



CHAPTER III

RESULT

The Content of IDM in IDM-Carrier powders

IDM-Mannitol powder

The percentage of IDM content from both mixture system and coprecipitate were shown in Table 10 (page 190). Each datum came from three determinations. It was a little difference of IDM percentage from physical mixture and coprecipitate, but the coprecipitate trended to having about 0.02% and 0.36% less IDM content in the 1:1 and 1:5 physical mixture, and about 0.2% higher in the 1:10 coprecipitate than in the same ratio of physical mixture.

IDM-PEG 4000 powder

The content of IDM from IDM-PEG 4000 system were illustrated in the Table 11 (page 190). The coprecipitate showed higher IDM percentage than the physical mixture. The percentages of IDM from physical mixture were about 1.9%, 0.8% and 1.5% less than coprecipitate with the ratio of 1:1, 1:5 and 1:10 respectively.

IDM-PVP K 30 powder

The amount of IDM in the IDM-PVP K 30 systems were illustrated in the Table 12 (page 190). The same pattern of IDM percentage as IDM-PEG 4000 system, the physical mixture showed less IDM percentage than the coprecipitate. In addition, the coprecipitate displayed about 1.25%, 3.4% and 1% greater IDM percentage than the physical mixture with the ratio of 1:1, 1:5 and 1:10 consequently.

IDM-SLS powder

The same pattern of increasing content of IDM in coprecipitate as IDM-PVP K 30 system, the amount of IDM from IDM-SLS systems were seen in Table 13 (page 190). The coprecipitate showed 1.7%, 0.6% and 0.9% higher IDM content than physical mixture in the ratio of 1:0.1, 1:0.5 and 1:1.0 respectively.

Dissolution Studies

Pure IDM

Dissolution profiles of IDM from untreated and treated IDM in both powders and capsules were shown in Figure 8-11 and Table 14, 15. Each datum represented the average value obtained from (page 191) six determinations at a given sampling time.

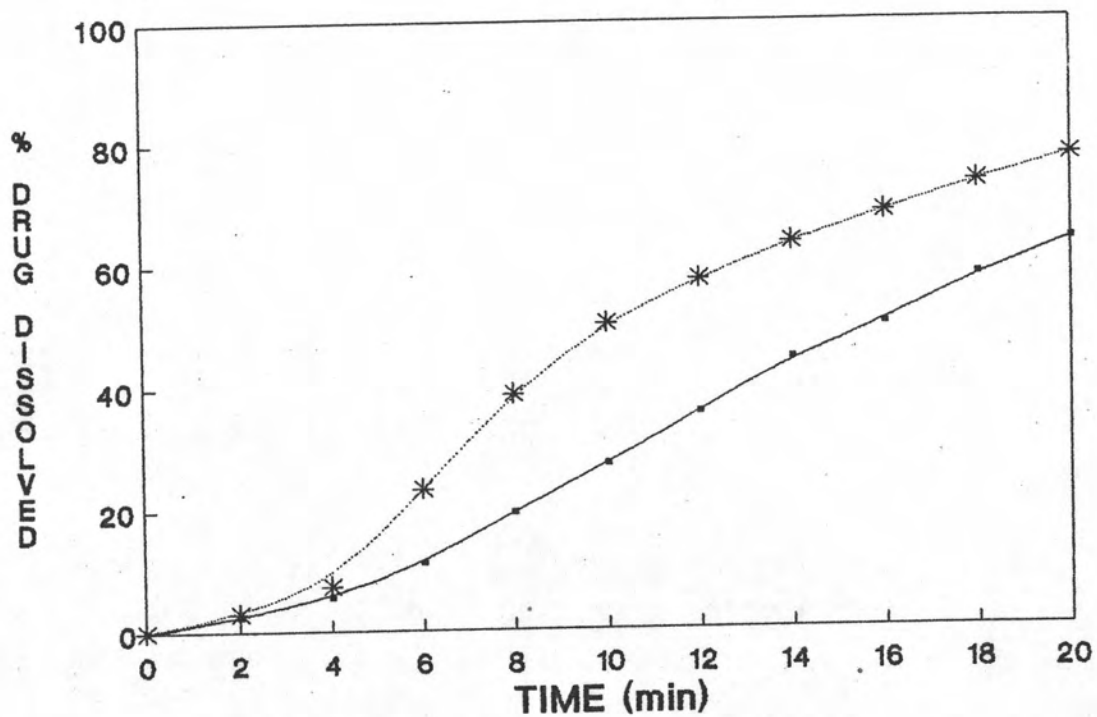


Figure 7 Dissolution profiles of Indomethacin both powder (•) and capsule (*)

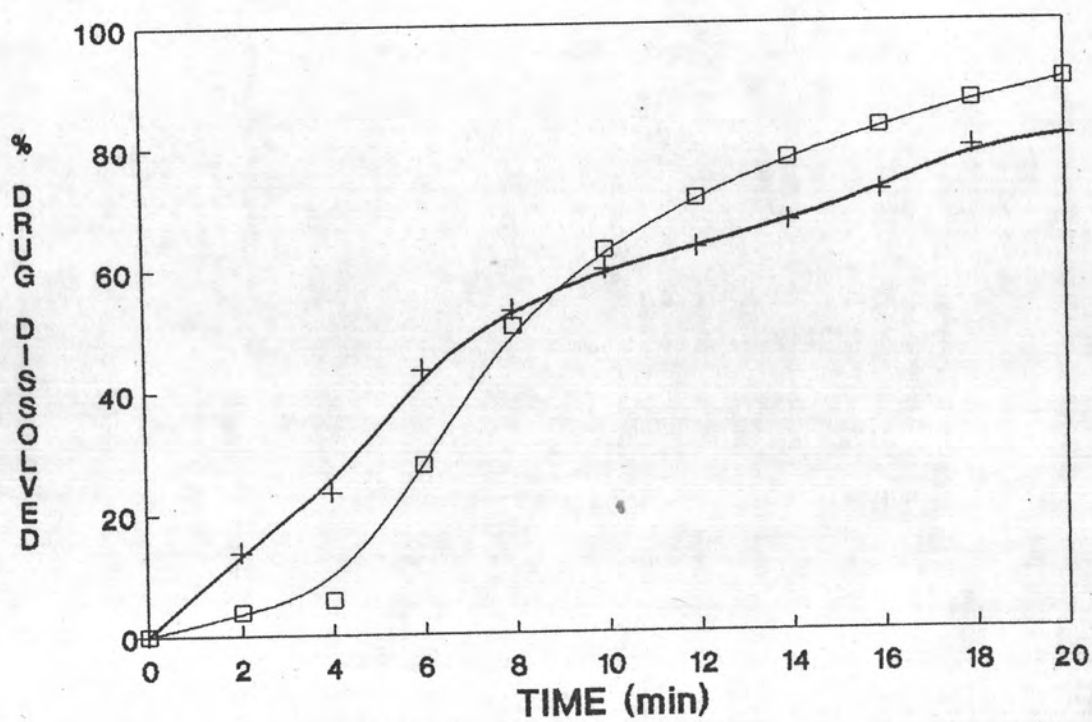


Figure 8 Dissolution profiles of IDM from Treated Indomethacin both powder (+) and capsule (□).

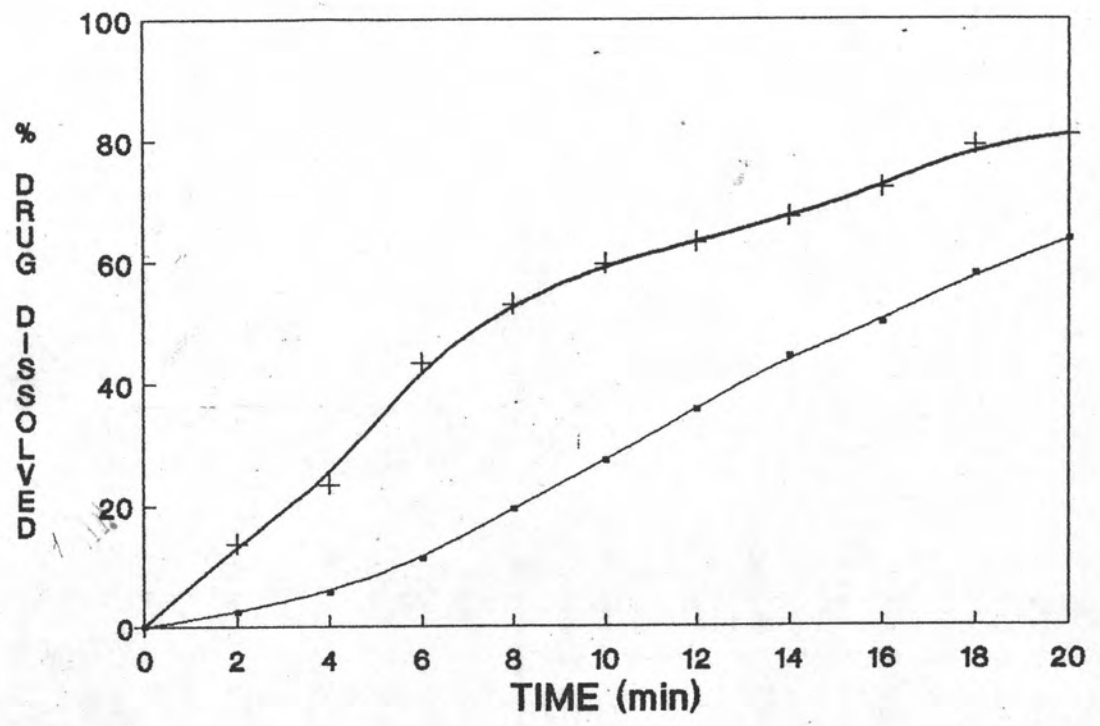


Figure 9 The dissolution profiles of IDM powders both untreated (.) and treated (+).

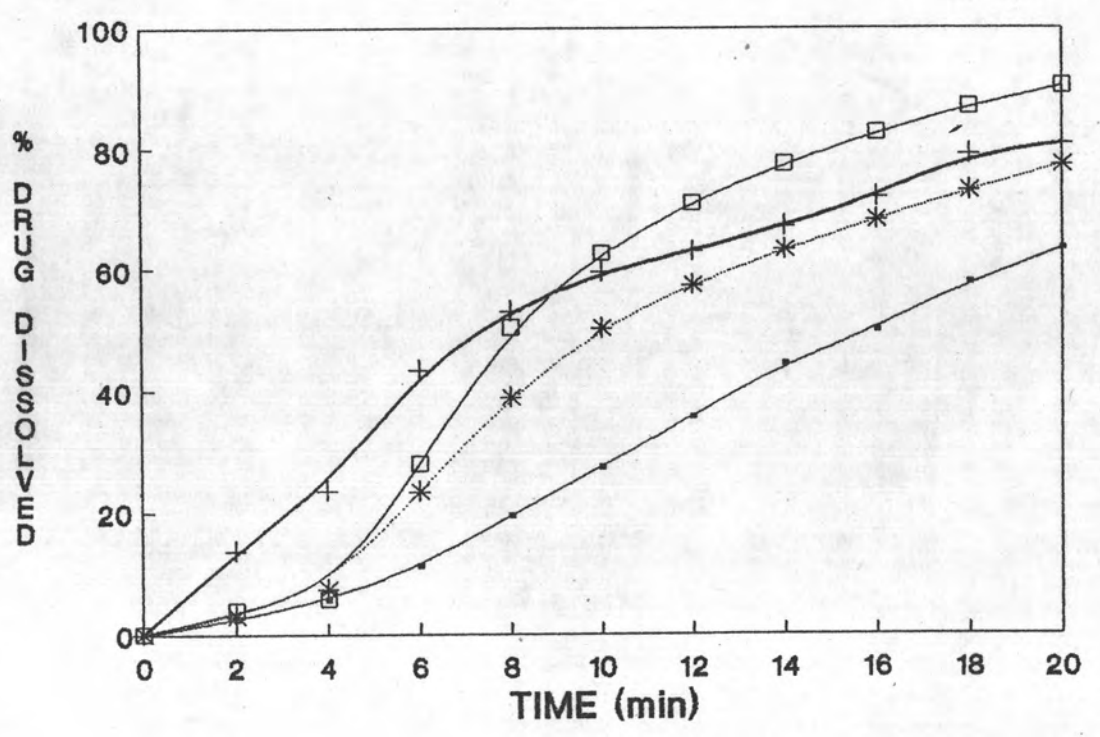


Figure 10 The dissolution profiles of IDM from powder (•), treated IDM (+), IDM capsule (*), and treated IDM capsule in phosphate buffer of pH 7.2 : water (1:4) (□)

The comparison of dissolution profiles of IDM between IDM and treated IDM in powder, were shown in Figure 10. The percentage amount of IDM in treated IDM powder was about 25% higher than untreated IDM, while the percentage of IDM in treated IDM capsule was about 16% greater than untreated IDM capsule. Moreover, the percentage of IDM dissolution in capsule from each preparation gave higher than in powder. The time 80% is the time that was taken to dissolve 80% of IDM. This time could be measured by extrapolating the 80% of IDM to the dissolution-time curve. The time 80% of IDM from treated IDM powder and capsule was about 19 minutes 5 seconds and 15 minutes 26 seconds respectively. Untreated IDM powder and capsule were required more than 20 minutes to dissolve 80% of IDM, Table 40 (page 200).

IDM-Mannitol

Powder

The dissolution profiles of IDM from IDM-Mannitol system were shown in Figure 11-13 and Table 16-18 (page 192), 28-30 (page 196). The IDM-Mannitol with various ratio in both coprecipitate and physical mixture were higher percentage of IDM dissolution than IDM and treated IDM, except the 1:1 physical mixture ratio that was lower than treated IDM. The dissolution of IDM in the ratio of 1:1, 1:5 and 1:10 physical mixture were about 20%, 30% and 29%, respectively, higher than untreated IDM powder.

The IDM dissolution of IDM in the ratio of 1:5 and 1:10 coprecipitate gave about 20% and 10%, respectively, greater than treated IDM powder, while the ratio of 1:1 coprecipitate yielded equally to treated IDM powder. The fastest time 80% from the ratio of 1:5 coprecipitate was 4 minutes 16 seconds, while the ratio of 1:1 and 1:10 coprecipitate were 17 minutes 53 seconds and 8 minutes respectively. However, the 1:1 physical mixture ratio could not dissolve 80% IDM before 20 minutes, the time 80% of the 1:5 and 1:10 were 15 minutes 14 seconds and 14 minutes 50 seconds, consequently, Table 40 (page 200).

Capsule

Dissolution profiles of IDM from IDM-Mannitol capsule were illustrated in Figure 23, and Table 45, 46. It was noted that coprecipitate capsule showed about 28% higher IDM dissolution than physical mixture capsule. The physical mixture capsule displayed about 2% lower dissolution of IDM than the treated IDM capsule, but about 13% higher than the untreated IDM capsule.

The markedly IDM dissolution increasing was seen after about 4 minutes. The time 80% of coprecipitate capsule was 9 minutes 13 seconds, and the physical mixture capsule was 17 minutes 21 seconds, Table 41 (page 200).

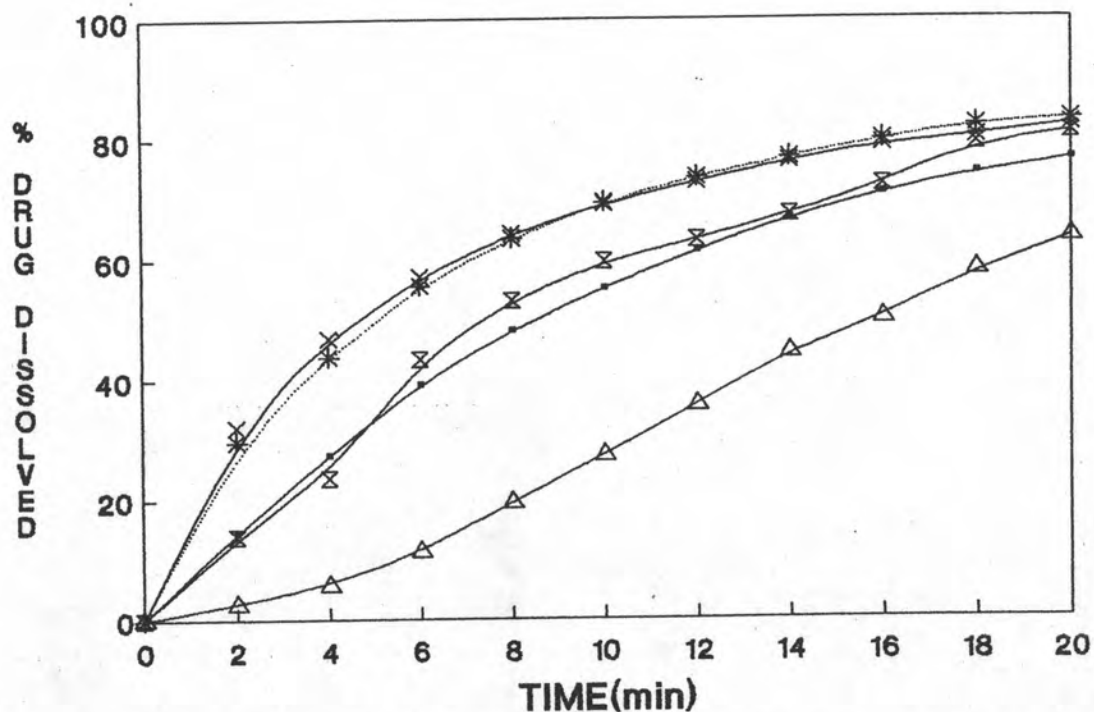


Figure 11 Dissolution profiles of IDM from IDM-Mannitol physical mixture powder with the ratio of 1:1 (.), 1:5 (*) and 1:10 (x) including IDM (Δ) and treated IDM (\times) in phosphate buffer of pH 7.2 : water (1:4).

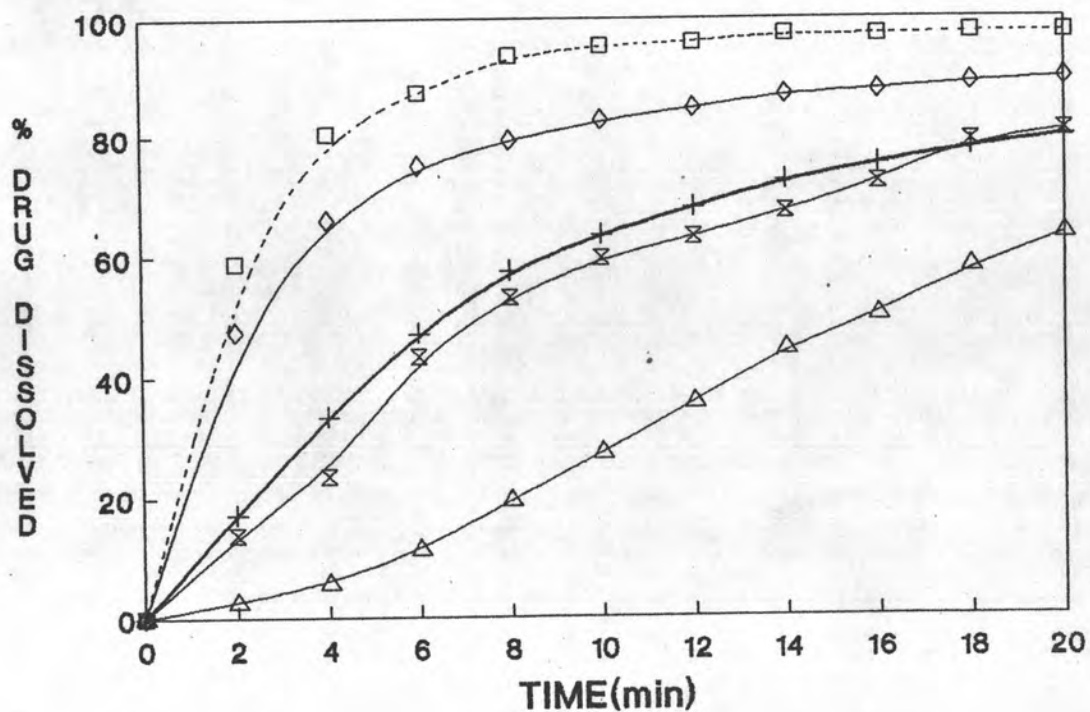


Figure 12 Dissolution profiles of IDM from IDM-Mannitol solid dispersion powder with the ratio of 1:1 (+), 1:5 (\square) and 1:10 (\diamond) including IDM (Δ) and treated IDM (\times) in phosphate buffer of pH 7.2 : water (1:4).

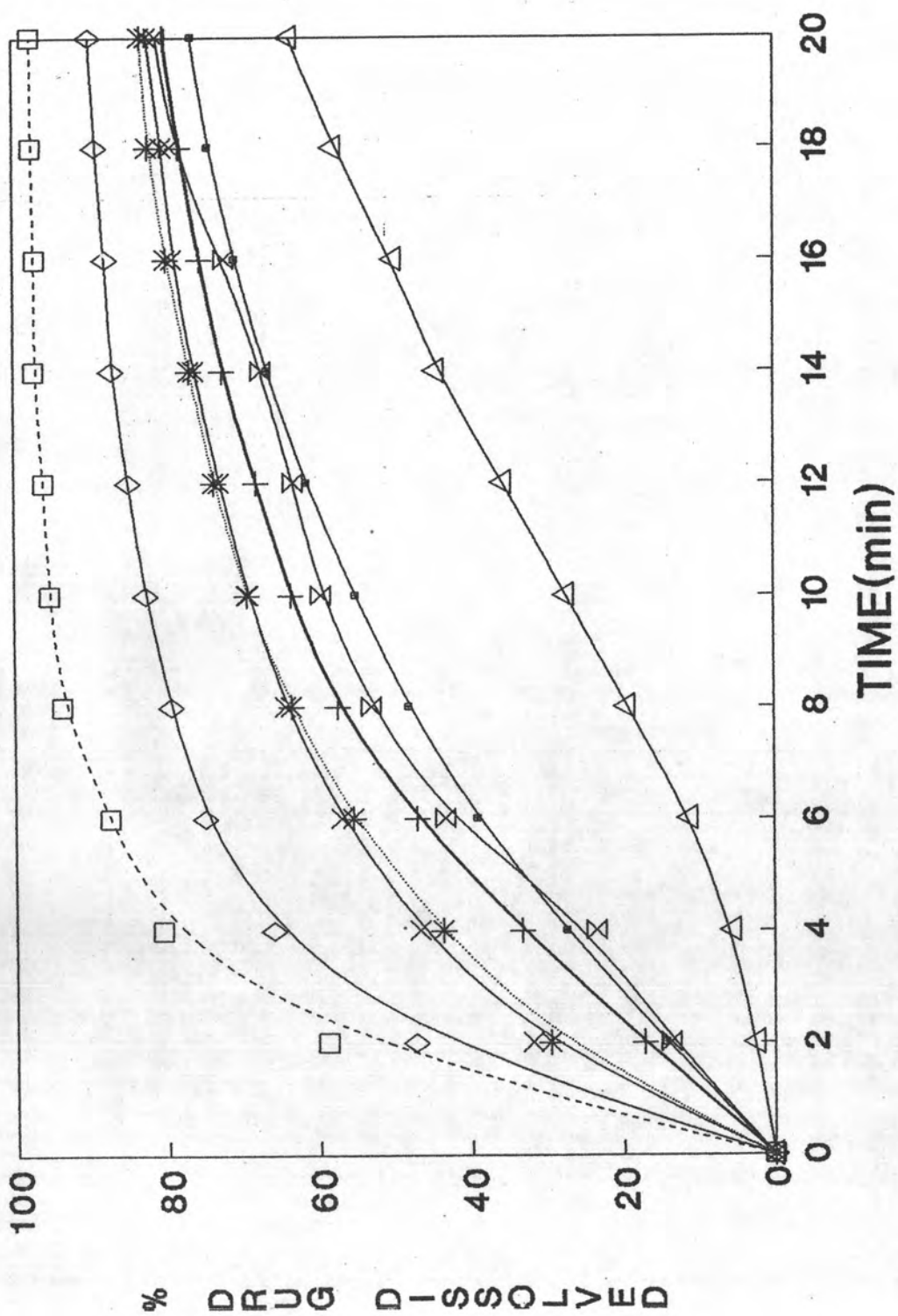


Figure 13
 Dissolution profiles of IDM from IDM-Mannitol powders both physical mixture with ratio of 1:1 (•), 1:5 (*) and 1:10 (x) and solid dispersion with the ratio of 1:1 (+), 1:5 (□) and 1:10 (◇) including IDM (Δ) and treated IDM (X) from various ratio in phosphate buffer of pH 7.2 : water (1:4)

IDM-PEG 4000

Powder

Dissolution profiles of IDM from IDM-PEG 4000 system were displayed in Figure 14-16 and Table 19-21 (page 193), 31-33 (page 197), IDM and treated IDM powders illustrated lower dissolution of IDM than all ratio of IDM-PEG 4000 systems, except the ratio of 1:1 and 1:5 physical mixture which these both ratio of physical mixture displayed lower dissolution of IDM than treated IDM about 18% and 14% respectively at the twentieth minute. The treated IDM powder gave lower dissolution of IDM than that both ratio of physical mixture before 8 minutes, but after that time it showed higher until 20 minutes. The ratio of 1:5 physical mixture showed about 10% higher dissolution of IDM than treated IDM powder until 18 minutes. The 1:10 coprecipitate ratio gave the fastest dissolution of IDM that about 10% greater than the 1:5 coprecipitate ratio before 4 minutes and after 8 minutes the dissolution of IDM was equal with each other. The ratio of 1:1 coprecipitate was average about 20% less IDM dissolution than the 1:10 coprecipitate ratio during 20 minutes. The coprecipitate powder showed more IDM dissolution than the physical mixture powders. Moreover, increasing weight fraction of PEG 4000 increased in the dissolution of IDM both physical mixture and coprecipitate in all ratio. The time 80% of the 1:1 and 1:5 coprecipitate ratios were 15 minutes 30 seconds and 3

minutes 40 seconds, consequently, while the fast time 80% from the ratio of 1:5 coprecipitate was 2 minutes 20 seconds. It took more than 20 minutes to dissolve 80% of IDM in the ratio of 1:1 and 1:5 physical mixture, but the 1:10 physical mixture ratio took 17 minutes 30 seconds to dissolve 80% of IDM, Table 40 (page 200).

Capsule

Dissolution profiles of IDM from IDM-PEG 4000 capsules were shown in Figure 24 and Table 47-48 (page 203). The same pattern of IDM dissolution profile as IDM-Mannitol, the coprecipitate capsule showed the highest dissolution of IDM, while the physical mixture capsule showed the IDM dissolution between treated IDM capsule and untreated IDM capsule, that was about 6% less than treated IDM capsule, but it was about 10% greater than untreated IDM capsule at the twentieth minute. The markedly increasing of IDM dissolution was appeared after about 4 minutes, it implied that the capsules were disintegrated. The coprecipitate capsule took 11 minutes 56 seconds for dissolution 80% IDM, and about 30% greater than the physical mixture capsule at the twentieth minute. The time 80% of the physical mixture capsule was 16 minutes 33 seconds Table 41.

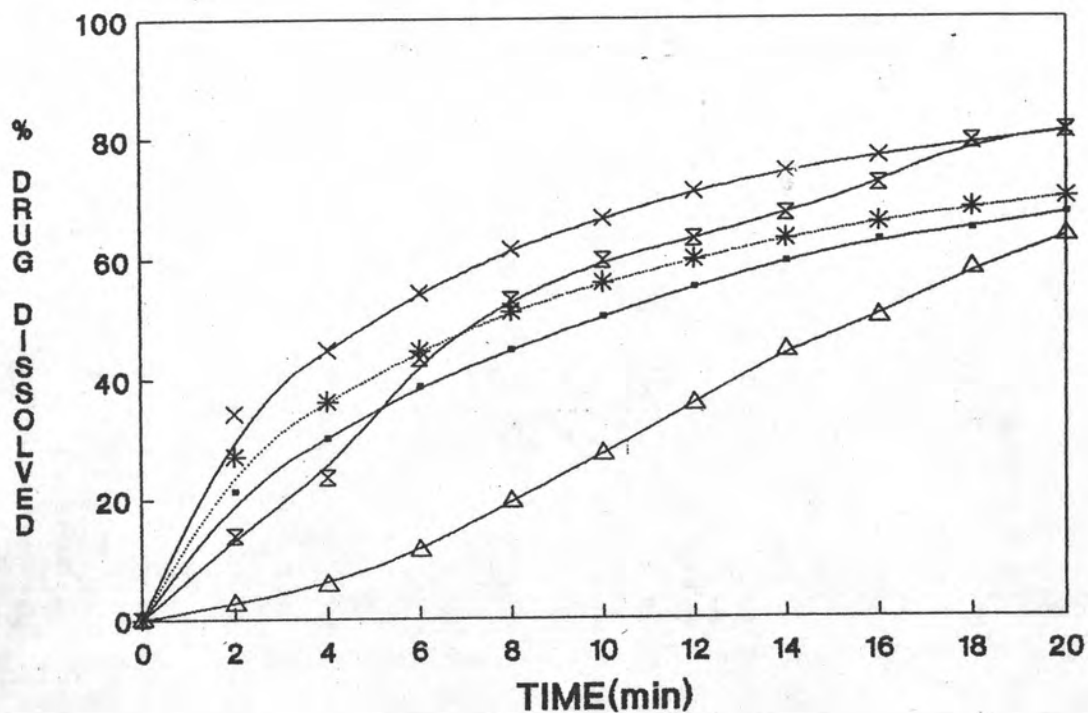


Figure 14 Dissolution profiles of IDM from IDM-PEG 4000 physical mixture powder with the ratio of 1:1 (.), 1:5 (*) and 1:10 (x) including IDM (Δ) and treated IDM (\times) in phosphate buffer of pH 7.2 : water (1:4).

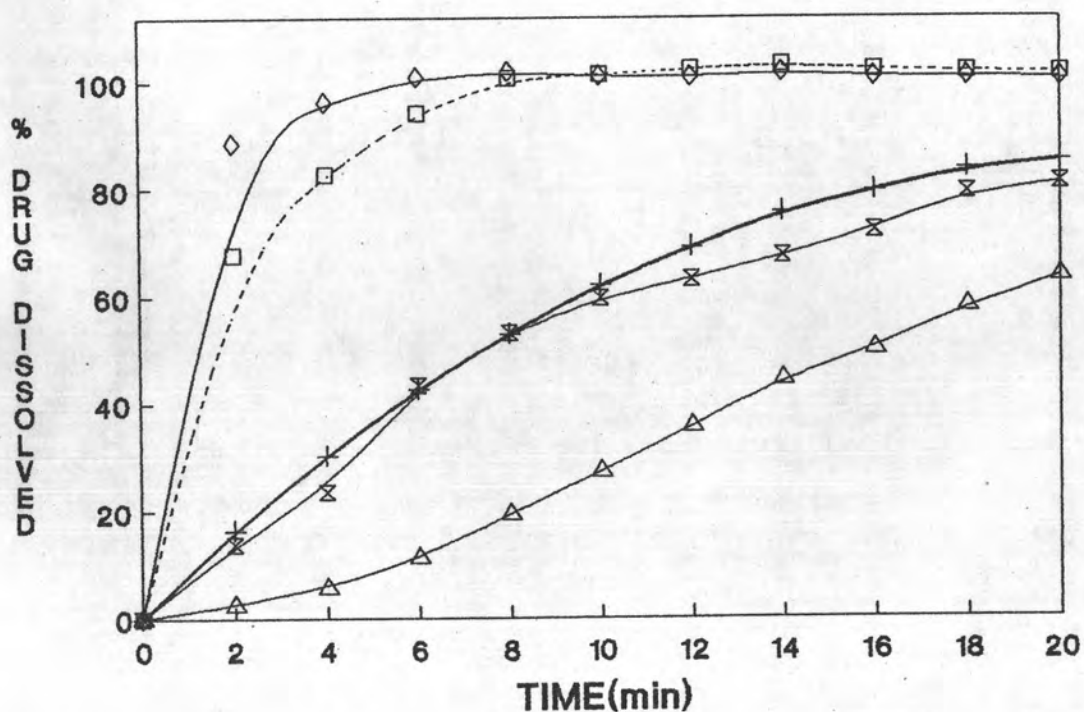


Figure 15 Dissolution profiles of IDM from IDM-PEG 4000 solid dispersion powder with the ratio of 1:1 (+), 1:5 (□) and 1:10 (◇) including IDM (Δ) and treated IDM (\times) in phosphate buffer of pH 7.2 : water (1:4).

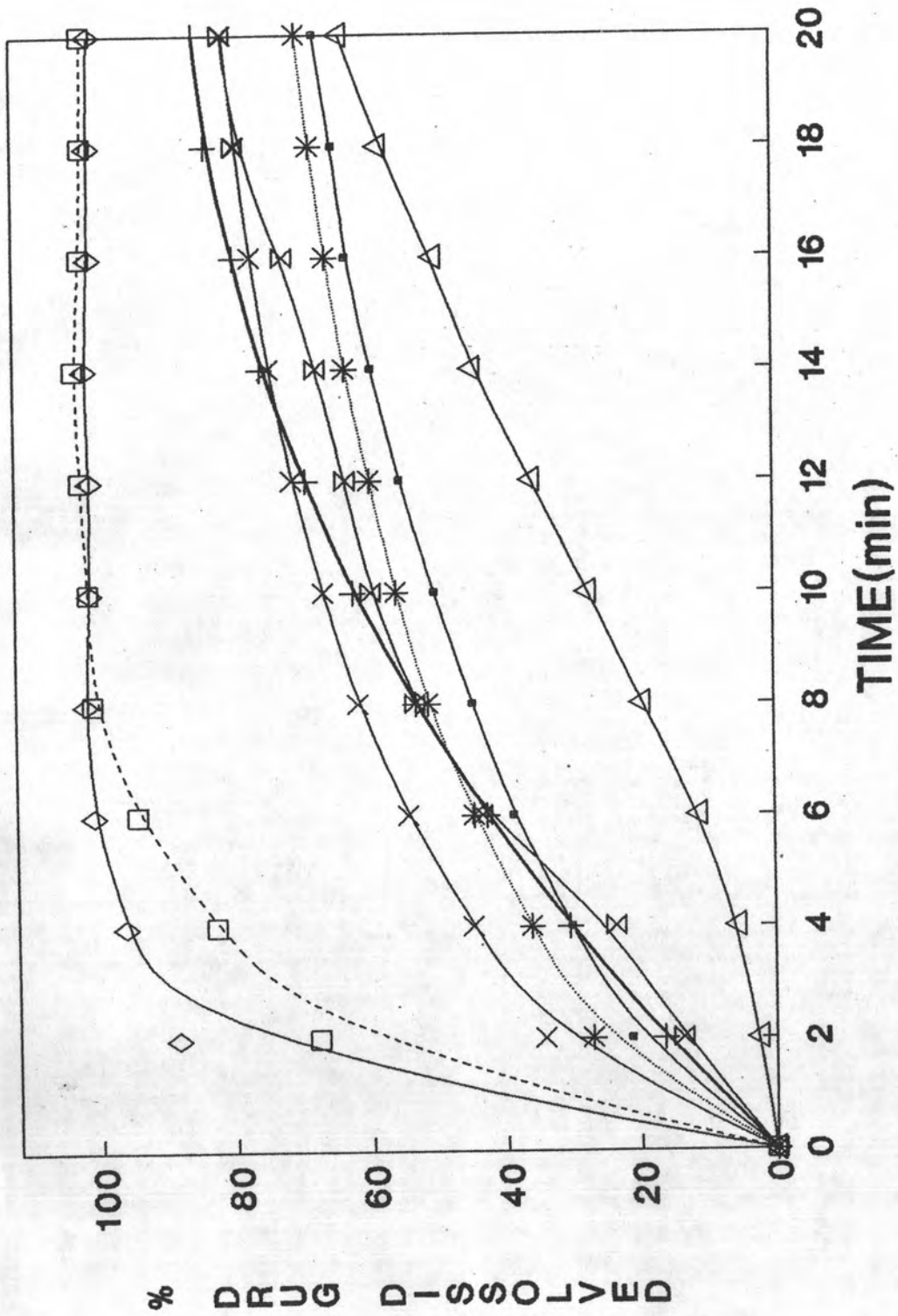


Figure 16

Dissolution profiles of IDM from IDM-PEG 4000 powders both physical mixture with ratio of 1:1 (•), 1:5 (*) and 1:10 (x) and solid dispersion with the ratio of 1:1 (+), 1:5 (◊) and 1:10 (◊) including IDM (Δ) and treated IDM (x) from various ratio in phosphate buffer of pH 7.2 : water (1:4)

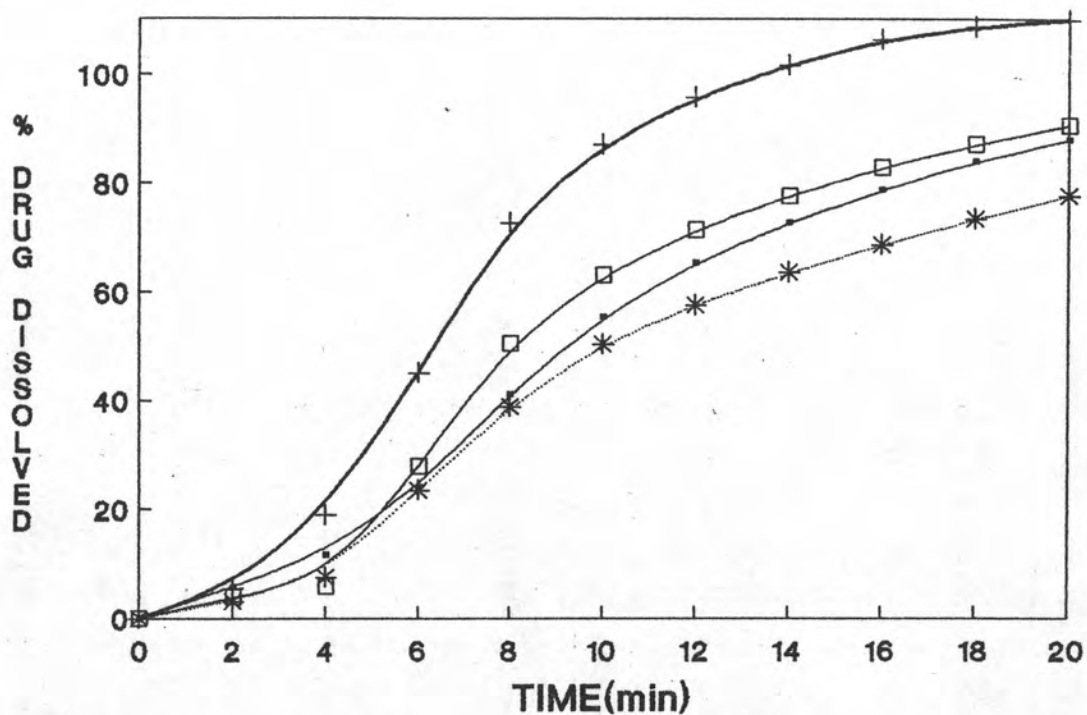


Figure 23 Dissolution profiles of IDM from IDM-Mannitol capsules both physical mixture (.) and solid dispersion (+) from ratio 1:1, including IDM (*) and treated IDM (□) in phosphate buffer of pH 7.2 : water (1.4)

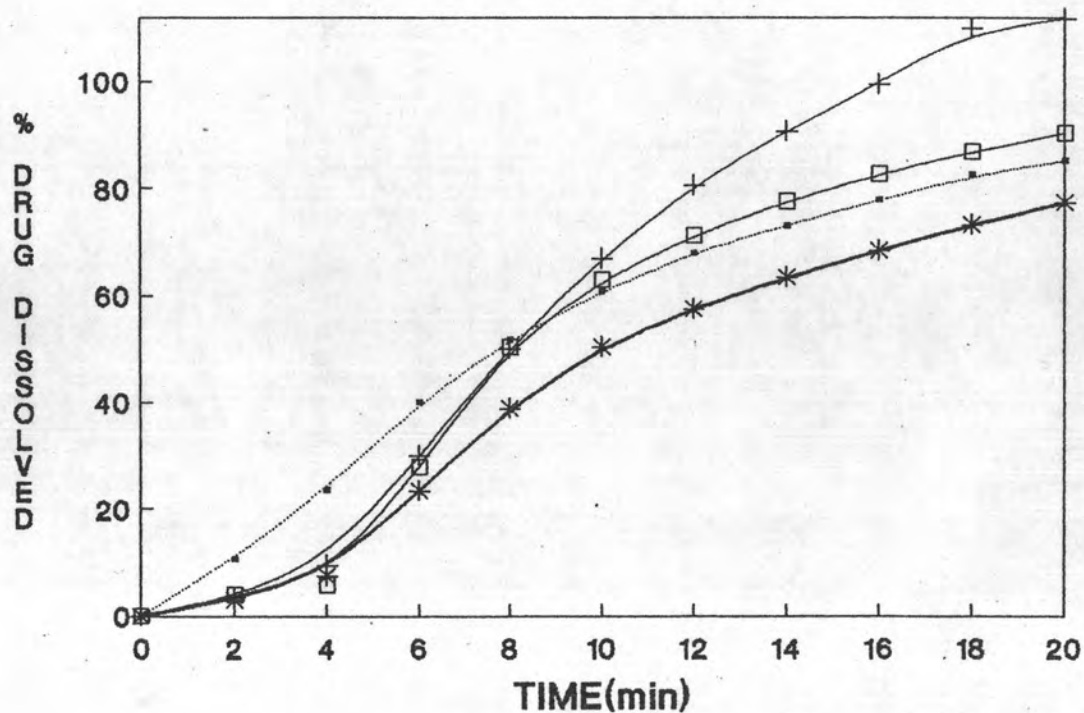


Figure 24 Dissolution profiles of IDM from IDM-PEG 4000 capsules both physical mixture (.) and solid dispersion (+) from ratio 1:1, including IDM (*) and treated IDM (□) in phosphate buffer of pH 7.2 : water (1.4)

IDM-PVP K 30

Powder

Dissolution profiles of IDM from IDM-PVP K 30 systems were demonstrated in Figure 17-19 and Table 22-24 (page 194), 34-36 (page 198). The more amount of PVP K 30 were in systems, the more dissolution of IDM from IDM-PVP K 30 system appeared. All ratio of coprecipitate illustrated faster IDM dissolution than all ratio of physical mixture. The ratio of 1:5 physical mixture was 9% greater IDM dissolution than the ratio of 1:1 physical mixture, and 5% less than the ratio of 1:10 physical mixture. All ratios of physical mixture were lower IDM dissolution than treated IDM powder after 5 minutes, but greater than IDM dissolution than treated IDM powder after 5 minutes, but greater than untreated IDM powder until 16 minutes. The treated IDM powder was about 59%, 45% and 37% greater IDM dissolution from the ratio of 1:1, 1:5 and 1:10 physical mixture.

The 1:10 coprecipitate displayed IDM dissolution about 16% greater than the 1:5 coprecipitate and about 30% greater than the 1:1 coprecipitate before 10 minutes; afterward, the ratio of 1:1 coprecipitate showed about 5% greater than the ratio of 1:5 coprecipitate. The 1:10 coprecipitate demonstrated IDM dissolution 61% greater than the same ratio of physical mixture, while IDM dissolution was 54% and 77% greater in the ratio of 1:1

and 1:5 coprecipitate than the same ratio of physical mixture respectively. It took more than 20 minutes to dissolve 80% IDM in all ratio of physical mixture. The fastest time 80% was 2 minutes 20 seconds in the 1:10 coprecipitate, while the ratio of 1:1 and 1:5 coprecipitate took 7 minutes 20 seconds and 5 minutes, respectively for dissolving 80% of IDM, Table 40 (page 200).

Capsule

Dissolution profiles of IDM from IDM-PVP K 30 system were shown in Figure 25 and Table 49-50 (page 204). The coprecipitate capsule displayed about 28% higher dissolution of IDM than the physical mixture capsule and 17.6%, 37% higher than treated IDM, untreated IDM respectively. IDM dissolution from physical mixture was about 10% less than treated IDM capsule, but about 6% higher than IDM capsule in the twentieth minute. The fastest time 80% was 8 minutes 42 seconds from coprecipitate capsule, while the physical mixture capsule took 19 minutes 40 seconds for dissolving 80% IDM, Table 41 (page 200).

IDM-SLS

Powder

Dissolution profiles of IDM from IDM-SLS system were displayed in Figure 20-22 and Table 25-27 (page 195), 37-39 (page 197). All ratio of IDM-SLS system

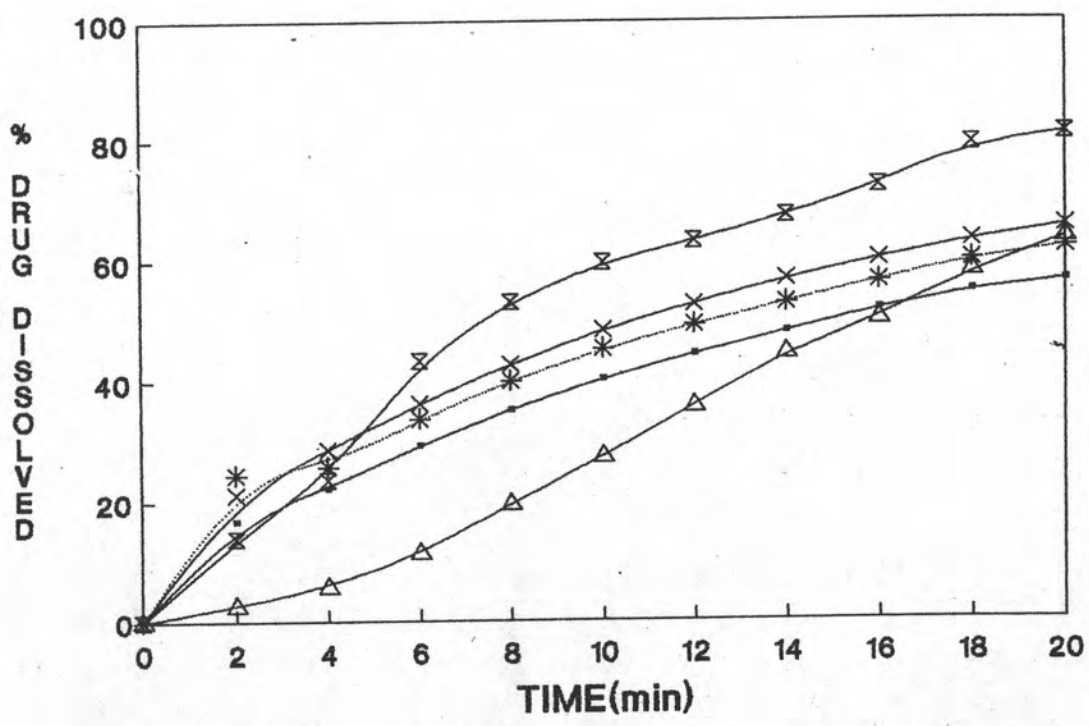


Figure 17 Dissolution profiles of IDM from IDM-PVP K 30 physical mixture powder with the ratio of 1:1 (.), 1:5 (*) and 1:10 (x) including IDM (Δ) and treated IDM (⊗) in phosphate buffer of pH 7.2 : water (1:4).

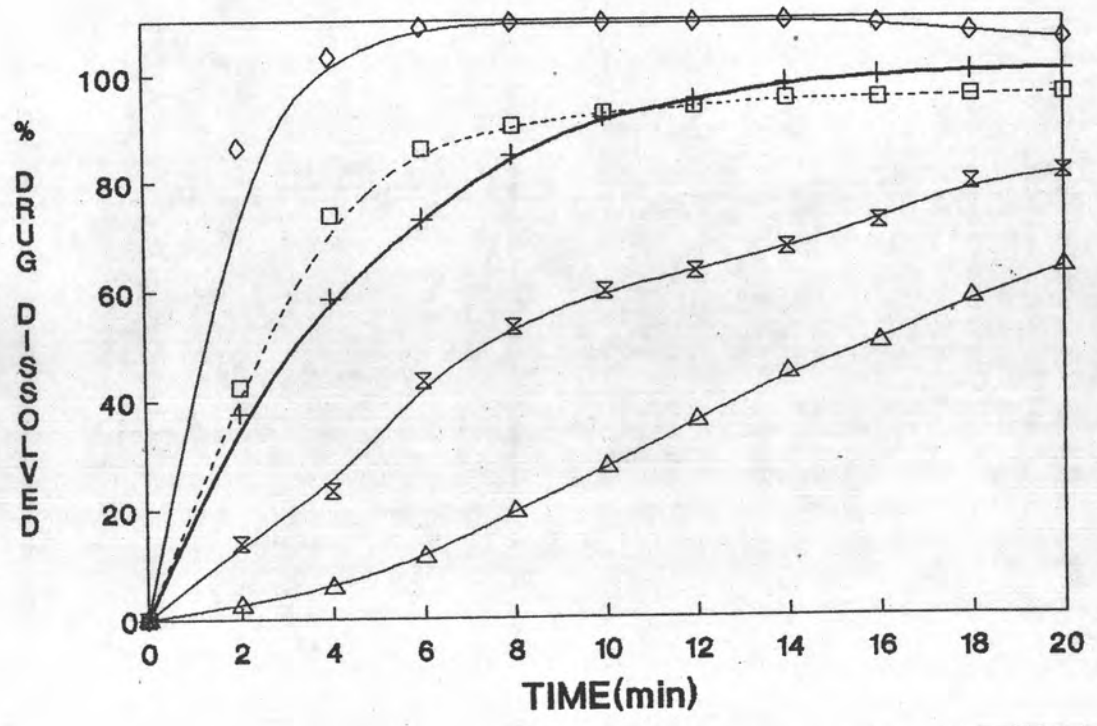


Figure 18 Dissolution profiles of IDM from IDM-PVP K 30 solid dispersion powder with the ratio of 1:1 (+), 1:5 (□) and 1:10 (◇) including IDM (Δ) and treated IDM (⊗) in phosphate buffer of pH 7.2 : water (1:4).

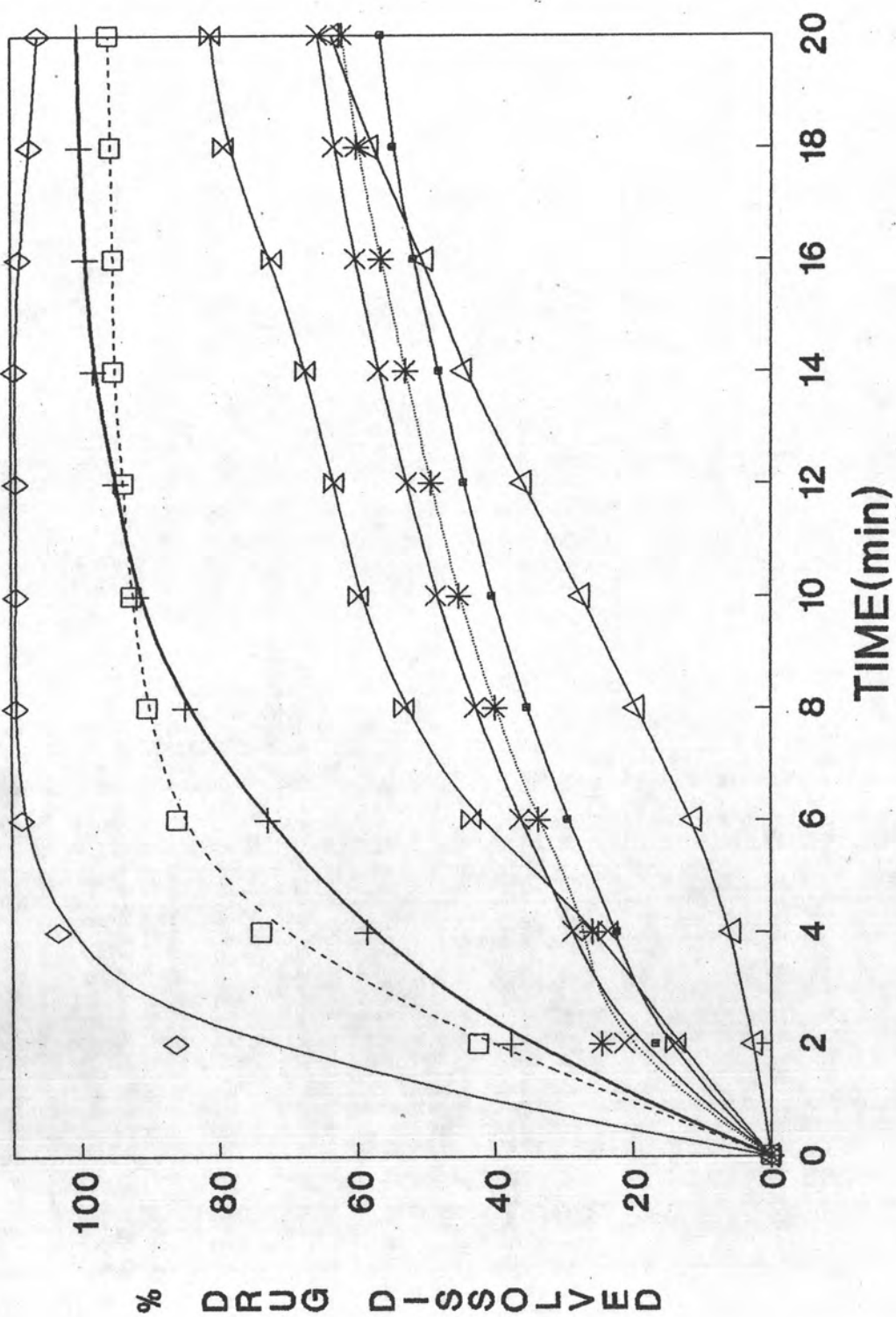


Figure 19 Dissolution profiles of IDM from IDM-FVP K 30 powders both physical mixture with ratio of 1:1 (.), 1:5 (*) and 1:10 (x) and solid dispersion with the ratio of 1:1 (+), 1:5 (□) and 1:10 (◇) including IDM (Δ) and treated IDM (X) from various ratio in phosphate buffer of pH 7.2 : water (1:4)

demonstrated higher dissolution of IDM than untreated IDM and treated IDM. In physical mixture powder, the more weight fraction of SLS was, the less dissolution of IDM appeared. It was about 7% and 14% higher IDM dissolution in the ratio of 1:0.1 physical mixture than the ratio of 1:0.5 and 1:1 physical mixture, respectively. In the contrary, the coprecipitate showed the increasing dissolution of IDM with increasing amount of SLS. Moreover, the coprecipitate also displayed higher dissolution of IDM than the physical mixture. The ratio of 1:1 coprecipitate gave 10% and 0.7% higher IDM dissolution than the ratio of 1:0.1 and 1:0.5 coprecipitate respectively. In addition, the time 80% of the 1:1 coprecipitate ratio was 2 minutes 53 seconds, while the ratio of 1:0.1 and 1:0.5 coprecipitate were 7 minutes 13 seconds and 4 minutes 16 seconds, respectively. It took more time for dissolving 80% in physical mixture that were 8 minutes 13 seconds in the ratio of 1:0.1, 11 minutes 26 seconds in the ratio of 1:0.5 and finally 15 minutes 40 seconds in the ratio of 1:1.0, Table 40 (page 200).

Capsule

Dissolution profiles of IDM from IDM-SLS capsule system were given in Figure 26 and Table 51-52 (page 205). It looked the same pattern of IDM dissolution as the other systems. The physical mixture capsule was 14% higher and

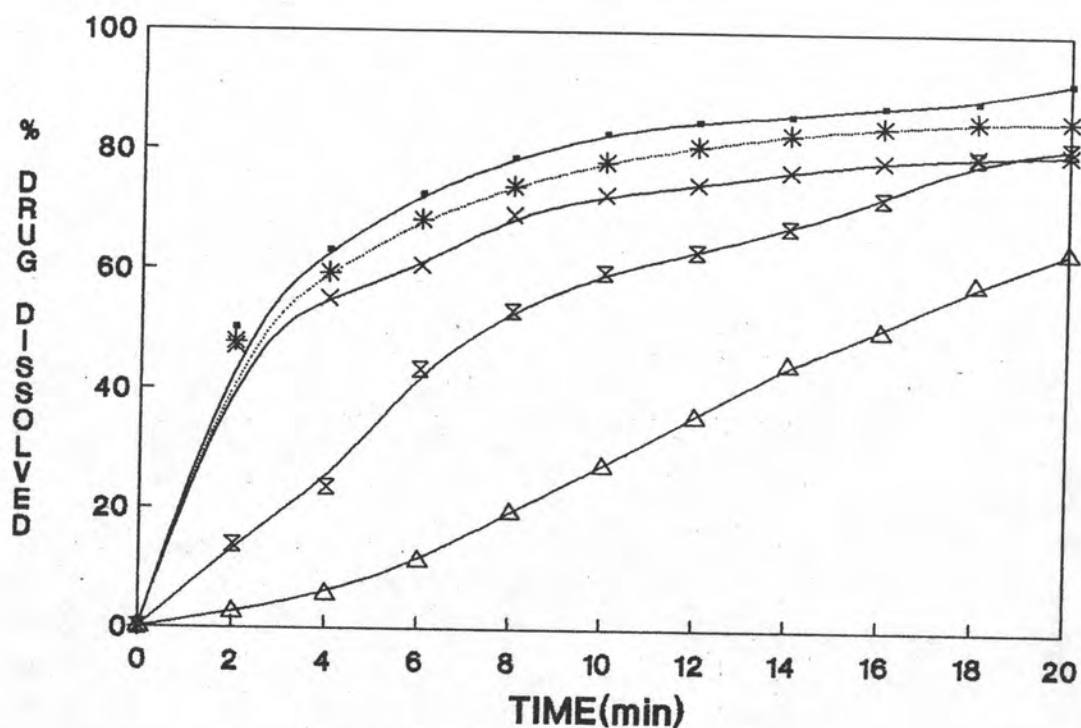


Figure 20 Dissolution profiles of IDM from IDM-SLS physical mixture powder with the ratio of 1:0.1 (.), 1:0.5, and 1:1.0 (x) including IDM (Δ) and treated IDM (\times) in phosphate buffer of pH 7.2 : water (1:4).

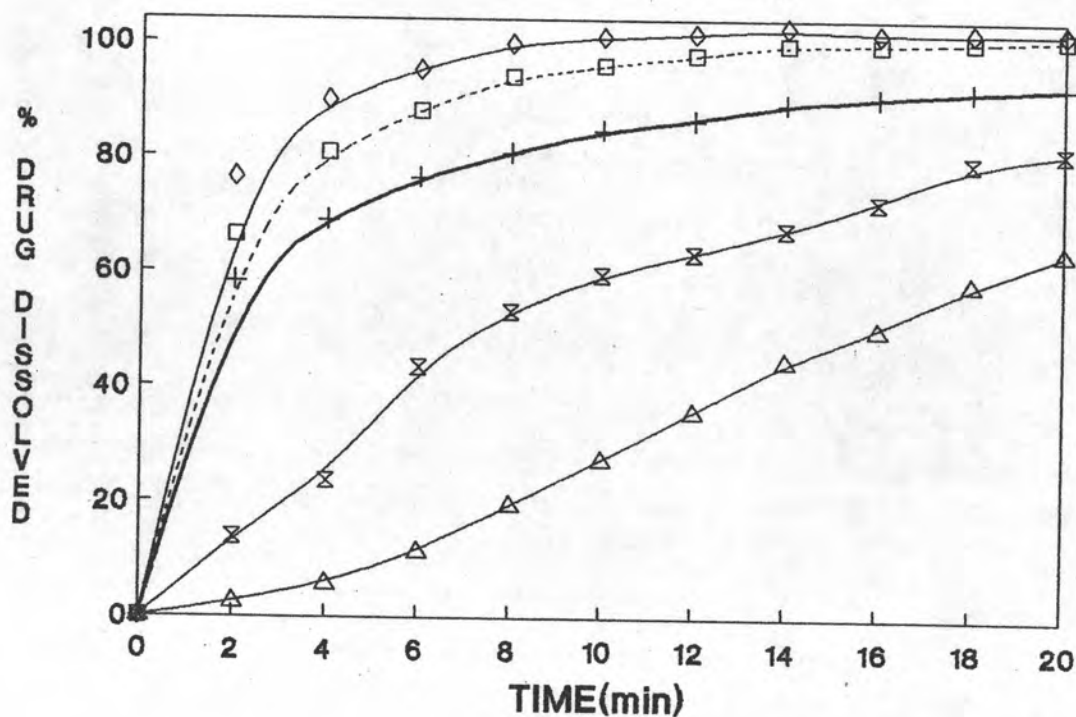


Figure 21 Dissolution profiles of IDM from IDM-SLS solid dispersion powder with the ratio of 1:0.1 (+), 1:0.5 (\square) and 1:1.0 (\diamond) including IDM (Δ) and treated IDM (\times) in phosphate buffer of pH 7.2 : water (1:4).

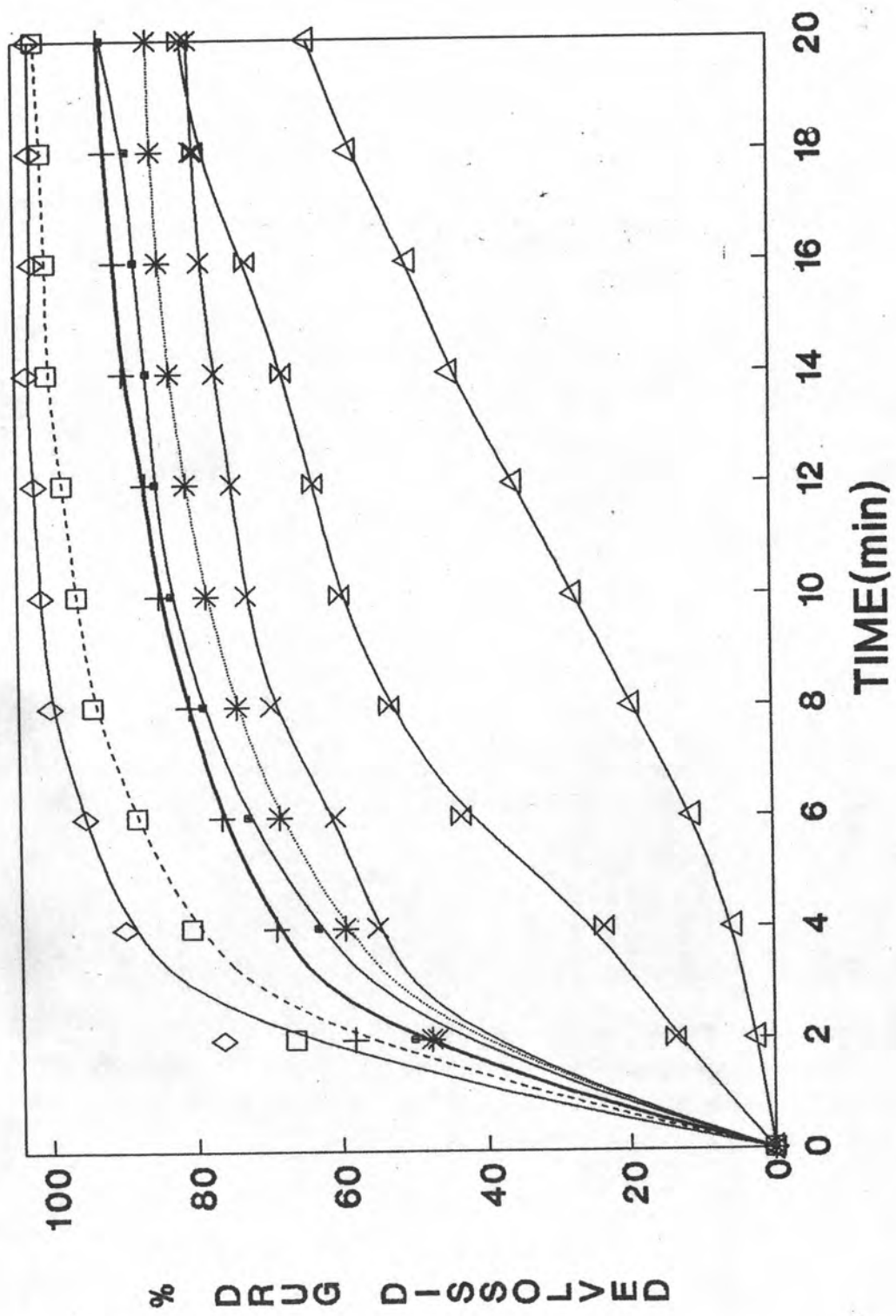


Figure 22
 Dissolution profiles of IDM from IDM-SLS powders both physical mixture with the ratio of 1:0.1 (.), 1:0.5 (*) and 1:1.0 (x) and solid dispersion with the ratio of 1:0.1 (+), 1:5 (◇) and 1:1.0 (△) from various ratio in phosphate buffer of pH 7.2 : water (1:4)

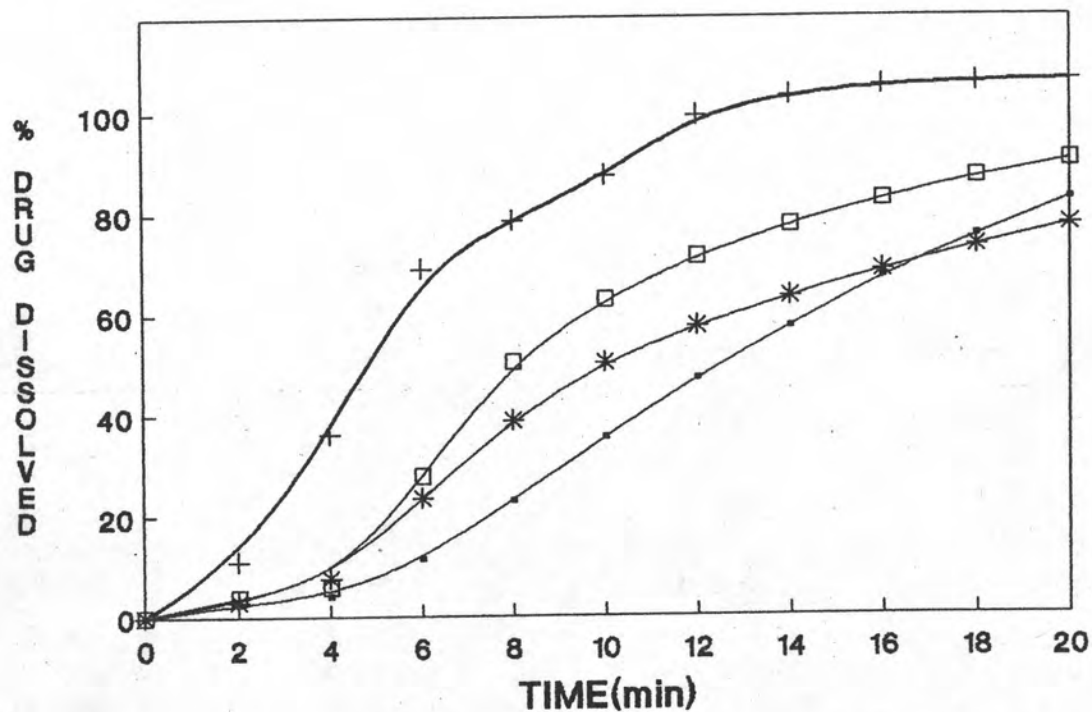


Figure 25 Dissolution profiles of IDM from IDM-PVP K 30 capsules both physical mixture (.) and solid dispersion (+) from ratio 1:1, including IDM (*) and treated IDM (□) in phosphate buffer of pH 7.2 : water (1.4)

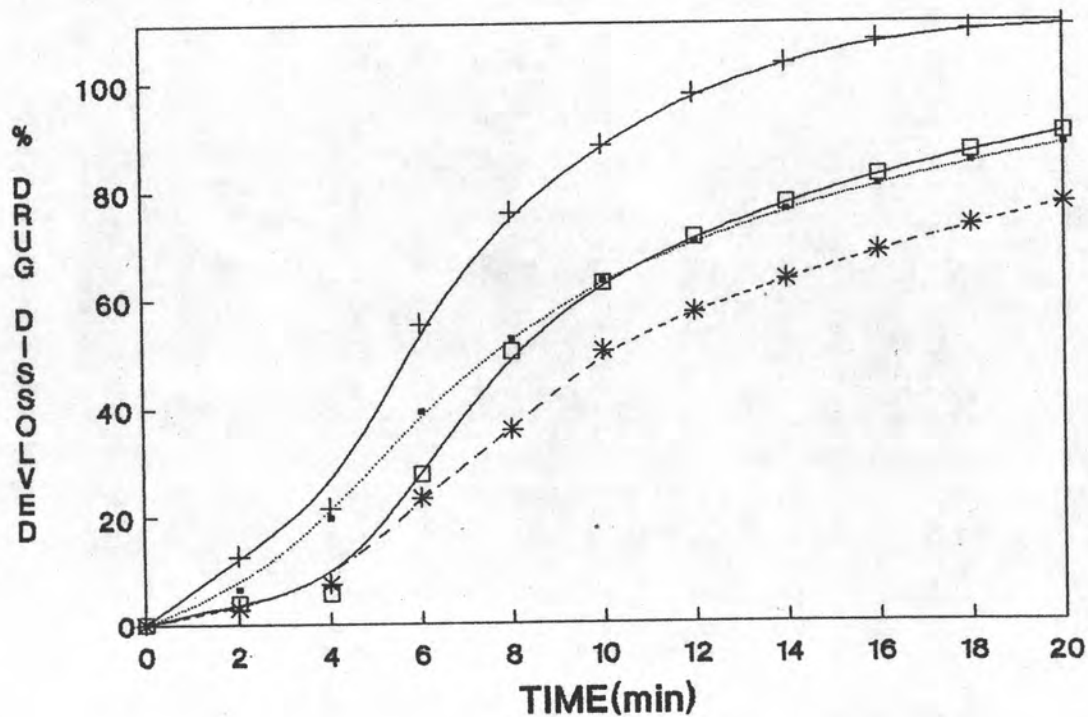


Figure 26 Dissolution profiles of IDM from IDM-SLS capsules both physical mixture (.) and solid dispersion (+) from ratio 1:1, including IDM (*) and treated IDM (□) in phosphate buffer of pH 7.2 : water (1.4)

2% less IDM dissolution than IDM and treated IDM capsule, respectively, while the coprecipitate capsule gave 25% higher IDM dissolution than the physical mixture. It took 16 minutes 36 seconds in the physical mixture capsule and 8 minutes 21 seconds in the coprecipitate capsule for dissolving 80% of IDM.

From all dissolution of IDM data from various ratio and types of carriers, the 1:10 IDM-PVP K 30 coprecipitate powder and 1:10 IDM-PEG 4000 coprecipitate were the fastest dissolution of IDM and IDM-SLS capsule was also the same.

Moreover, the only IDM-PVP physical mixture powder, were slower dissolution of IDM than treated IDM. All physical mixture capsule were also less IDM dissolution than treated IDM capsule, but most of them gave higher IDM dissolution than untreated IDM capsule.

The resulting coprecipitates

During evaporation step, IDM-PEG 4000 systems and IDM-PVP K 30 systems in absolute ethanol over the water bath were yellow and viscous solutions; whereas, IDM-mannitol systems and IDM-SLS system gave two distinct phases, yellow solution and white precipitate.

After drying in an incubator, mannitol coprecipitates were creamy white mass, PEG 4000 coprecipitates were pale yellowish brittle wax-like mass,

and SLS coprecipitates were pale yellow wax-like mass, as well. These three types of coprecipitates were easily pulverized and easily screened through a # 40 mesh. It took longer time for IDM-PVP K 30 coprecipitates to solidify. After drying the coprecipitates were yellow brittle and transparent mass. When IDM-PVP K 30 coprecipitates were ground, it should avoid using high temperature because this mass could melt at high temperature and would stick to the blender; thus, the powder of IDM-PVP K 30 could not be collected.

The IDM in absolute ethanol was yellow solution during the evaporation procedure. After drying, treated IDM appeared to be creamy white bulky mass. Moreover, treated IDM was easily ground and easily screened through a # 40 mesh.

Particle Size Appearance

The photomicrographs from the Scanning Electron Microscope illustrated the following powder appearance.

IDM was irregular crystal, from Figure 27a, 27b. Moreover, the picture also displayed some of the aggregations of IDM crystals. After treated with absolute ethanol. IDM appearances changed from irregular crystal to needle crystalline forms (Figure 27c, 27d).

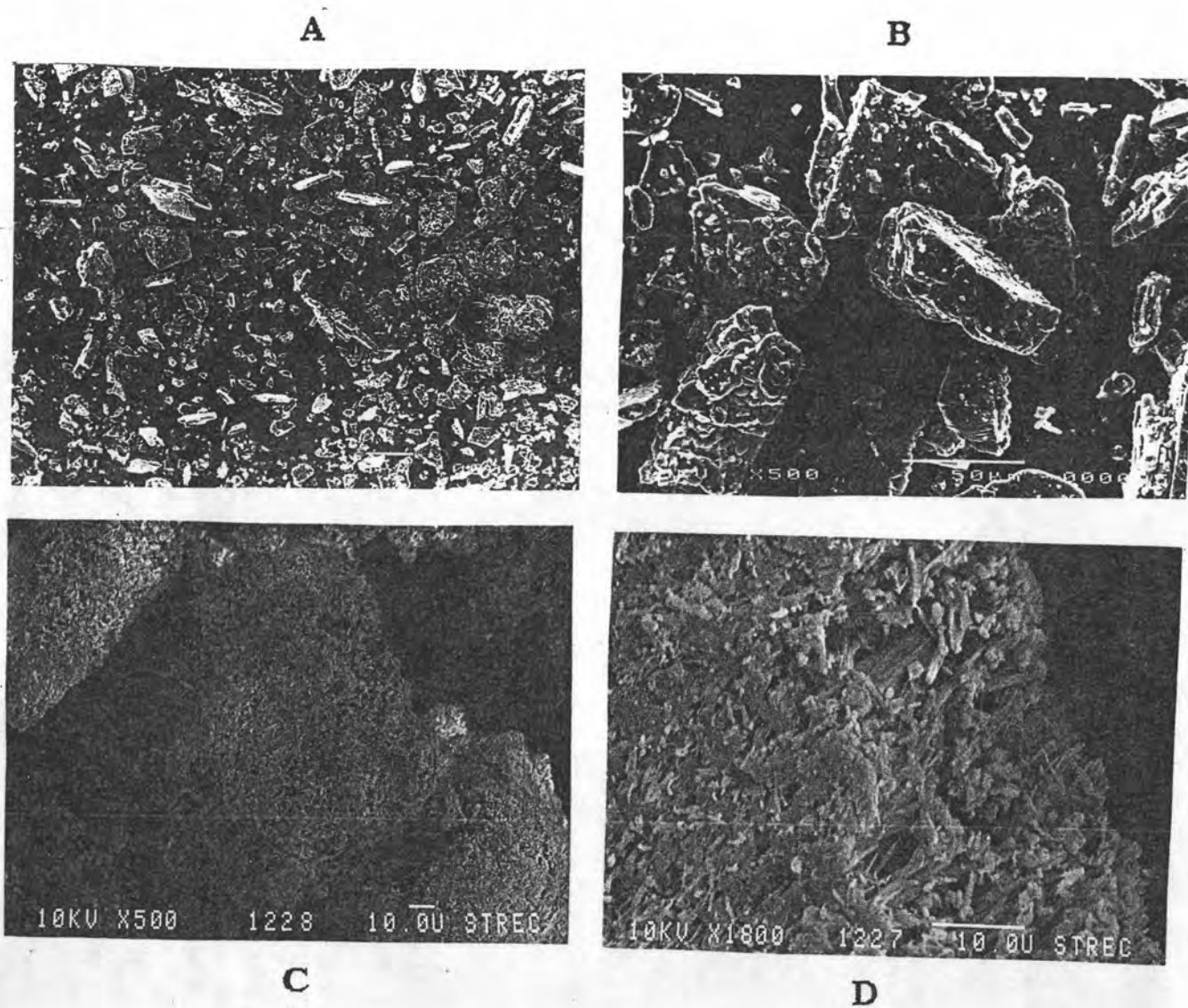


Figure 27

The photomicrographs of Indomethacin (key : A and B are Indomethacin powder, A x 100, B x 500; C and D are treated Indomethacin powder, A x 100, B x 1800)

In addition, the cluster of needle crystals of IDM was shown and the size of the aggregations of treated IDM was larger than IDM crystals. The length of needle crystals was about 10 to 40 μm .

Mannitol

Mannitol was an aggregate orthorombic crystal with a little fine needle crystals on the surface (Figure 28a, 28b). The pictures showed that the orthorombic size was about 150 x 200 μm . There was no fine needle crystals on the surface of crystal after it was treated with absolute ethanol (Figure 28c, 28d) and the sizes were quite equal to the untreated mannitol.

The amounts of IDM crystal and mannitol were rather equal in the 1:1 physical mixture (Figure 29a, 29b). A lot of fine needle crystals of IDM were deposited on the surface of mannitol in an cluster form in the 1:1 coprecipitate (Figure 29c, 29d). In physical mixture, the picture showed smaller size of mannitol than pure mannitol. However, the particle size of IDM-Mannitol coprecipitate from the pictures showed larger than that of physical mixture.

Less amounts of IDM crystal was in the ratio of 1.5 physical mixture (Figure 30a, 30b) than the ratio of 1:1, but some mannitol crystals were smaller than pure mannitol. Moreover, in the 1:5 coprecipitate showed

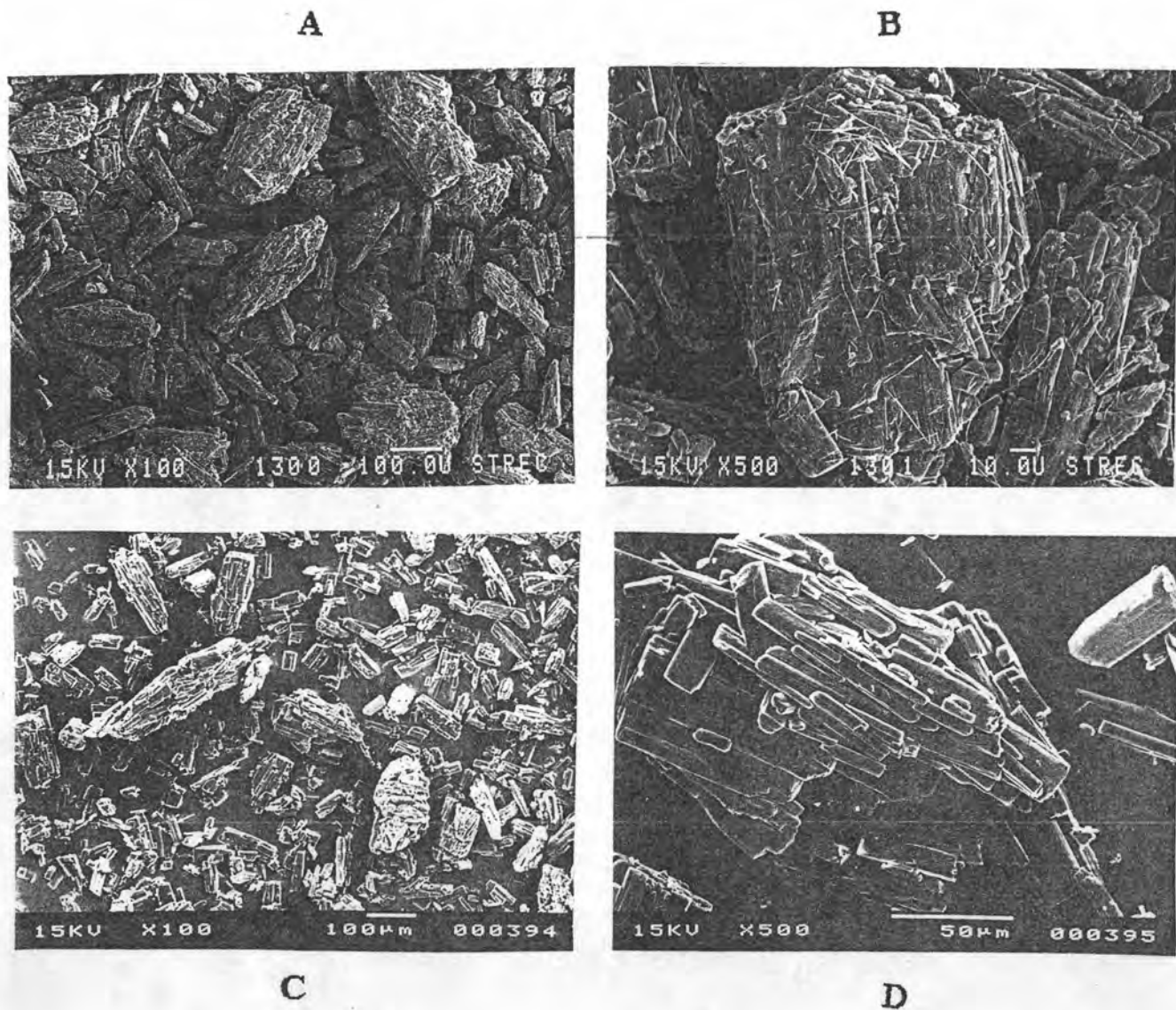


Figure 28

The photomicrographs of Mannitol (key : A and B are Mannitol powder, A x 100, B x 500; C and D are treated Mannitol powder, A x 500, B x 500)

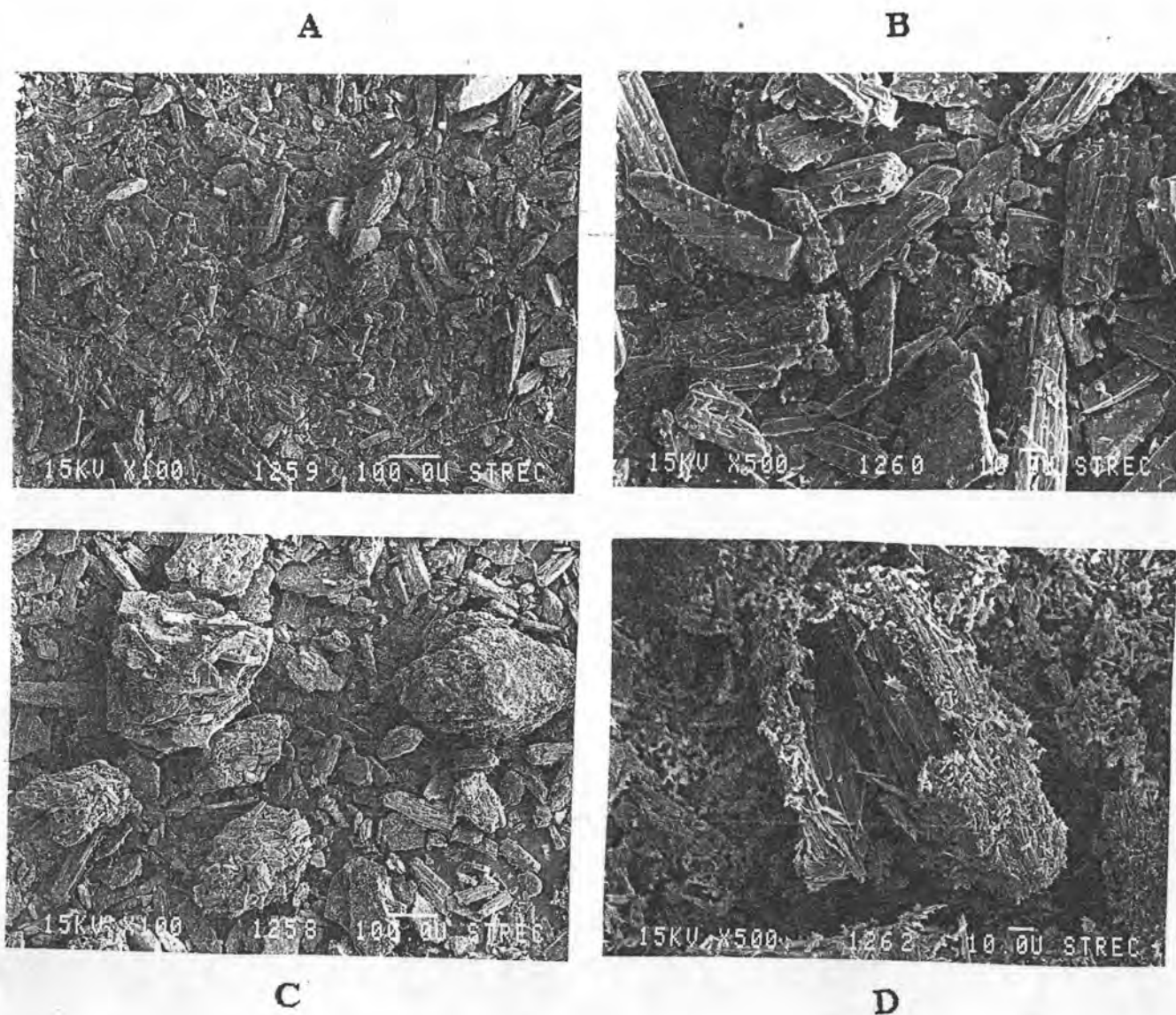


Figure 29

The photomicrographs of IDM-Mannitol ratio 1:1
 (key : A and B are physical mixture, A x 100,
 B x 500; C and D are coprecipitate, A x 100, B
 x 500)

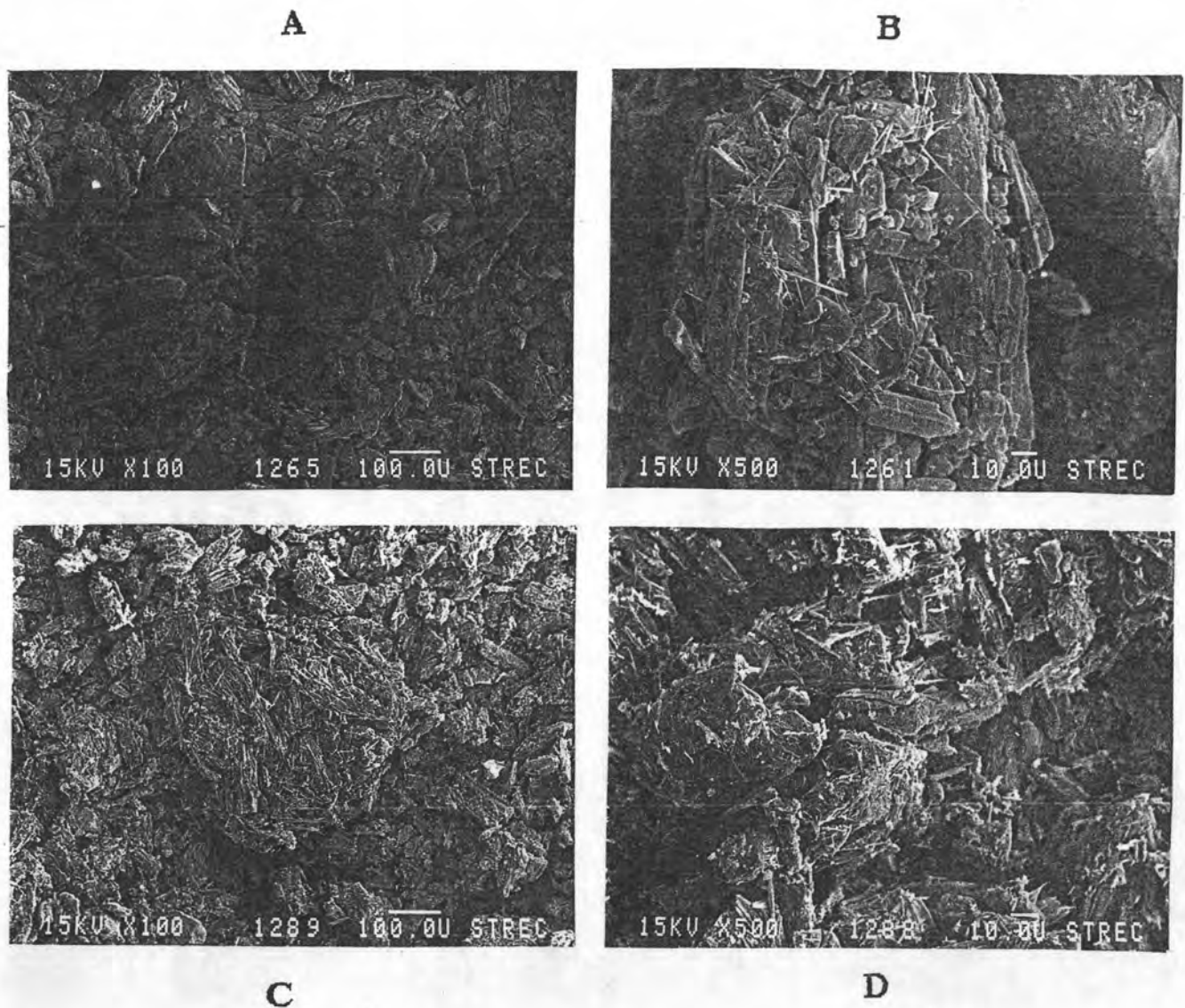


Figure 30 The photomicrographs of IDM-Mannitol ratio 1:5
(key : A and B are physical mixture, A x 100,
B x 500; C and D are coprecipitate, A x 100, B
x 500)

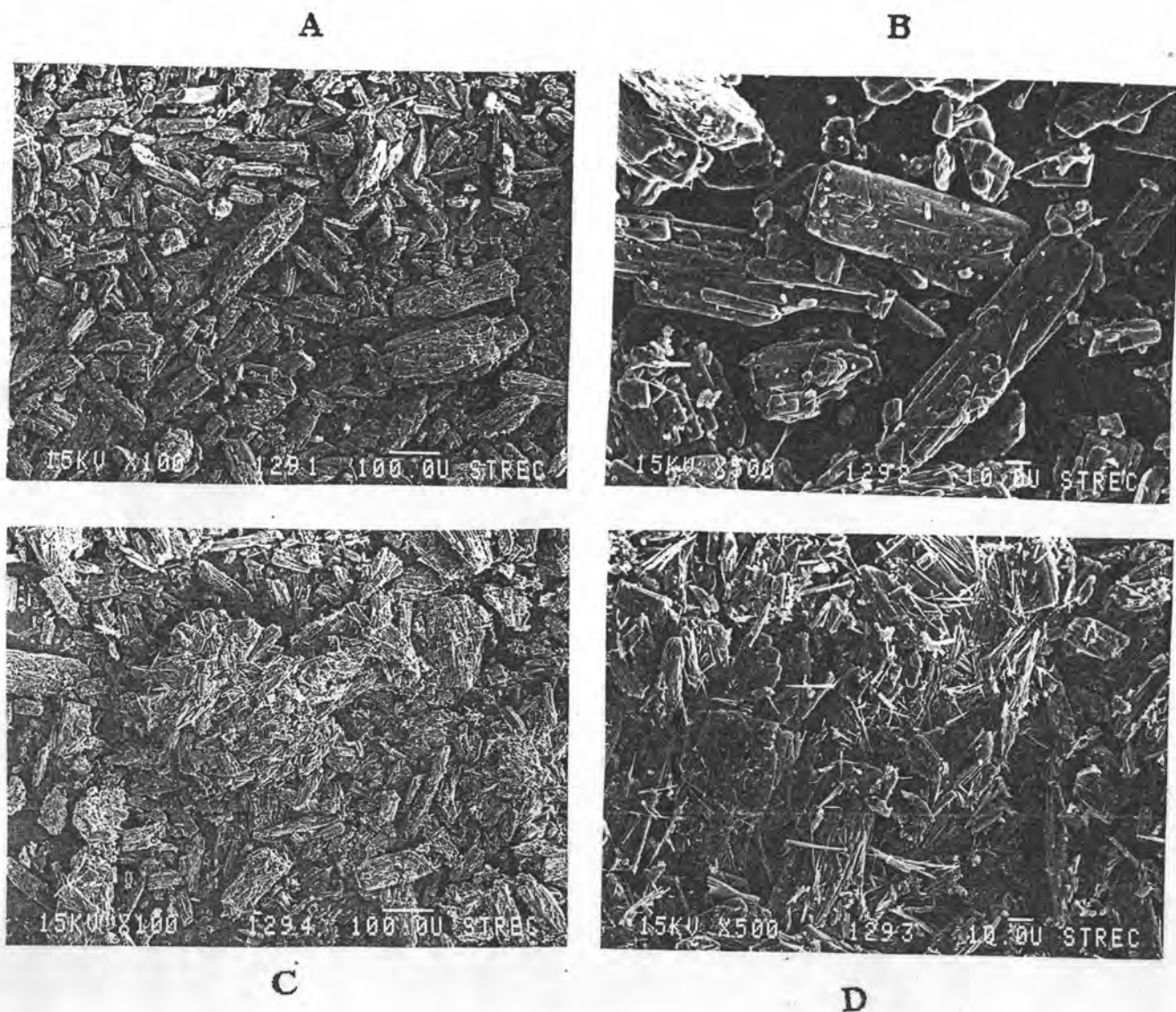


Figure 31 The photomicrographs of IDM-Mannitol ratio 1:10 (key : A and B are physical mixture, A x 100, B x 500; C and D are coprecipitate, A x 100, B x 500)

larger cluster size of IDM-Mannitol than its physical mixture and the needle crystals of IDM deposited on the surface of mannitol in less aggregated form.(Figure 30c, 30d). Finally, the 1:10 physical mixture contained the least amount of IDM crystals and the size of mannitol crystals were smaller than pure mannitol (Figure 31a, 31b). After treated with absolute ethanol, the needle crystal of IDM were larger than the other two ratio and quite individually seperated on the surface of mannitol (Figure 31c, 31d). The size of coprecipitate were larger than that of physical mixture.

PEG 4000

PEG 4000 showed various shapes and sizes such as globular with diameter about 300 to 500 um, flakes or tubular types that were seen in Figure 32a, 32b, while the treated PEG 4000 was irregular shape with much rougher surface than untreated PEG 4000 (Figure 32c, 32d).

The photomicrographs showed that IDM crystal was on the surface of PEG 4000 in physical mixture. The more amount of PEG 4000 existed, the less IDM crystals were on the surface (Figure 33-35a, b). Some of IDM in physical mixture were smaller than pure IDM. The 1:1 coprecipitate was partially porous mass (Figure 33c, 33d). The pores looked like needle crystals of IDM that was immersed in the solid mass. In the 1:5 and 1:10 coprecipitates (Figure 34-35c, d), the pictures also displayed fine

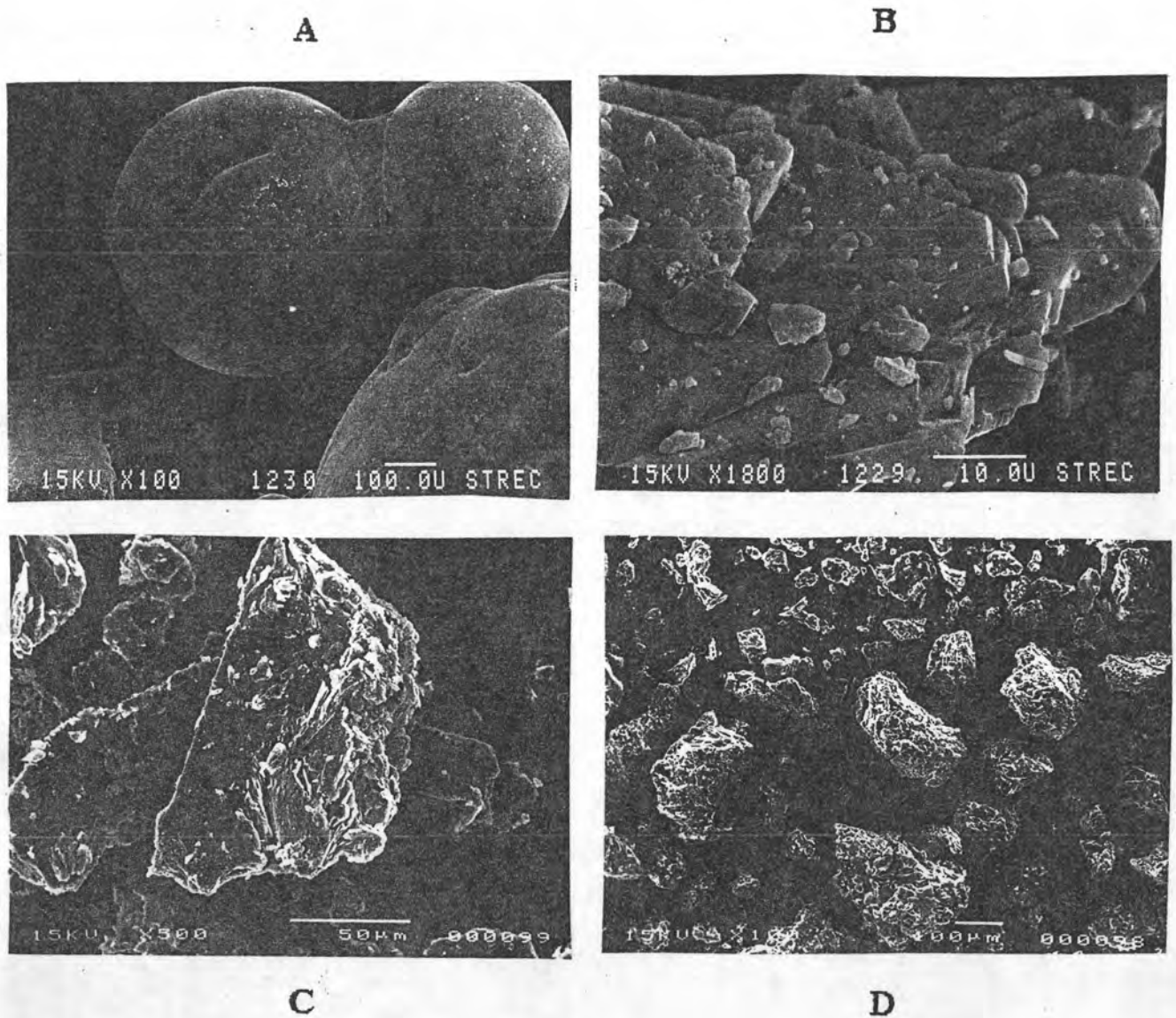


Figure 32 The photomicrographs of PEG 4000 (key : A and B are PEG 4000, A x 100, B x 1800 C and D are treat PEG 4000, C x 500, D x 100)

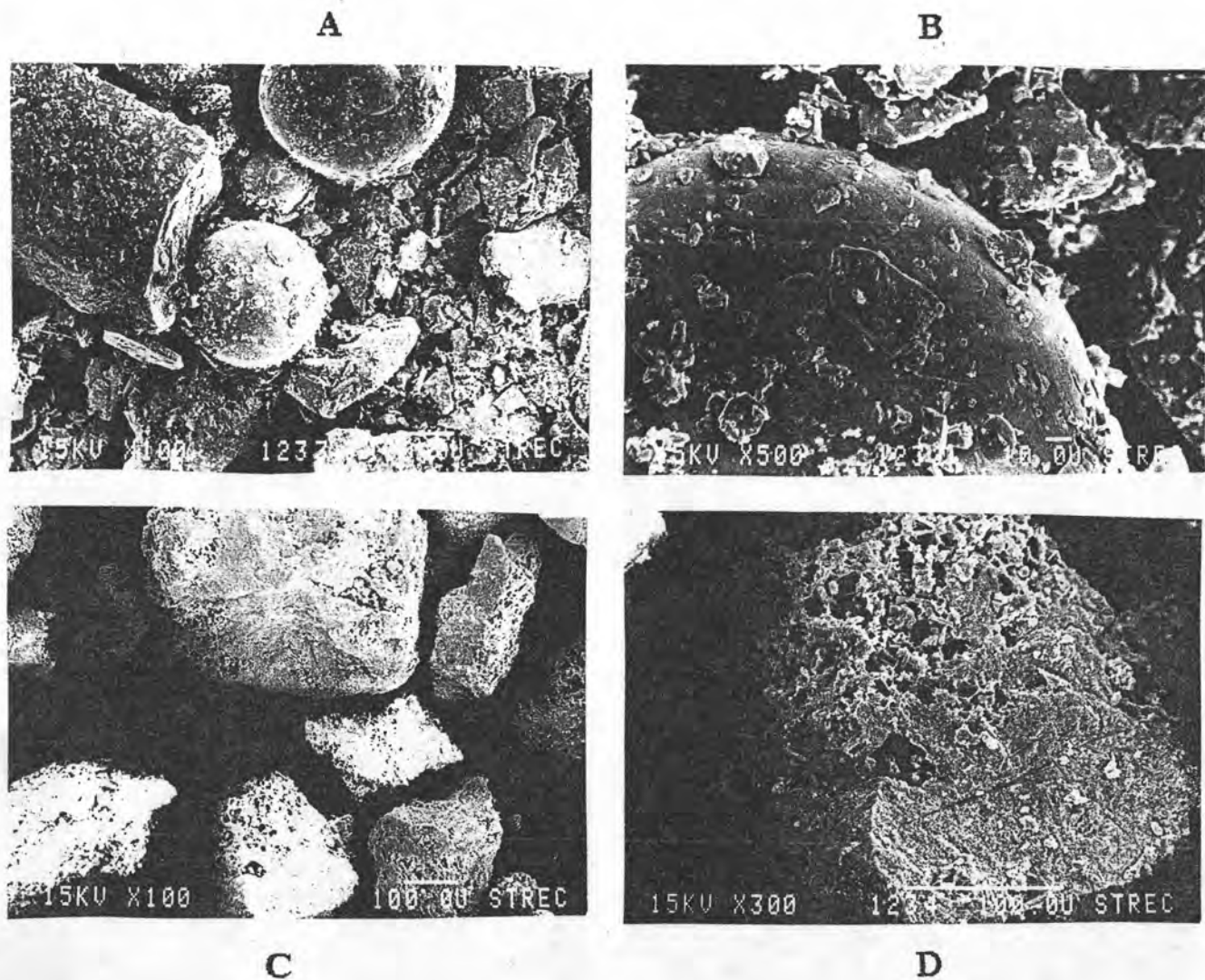


Figure 33

The photomicrographs of IDM-PEG 4000 ratio 1:1
 (key : A and B are physical mixtures, A x
 100, B x 500; C and D are coprecipitates, C x
 100, D x 500)

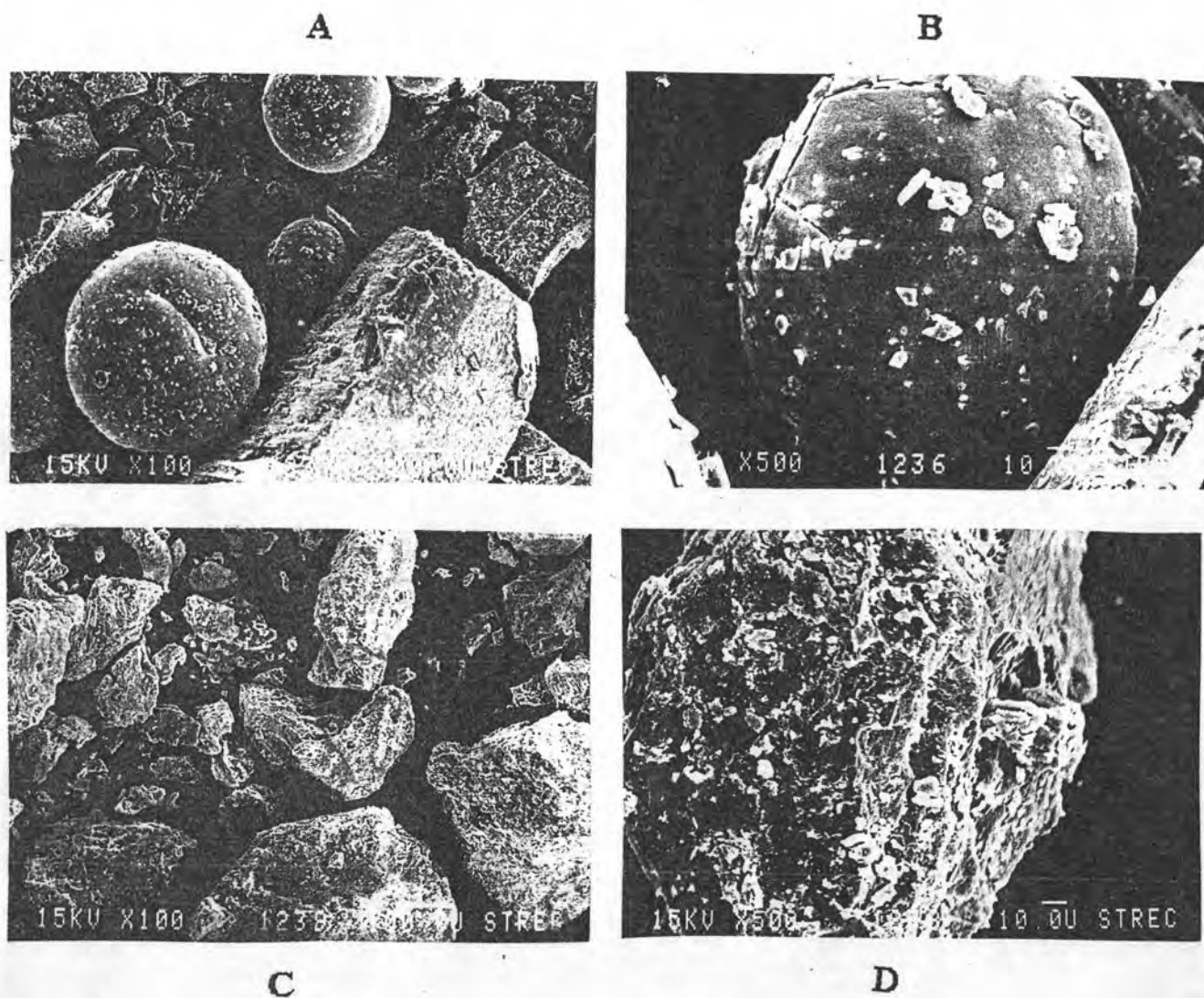


Figure 34

The photomicrographs of IDM-PEG 4000 ratio 1:5
 (key : A and B are physical mixtures, A x
 100, B x 500; C and D are coprecipitates, C x
 100, D x 500)

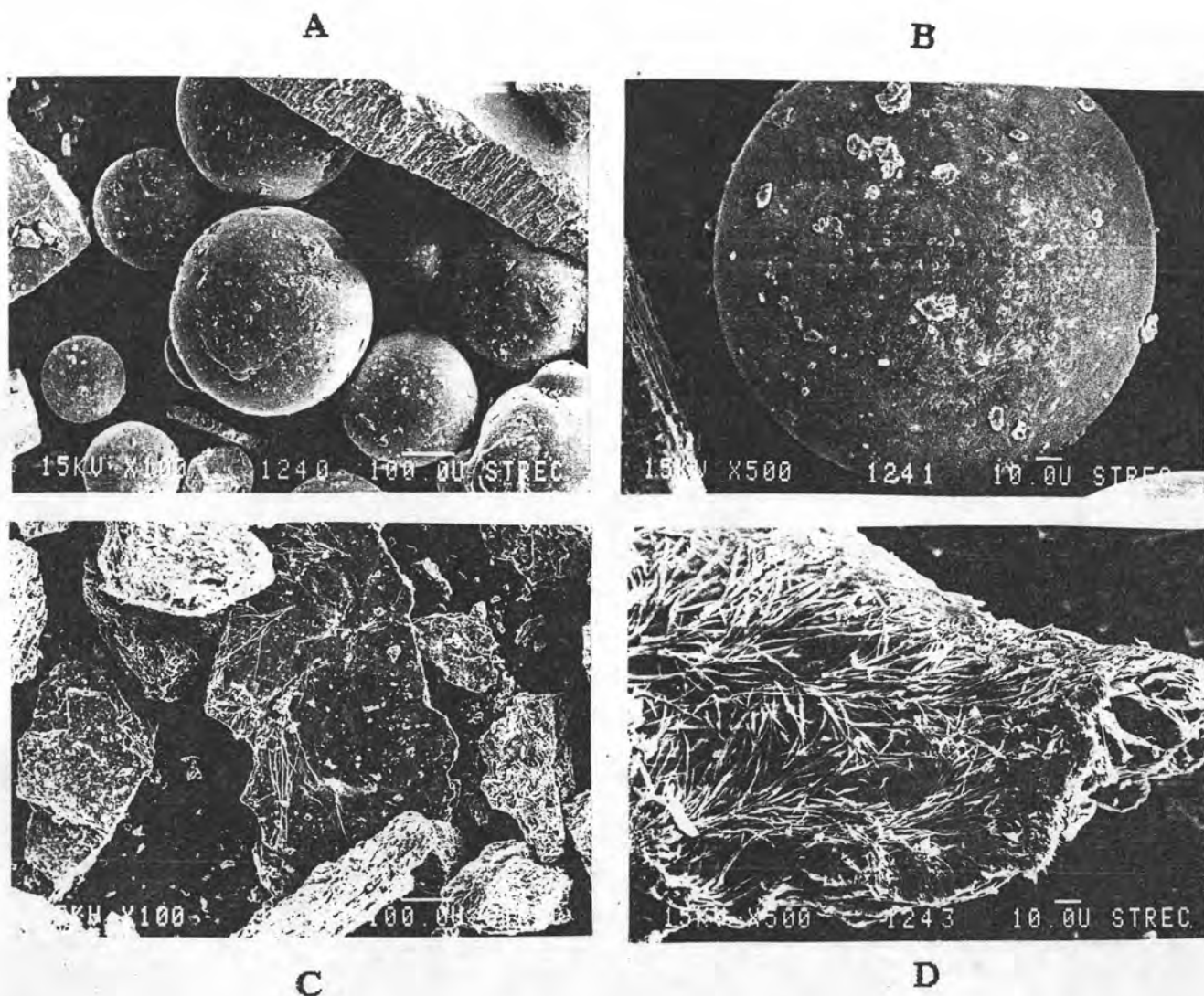


Figure 35 The photomicrographs of IDM-PEG 4000 ratio 1:10 (key : A and B are physical mixtures, A x 100, B x 500; C and D are coprecipitates, C x 100, D x 500)

needle crystal of IDM on the surface of the coprecipitate mass, but the 1:1 coprecipitate obviously showed needle crystal of IDM on the surface more than the 1:5 coprecipitate. The coprecipitates were irregular shapes with various size and the surface of the mass were much rougher than the surface of physical mixtures.

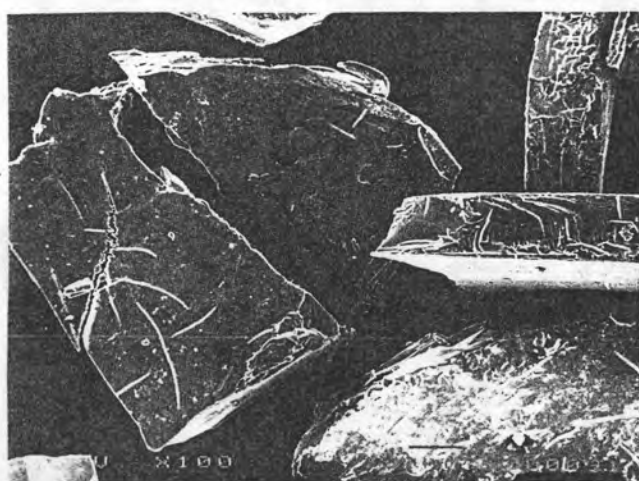
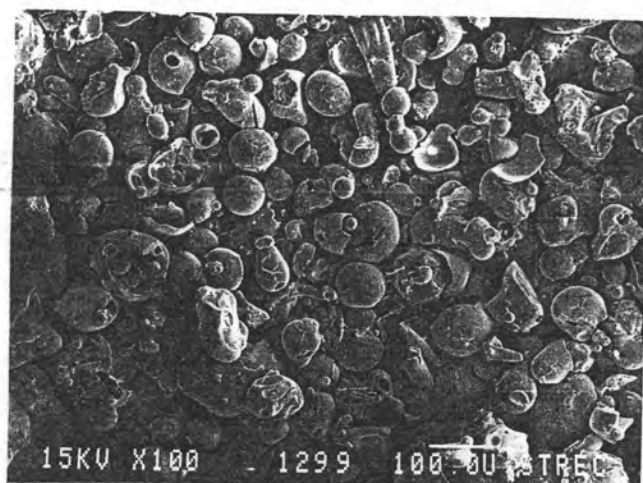
PVP K 30

PVP K 30, in Figure 36a, was almost spherical shape with a diameter about 10 to 100 μm . After treated with absolute ethanol, spherical shape of PVP K 30 were changed to bigger irregular mass with smooth surface that could be seen in Figure 36b, 36c.

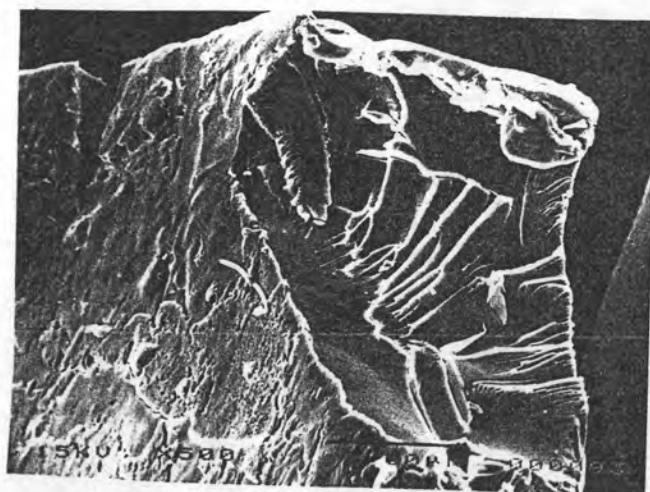
The physical mixture of more weight fraction of PVP K 30 in system showed that the more loosely of IDM crystals deposited on the surface of PVP K 30 (Figure 37-39a, b). Moreover, the particle size of IDM crystal were smaller than pure IDM, which the sizes and shapes of PVP K 30 were rather the same as pure materials.

From Figure 37-39c, d, the coprecipitate mass were irregular shapes with smooth surface, except the ratio of 1:1 that appeared a little rougher surface. The sizes of coprecipitate were varied. Some of them were larger than the particle size of IDM and PVP K 30 in physical mixture.

A



B



C

Figure 36 The photomicrographs of PVP K 30 (key : A is PVP k 30 powder, A x 100; B and C are treated PVP k 30, B x 100, C x 500)

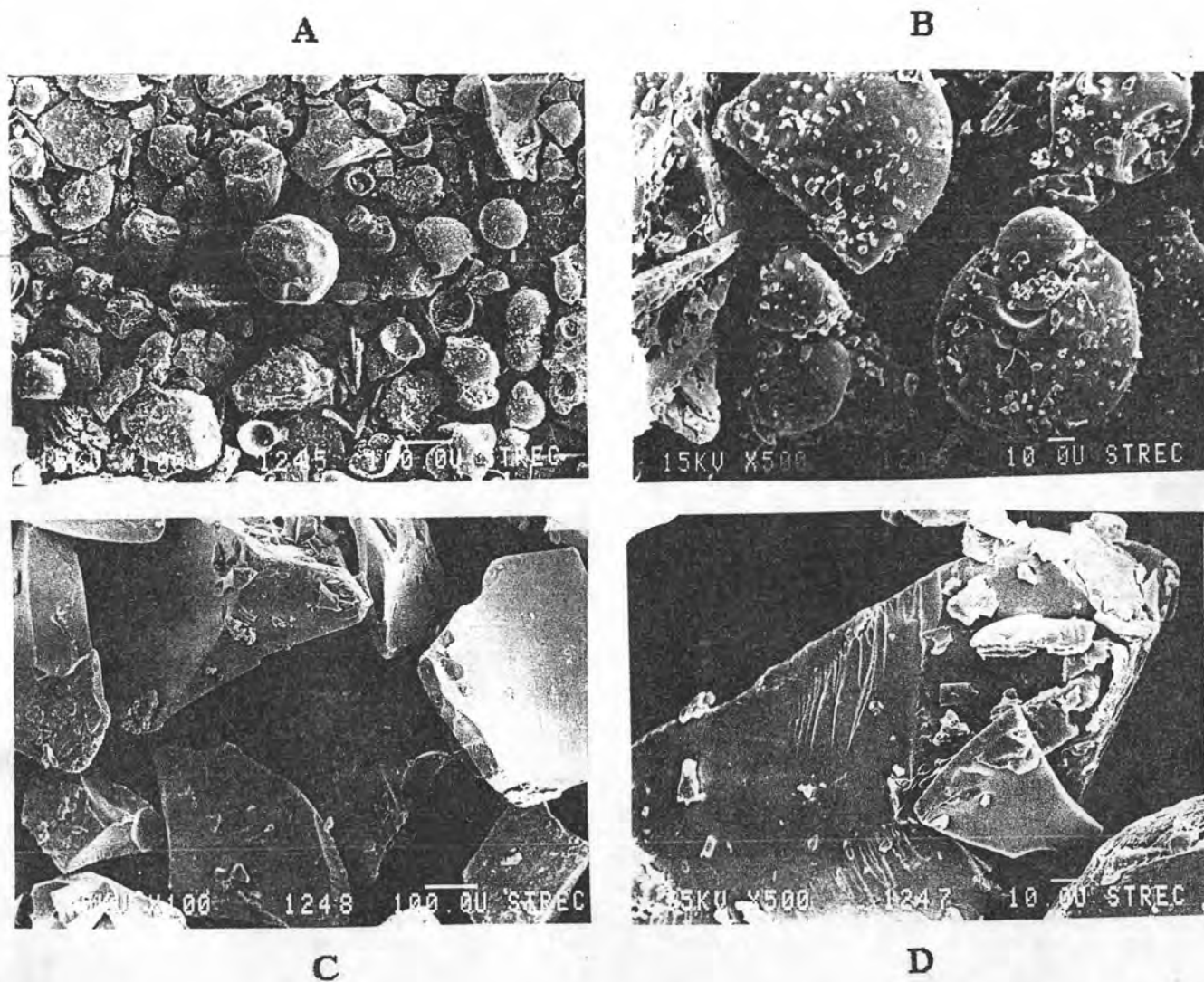


Figure 37

The photomicrographs of IDM-PVP K 30 ratio 1:1
 (key : A and B are physical mixtures, A x
 100, B x 500; C and D are coprecipitates, C x
 100, D x 500)

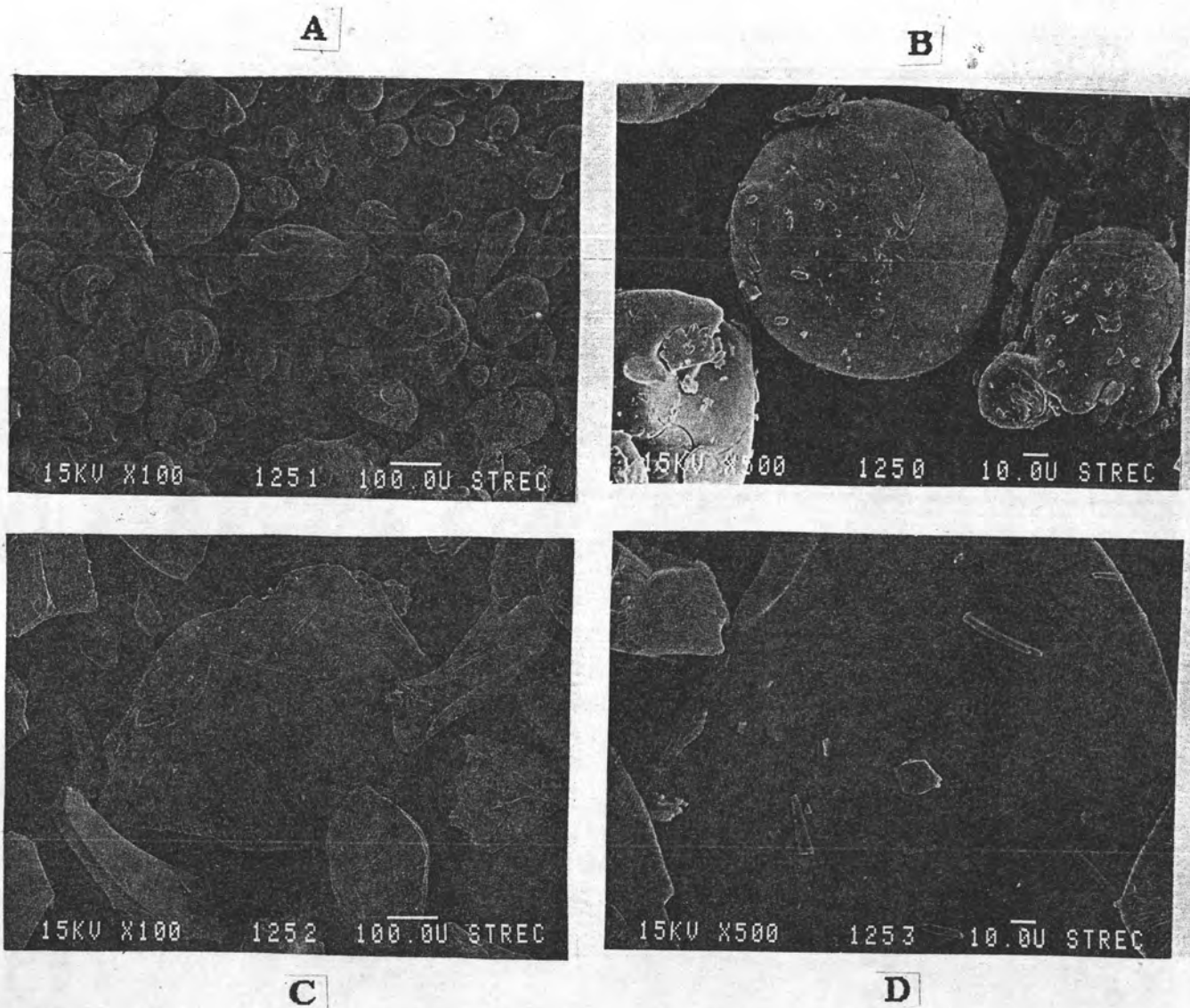


Figure 38 The photomicrographs of IDM-PVP k 30 ratio 1:5
 (key : A and B are physical mixtures, A x
 100, B x 500; C and D are coprecipitates, C x
 100, D x 500)

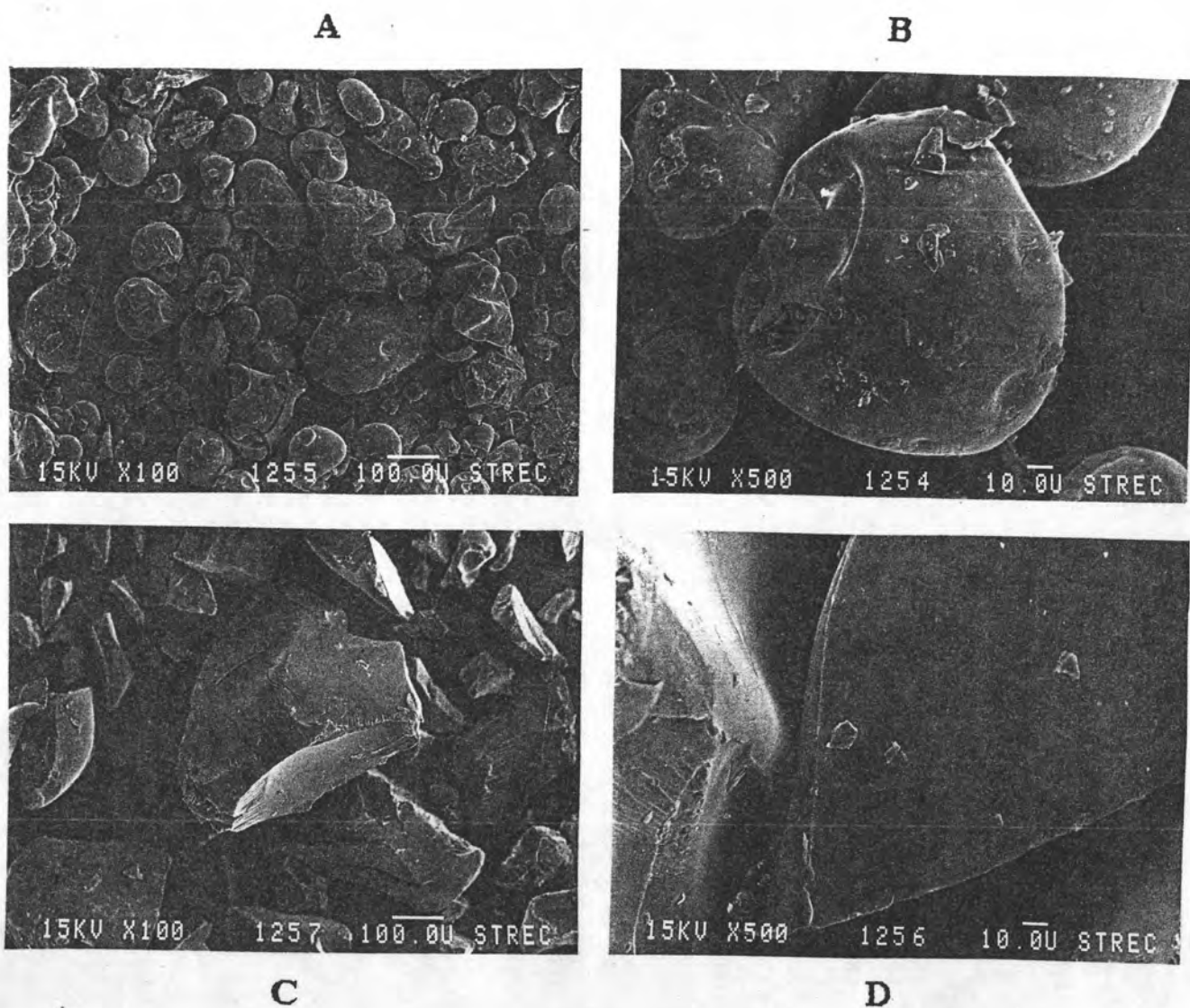


Figure 39 - The photomicrographs of IDM-PVP k 30 ratio 1:10
(key : A and B are physical mixtures, A x 100, B x 500; C and D are coprecipitates, C x 100, D x 500)

SLS

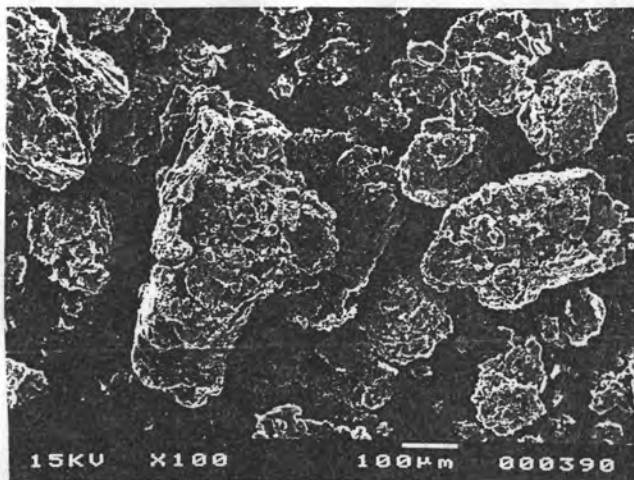
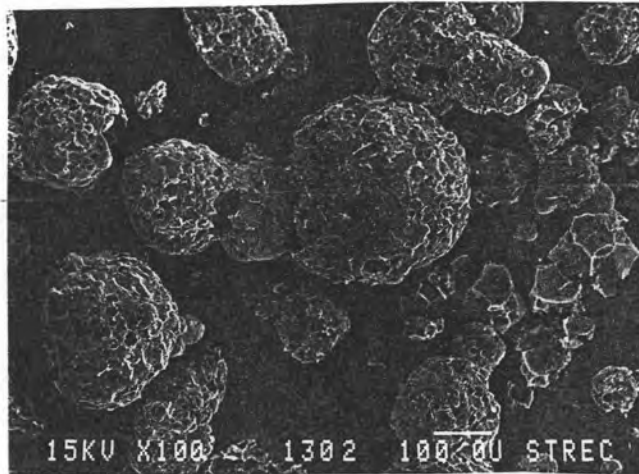
The photomicrograph of sodium lauryl sulfate was in Figure 40a. Its shape was spherical and diameter was about 100 to 300 μm . It was also porous and hollow spherical. There were some fracture of SLS spherical; thus, it implied that SLS could be broken. After treated with absolute ethanol, the shape of SLS was rough and irregular with various size (Figure 40b, 40c).

The fractures of SLS were on the surface of IDM crystal in the 1:0.1 physical mixture (Figure 41a, 41b). However, the picture of the 1:0.1 coprecipitate displayed aggregated needle crystals of IDM and little mass of SLS (Figure 41c, 41d). The size of physical mixture and coprecipitate were rather equal, but some of coprecipitate were larger than physical mixture.

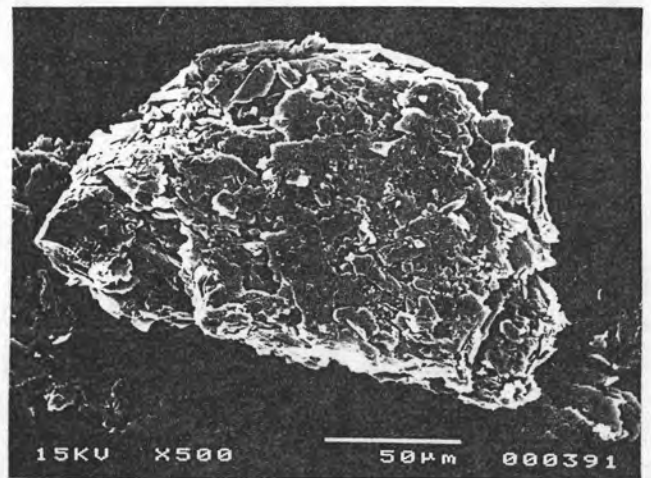
In the ratio of 1:0.5, there were some spherical shape of SLS in physical mixture and also some fractures (Figure 42a, 42b). The coprecipitate pictures showed that IDM needle crystal deposited on the surface and some immersed in IDM-SLS coprecipitate (Figure 42c, 42d). The particle sizes of coprecipitate mass were larger than that of physical mixture.

Finally, the 1:1 IDM-SLS system were shown in Figure 43a-d. The physical mixture, in Figure 43a, 43b, showed that there were some remained SLS globular appearance and some of globular SLS were fracture.

A



B



C

Figure 40

The photomicrographs of SLS (key : A is SLS powder, A x 100; B and C are Treated SLS, B x 100, C x 500)

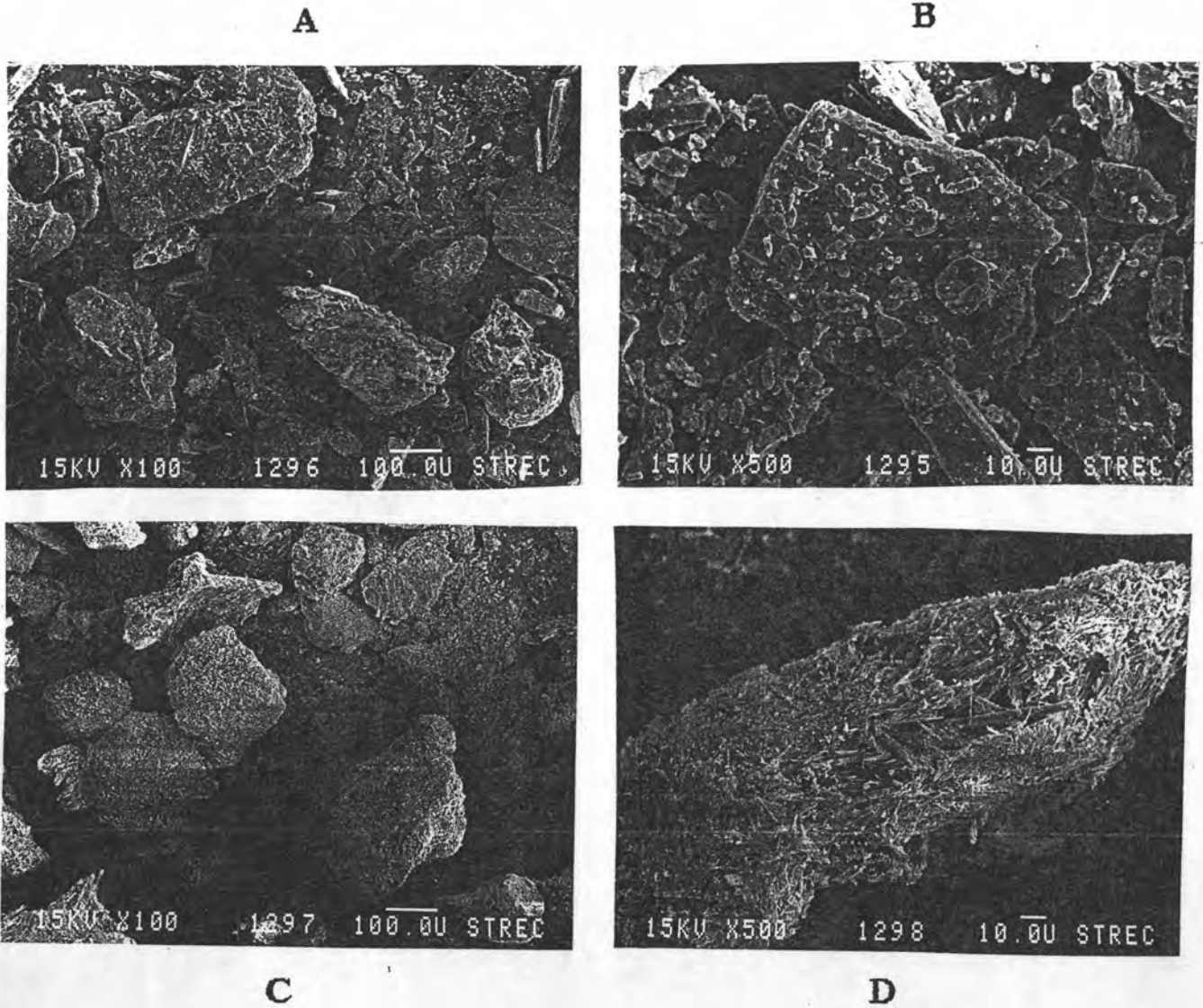


Figure 41 The photomicrographs of IDM-SLS ratio 1:0.1 (key : A and B are physical mixtures, A x 100, B x 500; C and D are coprecipitates, C x 100, D x 500)

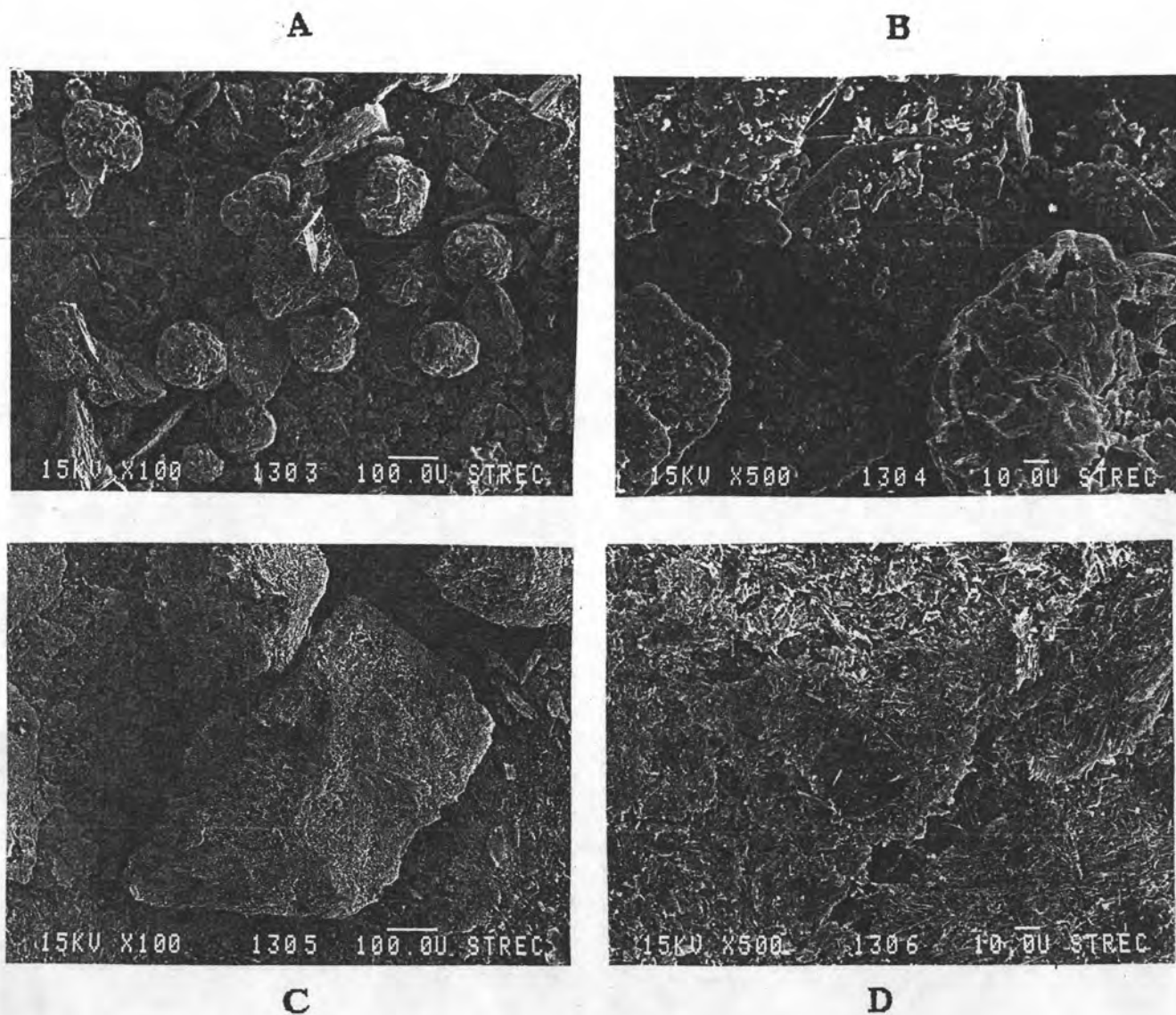


Figure 42 The photomicrographs of IDM-SLS ratio 1:0.5
 (key : A and B are physical mixtures, A x
 100, B x 500; C and D are coprecipitates, C x
 100, D x 500)

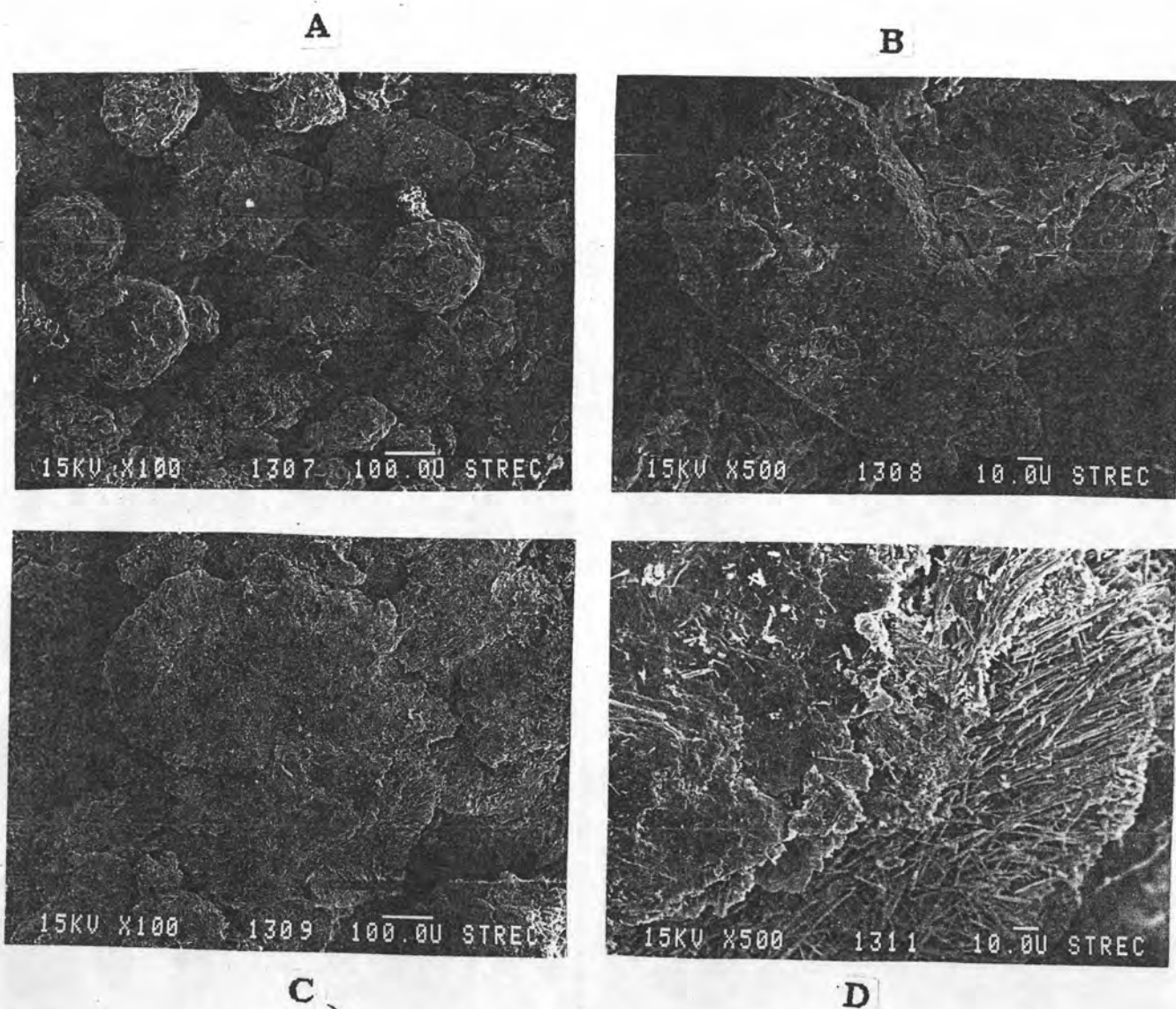


Figure 43 The photomicrographs of IDM-SLS ratio 1:10
 (key : A and B are physical mixtures, A x
 100, B x 500; C and D are coprecipitates, C x
 100, D x 500)

Moreover, the amount of spherical SLS were equal to the amount of IDM crystals. It was clearly displayed that needle crystals of IDM were deposited on surface and some were immersed in the mass. The needle crystal were also aggregated in Figure 43c, 43d. The size of the component in physical mixture were more minute than that of coprecipitate, but the size distribution of physical mixture from photomicrograph was not much different from coprecipitate.

The Infrared Spectra

The IR spectra of untreated and treated IDM powder were shown in Figure 44. The IR spectra of both IDM forms showed major peaks of C-O stretching at 1690 and 1720 cm^{-1} . The peak at 1690 cm^{-1} indicated C-O stretching of ketone group and at 1720 cm^{-1} referred to C-O stretching of carboxylic group from IDM molecules. After treated with absolute ethanol, their IR spectra were different from untreated, IDM spectra that treated IDM spectra showed interesting peaks at 1675, 1690 and 1730 cm^{-1} and a broad peak from 3100 to 3300 cm^{-1} . The broad peak referred to O-H stretching.

The IR spectra of the 1:1 IDM-Mannitol, Figure 45, showed the combination of peaks of mannitol and IDM. This combination was confirmed by peaks at 1720 and 1690 cm^{-1} of untreated IDM and a broad peak from 3300 to 3400 cm^{-1} of mannitol. In the same ratio of coprecipitate, the IR

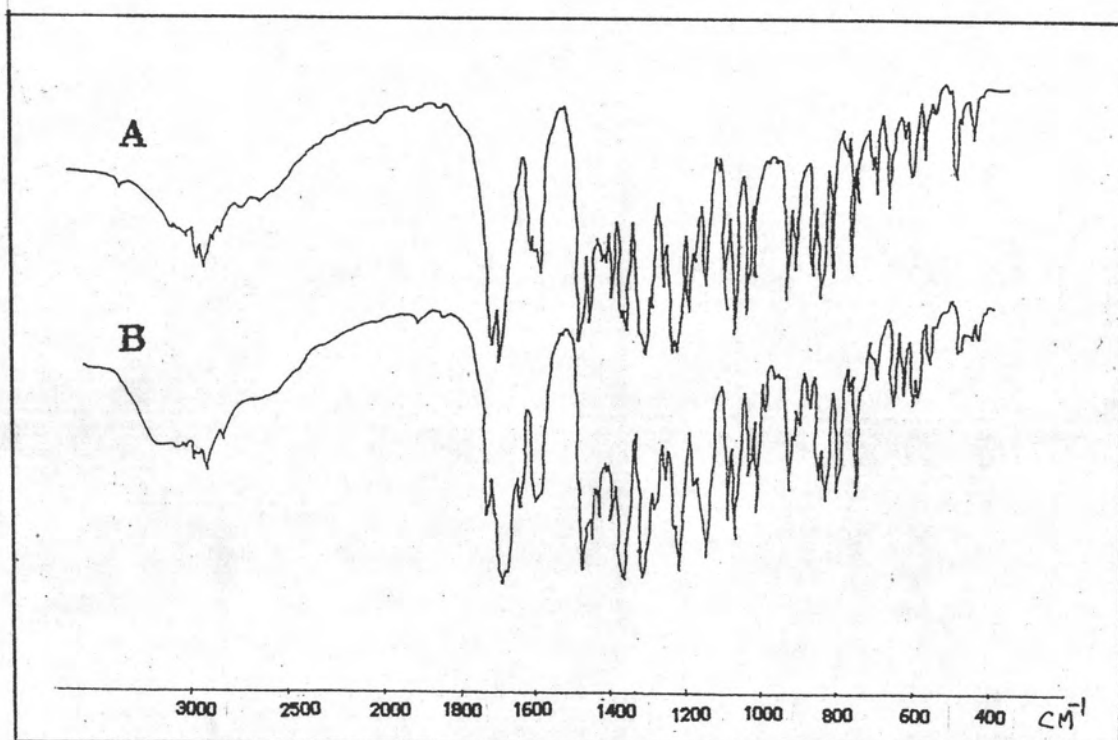


Figure 44 IR spectra of Indomethacin (key : A - IDM powder; B - treated IDM)

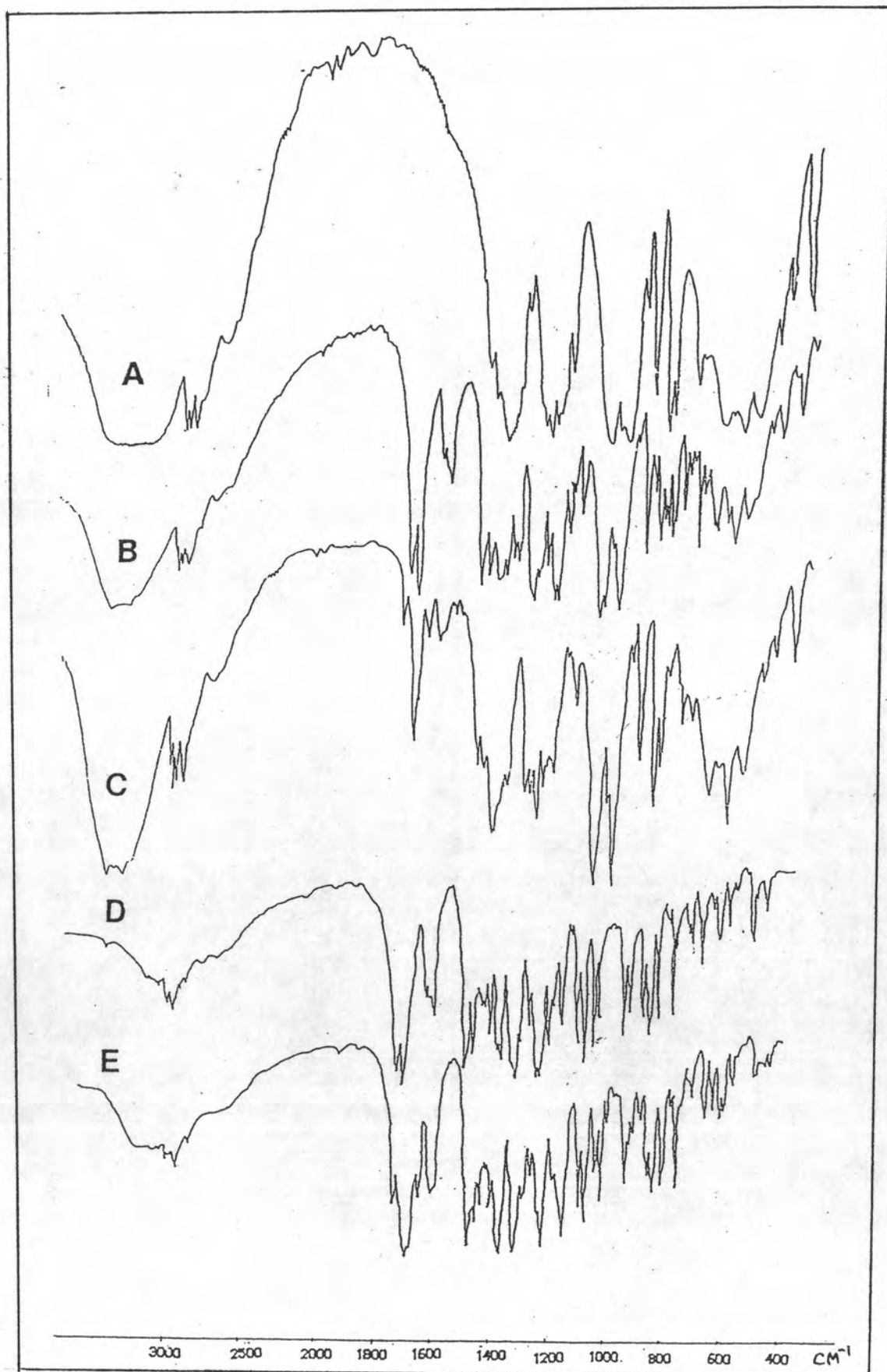


Figure 45

The IR spectra of Mannitol (A) and IDM-Mannitol systems, the 1:1 physical mixture (B) and the 1:1 coprecipitate (C), including untreated IDM (D) and treated IDM (E).

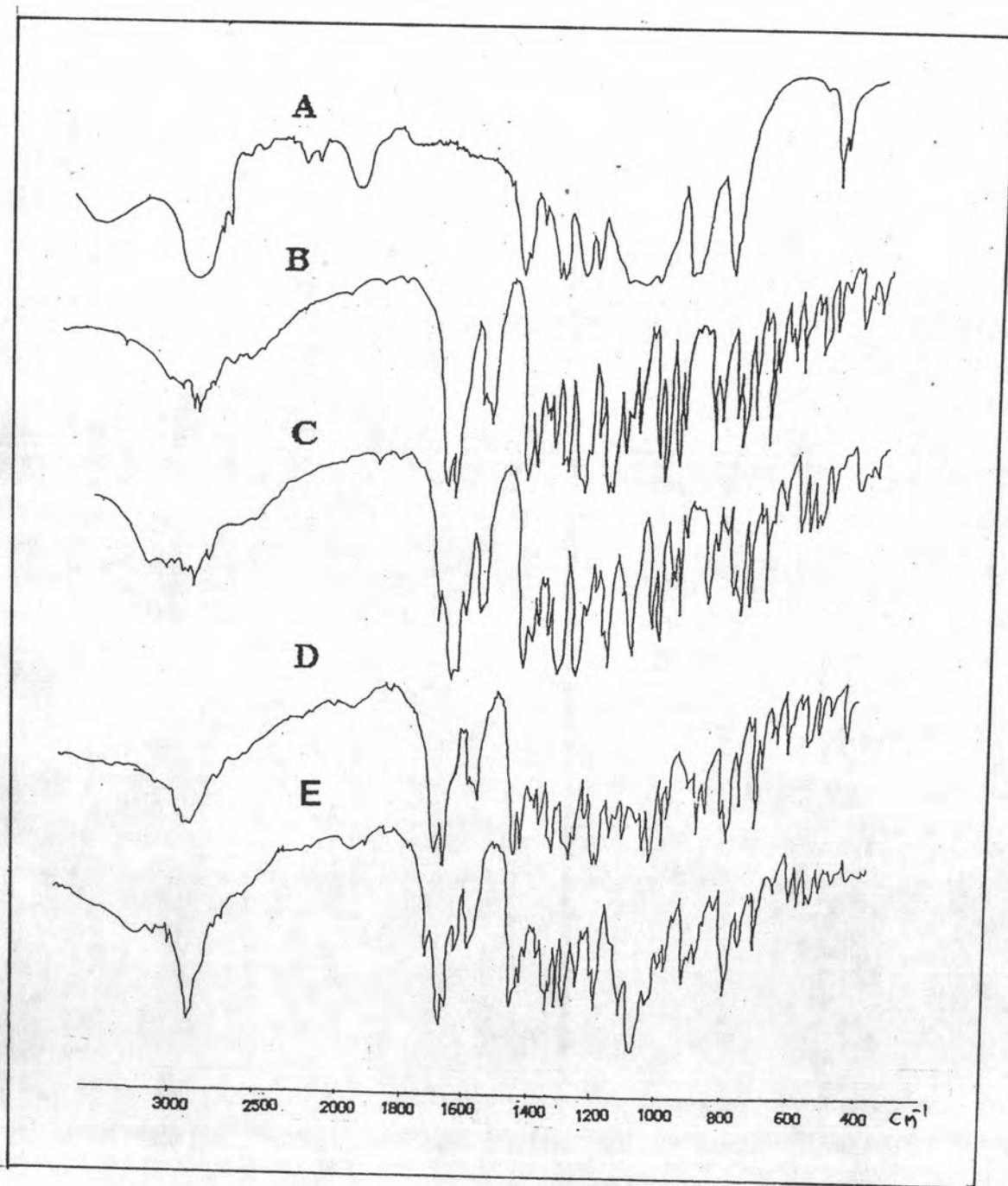


Figure 46

The IR spectra of PEG 4000 (A) and IDM-PEG 4000 systems, the 1:1 physical mixture (B) and the 1:1 coprecipitate (C), including untreated IDM (D) and treated IDM (E).

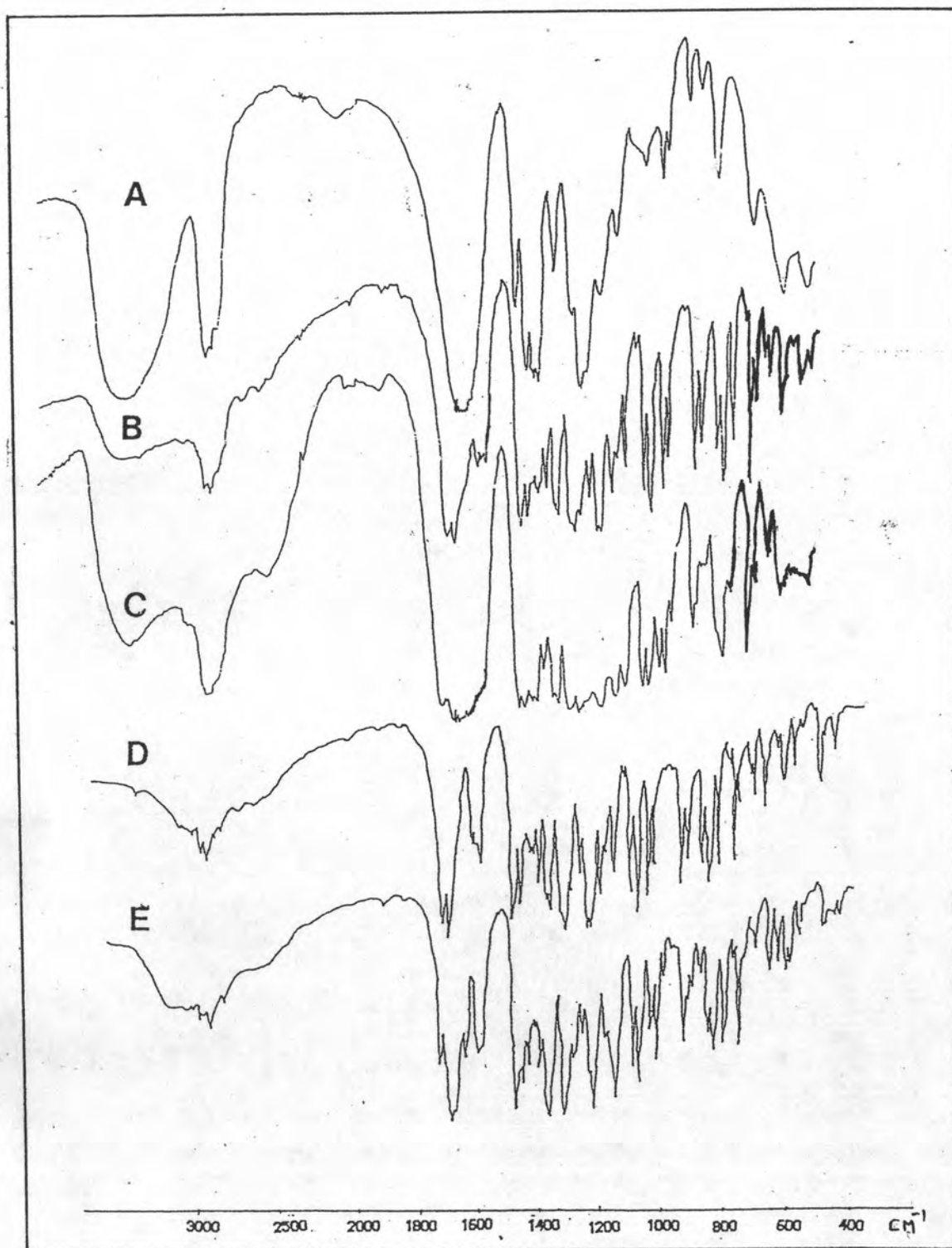


Figure 47

The IR spectra of PVP K 30 (A) and IDM-PVP K 30 systems, the 1:1 physical mixture (B) and the 1:1 coprecipitate (C), including untreated IDM (D) and treated IDM (E).

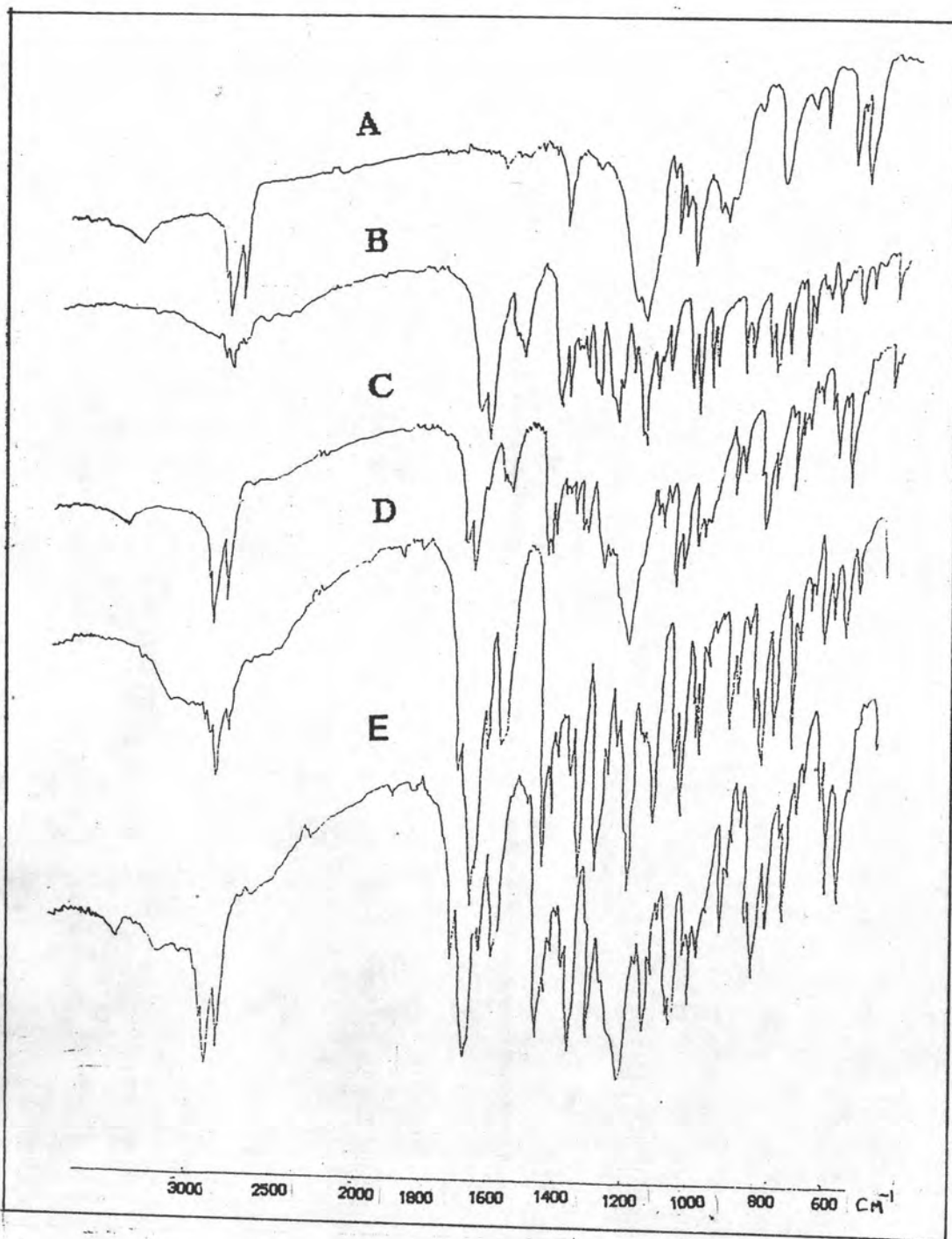


Figure 48

The IR spectra of SLS (A) and IDM-SLS systems, the physical mixture of IDM-SLS with of 1:0.1 (B) and 1:1.0 (C), corresponding with coprecipitate with ratio of 1:0.1 (D) and 1:1.0 (E).

spectra of mannitol were still the same with the similar spectra as treated IDM at 1730, 1690 and 1680 cm^{-1} .

The IR spectra of PEG 4000, figure 46, showed peaks at 1960 cm^{-1} , triple board peaks from 2800 to 2990 cm^{-1} , from 3300 to 3600 cm^{-1} and from 1000 to 1200 cm^{-1} . The 1:1 IDM-PEG 4000 physical mixture showed interesting peaks at 1690, 1720 cm^{-1} and a broad peak from 2800 to 2990 cm^{-1} . The two former peaks were the peak of C-O stretching in untreated IDM and the latter board peak indicated PEG 4000 spectra. The 1:1 IDM-PEG 4000 coprecipitate, figure 46, illustrated the C-O stretching peaks of IDM as same as treated IDM at 1675, 1690 and 1730 cm^{-1} , and one board peak between 3100 and 3300 cm^{-1} . Moreover, the double board peaks at 1000 to 1200 cm^{-1} and 2800 to 2980 cm^{-1} in the coprecipitate were more obviously noticed than in the physical mixture.

The IR spectra of PVP K 30 showed the interesting peaks at 1480 cm^{-1} and a board peak at 3340 cm^{-1} . The peak at 1480 cm^{-1} indicated C-N stretching and a board peak indicated water molecule in PVP K 30, Figure 47. The coprecipitate spectra showed that there was a shift of peak from 1480 cm^{-1} to 1430 cm^{-1} . This peak indicated both C-N stretching of PVP K 30 and C-N stretching or C-C in ring stretching of IDM molecule, while the physical mixture showed the combination of peaks from untreated IDM at 1720 and 1690 cm^{-1} and PVP K 30 at 2960 and 2920 cm^{-1} .

The IR spectra of SLS was shown in Figure 48. The peaks that showed in SLS spectra at 1210 and 1240 cm^{-1} indicated C-O stretching in SLS molecule, and at 1460 cm^{-1} referred to O=S=O stretching. Moreover, the peaks at 2820, 2900 and 2920 cm^{-1} showed C-H stretching peaks. From physical mixture spectra, Figure 48, it illustrated that the more amount of SLS, the peaks at 2820, 2910 and 2920 cm^{-1} were more intensity and the broad peak from 1160 to 1270 cm^{-1} was more obviously seen. The peaks of untreated IDM spectra also showed at 1690 and 1720 cm^{-1} . There were some differences of peaks in both the physical mixture and the coprecipitate. The first difference was IDM peaks from coprecipitate were similar patterns to treated IDM, but there was a little shift of C-O stretching at 1690 to 1680 cm^{-1} when increasing the amount of SLS. Secondly, there was an absence of peak at 1460 cm^{-1} in both ratio of coprecipitate which this peak may be fused to IDM peaks. Finally, the more amount of SLS in coprecipitate, the more intensities of peaks at 2820, 2900 and 2920 cm^{-1} appeared.

The investigation of Microenvironment

According to the NMR spectra, it was not able to interpret because the limit of NMR equipment is used only for clear solution. The tested solution of IDM-PVP K 30 coprecipitate both physical mixture and coprecipitate gave a suspension in D_2O . Thus, it was very difficult to

investigation of NMR spectra from the tested suspension. It should be evaluated by the solid-type NMR, but it was the limitation of these experiments.

The X-Ray diffractograms

The X-ray diffractograms of IDM and treated IDM were different and shown in Figure 49. The major peaks of IDM were particularly at 11.60° (2θ), 17° (2θ), 19.6° (2θ) and 21.80° (2θ), while the major peaks of treated IDM showed different peaks at 8.80° (2θ), 11.85° (2θ), 14.45° (2θ), 22.02° (2θ), 22.60° (2θ) and 23.35° (2θ).

IDM-Mannitol

The IDM, treated IDM, mannitol and IDM-Mannitol coprecipitate with ratio 1:1 X-ray diffraction spectra were shown in Figure 50. IDM-Mannitol coprecipitate diffractograms seemed to be combined with treated IDM and mannitol since this diffractograms displayed major peaks at 8.8° (2θ), 14° (2θ), 17° (2θ), 24° (2θ), while mannitol diffractograms showed the major peaks at 10° (2θ), 14° (2θ), 17° (2θ) and 24° (2θ). However, the intensity of diffractograms peaks were lower in coprecipitate than pure compound.

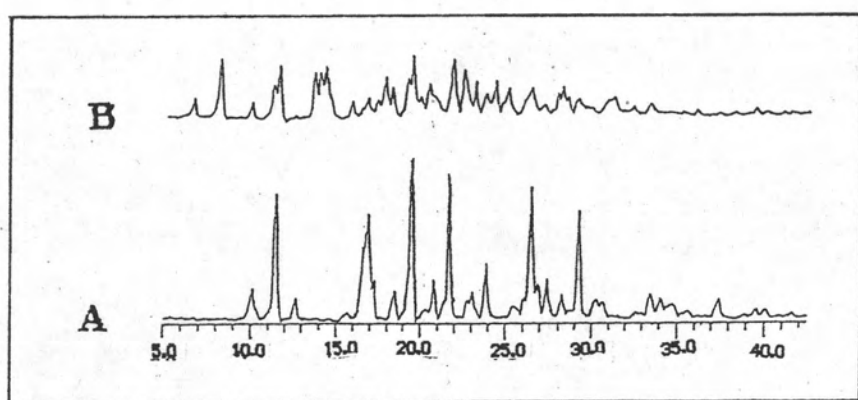


Figure 49 . X-ray diffractograms of Indomethacin (key :
A - IDM powder; B - treated IDM)

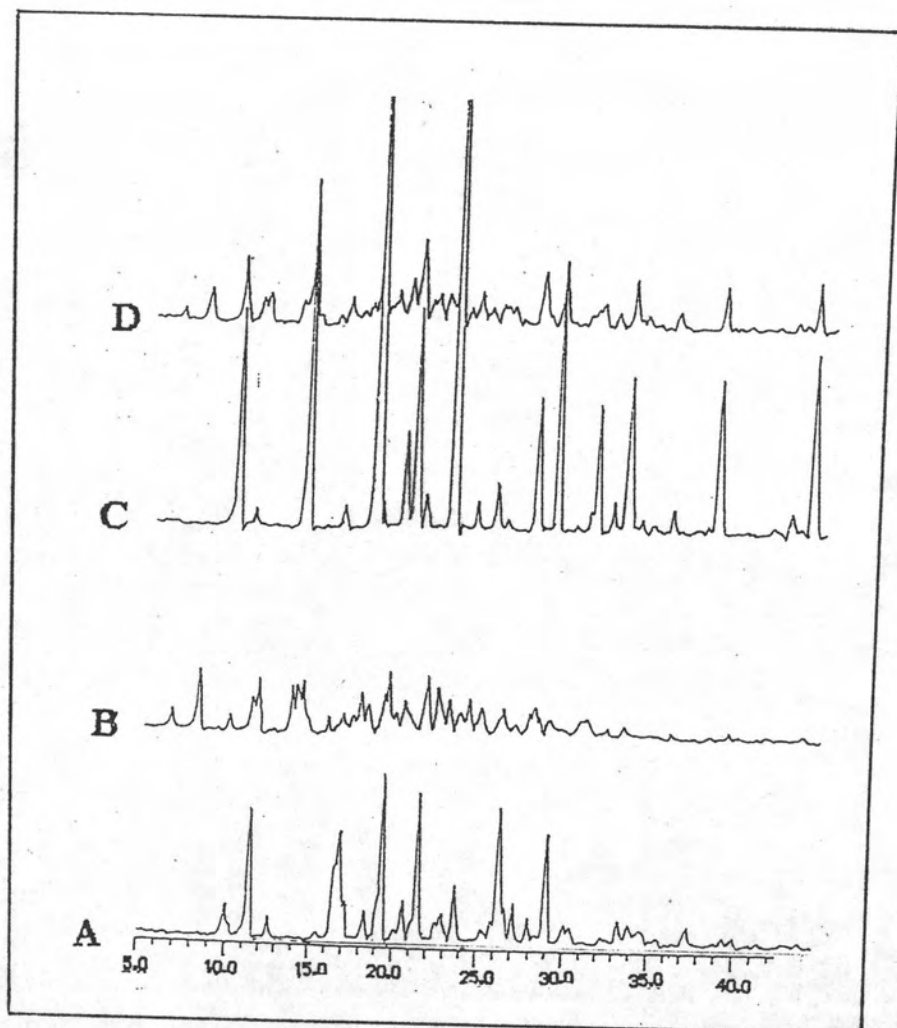


Figure 50 X-ray diffractograms of IDM-Mannitol (key : A - IDM powder; B - treated IDM; C - IDM-Mannitol ratio 1:1 coprecipitate; D - Mannitol)

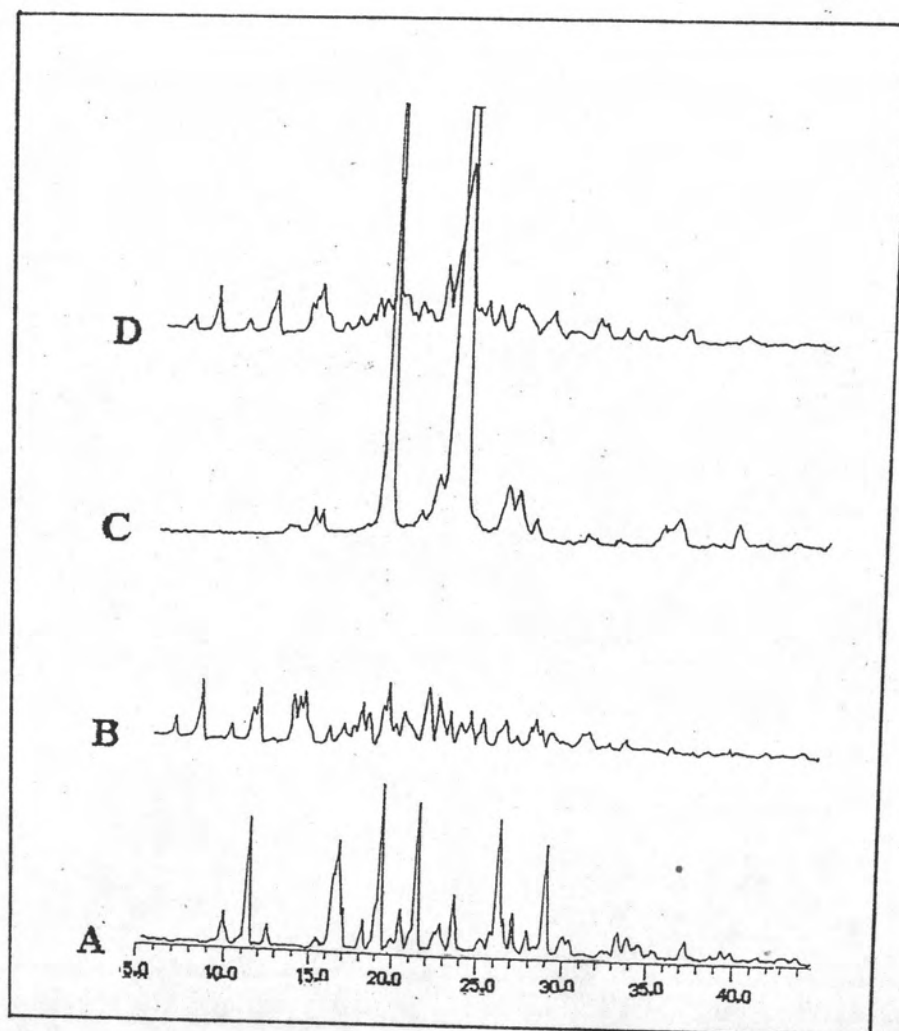


Figure 51

X-ray diffractograms of IDM-PEG 4000 (key :
A - IDM powder; B - treated IDM; C - IDM-PEG
4000 ratio 1:1 coprecipitate; D - PEG 4000)

IDM-PEG 4000

The IDM, treated IDM, PEG 4000 and IDM-PEG 4000 coprecipitate with ratio 1:1 were illustrated in Figure 51. The same with diffractograms of IDM-Mannitol coprecipitate, the combination peaks of treated IDM and PEG 4000 occurred. It showed peaks at 8.80° (2θ), 11° (2θ), 14° (2θ), 19° (2θ), and 23° (2θ), while pure PEG 4000 displayed at 19° (2θ) and 23° (2θ). The peaks intensity of coprecipitate were lower than pure materials.

IDM-PVP K 30

The IDM, treated IDM, PVP K 30 and IDM-PVP K 30 coprecipitate with ratio 1:1 were displayed in Figure 52. PVP K 30 diffractograms gave no sharp peaks, and the coprecipitate also illustrated the same diffractogram pattern as PVP K 30 diffractogram's, but the coprecipitate showed only one small board basement, while PVP K 30 illustrated double board basement.

IDM-SLS

The diffractograms of IDM, treated IDM, SLS and IDM-SLS coprecipitate with ratio 1:0.1 were demonstrated in Figure 53. The coprecipitate diffractograms showed the major peak similar to the peaks from diffractograms of treated IDM, but little intensity peaks at 6° (2θ) and 20° (2θ) were detected. However, the higher intensity of peak

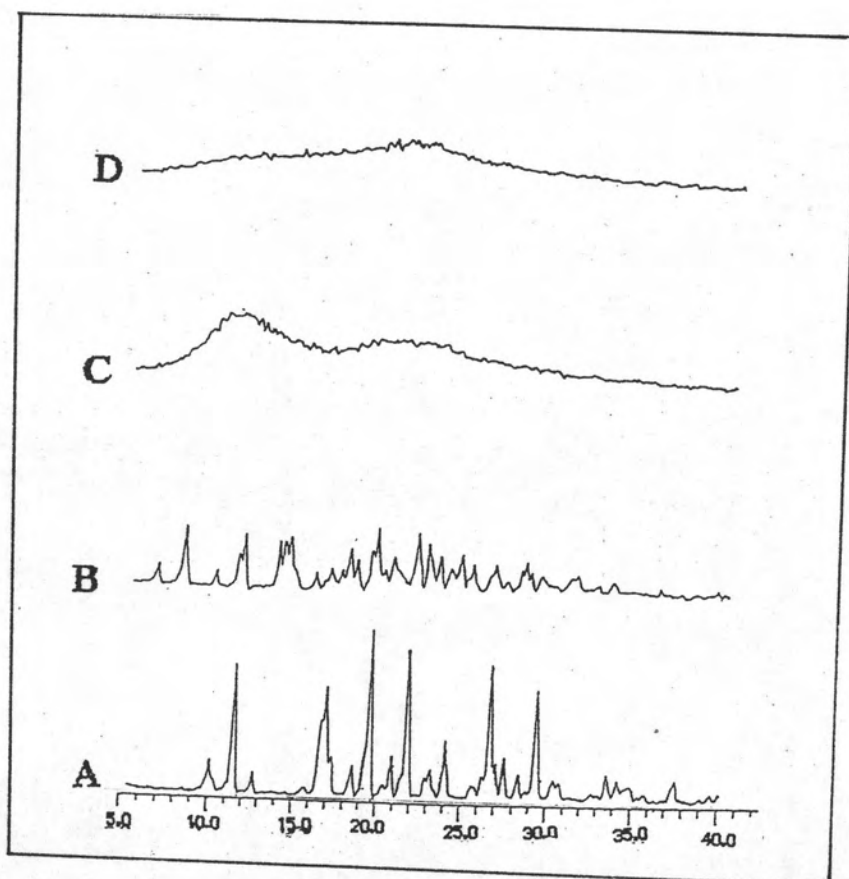


Figure 52 X-ray diffractograms of IDM-PVP K 30 (key :
A - IDM powder; B - treated IDM; C - IDM-PVP
K 30 ratio 1:1 coprecipitate; D - PVP K 30)

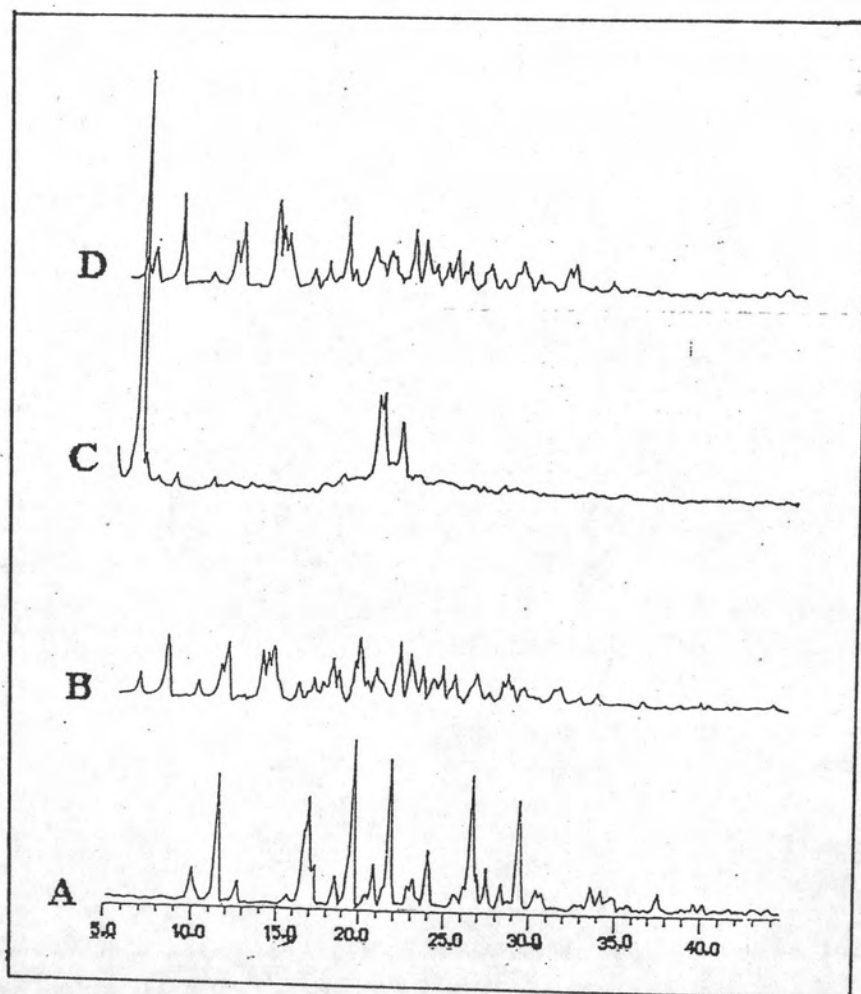


Figure 53 X-ray diffractograms of IDM-SLS (key : A - IDM powder; B - treated IDM; C - IDM-SLS ratio 1:0.1 coprecipitate; D - SLS)

at 6° (2θ) than at 20° (2θ) was appeared in SLS powder, in coprecipitate diffractograms did not display the same ratio of peak height as SLS diffractograms that was 7:1 [the height at 6° (2θ) : the height at 20° (2θ)] in SLS diffractogram and 3:7 in the coprecipitate. It could be implied that there were some changes in SLS powder. It may also be the changing form of SLS in physical properties.

DTA Thermograms

The thermograms of IDM, treated IDM, carriers, corresponding physical mixture and solid dispersion of IDM with various amount and types of carriers preparations were illustrated in Figure 54 to 57. The thermogram of IDM gave the characteristic melting endotherm at 162°C , while treated IDM showed the endothermic peak at 154°C . Mannitol and PEG 4000 displayed the melting endothermic peaks at 180°C and 75°C respectively. PVP K 30 showed the broad melting endotherm from 43°C to 120°C . SLS displayed the two melting endotherm at 104°C and 190°C .

IDM-Mannitol thermograms

The thermograms were shown in Figure 55. The thermograms of IDM-Mannitol coprecipitate showed the two melting endotherms. The first point in all ratio at 155°C which was the same point as the endotherm peaks of treated IDM and the second point at 170°C , 173°C and 176°C in the coprecipitate ratio of 1:1, 1:5 and 1:10 respectively.

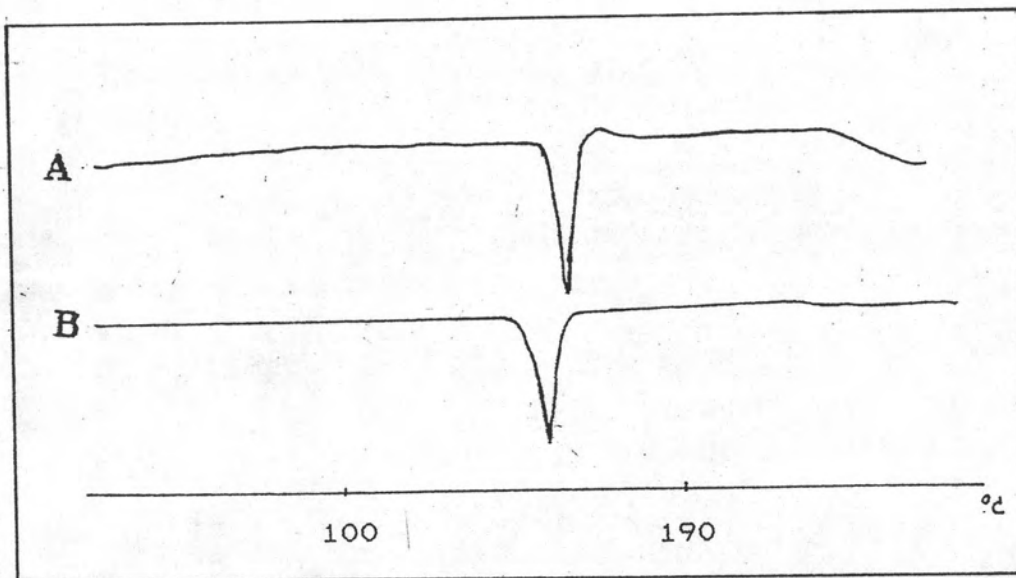


Figure 54 Thermograms of IDM (key : A - IDM powder; B - treated IDM)

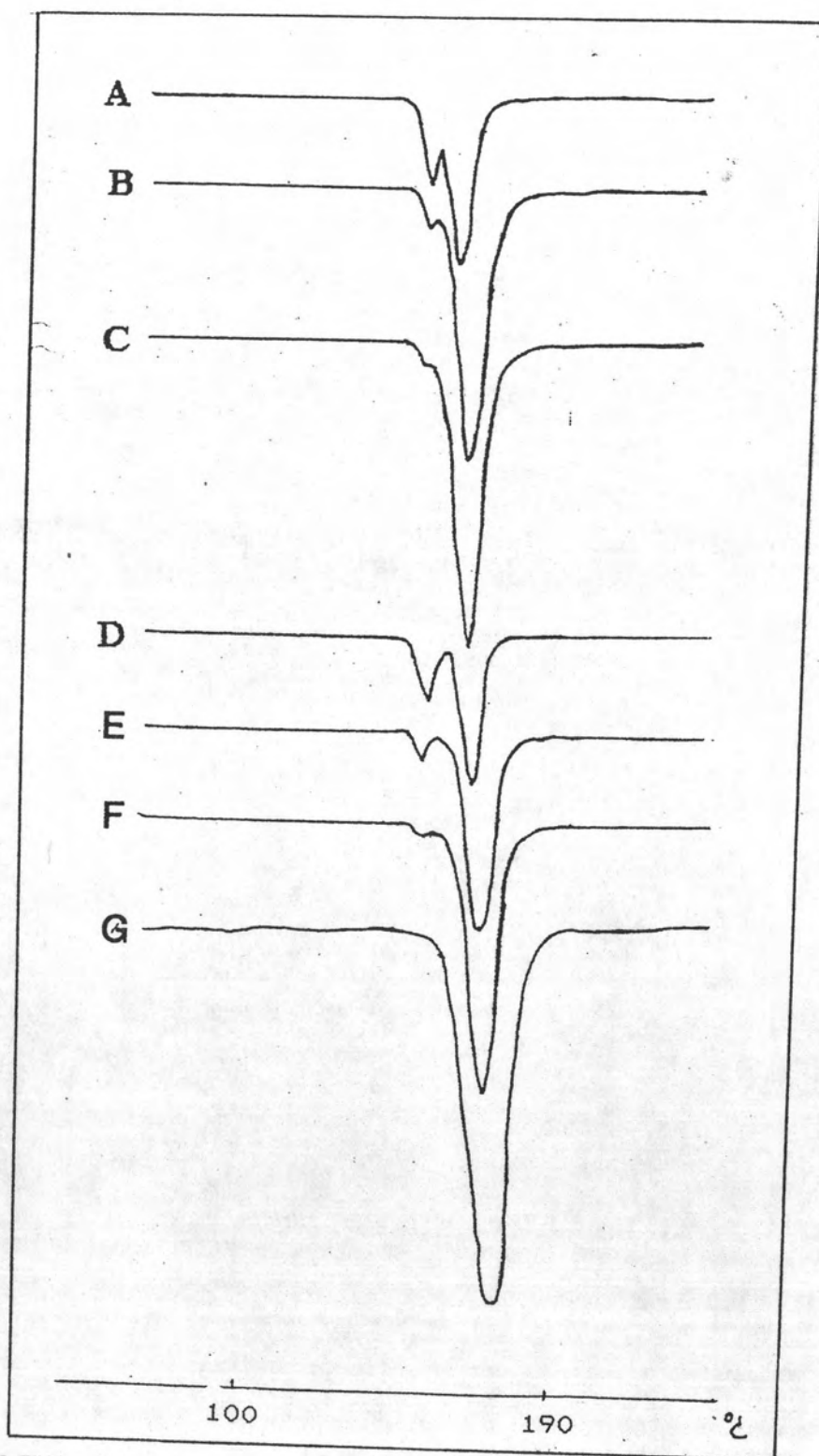


Figure 55

The thermograms of IDM-Mannitol systems both the physical mixture with ratio of 1:1 (A), 1:5 (B), and 1:10 (C), the solid dispersion with ratio of 1:1 (D), 1:5 (E) and 1:10 (F), corresponding Mannitol (G).

These thermograms implied that there were a combination of treated IDM and mannitol, so it may bring the positive shift of endotherms of mannitol to higher temperature with decreasing amount of IDM.

The corresponding physical mixture also showed the double melting endotherms. The first point of all ratio at 162°C that was the same point as IDM crystal, and the second point at 175°C, 160°C and 180°C in physical mixture ratio of 1:1, 1:5 and 1:10 respectively. This was implied as the same as the coprecipitate, but the second endothermic peak shift in physical mixture was less than in solid dispersion, moreover, the second endotherm in physical mixture was also higher temperature than the coprecipitate.

IDM-PEG 4000 thermograms

The thermograms were shown in Figure 56. Both thermograms of physical mixture and solid dispersion with the ratio of 1:1, 1:5 and 1:10 illustrated no endotherms of either IDM or treated IDM. Moreover, the thermograms of physical mixture showed only the single melting endothermic peak at 68°C, 72°C and 74°C in the ratio of 1:1, 1:5 and 1:10 respectively, the thermograms of coprecipitate showed nearly the same endothermic point as physical mixture at 70°C, 73°C and 74°C in the ratio of 1:1, 1:5 and 1:10 respectively. Both endotherms from physical mixture and coprecipitates displayed similar

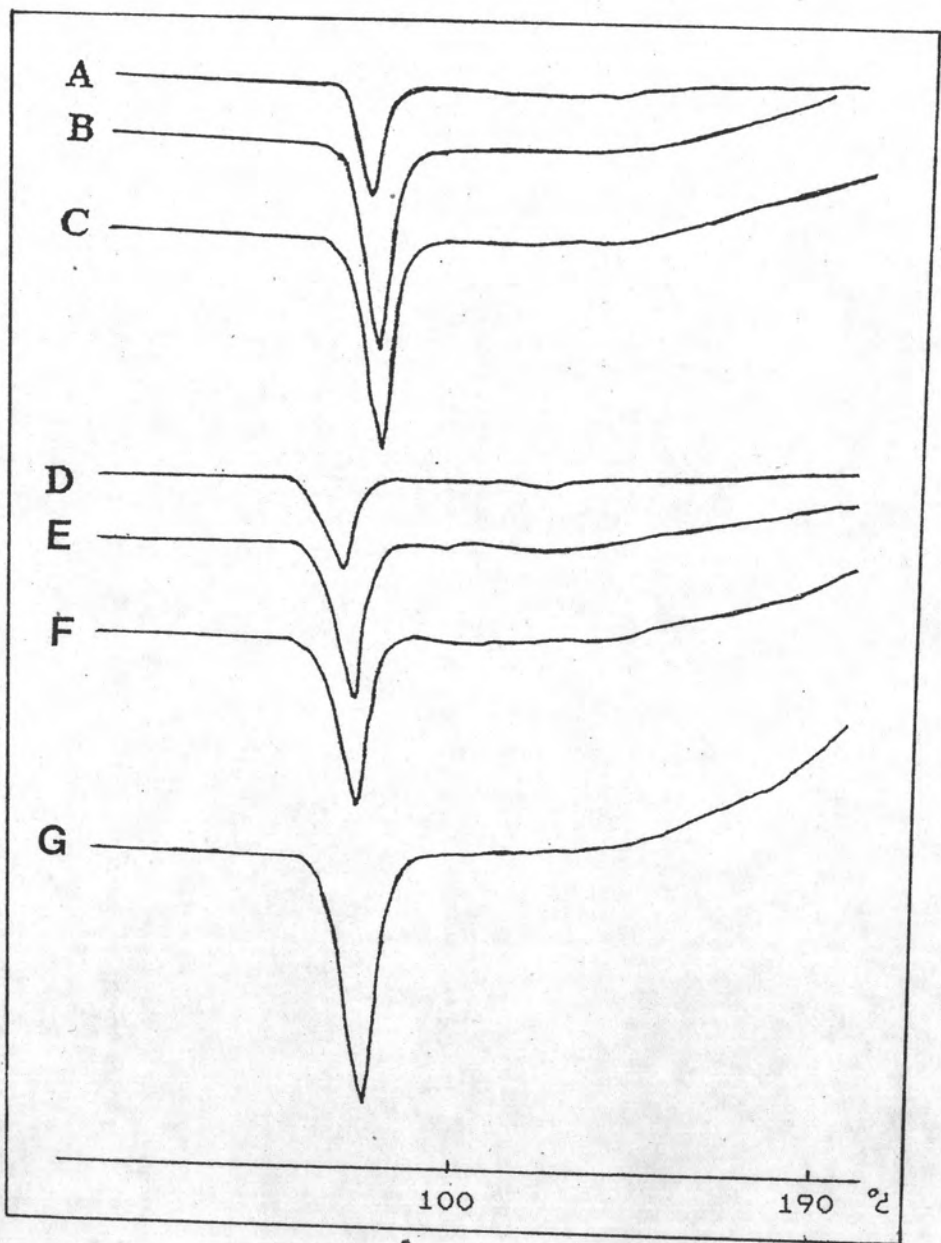


Figure 56

The thermograms of IDM-PEG 4000 (G) systems both the physical mixture with ratio of 1:1 (A), 1:5 (B), and 1:10 (C), the solid dispersion with ratio of 1:1 (D), 1:5 (E) and 1:10 (F), corresponding PEG 4000 (G).

pattern of thermograms that was different from pure PEG 4000 thermogram. The difference from pure PEG 4000 endotherm was the slope of endotherms after 100°C which pure PEG 4000 endotherm showed higher slope than the others, but the slope was decreased with increasing amount of IDM.

IDM-PVP K 30 thermograms

The thermogram were seen is Figure 57. The thermograms of physical mixture illustrated double melting endotherms. The first board endotherm in all ratio was from 43°C to 120°C that was the same board endothermic peak of PVP K 30, and the second point at 160°C which was the same point as pure IDM. The intensity of second endotherms was decreased with decreasing amount of IDM. It was seemed that the thermograms of physical mixture composed of endotherms of IDM and PVP K 30. The coprecipitate endotherms also demonstrated the same first endothermic peak, but lower intensity than physical mixture. The second endotherms of coprecipitates were shifted to 128°C , 138°C and 138°C in ratio of 1:1, 1:5 and 1:10 respectively.

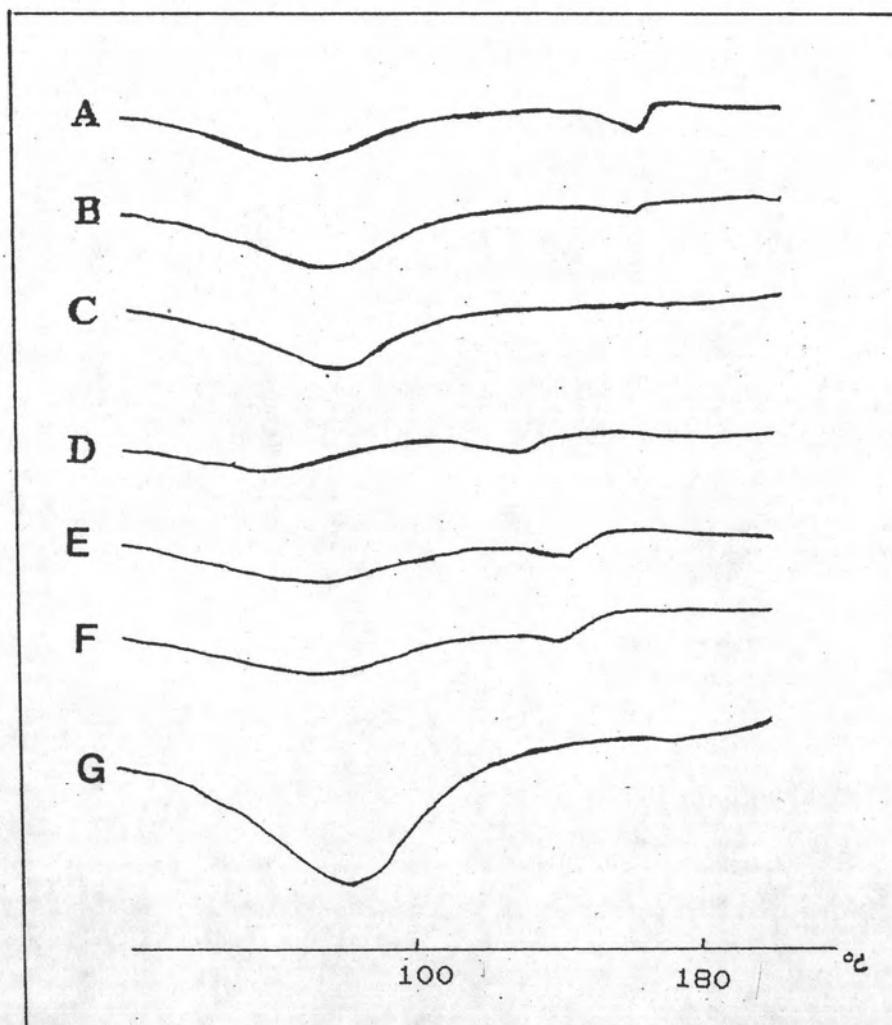


Figure 57

The thermograms of IDM-PVP K 30 systems both the physical mixture with ratio of 1:1 (A), 1:5 (B), and 1:10 (C), the solid dispersion with ratio of 1:1 (D), 1:5 (E) and 1:10 (F), corresponding PVP K 30 (G).

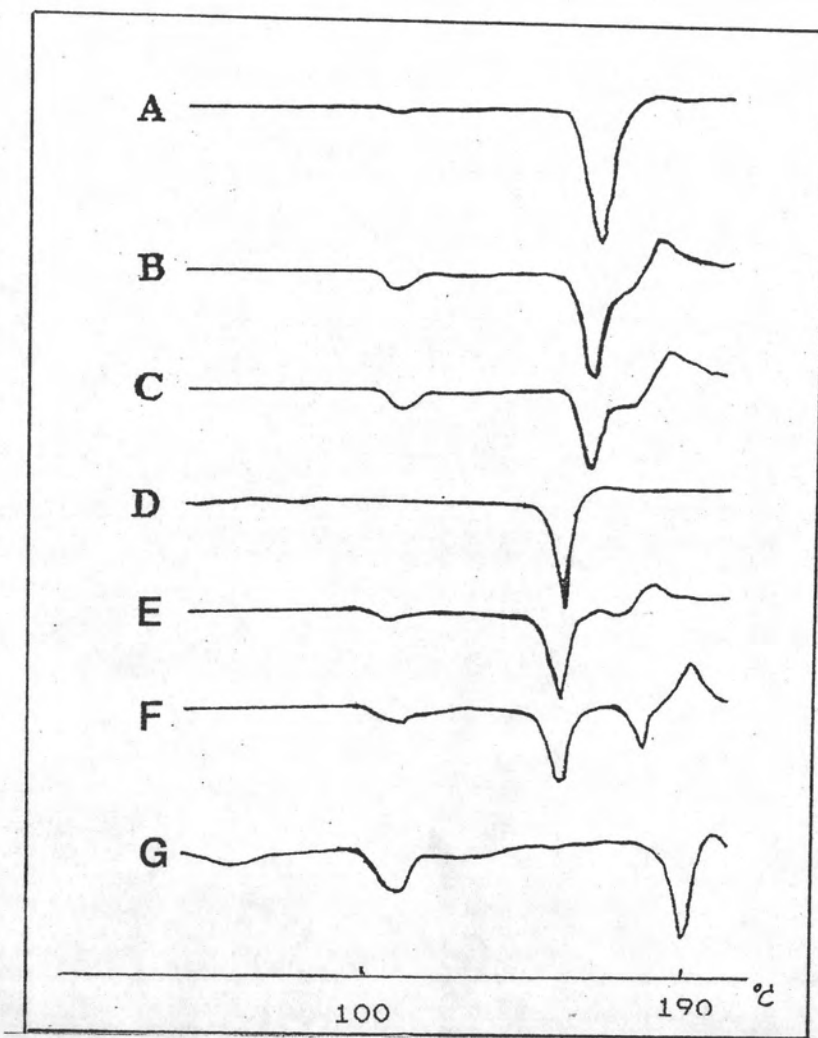


Figure 58

The thermograms of IDM-SLS systems both the physical mixture with ratio of 1:0.1 (A), 1:0.5 (B), and 1:1.0 (C), the solid dispersion with ratio of 1:0.1 (D), 1:0.5 (E) and 1:1.0 (F), corresponding SLS (G).

IDM-SLS thermograms

The thermogram were shown in Figure 58. The thermograms of physical mixture in ratio of 1:0.1 illustrated double melting endothermic peaks at 104°C and 161°C which the former was the endotherm of SLS and the latter was the endothermic peak of pure IDM. Because of the small amount of SLS in ratio 1:0.1, the endothermic peaks of SLS could not clearly be seen. However, the higher amount of SLS in the physical mixture also displayed the triple melting endothermic peaks at 104°C, 160°C and 181°C which the peak at 104°C and 181°C indicated the peak of SLS; whereas, the point at 161°C referred to pure IDM. The thermograms of coprecipitate in ratio of 1:0.1 also exhibited double endotherms at 105°C and 154°C which the latter should be claimed as treated IDM and the former indicated SLS.

The ratio of 1:0.5 coprecipitate demonstrated triple peaks, but different from physical mixture, the coprecipitate endotherms illustrated the two melting endotherm at 105°C and 154°C that referred to SLS and treated IDM respectively. Another exothermic peak at 178°C. Different thermograms from physical mixture, the ratio of 1:1 coprecipitate displayed four peaks, three melting endotherm at 105°C, 154°C and 178°C that indicated SLS and treated IDM. Another single melting exotherm at 190°C.

The Solubility

The saturated solubilities of IDM in medium, phosphate buffer of pH 7.2 : water, 1:4, from all powders were shown in Table 54. Before filtration of saturated solutions, IDM-PVP K 30 coprecipitates produced turbid and milky-like dispersion, while other systems gave two distinct phases, supernatant and solid coprecipitates.

The solubility of treated IDM was about 10% higher than pure IDM. Lower solubilities than pure IDM and treated IDM were displayed in both IDM-Mannitol systems. However, IDM solubility in IDM-Mannitol coprecipitate was about 20% higher than the physical mixture during the ratio of 1:5 and 1:10. In this system, the solubility of IDM was the highest in the 1:5 ratio both physical mixture and solid dispersion, while the ratio of 1:1 and 1:10 coprecipitate showed higher solubilities of IDM that was about 4% and 20% greater than physical mixture, respectively.

IDM solubility in IDM-PEG 4000 systems showed that the coprecipitate displayed more solubility of IDM than physical mixture. The percents of increasing solubility of IDM from physical mixture to coprecipitate decreased with more weight fraction of PEG 4000 in the system. There were about 42%, 22% and 8% increasing IDM solubility from physical mixture to coprecipitate in the ratio of 1:1, 1:5 and 1:10, respectively. Moreover, the

TABLE 54 THE SOLUBILITY OF IDM FROM POWDER
IN PHOSPHATE BUFFER OF pH 7.2 : WATER (1:4)

SAMPLE	CONCENTRATION (mg/ml)	SD	%CV
IDM	10.13	0.01	0.12
TREATED IDM	11.10	0.05	0.46
MAN PHY 1:1	8.07	0.03	0.31
MAN PHY 1:5	8.21	0.01	0.15
MAN PHY 1:10	7.09	0.01	0.18
MAN SOL 1:1	8.45	0.03	0.30
MAN SOL 1:5	9.89	0.03	0.26
MAN SOL 1:10	8.57	0.05	0.59
PEG PHY 1:1	10.84	0.01	0.12
PEG PHY 1:5	15.79	0.01	0.08
PEG PHY 1:10	15.01	0.04	0.25
PEG SOL 1:1	15.43	0.03	0.16
PEG SOL 1:5	19.38	0.01	0.07
PEG SOL 1:10	16.30	0.01	0.08
PVP PHY 1:1	12.58	0.04	0.30
PVP PHY 1:5	11.77	0.01	0.11
PVP PHY 1:10	9.04	0.01	0.14
PVP SOL 1:1	15.64	0.01	0.08
PVP SOL 1:5	35.28	0.05	0.72
PVP SOL 1:10	45.84	0.01	0.14
SLS PHY 1:0.1	10.05	0.04	0.38
SLS PHY 1:0.5	21.80	0.03	0.12
SLS PHY 1:1.0	32.87	0.03	0.38
SLS SOL 1:0.1	17.52	0.03	0.14
SLS SOL 1:0.5	35.66	0.03	0.35
SLS SOL 1:1.0	70.49	0.04	0.27

solubility of IDM in IDM-PEG 4000 system were higher than solubility of IDM from pure IDM and treated IDM.

From the solubilities of IDM in IDM-PVP K 30 system, the IDM solubility demonstrated that markedly increased solubility were in coprecipitate than physical mixture. The more amount of PVP K 30 presented in the coprecipitate system, the higher of IDM solubility were shown. Inversely, the more weight fraction of PVP K 30 in the physical mixture, the less of IDM solubility appeared. However, the percentage of increasing solubility of IDM from physical mixture in ratio of 1:1 was about 24%, while IDM solubilities in the ratio of 1:5 and 1:10 coprecipitate were consequently about 200% and 400% greater than in physical mixture. All IDM solubilities of IDM-PVP K 30 systems were higher than IDM solubility in pure IDM powder, except IDM-PVP K 30 the ratio of 1:10 physical mixture.

Undoubtedly, increasing solubility of IDM from IDM-SLS system was higher with increasing amount of SLS from both physical mixture and solid dispersion and all solubilities of IDM in these systems were higher than from IDM powder. It was about 74% and 63% of increasing solubility of IDM from physical mixture to coprecipitate in the ratio of 1:0.1 and 1:0.5. Moreover, IDM solubility in the 1:1.0 coprecipitate ratio was 114% greater than IDM solubility in the physical mixture at the same ratio. The solubility of IDM was the highest in the ratio of 1:1.0

coprecipitate that was about 98% and 300% greater than those from the ratio of 1:0.5 and 1:0.1 coprecipitate respectively. While IDM solubility in physical mixture showed about 120% and 200% greater in the ratio of 1:0.5 and 1:1.0, consequently, than that from the ratio of 1:0.1. The solubility of IDM from the 1:1.0 coprecipitate of IDM-SLS system was the highest in this experiment.

The viscosities of IDM-PVP K 30 solutions were higher than other IDM carrier solutions, and all viscosities of solutions were shown in Table 58 (page 208). Physical mixture of IDM-mannitol system solutions were displayed higher viscosity of solution than coprecipitate system solution, except the ratio of 1:1 from both systems that was quite equal. The solutions in the ratio of 1:5 and 1:10 in these system decreased in viscosity about 35% and 19%, respectively, from physical mixture to coprecipitate.

However, much decreasing of solution viscosities in coprecipitate occurred in some IDM-PEG 4000 systems. There was little different in the ratio of 1:1 from both physical mixture and coprecipitate solutions, but there were markedly decreased in viscosities from physical mixture solution to coprecipitate solution, both about 80%.

On the other hand, the solution viscosities of IDM-PVP K 30 systems were increased much more in solid dispersion solution than physical mixture solution. The both ratio of 1:1 and 1:5 coprecipitate displayed increasing viscosities of 20% and 37% from physical mixture solution, while the viscosity of ratio 1:10 coprecipitate solution showed 124% greater than viscosity in physical mixture solution.

The same pattern of viscosity changing as IDM-PEG 4000 system, the viscosities of IDM-SLS system solutions showed decreasing in coprecipitate solution. The ratio of 1:0.5 illustrated markedly decreasing viscosity, about 26%, from physical mixture. While the ratio of 1:0.1 and 1:1.0 showed 14% and 5% decreasing from physical mixture.

The densities of all solutions were shown in Table 59 (page 210). Moreover, all densities illustrated value of nearly 1 gm/ml. Density of treated IDM solution was a little bit higher than IDM, and density of pure IDM was the lowest.

In IDM-Mannitol system showed that there was a little changes in densities of all these solution system. IDM-Mannitol solution showed an increasing density, about 0.3%, in the ratio of 1:1 coprecipitate solution from physical mixture solution, but an decreasing density in the ratio of 1:5 and 1:10 coprecipitate solution were 2.3% and 1.9% from physical mixture solutions respectively.

IDM-PEG 4000 systems and IDM-PVP K 30 systems displayed the same pattern of density changing as IDM-Mannitol system. Densities of IDM-PEG 4000 systems were illustrated an increasing as 0.9% and an decreasing as 2.42% and 1.84%, consequently, in the ratio of 1:1, 1:5 and 1:10 coprecipitate solutions from physical mixture solution, while densities of IDM-PVP K 30 systems were displayed an increasing as 0.49% and an decreasing as 1.75% and 1.46% in the ratio of 1:1, 1:5 and 1:10 respectively. Densities of IDM-SLS systems were different from the other system, they showed decreasing in both ratio of 1:1 and 1:5 coprecipitate solution 0.69% and 0.2% respectively, from physical mixture solution while a solution density of the ratio of 1:10 coprecipitate solution displayed increasing 0.5% from physical mixture solution.

The surface tensions of IDM-carrier powder solutions were displayed in Table 56 (page 206). The surface tension of IDM-Mannitol solutions decreased from physical mixture to coprecipitate except the ratio of 1:10. The decreasing tensions in the ratio of 1:1 and 1:5 physical mixture solutions were about 13% and 19%, respectively. While an increasing tension of 1:10 coprecipitate solution was about 5% from physical mixture solution. Inversely changing of surface tension pattern of IDM-Mannitol, solutions of IDM-PEG 4000 system displayed decreasing tension, 7%, in the ratio of 1:10

from physical mixture solution, while the other ratios displayed increasing tension, 6% and 9% in the ratio of 1:1 and 1:5 respectively. Increasing amount of PVP K 30, the percentages of increasing tension were appeared. In ratio of 1:1, 1:5 and 1:10 coprecipitate solutions showed the increasing tension, about 3%, 9% and 16% from physical mixture, respectively. All surface tensions of solution were in the range of 44 dyne/cm to 56 dyne/cm, except the surface tensions of IDM-SLS system solutions that were illustrated rather equal value of 31.74 dyne/cm.

The Wettability Determinations

The acquired times, that the saturated solution passed through a powder bed of given powder of 0.5 cm height, were different in all powder system (Table 60, page 210)). Each contact angle was calculated from the average of six determinations from the penetration time and the average of three values from the surface tension. Moreover, the average of three determinations from the viscosity was also used for calculation. The saturated solution of IDM-PVP K 30 systems were viscous liquid; thus, they could not pass through the given powder bed of IDM-PVP K 30 systems. In addition, the powder bed of IDM-PVP K 30 systems were not easily allowed the investigated solvent, the saturated of IDM in IDM-PVP K 30 solution, passed through.

TABLE 55 THE CONTACT ANGLE OF POWDER

SAMPLE	COS θ	ACOS θ	θ
IDM	0.000	1.571	89.90
TREATED IDM	0.000	1.571	89.88
MAN PHY 1:1	0.002	1.568	88.66
MAN PHY 1:5	0.006	1.565	86.77
MAN PHY 1:10	0.002	1.569	88.69
MAN SOL 1:1	0.001	1.569	89.21
MAN SOL 1:5	0.006	1.565	86.55
MAN SOL 1:10	0.006	1.565	86.84
PEG PHY 1:1	0.004	1.567	87.79
PEG PHY 1:5	0.026	1.544	88.49
PEG PHY 1:10	0.026	1.545	88.50
PEG SOL 1:1	0.003	1.568	88.45
PEG SOL 1:5	0.002	1.569	88.43
PEG SOL 1:10	0.003	1.568	88.72
PVP PHY 1:1	-	-	-
PVP PHY 1:5	-	-	-
PVP PHY 1:10	-	-	-
PVP SOL 1:1	-	-	-
PVP SOL 1:5	-	-	-
PVP SOL 1:10	-	-	-
SLS PHY 1:0.1	0.004	1.567	87.68
SLS PHY 1:0.5	0.007	1.564	85.87
SLS PHY 1:1.0	0.007	1.564	85.96
SLS SOL 1:0.1	0.003	1.568	88.33
SLS SOL 1:0.5	0.002	1.569	88.93
SLS SOL 1:1.0	0.002	1.569	89.11

The contact angles (θ) of all powders were shown in Table 55. IDM powder gave higher degree of contact angle than all powders, except the 1:5 IDM-SLS coprecipitate. The contact angles of all powders were not much different between physical mixture and solid dispersion. From IDM-Mannitol system the contact angle degree of the 1:10 coprecipitate was less than the same ratio of physical mixture, about 2%. the other ratio indicated less than 1% changing of contact angle degree from physical mixture to coprecipitate. It implied that powder of IDM-Mannitol coprecipitate gave better wettability than physical mixture. There were a little changes of contact angle degree in IDM-PEG 4000 system. It was about 0.7% less degree in physical mixture than coprecipitate in the ratio of 1:1. The both rest ratio gave very little changes, less than 0.4%, from physical mixture to coprecipitate. The 1:5 coprecipitate was less degree, about 0.4% than the same ratio of physical mixture, but the 1:10 coprecipitate showed about 0.2% greater degree of contact angle than the same ratio of physical mixture. The range of contact angle degree of these system was 87.79° to 88.72° . It was very interesting that the contact angle degree of powder in IDM-SLS systems were greater in solid dispersion than in physical mixture. The increasing of contact angle degree from physical mixture to solid dispersion was about 0.7%, 3.5% and 3.6% in the ratio of 1:0.1, 1:0.5 and 1:1.0. It was implied that IDM-SLS physical mixture powders

illustrated better wettability than those solid dispersion powders.

The content uniformity of IDM in capsule

The content uniformity of all capsules were shown in the Table 42 (page 201). All of IDM percentage from capsules were in the range of 98.52 - 104.48%. The amount of IDM from both IDM capsule and treated IDM capsule were quite equal each other. IDM-Mannitol capsule showed that the physical mixture was higher IDM percentage, than the coprecipitate, about 2.6%. On the other hand, both IDM-PEG 4000 and IDM-PVP K 30 system showed that the coprecipitate was about 1.3% and 2.7% of IDM content higher than the physical mixture, consequently. Finally, the IDM-SLS capsule displayed that the physical mixture was about 2.23% less than the coprecipitate.

The contents of all capsule were in the range of the limitation in USP XXII that the percentage of IDM capsule is in the range of $100 \pm 10\%$.

The weight variation of capsule

The weight variation of all capsules were in the Table 43 (page 201). It was seen that the average weight of IDM capsule was higher than those of treated IDM capsule, about 1.4%. IDM-Mannitol physical mixture capsule showed about 2% more average weight than those of

coprecipitate capsule; whereas, IDM-PEG 4000 physical mixture capsule showed about 1.6% greater than those of coprecipitate capsule. In IDM-PVP K 30 capsule, the physical mixture also displayed about 2.69% less than coprecipitate capsule. The system of IDM-SLS capsule showed that the physical mixture was 2.34% higher average weight than the coprecipitate. From all weight variation, the all of capsule gave no more 5% of coefficientn of variation.

The disintegration time of capsule

The disintegrations time of capsules were shown in the Table 44 (page 201). The IDM-SLS capsule showed the fastest disintegration of all capsule, while the other systems took more time for disintegration. The untreated IDM and treated IDM capsule were disintegrated more rapidly than IDM-Mannitol, IDM-PEG 4000, and IDM-PVP K 30 system.