CHAPTER I

INTRODUCTION

Rationale

Ergoloid mesylate belongs to the ergotoxine group of peptide ergot alkaloids (Peptide ergot alkaloids have been divided into three groups: ergotamine, ergoxine, and ergotoxine) (Bianchi, 1982). It is a mixture of the methanesulfonate salts of the three hydrogenated alkaloids, dihydroergocristine, dihydroergocornine and dihydroergocryptine, in an approximate weight ratio of 1:1:1. Dihydroergocryptine mesylate exists as mixture of alpha- and beta-isomers. The ratio of alpha- to beta-isomer is not less than 1.5:1.0 and not more than 2.5:1.0 (Budavari, 1989; Gennoro et al., 1975; Hartmann et al., 1978; Her Majesty's stationery office, 1988; Mcevoy, 1989; United States Pharmacopeia Convention, 1990).

Ergoloid mesylate is widely used and accepted clinically as a potent, sympatholytic agent. It has been shown to be useful in several clinical conditions where treatment of cerebro-vascular, peripheral vascular and hypertension in the elderly is imperative (Dominiak et al., 1988).

Ergoloid mesylate is slightly soluble in water (Mcevoy, 1989). The rapid dissolution rate of the drug from the dosage form is, therefore, considerably important in manufacture of this tablet product. It was claimed that the products which

produced high drug concentration at the site of absorption could exhibite higher bioavailability. Hunt et al. (1981) conducted dissolution test of ergoloid mesylate tablets commercially available in the United State. It was shown that there were brand to brand and lot to lot dissolution differrences. Some brands failed to achieve satisfactory dissolution.

An effort had been made to increase the dissolution rate of ergoloid mesylate. Intermolecular complexation between a mixture of ergoloid mesylate and several xanthines were investigated (Zogliu and Manlding, 1970). It was found that the dissolution and solubility of the complexes were substantially increased. However, xanthines possess the pharmacological response, it is not suitable to be used as dissolution promoting excipient for ergoloid mesylate in tablet dosage forms.

As it is known, solid dispersions is one of several methods which could be employed to improve dissolution property of poorly water soluble drug (Bloch and Speiser, 1987). But no report of the investigation on solid dispersion of ergoloid mesylate has been found as far as the literature search has been done. Therefore, it is of interest to explore solid dispersion systems of this drug substance and to apply then in producing the tablet which may enhance dissolution property of the drug in comparing with the conventional method of tablet making.

The following carrier materials were assigned in preparing solid dispersions of the drug:polyethylene glycol (PEG

4000 and PEG 6000), polyvinylpyrrolidone (PVP K-30 and PVP K-90), polyethylene-propylene glycol (poloxamer 188) and the mixture of PVP and poloxamer 188. PVP and PEG are common carriers frequently used for solid dispersions. Poloxamer 188 was chosen because it is a nontoxic surfactant which is soluble in both water and organic solvents and it is reported to inhibit crystallization of the drug. The mixture of PVP and poloxamer are selected because it was reported that the combined water soluble carrier produced a faster dissolution of a model drug than did the single water soluble carrier alone.

On the basis of explanation mentioned earlier, the purposes of the present investigation were, therefore, concerned with:

1. the method of preparation of solid dispersion of ergoloid mesylate with various carriers and assessment of their physicochemical properties.

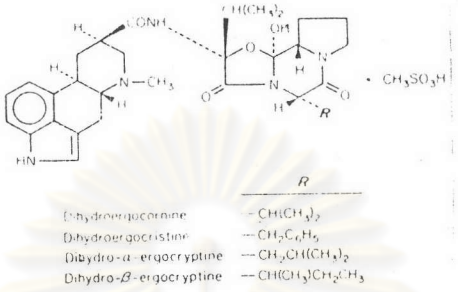
2. the examination of the dissolution behavior of all solid dispersion systems prepared.

3. the application of the solid dispersion of the drug in producing the tablets and evaluate their physical property in comparing with the other conventional method of tablet preparation.

4. comparative studies of dissolution rate of prepared tablets with the tablet products commercially available.

Ergoloid mesylate

1. Formula (Schoenleber, Jacobs and Brewer, 1978; United States Pharmacopeia Convention, 1990)



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Dihydroergocornine	$-CH(CH_3)_2$
Dihydroergocristine	$-CH_2C_6H_5$
Dihydro-α-ergocryptine	$-CH_2CH(CH_3)_2$
Dihydro-β-ergocryptine	$-CH(CH_3)CH_2CH_3$

Name	Empirical formula	Molecular weight
Dihydroergocornine mesylate	$C_{31}H_{41}N_5O_5.CH_4O_3S$	659.80
Dihydroergocristine mesylate	$C_{35}H_{41}N_5O_5.CH_4O_3S$	707.84
Dihydro α-ergocryptine mesylate	$C_{32}H_{43}N_5O_5.CH_4O_3S$	673.82
Dihydro β-ergocryptine mesylate	$C_{32}H_{43}N_5O_5.CH_4O_3S$	673.82

2. Synonym

Dihydroergotoxine mesylate (Mcevoy, 1989)

Dihydroergotoxine methanesulfonate (Schoenleber et al., 1978)

Hydrogenated ergot alkaloid (Mcevoy, 1989)

Co-dergocrine mesylate (Her Majesty's Stationery Office, 1988)

3. Characteristics

Ergoloid mesylate occurs as a white to yellowish-white, practically odorless, crystalline powder (Her Majesty's Stationery Office, 1988; Mcevoy, 1989).

4. Solubility

Ergoloid mesylate is slightly soluble in water, soluble in alcohol, and practically insoluble in ether and petroleum ether (Mcevoy,1989; Schoenleber et al. 1978).

5. Stability

Ergoloid mesylate is unstable in the presence of light, moisture, or temperatures above 30^{o}C (Mcevoy, 1989).

6. Pharmacology

Ergoloid mesylate has some peripheral adrenergic blocking action, but has little or no vasoconstrictor activity and no oxytocic activity. The drug usually causes peripheral vasodilation primarily due to CNS depression of vasomotor nerve activity and cause a slight decrease in blood pressure and heart rate. A few studies have shown that the drug may improve cerebral blood flow and EEG tracings, but other studies indicate that the drug does not significantly alter cerebral blood flow. It has been postulated that ergoloid mesylate may increase oxygen utilization in the brain via stabilization of ganglion cell metabolism, thus increasing cerebral blood flow indirectly rather than by direct dilation of cerebrovascular smooth muscle. There is no conclusive evidence that ergoloid mesylate affects cerebral arteriosclerosis or cerebrovascular insufficiency (Eto and Yoshikawa, 1985; Mcconnachie, 1981; Mcevoy, 1989).

7. Pharmacokinetics

The absorption of ergoloid mesylate after oral administration amounts to 25%. Maximal plasma concentrations are reached after 0.5 to 1.5 hours. Due to the first-pass effect, the bioavailability is between 5 and 12%. The volume of distribution is 1100 litres (Approximate 16 litres/Kg.) and the plasma-protein binding 81%. Administration of drug with food has no effect on the extent of absorption but lowered the absorption rate. The elimination is biphasic with a short half-life of 1.5 to 2.5 hours and a longer one of is to 13 hours. Ergoloid mesylate is mainly excreted with the bile into the faeces. Elimination in the urine amounts to 2% for the unchanged drug and its metabolites and to less than 1% for the unchanged substance alone. Total clearance is about 1,800 ml./min.. In elderly patients the plasma concentrations are somewhat higher than in younger subjects. In patients with renal insufficiency, a reduction in dose is scarcely necessary because only a minor amout of the drug and its metabolites is eliminated by the kidney (Dominiak et al., 1988; Franz, Vonderscher, and Voges, 1980; Mcevoy ed., 1989; Schran, Mcdonald, and Lehr, 1988; Segre et al., 1983; Sorgel et al., 1988).

8. Use

Ergoloid mesylate is widely used in the treatment of cerebrovascular and peripheral vascular diseases and in the treatment of hypertension in the elderly (Dominiak et al., 1988; Sorgel et al., 1984)

9. Adverse effects

Sublingual or oral administration of ergoloid mesylate has not produced any serious adverse effects. Sublingual irritation, rashes, increased nasopharyngeal secretions or nasal stuffiness, blurred vision, orthostatic hypotension, flushing, sinus bradycardia, lightheadness, anoroxia, transient nausea, and vomiting, or other mild GI disturbances have been reported infrequently (Mcevoy, 1989).

10. Administration

Ergoloid mesylate is administered sublingually, orally or injection (Mcevoy, 1989).

11. Dosage

The usual dosage of ergoloid mesylate is 1 mg. 3 times daily. Therapeutic response to ergoloid mesylate is usually gradual and beneficial effects may not be observed until after 3-4 weeks of therapy. The optimum dosage of ergoloid mesylate has not been established, but dosage has ranged from 1.5-12 mg. daily. Some clinicians suggest a dosage of at least 6 mg. daily and recommend a treatment period of 6 months to ensure an adequate trial of therapy with continuing, use of a lower dosage may be attempted; if no benefit is evident the drug should be discontinued (Mcevoy, 1989).

12. Preparations in Thailand (Yukon, 1989; Gwendolene, 1990)

Ergoloid mesylate preparations in Thailand are described in trade name, distributor, dosage form, dose per dosage form in Table 1.

Table 1 Ergoloid mesylate products in Thailand

Trade name	Distributor	Dosage form	Dose/Dosage form
1. Cebralest	Pacific Healthcare	Tablet	1.5 mg.
2. Codergine	Shiwa Chemicals	Tablet	1.0 mg.
3. Hergene	Modren Manu	Tablet	1.0 mg.
4. Holcon	Polipharm	Tablet	1.0 mg.
5. Hyceral	Condrugs	Tablet	1.0 mg.
6. Hydergine	Sandoz	Tablet	1.0 and 4.5 mg.
		Injection	0.3 mg./ ml.
7. Hydrine	T.O.Chemicals	Tablet	1.0 mg.
8. Hymed	Medifive	Tablet	1.0 mg.
9. Memoxy	Galephar (Thailand)	Capsule	1.0 and 1.5 mg.
10. Naline	Pharmaland	Tablet	1.0 mg.
11. Novofluen	International Pharm	Tablet	1 ,1.5 and 4.5 mg.
12. Perenan	Sanofi	Capsule	2.5 mg.
13. Redergin	Rx Co.	Tablet	1.5 and 4.5 mg.
		Injection	0.3 mg./ ml.
14. Siderine	Siam Pharmaceutical	Tablet	1.0 mg.
15. Trigogine	Atlantic	Tablet	1.0 mg.
16. Vasculin	Biopharm	Tablet	1.0 mg.
		Injection	0.3 mg./ ml.
17. Vasian	Asian Pharm	Tablet	1.0 mg.

Literature review

1. Historical background of solid dispersion

It has been observed that the rate of absorption of many poorly-water-soluble drugs from the gastrointestinal tract is limited by the rate of dissolution of the drug substance (Florence and Attwood, 1981). Enhancement of dissolution properties generally improves the rate and extent of gastrointestinal absorption and the bioavailability of such drug.

Many methods have been used to enhanced dissolution rate of poorly-water-soluble or insoluble drugs; these include formation of polymorphs and salts, complexation, particle-size reduction, surface adsorption, and solid dispersion (Mcginity, 1978). Among these methods, reduction of particle size remains the most accepted method for increasing drug dissolution. Particle size reduction is usually achieved by: (a) conventional trituration and grinding; (b) ball milling; (c) fluid energy micronization; (d) controlled precipitation by change of solvent or temperature on 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 salts of poorly soluble compounds form which the parent, neutral forms may precipitate in ultrafine form in GI fluids (Chiou and Riegelman, 1971; Khan, 1981).

However, easily and directly the reduction of particle size can be accomplished by the first four methods (a-d), the

resultant fine particles may not produce the expected faster dissolution and absorption. This is primarily due to the the possible aggregation and agglomeration of the fine particles and air adsorption caused by their increased surface energy and the subsequent stronger Van Der Waal's attraction between nonpolar molecules, or their poor wettability in water. Moreover, drug with plastic properties are difficult to subdivide by method a-c. Controlled precipitation by change of solvent by method e is not frequently employed in commercial market due to such reasons as selection of a nontoxic solvent, limitation to low dose, and high costs of production. The water-soluble salts of many poorly soluble acidic or basic drugs have been widely used clinically in solid dosage forms and have been shown frequently to produce better absorption than their parent compounds. Nevertheless, the sodium and potassium salts may react with atmospheric carbon dioxide and water to precipitate out poorly soluble parent compounds. This occurs especially on the outer layer of a dosage form and thereby retards the rate of dissolution and absorption. In addition, the alkalinity of some salts may cause epigastric distress following administration (Chiou and Riegelman, 1971; Ford, 1986; Bloch and Speiser, 1987).

The concept of solid dispersion was introduced by Sekiguchi and Obi (1961). They proposed the formation of a eutectic mixture or molecular dispersion of a poorly soluble drug, sulfathiazole, and the physiologically inert, water-soluble carrier, urea. It possessed higher absorption and excretion after oral administration than sulphathiazole alone. Since then,

extensive studies and excellent work were made and modifications of this technique have been suggested (Anastasiaduo et al., 1983; Attia and Habib, 1985; Babar and Jarowski, 1983).

2. Terminology

The term " solid dispersions " was defined by Chiou and Riegelman (1971) and refer to the dispersion of one or more active ingredients in an inert carrier or matrix at solid state prepared by the melting (fusion), solvent or melting-solvent method. Not include in this category are dispersions of drugs in solid diluents by traditional mechanical mixing but complexes may also be classed as solid dispersion. Since the dissolution rate of a component from a surface is affected by the second component in a multiple component mixture, the selection of the carrier has an ultimate influence on the dissolution characteristics of the dispersed drug. Therefore, a poorly water-soluble drug combined with a water-soluble carrier results in a fast release of the drug and a good water-soluble drug combined with a slightly water-soluble carrier leads to a retardation of drug release from matrix. Since this technique is commonly used for increasing dissolution, this review emphasizes on fast-release solid dispersion. However, some of the principles may also be applied to slow-release solid dispersion systems (Chiou and Riegelman, 1971; Bloch and Speiser, 1987; Ford, 1986).

The solid dispersion may also be called under a variety of names, including solid-state dispersion, solid solution, eutectics, fast-release solid dispersion and coprecipitates, The

term " coprecipitates " has also been frequently used to refer to those preparations obtained by the solvent methods such as reserpine-PVP coprecipitates (Geneidi, Ali and Salama, 1978; Miralles, Mcginty and Martin, 1982; Reddy, Khahl, and Gouda, 1976; Simonelli, Mehta, and Higuchi, 1969; Stupak, and Bates, 1972).

3. Methods of preparation of solid dispersions

Broadly speaking there are only three methods of preparing solid dispersions, namely by melting, solvent or melting-solvent processes.

3.1 Melting method

The melting or fusion method was first used by Sekiguchi and Obi (1961) and was subsequently employed some modification by many investigations (Ford adn Elliott, 1985; Jachowicz, 1987; Jain and Parikh, 1986; Ravis and Chen, 1981). Carriers that have been employed during the past 15 years include urea, polyethylene glycol 4000, 6000 and 20,000, citric acid, succinic acid, pentacrythritol, pentacrythrityl tetraacetate, mannitol, dextrose, and other sugar (Mcginity, 1978). A schematic diagram of preparation steps is shown in Figure 1.

The advantage of melting method are:

1. Its simplicity and economy.

2. A supersaturation of a solute or drug in a system can often be obtained by quenching the melt rapidly from a

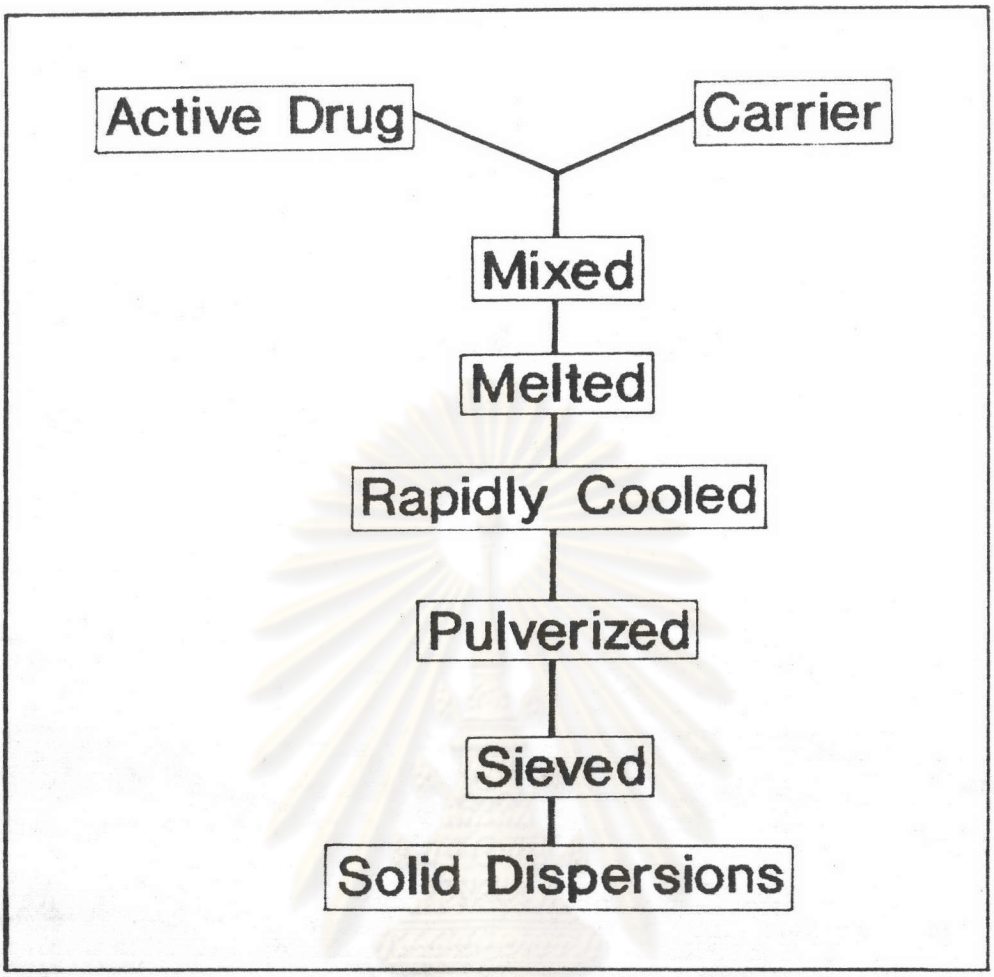

Figure 1 A schematic diagram for preparing solid dispersions by melting method

high temperature.

3. A much finer dispersion of crystallites was obtained for systems of simple eutectic mixtures if such quenching techniques were used.

The disadvantages are:

1. Many substances, either drugs or carriers may decompose or evaporate during the fusion process at high temperature.

2. Only low melting carriers can be used.

3. The resulting product from melting method is always difficult to be pulverized.

3.2 Solvent method

This method was initially used by Tachibana and Nakamura (Tachibana and Nakamura, quoted in Ford, 1986). After that it was widely used in the preparation of many solid dispersion systems, such as Chlorpropamide-PVP (Deshpande and Agrawal, 1984), Frusemide-PVP (Doherty and York, 1987), Nalidixic acid-Myrj$^{(R)}$ (Elgindy, Shalaby, and Elkhalek, 1983), Corticosteroid-PEG (Khalil, Elfattah, and Mortada, 1984), Prednisolone-gelatin (Kimura et al., 1990).

Solid dispersions prepared by solvent removal processes were termed by Bates (1969) as " coprecipitates " and this term has been misconstrued by many other wokers. They should, more correctly, be designated as " coevaporates ", a term

that has been recently adopted (Sekikawa et al., 1983). A schematic diagram of this method is shown in Figure 2.

The advantages of the solvent method are:

1. Thermal decomposition of drugs or carriers can be prevented because of the low temperature required for the evaporation of organic solvents.

2. High melting carriers can be used.

The disadvantages are:

1. The higher cost of preparation.

2. The difficulty in completely removing liquid solvent which may affect the chemical stability of the drug.

3. The difficulty in selecting a common volatile solvent.

4. The difficulty of reproducing crystal forms.

5. A supersaturation of the solute in the solid system cannot be attained except in system showing highly viscous properties.

6. Solvent flammability and toxicity.

3.3 Melting-solvent method

This method is derived from melting method by

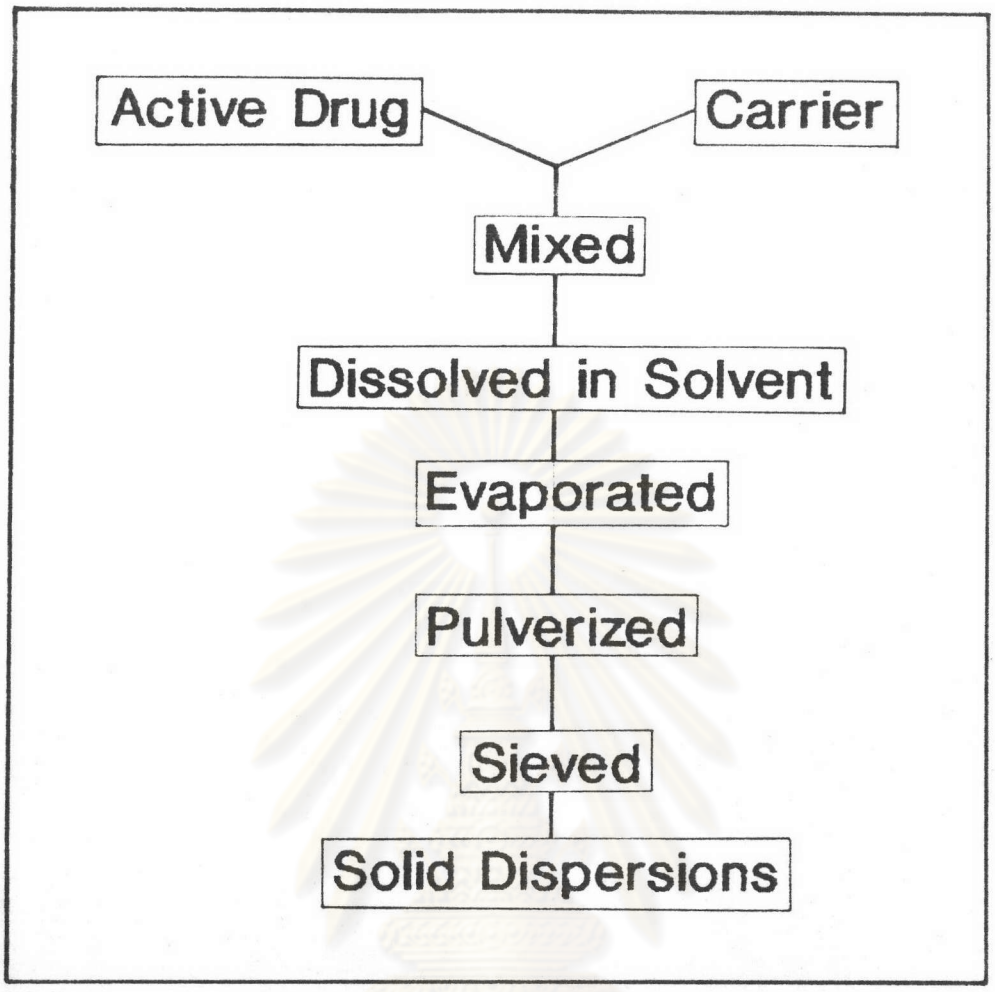

Figure 2 A schematic diagram for preparing solid dispersions by solvent method

Chiou and Smith (1971). It was shown recently that 5-10% (w/w) of liquid compounds could be incorporated into PEG 6000 without significant loss of its solid property. Hence, it is possible to prepare solid dispersions by first dissolving a drug in a suitable liquid solvent and then incorporating the solution directly into the melt of PEG, obtainable below 70°C, without removing the liquid solvent. A schematic diagram of this method is show in Figure 3. The feasibility of this method was demonstrated on spironolactone-PEG 6000 and griseofulvin-PEG 6000 systems (Chiou and Riegelman, 1971).

The advantages of both the melting and solvent methods, from a practical standpoint, are only limited to drugs with a low therapeutic dose, e.g., below 50 mg. (Chiou and Riegelman, 1971).

4. Methods for determination of types of solid dispersion systems

Many methods are available for contributing information regarding the physical nature of a solid dispersion system. In many instances, a combination of two or more methods is required to study its complete picture (Chiou and Riegelman, 1971; Mcginity, 1978).

4.1 Thermal analysis

This is the most common approach used to study the physicochemical interactions of two or more component systems. Several modified techniques are utilized the same

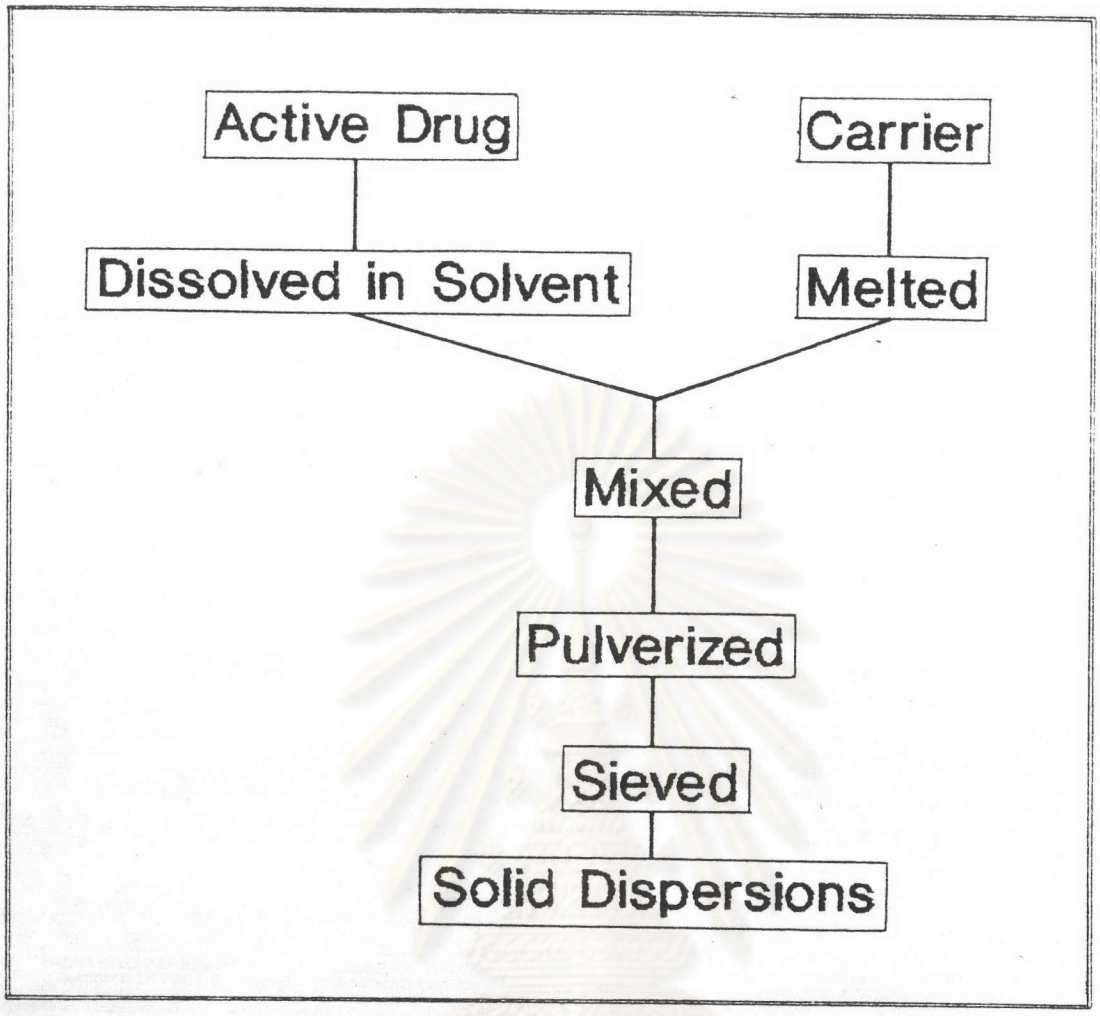

Figure 3 A schematic diagram for preparing solid dispersions by melting - solvent method

principle of change of thermal energy as a function of temperature.

4.1.1 Zone melting method

This technique was first introduced in 1952 and has been primarily used for ultrapurification of metals and inorganic and organic compound. The phase diagram can be constructed. A molten zone effected by a heater traverses a cylindrical ingot or solidified melt at a rate of about 0.5-0.001 cm. per hour. A mechanical stirring device is also required for the mixing of the liquid in molten zone. After zone melting is finish, the bar is sectioned and analyzed for its chemical composition. A phase diagram of a binary or multicomponent can be constructed from their chemical compositions and freezing temperatures of the corresponding sections. This method is limited to compound with low volatility and high thermal stability (Chiou and Riegelman, 1971).

4.1.2 Thermomicroscopic method

In this method, polarized microscopy with a hot stage is used to study phase diagram of binary system. The physical mixture is placed on a slide covered with a cover slip and sealed with silicon grease to prevent sublimation. The mixture is heated until a homogeneous melt is obtained. After cooling, the mixture is heated at the rate of $4^{o}C$ per minute. The thaw and melting points are determined by visual observation and various forms of phase diagrams can be constructed. The Kofler contact method, also utilizing

polarizing microscopes was proposed to establish various forms of phase diagrams and used to require a good knowledge of crystallography (Chiou and Riegelman, 1971; Ford and Rubinstein, 1978).

4.1.3 Cooling curve method

In this method, the physical mixtures of various composition are heated until it completely liquifies. The temperature of the mixture is then recorded as a function of time. From a series of temperature-time curve, the phase diagram can be established. This method was recently used to determine phase diagrams of deoxycholic acid-menadione and caffeine-phenobarbioal (Chiou and Riegelman, 1971).

4.1.4 Thaw-melt method

In this method, a sample of solidified mixtures in a capillary melting-point tube is heated gradually and the thaw point is determined. The thaw point is the temperature on crossing a solidus line. Such method was modified and utilized by using a stirring device in capillary tube for more accurate reults, the stirring facilitates the attainment of a homogenous system (Chiou and Riegelman, 1971).

4.1.5 Differential thermal analysis and differential scanning calorimetry

These are effective thermal method for studying phase equilibria of either a pure compound or a mixture.

Differential effects, associated with physical or chemical changes, are automatically recorded as a function of temperature or time as the substance is heated at a uniform rate. In addition to thawing and melting, polymorphic transitions, sublimation, evaporation, desolvation, and other type of decomposition can be detected. These techniques are especially valuable in detecting the presence of a small amount of eutectic in the mixture, because its melting at the eutectic temperature can be sensitively detected, the observation of such small fractions of melting at eutectic temperature can often be missed when employing thaw-melt or thermomicroscopic methods (Chiou, 1971; Chiou and Niazi, 1971; Chiou and Riegelman, 1971; Ford, 1978; Ford and Rubinstein, 1977).

4.2 Microscopic method

Microscopy has been used quite often to study the morphology and polymorphism of solid dispersions. The polarizing microscope was used to study the fine particles of crystallization in the glassy PVP matrix. The dispersed particle size of iopanoic acid in PVP and hydrocortisone in PEG can be readily detected by the high resolution of an electron microscope. The application of the electron microscope technique is, however, usually limited to chemical with high atomic numbers. Photoplan microscope was also used to study aging of indomethacin-PEG 6000 solid dispersions (Chiou and Riegelman, 1971; Ford and Rubinstein, 1979; Kaur, Grant, and Eaves, 1980).

4.3 Spectroscopic method

IR spectroscopy is usually used to study polymorphic phenomena or complex formation in solid dispersions systems. For example, the utilization of IR spectrum could indicate the complexation between PVP and glibenclamide in the solvent method (Chiou and Riegelman, 1971; Geneidi, Adel, and Shehata, 1980).

4.4 X-ray diffraction method

In this method, the intensity of the X-ray diffraction (or reflection) from a sample is measured as a function of diffraction angles. X-ray diffraction also serves as a means for isolating X-ray of a particular wavelength in an X-ray spectrometer. This is similar to what is done with a prism or grating in conventional visible or ultraviolet spectrophotometers.

The diffraction method is a very important and efficient tool in studying the physical nature of solid dispersions. It is also valuable in detecting compound or complex formation since it spectra or lattice parameters are markedly different from those of pure components. It has been used to study quantitatively the concentration of a crystalline component in the mixture. This method was used to study various dispersion systems (Chiou, 1971; Chiou and Niazi, 1971; Chiou and Riegelman, 1971; Christian and Oreilly, 1986; Ravis and Chen, 1981; Takayama, Nambu and Nagai, 1982).

4.5 Thermodynamic method

The phase diagram of eutectic and solid solution systems can be constructed on the basis of some thermodynamic parameters. A knowledge of heats of fusion, entropies, and partial pressures at various compositions enables one to determine the solubility gap below the solid-liquid equilibrium temperature (Chiou and Riegelman, 1971).

4.6 Dissolution-rate method

Allen and Kwan (1969) proposed the dissolution-rate method to study the degree of crystallinity in solid-solid equilibria, especially in temperature regions below solid- liquid equilibria. The method involves comparing the in-vitro dissolution rates of the solute component from a constant-surface tablet made from molecular dispersion with a physical mixture of the same chemical composition.

The application of this method also requires: (a) the observed dissolution rate to be proportional to the surface area, (b) a reasonably large difference between the dissolution rate of the physical mixture and the corresponding solid solution, and (c) the use of the same polymorphic form of a drug in the tablet of the physical mixture as that precipitated out from the solid dispersions. Furthermore, one must assume in this dissolution method that the distribution of particle size. (may be as small as on the subcolloidal range) precipitated from the solid solution or glass solution dose not affect the dissolution rate. Such assumption need to be proved experimentally.

5. Physicochemical structures of solid dispersions

The physicochemistry and thermodynamic of these dispersions play an important role in controlling their drug release. Although solid dispersions systems may include more than two components, for the sake of simplicity and practicality, this review is primarity limited to binary systems. On the basis of their major fast-release mechanisms, six representatives have been outlined as representative of interactions between carrier and drug (Bloch and Speiser, 1987; Chiou and Riegelman, 1971; Ford, 1986).

1. Simple eutectic mixtures
2. Solid solutions
3. Glass solutions and glass suspensions
4. Amorphous precipitation in a crystalline carrier
5. Compound or complex formation
6. Combinations

5.1 Simple eutectic mixtures

The simple eutectic mixture is usually prepared by rapid solidification of two melted components which show complete miscibility in the liquid state and negligible solid-solid solubility. These properties are characterized by a typical melting point depression and can be illustated in a phase diagram (Figure 4). Thermodynamically, such a system is regarded as an intimately blended physical mixture of its two crystalline

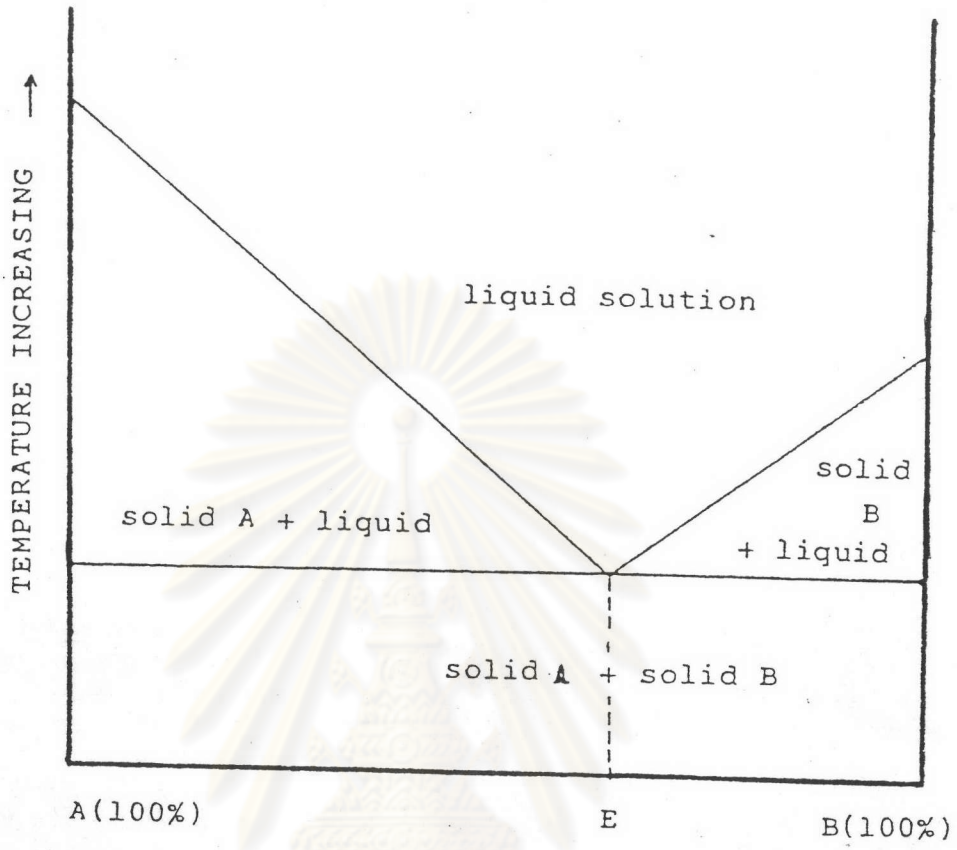

Figure 4 A typical phase diagram of a simple eutectic mixture with negligible solid solubility

components (Chiou and Riegelman, 1971).

When a eutectic composed of a poorly soluble drug is exposed to water or GI fluids, both components may simultaneously crystallize out in very small particulate sizes. The increases of the specific area due to this reduction of particle size generally increases rates of dissolution and peroral absorption of poorly soluble drugs (Bloch and Speiser, 1987; Chiou and Riegelman, 1971).

In addition to the reduction of the crystallite size, the following factors may contribute to the faster dissolution rate of a drug dispersed in the eutectic.

1. The increase of drug specific surface area due to its extremely small crystallites, consequently an increase in drug solubility may occur.

2. The absence of agglomeration and aggregation between fine crystallites of the pure hydrophobic drug because the individually dispersed particles are surrounded in the matrix by carrier particles.

3. A possible solubilization effect by the carrier 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. This was demonstrated by the faster dissolution rate of acetaminophen from its physical mixture with comparable particle size (Chiou and Riegelman, 1971; Goldberg et al., 1966).

4. An increased rate of dissolution and absorption may also occur if a drug crystallizes in a metastable form after solidification from the fused solution. A metastable, crystalline form has a higher solubility which, in turn, leads to a faster dissolution rate according to the well-known Noyes-Whitney equation (Appendix 1) (Chiou and Riegelman, 1971).

5. Excellent wettability and dispersibility of a drug from a eutectic or other solid dispersions system prepared with a water-soluble matrix result in an increased dissolution rate of the drug in aqueous media. This is due to the fact that each single crystallite of the drug is very intimately encircled by the soluble carrier which can readily dissolve and cause the water to contact and wet the drug particle. The encycling carrier also prevents the drug powders from being surrounded by the non-polar air. In contrast, the aggregates and agglomerates of poorly soluble pure powders are surrounded by the non-polar air, which is hard to penetrate or displace by water (Chiou and Riegelman, 1971).

The composition of a eutectic may have a significant effect on the particle size of the crystallite. If it is made up of a high weight fraction of drug, an ultrafine crystallization of the drug may not be obtained. This is logical if one expects that the higher the dilution, the finer the crystalline size of its precipitate.

In addition to the possible aforementioned differences between the eutectics and the physical or mechanical mixture, the rapidly crystallized (quenched) eutectics are characterized by increased hardness. This was explained on the bases of a high degree of strain resulting from the action of mechanical forces. The effect of such increased hardness on the dissolution rate, however, remains to be explored. It is believed that the hardening effect of the eutectic may also play a role in retarding dissolution rate of acetaminophen from the eutectic with urea which contains 52% of the acetaminophen (Chiou and Riegelman, 1971; Goldberg, Gibaldi, and Kanig, 1966).

5.2 Solid solution

Compared to a liquid solution, a solid solution is made up of a solid solute dissolved in a solid solvent. The two components crystallize together in a homogeneous one-phase system, so it is often called a mixed crystal . Goldberg, Gibaldi, and Kanig (1965) suggested that a solid solution of a poorly soluble drug in a rapidly soluble carrier achieves a faster dissolution rate than a eutectic mixture because the particle size of the drug in the solid solution is reduced to a minimum state, i.e., its molecular size. In addition to such maximum size reduction, other factors discussed under simple eutectic mixture may contribute to increased rate of dissolution and absorption of drugs dispersed in solid solutions. However, due to the maximum particle-size reduction in the solid solution and to the possible solubilization effect of the carrier in the

microenvironmental diffusion layer of bulk fluids, the drug may temporarity result in a high supersaturation of the bulk fluids. Obviously, this is temporary and would lead to precipitation if the drug is not being absorbed or removed by other processes (Chiou and Riegilman, 1971).

Two methods are used to classify solid solutions. On the basis of the extent of miscibility between the two components, they can be divided into two groups: continuous (or isomorphous, unlimited, complete) solid solutions and discontinuous (or limited, restricted, partial, incomplete) solid solutions. The second classification is based on the crystalline structure of the solid solutions, they can also be divided into two groups: substitutional solid solutions and interstitial solid solutions.

5.2.1 Continuous solid solutions

In this system, the two components are miscible or soluble at solid state in all proportions (Figure 5). The presence of a small amount of the soluble carrier in the crystalline lattice of the poorly soluble drug may also produce a dissolution rate faster than the pure compound with similar particle size. This may be due to a small number of the neighboring drug molecules holding the dissolving drug molecule after the rapid dissolution of the neighboring water-soluble carrier. The solid solutions above the temperature of the miscibility gap, as shown in Figure 5, is also thermodynamically stable, with a free energy lower than that anticipated from the

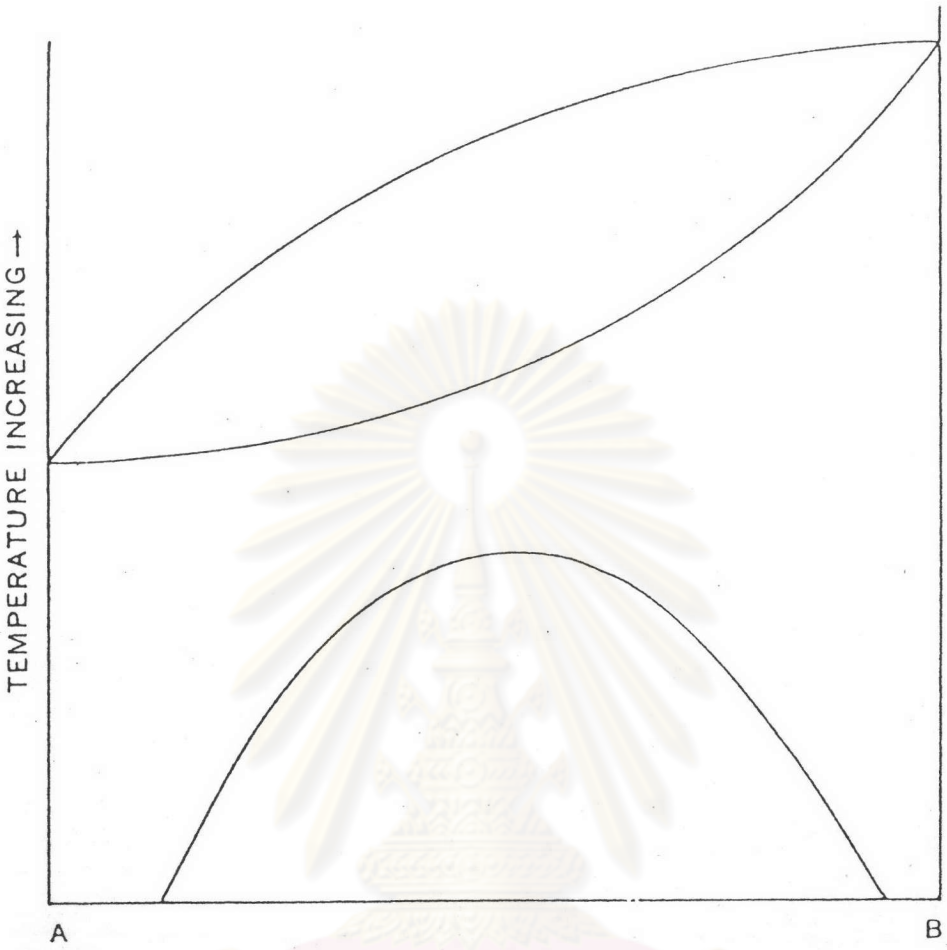

Figure 5 A typical phase diagram of continuous solid solution of a binary system , A and B

mixture law. The miscibility gap noted in Figure 5 may occur as a result of limited solid-state solubility at lower temperatures.

5.2.2 Discontinuous solid solution

In this system, there is a limited solubility of a solute in a solid solvent. This can be best depicted in a standard phase diagram (Figure 6) the regions of solid solution in the diagram are marked as the α and β regions. In these regions, one component is dissolved in the other component to a certain degree above the eutectic temperature. However, as the temperature is lowered, the solid solution regions become narrower, The free energy of a stable, limited solid solution is also lower than that of the pure solvent (Chiou and Riegelman, 1971).

An example of this type of solid solution was reported by Chiou and Niazi (1976). The system comprised griseofulvin and succinic acid and was believed to be a simple eutectic mixture with limited solid solubility of griseofulvin in succinic acid.

5.2.3 Substitutional solid solution

In this system, a schematic diagram is shown in Figure 7. The solute molecule substitutes for the solvent molecule in the crystal lattice of the solid solvent. It can form continuous or discontinuous solid solution. The size and steric factors of the solute molecule were shown to play a decisive role in the formation of solid solutions. The size of

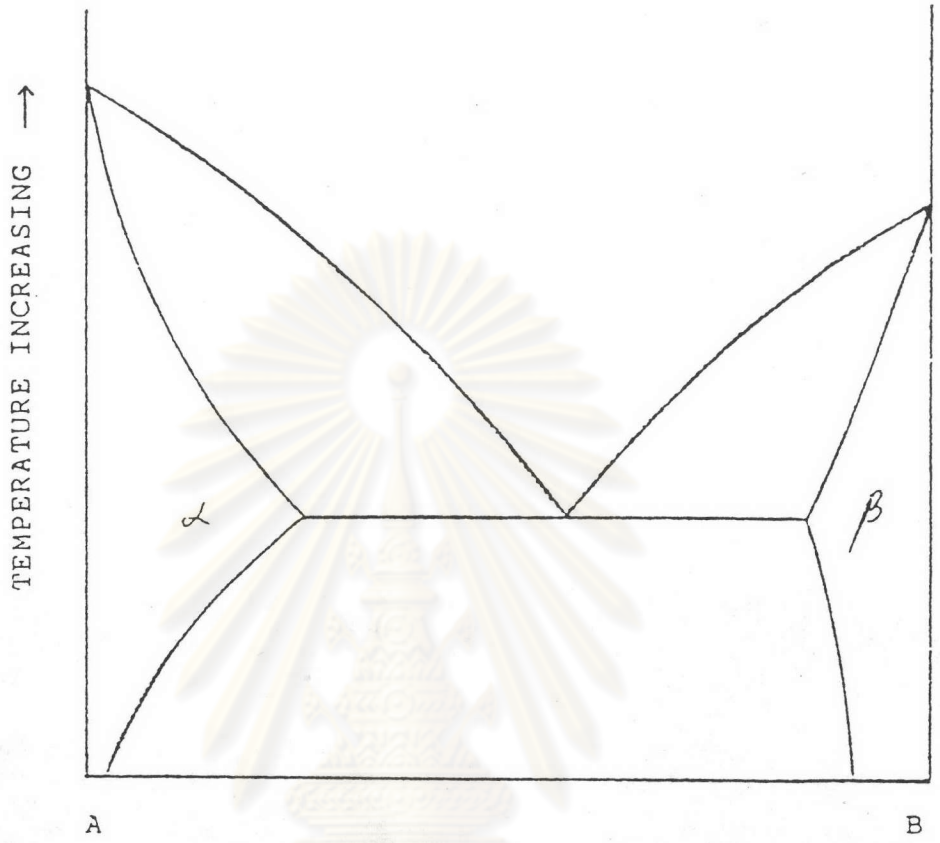

Figure 6 A typical phase diagram of discontinuous solid solution of a binary system , A and B

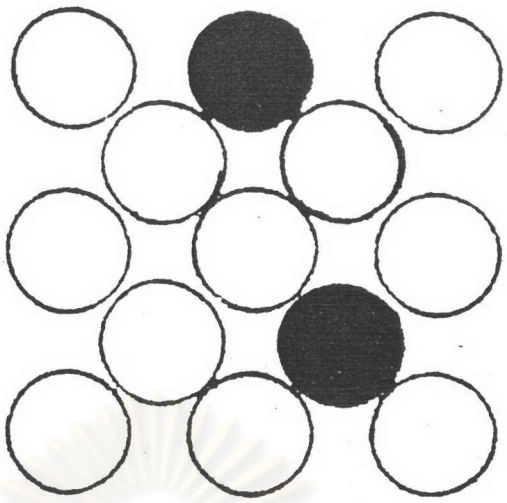

Figure 7 A diagram of a substitutional solid solution (Dark circles indicate solute atoms or molecules , while open circles indicate solvent atoms or molecules.)

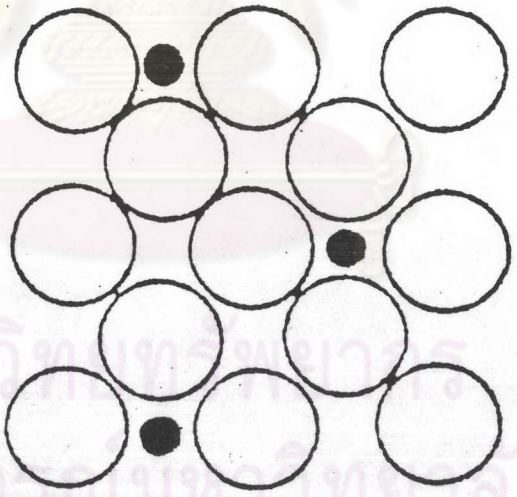

Figure 8 A diagram of an interstitial solid solution (Dark circles indicate solute atoms or molecules , while open circles indicate solvent atoms or molecules.)

the solute and the solvent molecule should be as close as possible. Example of substitutional solid solution were griseofulvin-pentaerythritol (Chiou and Riegelman, 1969; Chiou and Riegelman, 1971).

5.2.4 Interstitial solid solution

In this system, a schematic diagram is shown in Figure 8. The solute molecule occupies the interstitial space of the solvent lattice. It usually forms only a discontinuous (limitted) solid solution. The size of the solute is critical in order to fit into the interstices. It was found that the apparent diameter of the solute atom should be less than 0.59 that of the solvent and the volume of the solute shold be less than 20% of the solvent. Examples of interstitial solid solutions were indomethacin-PEG 6000, Hydrocortisone acetate-PEG 6000, and digitoxin-PEG 6000 (Chiou and Riegelman, 1971; Ford and Rubinstein, 1978).

5.3 Glass solutions and glass suspension

A glass solution is a homogeneuos, glassy or vitreous system in which a solute dissolves in a glassy solvent. Often it is characterized by transparency and brittleness below the glass-transforming temperature. On heating, it softens progressively and continuously without a sharp melting point. It is due to the facts that the chemical bonds in the glass differ considerably in length, strength and there is no one temperature at which all the bond become loosened simultaneously. A glass or

glass solution is metastable. It produces only weak and diffusion diffraction effect, while crystallites can give strong and sharp diffraction effects. The lattice energy in the glass solution is much less than in a solid solution and the solute particle size of crystallization in the glass solution is much smaller than it in solid solution. Therefore, if everything is equal, the dissolution rate of drugs in the glass solution should be theoretically faster than that in the solid solution. Carriers favouring glass formation include sucrose, dextrose, galactose (Allin, Yanchick and Maness, 1977), sorbitol, citric acid (Summmers and Enever, 1976), PVP (Resetarits et al., 1979; Stupak and Bates, 1972; Stupak and Bates, 1973), and urea (Ford and Rubinstein, 1977). Glass suspensions rather than glass solutions are formed when the drug and carrier do not show interaction and are immiscible in the liquid state (Chiou and Reigelman, 1971; Ford, 1986).

5.4 Amorphous precipitations in a crystalline carrier

This is the system which the drug precipitates out as an amorphous form in the crystalline carrier from a melting or a solvent method of preparation. Since the amorphous form is the highest energy form of a pure drug, it should produce faster dissolution and absorption rates than the crystalline form whether the crystals are or are not dispersed in a carrier. For example, amorphous sulfathiazole dispersed in the crystalline urea was believed to be a contributing factor in increasing sulfathiazole dissolution rate (Chiou and Niazi, 1971). Amorphous

deposits of the drug is metastable and convert on storage to more crystalline forms. Systems containing long- chain polymers may crystallize only slowly and because of steric hindrance will never reach 100% crystallinity. Consequently dispersion in PEG_s and other long chain polymers may show gradual increase in crystallinity of amorphous areas during storage (Chiou and Reigelman, 1971; Ford, 1986).

5.5 Compound or complex formations

In a strict sense, the modification of a dosage form by a compound or complex formation (DnCm) between a drug (D) and an inert soluble carrier (C) should not be classified under the application of solid dispersions systems (Bloch and Speiser, 1987; Chiou and Riegelman, 1971).

Figure 9 shows that the bioavailability of the drug (D) depends on the solubility, the dissociation constant, and the intrinsic absorption rate of the complex. Although complex formation should not be classified as one of solid dispersions systems, such interaction between a drug and an inert soluble carrier frequently occurs during dispersion preparation. It is believed that the rates of dissolution and absorption can be increased by the formation of complex, eg. glibenclamide-PVP (Geneidi, Adel, and Shehata, 1980), and hydroflumethiazide-PVP (Corrigan and Timoney, 1975). On the contrary, PVP was shown to retard the pharmacological action of numerous compounds such as penicillin, prostigmine and quinine. However, some interactions may not have any effect on drug activities. For instance, the

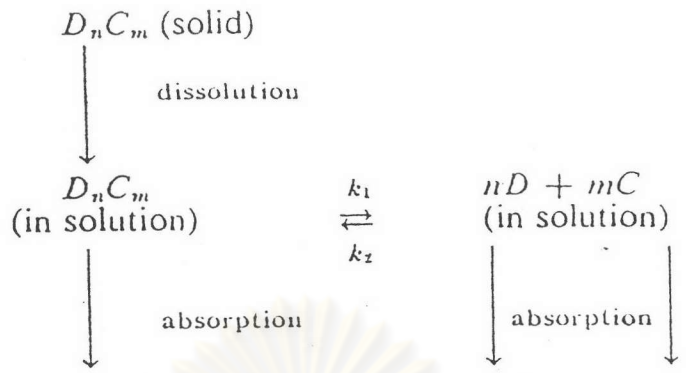

Figure 9 A schematic diagram of the dissolution and absorption of drug into the body from a complex or compound

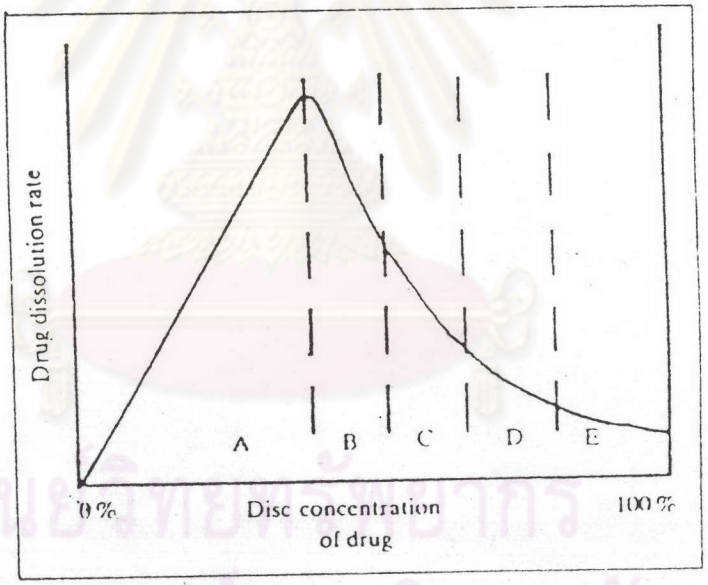

Figure 10 A schematic diagram showing the effect of composition on the dissolution rate of solid dispersions , as measured from constant surface area discs

bacteriological activity of sulfamethoxazole dispersions was not changed in spite of the complex formation between sulfamethoxazole and reducing sugars (Ghanem, Meshali, and Ibraheem, 1980).

5.6 Combinations and miscellaneous mechanisms

Phase interactions between drugs and carriers are often difficult to quantify because dispersions may be combination of these phase interaction, and thus quantification is made more difficult by the structure of the dispersion being often dependent on the methods of preparation and age of the dispersion. The sulfathiazole dispersed at high concentration in PVP, for instance, may be present as individual sulfathiazole and sulfathiazole-PVP complex molecules, amorphous and polymorphic sulfathiazole, and possibly an amorphous sulfathiazole-PVP complex (Chiou and Reigelman, 1971; Ford, 1986).

Drug concentration in solid dispersion is one of many factors effected on the dissolution rate. In selection of the optimum drug concentration, it should be exhibited the highest dissolution rate. Figure 10 may be invented which relates the ratio of drug-carrier to dissolution rates measured by constant surface area discs.

6. The future of solid dispersions

Solid dispersions possess tremendous potential to increase the dissolution rate and bioavailability of drugs whose absorption is limited by solubility or dissolution rate. The techniques are therefore unsuitable for drugs which are actively absorbed. The problems of total solvent removal in dispersions prepared by solvent methods and of thermal instabilities in melting prepared dispersions warrant careful choice of the carrier. The chosen drug: carrier ratio should be one which both prevents decomposition and minimizes age-changes during storage. Current indications are that this latter level is a ratio which contains a large proportion of carrier, and this is not conducive to the use of solid dispersions of high-dosage drugs (Ford, 1986).

In solvent method organic solvent has a significant effect on the composition and properties of the final coevaporate. For example, if the solubility of drug and carrier are not different, both drug and carrier should coevaporate out of solution at the same rate. If, however,both solubilities are difference, the lower solubility should have been coevapotated before the saturation concentration of the higher solubility has been exceeded. To overcome this problem and have the solubility of the drug and carrier similar to one another, one can utilize mixed solvent systems, however, a constant-boiling-point (or azeotropic) mixture should be used so that the composition of the solvent dose not change during evaporation (Mcginity, 1978).

The two most commonly used carrier, PVP and PEG, have traditional usage as tablet binders and consequently their formulation requires the addition of disintegrants whose action may be lost by the high local viscosity these polymers produce on dissolving. However, high-levels of PEG are difficult to compress due to the elastic nature of the polymer. Additionally formulation of the dispersions may reduce the large dissolution rates of the unformulated dispersions (Ford, 1986).

However, the four advantages of maintaining a drug in a bioavailable form, dosage reduction, true coevaporate, or cleaner manufacturing conditions provide scope for the continued interest in solid dispersions.