CHAPTER IV

DISCUSSION AND CONCLUSION

Discussion

IDM incorporated in solid dispersion with mannitol, PEG 4000, PVP K 30 or SLS illustrated faster dissolution of IDM than its corresponding physical mixture, including both alcohol-treated drug and untreated powder. The more amount of carrier gave more dissolution of drug; moreover, the type of carrier also showed the differences of drug dissolution. This differences depended on enhancing mechanisms of those systems.

The mechanism of increasing dissolution of IDM by the solid dispersion technique may be contributed to various types. Many methods were used for evaluating of the possible mechanism(s). Hence, the clues for determining the enhancing dissolution mechanisms were illustrated

The mechanism	Evaluating method
- Reduction of Particle Size	- Scanning Electron Microscope (SEM)
- Deaggregation or Deagglomeration	- Scanning Electron Microscope (SEM)
- Complexation formation	- Infrared Spectrophotometer, Differential thermal Analysis (DTA), X-ray diffractometer
- Changing of Crystallinity	- Infrared Spectrophotometer, Differential thermal Analysis (DTA), X-ray diffractometer, Scanning Electron microscope
- Changing of Microenvironmental of drug molecule	- Nuclear Magnetic Resonance (NMR)
- Increased Wettability	- Penetration method

For the investigating of the changing of drug microenvironment, it was non-determinable because of the limitation of equipment. However, this mechanism was elucidated from the SEM of the resulting mass of coprecipitate.

IDM

The dissolution profiles of IDM and treated IDM showed that treated IDM was more soluble than untreated IDM. It was explained by the altering in polymorph of IDM from Form I to Form II. This changing was evidenced by the particle appearances, the thermograms, X-ray diffractograms and IR spectra. Borka (1974) revealed that IDM have four polymorphs, Form I, Form II, Form III and Form IV. They were prepared by various organic solvents (Figure 59). Form I was the most stable form and mostly found in commercial grade. Form II could be grown from several solvents if IDM was dissolved and the solvent was evaporated at room temperature (Table 62). Form III was prepared by a crystal film and placing it on the koffer hot bench at 110-115^{o}C. Form III could not be separated in pure form. Finally, Form IV grew readily between 70 and 90^{o}C in a crystal film, placed on the koffer hot bench. None of the solvents except warm methanol yielded Form III.

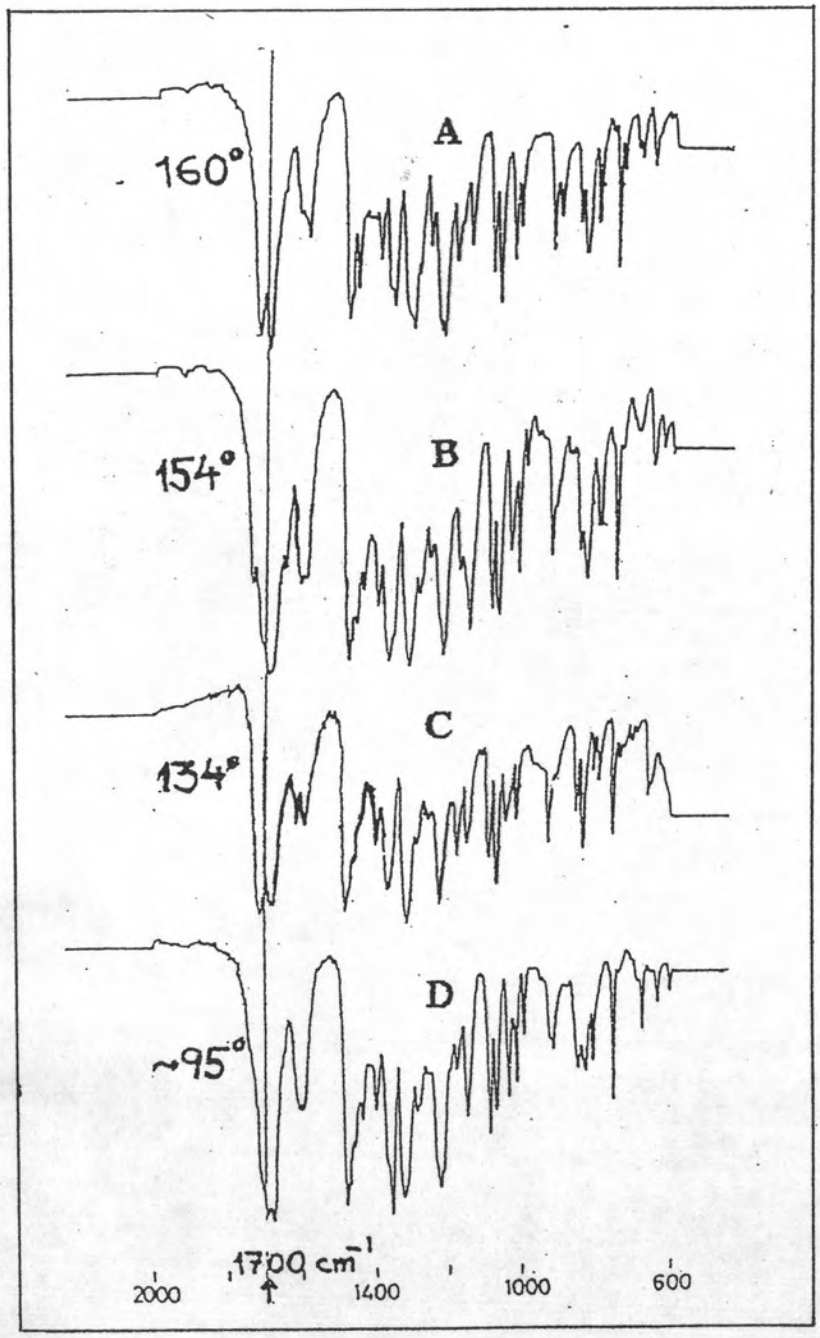

Figure 59 The IR spectra of four polymorphic modifications of Indomethacin (KBr disc). From the top : Form I (A), Form II (B), Form IV (C), and the solvent-containing form (D).

TABLE 62 SOME CHARACTERISTICS OF INDOMETHACIN POLYMORPHS GROWN FROM DIFFERENT SOLVENT (BORKA,1974)

SOLVENT	W/W PERCENT SOLVENT REST		MOL PERCENT SOLVENT REST		IR SPECTRA		M.P. AFTER AIR DRYING CELCIUS DEGREE
	AFTER AIR DRYING	AFTER HEATING 105/30 MIN	AFTER AIR DRYING	AFTER HEATING 105/30 MIN	AFTER AIR DRYING MOD. FORM	AFTER HEATING 105/30 MIN MOD. TO FORM	
METHANOL	0.1	0.0	1.0	0.0	II	II	152-154
"	0.1	0.0	1.0	0.0	IV	IV	134
"	0.1	0.0	1.0	0.0	solvate	I	98
ETHANOL	0.8	0.3	7.0	3.0	II	II	152-154
1-PROPANOL	6.0	0.7	42.0	5.0	solvate	I+II	92-100
DIETHY ETHER	1.0	0.8	6.0	5.0	solvate	II	95
"	0.0	0.0	0.0	0.0	I	I	160
BENZENE	4.7	0.0	26.0	0.0	solvate	II	95
DICHLOROMETHANE	1.1	0.0	6.0	0.0	solvate	I	90-96
CHLOROFORM	10.5	1.0	42.0	4.0	solvate	I	97
"	10.5	1.0	42.0	4.0	solvate	II	97
DIMETHY-FORMAMIDE	1.4	0.0	8.0	0.0	II	II	152-153
GLACIAL ACETIC-ACID	0.5	0.0	3.0	0.0	II	II	152-154
ACETRONITRILE	0.0	0.0	0.0	0.0	I	I	162
"	3.0	0.0	5.0	0.0	II	II	153
ETHY ACETATE	1.1	0.0	5.0	0.0	II	II	153
ACETONE	6.0	1.4	43.0	10.0	solvate	I	90-95
WATER	0.0	0.0	0.0	0.0	II	II	148-152

MOD. : MODIFICATION
M.P. : MELTING POINT

It was rather clearly evidenced that treated IDM was pure polymorphic form Form II. Moreover, the IR spectra of treated IDM showed that the more free O-H stretching at 3200 cm^{-1}, due to the intermolecular hydrogen bond, which may occur from H-atom of carboxylic group with O-atom of carboxylic group or with O-atom of ketone group of IDM molecule, was broken. There was a little shift of C-O stretching peak from treated IDM spectra. It implied that free ketone group of IDM molecule occurred, while carbonyl stretching of carboxylic group showed the same peak at 1690 cm^{-1}. However, there was a little peak at 1625 cm^{-1}, it might be C-O stretching from interaction of IDM molecules. The different spectra of IDM implied that the treated IDM was higher amount of free OH group than IDM, so the treated IDM might interact with medium easier than IDM. Moreover, it implied that treated IDM was in smaller particle size than untreated IDM.

However, the photomicrographs exihibited the agglomeration of fine needle crystalline of treated IDM. It may be reduced or increased the surface area of IDM to expose to medium for dissolution. The solubility of treated IDM was higher than IDM because of the less stable form of Form II. In addition, the wettability of treated IDM also revealed better than that of IDM, it may be caused by less hydrophobicity of powder or a very small size of treated IDM or changing of polymorphs.

IDM-Mannitol powder sytem

The time 80% IDM-ratio of carrier curve showed that the more amount of mannitol in physical mixture brought less time for dissolving 80% IDM. Although, the under ratio of 1:5 coprecipitate curve displayed that the less amount of drug illustrated shorter time 80%, the over ratio of 1:5 coprecipitate showed increasing time 80% (Figure 60). Moreover, the solubility of IDM and the wettability of powder were rather directly correlated (Figure 64, 68). The solubility of IDM below the ratio of 1:1 of both systems was decline, it may be caused by two factors, the more aggregate form of IDM and the solubility effect of mannitol. With increasing solubility of IDM from the ratio of 1:1 to 1:5, it may be contributed to the cosolvent effect of mannitol solution. Therefore, the decline again may be possible resulted from the higher solubility of mannitol, that presented in the same volume with others, than untreated and treated IDM. Moreover, the higher viscosity of medium in the ratio of 1:1 may effect the wettability of powder bed; hence, powder wettability occurred with increasing amount of mannitol that was greater than the ratio of 1:5.

During the coprecipitate preparation, IDM was dissolved in absolute ethanol while some mannitol was still undissolved because the mannitol solubility in absolute alcohol is not high (1:83), so the dissolved mannitol in alcohol may not retard crystallization of IDM.

The photomicrograph also showed the heterogenous solid of mannitol and IDM. This coprecipitate may be not only solid dispersion but also solid-deposited surface. Solid-deposition or solid-surface deposition system is also one of the techniques that improve dissolution of poorly insoluble drug. This technique described as the formation of drug adsorbates with inert and insoluble carrier (Monkhouse and Lach, 1972).

From pictures of both physical mixture and coprecipitate, it was also implied that the microenvironment of drug did not change because it could be seen the distinct phase of both IDM and mannitol. The physical mixture picture showed smaller size of mannitol and IDM because some agglomerated particle was broken by mixing force; whereas, the coprecipitate picture showed agglomerated form of needle crystal of IDM, and some of coprecipitate gave larger size than physical mixture that it might be caused by the coprecipitation of two substances.

The thermograms, X-ray diffractograms and IR spectra confirmedly showed the evidence that there was no complex occurred between IDM and mannitol in coprecipitate and physical mixture. Furthermore, IDM also changed its polymorphic form Form I to Form II when it was treated with absolute ethanol.

The major mechanism of enhancing dissolution of IDM from IDM-Mannitol coprecipitate may be

1. The reduction of particle size
2. The transformation of polymorphic form (Form I to Form II)
3. The better wettability of powder
4. The combination of three mechanisms

IDM-PEG 4000 powder system

The more amount of PEG in the system, the less time for dissolving 80% of IDM, Figure 61. The ratio of 1:10 coprecipitate expressed the fastest time 80% IDM, followed by the ratio of 1:5 and 1:1 coprecipitate, 1:10 physical mixture respectively. The ratio of 1:5 and 1:1 physical mixture took more than 20 minutes for dissolving 80% of IDM.

The photomicrograph showed that the IDM-PEG 4000 coprecipitates were less porous homogenous solid with increasing the amount of PEG 4000. Moreover, it seemed that the microenvironment of IDM was covered with PEG 4000 and displayed homogenous phase. It implied that there might be a changing of microenviroment of drug particle.

Generally, PEG molecular structures are semi-crystalline, containing both ordered and amorphous components. In the crystalline state, the chains are presented as double helices containing approximately 15

monomers within a repeat unit. The helices are arranged as plate-like structure (lamellae), from which the hydroxyl end groups are rejected onto the surface. The chains within the lamellae may be extended or folded, the latter arranged in spherical structure (spherulites). In general the higher the molecular weight of PEG, the more stable the folded chain form within the lamellae (Craig, 1990). It was predicted that significant amounts of drug could be entrapped in the helical interstitial space when IDM and PEG 4000 were coprecipitated over the steam bath. The PEG was expected to give an ultrafine or colloidal crystallization of the pure drug-PEG that was melt and solidified immediately (Chiou and Reigelman, 1969). This was mainly due to the difficulty of growth of the crystallite in a highly viscous medium and the short time interval for the completion of solidification. It was also the method by which doped crystals were prepared to render specific physical properties in a system in which a material was crystallized in a retard manner due to solute depletion in the environment affecting crystal growth. The highly possible physical-chemical interaction between the drug and PEG may also play a role in preventing the crystalline growth.

The X-ray diffractograms also showed that IDM was changed its polymorphic form from Form I to Form II in the coprecipitate. Moreover, the thermograms of IDM-PEG revealed the same pattern in both physical mixture and

solid dispersion. Furthermore, the less amount of carrier, 1:0.5 and 1:0.3, also showed the same pattern, but these two ratios gave two melting points which the 1:0.5 physical mixture showed two melting points at 62 and 138°C and the 1:0.5 coprecipitate displayed at 58 and 137°C. The 1:0.3 physical mixture illustrated the melting point at 62 and 147°C, while the coprecipitate showed at 57 and 145°C. From the datum, it could be drawn the phase diagram of IDM-PEG 4000, Figure 71. It could be described such pattern to the presence of the monotectic system. Monotectic phase diagrams occur when the liquid-liquid bonds between two molten components are of comparable strength to those between the higher melting point component; whereas, with eutectic system the bonds between the two are stronger than those of either pure component. The monotectics represent system whereby one component is presented in the other as discreet crystalline particle, while eutectics is revealed a microfine dispersion of the two components (Craig, 1990).

To evaluate monotectic mixture,DTA or DSC are effective methods. There were no changing of solid state in fusion process of low drug concentration from physical mixture monotectic phase diagrams (Hargreave cited by Craig, 1990). Moreover, YenKataram and Roger (1984) reported that electron micrograph studies on griseofulvin-dimyristoyl phosphatidyl choline systems showed the drug particles to remain essentially unchanged in appearance

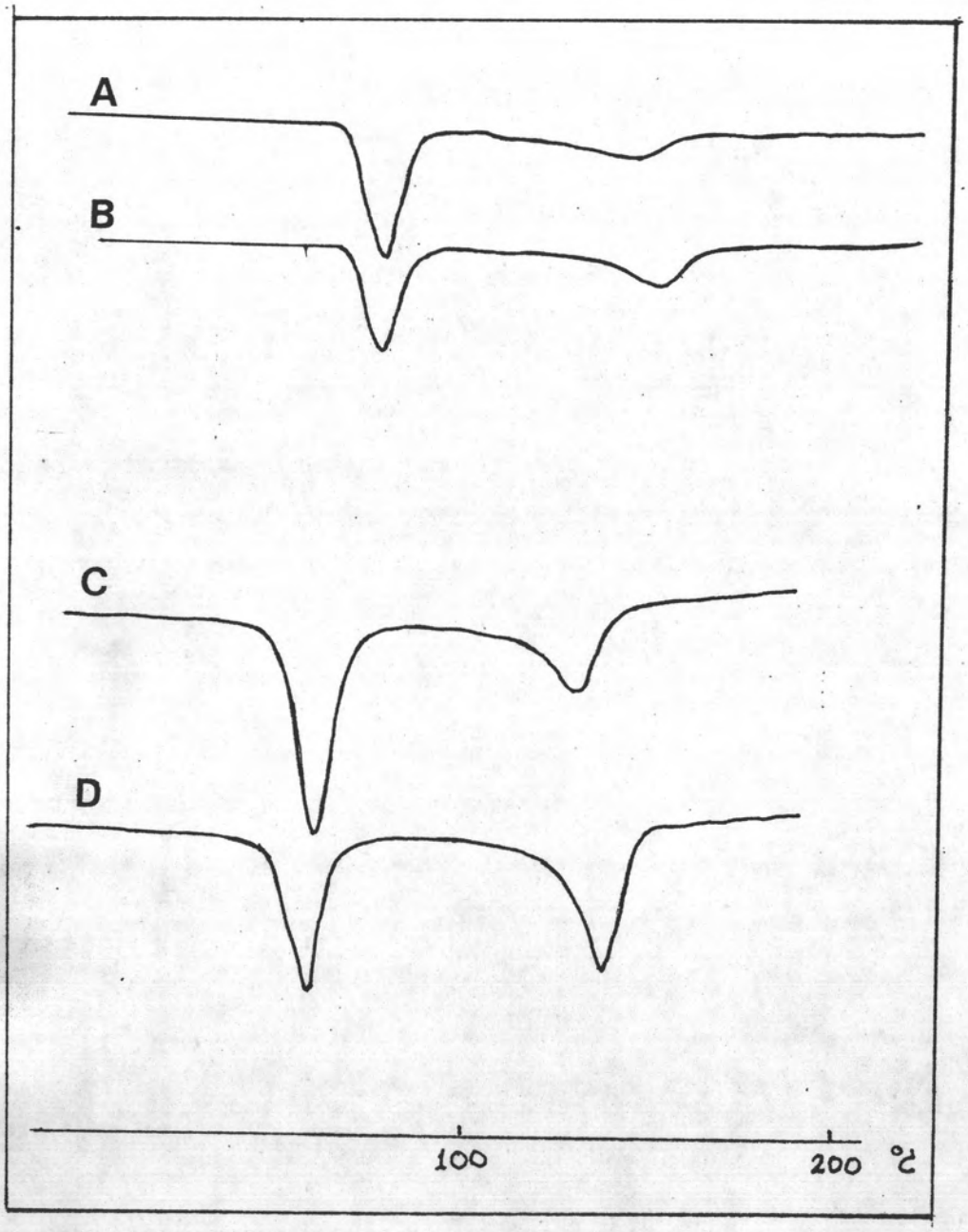

Figure 71 The thermograms of IDM-PEG 4000 both physical mixture ratio 1:0.5 (A), 1:0.3 (B) and solid dispersion ratio 1:0.5 (C), 1:0.3 (D)

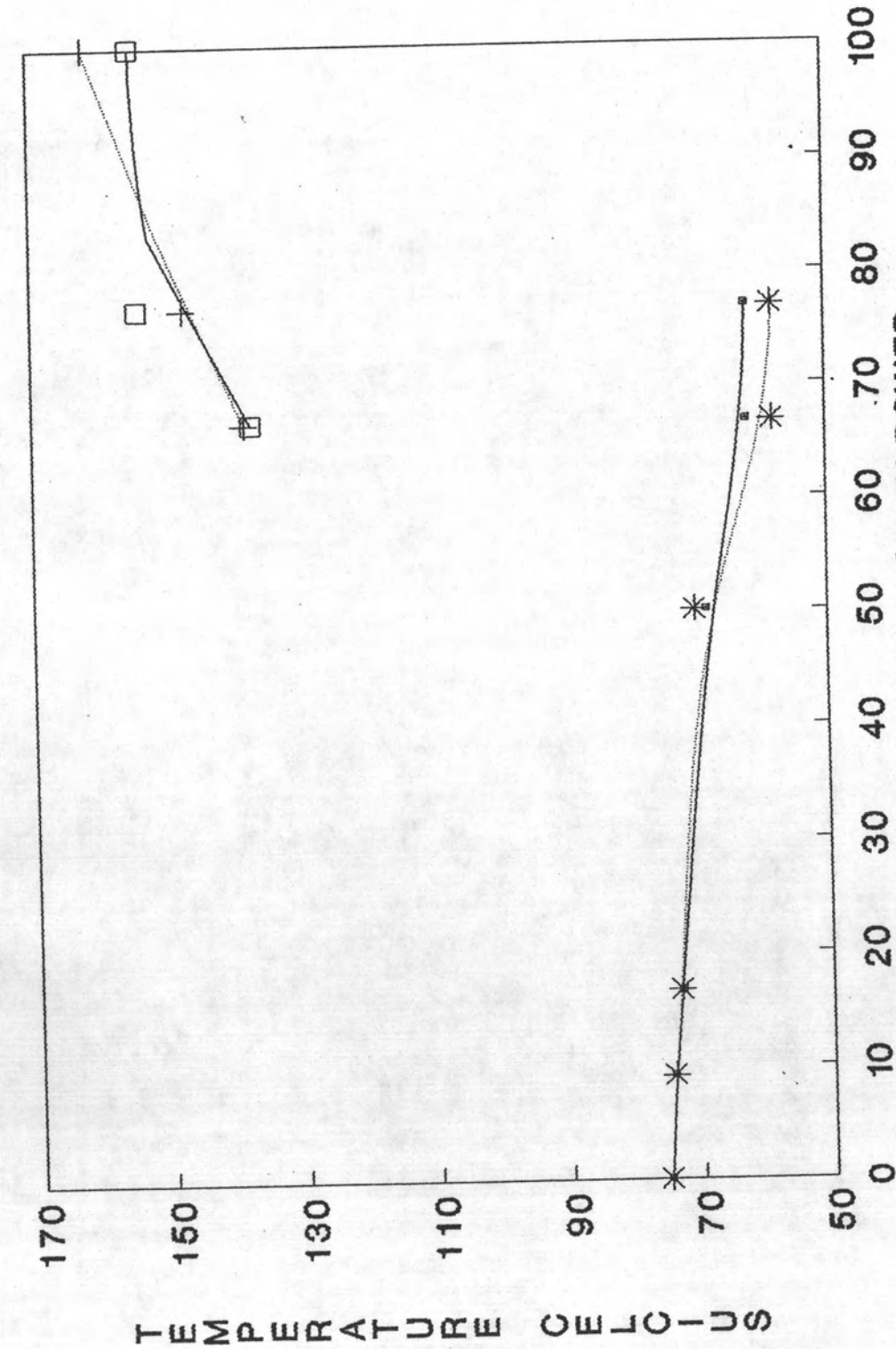

Figure 72 The phase diagram of IDM-PEG 4000 systems both physical mixture and solid dispersion

before and after coevaporation; in addition, the corresponding phase diagram was monotectic in nature.

The solubility of IDM in the IDM-PEG 4000 were increasing until the ratio 1:15 and then decreased Figure 65. In the decline solubility of IDM, it may be caused by viscosity effect of PEG solution. These high viscosity would retard the dissolution of IDM. Moreover, the contact angle of powders was increased when more amount of PEG presented in the system, Figure 69. It implied poorer wettability with more weight fraction of carrier.

The increased solubility of IDM from the ratio of 1:1 to 1:5 may be reasoned by the cosolvent effect of PEG 4000 and the solubility of IDM in the coprecipitation were greater than physical mixture. Najib and Salum (1987) found that the solubility of Ibuprofen from PEG with increasing weight fraction of PEG, resulting decrease solubility. Moreover, they also found that the solid dispersion gave higher solubility of drug than the physical mixture. This difference in solubility could be due to the different crystalline structure and hence energies of the dispersed system obtained by the solid dispersion technique. Higher heat of solution are associated with higher lattice energy and therefore a large amount of heat has to be absorbed before dissolution take place. Their experimental data displayed that the Drug : PEG dispersion exihibited 5.6 kJk^{-1} mol^{1} which was

lower heat of solution than pure drug, 19.12 kJk^{-1} mol^{-1}, and Drug : PEG physical mixture, 16.08 kJk^{-1} mol^{-1}, so the dispersed system showed a great solubility of drug.

In coprecipitate system, IDM changed its polymorphic form from to Form II which was more soluble than Form Form I.

From IR spectra, it supported for changing polymorphic form of IDM in solid dispersion. Moreover, the spectra indicated that the O-H stretching at 3200 cm^{-1} in the coprecipitate was more intensity than physical mixture. It implied that the intermolecular bonds of IDM were broken, so IDM was in a smaller size, or deaggregation and deagglomeration in the coprecipitate. Furthermore, IDM-PEG 4000 coprecipitate IR spectra also obviously showed peaks of both treated IDM and PEG 4000 so, it revealed that the coprecipitate was more homogenous dispersed than the physical mixture.

The both physical mixture and solid dispersion powders also illustrated the less degree of contact angle than both treated and untreated IDM. The 1:1 coprecipitate showed better wettability than other ratio from both the physical mixture and the coprecipitate. The higher amount of PEG brought higher viscosity of solution, so it would bring more time to penetration through the powder bed. These systems showed better wettability than treated and untreated drug.

The possible mechanism for enhancing IDM dissolution by these systems should be

1. Reduction of particle size
2. Deaggregation and deagglomeratio of IDM particle
3. The changing of the crystallinity from Form I to Form II
4. The changing of microenvironment of IDM
5. The combination of aforementioned mechanism

IDM-PVP K 30

The more weight fraction of PVP K 30 presented in solid dispersion, the faster dissolution of IDM was shown. In the physical mixture system, the dissolution pattern of IDM was shown in the same way as the solid dispersion´s.

The time 80% of IDM in the IDM-PVP K 30 system was illustrated in Figure 62. The 1:10 coprecipitate exhibited the fastest dissolution of IDM, followed by the 1:5 coprecipitate, the 1:1 coprecipitate, the 1:10 physical mixture, the 1:5 physical mixture, the 1:1 physical mixture, respectively. The faster dissolution of IDM from coprecipitate may be caused by an amorphous form of IDM or it might also be a glass formation of IDM in IDM-PVP K 30 system.

The pure polyvinylpyrrolidone and some other polymer dissolved in the organic solvent may become glassy after the evaporation of the solvent.

Glass is generally prepared by rapid quenching of a liquid melt. It appears that most liquid can be made to solidify to a glass if they are cooled through the crystallization temperature range more rapidly than the time required for crystal nuclei to form. This can be easily accomphished if the symmetry of the molecule is of low order, or the rotational isomerization from the equilibrium rotamer distribution to that required for crystallization is low at temperature equal to or low at the melting point. A high melt viscosity at or low the melting point along with the ability to hydrogen bond and steric considerations of the molecule may aid in the vitrification process (Timko and Lordi, 1984). Thus, it is possible that the precipitation of drug introduced into the sytem is inhibited due to the increase in viscosity as solvent evaporate. Such prevention may also be facilitated by the possible complexation between the drug and polymer. Thereby a transparent, brittle, glassy solution is formed. The lattice energy in the glass or glass solution is expected to be much less because of its similarity with the liquid solution. A glass or liquid can only produce weak and diffuse diffraction effects, while crystallites can give strong and sharp diffraction effect. Thus, a glass is also amorphous to X-ray

diffraction. Therefore, a glass or glass solution is a metastable form.

The IDM-PVP K 30 coprecipitates were brittle, transparent mass, so this mass may be a glass dispersion. Moreover, the X-ray diffraction displayed no sharp peaks, it implied that IDM crystals in IDM-PVP K 30 coprecipitate was an amorphous form. For investigation of a glass transition temperature (Tg) of this mass, the thermograms of 1:10 IDM-PVP K 30 coprecipitate show the board peak between 30-100^{o}C. These board melting point also present in the thermogram of pure PVP K 30, thus this board peak should be referred to board melting point of pure PVP K 30.

The Tg is the temperature that a glass begins to soften. This Tg should be different from pure substance. Thus, this mass might not be a glass structure. However, the amorphous form of IDM is presented at the melting temperature of 55-57^{o}C. It seemed that this melting point of an amorphous form of IDM was combined with that peak of PVP K 30.

The photomicrographs of the coprecipitates exhibited the homogenous mass with smooth surface, while the physical mixture showed only the combination of two substances. The particle size of IDM may be very fine in a mass of IDM-PVP K 30 coprecipitate, owing to the difficult growth of the crystal in its viscous medium. The particles of IDM in the physical mixture were also

reduced since the particles were broken by the mixing force.

The solubility of IDM was increased with increasing weight fraction of PVP K 30 in coprecipitate, Figure 66, it might be resulted from the very fine particle size or an amorphous form of IDM in this coprecipitate. On the other hand, the physical mixture displayed decreasing of IDM with increasing amount of PVP K 30. In this reversed effects should be resulted from the unchanged form of IDM and the increasing viscosity of polymer solutions, thereby retarding of IDM dissolution. The viscosity of IDM-PVP K 30 system is more viscous than other systems; thus, it was very obstructive to investigate the powder wettabilities by the penetration technique. Moreover, the powder bed in the tube, that was for investigation of wettability, was not easily allowed the solvent pass through because of its surface swelling phenomenon.

The IR spectra of 1:1 IDM-PVP K 30 coprecipitate showed the shift peak of C-N stretching of both IDM and PVP K 30 to lower wave number. This shift indicated that the energy for C-N stretching was lower than pure compound, so there was an interaction of IDM and PVP K 30. The possible interaction occurred between C-N of PVP K 30 and benzene ring of IDM. This interaction brought the substance higher melting point than PVP K 30. This implied that the higher weight fraction of PVP K 30 would

bring the same interaction as the 1:1 copreceipitate. However, the 1:1 physical mixture IR spectra displayed the combination peaks of IDM and PVP K 30. It was revealed that there was no interaction between IDM and PVP K 30 in the physical mixture.

The thermograms of the coprecipitates showed two melting board peaks. The first peak indicated PVP K 30, while the second peak indicated that a new compound was occurred from the interaction between IDM and PVP K 30. The second melting point presented all ratios of coprecipitate. It was confirmed that higher amount of PVP K 30 brought an interaction of both substances as the same as the 1:1 coprecipitate. The physical mixture thermograms illustrated that there was no such changing of melting point of both substances. It was also evident that there was no new compound between IDM and PVP K 30 in physical mixture

The possible mechanism for enhancing dissolution to IDM from these system shold be

1. The reduction size of IDM
2. The deaggregation or deagglomeration of IDM
3. The changing crystallinity to amorphous form
4. The changing of microenvironment of IDM molecule
5. The interaction of IDM and PVP K 30
6. The combination of aforemendtioned mechanisms

IDM-SLS powder system

The dissolution of IDM in IDM-SLS was very interesting. The more amount of SLS in the coprecipitates, the faster the dissolution; whereas, the dissolution in the physical mixture illustrated inversely. The time 80% of IDM in these systems was displayed in Figure 63. The 1:10 coprecipitate showed the fastest IDM dissolution, followed by the 1:0.5, 1:0.1 coprecipitate, 1:0.1, 1:0.5 and 1:1.0 physical mixture.

In view of the relationship between solubility and dissolution rate as derived in the Noyes-Whitney equation, the enhanced solubility of a drug in a micellar solution of surfactant should result in a proportional increase in the dissolution rate. While the IDM-SLS physical mixtures were failure to achieve pertinent to the influence of interacting colloids, such as micelles, on mass transport. Higuchi (1967) concluded that dissolution rate in micellar solution under sink condition could be described by

$$dM/dt = DC_s/h + D_mC_m/h \quad \ldots\ldots\ldots (3)$$

Where D and D_m are the diffusion coefficients for the free drug and micelle-solubilized drug species, respectively, C_s is the solubility of the drug, C_m is the solubility increase due to solubilization, and h is the effective diffusion layer thickness. From the equation, the influence of micellar solubilization on the

dissolution rate of drugs from conventional dosage form will be significantly greater than that predicted by Noyes-Whitney relationship.

The surfactant concentration below the critical micellar concentration (CMC) would obey this equation, but the exceed CMC of surfactant would decrease the dissolution rates. Braun and Parrott (1972) reported about the presence of surfactant over CMC that at concentration of polysorbate 80 exceeding the concentration corresponding to the maximum dissolution rate, the dissolution rate is decreased as the concentration of surfactant is increased. Since the dissolution rate is inversely the viscosity of the micellar solution to the extent that the dissolution rate is slow although the total solubility is greatly increased.

The CMC of SLS in phosphate buffer of pH 7.2 : water (1:4) was 0.03162 mg/ml. These data were obtained by using surface tension method (Mittal, 1972) that was shown in Figure 72 and Table 61. The more amount of SLS in physical mixture brought less dissolution of IDM. It might be contributed to the formation of micelles that the increasing amount of SLS gave the SLS concentration above CMC.

TABLE 61 THE SURFACE TENSION OF SLS SOLUTION

SAMPLE	CONCENTRATION (m⁻/ml)	LOG(CON)	SURFACE TENSION (DYNE/CM) 1	2	3	AVERAGE	SD	%CV
1	0.0075	-2.125	58.20	58.00	58.00	58.07	0.09	0.16
2	0.0097	-2.014	54.10	55.10	56.10	55.10	0.82	1.48
3	0.0150	-1.824	50.00	50.50	50.00	50.17	0.24	0.47
4	0.0300	-1.523	45.40	45.50	46.00	45.63	0.26	0.58
5	0.0485	-1.315	42.20	42.30	42.30	42.27	0.05	0.11
6	0.0969	-1.014	38.70	38.10	37.95	38.25	0.32	0.85
7	0.1938	-0.713	35.10	35.40	35.60	35.37	0.21	0.58
8	0.5815	-0.235	32.40	32.80	32.90	32.70	0.22	0.66
9	0.9692	-0.014	31.00	30.50	30.50	30.67	0.24	0.77

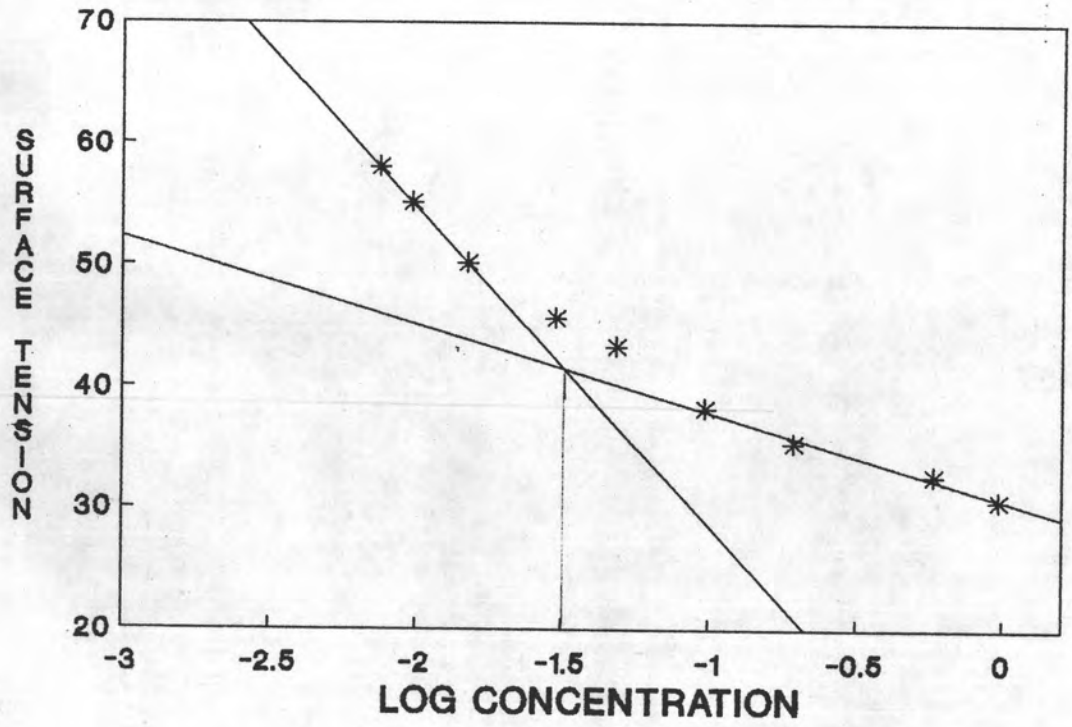

Figure 73 The curve of critical micellar concentration of sodium lauryl sulfate in phosphate buffer of pH 7.2 : water (1:4)

The concentration of SLS in the ratio of 1:1.0 physical mixture in test medium was greater than CMC, so it might bring more drug entrapment in micelle. In higher amount of SLS in physical mixture, the viscosity of solution also showed increasing. From these evidents, the increasing of SLS would allow decreasing dissolution of IDM. Although the concentration of SLS in the ratio of 1:0.5 physical mixture was not up to CMC, the dissolution of CMC, the dissolution of IDM was less than the ratio of 1:0.1, it was contributed to the higher viscosity of solution.

The thermograms of IDM-SLS coprecipitate system illustrated the shift of melting point of IDM. It implied that IDM also changed the polymorphic form from Form I to Form II. Moreover, the 1:1 IDM-SLS coprecipitate thermogram showed the exotheromic peak at 190^{o}C while the 1:0.5 showed at 178^{o}C. It implied that SLS in coprecipitate also changed its form. The X-ray diffractograms also demonstrated that there was no sharp peak of SLS at 6^{o} (2θ) in the coprecipitate, while the peak of SLS still existed at 20^{o} (2θ). It was confirmed that there were some changes of SLS in the coprecipitate. IR spectra showed that there was more board peak OH stretching in the coprecipitate; consequently, it was referred that the intermolecular bond was broken. Moreover, there was a shift of C-O stretching of IDM, it implied that there was an interaction of compound. In

this system, IDM was an acidic drug and SLS was an anionic surfactant; thus, complex formation between IDM and SLS might occur. Its interaction might be an ionic interaction.

In coprecipitate, the more weight fraction of SLS was in the system, the more the dissolution of IDM occurred. Since the changing of SLS form also played an important role for changing pattern of IDM dissolution from physical mixture. Moreover, the wettabilities of coprecipitate powders were less than physical mixture, Figure 70. However, the solubilities of IDM in both physical mixture and solid dispersion were increased with the increasing amount of SLS in system. The IDM solubilities in coprecipitate were higher than physical mixture, Figure 67. These increasing of IDM solubility was caused by the micellar formation of SLS in medium; thus, the more amount of SLS in medium, the more micelle occurred.

The photomicrograph displayed fine needle crystal of IDM in the coprecipitate, while the physical mixture still showed the crystal of IDM. The fine needle of IDM could be seen obviously in the 1:1 coprecipitate. The physical mixtures showed that there were some fractures of SLS. This fracture might be resulted from the mixing force.

IDM in coprecipitate was not in Form I as physical mixture, it changed into Form II. That changing was confirmed by changing size and shape of IDM crystal, changing of IR spectra and X-ray diffractograms, and also shifting of the melting point to a lower temperature, 154°C.

From all resulted investigation, the possible mechanisms for enhancing IDM dissolution in these system should be

1. The reduction of particle size of IDM
2. The complex formation of IDM-SLS coprecipitate
3. The changing polymorphic form of IDM from Form I to Form II
4. The increased wettability of powder
5. The combination of aforementioned mechanism

IDM capsule and its corresponding

The untreated IDM capsule could not dissolve 80% of IDM within 20 minutes, but its dissolution of IDM was greater than IDM powder. The fastest of 80% IDM dissolution was the 1:1 IDM-SLS coprecipitate capsule, 8 minutes 21 seconds, and this capsule also showed greater dissolution of IDM than that of capsule from IDM-PVP K 30 coprecipitate, IDM-Mannitol coprecipitate, IDM-PEG 4000 coprecipitate, treated IDM, IDM-PEG 4000 physical mixture, IDM-SLS physical mixture, IDM-Mannitol physical mixture and IDM-PVP physical mixture, respectively.

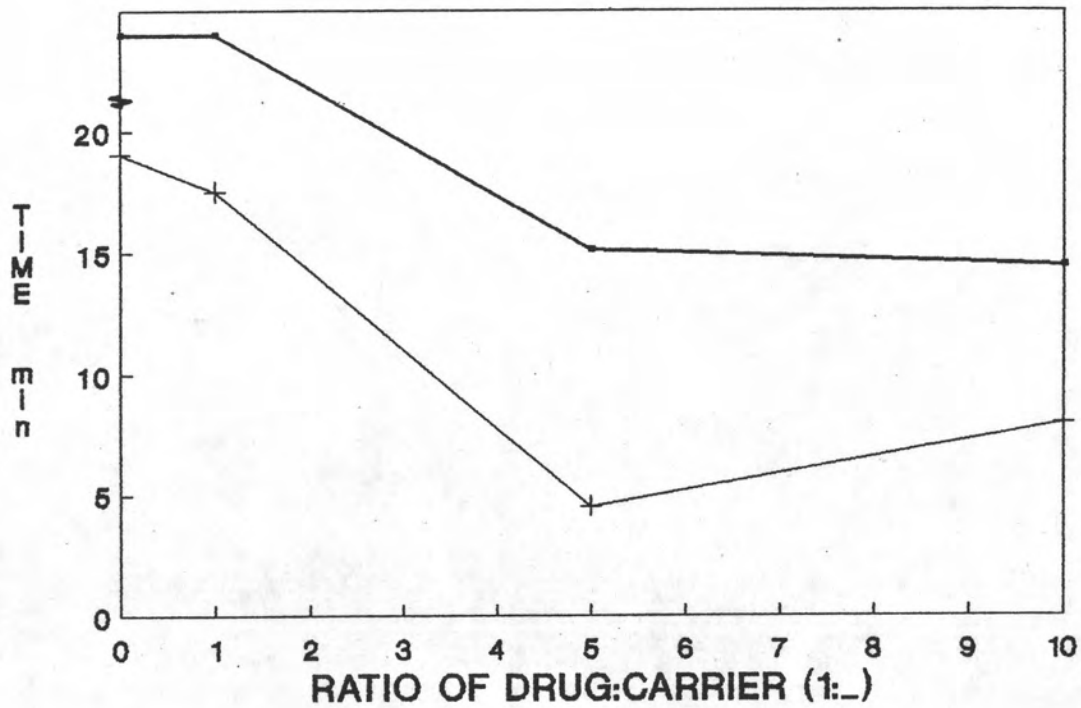

Figure 60 The comparison curve of Time 80% of IDM from IDM-Mannitol powder with various ratio from both physical mixture (•) and solid dispersion (+).

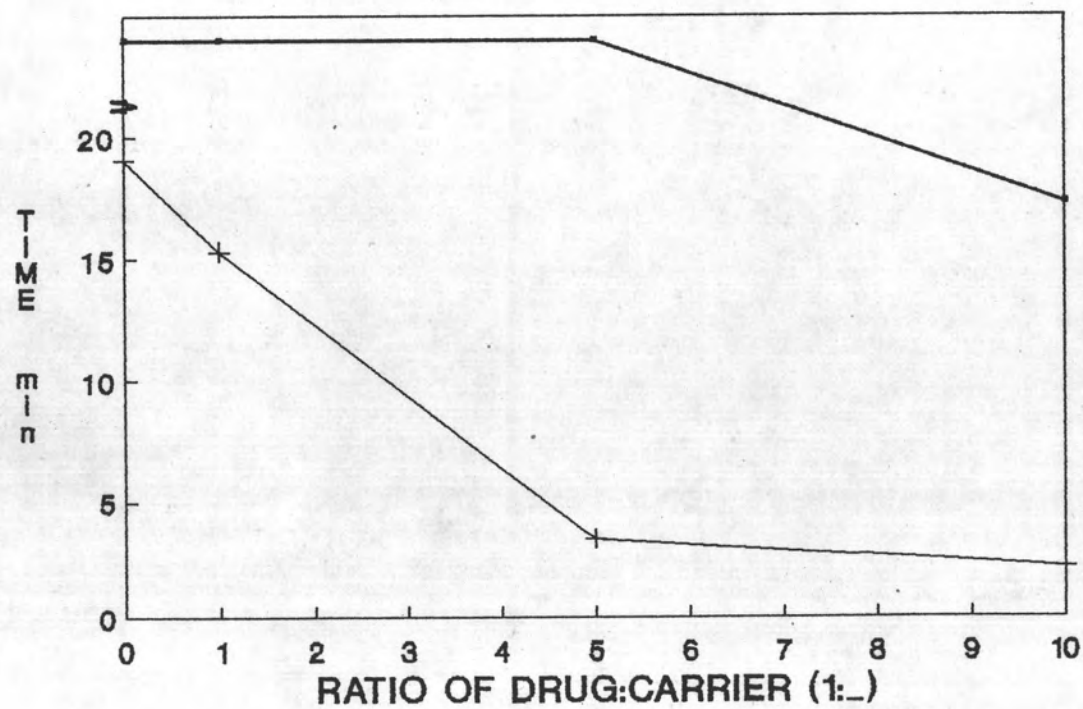

Figure 61 The comparison curve of Time 80% of IDM from IDM-PEG 4000 powder with various ratio from both physical mixture (•) and solid dispersion (+).

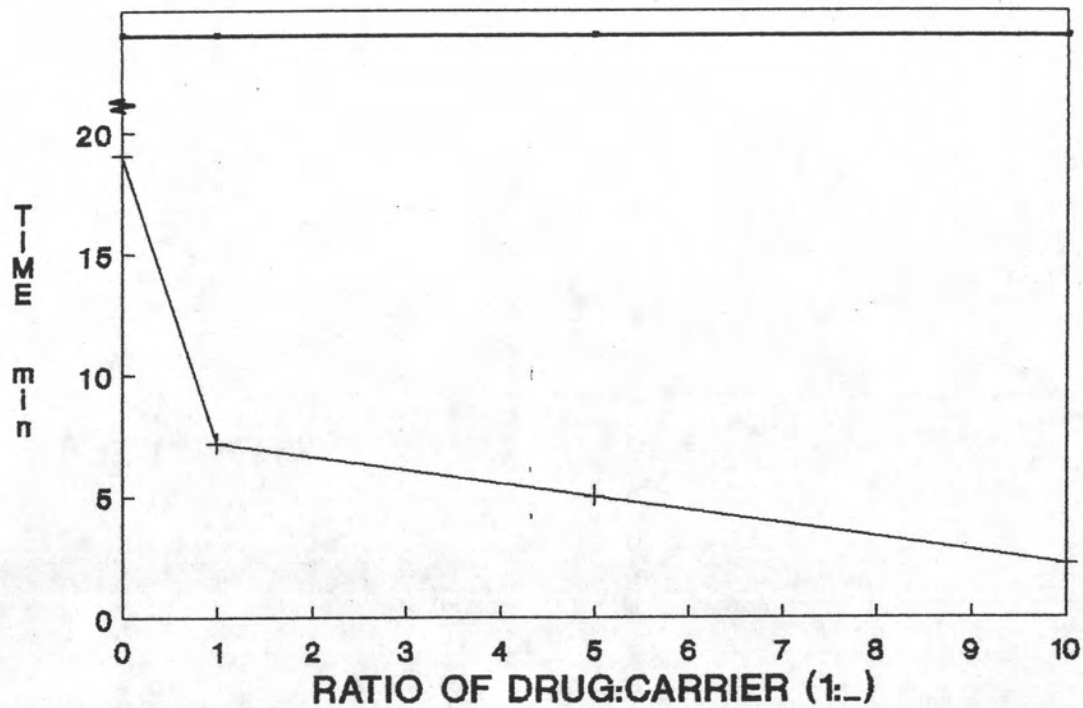

Figure 62 The comparison curve of Time 80% of IDM from IDM-PVP k 30 powder with various ratio from both physical mixture (•) and solid dispersion (+).

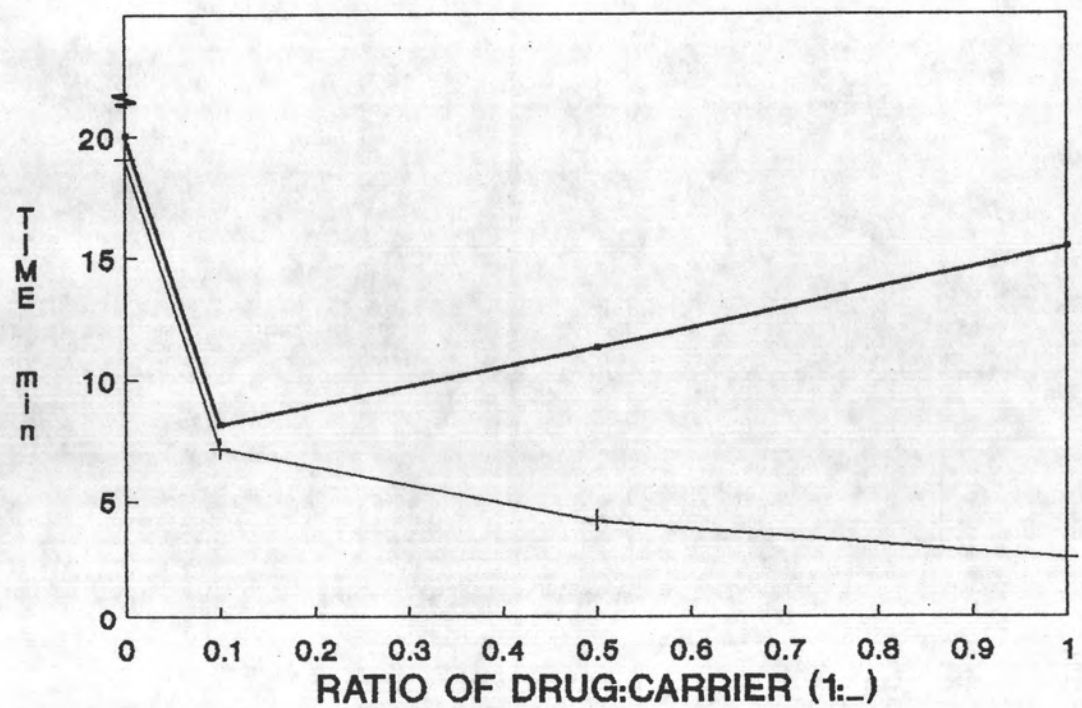

Figure 63 The comparison curve of Time 80% of IDM from IDM-SLS powder with various ratio from both physical mixture (•) and solid dispersion (+).

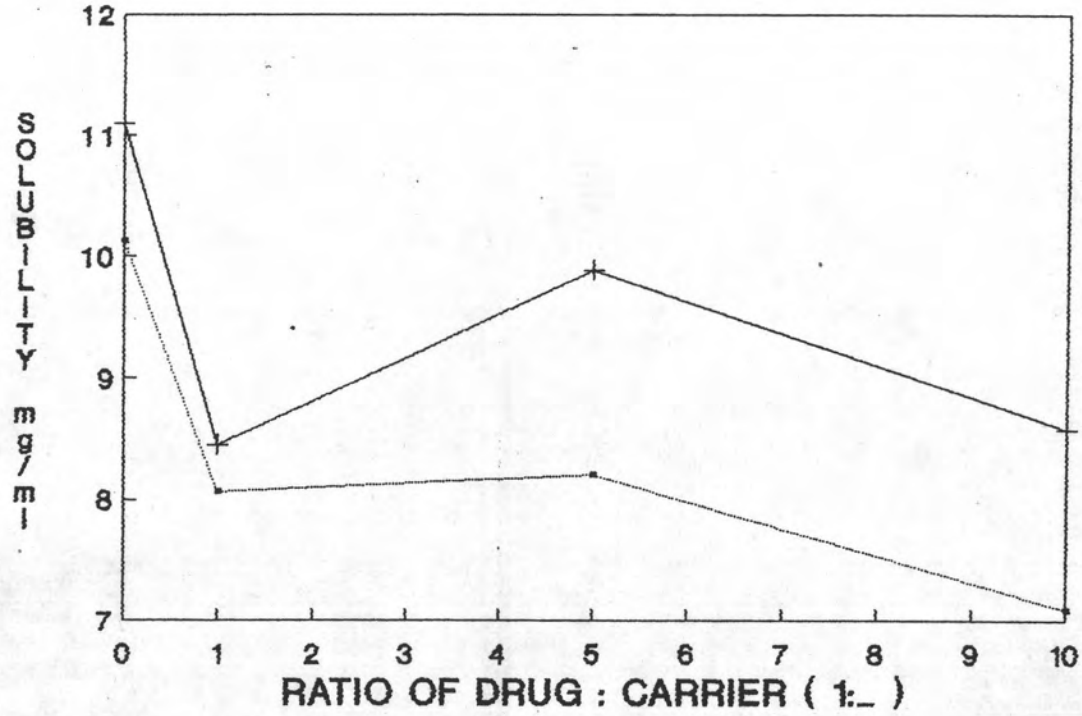

Figure 64 . The comparison curve of solubility of IDM from IDM-Mannitol powder with various ratio from both physical mixture (.) and solid dispersion (+).

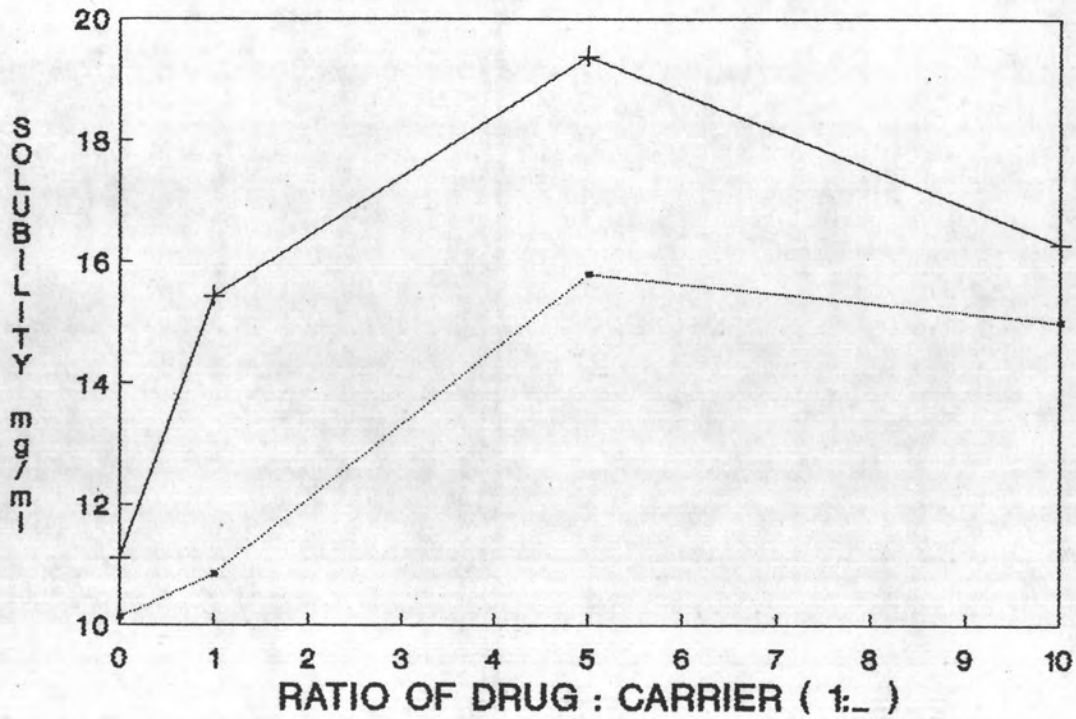

Figure 65 The comparison curve of solubility of IDM from IDM-PEG 4000 powder with various ratio from both physical mixture and solid dispersion (+)

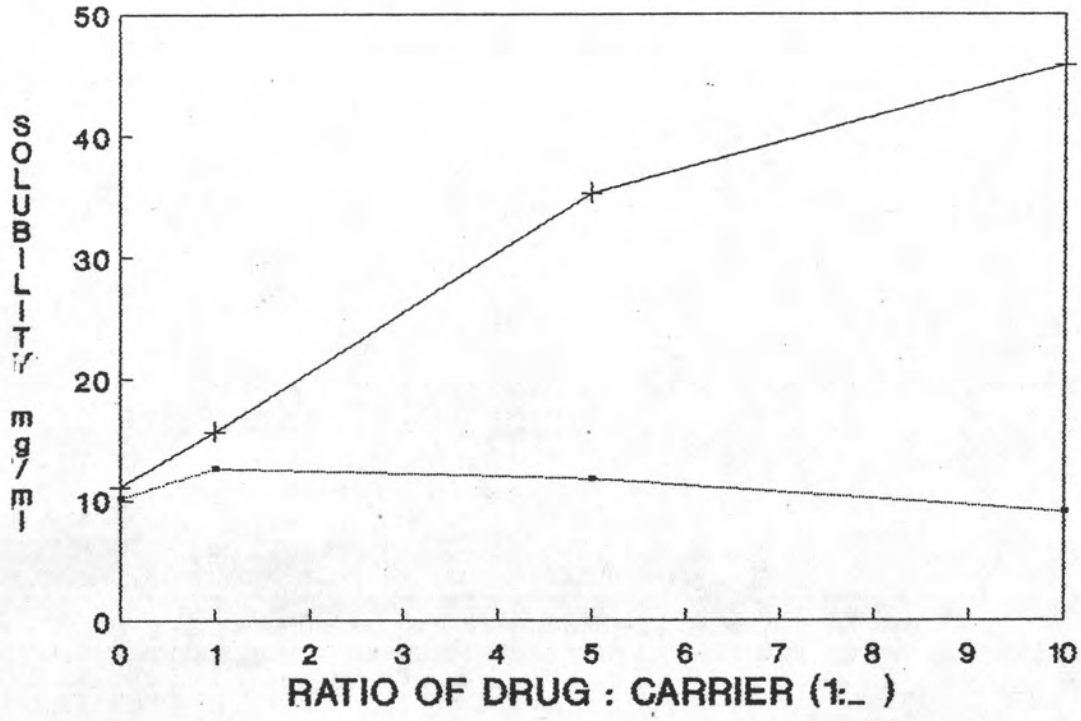

Figure 66 The comparison curve of solubility of IDM from IDM-PVP K 30 powder with various ratio from both physical mixture (•) and solid dispersion (+).

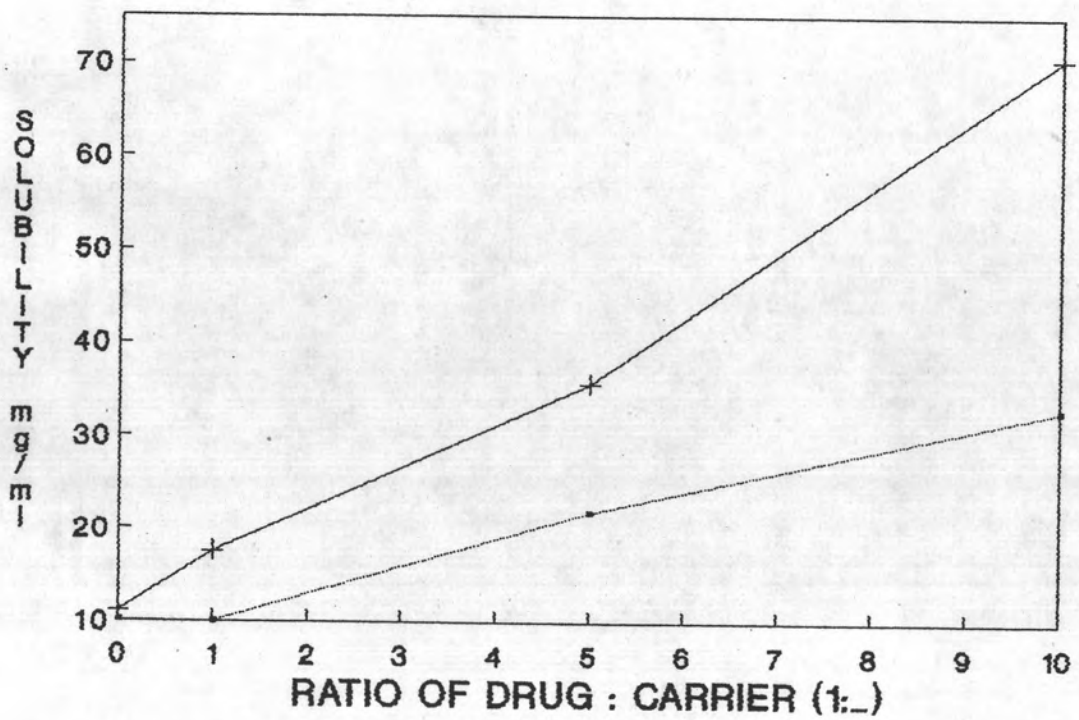

Figure 67 The comparison curve of solubility of IDM from IDM-SLS powder with various ratio from both physical mixture (•) and solid dispersion (+).

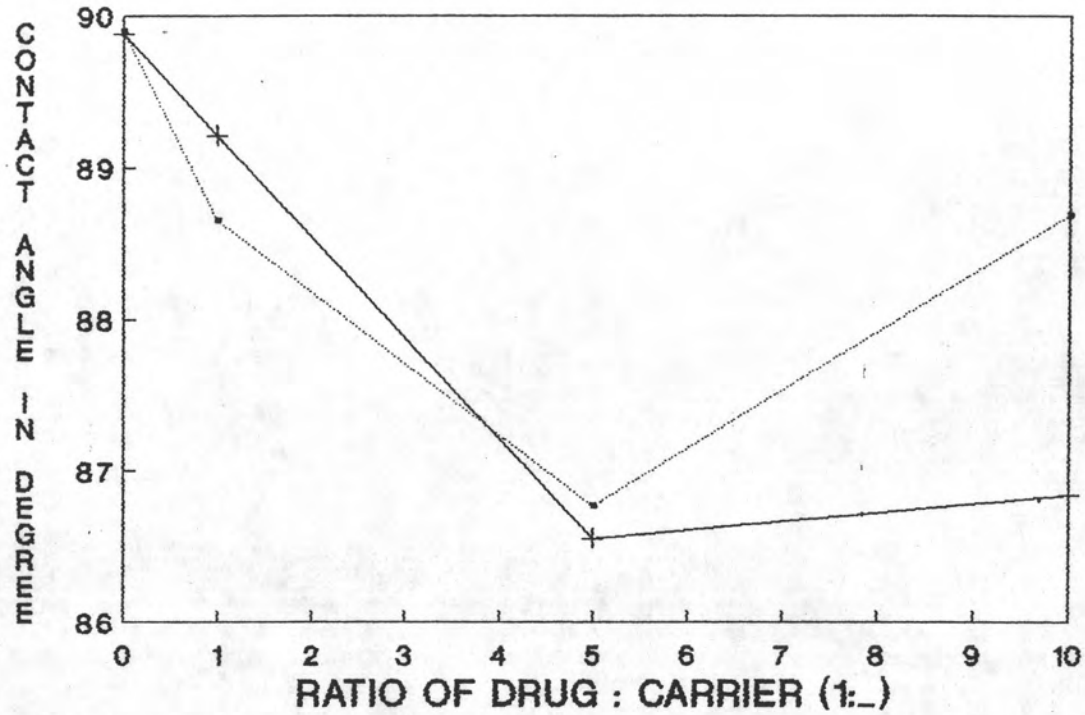

Figure 68 The comparison curve of contact angle of powder from IDM-Mannitol system from both physical mixture (.) and solid dispersion (+).

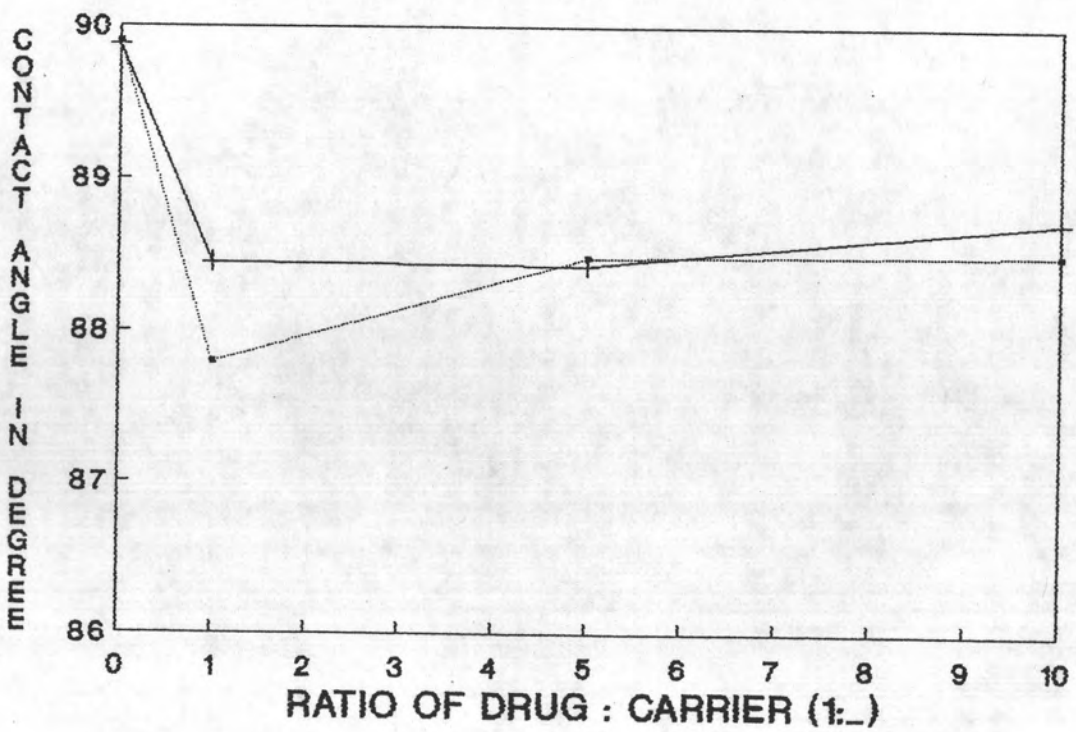

Figure 69 The comparison curve of contact angle of powder from IDM-PEG 4000 system from both physical mixture (.) and solid dispersion (+).

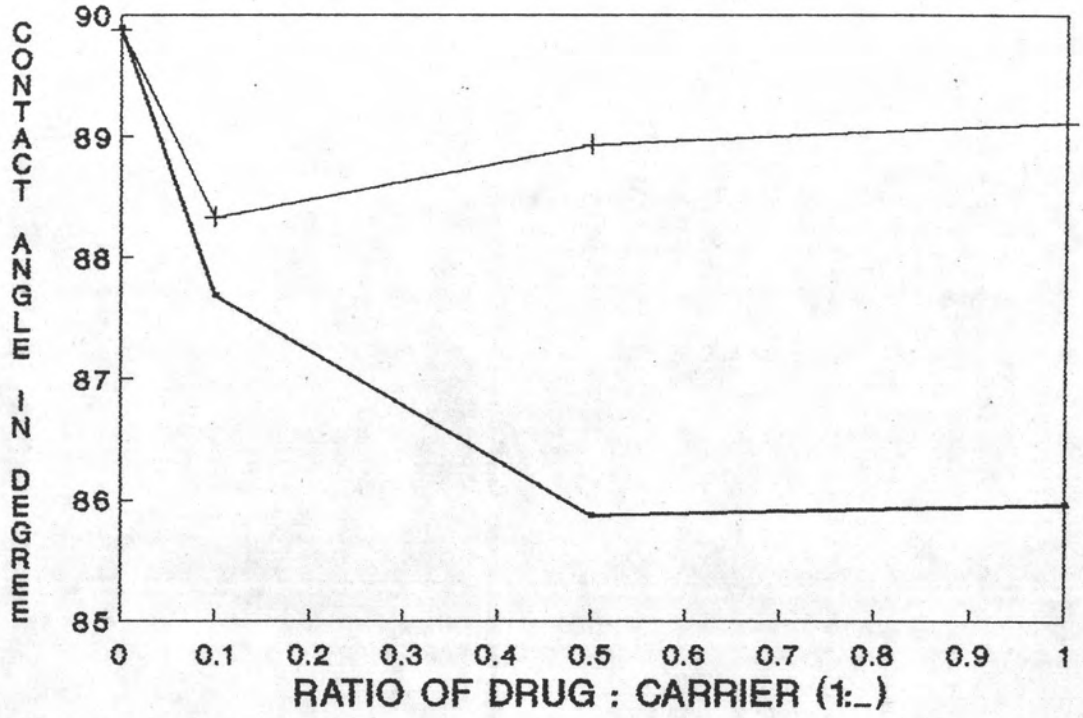

Figure 70 The comparison curve of contact angle of powder from IDM-SLS system from both physical mixture (.) and solid dispersion (+).

It seemed that the components in the capsule help to enhance dissolution of IDM because all capsules gave higher IDM dissolution than the same ratio of powder, except IDM-SLS system. The higher dissolution of IDM in capsule than powder may be resulted form the reduction of particle size or deaggregation and deagglomeration by mixing forces. It was also caused by increasing wettability due to freely soluble diluent, lactose. However, IDM-SLS systems displayed inversely that may be resulted from the effect of undissolved diluent, corn starch, which was covered the surface of drug and the coprecipitate.

The IDM dissolution from capsule implied that using the solid dispersion technique with a small amount of carrier, the ratio of 1:1 for mannitol, PEG 4000, PVP K 30, and the ratio of 1:0.1 for SLS, can improve dissolution of IDM. Moreover, the size of capsule was also the same as commercial capsule; thus, it is very convincing that the application of IDM dissolution by using the solid dispersion technique will be valid in manufacturing scale.

From all dissolution data of all IDM-carrier powder, the 1:10 IDM-PVP K 30 coprecipitate and the 1:10 IDM-PEG 4000 coprecipitate display nearly the same time 80% which is the fastest dissolution from all powders. However, it is unconvenient to prepare IDM-PVP K 30 coprecipitate due to the stickiness of mass and the

difficulty in grinding mass. In practical for the fastest IDM dissolution preparation, PEG 4000 is more suitable than PVP K 30 because IDM-PEG 4000 coprecipitate can be easily ground and screened through a sieve.

However, the more weight fraction of carrier brings the larger of capsule size the leads to larger container, so the cost of manufacturing must be increased. Moreover, larger capsule brings less patient compliance, so it will be a problem for curing deseases. Hence, the small amount of carrier should be considered for capsule preparation.

From the investigation, the 1:0.1 IDM-SLS coprecipitate capsule gives the fastest 80% dissolution of IDM, 8 minutes 21 seconds. The Pharmacopoeia requires 20 munutes for dissolution 80% of IDM, so the IDM-SLS coprecipitate capsule showed about 2.4 times faster than the required time from USP XXII. Furthermore, the capsule contains only 2.5 mg of SLS. Hence, in practical industrial process, SLS might be a choice of carrier for preparing the solid dispersion capsule.

Conclusion

This investigation is focused on the possible enhancing dissolution mechanisms of IDM from various types and amounts of carriers. The mechanisms from both the physical mixture and the coprecipitate are tabulated in

the Table 63 and Table 64, respectively. Moreover, the relation of amount of carrier which reflexes the ability of increasing dissolution mechanisms from both the physical mixture and the solid dispersion are shown in Table 65 and Table 66 consequently.

All systems of IDM coprecipitate give higher IDM dissolution than physical mixture and drug alone. In capsule, it brings in the same way as powder dissolution. The 1:0.1 IDM-SLS coprecipitate capsule shows the best system in the dissolution of IDM.

Table 63 The possible mechanism(s) of enhancing dissolution of IDM from physical mixture powder.

Mechanism	System			
	IDM-MAN	IDM-PEG	IDM-PVP	IDM-SLS
Particle Size reduction	-	+	+	-
Deaggreation Deagglomeration	+	+	+	-
Complex formation	-	-	-	-
Changing microenvironment of drug	a	a	a	a
Changing crystallinity	-	-	-	-
Wettability Increased	+	+	a	+

+ : positive

- : negative

a : unknown

Table 64 The possible mechanism(s) of enhancing dissolution of IDM from coprecipitate powder

Mechanism	System			
	IDM-MAN	IDM-PEG	IDM-PVP	IDM-SLS
Particle Size reduction	+	+(d)	+(e)	+
Deaggreation Deagglomeration	+	+(d)	+(e)	+
Complex formation	-	-	+	+
Changing microenvironment of drug	a	+	+	a
Changing crystallinity	b	b	c	b
Wettability Increased	+	+	a	+

+ : positive

- : negative

a : unknown

b : Form I to Form II

c : Form I to amorphous form

d : monotectic mixture

e : might be a glass formation

Table 65 The relation of increasing amount of carrier and mechanism(s) from the physical mixture powder

Mechanism	System			
	IDM-MAN*	IDM-PEG*	IDM-PVP*	IDM-SLS**
Particle Size reduction	-	smaller	smaller	-
Deaggreation Deagglomeration	more	more	more	-
Complex formation	-	-	-	-
Changing microenvironment of drug	a	a	a	a
Changing crystallinity	-	-	-	-
Wettability (contact angle)	88.66 to 86.77 to 88.69	87.79 to 88.49 to 88.50	a	87.68 to 85.87 to 85.96

- : negative

a : unknown

* : 1:1 to 1:5 to 1:10

** : 1:0.1 to 1:0.5 to 1:1.0

Table 66 The relation of increasing amount of carrier and mechanism(s) from the coprecipitate powder

Mechanisms	System			
	IDM-MAN*	IDM-PEG*	IDM-PVP*	IDM-SLS**
Particle Size reduction	smaller	+(e)	+(e)	smaller
Deaggreation Deagglomeration	more	more	a	more
Complex formation	-	-	+	+(b)
Changing microenvironment of drug	a	+(e)	+(e)	a
Changing crystallinity	c	c	d	c
Wettability (contact angle)	89.21 to 86.55 to 86.84	88.45 to 88.43 to 88.72	a	88.33 to 88.93 to 89.11

+ : positive

- : negative

a : unknown

b : occurred in higher ratio

c : Form I to Form II

d : Form I to amorphous form

e : can not measure

* : 1:1 to 1:5 to 1:10

** : 1:0.1 to 1:0.5 to 1:1.0