1.Introduction

Dissolution of water insoluble drugs has always been problem for formulation with pharmaceutical industries and the realization of the fact that formulation factors are significant in affecting the biological availability of a drug in a dosage form has led to continuous development and expansion of novel drug delivery systems.

For orally administered solid particles containing the drug, the dissolution process is the rate limiting process with respect to absorption process. It is because dissolution is going to exert an effect on the rate and amount of drug appearing in the body. The poor dissolution characteristics of relatively insoluble drugs have been a problem to pharmaceutical industry.

For improvement of solubility and dissolution rate of such poorly soluble drugs numerous new techniques such as liquisolid, in which drug in solution state or dissolved drug is adsorbed over insoluble carriers, nanomorph; a patented technology of Soliqs® for controlled crystallization of drug, in situ micronisation, coprecipitation using antisolvent, self emulsifying drug delivery systems, microemulsions and old techniques like solid dispersion and micronisation are available.

In present vocation self emulsifying drug delivery systems, liquisolid systems, solid dispersions and nanocrystals were prepared to study their comparative dissolution enhancement efficiency. Since varying physicochemical properties of drugs affect the efficiency of systems 3 different drugs carbamazepine, oxcarbamazepine and gabapentine were exercised for study. All the 3 drugs are used in epilepsy. Improvement of dissolution and bioavailability characteristics of these drugs will help to improve the therapy.

Self emulsifying drug delivery system is isotropic mixtures of an oil, surfactant, cosurfactant (or solubilizer), and drug. The basic principle of this system is its ability to form fine oil-in-water (o/w) emulsions under gentle agitation following dilution by aqueous phases. That is the digestive motility of the stomach and intestine providing the agitation required for self-emulsification *in vivo*. The spontaneous formation of an emulsion upon drug release in the GI tract advantageously presents the drug in a dissolved form and the small droplet size provides a large interfacial surface area for drug absorption.

Liquisolid systems are acceptably flowing and compressible powdered forms of liquid medications. According to the concept of liquisolid systems, liquid lipophilic drugs or water insoluble solid drugs dissolved in suitable non-volatile solvents, may be converted into free flowing and readily compressible powder by simple admixture with selected powder excipients referred to as carrier or coating materials. Various grades of microcrystalline or amorphous cellulose may be used as carriers, whereas very fine particle size silica powders may be used as coating materials.

Solid dispersion is also one of promising methods to formulators due to its ease of preparation, ease of optimization and reproducibility. Poorly soluble drug when dispersed in an inert hydrophilic polymer or matrix by melting, solution formation or solvent melting yields solid dispersion.

In case of microcrystals, the coarse crystalline drug substances were transformed into a microdispersed amorphous state, without any physical milling or grinding procedures. This lead to the preparation of amorphous microcrystals.

The developed formulations were studied for their *in vivo* behavior in rabbits.

Review of novel techniques utilized for dissolution enhancement of poorly soluble drugs.

1.1. Self-emulsification (SEDDS).

Much attention has been focused on lipid based formulations in recent years (Humberstone and Charman, **1997**) with particular emphasis on self-emulsifying drug delivery systems (SEDDS) for the improvement of oral bioavailability of lipophilic drugs (Constantinides, **1995** , Pouton, **1997**). In the absence of external phase (water), the mixture of oil, surfactant, cosurfactant, one or more hydrophilic solvents and cosolvent forms a transparent isotropic solution that is known as the self-emulsifying drug delivery system (SEDDS). This forms fine O/W emulsions or microemulsions spontaneously upon dilution in the aqueous phase and is used for improving lipophilic drug dissolution and absorption (Gershanik and Benita, **2000,** Gershanik, *et al.*, **1998**). The digestive motility of the stomach and intestine provide the agitation necessary for self-emulsification *in vivo*. Factors controlling the *in vivo* performance of SEDDS include their ability to form small droplets of oil (<5 μm) and the polarity of the oil droplets to promote faster drug release into aqueous phase (Shah, *et al.*, **1994**). The smaller oil droplets provide a large interfacial area for pancreatic lipase to hydrolyze triglycerides and thereby promote the rapid release of the drug and/or formation of mixed micelles of the bile salts containing the drug (Tarr and Yalkowsky, **1989**). The surfactants used in such formulations are known to improve the bioavailability by various mechanisms like,

i. improved drug dissolution (Constantinides, **1995,** Muranishi, *et al.*, **1980**)
ii. intestinal epithelial permeability (Swenson and Curatolo, **1992**)
iii. increased tight junction permeability (Lindmark, *et al.*, **1995**)
iv. decreased or inhibited p-glycoprotein drug efflux (Lo, *et al.*, **1998,** Nerurkar, *et al.*, **1996,** Nerurkar, *et al.*, **1997,** Yu, *et al.*, **1999**).

Recently a threefold increase in the bioavailability of a poorly soluble compound when formulated as SEDDS has been reported (Shah, *et al.*, **1994**). A marketed formulation of cyclosporine (Sandimmune Neoral®), a microemulsion preconcentrate with self-emulsifying properties, is reported to improve oral bioavailability and reduce inter and intra subject variability in cyclosporine pharmacokinetics i.e improves the reproducibility of the plasma level–time profile (Armstrong and James, **1980,** Friman and Backman, **1996**). A few other studies have reported enhancement in the bioavailability of poorly soluble drugs when formulated as SEDDS (Charman, *et al.*, **1992,** Hauss, *et al.*, **1998,** Klem, *et al.*, **1993,** Lin, *et al.*, **1991,** Matuszewska, *et al.*, **1996**). SEDDS are accounted for enhancement of the oral delivery of Coenzyme Q_{10} (Kommuru, *et al.*, **2001**). For selecting a suitable self-emulsifying vehicle, it is important to assess,

i. the drug solubility in various components
ii. the area of self-emulsifying region in the phase diagram and
iii. droplet size distribution following self-emulsification.

The self-emulsification process is specific to the nature of the oil/surfactant pair, surfactant concentration, oil/surfactant ratio and temperature at which self-emulsification occurs. The ease of emulsification could be associated with the ease of water penetrating into the various liquid crystalline or gel phases formed on the surface of the droplet. A few parameters have been proposed to characterize the self-emulsifying performance including the rate of emulsification, the emulsion size distribution and the charge of resulting droplets.

Among them, emulsion droplet size is considered to be a decisive factor in self emulsification/dispersion performance, since it determines the rate and extent of drug release and absorption (Shah, *et al.*, **1994,** Tarr and Yalkowsky, **1989**). In addition, positively charged emulsion droplets could be obtained by incorporation of a small amount of cationic lipid (oleylamine) into such system (Gershanik and Benita, **1996a,** Gershanik, *et al.*, **1998**). The oral bioavailability of progesterone was significantly enhanced in rats by forming positively charged emulsion in comparison to the corresponding negatively charged formulation (Gershanik and Benita, **1996a**).

One of the advantages of SEDDS in relation to scale-up and manufacture is that they form spontaneously upon mixing their components under mild agitation and they are thermodynamically stable. The drawbacks of this system include chemical instabilities of drugs and high surfactant concentrations. The large quantity of surfactant in self-emulsifying formulations (30-60%) irritates GIT. Consequently, the safety aspect of the surfactant vehicle had to be considered. Moreover, volatile cosolvents in the conventional self-emulsifying formulations are known to migrate into the shells of soft or hard gelatin capsules, resulting in the precipitation of the lipophilic drugs. As an example of self-emulsification, Neoral® is composed of ethanol, corn oil mono-di-triglycerides, cremophor RH 40 and propylene glycol. It exhibits less variability and better drug uptake compared to Sandimmune®.

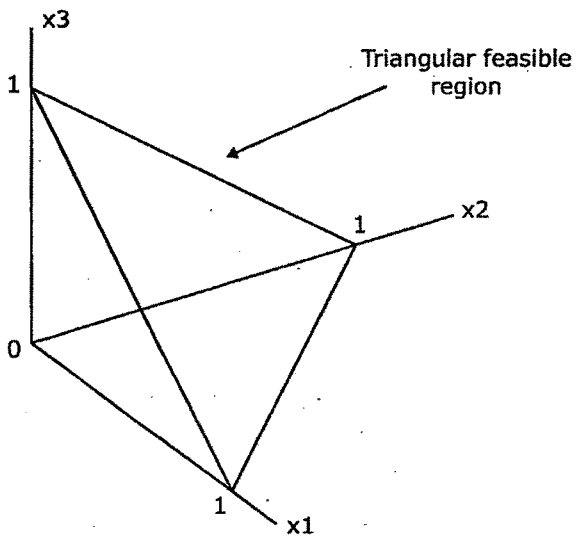
Table 1.1 Selected examples of self-emulsifying drug delivery systems (SEDDS).

Compound	Study Type	Formulation	Observations and comments
WIN 54954	In vitro emulsification, oral BA in dogs	Neobee-M5 / Tagat- TO	BA from SEDDS ≅ PEG 600, less variability with SEDDS
CCK_B receptor antagonist	In vitro assessment	Labrafil M 2125 Tween 80	Addition of drug to SEDD system altered droplet size distribution
CCK_B receptor antagonist	Oral BA in dogs	Labrafil M 2125 Tween 80	BA from SEDDS ≅ PEG 6004 conventional tablets
Ro 15-0778	Oral BA in dogs, physicochemical assessment	Neobee-N5/ Peanut oil	BA from SEDDS ≥ PEG 400. Tablet (crystalline drug). Drug release a function of polarity and emulsion droplet size

1.1.1. Formulation design of SEDDS

SEDDS are essentially mixtures of oil(s), surfactant and a cosurfactant and the properties of a mixture are always a function of the relative proportions of the ingredients rather than their absolute amounts. Therefore in experiments with mixtures, a factor's value is its proportion in the mixture, which falls between 0 and 1. The sum of the proportions in any mixture recipe is 1 (100%). Designs for mixture experiments are fundamentally different from those for screening. Screening experiments are orthogonal. Which means that, over the course of an experiment, the setting of one factor varies independently of any other factor. Figure 1.1 illustrates the experimental domain for design of SEDDS. The interpretation of screening experiments is simple, because the effects of the factors on the response are separable. With mixtures it is impossible to vary one factor independently of all the others. When you change the proportion of one ingredient, the proportion of one or more other ingredients must also change to compensate. Because the proportions sum to one, mixture designs have an interesting geometry. The feasible region for a mixture takes the form of a simplex. In present work Simplex Lattice Design was employed for the design of experiments. The simplex lattice design is a space-filling design that creates a triangular grid of runs. The design is the set of all combinations where the factors' values are i / m, where i is an integer from 0 to m such that the sum of the factors is 1.

Figure 1.1 Experimental domain for design of SEDDS.



1.1.2. Evaluation of SEDDS

Literature has proposed few methods for the characterization of the self-emulsifying performance of systems. Visual assessment is the one which may provide important information about the self-emulsifying properties of the mixture and about the resulting dispersion system. However more criteria are required for efficient SEDDS evaluation and comparison. Pouton proposed the estimation of the efficiency of self-emulsification by evaluation of the rate of emulsification and the particle size distribution. He used turbidity measurements to identify efficient self-emulsifying systems by establishing whether the dispersion reached equilibrium rapidly and in a reproducible time (Pouton, **1985a**). Shah et al pointed out the role of emulsion droplet polarity, in addition to droplet size, as an important emulsion characteristic (Shah, **1994**). The polarity of the oil droplets is governed by the HLB, the chain length and degree of unsaturation of the fatty acid, the molecular weight of the hydrophilic portion and the concentration of the emulsifier. Size of the emulsion droplet is considered to be a decisive factor in self- emulsification/dispersion performance, since it determines the rate and extent of drug release and absorption. Droplet/particle size is usually established by the photon correlation spectroscopy (PCS) method (Gershanik and Benita, **1996b,** Shah, **1994**). Efficient emulsification was arbitrarily defined by Shah et al., as a system which produces mean emulsion droplet diameter values of less than 5 μm. Further reduction of droplet size led to the development of SEDDS capable of forming thermodynamically stable, isotropic, clear o/w dispersions. Positively charged SEDDS recently developed by Gershanik and Benita introduced a new parameter for SEDDS characterization: the charge of the resulting droplets. The emulsion droplets resulting from the aqueous dilution of conventional SEDDS formed by traditional oil/non-ionic surfactant blend carry some negative charge, possibly provided by free fatty acids present in the mixture. Incorporation of a small amount of a cationic lipid, oleylamine [2.5-3%] into such a system reversed the charge nature, leading to the formation of emulsion droplets, which exhibit a positive -potential value of about 35-45mV. This positive potential value was also preserved after the incorporation of the model drug (Gershanik and Benita, **1996b**).

1.1.2.1. Literature cited for SEDDS as dissolution enhancer

Groves et al. have (Groves and De Galindez, **1976**) developed a method for measuring the rate of emulsification of oil – surfactant systems (which provided a correlation with a subjective assessment of self-emulsification). They also investigated the mechanism of self-emulsification (Groves and Mustafa, **1974,** Groves, *et al.*, **1974**). They found a relationship between the rapidity of emulsification and the formation of a liquid crystal phase on dilution of the oil – surfactant mixture with water. This suggested that efficient self-emulsification occurred when the lipid-based structure formed on initial uptake of water allowed facile penetration of water leading to rapid expansion of the oil-water interface.

Pouton developed a method for assessing both the rate of emulsification and the resulting particle size range formed from potential SEDDS formulations by assessing various combinations of Miglyol 812 or Miglyol 840 lipids (fractionated coconut oils) and Tween 85 (Pouton, **1985b**). The observations of these studies indicated the highly specific nature of the self-emulsification process and the need for individual selection of lipids, surfactants and their relative compositions.

Wakerley et al. screened a range of non-ionic surfactants and oils for self-emulsifying behaviour (Wakerly, *et al.*, **1986**). It was postulated that unsaturated ester-based surfactants were more efficient at forming self-emulsifying systems than the corresponding saturated ether-based surfactants with either a medium chain triglyceride lipid or arachis oil. Binary mixtures of Tagat TO and Miglyol 812 were studied in greater detail and efficient self-emulsification was demonstrated from mixtures containing 35 to 52.5% Tagat TO, with a minimum droplet size of 100–200 nm

Charman et al. formulated and evaluated a self-emulsifying formulation for the delivery of an investigational lipophilic anti-viral compound (WIN 54954) utilizing a medium chain triglyceride lipid and non-ionic surfactant (Charman, *et al.*, **1992**) at a constant surfactant concentration of 30% which was previously been reported to exhibit efficient self-emulsification (Pouton, **1985b,** Wakerly, *et al.*, **1986**). The effect of WIN 54954 inclusion on the self-emulsification of the lipid – surfactant mixture was investigated. Acceptable emulsions, where the mean emulsion droplet size was less than 3 μm, were produced by oil – surfactant mixtures containing up to 35% WIN 54954. Their observations demonstrated that substantial proportions of WIN 54954 could be successfully incorporated into a self-emulsifying mixture. Through the application of partial equilibrium phase diagrams it was demonstrated that a transparent liquid crystalline phase was formed when the oil/surfactant/WIN 54954 mixtures were equilibrated with up to 10% water for WIN 54954 concentrations as high as 25%, although at drug concentrations as high as 30–40% a turbid phase was formed. It was suggested that the application of phase diagrams were an important aspect for identifying the phase behaviour of the oil – surfactant – WIN 54954 mixtures, but that the overall efficiency of self-emulsification could not necessarily be predicted from such a study due to problems associated with assignment of the phases and the inability to ascribe self-emulsification to the formation of a particular phase.

The bioavailability of L-365 260 prepared as either a SEDDS formulation containing 56% Labrafil M2125 and 30% Tween 80, a tablet or suspension formulation and a PEG 600 formulation was assessed in dogs (Lin, *et al.*, **1991**). The Cmax and relative bioavailabilities of L-365 260 when administered as the SEDDS formulation were 7–8-fold higher than from the tablet or suspension formulations, although the plasma profiles after administration of the SEDDS formulation were similar to those observed after administration of a simple PEG 600 solution formulation. The reported data suggested that dissolution was most likely the limiting feature of solid L-365 260 formulations and that

both the lipid based SEDDS and solution PEG 600 formulation were able to effectively deliver the compound by avoiding this limitation, although by different mechanisms.

1.2. Liquisolids

Liquisolid systems are acceptably flowing and compressible powdered forms of liquid medications. According to the concept of liquisolid systems, liquid lipophilic drugs, or water-insoluble solid drugs dissolved in suitable nonvolatile solvents, may be converted into free-flowing and readily compressible powders by a simple admixture with selected powder excipients referred to as the carrier and coating materials. Various grades of microcrystalline or amorphous cellulose may be used as carriers, whereas very fine particle size silica powders may be used as coating materials. Based on the theory that the carrier and coating materials can retain only certain amounts of liquid and at the same time maintain acceptable flow and compression properties, a formulation-mathematical model was provided by (Spireas, **1988**) to calculate the optimum quantities of carrier and coating materials required to yield acceptably flowing and compressible liquid/powder admixtures.

The concept of powdered solutions was exploited to formulate drug solutions or liquid drugs in powders termed as liquisolid systems. A liquid drug or a poorly water-soluble solid drug dissolved in a suitable nonvolatile solvent can be converted into a dry, nonadherent, free-flowing, and readily compressible powder mass by its simple admixture with selected carrier and coating materials. This method does not involve drying or evaporation. It is well established that better bioavailability of a relatively water-insoluble drug is achieved when the drug is in solution form (Nelson, **1962**). That is why soft gelatin capsules of such drugs demonstrate higher bioavailability compared to the conventional oral solid dosage forms (Ebert, **1977**). The same principle governs powdered solutions and is solely responsible for their improved dissolution profiles. In this instance, even though the drug is in a tableted or encapsulated dosage form, it is held in solution thus enhancing its release (Spireas, **1988**). Several investigators have utilized the concept of powdered solutions to improve the dissolution profile of poorly water-soluble drugs (Liao, **1983,** Lin, **1986,** Sheth and Jarowski, **1990,** Spireas, **1988**). Lipophilic liquid drugs (e.g., chlorpheniramine and clofibrate) or solid drugs (e.g., prednisone, prednisolone, hydrocortisone, theophylline, polythiazide, and spironolactone) dissolved in nonvolatile, highboiling point solvent systems (e.g., polyethylene and propylene glycols, glycerin, N, N-dimethylacetamide, and various oils) have been formulated in powdered solutions by admixture with various carriers (e.g., celluloses) and coating materials (e.g., silicas). This technique has been reported to produce improved dissolution profiles as compared to the commercially available products. Liao (Liao, **1983**) proposed mathematical expressions for the calculation of the amount of excipients needed for powdered solution formulations. In this study, microcrystalline cellulose and silica were used as the carrier and coating material, respectively. The major drawback of this approach was that the final product exhibited poor and erratic flowability due to the inadequacy of the proposed model to

calculate the appropriate amount of excipients required to produce powder admixtures of acceptable and consistent flow properties. The purpose of the present article is to propose a theoretical model for the formulation of powdered solutions. Mathematical expressions based on powder properties and the fundamental principles and mechanism of powdered solutions are derived. A new physical property of powders, termed the flowable liquid-retention potential (Φ value), is introduced. It is shown that these mathematical expressions can be used to calculate the optimum amount of excipients required to yield free-flowing powdered solution formulations. The validity and applicability of the proposed relationships have been verified experimentally using clofibrate and prednisolone as test materials.

1.2.1. Theoretical considerations in liquisolid or powdered solution formulations

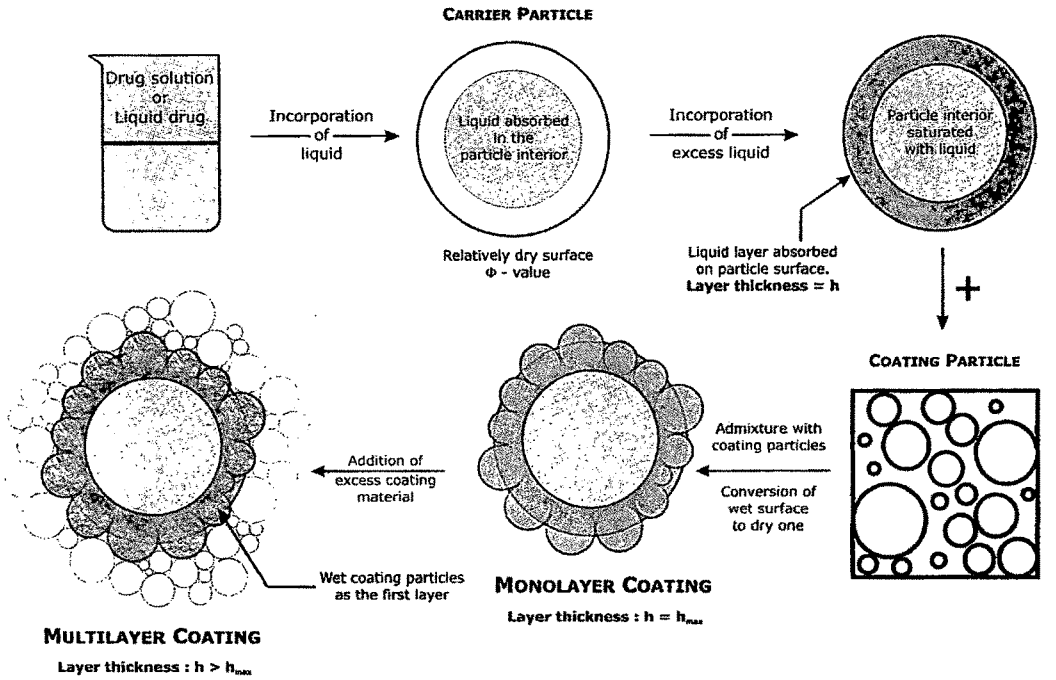
Flowable Liquid-Retention Potential (Φ, Value) of a Powder Absorption of a liquid by a powder material occurs when the absorbate molecules diffuse inside the absorbent and are eventually captured and held by the powder particles within their bulk. In some cases, the liquid is not truly absorbed, and instead of being dispersed throughout the interior of the solid, the liquid molecules only cling to its available surface, i.e., internal and external. This process is known as adsorption (Martin, *et al.*, **1983**). Sometimes, however, depending on the sorbent properties, both of these processes may occur simultaneously. The combined process is termed sorption. For instance, if a liquid is incorporated into a material which has a porous surface and closely matted fibers in its interior, e.g., cellulose, both absorption and adsorption take place. The liquid is initially absorbed in the interior of the particles captured by its internal structure, and after the saturation of this process, adsorption of the liquid onto the internal and external surfaces of the porous carrier particles occurs. One can generalize this liquid retention capacity of the powder material by referring to it as the total liquid-retention potential or "holding capacity" of the sorbent. The flowable liquid-retention potential (Φ value) of a powder material describes its ability to retain a specific amount of liquid while maintaining good flow properties. **Equation 1.1** shows the determination of Φ value which is defined as the maximum weight of liquid, W_{Liquid} that can be retained per unit weight of the sorbent, W_{Solid} yielding a mixture with acceptable flowability.

Equation 1.1

$$\Phi = \frac{W_{Liquid}}{W_{Solid}}$$

As the flowable liquid-retention potential of the carrier material is approached, the liquid is held entirely in the interior of the particles maintaining their surfaces relatively drier, thus yielding powders with acceptable flow properties. When the Φ value is exceeded, the interior of the particles becomes saturated, resulting in the formation of a liquid layer on the carrier particles' available surface which is depicted in Figure 1.2

Figure 1.2 Theoretical model of powdered solutions. When the weight of incorporated liquid per unit weight of carrier material exceeds the Φ value of the carrier material, a liquid layer is formed around the carrier particle which must be effectively covered by coating particles. Depending on the amount of coating material, the coating may be monolayered or multilayered.



For the clarity of theories proposed in this article, the following terms must be well distinguished. The term "interior of the particles" implies the solid bulk of the powder particles, which is assumed to be a homogeneous mass of closely packed material, excluding pores, that constitutes the solid intrastructure of each particle. The term "internal surface of the particles" implies surfaces created throughout the interior of the particles by the scattered penetrating pore network. Internal surface is a direct indication of the porosity of the material. The term "external surface of the particles" implies their outer surface, with which particles come in contact with each other. Therefore, the sum of internal and external surfaces is termed the total surface of the particle; and the total surface area per unit weight of the material represents its specific surface. Since internal and external surfaces of the particle are physically interconnected, the thickness of the liquid layer formed around them is assumed to be uniform.

1.2.2. Principle Hypothesis for the Mechanism of Powdered Solutions

A liquid drug or drug solution having a total volume V is incorporated into a carrier powder material. Depending on the holding capacity of the material, a part of the liquid, say, V_Φ is absorbed and retained in the interior of the carrier particles. This volume is dependent on the flowable liquid-retention potential (Φ) of the carrier material. The remaining liquid, v_L, is uniformly distributed and adsorbed onto the internal and external surfaces of the particles, forming a layer of certain thickness, h (Figure 1.2). Thus, mathematically, the volume distribution can be expressed by Equation 1.2.

Equation 1.2 $$V = V_\Phi + v_L$$

When a coating material, having a very small particle size, large specific surface, and high flowable liquid retention potential, e.g., silica, is added to such a mixture, its fine particles will cover the wet carrier material retaining the excess liquid, thereby maintaining acceptable flow properties. Eventually a dry, nonadherent, and free-flowing powder mixture will be produced. Depending on the amount of coating material required to yield such powdered solutions, the type of coating may be monolayer or multilayer (Figure 1.2). If only a specific volume (e.g., V) of liquid is incorporated into the carrier material, the liquid would be absorbed in the interior of the particles without significantly wetting their surface, and consequently, the powder would be dry and free-flowing. This portion of the liquid is represented by V since it depends on the flowable liquid-retention potential Φ, and the quantity, Q, of the carrier material used. Since $W_{Solid} = Q$ and $W_{Liquid} = V_\Phi \rho$, where ρ is the density of the liquid incorporated into the carrier material, Equation 1.1 can be expressed as Equation 1.3.

Equation 1.3 $$\Phi = \frac{V_\Phi \rho}{Q}$$

Equation 1.3 can be further rearranged to Equation 1.4.

Equation 1.4 $$V_\Phi = \frac{Q\Phi}{\rho}$$

1.2.2.1. Principle of Sufficient Coating

Since the coating should be sufficient to convert the wet surface of the carrier particles to dry surface, the volume V_L, of the adsorbed liquid must be retained by the coating particles while maintaining their free-flowing texture (

Figure 1.3). This means that the volume V_L, must be equal to a volume, v_ϕ, of the liquid which a quantity, q, of the coating particles can retain and with maintaining acceptable flowability. Therefore Equation 1.2 can be rewritten as

Equation 1.5 $$V = V_{\Phi} + v_{\phi}$$

According to definition, v_{ϕ} represents the same characteristics of the coating material as represented by V_{Φ}, for the carrier material in Equation 1.4. Using the same logic as was used in deriving Equation 1.3, it can be concluded that,

Equation 1.6 $$v_{\phi} = \frac{q\phi}{\rho}$$

Where ϕ is the flowable liquid retention potential of the coating material. Thus, v_{ϕ} is dependent on the flowable liquid retention potential, ϕ, and quantity, q, of the coating material.[1]

Substituting the values of V_{Φ} (Equation 1.4) and v_{ϕ} (**Equation 1.6**) in **Equation 1.5**,

Equation 1.7 $$V = \frac{(Q\Phi) + (q\phi)}{\rho}$$

Equation 1.7 can be rearranged in terms of Q (the quantity of the carrier material required to retain a specific volume V of liquid), as

Equation 1.8 $$Q = \frac{(V\rho) - (q\phi)}{\Phi}$$

Similarly Equation 1.7 can be rearranged in terms of q (the quantity of the coating material required to cover the wet carrier particles effectively), as

Equation 1.9 $$q = \frac{(V\rho) - (Q\Phi)}{\phi}$$

Excipient Ratio (R)

In some cases, however the dosage formulation may require a specific ratio of carrier / coating material in the final powder admixture. This ratio may be termed as the excipients ratio, R and written as

Equation 1.10 $$R = \frac{\text{Amount of carrier material}}{\text{Amount of coating material}} = \frac{Q}{q}$$

Combining Equation 1.7 and Equation 1.10 with a consideration of predetermined quantity, Q, of the carrier material,

[1] Capital letters, i.e., Q, V_{Φ}, Φ and A, represent the quantity, volume of liquid retained, flowable liquid retention potential and specific surface respectively of the carrier material, whereas lowercase letters q, v_{ϕ}, ϕ, and a, refer to the same values of the coating material.

Equation 1.11

$$V = \frac{Q[(R\Phi) + \phi]}{R\rho}$$

Solving Equation 1.11 for Q,

Equation 1.12

$$Q = \frac{V\rho R}{(R\Phi) + \phi}$$

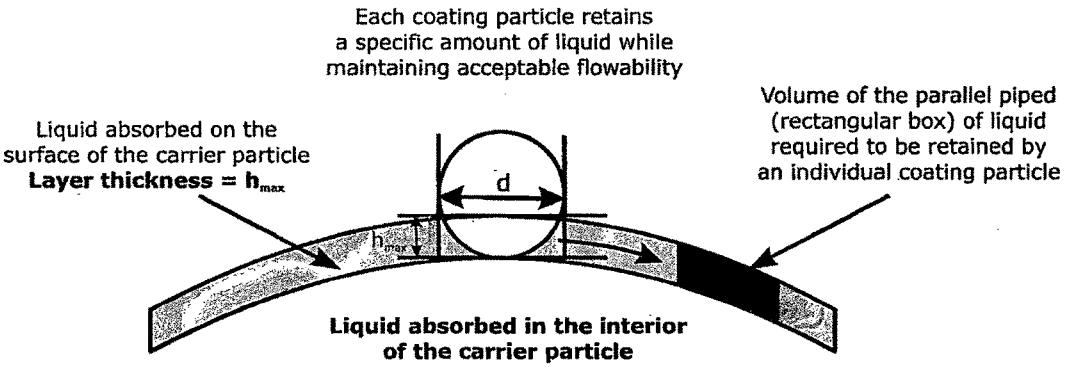
Similarly combining Equation 1.7 and Equation 1.10 with a consideration of predetermined quantity, q, of coating material and solving the equation for q,

Equation 1.13

$$q = \frac{V\rho}{(R\Phi) + \phi}$$

From Equation 1.12 and Equation 1.13 the quantity of carrier and coating material of desired liquid load can be calculated.

Figure 1.3 Diagrammatic representation of monolayer coating. The shaded box represents the portion of liquid that must be efficiently retained by a single coating particle.



1.2.3. Literature cited for liquisolid systems as dissolution enhancer

Being a patented technique much less literature has been cited by scientific community for development of liquisolid systems for commercial exploitation. However in academics point of view it is the technique that has to be further furnished for more ease in optimization of liquisolid tablet formulation. Use of different and modified excipients with different modes of mixing may result in better results.

Javadzadeh, Siahi-Shadbad, Barzegar-Jalali and Nokhodchi utilized piroxicam a poorly soluble, highly permeable drug with the rate of its oral absorption often controlled by the dissolution rate in the gastrointestinal for preparation of liquisolid systems. They investigated the dissolution behaviour of piroxicam from liquisolid compacts in simulated gastric fluid (SGF, pH 1.2) and simulated intestinal fluid (SIF, pH 7.2). Several liquisolid tablet formulations containing various ratios of drug : Tween 80 (ranging from 10% to

50% w/w) were prepared. The ratio of MCC (carrier) to silica (coating powder material) was kept constant in all formulations. The results showed that liquisolid compacts demonstrated significantly higher drug release rates than those of conventionally made (capsules and directly compressed tablets containing micronized piroxicam). This was due to an increase in wetting properties and surface of drug available for dissolution (Javadzadeh, *et al.*, **2005**).

Khaled, Asiri and El-Sayed evaluated the absorption characteristics of experimentally developed hydrochlorothiazide liquisolid tablets using six male beagle dogs. They compared the data with reference commercial tablets. The drug was administered orally as a single 25 mg dose of commercial and liquisolid tablets on two occasions in a randomized two-way crossover design. The pharmacokinetic parameters of the drug post intravenous dosing were reported for the first time. The results of the oral administration revealed statistically significant differences between the liquisolid and the commercial tablets in the area under the plasma concentration-time curve, the peak plasma concentration, and the absolute bioavailability. On the other hand, no significant differences were observed between the two formulations with regard to the mean residence time, the mean absorption time and the rate of absorption. The absolute bioavailability of the drug from the liquisolid tablets was 15% higher than that from the commercial one. The parametric 90% confidence intervals for the different parameters were higher than the commonly expected intervals for bioequivalency, indicating greater bioavailability of the liquisolid tablets (Khaled, *et al.*, **2001**).

Nokhodchi, Javadzadeh, Siahi-Shadbad and Barzegar-Jalali studied the solubility and dissolution behaviour of indomethacin (key determinants of its oral bioavailability). They prepared several formulations of liquisolid compacts containing various ratios of drug : propylene glycol (ranging from 1:1 to 1:4). In this study the ratio of microcrystalline cellulose (carrier) to silica (coating powder material) was 20 in all formulations. The dissolution behaviour of indomethacin from liquisolid compacts and conventional formulations was investigated at different pHs (1.2 and 7.2). The results showed that liquisolid compacts demonstrated considerably higher drug dissolution rates than those of conventionally made capsules and directly compressed tablets containing indomethacin. This was due to increased wetting properties and surface of drug available for dissolution. They inferred that the fraction of molecularly dispersed drug in the liquid medication of liquisolid systems was directly proportional to their indomethacin dissolution rates. They attempted to correlate the percentage drug dissolved in 10-min with the solubility of indomethacin in different vehicles. A plot of the percentage drug dissolved against the solubility of indomethacin showed that the amount of drug dissolved increased linearly (R^2 = 0.9994 and 0.996 at pH 7.2 and 1.2 respectively) with an increase in solubility of indomethacin in the vehicles. The liquisolid compacts technique can be a promising alternative for the formulation of water insoluble drugs, such as indomethacin into rapid release tablets (Nokhodchi, *et al.*, **2005**).

Spireas, Sadu and Grover studied the potential of liquisolid systems to improve the dissolution properties of water-insoluble agents using hydrocortisone as the model medication. The in vitro release patterns of this very slightly water-soluble corticosteroid, formulated in directly compressed tablets and liquisolid compacts, were studied at different dissolution conditions. The new formulation technique of liquisolid compacts was used to convert liquid medications such as solutions or suspensions of hydrocortisone in propylene glycol, a nonvolatile liquid vehicle, into acceptably flowing and compressible powders by blending with selective powder excipients. Several liquisolid tablet formulations were prepared using a new mathematical model to calculate the appropriate quantities of powder and liquid ingredients required to produce acceptably flowing and compressible admixtures. Due to their increased wetting properties and surface of drug available for dissolution, liquisolid compacts demonstrated significantly higher drug release rates than those of conventionally made, directly compressed tablets containing micronized hydrocortisone. The in vitro drug dissolution rates of liquisolid tablets were found to be consistent and independent of the volume of dissolution medium used, in contrast to the plain tablets which exhibited declining drug release patterns with decreasing dissolution volumes. It has been also shown that the fraction of molecularly dispersed drug in the liquid medication of liquisolid systems is directly proportional to their hydrocortisone dissolution rates (Spireas, *et al.*, **1998**).

Spireas, Wang and Grover depicted the effects of powder substrate composition on the *in vitro* release properties of methyclothiazide liquisolid compacts. The dissolution patterns of methyclothiazide when formulated in liquisolid tablets were also compared to those of commercial products. According to the new liquisolid technique, liquid medications such as solutions or suspensions of water-insoluble drugs in suitable nonvolatile liquid vehicles can be converted into acceptably flowing and readily compressible powders by a simple admixture with certain powder substrates, referred as carrier and coating materials. Enhanced release profiles may be exhibited by such systems due to the increased wetting properties and surface of drug available for dissolution. The release rates of such products were assessed using the USP dissolution test and were compared to those of their commercial counterparts. It was observed that maximum drug dissolution rates can be exhibited by systems that have powder substrates with optimum carrier-to-coating ratios. In addition, liquisolid tablets displayed significantly enhanced dissolution profiles compared to those of marketed products (Spireas, *et al.*, **1999**).

Grover, Spireas and Lau-Cam developed and validated a simple spectrophotometric procedure to indirectly assess the quantities of propylene glycol remaining in compressed liquid/powder admixtures. Such simplified quantitation may facilitate several testing procedures related to various aspects of formulation development and material testing of pharmaceutical powder excipients using various nonvolatile liquids as the diluents. In the present study, this new and simple approach for PG quantitation was developed as an integral part of a new method termed the liquisolid compressibility (LSC) test, used to characterize the compaction behavior of powder excipients. According to LSC testing,

several admixtures of a nonvolatile liquid (in this case PG) and a powder, differing in their PG/powder weight ratio, are compressed in order to assess their compactabilities. The PG content of such compacts may then be directly quantitated by the USP gas chromatographic method or, indirectly, by this new simple spectrophotometric procedure. The new approach involves the addition of a dye marker to the PG prior to its incorporation into the powder. After compression, the PG amount remaining in the compacts may be determined by simply extracting the dye from the tablets and analyzing the extracts spectrophotometrically. In this manner, the dye content thus obtained may be extrapolated to the respective net amount of PG originally added as a dye/PG solution to the powder. Statistical comparison of the results obtained from both methods revealed almost absolute correlation (Grover, *et al.*, **1998**).

1.3. Solid Dispersions

Solid dispersion was firstly introduced to overcome the low bioavailability of lipophilic drugs by forming of eutectic mixtures of drugs with water-soluble carriers (Sekiguchi and Obi, **1961**). The term 'solid dispersion' has been exploited to describe a family of dosage forms where the drug is dispersed in a biologically inert matrix, usually with a logical view of enhancing oral bioavailability. Figure 1.4 shows the Schematic representation of the bioavailability enhancement of a poorly water-soluble drug by solid dispersion compared with conventional tablet or capsule.

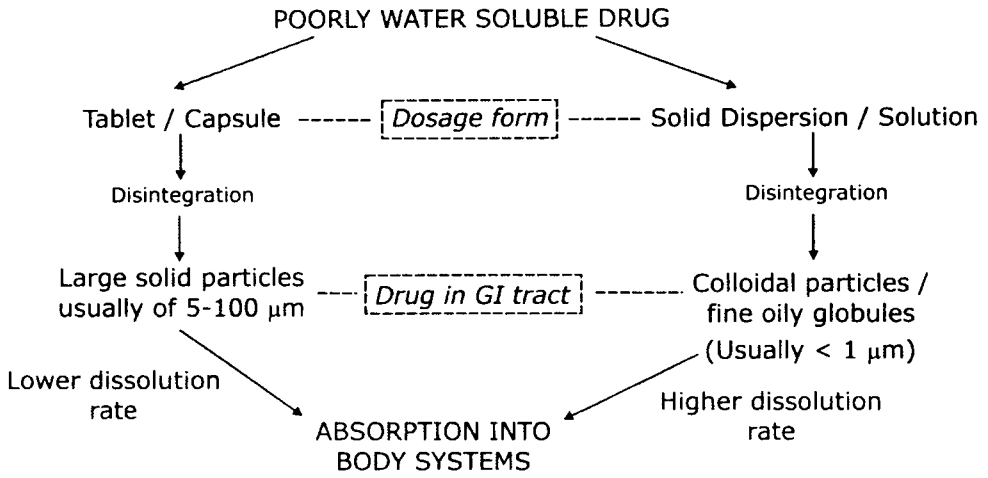
In practice, these dosage forms have been traditionally regarded as being synonymous with systems whereby the *in vitro* release of drug is enhanced when compared to conventional dosage forms, with concomitant implications for *in vivo* release. Furthermore, the carrier used has, again traditionally, been a water-soluble or water miscible polymer such as polyethylene glycol (PEG) or polyvinylpyrrolidone (PVP) or low molecular weight materials such as sugars. However, the proliferation of publications in the area since the first solid dispersions were described (Sekiguchi and Obi, **1961**) has led to a broadening of these definitions to include water insoluble matrices such as Gelucires and Eudragits that may yield either slow or rapid release or absorption.

Just as the broadness of the definition of solid dispersions they can exist in various forms. Table 1.2 illustrates the different types of solid dispersion based on their phase composition.

Table 1.2 Classification of solid dispersions based on their phase composition

Type	Characteristic
Eutectic mixture	Two or more crystalline phases
Solid solution	Single crystalline phase
Complex	Single amorphous or crystalline phase
Glass solution	Single amorphous phase
Amorphous suspension	Two partial or complete amorphous phases

Figure 1.4 Schematic representation of the bioavailability enhancement of a poorly water-soluble drug by solid dispersion compared with conventional tablet or capsule (Serajuddin, 1999).



Numerous reviews have appeared in the literature (Chiou and Riegelman, **1971b,** Craig, **1990,** Ford, **1986,** Serajuddin, **1999**) attempting to bring together the various publications and ideas associated with these dosage forms. The latest of these (Serajuddin, **1999**) gives details of some more recent approaches such as the use of surface active carriers and the use of melt-extrusion of PVP dispersions as a means of manufacturing viable dosage forms using this technology. One aspect of solid dispersion technology on which most workers in the field would agree is that the number of marketed products arising from this approach has been disappointing. The sheer simplicity of the solid dispersion manufacturing method, with the general fact that only drug and carrier are required, alongwith frequently reported improvements in both the dissolution rate and bioavailability would definitely make one expect that the transfer to the market place would be rapid and widespread. But the actual case is quite diverse, despite approximately 500 papers with different carrier polymers having been published on the subject (Leuner and Dressman, **2000**). The reason for such failure can be attributed a large extent to manufacturing and physical as well as chemical stability considerations (Craig, **2002,** Franco, *et al.*, **2001,** Serajuddin, **1999**). It is also argued that a primary reason for such scenario is poor predictability of solid dispersion behaviour due to the lack of a basic understanding of its properties. Only two commercial products, a griseofulvin in polyethylene glycol 8000 solid dispersion (Gris-PEG, Novartis) and a nabilone in povidone solid dispersion (Cesamet, Lilly) were marketed during the last four decades following the initial work of Sekiguchi and Obi. Table 1.3 shows Solubilizing carriers reported for enhancing drug solubility in solid dispersions.

Table 1.3 Solubilizing carriers reported for enhancing drug solubility in solid dispersions.

Solubilizing Carrier	Drug
PEG	Griseofulvin, Phenytoin, Prednisolone, Nortriptyline HCl, Piroxicam, Oxazepam, Fenofibrate, Ketoprofen, Glyburide, Nifedipine, Carbamazepine, Ibuprofen and Zolpidem.
PVP	Griseofulvin, Sulphathiazole, Hydrochlorothiazide, Carbamazepine, Fur, NSAIDs (Mefenamic acid, Azapropazone, Glafenin and Flotafenin), Oxodipine, Etoposide, Benidipine HCl, Atenolol, Piroxicam, Clofazimine, Lonidamine, CEL.
PVP/VA	Carbamazepine, Atenolol.
HPMC	Benidipine, Niluadipine, Albendazole.
PVM/MA	Griseofulvin, Clofazimine.
Crospovidone	FUR
Croscarmellose Na	Itraconazole
Sorbitol	Prednisolone
Mannitol	Triamterene
Lactose	Nitrazepam
Urea	Ofloxacin
Chitosan	Nifedipine
Gellita collagel	Oxazepam
Egg albumin	Mefenamic acid

1.3.1. Challenges

Past four decades have shown a great interest in solid dispersion design and development but its commercial utilization is very limited. Potential problems with solid dispersion are as,

1.3.2. The solid state structure.

It is still not clear how the drug is dispersed within the matrix in the majority of cases. Methods such as DSC, XRD and hot stage microscopy have been widely employed but the question as to whether the drug is present as a molecular, a crystalline particulate or an amorphous particulate dispersion is far from clear in the majority of cases. Fortunately, this issue has been studied in more detail in recent years, with techniques such FTIR, Raman spectroscopy and solid state NMR being employed in addition to the aforementioned methods, particularly to study the nature of the molecular interactions between the drug and the carrier in amorphous systems (Forster, *et al.*, **2001**, Matsumoto and Zografi, **1999**).

1.3.3. The mechanism by which dissolution enhancement occurs.

While a number of theories have been proposed the mechanism by which the dissolution rate is improved in relation to conventional dosage forms is not fully understood.

1.3.3.1. Drug release from solid dispersions

While a number of potential and realized advantages of solid dispersions have been described in the literature, the single most widely cited consideration is the improvement in dissolution rate, with concomitant implications for improving the bioavailability of poorly water-soluble drugs. Such improvements in dissolution rate are often considerable, with increases of up to four hundred fold having been reported. It is therefore all the more remarkable that the mechanism underpinning these increases is so poorly understood. This may be largely because there are comparatively few papers available whereby elucidation of the mechanism(s) involved is a specific objective (Craig, **2002**).

The currently accepted range of possible mechanisms of enhanced dissolution effectively emerges from the seminal review by Chiou and Riegelman (1971). These include the following:

1.3.3.2. Particle size reduction and reduced agglomeration

Since both are related to increase in the exposed surface area of drug these can be usefully considered together. Size reduction has been classically considered to be a result of eutectic or solid solution formation; it is worth noting that this mechanism suggests an intrinsic link between solid state structure and release. Similarly it has been suggested that the presentation of particles to the dissolution medium as physically separate entities may reduce aggregation. In addition, many of the carriers used for solid dispersions may have some wetting properties; hence it is suggested that improved wetting may lead to reduced agglomeration and hence increased surface area.

1.3.3.3. Increased solubility or dissolution rate of the drug

Carriers used are chosen in such way that they increase the solubility of the drug. This mechanism is under debate as solubility studies have indicated that at the concentrations used for *in vitro* experiments the carriers often elicit a minimal solubility increase. It is the foresight of the assumption that concentration of the carrier after complete dissolution in the water bath (e.g. 0.5 gm/L) may be used as a model of behaviour at dissolving surface. Similarly, in case of cyclodextrins carrier and drug may form a soluble complex. The evidence for this occurring with other carriers is feeble. Finally, changes to the physical properties of the drug such as degree of crystallinity and polymorphic form possibly will also be considered under this category.

Corrigan, Ford and Nystrom in the 1980s had influential papers which fetched this type of approach, though it has not yet been fully incorporated into the common parlance within the field, despite the possibilities for dissolution prediction that it appears to offer.

Corrigan provided a very valuable contribution by not only measuring the dissolution rate of the incorporated drug but also assessing that of the polymer itself (Corrigan, **1985, 1986**). The authors found that dissolution rate of the drug in the polymer and the polymer alone were in fact equivalent, leading to the suggestion of carrier-controlled dissolution whereby the dissolution rate of the drug is controlled by that of the inert carrier. It is also noted that the dissolution rates of a range of drugs in a single carrier, prepared under comparable conditions, were identical in most cases (Dubois and Ford, **1985**). This means that it is the dissolution rate of the carrier and not the drug that dominates the process. Craig and Newton indicated that a log-linear relationship existed between the molecular weight of the PEG carrier and the dissolution rate, implying that the properties of the polymer were dominating the dissolution process (Craig and Newton, **1992**).

1.3.4. Poor understanding of the *in vitro in vivo* correlation.

In vitro in vivo correlation (IVIVC) is a mathematical tool for gaining better understanding of drug absorption and its dependence on *in vitro* release processes (Cardot and Beyssac, **1993**). In the case of solid dispersions numerous studies have reported enhanced dissolution rates and absorption rates from solid dispersions the correlation between the two is not straightforward. It should also be born in mind that the literature tends to be success led, hence examples of poor absorption improvement are less likely to be brought to the scientific community's attention.

In spite of such scenario excellent linear correlations were obtained for several *in vitro in vivo* data of solid dispersion systems. A linear correlation was found between the amount of reserpine dissolved in 25 minutes from some of the drug/PVP test systems and the cumulative amount of reserpine equivalents excreted in the urine in either 4 or 48 hours (Stupak, *et al.*, **1974**) and between the amount of nitrofurantoin dissolved in acidic as well as basic medium after 30 and 90 minutes and the cumulative amount of unchanged drug excreted after 12 hours using solid dispersions of drug in PVP, PEG, or mannitol (Ali and A.S., **1984**). In the case of mebendazole/PVP complex, for the *in vivo* parameters related to the amount of absorbed drug (AUC and C_{max}), the best correlation was obtained with the *in vitro* characteristics related to solubility (C_s, T_m, (mean dissolution time)) (Daniel-Mwambete, *et al.*, **2004**). Good correlations were also obtained between T_{max} and log P and log k_w' (k_w' being the capacity factor determined by HPLC), the *in vitro* lipophilia / hydrophilia relation parameters.

Table 1.4 Comparison of *in vitro* and *in vivo* advantage with solid dispersions (Kaushal, *et al.*, **2004**).

Drug-Carrier System	Dissolution ratio	BA parameter	
		C_{max} ratio	AUC ratio
Mefenamic acid : Egg albumin (1:3)	6.00	2.77	2.13
dl-a-Tocopherol : Egg albumin (1:5)	10	1.30	1.15
Albendazole : HPMC : HPMCP (1:5:5)	8.00	1.14	1.42
ER-34122*: HPMC (1:1)	200.00	82.00	113.48
TAS-301* : Calcium silicate (1:2)	1.67	2.96	2.50
Lonidamine : PVP(1:9)	350.00	1.07	1.74
Lonidamine: PEG (1:9)	30.00	1.43	1.43
Mebendazole : PVP (1:20)	5.54	5.54	2.78

1.3.5. Method of preparation

More precisely, (Chiou and Riegelman, **1971b**), in their archetypal review, defined solid dispersions as 'the dispersion of one or more active ingredients in an inert carrier matrix at solid-state prepared by the melting (fusion), solvent or melting-solvent method', whereas (Corrigan, **1985**) suggested the definition as 'a product formed by converting a fluid drug-carrier combination to the solid state'. Preparation techniques for solid dispersions include fusion/melt method (Chiou and Riegelman, **1971a**, Sekiguchi and Obi, **1961**), hot melt extrusion (El-Egakey, *et al.*, **1971**), solution evaporation method (Tachibana and Nakamura, **1965**) and supercritical fluid technology (Juppo, *et al.*, **2003**) which yield a totally or partially amorphous drug present as a molecular or particulate dispersion within a carrier matrix.High melting temperature may chemically decompose drugs and carriers. No report addresses how much residual solvent is present in solid dispersions when different solvents, carriers or drying techniques are used.

1.3.5.1. Reproducibility of physicochemical properties

Various investigators observe that heating rate, maximum temperature used, holding time at a high temperature, cooling method and rate, method of pulverization and particle size distribution may influence the properties of solid dispersions prepared by the melting method. In addition, the nature of solvent used, ratios of drug/solvent or carrier/solvent, solvent evaporation method and rate may significantly affect the physicochemical properties of solid dispersions formed.

1.3.5.2. Dosage form development

Very few reports address the difficulty of pulverization and sieving of the solid dispersion. Solid dispersions are usually soft, tacky and with poor flow and mixing properties. Thus,

poor compressibility, drug-carrier incompatibility and poor stability of the related dosage forms are resulted.

1.3.5.3. Scale-up of manufacturing processes

Most of solid dispersions reported in literatures are prepared in lab-scale. The scale-up of the preparation methods is generally very challenging. The physicochemical properties and stability of solid dispersions may be affected by scale-up because heating and cooling rates of solid dispersion in large scale differ from small-scale. It is also not practical and high-cost to evaporate hundreds and even thousands of liters of organic solvents to prepare solid dispersion for kilogram quantities of drugs. Removal of residual toxic organic solvent may be difficult because the solid dispersions are usually amorphous and may exist in viscous and waxy forms.

1.3.6. Stability

The physical instability of solid dispersions due to crystallization of amorphous drugs is the subject of most published reports (Khalil and Mortada, **1978,** Vila Jato, *et al.*, **1984**). In a solid dispersion prepared by the melt method, a certain fraction of the drug may remain molecularly dispersed depending on its solubility in the carrier. The excess drug existing may greatly depend on the manufacture method. It may form a supersaturated solution, separate out as an amorphous phase or crystallize out. The supersaturated and amorphous forms may, in turn, crystallize out on aging. Certain carriers may also exist in thermodynamically unstable states in solid dispersions and undergo changes with time. As reported, polyvinyl pyrrolidone acts as stabilizer in the solid dispersion by retarding crystallization of drug at a low humidity. Hydrogen bonds between the drug and PVP restrain drug crystallization (Taylor and Zografi, **1997**).

1.3.6.1. Literature cited for solid dispersions as dissolution enhancer

Abd-el-Fattah, Boraie and Hassan prepared solid dispersions of hydrochlorothiazide in mannitol and in dihydroxypropyltheophylline by melting and solvent methods. For both systems, phase diagrams of simple eutectic type were obtained. A significant increase in dissolution rate was observed for 1:2 and 1:3 physical mixtures and solid dispersion as compared to pure drug. Solubility of hydrochlorothiazide in mannitol and in dihydroxypropyltheophylline solution at 27 ^{o}C and 37 ^{o}C was studied. At 37 ^{o}C the water solubility of the drug increased 3.7 times using 0.4 mol of dihydroxypropyltheophylline. The solubilization of the drug by dihydroxypropyltheophylline in water was due to the formation 1:1 soluble complex. Tablets from physical mixtures and solid dispersion were prepared (Abd el-Fattah, *et al.*, **1986**).

Arias, Gines, Moyano, Perez-Barrales, Vela and Rabasco designed project to substantiate further contention concerning the universality of the utilization of PEG polymers as matrix

carriers. They attempted to enhance the dissolution rate of triamterene, with the subsequent enhancement in its absorption rate, via solid dispersion using PEG 4000. The approach of solid dispersions was found useful for optimizing the pharmacokinetic of triamterene in rats (Arias, *et al.*, **1994**).

Arima, Yunomae, Miyake, Irie, Hirayama and Uekama showed the enhancing effects of cyclodextrins (CDs) on solubility, dissolution rate, and bioavailability of tacrolimus after oral administration to rats. They also compared the data with those after administration of a PROGRAF capsule containing the solid dispersion formulation of tacrolimus. Of the natural CDs, the solubility of tacrolimus increased in the addition of βCD, indicating that the cavity of βCD comfortably fitted the drug. Of the βCD derivatives, DM-βCD had the greatest solubilizing activity and gave phase solubility curve as defined by Higuchi and Connors, suggesting the formation of higher-order complexes. The result of Van't Hoff plot suggests that the enthalpy is dominant for the complexation of tacrolimus with DM-β-CD. The dissolution rate of tacrolimus was markedly augmented by the complexation with DM-β-CD, reflecting its solubilizing activity. An *in vivo* study revealed that DM-β-CD increased the bioavailability of tacrolimus with low variability in the absorption after oral administration of the tacrolimus suspension to rats. The present results suggest that DM-β-CD is particularly useful in designing oral preparations of tacrolimus with an enhanced bioavailability and a reduced variability in absorption (Arima, *et al.*, **2001**).

Aso, Yoshioka and Kojima determined the overall crystallization rates and mean relaxation times of amorphous nifedipine and phenobarbital in the presence of polyvinylpyrrolidone (PVP) at various temperatures to gain further insight into the effect of molecular mobility on the crystallization rates of amorphous drugs and the possibility of predicting stability from their molecular mobility. Nifedipine-PVP (9:1 w/w) and phenobarbital-PVP (95:5 w/w) solid dispersions were prepared by melting and rapidly cooling mixtures of each drug and PVP. The amount of amorphous nifedipine remaining in the solid dispersion was calculated from the heat of crystallization, which was obtained by DSC. The amount of amorphous phenobarbital remaining in the solid dispersion was estimated from the change in the heat capacity at its glass transition temperature T_G. The time required for the amount of amorphous drug remaining to fall to 10%, t_{90} was calculated from the profile of time versus the amount of amorphous drug remaining. The t_{90} values for the solid dispersions studied were 100-1000 times lesser than those of pure amorphous drugs when compared at the same temperature. Enthalpy relaxation of the amorphous drugs in the solid dispersions was reduced compared with that in the pure amorphous drugs, indicating that the molecular mobility of the amorphous drugs is reduced in the presence of PVP. The temperature dependence of mean relaxation time (τ) for the nifedipine-PVP solid dispersion was calculated using the Adam-Gibbs-Vogel equation. Parameters D and T_0 in the equation were estimated from the heating rate dependence of T_G. Similar temperature dependence was observed for t_{90} and τ values of the solid dispersion, indicating that the information on the temperature dependence of the molecular mobility, along with the crystallization data

obtained at around the T_G, are useful for estimating the t_{90} of overall crystallization at temperatures below T_G in the presence of excipients (Aso, *et al.*, **2004**).

Aso and Yoshioka prepared amorphous nifedipine-PVP and phenobarbital-PVP solid dispersions with various drug contents by melting and subsequent rapid cooling of mixtures of PVP and nifedipine, or phenobarbital. Chemical shifts and spin-lattice relaxation times of PVP, nifedipine, and phenobarbital carbons were determined by ^{13}C-CP/MAS NMR to elucidate drug-PVP interactions and the localized molecular mobility of drug and PVP in the solid dispersions. The chemical shift of the PVP carbonyl carbon increased as the drug content increased, appearing to reach a plateau at a molar ratio of drug to PVP monomer unit of approximately 1:1, suggesting hydrogen bond interactions between the PVP carbonyl group and the drugs. T(1) of the PVP carbonyl carbon in the solid dispersions increased as the drug content increased, indicating that the mobility of the PVP carbonyl carbon was decreased by hydrogen bond interactions. T(1) of the drug carbons increased as the PVP content increased, and this increase in T(1) became less obvious when the molar ratio of PVP monomer unit to drug exceeded approximately 1:1. These results suggest that the localized motion of the PVP pyrrolidone ring and the drug molecules is reduced by hydrogen bond interactions. Decreases in localized mobility appeared to be one of the factors that stabilized the amorphous state of drugs (Aso and Yoshioka, **2006**).

Chiou and Niazi studied the dissolution profile of the griseofulvin-succinic acid eutectic mixture system. The system was evaluated using the powder and constant-surface tablet methods. Factors contributing to the enhancement of griseofulvin dissolution from the dispersion in succinic acid were discussed. Contrary to the original proposal of Sekiguchi and coworkers, dissolution rates of driseofulvin from solid dispersions were found to be markedly affected by the particle size of solid dispersions (Chiou and Niazi, **1976**).

Chiou used the X-ray diffraction method to characterize physiochemical properties of griseofulvin dispersed in polyethylene glycol 4000 and 6000. Results indicated a negligible or very limited solid solubility of griseofulvin in the pulverized solid dispersions. Pulverization and aging had pronounced effects on the X-ray diffraction spectrum. Results from aqueous solubility studies of griseofulvin in various concentrations of polyethylene glycol 6000 further indicate weak or insignificant interactions between the drug and the carrier. Mechanisms were postulated to account for the reported marked enhancement of dissolution rates and oral adsorption of griseofulvin dispersed in these carriers (Chiou, **1977**).

Chokshi, Sandhu, Iyer, Shah, Malick and Zia studied characterization of the physical and viscoelastic properties of binary mixtures of drug and selected polymers to assess their suitability for use in the hot-melt extrusion (HME) process as a means to improve solubility by manufacturing either solid dispersion or solid solution. They selected indomethacin (INM) as a model drug. Based on comparable solubility parameters, the selected polymers were Eudragit EPO (EPO), PVP-VA copolymer, PVP K30 and poloxamer 188. The various

drug and polymer systems were characterized for thermal and rheological properties as a function of drug concentration to provide an insight into miscibility and processibility of these systems. From the thermal analysis studies, a single T_G was observed for the binary mixtures of INM/EPO, INM/PVP-VA, and INM/PVP K30, indicating miscibility of drug and polymer in the given ratios. In the case of mixtures of INM/Poloxomer 188, two melting endotherms were observed with decreasing drug melting point as a function of polymer concentration indicating partial miscibility of drug in polymer. As part of the rheological evaluation, zero rate viscosity ε_0 and activation energy ε_a was determined for the various systems using torque rheometer at varying shear rates and temperatures. The ε_0 for binary mixtures of drug and EPO, PVP-VA and PVP K30 were found to be significantly lower as compared to pure polymer, indicating disruption of the polymer structure due to miscibility of the drug. On the other hand, INM/P188 mixtures showed a higher ε_0 compared to pure polymer indicating partial miscibility of drug and polymer. With respect to ε_a, the mixtures of INM/EPO showed an increase in ε_a with increasing drug concentration, suggesting antiplasticization effect of the drug. These findings corroborated the thermal analysis results showing increase T_G for the various binary mixtures. The mixtures of INM/PVP-VA showed a decrease in the ε_a with the increasing drug concentration suggesting a plasticization effect of the drug. The understanding of thermal and rheological properties of the various drug/polymer mixtures help established the processing conditions for hot melt extrusion (such as extrusion temperatures and motor load) as well as provided insight into the properties of the final extrudates. Using the actual hot-melt processing, a model was developed correlating the zero rate viscosity to the motor load determined by rheological evaluation (Chokshi, *et al.*, **2005**).

Chowdary and Rao prepared solid dispersions of itraconazole (ITR) in lactose, microcrystalline cellulose (MCC), and three superdisintegrants (Primogel, Kollidon CL, and Ac-Di-Sol) and formulated them into tablets. Solid dispersions and tablets were investigated with an objective of enhancing the dissolution rate of ITR from tablet formulations. X-ray diffraction (XRD) and DSC were used to characterize the dispersions. A marked enhancement in the dissolution rate of ITR was observed with all the excipients. The order for the excipients to enhance the dissolution rate was Ac-Di-Sol > Kollidon CL > Primogel > MCC > lactose. Solid dispersions in superdisintegrants gave much higher rates of dissolution than the dispersions in other excipients. Ac-Di-Sol gave the most improvement (28-fold) in the dissolution rate of ITR at a 1:1 drug:excipient ratio. Solid dispersions in superdisintegrants could be formulated into tablets. These tablets, apart from fulfilling all official and other specifications, exhibited higher rates of dissolution and dissolution efficiency (DE) values. XRD indicated the presence of ITR in amorphous form in the dispersions. DSC indicated a weak interaction between ITR and the excipients. Micronization and conversion of the drug into the amorphous form and the fast disintegrating and dispersing action of the superdisintegrants contributed to the enhancement of the dissolution rate of ITR from its solid dispersions in superdisintegrants and their corresponding tablet formulations (Chowdary and Rao, **2000**).

Chutimaworapan, Ritthidej, Yonemochi, Oguchi and Yamamoto designed and developed solid dispersions of nifedipine (NP) with polyethylene glycols (PEG4000 and PEG6000), hydroxypropyl-beta-cyclodextrin (HP-βCD), and poloxamer 407 (PXM 407) in four mixing ratios by melting, solvent, and kneading methods in order to improve the dissolution of NP. The enhancement of the dissolution rate and the time for 80% NP dissolution T_{80}% depended on the mixing ratio and the preparation method. The highest dissolution rate and the T_{80}% as short as 15 min were obtained from PXM 407 solid dispersion prepared by the melting method at the mixing ratio of 1:10. The X-ray diffraction (XRD) patterns of solid dispersions at higher proportions of carriers demonstrated consistent with the results from DSC thermograms that NP existed in the amorphous state. The wettability and solubility were markedly improved in the PXM 407 system. The presence of intermolecular hydrogen bonding between NP and PEGs and between HP-β-CD and PXM 407 was shown by infrared (IR) spectroscopy (Chutimaworapan, *et al.*, **2000**).

Dannenfelser, He, Joshi, Bateman and Serajuddin evaluated different formulation approaches to ensure that the formulation of a poorly water soluble compound chosen during early development achieves optimum bioavailability. The insoluble compound has an aqueous solubility of 0.17 μg/mL at 25±1 ^{0}C, a relatively high permeability Caco2 P_{app} = $6.1x10^{-4}$ cm/min), and poor bioavailability in dogs (dry blend formulation). Based on the prediction by GastroPlus, the oral absorption of this compound is sensitive to its apparent solubility and particle size. The oral bioavailability of three different formulations was compared in a dog model: a cosolvent-surfactant solution, a solid dispersion in a mixture of polyethylene glycol 3350 and polysorbate 80, and a dry blend of micronized drug with microcrystalline cellulose. In absence of a parenteral injection, the bioavailability of the solution was considered to be 100%, and the relative oral bioavailability of the three formulations was 100, 99.1 and 9.8 respectively. Comparable bioavailability was obtained with the solid dispersion and the cosolvent-surfactant solution, both of which showed a 10-fold higher bioavailability than the dry blend. Thus, a 20 mg dose strength capsule containing the solid dispersion formulation was selected for clinical development. The selected solid dispersion system was physically and chemically stable for at least 16 months at 25 ^{0}C/60% RH. They also concluded that, the bioavailability of a poorly water soluble drug was greatly enhanced using the solid dispersion formulation containing a water soluble polymer with a surface active agent (Dannenfelser, *et al.*, **2004**).

Doherty and York hypothesized the dependence of the dissolution rate on the pH of the buffered medium, using constant surface area discs for crystalline frusemide, a semi-crystalline frusemide-PVP solid dispersion and an X-ray amorphous frusemide-PVP dispersion. The marked changes observed in the pH-dissolution profiles indicated that differing dissolution mechanisms operate in the amorphous regions. This conclusion was further supported by the comparison of pH-dissolution and pH-equilibrium solubility profiles that suggested a supersaturation effect to be the relevant term in describing the dissolution enhancing effects of amorphous regions. A marked dissolution enhancement, relative to crystalline frusemide, was shown by the X-ray amorphous solid dispersion in

weakly acidic solutions. A similar effect was observed in the dissolution characteristics of gelatin capsule formulations in simulated gastric and intestinal media. In a human bioavailability study, the X-ray amorphous frusemide-PVP solid dispersion exhibited a significant reduction in the time for maximum effect in comparison to crystalline frusemide and a semi-crystalline solid dispersion. This effect, demonstrated by the primary end organ response in seven healthy subjects, concurred with the in-vitro prediction of dissolution enhancement in weakly acidic media (Doherty and York, **1989**).

Gong, Viboonkiat, Rehman, Buckton and Darr utilized supercritical carbon dioxide (sc-CO_2) to prepare coprecipitates of indomethacin (IM) and PVP with the aim to improve the dissolution rate of IM. The coprecipitates of IM and PVP at various proportions were prepared using a stirred batch reactor containing sc-CO2 as a gas saturated solution (i.e. the compressible CO_2 is dissolved in the molten compound). Temperatures between 40 and 90 ^{o}C and pressure of 150 or 200 bar were employed. The coprecipitates prepared at 75 ^{o}C and 150 bar were characterized using DSC, XRPD, SEM (SEM) and dissolution testing. The results suggested that IM was totally amorphous at PVP weight fraction of 0.80 and above (as a molecular composite in which the drug molecules interacted with the polymer backbone). As the PVP weight fraction decreased, IM displayed an increasing amount of crystalline material. The SEM photographs of coprecipitates showed a foamed and porous structure. The dissolution rate of IM was increased by incorporation of PVP. IM and PVP at various weight fractions exhibited comparatively higher dissolution rates than that of crystalline IM alone. The sc-CO_2 based process produced a solvent free, completely amorphous porous IM solid dispersion with a rapid dissolution rate (Gong, *et al.*, **2005**).

Greenhalgh, Williams, Timmins and York reported interactions and possible incompatibilities in solid dispersions of hydrophobic drugs with hydrophilic carriers, with solubility parameters employed as a means of interpreting results. Systems containing ibuprofen (IB) and xylitol (XYL) in varying proportions and systems of IB with other sugars and a sugar polymer were produced using solvent evaporation and fusion methods. Additionally, bridging agents were employed with IB/XYL systems to facilitate the production of a solid dispersion. Results show that IB formed no interactions with any of the sugar carriers but interacted with all the bridging agents studied. The bridging agents were immiscible with XYL in the liquid state. Results of other reported drug/carrier systems and those from the systems studied in this paper were interpreted using Hildebrand solubility parameters. A trend between differences in drug/carrier solubility parameters and immiscibility was identified with incompatibilities evidence when large solubility parameter differences exist between drug and carrier. It was concluded that Hildebrand parameters give an indication of possible incompatibilities between drugs and carriers in solid dispersions, but that the use of partial solubility parameters may provide a more accurate prediction of interactions in and between materials and could provide more accurate indications of potential incompatibilities (Greenhalgh, *et al.*, **1999**).

Gupta, Goldman, Bogner and Tseng employed a combination of solid dispersion and surface adsorption techniques to enhance the dissolution of a poorly water-soluble drug, BAY 12-9566. In addition to dissolution enhancement, this method allowed compression of the granulated dispersion into tablets. Gelucire 50/13 (polyglycolized glycerides) was used as the solid dispersion carrier. Hot-melt granulation was performed to adsorb the melt of the drug and Gelucire 50/13 onto the surface of Neusilin US2 (magnesium alumino silicate), the surface adsorbent. Dispersion granules using various ratios of drug-Gelucire 50/13-Neusilin US2 were thus prepared. The dissolution profiles of BAY 12-9566 from the dispersion granules and corresponding physical mixtures were evaluated using USP Type II apparatus at 75 rpm with 0.1 N hydrochloric acid (HCl) and 1% w/v sodium lauryl sulfate (SLS) as dissolution medium. Dissolution of BAY 12-9566 from the dispersion granules was enhanced compared to the physical mixture. The dissolution of BAY 12-9566 increased as a function of increased Gelucire 50/13 and Neusilin US2 loading and decreased with increased drug loading. In contrast to the usually observed decrease in dissolution on storage, an enhancement in dissolution was observed for the dispersion granules stored at 40 ^{o}C/75% relative humidity (RH) for 2 and 4 weeks. Additionally, the flow and compressibility properties of dispersion granules were improved significantly when compared to the drug alone or the corresponding physical mixture. The ternary dispersion granules were compressed easily into tablets with up to 30% w/w drug loading. The extent of dissolution of drug from these tablets was greater than that from the uncompressed dispersion granules (Gupta, *et al.*, **2001**).

Hamaura and Newton gave indispensable information on the interaction between water and polymers for manufacturing solid dispersion of a drug by hot-melt extrusion because this interaction affected various properties of the water-polymer mixtures, such as their viscoelastic properties. In their study, polyvinylpyrrolidone K30 (PVP) containing 0%, 10%, and 20% polyethylene glycol 400 (PEG) was used as model amorphous polymers. The interaction of water with these polymers was assessed by the evaluation of the glass transition temperature (T_G), the point on the isotherm corresponding to the weight of sorbed water required to form a complete monolayer on the solid surface (apparent Wm), and the maximal amount of nonfreezing water, which were measured by *DSC* and water sorption isotherms. In all of the systems with a water content below a certain water fraction (0.1 for PVP, 0.12 for PVP-PEG 10%, and 0.16 for PVP-PEG 20%), the T_G values were successfully predicted using theoretical equations, whereas the experimental T_G values were higher than predicted for those with a water content above these water fraction levels. In addition, these values of water fraction were similar to the apparent Wm values determined using the Guggenheim-Anderson-DeBoer (GAB) equation (0.110, 0.117, and 0.147 weight fraction of water for PVP, PVP-PEG 10%, and PVP-PEG 20%, respectively). Nonfreezing water was detected above 0.47, 0.49, and 0.51 weight fraction of water for PVP, PVP-PEG 10%, and PVP-PEG 20%, respectively. Miscibility between water and PVP or PVP-PEG seemed to change according to the water content in the system. All parameters increase with the concentration of PEG in the sample. This was explained by

the fact that PEG has a larger number of polymer repeating units, which may therefore interact with water more than PVP (Hamaura and Newton, **1999**).

Imai, Nohdomi, Acarturk and Otagiri proposed the dissolution behavior and absorption of mefenamic acid following oral and rectal administration from drug:egg albumin solid dispersions in comparison with those of the drug alone. The interaction of drug with egg albumin in aqueous solution and solid state were examined by solubility analysis, dialysis experiments, and X-ray diffractometry. The results showed that the dissolution rate of mefenamic acid, and also the release of drug from witepsol H-15 suppositories, were significantly increased by using egg albumin:drug solid dispersions. Although egg albumin:drug solid dispersion enhanced the mean serum levels and the area under serum concentration-time curves after oral and rectal administration compared with those of the drug alone, no significant differences were found between the mean residence time values of drug and its solid dispersion. It was also noted that the extent of bioavailability of mefenamic acid and its solid dispersion following oral administration was significantly greater than that following rectal administration (Imai, *et al.*, **1991**).

Khan and Craig studied Gelucire 50/13 alone and solid dispersions in this material containing two model drugs (10% w/w caffeine and paracetamol) with a view to establish the mechanism underpinning changes in drug-release characteristics as a function of storage time and temperature. The lipid systems were fabricated into tablets and stored for up to 180 days at temperatures of 20 and 37 ^{o}C. The dispersions were studied using DSC, SEM, and dissolution testing. DSC studies indicated that the Gelucire 50/13 exists in two principal melting forms (melting points 38 and 43 ^{o}C) that undergo transformation to the higher melting form on storage at 37 ^{o}C. SEM studies indicated that the systems exhibit "blooming," with crystal formation on the surface being apparent on storage at both temperatures. The dissolution rate increased on storage, with the effect being particularly marked at higher storage temperatures and for the paracetamol systems. However, whereas these changes corresponded well to those seen for the morphology, the correlation between the changes in dissolution and those of the DSC profiles was poor. The study suggested a novel explanation for the storage instability of Gelucire 50/13 whereby the change in dissolution was not associated with molecular rearrangement as such but with the gross distribution of the constituent components, which in turn altered the physical integrity of the lipid bases (Khan and Craig, **2004**).

Khougaz and Clas investigated the effects of polyvinylpyrrolidone (PVP) molecular weight, composition, and content on the crystallization of a model drug, MK-0591 (Form I). Solid dispersions of crystalline MK-0591 with PVP homopolymers of different molecular weights (2500 x 10^6 g/mol) and with a copolymer containing polyvinyl acetate (PVA), (PVP/VA, 60:40, 5.8 x 10^4 g/mol) were prepared by the solvent method. MK-0591 in the solid dispersions was found to be X-ray amorphous. One glass transition temperature T_G was observed suggesting drug-polymer miscibility. The T_G values were higher than predicted by the Gordon-Taylor equation, indicating drug-polymer interactions. The extent of

crystallization inhibition increased with PVP molecular weight and, for a comparable PVP molecular weight, the homopolymer was more effective in the crystallization inhibition of the drug than the copolymer. The first onset temperature of crystallization $Tc_{(obs)}$ increased with polymer content. The $Tc_{(obs)}$ values (normalized to polymer content) were a function of the difference between the T_G of the polymer and drug. For PVP K-90, K-30, and K-17 dispersions, the $Tc_{(obs)}$ values increased proportionally to the T_G of the dispersions. However, for PVP K-12 and PVP/VA, the increase in $Tc_{(obs)}$ values corresponded to a small decrease in the T_G values of the dispersions. This result suggested that additional factors other than the reduction in mobility affect the crystallization behavior of MK-0591 in the solid dispersions, such as specific interactions. By Fourier transform-infrared spectroscopy, changes in the carbonyl-stretching band of PVP in the solid dispersions were observed. The existence of an ion-dipole interaction between COO^-Na^+ of the drug and the cyclic amide group of PVP was postulated (Khougaz and Clas, **2000**).

Kushida, Ichikawa and Asakawa attempted several formulation approaches to improve the dissolution and the oral absorption of ER-34122, which is a novel dual 5-lipoxygenase/cyclooxygenase inhibitor with potent anti-inflammatory activity. The solid dispersion of ER-34122 with hydroxypropylmethylcellulose (TC-5RW), an inert solid carrier, resulted a significant improvement in the dissolution rate of ER-34122. The solid dispersion was prepared by a solvent evaporation method using ethanol and water. The solid-state characteristics of the solid dispersion, the corresponding physical mixture, and ER-34122 alone were investigated by XRPD, FTIR and an automated controlled-atmosphere microbalance. The XRPD patterns suggested that the solid dispersion existed in a totally amorphous state and the others existed in crystalline state. The FTIR spectra results suggested that ER-34122 can interact with TC-5RW through intermolecular hydrogen bonding in the solid dispersion. This interaction may cause a stabilization of ER-34122 in the higher-energy, faster-dissolving amorphous state. The dissolution rate of ER-34122 from the solid dispersion was significantly greater than that from the physical mixture or the pure drug. Furthermore, when orally administrated to beagle dogs, ER-34122 showed about a 100-fold increase in both maximum concentration C_{max} and area under the curve of concentration versus time (AUC) compared with the pure drug. Consequently, it was determined that the solid dispersion technique with TC-5RW provides a promising way to increase the dissolution rate and the oral absorption of poorly water-soluble drugs such as ER-34122 (Kushida, *et al.*, **2002**).

Law et. al. performed a systematic study of the properties of ritonavir and the influence of PEG 8000 on ritonavir. They revealed that amorphous ritonavir dispersions in PEG would have an improved dissolution profile and could exhibit long-term stability. Ritonavir, a human immunodeficiency virus (HIV) protease inhibitor, is highly lipophilic [distribution coefficient (log D) = 4.3, 25 ^oC, pH 6.8], poorly water soluble (400 µg/mL in 0.1 N HCl, 1 ± µg/mL at pH 6.8, 37 ^oC), and exhibited an exceedingly slow dissolution rate (0.03 $mg/cm^2/min$ in 0.1 N HCl at 37 ^oC). These properties indicated that a solid dispersion containing ritonavir might be useful for overcoming problems associated with slow

dissolution. In addition, ritonavir has good glass former [glass-transition temperature T_G melting point, Tm > 0.7]. Amorphous ritonavir had an apparent solubility of 4 mg/mL in 0.1 N HCl at 37 ^{o}C and showed reasonable stability at 25 ^{o}C. Amorphous ritonavir had properties desirable for preparing a solid dispersion containing this phase. Since PEG, a commonly used polymer, improved the aqueous solubility of crystalline ritonavir, it was expected to have a positive influence on the dissolution rate of ritonavir. Moreover, PEG was found to have negligible plasticizing effect on amorphous ritonavir, which was beneficial for the stability of the dispersion. Solid dispersions of amorphous ritonavir in PEG were prepared, and these dispersions had improved *in vitro* dissolution rate and were physically stable for > 1.5 years at 25 ^{o}C when protected from moisture. The performance of this solid dispersion has been attributed to the physicochemical properties of amorphous ritonavir. *In vivo* study results indicate that amorphous solid dispersions containing 10-30% drug exhibited significant increases in area under the curve of concentration versus time (AUC) and maximum concentration C_{max} over crystalline drug. 10% amorphous dispersion exhibited increases of 22 and 13.7 fold in AUC and C_{max} respectively. Both *in vitro* dissolution and bioavailability decreased with increasing drug load, which led to the construction of a multiple Level C *in vitro in vivo* relationship for this Class IV compound (Law, *et al.*, **2001,** Law, *et al.*, **2004,** Law, *et al.*, **2003**).

Law, Wang, Schmitt, Qiu, Krill and Fort postulated that Polyethylene glycol or PEG is an ideal inactive component for preparing simple binary eutectic mixtures because of its low entropy of fusion (approximately 0.0076 J/mol˙K), lower melting point (approximately 62 ^{o}C) compared to most pharmaceuticals, miscibility with drugs at elevated temperatures, and its covalent crystalline lattice. Implication of these physicochemical properties on eutectic crystallization and size reduction of the drug is discussed. Enhancement of the dissolution rate of a poorly soluble compound through the formation of PEG-drug eutectics was investigated using fenofibrate. Solid dispersions of PEG-fenofibrate when characterized revealed that PEG and fenofibrate form a simple eutectic mixture containing 20-25% (w/w) fenofibrate at the eutectic point. Eutectic crystallization led to the formation of an irregular microstructure in which fenofibrate crystals were found to be less than 10 mm in size. Dissolution rate improvement of fenofibrate was correlated with the phase diagram, and the amount of fenofibrate released from the dispersions that contained fenofibrate as a eutectic mixture was at least 10-fold higher compared to untreated fenofibrate. On aging, the dissolution rate of the dispersion containing 15% (w/w) fenofibrate in PEG remained unaltered. The results indicate that PEG-drug eutectic formation is a valuable option for particle size reduction and subsequent dissolution rate improvement (Law, *et al.*, **2003**).

Liu and Desai studied dissolution rate enhancement of valdecoxib using its solid dispersions (SDs) with polyethylene glycol (PEG) 4000. The phase solubility behavior of valdecoxib in the presence of various concentrations of PEG 4000 in water was obtained at 37 ^{o}C. The solubility of valdecoxib increased with increasing amount of PEG 4000 in water. Gibbs free energy values were all negative, indicating the spontaneous nature of

valdecoxib solubilization, and they decreased with increase in the PEG 4000 concentration, demonstrating that the reaction conditions became more favorable as the concentration of PEG 4000 increased. The SDs of valdecoxib with PEG 4000 were prepared at 1:1, 1:2, 1:5, and 1:10 (valdecoxib: PEG 4000) ratio by melting method. Evaluation of the properties of the SDs was performed by using dissolution, Fourier-transform infrared (FTIR) spectroscopy, DSC, XRPD, and SEM studies. The SDs of valdecoxib with PEG 4000 exhibited enhanced dissolution rate of valdecoxib, and the rate increased with increasing concentration of PEG 4000 in SDs. Mean dissolution time (MDT) of valdecoxib decreased significantly after preparation of SDs and physical mixture with PEG 4000. The FTIR spectroscopic studies showed the stability of valdecoxib and absence of well-defined valdecoxib-PEG 4000 interaction. The DSC and XRD studies indicated the amorphous state of valdecoxib in SDs of valdecoxib with PEG 4000. The SEM pictures showed the formation of effective SDs of valdecoxib with PEG 4000, since well-defined changes in the surface nature of valdecoxib, SDs, and physical mixture were observed (Liu and Desai, **2005**).

Lloyd, Craig and Smith studied the melting behavior of paracetamol and polyethylene glycol (PEG) 4000, both individually and as binary systems using *DSC*. The appearance of the PEG peaks was shown to be highly dependent on scanning rate, with evidence for the existence of once-folded and extended chain forms being noted at slower scanning speeds. The melting peak of paracetamol was found to be profoundly influenced by the presence of the PEG 4000; when observed at all, the endotherm became broader and occurred at a lower temperature on mixing with the polymer. The thermal behavior of the binary mixes was again highly dependent on scanning rate, with faster rates leading to the appearance of the paracetamol peak at lower concentrations. The mixes were then thermally cycled to mimic production of solid dispersions, showing that the temperature cycling of the PEG 4000 could result in binary melting with the paracetamol peak disappearing (Lloyd, *et al.*, **1997**).

Maulding studied the dissolution rates of a number of drug-urethan solid-state dispersion systems. A marked enhancement of the initial dissolution rates of several poorly water-soluble drugs was found when they were incorporated into a urethan matrix by heat fusion. These differences were considerable when pure substances such as griseofulvin, hydrocortisone, chloramphenicol, and acetaminophen were compared to the urethan-drug solid dispersion. Physical mixtures of the medicinal agents with urethan also gave a marked increase in the amount of drug in solution, with the value in most cases being over one-half that of the solid-state dispersion. Data are given, comparing ultrafiltration with samples filtered through cotton, regarding drug content remaining in solution (Maulding, **1978**).

Miyazaki, Yoshioka, Aso and Kojima studied the inhibition of crystallization of amorphous acetaminophen (ACTA) by polyvinylpyrrolidone (PVP) and polyacrylic acid (PAA) using amorphous solid dispersions prepared by melt quenching. Co-melting with PVP and PAA decreased the average molecular mobility, which was indicated by increases in glass

transition temperature and enthalpy relaxation time. The ACTA/PAA dispersion exhibited much slower crystallization than the ACTA/PVP dispersion with a similar glass transition temperature value, indicating that interaction between ACTA and polymers also contributed to the stabilizing effect of these polymers. The carboxyl group of PAA may interact with the hydroxyl group of ACTA more intensely than the carbonyl group of PVP does, resulting in the stronger stabilizing effect of PAA. Dielectric relaxation spectroscopy showed that the number of water molecules tightly binding to PVP per monomer unit was larger than that to PAA. Furthermore, a small amount of absorbed water decreased the stabilizing effect of PVP, but not that of PAA. These findings suggest that the stronger stabilizing effect of PAA is due to the stronger interaction with ACTA. The ability of PAA to decrease the molecular mobility of solid dispersion was also larger than that of PVP, as indicated by the longer enthalpy relaxation time (Miyazaki, *et al.*, **2004**).

Moneghini, Kikic, Voinovich, Perissutti and Filipovic-Grcic applied the attractive technique of supercritical fluid to the preparation of solvent-free solid dispersions. In particular, the gas antisolvent crystallisation technique (GAS), using supercritical carbon dioxide as processing medium, was considered to prepare dosage form with an enhanced release for the poorly soluble carbamazepine, employing PEG 4000 as a hydrophilic carrier. The physical characterisation of the systems using laser granulometer, XRPD, thermal analyses, and SEM was carried out in order to understand the influence of this technological process on the physical status of the drug. The results of the physical characterization attested a substantial correspondence of the solid state of the drug before and after treatment with GAS technique, whereas a pronounced change in size and morphology of the drug crystals was noticed. The dramatic reduction of the dimensions and the better crystal shape, together with the presence of the hydrophilic polymer determined a remarkable enhancement of the *in vitro* drug dissolution rate (Moneghini, *et al.*, **2001**).

Murali Mohan Babu, Prasad Ch and Ramana Murthy employed a recently developed excipient, Modified gum karaya (MGK) for dissolution enhancement of poorly soluble drug, nimodipine (NM). The advantages of MGK over the parent gum karaya (GK) were illustrated by differences in the *in vitro* dissolution profiles of respective solid mixtures prepared by co-grinding technique. The influence of process variable, such as polysaccharide concentration and method of preparation of solid mixture on dissolution rate was studied. Solubility studies were also performed to explain the differences in dissolution rate. Solid mixtures were characterized by DSC, XRD and SEM. The dissolution rate of NM was increased as the MGK concentration increased and optimum ratio was found to be 1:9 w/w ratio (NM:MGK). It is found that method of preparation of solid mixtures was significantly effected the dissolution rate of NM from solid mixtures. The order of method of preparation in according to their dissolution efficiency was physical mixture < co-grinding mixture < swollen carrier mixture < kneading mixture (water as kneading agent) < kneading mixture (70% v/v ethanol as kneading agent) <solid dispersion. Though, the solid mixtures prepared by other methods like solid dispersion,

swollen carrier mixture and kneading technique gave faster release, co-grinding mixture prepared in 1:9 w/w ratio (NM:MGK) was found to exhibit a significant improvement in dissolution rate without requiring addition of organic solvents or high temperatures for its preparation and the process is less cumbersome. Hence, co-grinding technique appears to be easier and the most convenient method from a practical point of view (Murali Mohan Babu, *et al.*, **2002**).

Nagarsenker, Meshram and Ramprakash studied Ketorolac, a non-steroidal anti-inflammatory drug, with strong analgesic activity for dissolution enhancement. The study described the formulation of solid dispersions of ketorolac using hydroxypropyl beta-cyclodextrin (HPBCD) and beta-cyclodextin (BCD) as carriers, to improve the aqueous solubility of the drug, thus enhancing its bioavailability. Also, reduction in ulcerogenicity was anticipated. *DSC* and X-ray diffraction studies indicated loss of crystalline nature of the drug, in the dispersions prepared with HPbeta-CyD. NMR studies revealed a strong interaction between drug and HPbeta-CyD. Solid dispersions of drug with beta-CyD retained the crystalline nature of the drug. All the solid dispersions showed a remarkable improvement in the rate and extent of dissolution of ketorolac. The kneaded dispersion with HP-β-CD prepared using a 1:1 alcohol-water mixture showed promise in reducing the ulcer-inducing effect of ketorolac in rats. Oral administration of this dispersion was found to inhibit carrageenan-induced paw oedema in rats to a significantly greater extent compared with ketorolac or its trometamol salt. Though βCD as a carrier for ketorolac gave faster release of the poorly soluble drug, HP-βCD proved to be superior to βCD, as a carrier in the kneaded dispersion prepared using 1:1 alcohol-water mixture. These results suggest that solid dispersions of ketorolac with HP-βCD aid in faster dissolution and better bioavailability of the drug. The higher solubility of the drug in the presence of HP-βCD also reduces local gastrointestinal side-effects of the drug (Nagarsenker, *et al.*, **2000**).

Nang, Cosnier, Terrie and Moleyre improved dissolution of a poorly water-soluble experimental antianginal drug by solid dispersion preparation. Its solubility decreased with rising chloride ion concentration and biological responses in dogs varied with the gastrointestinal administration site. A correlation seemed to exist between the apparent solubility and the heart rate activity (Nang, *et al.*, **1977**).

Ozdemir and Ordu prepared the solid dispersions of furosemide, a substance that is poor-soluble in water, with polyethylene glycol 6000, 10,000 and 20,000 with the aim of enhancement of the dissolution rate of furosemide. Solid dispersions were prepared by the fusion method in proportions of 1:4, 1:6 and 1:10 (active material/polymer). The formation of solid dispersion was tested by the techniques of X-ray diffraction, differential calorimetry (DSC) and infrared spectroscopy (IR). The release rate of active material from the solid dispersions prepared was examined by using the flow through cell method. Also, the effect of particle size of the complexes obtained, on the dissolution rate and the stabilities of these complexes were studied. It was determined that the dissolution rate of furosemide was markedly increased along with the formation of the complex and that a

better dissolution profile was obtained even in the physical mixtures prepared for the purposes of comparison. It was found that the molecular weights of different kinds of polyethylene glycols and the various proportions of active material/polymer complexes as well as the particle sizes of the solid dispersions were not efficient in the release rate of active material. It was concluded that the increase of the dissolution rate was being a result of both wettability and solubility enhancing effects of polyethylene glycols (Ozdemir and Ordu, **1997**).

Pan, Chen and Chen prepared solid dispersion systems of water-insoluble piroxicam in polyethylene glycol (PEG) 4000 and in urea by fusion and solvent methods and were characterized. The *in vitro* dissolution studies showed that the dispersion systems containing piroxicam and PEG4000 or urea gave faster dissolution than the corresponding simple mixtures. The DSC study indicated that the piroxicam-PEG system prepared by the fusion method is a solid dispersion, while the piroxicam-urea system prepared by the solvent method was likely to be a solid solution of piroxicam in urea. The storage testings showed that all dispersions were stable, except that uptake of water during storage may occur in the PEG system. A single-dose study with rabbits showed that the dispersion systems provided statistically significant to a higher extent and rate of bioavailability than the corresponding physical mixture ($p<0.05$) (Pan, *et al.*, **2000**).

Paradkar, Ambike, Jadhav and Mahadik studied solid dispersion systems of Curcumin, a naturally occurring highly lipophilic molecule having wide range of pharmacological activities. Solid dispersions of curcumin in different ratios with PVP were prepared by spray drying. Physical characterization by SEM, IR, DSC, and XRPD studies, in comparison with corresponding physical mixtures revealed the changes in solid state during the formation of dispersion and justified the formation of high-energy amorphous phase. Dissolution studies of curcumin and its physical mixtures in 0.1N HCl showed negligible release even after 90 min. Whereas, solid dispersions showed complete dissolution within 30 min. It was concluded that this increase in dissolution may aid in improving bioavailability and dose reduction of the drug (Paradkar, *et al.*, **2004**).

Prabhu, Brocks and Betageri improved the dissolution properties of a poorly water soluble and bioavailable drug, ethopropazine HCl (ET), by incorporating the drug in three different types of solid dispersion systems. Solid dispersions of ET were prepared using 1:1 (w/w) ratios of phospholipid (1,2-dimyristoyl-sn-glycerophosphocholine) (DMPC), PEG 8000 and a novel combination of both DMPC and PEG 8000. Using the solvent method of preparation, ET and DMPC and/or PEG were dissolved in chloroform, and solvent subsequently was evaporated using nitrogen gas. The resulting solid dispersions were passed through a 60-mesh sieve. Characterization of ET/DMPC solid dispersion was performed by DSC and XRD studies. They conducted dissolution studies in phosphate buffered saline (PBS) (pH 7.4, $37^{\circ}C \pm 0.5^{\circ}C$) using the USP type II (paddle) dissolution apparatus showed significant increases in the dissolution rate of ET with all the solid dispersions in this study. Specifically, within the first 5 min (D5), solid dispersions containing ET/DMPC (1:1) showed

an eightfold increase in dissolution; in combination with DMPC and PEG 8000 (1:1), there was an approximately six folds increase; and a four fold increase was observed with PEG 8000 (1:1). Complete dissolution of all solid dispersions occurred within 60 min (D60) of the run. Storage of the ET/DMPC sample for over 4.5 months revealed a decrease in the dissolution rate when compared to freshly prepared sample. Overall, it was concluded that the dissolution rate of ET significantly improved when dispersed in all the selected carrier systems. However, the solid dispersion of ET/DMPC was observed to be superior to the other combinations used (Prabhu, *et al.*, **2001**).

Sethia and Squillante formulated solid dispersions of carbamazepine (CBZ) by supercritical fluid processing (SCP) and conventional solvent evaporation in PEG 8000 with either Gelucire 44/14 or vitamin E TPGS NF (d-α-tocopheryl PEG 1000 succinate). Formulations were evaluated by dissolution, SEM, XRPD, and DSC studies whereas excipient cytotoxicity in Caco-2 cells was by MTS [3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium, inner salt] assay. CBZ release was enhanced from supercritical fluid-treated CBZ and the CBZ/PEG 8000 (1:5), CBZ/PEG 8000/TPGS or Gelucire 44/14 (1:4:1) solid dispersions. The radically altered morphologies of SCP samples seen by SEM suggested polymorphic change that was confirmed by the X-ray diffraction and *DSC*. Disappearance of the characteristic CBZ melting peak indicated that CBZ was dissolved inside the carrier system. Polymorphic change of CBZ during SCP led to faster dissolution. Therefore, SCP provides advantages over solid dispersions prepared by conventional processes.

They also studied improvement in the CBZ bioavailability of solid dispersions along with the elucidation of the mechanism of improved absorption. Directional transport through Caco-2 cell monolayers was determined in the presence and absence of TPGS. Cell viability in presence of various concentrations of amphiphilic carriers was seen. *In vivo* oral bioavailability was determined in rats. The apparent intrinsic dissolution rates (IDR) of both conventional- and SCF-CBZ/PEG 8000/TPGS solid dispersions were increased by 13 and 10.6 fold, respectively, relative to neat CBZ. CBZ was not a substrate of P-glycoprotein. Higher CBZ permeability was seen in presence of 0.1% TPGS. Cell viability studies showed significant cytotoxicity only at or above 0.1% amphiphilic carrier. Supercritical treated formulation (without amphiphilic carrier) displayed oral bioavailability on par with those conventional solid dispersions augmented with amphiphilic carriers. An *in vitro-in vivo* correlation was seen between IDR and the AUC of the various CBZ solid dispersions. Bioavailability of CBZ was more a function of dissolution as opposed to membrane effects. Although bioavailability from SCF processed dispersions was better than conventionally processed counterparts (except for one formulation containing Gelucire 44/14), an interaction of processing method and inclusion of an amphiphilic carrier, rather by one factor alone contributed to optimal absorption, thus giving contradictory results for Gelucire 44/14 and TPGS formulations (Sethia and Squillante, **2002, 2004**).

Six, Verreck, Peeters, Brewster and Van Den Mooter prepared solid dispersions were of itraconazole-Eudragit E100, itraconazole-PVPVA64, and itraconazole-Eudragit E100/PVPVA64 using a corotating twin-screw hot-stage extruder. Modulated temperature differential scanning calorimetry (MTDSC) was used to evaluate the miscibility of the extrudates, and dissolution experiments were performed in simulated gastric fluid without pepsin SGF_{wp}. Itraconazole and Eudragit E100 are miscible up to 13% w/w drug loading. From that concentration on, phase separation is observed. Pharmaceutical performance of this dispersion was satisfactory because 80% of the drug dissolved after 30 min. Extrudates of itraconazole and PVPVA64 were completely miscible but the pharmaceutical performance was low, with 45% of drug dissolved after 3 h. Combination of both polymers in different ratios, with a fixed drug loading of 40% w/w, was evaluated. MTDSC results clearly indicated a two-phase system consisting of itraconazole-Eudragit E100 and itraconazole-PVPVA64 phases. In these extrudates, no free crystalline or glassy clusters of itraconazole were observed; all itraconazole was mixed with one of both polymers. The pharmaceutical performance was tested in SGF_{wp} for different polymer ratios, and Eudragit E100/PVPVA64 ratios of 50/50 and 60/40 showed significant increases in dissolution rate and level. Polymer ratios of 70/30 and 80/20, on the other hand, had a release of 85% after 30 min. Precipitation of the drug was never observed. The combination of the two polymers provides a solid dispersion with good dissolution properties and improved physical stability compared with the binary solid dispersions of itraconazole (Six, *et al.*, **2004**).

Tong and Zografi prepared amorphous solid dispersions of indomethacin (IMC) and sodium indomethacin (NaIMC) over a range of compositions by physical mixing as well as by coprecipitation from methanol solution. Measurement of glass transition temperatures, T_G for the physical mixtures revealed two values indicating, as expected, phase separation. In contrast, all samples of coprecipitated materials exhibited one value of T_G, which was greater than that predicted for ideal miscibility in the formation of a molecular dispersion. Such nonideality suggests a stronger acid-salt interaction in the amorphous state than that between acid-acid and salt-salt. FTIR spectroscopic analysis provides evidence for interactions between NaIMC and IMC through a combination of hydrogen bonding and ion-dipole interactions between the carboxylic group of the acid and the carboxylate anion of the salt. The inhibition of isothermal crystallization of IMC by NaIMC only when in molecular dispersion is believed to result from the interaction between the acid and the salt, which prevents the formation of hydrogen-bonded carboxylic acid dimers for IMC, required for the formation of crystal nuclei and crystallization.

Van Drooge, Hinrichs and Frijlink studied and evaluated a new and robust method to prepare physically stable solid dispersions. Trehalose, sucrose, and two inulins having different chain lengths were used as carrier. Diazepam, nifedipine, Δ (9)-tetrahydrocannabinol, and cyclosporine A were used as model drugs. The sugar was dissolved in water and the drug in tertiary butyl alcohol (TBA). The two solutions were mixed in a 4/6 TBA/water volume ratio and subsequently freeze dried. Diazepam could be

incorporated at drug loads up to 63% w/w. DSC measurements showed that, except in some sucrose dispersions, 97-100% of the diazepam was amorphous. In sucrose dispersions with high drug loads, about 10% of the diazepam had crystallised. After 60 days of exposure at 20 ^{o}C and 45% relative humidity (RH), diazepam remained fully amorphous in inulin dispersions, whereas in trehalose and sucrose crystallization of diazepam occurred. The excellent physical stability of inulin containing solid dispersions can be attributed to the high glass transition temperature T_G of inulin. For the other drugs similar results were obtained. The residual amount of the low toxic TBA was only 0.1-0.5% w/w after freeze drying and exposure to 45% RH and 20 ^{o}C. Therefore, residual TBA will not cause any toxicity problems. This study provides a versatile technique, to produce solid dispersions. Inulin glasses are preferred because they provide an excellent physical stability of the incorporated amorphous lipophilic drugs (Tong and Zografi, **2001**).

Velaz, Sanchez, Martin and Martinez-Oharriz made use of Naproxen, a nonsteroidal anti-inflammatory drug characterized by its low wettability and poor water solubility for the dissolution enhancement using solid dispersion preparation. Solid dispersions naproxen:PEG 4000 were prepared in order to improve the solubility and dissolution rate of the drug, since these factors were the limiting steps for absorption and bioavailability of poorly soluble drugs. X-ray diffraction analysis, infrared spectroscopy and *DSC* detected no physico-chemical interaction between the drug and the inert carrier PEG 4000. The phase diagram of the naproxen-PEG 4000 system produced by DSC and hot stage microscopy is reported. The intrinsic dissolution rate of naproxen is calculated. The dissolution kinetics of solid dispersions prepared by the solvent and melt methods was compared with those of free drug and physical mixture. The studies were carried out at 37 ^{o}C and pH 1.2 according to the dispersed amount method. The dissolution profiles obtained indicated a significant dissolution enhancement with solid dispersions in comparison with the physical mixture. In addition, the physical mixture showed a dissolution rate higher than the free drug (Velaz, *et al.*, **1998**).

Verreck, Vandecruys, De Conde, Baert, Peeters and Brewster designed a bioavailable formulation for a water-insoluble microsomal triglyceride transfer protein inhibitor, R103757 using solid dispersion technology. The need for an advanced formulation was tested in the dog by assessing the oral bioavailability of three generic concepts: a tablet (crystalline drug), a capsule (film-coated beads), and an oral solution. These screening studies steered further development in the direction of a solid dispersion. Three solid dispersion platforms were assessed: melt extrusion, film-coated beads, and a glass thermoplastic system. Thermal and spectrophotometric analysis revealed that no crystalline drug was present in any of the formulations. The dissolution profiles of the three dispersion systems showed that release was improved compared with the unmanipulated drug. In addition, stability studies confirmed the physical and chemical integrity of the formulation. A human clinical trial was performed to assess the pharmacokinetics of the three amorphous dispersions. Plasma levels were obtained after single oral administration in both the fasting and fed state. The study indicated that all three approaches improved

the bioavailability of R103757 with the glass thermoplastic system providing the best performance. These studies point to the potential usefulness of solid dispersion approaches and expand the possible number of ways to implement these methodologies (Verreck, *et al.*, **2004**).

Yamada, Saito, Anraku, Imai and Otagiri undertook a study to improve the oral absorption of KCA-098, an antiosteoporosis drug. In this study, the form 2 of KCA-098 was used as a desirable crystal form for pharmaceutical formation among three kinds of crystal forms, 1, 2, and 3. Solid dispersions of KCA-098 with hydroxypropylcellulose (HPC) and polyvinylpyrrolidone (PVP) were prepared by the solvent method. The physicopharmaceutical properties of the solid dispersions were characterized by XRPD, FTIR spectroscopy, and DSC. The powder x-ray diffractograms suggested that KCA-098 in the HPC-SL solid dispersion existed in a partial crystalline state as a new crystal form that could be produced by recrystallization from the solvent. Dissolution from the solid dispersions was markedly enhanced in comparison with that of the drug alone. The dissolution enhancement was observed to be greater for the solid dispersion with HPC-SL than for that with PVP. The KCA-098/HPC-SL (1:2) solid dispersion capsule showed a 3.5-fold increase in the initial concentration and 2.5-fold increase in initial concentration of dissolved drug after 60 min, compared with the values for a physical mixture of KCA-098 (form 2)/lactose (1:2). The *in vivo* absorption of the drug was investigated after oral administration of KCA-098 or its solid dispersion. The area under the plasma concentration curve of KCA-098 after oral administration of the KCA-098/HPC-SL (1:2) solid dispersion capsule was three-fold greater than that for the drug itself (Yamada, *et al.*, **2000**).

Zajc, Obreza, Bele and Srcic prepared solid dispersions of nifedipine (NIF) with mannitol in preparations containing 10 and 50% (w/w) of drug, manufactured by the hot melt method. Physical properties and the dissolution behaviour of binary systems as physical mixtures and solid dispersions were investigated. In all samples, the crystal structure of NIF was confirmed using DSC and SEM. FTIR studies revealed, there was no interaction between drug and carrier, however, FTIR spectra indicated formation of thermodynamically less stable polymorph of mannitol. The dissolution rate of NIF from solid dispersions was markedly enhanced, the effect being stronger at higher drug loading (50%, w/w, NIF). The dissolution rate enhancement was attributed to improved wetting of NIF crystals due to mannitol particles, attached on the surface, as inspected by means of SEM. Thermal stability of NIF, mannitol and two other potential carbohydrate carriers (lactose and saccharose) during the hot melt procedure was investigated using 1H NMR. NIF was found to be thermally stable under conditions applied. As expected, among carriers only mannitol demonstrated suitable resistance to high temperature used in experiments (Zajc, *et al.*, **2005**).

Zerrouk, Chemtob, Arnaud, Toscani and Dugue extended previous physico-chemical investigations on the effects of solid dispersion on the solubility, dissolution rate and the pharmacokinetic profile of carbamazepine. Solubility studies showed a linear increase in

carbamazepine solubility with the increase of PEG 6000 concentration. There is no marked difference between physical mixtures and solid dispersions for the enhancement of carbamazepine solubility by PEG 6000. Less than 60% of pure carbamazepine was dissolved in 90 min. Physical mixtures and solid dispersions dissolution rates were higher in comparison of the parent drug. In solid dispersions there was a remarkable enhancement in the dissolution rates of the drug in the vicinity of the eutectic composition as compared with those of corresponding physical mixtures. Hence, the optimum value for the solid dispersion was 80.5±1.7% of carbamazepine having dissolved within the first 10 min compared to 40±1% for the corresponding physical mixtures of the same composition. Statistical analysis of pharmacokinetic parameters confirmed that the carbamazepine:PEG 6000 binary systems displayed higher bioavailability of the drug than the pure carbamazepine. The area under the curve (AUC) values highlighted the evidence that only slight differences in the bioavailability of the drug occur between physical mixtures and solid dispersions prepared at the 80:20 and 50:50 drug:carrier compositions. However, the mean normalized plasma concentrations showed that standard error deviations are rather wide intervals for pure drug and physical mixtures in comparison to solid dispersions. One additional interesting point to consider was the disappearance of the multiple peaks on the individual kinetic curve of the 50:50 solid dispersion compositions. Furthermore investigations highlighted the interest of solid dispersions prepared at near eutectic composition as preliminary data showed that the plasma concentration of the drug for the 15:85 dispersed sample containing 150 mg of carbamazepine was not significantly different from that obtained for the 50:50 dispersed sample containing 300 mg of the drug (Zerrouk, *et al.*, **2001**).

1.4. Solubilization and surfactants

One approach to increase the bioavailability of lipophilic drugs is the solubilization of the drugs by means of pH adjustment, cosolvent, microemulsification, self-emulsification, micelles, liposomes and emulsions (Strickley, **2004**). Each has its advantages and limitations.

Table 1.5 Solubilizing excipients used in commercially available oral and injectable formulations.

Water-soluble	Water-insoluble	Surfactants
Dimethylacetamide (DMA)	Beeswax	Polyoxyl 35 castor oil (Cremophor EL)
Dimethyl sulfoxide (DMSO)	Oleic acid	Polyoxyl 40 hydrogenated castor oil (Cremophor RH 40)
Ethanol	Soy fatty acids	Polyoxyl 60 hydrogenated castor oil (Cremophor RH 60)
Glycerin	δ–α-tocopherol (Vitamin E)	Polysorbate 20 (Tween 20)
N-methyl-2-pvrrolidone (NMP)	Corn oil mono-di-triglycerides Medium chain (C_8/C_{10}) mono and diglycerides	Polysorbate 80 (Tween 80)
PEG 300	**Long-chain triglycerides**	δ–α-tocopheryl polyethylene glycol 1000 succinate (TPGS)
PEG 400	Castor oil	Solutol HS-15
Poloxamer 407	Corn oil	Sorbitan monooleate (Span 20)
Propylene glycol	Cottonseed oil	PEG 300 caprylic/capric glycerides (Softigen 767)
Hydroxypropyl-β-cyclodextrin	Olive oil	PEG 400 caprylic/capric glycerides (Labrasol)
Sulfobutylether-β-cyelodexlrin (Caplisol®)	Peanut oil	PEG 300 oleic glycerides (Labrafil M-1944CS)
α-cyclodexlrin	Peppermint oil	PEG 300 Imoleic'glycendcs (Labrafil M-2125CS)
Phospholipids	Safflower oil	Polyoxyl 8 stearate (PEG 400 monosterate)
Hydrogenated soy phosphatidylcholine (HSPC)	Sesame oil	Polyoxyl 40 stearate (PEG 1750 monosterale)
Distearoylphosphatidylglycerol (DSPG)	Soybean oil	Peppermint oil
L-α-dimyristoylphosphatidyl-choline(DMPC)	Hydrogenated soybean oil	
L-α-dimyristoylphosphatidyl-Glycerol (DMPG)	Hydrogenated vegetable oils	
	Medium-chain triglycerides	
	Caprylic/capric triglycerides derived from coconut oil or palm see oil	

1.5. pH adjustment

pH adjustment is the simplest and most commonly used method to increase water solubility of ionizable compounds. However, this salt formation is infeasible for unionized compounds. The formed salts may also converse to respective acid or base forms in gastrointestinal-tract (GIT).

1.6. Colsovent

Colsolvents are the mixtures of miscible solvents often used to solubilize lipophilic drugs. The solubilizing excipients used in commercially available oral and injectable formulations are listed in Table 1. Currently, the water-soluble organic solvents are PEG 400, ethanol, propylene glycol, and glycerin. For example, Procardia® (nifedipine) was developed by Pfizer contains glycerin, peppermint oil, PEG 400 and sodium saccharin in soft gelatin capsules. The water-insoluble solvents include long-chain triglycerides (i.e. peanut oil, corn oil, soybean oil, sesame oil, olive oil, peppermint oil, hydrogenated vegetable oil and hydrogenated soybean oil), medium-chain triglycerides (Miglyol 812), beeswax, δ–α–tocopherol (vitamin E) and oleic acid. Progesterone is a water-insoluble steroid and is solubilized in peanut oil (Prometrium®).

1.7. Microemulsion

Microemulsion is a thermodynamically stable isotropical dispersion composed of a polar solvent, oil, a surfactant and a cosurfactant. The formation of microemulsions is spontaneous and does not involve the input of external energy. One theory considers negative interfacial tension while another considers swollen micelles. The surfactant and the cosurfactant alternate each other forming a mixed film at the interface contributing to the stability of the microemulsion. Microemulsions are potential drug delivery systems for poorly water soluble drugs due to their ability to solubilize the drugs in the oil phase, thus increasing their dissolution rate (Kawakami, *et al.*, **2002**). Even if the microemulsions are diluted after oral administration below the critical micelles concentration (CMC), the resultant drug precipitates have a fine particle size allowing enhanced absorption (Lieberman, *et al.*, **1988**).

1.8. Modification of polymorphs

Polymorphs are different crystalline forms of a drug that may have different physicochemical properties and biological activities, such as shelf-life, melting point, vapor pressure, solubility, morphology, density and bioavailability (Kachi, *et al.*, **1998,** Kobayashi, *et al.*, **2001**). Metastable forms are associated with higher energy with increased surface area, subsequently solubility, bioavailability and efficacy (Kachi, *et al.*, **1998,** Vippagunta, *et al.*, **2001**). With regard to bioavailability, it is preferable to change drug from crystal forms into metastable or amorphous forms. However, the possibility of a conversion of the high energy amorphous or metastable polymorph into a low energy crystal form having low solubility can not be ruled out during manufacture and storage. It is preferable to develop the most thermodynamically stable polymorph of the drug to assure reproducible bioavailability of the product over its shelf-life under a variety of real-

world storage conditions. For instance, ritonavir is the active ingredient in Norvir®, a protease inhibitor used to treat HIV/AIDS. It was launched by Abbott Laboratories in 1996 as an amorphous semisolid dispersion consisting of medium chain triglycerides, polyoxyl 35 castor oil, citric acid, ethanol, polyglycolyzed glycerides, polysorbate 80, propylene glycol and 100 mg of ritonavir. The dissolution and the oral bioavailability were decreased due to crystallization of amorphous ritonavir into an insoluble crystal form during storage. This polymorph (form II) was 50% less soluble than the original form in the market, and caused the drug to fail its regulatory dissolution specifications (Pharmacy Today, 1999). Finally, the drug was relaunched with the form II polymorph in a soft gelatin formulation that required refrigeration. Therefore, it is important to note that the selection of a polymorph of a drug should balance between solubility and stability to maintain its potency over the shelf-life period.

1.9. Reduction in particle size

Micro/nanonization is one of the most promising approaches to improve the bioavailability of lipophilic drugs by an increase in surface area and saturation solubility via reduction of the particle size to less than 1 μm (Merisko Liversidge, 2003). Such size reduction cannot be achieved by the conventional milling techniques. Patented engineering processes have come up based on the principles of pearl milling (NanoCrystals®), high-pressure homogenization (DissoCubes®), solution enhanced dispersion by supercritical fluids (SEDS), rapid expansion from supercritical to aqueous solution (RESAS), spray freezing into liquid (SFL) and evaporative precipitation into aqueous solution (EPAS) (Hu, *et al.*, **2004**).

1.10. Microcrystals/Nanocrystals/ Nanomorphs®

Well-known method for increasing the dissolution rate is the forming of a high specific surface area by micronization. The process which is usually used to obtain small particles is the disruption of large crystals by micronization of sparingly water soluble drugs using jar mills and fluid energy mills (Chaumeil, **1998**). However micronization process using mills is extremely unproductive (Parrott, **1990**). High energy input led disruptions in the crystal lattice obviously can cause physical or chemical instability. Disordered regions in the resulting product are thermodynamically unstable. These disordered structures were detected and can be analyzed by dynamic vapor sorption analysis (Ticehurst, *et al.*, **2000**). Amorphous or disordered material tends to recrystallize, especially when water from the atmosphere is adsorbed which is the result of a reduction of the glass transition temperature, the energy threshold to recrystallization is decreased (Elamin, *et al.*, **1995**). These disordered structures in the material can also influence the performance in

formulations (Buckton, **1997**). The conversion of crystalline solid surfaces into partially amorphous solid surfaces leads to a dynamic nature of the micronized drug (Ward and Schultz, **1995**). Surface energy changes can also influence processing properties such as the powder flow. Micronized powders with a higher energetic surface (measured by inverse gas chromatography) show poorer flow properties (Feeley, *et al.*, **1998**). Due to their high specific surface, micronized particles are often agglomerated. Because of fracture, electrostatic effects can occur.

Microsized drug particles of poorly water-soluble drugs when used in oral administration forms, it enhances the drug dissolution rate. Because the drug powders are prepared directly in the micronized state during the particle formation without any further size reduction, this technique can be described as an *in situ* micronization technique. The molecularly dispersed drug is transformed to particles in the desired size and stabilized in the formed dispersion. A stabilizing agent can be used to stabilize the associated drug preserve in small particle size against crystal growth. Furthermore, the use of an effective stabilizer is important to obtain a drug powder with a drug load as high as possible. By the use of a suitable stabilizer, the crystal germs can be stabilized. To find a stabilizer with high affinity to the newly created high surface, several potential stabilizing agents can be compared.

Crystallization can be conducted using the solvent change method by instantaneously mixing two liquids in the presence of a stabilizing agent as described by Rasenack and Müller (Rasenack and Müller, **2002**).

Coevaporation with some polymers can also give rise to a high energy solid state particles (Simonelli, *et al.*, **1976**) or inhibit the crystallisation of the drug, thus leading to an amorphous solid state (Kearney, *et al.*, **1994**, Sekikawa, *et al.*, **1978**). The formation of high-energy complexes (Simonelli, *et al.*, **1969, 1976**), the presence of amorphous drug and the interaction between PVP and drugs such as hydrogen bonding (Doherty and York, **1987**, Shefter and Cheng, **1980**, Tantishaiyakul, *et al.*, **1996**) can explain the solubility enhancement. (Sekikawa, *et al.*, **1979**) noticed that coacervate formation is responsible for the enhanced dissolution of sulfamethizole.

1.10.1. Literature cited for microcrystals/nanocrystals as dissolution enhancer

Rasenack and Muller evaluated a novel in situ micronization method avoiding any milling techniques to produce nano or microsized drug particles by controlled crystallization to enhance the dissolution rate of poorly water-soluble drugs. They prepared microcrystals of ibuprofen, itraconazole and ketoconazole by the association of the previously molecularly dispersed drug using a rapid solvent change process. The drug was precipitated in the presence of stabilizing agents, such as hydrocolloids. The obtained dispersion was spray-dried. Particle size, morphology, dissolution rate, specific surface area, and wettability

were analyzed. Physicochemical properties were characterized using differential scanning calorimetry and X-ray diffractometry. The obtained dispersions showed a homogeneous particle size distribution. Drugs were obtained in a mean particle size of approximately 2 μm and below. A high specific surface area was created and in situ stabilized. Different stabilizers showed differences in protecting the precipitated drug from crystal growth. The surface was hydrophilized because of the adsorbed stabilizer. Thus, a drug powder with markedly enhanced dissolution rate was obtained. Compared to milled products drug properties are optimized as all particle surfaces are naturally grown, the particle size is more uniformly distributed and the powder is less cohesive (Rasenack and Muller, **2002**).

Rasenack, Hartenhauer and Muller improved the poor dissolution rate of ECU-01, a low molecular enzyme-inhibitor with anti-inflammatory properties. In their study microcrystals were not produced using any cutting up techniques, but only by association. Naturally grown microcrystals were prepared by a precipitation method in the presence of stabilizing agents (e.g. gelatin, chitosan, different types of cellulose ethers) followed by spray-drying of the formed dispersion. First the drug was dissolved in acetone and then precipitated by rapid pouring an aqueous solution of the stabilizer into the drug solution. Particularly, cellulose ethers were able to form stable and homogeneous dispersions of microcrystals (mean particle size = 1 μm) showing a tight particle size distribution. By spray-drying, the drug powder was obtained. The dissolution rate is significantly enhanced due to the large surface, which is hydrophilized by adsorbed stabilizers (Rasenack, *et al.*, **2003**).

Ma, Rong, Wu and Zhou prepared D860 (tolbutamide) solid dispersions with urea, polyvinyl pyrrolidone (PVP) and polyethylene glycol (PEG) 6000 as carriers. Solid dispersions were studied by X-ray diffraction, relating to their dissolution rates. D860 in D860-PVP dispersion was shown to be in an amorphous state and to have greater dissolution rate. D860-urea and D860-PEG melts were found to be partly in miscible solid solution state and partly in microcrystal state and possess higher activity and greater dissolution rate. D860-PEG coprecipitate was a physical mixture and its dissolution rate is slower than its melt. No variation in the crystal structure of the D860 dispersions was observed during the ageing test (Ma, *et al.*, **1992**).

Hecq, Deleers, Fanara, Vranckx and Amighi prepared nanoparticles of poorly water soluble drug nifedipine using high pressure homogenization. The homogenization procedure was first optimized in regard to particle size and size distribution. Nanoparticles were characterized in terms of size, morphology and redispersion characteristics. Saturation solubility and dissolution characteristics were investigated and compared to the unmilled commercial nifedipine to verify the theoretical hypothesis on the benefit of increased surface area. Crystalline state evaluation before and following particle size reduction was also conducted through DSC and XRPD to denote eventual transformation to amorphous state during the homogenization process. Through this study, it was shown that initial crystalline state was maintained following particle size reduction and that the dissolution characteristics of nifedipine nanoparticles were significantly increased in regards to the

commercial product. They showed that the method was simple and easy to scale up, which should have a general applicability to many poorly water soluble drug entities (Hecq, *et al.*, **2005**).

Lee and Cheng explained drying procedures to convert liquid nanocrystal dispersions into solid dosage forms. The solid dosage form should consist of nanocrystals that can readily reconstitute into their original size upon dissolution in water. They used the freeze drying process for this purpose. Nanocrystal dispersions were examined at varying freezing rates (speed of freezing interface). As freezing rate decreased, more particle-particle aggregation developed. A critical freezing rate, below which the dried nanocrystals cannot be redispersed, was identified based on the plot of the particle size of reconstituted nanocrystals versus freezing rate. Freeze drying at a freezing rate near the critical value produces dry powders of bimodal particle size distribution after redispersion. In addition, API concentration was found to significantly affect the critical freezing rate and therefore the redispersibility of dry powders. The concept of critical freezing rate is decisive for the development of solid dosage forms of liquid nanocrystal dispersions (Lee and Cheng, **2006**).

Moschwitzer and Muller employed high pressure homogenization to produce drug nanocrystals with a number of advantages, like improved solubility behaviors, better drug targeting or even increased mucoadhesiveness. Their study showed the feasibility to use a mucoadhesive nanosuspension of poorly soluble hydrocortisone acetate produced by high pressure homogenization as layering dispersion in a fluidized bed process, followed by the application of an enteric coating to achieve a controlled drug release. To point out the advantages of drug nanocrystals the new fomulation was compared with a formulation containing micronized drug. Both formulations were characterized with regard to their particle size and crystallinity by using laser diffractometry, photon correlation spectroscopy and X-ray diffraction. The pellet morphology was characterized by using the environmental scanning electron microscopy (ESEM). In the *in vitro* dissolution tests an accelerated dissolution velocity and an increased drug release was observed for the pellets containing drug nanocrystals. (Moschwitzer and Muller, **2006**)

1.11. Some other vital techniques from future perspective

1.11.1. Pearl milling.

NanoCrystals® involves filling an aqueous suspension of drug into a pearl mill containing glass or zirconium oxide pearls as milling media. The drug microparticles are ground to nanoparticles (< 400 nm) in between the moving milling pearls over a few days. The milling efficiency is dependent on the properties of the drug, the medium and the stabilizer. Rapamune®, an immune suppressant agent, is the first FDA approved

nanoparticle drug using NanoCrystals® technology developed by Elan Drug Delivery. Emend® is another product containing 80 or 125 mg formulated by this technique. The limitation of the pearl milling process is the introduction of contamination to the product from the grinding material, batch-to-batch variations and the risk of microbiological problems after milling in an aqueous environment for a few days.

1.11.2. High pressure homogenization

DissoCubes® manufacture involves dispersing a drug powder in an aqueous surfactant solution and passing through a high pressure homogenizer, subsequently nanosuspensions are obtained. The cavitation force experienced is sufficient to disintegrate drug from microparticles to nanoparticles. The particle size is dependent on the hardness of the drug substance, the processing pressure and the number of cycles applied. The possible interesting features of nanosuspensions are (Müller, *et al.*, **2001**) :

- Increase in saturation solubility and dissolution rate of drug
- Increase in adhesive nature, thus resulting in enhanced bioavailability
- Increase the amorphous fraction in the particles, leading to a potential change in the crystalline structure and higher solubility
- Possibility of surface modification of nanosuspensions for site specific delivery
- Possibility of large-scale production, the prerequisite for the introduction of a delivery system to the market.

However, only brittle drug candidates might be broken up into nanoparticles by this technique. A few points have to be considered, such as chemical instability of fragile drugs under the harsh production conditions, Ostwald ripening in long-term storage, toxicity of surfactants, redispersibility of the dried powder, batch-to-batch variation in crystallinity level and finally the difficulty of quality control and the stability of the partially amorphous nanosuspensions.

Solution enhanced dispersion by the supercritical fluids (SEDS). The SEDS process was developed and patented by the University of Bradford (Hanna and York, **1998**). The use of a coaxial nozzle provides a means whereby the drug in the organic solvent solution mixes with the compressed fluid CO_2 (antisolvent) in the mixing chamber of the nozzle prior to dispersion, and flows into a particle-formation vessel via a restricted orifice. Such nozzle achieves solution breakup through the impaction of the solution by a higher velocity fluid. The high velocity fluid creates high frictional surface forces, causing the solution to disintegrate into droplets. A wide range of materials has been prepared as carriers of microparticles and nanoparticles using the SEDS process (York, 1999; Hanna and York, 1998). A key step in the formation of nanoparticles is to enhance the mass transfer rate between the droplets and the antisolvent before the droplets coalesce to form bigger droplets. In another study, a significant decrease in the particle size is achieved by using

the ultrasonic nozzle-based supercritical antisolvent process (Subramaniam, *et al.*, **1997**) (Subramaniam et al., 1997A; 1997B).

1.11.3. Rapid expansion from supercritical to aqueous solution (RESAS)

This process induces rapid nucleation of the supercritical fluid dissolved drugs and surfactants resulting in particle formation with a desirable size distribution in a very short time. The surfactants in the supercritical fluid stabilize the newly formed small particles and suppress any tendency of particle agglomeration or particle growth when spraying this solution (drug+surfactant+CO_2) into an aqueous solution containing a second surface modifier (Pace, *et al.*, **2001,** Young, *et al.*, **2000**). The low solubility of poorly water soluble drugs and surfactants in supercritical CO_2 and the high pressure required for these processes restrict the utility of this technology in pharmaceutical industry.

1.11.4. Spray freezing into liquid (SFL)

The SFL technology was developed and patented by the University of Texas at Austin in 2003 and commercialized by the Dow Chemical Company. This technique involves atomizing an aqueous, organic, aqueous organic cosolvent solution, aqueous-organic emulsion or suspension containing a drug and pharmaceutical excipients directly into a compressed gas (i.e. CO_2, helium, propane, ethane), or the cryogenic liquids (i.e. nitrogen, argon, or hydrofluoroethers).

The frozen particles are then lyophilized to obtain dry and free-flowing micronized powders (Williams, *et al.*, **2003**). Use of acetonitrile as the solvent increased the drug loading and decreased the drying time for lyophilization. The dissolution rate was remarkably enhanced from the SFL powder contained amorphous nanostructured aggregates with high surface area and excellent wettability (Hu, *et al.*, **2003,** Hu, *et al.*, **2002,** Rogers, *et al.*, **2002a,** Rogers, *et al.*, **2002b**).

1.11.5. Evaporative precipitation into aqueous solution (EPAS).

The EPAS process utilizes rapid phase separation to nucleate and grow nanoparticles and microparticles of lipophilic drugs. The drug is first dissolved in a low boiling point organic solvent. This solution is pumped through a tube where it is heated under pressure to a temperature above the solvent's boiling point and then sprayed through a fine atomizing nozzle into a heated aqueous solution. Surfactants are added to the organic solution and the aqueous solution to optimize particle formation and stabilization. In EPAS, the surfactant migrates to the drug-water interface during particle formation, and the hydrophilic segment is oriented towards the aqueous continuous phase (Chen, *et al.*,

2002). The hydrophilic stabilizer on the surface inhibits crystallization of the growing particles and therefore facilitates dissolution rates.

1.11.6. Complexation

Cyclodextrins and their derivatives have been employed as complexing agents to increase water solubility, dissolution rate and bioavailability of lipophilic drugs for oral or parenteral delivery (Choi, *et al.*, **2003,** Koester, *et al.*, **2004,** Sridevi, *et al.*, **2003**). The solubility enhancement factors of pancratistatin, hydrocortisone, and paclitaxel are 7.5, 72.7 and 99000 by forming complexes with cyclodextrin derivatives (Loftsson and Brewster, **1996**). The lower the aqueous solubility of the pure drug, the greater the relative solubility enhancement obtained through cyclodextrin complexation. Pharmaceutical applications of cyclodextrins in drug solubilization and stabilization (Loftsson and Brewster, **1996**), *in vivo* drug delivery (Rajewski and Stella, **1996**), toxicological issues and safety evaluation (Irie and Uekama, **1997**) and mechanisms of cyclodextrins modifying drug release from polymeric drug delivery systems (Bibby, *et al.*, **2000**) have been previously reviewed.

1.12. References

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OBJECTIVES OF THE WORK

SEDDS, liquisolid systems, solid dispersions and microcrystals were designed and developed to enhance the dissolution properties of water insoluble drugs carbamazepine, oxcarbamazepine and gabapentin, thereby efficacy of drug in dosage form is improved and quick therapeutic response is obtained.

So the prime objectives in carrying out the work were,

1. To design and construct SEDDS, Liquisolid systems, Solid Dispersions and Microcrystals systems of 3 different active pharmaceutical ingredients.
2. To identify and investigate the critical factors involved in the dissolution enhancement of all the systems developed using Experimental design approach and thereby constructing contour plots.
3. To investigate *in vitro* drug release pattern of all the systems prepared.
4. To compare the data obtained for systems developed with marketed conventional dosage forms.
5. To investigate the *in vivo* bioavailability of systems developed and marketed conventional dosage forms using rabbits.

1.13. Drug Profiles

In the present work 3 drugs namely Carbamazepine, Oxcarbamazepine and Gabapentine of same category but different physicochemical characteristics were used. First two are classified as BCS class II (Poor solubility but High permeability) drugs and the last is classified as BCS Class III (High solubility but Poor permeability) drug.

Table 1.6 gives physicochemical characteristics for CBZ, OCBZ and GPN.

Table 1.6 Detailed drug profiles.

	Drugs		
	Carbamazepine	**Oxcarbamazepine**	**Gabapentine**
IUPAC name	5H-Dibenz[b,f]azepine-5-carboxamide	10,11-Dihydro-10-oxo-5H-dibenz[b,f]azepine-5-carboxamide	1-(Aminomethyl)cyclohexaneacetic acid
Molecular formula	$C_{15}H_{12}N_2O$	$C_{15}H_{12}N_2O_2$	$C_9H_{17}NO_2$
MW	236.3	252.3	171.2
MP	189° to 193°	215° to 216°	162° to 166°
Solubility	Practically insoluble in water and ether; soluble in alcohol, acetone chloroform, and propylene glycol.	Practically insoluble in water, ether and ethanol; slightly soluble in chloroform, dichloromethane, acetone and methanol.	It is freely soluble in water (4491 mg/L at 25°), basic and acidic aqueous solutions.
pKa	7	4.6	3.68 and 10.7
Log P (octanol/water)	2.45	1.11	-1.1
UV maxima (nm)	237 and 285	256 and 306	------
Bioavailability	Upto 70%	upto 75%	Upto 60%, but as dose increases, bioavailability decreases.
Volume of distribution.	About 1.4 L/kg.		0.6 to 0.8 L/kg.