Binary Amorphous Solid dispersion: - Methods and Applications

Asmita K. Kedar, Dr. Abhijeet D. Kulkarni

Department of Pharmaceutical Quality Assurance (PG), Sanjivani College Of
Pharmaceutical Education and Research, Kopargaon
Maharashtra- 423603, India.

Department of Pharmaceutical Quality Assurance (PG), Sanjivani College Of
Pharmaceutical Education and Research, Kopargaon
Maharashtra - 423603, India.

Abstract: Binary amorphous solid dispersion system have been realized as extremely useful tool in improve the dissolution and solubility properties of poorly water soluble drugs. In recent years, a great deal of knowledge has been accumulated about technology, but their commercial application is limited. Various methods are tried recently to beat the limitation and make the preparation practically feasible. The problems involved in incorporating into formulation of dosage forms are gradually resolved with the arrival of other strategies. The use of this techniques has immensely increased in enabling the delivery of the difficult to solubilize compounds.

Keyword: Binary Amorphous Solid dispersion, Introduction, Methods, Applications, Examples of Marketed Preparations.

Introduction:

The idea of stable dispersion turned into in the beginning proposed by Sekiguchi and Obi. solid dispersion is help to increasing the dissolution, absorption and therapeutic efficacy of drugs. solid dispersion has become a long time solubilization generation for poorly water soluble drugs. Stable dispersion is basically a drug-polymer two system. stable dispersion is now firmly set up as platform for the poorly water soluble drugs.

The term solid dispersion became defined as dispersion of one or more active ingredients in an inert polymer or polymer matrix or in a carrier. solid dispersion of a hydrophobic drug in a water-soluble polymer is one of the favourite technique to enhance the drug dissolution. The low solubility often results in low absorption, which ultimately decreases the oral bioavailability. One of the promising method to increase the solubility is solid dispersion by the solvent evaporation method.

The enhancement of oral bioavailability of poorly water soluble drugs remains one of the most challenging aspect of drug development. Although salt formation, co-solubilization and particle size reduction have commonly been wont to increase dissolution rate and thereby oral absorption and bioavailability of such drugs, there are practical limitations of these techniques. The salt formation technique is not feasible for neutral compound and also the synthesis of appropriate salt form of drugs that are weakly acidic or weakly basic may often not be practical.
Advantages Of Solid Dispersion:
1. To reduced particle size.
2. To enhance wettability.
3. To enhance porosity of drug.
4. To decrease the crystalline structure of a drug into amorphous form.
5. To enhance dissolvability in water of a poorly water soluble drugs.

Disadvantages of Solid Dispersion:
1. The upper cost of preparation.
2. The problem in completely removing liquid solvent.
3. Tough handling due to tackiness.

Binary Amorphous Solid Dispersion:
Amorphous solid dispersion is one among the techniques utilized in the formulation development of poorly soluble compounds, thanks to the advancement within the basic physicochemical understanding of amorphous systems, the use of this techniques has immensely increased in enabling the delivery of the difficult to solubilize compounds. Binary amorphous solid dispersion defined as a dispersion contain a drug dispersed during a single polymer matrix is named as binary amorphous solid dispersion.

Ternary Amorphous Solid Dispersion:
Ternary amorphous solid dispersion is defined as dispersion contain a drug among the challenges related to developing ternary amorphous solid dispersion is that the selection of appropriate polymers/surfactant and their combination .The parameters studied in solution state screening studies usually are the power of polymers or their combination to inhibit precipitation and maintaining supersaturation.

The prepared ternary solid dispersion are often characterized by techniques like DSC/MDSC, PXRD, and FTIR .These techniques are wont to determine important parameters like glass-transition temperature of amorphous components the crystallinity of the drug and therefore the molecular interaction between drug and excipient.

Principle Involved In The Solid Dispersion:
The basic principal includes the complete removal of drug crystallinity and molecular dispersion of the poorly soluble compounds in a hydrophilic polymeric carrier. When the solid dispersion is exposed to aqueous media, the carrier dissolves and therefore the drug releases as fine colloidal particles .This increases area of dissolution rate and hence bioavailability of poorly water soluble drugs .Drug in
soluble hydrophilic carrier improves the dissolution rate by reducing particle size and increasing the particle porosity. Remaining drug is in amorphous state and improving wettability and hence bioavailability for poorly water soluble drug. The potential advantages of this technique is enormous. Recently surfactants have been included for betterment of formulation as in many cases. Thermodynamic instability and recrystallization of drug becomes a problem. Hence surfactant are used to avoid recrystallization and potentiating their solubility.

**Different Methods Used For Solid Dispersion:**

1) **Spray Drying:**

Spray drying is help to meet the needs for the formulation of amorphous solid dispersions for most poorly soluble APIs and are likely to keep playing important roles in pharmaceutical product design. Spray drying is an established processing technology for the pharmaceutical industry by co-precipitating API with a polymer in a stable amorphous solid dispersion, spray drying improves dissolution rates and enhances the bioavailability of poorly soluble compounds.

**Benefits:**
1) Enhance bioavailability of poorly soluble compounds.
2) Provides a physically stable drug form that enables processing of the dispersion into solid dosage form.
3) Improved therapeutic efficacy, safety, and patient compliance.
4) Lowering dosage costs.
5) Extending product life cycle.

**Advantages:**
1) Creation of an amorphous solid dispersion.
2) Fast and Continuous process.
3) Suitable for heat-sensitive product.
4) Improved solubility without physical milling.
5) Processing of aqueous and organic solvent system.

2) **Freeze Drying:**

Freeze drying is also known as lyophilization or cryodesiccation, is low temperature dehydration process that involves freezing the product, lowering pressures, then removing the ice by sublimation. This is in contrast to dehydration by most conventional methods that evaporate water using heat. Freeze drying results in a high quality product because of the low temperature used in processing. The original shape of the product is maintained and quality of the rehydrated product is excellent.
Advantages:

1) Removal of water at low temperature.
2) Thermolabile materials can be dried.
3) Compatible with aseptic operation.
4) Sterility can be maintained.

Disadvantages:

1) Long time process.
2) Cost may be an issue, depending on the product.
3) Many biological molecules are damaged by the stress associated with freezing, freeze drying, or both.

3) Rotary Evaporation:

Rotary evaporation is the process of reducing the volume of a solvent by distributing it in thin film across the interior of a vessel at elevated temperature and reduced pressure. This promotes the rapid removal of excess solvent from less volatile samples. Most rotary evaporator have four major components: heat bath, rotor, condenser, and solvent trap.

Rotary evaporation can be used to separate solvent from many organics inorganics.

Advantages:

1) High heat transfer rates at higher temperature differences results in quick process.
2) Ease of cleaning.
3) Relatively inexpensive.

Disadvantages:

1) Large floor space and weight.
2) Poor heat transfer at coldness differences.
3) Not used for thermo-labile products.

4) Fusion Method:

The fusion method sometimes mentioned because the melt method, which is correct only the starting materials are crystalline. The first solid dispersions are created for pharmaceutical applications were prepared by the fusion method.
Advantage:
1) The main advantage of direct melting method is its simplicity and economy.
2) In addition melting under vacuum of an noble gas like nitrogen could also be employed to stop oxidation of drug or carrier.

Disadvantage:
1) The method are often only be applied when drug and matrix are compatible once they mix well at the heating temperature.
2) When drug and matrix are incompatible two liquid phases are often observed within the heated mixture which ends up in an in-homogenous solid dispersion.

4) Electro-spinning Method:
Electros pinning could also be a process during which solid fibers are produced from a polymeric fluid stream solution or melt delivered through millimeter scale nozzles. This process involves the appliance of a robust electric field over a conductive capillary attaching to reservoir containing a polymer solution or melt and a conductive collection screen upon increasing the electrical field intensity 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.

Advantages:
1) This technique has tremendous potential for the preparation of Nano fibers and controlling the release of biomedicine.
2) This technique can be utilized for the preparation of solid dispersion in future.

Disadvantages:
1) This technique can be utilized for the preparation of solid dispersion in future.

5) Melting solvent method :
In this method drug is first dissolved during an appropriate liquid solvent solution is then incorporate directly into the melt of polyethylene glycol obtainable below 70ºc without removing the liquid solvent.It has been shown that 5-10 %(w/w)of liquid compound might be incorporated into polyethylene glycol 6000without significant loss of its solid property.
Advantages
1) During this method thermal decomposition of medicine or carriers are often prevented due to the coldness required for evaporation of organic solvent.

Disadvantage
1) Because the practical point of view ,the melting –solvent method is restricted to drugs with a coffee therapeutic dose .

2) It's impossible that the chosen solvent or dissolved drug might not be miscible with the melt of polyethylene glycol.

7) Supercritical Fluid Methods:
Supercritical fluid methods are mostly applied with CO2 which is used as either a solvent for drug and matrix or as an ant solvent .When supercritical fluid CO2 is employed 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 expansions of the mixture leads to rapid cooling .This technique doesn't require the utilization of organic solvents and since CO2 is taken into account environmentally friendly ,this technique is reffered to as “solvent free”. this system is known as Rapid Expansion of Supercritical Solution.

Advantage:
1) The supercritical anti solvent penetrates into the droplets,in which drug and matrix become supersaturated ,crystalline and form particles.

2) The overall term for this process is precipitation with compressed anti oven  More specific samples of PCA are Supercritical Anti solvent when supercritical CO2 is employed or aerosol solvent extraction systems, and solution enhanced dispersion by supercritical fluids.

8) Dropping Method Solution:
The dropping method, developed by Ulrich et al.,(1997) to facilitate the crystallization of varied chemicals ,is a new procedure for producing round particles from melted solid dispersion. This system may overcome variety of the difficulties inherent within the opposite method. For laboratory scale preparation, a solid dispersion of a melted drug –carrier mixtures is pipette then dropped onto a plate, where it solidifies into round particles. The utilization of carriers that solidify at temperature may aid the dropping process. The dropping method not only simplifies the manufacturing process, but also gives a far better dissolution rate.
9) Gel Entrapment Technique:

Hydroxyl Propyl methyl Cellulose is dissolved in organic solvent to make a transparent and transparent gel. Then drug is dissolved in gel by sonication for jiffy. Organic solvent is evaporated under vaccum. Solid dispersion are reduced in size by mortar and sieved.

<table>
<thead>
<tr>
<th>Drug+ Polymer</th>
<th>Methods</th>
<th>Applications</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin + Cyclodextrin</td>
<td>1) Kneading Method</td>
<td>1) Enhance the solubility and dissolution of Atorvastatin</td>
<td>1) The increase in solubility and dissolution rate of ATR</td>
</tr>
<tr>
<td></td>
<td>2) Freezing Method</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Repaglinide + Lutrol F127+</td>
<td>1) Melting Method</td>
<td>1) Enhance the solubility</td>
<td>1) Solid dispersions showed dissolution improvement of pure drug to 2) Lutrol F127 as the most promising carrier.</td>
</tr>
<tr>
<td>PEG 6000 + Gelucire 44/14</td>
<td>2) Melting Solvent Method</td>
<td>2) Enhance the Bioavailability</td>
<td></td>
</tr>
<tr>
<td>Norfloxacin + β-CD +</td>
<td>1) Melting Method</td>
<td>1) Increase in the poor water solubility</td>
<td>1) The increase in dissolution rate of norfloxacin can be achieved.</td>
</tr>
<tr>
<td>Hydroxypropyl β-CD</td>
<td></td>
<td>2) Increase in the solubility</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1) Spray Drying</td>
<td>1) Enhance the dissolution Rate</td>
<td>1) Increase in the dissolution rate</td>
</tr>
<tr>
<td>Raloxifene + HPMC + PVP K 30</td>
<td></td>
<td>2) Enhance the bioavailability</td>
<td>2) Increase in the bioavailability</td>
</tr>
<tr>
<td>Drug Combination</td>
<td>Method Used</td>
<td>Objectives</td>
<td>Results</td>
</tr>
<tr>
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</tr>
<tr>
<td>Raloxifene + HPC + Poloxomer series + PVP K 30</td>
<td>1) Spray Drying</td>
<td>1) Improve the Physicochemical properties 2) Improve the bioavailability of poorly water soluble drug</td>
<td>1) RXF-loaded SD exhibited a significant increase in solubility and dissolution rate. 2) Bioavailability of RXF was markedly higher as compared with RXF powder</td>
</tr>
<tr>
<td>Raloxifene + β-CD</td>
<td>1) Kneading Method</td>
<td>1) To study the Effect and influence of β-CD on the solubility and dissolution rate of this poorly aqueous soluble drug.</td>
<td>1) Solubility of raloxifene significantly increased in the presence of β-CD. 2) The improvement in dissolution rate of Raloxifene</td>
</tr>
<tr>
<td>Carvedilol + Soluplus</td>
<td>1) Solvent evaporation method 2) Spray drying method 3) Freeze Drying method</td>
<td>1) Improving the solubility of poorly water soluble drug 2) Improving the dissolution rate of poorly water soluble drug</td>
<td>1) Solubility of carvedilol significantly increased 2) The Improvement in dissolution rate of Carvedilol</td>
</tr>
<tr>
<td>Atorvastatin calcium + Soluplus</td>
<td>1) Spray drying</td>
<td>1) Improve the oral bioavailability of Atorvastatin calcium. 2) Improve the solubility of Atorvastatin calcium.</td>
<td>1) Improved the oral bioavailability of atorvastatin calcium. 2) Improved the solubility of Atorvastatin calcium.</td>
</tr>
<tr>
<td>Drug Combinations</td>
<td>Preparation Method</td>
<td>Solubility Enhancement</td>
<td>Dissolution Improvement</td>
</tr>
<tr>
<td>----------------------------------------</td>
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</tr>
<tr>
<td>Bicalutamide+ PVP K29/32 +sodium lauryl sulphate</td>
<td>1) Solvent Evaporation 2) Spray drying</td>
<td>1) Enhancement of apparent solubility 2)Enhancement of dissolution</td>
<td>1) Increase the dissolution efficiency. 2) Increases the solubility of solid dispersion.</td>
</tr>
<tr>
<td>Raloxifene + PVP K30</td>
<td>1) Spray drying</td>
<td>1) Enhancement the dissolution rate 2) Enhancement of bioavailability</td>
<td>1) Increase the dissolution rate of poorly water soluble RXF 2) Enhanced the bioavailability</td>
</tr>
<tr>
<td>Etoricoxib + Sugar carriers (Lactose,Sucrose,Mannitol)</td>
<td>1) Solvent Evaporation</td>
<td>1) Improve Solubility. 2) Enhancement of dissolution</td>
<td>1) solubility of poorly aqueous soluble etoricoxib can be enhanced. 2) Dissolution of poorly aqueous soluble etoricoxib can be enhanced.</td>
</tr>
<tr>
<td>Carvedilol + PVP K30</td>
<td>1) Solvent Evaporation</td>
<td>1) Increase the Solubility 2) Increase the dissolution</td>
<td>1) Increased the solubility of drug. 2) Increased the dissolution of drug.</td>
</tr>
</tbody>
</table>

**Marketed Preparations:**

<table>
<thead>
<tr>
<th>Product</th>
<th>Drug</th>
<th>Dispersion Method</th>
<th>Polymer</th>
<th>Dose (mg)</th>
<th>Tablets per day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norvir</td>
<td>Ritonavir</td>
<td>Hot melt extrusion</td>
<td>PVP-VA64</td>
<td>100</td>
<td>6</td>
</tr>
<tr>
<td>Kaletra</td>
<td>Ritonavir/Lopinavir</td>
<td>Hot melt extrusion</td>
<td>PVP-VA64</td>
<td>50/200</td>
<td>4-8</td>
</tr>
<tr>
<td>Indvek</td>
<td>Telaprevir</td>
<td>Spray drying</td>
<td>HPMC-AS</td>
<td>250</td>
<td>6</td>
</tr>
<tr>
<td>Zelboraf</td>
<td>Vemurafenib</td>
<td>Co-precipitation</td>
<td>HPMC-AS</td>
<td>240</td>
<td>6</td>
</tr>
<tr>
<td>Kalydeco</td>
<td>Ivacaftor</td>
<td>Spray drying</td>
<td>HPMC-AS</td>
<td>150</td>
<td>2</td>
</tr>
</tbody>
</table>
Conclusion:

Solid dispersion systems have been realized as extremely useful tool in improving the dissolution properties of poorly water-soluble drugs. In recent years, a great deal of knowledge has been accumulated about solid dispersion technology, but their commercial application is limited. Various methods have been tried recently to overcome the limitation and make the preparation practically feasible. The problems involved in incorporating into formulation of dosage forms have been gradually resolved with the advent of alternative strategies. These include methods like spraying on sugar beads and direct capsule filling. Although there are some hurdles like scale up and manufacturing cost to overcome, there lies a great promise that solid dispersion technology will hasten the drug release profile of poorly water soluble drugs.

References:


