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# Solid Dispersion-Method of Enhancement of Dissolution Rate and Increase Bioavailability

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## Abstract

To improve the dissolution of poorly water-soluble drugs and thus enhance their bioavailability, the dispersion of one or more active pharmaceutical ingredients in a carrier at solid-state is used. It has engrossed significant interest as an efficient means of improving the dissolution rate. It happens due to the dispersions of poorly water-soluble drugs with water-soluble carriers. One of the most challenging aspects in formulation development is solubility behavior of drugs. The number of poor water-soluble compounds has radically increased. Compared to conventional formulations such as tablets or capsules, solid dispersions prepared by various methods can be used which have many benefits over the above conventional dosage form. The focus of this review article is on the advantages, limitations, various methods of preparation and characterization of the solid dispersion. The different types of solid dispersions based on their 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 have also been discussed. In this review, it is intended to discuss the prospects related to the area of solid dispersion manufacturing.

**Keywords**

Solid Dispersion, Introduction, Technique

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## INTRODUCTION

The drugs which are having poor water solubility often show poor oral bioavailability due to the low levels of absorption. Drugs that undergo dissolution rate limited absorption, their dissolution rate can be enhanced by micronisation or size reduction, but this leads to aggregation of particles which leads to poor wettability[1]. Various other approaches for increasing the bioavailability of poorly water-soluble drugs include salt formation, solubilization using a co-solvent, complexation with cyclodextrin and particle size reduction; all these approaches have various limitations. Development of solid dispersions of poorly bioavailable drugs overcame the drawbacks of the previous approaches. Solid dispersion is defined as dispersion of one or more active ingredients (hydrophobic) in an inert carrier (hydrophilic) at solid state prepared by melting (fusion) method, solvent, or melting solvent method. When the solid dispersion meets the aqueous medium, the inert carrier dissolves and the drug is released, the increased surface area produces a higher dissolution rate thus increasing the bioavailability of the poorly soluble drug[2].

The first drug whose rate and extent of absorption was significantly enhanced using solid dispersion was sulfathiazole, in which a eutectic mixture of

sulfathiazole with urea as the inert carrier was formed. Lyophilization is a molecular mixing technique where the drug and carrier are co-dissolved in cyclohexanol, frozen and then sublimed under a vacuum to obtain a lyophilized molecular dispersion[3].

**Solid Dispersions:**
Solid dispersion is a process in which one or more active ingredients in an inert carrier or matrix solid state are prepared by using different methods such as the melting (fusion), solvent evaporation and melting-solvent method. In a solid diluent or diluents, the dispersion of a drug or drugs by traditional mechanical mixing is not included in this category. The solid dispersions may also be called solid-state dispersions.[5]

**Types of Solid Dispersions:**
1. based on the carrier used
2. based on their molecular arrangement

**Based on carrier used:**
Based on carrier used solid dispersions can be classified into three generations:
**First generation:** Using crystalline carriers such as urea and sugars, first-generation solid dispersions were prepared which were the first carriers to be employed in solid dispersions. They have the demerits of forming crystalline solid dispersions and did not release the drug as quickly as amorphous ones.[6]

**Second generation:**
Second generation solid dispersions include amorphous carriers instead of crystalline carriers which are usually polymers. These polymers include synthetic. polymers such as povidone (PVP), polyethylene glycols (PEG) and polymethacrylates as well as natural products-based polymers such as hydroxyl propyl methylcellulose (HPMC), ethyl cellulose, and hydroxypropyl cellulose or starch derivatives like cyclodextrins.
**Third generation:** Recently, it has been shown that the dissolution profile can be improved if the carrier has surface activity or self-emulsifying properties. Therefore, third generation solid dispersions appeared. The use of surfactants such as inulin, inutec SP1, compritol 888 ATO, gelucire 44/14 and poloxamer 407 as carriers was shown to be effective in originating high polymorphic purity and enhanced in vivo bioavailability.

**Based on their molecular arrangement:** Solid dispersions can be classified in following types:

**Eutectics Systems:** This mixture consists of two compounds which in the liquid state are completely miscible but in the solid state only to a very limited extent. By rapid solidification of the fused melt of two components these are prepared and that show complete liquid miscibility and minor solid-solid solubility as show in fig1.

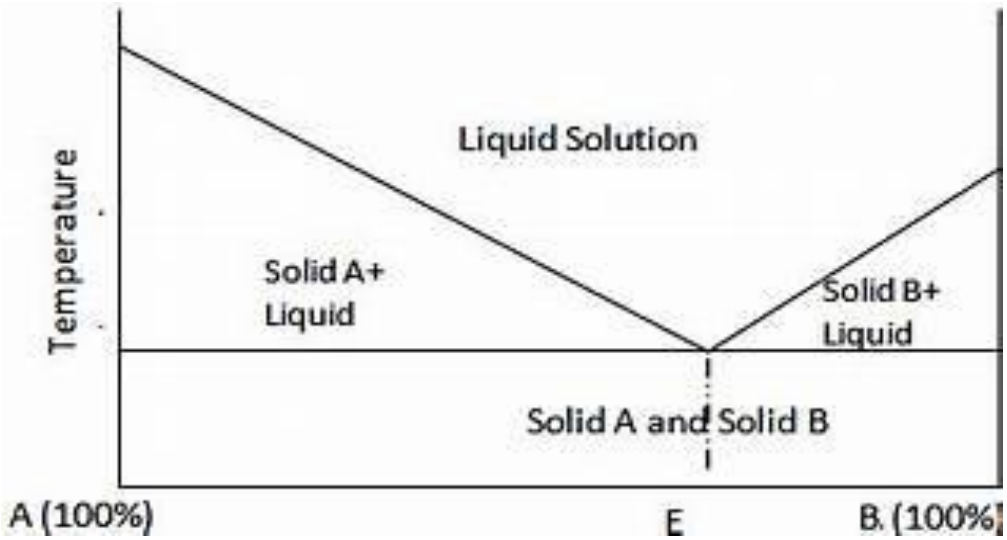


**Fig 1: Phase diagram of an eutectics system**

Thermodynamically, such a system is an intimately blended physical mixture of two crystalline components. When the mixture of A and B with a fix composition 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. When a mixture containing slightly soluble drug and carrier as an inert substance and highly water soluble is dissolved in an aqueous medium, the carrier will dissolve fast, releasing very fine crystals of the drug.

**Amorphous precipitation in a crystalline carrier:**

In the crystalline carrier the drug may also precipitate in an amorphous form instead of simultaneous crystallization of the drug and the carrier (eutectic system). The amorphous solid state is shown in Fig. 2. The high energy state of the drug in this system generally produces much greater dissolution rates than the corresponding crystalline forms of the drug.

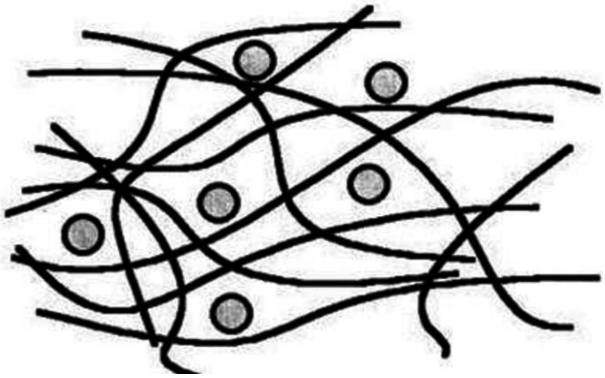

**Fig:2 - Amorphous solid solution**

**Glass solutions and suspensions:**

These are the homogeneous glassy system in which solute is dissolved in glass carrier. Glass suspensions are mixtures in which precipitated particles are suspended in glass solvent. Lattice energy is much lower in glass solutions and suspensions. Melting points of glasses is not sharp while they soften progressively on heating. Examples of carriers that form glass solutions and suspensions are citric acid, PVP, urea, PEG, sugars such as dextrose, sucrose, and galactose.

**Solid Solutions:**

In this system a homogeneous one phase system is formed when the two components crystallize together. The particle size of the drug is reduced to its molecular size in the solid solution. Thus, a faster dissolution rate is achieved in a solid solution than the corresponding eutectic mixture. Solid solutions can be classified as continuous or discontinuous according to the extent of miscibility of the two components. In continuous solid solutions, the two components are miscible in the solid state in all proportions.

**Continuous Solid Solutions:**

The components are miscible in all proportions in a continuous solid solution. Hypothetically, this means that stronger the bonding strength between the two components than the bonding strength between the molecules of each of the individual components.

**Discontinuous Solid Dispersions:**

The solubility of each of the components in the other component is limited in the case of discontinuous solid solutions. A typical phase diagram (**Fig.3**) shows the regions of true solid solutions. One of the solid components is completely dissolved in the other solid component in these regions. The mutual solubilities of the two components start to decrease below a certain temperature. Goldberg reported that the term 'solid solution' should only be applied when the mutual solubility of the two components exceeds 5%.

**Mechanism of Enhanced Dissolution in Solid Dispersion: -**

A number of factors may influence or increase the dissolution rate for solid dispersion.

These factors include the following: -

**Reduced Particle size or Reduced Agglomeration:**

Both are related to reduction of particle size and increase in the exposed surface area of the drug. Size reduction has been resulting of eutectic or solid solution formation. It has also been suggested that to the dissolution medium as physically separate entities the presentation of particles may reduce aggregation. For solid dispersion many of the carriers used may have some wetting properties and may lead to reduce agglomeration and increase surface area by improved wetting.

**Increased solubility or Dissolution rate of the drug:**

The solubility of the drug may increase by using many of the carriers. Therefore, carrier controlled the release of drug that is controlled by the carrier and is independent of drug properties. Secondly some

system shows release behaviour that is dependent on the properties of the drug rather than polymer.

**From crystalline to amorphous state transformation/ Formation of high Energy State: -**
Amorphous drugs have the higher energy state, minimum stability and can be considered as cooled liquids. The energy required to transfer a molecule from crystal is greater than required for non-crystalline (amorphous) solid, so they have grater aqueous solubility than crystalline forms. For example, the solubility of amorphous state of novobiocin is 10 times more than crystalline form.

**Wetting: -**
The liquid forms a film over the surface of the solid when a strong affinity exists between a liquid and solid. When this affinity is non-existent or weak the liquid has difficulty dispensing the air and there exist an angle of contact between the liquid and the solid. This contact angle results from an equilibrium involving three interfacial tensions.

**Polymer used in solid dispersion: -**
1- **Polyethylene Glycol-**
Polyethylene glycols are obtained from a reaction of ethylene glycol with ethylene oxide. Phospholipids: The complexity of glycerides

2- **Phospholipids**-
The complexity of glycerides advances by modification of the terminal hydroxyl with phosphate linked head groups to form phospholipids, common phospholipid head groups include choline, ethanolamine, serine, inositol and inositol phosphate, and glycerol esters.

3- **Polyvinyl Pyrrolidone**: -
PVP molecular weight ranges from 2500 to 3000000. It is having solubility in solvents like water, ethanol, chloroform, and isopropyl alcohol. PVP gets decomposed at high temperature. Therefore, it is not suitable for preparation of solid dispersions prepared by melt method because melting takes place at a very high temperature.

4- **Cyclodextrins:** -
Cyclodextrins are used to enhance solubility, chemical protection, taste masking and improved handling by the conversion of liquids into solids by entrapment.[9]

**POLYMERS USED IN SOLID DISPERSIONS: [9]**
Polyethylene Glycol (PEG): These are compounds.

1.**Techniques for Solid Dispersions:**
Various methods of preparation solid dispersions are summarized as: -

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

**Solvent method**
This method is also known as solvent evaporation method in which physical mixture of the drug and the carrier is dissolved in a common solvent and is evaporated until a clear solvent-free film is obtained. The main advantage is that the thermal decomposition of the drug or the carrier can be prevented because the organic solvents require a low temp for evaporation. The disadvantage of this method is difficulty in removing the solvent and higher cost of preparation.

**Co-precipitation method**
Required amount of drug is added to the solution of carrier. The system is kept under magnetic agitation and protected from the light. The formed precipitate is separated by vacuum filtration and dried at room temperature to avoid the loss of the structure water from the inclusion complex.

**Melting method**
The melting method is suitable for heat-stable materials with low melting points. The basic principle of the method consists of melting together the drug and carrier at a temperature slightly above their eutectic point, mixing the liquefied components. It is then cooled to acquire a congealed mass. It is crushed and sieved.
Ex. albendazole and urea solid dispersion were prepared by this method.

**Co-grinding method**
Physical mixture of drug and carrier is mixed for some time employing a blender at a particular speed. The mixture is then charged into the chamber of a vibration ball mill steel balls are added. The powder mixture is pulverized. Then the sample is collected and kept at room temperature in a screw capped glass vial until use. Ex. chlordiazepoxide and mannitol solid dispersion was prepared by this method.

**Gel entrapment technique.**
Hydroxyl propyl methyl cellulose is dissolved in organic solvent to form a clear and transparent gel. Then the drug for example is dissolved in gel by

sonication for a few minutes. Organic solvent is evaporated under vacuum. Solid dispersions are reduced in size by mortar and sieved.

**Spray-drying method.**
Drug is dissolved in suitable solvent and the required amount of carrier is dissolved in water. Solutions are then mixed by sonication or other suitable method to produce a clear solution, which is then spray dried using spray dryer.[6]

Melting method: In melting or fusion method a Solvent evaporation
-Hot-melt extrusion
-Fusion method
-Solvent melt method
-Kneading technique
-Inclusion complexes
-Direct capsule filling
-Surface active carriers
-Particle size reduction

**Advantages of Solid Dispersion: -**
The solid dispersions technique offers the following pharmaceutical advantages.
Solid dispersion technique is useful to enhance solubility.

1. It is easier to produce and is more applicable.
2. It leads to increase in extent and rate absorption.
3. It leads to increase in extent and rate absorption of a drug, hence rapid dissolution rate occurs.
4. Solid dispersion technique is useful to enhance solubility and bioavailability of poorly water-soluble drug.
5. It is easier to produce and is more applicable.
6. It is used to mask the bitter taste of drug.
7. It is used to improve porosity of drug.
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10. It is used to mask the bitter taste of drug.
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12. It is used to mask the bitter taste of drug.
13. It is used to improve porosity of drug.
14. It is used to mask the bitter taste of drug.
15. It is used to improve porosity of drug.

**Disadvantage of Solid Dispersion: -**
The disadvantages of solid dispersion are enlisted below: -

1. It leads to the poor scale-up for the purpose of
2. It leads to the poor scale-up for the purpose of manufacturing.
3. It is laborious method of preparation.
4. The polymer used in solid dispersion can absorb moisture and cause phase-separation, crystal growth and convert amorphous from into crystalline form. Thus, result in decrease solubility and dissolution rate.
5. It causes reproducibility of physiochemical characteristics.

**APPLICATION OF THE SOLID DESPERSION**

1. Formulation of sustained release dosage form.
2. Masking of unpleasant taste and smell of drugs.
3. Solid dispersion also acts as the functional carriers that offer Solid dispersion also act as the functional carriers that offer the added benefit of the targeting the release of the highly soluble forms of the poorly water-soluble drugs for absorption to an optimum site.
4. Reduction in the inactivation of drugs like morphine and progesterone in pre systemic circulation.
5. It increases the solubility of poorly soluble drugs and thus increases the dissolution rate, which enhances the absorption and bioavailability of the drug.

**CONCLUSION**
To improve the dissolution of poorly water-soluble drugs and thus enhance their bioavailability, the dispersion of one or more active pharmaceutical ingredient in a carrier at solid state is used. Solid dispersion is a most simple and efficient technique for increasing the aqueous solubility of a drug.

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