CHAPTER I

INTRODUCTION

A. Literature Reviews

It has been observed that the rate of absorption of many poorly water-soluble drugs from the gastro-intestinal tract is limited by the rate of dissolution of the drug substance (1). Therefore, efforts have been made to increase the dissolution rate of the poorly water-soluble drugs. Many methods have been used to enhance the dissolution rate of poorly water-soluble drugs. The methods include:-

1. Prodrug Approach (2-6)
2. Reduction in particle size (7-12)
3. Application of polymorphism properties of the drugs (13-21)
4. Application of solid dispersion systems. (11, 22-35)
5. Application of solid surface dispersion systems (36-51)
6. Reduction in hydrophobicity (52-57)
7. Other approach methods (54, 57-61)

I. Prodrug Approach

The use of derivatives to increase the aqueous solubility of poorly water-soluble drugs has been recognized as an effective design strategy (2). Method of drug derivation can be divided into two categories: irreversible or reversible (3).

Irreversible derivatives or analogs are usually synthesized for the purpose of finding a similar, new, biologically active entity processing increased potency, a broader spectrum of activity, or some other desirable property not possesed by the parent compound.

Reversible derivatives utilize a chemical moiety of proven biological activity (The parent molecule) and seek to deliver them to the site of action while overcoming some inherent drawback to the use of the parent compound. This method will focus on chemical modification of existing drug substances whose biological effects are known. It will be limited solely to biologically reversible derivatives, ie, those compounds that, upon introduction to the appropriate biological system, revert back to the parent molecule by virtue of enzymatic and / or chemical lability.

A more soluble derivative of poorly water-soluble drugs can be modified by synthesizing the reversible derivative, because the reversible derivative can be modified at any functionality without undue concern for its involvement at the receptor level. In case of the irreversible derivative, functional group can be modified, but it may be destroyed all bioactivity.

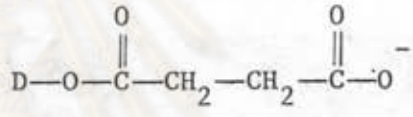
Two strategies can be employed to synthesize a reversible derivative, which increasing its solubility.

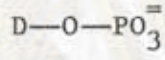
(1) Introduction of an ionic or ionizable group.

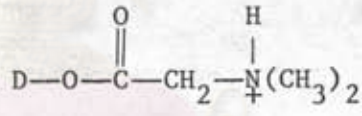
The synthesis of an ionic or ionizable derivative of a poorly water-soluble drug is the common of the "prodrug" solubilization strategies.

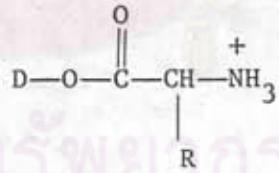
TABLE 1 Examples of Solubilizing Progroups for Drug D-X

X = OH

Hemisuccinates 

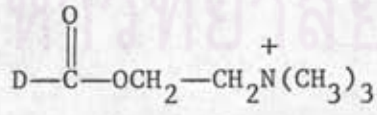
Phosphates 

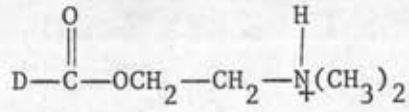
Dimethylaminoacetates 

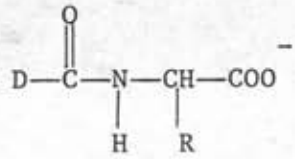
Amino acid esters 

(R = amino acid side chain)

X = COOH

Choline esters 

-dimethylamonoethyl esters 

Amino acid esters 

(R = amino acid side chain)

TABLE 1 lists some progroups used for synthesis the ionic or ionizable derivatives of poorly water-soluble drug (2)

The basis for this approach is well-known as solubility-PH relationships for weak acids and bases.

Letting So represent the solubility of the unionized species then for acids

$$HA \overset{Ka}{\rightleftharpoons} A^- + H^+$$

$$Ka = \frac{[A^-]\,[H^+]}{[HA]} \qquad \text{.....(1)}$$

$$S_o = S_{HA}$$

$$S_T = S_{HA} + [A^-] = S_o \left[1 + \frac{Ka}{[H^+]} \right] \qquad \text{.....(2)}$$

and for bases

$$BH^+ \overset{Ka'}{\rightleftharpoons} B + H^+$$

$$Ka' = \frac{[H^+]\,[B]}{[BH^+]} \qquad \text{.....(3)}$$

in term of Kb

$$B + H_2O \overset{Kb}{\rightleftharpoons} BH^+ + OH^-$$

$$Kb = \frac{[BH^+]\,[OH^-]}{[B]} \qquad \text{.....(4)}$$

$$Kw = [H^+]\,[OH^-] \qquad \text{.....(5)}$$

Hence $Kb = \frac{Kw}{Ka'}$ .....(6)

$So = S_B$

$S_T = S_B + [BH^+]$

$= So \left(1 + \frac{[H^+]}{Ka'}\right)$ .....(7)

However, both equations only hold up to the point where the total solubility approaches that of the ionic species. The complete curves is obtained by a similar analysis to that above for salt form for acids.

$S_O = S_{A^-}$

$S_T = S_{A^-} + [HA]$

$S_T = S_O \left(1 + \frac{[H^+]}{Ka}\right)$ .....(8)

and bases

$S_O = S_{BH^+}$

$S_T = S_{BH^+} + [B]$

$S_T = S_O \left[1 + \frac{Ka'}{[H^+]}\right]$ .....(9)

Figure 1 shows the general shape of the curves of solubility-pH profile for an acid.

Figure 2 shows the solubility-pH profile for the case in which both acid and salt have equal solubilities.

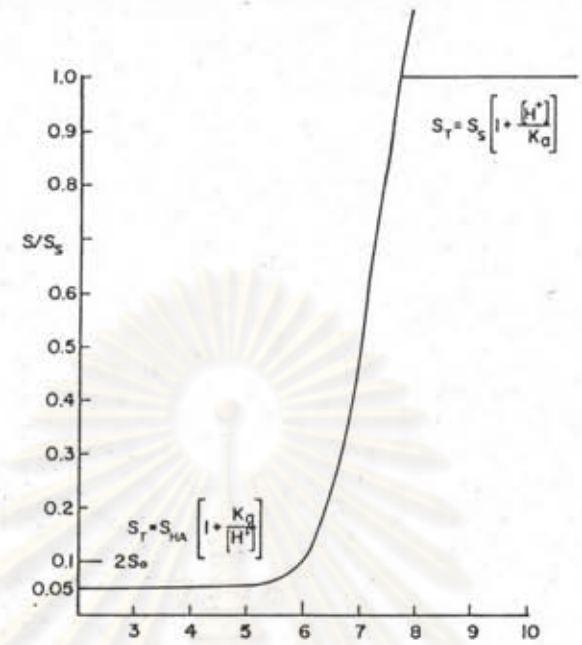


Figure 1 : Solubility-pH profile for an acid

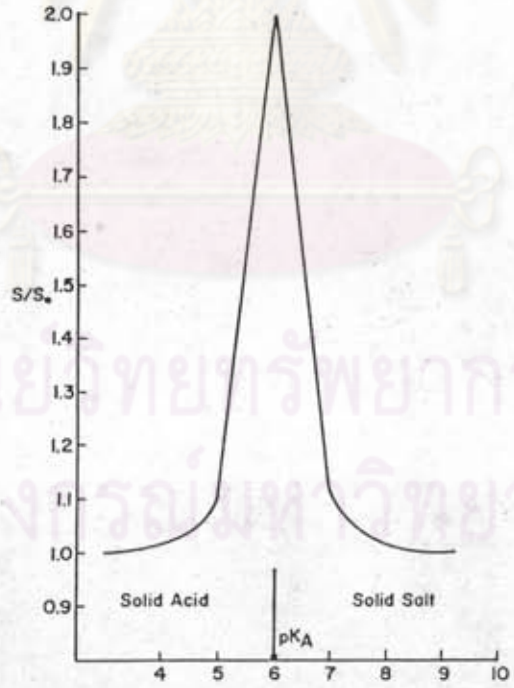


Figure 2 : Solubility-pH profile for the case in which both acid and salt have equal solubilities

The maximum solubility occurs at pH = pKa and is twice of So. At this point equal amount of ionized and un-ionized species are in solution. A change in pH in either direction results in a reduction of solubility and precipitation of either the acid or salt as shown in figure 2.

(2) Introduction of a group which decreases the melting point of the parent drug.

The basis for this strategy is that in order to dissolve, molecules must be removed from crystal lattice. Any modification which reduces this crystal lattice energy, hence melting point, would tend to increase solubility.

It has been found that the relationship between ideal solubility, melting point is followed by the equation (2)

$$\log S_0 = -0.01\ T_M + C \qquad \text{.....(10)}$$

where S_0, T_M, C are ideal solubility (mg/ml), melting point (°C) and experimental constant respectively. This equation shows that a decrease in melting point by 100° C would increase the solubility by a factor of 10. The step from estimating the ideal solubility to estimating aqueous solubility is nontrivial. If the assumption is made that solubility in octanol is given by equation (10), and interpreting the partition coefficient between octanol and water as a solubility ratio So/Sw, the aqueous solubility Sw can be calculated.

$$\log PC = \log \frac{So}{Sw}$$

$$\log Sw = \log S_o - \log PC \quad \text{.....(11)}$$

and using Equation (10)

$$\log Sw = -\log PC - 0.01T_M + C' \quad \text{.....(12)}$$

where PC is the octanol/water partition coefficient, T_M the melting point in degree celsius and C' the experimental constant.

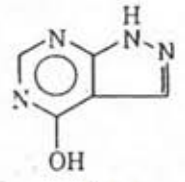
The beauty of this equation is probably in its simplicity and utility, with both the partition coefficient and melting point dependence of solubility simply displayed. In making derivatives of a drug, then the changes in aqueous solubility will result directly from changes in PC and T_M It is possible to choose a derivative that increase PC (hence would reduce Sw) while reducing melting point, with the net effect of increasing Sw. According to melting point changes as a solubilization strategy, two points may be considered.

(1) Should thermal decomposition of a compound begin to occur prior to melting, then the observed melting point would not be a true reflection of the crystalline forces and consequently its use in Equation (10) would lead to errors.

(2) High melting point drug would be the best candidate for this strategy, since the melting point coefficient in Equation (10) is only -0.01.

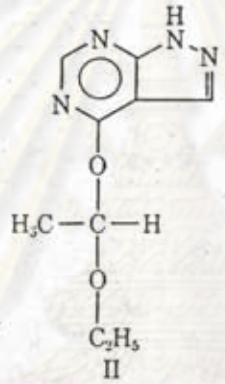
Examples of the first strategy, introduction of an ionic or ionizable group to the prodrug. The numerous steroid phosphate esters are typical examples. The more soluble phosphate ester salt is reconstituted prior to administration and is subsequently enzymatically hydrolyzed to the active agent in body fluids (2). Phosphate esters have the very desirable qualities of both good chemical stability and good biological liability. Phosphate group is also the most commonly used progroup to increase the solubility of prodrug. Succinate esters represent the second common progroup used in solubilization. While chemical stability appears to be satisfactory, their biological liability does not appear to be as good as that of phosphate monoesters. Succinates esters are generally not very good substrates for esterases, and consequently prodrug may be eliminated from the body at a rate near that for the hydrolysis to the active agent (2). An example of succinate esters is hydrocortisone succinate. Amino acid esters have been suggested as being potentially very useful progroups (2, 4). The combine low toxicity with a wide choice in physical properties. Biological reconversion may be very efficient through protease activity (2), and they appear to provide a means of overcoming the solubility partition coefficient compromise.

Examples of the second strategy melting point changes on solubility are allopurinol and Ara - A (5, 6) For allopurinol, the high melting point of allopurinol (365 °C) suggestes that transient blocking of some polar groups in the molecule might decrease inter-molecular hydrogen bonding and enhance the solubility.



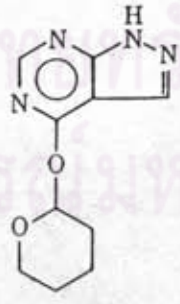
I

(I) allopurinol ; solubility = 0.78 mg/ml



II

(II) 1-ethoxyethyl-4-allopurinyl ether ; solubility 1.91 mg/ml



III

(III) 2-tetrahydropyran-4-allopurinyl ether ; solubility (3.64 mg/ml)

the strategy of blocking polar groups in allopurinol molecule can be made by synthesizing the 1-ethoxyethyl-4-allopurinylether and 2 - tetrahydropyran - 4 - allopurinylether. These compounds have lower melting points. The melting points of the ethylvinylether and the dihydropyran derivatives are 185°C and 203°C respectively. The approximately 150°C decrease in melting point of both derivatives would, on the basis of equation (12), lead to a 1.5 log unit (30-fold) increase solubility. The observed three to five fold increase in solubility is at least in part due to a compensating increase in partition coefficient.

The increase in solubility observed for both derivatives compared with the parent compound is probable due to the decrease in the solute - solute intermolecular forces in the crystal form caused by blocking the hydroxyl group in allopurinol. Figure 3 shows rate of dissolution of tablets containing allopurinol, 1-ethoxyethyl-4-allopurinyl ether, and 2-tetrahydropyran-4-allopurinylether at 25°C.

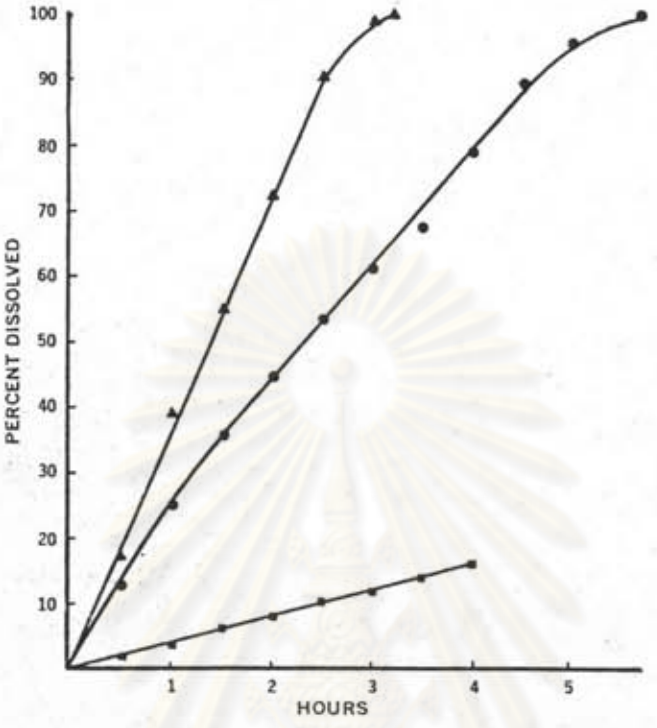


Figure 3: Rate of dissolution of tablets containing allopurinol (■) 1-ethoxyethyl-4-allopurinylether (●) and 2-tetrahydropyran-4-allopurinyl ether (▲) at 25°C

For. Ara - A, the 85 degree change in melting point of its derivative would give a seven fold increase solubilities.

The observed increase of 60 is in part due to this changes in melting point (5).

II. Reduction in Particle Sizes.

Whether the solution process takes place in laboratory or in-vivo there is one law which defines the rate of solution of solids when the process is diffusion controlled and involves no chemical reaction. This is the Noyes-Whitney equation (1).

$$\frac{dQ}{dt} = K (Cs - C) \qquad \text{.....(13)}$$

where $K = DA/t$

The terms of the equation are: $\frac{dQ}{dt}$, The rate of increase of the amount of material in solution dissolving from a solid; k, The rate constant of dissolution ($time^{-1}$); Cs, the saturation solubility of the solvate in bulk. A is the area of the solvate particles exposed to the solvent; t, the thickness of the diffusion layer, and D the diffusion coefficient of the dissolved solute.

It has generally been believed that only substances in the molecularly dispersed form (that is, in solution) are transported across the intestinal wall and absorbed into the systemic circulation. However very small particles in the nanometer size range can also be transported through enterocytes by way of pinocytosis. In fact, the opportunity for molecules to penetrate the cell membrane is obviously higher than that for particles, because of the much greater absortive area available to molecules.

The Noyes - Whitney equation demonstrates that the surface area, A of the particles is one of the main factors determining rate of solution. When the rate of solution is less than the rate of absorption the solution process becomes rate limiting. 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 is only when comminution reduces particle size below 0.1 um that there is an effect on the intrinsic solubility of the substance, and thus on its intrinsic dissolution rate (1). Very small particles have a very high surface / bulk ratio. If the surface layer has a higher energy than the bulk, as is the case with these small particles, they will interact more readily with solvent to produce higher degrees of solubility. Reduction of particle size to expose larger surface areas to the dissolution medium is perhaps the most obvious choice for improving dissolution (1). The literature contains several examples where bioavailability was increased following particle size reduction (7). Ridolfo et al. (8) had shown that the bioavailability of benaxaprofen, a anti - inflammatory agent, was increased by reducing particle size. The therapeutic dose of griseofulvin was reduced to 50% by micronization and it also produced a more constant and reliable blood level (9). The commercial dose of spironolactone was also decreased to half by just a slight reduction of particle size (9). Carless et al. (10) have been investigated the influence of particle size on the bioavailability of digoxin.

Althrough particle size seems to be easiest and most controllable factor, in practice, reduction of the particle size is often associated with the following problems :-

a) Increased rate of degradation of relatively unstable drugs.

Particle size reduction may increase the rate of moisture uptake by hygroscopic and moisture sensitive drugs. Therefore, extra care and humidity control might be required for the processing of fine powders of relatively unstable drugs. A drug which is sensitive to oxidation process particle size reduction of the drug may also increase the rate of degradation. When a drug is unstable in the gastric fluid, then rapid dissolution may enhance degradation and the net effect, may be reduced availability (7). It had been said that the particle size reduction of acid unstables drugs such as penicillin G and erythromycin may, in fact, reduced their bioavailability (7). This, of course, assumed that the rate of degradation is faster than the rate of absorption. Since both absorption and degradation will occur only after dissolution. The extent and rate of availability will depend on the overall balance between the rates of absorption and degradation and the respective kinetics of the two processes.

b) Dustiness and difficulties of handling fine powders, poor flow property.

Reduction of particle size increases dustiness and problems of handling bulk drugs. The environmetal risk has to be reduced by taking extra precautions (wearing of masks etc.), which inevitably places constraints on both operators and production.

The problems associated with the poor flow of fine powders was also well known (11).

c) The resultant fine particles may not produce the expected faster dissolution. This primarily results from the possible aggregation and agglomeration of the fine particle due to their increased surface energy and the subsequent stronger Van der waal's attraction between nonpolar molecules. This was demonstrated by many researchers, for examples :-

Lin et al. (12) showed that the in-vitro dissolution rate of micronized glutethimide was slower than those of their coarser particles.

It was shown that dissolution rate of phenacetin powder increased with increasing particle size. In fact, the smaller phenacetin particles had more air adsorbed on their surfaces and actually floated on the dissolution medium (11).

d) The disadvantage of fine powders of poorly water-soluble drug is their poor wettability in water.

The wetting of powders is the first step for them to dissolve and sometimes disperse in fluid (9).

e) Drugs with plastic properties are difficult to subdivide and they have more tendency to stick together, even if fine powders can be produced by a suitable method (9). The comminution process can significantly modify the particle size distribution of a starting drug. If the drug compacts by plastic deformations we might expect a reduction in surface area. However, if the drug consolidates by the process of fragmentation, the particle size may by reduced (11).

f) Increased side - effect in some drugs.

For example, Rapid solution of nitrofurantoin from tablets of fine particulate material led to a high incidence of nausea in patients, as local high concentration of the drug produce a centrally mediated nausea (1). Development of macrocrystalline nitrofurantoin (Macrodantin^{R}) has led to the introduction of a form of therapy in which the incidence of nausea is reduced.

In conclusion, it is generally accepted that the reduction in particle size of poorly water-soluble drugs increase the rate of absorption. However formulators must be aware that particle size reduction, on its own, may not improve dissolution rates of some hydrophobic systems, and some drugs compacts by plastic deformation. Therefore, a suitable method, treatment with hydrophobic materials, another particle size reduction processing, and formulation adjustments may be required.

III. Application of polymorphism properties of Drugs

Many drugs are crystalline subtances. The crystalline properties of the solid state of drugs are considerable interest as they can affect both the production of the dosage forms and the biological behavior of the finished forms (1).

The nature of the crystalline form of a drug substance may affect its stability in the solid state, its flow properties and its biological availability, the last mainly through the effect of crystal properties on dissolution rates (13). Many drug substances can exist in more than one crystalline form, the different forms being termed "polymorphs" and the condition "polymorphism". A polymorph of a drug substance can be defined as a solid crystalline phase of the drug resulting from the possibility of at least two different arrangements of the molecule of that compound in the solid state (1, 13). The more soluble forms of crystalline drugs, having less internal cohesion, high thermodynamic activity, are less stable and transformation into stable modifications can occur by a process which may be rapid or slow (1, 13). Use of polymorphism properties of poorly water-soluble drugs to enhance the dissolution rate may be useful in the present day. However the more soluble, but metastable polymorphic forms of poorly water-soluble drugs may present special pharmaceutical problems.

Examples of the application of polymorphism property of poorly water-soluble drugs to enhance dissolution rates.

Mullins and Macek (14) working on pharmaceutical properties of novobiocin identified two polymorphic forms of novobiocin, one of which was crystalline and the other amorphous. They found that the crystalline novobiocin acid was poorly absorbed and did not provide therapeutically adequate systemic levels following oral administration, but the amorphous novobiocin acid was readily absorbed and therapeutically active. This difference in availability was due to difference in solubility in aqueous systems.

Aguiar et al. (15) investigated the absorption of polymorph A and B of chloramphenicol palmitate in chloramphenicol palmitate suspension. In the studies the highest mean blood levels were obtained with suspensions containing only form B. The blood levels decreased proportionately as the concentration of form A increased. The relative large free evergy difference (-774 cal/mole) found between polymorph A and B may explain the higher and faster absorption observed with polymorph B in comparison to polymorph A.

Polymorphic forms of Ampicillin had been shown the difference in absorption. It was found that in-vivo experiment, the anhydrous form produced higher and earlier peaks in blood serum than trihydrate form (1).

Hamlin et al. (16) using two polymorphs of methyl-prednisolone (Forms I and II), prepared constant surface pellets and determined their dissolution rates, both in-vitro and in-vivo. They found that both in-vitro and in-vivo experiment, the dissolution rate of form II was greater than form I, the thermodynamically more stable form at room temperature.

Tawashi (17) reported on the dissolution of two polymorphic forms of aspirin where form II dissolves 50% faster than form I. Levy (18) also reported on the comparative dissolution and absorption rates of different commercial aspirin tablets and indicated that since the inital absorption of aspirin occured from the stomach, and since the rate of absorption was proportional to the amount of aspirin dissolved in the gastric fluids, the in-vivo dissolution rate of aspirin in tablet form in the stomach would be reflected. It was possible that polymorphism may also be involved with availability from commercial aspirin tablets.

Tuladhar et al. (19) characterized five difference polymorphic forms of phenylbutazone as polymorphs A, B, C, D and E by differential scanning calorimetry, X-ray diffraction and IR spectroscopy. They reported that the in-vitro dissolution of crystals forms was in order of form C> form E> form B > form D> form A.

Trottier et al. (20) prepared the three polymorphs of analgesic 6-benzoylbenzoxazolidinone (CERM 10194) by solid dispersion and solvent deposition. The different polymorphic forms was characterized by X-ray diffraction, DTA and IR spectroscopy. The polymorphic form was designated, raw material as form I, the solid dispersion of CERM 10194 in polyvinylpyrrolidone (PVP) 9:1 as from II and the solvent deposition of CERM 10194 on colloidal silica (9:1) as form III. They reported that form II and form III gave a high dissolution rate in-vitro. Form II and Form III were also stable for six months without special handling.

In conclusion, the application of polymorphism properties of poorly water-soluble drugs can be used to choose for a pharmaceutical formulation, that polymorph having the rate of dissolution desired. However, before choosing suitable polymorphic form, free-energy difference must be considerred. It is suggested that large differences in the free energy content of the polymorphs, as was demonstrated in the case of chloramphenical palmitate may affect significantly the absorption and resulting blood levels (21). On the other hand, a small difference as was seen with mefenamic acid did not appear to affect the absorbability of the drug (21).

IV. Solid dispersion of the drug using inert water-soluble carriers.

The novel use of solid dispersion technique to increase the dissolution rate and absorption of poorly water-soluble drugs was firstly proposed by Sekiguchi and co-workers in 1961 (22). The term "solid dispersion" refered to the dispersed system of one or more active ingredients to an inert water-soluble carrier or matrix at solid state prepared by melting, solvent, or melting-solvent method (23). Methods of preparation of solid dispersion :-

a) Melting method (Fusion method.)

This method is prepared by heating the physical mixture of drug and water-soluble carrier to a temperture at which melting occurs and a solution forms. The melted mixture is then usually cooled rapidly to entrap the drug particles in the matrix in as fine state as possible. The cooling rate of a eutectic mixture can influence the physical state of the solid obtained and the particle size of the crystals formed (23).

The main advantage of this direct melting method is its simplicity and economy. In addition, a supersaturation of a solute or drug in a system can often be obtained by quenching the melt rapidly from a high temperature and a much finer dispersion of crystallites is obtained for systems of simple eutectic mixtures if such quenching techniques is used (24). The disadvantage of this procedure is the possibility of decomposition and/or evaporation of a component at the elevated temperatures required. This method was first proposed by Sekiguchi and Obi and was subsequently employed with some modification by many investigators (25-27).

b) Solvent Method (Coprecipitation method)

This method is prepared by dissolving the drug and a water-soluble carrier in a common solvent. The solvent is then taken off by evaporation with / without the aid of vaccum pump. Sometimes heat is used to assist in the evaporation of the solvent (23).

The main advantage of the solvent method is that thermal decomposition of drugs or carriers can be prevented because of the low temperature required for evaporation of organic solvents. However some disadvantages associated with this method are the higher cost of preparation, the diffculty in completely removing liquid solvent, the possible adverse effect of the supposedly negligible amount of the solvent on the chemical stability of the drug, the selection of a common volatile solvent and the difficulty of reproducing crystal forms. This method was used to prepared several solid dispersions (28, 29, 30, 31).

c) Melting - Solvent method.

The melting-solvent method is prepared by first dissolving a drug in a suitable solvent and then incorporating the solution directly into the melt of water-soluble carrier. The solvent is then taken off by evaporation with/without the aid of heat. This method possesses the advantages of both the melting and solvents methods. However, it is possible that the selected solvent or dissolved drug may not be miscible with the melt of water-soluble carrier, and the polymorphic form of the drug precipitated in the solid dispersion may be affected by the liquid solvent used. The feasibility of the melting-solvent method was demonstrated on spironolactone-PEG 6000 and griseofulvin-PEG 6000 systems (23). Carrier has an ultimate influence on the dissolution characteristics of solid dispersion systems (23). Goldberg et al.(23, 24) proposed that in order to produce the enhancement of dissolution, carriers for solid dispersions prepared by melting method should meet the following criteria. First are soluble in water, physiologically inert, melting not more than 200°C , thermal stable up to its melting point, and relatively low vapor pressure. In addition to carriers for solid dispersions prepared by solvent method should meet the criteria, that be soluble in variety of organic solvents. The widely utilized carrier are :-

polyethylene glycol; polyvinylpyrrolidone; urea; sugars. (e.g. fructose, galactose, sucrose); polyols (e.g. mannitol, sorbitol); Poly acids (e.g. citric acid); cholesterol, cholesterol esters, bile acid, bile salts, xylitol, urethan, etc. (23-32).

The mechanisms of solid dispersion to enhance dissolution rate of durgs are

1.) Solid dispersion gives the very fine dispersion of the drug in the water-soluble carrier (23).

2.) A possible solubilization effect by water-soluble carrier may operate in the microenvironment (diffusion layer) immediately surrounding the drug particle in the early stage of dissolution since the carrier completely dissolves in a short time (23).

3.) The absence of aggregation and agglomeration between fine crystallites of the pure hydrophobic drug (23).

4.) Increase wettability and dispersibility of a drug (23).

5.) The formation of soluble compound or complex between drug and carrier (23).

It is believed that the solid dispersion technique is a field of pharmaceutical techniques and principles will play an important role in increasing dissolution, absorption, and therapeutic efficacy of poorly water-soluble drugs in future dosage forms. However, the solid dispersion systems have been of limited application to manufacturing because of the processing problem of solid dispersions, which tend to be like sticky masses (32), poor flowability and a number of problems have not yet been solved are listed below :-

a) The use of solid dispersions is limited to low dose drugs. A large amount of carrier is often required to improve the dissolution of the drug and this limits the use of solid dispersions to low and in a few cases of medium dose drug (11).

b) The process of preparing solid dispersion might cause degradation of drugs or excipients used. Thermolabile drugs may break down during the preparation of solid dispersion. Some of the problems are discussed in the literature (33, 34, 35).

c) The physicochemical stability of solid dispersions is generally poor. It was found that although tablets freshly made from the solid dispersion had superior disintegration and dissolution properties to tablets made by traditional methods, they became harder on aging and tended to have decreased dissolution rates. Solid dispersion tablets were moisture sensitive and less stable than conventional tablets, when stored at 35 and 45°C (11).

d) For tabletting, other excipients are required to aid the flow, compaction and disintegration of solid solution. These materials increase the tablet size, hence the tablets may be difficult to be swallowed (11).

e) The compaction process often destroys the improved dissolution achieved by solid dispersion.

Some of the hydrophilic carriers also act as tablet binders, and the improvement in dissolution achieved by solid dispersion may therefore be destroyed if tablet disintegration is delayed (11).

V. Application of solid surface dispersion systems

The dissolution characteristics of drug can be altered by dispersing it on the surface of an inert carrier (36-46). The solid surface dispersion systems are defined as the systems in which the drug is distributed on the surface of an inert carrier to increase dissolution rate of the drug (36). The new approch "solid surface dispersion" to increase the dissolution rate of poorly water-soluble drugs is based on the concept of increasing the surface area of the drugs available for contact with dissolution media (36, 45, 46). The solid surface dispersion systems is achieved by two methods, frictional deposition (or mechanical deposition) and solvent deposition (36-46). Frictional deposition method is accomplished by grinding the drugs with inert carrier. The second method, solvent deposition is prepared by dissolving the drugs in a suitable organic solvent and then the solution of drug is dispersed on the surface area of an inert carrier with an extensive surface area. The solvent is taken off by evaporation with/without the aid of heat.

In manufacturing powdered preparation, grinding generally use for reducing the particle size of a solid, since the dissolution rate of poorly water-soluble drug is strongly affected by particle size (1). It had been reported that a strong grinding force gave to crystalline solid an increase in the activation energy on the surface and in the distortion of crystal lattice together with reducing the size (37, 38, 39).

These phenomena occured in all crystalline medicinals independent of the molecular properties, such as structure, size and polarity (37).

In many studies (37-42), amorphous state of organic crystalline medicinal was obtained by grinding of the medicinal with microcrystalline cellulose or other materials such as β-cyclodextrin, lactose and sucrose.

Hersey (40) reviewed the effect of grinding on particle size reduction and proposed that grinding could also induce "mechanical activation" which in turn could lead to an increase in solubility and dissolution rate.

Yamamoto et al. (41) found that a ground mixture of griseofulvin and microcrystalline cellulose (1:9) prepared by grinding them in a vibration ball mill, were shown to be significantly greater in the dissolution rate and bioavailability than those from micronized griseofulvin powder. They proposed that the possible transformations may take place during the vibration ball mill process were :-

a) initial size reduction of griseofulvin crystals

b) formation of an amorphous structure either by partial melting of the crystalline powder and its interaction with cellulose, which has also become amorphous during the milling process, or by production of lattice defect due to shear stress and impact stress.

A marked influence of dispersion method such as simple blending, solvent deposition, ball milling and muller milling on the dissolution rate and bioavailability of digoxin had been reported

(43, 44). A ground mixture prepared by ball milling and muller milling was shown to be significantly greater in dissolution rate and bioavailability than simple blending and solvent deposition. The greater difference in dissolution rate and bioavailability between ball milling and simple blending may be due to an increase in the activation energy, on the surface and/or the distortion of crystal lattice. (43, 44).

Yamamoto et al.(42) demonstrated that the ground mixture of phenytoin and microcrystalline cellulose prepared be grinding in a vibration ball mill gave a greater dissolution rate and bioavailability than the fine powder of phenytoin. The exact physical nature of the ground mixture was not determined. However it was proposed that the drug molecules in the ground mixture were probably dispersed on the surface of the cellulose and were presented in an amorphous state. Their energy level was expected to be higher than those of the original crystals. In addition, the hydrophilic nature of the cellulose, reduced hydrophobicity of the drug in the ground mixture and improve its wettability.

Solvent deposition is the second method in which gives the solid surface dispersion systems. Monkhouse and Lach (45, 46) used inert water-insoluble adsorbents, such as fumed silicon dioxide and silicic acid, as supports for the solvent deposition of a number of drugs. The solution of the drug in suitable organic solvent was dispersed on the surface of the support material and the solvent was taken off by evaporation. The resulting material contained the drug in a "molecularly micronized" state on the

surface of the carrier. The term "minuscular form" was used to describe the state that the drug has undergone molecular micronization when its dispersed on the extensive surface area of the adsorbents. The dissolution rate of the drug in "minuscular form" was found significantly greater than the drug powder alone. The fast dissolution rates of these systems were also found to be dependent on the weight ratio of drug to adsorbent. When low fractions of drug were used, the dissolution rate was maximized (45). This implied that the surface area of the adsorbent was covered by a drug monolayer that controlled the dissolution rate.

In conclusion the solid surface dispersion system can be regarded as drug in a microparticulate form molecularly dispersed on the surface of inert carrier. The resulting decrease in particle size and the concomitant increase in surface area serve to increase the thermodynamic activity of the drug in the dispersed state which, in turn, greatly enhances the dissolution rates (36-46). The solid surface dispersion system is a pharmaceutical technique, in which can play an important role in increasing dissolution rate of poorly water-soluble drug. However the solid surface dispersion system may have the problems since drug-excipient interaction can readily occur in normal manufacturing process and since these interactions not only alter the physical and chemical properties of the drug but also appreciably affect the physiological availability of the drug from the dosage from, resulting decrease in therapeutic action of the drug (46-51).

VI. Reduction in hydrophobicity of the drugs.

A major problem of traditional particle size reduction of the poorly water soluble drugs is that it results in a very cohesive powder and the high surface energy results in the formation of aggregates and agglomerates. The drug particle aggregates tend to be hydrophobic and are, thus, difficult to wet. This problem is overcome by reduction in hydrophobicity of the drugs. The approach "reduction in hydrophobicity" of the drugs to enhance the dissolution rate of poorly water-soluble drug is based on the concepts of reducing the particle size of hydrophobic drug may give greater problems with wetting and liquid penetration in solid dosage form and since liquid penetration is the first step in the disintegration and dissolution of the solid dosage froms, the overall process may be penetration limited, thus reduction in hydrophobicity of the drugs may be an effective method (52). In an ideal situation, the drug would be released from the solid dosage forms as discrete, well-wetted particle, so that the maximum surface area afforded by the powder would be exposed to the dissolution medium. For hydrophobic drugs, such a situation may be difficult; but it may be possible to achieve if the surface properties of the drugs are changed from hydrophobic into a hydrophilic drugs. The changes of hydrophobicity of the drugs may be accomplished by several methods, such as by coating the hydrophobic drugs with a hydrophilic material, using surface active agent, and mixing with a hydrophilic material (52).

Lerk et al. (52) sucessfully used a technique for reducing the hydrophocity of drugs with a hydrophilic polymer to enhance dissolution rate of poorly water-soluble drugs. They also found that the dissolution rate was dependent on the amounts of hydrophilic polymers used and there are the optimum percentage of the hydrophilic polymers used to increase the dissolution rate of the drugs. The method appears similar to a conventional granulation technique and simply relies on improving the wettability and solubilization of a hydrophobic drug partically coated with hydrophilic polymer.

Many investigators had reported that the surface-active agents could also enhance the dissolution rate of many poorly water soluble drugs by reducing of hydrophobicity of the drugs (53-57). According to Nogami (63, 64, 65), the rate-determining step in tablet disintegration was the penetration of media through the pores in the tablet. An equation was derived (54). Which was found applicable to tablets.

$$L^2 = \frac{rs\cos\theta}{2n} t = kt \quad \ldots\ldots\ldots\ldots (14)$$

Where L is the length penetrated at time t, k the coefficient of penetration, r the average radius of the void space, the contact angle, s and n the surface tension and viscosity, respectively.

Equation (14) indicates that a surface-active agent has two effects on penetration of a liquid into the tablet. The addition of a surface-active agents lowers the surface-tension and decrease the

contact angle. Thus, the overall coefficient of penetration of a liquid into the tablet rises in the presence of surface-active agents and increased penetration generally enhance disintegration.

The surface-active agents, dioctyl sodium sulfosuccinate and poloxamer 188, have been shown to improve the dissolution rates and absorption characteristics of various sulfonamides (55, 56). In conclusion, the dissolution rate of poorly water-soluble drug may be enhance by administered with surface-active agent. Another method in reduction of hydrophobicity of the hydrophobic drugs is mixing with a hydrophilic filler, such as starch, microcrystalline cellulose, polyvinylpyrrolidone, etc. Starch, has been shown to enhance the dissolution of poorly water-soluble drugs, particularly when it was granulated with the drug. Marlowe and Shangraw (57) prepared sodium salicylate tablets by wet granulation techniques using either lactose or a mixture of lactose and corn starch as filler. They found that the presence of starch dramatically increased the dissolution rate.

VII. Other methods;

Although several methods are used to enhance the dissolution rate of poorly water-soluble drugs, the application of the following other methods are still effective methods of improving dissolution properties of solid dosage forms.

The formation of molecular complexes can increase the apparent solubility of many drugs, thus increase the dissolution rate of the drugs from solid dosage forms.

Higuchi and Ikeda (58) prepared a rapidly dissolving form of digoxin by complexing the drug with hydroquinone. They suggested that the formation of a complex may overcome the processing problems associated with digoxin solid dosage forms because the complex completely dissociated when dissolved. In the studies with the benzocaine-caffeine complex, Higuchi et al. (59) found that the fastest rate of dissolution for either compound occured when the molar ratio was 1:1 Zoglio et al. (60) later found that caffeine forms soluble complexes with the ergot alkaloids. However, the formation of molecular complexes not only increase the apparent solubility of many drugs but also decrease its apparent solubility. Bettis et al. (61) found that the complexation of theophylline to barbiturate resulted in significant decrease in dissolution rate of theopylline.

It is well known that the preparation of solid dosage form involves the use of excipients. These excipients can influence the disintegration time, dissolution rate, and therapeutic effectiveness of the medicament, thus the use of suitable excipient, may be effective to improve the bioavailability of the drugs. In tablet formulation, excipient are added as binding agents, lubricants, disintegrants, and other diluents are nescessary for the preparation of a good-quality drug product.

Marlowe and Shangraw (57) demonstrated the hydrophilic excipient, such as starch, enhanced the dissolution rate of sodium salicylate tablet. Type of disintegrants, lubricants, its concentration, and the method of incorporation during tablet preparation were greatly affected the dissolution rate of the drugs (54).

The effect of compression force on the dissolution of nondisintegrating tablet and disintegrating tablet are difference. In the case of nondisintegrating tablet the dissolution rate of drug is almost independent of compression force, but in the disintegrating tablet, the effect of compressional force on the dissolution rate is difficult to predict. However, for a conventional tablet the dissolution rate of disintegrating tablet is dependent on the pressure range, and the properties of the medical compound and excipients. If fragmentation of the granules occur during compression, the dissolution is faster as the compressional force is increased. If the bonding of the particles is the predomonate phenomenon in compression, the increase in compressional forces causes a decrease in dissolution (54). In generally the relationship between compressional force and dissolution rate of the drug in the individual tablet formulation is unknown, thus, the optimum range of compression force must be find out in the individual tablet formulation.

In conclusion, although various methods have been suggested to enhance the dissolution rate of poorly water-soluble drugs, the most suitable method of the drugs must be condidered.

B. Rationale.

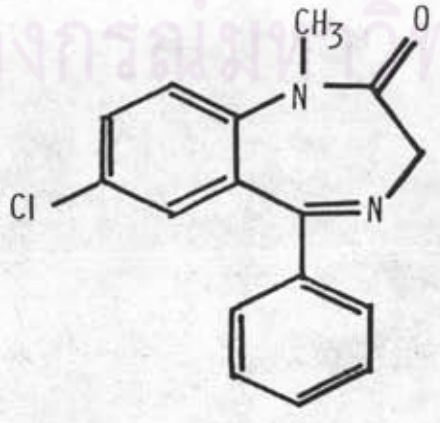
The poor dissolution characteristics of poorly water-soluble drugs has long been a problem to the pharmaceutical industry (1). When the poorly water-soluble drug is administered orally, the rate of absorption and/or the extent of bioavailability are controlled by its dissolution rate in the GI fluids (1). Therefore, efforts

have been made to increase the dissolution rate of poorly water-soluble drugs. When synthesis of a more soluble chemical derivative is not feasible, diminution of the particle size (7-12), or utilization of another polymorphic form (13-21), or solid dispersion of the drug using inert water soluble carriers (11, 22-35), or grinding with/or adsorption onto, an inert compound (36-51), reduction in hydrophobicity (52-57) and other method (54, 57-61) may increase its biological availability.

The diazepam was chosen to be the model drug, is due to the wide-spread used of diazepam as a tranguilizer and it is a psychotropic benzodiazipine exhibiting poorly water-soluble and absorption irregularities (75). The ten commercial diazepam tablets from different manufactures possessed different dissolution characteristics. The time required for the tablets to release 60% of diazepam varies among ten brands and range from 1-13 minutes (62).

Diazepam:

(7-chloro-1-methyl-5-phenyl-1, 3 dihydro-2H-1, 4 benzodiazepine-2-one)



Diazepam is yellowish-white crystalline powder. Its melting point is between 130 and 133°C. It is poorly soluble in water, but soluble in ethanol, methanol, chloroform, ether, acetone, and propylene glycol; the pKa is 3.3

Nakai et al. (37, 38, 39) found that crystalline medicinals changed in their physical properties during grinding the mixture of a 10% medicinals in microcrystalline cellulose. There was the critical content of medicinals in the ground mixture to show the halo pattern on the X-Ray diffraction patern and no heat of fusion on the thermogram. The ground mixture was regarded as an "entropy frozen solution" of the medicinal in cellulose molecules. These phenomena occured in all crystalline medicinals independent of the molecular properties, such as structure, size, and polarity. It was estimated that the medicinal molecules were dispersed within the cellulose as a molecule or microassembly of the molecules having no preferred orientation by hydrogen bond.

Yamamoto et al. (41) described that the possible transformations of ground mixture of griseofulvin and microcrystalline cellulose (1:9) prepared by grinding them in a vibration ball mill were :-

1) initial size reduction of griseofulvin crystals

2) formation of an amorphous structure either by partial melting of crystalline powder and its interaction with cellulose, or by production of lattice defect due to shear stress and impact stress.

They found that a ground mixture of griseofulvin and microcrystalline cellulose (1:9) were shown to be significantly greater in the dissolution rate and bioavailability than those from a micronized griseofulvin powder.

They also found that crystalline powder of griseofulvin was ground in a similar manner, but in the absence of microcrystalline cellulose, the crystalline structure has been retained as judged by X-Ray diffraction measurements. The dispersion method described above may be called "mechanical deposition or frictional deposition."

Monkhouse and Lach (45, 46) invented an approach "solvent deposition" method to enhance dissolution rate of poorly water-soluble drugs. Solvent deposition was prepared by dispersing the solution of the drug in suitable organic solvent on the surface of the support material and the solvent was taken off by evaporation. The resulting material contained the drug in a molecular micronized state called "minuscular form". The dissolution rate of the drug in "minuscular form" was found significantly greater than the drug powder alone.

Shelter (36) defined the mechanical deposition and solvent deposition as "the solid-surface dispersion system".

According to the experiments, it is possible to improve the dissolution rate of the diazepam by means of "solid surface dispersion systems" because diazepam is a crystalline powder, exhibiting poorly water soluble and absorption irregularities. (62)

The diluents used in the experiments, commonly employed as components of capsule formulation are classified in two groups.

1. Water-soluble diluents groups i.e.,
   mannitol, and sucrose
2. Water-insoluble diluents groups i.e.,
   dibasic calcium phosphate and microcrystalline cellulose

and the dispersion methods used in the study are

1. Simple Blending Method
2. Solvent deposition method
3. Mechanical or Frictional deposition method

C Purpose of the study:

1. To study the influence of dispersion methods on dissolution rate of diazepam capsules.

2. To study the dissolution behavior of diazepam capsules prepared by different dispersion methods.

3. To perform comparative studies of the effects of various diluents in the dispersion systems on dissolution behavior of diazepam capules.

4. To persude and facillitate the local manufacturers in order to develop their own product formulations by using the suitable dispersion systems with an objective of optimizing the dissolution of diazepam capsules.