Enhancement of Solubility of Poorly Soluble Drugs by Using Solid Dispersion Technique

D. Venkata Shashanka*, P. Dinesh Kumar, A. Seetha Devi, K. Rajarao and P. Nagaraju

Department of Pharmaceutics, Hindu College of Pharmacy, Guntur, Andhra Pradesh, India.

ABSTRACT

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 improving wettability and forming amorphous particles. The term solid dispersion refers to a group of solid products consisting of at least two different components, generally a hydrophilic inert carrier or matrix and a hydrophobic drug.

Keywords: Poorly soluble drug; solid dispersion; solubility enhancement.

INTRODUCTION

The oral route of drug administration is the most common and preferred method of delivery due to convenience and ease of ingestion. One of the reasons is limited drug absorption which results in poor bioavailability of drug which is the one amongst the potential problems that can be encountered when delivering an active agent via the oral route. An improvement of oral bioavailability of poor water-soluble drugs remains one of the most challenging aspects of drug development. Therefore, a drug with poor aqueous solubility will typically exhibit dissolution rate limited absorption, and a drug with poor membrane permeability will typically exhibit permeation rate limited absorption.

Biopharmaceutical classification system

Drugs can be classified according to their Biopharmaceutical classification (Table 1). In the Biopharmaceutical Classification System (BCS) drugs with low aqueous solubility and high membrane permeability are categorized as Class II drugs. Therefore, solid dispersion technologies are particularly promising for improving the oral absorption and bioavailability of BCS Class II drugs.

Table 1: Biopharmaceutical classification system

<table>
<thead>
<tr>
<th>Class</th>
<th>Dissolution in aqueous environment</th>
<th>Permeation over intestinal membrane</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Fast</td>
<td>Fast</td>
</tr>
<tr>
<td>II</td>
<td>Slow</td>
<td>Fast</td>
</tr>
<tr>
<td>III</td>
<td>Fast</td>
<td>Slow</td>
</tr>
<tr>
<td>IV</td>
<td>Slow</td>
<td>Slow</td>
</tr>
</tbody>
</table>

An increasing number of poorly water-soluble drugs are being identified as potential therapeutic agents. In fact, about 40% of new chemical entities currently being discovered are poorly water-soluble. The solubility of any drug can be categorized as given in table 2. The drugs which are practically insoluble in water hence show poor bioavailability. Such drugs can be solubilized by various techniques, which is useful for the enhancement of solubility of poorly water soluble drug and hence, its bioavailability.
Table 2: Solubility profile of the drug

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Descriptive phrase (Category)</th>
<th>Approximate quantities of solvent by volume for one part of solute by weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Very soluble</td>
<td>1 in 1 part of solvent</td>
</tr>
<tr>
<td>2.</td>
<td>Freely soluble</td>
<td>1 in 10 parts of solvent</td>
</tr>
<tr>
<td>3.</td>
<td>Soluble</td>
<td>1 in 30 parts of solvent</td>
</tr>
<tr>
<td>4.</td>
<td>Sparingly soluble</td>
<td>1 in 50 parts of solvent</td>
</tr>
<tr>
<td>5.</td>
<td>Slightly soluble</td>
<td>1 in 100 parts of solvent</td>
</tr>
<tr>
<td>6.</td>
<td>Very slightly soluble</td>
<td>1 in 1000 parts of solvent</td>
</tr>
<tr>
<td>7.</td>
<td>Practically insoluble</td>
<td>1 in &gt;10,000 parts of solvent</td>
</tr>
</tbody>
</table>

Mechanism of enhancement of solubility and permeability

Fig. 1: Mechanism of technology showing solubility and permeability of the drugs

Approaches for increasing solubility

A) Formulation approach
   a) Reduction in particle size by
      i) Micronization technique
      ii) Nanosuspension formulation.
   b) Modification of the crystal habits
   c) Complexation of drug as
      i) Inclusion complex
      ii) Ion exchange complex
   d) Solubilization and surfactants
      i) Micronization
      ii) Micelles formation
      iii) Formulation of self-emulsifying drug delivery systems
   e) Formation of solid dispersions with water soluble carriers.

B) Chemical modification
   a) Salt formation
   b) Prodrug formation
   c) Polar group incorporation

Introduction to solid dispersion

Solid dispersions are one of the most promising strategies to improve the oral bioavailability of poorly water soluble drugs. By reducing drug particle size to the absolute minimum, and hence improving drug wettability, solubility increases hence bioavailability may be significantly improved. They are usually presented as amorphous products, mainly obtained by different methods.
Fig. 2: A schematic representation of the bioavailability enhancement of a poorly soluble drug by solid dispersion compared with conventional tablet or capsule

Advantages of solid dispersion
- Particles with reduced particle size
- Particles with improved wettability
- Particles with higher porosity
- Drugs in amorphous state

Preparation of solid dispersions: Various methods are used for the preparation of solid dispersions. They are

A. Hot melt extrusion: A "hot-melt" is any material that undergoes a transition from a solid or semi-solid state at a lower temperature, to a liquid or semi-liquid state at a higher temperature. Hot-melt extrusion (HME) is the process of pumping raw materials with a rotating screw under elevated temperature through a die into a product of uniform shape. It is a process used to disperse or dissolve a drug in a molten polymer, has become increasingly important in pharmaceuticals due to the possibility of dissolving poorly soluble drugs in a solid solution.

It is a process that involves forcing a raw material or blend through a die or orifice under set conditions such as temperature, pressure, rate of mixing and feed-rate, for the purpose of producing a stable product of uniform shape and density.

Melt extrusion is commonly used to prepare solid dispersions by:
1. Softening the polymer and any desired adjuvants in a twin screw extruder
2. Adding the API to the molten mixture and mixing it into the system as it flows through the extruder
3. Rapidly cooling the extrudate to form strands of polymeric glass with embedded API and
4. Milling the glass strands into a powder suitable for subsequent finished formulation.

In the hot melt extrusion process, the formulation is processed above the glass transition temperature of the polymer/API/adjuvant system to mix the active ingredient with the polymer on a molecular level. When carried out in a twin screw extruder,

Working principle of co-rotating twin screw extruder

Because of their excellent mixing behavior and degassing possibilities, co-rotating twin-screws are particularly suitable for hot melt extrusion.
Individual steps, such as melting, dispersive mixing, distributive mixing, degassing and pressure build-up, can be controlled very selectively and very effectively. For many APIs, the delta in temperature between the softening point of the polymer and the degradation temperature of the API is very narrow and therefore offers only a very small operating window. Thus, tight process control is critical.

**Intermeshing profile of the twin screws**

This continuous process offers numerous advantages over other melt processing methods, including:

- A short residence time at elevated temperatures.
- A high reproducibility
- Intensive mixing (dispersive or distributive mixing)
- High throughput rates
- A self-wiping effect from the closely intermeshing screws
- It is non-solvent technology
- Good method of granulation of poorly soluble drugs
- Uniform dispersion of fine particles occurs
- Good stability at varying pH and moisture levels
- Fewer processing steps needed thus time consuming drying steps eliminated
- Applicable in formulation of matrix tablets and hard gelatine capsules.
- The hot melt extrusion process and hot melt extrusion equipment are readily scalable, from lab- to pilot plant-scale, through to commercial production

**Applications of hot-melt technique**

- Improving dissolution rate and bioavailability of drug.
- Controlling or modifying drug release.
- Masking the bitter taste of active drug.

**B. Fusion method**

The fusion method is also referred as the melt method, which is done only when the starting materials are crystalline. Therefore, the more general term fusion method is preferred. The first solid dispersions created for pharmaceutical applications were prepared by the fusion method. The dispersion consisted of sulfathiazole and urea as a matrix which were melted using a physical mixture at the eutectic composition, followed by a cooling step. The eutectic composition was chosen to obtain simultaneous crystallization of drug and matrix during cooling. This procedure resulted in solid dispersions of type I. Poly(ethylene glycol) (PEG) is a hydrophilic polymer often used to prepare solid dispersions with the fusion method. This often results in solid dispersions of type III since many drugs are incorporated as separate molecules in the helical structure present in a crystalline PEG.

When drug and matrix are incompatible, two liquid phases or a suspension can be observed in the heated mixture, which results in an non-homogeneous solid dispersion. This can be prevented by using surfactants. Secondly, a problem can arise during cooling when the drug-matrix miscibility changes. In such 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 up to temperatures which is necessary to fuse matrix and drug. For example, to melt a sugar matrix of galactose, a temperature of 169°C was required and in order to get the glassy PVP in the rubbery Poly ethylene glycols, it should be melt at around 70°C and are therefore often used for the preparation of solid dispersions with the fusion method.

**C. Solvent method**

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 of both drug and polymer at the molecular level was preferred, because this leads to optimal dissolution properties. Using the solvent method, the two challenges were observed. The first challenge is to mix both drug and matrix material in one solution, which is difficult when they differ significantly in polarity. To minimize the drug particle size in the solid dispersion, the drug and matrix material have to be dispersed in the solvent as fine as possible, preferably drug and matrix material are in the dissolved state in one solution. Solubilizers like cyclodextrins or surfactants like Tween80® increase the aqueous solubility of the drug substantially. On the other hand, at high temperatures the molecular mobility of
drug and matrix remains high, favoring phase separation (e.g. crystallization).

**Fig. 4: Overall crystallization rate as a function of temperature. Tg is the glass transition temperature and Tm is the melting temperature**

To dry the solutions, vacuum drying is often used. The solution is dried by the application of vacuum and moderate heating. Sometimes, the solvent evaporation is accelerated by using a rotary evaporator. Afterwards, the formed solid dispersion is often stored in a vacuum desiccator to remove the residual solvent. Vacuum drying at elevated temperature bears the risk of phase separation because the mobility of drug and matrix decreases slowly.

**D. Solvent-melting method (melt evaporation)**

This method involves dissolving the drug in a suitable organic solvent and then incorporating the solution directly into the molten carrier, which is then evaporated until a clear, solvent free film is left. The film is further dried to constant weight. This method is particularly useful for drugs having high melting points or which are thermolabile. 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.

**E. Spray drying**

This technique is poorly exploited for the preparation of solid dispersions. One of the reasons might be the low freezing temperature of most organic solvents. Obviously, sublimation during freeze drying is only possible when the solvent stays frozen. In addition, when the formation of a glass is envisaged, the sample temperature should be kept below the Tg of the maximally freeze concentrated fraction. Therefore, low sample temperatures are required which slows down the process. Betageri and Makarla, used a condenser temperature of -75°C, to dry a solution with cyclohexanol as the solvent. To obtain a lyophilization process of acceptable duration, the solvent should have a sufficiently high vapour pressure. As can be seen, dimethylsulphoxide (DMSO) has a high melting temperature but it has a very low vapour pressure. Therefore, DMSO is not suitable as a solvent for freeze drying. A suitable solvent that meets both requirements is 2- methyl-2-propanol or tertiary butanol (TBA), because it has a high melting temperature as well as a high vapour pressure. Also mixtures of solvents can be considered.

**F. Surface-active carriers**

The surface-active 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 (Gattefosse Corp, Gennevilliers, France) 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 macrogolglycerides; the suffixes 44 and 14 in its name refer, respectively, to its melting point and hydrophiliclipophilic balance (HLB) value.

**G. Supercritical fluid methods**

Supercritical fluid methods are mostly applied with carbon dioxide (CO2), which is used as either a solvent for drug and matrix or as an anti-solvent. When supercritical CO2 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 CO2 is considered environmentally friendly, this technique is referred to as ‘solvent free’. In fact, these techniques represent alternative methods to remove solvents from a solution containing typically a drug and a polymer. Moneghini and co-workers (2001) reported their method as solvent-free, but they dissolved PEG and carbamazepine in acetone. They used a technique that is called the Gas-Anti-Solvent technique (GAS) or Precipitation from Gas Saturated Solutions (PGSS).
Characterization of solid dispersion

A. Detection of crystallinity in solid dispersions:

Several different molecular structures of the drug in the matrix can be encountered in solid dispersions.

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

1. Powder X-ray diffraction can be used qualitatively to detect the crystallinity of material. X-ray diffraction is nondestructive method that can quantitatively measure residual stress in crystalline and semi-crystalline materials. Sharper diffraction peaks indicate more crystalline material.\(^{19,20}\)

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 accurately to detect crystallinities ranging from 1 to 99\% in pure material.\(^{21,22}\) However in solid dispersions only qualitative detection was possible.

3. Water vapour sorption can be used to differentiate 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 Microcalorimetry (IM) measures the crystallization energy of amorphous material that is heated above its glass transition temperature (T_g). However, this technique has some limitations. Firstly, this technique can only be applied if the physical stability is such that only during the measurement of crystallization takes place. Secondly, it has to be assumed that all amorphous material crystallizes.

5. Dissolution Calorimetry 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 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.

B. Detection of molecular structure in amorphous solid dispersions

The properties of a solid dispersion are highly affected by the uniformity of the distribution of the drug in the matrix.

1. Confocal Raman Spectroscopy (CRS) 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\mum, 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 (TMDSC) 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.

Alternative strategies

A. Spraying on sugar beads using a fluidized bed coating system\(^{25}\)

B. Direct capsule filling

C. Cotton Candy Process
Table 3: List of Patented Technologies for cotton candy process

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Patented Technologies</th>
<th>Inventors</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Zydis technology</td>
<td>Zydis</td>
</tr>
<tr>
<td>2.</td>
<td>Takeda technology</td>
<td>Takeda (Osaka, Japan)</td>
</tr>
<tr>
<td>3.</td>
<td>Novartis technology</td>
<td>Novartis Consumer Health (Basel, Switzerland)</td>
</tr>
<tr>
<td>4.</td>
<td>Nippon Shinyaku technology</td>
<td>Nippon Shinyaku (Kyoto, Japan)</td>
</tr>
<tr>
<td>5.</td>
<td>Flashtab technology</td>
<td>Ethypharm (Paris, France)</td>
</tr>
<tr>
<td>6.</td>
<td>Wowtab technology</td>
<td>Yamanouchi (Tokyo, Japan)</td>
</tr>
<tr>
<td>7.</td>
<td>Dalichi technology</td>
<td>Dalichi (Tokyo, Japan)</td>
</tr>
<tr>
<td>8.</td>
<td>Orasolv technology</td>
<td>Cima Labs (Eden Prairie, MN)</td>
</tr>
<tr>
<td>9.</td>
<td>Zipllets technology</td>
<td>Eurand (Pessano con Bornago, Italy)</td>
</tr>
<tr>
<td>10.</td>
<td>Lyoc technology</td>
<td>Pharmalyoc</td>
</tr>
<tr>
<td>11.</td>
<td>Nanocrystal technology</td>
<td>Elan, King of Prussia</td>
</tr>
<tr>
<td>12.</td>
<td>Pharmabrust technology</td>
<td>SPI Pharma</td>
</tr>
<tr>
<td>13.</td>
<td>Advantol technology</td>
<td>Akina</td>
</tr>
<tr>
<td>14.</td>
<td>Frosta technology</td>
<td>Lavipharm Laboratories Inc. (Lavipharm)</td>
</tr>
</tbody>
</table>

D. Electrostatic spinning method

Thermodynamic and Kinetically Stabilization of Solid Dispersions

Typically solid dispersions are developed ideally in such a way that the poorly water soluble drug substance is soluble in the carrier/polymer and kept below its solid saturation solubility (thermo-dynamic stabilization). DSC is a good tool to monitor the Tg of the systems. Each phase separation (e.g. separation of the amorphous drug substance phase from the polymer or the solution phase) can lead to separation of individual glass transition signals as depicted in figure 5.

![DSC-Based Determination of Miscibility](image)

**Fig. 5: Thermodynamic and Kinetical Stabilization of Solid Dispersions**

CONCLUSION

By this article we conclude that, solubility of the drug is the most important factor that controls the formulation of the drug as well as therapeutic efficacy of the drug, hence the most critical factor in the formulation development. Dissolution of drug is the rate determining step for oral absorption of the poorly water soluble drugs and solubility is also the basic requirement for the formulation and development of different dosage form of different drugs. The various techniques described above alone or in combination can be used to enhance the solubility of the drug. Solubility can be enhanced by many techniques and number of folds increase in solubility. Because of solubility problem of many drugs the bioavailability of them gets affected and hence solubility enhancement becomes necessary. It is now possible that to increase the solubility of poorly soluble drugs with the help of various techniques as mentioned above.

REFERENCES


30. Linn M., Collnot E., Djuric D., Hempel K., Fabian E., Copovidone_ as an effective
37. Tiwari R., Tiwari G., Srivastava B.; Solid dispersion: An Overview to modify bioavailability of poorly water soluble drugs.