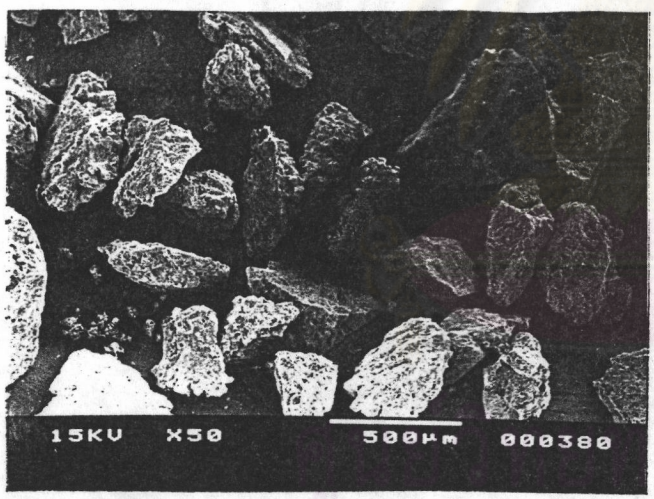
Figure 43 The photomicrographs of indomethacin-ϑ-cyclodextrin systems ratio 1:3 (key : A and B are grounded mixture, AX500, BX1500; C and D are kneaded mixture, CX50, DX500; E and F are solvent deposition, EX50, FX500).



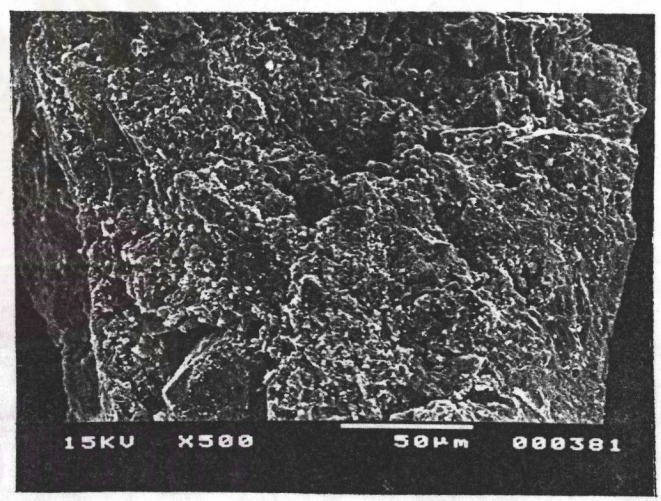
A



B

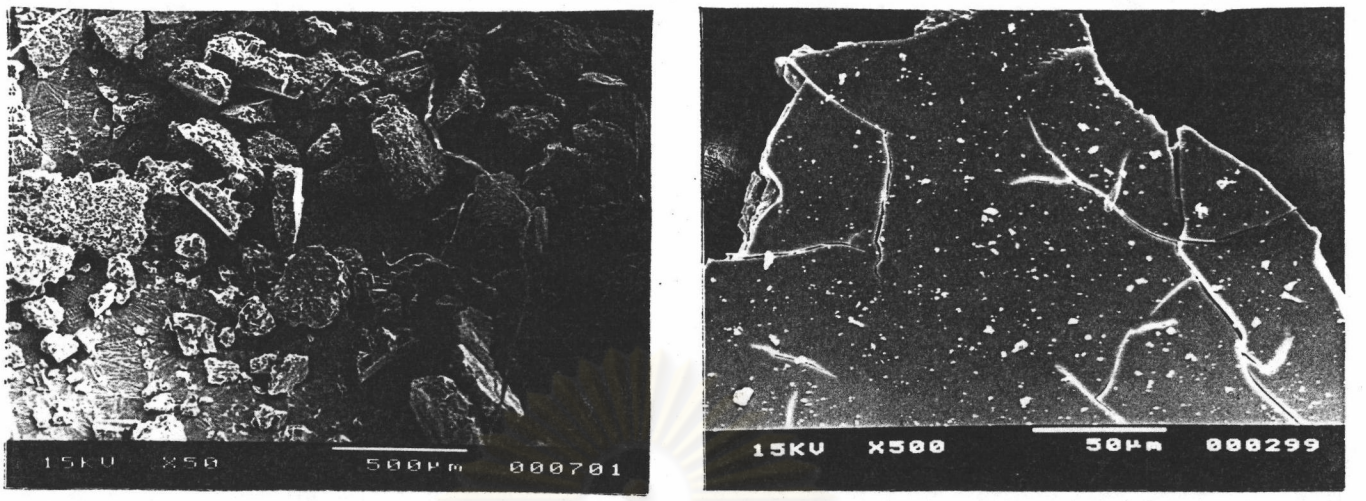


C



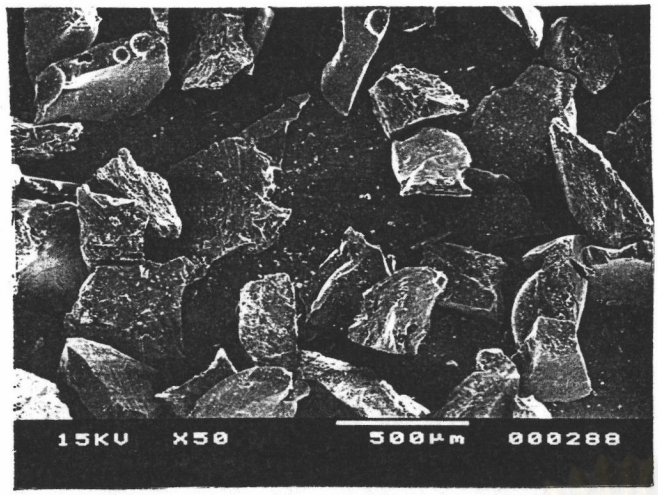
D

Figure 44 The photomicrographs of indomethacin-dimethyl-β-cyclodextrin (key : A and B are grounded mixture, AX500, BX1500; C and D are kneaded mixture, CX50, DX500).

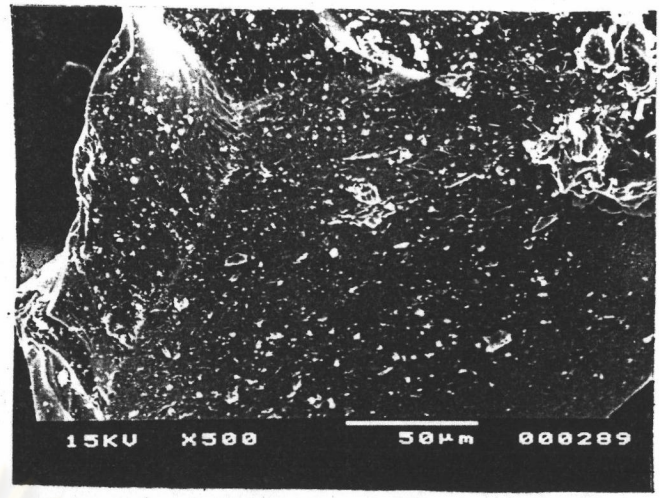


A B

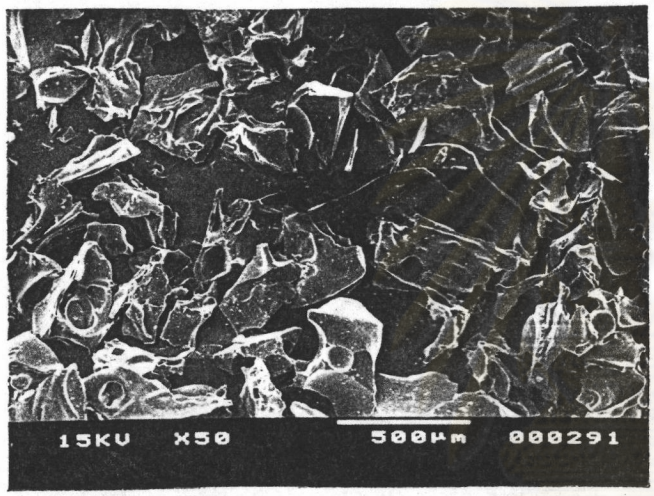
Figure 45 The photomicrographs of treated dimethyl-β-cyclodextrin (key : AX50, BX500).



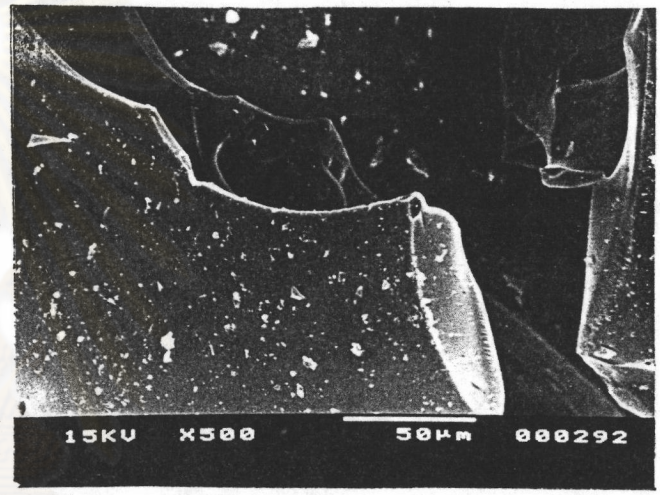
A



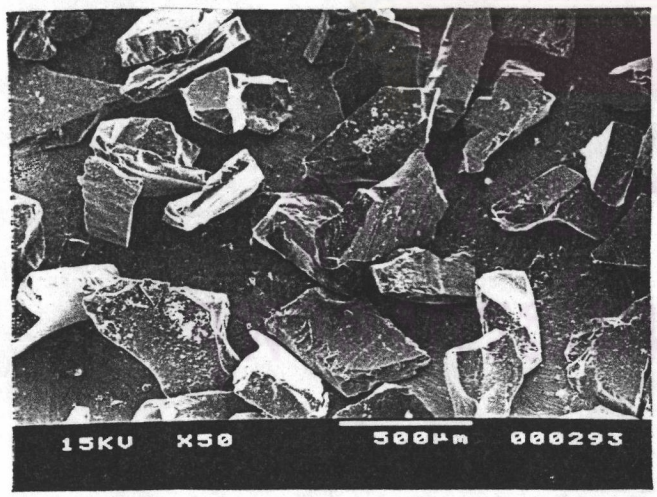
B



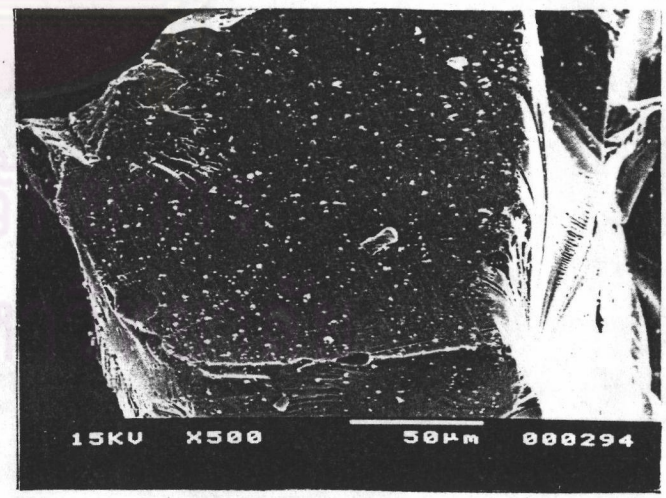
C



D



E



F

Figure 46 The photomicrographs of indomethacin-dimethyl-β-cyclodextrin coevaporates (key : A and B are ratio 1:1, AX50, BX500; C and D are ratio 1:2, CX50, DX500; E and F are ratio 1:3, EX50, FX500).

treated DIMEB but the size was relatively bigger than treated DIMEB. There was observed that the ratio of 1:1 drug : DIMEB coevaporation was composed of fine small needle on the surface while there was not seen in the ratio of 1:2 and 1:3 coevaporate particles.

2. Infrared spectra

The IR spectra of pure indomethacin, treated drug, cyclodextrins, grounded mixture, kneadeded mixture and solvent mixture are presented in Figures 47 - 52 .

The IR spectra of pure drug and treated drug is shown in Figure 47 . The IR spectra of pure drug showed the major peaks at 1692 and 1716 cm^{-1}, indicated C-O stretching of ketone group and of carboxylic group from IDM molecule, respectively (Borka, 1974; Brien, McCauley and Cohen, 1984). The peak at 1593 cm^{-1} referred to C=C stretching of aromatic ring and broad peak at 3300-3600 cm^{-1}, resulted from O-H stretching. After treated with absolute ethanol, treated drug showed peaks at 1650, 1692 and 1753 cm^{-1}(Borka, 1974; Somlak, 1991).

The absorption band characteristic of indomethacin was probably unaffected in grounded mixture systems and kneaded mixture systems of α-, β-, δ-CD and DIMEB. And IR spectra showed the combination peaks of IDM and cyclodextrins, further investigation need to be done. In solvent deposition, spectra of α-, β- and δ-CD were similar as treated drug as indicate by the position of the

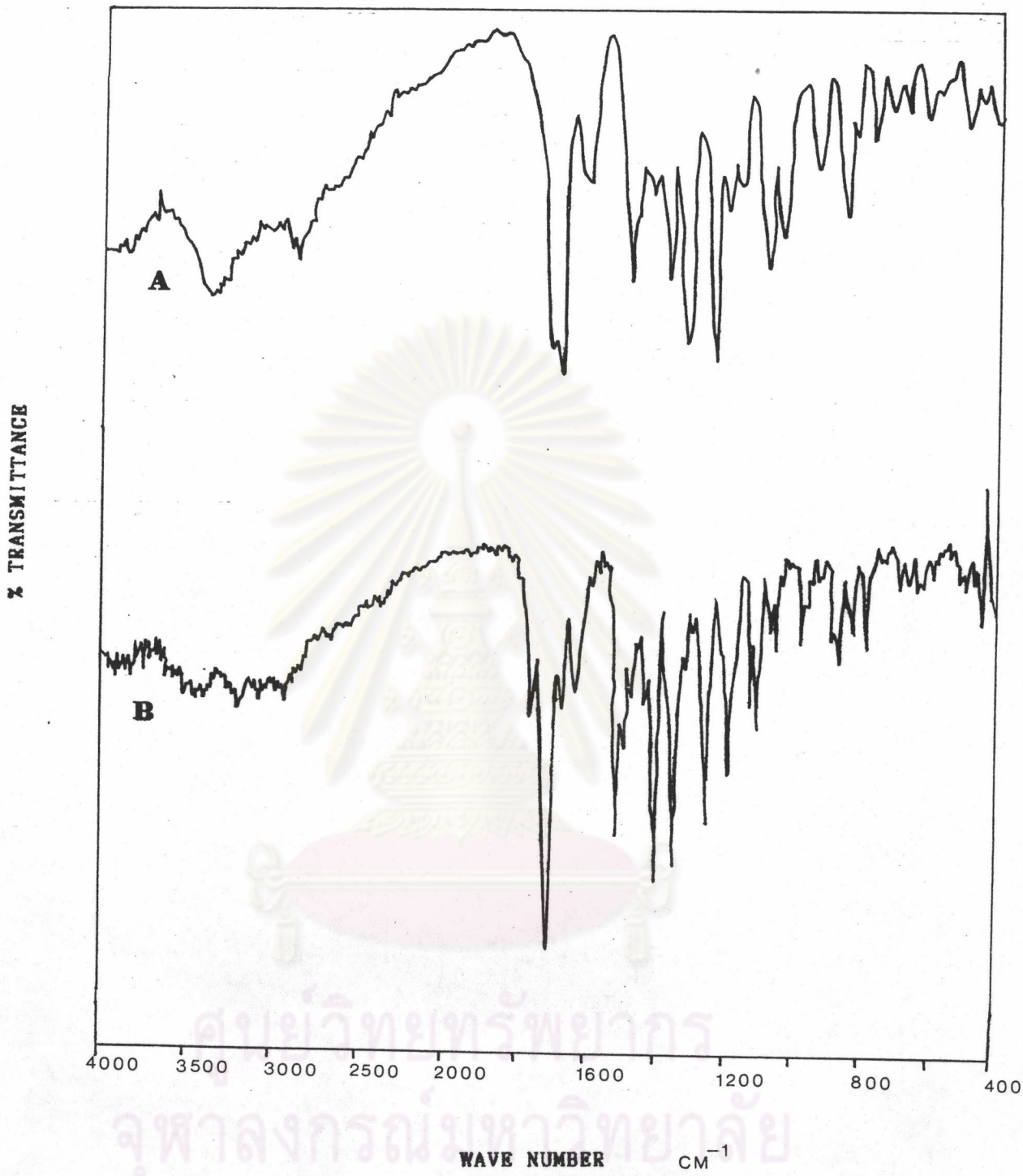


Figure 47 IR spectra of (A) IDM; (B) TD.

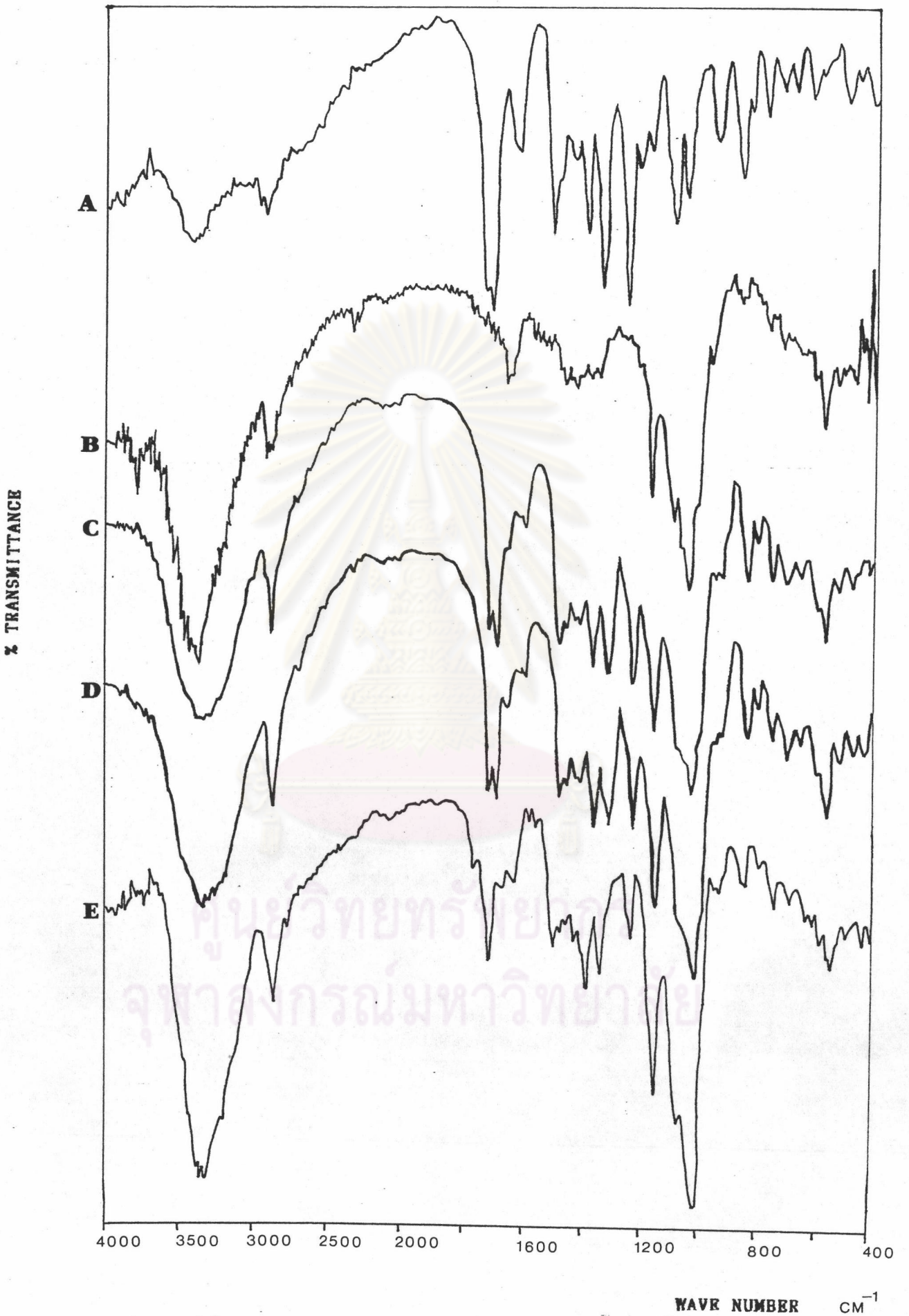


Figure 48 IR spectra of (A) IDM; (B) α-CD and (C),(D),(E) are IDM-α-CD dispersed systems; (C) GM 1:3; (D) KM 1:3; (E)

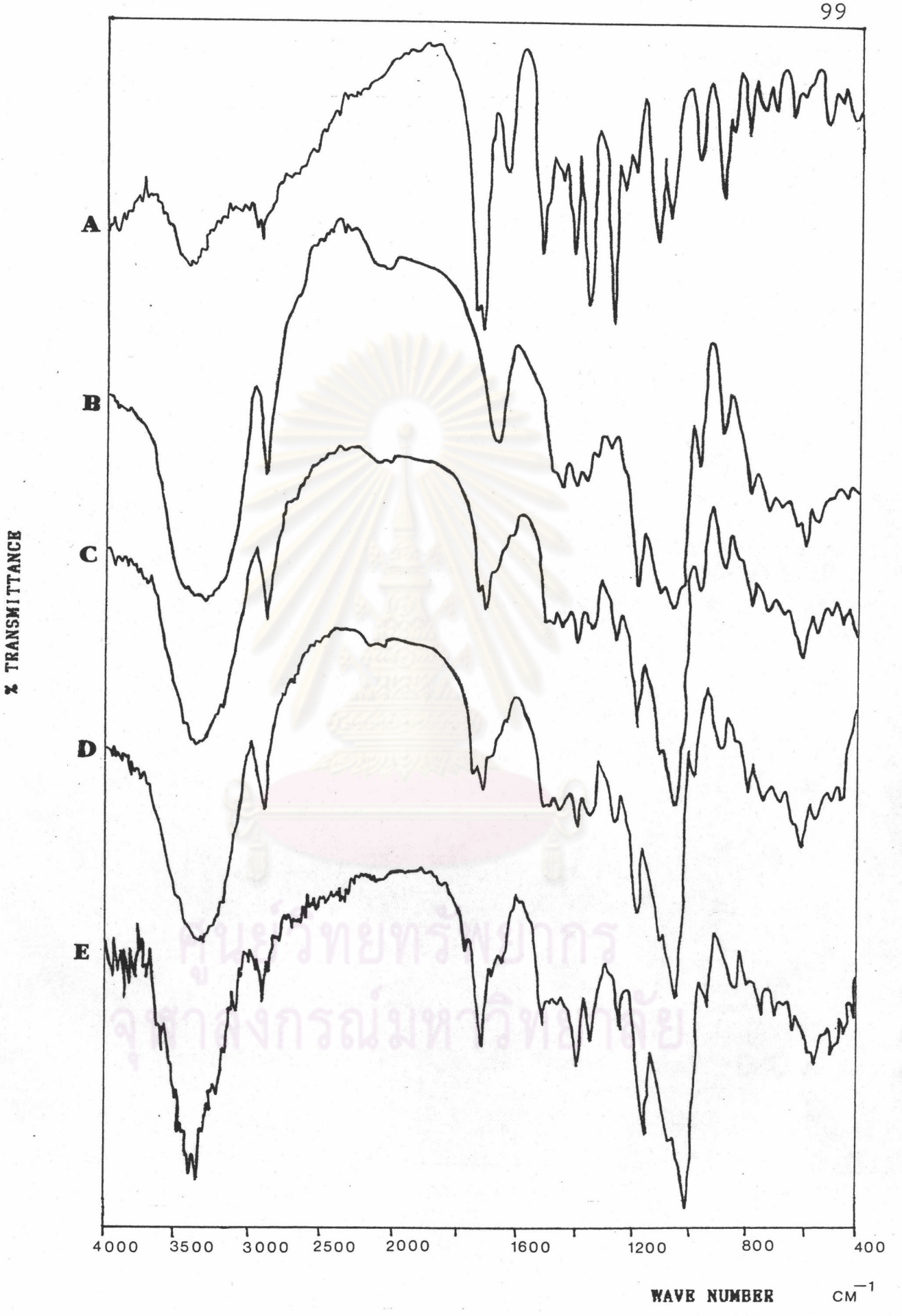


Figure 49 IR spectra of (A) IDM; (B) β-CD and (C),(D),(E) are IDM-β-CD dispersed systems; (C) GM 1:10; (D) KM 1:10; (E) SM 1:2

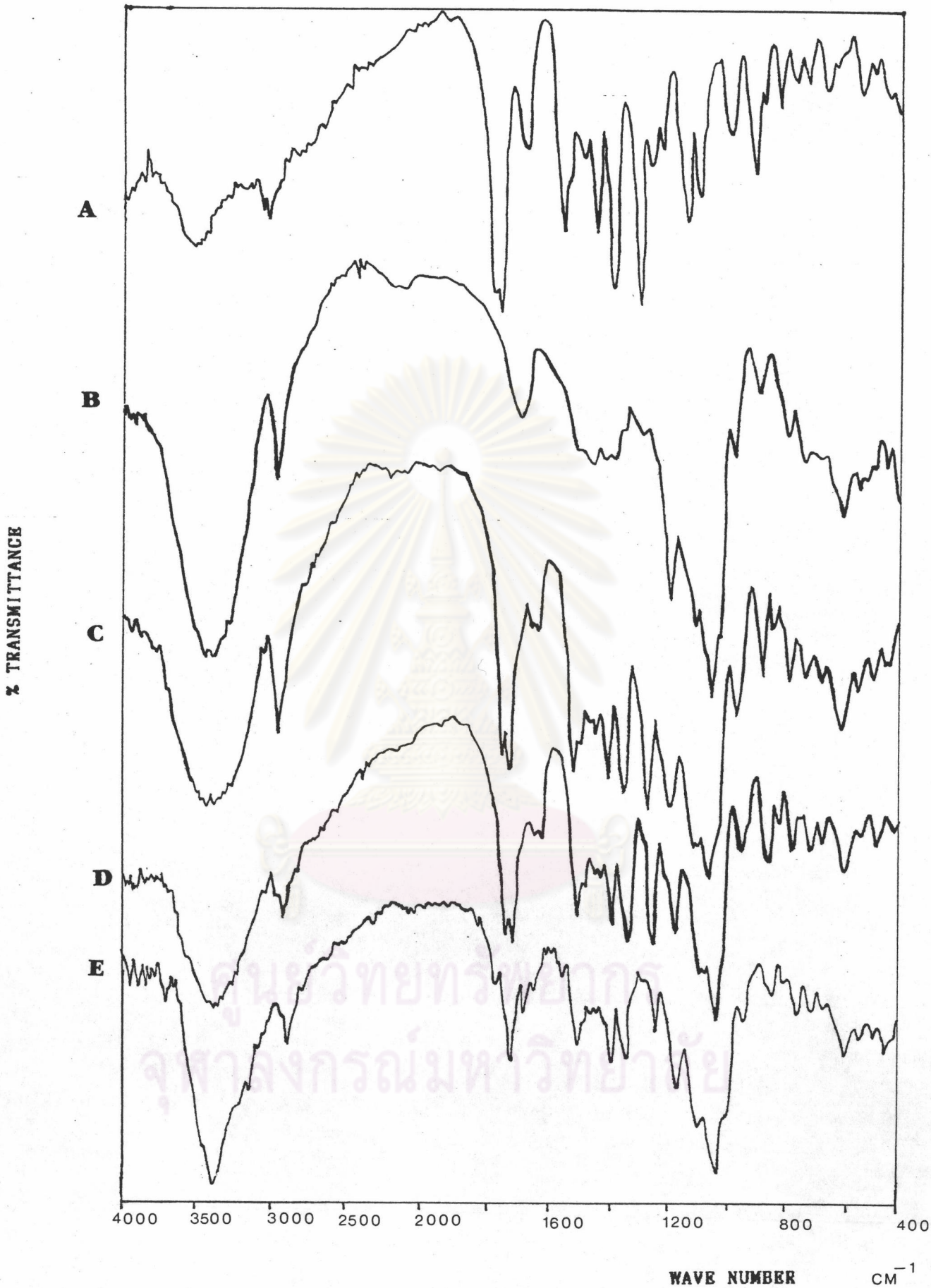


Figure 50 IR spectra of (A) IDM; (B) δ-CD and (C),(D),(E) are IDM-δ-CD dispersed systems; (C) GM 1:3; (D) KM 1:3; (E) SM 1:3.

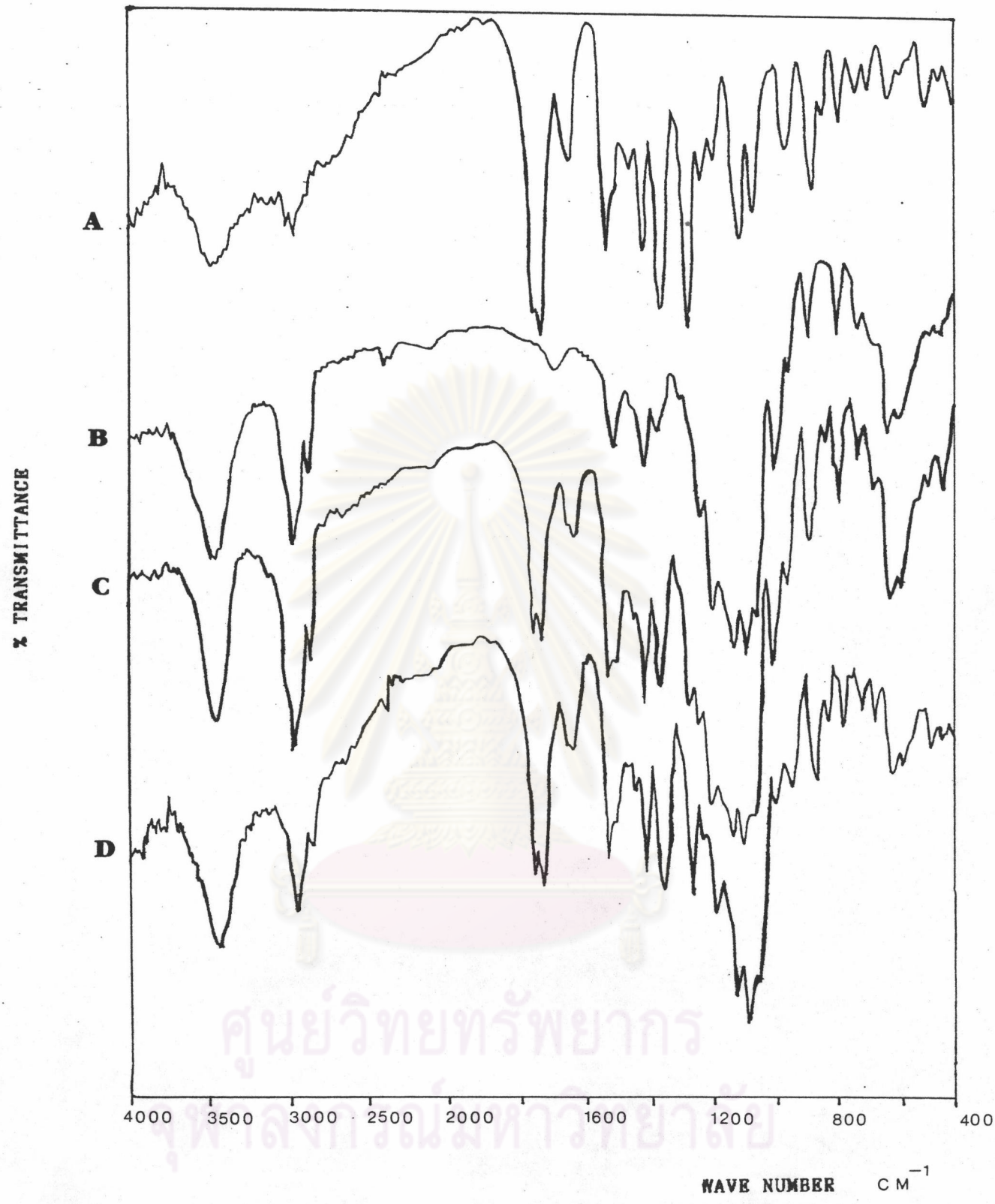


Figure 51 IR spectra of (A) IDM; (B) DIMEB and (C),(D) are IDM-DIMEB dispersed systems; (C) GM 1:3; (D) KM 1:3.

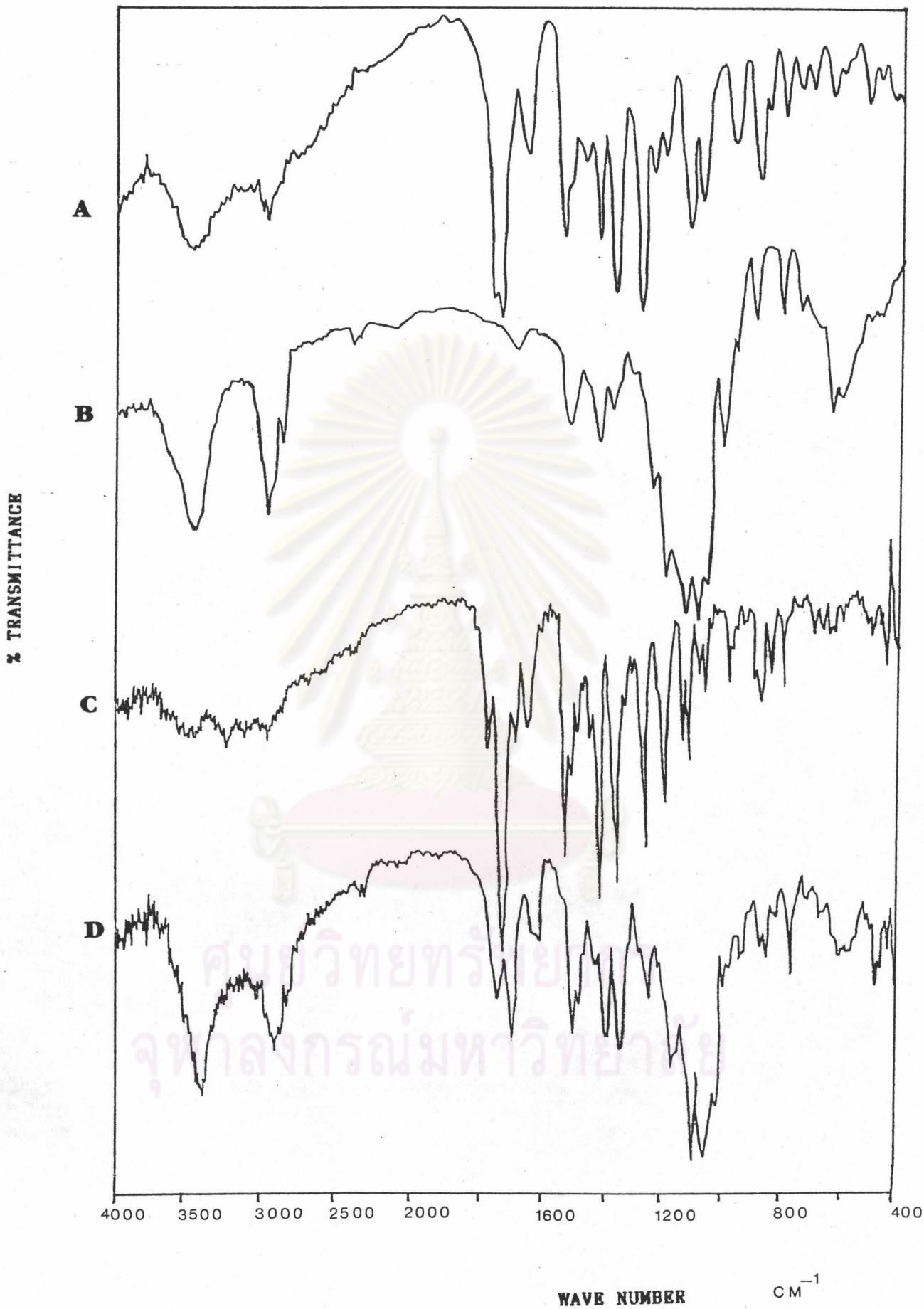


Figure 52 IR spectra of (A) IDM; (B) DIMEB; (C) treated IDM and (D),(E),(F) are IDM-DIMEB dispersed systems; (D) coevaporated 1:1; (E) coevaporated 1:2; (F) coevaporated

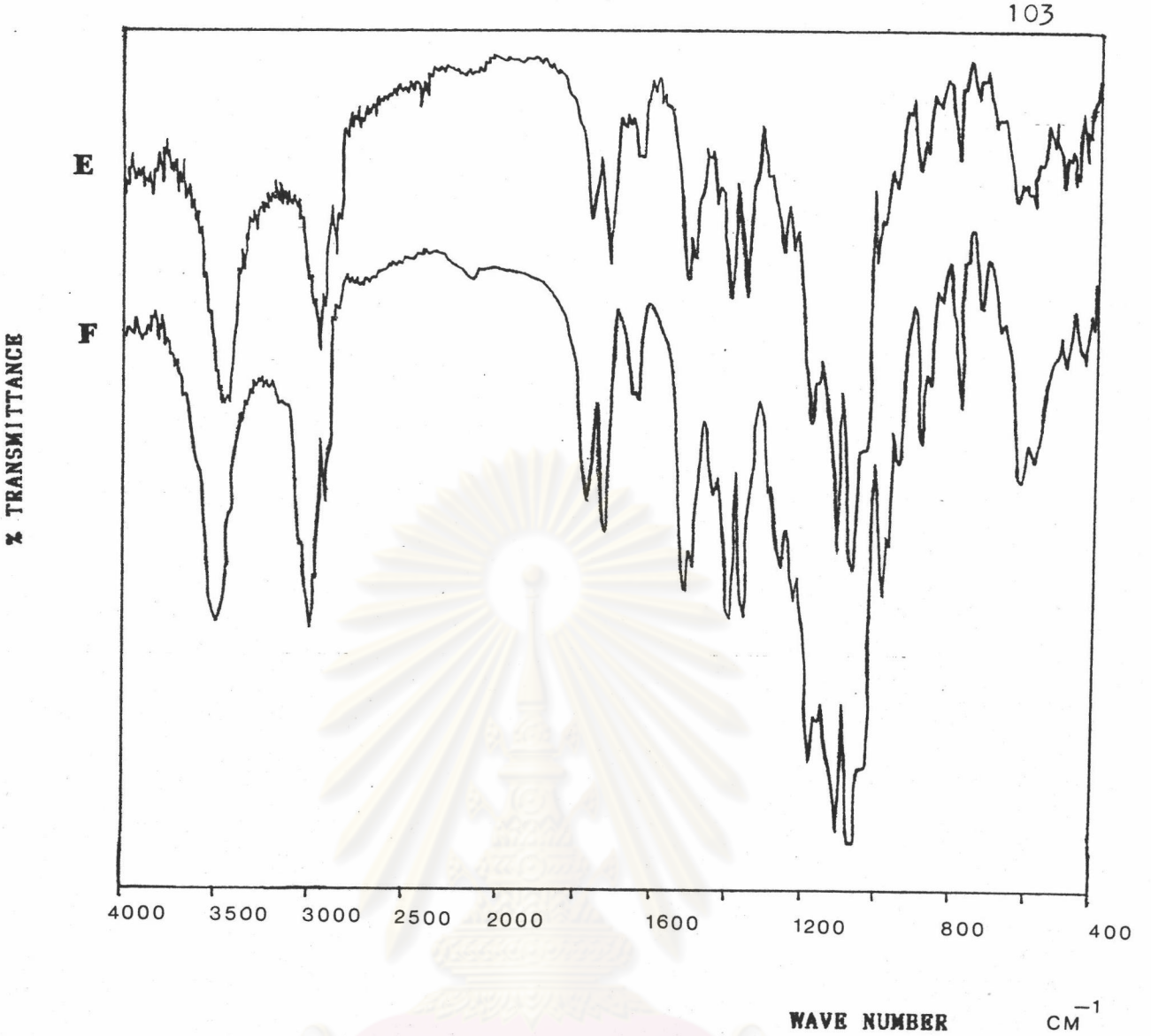


Figure 52 (cont.) IR spectra of (A) IDM; (B) DIMEB; (C) treated IDM and (D),(E),(F) are IDM-DIMEB dispersed systems; (D) coevaporated 1:1; (E) coevaporated 1:2; (F) coevaporated 1:3.

peaks at 1650, 1692 and 1735 cm^{-1}. While the coevaporation spectra of DIMEB showed a shift of the major peaks of indomethacin from 1692 cm^{-1} to 1687, 1686, 1687 cm^{-1} and from 1718 cm^{-1} to 1732, 1736, 1735 cm^{-1} in 1:1, 1:2, 1:3 indomethacin : DIMEB, respectively.

3. DTA thermograms

Thermograms of pure drug, grounded drug, kneaded drug, treated drug, cyclodextrins, grounded mixtures, kneaded mixtures and solvent mixtures are presented in Figures 53 - 59 . The thermogram of pure drug gave the characteristic melting endotherm at 160 °C. Grounded drug and Kneaded drug showed the same melting endotherm at 158 °C while treated drug gave melting endotherm at 153 °and broad endotherm at 310 °C.

3.1 α-CD systems

The α-CD displayed two broad melting endotherm at 57 °and 88 ° C and small endothermic peak at 138 °C. The thermogram of grounded mixture showed three endothermic peaks at 60 °, 87 ° and 160 ° C with small exothermic peak at 203 °C. For kneaded mixtures, there was a little shift of IDM endothermic peak from 160 ° to 159°, 157 °, 158 °C in 1:1, 1:2, 1:3 indomethacin : α-CD, respectively. Moreover, there were three endothermic peaks similar as α-CD at 50°- 60 °, 78°- 88°C and 137°- 138°C with including small exothermic peak at 200°- 206°C. The peak at 137 °- 138 °C increased as the amount of α-CD increased (Figure 54).

3.2 β-CD systems

The thermogram of β-CD systems are presented in Figures 55 - 56. β-CD showed broad endothermic around 92°C and no characteristic peak between 100°- 200°C. In grounded mixtures and kneaded mixtures combined the features of the thermograms of each component. But indomethacin showed only a small endotherm and a little shift from 160° to 157°C with increasing the amount of β-CD. And there was small endothermic peak at 215°- 217°C with increased intensity when increased the quantity of β-CD in both systems.

3.3 δ-CD systems

δ-CD had no endothermic peak around 100°- 300°C, there was only broad endotherm at 78°C. There were a combination of IDM and δ-CD thermograms in grounded mixtures and kneaded mixtures. They showed nearly the same endothermic point as IDM at 159°, 160°, 159°, 156°C in 1:3 grounded mixture, 1:1, 1:2, 1:3 kneaded mixtures, respectively (Figure 57).

In solvent deposition of α-CD and δ-CD obtained the similar thermogram. There was two endothermic peaks, the first was broad peak at 80° and 62°C for α-CD and δ-CD. The second was the sharp peak at 150°C. For β-CD solvent deposition, there were three endothermic peaks, broad peak at 68°C, sharp peak at 147°C and small endothermic peak at 214°C (Figure 58).

3.4 DIMEB systems

Thermograms of the DIMEB systems are exhibited in Figure 59 . There was not founded the characteristic peak of DIMEB during scanning range of temperature of the DTA studied.For grounded mixtures and kneaded mixtures, there were a shift of endothermic peak from 160 °to 148°, 147°, 149°, 148°, 148°, 150°C in 1:1, 1:2, 1:3 indomethacin : DIMEB grounded mixtures and 1:1, 1:2, 1:3 kneaded mixtures, respectively. In 1:1 drug : DIMEB coevaporation showed the small endothermic peak at 143°C but did not show the melting endotherm of indomethacin in 1:2 and 1:3 coevaporation.

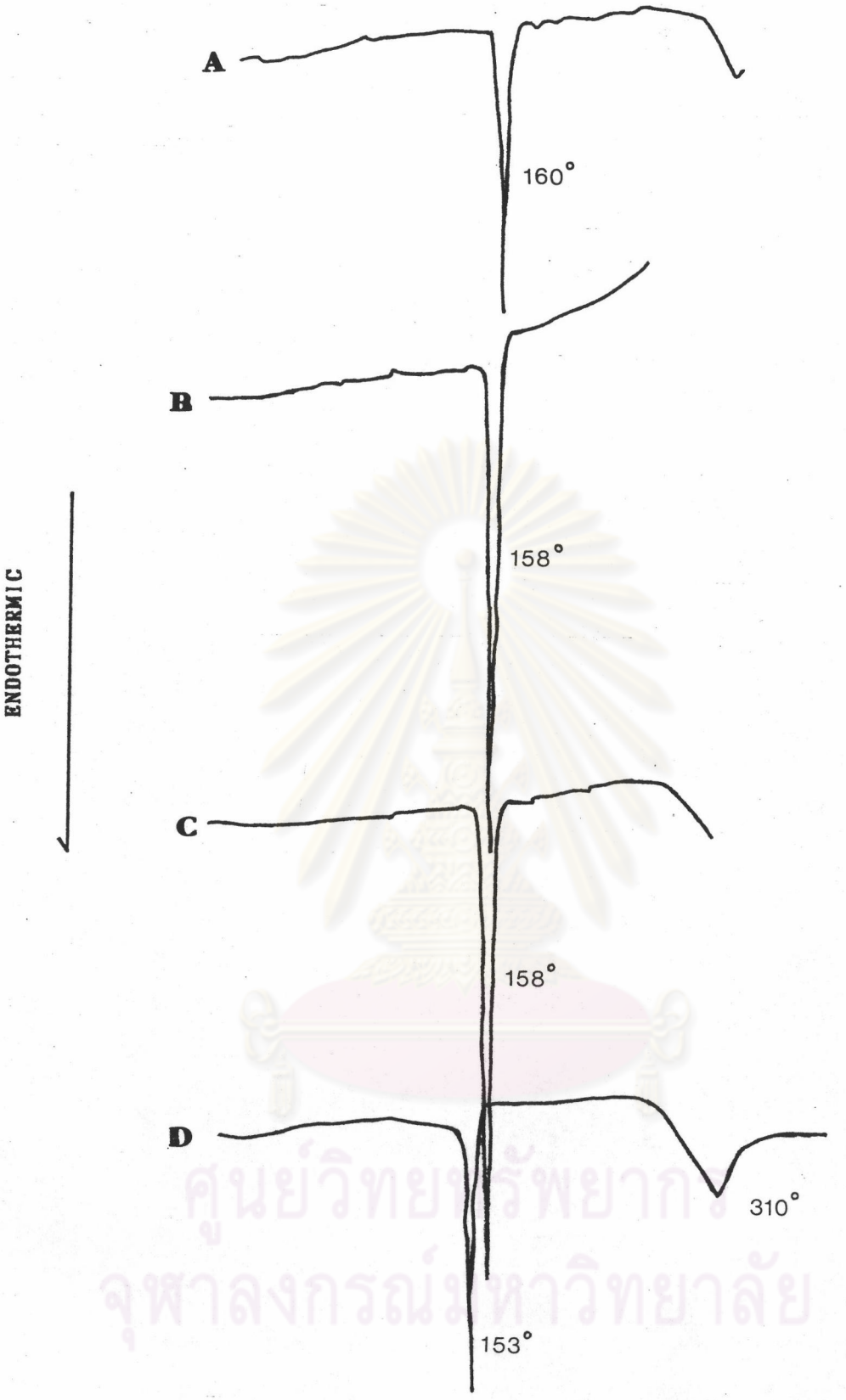


Figure 53 DTA thermograms of (A) IDM; (B) GD; (C) KD; (D) TD.

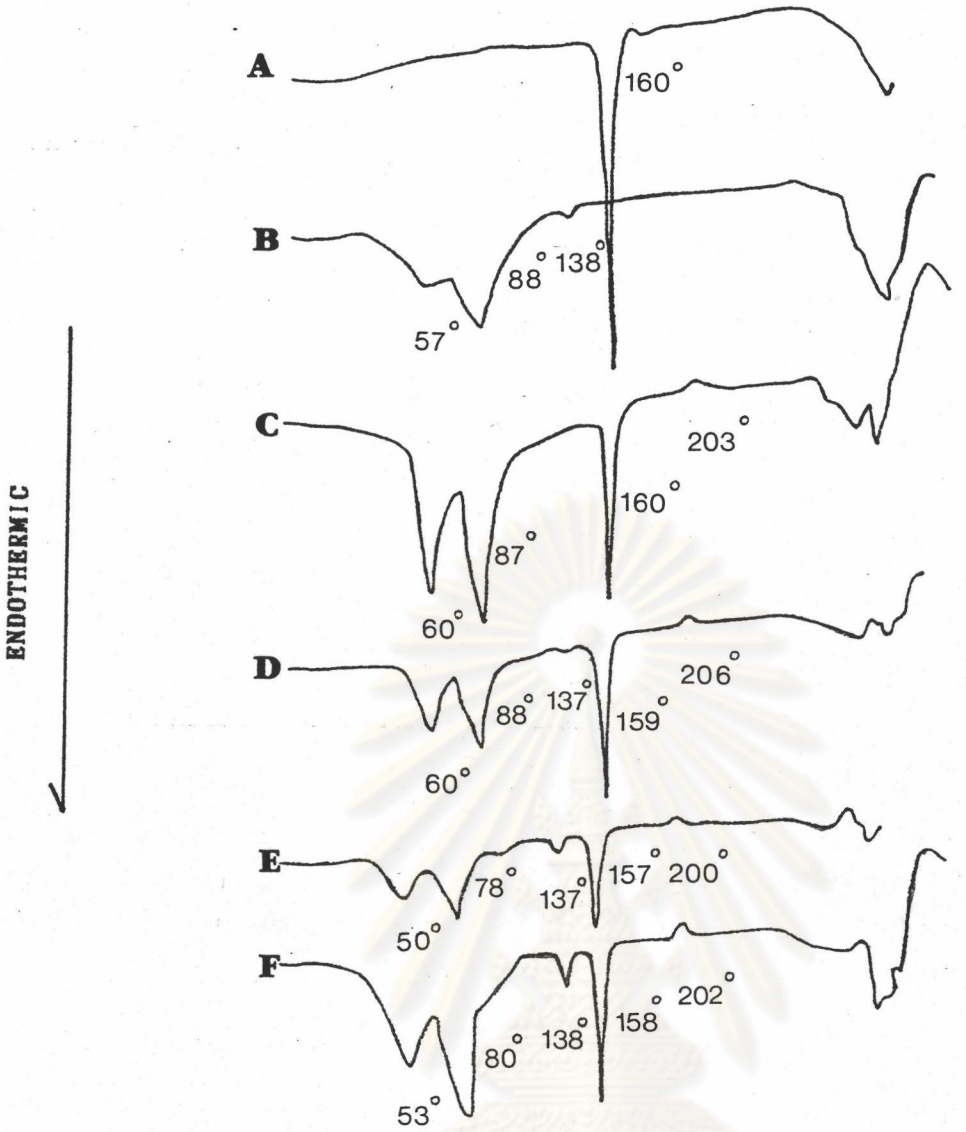


Figure 54 DTA thermograms of (A) IDM; (B) α-CD and (C),(D), (E),(F) are IDM-α-CD dispersed systems; (C) GM 1:3;(D) KM 1:1; (E) KM 1:2; (F) KM 1:3.

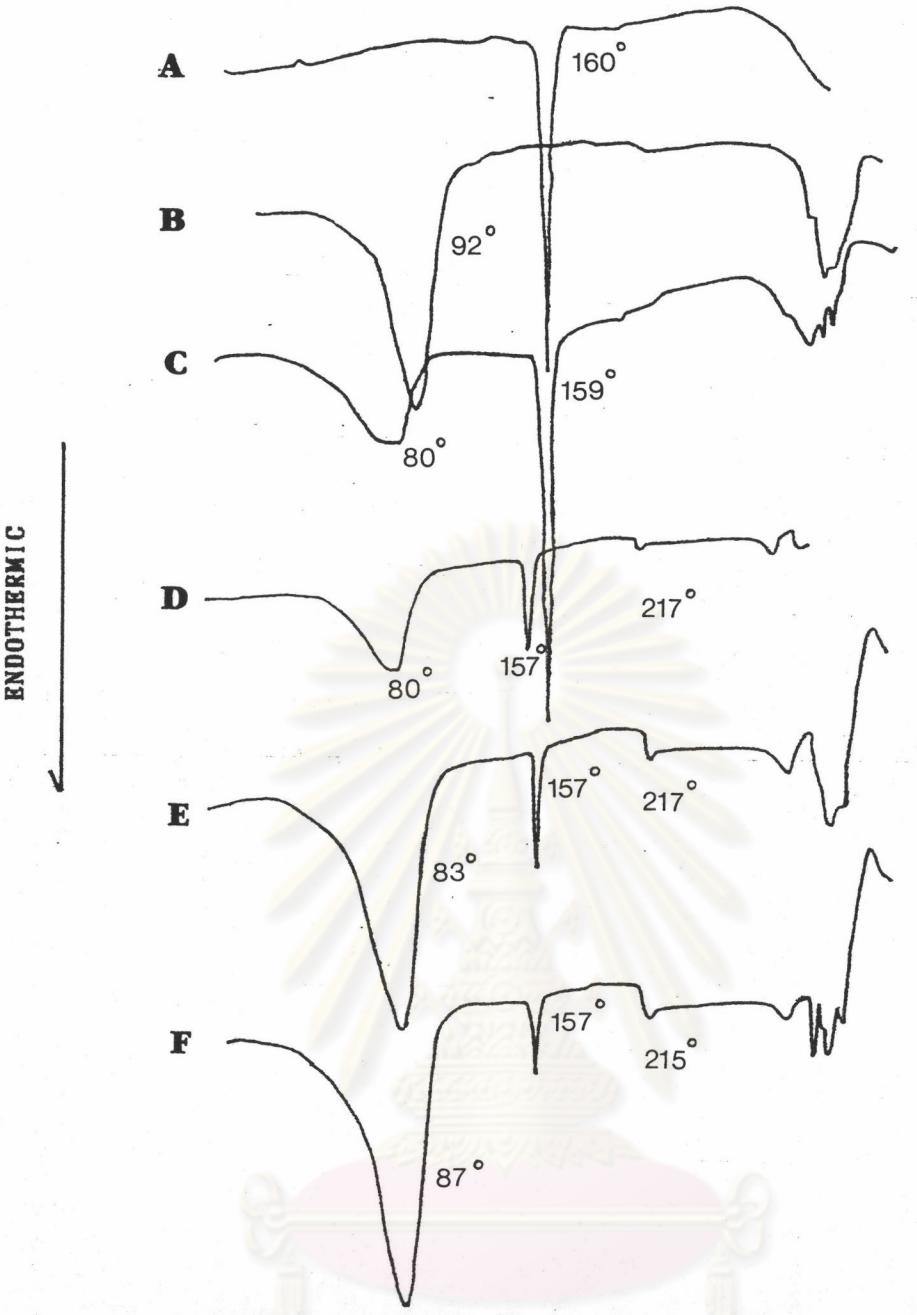


Figure 55 DTA thermograms of (A) IDM; (B) β-CD and (C),(D), (E),(F) are IDM-β-CD dispersed systems; (C) GM 1:0.5; (D) GM 1:3; (E) GM 1:6; (F) GM 1:10.

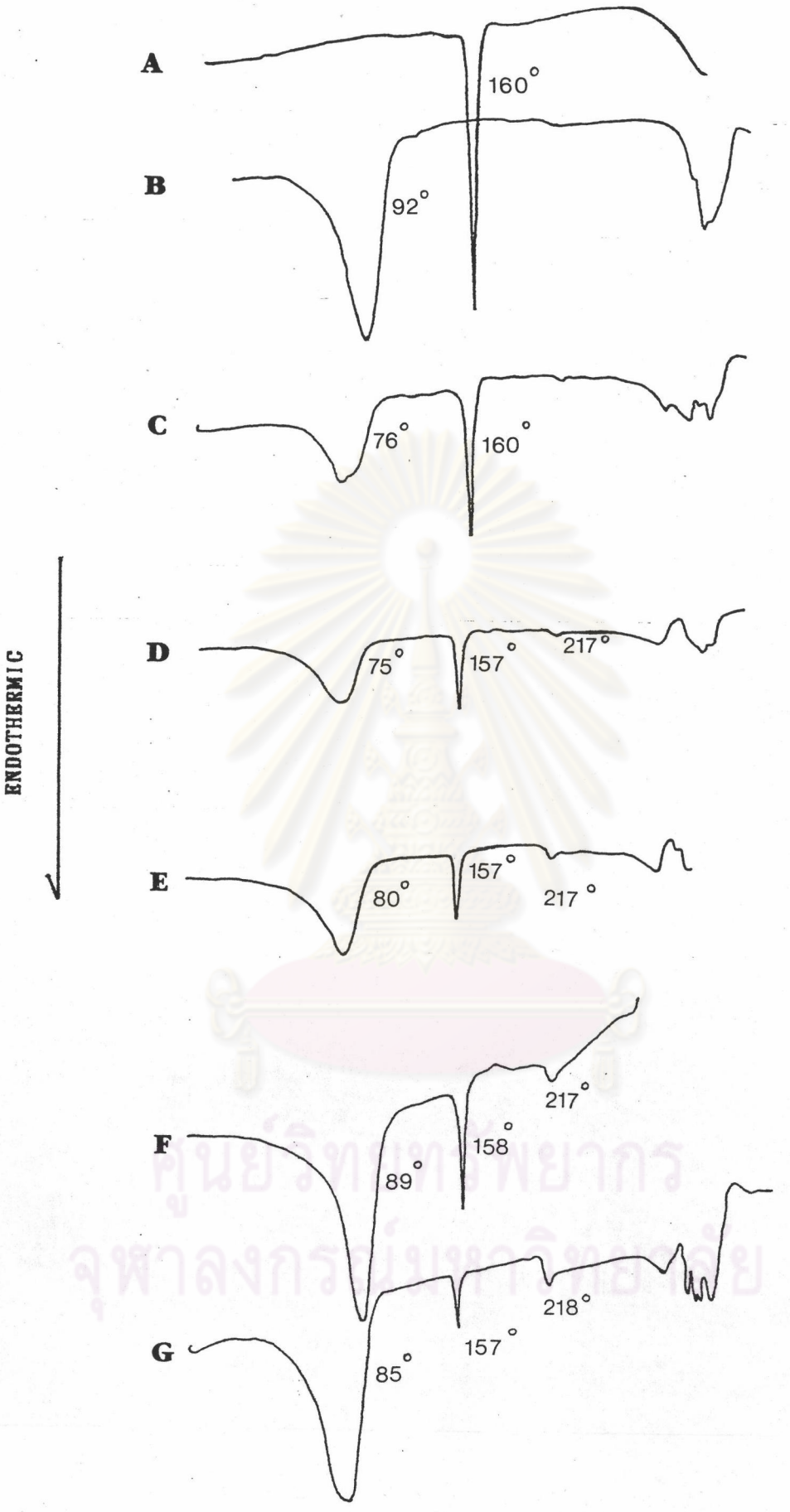


Figure 56 DTA thermograms of (A) IDM; (B) β-CD and (C),(D), (E),(F),(G) are IDM-β-CD dispersed systems; (C) KM 1:1; (D) KM 1:2; (E) KM 1:3; (F) KM 1:6; (G) KM 1:10.

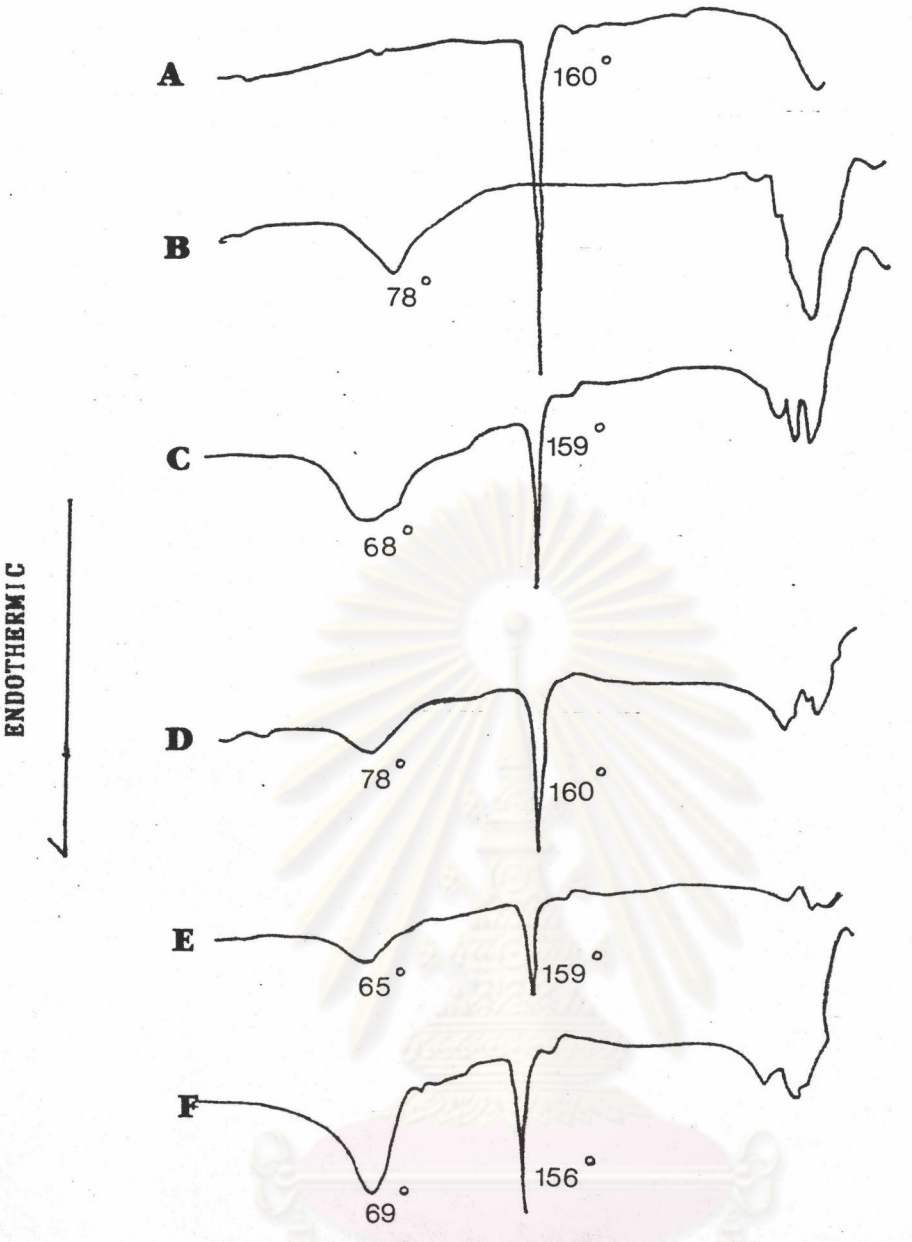


Figure 57 DTA thermograms of (A) IDM; (B) ŏ-CD and (C),(D), (E),(F) are IDM-ŏ-CD dispersed systems; (C) GM 1:3; (D) KM 1:1; (E) KM 1:2; (F) KM 1:3.

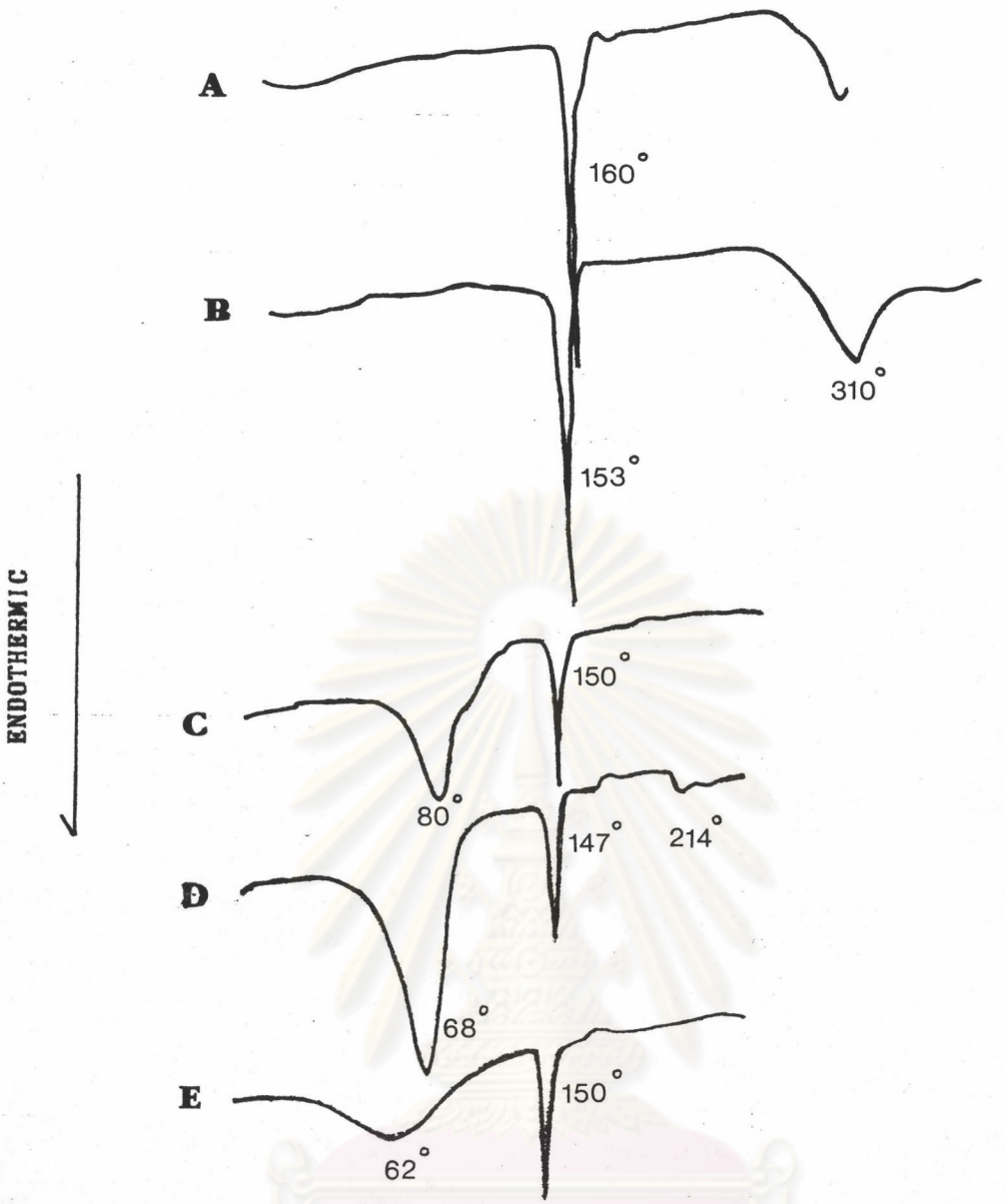


Figure 58 DTA thermograms of (A) IDM; (B) TD; (C) SM 1:3 IDM : α-CD; (D) SM 1:3 IDM : β-CD; (E) SM 1:3 IDM : δ-CD.

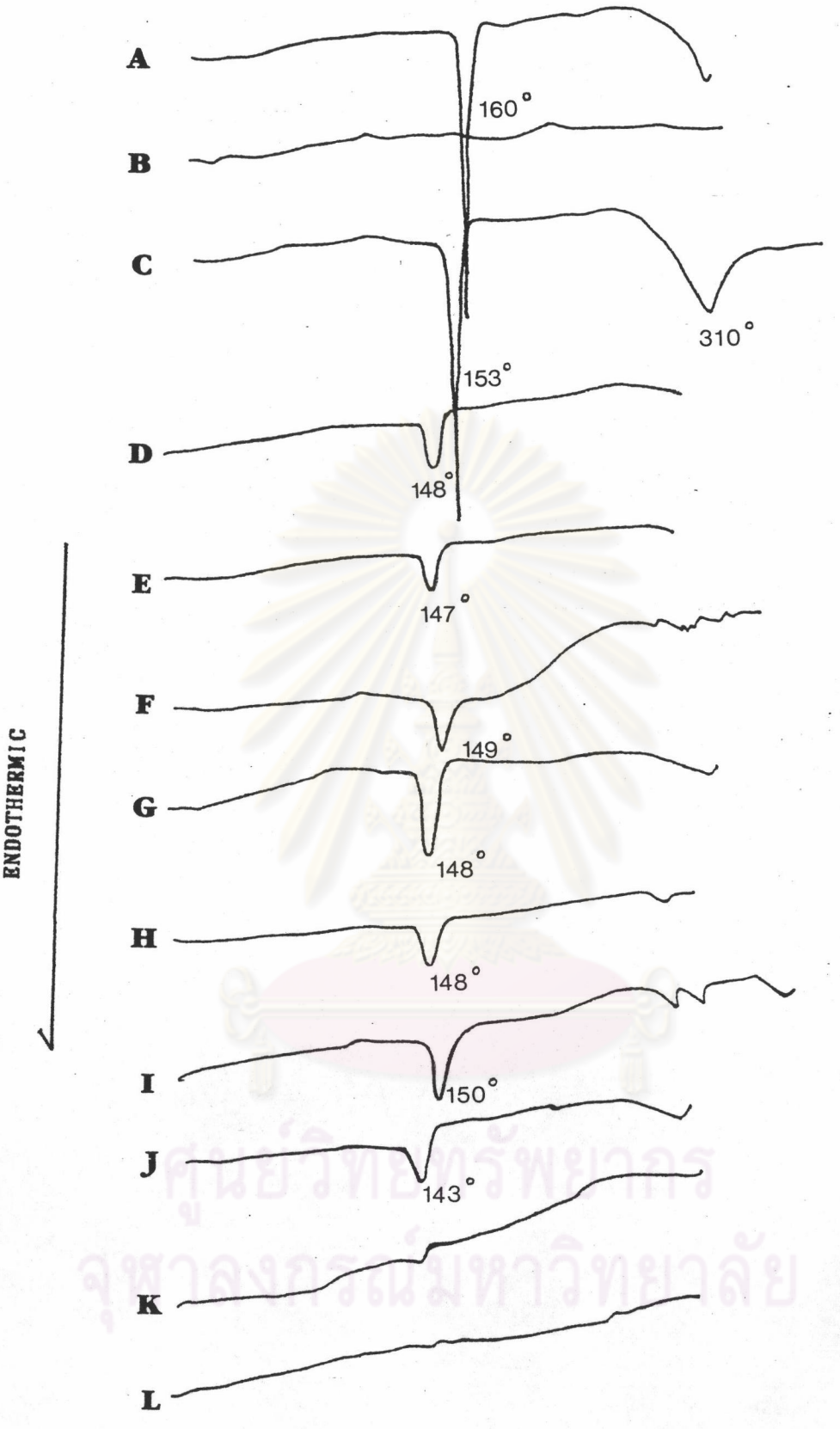


Figure 59 DTA thermograms of (A)IDM; (B)DIMEB; (C)treated IDM and (D),(E),(F),(G),(H),(I),(J),(K),(L) are IDM : DIMEB dispersed systems; (D)GM 1:1; (E)GM 1:2; (F) GM 1:3; (G) KM 1:1; (H)KM 1:2; (I)KM 1:3; (J)coevaporated 1:1; (K) coevaporated 1:2; (L) coevaporated 1:3.

Table 13 The summary of melting point peaks of IDM and IDM prepared from different methods with various type of cyclodextrins.

sample	melting point peak (degree celcius)				
IDM	–	–	–	160	–
GD	–	–	–	158	–
KD	–	–	–	158	–
TD	–	–	–	153	B 310
α-CD	B 57	B 88	S 138	-	-
α-CD GM 1:3	60	87	-	160	-
α-CD KM 1:1	B 60	B 88	S 137	159	E 206
α-CD KM 1:2	B 50	B 78	S 137	157	E 200
α-CD KM 1:3	B 53	B 80	138	158	E 202
α-CD SM 1:3	-	B 80	-	150	-
β-CD	-	B 92	-	-	-
β-CD GM 1:0.5	-	B 80	-	159	-
β-CD GM 1:3	-	B 80	-	157	S 217
β-CD GM 1:6	-	B 83	-	157	S 217
β-CD GM 1:10	-	B 87	-	157	S 217
β-CD KM 1:1	-	B 76	-	160	-
β-CD KM 1:2	-	B 75	-	157	S 217
β-CD KM 1:3	-	B 80	-	157	S 217
β-CD KM 1:6	-	B 89	-	158	S 218
β-CD KM 1:10	-	B 85	-	157	S 218
β-CD SM 1:3	-	B 68	-	147	S 21

Table13 (cont.) The summary of melting point peaks of IDM and IDM prepared from different methods with various type of cyclodextrins.

sample	melting point peak (degree celcius)				
ð-CD	-	B 78	-	-	-
ð-CD GM 1:3	-	B 68	-	159	-
ð-CD KM 1:1	-	B 78	-	160	-
ð-CD KM 1:2	-	B 65	-	159	-
ð-CD KM 1:3	-	B 69	-	156	-
ð-CD SM 1:3	-	B 62	-	150	-
DIMEB	-	-	-	-	-
DIMEB GM 1:1	-	-	-	148	-
DIMEB GM 1:2	-	-	-	147	-
DIMEB GM 1:3	-	-	-	149	-
DIMEB KM 1:1	-	-	-	148	-
DIMEB KM 1:2	-	-	-	148	-
DIMEB KM 1:3	-	-	-	150	-
DIMEB SM 1:1	-	-	-	143	-
DIMEB SM 1:2	-	-	-	-	-
DIMEB SM 1:3	-	-	-	-	-

NOTE : B : BOARD OF PEAK

E : EXOTHERMIC PEAK

S : SMALL PEAK

3.5 X-ray diffraction spectra

X-ray diffraction patterns for IDM and treated IDM are shown in Figure 60 . Major X-ray diffraction peaks particularly at 10.2°, 11.5°, 17.0°, 19.6°, 21.8°, 25.6° and 29.3° are presented in pure indomethacin while the major peaks of treated drug showed at 6.9°, 8.4°, 10.2°, 11.8°, 14.2°, 14.4°, 17.5°, 18.0°, 18.4°, 19.7°, 20.6°, 22.0°, 22.6°, 23.3°, 24.6° and 28.4°, respectively.

X-ray diffractograms of DIMEB, 1:3 indomethacin : DIMEB grounded mixture, kneaded mixture and coevaporation are presented in Figures 62–63 . For DIMEB diffraction peaks showed at 8.5°, 10.2°, 12.2°, 17.0°, 19.0° and 21.3°. In the case of grounded and kneaded mixture systems, the diffraction patterns were nearly the same as DIMEB but the intensity was higher and showed the changing of diffraction peaks at 5.4°, 6.9°, 7.8°, 8.6°, 11°, 11.5°, 16.9° and 20.8°; moreover the diffraction peak of grounded mixture obtained more intensity than that of kneaded mixture. In the case of coevaporation at the ratio 1:1, the X-ray diffraction spectrum also exhibited the diffraction peaks of IDM while in the ratio 1:2 and 1:3 coevaporated showed the halo pattern.

3.6 Solubility studied

The solubility of IDM in four cyclodextrin solutions at various concentrations are presented in Table 14 and Figure 64 . It was observed that the concentration of drug dissolved reached the equilibrium level after shaking for 24 hours. The solubility of IDM

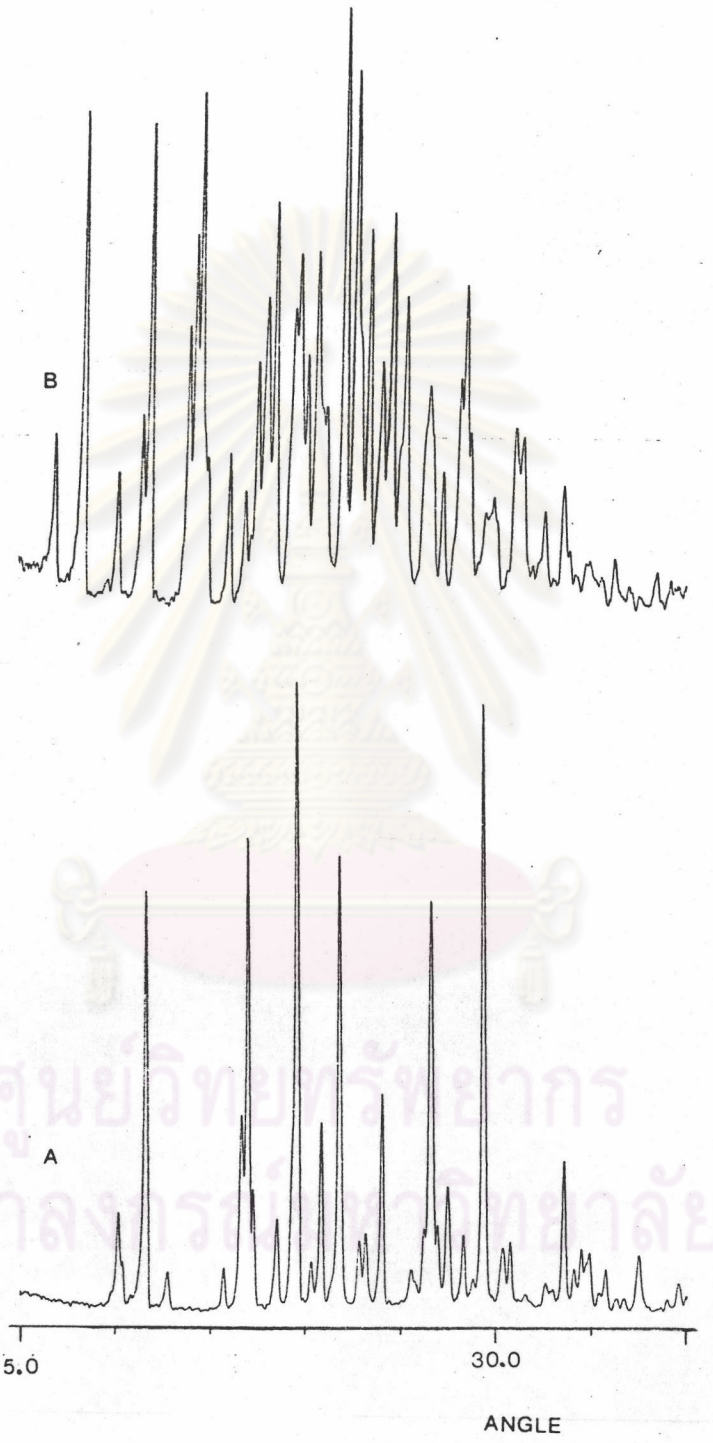


Figure 60 X-ray diffractograms of (A) IDM; (B) treated IDM.

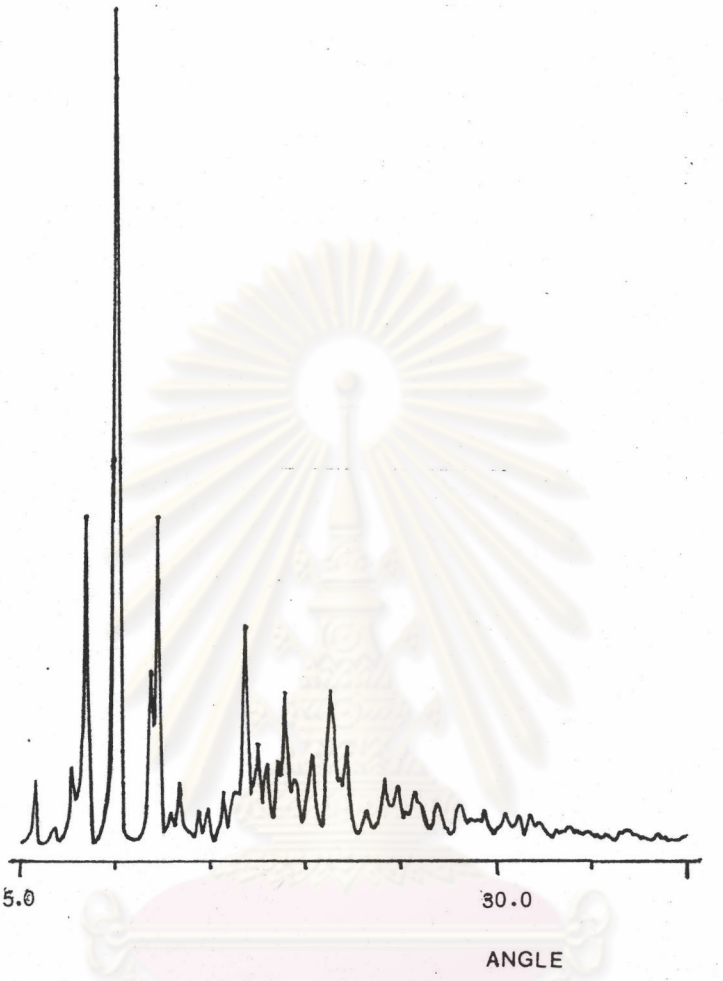


Figure 61 X-ray diffractogram of DIMEB.

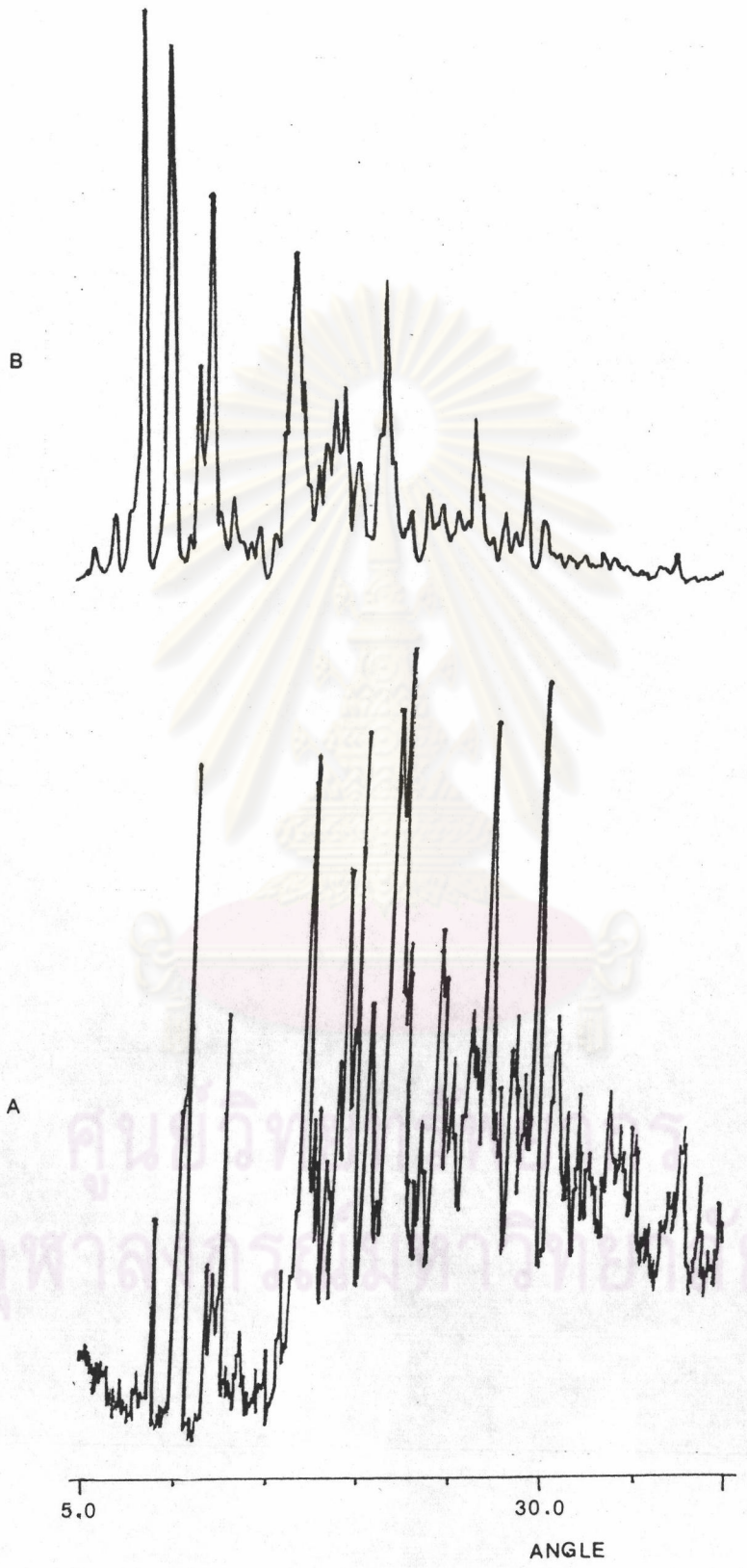


Figure 62 X-ray diffractograms of (A) GMDM 1:3 ;
(B) KMDM 1:3.

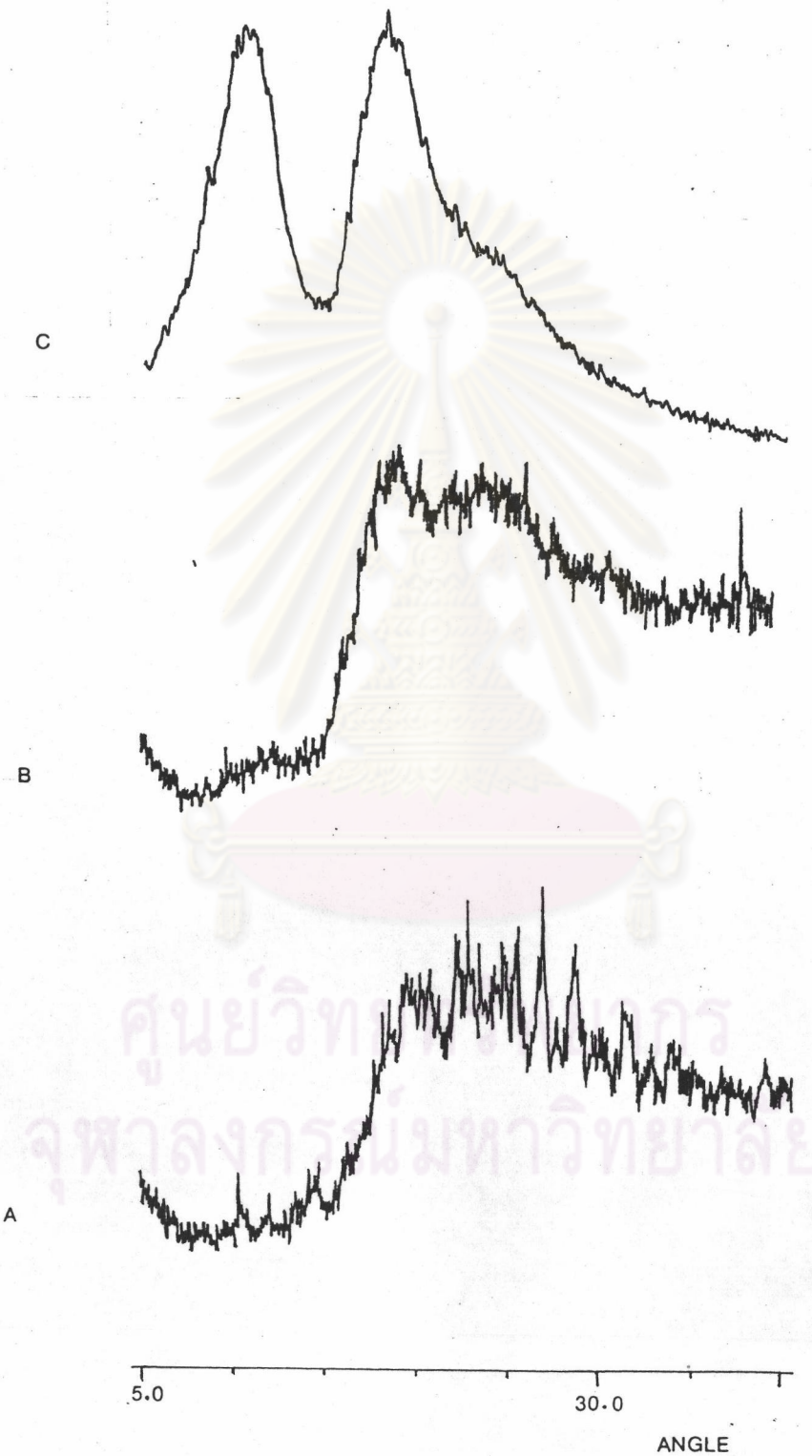


Figure 63 X-ray diffractograms of (A) CODM 1:1; (B) CODM 1:2 ; (C) CODM 1:3.

Table 14 Effect of cyclodextrins at various concentrations on solubility of indomethacin in the mixture of phosphate buffer solution of pH 7.2 : deionized water (1:4) at 37°C.

cyclodextrins	Conc. of CDS (x 10^{-3}, M)	Amount of IDM dissolved (mg/100 ml)
alpha-CD	0	97.26
	20	120.60
	40	147.36
	60	163.22
	80	170.20
	100	177.17
beta-CD	0	97.26
	4	111.97
	8	127.70
	12	142.52
	16	156.37
	20	160.43
gamma-CD	0	97.26
	20	115.78
	40	139.63
	60	143.94
	80	150.03
	100	154.09
DIMEB	0	97.26
	4	122.76
	8	148.89
	12	158.02
	16	165.76
	20	166.52

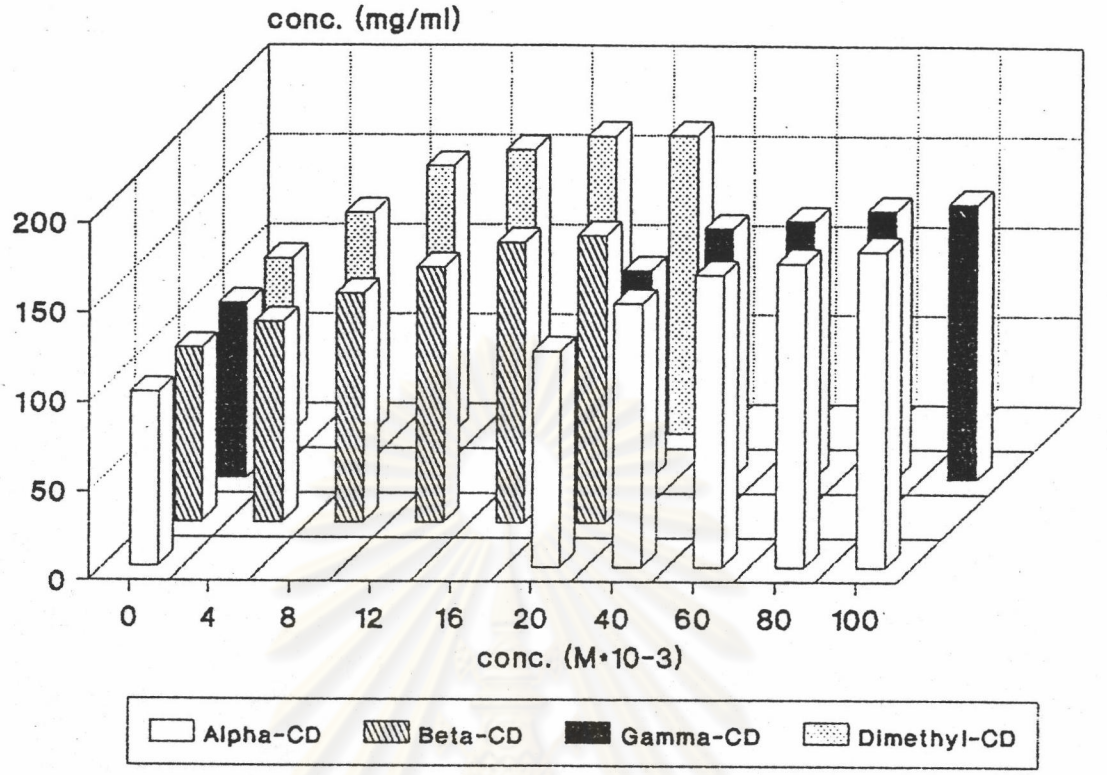


Figure 64 The solubility of indomethacin in the presence of α-,β-,δ-CD and dimethyl-β-cyclodextrins at various concentratious.

obviously increased with increasing the concentration of cyclodextrins. The experimental solubility of IDM was approximately 97.26 mg/100 ml. The equilibrium solubility of drug in 0.020 M of various type of cyclodextrins were ranked as follow : DIMEB > β-CD > α-CD > ϑ-CD. It should be noted that the solubility studies were performed in the mixture of pH 7.2 phosphate buffer : DIW (1:4), not in water, with the aim of being correspond to the dissolution study of indomethacin powders and capsules.

Capsule Evaluation

Seven capsule formulations of various methods of indomethacin preparation were manufactured and the physical properties such as weight variation, content uniformity and disintegration time are presented in Appendix 19 and found to meet the USP XXII requirement.

Dissolution profiles and data of seven indomethacin capsules are shown in Figures65 - 72 and Appendix 20, respectively. The dissolution profiles was ranked as follow : 1:2 coevaporation > 1:0.5 kneaded mixture > 1:0.5 grounded mixture > grounded drug > treated drug > pure drug > kneaded drug. There was the same dissolution profile of grounded mixture and kneaded mixture in the initial stage, but after 12 minutes kneaded mixture gave the higher dissolution profile than grounded mixture. And there was slightly different in dissolution profiles of pure drug and treated drug.

By comparing dissolution profiles between capsule and corresponding towder, it was found that the dissolution profile of capsule was lower than powder at the initial profile and gave higher dissolution rate than powder later in grounded drug,kneaded drug and treated drug except pure drug capsule and powder obtained nearly the same profile. For grounded mixture, kneaded mixture and coevaporation, the dissolution profile of powder gave higher dissolution profile than that of capsule.

The time required for 80 percent of seven indomethacin capsules to dissolve(T80%) are presented in Table and Figure . There was found that the T80% was less than 20 minutes and meet the requirement in grounded drug capsule, grounded mixture, kneaded mixture, solvent mixture of both capsule and powder. For pure drug, grounded drug, kneaded drug and treated drug capsules gave the lower T80% than that of corresponding powder while grounded mixture, kneaded mixture and solvent mixture capsules obtained T80% higher than that of powder.

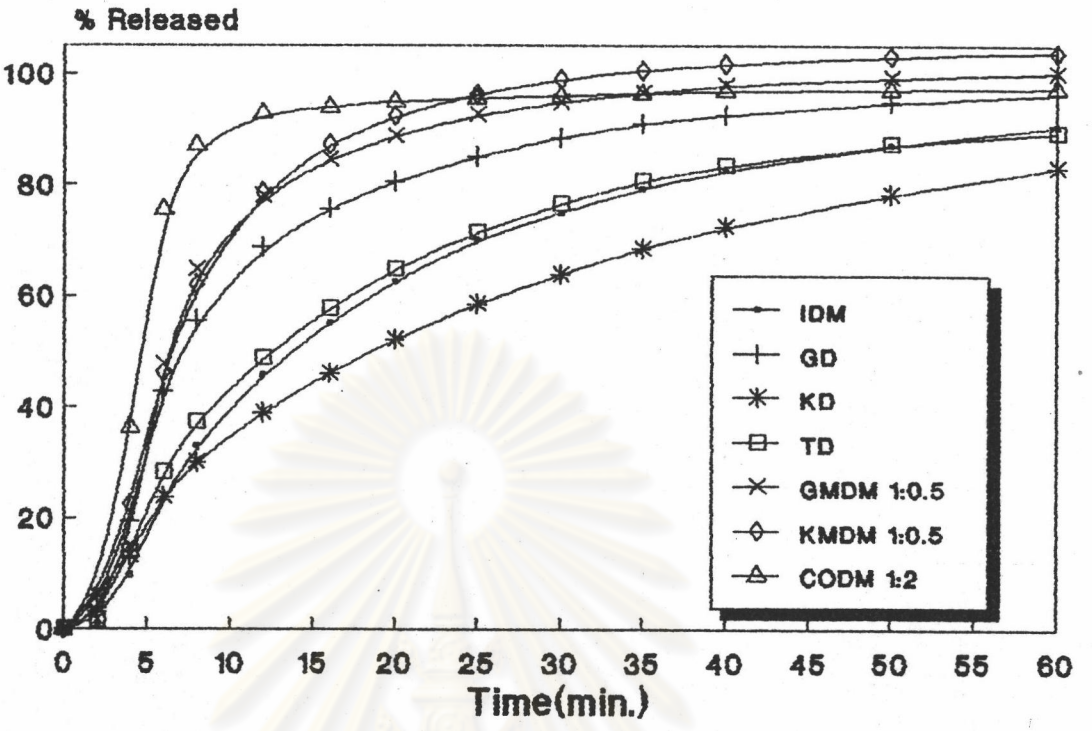


Figure 65 Dissolution profiles of indomethacin capsules (key : Indomethacin(IDM); Grounded drug(GD); Kneaded drug(KD); Treated drug(TD); Grounded mixture of IDM : DIMEB = 1:0.5 (GMDM 1:0.5); Kneaded mixture of IDM : DIMEB = 1:0.5 (KMDM 1: 0.5) and Coevaporated of IDM : DIMEB = 1:2 (CODM 1:2).

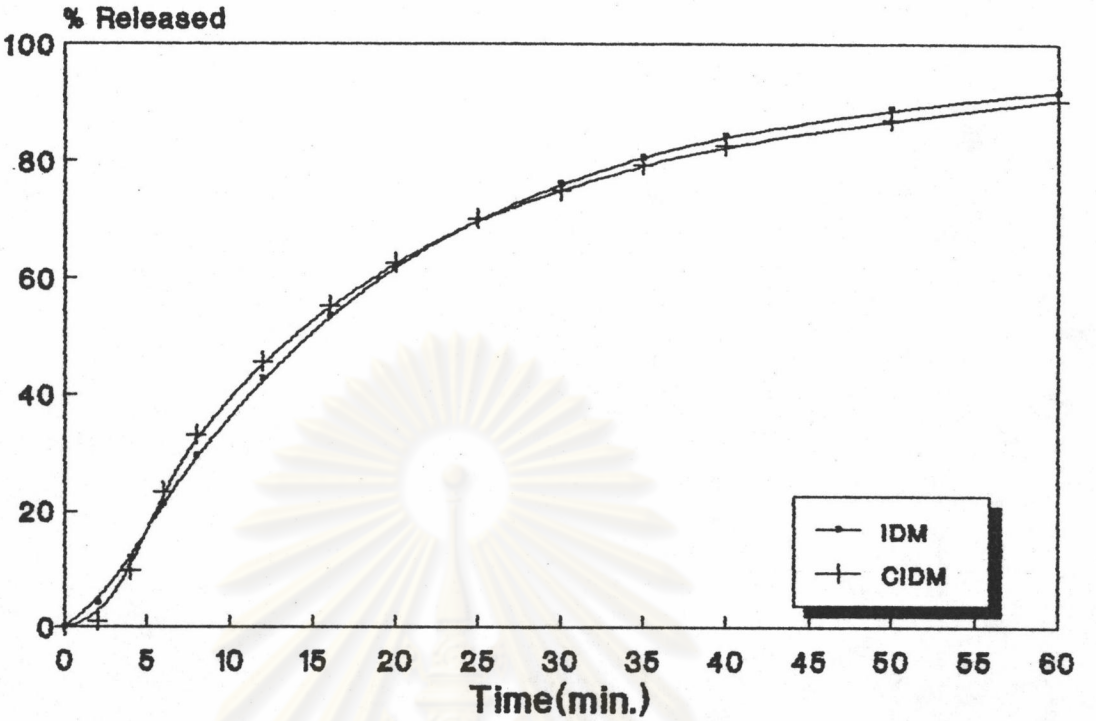


Figure 66 Dissolution profiles of indomethacin powder (IDM) and indomethacin capsule (CIDM).

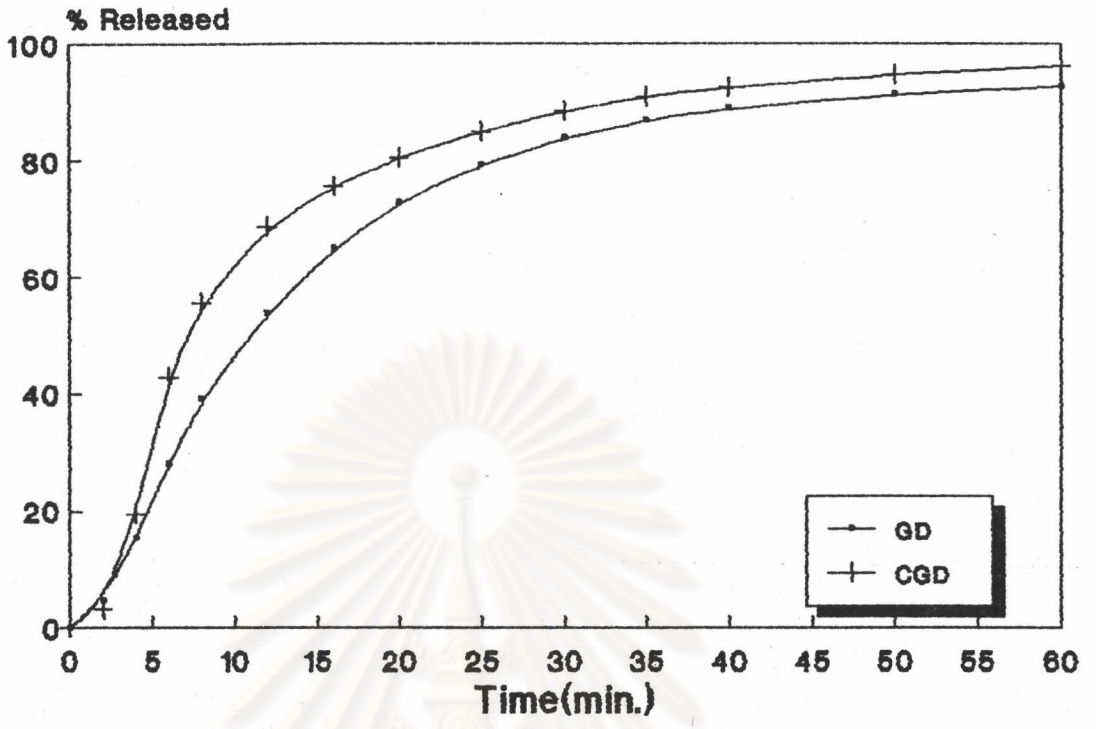


Figure 67 Dissolution profiles of grounded drug powder (GD) and capsule (CGD).

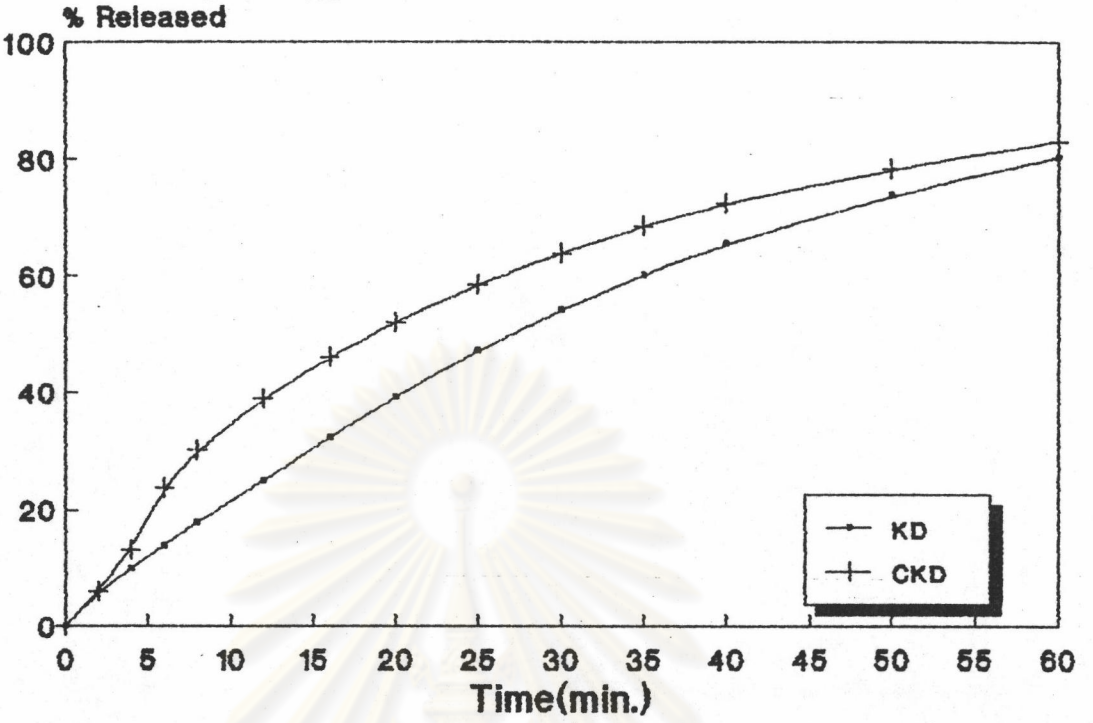


Figure 68 Dissolution profiles of kneaded drug powder (KD) and capsule (CKD).

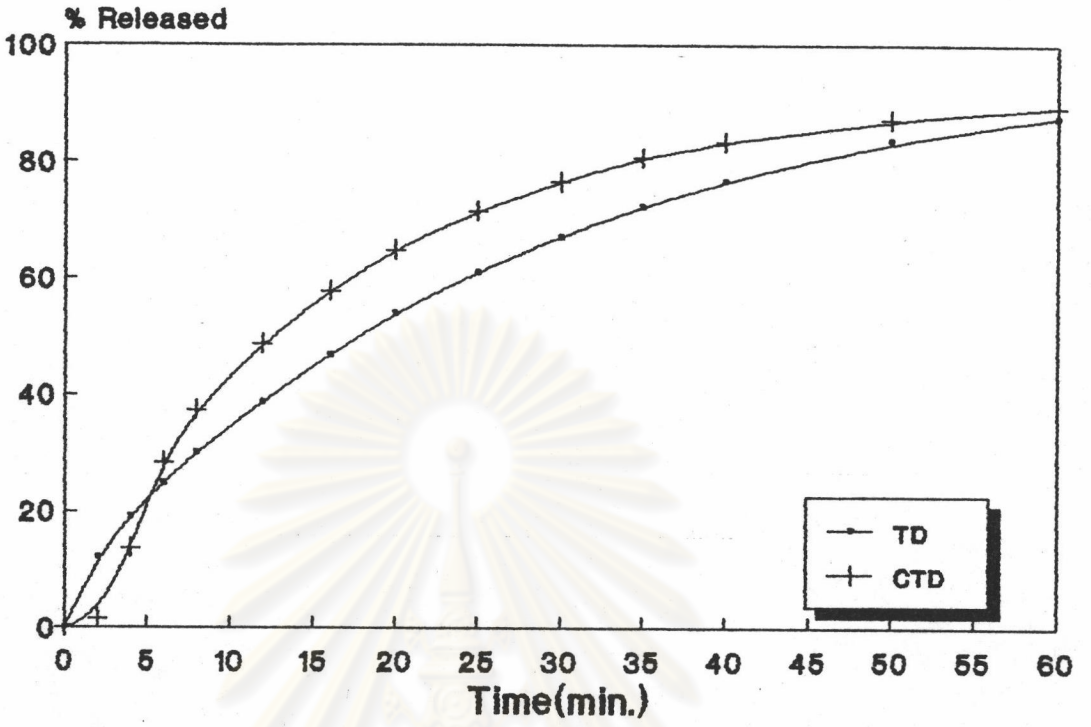


Figure 69 Dissolution profiles of treated drug powder (TD) and capsule (CTD).

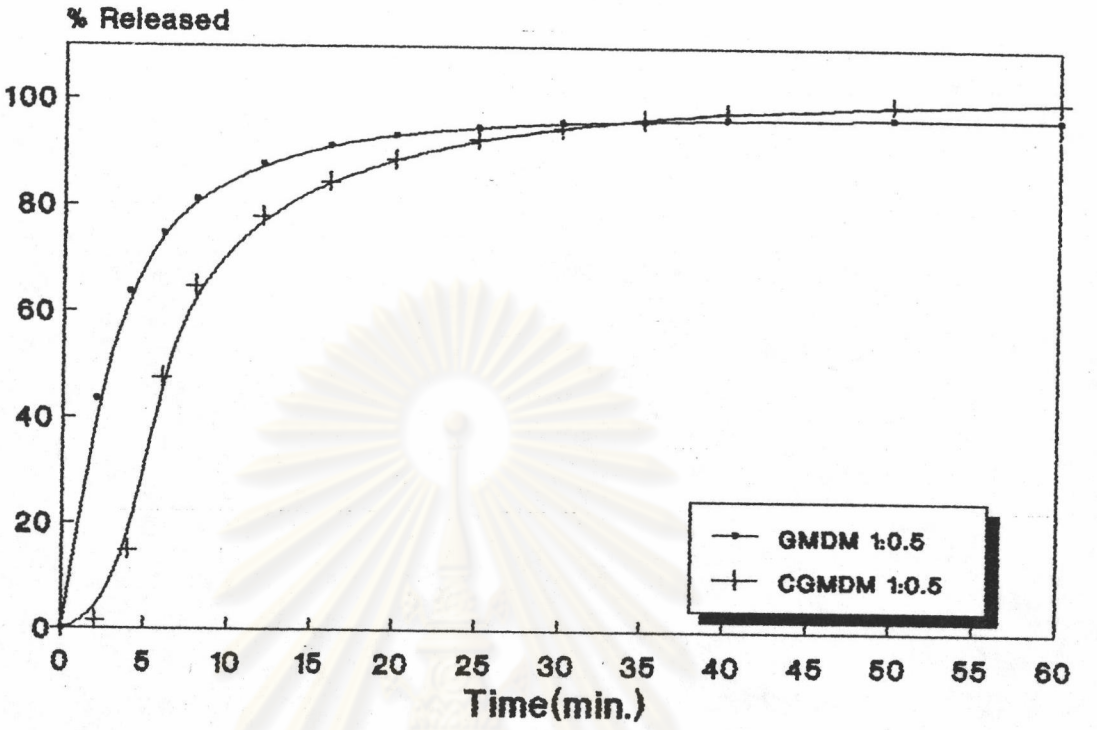


Figure 70 Dissolution profiles of 1:0.5 IDM : DIMEB grounded mixture powder (GMDM 1:0.5) and capsule(CGMDM 1:0.5).

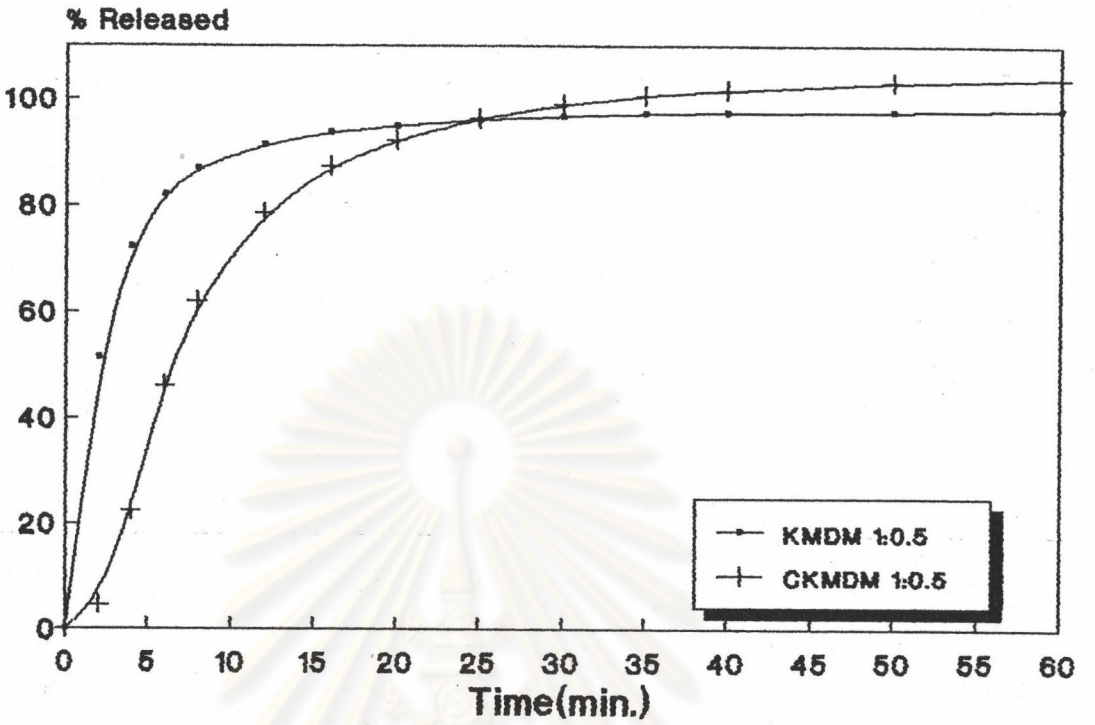


Figure 71 Dissolution profiles of 1:0.5 IDM : DIMEB kneaded kneaded mixture powder (KMDM 1:0.5) and capsule (CKMDM 1:0.5).

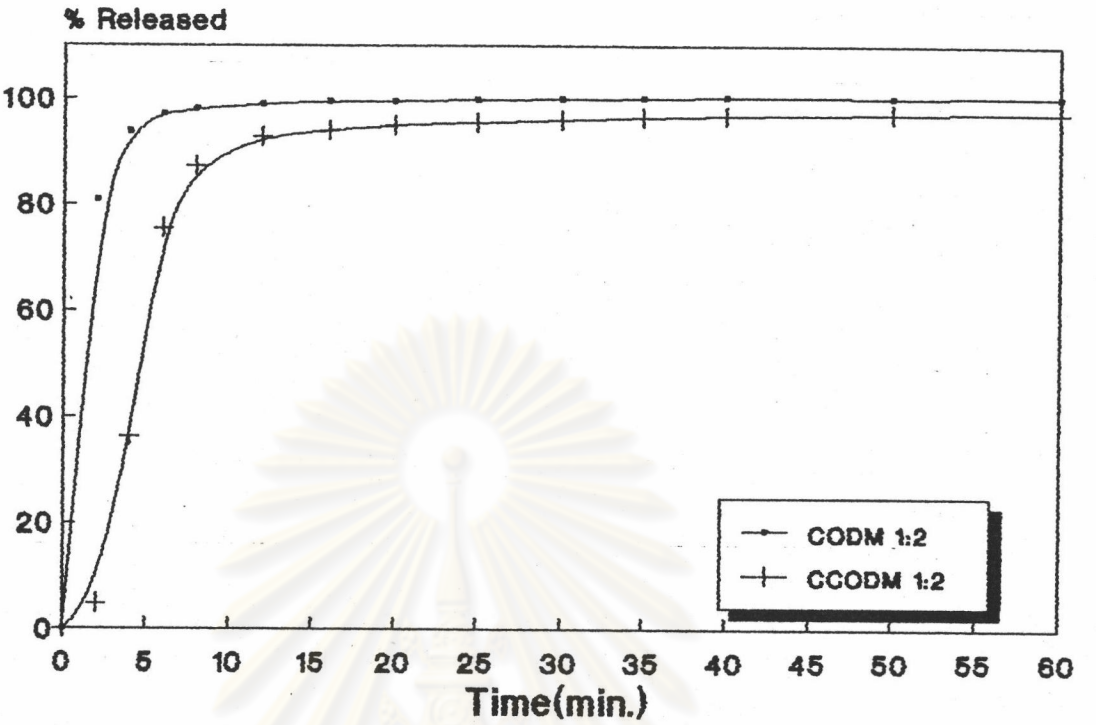


Figure 72 Dissolution profiles of 1:2 IDM : DIMEB coevaporated powder (CODM 1:2) and capsule (CCODM 1:2).

Table 15 Effect of type of preparations on time of 80% released of indomethacin powders and capsules.

Type of preparations	T 80% released (min.)	
	Powder	Capsule
IDM	34.23	34.29
GD	25.58	19.05
KD	60.15	50.48
TD	45.38	30.95
GMDM 1:0.5	8.00	13.02
KMDM 1:0.5	5.77	12.56
CODM 1:2	2.50	6.88

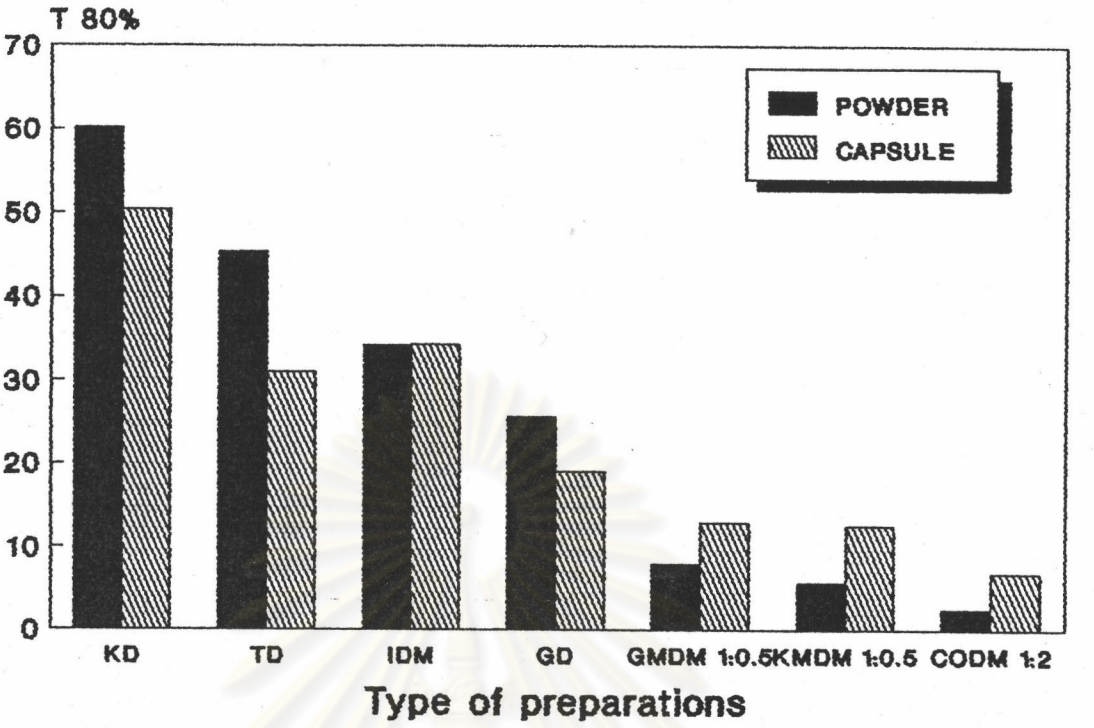


Figure 73 Time of 80% released of IDM from powder and capsule.