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Review Article

A REVIEW: SOLID DISPERSION, A TECHNIQUE OF SOLUBILITY ENHANCEMENT

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ABSTRACT

Purpose: The aim of the study was to explore the necessity, advantages and different techniques of solid dispersion for enhancing solubility of poorly soluble drugs.

Approach: Different types of solid dispersion have been explained briefly along with the various techniques of solid dispersion in detail.

Findings: Solid dispersions of poorly soluble drugs have been found to give positive results in enhancing its solubility and dissolution characters.

Conclusion: Solid dispersion techniques improve solubility and bioavailability of poorly soluble drugs. Solid dispersions can be incorporated into various dosage forms with wide range of applicability.

Keywords: *solid dispersion techniques, solubility, advantages, disadvantages, carriers.*

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INTRODUCTION

The oral route of administration is the most preferred route of drug administration. The oral route of drug offers convenience and easy intake without any pain. However, poorly soluble drugs face an immense solubility problem via oral delivery.[1] High oral solubility and bioavailability is must in order to provide optimum therapeutic level. Salt formation, size reduction, use of lipid vesicles, cosolvency, complexation, use of prodrugs, surfactants etc have been used to improve solubility profiles.[2] Preparation of solid dispersions has widely been accepted and one of the most employed technique for solubility enhancement.[3]

Solid dispersion is defined as the dispersion of one or more active ingredients in an inert carrier at solid state prepared by fusion, solvent or solvent fusion method.[4] The classification of solid dispersion is given in figure 1.

Solid dispersion technique has been used for a variety of poorly aqueous soluble drugs such as nimesulide, ketoprofen, tenoxicam, nifedipine, nimodipine, etc. Various hydrophilic carriers such as PEG 6000, PVP, HPMC, gums, sugars, and mannitol have been used for improvement of dissolution characteristics and solubility of poorly water soluble drugs.[5] Solid dispersions can be prepared by various methods such as melting, solvent evaporation, solvent melting, spray drying, supercritical fluid techniques, etc.[6] The list of marketed products using solid dispersion techniques is given in table 1.

Advantages of solid dispersion

i. Particles with reduced particle size increased surface area.
After carrier dissolution, the drug is molecularly dispersed in the dissolution medium, thereby resulting in reduced particle size or increased surface area.[7,8.]

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ii. Particles with improved wettability.
Drug solubility increases as wettability increases. Use of carriers without surface activity such as urea, and with surface activity such as cholic acid and bile salts improve drug wettability. Carriers enhance drug dissolution profile by direct dissolution or co-solvent effect.[7]

iii. Particles with high porosity.
Studies have shown that the particles in solid dispersions have a high degree of porosity. The porosity depends on the properties of carriers used. For example, a solid dispersion containing linear polymers produces larger and more porous particles than those containing reticular polymers and hence results in a higher dissolution rate and bioavailability.[8]

iv. Particles in amorphous state
The solubility of drugs in amorphous state is higher than the crystalline drugs as latter requires energy to break the crystal lattice. Hence in solid dispersion, the drug exists as supersaturated solution after system dissolution and when the precipitation of drug occurs, it exists as a metastable polymorphic form with enhanced dissolution than the crystal form.[7]

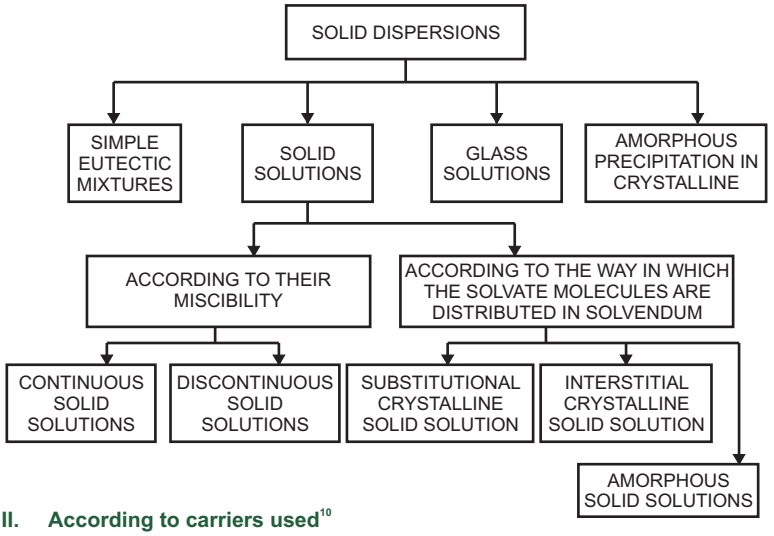
Disadvantages of solid dispersion

i. Instability
ii. By absorbing moisture, phase separation, crystal growth or a change from metastable crystalline form to stable form can take place resulting in reduction of drug solubility
iii. Difficulty in handling because of tackiness[9]

Limitation of solid dispersion

i. Physical and chemical stability of drugs and vehicles
ii. Method of preparation
iii. Reproducibility of solid dispersion into dosage form
iv. Scale-up of manufacturing processes
v. Poor predictability of solid dispersions behavior[7]

I. ACCORDING TO MOLECULAR ARRANGEMENT[10]



II. According to carriers used[10]

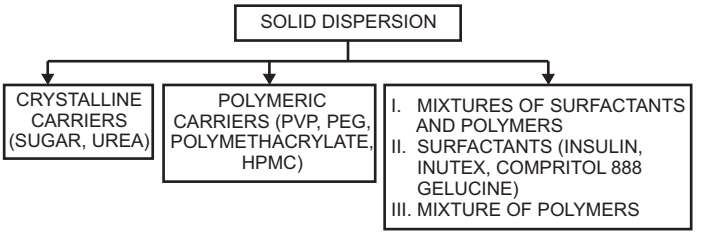


Fig. 1 : Classification of solid dispersion

1) Simple eutectic mixtures

It consists of two compounds which are completely miscible in the liquid state but only to a very limited extent in the solid state. Preparation involves rapid solidification of fused melt of two components that shows complete liquid miscibility but negligible solid-solid solution.[12]

1) Solid solutions

It is further categorized as shown in the diagram above:

a) **Continuous solid solutions(one phase)**
In this type, the components are miscible in all proportions which imply that the bonding strength between 2 components is stronger than the bonding strength between the molecules of each of the individual components.[13]

b) **Discontinuous solid solutions (two phase)**
Here, the solubility of each of the components in the other component is limited.[13] It includes 2 phases even though drug is molecularly dispersed.[10]

c) **Substitutional solid solutions (one or two phase)**
It is a type of solid dispersion having a crystalline structure in which the solute molecules substitute for solvent molecules in the crystal lattice. If the size of the solute molecules differs by less than 15% from that of the solvent molecules, only then the substitution takes place.[11]

d) **Interstitial crystalline solid solution (two phase)**
In this type, the interstitial spaces between the solvent molecules in the crystal lattice are occupied by the dissolved molecules. Here, the molecular diameter of solute molecules should not be greater than 0.59 of the solvent molecule's molecular diameter and also the volume of solute molecules should be less than 20% of the solvent.[11]

e) **Amorphous solid solutions**
It includes irregularly dispersed solute molecules within the amorphous solvent. Example the formation of an amorphous solid solution using griseofulvin in citric acid to improve drug's dissolution properties.[11]

2) Amorphous precipitation in crystalline matrix

These are similar to eutectic mixtures but the only difference is that the drug is precipitated out in an amorphous form.[12]

3) Glass solutions and glass suspensions

A glass solution is a homogeneous glassy system in which a solute dissolves in a glassy solvent.[11] Glass suspensions are mixtures in which precipitated particles are suspended in glass solvent. The lattice energy is much lower in glass solution and suspension.[12]

Selection of carrier

Criteria to be met by a carrier in order to be incorporated into various solid dispersions are as follows:

- Freely water-soluble with rapid intrinsic dissolution properties
- Non-toxic and pharmacologically inert
- Heat stable with a low melting point for the temperature dependent preparation methods
- Soluble in a wide range of solvents
- Does not interact chemically with the active ingredients[11]

Preparation of Solid dispersions

Many methods are used for the preparation of solid dispersion systems and some of them are enlisted as follows:

i. Fusion/Melting method
ii. Solvent method
iii. Melting solvent method(melt evaporation)
iv. Melt extrusion method
v. Lyophilization techniques
vi. Melt agglomeration process
vii. Use of surfactants
viii. Electrospinning
ix. Super critical fluid technology
x. Kneading method
xi. Co-grinding method

i. Fusion/Melting method

The method involves preparation of physical mixture of a drug and a water-

soluble carrier by heating it directly until it melts, followed by rapid solidification in an ice-bath with a vigorous stirring. The final solid mass is crushed, pulverized and sieved. This method is economic and simple.

Disadvantages of this method include :

- Decomposition of either drug or carrier during the fusion process at high temperatures.
- Drug-matrix miscibility changes during cooling.
- Applied only when the drug and matrix are compatible and mix well at heating temperature.[11,13]

ii. **Solvent method**

The method involves preparation of a solution containing both matrix material and drug in a common volatile solvent followed by the evaporation of the solvent at either room temperature or elevated temperature with/without vacuum. It results in a solvent free film which is further dried to constant weight.[11,13]

iii. **Melting solvent method (melt evaporation)**

In this method, the drug is dissolved in a suitable liquid solvent followed by incorporation of the solution directly into the melt of a suitable carrier which is then evaporated until a clear, solvent-free film is left. This technique has an advantage of both the fusion and solvent evaporation methods. It is only limited to drugs with a low therapeutic dose (below 50 mg) and applicable for drugs that are thermolabile or have high melting points.[11,12]

iv. **Melt extrusion method**

It consists of extruding the previously mixed drug and carrier, at high rotational speed, at melting temperature for a small period of time.[11] In this method, drug carrier mix is simultaneously melted, homogenized, and processed using a twin-screw extruder. The extrudate may be shaped as granules, pellets, sheets or powder form, which can be further processed into conventional tablets.[12]

Polymeric materials such as vinyl polymers (PVP, PVP-vinyl acetate), polyethylene oxide, PEG, etc are used in hot-melt extrusion.

The advantages of this method include absence of solvents, few processing steps, continuous operation, low temperature, short residence time which prevents the thermal degradation of the drug-carrier mixture.

Some disadvantages of this method include:

- Production of high local temperature in the extruder due to high shear forces, which may affect heat sensitive ingredients.
- Miscibility of drug and carrier can be a problem.[11]

v. **Lyophilization techniques**

It is molecular mixing technique where the drug and carrier are co-dissolved in a common solvent, frozen and sublimed to obtain a lyophilized molecular dispersion. An advantage of this method is that the drug is subjected to minimal thermal stress during the formation of the solid dispersion and the risk of phase separation is minimized as soon as the solution is converted into glass or a glassy substance.[11]

vi. **Melt agglomeration process**

This technique has been used to prepare solid dispersion in which the binder acts as a carrier. Solid dispersions are prepared either by heating binder, drug and excipient to a temperature above the melting point of the binder (melt- in procedure) or by spraying a dispersion of drug in molten binder on the heated excipient (spray-on procedure). Instruments like rotary processor is preferable for high melt agglomeration as it is easier to control temperature and higher binder content can be incorporated in the agglomerates. Melt-in method gives a higher dissolution rates than the spray-on method with PEG 3000, poloxamer 188 and gelucire 50/13. Enhanced homogeneous distribution of drug in agglomerate can be achieved by the melt-in method. Larger particles results in densification of agglomerates

where as fine particles cause complete adhesion to the mass after melting.[11]

vii. **Use of surfactants**

Adsorption of surfactant on solid surface modifies their hydrophobicity, surface charge, and also controls other interfacial properties such as flocculation/dispersion, floating, wetting, solubilization, corrosion inhibition and enhanced oil recovery.

Use of surfactants results in solvation/ plasticization, reduction of melting active pharmaceutical ingredient, glass transition temperature and combined glass transition temperature of solid dispersion.[11]

viii. **Electrospinning**

Electrospinning is a process in which solid fibers are produced from a polymeric fluid stream solution or melt delivered through a millimeter-scale nozzle. It involves application of a strong electrostatic field over a conductive capillary attached to a reservoir containing polymer solution or melt and a conductive collection screen. Increasing the electrostatic field strength, not exceeding a critical value, results in accumulation of charged species on the surface of a pendant drop that destabilize the hemispherical shape into a conical shape. Beyond the critical value, ejection of a charged polymer jet from the apex of the cone occurs. The ejected charged jet is then carried to the collection screen via the electrostatic force. Thinning down of the charged jet is limited. Increase in viscosity results in drying of the charged jet.[11]

ix. Super critical fluid technology

This technique can be employed for the preparation of solvent free dosage forms. Super critical fluid is the one which exists as a single fluid phase above their critical temperature and pressure. Carbondioxide is the most commonly used super critical fluid as it is chemically inert, non-toxic and non-flammable. After the drug particles are solubilized within super critical fluid, they can be recrystallized with reduced particle sizes as per the requirement.[13]

x. Kneading method

Here, a mixture of accurately weighed drug and carrier is wetted with solvent and kneaded thoroughly in glass mortar.[10]

xi. Co-grinding method

Drug and carrier are weighed accurately and mixed using a suitable blender. The blend is then grinded using ball mill or other as per the need.[10]

Characterization of solid dispersions

1. Physical appearance
2. Drug content
3. Dissolution studies
4. X-ray diffraction
5. Differential scanning calorimetry
6. Scanning electron microscopy
7. Fourier transform Infra red(FTIR) spectroscopy

1. **Physical appearance**

It includes visual inspection of solid dispersions.[13]

2. **Drug content**

For the drug content analysis, a definite amount of solid dispersion containing drug is taken and dissolved in a suitable solvent in which it is freely soluble . It is then diluted to appropriate concentration and the absorbance is measured by UV-spectro-photometer.[13]

3. **Dissolution studies**

It is carried out to determine the rate and extent of dissolution. The study is performed in 500 ml of suitable dissolution medium at 37 ± 0.5□ C using USP-II paddle apparatus at 75 rpm. Aliquots are withdrawn at suitable time intervals and diluted with suitable medium so that the drug concentration lies within the Beer's range . Absorbance is measured to determine drug release. [13]

4. **X-ray diffraction**

Powder XRD patterns are traced using X-ray diffractometer for different samples using suitable wavelength range.[14, 15]

5. **Differential scanning calorimetry**

All samples are weighed (8-10mg) in aluminium pans or lids and heated at a scanning rate of 10□ C/min under dry nitrogen flow (20ml/min) between 50-300^{0}C or as per the thermal character of the

respective drug.[14,15]

6. **Scanning electron microscopy**
   It is carried out using a scanning electron microscope. Samples are mounted on aluminium slab using a double sided adhesive tape and making it electrically conductive by coating with a thin layer of gold in vacuum.[14]

7. **Fourier transform Infra red (FTIR) spectroscopy**
   This study is carried out to explore the interaction between drug and carrier used in formulation of solid dispersion by potassium bromide disc method in an Infra red spectrophotometer.[13]

Table 1: List of marketed products using solid dispersion techniques[7]

Product/substance	Dispersion polymers or carriers	Technology used	Company
Gris-PEG® (Griseofulvin)	PEG	Melt process	Novartis
Cesamet®(Nabilone)	Povidone	Process unknown	Lilly
Spromax capsules (Itraconazole)	HPMC	Spray layering	Janseen pharma-ceuticals
Kaletra(lopinavir and ritonavir)	PVP/polyvinyl acetate	Melt-extrusion	Abbott labora-tories
Torcetrapib	HPMC acetate/succinate	Spray drying	Pfizer
Ibuprofen	Various	Melt-extrusion	Soliqs
Isoptin SRE-240 (Verapamil)	Various	Melt-extrusion	Soliqs
Rezulin(Troflitazone)	PVP	Melt-extrusion	Soliqs
LCP-Tacro (Tacrolimus)	HPMC	Melt-granulation	Lifecycle pharma
Intelene(Etavirine)	HPMC	Spray drying	Tibotec
Certican(Everolimus)	HPMC	Melt or Spray drying	Novartis
Afeditab(Nifedipine)	Poloxamer or PVP	Melt/absorb on carrier	Elan corp

Pharmaceuticals applications of solid dispersions

- To enhance the absorption of drug.
- To obtain a homogeneous distribution of a small amount of drug in solid state.
- To stabilize unstable drugs and protect against decomposition by process such as oxidation, hydrolysis, racemization, photo oxidation, etc.
- To dispense liquid or gaseous compounds.
- To formulate a fast releasing priming dose in a sustained release dosage form.
- To formulate sustained release preparation of soluble drugs by dispersing the drug in poorly soluble or insoluble carrier.
- To reduce side effects
  a. The binding ability of drugs for example to the erythrocyte membrane is decreased by making its inclusion complex.
  b. The damage to the stomach mucous membranes by certain non-steroidal anti-inflammatory drugs can be reduced by administration as an inclusion compound.
- To mask unpleasant taste and smell.
- To convert liquid compounds into formulations. Liquid drugs can be manufactured as solid drug formulations via solid dispersions.

To reduce pre systemic inactivation of drugs like morphine and progesterone.[16,17]

CONCLUSION

The solubility of a poorly soluble drug can be significantly improved by incorporating the drug into solid dispersion using a wide range of carriers/polymers. Solid dispersion improves drug dissolution characteristic and also increases the oral bioavailability. In prior to the development of a solid dispersion of a poorly soluble drug, it is must to study the physicochemical properties of the drug and carrier. Solid dispersion techniques are easy to handle, highly efficient, economic and in most of the cases environmentally and biologically safe. Solid dispersion is one of the best way to improve drug solubility but still a lot needs to be explored and studied further about the development of new solid dispersions.

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