CHAPTER I

INTRODUCTION

The method of enhancing drug dissolution by incorporating a poor water soluble drug in a carrier was first proposed by Seikiguchi and Obi in 1961 in an attempt to improve the biopharmaceutical properties of many drugs of low aqueous solubility. The pharmaceutical applications of solid dispersion are to date two marketing solid dispersion systems, Grispeg [R] (Sandoz-Wander) a griseofulvin-polyethylene glycol solid dispersion and Cesamet [R] (Lilly) a nabilone-PVP solid dispersion.

While there is a large volume of experimental data showing dissolution rate improvement by solid dispersion formulations (Akbûga, Gürsoy, and kendi, 1988; Badawi, El-Sayed, 1980; Desphpande, and Agrawal, 1984; Ford, 1986; McGinity, 1978; Khan, 1981), little incidence is given to elucidate the mechanism(s) responsiple (Doherty and York, 1987; Craig, 1985). An understanding of mechanism(s) of drug that releases from solid dispersion would allow the formulator to predict the potential gain in dissolution resulting from a given solid dispersion such as knowing amount of carrier that should be suited for a given drug type of carrier that should be selected for the drug and the process that why the carrier produce the increase

dissolution for this preparation. Moreover, to investigate the exact mechanism(s) is a basic research for the other drugs poorly soluble drugs.

This study will focus on IDM-carrier solid dispersion system in depth to elucidate specific mechanisms effecting dissolution enhancement. Solvent technique was used for preparation; moreover, the amount and type of carriers are varied. The model drug, indomethacin was chosen based on its low solubility in water (Methew, James, and Edward, 1984). Freely soluble, inert and nontoxic substances PEG 4000, PVP K 30, mannitol and sodium lauryl sulfate were selected as carries used for this research. These carriers vary widely in chemical and physicochemical properties. They can be catagoried as sugar, soluble polymer, or surfactant.

Purposes for investigation

1. To elucidate mechanism(s) of increasing dissolution of indomethacin solid dispersion prepared by different carriers; sugar, polymer, and surfactant of various ratios. The investigation involves particle size reduction, solubility, complexation, crystallinity and wettability.

2. To study and compare the dissolution of IDM from powders prepared by solid dispersion and physical mixture.

3. To investigate the relationship between mechanisms of increasing dissolution of different indomethacin solid dispersions and their drug dissolutions.

4. To compare and study the dissolution of indomethacin capsule composed of pure drug, treated drug, physical mixtures and solid dispersion.

5. To use the solid dispersion technique both to increase dissolution; thus, improve drug bioavailability and to develop a formula for poorly soluble drug in dosage form for a manufacturing process.

Literature Review

Solid dispersion is a technique for changing pattern of dissolution rate. It can change into two ways, increasing or decreasing, depending on the types of carriers (Chiou, and Riegelman, 1971). The water soluble carrier combined with a poorly water-soluble drug results in a fast release of the drug from the matrix; whereas, the poorly soluble or insoluble carrier combined with a good water-soluble drug leads to a retardation of drug release from the matrix.

Solid dispersion was defined by Chiou and Reigelman in 1971 as "a dispersion of one or more active ingredients in an inert carrier or matrix at a molecular level in a solid state prepared by the melting or fusion, solvent, or melting-solvent method."

The various possible mechanisms of increasing dissolution rate from solid dispersion are (Ford, 1981; Chion and Riegelman, 1971) :

1. Reduction of particle size

2. Deaggregation or deagglomeration of particles

3. Soluble complex formation

4. Changing crystallinity of active ingredients

5. Changing the microenvironment of powder in solid dispersion

6. Increased wettability of powder

7. Combination of the aforementioned mechanisms

I. REDUCTION OF PARTICLE SIZE

The effect of particle size reduction on dissolution rate is one primarily of exposure of increasing amounts of surface area of the drug to the solvent. It can be predicted that dissolution rate will increase as particle size decreases; owing to Noyes-Whitney equation (Higuchi, 1967).

$$dc/dt \quad = \quad kA \, (C_s - C_t) \quad \ldots\ldots\ldots\ldots (1)$$

where dc/dt is the amount of solute dissolved per unit time.

A   is the surface area explosed to solvent.

k   is the dissolution rate constant.

C_s is the saturation solubility of the solute in medium.

C_t is its concentration at any given time.

In equation 1, the rate of dissolution vary directly to the suface area of the powder. The reduced particle size produced greater surface area; thus, the smaller size of drug particle brought gerally more dissolution of drug. Particle size reduction is usually achieved by (Russell, 1990).

A : Conventional trituration and grinding

B : Ball milling

C : Fluid energy micronization

D : Controlled precipitation by changing of solvent or temperature application of ultrasonic waves and spray drying.

E : Administration of liquid solution from which upon dilution with gastric fluids, the dissolved drug may precipitate in very fine particles.

F : Administration of water-soluble salt of poorly soluble compounds from which the parent, nutral forms may precipitate in ultrafine form in Gastrointestinal fluids

The physicochemical structures of solid dispersions that involve particle size reduction are three structures : eutectic formation, solid solution and glass formation.

a. The Eutectic Mixture

When two substances are completely miscible in their molten state they will harden to form a eutectic mixture. These properties can be illustrated in a phase diagram (Figure 1) which these materials are not able to form solid solution (Shefter, 1981). When a eutectic composed of a poorly soluble drug is exposed to water or GI fluids, the carrier may be released into aqueous medium
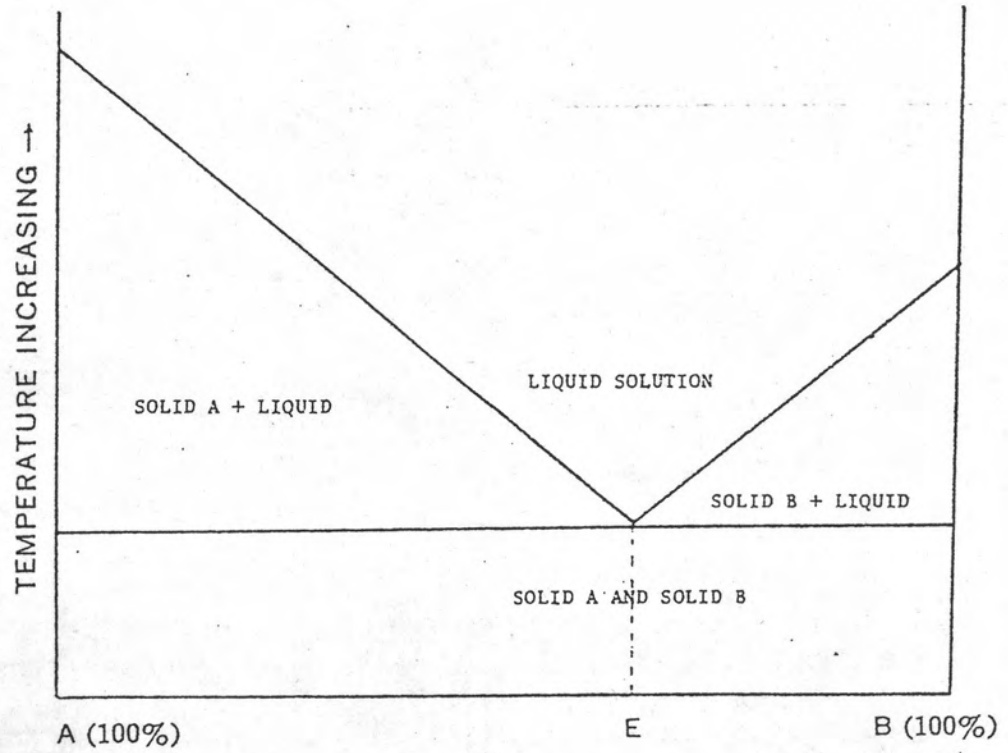
Figure 1   Phase diagram of a simple eutectic mixture
            with negligible solid solubility

in fine crystalline form (Goldberg, Gibaldi, and Kanig, 1965). This is based on the assumption that both components may simultaneously crystalize out in very small particulate size. Ultrafine or colloidal crystallines of eutectics can be found in such a sample as tin-lead system (Gennaro, Chase, Gibson, Cramberg, King, et al, 1985). The composition of eutectic may have a significant effect on the particle size of the crystalline. If it is made up of high weight fraction of drug, an ultrafine crystallization of drug may not be obtained.

This is logical if one expects that the higher the dilution, the finer the crystalline size of its precipitate. This probably accounts for the failure to find an increased dissolution rate of acetaminophen from the eutectic with urea which contain 52% of acetaminophen (Goldberg, Gibaldi and Kanig, 1966a). It is believed that the hardening effect of the eutectic may also play a role in retarding its dissolution.

It can be seen that the particle size of component of the eutectic mixture may be affected by rate of solidification, type of materials comprising the mixture, and composition of the mixture. In case of the increase in dissolution rate, that were observed for eutectic mixtures, can be proposed by other mechanisms too.

Except phase diagram, the eutectic mixture investigation can be evaluated by X-ray diffraction, differential thermal analysis and microthermal microscope (Chiou and Riegelman, 1871)..

b. Solid Solution

A solid solution, compared with liquid solution, is made up of a solid solute dissolved in a solid solvent. It is often called a mixed crystal because the two components crystallize together in homogenous one phase system. Goldberg et al. (1966) suggested that a solid solution of poorly soluble drug in a rapidly soluble carrier achieved a faster dissolution rate than a eutectic mixture because the particle size of the drug in the solid solution was reduced to a minimum state, its molecular size. It must be focused that the advantage of a solid solution if exposed to a medium with a volume much less capable to dissolve all the drug. Under these condition, a drug may precipitate. However, due to maximum particle size reduction in the solid solution and to the possible solubilization effect of the carrier in the microenvironment, diffusion layer of bulk fluids, the drug may temporarily result in a high supersaturation of the bulk fluid. Obviously, it is temporary and would lead to precipitation if this is not being absorbed or removed by other processes.

The classification of solid solution can be devided into two catagories. The first classification (Chiou, and Rieglman, 1971) depended on their solid miscibility, and separated into two groups.

I. The continuous (isomorphous, non-restricted, complete) solid solution. In this system, two components are miscible or soluble at solid state in all proportions. The bond strength between the different components is greater than the bond strength between the same species of molecules. As, yet no solid dispersion falls into this catagory (Figure 2).

II. The discontinuous solid solution - In contrast to the continuous solid solution, there is only a limited solubility of a solute in a solid solvent in this group of solid solution. Therefore, each component is capable of dissolving the other to some extent at the eutectic temperature but as the temperature is lowered the degree of solubility decreases consequently the degree of solubility predicted by phase analysis at the eutectic temperature is reduced at ambient resulting in phase separation and crystallization (Figure 3).

The second classification (Shefter, 1981) is based on the molecular size of the two components and solutions are terms of substitutional, interstitional and imperfectional (Figure 4).
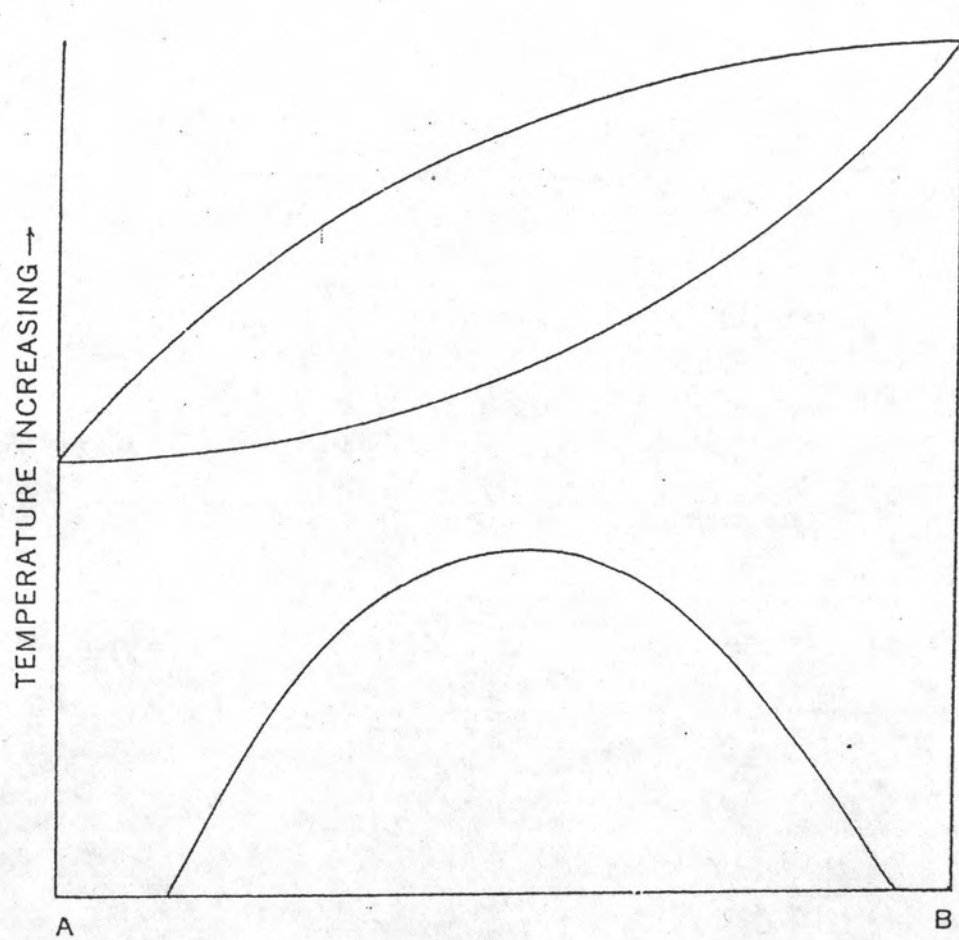
Figure 2   A typical phase diagram of continuous solid
solution of a binary system, A and B. The
lowest curve indicates a solubility gap at
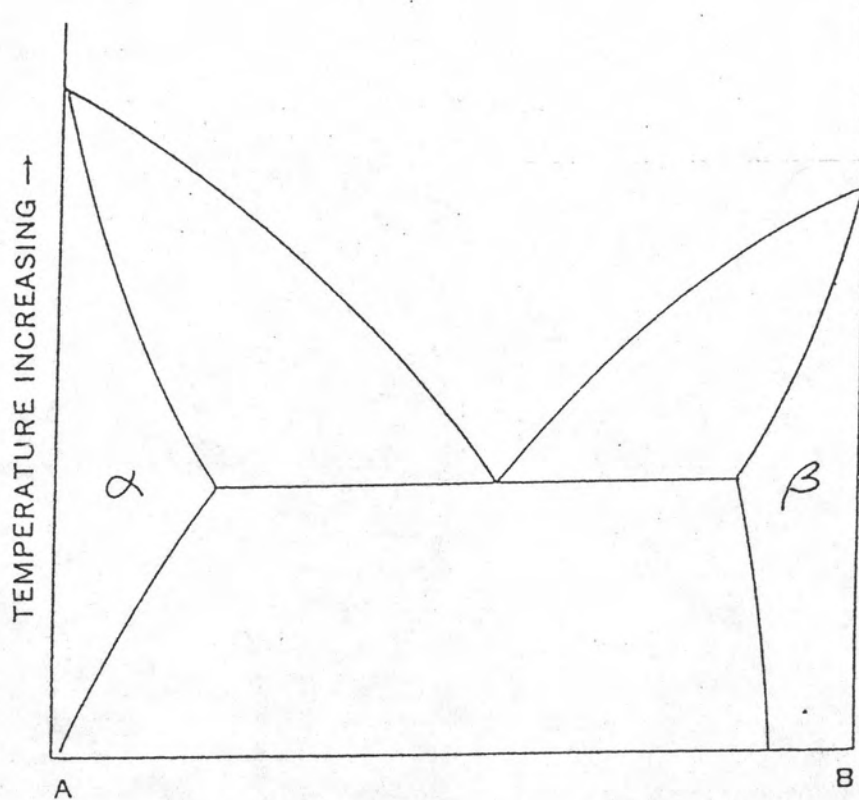lower temperatures.

Figure 3   A typical phase diagram of a discontinuous
solid solution of a binary system, A and B.
and are regions of solid solution formation.

SUBSTITIONAL   INTERSTITIAL
                          SPACE

IMPERFECTIONS
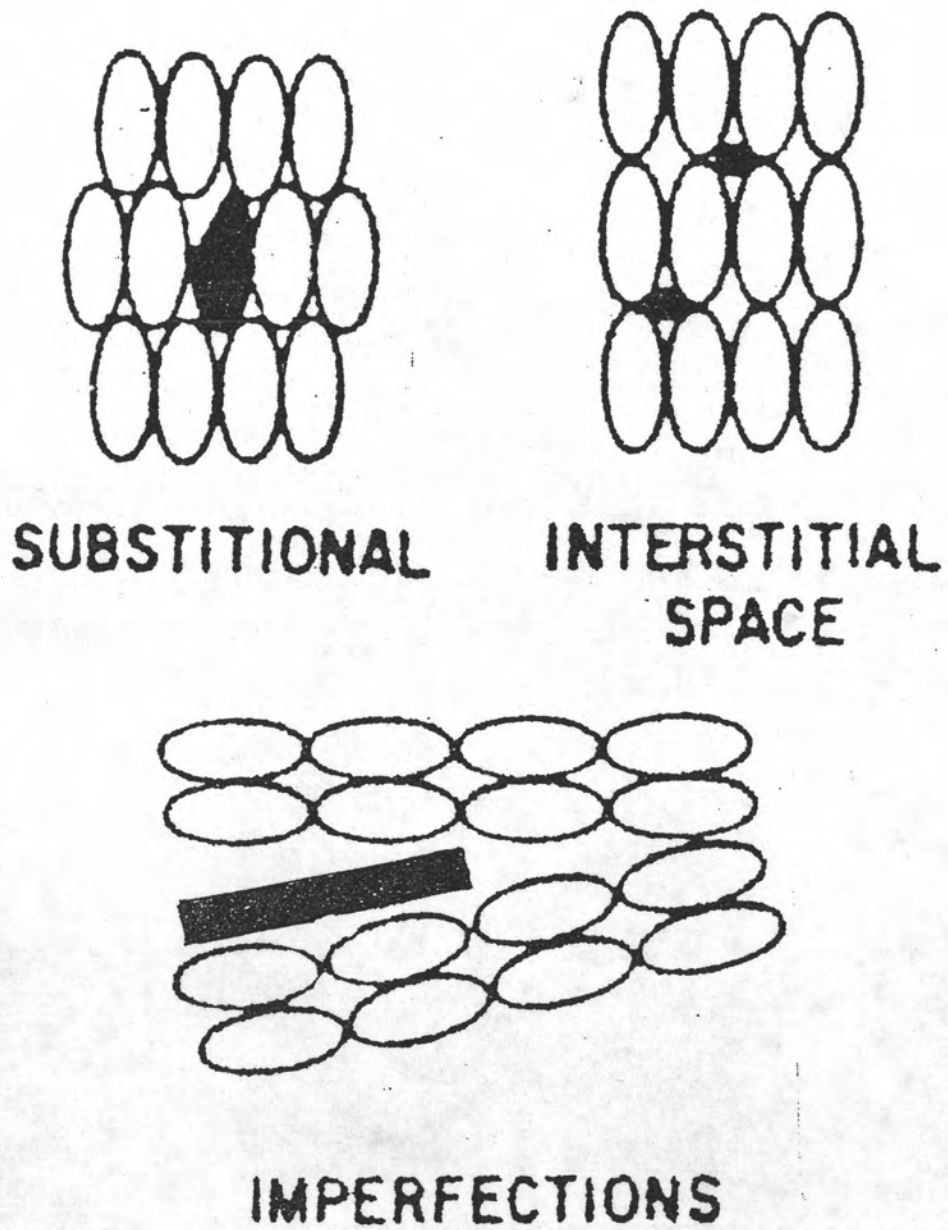
Figure 4   Schematic (2-dimensional) of the types of
                  substitution which may occur in crystalline
                  material.

- The substitutional solid solution requires as higher degree of topological and chemical similarity between molecules. The molecular size of the two components should not differ by more than 15%, and the solute molecule substitutes for the solvent molecule in the crystal lattice of the solid solvent.

- The interstitial solid solution - the solute molecule occupied the interstitial space between the solvent molecule. The size of molecule is again critical and the solute molecule diameter should be less than 0.59 that of the solvent molecule, and that the volume of the solute molecule should be less than 20% of that of the solvent. Large crystalline polymer, e.g. polyethylene glycols trends to form this type of solid solution. Moreover, other factors such as high viscosity, supercooling, and physical-chemical interaction between the drugs and the polymers may contribute to the formation of metastable solid solution if the drug-polyethylene glycol (Craig, 1990) melt is solidified rapidly. The melt of polyethylene glycol polymers is high viscous, even at temperature at 200 degree; in an addition, the viscosity increases rapidly with the decrease in temperature. Therefore, as drug-polyethylene glycol melt is allowed to solidify quickly, the crystallization of the drug is retarded, due to reduce solute migration and the difficulty in nucleation of the drug in the viscous medium.

- The imperfection type - At the sites of imperfections, these foreign substances could be entrapped. It is possible that dispersions of drugs at the molecular level could be achieved in this way.

c. **The glassy solutions or dispersions**

A glass solution (Gennaro, Chase, Gibson, Granbberg, King, Martin, 1985; Shefter, 1981; Ford, 1986) is a homogenous glassy system in which a solute dissolves in a glassy solvent. It is thought of a specific, non-conducting, transparent, brittle solid over the glass-transition forming temperature (Tg).

The familiar term "glass", however, can be used to describe either a pure chemical or a mixture of chemical (window glass is a mixture of inorganic oxides) in a glassy or vitreous state. The glassy or vitreous state is usually obtained by an abrupt quenching of the melt. On heating, it softens, progressively and continuously without a sharp melting point. This is primarily due to the facts that the chemical bonds in the glass differ considerably in length and therefore, in strength and that there is no one temperature at which all the bonds become lossened simultaneously. The glassy form of pure compound can often be transformed to a crystalline state upon heating. It is also interesting to know that any liquid or supercooled liquid whose viscosity is greater than 10^3 poises is generally called glass.

A crystallization solid processes both long range and short range orders of structure; whereas, a glass or liquid has a structure only with a short range order. Glass formation is common in many polyhydroxyl molecules such a sugar, presumably due to their strong hydrogen bonding which may prevent their crystallization. There is usually a relatively strong chemical bonding between the solute and the solvent in the solid solution, while the lattice energy in the glass solution is expected to be, much less because of its similarity with the liquid solution. Similarly, the dissolution rate from a crystal is usually slower than from an amorphous or glassy solid of the same chemical identity. Therefore, if everything is equal, the dissolution rate of drug in the glass solution should be theoretically faster than that in the solid solution. There is another important advantage of glass solution over solid solution when the content of the solute exceeds the solubility in both solution at ambient temperature. The particle size of crystallization of the solute is much smaller in the glass solution due to the different growth of the crystal in its viscous medium.

The properties of a glassy may be related to the method of solidification or cooling. The particle size distribution in the crystallization of benzophenone in hydrocarbon glass was shown to be a function of the cooling rate; ranging from being viscible to opaque in appearance as the rate of cooling was prolonged.

A term of glass suspension is referred to mixture in which precipitated particles are supported in a glassy solvent.

Pure Polyvinylpyrrolidone and some other substances (citric acid, Urea, PEG, sugar such as dextrose, sucrose and galactose) (Ford, 1981; Allem, victor, Yanchick and Maness, 1977) dissolved in the organic solvent may become glassy after the evaporation of the solvent. It is possible that the precipitation of drugs introduced into the system is inhibited due to the increase in viscosity as the solvent evaporated. Such inhibition may also be facilitated by the possible complexation between the drug and the polymer. Thereby, a transparent, brittle glassy solution is formed. Evidence for molecular dispersion of drug in polyvinylpyrrolidone, i.e. a glass solution (Chiou and Reigelman, 1971) is provided by using of the UV method for a carrier, high resolution electron microscope method for iopanic acid and X-ray diffraction method for sulfathiazol (Niazi, 1976). For the polyethylene glycol carrier, the crystalline size of the drug may also be very fine if the drug concentration greatly exceeds its solubility in polyvinylpyrrolidone.

The basic processes employed for measurement of fine solid particle involve direct and indirect techniques. Direct methods measure the actual dimensions of the particle by using of a calibration scale in

microscop and by using a sieve. Indirect measurement make use of some characteristics of the particle that can be related to particle size such as sedimentation rates, permeability and optical properties. There are some examples of particle size measurement shown at table 1.

Electron microscope was chosen because it can supply information about the shape and thickness that can not be obtained by other methods and in addition supply a permanent record through use of photomicrographs.

Table 1 Common Particle Counting Method.

| Method of counting	Size range covered (approximate)
1. Sieve	44 and greater (325 mesh)
2. Light scattering	1-200 μm (70 mesh)
3. Electronic sensing zone	1-300 μm (50 mesh)
4. Light obstruction	2-300 μm (50 mesh)
5. Air permeation	0.05-150 μm (100 mesh)
6. Sedimentation in gas or liquid	2-200 μm (700 mesh)
7. Optical microscope	0.5-100 μm (140 mesh)

2. DEAGGREGATION AND DEAGGLOMERATION

The aggregation and agglomeration between fine
crystallinity of the pure hydrophobic drug may play a far
more important role in disturbing rate of dissolution and
absorption (Chiou, Riegelman, 1971). An aggregation is
defined as a particle or an assembly of particles held
together by strong inter-or intra molecular or atomic
cohesive forces. Usually the aggreagate is stable to
high-speed mixing or ultrasonic forces. An agglomerate is
defined as a gathering of two or more particles and/or
aggregates held together by relatively week cohesive
forces. In many cases, these forces are due to an
electron static surface charges gathered during handling
or processing operation. It is also likely that these
electrostatic forces may be involved only in bringing
particle together, but they are not responsible for
holding them together. Such agglomeration is more severe
for very finely divided particles about 0.1 um, due to the
greater specific surface changes. Although the
agglomerates may be broken, their dispersion in the mildly
stirred GI fluids may not be very efficient. These
problems of agglomeration and aggregation are most
determined to the application and efficacy of pure fine
particle between their effective specific surface area is
markedly reduced. Serious drawbacks of aggregation and
agglomeration and lumping in the dissolution medium
between pure drug particle are, however, rarely presented

in most solid dispersion systems because the individually dispersed particles are surrounded in the matrix by carrier particle. It must be emphasized that the agglomeration and aggregation of solid dispersion powders may not significantly affect the dissolution of the drug which can still disintegrate quickly due to the more rapid dissolution of soluble carrier.

The methods of studying the deaggregation and deagglomeration are similar to the methods used for studying particle size.

3. SOLUBLE COMPLEX FORMATION

Complex is defined as a species formed by the association of two or more interactant molecules or ions (Repta, 1981). Complexation may be defined as the reversible association of (m) molecules of substrate (S) with (n) molecules of a ligand species (L) to form a new species (SmLn) as shown.

$$mS + nL \underset{}{\overset{K_{m,n}}{\rightleftharpoons}} SmLn$$
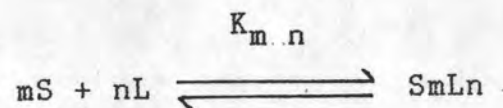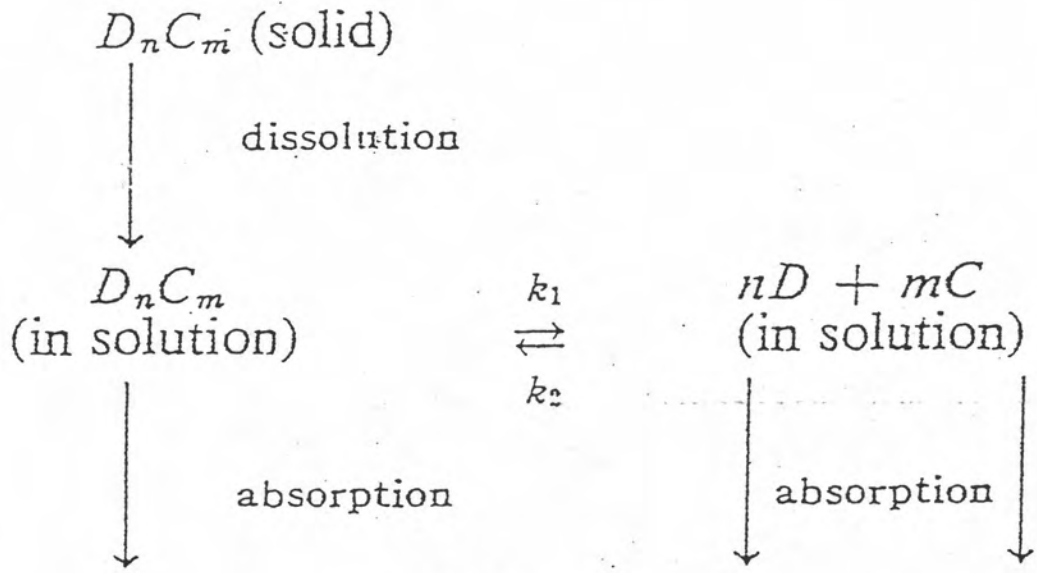
The definition of a complex leads to a classification into two groups based on the type of chemical bonding (Gennaro, Chase, Gibson, Granbberg, King, Marten et al, 1990). There are :

I. Coordination complexes - these complexes are formed by coordinate bonds in which a pair of electron is, in some degree, transfered from an interactant to the other. The most important examples are the metal ion coordination, complexes between metal ions and bases. Such complex can be viewed as products of Lewis acid-base interaction. Proton acids then constitute a special cases of this type.

II. Molecular complexes - These species are formed by noncovalent interactions between the substrate and ligand. The noncovalent forces arise from electrostatic, induction and dispersion interactions, and they include, or give rise to, hydrogen-bonding, charge-transfer and hydrophobic effect. Among the kinds of complex species that are included in this class are small molecule-small molecule compounds, small molecule-macro molecule species (for example, drug-protein and enzyme substrate complex), ion-pairs, dimers and other self-associated species, inclusion complexes, intra molecular interaction (such as bases-bases interactions in the DNA helix) and clathrate complexes, in which a crystal structure of one interactant encloses molecules of the second interactant. It can be classified molecular complex in term of the kind of interaction involved in their formation, the kinds of interactants involved or the kinds of complex formed, as shown in the Table 2.

Table   2   Classification of Molecular Complexes

I.	Types of Bonding or Interaction
	- Charge-transfer
	- Hydrogen bonding
	- Hydrophobic interaction
	- Stacking interaction
II.	Type or Structure of Interactants
	- Small molecule-small molecule complex
	- Small molecule-macromolecule binding
	- Drug-protein binding
	- Enzyme-substrate complex
	- Antigen-Antibody complex
III.	Type of Structure of Complex
	- Self-associated aggregate
	- Micelle
	- Inclusion complex
	- Clathrate

$$D_n C_m \text{ (solid)}$$

$$\downarrow \text{dissolution}$$

$$D_n C_m \text{ (in solution)} \quad \underset{k_2}{\overset{k_1}{\rightleftarrows}} \quad nD + mC \text{ (in solution)}$$

$$\downarrow \text{absorption} \qquad\qquad \downarrow \text{absorption}$$

Scheme I

Figure 5   The dissolution and adsorption of a drug into the body from a complex or a compound.
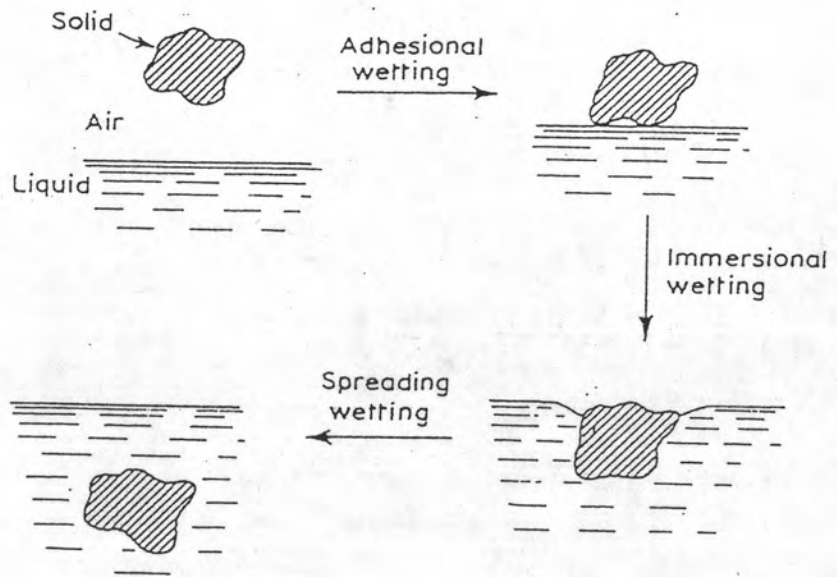

Figure 6   The process of powder wetting.

The dissolution and absorption of drug into the body from a complex or a compound are schematically shown in Figure 5 (Chiou, and Reigelman, 1971). Which D_nC_m is a compound or complex formation between a drug (D) and an inert soluble carrier (C).

It is clear from scheme I that the availability of drug depends on the solubility, the dissociation constant, and the intrinsic absorption rate of the complex. Although the water-soluble polymers have been considered as ideal carrier for the solid dispersion of poorly soluble drug, the implication of the possible complexation should not be overlooked. Polyvinylpyrrolidone was shown to retard the pharmacological action of numerous compounds such as pennicillin, novocain, prostigmine, hexobarbitol, quinine and hexylresorcinol (Chiou and Reigelman, 1971). The formation of an insoluble complex between phenobarbitol and PEG 4000 or 6000 (Kono, Takeda, Nogani, and Nagai, 1971) was shown to reduce rates of dissolution and permeation of phenobarbitol through everted guts of rats. The complexation between griseofulvin and polyethylene glycol 6000 (Chiou, and Reigelman, 1970) may be thought to occur on the basic of traditional solubility study. It is believed that in comparison with pure, insoluble solid drugs, the rates of dissolution and GI absorption can be increased by the formation a soluble complex with a low association constant.

Any methodologies which can relate the changes in one or more properties of the system which are caused by intermolecular interaction may be utilized. Methods (Repta, 1981) which have been used to studying complexes include (but are not limited to) calorimeter, refractive index, optical rotary dispersion, nuclear magnetic resonance spectrometer, spectrophotometry, kinetics and solubility technique.

4. THE CHANGING CRYSTALLINITY OF ACTIVE INGREDIENTS

The crystallinity of drug may be altered during preparation into another form, polymorph or amorphous.

A polymorph (John, Walter, 1969) is a solid crystalline phase of a given compound resulting from the possibility of at least two different arrangements of the molecules of that compound in the solid state. Polymorphism is the ability of any element or compound to crystallize as more than one distinct crystal species (e.g., carbon as cubic diamond or hexagonal graphite). Different polymorph of a given compound are, in general, as different in structure and properties as the crystals of two different compound. Solubility, melting point, density, hardness, crystal shape, optical and electrical properties, vapor pressure, etc., all vary with the polymorphic form. In general, it should be possible to obtain different crystal forms of a drug and thus modify the performance properties for that compound. A number of

technique have been used to identify different polymorphic form of compound. Each of these techniques could be successful in identifying the phase, but a combination of methods provide a powerful means for identification and isolation of each crystalline modification. The various ways are microscopy method, X-ray diffraction, infrared spectroscopy, different thermal analysis etc.

In other forms, amorphous, the drug may also precipitate out in an amorphous form which is the highest energy form of a pure drug, under almost all condition produce faster dissolution and absorption rates than the crystalline form whether the crystal are or are not dispersed in a carrier. A larger amorphous mass with entrapped air probably will not dissolve faster than microcrystals dispersed in a water soluble carrier.

The techniques which identify amorphous form are almost the same as the methods used for investigation of polymorphism. However, the X-ray diffraction is a method of choice.

5. **THE CHANGING MICROENVIRONMENT OF POWDER IN SOLID DISPERSION** (Ford, 1986).

The possible solubilization effect by the carrier may operate in the microenvironment immediately surrounding the drug particle in the early stage of dissolution studies. Micellar solubilization and/or

lowering surface tension of liquid by carrier can lead to the decreased diffusion layer thickness and increased dissolution rate of drug (Yalkosky, 1981). Some carriers, such as urea (Feldman, and Gibbaldi, 1967), can solubilize drugs by effectively breaking up the clusters of hydrogen-boned water molecules in aqueous solution resulting in an increase in the enthalpy of the system and an increase in water solubility of the drug molecule. This mechanism is thought to be partly accounted for the increase in dissolution rate of hydroflumethiazide-PVP (Corrigan, and Timoney, 1975).

Soluble, hydrophillic polymers can affect the solution behavior. Probably the most important solution effect caused by hydrophyllic macromolecules is an in solution viscosity. The microenvironmental viscosity is a true reflection of resistance of flow by molecules in solution. The microviscovity of the formulation may be investigated by a variety of spectroscopic techniques, including nuclear magnetic resonance and electron spin resonance, but little attention has been given to the use of photon correlation spectroscopy (PCS). (Al-khamis, Davis, Hadgraft, 1986; Flounce, Elworthy, Rahman, 1973). Thus, the measured microviscosity implied the changing of microenvironment of drug molecule. If microviscosity of drug molecule was altered, it might change the dissolution rate of drug. It may be according to the Noyes-whitney equation that the more viscosity of solution causes the

less dissolution rate of molecule. For investigating this type of mechanism, NMR was chosen because the changing of relaxation time of drug can point the changing of microviscosity of drug in the equal amount of used power.

6. THE INCREASED WETTABILITY OF POWDER

The increasing dissolution phenomena from solid dispersion may be caused by increased wettability of the poorly soluble drug in the soluble carrier matrix (Florence, 1981). This is due to the fact that each single crystalline of drug is very intimately encircled by the soluble carrier which can readily dissolved and causes the water to contact and wets the drug particle. As a consequence, a fine homogenous suspension of a drug can be easily obtained with minimum stirring.

The wetting of solid materials usually implies the replacement of air on the surface of a solid by liquid (Stamn, Gissinger and Boymond, 1984). In addition to the component of the system, the type of wetting is also important. There are three types (Buckton and Newton, 1985) of wetting namely those of adhesion, immersion and spreading (Figure 6). The contact angle is a parameter that was used for determining the wettability. Pharmaceutically wetting is not an end in itself but it is the preliminary step in another process, e.g. dispersion or dissolution, both in vitro and in vivo. In the preparation of dispersion, surfactants are often employed

to aid in the wetting of insoluble powders (Chiou, Chen and Atharikar, 1976; Andererg, Bisrat and Nystrom, 1988). The role of wetting in the dissolution of drug is not established. Solvang and Filwl (1970) stated that the change to a hydrophilic character probably was responsible for the increased dissolution rate of hydrophobic drug after granulation with a binder. Kawashima (1975) concluded that improvement in wetting caused the increased dissolution rate of salicylic acid powder after spray with acacia. Allen and Davies (1975) reported increase in the dissolution rate and amount of absorption of a highly lipid-soluble drug after admixture with lactose, seemingly due to increased wettability.

The wetting of powders can be evaluated by different manner (Stamn, Gissinger and Boymond, 1984) :

- Direct measurement of the solid-liquid contact angle
- Indirect measurement of that angle (h and e method), liquid penetration rate into a powder bed

In this research, the liquid penetration was selected. Since wetting was also an interpretted indirectly by the rate of penetration of a liquid into a powder bed (Jaiyeoa and Spring, 1980). According to Washburn, a tablet can roughly be considered as a powder bed in which are small capillars of constant radius. If

this is the case, the penetration rate of a liquid into the powder is given by the Washburu equation (Yang and Zografi, 1986) :

$$L^2 = \frac{R.r.\ \cos\theta.t}{2\eta} \qquad \text{eq (2)}$$

Where

L is the length of liquid penetration (cm)

R is the capillar radius (cm)

r is the liquid surface tension (dyne/cm)

θ is the contact angle (degree)

t is the time (second)

η is the liquid viscosity (poise)

This relationship between length of penetration and the time is only verified when the powder bed is homogeneous, and its structure can be kept unchanged during all the experiment (no dissolution should occur). If these conditions can be verified, the Wasburn equation can be used to calculate the contact angle.

7. COMBINATION OF THE PREVIOUS MECHANISM(S)

Quite often a solid dispersion does not entirely belongs to any of the aforementioned mechanisms discussed but it may be made up of combinations of different mechanism(s). Therefore, the observed increase in dissolution and absorption rates may be the contribution of various groups of mechanisms.

Indomethacin (Methew, James and Edward, 1984; Borka, 1974)

The molecular structure of IDM is shown below
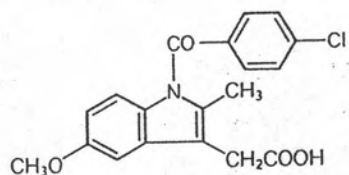
The empirical structure is $C_{19}H_{16}ClNO_4$ with molecular weight 357.81. IDM is a white to yellow-tan, odourless or almost odourless, crystalline powder with a faintly astringent taste. Its melting range is according to the Table 3.

Table 3   Melting points of IDM polymorphs.

Form	metting point (^{o}C)
form I (type γ)	160-161.5
	160
form II (type α)	154-155.5
	154
form III	148
form IV	134
type β	158-160.5

Its solubility data are represented in Table 4.

Table 4   The solubility of IDM from various solvents.

Solvent	temp(^{o}C)	Solubility
Water	25	0.4 mg/100 ml[a]
		0.42 mg/100 ml[b]
		0.88 mg/100 ml[c]
Water	RT	practically insoluble
phosphate buffer pH 5.6	25	3 mg/100 ml[a]
		5 ml/100 ml[b]
phosphate buffer pH 6.2	25	11 mg/100 ml[a]
		16 mg/100 ml
phosphate buffer pH 7.0	25	54 mg/100 ml[a]
		80 mg/100 ml[b]
Ethyl alcohol (95%)	RT	1:50
Chloroform	RT	1:30
Ether	RT	1:45
Methanol	25	32 mg/gm
Benzene	25	5 mg/gm
n-butanol	25	19 mg/gm
sec-butanol	25	27 mg/gm

a - form I

b - form II

c - form III

Form I is the highest melting and the lowest solubility polymorph and is, therefore, the thermodynamically stable crystalline modification of indomethacin. However, from a practical view, Form I and Form II are equally biologically available and active.

IDM is an NSAID that has been used effectiely in the management of patients with moderate to severe rheumatoid arthritis, ankylosing spondylitis, osteoathritis, acute painful shoulder (bursitis and/or tendinitis) and acute gouty arthritis. Moreover, IDM has been found effectively in the treatment of neonates with patent ductus arteriosus and in patients with cystoid macular edema following cataract surgery.

The dose is following to the Table 5.

Table 5 The dose of IDM administration.

| |
|---|
| Adult - oral 50 mg. Maximum 200 mg daily in individual dose.
     - Injection IM 25-150 mg/day. Maximum 3 dose/day which is injected at different sites. Maximum single dose 50 mg. |
| Childern $\geq$ 2 year using 2 mg/kg/day in individual dose bid-tid Increased weekly as requested. Maximum daily dose > 150-200 mg/day or 4 mg/kg/day whichever is less. |

Pharmacokinetic parameter

Indomethacin

Time to Peak levels (hrs)	1-2
Half life (hrs)	4.5-6
Analgesic Action	
- onset (hrs)	0.5
- Duration (hrs)	4-6
Antirheumatic Action	
- onset (days)	up to 7
- Peak (weeks)	1-2
maximum recommended daily dose (mg)	200

Mannitol (American Pharmaceutical Association, 1986)

The molecular structure of mannitol is shown below.

$$
\begin{array}{c}
CH_2OH \\
| \\
HO-C-H \\
| \\
HO-C-H \\
| \\
H-C-OH \\
| \\
H-C-OH \\
| \\
CH_2OH
\end{array}
$$
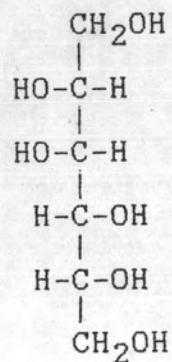
And its empirical structure is $C_6H_{14}O_6$ with molecular weight 182.17. Mannitol is a white, odorless, crystalline powder or free-flowing granules. Its microscopically appearance is orthorhombic needles when crystallized from alcohol. Mannitol is one half as sweet as sucrose and about as sweet as glucose. Its melting range is $165^{o}C$ - $169^{o}C$. The solubility follows to Table 6.

Table 6   The solubility of mannitol from various solvent.

| Solvent	gm in 100 ml	
	at $25^{o}C$	at $60^{o}C$
Purified water	16.7	-
Aqueous buffers over pH range 2 to 9; teore 11 and stengagen phosphate citrate-bosate	16.7	40
Ethanol	1.3	
Propan-2-ol	1.0	
Glycerol	5.6	

Mannitol is used as a filler (10 - 90%) in conventional tablets. It is of special value when moisture-sensitive drugs are being tabletted because of its non-hygroscopicity; the granular form is earily dried. Moreover, it has been used as water soluble carrier in several solid dispersion system. In 1974, Mc Gnity

et al., prepared sulfacetamide-mannitol solid dispersions by both melting and solvent methods and found that coprecipitates produced faster dissolution rate than the melting process. Mannitol dispersions were also shown to increase the dissolution rate of glibenclamide (Geneidi, Adel and Shehata, 1980), sulfamethoxazole (Ghanenm, Meshali, and Ibrahum, 1980), prednisolone and hydrocortisone (Allen, Levinson and Martono, 1978).

Polyethylene Glycol 4000
(American Pharmaceutical Association, 1986)

The molecular structure of Polyethylene glycol 4000 is demonstrated below.

$$HOCH_2 \ (CH_2OCH_2)_{69-84} \ CH_2OH$$
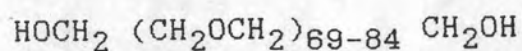
Its molecular weight is 3000 - 4000. Polyethylene glycol is an almost tasteless, creamy white, hard, wax-like solid or flakes or white free-flowing powder with a faint characteristic odour. Its melting range is $50^{\circ}C$ - $58^{\circ}C$. It is solule with 1:3 water, 1:2 alcohol and chloroform and practically insoluble in ether. Polyethylene glycol is used as stabilizers of emulsion, water miscible bases for ointments or bases for suppositories. Moreover, the aqueous solubility or dissolution characteristics of poorly soluble compounds can be enhanced by making solid dispersion such as

diazepam (Anastasidou, Henry, Legendse, Soulean and Duchene, 1983), griseofulvin (Kaur, Grant and Eaves, 1980).

Polyvinylpyrrolidone K 30

(American Pharmaceutical Association, 1986)

The molecular structure is shown below.

$$\left[\begin{array}{c} \overset{\displaystyle N}{\underset{\displaystyle -CH-CH_2-}{\bigcirc\!\!=\!\!O}} \end{array} \right]_n$$
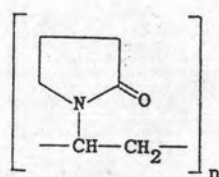
Its molecular weight is 40,000. PVP K 30 is a white to creamy white odorless or almost odorless, hygroscopic powder. Its melting range is over $275^{\circ}C$ with decomposition. . PVP K 30 can be readily soluble in water up to 60% and freely soluble in many organic solvents, including monohydric (ethanol, methanol) and polyhydric alcohol, acids, esters, ketones, methylene chloride, chloroform. In addition, its is essentially insoluble in ether, hydrocarbon, carbon tetrachloride, ethyl acetate and mineral oil.

PVP K 30 can be used as dispersing agent, suspending agent or viscosity builder, tablet binder, coating agent. Moreover, it can be utilized in preparing solid dispersions as a carrier such as

furosemide (Akbuga, Gursoy and Kendi, 1988), sulfathiazole (Badawi and El-sayed, 1980).

Sodium Lauryl Sulfate

(American Pharmaceutical Association, 1986)

The molecular structure is exhibited below.

$$[CH_3-(CH_2)_{10}-CH_2-O-\underset{\underset{O}{\overset{\overset{O}{\|}}{\|}}}{S}-O]^- Na^+$$
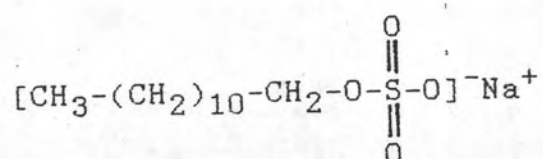
The empirical structure is $C_{12}H_{25}NaO_4S$ with molecular weight 288.38. SLS is a white or cream-colored to pale yellow crystal, flake or powder. It has a smooth feel, a soapy, bitter taste and a faint odor of fatty substances. Its melting range is $204^{O}C$ - $207^{O}C$ (pure substance). SLS is freely solule in water, giving an opalesent solution, and partly soluble in alcohol. SLS is used as wetting agent, solubilizer in concentrations greater than critical micellar concentration (CMC).