ENHANCING DRUG SOLUBILITY AND ORAL BIOAVAILABILITY USING SOLID DISPERSIONS: A REVIEW

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ABSTRACT

The solubility behavior of drugs remains one of the most challenging aspects in formulation development. Solid dispersions have tremendous potential for improving drug solubility. The present review is devoted to production of solid dispersions, various carriers used and the advantageous properties of solid dispersion. With the introduction of new manufacturing technologies such as hot melt extrusion, freeze drying, spray drying etc. it should be possible to overcome problems in scale-up and for this reason solid solutions are enjoying a renaissance. 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, bioavailability may be significantly improved. Recently, surfactants have been included to stabilize the formulations, thus avoiding drug recrystallization and potentiating their solubility. New manufacturing processes to obtain solid dispersions have also been developed to reduce the drawbacks of the initial process. This article begins with an overview of the historical background and definitions of the various systems including solid dispersions and solid solutions.

Key words: solid dispersion, solubility enhancement, BCS class, amorphous solids.

INTRODUCTION

In the recent years the progress in treatment of diseases has been evident with an upsurge in development of new drugs. An estimated 40% of these drugs are poorly water soluble. Although most of the drugs have encouraging experimental data obtained in vitro, in vivo results have been disappointing. The attributes include
1. Poor absorption, rapid degradation, and lamination (peptides and protein) resulting in insufficient concentration,
2. Drug distribution to other tissues with high drug toxicities (anticancer drugs),
3. Poor solubility of drugs
4. Fluctuations in plasma levels owing to unpredictable bioavailability.

The enhancement of oral bioavailability of such poorly water soluble drugs remains one of the most challenging aspects of drug development (Hamsaraj Karanth et al., 2006).

The therapeutic effect of drugs depends on the drug concentration at the site of action. The absorption of the drug into the systemic circulation is a prerequisite to reach the site of action for all drugs, except for those drugs that are applied at the site of action or those that are intravenously injected. After oral administration (gastrointestinal route), many factors determine the bioavailability (fraction of drug reaching the systemic
circulation). Since only dissolved drug can pass the gastrointestinal membrane, dissolution is one of those factors. However, drug metabolism in the intestinal lumen, the intestinal wall and the liver may also reduce its bioavailability (Ambike AA et al., 2005). In general it can be stated that the rate of absorption, ergo the onset and extend of the clinical effect, is determined by the dissolution of the drug and the subsequent transport over the intestinal membrane and passage of the liver (Ambike AA et al., 2005). The two important parameters controlling drug absorption are solubility and permeability.

Various approaches has been used to improve the solubility of drug which in turn leads to increase in invitro drug release. The approaches are preparation of amorphous form, prodrug, solid dispersion and complexation with various natural and synthetic cyclodextrins. Out of which preparation of amorphous form is the convenient way to enhance aqueous solubility and dissolution profile of poorly water soluble drugs.

Different techniques used to convert crystalline form of a drug to the amorphous form are spray drying, jet milling, hot melt extrusion or drug-polymer co-precipitation. Materials in the amorphous form are less thermodynamically stable than any crystalline form, leading to a tendency for amorphous materials to transform to a known or potentially unknown crystalline form. The time scale for any transformation is also unknown and is evaluated through stability studies. Amorphous state is characterized by the randomly arranged molecules of which the motions are kinetically frozen. A little provocation by different stressors can accelerate the mobility of molecules and facilitate the achievement of most stable and ordered crystalline states. Crystalline and amorphous states of a solid exhibit altered molecular interactions, which may pose as energy barrier for phase transformations between them (Lian Y et al., 2001).

**Approaches for increasing solubility** (Bell LN et al., 1995)

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
   1) Micronization
   2) Micelles formation.
   3) 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

**A) Formulation approach** (Andronis V et al., 1997; Lian Y et al., 2001)

a) Reduction of particle size

Both micronization and the nanosuspension approaches employ reduction of the drug particle size for improving its bioavailability. Increasing the dissolution rate by increasing the surface area exposed to GI fluid is the major mechanism by which micronized drug particles improve absorption. Nanosuspension improves bioavailability because of large surface area for absorption as well as due to its mucoadhesive property. Agglomeration of the micronized particle is the major concern related to successful formulation.

b) Modification of the crystal habits

Many drugs exhibit polymorphism whereby they tend to crystallize in more than one crystalline form. Bioavailability of the compound can be enhanced if appropriate studies are conducted to detect polymorphs with higher solubility prior to formulation. Metastable forms are associated with higher energy and thus higher solubility. Similarly the amorphous forms have high solubility due to higher energy associated and increased surface area.

c) Complexation (Aithal KS et al., 1995)

Complexation is the one of the several ways to favorably enhance the physiochemical properties of pharmaceutical compounds. It involves reversible association of the substrate and ligand to form a new species. The differentiation of complexes is usually based on the types of the interactions and species involved, e.g., metal complexes, inclusion complexes, and ion exchange complexes.

d) Solubilization and surfactant

The bioavailability of poorly soluble drug can also be improved by solubilization of the drug by means of the surfactants. It involves formulating the drug as microemulsions or Self-Emulsifying Drug Delivery Systems (SEDDS).

e) Solid dispersion

It involves dispersion of one or more active ingredients in an inert carrier or matrix at solid state. Melting (fusion) method, solvent evaporation method or melting evaporation methods can be employed for the preparation of the solid dispersions. The dissolution rate of the solid dispersion depends on the type of carriers used or the type of the matrix forming polymers used (Gupta P et al., 2005).
B) Chemical modification

Chemical modification can be brought about by incorporating polar or ionisable group or groups that decrease melting point without altering the basic pharmacophore structure of the compound or by using prodrug or more soluble salts of drug.

Amorphous State (Lian Y et al., 2001)

An amorphous solid (glass) can be defined with reference to a crystalline solid: similar to a crystalline solid, an amorphous solid may have short-range molecular order (i.e., in relationship to neighboring molecules); but unlike a crystalline solid, an amorphous solid has no long-range order of molecular packing or well-defined molecular conformation if the constituent molecules are conformationally flexible. Amorphous form is important in industries such as polymers, ceramics, metals, optical materials (glasses and fibers), foods, and pharmaceuticals. Some properties of amorphous systems are:

- Amorphous forms are having higher solubility, higher dissolution rate, and sometimes better compression characteristics than corresponding crystals.
- But, the problem exist with amorphous solid is amorphous form are generally less stable physically and chemically than corresponding crystals. Amorphous solids can be produced by standard pharmaceutical processes and are the common form of certain materials (e.g., proteins, peptides, some sugars and polymers).

Although the amorphous solid has always been an essential part of pharmaceutical research, the current interest has been elevated by two developments:
1. A growing attention to pharmaceutical solids in general, especially polymorphs and solvates and
2. A revived interest in the science of glasses and the glass transition. Studies of crystalline and amorphous solids are often so intertwined that it is natural to treat the two solids as “polymorphs” of each other. This view is harmonious with one definition of polymorphism (i.e., any solids that share the same liquid state), and with the “energy landscape” model of solids, which regards crystalline and amorphous states as connected minima on a multi-dimensional potential energy surface corresponding to different molecular packing, conformations, etc. The amorphous phase is characterized by high molecular mobility even below \( T_g \), thus hampering its biopharmaceutical advantage of higher dissolution rate due to diversification on storage (Ambike AA et al., 2005).

Pharmaceutical materials that are processed by high energy processes such as freeze drying, spray drying, jet milling, melt extrusion and so forth are often rendered at least partially amorphous. This occurs by the virtue of the fact that can prevent crystallization or mechanically disrupt the structure of an existing crystalline material (Hamsaraj Karanth et al., 2006).

A) Freeze drying: - For freeze-drying, drug is dissolved in specified solvent and polymer in water. The mixture of both solutions is stirred at room temperature for 24 hrs, which is then freeze-dried for optimized time span to obtain inclusion complexes.

Freeze drying with liquid nitrogen is also widely used technique for the preparation of amorphous solids. Acetaminophen with Cyclodextrin complexation is freeze dried which gives amorphous acetaminophen (Johori GP et al., 1990).

B) Melt extrusion: - Drug and water are added to an extruder. Extruded complex is placed in an oven to dry. Degree of mixing, amount of heating, heating time can be controlled in the barrel of extruder. This processing technique is currently being investigated for application in formulation of drug/polymer solid dispersions (Ghaderi R et al., 1999).

C) Quench cooling: - The simplest method to prepare amorphous form of drug is by heating the crystalline drug or its physical mixture with additives up to 175°C, hold isothermally for 1 min and then quench cooling over crushed ice (Charumanee S et al., 2004).

D) Spray drying: - It is often used for the physical transformation of a drug substance into the amorphous or partially amorphous phase (Hancock BC et al., 1994; Hancock BC et al., 1997).

E) Co-Grinding: - Amorphous form of a drug can also be prepared by co-grinding the drug with the polymer in a mortar in a suitable proportion (Karavas E et al., 2006).

F) Co-evaporation method: - The aqueous solution of polymer is added to solution of drug in solvent or solvent blend. The resulting mixture is stirred and solvent is evaporated at specific temperature (Leuner C et al., 2000).

G) Microwave oven method: - In this method physical mixture of drug and polymer are heated in microwave oven at different power for different periods of time (Ghaderi R et al., 1999).

H) Kneading: - It involves addition of a guest to slurry of polymer and kneading thoroughly to obtain a paste, which is then dried. The product is washed with organic solvent to remove free drug (Johori GP et al., 1990).

In rare cases pharmaceutical solids exist as 100% crystalline or 100% amorphous form. Hence it is necessary to study the concept how particular crystalline or amorphous systems are likely to behave. When thermodynamically states of a material exist differently will probably result in:
- Significant heterogeneities and
- Batch to batch variation in physical properties.

A successful design and production of amorphous pharmaceutical systems depends upon the ability to distinguish between crystalline and amorphous states of a material and to be able to quantify one phase.
Characterization of Drug - Polymer Amorphous System (Leuner C et al., 2000)

In the characterization of amorphous system the DSC thermogram of solid dispersion presented a straight line with absence of any thermodynamic transitions. The absence of melting peak clearly indicated the existence of amorphous state of drug, which was also confirmed by XRPD showing a halo, characteristic to amorphous form. Ideally, as the thermogram of solid dispersion presented no incidence of crystallinity, it should indicate the presence of Tg (Chokshi R et al., 2004).

Except above techniques some techniques like density, viscosity and heat capacity which measure these properties (directly or indirectly) can be used to detect the presence of an amorphous material (glass or rubber).

Physical techniques for characterizing amorphous solids

a) Powder X-ray diffraction

Powder X-ray diffraction analysis is used in the characterization of crystalline structure. A comparison of the diffractograms of the assumed complex with a physical mixture of guest and carrier, in pure form has to be made. In powder X-ray diffraction analysis a characteristic fingerprint region in the diffraction pattern reflects the crystallinity of the sample. A reduction in, or even the disappearance of the characteristic maxima in the powder diagram of the guest molecule and carrier with the new peaks in the diffraction pattern of the complex are the indications of formation of complex (Lian Y et al., 2001).

b) IR spectroscopy

IR spectroscopy is used to assess the interaction between carrier or complexing agent and guest molecule in solid state. Because of their high structural resolution this technique is valuable for characterization of an amorphous system. Bands, which could be assigned to the included part of the guest molecules, are easily masked by the band of complexing agent. The application of IR spectroscopy is limited to the guests having some characteristic bands such as carbonyl, sulphonyle groups etc (Charumanee S et al., 2004).

c) Thin layer chromatography (TLC)

To a very limited extent, TLC has also been used to support the formation of drug-carrier complexes. The change in the Rf value of the complex compared to that of the drug alone or physical mixture gives an indication for the formation of complex. Generally the Rf value obtained with a physical mixture is between the Rf of the pure guest molecule and that of the complex (Yonemochi E et al., 1994).

d) Thermal analytical methods

Thermal analysis includes thermogravimetry (thermogravimetric analysis, TGA), differential thermal analysis (DTA) and differential scanning calorimetry (DSC). These techniques for determining the degree of crystallinity. Amorphous solids may co-exist with and have the potential to convert to crystalline solids (Rao GC et al., 2004; Serajuddin AT et al., 1999).

e) Nuclear magnetic resonance spectroscopy (NMR)

The interpretation of the proton shift of a carrier or that of the drug help to investigate whether the type of interactions is hydrogen bond formation, van der Waals forces or dipole-dipole interaction (Vasanthvada M et al., 2005).

f) Dissolution studies

The rotating disk method and dispersed amount technique are most commonly used dissolution techniques. In rotating disk method formulations are pressed into tablets and placed on rotating disks apparatus. At appropriate intervals samples are removed and analyzed for the guest content. In dispersed amount technique unconsolidated powder mass is used instead of tablet (Wade A 1994).

Molecular Interaction in Amorphous system

Amorphous form is characterized by randomly arranged molecules, whose motions are kinetically-frozen, at least on experimental time scales. A little provocation by different stressors can accelerate the mobility of molecules and facilitate the achievement of most stable and ordered crystalline state. These issues gain greater importance during pharmaceutical manufacturing processes, wherein a solid experiences variable extent of stress (Modi A et al., 2006).

Crystalline and amorphous states of a solid exhibit altered molecular interactions, which may pose as energy barriers for phase-transformations. These structural changes depend on adjustment in the nearest-neighbor relationships, including parameters such as intermolecular distances and patterns in hydrogen bonding. The process can be envisioned as decrease in configurational entropy with simultaneous increase in number of molecules constituting co-operatively rearranging regions, favoring gain of molecular order (Charumanee S et al., 2004).

The hydrogen bonding between the drug and polymer is most predominant mechanism for interaction between drug and polymer. Polar solvent like methanol will favour hydrogen bonding between silanol groups of colloidal silicon dioxide (Aerosil 200) and carbonyl group of simvastatin (Gupta P et al., 2005). A molecular interaction between the drug and additives can influence their Tg. A stronger bonding between unlike molecules raises the Tg from values expected from ideal mixing due to reduced mobility of a molecule in the complexed state. Hydrogen bonding between hydroxyl group of β-Cyclodextrin and drug leads to the enhanced stabilization of drug in the amorphous phase. Due to combined role of cyclodextrin and hydrophilic polymer in hydrogen...
bonding, ternary system has significantly higher stability than binary system (Johori GP et al., 1990).

**Advantages of solid dispersions over other strategies to improve bioavailability of poorly water soluble drugs**

Improving drug bioavailability by changing their water solubility has been possible by chemical or formulation approaches, chemical approaches to improving bioavailability without changing the active target can be achieved by salt formation or by incorporating polar or ionizable groups in the main drug structure, resulting in the formation of a pro-drug. Solid dispersions appear to be a better approach to improve drug solubility than these techniques, because they are easier to produce and more applicable. For instance, salt formation can only be used form weakly acidic or basic drugs and not for neutral. Furthermore, it is common that salt formation does not achieve better bioavailability because of its in vivo conversion into acidic or basic forms. Moreover, these type of approaches have the major disadvantage that the sponsoring company is obliged to perform clinical trials on these forms, since the product represents a NCE (Watanabe T et al., 2002). Formulation approaches include solubilization and particle size reduction techniques, and solid dispersions, among others. Solid dispersions are more acceptable to patients than solubilization products, since they give rise to solid oral dosage forms instead of liquid as solubilization products usually do. Milling or micronization for particle size reduction are commonly performed as approaches to improve solubility, on the basis of the increase in surface area. Solid dispersions are more efficient than these particle size reduction techniques, since the latter have a particle size reduction limit around 2–5 mm which frequently is not enough to improve considerably the drug solubility or drug release in the small intestine and, consequently, to improve the bioavailability. Moreover, solid powders with such a low particle size have poor mechanical properties, such as low flow and high adhesion, and are extremely difficult to handle (Yonemochi E et al., 1994).

**The advantageous properties of solid dispersions**

Management of the drug release profile using solid dispersions is achieved by manipulation of the carrier and solid dispersion particles properties. Parameters, such as carrier molecular weight and composition, drug crystallinity and particle porosity and wettability, when successfully controlled, can produce improvements in bioavailability (Zhang J et al., 2006).

**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 (Zhang J et al., 2006).

**Particles with improved wettability**

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 properties of drugs. Moreover, carriers can influence the drug dissolution profile by direct dissolution or co-solvent effects. Recently, the inclusion of surfactants in the third generation solid dispersions reinforced the importance of this property (Yonemochi E et al., 1994).

**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 (Zhang J et al., 2006).

**Disadvantages of Solid dispersions**

Despite extensive expertise with solid dispersions, they are not broadly used in commercial products, mainly because there is the possibility that during processing (mechanical stress) or storage (temperature and humidity stress) the amorphous state may undergo crystallization. The effect of moisture on the storage stability of amorphous pharmaceuticals is also a significant concern, because it may increase drug mobility and promote drug crystallization. Moreover, most of the polymers used in solid dispersions can absorb moisture, which may result in phase separation, crystal growth or conversion from the amorphous to the crystalline state or from a metastable crystalline form to a more stable structure during storage. This may result in decreased solubility and dissolution rate. Therefore, exploitation of the full potential of amorphous solids requires their stabilization in solid state, as well as during in vivo performance. Another drawback of solid dispersions is their poor scale-up for the purposes of manufacturing. Strategies to overcome the manufacturing process drawbacks will be discussed later (Zhang J et al., 2006).

**Pharmaceutical Applications of an Amorphous System**

The amorphous solid state possesses several applications in comparison to the crystalline state which allows enhanced forms of drugs to be produced. Many drugs when produced as an amorphous form will exhibit one or more of the following applications.
a) Amorphous drugs have better compression characteristics than corresponding crystalline drugs thus, facilitating the pharmaceutical processing. e.g. Lactose (Chokshi R et al., 2004).

b) Stabilization of drug in amorphous phase can be achieved by Cyclodextrin complexation. e.g. acetaminophen (Karavas E et al., 2006).

c) Nanoparticles can be formulated as injections consisting of spherical amorphous particles which do not aggregate hence they can be safely administered by intravenous route (Bruno C et al., 1998).

d) Amorphous drugs have higher solubility, higher dissolution rate and thus higher bioavailability than corresponding crystalline drug (Kerc L et al., 1998). Nanoparticles formulated as an amorphous spheres offer high solubility than the standard crystalline formulation, thus improving the poor aqueous solubility of the drug and hence its bioavailability (Gupta P et al., 2005). Improvement in the drug solubility can be synergistic with use of cyclodextrin for preparation of amorphous drugs. e.g. Acetaminophen (Karavas E et al., 2006).

e) It is also important in determining the behavior and properties of pharmaceutical solids in the various steps of processing the pharmaceuticals (Ambike AA et al., 2005).

Table 1: Measured physical properties of some amorphous pharmaceuticals (Bruno C et al., 1998; Charumanee S et al., 2004)

<table>
<thead>
<tr>
<th>Material</th>
<th>M_w</th>
<th>T_m(K)</th>
<th>T_g(K)</th>
<th>T_m/T_g</th>
<th>ΔC_p</th>
<th>ρ_crystal</th>
<th>ρ_amorphous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indomethcin</td>
<td>358</td>
<td>438</td>
<td>320</td>
<td>1.37</td>
<td>0.446</td>
<td>1.38</td>
<td>1.32</td>
</tr>
<tr>
<td>Sucrose</td>
<td>342</td>
<td>453</td>
<td>348</td>
<td>1.30</td>
<td>0.544</td>
<td>1.59</td>
<td>1.43</td>
</tr>
<tr>
<td>Lactose (anhydrous)</td>
<td>342</td>
<td>486</td>
<td>383</td>
<td>1.27</td>
<td>0.472</td>
<td>1.60</td>
<td>1.48</td>
</tr>
<tr>
<td>Trehalose (anhydrous)</td>
<td>342</td>
<td>476</td>
<td>385</td>
<td>1.24</td>
<td>0.534</td>
<td>1.58</td>
<td>1.49</td>
</tr>
<tr>
<td>Dextran</td>
<td>≈5x10^5</td>
<td>498</td>
<td>---</td>
<td>0.400</td>
<td>0.92</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poly (vinyl Pyrrolidone)</td>
<td>≈1x10^6</td>
<td>458</td>
<td>---</td>
<td>0.260</td>
<td>1.25</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Water</td>
<td>18</td>
<td>273</td>
<td>136</td>
<td>2.01</td>
<td>0.100</td>
<td>&lt;0.95</td>
<td>≈0.95</td>
</tr>
</tbody>
</table>

M_w = Molecular mass  
 T_m = Melting temperature  
 T_g = Glass transition temperature  
 ΔC_p = Heat capacity change at T_g  
 ρ = Density

Figure 1: The Biopharmaceutical Classification System
Figure 2: Different physical forms of Drug substances (Modi A et al., 2006)

Figure 3: Various methods for formation of amorphous form

Figure 4: Manufacturing processes used to produce solid dispersions
CONCLUSION

Most of the promising NCEs are poorly water soluble drugs, which may present a lack of therapeutic effect, because of their low bioavailability. Solid dispersions are one of the most attractive processes to improve drugs’ poor water solubility. Various solubility enhancers like water-soluble carriers, co solvents, surfactants and superdisintegrants via solid dispersion approach (fusion method and solvent evaporation method) aids in solubility enhancement. These significantly help to improve the bioavailability and bioequivalence. Solid dispersions can improve their stability and performance by increasing drug-polymer solubility, amorphous fraction, particle wettability and particle porosity. Moreover, new, optimized manufacturing techniques that are easily scalable are also coming out of academic and industrial research.

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