

Review Article

## Solid dispersion a promising tool for drug solubility improvement

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### ARTICLE INFO

- Received 22 Jul 2018
- Revised 18 Aug 2018
- Accepted 28 Aug 2018

### Keywords:

- Solid dispersion
- Poorly soluble drugs
- Hydrophilic
- Matrix system
- Bioavailability

### ABSTRACT

The term solid dispersion refers to a group of solid products consisting of at least two different components, generally a hydrophilic matrix and hydrophobic drugs. The matrix can be either crystalline or amorphous. The drug can be dispersed molecularly, in amorphous particles or in crystalline particles. The formation of solid dispersion is a useful approach to enhance the dissolution rate of sparingly soluble drugs. The dissolution behavior is mostly affected, if the drug is present in the amorphous state or even dissolved in the carrier. However, such systems may be metastable and they tend to return to a more stable state, which can result in the recrystallization of the drugs. The different types of solid dispersions based on the molecular arrangement have been highlighted. Some of the practical aspects to be considered for the preparation of solid dispersions, such as selection of carrier and methods of physicochemical characterization are discussed. The development of solid dispersion as a practically viable method to enhance bioavailability of poorly water –soluble drugs overcome the limitation of previous approaches such as salt formation, solubilization by cosolvents, and particle size reduction.

### 1. INTRODUCTION

The term solid dispersion refers to a group of solid products consisting of at least two different components, generally a hydrophilic matrix and hydrophobic drugs. The matrix can be either crystalline or amorphous. The drug can be dispersed molecularly, in amorphous particles or in crystalline particles. In 1961, Sekiguchi and Obi developed this solid dispersion technology. This is an oral route of administration and it is most common and preferred method of delivery. Solid dispersion is improving the oral bioavailability of drugs with increase solubility and dissolution rate of poorly water soluble drugs [1].

Oral bioavailability of drugs depends on its solubility and/or dissolution rate, therefore major problems associated with these drugs was its very low solubility in biological fluids, which result into poor bioavailability after oral administration. A drug with poor aqueous solubility will typically exhibit dissolution rate limited absorption, and a drug with poor membrane permeation rate limited absorption. Therefore, pharmaceutical researcher's focuses on two areas for improving the oral bioavailability of drugs include:

- Enhancing solubility and dissolution rate of poorly water-soluble drugs.
- Enhancing permeability of poorly permeable drugs.

It has been estimated that 40% of new chemical entities currently being discovered are poorly water soluble. Unfortunately, many of these potential drugs are abandoned in the early stages of development due to the solubility problems. It is therefore important to realize the solubility problems of these drugs and methods for overcoming the solubility limitations are identified and applied commercially so that potential therapeutic benefits of these active molecules can be realized. Therefore lots of efforts have been made to increase dissolution of drugs [2].

Solid dispersion is one of such methods and involves a dispersion of one or more active ingredients in an inert carrier or matrix in solid state prepared by melting, dissolution in solvent or melting solvent method. There are various techniques such as, Particle size reduction, micronization, physical modification, nano-suspension, modification of crystal habit such as, polymorphs, pseudopolymorphs, complexation, solubilization, salt formation and use of cyclodextrins which can enhance the solubility and

dissolution rate of insoluble drug. But, these techniques are having some practical limitations. Solid dispersion technique overcomes these practical limitations. The formation of solid dispersion is a useful approach to enhance the dissolution rate of sparingly soluble drugs. The dissolution behavior is mostly affected, if the drug is present in the amorphous state or even dissolved in the carrier. However, such systems may be metastable and they tend to return to a more stable state, which can result in the recrystallization of the drugs. Therefore, the effects of an addition of high amounts of recrystallization inhibitors to the hydrophilic PEG on the properties of the solid dispersion were investigated. It is readily absorbed in GIT and transported through bound plasma proteins. It treats diabetes mellitus by reducing the platelet adhesiveness and aggregation by antagonizing the abnormal fibrin deposition on the vessel wall and by reducing the excessive response of the diabetes micro vessel. It is practically insoluble in water, sparingly soluble in acetone, slightly soluble in ethanol (96%) and freely soluble in dichloromethane [3].

The development of solid dispersion is a practically viable method to enhance bioavailability of poorly water –soluble drugs and it overcomes the limitation of previous approaches such as salt formation, solubilization by co-solvents and particle size reduction. Studies revealed that drugs in solid dispersion need not necessarily exist in the micronized state. A fraction of the drug might molecularly disperse in the matrix, thereby forming a solid dispersion. When the solid dispersion is exposed to aqueous media, the carrier dissolves and it releases as fine colloidal particles [4,5].

## 2. ADVANTAGES OF SOLID DISPERSIONS

There are various reasons for the improvement of solubility of poorly water-soluble drug using solid dispersion technology. The advantages of solid dispersions are as follows:

- Particles with reduced particle size.
- Particles with improved wettability.
- Particles with higher porosity.
- Drugs in amorphous state.
- Decreased crystalline structure of drug in to amorphous form.
- Improved dissolvability in water of a poorly water-soluble drug in a pharmaceutical.
- Masking the taste of the drug substance.
- Rapid disintegration oral tablets.
- Homogenous distribution of small amount of drugs at solid state.
- Stabilized unstable drugs.
- Dispense liquid or gaseous compounds.
- Formulate a faster release priming dose in a sustained release dosage form.

- Formulate sustained release dosage or prolonged release regimens of soluble drugs using poorly soluble or insoluble carriers [6-11].

## 3. TYPES OF SOLID DISPERSIONS

There are three types of solid dispersion

- Binary Solid Dispersion: It consists of drug and a polymeric carrier.
- Ternary Solid Dispersion: It consists of drug, a polymeric carrier and a surfactant.
- Surface Solid Dispersion: Surface solid dispersion is formulated with polymers such as polyvinyl pyrrolidone, polyethylene glycol and polyvinyl pyrrolidone-vinyl acetate polymer by fusion technique to improve its solubility [12-16].

## 4. METHODS OF PREPARATION OF SOLID DISPERSION

Various methods are used for preparation of solid dispersion. These methods are given bellow:-

- Melting/Fusion method
- Solvent method
- Melt extrusion methods
- Lyophilization techniques
- Melt agglomeration Process
- Spray drying method
- Electrospinning
- Super Critical Fluid (Scf) technology
- Kneading technique

### 4.1. Melting method or Fusion method

The melting or fusion method, first proposed by (Sekiguchi and Obi 1961) involves the preparation of physical mixture of a drug and a water-soluble carrier and heating it directly until it melted. The melted mixture is then solidified rapidly in an ice-bath under vigorous stirring. The final solid mass is crushed, pulverized and sieved. 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 supersaturation 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 on process. The quenching technique gives a much finer dispersion of crystallites when used for simple eutectic mixture [17].

The fusion method is sometimes called melt method, which is correct only when the starting materials are crystalline. Therefore, the more general term “fusion method” is preferred. The main advantages of this method are its simplicity and economy. Firstly, a major disadvantage is that the method is only

applied when the drug and matrix are compatible and when they mix well at the heating temperature. Traditional fusion method usually produces soft, tacky materials with poor flow properties and compressibility [17].

#### 4.2. Solvent 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. 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 that the thermal decomposition of drugs or carriers can be prevented because of the relatively low temperatures required for the evaporation of organic solvents. However, some disadvantages are associated with this method such as higher cost of preparation, difficulty in completely removing liquid solvent and possible adverse effect of traces of the solvent on the chemical stability [18].

#### 4.3. Hot-melt extrusion

This technology was first utilized predominantly in the plastic industry and to lesser extent in the food industry since 1930's. Many advantages of hot melt extrusion over conventional solid dosage form manufacturing picked the interest of pharmaceutical industry and researchers for the useful technology to prepare novel drug delivery system. This technique employs the use of extruders which consists of conveying system, for transportation and mixing of materials, and die system, which shapes the melt into required shape like pellets, granules, or powder. In this method solvents are not used therefore, it is environmentally friendly, economical and no residual solvent in the final product. Advantage of hot melt extrusion technique over melting method is the use of low temperature and short residence time which prevents the drug-carrier mixture from thermal degradation. Another advantage is that production is continuous therefore fewer batches are required and efficient scale-up from laboratory to large-scale production required. This method has several disadvantages these are: (i) high shear forces may produce high local temperature in the extruder therefore it may create a problem for heat sensitive materials, (ii) just like traditional fusion method, miscibility of drug and carrier matrix can be a problem [19].

#### 4.4. Spray drying

Spray drying method consists of dissolving or suspending the drug and polymer in a common solvent or solvent mixture and then drying it into a stream of heated air flow to remove the solvent. Due to the large surface area of the droplets, the solvent rapidly evaporates and solid dispersion is formed within seconds, which may be fast enough to phase separation. Spray drying usually yields drugs in the amorphous state, but sometimes

the drug may be partially crystallized during processing. Polyglycolized glycerides (Gelucire) are available with a range of properties depending on their hydrophilic lipophilic balance (HLB) over the range of 1 to 18 and melting point between 33° and 70°C. Preparation of SDs by conventional spray drying with polyglycolized glycerides has been problematic because a sticky and tacky mass of polyglycolized glycerides is obtained. Therefore, spray drying technique for polyglycolized glycerides has been used with combination with high melting lipids to solve this problem. Chauhan et al. in 2005, prepared solid dispersions of etoricoxib using spray drying technique with lipid carriers, mainly polyglycolized glycerides (Gelucire 50/13) and high melting lipids, namely, Compritol (atomized glyceryl dibehenate) or Sterotex K NF (hydrogenated cottonseed oil). They concluded that SDs of the purely water soluble drug etoricoxib was successfully prepared by spray drying using lipid carriers [20].

#### 4.5. Lyophilization (freeze drying)

An important advantage of freeze drying is that the drug is subjected to minimal thermal stress during the formation of the SDs. However, the most important advantage is that the risk of phase separation is minimized as soon as the solution is vitrified. Singh et al., in 2011, dissolved some selected solid dispersions in a minimum amount of cyclohexanol. Then this solution was rapidly solidified by transferring small portions with a Pasteur pipette onto the inner surface of a cold flask rotating in a -50°C methanol bath. After achieving a certain layer thickness, the flask was attached to the vacuum adaptor of the lyophilizer. The solvent was then sublimed under a pressure of 8-10mmHg and condensed onto a -75°C condenser. When the solvent was completely removed, they found that the nature of the powder residue was porous, light and fluffy mass [18].

#### 4.6. Electrostatic spinning method

Electrostatic spinning method involves the introduction of a liquid into an electric field whereby the liquid is caused to produce fibers. After being drawn from the liquid the fibers harden, which may involve mere cooling, chemical hardening or evaporation of solvent, and then hardened fibers may be collected upon a suitably charged surface. Tubular products comprising polyurethane fibers can be prepared by this electrostatic spinning method. One example of this type of tubular product is a vascular prosthesis, particularly a synthetic blood vessel. Other applications of this type of tubular products include the use of different kinds of ducts, e.g. urinary, air or bile as well as conduit through which for example a wire or other device or structure may pass or lie. The electrostatic spinning method has a few applications in pharmaceutical industry. In this method a drug-matrix solution is pumped through an orifice and then subjected to an electrical field to form fibers with a diameter of micro- or nano-scale. This method is limited to a few matrices because only a few high molecular weight materials are fiber forming materials. In this method electrical forces are used to

overcome the surface tension of drug-polymer solution at air interface, the fibers of submicron diameters are formed whose diameter depends upon feeding rate, dielectric constant, surface tension and electric field strength [19].

#### 4.7. Supercritical fluid technology

Supercritical fluid (SCF) technology offers tremendous potential and the low operating conditions (temperature and pressure) make the method more attractive for pharmaceutical research. In the pharmaceutical field, the supercritical fluid technology was industrially applied in the early 1980's. A supercritical fluid exists as a single phase above its critical temperature and pressure. The most commonly used supercritical fluids for a variety of applications include supercritical fluid carbon dioxide, nitrous oxide, water, methanol, ethanol, ethane, propane, n-hexane and ammonia. Carbon dioxide is one of the most commonly used SCFs because of its low critical temperature ( $T_c = 31.1^\circ\text{C}$ ) and pressure ( $P_c = 73.8$  bar). Apart from being nontoxic, nonflammable, and inexpensive, the low critical temperature of  $\text{CO}_2$  makes it attractive for processing heat-labile molecules. This technique consists of dissolving the drug and the inert carrier in a common solvent that is introduced into a particle formation vessel through a nozzle, simultaneously with  $\text{CO}_2$ . When the solution is sprayed, the solvent is rapidly extracted by the SCF, resulting in the precipitation of solid dispersion particles on the walls and bottom of the vessel. This SCF technology provides a novel alternative method of preparation of small particles with higher surface area, free flowing property, and a very low content of residual organic solvent and this technology also avoids most of the drawbacks of the traditional methods [20].

#### 4.8. Kneading technique

In this method, carrier is permeated with water and transformed to paste. Drug is then added and kneaded for particular time. The kneaded mixture is then dried and passed through sieve if necessary [20].

#### 4.9. Melt agglomeration process

This technique has been used to prepare solid dispersion where the binder acts as a carrier. SD(s) are prepared either by heating the binder, drug and excipient to a temperature above the melting point of the binder or by spraying a dispersion of drug in molten binder on the heated excipient by using a high shear mixer [20].

### 5. EVALUATION OF SOLID DISPERSIONS

#### 5.1. Determination of % practical yield

Determination of practical yield is useful to determine the efficiency of a preparation technique

#### 5.2. Physical characterization and saturation solubility study

The excess amount of the formulations (PMs and SDs) was added to conical flasks containing 10 ml of distilled water and subjected to shaking on a rotary shaker for 48 hours at  $37^\circ\text{C}$ .

Then the flasks were removed and filtered. Suitable aliquots were withdrawn from the filtered solution and analyzed for the drug content after appropriate dilution with distilled water and compared with pure drug solubility.

#### 5.3. Study of pure drug and all preparations

For all the formulations and drug the pellets have been prepared using potassium bromide (KBr) for FT-IR study. The pellets were subjected to FT-IR instrument 'Perkin Elmer FTIR spectrometer, spectrum 1000 Germany' for the collection of IR spectra.

#### 5.4. Drug content analysis

Preparations equivalent to 20 mg was weighed accurately and transferred to 100 ml volumetric flask and dissolved in solvent. The volume was made up with solvent up to the mark. After suitable dilution, the absorbance of the above solution was measured using appropriate blank solution. The drug content of drug was calculated using calibration curve.

#### 5.5. *In-Vitro* release studies

Accurately weighed amount of sample was taken for dissolution studies. Aliquots of sample were withdrawn at predetermined intervals of time and analyzed for drug release by measuring the absorbance using dissolution medium. The volume withdrawn at each time intervals were replaced with same quantity of fresh medium.

#### 5.6. Stability studies

Each SDs formulation was prepared in duplicate and each analysis was duplicated. Effect of formulation variables release parameters (t50% and t80%) were tested for significance by using analysis of variance (ANOVA: single factor) with the aid of Microsoft® Excel2002. Difference was considered significant when  $P < 0.05$  [19-21].

### 6. CONCLUSION

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. The solid dispersion method is one of the effective approaches to achieve the goal of solubility enhancement of poorly water-soluble drugs. The enhancement of oral bioavailability of poorly water soluble drugs remains one of the most challenging aspects of drug development. Dissolution of drug is the rate determining step for oral absorption of drugs which can subsequently affect the *in-vivo* absorption of drug. So,

to improve the aqueous solubility of the drugs, many techniques have been adopted since decades and solid dispersion is one of those techniques. Use of solid dispersions for the development of the release rate and oral bioavailability of poorly water soluble drugs, by careful choice of the carrier it is also feasible to delay or slow down the release pattern of a drug by formulating it into solid dispersion.

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