



## A REVIEW ON SOLID DISPERSION



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### Abstract

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The poor solubility and low dissolution rate of poorly water soluble drugs in the aqueous gastro-intestinal fluids often cause insufficient bioavailability rather than the limited permeation through the epithelial and the formulation of poorly soluble drugs for oral delivery now presents one of the major challenges to formulation scientists in the industries. The term 'solubility' is defined as maximum amount of solute that can be dissolved in a given amount of solvent. Quantitatively it is defined as the concentration of the solute in a saturated solution at a certain temperature. In qualitative terms, solubility may be defined as the spontaneous interaction of two or more substances to form a homogenous molecular dispersion. Improving oral bioavailability of drugs those given as solid dosage forms remains a challenge for the formulation scientists due to solubility problems. The dissolution rate could be the rate-limiting process in the absorption of a drug from a solid dosage form of relatively insoluble drugs. Therefore increase in dissolution of poorly soluble drugs by solid dispersion technique presents a challenge to the formulation scientists. Solid dispersion techniques have attracted considerable interest of improving the dissolution rate of highly lipophilic drugs thereby improving their bioavailability by reducing drug particle size, improving wettability and forming amorphous particles. Solubility is a most important parameter for the oral bio availability of poorly soluble drugs. Dissolution of drug is the rate determining step for oral absorption of the poorly water soluble drugs, which can subsequently affect the in vivo absorption of drug.

## **INTRODUCTION:**

Solid dispersion was introduced in the early 1970s, refers to a group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug. There are different approaches which can be used for increasing the dissolution of the poorly soluble drugs. Chiou and Riegelman defined the term solid dispersion as “a dispersion involving the formation of eutectic mixtures of drugs with water soluble carriers by melting of their physical mixtures”; they classified solid dispersions into the following representative types <sup>[1,2]</sup>

- ❖ Simple eutectic mixtures,
- ❖ solid solutions,
- ❖ glass solutions and glass suspensions,
- ❖ amorphous precipitations in a crystalline carrier,
- ❖ compound or complex formation, and
- ❖ Combinations of the previous five types.

While Corrigan (1985) suggested the definition as being a ‘product formed by converting a fluid drug-carrier combination to the solid state’. This strategy includes

complete removal of drug crystallinity, and molecular dispersion of the poorly soluble compound in a hydrophilic polymeric carrier. Solid dispersion is a promising approach to improve the dissolution and bioavailability of hydrophobic drugs. The preparation and storage conditions of solid dispersions are crucial since changes may alter the dissolution characteristics of the active ingredients. The development of solid dispersions as a practically viable method to enhance bioavailability of poorly water-soluble drugs overcame the limitations of previous approaches such as salt formation, solubilization by co solvents, and particle size reduction. When the solid dispersion 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 <sup>[3,4]</sup>.

The solubility of Cefixime Trihydrate is soluble in methanol but insoluble in water. Cefixime Trihydrate is absorbed orally as 40 – 50% and 50% excreted unchanged in Urine. Its serum half life is 3 – 4 hours. Because of poor solubility of Cefixime Trihydrate it is prepared as sold dispersions

by using various techniques like Physical mixing, Co – grinding method , kneading technique and solvent evaporation technique <sup>[5,6]</sup>.

Limited in drug absorption results poor bioavailability of drug. In GI Tract the absorption of drug can be limited by the various factors with the most poor aqueous solubility or poor membrane permeability of the drug molecule. When the active ingredient can be delivered as GIT orally, it first dissolved in intestinal fluids before it reach to systemic circulation. Therefore a drug having poor aqueous solubility will typically exhibit in dissolution rate limitation and absorption and a drug with poor membrane permeability will exhibit the permeation rate absorption limited. So that oral bioavailability of drugs can be improved by the enhancing solubility and dissolution rate of poorly water soluble drugs , and another is enhancing the permeability of poor permeable drugs.

#### **PREPARATION OF SOLID DISPERSIONS**

Solid dispersions can be prepared by the various methods those are deals with the mixing of matrix and a drug, preferably on a molecular level, while the matrix and drug

are generally poorly miscible. During the preparation of solid dispersion techniques, de-mixing and formation of different phases are observed. Phase separations like crystallization or amorphous of drug clusters formation are difficult to control and therefore unwanted. So the phase separation can be minimized by the rapid cooling procedure. In generally phase separation can be prevented by maintaining a low molecular mobility of matrix and drug during preparation. And also, maintain the driving force by keep the mixture at an elevated temperature, there by maintain miscibility for as long as possible <sup>[6,7]</sup>.

#### **ADVANTAGES OF SOLID DISPERSIONS** <sup>[8,9,10]</sup>

##### **Particles with reduced particle size**

Molecular dispersions, as solid dispersions, represent the last state on particle size reduction, and after carrier dissolution the drug is molecularly dispersed in the dissolution medium. Solid dispersions apply this principle to drug release by creating a mixture of a poorly water soluble drug and highly soluble carriers. A high surface area is formed, resulting in an increased dissolution rate and, consequently, improved bioavailability.

### **Particles with improved wet ability**

A strong contribution to the enhancement of drug solubility is related to the drug wettability improvement verified in solid dispersions. It was observed that even carriers without any surface activity, such as urea improved drug wettability. Carriers with surface activity, such as cholic acid and bile salts. When used, can significantly increase the wettability property of drug. Moreover, carriers can influence the drug dissolution profile by direct dissolution or co-solvent effects.

### **Particles with higher porosity**

Particles in solid dispersions have been found to have a higher degree of porosity. The increase in porosity also depends on the carrier properties; for instance, solid dispersions containing linear polymers produce larger and more porous particles than those containing reticular polymers and, therefore, result in a higher dissolution rate. The increased porosity of solid dispersion particles also hastens the drug release profile.

### **Drugs in amorphous state**

Poorly water soluble crystalline drugs, when in the amorphous state tend to have higher solubility. The enhancement of drug release can usually be achieved using the drug in its amorphous state, because no energy is required to break up the crystal lattice during the dissolution process. In solid dispersions, drugs are presented as supersaturated solutions after system dissolution, and it is speculated that, if drugs precipitate, it is as a meta stable polymorphic form with higher solubility than the most stable crystal form. For drugs with low crystal energy (low melting temperature or heat of fusion), the amorphous composition is primarily dictated by the difference in melting temperature between drug and carrier. For drugs with high crystal energy, higher amorphous compositions can be obtained by choosing carriers, which exhibit specific interactions with them.

### **EVALUATION OF PREPARED SOLID DISPERSIONS** <sup>[11,12]</sup>

#### **Percentage yield**

Percentage practical yield were calculated to know about percent yield or efficiency of

any Method, thus it helps in selection of appropriate method of production. Solid dispersions were collected and weighed to determine practical yield (PY) from the following equation

Practical mass

### Drug content

The Physical mixture and solid dispersion equivalent to 50 mg of drug were taken and dissolved separately in 100 ml of phosphate buffer pH 7.2. The solutions were filtered and were further diluted such that the absorbance falls within the range of standard curve. The absorbance's of solutions were determined at 288 nm by UV-visible spectrophotometer. The actual drug content was calculated using the following equation as follows

Theoretical drug content

SOLID DISPERSION TECHNIQUES [13,14,15]

Solvent evaporation method

Basic process of preparing solid dispersion consists of dissolving the drug and the polymeric carrier in a common solvent such as ethanol, chloroform, or a mixture of ethanol and dichloromethane. In some

cases, large volume of solvents as well as heating may be required to enable complete dissolution of drug and carrier. To minimize the volume of organic solvent required, some investigators have reported the use of co-solvents. The main advantage of the solvent method is thermal decomposition of drugs or carriers can be prevented because of the relatively low temperatures required for the evaporation of organic solvents. However, solvent methods show many disadvantages such as; expensive, ecological, and difficult to find common and removable solvents, difficulty in completely removing liquid solvent, difficulty of reproducing crystal form.

Solvent	Melting point(°c)	Boiling point(°c)	Vapour pressure at 25°C (kPa)
Water	0	100	3.16
Methanol	-93.9	65	16.9
Ethanol	-117	78.5	5.79
1-propanol	-85.8	97.4	2.27
2-propanol	-127	82.4	5.85
Chloroform	-63	62	26.1
Dimethylsulphoxide	19	189	0.08
Acetic acid	17	118	1.64
1,4-dioxane	12	102	4.92
2-methyl-2-propanol (TBA)	25	82	5.49

Table 1.1: Different solvents used in solvent Evaporation method

#### Fusion method/Melting Method

The fusion method is sometimes referred to as the melt method. The first solid dispersions created for pharmaceutical applications were prepared by the fusion method. The melting or fusion method was first proposed by Sekiguchi and Obi to prepare fast release solid dispersion dosage forms. The physical mixture of a drug and a water-soluble carrier was heated directly until it gets melted. The melted mixture was then cooled and solidified rapidly in an ice bath under rigorous stirring. The final solid mass was crushed, pulverized, and sieved. Such a technique was subsequently employed with some modification by Goldberg et al. and Chiou and Riegelman. The solidified masses were often found to require storage of 1 or more days in desiccators at ambient temperatures for hardening and ease of powdering. The fusion method has serious limitations. Firstly, a major disadvantage is that the method can only be applied when drug and matrix are compatible and when they mix well at the heating temperature. When drug and matrix are incompatible two liquid phases or a suspension can be observed in the heated mixture, which results in an

inhomogeneous solid dispersion. This can be prevented by using surfactants. Secondly, a problem can arise during cooling when the drug-matrix miscibility changes. In this case phase separation can occur. Indeed, it was observed that when the mixture was slowly cooled, crystalline drug occurred, whereas fast cooling yielded amorphous solid dispersions. Thirdly, degradation of the drug and or matrix can occur during heating to temperatures necessary to fuse matrix and drug.

#### Hot melt extrusion

Hot-melt extrusion (HME) technique represents a novel application of polymer processing technology to prepare pharmaceutical dosage forms. The process involves embedding a drug in a polymer while shaping the composite material to form a pharmaceutical product. This technique is same as the fusion method. The only difference is that in this method, intense mixing of the components is induced by the extruder. High shear forces results in to the high local temperature in the extruder and that can be problematic for the heat sensitive materials. When compared to melting in a vessel, the

product stability and dissolution are similar, but melt extrusion offers the potential to shape the heated drug-matrix mixture into implants, ophthalmic inserts, or oral dosage forms. Just like in the traditional fusion process, miscibility of drug and matrix can be a problem. Solubility parameters are investigated to predict the solid state miscibility and to select matrices suitable for melt extrusion. High shear forces resulting in high local temperatures in the extruder are a problem for heat sensitive materials.

#### Supercritical fluid technology (SCF)

SCF techniques can be adopted for the preparation of solvent free solid dispersion dosage forms to enhance the solubility of poorly soluble compounds. Super critical fluid is the one where substances existing as a single fluid phase above their critical temperature and pressure. Methodology includes a very fine dispersion of hydrophobic drug in the hydrophilic carrier. Carbon dioxide is the most commonly used SCF because it is chemically inert, non toxic and non flammable:

#### Dropping method

The dropping method was developed by Bulau and Ulrich (1977) to facilitate the crystallization of different chemicals. This method is a new procedure for producing round particles from melted solid dispersions. Methodology includes that the solid dispersion of a melted drug-carrier mixture is dropped onto a cooling plate, where it get solidifies into round particles. The size and shape of the particles can be influenced by factors such as the viscosity of the melt and the size of the pipette. As viscosity is highly temperature dependent, it is very important to adjust the temperature so that, when the melt is dropped onto the plate, it solidifies into a spherical shape. The dropping method does not use organic solvents and therefore has none of the problems associated with solvent evaporation.

#### Electrostatic Spinning Method

This technology is used in polymer industry where in it combines solid solution/dispersion technology with nanotechnology. In this process, a potential between 5 and 30 kV is applied on the liquid stream of a drug/polymer solution. And as when the electrical forces overcome

the surface tension of the drug/polymer solution at the air interface, fibers of submicron diameter are formed. After evaporating the solvent, the formed fibers can be collected on a screen.

#### Co-precipitation method

In this method, while during constant stirring, a non solvent is added drop wise to the drug and carrier solution and the drug and carrier are co-precipitated to get micro particles, and then this micro particle suspension is filtered and dried.

#### Characterization of solid dispersion

Detection of crystallinity in solid dispersions<sup>[16, 17]</sup>

Several different molecular structures of the drug in the matrix can be encountered in solid dispersions. Many attempts have been made to investigate the molecular arrangement in solid dispersions. However, most effort has been put into differentiate between amorphous and crystalline material. For that purpose many techniques are available which detect the amount of crystalline material in the dispersion. The amount of amorphous material is never measured directly but is

mostly derived from the amount of crystalline material in the sample. It should be noted that through the assessment of crystallinity as method to determine the amount of amorphous drug it will not be revealed whether the drug is present as amorphous drug particles or as molecularly dispersed molecules.

Currently, the following techniques are available to detect the degree of crystallinity

1. Powder X-ray diffraction can be used to qualitatively detect material with long range order. Sharper diffraction peaks indicate more crystalline material. Recently developed X-ray equipment is semi-quantitative.
2. Infrared spectroscopy (IR) can be used to detect the variation in the energy distribution of interactions between drug and matrix. Sharp vibrational bands indicate crystallinity. Fourier Transformed Infrared Spectroscopy (FTIR) was used to accurately detect crystallinities ranging from 1 to 99% in pure material. However in solid dispersions only qualitative detection was possible



3. Water vapour sorption can be used to discriminate between amorphous and crystalline material when the hygroscopicity is different. This method requires accurate data on the hygroscopicity of both completely crystalline and completely amorphous samples.

#### 4. Isothermal Micro calorimetry

Measures the crystallization energy of amorphous material that is heated above its glass transition temperature. However, this technique has some limitations. Firstly, this technique can only be applied if the physical stability is such that only during the measurement crystallization takes place. Secondly, it has to be assumed that all amorphous material crystallizes. Thirdly, in a binary mixture of two amorphous compounds a distinction between crystallization energies of drug and matrix is difficult.

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

6. Macroscopic techniques that measure mechanical properties that are different for amorphous and crystalline material can be indicative for the degree of crystallinity. Density measurements and Dynamic Mechanical Analysis (DMA) determine the modulus of elasticity and viscosity and thus affected by the degree of crystallinity. However, also these techniques require knowledge about the additivity of these properties in intimately mixed binary solids.

7. A frequently used technique to detect the amount of crystalline material is Differential Scanning Calorimetry. In DSC, samples are heated with a constant heating rate and the amount of energy necessary for that is detected. With DSC the temperatures at which thermal events occur can be detected. Thermal events can be a glass to rubber transition, (re)crystallization, melting or degradation. Furthermore, the melting and (re)crystallization energy can be quantified. The melting energy can be used to detect the amount of crystalline material. Possibly, the re crystallization energy can be used to calculate the amount of amorphous material provided, that all amorphous

material is transformed to the crystalline state.

Detection of molecular structure in amorphous solid dispersions<sup>[17,18]</sup>

The properties of a solid dispersion are highly affected by the uniformity of the distribution of the drug in the matrix. The stability and dissolution behavior could be different for solid dispersions that do not contain any crystalline drug particles, i.e. solid dispersions of type V and VI or for type II and III. However, not only the Knowledge on the physical state (crystalline or amorphous) is important; the distribution of the drug as amorphous or crystalline particles or as separate drug molecules is relevant to the properties of the solid dispersion too. Nevertheless, only very few studies focus on the discrimination between amorphous incorporated particles versus molecular distribution or homogeneous mixtures.

1. Confocal Raman Spectroscopy was used to measure the homogeneity of the solid mixture of ibuprofen in PVP. It was described that a standard deviation in drug content smaller than 10% was indicative of homogeneous distribution. Because of the

pixel size of 2  $\mu\text{m}^3$ , uncertainty remains about the presence of nano-sized amorphous drug particles.

2. Using IR or FTIR, the extent of interactions between drug and matrix can be measured. The interactions are indicative for the mode of incorporation of the drug, because separately dispersed drug molecules will have more drug-matrix interactions than when the drug is present in amorphous clusters or other multi-molecule arrangements

3. Temperature Modulated Differential

Scanning Calorimetry 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 transitions (reversible) are separated from crystallization or relaxation (irreversible) in amorphous materials. Furthermore, the value of the T<sub>g</sub> is a function of the composition of the homogeneously mixed solid dispersion. It has been shown that the sensitivity of TMDSC is higher than conventional DSC. Therefore this technique can be used to assess the amount of molecularly dispersed drug, and from that the fraction of drug

that is dispersed as separate molecules is calculated.

### Alternative strategies

#### Spraying on sugar beads using a fluidized bed coating system<sup>[18]</sup>

The approach involves a fluidized bed coating system, wherein a drug-carrier solution is sprayed onto the granular surface of excipients or sugar spheres to produce either granules ready for tableting or drug-coated pellets for encapsulation in one step. The method has been applied for both controlled- and immediate-release solid dispersions.

Itraconazole coated on sugar sphere, is made by layering onto sugar beads a solution of drug and hydroxyl propyl methylcellulose (HPMC) in an organic solvent of dichloromethane and ethanol. A solid solution of drug in HPMC is produced upon coating (co solvent evaporation) and controlled drying of coated beads in a closed Wurster process. As this thin film dissolves in water or gastric fluid, the molecularly dispersed itraconazole is released at supersaturated concentration. HPMC acts as a stabilizer to inhibit recrystallization of the itraconazole.

The supersaturated solutions of itraconazole are sufficiently stable to allow for absorption and distribution<sup>12</sup>.

#### Direct capsule filling

Direct filling of hard gelatin capsules with the liquid melt of solid dispersions avoids grinding-induced changes in the crystallinity of the drug. The filling of hard gelatin capsules has been feasible in molten dispersions of Triamterene-PEG 500 using a Zanasi LZ 64 capsule-filling machine. However, PEG was not a suitable carrier for the direct capsule-filling method as the water-soluble carrier dissolved more rapidly than the drug, resulting in drug-rich layers formed over the surface of dissolving plugs, which prevented further dissolution of the drug. A surfactant must be mixed with the carrier to avoid formation of a drug-rich surface layer (e.g., polysorbate 80 with PEG, phosphatidylcholine with PEG). The temperature of the molten solution should not exceed ~70°C because it might compromise the hard-gelatin capsule shell.

#### Surface-active carriers

The surface-active and self-emulsifying carriers for solid dispersion of poorly water-soluble drugs have been of great interest in

recent years. A surface-active carrier may be preferable in almost all cases for the solid dispersion of poorly water-soluble drugs. Two of the important surface-active carriers are Gelucire 44/14 and Vitamin E R-alpha-tocopheryl polyethylene glycol 1000 succinate (TPGS). Gelucire 44/14 has commonly been used in solid dispersion for the bioavailability enhancement of drugs. Gelucire 44/14 is a mixture of glyceryl and PEG 1500 esters of long-chain fatty acids and is official in the European Pharmacopoeia as lauryl macroglycerides; the suffixes 44 and 14 in its name refer, respectively, to its melting point and hydrophilic-lipophilic balance (HLB) value. Vitamin E TPGS National Formulary (NF) (Eastman, Kingsport, TN) is prepared by the esterification of the acid group of d-R-tocopheryl acid succinate by PEG 1000. The material has an HLB value of 13 and is miscible with water in all parts. Its melting point, however, is relatively low (38°C), and it may require mixing with other carriers to increase melting temperatures of formulations.

A commonly used surfactant, Polysorbate 80, when mixed with solid PEG, has also been reported to be an alternative surface-

active carrier. Polysorbate 80 is liquid at room temperature; it forms a solid matrix when it is mixed with a PEG because it incorporates within the amorphous regions of PEG solid structure. As much as 75% (wt/wt) Polysorbate 80 was incorporated, PEG remained semisolid, and the lowering of the melting temperature of the PEG used was <12°C. The PEG-polysorbate carriers have been found to enhance dissolution<sup>36</sup> and bioavailability of drugs from the solid dispersions. Incorporation of 5% (wt/wt) phosphatidyl-choline resulted in enhanced dissolution rate of nifedipine from a PEG-based solid dispersion. Pulverized solid dispersions in PEG containing varying amounts of ionic and nonionic surfactants, including sodium dodecyl sulfate and Polysorbate 80 gave increased dissolution rate of drug.

### **Conclusion**

Improving oral bioavailability of drugs those given as solid dosage forms remains a challenge for the formulation scientists due to solubility problems. The dissolution rate could be the rate-limiting process in the absorption of a drug from a solid dosage form of relatively insoluble drugs. Therefore

increase in dissolution of poorly soluble drugs by solid dispersion technique presents a challenge to the formulation scientists. Solid dispersion techniques have attracted considerable interest of improving the dissolution rate of highly lipophilic drugs thereby improving their bioavailability by reducing drug particle size, improving wettability and forming amorphous particles. Solubility is a most important parameter for the oral bio availability of poorly soluble drugs. Dissolution of drug is the rate determining step for oral absorption of the poorly water soluble drugs, which can subsequently

affect the in vivo absorption of drug. Currently only 8% of new drug candidates have both high solubility and permeability. Because of solubility problem of many drugs the bio availability of them gets affected and hence solubility enhancement becomes necessary. Solid dispersion technology is one of the possible modes that increase the solubility of poorly soluble drugs.

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