Bulletin of Pharmaceutical Research 2011;1(1):75-87
An Official Publication of Association of Pharmacy Professionals
ISSN: 2249-6041 (Print); ISSN: 2249-9245 (Online)

REVIEW ARTICLE

SOLID DISPERSIONS: AN INDUSTRIALLY FEASIBLE ALTERNATIVE APPROACH TO FORMULATE BRICK DUST MOLECULES

Nikhil K. Sachan* and Seema Pushkar

Department of Pharmaceutics, University Institute of Pharmacy, C.S.J.M. University, Kanpur - 208 024, Uttar Pradesh, India.

**E-mails*: nikhilsachan@gmail.com, seemapushkar@gmail.com
Tel.: +91-9307755497.

Received: February 08, 2011 / Revised: April 22, 2011 / Accepted: April 27, 2011

The enhancement of oral bioavailability of poorly water-soluble drugs remains one of the most challenging aspects of drug development. The solid dispersions have attracted considerable interest as an efficient means of improving the dissolution rate and thereby the bioavailability of poorly soluble therapeutic substances which were otherwise to be formulated through nanomiling or prodrug formation. This review compiles historical background, definitions, rationale and scope, formulation aspects and carriers used, preparation methods, drug release mechanisms, characterization and advantages of solid dispersion system along with its limitations as well as alternative approaches to overcome these limitations which are responsible for its little commercialization.

Key words: Solubility enhancement, Drug delivery, Dissolution, Bioavailability.

INTRODUCTION

The drug substances are rarely administered in its pure chemical form, rather a suitable dosage form needs to be formulated which carry and deliver the drug to proper site of absorption at an optimum rate. The dosage forms so formulated may be administered through topical, oral or parenteral route. The oral route is most important for administering drugs for systemic effects. When a new drug is discovered, one of the first questions, a pharmaceutical company asks is whether or not the drug can be effectively administered by the oral route, for its intended effect. From a patient's perspective, swallowing a dosage form is comfortable and familiar means of taking medication. As a result, patient compliance and hence drug treatment is typically more effective with orally administered medications as compared to the non-conventional routes of administration (Dhirendra *et al* 2009). The development of oral dosage forms especially for poorly water soluble drugs has been a challenge to formulation scientists because of many self-dependant variables in the absorption of drug from gastrointestinal tract. The formulation scientist must have to take an account of relationship between drug release from product and absorption process. In this respect, the rate-limiting step is of primary relevance. The bioavailability and therefore *in vivo* performance of the drug will be dependent on the solubility parameter, if dissolution / drug release is the rate limiting step for dosage form. In contrast, as long as the permeation through bio-membranes is rate-limiting process, bioavailability and bioequivalence are not so much dependent upon the drug release behavior of the dosage form. A drug must possess some aqueous solubility and

go in solution in order to enter systemic circulation, to reach to site of action, and for being therapeutically effective. Therefore the solubility and dissolution behavior of a drug is key determinant to its oral bioavailability and formulation of a drug into oral dosage form become problematic for so-called '*Brick dust*' molecules having extremely low water solubility. The poorly water soluble compounds are classically defined as those dissolving less than one part per thousand part of water. With recent advances in technology, molecular screening methods, innovation of combinatorial chemistry and high throughput screening; an increasing number of poorly water soluble molecules are being identified as potential drug candidates. It is reported that about 35-40% of new chemical entities currently being discovered suffer from poor aqueous solubility. The solubility issue complicates the delivery of these drugs and remains one of the most challenging aspects of drug development. Although salt formation, solubilization and particle size reduction have commonly been used to increase the dissolution rate and there by oral absorption and bioavailability of such drugs, the salt formation is not feasible for neutral compounds and the synthesis of appropriate salt forms of drugs that are weakly acidic or weakly basic may often not be practical. The solubilization of the drugs in organic solvents or in aqueous media by the use of surfactants and co-solvents leads to liquid formulations that are usually less desirable from the view points of patient's acceptability and commercialization. The use of very fine powder in a dosage forms may also be problematic because of handling difficulties, electrostatic charges and poor wettability. Therefore, alternative formulation approaches are being explored to enhance the bioavailability of poorly water soluble drugs. One such promising approach to formulate poorly soluble drugs for enhancing their absorption is to prepare solid dispersion. The term solid dispersions (SD) has been utilized to describe a family of dosage forms consisting of at least two different components, generally a hydrophobic drug dispersed into an inert hydrophilic matrix which can be either crystalline or amorphous. Sekiguchi and Obi (1961) suggested that the drug was present in a eutectic mixture in a microcrystalline state. Later, Goldberg *et al* (1966) demonstrated that all the drug in a SD might not necessarily exist in a microcrystalline state, a certain fraction of the drug might be molecularly dispersed in the matrix, thereby forming a solid solution. When the SD system is exposed to aqueous media, the carrier dissolves and the drug releases as fine colloidal particles. The resulting enhanced surface area produces higher dissolution rate and bioavailability of poorly water soluble drugs. Much of research has been reported on SD technologies that explored a variety of processing and excipients option allowing flexibility for formulation of poorly water soluble drugs into oral drug delivery systems. The Biopharmaceutical Classification System (BCS) has provided guidance for the drugs suitable for implementing solubility enhancement strategy in formulation development. Therefore the SD systems are generally suitable for the drugs categorized as Class II drugs in BCS which require more time to dissolve in gastrointestinal fluid than it take to be absorbed into systemic circulation from gastrointestinal tract. The SD systems, although enjoy several advantages as discussed earlier but their commercial use have been limited because of some manufacturing problems and limitations of this technology. The limitations include (1) laborious and expensive methods of preparation, (2) reproducibility of physicochemical characteristics, (3) difficulty in incorporating into formulations of dosage forms, (4) scale-up of manufacturing process, and (5) stability of drug in vehicle. Various remedial measures including modified processes have been tried to overcome formulation and manufacturing problem which will be briefly reviewed.

ADVANTAGES OF SD SYSTEMS IN FORMULATION

Particles with reduced particle size

The SDs contain drug present in the form of molecular dispersion that is highest possible micronized state dispersed in matrix. This increases the surface area resulting in increased dissolution rate and thereby improved bioabsorption (Leuner and Dressman, 2000; Kang *et al* 2004).

Improved particle wettability

Wetting of particles is an important criterion in dissolution of the drugs into gastrointestinal fluid. In SDs, the hydrophilic matrix releases the drug by itself going into the solution therefore it offers improved wettability even with the carriers having no surface activity. This is further enhanced when the carriers with surface activity, such as cholic acid and bile salts, are

used (Sekiguchi *et al* 1964).

Particles with higher porosity

In SDs, the particles are found to have higher degree of porosity. The properties of carrier also affect the porosity, as the highly branched polymers in matrix render more porous structure.

Drugs in amorphous state

Poorly water soluble crystalline drugs, when in the amorphous state tend to have higher solubility (Pokharkar *et al* 2006; Lloyd *et al* 1999). The enhancement of drug release can usually be achieved using the drug in its amorphous form because no energy is required to break up the crystal lattice during the dissolution process (Taylor and Zografi, 1997). In SDs, drugs are presented as supersaturated solutions after system dissolution, and it is speculated that, if drug precipitates it as a metastable polymorphic form with higher solubility than the most stable crystal form (Leuner and Dressman, 2000; Karavas *et al* 2006). **Figure 1** represents the bioavailability enhancement of a poorly water soluble drug by solid dispersions compared to conventional tablets and capsules.

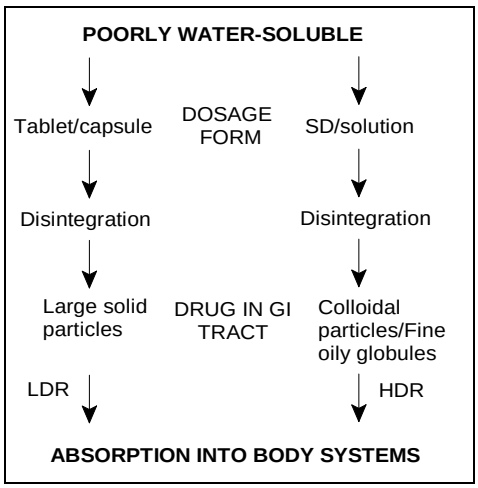

Figure 1. Schematic representation of the bioavailability enhancement of a poorly water-soluble drug by solid dispersions compared with conventional tablet or capsule

Types of SDs

There are following major types of SDs formulated by researchers (**Table 1**).

Simple eutectic mixtures

These are prepared by rapid solidification of the fused melt of two components that show complete liquid miscibility but negligible solid-solid solubility. Thermodynamically, such a system is an intimately blended physical mixture of its two crystalline components. Thus, the X-Ray diffraction patterns of eutectic constituents are additive composite of the two components (Sekiguchi and Obi, 1961; Goldberg *et al* 1966).

Solid solutions

In solid solutions, the two components crystallize together in a homogeneous one-phase system. The particle size of drug in a solid solution is reduced to its molecular size. Thus, a solid solution can achieve a faster dissolution rate than the corresponding eutectic mixtures. Solid solution can be classified by two methods. According to the extent of miscibility of the two components, they may be classified as continuous or discontinuous. In continuous solid solutions, the two components are miscible in solid state in all proportions. Discontinuous solid solutions exist at extremes of composition. According to the criterion of molecular size of the two components, the solid solutions are classified as substitutional or interstitial. In the substitutional type, the solute molecule substitutes for the solvent molecule in crystal lattice. An interstitial solid solution is obtained when the solute molecule occupies the interstitial space in the solvent lattice (Goldberg *et al* 1966).

Glass solutions and suspension

A glass solution is a homogenous glassy system in which a solute dissolves in the glassy carrier. A glass suspension refers to a mixture in which precipitated particles are suspended in a glassy solvent. The glassy state is characterized by transparency and brittleness below the glass transition temperature. Glasses do not have sharp melting points. Instead, they soften progressively on heating. The lattice energy, which represents a barrier to rapid dissolution, is much lower in glass solutions than in solid solution.

Amorphous precipitations in a crystalline carrier

This type of SD is distinguished from a simple eutectic mixture by the fact that the drug is precipitated out in an amorphous form. It is postulated that a drug with a propensity to super cooling has more tendency to solidify as an amorphous form in the presence of a carrier (Dua *et al* 2009).

Table 1. Types of solid dispersion (Dhirendra *et al* 2009)

Solid dispersion type		Matrix*	Drug**	Remarks	No. of phases
I	Eutectics	C	C	The first type of solid dispersion prepared	2
II	Amorphous precipitations in crystalline matrix	C	A	Rarely encountered	2
III	Solid solutions				
	Continuous solid solutions	C	M	Miscible at all composition, never prepared	1
	Discontinuous solid solutions	C	M	Partially miscible, 2 phases even though drug is molecularly dispersed.	2
	Substitutional solid solutions	C	M	Molecular diameter of drug (solute) differs less than 15% from the matrix (solvent) diameter. In that case the drug and matrix are substitutional. Can be continuous or discontinuous. When discontinuous: 2 phases even though drug is molecularly dispersed.	1 or 2
	Interstitial solid solutions	C	M	Drug (solute) molecular diameter less than 59% of matrix (solvent) diameter. Usually limited miscibility, discontinuous. Example: Drug in helical interstitial spaces of PEG.	2
IV	Glass suspension	A	C	Particle size of dispersed phase dependent on cooling/evaporation rate. Obtained after crystallization of drug in amorphous matrix	2
V	Glass suspension	A	A	Particle size of dispersed phase dependent on cooling/evaporation rate many solid dispersions are of this type	2
VI	Glass solution	A	M	Requires miscibility OR solid solubility, complex formation or upon fast cooling OR evaporation during preparation, many (recent) examples especially with PVP	1

*A: matrix in the amorphous state, C: matrix in the crystalline state, **A: drug dispersed as amorphous clusters in the matrix, C: drug dispersed as crystalline particles in the matrix, M: drug molecularly dispersed throughout the matrix

Compound or complex formation

When two substances form a molecular compound, it usually gives rise to a maximum in the phase diagram. An example of this is the quinine-phenobarbital system.

Preparation methods of SDs

The two basic procedures used to prepare SDs are the fusion and co solvent techniques. Modifications of these methods and combinations of them have also been used. Recently, application of supercritical fluid process has been explored to form pharmaceutical SDs.

Melting or fusion method

In this method, the physical mixture of an active agent and water-soluble carrier is heated until it is melted. The melt is solidified rapidly in an ice bath under vigorous stirring, pulverizing and then sieving. Rapid congealing is desirable because it results in super saturation of the drug as a result of entrapment of solute molecules in the solvent matrix by instantaneous solidification. Two advantages of the melt method are its simplicity and its economy, as no solvents are involved. However, the method may not be suitable if the drug or the carrier is unstable at the fusion temperature or evaporates at high temperature.

Solvent method

Tachibana and Nakamura (1965) first used this method to prepare a SD of β-carotene in PVP by

using chloroform as a co solvent. The solvent is usually removed by evaporation under reduced pressure at varying temperature. The choice of solvent and its removal rate are critical to the quality of the dispersion. A mixed solvent system may be used. Some examples of SDs prepared by this method include sulfathiozole-PVP, reserpine-PVP, reserpine-dioxycholic acid and griseofulvin-PVP. The major advantage of the solvent method is that thermal decomposition of drugs and carriers associated with fusion method can be avoided.

Melting solvent method (melt evaporation)

It involves preparation of solid dispersions by dissolving the drug in a suitable liquid solvent and then incorporating the solution directly into the melt of polyethylene glycol, which is then evaporated until a clear, solvent free film is left. The film is further dried to constant weight. The 5-10% (*w/w*) of liquid can be incorporated into melted PEG 6000 without significant loss of its solid property. It is possible that the selected solvent or dissolved drug may not be miscible with the melt of the PEG. Also the liquid solvent used may affect the polymorphic form of the drug, which precipitates as the solid dispersion. This technique possesses unique advantages of both the fusion and solvent evaporation methods. From a practical standpoint, it is only limited to drugs with a low therapeutic dose *e.g.* below 50 mg (Goldberg *et al* 1966).

Super critical fluid process

This technology has been introduced in late 1980s and early 1990s, and experimental proofs of concept are abundant in scientific literature (Phillips and Stella, 1993). From the very beginning of supercritical fluid particle generation research, the formation of biocompatible polymer and drug loaded biopolymer micro-particles has been studied by a number of research groups for pharmaceutical applications (Muhrer *et al* 2006). Particle size reduction *via* super critical fluid process is a novel nanosizing and solubilization technology (Hite *et al* 2003). For any substances, at the critical temperature (Tc) and critical pressure (Pc), the liquid and vapor states coexist. A substance whose temperature and pressure are simultaneously higher than their critical point is referred to as a super critical fluid-SCF (Jovanovic *et al* 2004). Super critical CO_2 is a good solvent for water-insoluble as well as water–soluble compounds under suitable conditions of temperature and pressure. The typical operating temperature and pressure for SCFs are 1.01–1.1T/Tc, where T is the temperature at which the fluid is maintained and 1.01 – 1.1P/ Pc, where P is the pressure at which the pressure is maintained. SCFs show properties attributable to both liquids and gases. They offer liquid like densities, gas like viscosities and compressibility and higher diffusivities than liquids. At near critical temperature, SCFs are highly compressible allowing moderate changes in pressure to greatly alter the density and mass transport characteristics of the fluids. This confers enormous solvent power to the SCF (Ghaderi, 2000). Insoluble drug particles are solubilized within the SCF due to its high density and diffusivity. The particles may then be recrystallized at greatly reduced particle size. The particles obtained are nanosized and have a narrow size distribution. Some commonly used super critical solvents include carbon dioxide, nitrous oxide, ethylene, propylene, propane, n-pentane, ethanol, ammonia, and water. Depending on the use of the SCF as a solvent or anti solvent the processes are broadly two types namely: RESS- Rapid expansion of super critical solution and GAS-Gas anti solvent precipitation.

In the RESS process, the drug or a drug–polymer mixture is solubilized in the SCF (carbon dioxide). This solution is then sprayed into a lower pressure environment via a conventional nozzle or capillary tube. The SCF solution expands at super sonic velocities reducing the density and consequently the solvent power of CO_2. The sprayed solution becomes super saturated causing the drug to recrystallize or precipitate at a reduced particle size. Cosolvents such as methanol or acetone and others can be mixed with the SCF to increase the solvating power of the SCF.

In the GAS precipitation process the SCF acts as an anti solvent and hence the drug or solute is to be miscible with the SCF. The solute is dissolved in a conventional solvent i.e. miscible with the SCF. The solution is then expended by introducing the SCF into it. The diffusion of the SCF into the solution causes the precipitation of drug particles.

The advantages of SCF process includes:

1) No degradation due to mechanical stress as evident in crushing, milling.
2) No extensive uses of organic solvents as needed for recrystallization processes.
3) Suitable for thermo labile moieties.

4) The organic solvent used is removed along with the SCF.
5) Light, oxygen and possibly moisture free atmosphere during processing.

Common carriers used in SD (Serajuddin, 1999)
Sugars: dextrose, sucrose, galactose, sorbitol, maltose, xylitol, mannitol, lactose
Acids: citric acid, succinic acid
Polymeric materials: povidone (PVP), poly-ethylene glycols (PEG), hydroxypropyl-methyl cellulose, methyl cellulose, hydroxylethyl cellulose, cyclodextrins, hydroxylpropyl cellulose, pectin, galactomannan
Insoluble or enteric polymers: hydroxypropyl methylcellulosephthalate, eudragit L-100, eudragit S-100, eutragit RL, eutragit RS
Surfactants: polyoxyethylene stearate, renex, poloxamer 188, texafor AIP, deoxycholic acid, tweens, spans
Miscellaneous: pantaerythritol, pentaerythrityl-tetracetate, urea urethane, hydroxyalkyl-xanthins.

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

Particle size reduction and reduced agglomeration
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 SDs may have some wetting properties; hence it is reasonable to suggest that improved wetting may lead to reduced agglomeration and hence increased surface area.

Increased solubility or dissolution rate of the drug
Again, many of the carriers used may increase the solubility of the drug. There has been some debate over this mechanism as solubility studies have indicated that at the concentrations used for in-vitro experiments the carriers of an elicit minimal solubility increases. Similarly, the carrier and drug may form a soluble complex, as is well established for cyclodextrins, although the evidence for this occurring with other carrier is weaker. Finally, changes to the physical properties of the drug such as degree of crystallinity and polymorphic form may also be considered under this category. Corrigan provided a very valuable contribution by measuring the dissolution rate of the incorporated drug and also assessing dissolution rate of the polymer itself. It was found that the dissolution rate of the drug in the polymer and polymer alone were in fact equivalent, leading to the suggestion of carrier-controlled dissolution where by the dissolution rate of the drug is controlled by that of the inert carrier. This finding was supported by the work of Dubois and Ford (1985) who noted that the dissolution rates of a range of drugs in a single carrier, prepared under comparable conditions were identical in most cases.

Drug controlled versus carrier controlled dissolution
Corrigan has suggested that carrier-controlled dissolution may be modeled in terms of the approach outlined by Higuchi (1967), where by the dissolution of two-compartment system is considered. Upon exposure to the solvent both component dissolve at rates proportional to their respective solubility (Cs) and diffusion coefficient (D) in the dissolving medium, as predicted for single component systems by the well known modified Noyes-Whitney equation. This model predicts that the interfacial layer between the dissolving front and the solvent will become depleted in the more rapidly dissolving component, leading to the creation of a surface layer rich in one component through which other must diffuse prior to release into the bulk phase.
Leading from these studies, Lloyd *et al* (1999) argued that if dissolution was dominated by the properties of the carrier and not the drug then the physical form of the drug should be irrelevant to the release rate. A homologous series of drugs (para-aminobenzoates) in PEG 6000 is already used in an attempt to interrelate the solid-state structure, drug solubility and dissolution rate. Authors noted that there was a linear relationship between the intrinsic dissolution rate of the model drugs in the dispersions and the drug solubility, clearly linking the properties of the drug to the dissolution rate; it may be helpful at this stage to

refer to such behavior as drug–controlled dissolution is opposed to carrier-controlled dissolution. It was also noted that as the concentration of the drug increased the dissolution rate become effectively independent of composition and very similar to the drug alone; in this respect therefore the behavior corresponds to the Higuchi model when the drug is the dominant component.

CHARACTERIZATION OF SDs

Detection of crystallinity in SDs

There are several techniques employed to determine the fraction of crystalline phase in SDs. The amorphous amount is not usually measured directly rather derived from the amount of crystalline material in the sample (Kaushal *et al* 2004). Currently the following techniques are available to detect the degree of crystallinity in sample.

Differential scanning calorimetry

DSC is the most widely used, highly regarded method. DSC enables the quantitative detection of all process in which energy is required or produced (*i.e.* endothermic and exothermic phase transformations). Exothermic transitions, such as conversion of one polymorph to another polymorph, can also be detected. Lack of melting peak in the DSC of a SD indicates that drug is present in the amorphous rather than crystalline form. Since the method is quantitative in nature, the degree of crystallinity can be also calculated for the system in which drug is partially amorphous and partially crystalline. However, crystallinities of fewer than 2% cannot generally be detected with DSC.

X-ray diffractometry

X-ray have been used in crystal structure studies in two different ways: (1) Single crystal X-ray crystallography dealing with the determination of bond angle and inter-atomic distance and (2) Powder x-ray diffraction dealing with the study of crystal lattice parameters, where the x-ray intensity from a sample ins measured as a function of diffraction angle. Thus changes in the diffraction pattern indicate changes in crystal structure. The relationship between wavelength (λ) of the x-ray, the angle of diffraction, θ, and the distance between each set of atomic planes of crystal lattice, d, is given by equation (Willard *et al* 1965)

$$M\lambda = 2d\sin\theta$$

where M represents the order of diffraction

X-ray diffraction spectrum of simple eutectic system shows peaks of each crystalline component. Therefore, it is possible with X-ray diffraction to differentiate between solid solutions, in which the drug is amorphous, and SDs, in which it is at least partly present in the crystalline form, regardless of whether the carrier is amorphous or crystalline. However, crystallinities of under 5-10% cannot generally be detected with X-ray diffraction.

IR spectroscopy

Structural changes and lack of crystal structure can lead to changes in bonding between functional groups, which can be detected by IR spectroscopy. Since not all peaks in the IR spectrum are sensitive to crystalline changes, it is possible to differentiate between those that are sensitive to changes in crystallinity and those that are not.

Thermomicroscopical analysis

This is visual method of analysis using a polarized microscope with a hot stage to determine the thaw and melting points of solids. Its advantages are the small amount of sample required and direct observation of the changes taking places in the sample though the thaw and melts stages. This technique has been used to support DTA or DSC (Ford and Robinstein, 1978; Daabis *et al* 1974).

Dissolution calorimetry

It measures the energy of dissolution which is dependent on the crystallinity of sample. Usually dissolution of crystalline material is endothermic, whereas that of amorphous material is exothermic.

Water vapour sorption

Water vapour sorption studies can be used to discriminate between the amorphous and crystalline material when the hygroscopicity of the two is different (Buckton and Darcy, 1995). This technique requires accurate data on the hygroscopicity of both, completely crystalline and completely amorphous material.

Isothermal microcalorimetry

This measures the crystallization energy of amorphous material that is heated above its glass transition temperature (Tg) (Sebhatu *et al* 1994). However, this method has some

limitations; (1) this technique can only be applied if the physical stability is such that only during the measurement crystallization takes place (2) it has to be assumed that all amorphous material crystallizes (3) in a binary mixture of two amorphous compounds a distinction between crystallization energies of the drug and matrix is difficult.

Among these the most important methods are thermoanalytical, X–ray diffraction, infrared spectroscopy and measurement of the release rate of the drug. In addition to characterizing the SD, these methods can be used to differentiate between solid solution (molecularly dispersed drug), SDs in which drug is only partially molecularly dispersed and physical mixture of drug and carrier. It is usually assumed that dispersions in which no crystallinity can be detected are molecularly dispersed and the absence of crystallinity is used as a criterion to differentiate between the solid solutions and SDs.

Detection of molecular structure in amorphous SDs

The properties of SDs are highly affected by the uniformity of the distribution of the drug in the matrix. For the SDs that do not contain any crystalline particles, the dissolution and stability profile could be different, *i.e.* SD of type V and type IV or for type II and III. The distribution of drug as crystalline or amorphous particles or as separate drug molecule is also important along with the knowledge of physical state (amorphous and crystalline) is important.

Temperature modulated differential scanning calorimrtry (TMDSC)

It can be used to assess the degree of mixing of an incorporated drug. Due to the modulation, reversible and irreversible events can be separated. For example, 'glass transition', a reversible event can be separated from 'crystallization' or 'relaxation' which is irreversible. The value of glass transition is a function of composition of homogeneously mixed SD. It has been shown that the sensitivity of TMDSC is higher than conventional DSC (De Meuter *et al* 1999). Therefore it can be used to assess the amount of molecularly dispersed drug (Cilurzo *et al* 2002) and the fraction that is dispersed as separate molecules (Vasanthavada *et al* 2004).

Dissolution method

Release rate experiments cannot be used on a stand–alone basis to determine whether a solid solution has been formed or not. However, in conjunction with other physicochemical data, they provide a strong evidence for the formation of a molecularly disperse or nearly molecularly dispersed system. When the goal of preparing a SD is to improve the dissolution characteristics of the drug in question, the results of release rate experiments are obviously of prime importance in assessing the success of the approach. A well-designed release experiment will show whether the solubility of the drug and its dissolution rate has been enhanced, and also whether the resulting supersaturated solution is stable or tends to precipitate quickly. Comparison of results with those for pure drug powder and physical mixtures of the drug and carrier can help to indicate the mechanism by which the carrier improves dissolution: *via* solubilization and wetting effects which could be affected by a simple mixture of the components, or by formation of a SD/ solution.

Applications of SD

1) The rapid dissolution rates that result in an increase in the rate and extent of the absorption of drug and a reduction in pre-systemic metabolism
2) Transformation of the liquid form of the drug into a solid form (e.g. clofibrate and benzoylbenzoate) can be incorporated into PEG 6000 to give a solid (Chiou and Smith, 1971)
3) Avoidance of polymorphic changes and there by bioavailability problems, (as in the case of nabilon and PVP dispersions) (Thakkar *et al* 1977)
4) Protection of certain drugs by PEGs (e.g. cardiac glycosides) against decomposition by saliva to allow buccal absorption (Aleem, 2006)

The advantages of SD, compared with conventional capsule and tablet formulations, are schematically presented in the **Figure 1**.

Limitations of SD

1) Reproducibility of the physicochemical characteristics
2) Difficult handling and tackiness mainly due to conventional method of preparation and with some carriers like PEGs and PVP

3) Difficulty in incorporating into formulation of dosage forms due to increased bulk of the SD systems
4) Scale-up problems in manufacturing processes from laboratory research scale to that required for industrial level large scale production
5) Instability of the drug and vehicle- Several systems have shown changes in crystallinity and a decrease in dissolution rate with aging. The crystallization of ritonavir from the supersaturated solution in a SD system was responsible for the withdrawal of the ritonavir capsule (Norvir, Abbott) from the market (Serajuddin, 1999). Moisture and temperature have more of a deteriorating effect on SDs than on physical mixtures

CHALLENGES AND REMEDIAL STRATEGIES

A few alternative measures have been adopted recently to overcome the aforementioned problems and led to industrial scale production. The recent breakthroughs in the formulation of SD systems involve (1) the development of technologies to fill SDs directly into hard gelatin capsule and (2) the availability of surface-active and self-emulsifying carriers (3) electrostatic spinning (4) hot melt extrusion and (5) spraying on sugar beads using fluidized bed coating. As a result, there is renewed interest in such systems for use in commercial development of drug products (Serajuddin, 1997a).

Direct capsule-filling

Chatham (1987) reported the possibility of preparing PEG- based SD by filling drug-PEG melts in hard gelatin capsules. By using PEG with molecular weights ranging from 1000-8000, Serajuddin *et al* (1988a) however, demonstrated that a PEG by itself might not be a suitable carrier for SD of poorly water soluble drugs intended for direct filling in to hard gelatin capsules. They dissolved a poorly water-soluble drug, REV5901, in molten PEG 1000, PEG 1450 and PEG 8000 and filled the hot melts into hard gelatin capsules. At room temperature, solid plugs were formed inside the capsules, where the drug remained molecularly dispersed in the carriers. The dissolution of drug from all PEG based SDs was incomplete, because the water-soluble carrier dissolved more rapidly than the drug, drug-rich layers were formed over the surfaces of dissolving plugs, which prevented further dissolution of drug from SDs. The dissolution was practically zero at pH>2, where the solubility of drug was low and a drug layer coated the surface of the solid plug as soon as the capsule shell disintegrated.

Lyophilization technique

Freeze drying involves transfer of heat and mass to and from the product under preparation (Tsinontides *et al* 2004). This technique was proposed as an alternative technique to solvent evaporation. Lyophilization has been thought of a molecular mixing technique where the drug and carrier are co-dissolved in common solvent, frozen and sublimed to obtain a lyophilized molecular dispersion. The potential applications of this technique in manufacturing of SDs have been studied by several researchers (Betageri and Makarla, 1995; El-Badry and Fathy, 2006; Fathy and Sheha, 2000). van Drooge *et al* (2005) suggested the spray drying as a potential alternative of conventional processes to manufacture SDs.

Surface-active carriers

Serajuddin *et al* (1997b) achieved a complete dissolution of drug from SDs by using surface active or self-emulsifying agents. The vehicles acted as dispersing or emulsifying agents for the liberated drug, thus preventing the formation of any water-insoluble surface layers. Although the liberated drug remained undissolved in the dissolution medium when its concentration exceeded its saturation solubility, it was dispersed or emulsified in a finely divided state because of surface activity of the dissolved vehicle (Serajuddin *et al* 1988a). The high surface area of a drug produced in this way would facilitate its dissolution in the gastrointestinal fluid, especially in the presence of bile salts, lecithin and lipid digestion mixtures (Serajuddin *et al* 1988b). Therefore, a surface-active carrier may be preferable in almost all cases for the SD of poorly water-soluble drugs.

One surface-active carrier that has commonly been used in SD for the bioavailability enhancement of drugs is Gelucire 44/14 (Gattefosse Corp; France). (Dennis *et al* 1990) the suffixes 44 and 14 in its name refer, respectively, to its melting point and hydrophilic-lipophilic balance (HLB) value.

Another surface-active carrier that generated certain interest in recent years is vitamin E TPGS NF (Eastman, Kingsport, TN) (Aungst *et al* 1997). In search of alternative surface-active carriers, Serajuddin and co-workers demonstrated that a

commonly used surfactant, polysorbate 80, could be used in SDs by mixing it with solid PEG (Serajuddin *et al* 2008). SD in surface-active carriers may not be the answer to all bioavailability problems with poorly water-soluble drugs. One of the limitations of bioavailability enhancement by this method might be the low solubility of drug in available carriers (Dordunoo *et al* 1991). The desired doses of a drug cannot be solubilized and filled into hard gelatin capsules if adequate solubility in a carrier cannot be obtained.

On the other hand, if the drug is dissolved by heating in excess of its solubility in the carrier under normal storage condition, it may subsequently crystallize out from the SD. The crystallization of ritonavir from the supersaturated solution in a SD system was responsible for the withdrawal of the ritonavir capsule (Norvir, Abbott) from the market (Gines *et al* 1995). To ensure that a drug would not crystallize out of SD at the desired storage temperature, it is important to screen the drug solubility in different carriers at such a temperature. The relative solubility of a drug in different carriers may be determined by equilibrating the drug at an elevated temperature where all the carriers exists in a liquid state.

Electrostatic spinning

This technology used in the polymer industry combines solid solution/dispersion technology with nanotechnology (Reneker and Chun, 1996). This technology is now applied in the pharmaceutical field. In this process, a liquid stream of a drug/polymer solution is subjected to a potential between 5 and 30 kV. When electrical force overcomes the surface tension of drug polymer solution at air interface, fibers of submicron diameters are formed. As the solvent evaporates, the formed fibers can be collected on a screen to give nonwoven fabric, or they can be collected on a spinning mandril. The fiber diameter depends on surface tension, dielectric constant feeding rate, and electric field strength. Polymers with water solubility are useful in formulation of immediate release dosage forms, and those are water insoluble, may be biodegradable or non biodegradable, used in controlling dissolution properties. Fabrics generated by the water soluble carriers could be used in oral dosage formulations by direct compression of materials into the capsules. Itraconazole/HPMC nanofibers have been prepared using this technique (Verreck *et al* 2003).

Hot melt extrusion

It was used as a manufacturing tool in pharmaceutical industry as early as 1971. Many studies have been done on this process for preparation of SDs. It has been reported that melt extrusion of a miscible component result in amorphous solid solution formation, whereas extrusion of an immiscible component leads to amorphous drug dispersed in crystalline excipient (Breitenbach, 2002). The process has been useful in the preparation of SDs in a single step. The drug carrier mix is used in the hopper and is conveyed, mixed, and melted by the extruder. The die then shapes the melt in required form that can be further processed into conventional tablets and capsules. The advantages of hot melt extrusion include lower temperature and shorter residence time of the drug carrier mix (<2 minutes), absence of organic solvents, continuous operation possibility, minimum product wastage, good control of operating parameters and possibility to scale-up. A fast release dosage form of carbamazapine was prepared using lactose as a hydrophilic filter and PEG 4000 as a binder at a temperature below its melting point (Perissutti *et al* 2002). Solubility and dissolution rate of 17-beta estradiol hemihydrates was improved using PEG 6000, polyvinyl pyrrolidone (PVP) or a vinyl pyrrolidone / vinyl acetate copolymer and sucroester WE15 or Gelucire 44/14 employing this process (Hulsmann *et al* 2000).

Spraying on sugar beads using fluidized bed

This approach involves a fluidized bed coating system, wherein a drug carrier solution is sprayed on to the granular surface of excipients or sugar spheres to produce, either granules ready for tabletting or drug coated pellets for encapsulation in one step. The method has been applied for both controlled and immediate release SDs (Beten *et al* 1995; Ho *et al* 1996). Itraconazole (Sporanox oral, Janssen Pharmaceutica, Titusville, NJ) coated on sugar sphere, is made by layering on to sugar beads, a solution of drug and hydroxypropyl methyl cellulose (HPMC) in an organic solvent of dichloromethane and ethanol. A solid solution of drug in HPMC is produced upon coating (cosolvent evaporation) and controlled drying of coated beads in closed Wourster's process. As this thin film dissolves in water or organic fluid,

the molecularly dispersed itraconazole is released at supersaturated concentration. HPMC acts as stabilizer to inhibit recrystallization of itraconazole. The supersaturated solutions of itraconazole are sufficiently stable to allow the absorption and distribution. A modification to this method is reported; wherein use of organic solvent is avoided, involving the hot melt fluid bed technique (Kennedy and Neibergall, 1996).

CONCLUSION

In conclusion, the SD systems have realized as very useful formulation strategy to overcome the solubility problem of brick-dust molecules. Successful development of SD systems for preclinical, clinical and commercial use has been feasible in recent years due to the availability of surface-active and self-emulsifying carriers with relatively low melting points. In addition to bioavailability enhancement, much recent research on SD systems was directed toward the development of extended-release dosage forms. In regard to manufacturing considerations, the problem of total solvent removal in dispersions prepared by the solvent method needs to be addressed. The method involving spray coating of nonpareils or any other inert core with drug-carrier solution provides a one step process of achieving a multiunit dosage form of SDs. The problem of instability of the supersaturated state upon dissolution, which results in a stable form, has been dealt with by addition of a retarding agent. The problems involved in incorporating into formulation of dosage forms have been gradually resolved with the advent of alternative strategies.

REFERENCES

Aleem MA. Solid dispersion - An approach to enhance the dissolution rate of aceclofenac, Rajiv Gandhi University of Health Sciences, Banglore, Karnatka (India), M.Pharm thesis, 2006;1-24.

Aungst BJ, Nguyen NH, Rogers NJ, Rowe SM, Hussain MA, White SJ, Shum L. Amphiphilic vehicles improve the oral bioavailability of a poorly soluble HIV protease inhibitor at high doses. *Int. J. Pharm.* 1997;156(1):79-88. [DOI: 10.1016/S0378-5173(97)00189-0]

Betageri GV, Makarla KR. Enhancement of dissolution of glyburide by solid dispersion and lyophilization techniques. *Int. J. Pharm.* 1995;126(1-2):155-60. [DOI: 10.1016/0378-5173(95)04114-1]

Beten DB, Amighi K, Moes AJ. Preparation of controlled-release coevaporates of dipyridamole by loading neutral pellets in a fluidized-bed coating system. *Pharm. Res.* 1995;12(9):1269-72. [DOI: 10.1023/A:1016253119194]

Breitenbach J. Melt extrusion: from process to drug delivery technology. *Eur. J. Pharm. Biopharm.* 2002;54(2):107-17. [DOI: 10.1016/S0939-6411(02)00061-9]

Buckton G, Darcy P. The use of gravimetric studies to assess the degree of crystallinity of predominantly crystalline powders. *Int. J. Pharm.* 1995;123(2):265-71. [DOI: 10.1016/0378-5173(95)00083-U]

Chatham SM. The use of bases in SSM formulations. *STP Pharm.* 1987;3:575-82.

Chiou WL, Riegelman S. Pharmaceutical applications of solid dispersion systems. *J. Pharm. Sci.* 1971;60(9): 1281-1302. [DOI: 10.1002/jps.2600600902]

Chiou WL, Smith LD. Solid dispersion approach to the formulation of organic liquid drugs using polyethylene glycol 6000 as a carrier. *J. Pharm. Sci.* 1971;60(1):125-7. [DOI: 10.1002/jps.2600600127]

Cilurzo F, Minghetti P, Casiraghi A, Montanari L. Characterization of nifedipine solid dispersions. *Int. J. Pharm.* 2002;242(1-2):313-7. [DOI: 10.1016/S0378-5173(02)00173-4]

Corrigan OI. Mechanisms of dissolution of fast release solid dispersions. *Drug Dev. Ind. Pharm.*1985;11(2-3):697-724. [DOI: 10.3109/03639048509056896]

Corrigan OI. Retardation of polymeric carrier dissolution by dispersed drugs: Factors influencing the dissolution of solid dispersions containing polyethlene glycols. *Drug Dev. Ind. Pharm.* 1986;12(11-13):1777-93. [DOI: 10.3109/03639048609042609]

Daabis NA, Abd-Elfattah S, el-Banna HM. Physicochemical study of drug binary systems. 2. Khellin-urea system, *Pharmazie* 1974;29(6):400-4.

De Meuter P, Rahier H, Van Mele B. The use of modulated temperature differential scanning calorimetry for the characterisation of food systems. *Int. J. Pharm.* 1999;192(1):77-84. [DOI: 10.1016/S0378-5173(99)00274-4]

Dennis AB, Farr SJ, Kellaway IW, Taylor G, Davidson R. In vivo evalution of rapid release and sustained release Gelucire capsule formulations. *Int. J. Pharm*. 1990;65(1-2):85-100. [DOI: 10.1016/0378-5173(90)90013-T]

Dhirendra K, Lewis S, Udupa N, Atin K. Solid dispersions: a review. *Pak. J. Pharm. Sci*. 2009;22(2):234-46.

Dordunoo SK, Ford JL, Rubinstein MH. Preformulation studies on solid dispersions containing triamterene or temazepam in polyethylene glycols or Gelucire 44/14 for liquid filling of hard gelatin capsules. *Drug Dev. Ind. Pharm.* 1991;17(12):1685-1713. [DOI: 10.3109/03639049109057315]

Dua K, Pabreja K, Sharma VK, Sara UVS, Ramana MV. Solid dispersion technology. *Pharmabiz* 2009; September 10, Thursday.

Dubois J-L, Ford JL. Similarities in the release rates of different drugs from polyethylene glycol 6000 solid dispersions. *J. Pharm. Pharm.* 1985;37(7):494-95. [DOI: 10.1111/j.2042-7158.1985.tb03048.x]

El-Badry M, Fathy M. Enhancement of the dissolution and permeation rates of meloxicam by formation of its freeze-dried solid dispersions in polyvinylpyrrolidone K-30. *Drug Dev. Ind. Pharm.* 2006;32(2):141-50. [DOI: 10.1080/03639040500465983]

Fathy M, Sheha M. *In vitro* and *in vivo* evaluation of an amylobarbitone/hydroxypropyl-beta-cyclodextrin complex prepared by a freeze-drying method. *Pharmazie* 2000;55(7):513-7.

Ford JL, Rubinstein MH. Phase equilibria and dissolution rates of indomethacin-polyethylene glycol 6000 solid dispersions. *Pharm. Acta Helv.* 1978;53(11):327-32.

Ghaderi R. A supercritical fluids extraction process for the production of drug loaded biodegradable microparticles, Acta Universitatis Upsaliensis, Ph.D Thesis, Uppsala University, Sweden, 2000;1-46.

Gines JM, Veiga MD, Arias MJ, Rabasco AM. Elaboration and thermal study of interactions between cinnarizine and gelucire® 53/10 physical mixtures and solid dispersions. *Int. J. Pharm.* 1995;126(1-2):287-91. [DOI: 10.1016/0378-5173(95)04140-0]

Goldberg AH, Gibaldi M, Kanig JL. Increasing dissolution rates and gastrointestinal absorption of drugs *via* solid solutions and eutectic mixtures II: Experimental evaluation of a eutectic mixture: Urea-acetaminophen system. *J. Pharm. Sci.* 1966;55(5):482-7. [DOI: 10.1002/jps.2600550507]

Higuchi WI. Diffusional models useful in biopharmaceutics. Drug release rate processes. *J. Pharm. Sci*. 1967;56(3):315-24. [DOI: 10.1002/jps.2600560302]

Hite M, Turner S, Federici C. Part 1: Oral delivery of poorly soluble drugs. *Pharmaceutical Manufacturing and Packing Sourcer* Summer 2003;03:1-3.

Ho H-O, Su H-L, Tsai T, Sheu M-T. The preparation and characterization of solid dispersions on pellets using a fluidized-bed system. *Int. J. Pharm.* 1996;139(1-2):223-9. [DOI: 10.1016/0378-5173(96)04594-2]

Hulsmann S, Backensfeld T, Keitel S, Bodmeier R. Melt extrusion-an alternative method for enhancing the dissolution rate of 17β-estradiol hemihydrate. *Eur. J. Pharm. Biopharm.* 2000;49(3):237-42. [DOI: 10.1016/S0939-6411(00)00077-1]

Jovanovic N, Bouchard A, Hofland GW, Witkamp G-J, Crommelin DJA, Jiskoot W. Stabilization of proteins in dry powder formulations using supercritical fluid technology. *Pharm. Res.* 2004;21(11):1955-69. [DOI: 10.1023/B:PHAM.0000048185.09483.e7]

Kang BK, Lee JS, Chon SK, Jeong SY, Yuk SH, Khang G, Lee HB, Cho SH. Development of self-microemulsifying drug delivery systems (SMEDDS) for oral bioavailability enhancement of simvastatin in beagle dogs. *Int. J. Pharm.* 2004;274(1-2):65-73. [DOI: 10.1016/j.ijpharm.2003.12.028]

Karavas E, Ktistis G, Xenakis A, Georgarakis E. Effect of hydrogen bonding interactions on the release mechanism of felodipine from nanodispersions with polyvinylpyrrolidone. *Eur. J. Pharm. Biopharm.* 2006;63(2):103-14. [DOI: 10.1016/j.ejpb.2006.01.016]

Kaushal AM, Gupta P, Bansal AK. Amorphous drug delivery systems: molecular aspects, design and performance. *Crit. Rev. Ther. Drug Carrier Syst.* 2004;21(3):133-93. [DOI: 10.1615/CritRevTherDrugCarrierSyst.v21.i3.10]

Kennedy JP, Neibergall PJ. Development and optimization of a solid dispersion hot-melt fluid bed coating method. *Pharm. Dev. Technol.* 1996;1(1):51-62. [DOI: 10.3109/10837459609031418]

Leuner C, Dressman J. Improving drug solubility for oral delivery using solid dispersions. *Eur. J. Pharm. Biopharm.* 2000;50(1):47-60. [DOI: 10.1016/S0939-6411100)00076-X]

Lloyd GR, Craig DQM, Smith A. A calorimetric investigation into the interaction between paracetamol and polyethylene glycol 4000 in physical mixes and solid dispersions. *Eur. J. Pharm. Biopharm.*1999;48(1):59-65. [DOI: 10.1016/S0939-6411(99)00022-3]

Muhrer G, Meier U, Fusaro F, Albano S, Mazzotti M. Use of compressed gas precipitation to enhance the dissolution behavior of a poorly water-soluble drug: Generation of drug microparticles and drug-polymer solid dispersions. *Int. J. Pharm.* 2006;308(1-2):69-83. [DOI: 10.1016/j.ijpharm.2005.10.026]

Perissutti B, Newton JM, Podczeck F, Rubessa F. Preparation of extruded carbamazepine and PEG 4000 as a potential rapid release dosage form. *Eur. J. Pharm. Biopharm.* 2002;53(1):125-32. [DOI: 10.1016/S0939-6411(01)00209-0]

Phillips EM, Stella VJ. Rapid expansion from supercritical solutions: applications to pharmaceutical processes. *Int. J. Pharm.* 1993;94(1-3):1-10. [DOI: 10.1016/0378-5173(93)90002-W]

Pokharkar VB, Mandpe LP, Padamwar MN, Ambike A, Mahadik KR, Paradkar A. Development, characterization and stabilization of amorphous form of low Tg drug. *Powder Technol*. 2006;167(1):20-5. [DOI: 10.1016/j.powtec.2006.05.012]

Reneker DH, Chun I. Nanometer diameter fibers of polymers produced by electro-spinning. *Nanotechnology* 1996;7(3):216-23. [DOI: 10.1088/0957-4484/7/3/009]

Sebhatu T, Angberg M, Ahlneck C. Assessment of the degree of disorder in crystalline solids by isothermal microcalorimetry. *Int. J. Pharm.* 1994;104(2):135-44. [DOI: 10.1016/0378-5173(94)90188-0]

Sekiguchi K, Obi N. Studies on absorption of eutectic mixture. I. A comparison of the behavior of eutectic mixture of sulphathiazole and that of ordinary sulphathiazole in man. *Chem. Pharm. Bull.* 1961;9(11):866-72.

Sekiguchi K, Obi N, Ueda Y. Studies on absorption of eutectic mixture. II. Absorption of fused conglomerates of chloramphenicol and urea in rabbits. *Chem. Pharm. Bull.* 1964;12(2):134-44.

Serajuddin ATM. Bioavailability enhancement of poorly water-soluble drugs by solid dispersion in surface-active vehicles: A recent breakthrough. *La Gazette de l'ApGI* (France) 1997a;14:144-5.

Serajuddin ATM. Solid dispersion of poorly water-soluble drugs: Early promises, subsequent problems, and recent breakthroughs. *J. Pharm. Sci.* 1999;88(10):1058-66. [DOI: 10.1021/js980403l]

Serajuddin ATM, Li P, Haefele TF. Development of lipid-based drug delivery systems for poorly water-soluble drugs as viable oral dosage forms - present status and future prospects. *Am. Pharm. Rev.* 2008;11(2):34-42.

Serajuddin ATM. Bioavailability enhancement of poorly water soluble drugs by solid dispersions in surface active and self-emulsifying vehicles. *Bull. Techniq. Gattefosse* 1997b;90:43-50.

Serajuddin ATM, Sheen P-C, Mufson D, Bernstein DF, Augustine MA. Effect of vehicle amphiphilicity on the dissolution and bioavailability of a poorly water-soluble drug from solid dispersions. *J. Pharm. Sci.* 1988a;77(5):414-7. [DOI: 10.1002/jps.2600770512]

Serajuddin ATM, Sheen P-C, Mufson D, Bernstein DF, Augustine MA. Physicochemical basis of increased bioavailability of a poorly water-soluble drug following oral administration as organic solutions. *J. Pharm. Sci.* 1988b;77(4):325-9. [DOI: 10.1002/jps.2600770409]

Squillante E, Neduvelil S. Preparation of sustained-release chlorpheniramine maleate powders using supercritical fluid processing technology. *AAPS Annual Meeting*, November 14-18, 1999; Poster 3617.

Tachibana T, Nakamura A. A method for preparing an aqueous colloidal dispersion of organic materials by using water-soluble polymers: dispersion of β-carotene by polyvinylpyrrolidone. *Colloid. Polym. Sci.* 1965;203(2):130-3. [DOI: 10.1007/BF01507758]

Taylor LS, Zografi G. Spectroscopic characterization of interactions between PVP and indomethacin in amorphous molecular dispersions. *Pharm. Res.* 1997;14(12):1691-8. [DOI: 10.1023/A:1012167410376]

Thakkar AL, Hirsch CA, Page JG. Solid dispersion approach for overcoming bioavailability problems due to polymorphism of nabilone, a cannabinoid derivative. *J. Pharm. Pharmacol.* 1977;29(1):783-4. [DOI: 10.1111/j.2042-7158.1977.tb11468.x]

Tsinontides SC, Rajniak P, Pham D, Hunke WA, Placek J, Reynolds SD. Freeze drying-principles and practice for successful scale-up to manufacturing. *Int. J. Pharm.* 2004;280(1-2):1-16. [DOI: 10.1016/j.ijpharm.2004.04.018]

van Drooge D-J, Hinrichs WL, Dickhoff BH, Elli MN, Visser MR, Zijlstra GS, Frijlink HW. Spray freeze drying to produce a stable Delta(9)-tetrahydrocannabinol containing inulin-based solid dispersion powder suitable for inhalation. *Eur. J. Pharm. Sci.* 2005;26(2):231-40. [DOI: 10.1016/j.ejps.2005.06.007]

Vasanthavada M, Tong W-Q, Joshi Y, Kislalioglu MS. Phase behavior of amorphous molecular dispersions I: Determination of the degree and mechanism of solid solubility. *Pharm. Res.* 2004;21(9):1598-1606. [DOI: 10.1023/B:PHAM.0000041454.76 342.0e]

Verreck G, Chun I, Peeters J, Rosenblatt J, Brewster ME. Preparation and characterization of nanofibers containing amorphous drug dispersions generated by electrostatic spinning. *Pharm. Res.* 2003;20(5):810-7. [DOI: 10.1023/A:1023450006281]

Willard HH, Merritt Jr LL, Dean JA. Instrumental methods of Analysis, 4th edition, Van Nostrand Reinhold Company: New York, 1965; 198-238.

*****