DIFFERENT TYPES OF METHOD FOR MODIFIED DOSAGE FORM FOR ENHANCEMENT OF DISSOLUTION RATE THROUGH SOLID DISPERSION

*Sameer H Lakade, Bhalekar M.R.

Address for Correspondence
1Department of Pharmaceutics, Karpagam University, Coimbatore (T.N) India, Department of Pharmaceutics, Sinhgad Institute of Pharmaceutical Sciences Lonavala-Pune-410401. E Mail sameer_patil97@rediffmail.com
2Department of Pharmaceutics, AISSMS College of Pharmacy Kennedy Road Pune-411001

ABSTRACT
Solid dispersions are used to obtain a homogeneous distribution of a small amount of drug in solid state. To stabilize the unstable drug. To dispense liquid (up to 10%) or gaseous compounds in a solid dosage. To formulate a fast release primary dose in a sustained released dosage form. To formulate sustained release regimen of soluble drugs by using poorly soluble or insoluble carriers. Polymorphs in a given system can be converted into isomorphous, solid solution, eutectic or molecular addition compounds. Many more different types of polymers are used to solve the solubility problem by using solid dispersion method, hence solid dispersion is an very use full method for Pharmaceutical point of view because of this simple & convenient reason this method is widely used to study various approaches & application of drug property & polymers used in Pharmaceutical research.

KEYWORDS Solid dispersion, Hydrophilic matrix, Swallowing, Reproducibility, Scale-up.

INTRODUCTION
The term solid dispersion refers to a group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug. The matrix can be either crystalline or amorphous. The drug can be dispersed molecularly, in amorphous particles (clusters) or in crystalline particles. Therefore, based on their molecular arrangement, six different types of solid dispersions can be distinguished. Moreover, certain combinations can be encountered, i.e in the same sample, some molecules are present in clusters while some are molecularly dispersed. Confusingly, in various studies the designation of solid dispersions is based on the method of preparation. However, since different preparation methods can result in the same subtypes or similar preparation methods can result in different subtypes, it can be argued that solid dispersions should preferably be designated according to their molecular arrangement. Moreover, not the preparation method but the molecular arrangement governs the properties of solid dispersions. Therefore, it is essential to use terms that indicate the molecular arrangement in the solid dispersion. The oral route of drug administration is the most common and preferred method of delivery due to convenience and ease of ingestion. From a patient’s perspective, swallowing a dosage form is a comfortable and a familiar means of taking medication. As a result, patient compliance and hence drug treatment is typically more effective with orally administered medications as compared with other routes of administration. 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. In addition, in solid dispersions, a portion of drug dissolves immediately to saturate the gastrointestinal tract fluid, and excess drug precipitates as fine colloidal particles or oily globules of submicron size. In spite of these advantages, only products have been marketed since the development of this technology 4 decades ago. The limitations of this technology have been a drawback for the commercialization of solid dispersions. The limitations include,

1. Laborious and expensive methods of preparation,
2. Reproducibility of physicochemical characteristics,
3. Difficulty in incorporating into formulation of dosage forms, scale-up of manufacturing process.

Solid dispersion technique has been extensively used to increase the solubility of a poorly water-soluble drug. According to this method, a drug is thoroughly dispersed in a water-soluble carrier
by suitable method of preparation. The mechanism by which the solubility and the dissolution rate of the drug is increased includes: firstly, the particle size of a drug is reduced to submicron size or to molecular size in the case where the solid solution is obtained. The particle size reduction generally increases the rate of dissolution; secondly, the drug is changed from crystalline to amorphous form, the high energetic state which is highly soluble; finally, the wettability of the drug particle is improved by the dissolved carrier. Despite these promising advantages, the application of solid dispersion in pharmaceutical industry has certain limitation.

Categories of Solid Dispersions

a. Simple eutectic mixtures
b. Solid solutions

According to their miscibility
1. Continuous
2. Discontinuous solid solutions

According to the way in which the solvate molecules are distributed in the solvendum
1. Substitutional crystalline solid solutions
2. Interstitial crystalline solid solutions
3. Amorphous solid solutions
c. Glass solutions
d. Amorphous precipitation in a crystalline carrier

Simple eutectic mixtures

When a mixture of A and B with composition E is cooled, A and B crystallize out simultaneously, whereas when other compositions are cooled, one of the components starts to crystallize out before the other. Solid eutectic mixtures are usually prepared by rapid cooling of a comet of the two compounds in order to obtain a physical mixture of very fine crystals of the two components.

Solid solutions

Continuous solid solutions

In a continuous solid solution, the components are miscible in all proportions. Theoretically, this means that the bonding strength between the two components is stronger than the bonding strength between the molecules of each of the individual components. Solid solutions of this type have not been reported in the pharmaceutical literature to date.

Discontinuous solid solutions

In the case of discontinuous solid solutions, the solubility of each of the components in the other component is limited. A typical phase diagram is shown in Fig.2. The regions of true solid solutions. In these regions, one of the solid components is completely dissolved in the other solid component. Note that below a certain temperature, the mutual solubilities of the two components start to decrease.

Substitutional crystalline, interstitial crystalline and amorphous solid solutions

Substitutional crystalline solid solutions

Classical solid solutions have a crystalline structure, in which the solute molecules can either substitute for solvent molecules in the crystal lattice or into the interstices between the solvent molecules. A substitutional crystalline solid dispersion is depicted in Fig.3.
Interstitial crystalline solid solutions
In interstitial solid solutions, the dissolved molecules occupy the interstitial spaces between the solvent molecules in the crystal lattice. As in the case of substitutional crystalline solid solutions, the relative molecular size is a crucial criterion for classifying the solid solution type. In the case of interstitial crystalline solid solutions, the solute molecules should have a molecular diameter that is no greater than 0.59 of the solvent molecule's molecular diameter. Furthermore, the volume of the solute molecules should be less than 20% of the solvent.\(^\text{4-5}\)

Amorphous solid solutions
In an amorphous solid solution, the solute molecules are dispersed molecularly but irregularly within the amorphous solvent. Using griseofulvin in citric acid, Chiou and Riegelman were the first to report the formation of an amorphous solid solution to improve a drug's dissolution properties.\(^\text{6-7}\)
Glass solutions and glass suspensions
Chiou and Riegelman first introduced the concept of formation of a glass solution as another potential modification of dosage forms in increasing drug dissolution and absorption. A glass solution is a homogenous, glassy system in which a solute dissolves in a glassy solvent.

![Solid state solid dispersion](image)

**Fig-5: Solid state solid dispersion**

**Methods of preparation of solid dispersion**

**A. Fusion method**
The fusion method is sometimes referred to as the melt method, which is correct 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.

**B. Hot melt extrusion**
Melt extrusion is essentially the same as the fusion method except that intense mixing of the components is induced by the extruder. 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. The theoretical approach to understanding the melt extrusion process is therefore, generally presented by dividing the process of flow into four sections:

1) Feeding of the extruder.
2) Conveying of mass (mixing and reduction of particle size).
3) Flow through the die.
4) Exit from the die and down-stream processing.

Generally, the extruder consists of one or two rotating screw inside a stationary cylindrical barrel. The barrel is often manufactured in sections, which are bolted or clamped together. An end-plate die, connected to the end of the barrel, determines the shape of the extruded product (fig-7 and fig-8).

**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 at the molecular level is preferred, because this leads to optimal dissolution properties. Using the solvent method, the pharmaceutical engineer faces two challenges. The first challenge is to mix both drug and matrix 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 have to be dispersed in the solvent as fine as possible preferably drug and matrix material are in the dissolved state in one solution. The second challenge in the solvent method is to prevent phase separation, e.g. crystallization of either drug or matrix, during removal of the solvent(s).
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 desiccators to remove the residual solvent.12-14

D. 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.
Table 1: Some SCF Along with Their Properties

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Molecular weight g/mol</th>
<th>Critical temperature K</th>
<th>Critical pressure MPa (atm)</th>
<th>Density g/cm³</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbon dioxide (CO_2)</td>
<td>44.01</td>
<td>304.1</td>
<td>7.38 (72.8)</td>
<td>0.469</td>
</tr>
<tr>
<td>Water (H_2O)</td>
<td>18.02</td>
<td>647.3</td>
<td>22.12 (218.3)</td>
<td>0.348</td>
</tr>
<tr>
<td>Methane (CH_4)</td>
<td>16.04</td>
<td>190.4</td>
<td>4.60 (45.4)</td>
<td>0.162</td>
</tr>
<tr>
<td>Ethane (C_2H_6)</td>
<td>30.07</td>
<td>305.3</td>
<td>4.87 (48.1)</td>
<td>0.203</td>
</tr>
<tr>
<td>Propane (C_3H_8)</td>
<td>44.09</td>
<td>369.8</td>
<td>4.25 (41.9)</td>
<td>0.217</td>
</tr>
<tr>
<td>Ethylene (C_2H_4)</td>
<td>28.05</td>
<td>282.4</td>
<td>5.04 (49.7)</td>
<td>0.215</td>
</tr>
<tr>
<td>Propylene (C_3H_6)</td>
<td>42.08</td>
<td>364.9</td>
<td>4.60 (45.4)</td>
<td>0.222</td>
</tr>
<tr>
<td>Methanol (CH_3OH)</td>
<td>32.04</td>
<td>512.6</td>
<td>8.09 (79.8)</td>
<td>0.272</td>
</tr>
</tbody>
</table>

The application of supercritical fluids (SCF) for the precipitation of pharmaceuticals and natural substances has attracted great attention due to the peculiar properties of these fluids. Supercritical fluid is any substance at a temperature and pressure above its thermodynamic critical point. It has the unique ability to diffuse through solids like a gas, and dissolve materials like a liquid. Additionally, it can readily change in density upon minor changes in temperature or pressure. Carbon dioxide and water are the most commonly used supercritical fluids.15-16

ALTERNATIVE STRATEGIES

A. Spraying on sugar beads using a fluidized bed Coating system

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 granule 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.17-18

C. Electrostatic spinning method

This technology used in the polymer industry combines solid solution/dispersion technology with nanotechnology in this process, a liquid stream of a drug/polymer solution is subjected to a potential between 5 and 30 kV.

B. 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.19-20

D. 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. The material has an HLB value of 13 and is miscible with water in all parts. Its melting point, however, is relatively low (38oC), and it may require mixing with other carriers to increase melting temperatures of formulations.21

Applications of solid dispersion

Apart from absorption enhancement, the solid dispersion technique may have numerous pharmaceutical applications, which should be further explored.

It is possible that such a technique be used

- To obtain a homogeneous distribution of a small amount of drug in solid state.
- To stabilize the unstable drug.
- To dispense liquid (up to 10%) or gaseous compounds in a solid dosage.
- To formulate a fast release primary dose in a sustained released dosage form.
- To formulate sustained release regimen of soluble drugs by using poorly soluble or insoluble carriers.
- To reduce pre systemic inactivation of drugs like morphine and progesterone.
- Polymorphs in a given system can be converted into isomorphous, solid
solution, eutectic or molecular addition compounds.\(^{22}\)

**Methods of determination of type of solid dispersion system**

Many methods are available that can contribute information regarding the physical nature of solid dispersion system. A combination of two or more methods is required to study its complete picture.

- Thermal analysis.
- Infrared spectrophotometry.
- Differential scanning colorimetry
- X-ray diffraction method.
- Microscopic method
- Spectroscopic method.
- Dissolution rate method.
- Thermodynamic method\(^{23}\)

**REFERENCES**