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## **SOLID DISPERSION:-A REVIEW**

Rohit M. Patil \*, Swati D. Yeole, Harshal. L.Tare.

TSPM's, Trimurti Institute of Pharmacy Jalgaon, Maharashtra, India

### **Keywords:**

Solubility, solid dispersion, bioavailability, carrier, and future prospects.

### **For Correspondence:**

**Rohit M. Patil**

TSPM's, Trimurti Institute  
of Pharmacy Jalgaon,  
Maharashtra, India

### **ABSTRACT**

Solid dispersion is one of the method is widely used to improve the solubility dissolution rates and bioavailability of a poorly water soluble drugs. If be improving the dissolution rate of the poorly water soluble drug. It be water soluble carries used in preparation of solid dispersion

In this review, solubility of drug, types and preparation of solid dispersion, techniques, characterization, advantage, disadvantages on the application of the solid dispersion

## INTRODUCTION

The simplest and easiest way of administering drugs is through oral route. Over other types of dosage forms the oral dosage forms have many advantages like accurate dosage, less bulk, greater stability and easy productions is possible. The drugs which are having poor water solubility they often show poor oral bioavailability due to the low level of absorption. Drugs that undergoes 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.

Solid dispersion is defined as one or more active ingredient (hydrophobic) in a n inert carrier (hydrophilic) at solid state prepared by melting (fusion) method, solvent, or melting solvent method. Poor water soluble compound, large dosage is required to produce desirable effect of the poor water soluble drug because they show the decrease release rate and poor bioavailability but large dose may leads to toxicity of the drug.

The first drug whose rate and extent of absorption was significantly enhanced using solid dispersion was sulfathiazole by sekiguchi and obi (sekiguchi, 1961), in which eutectic mixture of sulfathiazole with urea as the inert carrier was formed. Lyophilization is a molecular mixing technique where the drug and carrier were co-dissolved in cyclohexanol, frozen and then sublimed under vacuum to obtain a lyophilized molecular dispersion (Lin, 1980).

**Table 1: Definition of different solubility terms**

Description forms (solubility definition)	Parts of solvent required for one part of solute	Solubility range (mg/ml)	Solubility assigned (mg/ml)
Very soluble (VS)	<1	>1000	1000
Freely soluble (FS)	1 to 10	100 -1000	100
Soluble	10-30	33-100	33
Sparingly soluble (SPS)	30-100	10-33	10
Slightly soluble (SS)	100-1000	1-10	1
Very slightly soluble (VSS)	1000-10000	0.1-1	0.1
Practically insoluble (PI)	>10000	<0.1	0.01

### •SOLID DISPERSION

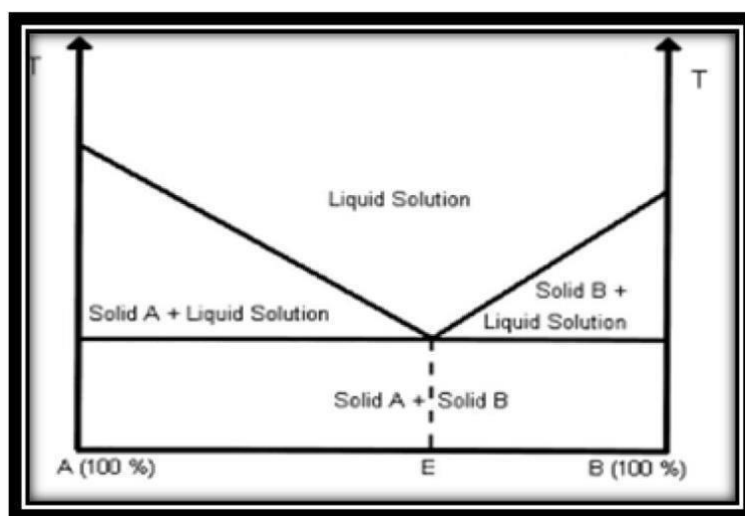
•Solid dispersion is defined as dispersion of one or more active ingredient (hydrophobic) is an inert carrier

(hydrophilic) at solid state prepared by melting (fusion), solvent, melting solvent method. The product formed contain different components i.e. a hydrophilic matrix and a hydrophobic drug.

### Classification of solid dispersion:

Depending on the molecular arraignment, solid dispersion can be following types:

1. **Eutectic mixture** – solid eutectic mixture are usually prepared by rapidly cooling the co-melt of the two components in order to obtain a physical mixture of very fine crystal of the two component

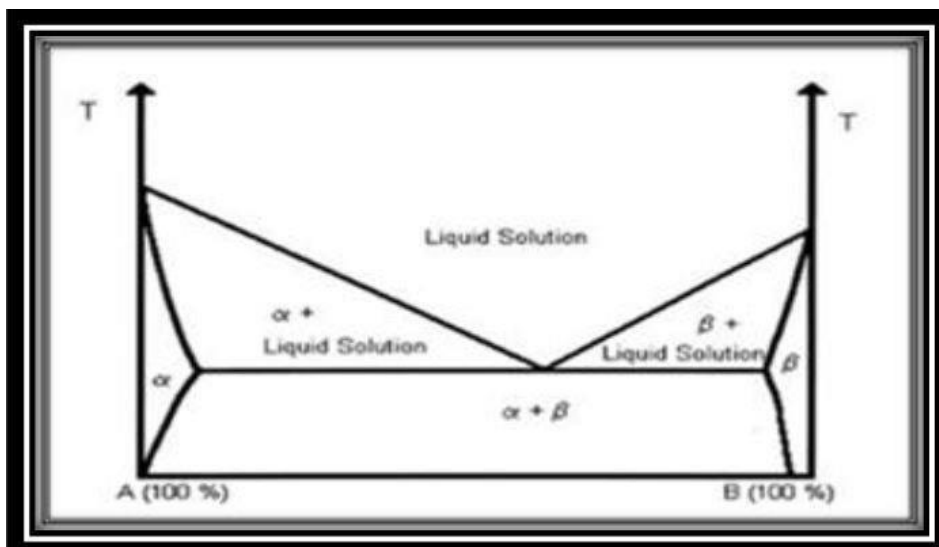


**Fig. 1: Phase diagram of an Eutectic System**

### 2. Solid solutions-

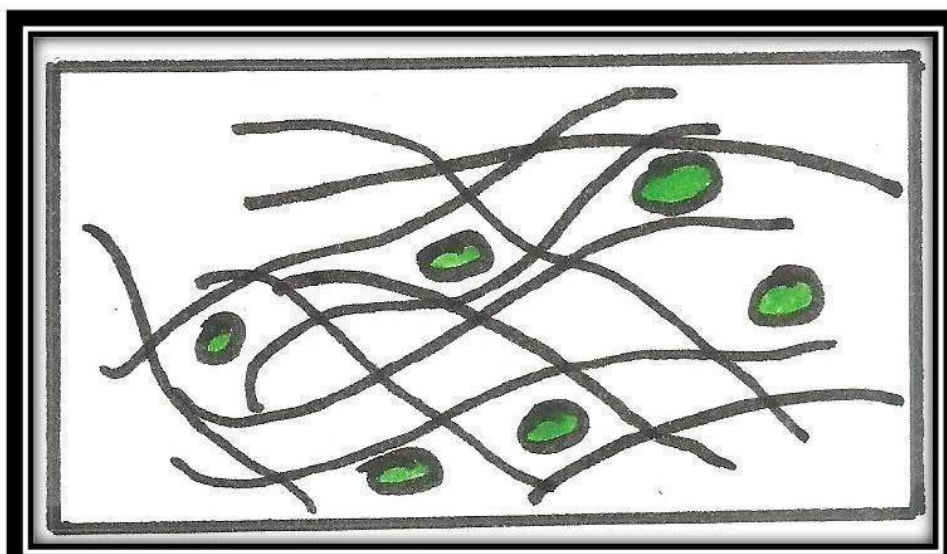
Depending on the miscibility, the two types of solid solutions are:

1. Continuous solid solutions-In continuous solid solutions, the components are miscible in all properties i.e. the bonding strength between the components is. Stronger than the bonding between the individual component.
2. Discontinuous solid solutions-In discontinuous solid solutions, the solubility of each of the component on other component is limited in nature.
3. Depending on distribution of solvates in the solvendum, solid solutions can be two types:
4. Substitutional crystalline solution-These are those solid solutions which have a crystalline structure, the solute molecules substitute for the solvent molecules in the crystal lattice.
5. Interstitial crystalline solid solution-These are those solid solutions in which the dissolved molecules occupy the interstitial spaces between the solvent molecules on crystal lattice



**Fig. 2: Phase Diagram for Discontinuous solution**

- 3. Amorphous solid solutions-** In amorphous solid solutions, the solute molecules are dispersed molecularly but irregularly within the amorphous solvent.



**Fig. 3: Amorphous solid solution**

- 4. Glass solutions and glass suspension-** A glass solution is a homogeneous system in which the solute dissolves in the glassy solvent. The glassy state is characterized by transparency and brittleness below the glass transition temperature. The term glass refers to a pure chemical or a mixture of pure chemicals in the glassy state.

**Classification of solid dispersion on the basis of recent advancement:**

1. First generation solid dispersion- These solid dispersions are prepared by using crystalline carriers. Urea and sugars were the first crystalline carriers that were used in

the preparation of solid dispersions. These have a disadvantage of being thermodynamically unstable and they do not release drug at a faster rate.

2. Second generation solid dispersion- These solid dispersions are prepared using amorphous carriers instead of crystalline carriers. The drug is molecularly dispersed in the polymeric carrier the polymeric carriers are divided into two groups:

- Synthetic polymer- povidone, polyethylene glycol and polymethacrylates.
- Natural polymers- hydroxypropylmethylcellulose, ethyl cellulose, starch derivatives like cyclodextrin.

3. Third generation solid dispersion- These solid dispersions contain a surfactant carrier, or a mixture of amorphous polymers and surfactants as carriers. These achieve the highest degree of bioavailability for the drugs that are having poor solubility. The surfactants being used in the third generation solid dispersion are such as insulin, poloxamer 407 etc.

#### **Advantages of solid dispersion :**

The solid dispersions technique offers the following pharmaceutical advantages.

- 1 It is easier to produce and is more applicable.
- 2 It leads to increase in extent and rate absorption of Drug, hence rapid dissolution rate occurred.
- 3 Transformation of various parameters and wettability can enhance the bioavailability of poorly water soluble drugs.
- 4 It is easier to produce rapid disintegration oral tablets by solid dispersion.
- 5 It is used to mask the bitter taste of drug.
- 6 It is used to improve porosity of drug.

#### **Disadvantages of solid dispersion:**

The disadvantages of solid dispersion are enlisted below:

It leads to the poor scale-up for the purpose of manufacturing.

- 1 The polymers used in solid dispersion can absorb moisture and cause phase- separation, crystal growth and convert amorphous form into crystalline form. Thus result in decrease solubility and dissolution rate.
- 2 It is laborious method of preparation.
- 3 It causes reproducibility of physicochemical characteristics

### **Selection of Carrier**

A carrier should possess the following characteristics to be suitable for increasing the rate of dissolution of a drug:

- 1 The carrier should be freely soluble in water with a high rate of dissolution.
- 2 It should be nontoxic in nature
- 3 It should be pharmacologically inert
- 4 Should possess heat stability with a low melting point
- 5 It should be able to enhance aqueous solubility of the drug
- 6 It should possess chemical compatibility with the drug, and should not form strongly bonded complexes with the drug
- 7 Economical.

### **Mechanisms of bioavailability enhancement**

- 1 Solid dispersion increase the dissolution rate of poorly water soluble drugs by one of the following mechanisms:
- 2 Reduction in particle size
- 3 Improvement in wettability and dispersibility
- 4 Changing crystalline form of drug to amorphous form
- 5 Reduction in aggregation and agglomeration of drug particles.

### **Application of the Solid Dispersion:**

- 1 The solid dispersion systems were shown to provide the bio available oral dosage forms for the anti- cancer drug, which could be substituted for the standard injection to improve the patient compliance and comfort.
- 2 Solid dispersion also act as the functional carriers that offer the added benefit of the targeting the release of the highly soluble drugs for absorption to an optimum site.
- 3 The solid dispersion systems were also found to reduce the food effect on the drug absorption , thus by increasing the convenience of the therapy as it is the need for some drugs to be taken with food was eliminated.
- 4 The solid dispersion formulations were demonstrated to accelerate the onset of action for the drugs such as NSAIDS (non- steroidal anti-inflammation drugs) where immediate action is crucial in relieving acute pain and inflammation.

Sr. No.	Category	Carriers
1	Sugars	Dextrose, sucrose, galactose, sorbitol, maltose, xylitol, manni
2	Acids	Citric acid, succinic acid
3	Polymeric materials	Polyvinyl pyrrolidone (PVP), polyethylene glycol (PEG), hydroxy methyl cellulose (HPMC), methyl cellulose (MC), hydroxy ethyl cell cyclodextrin, hydroxy propyl cellulose, pectin, galactomannan
4	Insoluble or enteric polymer	Hydroxy propyl methyl cellulose phthalate (HPMCP), eudrag E100, eudragit RL, eudragit RS
5	Surfactants	Polyoxyethylene stearate, poloxamer 188, deoxycholic acid, t
6	Miscellaneous	Pentaerythritol, pentaerythrityltetraacetate, urea, urethane, hyxanthins

Table No. 2: Different carriers used in solid dispersion

- 5 The improved absorption efficiency was demonstrated for the solid dispersion systems that allow for the reduction in the contents of the active agent per dose thus it decreases the cost associated with these drugs therapies.
- 6 The dry powder formulation consisting of the solid dispersion for use as inhalation is prepared in improving the immunosuppressive therapy in the lung transplant patients. Many problems can be avoided which includes use of local anesthesia and irritating solvents.

#### Methods of Preparation of Solid Dispersion:

Various methods used for preparation of solid dispersion system. These methods are given below.

1. Melting method
2. Solvent method
3. Melting solvent method (melt evaporation)
4. Melt extrusion methods
5. Lyophilization techniques
6. Melt agglomeration process
7. The use of surfactant
8. Electros pinning
9. Super Critical Fluid (SCF) technology

**1. Melting method:** In melting or fusion method a physical mixture of the drug and a water soluble carrier is prepared, by heating it directly until it melts. The final solid mass that is obtained is crushed, pulverized and sieved. However substances either the drug or the carrier may decompose due to high temperature during the melting process. A method to overcome this problem could be heating the mixture in a sealed container or under vacuum or in the presence of inert gases like nitrogen. The advantage is its simplicity and economical nature.

**2. Solvent method:** This method is also known as solvent evaporation method in which physical mixture of the drug and the carrier is dissolved in common 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 in this method is difficulty in removing the solvent and higher cost of preparation.

**3. Melting solvent method:** This method involves the dissolving the drug in an appropriate liquid solvent and then incorporating the solution formed directly into the melt of polyethylene glycol which is evaporated until a clear solvent free film is obtained. This technique is a combination of fusion and solvent evaporation method.

**4. Melt extrusion method:** using twin screw extruder, the drug/carrier mix is simultaneously melted homogenized and extruded and shaped in different forms such as tablets, granules, pellets, powder etc. The method is applicable for thermo labile drugs as the mixture of the drug and carrier is subjected to elevated temperature for about 1 min.

**5. Lyophilization:** It is a phenomenon of transfer of heat and mass from and to the product. It is an alternative technique to solvent evaporation in which molecular mixture technique is used where the drug and carrier is dissolved in common solvent, frozen and sublimed.

**6. Melt agglomeration technique:** In this technique binder is use as carrier. There are two method of preparation of solid dispersing, first is by spraying the drug on melted binder plus excipients and other one is melting of binder drug and excipient above the melting temperature of binder used. For using high binder content rotary process might be preferable for controlling temperature. This technique is advantageous in homogeneous mixing of drug but larger particle size cause densification and fines cause adhesion of mass.

**7. Electros pining method:** In this technique electric force is used to withdraw a Nano size fiber thread from the polymer sol/polymer melt. This a combination of solid dispersion with



nanotechnology use in polymer industry. Stream of polymer solution/melt is subjected to electric force (5 to 30kv) which cause body of the liquid becomes charged, and electrostatic repulsion counteracts the surface tension. This made a strong cohesive force between the particle and droplets of polymer and a stream of fiber is formed. The thinning and stretching of fiber to Nano diameter is done by using whipping process called electrostatic repulsion lead to formation of uniform fiber in Nano diameter. This process all depend on rate of feeding surface tension and electric force used.

**8. Supercritical fluid technology:**SCF is a substance above its critical temperature and pressure. Critical point represents the highest temperature and pressure at which the substance exists as vapor and liquid in equilibrium. In this technique SCF is used to form solid dispersion of insoluble material/polymer with drug cause increase in dissolution property. It is superior over conventional technique (spray drying, hot melt etc.), in this technique SCF carbon dioxide is mainly used which cause very rapid precipitation of solid mixture giving no time for separation of drug and polymer in preparation of solid dispersion. It form very stable small particle with higher surface area for good flow and low organic solvent residual. In recent solid dispersion of carbamazepine with PEG-4000 are made using SCF carbon dioxide in precipitation vessel. Resulting in formation of carbamazepine with increase rate and extent of dissolution with low solvent residual.

### **Characterization of solid dispersion**

Various characterization methods to assess the solid dispersion are as follows

#### **Drug-carriers miscibility**

- Hot stage microscopy
- Differential scanning calorimetry
- Powder X-ray diffraction
- Spectroscopic methods like Raman spectroscopy, FT-IR spectroscopy

#### **Physical structure**

- Scanning electron y
- Surface area analysis
- Surface properties
- Dynamic vapour sorption
- Inverse gas chromatograph

- Atomic force microscopy
- Raman microscopy

#### **Amorphous content**

- Polarised light optical microscopy
- Hot stage microscopy
- Humidity stage microscopy
- DSC (MTDSC)
- Powder X-ray diffraction

#### **Stability**

- Humidity studies
- Isothermal Calorimetry
- DSC (T<sub>g</sub>, Temperature recrystallization )
- Saturated solubility studies

#### **Dissolution enhancement**

- Dissolution
- Intrinsic dissolutions
- Dynamic solubility
- Dissolution in bio-relevant media

#### **Commercial solid dispersion product**

Paracetamol ,dizepam, lamotrigine, carbamazepine ,albendazole, Griseofulvin, nifedipine , prednisolone, ofloxacin, nimodipine

#### **CONCLUSION:**

Solid dispersions system has been realized as extremely useful tool in improving the dissolution properties of poorly water-soluble drugs. Because of the poor aqueous solubility the drug possess dissolution problem due to which the in vivo absorption of the drug is reduced and thus the bioavailability is reduced, making the drug inappropriate the oral consumption and therefore solubility enhancement become necessary for such drug candidate. In recent years, a great deal of knowledge has been accumulated\_about solid dispersion technology, but their commercial applications are limited. Various methods have been tried recently to overcome the limitations and make the preparation practically feasible. The problem involved in incorporating into formulation of dosage forms has been gradually

resolved with the advent of alternative strategies. These include method like spraying on sugar beads and direct capsule filling. Although there are some hurdles like scale up and manufacturing cost of overcome, there lies a great promise that solid dispersion technology will hasten the drug release profile of poorly water soluble drug.

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