



## A REVIEW ON SOLID DISPERSION: A MODERN FORMULATION APPROACH IN DRUG DELIVERY SYSTEM

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Drugs those are given as solid dosage form and having low solubility often have a lack of flexibility in drug formulation and administration. The dissolution rate could be the rate-limiting process in the absorption of a drug from a solid dosage form of relatively insoluble drugs. Solid dispersion technologies are promising techniques for improving the water solubility, and hence dissolution and bioavailability of hydrophobic drugs. It is done for Biopharmaceutical Classification System (BCS) II Class drugs. Solid dispersion is the dispersion of one or more active ingredients in hydrophilic inert carrier matrix at molecular level. Solid dispersions of poorly water-soluble drugs with water-soluble carriers have been reduced the incidence of these problems and enhanced dissolution. The focus of this review article is on advantages, disadvantages and the method of preparation, and characterization of the solid dispersion. This review also discusses the recent advances in the field of solid dispersion technology.

Keywords: Solubility, Solid Dispersions, Carrier, Bioavailability

### INTRODUCTION

The enhancements of oral bioavailability of poorly water-soluble drugs often show poor bioavailability because of low and erratic levels of absorption<sup>[1]</sup> Oral bioavailability of drugs depends on its solubility and/or dissolution rate, therefore major problems associated with the drugs is its very low solubility in biological fluids, which results into poor bioavailability after oral administration<sup>[2]</sup>. Therapeutic effectiveness of a drug depends upon the bioavailability and ultimately upon the solubility of drug molecules. Solubility behavior of a drug is one of the key determinants of its oral bioavailability. In recent years, the number of poorly soluble drug candidates has increased tremendously. The formulation of poorly soluble drugs for oral delivery presents a challenge to the scientist. So the pharmaceutical researcher's focuses on two areas for improving the oral bioavailability of drugs that includes, enhancing solubility and dissolution rate of poorly water-soluble drugs, and enhancing permeability of poorly permeable drugs. It has been estimated that 40% of new chemical entities currently being discovered are poorly water soluble. Therefore lots of efforts have been made to increase dissolution of drug. Methods available

to improve solubility include salt formation, micronization and addition of solvent or surface active agents, nanosuspension, microemulsion, modification of crystal habits, self micro emulsifying drug delivery system and solid dispersion etc.

Solid dispersion (SD) is one of such methods and involves a dispersion of one or more active ingredients in an inert carrier or matrix in solid state. Among the various approaches to improve solubility, the solid dispersion technique has often proved to be the most successful in improving the dissolution and bioavailability of poorly soluble drugs because it is simple, economic, and advantageous.<sup>[3]</sup> The term solid dispersion refers to a group of solid products consisting of at least two different components, a hydrophilic matrix and a hydrophobic drug. The drug can be dispersed molecularly, in amorphous particles (clusters) or in crystalline particles. Pharmaceutical polymers are used to create this matrix and their selection is based on many factors, including physicochemical (e.g. drug-polymer miscibility and stability) and pharmacokinetic (e.g. rate of absorption) constraints.<sup>[4]</sup>

### ADVANTAGES OF SOLID DISPERSIONS

1. To reduced particle size,
2. For taste masking of the drug substance,

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- To obtain a homogenous distribution of small amount of drugs at solid state.
- To stabilize unstable drugs,
- To formulate sustained release dosage or prolonged release regimens of soluble drugs using poorly soluble or insoluble carriers<sup>[5]</sup>

### DISADVANTAGES OF SOLID DISPERSION

Although a great research interest is in solid dispersion in the past four decades, the commercial utilization is very limited. Problems of solid dispersion involve

- The physical and chemical stability of drugs and vehicles,
- Method of preparation,
- Reproducibility of its physicochemical properties,
- Formulation of solid dispersion into dosage forms, and
- Scale-up of manufacturing processes<sup>[6]</sup>

### METHODS OF PREPARATION OF SOLID DISPERSIONS

#### 1. Melting method

The melting or fusion method, involves the preparation of physical mixture of a drug and a water-soluble carrier and heating it directly until it melts. The melted mixture is then solidified rapidly in an ice-bath under vigorous stirring. The final solid mass is crushed, pulverized and sieved<sup>[5]</sup>. Appropriately this has undergone many modifications in pouring the homogenous melt in the form of a thin layer onto a ferrite plate or a stainless steel plate and cooled by flowing air or water on the opposite side of the plate. In addition, a super-saturation of a solute or drug in a system can often be obtained by quenching the melt rapidly from a high temperature. Under such conditions, the solute molecule is arrested in the solvent matrix by the instantaneous solidification process.<sup>[6]</sup>

#### 2. Solvent Evaporation method

In this method, the physical mixture of the drug and carrier is dissolved in a common solvent, which is evaporated until a clear, solvent free film is left. The film is further dried to constant weight. The first step in the solvent method is the preparation of a solution

containing both matrix material and drug<sup>[7]</sup>. The second step involves the removal of solvent(s) resulting in formation of a solid dispersion. Mixing at the molecular level is preferred, because this leads to optimal dissolution properties. 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.<sup>[8]</sup>

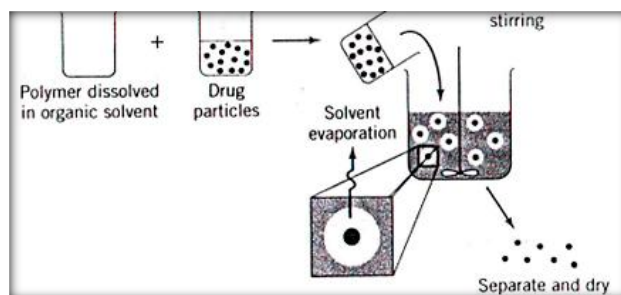


Fig 1: Solvent Evaporation Technique

#### 3. 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 compounds can be incorporated into polyethylene glycol6000 without significant loss of its solid property<sup>[9]</sup>. It is possible that the selected solvent or dissolved drug may not be miscible with the melt of the polyethylene glycol. 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.<sup>[10]</sup>

#### 4. Melt extrusion method

The drug/carrier mix is typically processed with a twin-screw extruder. The drug/carrier mix is simultaneously melted, homogenized and then extruded and shaped as tablets, granules, pellets, sheets, sticks or powder. The intermediates can then be further processed into

conventional tablets. An important advantage of the hot melt extrusion method is that the drug/carrier mix is only subjected to an elevated temperature for about 1 min, which enables drugs that are somewhat thermo labile to be processed.<sup>[11]</sup>

### 5. Lyophilisation Technique

Freeze-drying involves transfer of heat and mass to and from the product under preparation. This technique was proposed as an alternative technique to solvent evaporation. Lyophilisation has been thought of a molecular mixing technique where the drug and carrier are co dissolved in a common solvent, frozen and sublimed to obtain a lyophilized molecular dispersion. (Betageri GV et al). An important advantage of freeze drying is that the drug is subjected to minimal thermal stress during the formation of the solid dispersion. However, the most important advantage of freeze drying is that the risk of phase separation is minimized as soon as the solution is vitrified. An even more promising drying technique is spray-freeze drying. The solvent is sprayed into liquid nitrogen or cold dry air and the frozen droplets are subsequently lyophilized. The large surface area and direct contact with the cooling agent result in even faster vitrification, thereby decreasing the risk for phase separation to a minimum. Moreover, spray freeze drying offers the potential to customize the size of the particle to make them suitable for further processing or applications like pulmonary or nasal administration.<sup>[12]</sup>

### 6. Melt Agglomeration Process

This technique has been used to prepare SD wherein the binder acts as a carrier. In addition, SD(s) are prepared either by heating binder, drug and excipient to a temperature above the melting point of the binder (melt-in procedure) or by spraying a dispersion of drug in molten binder on the heated excipient (spray-on procedure) by using a high shear mixer. A rotary processor has been shown to be alternative equipment for melt agglomeration. The rotary processor might be preferable to the high melt agglomeration because it is easier to control the temperature and because a higher binder content can be incorporated in the agglomerates.

The effect of binder type, method of manufacturing and particle size are critical parameters in preparation of SD(s) by melt agglomeration. Since these parameters result in variations in dissolution rates, mechanism of agglomerate formation and growth, agglomerate size, agglomerate size distribution and densification of agglomerates. In addition the melt in procedure also results in homogenous distribution of drug in agglomerate.<sup>[13]</sup>

### 7. The use of surfactant

The utility of the surfactant systems in solubilization is well known. Adsorption of surfactant on solid surface can modify their hydrophobicity, surface charge, and other key properties that govern interfacial processes such as flocculation/dispersion, floatation, wetting, solubilization, detergency, enhanced oil recovery and corrosion inhibition<sup>[14]</sup>. Surfactants have also been reported to cause solvation/plasticization, manifesting in reduction of melting the active pharmaceutical ingredients, glass transition temperature and the combined glass transition temperature of solid dispersions. Because of these unique properties, surfactants have attracted the attention of investigators for preparation of solid dispersions.<sup>[15]</sup>

### 8. Electrospinning

Electrospinning is a process in which solid fibers are produced from a polymeric fluid stream solution or melt delivered through a millimeter-scale nozzle. This process involves the application of a strong electrostatic field over a conductive capillary attaching to a reservoir containing a polymer solution or melt and a conductive collection screen. Upon increasing the electrostatic field strength up to but not exceeding a critical value, charge species accumulated on the surface of a pendant drop destabilize the hemispherical shape into a conical shape (commonly known as Taylor's cone). Beyond the critical value, a charged polymer jet is ejected from the apex of the cone (as a way of relieving the charge built-up on the surface of the pendant drop). The ejected charged jet is then carried to the collection screen via the electrostatic force. The Coulombic repulsion force is responsible for the thinning of the charged jet during its

trajectory to the collection screen. The thinning down of the charged jet is limited by the viscosity increase, as the charged jet is dried. This technique has tremendous potential for the preparation of nanofibres and controlling the release of biomedicine, as it is simplest, the cheapest this technique can be utilized for the preparation of solid dispersions in future.<sup>[16]</sup>

### 9. Super Critical Fluid (SCF) Technology

Supercritical fluid methods are mostly applied with carbon dioxide (CO<sub>2</sub>), which is used as either a solvent for drug and matrix or as an anti-solvent. When supercritical CO<sub>2</sub> is used as solvent, matrix and drug are dissolved and sprayed through a nozzle, into an expansion vessel with lower pressure and particles are immediately formed. The adiabatic expansion of the mixture results in rapid cooling. This technique does not require the use of organic solvents and since CO<sub>2</sub> is considered environmentally friendly, this technique is referred to as 'solvent free'. The technique is known as Rapid Expansion of Supercritical Solution (RESS). However, the application of this technique is very limited, because the solubility in CO<sub>2</sub> of most pharmaceutical compounds is very low (<0.01wt- %) and decreases with increasing polarity. Therefore, scaling up this process to kilogram-scale will be impractical.<sup>[17]</sup>

### 10. 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. This molten dispersion forms a solid plug inside the capsule on cooling to room temperature, reducing cross contamination and operator exposure in a dust-free environment, better fill weight and content uniformity was obtained than with the powder-fill technique. 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.<sup>[18]</sup>

### 11. Dropping solution method

The dropping method facilitates the crystallization of different chemicals and produces round particles from melted solid dispersions. In laboratory-scale preparation, a solid dispersion of a melted drug-carrier mixture is pipetted and then dropped onto a plate, where it 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. Because 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 to a spherical shape. The use of carriers that solidify at room temperature may aid the dropping process. The dropping method not only simplifies the manufacturing process, but also gives a higher dissolution rate. It does not use organic solvents and, therefore, has none of the problems associated with solvent evaporation. The method also avoids the pulverization, sifting and compressibility difficulties encountered with the other melt methods. Disadvantages of the dropping method are that only thermo stable drugs can be used and the physical instability of solid dispersions is a further challenge.<sup>[19]</sup>

### 12. Co-precipitation method

Co-precipitation is a recognized technique for increasing the dissolution of poorly water soluble drugs, so as to consequently improve bioavailability. In this method nonsolvent is added drop wise to the drug and carrier solution, under constant stirring. In the course of the nonsolvent addition, the drug and carrier are co-precipitated to form micro particles. At the end, the resulted micro particle suspension is filtered and dried. The required quantity of polymer and the drug were mixed and then solvent was added to obtain clear solution. The Solution was first dried under vacuum at room temperature and kept inside incubator (37°C) for 12 hrs. Finally it was passed through sieves.<sup>[20]</sup>

### EVALUATION OF SOLID DISPERSION

**Estimation of drug content:** A quantity (100mg) of solid dispersion is placed in a beaker containing 100 ml of Phosphate buffer (7.4). The dispersion was vortexed

repeatedly to break up the solid dispersion and cause them to discharge their content completely. The solution is then filtered and analyzed spectrophotometrically using U V Spectrophotometry.<sup>[21]</sup>

**Drug Entrapment Efficiency (EE):** The drug entrapment efficiency can be calculated by following formula-

$$EE\% = \frac{\text{Actual drug content}}{\text{Theoretical drug content}} \times 100$$

**Particle Size Analysis and Morphological characteristics-** It can be done by using Scanning Electron Microscopy. Samples from each batch is to be taken and dispersed in Phosphate Buffer (pH 7.4).<sup>[22]</sup>

**Moisture Sorption Characteristics-** Solid dispersion is placed in Petridish and stored in an activated desiccating chamber at 10 degree C for one week to remove residual.<sup>[23]</sup>

#### Equilibrium Moisture Sorption

$$= \frac{\text{amount of moisture sorped at equilibrium}}{\text{dry weight of material}}$$

**In-vitro Drug Release Studies-** The dissolution profile for each solid dispersion as well as pure diclofenac powder is performed using rotatory paddle containing dissolution medium and further spectrophotometry is done.<sup>[24]</sup>

**Stability Study of the formulation-** is carried out on the best formulation and is packed in amber colored bottle, which is tightly plugged with cotton and capped with aluminium.<sup>[25]</sup>

**Differential Scanning Calorimetry (DSC)** Frequently used technique to detect the amount of crystalline material is Differential Scanning Calorimetry (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, recrystallization, melting or degradation. Furthermore, the melting & recrystallization energy can be quantified. The melting energy can be used to detect the amount of crystalline material.<sup>[26]</sup>

## CONCLUSIONS

Since the concept of solid dispersion technology was introduced in 1960s, great progresses have been made in

solid dispersion technology as solid dispersion offers a variety of opportunities. A single solid dispersion method cannot be universally accepted for a variety of drug materials. In developing a new solid dispersion system for a given drug, it is important to understand the physicochemical properties of the drug and carrier that best match the properties and find a solid dispersion method. The preparation method and the amount of the carrier also play a vital role in the enhancement of drug dissolution rate. Most of the solid dispersion work is in lab-scale setups; therefore the manufacturing process requires enough knowledge to scale up to the commercial scale.

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