**Solid Dispersion- A Review**

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**ABSTRACT**
Solid dispersion is an effective way of improving the dissolution rate of poorly water soluble drugs and hence its bioavailability. The water soluble carriers used in preparation of solid dispersion enhance the dissolution rate of the poorly water soluble drug. The review article focuses on the methods of preparation, advantages, disadvantages and characterization of the solid dispersions.

**Keywords:** solid dispersion, bioavailability, aqueous solubility, carrier, lyophilisation

**INTRODUCTION**
The drugs which are having poor water solubility they 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. Various other approaches for increasing the bioavailability of poorly water soluble drugs include salt formation, solubilisation 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 (hydrophillic) at solid state prepared by melting (fusion) method, solvent, or melting solvent method. The product formed contains different components i.e. a hydrophillic matrix and a hydrophobic drug.

**NOYES WHITNEY EQUATION**
The rate of dissolution can be expressed by using Noyes whitney equation, which provides various parameters that can help improve the bioavailability of a poorly soluble drug.

\[
\frac{dc}{dt} = \frac{AD(Cs - C)}{h}
\]

- \( \frac{dc}{dt} \) - is the rate of dissolution
- \( A \) - Surface area available for dissolution
- \( D \) - Diffusion coefficient of the compound
- \( Cs \) - solubility of the compound in the dissolution medium
- \( C \) - Concentration of drug in the medium at time t
- \( h \) - Thickness of diffusion boundary layer adjacent to the surface of dissolving compound

**SOLID DISPERSION**
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**CLASSIFICATION OF SOLID DISPERSION**
Depending on the molecular arrangement, solid dispersions can be of the following types:

1. **Eutectic mixtures** – solid eutectic mixtures are usually prepared by rapidly cooling the co-melt of the two components in order to obtain a physical mixture of very fine crystals of the two components.
2. Solid solutions
Depending on the miscibility, the two types of solid solutions are:

- Continuous solid solutions - In continuous solid solutions, the components are miscible in all proportions i.e. the bonding strength between the components is stronger than the bonding between the individual component.
- Discontinuous solid solutions - In discontinuous solid solutions, the solubility of each of the component in the other component is limited in nature.
- Depending on the distribution of the solvates in the solvendum, solid solutions can be of two types:
  - 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.
  - Interstitial crystalline solid solution - These are those solid solutions in which the dissolved molecules occupy the interstitial spaces between the solvent molecules in the crystal lattice.

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

4. Glass solutions and glass suspension – A glass solution is a homogenous system in which the solute dissolves in the glassy solvent. The glassy state is characterised 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: \[3\]

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 glycols 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 inulin, poloxamer 407 etc.

**ADVANTAGES OF SOLID DISPERSION**
- Solid dispersion results in particles with reduced particle size and thus the surface area are improved and increased dissolution rate is attained. Hence bioavailability is increased.\[4\]
- The carrier used in the solid dispersion plays a major role in improving the wettability of the particles. Improved wettability results in increased solubility thus improving the bioavailability.\[3\][5]
- In solid dispersion drugs are presented as supersaturated solutions which are considered to be metastable polymorphic form. Thus presenting the drug in amorphous form and increases the solubility of the particles.\[5\][6]

**DISADVANTAGES OF SOLID DISPERSION** \[7\]
- Major disadvantage is their instability. They show changes in crystallinity and a decrease in dissolution rate with ageing.
- Temperature and moisture have more deteriorating effect on solid dispersions than on physical mixtures.
- Difficulty in handling because of tackiness

**SELECTION OF CARRIER** \[3\]
A carrier should possess the following characteristics to be suitable for increasing the rate of dissolution of a drug.
• The carrier should be freely soluble in water with a high rate of dissolution
• It should be non toxic in nature
• It should be pharmacologically inert
• It should possess heat stability with a low melting point
• It should be able to enhance aqueous solubility of the drug
• It should possess chemical compatibility with the drug, and should not form strongly bonded complexes with the drug
• Economical

MECHANISM OF BIOAVAILABILITY ENHANCEMENT

Solid dispersions increase the dissolution rate of poorly water soluble drugs by one of the following mechanisms:
• Reduction in particle size
• Improvement in wettability and dispersibility
• Changing crystalline form of drug to amorphous form
• Reduction in aggregation and agglomeration of drug particles.

POLYMERS USED IN SOLID DISPERSIONS:

Polyethylene Glycol (PEG): These are compounds obtained from a reaction of ethylene glycol with ethylene oxide. PEGs whose molecular weight is above 300000 are commonly termed as polyethylene oxides.

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. As with the triglycerides, numerous species are possible by various combinations of different head groups and fatty acyl substitution at the first and second positions of the glycerol backbone, fluidity differences are evident as a function of the gel to liquid crystalline transition temperatures. Solubility of phospholipids is intimately linked to the confirmation of the aggregate material rather than strictly a chemical function of the molecule. Monoacyl phospholipids, which tend to form micelles, are usually more readily soluble in aqueous solutions

Polyvinyl Pyrrolidone (PVP): PVP molecular weight ranges from 2500 to 300000. 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.

Cyclodextrins: Cyclodextrins are primarily used to enhance solubility, chemical protection, taste masking and improved handling by the conversion of liquids into solids by entrapment.

Advantages of Cyclodextrins:
• Increasing the stability of the drug
• Release profile during gastrointestinal transit through modification of drug
• Release site and time profile
• Decreasing local tissue irritation
• Masking unpleasant taste.

METHODS OF PREPARATION OF SOLID DISPERSION:

Methods of preparation of solid dispersions: 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. Electrospinning
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 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 in this method is difficulty in removing the solvent and higher cost of preparation.

3. **Melting solvent method**: This method involves 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, pallets, 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 exipients and other one is melting of binder drug and exipient 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 homogenous mixing of drug but larger particle size cause densification and fines cause adhesion of mass.

7. **Electrosipinnig method**: In this technique electric force is used to withdraw a nano size fibre 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 or droplets of polymer and a stream of fibre is formed. Then thinning and stretching of fibre to nano diameter is done by using whipping process called electrostatic repulsion lead to formation of uniform fibre 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 vapour 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-carrier miscibility**
- Hot stage microscopy
- Differential scanning calorimetry
- Powder X-ray diffraction
- Spectroscopic methods like raman spectroscopy, FT-IR spectroscopy
Physical Structure
• Scanning electron microscopy
• 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 (Tg, Temperature recrystallization)
• Saturated solubility studies

Dissolution enhancement
• Dissolution
• Intrinsic dissolution
• Dynamic solubility
• Dissolution in bio-relevant media

Applications of solid dispersion
• It increases the solubility of poorly soluble drugs and thus increases the dissolution rate, which enhances the absorption and bioavailability of the drug.
• For stabilization of the unstable drugs against various decomposition procedures like hydrolysis, oxidation etc.
• For reducing the side effect of certain drugs.
• Masking of unpleasant taste and smell of drugs.
• To avoid undesirable incompatibilities.
• To obtain a homogeneous distribution of a small amount of drug in solid state.
• Dispensing of liquid (up to 10%) or gaseous compounds in a solid dosage.
• Formulation of sustained release dosage form
• Reduction in the inactivation of drugs like morphine and progesterone in pre systemic circulation

Ideal candidates for solid dispersion: Solid dispersion technologies use those drugs which are having poor aqueous solubility and are permeable through the biological membrane. Due to their poor solubility dissolution becomes difficult and thus absorption and bioavailability reduces. Solid dispersions are ideal for the class II drugs of the BCS classification which have poor aqueous solubility but high membrane permeability.

COMMERCIAL SOLID DISPERSION PRODUCTS
Griseofulvin, nifidipine, carbamazapine, albendazole, nimodipine, ofloxacin, prednisone, lamotrigine, diazepam, paracetamol etc.

MARKETED SOLID DISPERSION PRODUCTS
Some of the marketed solid dispersions are as follows:
• Troglitazone solid dispersion is marketed by Parke Davis
• Sporanox, a solid dispersion of itraconazole
• Gris-PEG®, solid dispersion of griseofulvin marketed by Novartis

CONCLUSION
Increasing the Bioavailability of a poorly soluble drug is a challenging aspect of drug development. Because of the poor aqueous solubility the drug possess dissolution problems due to which the in vivo absorption of the drug is reduced and thus the bioavailability is reduced, making the drug inappropriate for oral consumption and therefore solubility enhancement become necessary for such drug candidate. Solid dispersion is a most simple and efficient technique for increasing the aqueous solubility of a drug.

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