

A REVIEW ON SOLID DISPERSION METHOD TO INCREASES THE SOLUBILITY OF SCANCY WATER SOLUBLE DRUG

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ABSTRACT

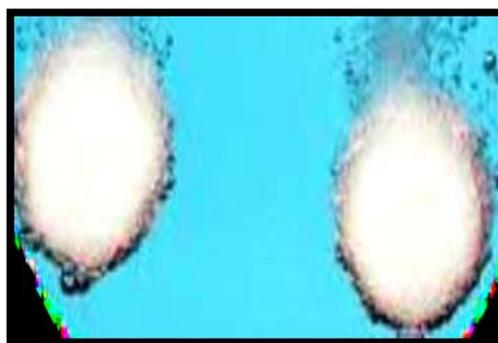
Solid dispersion method is the methods, which significantly increases the solubility, dissolution rate and also increases the bioavailability of the poorly soluble drugs. The solid dispersion is based on the concept of kneding method in that the drug is dispersed in an inert water-soluble carrier at solid state. Water soluble carriers such as cyclodextrin, methyl cellulose, urea, lactose, citric acid, polyvinyl pyrrolidone and polyethylene glycols are used as carriers for solid dispersion. This reviews background of solid dispersion technology, limitations, classification and various preparation techniques with its advantages and disadvantages.

KEYWORDS: Solid dispersion, Freeze-drying, Melt Agglomeration Process, Super Critical Fluid Technology, Dissolution rate.

INTRODUCTION

The solubility of drug administration is the most common and chosen method for delivery due to inconvenience and ease of ingestion but it is problematic if the drug is poorly soluble or poor membrane penetrability. Almost more than 90% drugs are orally administered. Drug absorption sufficient and reproducible bioavailability, pharmacokinetic profile of orally administered drug substances is highly dependent on solubility of that compound in aqueous medium.^[1] Therapeutic effectiveness of a drug depends upon the bioavailability and ultimately upon the solubility of drug molecules. Solubility is one of the important parameter to achieve desired concentration of drug in systemic circulation for pharmacological response to be shown. More than 40% of new candidates entering drug development pipeline fail because of non-optimal biopharmaceutical properties. Over the years, tools of drug discovery have caused a perceptible shift in biopharmaceutical properties. Poorly water-soluble drugs involve many difficulties in the development of pharmaceutical dosage forms for oral delivery systems due to their low bio-availability.^[2] Drug absorption from the gastrointestinal tract can be limited by a variety of factors, most significant contributors being poor aqueous solubility and poor membrane permeability of the drug molecule. When delivering an active agent orally it must first dissolve in gastric and/or intestinal fluids before it can permeate the membranes of the GI tract to reach systemic circulation. Hence, two areas of pharmaceutical research that focus on improving the oral bioavailability of active agents include; enhancing solubility and

dissolution rate of poorly water-soluble drugs and enhancing permeability of poorly water soluble drugs.^[3] The term solid dispersion" has been utilized to describe a family of dosage forms whereby the drug is dispersed in a biologically inert matrix, usually with a view to enhancing oral bioavailability. More specifically,^[4] Chiou and Riegelman defined these systems as „the dispersion of one or more active ingredients in an inert carrier matrix at solid-state prepared by the melting (fusion), solvent or melting- solvent method“,^[5] while Corrigan suggested the definition as being a „product formed by converting a fluid drug-carrier combination to the solid state“. In practice, these dosage forms have been traditionally regarded as being synonymous with systems whereby the in vitro release of the drug is enhanced compared to conventional dosage forms.^[6]

**Solid Dispersion^[7]**

The term solid dispersion refers to a group of solid products consisting of at least two different components,

generally a hydrophilic matrix and a hydrophobic drug.^[8] The matrix can be either crystalline or amorphous.⁷ The

drug can be dispersed molecularly, in amorphous particles (clusters) or in crystalline particles.^[9]

BCS classification system and solubility expression.^[9]

Solubility	Permeability	Example of drugs	Class
High solubility	High permeability	Benzapril Loxoprofen	I
High solubility	Low permeability	Valsartan Nimesulide	II
Low solubility	High permeability	Gabapentin Topiramate	III
Low solubility	Low permeability	Furosemide	IV

Advantages of Solid Dispersions

Particles with reduced particle size

Preparation of solid dispersions results in particles with reduced particle size and thus the surface area is improved and increased dissolution rate is attained.^[10] The ultimate result is improved bioavailability.

Particles with improved wettability^[11]

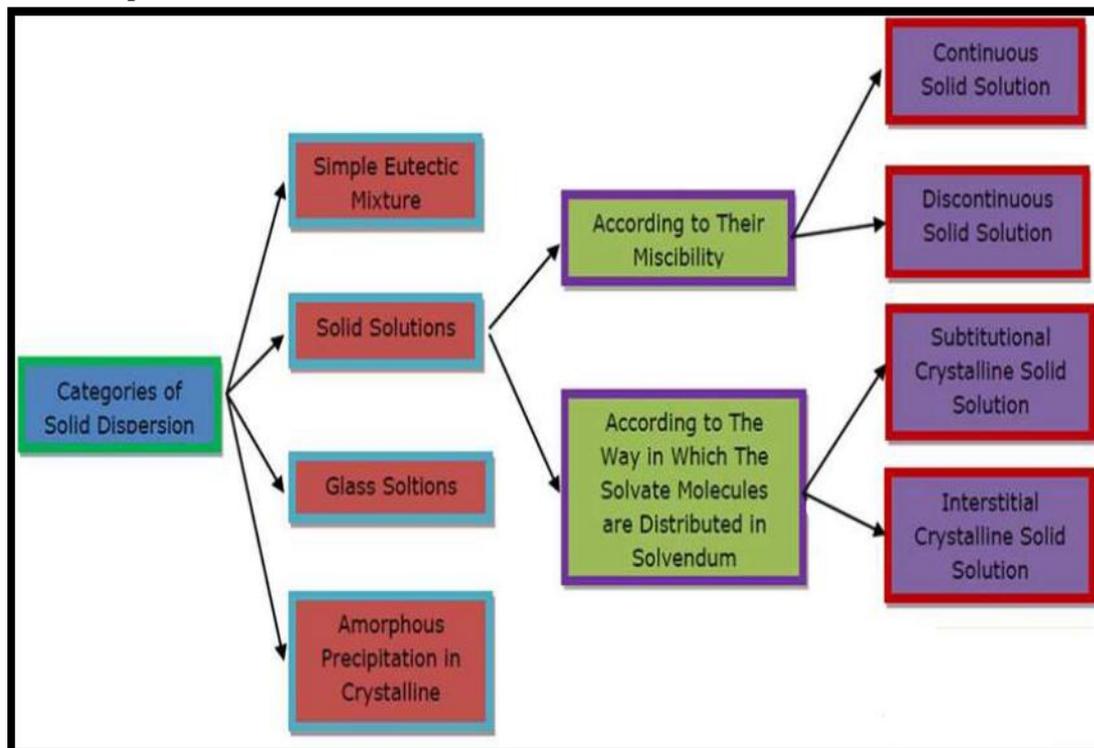
Wettability is improved during solid dispersion production. It has been suggested that the presentation of particles to the dissolution medium as physically separate entities may reduce aggregation. In addition, many of the carriers used for solid dispersions may have some wetting properties; hence improved wetting may lead to reduced agglomeration and increased surface area.^[12]

Disadvantages of Solid Dispersions

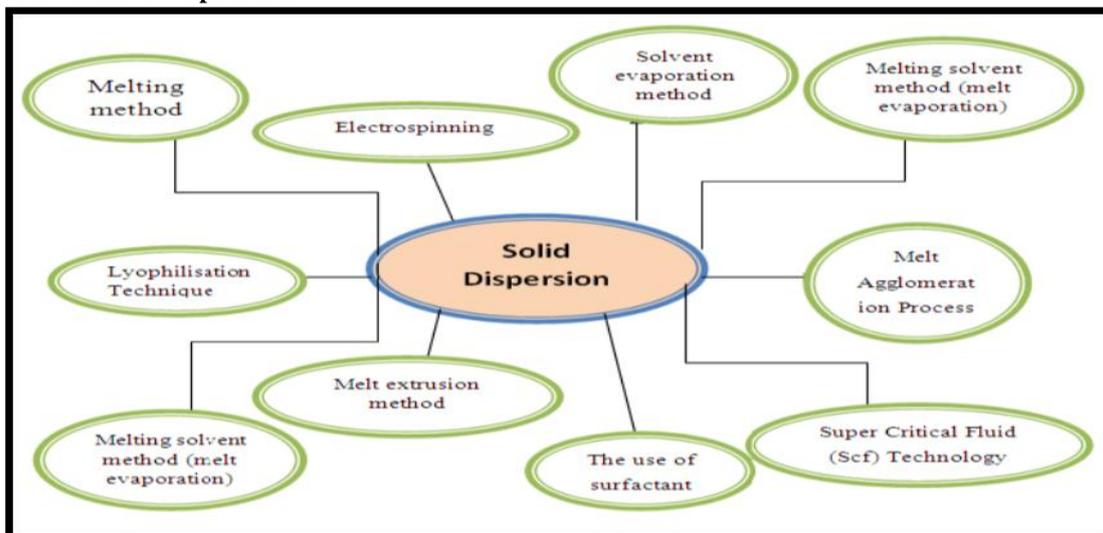
1. They are not broadly used in commercial products because there is the possibility that during

- processing (mechanical stress) or storage (temperature and humidity stress) the amorphous state may undergo crystallization.^[13]
- The effect of moisture on the storage stability of amorphous pharmaceuticals is also a significant concern, because it may increase drug mobility and promote drug crystallization.^[14]
- Most of the polymers used in solid dispersions can absorb moisture, which may result in phase separation, crystal growth or conversion from the amorphous to the crystalline state or from a metastable crystalline form to a more stable structure during storage.^[15]
- Poor scale-up for the purposes of manufacturing.
- Laborious and expensive methods of preparation.
- Reproducibility of physicochemical characteristics.
- Difficulty in incorporating into formulation of dosage forms.
- Scale-up of manufacturing process.

Types of Solid Dispersion^[16]



Preparation of Solid Dispersions



Method of SD

1. Fusion / 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. Fusion / Melting method^[17]

Fusion method is the preparation of physical mixture of a drug and a water-soluble carrier and heating it directly until it melts.^[18] The melted mixture is then solidified rapidly in an ice-bath under vigorous stirring. The final solid mass is crushed, pulverized and sieved. In addition, a super-saturation of a solute or drug in a system can often be obtained by quenching the melt rapidly from a high temperature.^[19]

2. Solvent method

The first step in the solvent method is the preparation of a solution containing both matrix material and drug.^[20] The second step involves the removal of solvent(s) resulting in formation of a solid dispersion. Mixing at the molecular level is preferred, because this leads to optimal

dissolution properties.^[21] The main advantage of the solvent method is thermal decomposition of drugs or carriers can be prevented because of the relatively low temperatures required for the evaporation of organic solvents.

3. Melting solvent method (melt evaporation)

The 5-10% (w/w) of liquid compounds can be incorporated into polyethylene glycol 6000 without significant loss of its solid property.^[22] Also the liquid solvent used may affect the polymorphic form of the drug, which precipitates as the solid dispersion. This technique possesses unique advantages of both the fusion and solvent evaporation methods.

4. Melt extrusion method

Hot-stage extrusion (HME) consists of the extrusion, at high rotational speed, of the drug and carrier, previously mixed, at melting temperature for a small period of time. Solid dispersion by this method is composed of active ingredient and carrier, and prepared by hot-stage extrusion using a co-rotating twin-screw extruder.^[23]

5. Lyophilization Technique (Freeze-drying)

Lyophilization has been thought of a molecular mixing technique where the drug and carrier are co dissolved in a common solvent, frozen and sublimed to obtain a

lyophilized molecular dispersion. This technique was proposed as an alternative technique to solvent evaporation.^[24]

6. Melt Agglomeration Process

This technique has been used to prepare solid dispersion wherein the binder acts as a carrier.^[25] In addition, 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) by using a high shear mixer.

7. The use of surfactant

The utility of the surfactant systems in solubilization is very important.^[26] Adsorption of surfactant on solid surface can modify their hydrophobicity, surface charge, and other key properties that govern interfacial processes such as flocculation/dispersion, floating, wetting, solubilization, detergency, and enhanced oil recovery and corrosion inhibition.^[27] Surfactants have also been reported to cause solvation/plasticization, manifesting in reduction of melting the active pharmaceutical ingredients, glass transition temperature and the combined glass transition temperature of solid dispersions.

8. 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.^[28] This process involves the application of a strong electrostatic field over a conductive capillary attaching to a reservoir

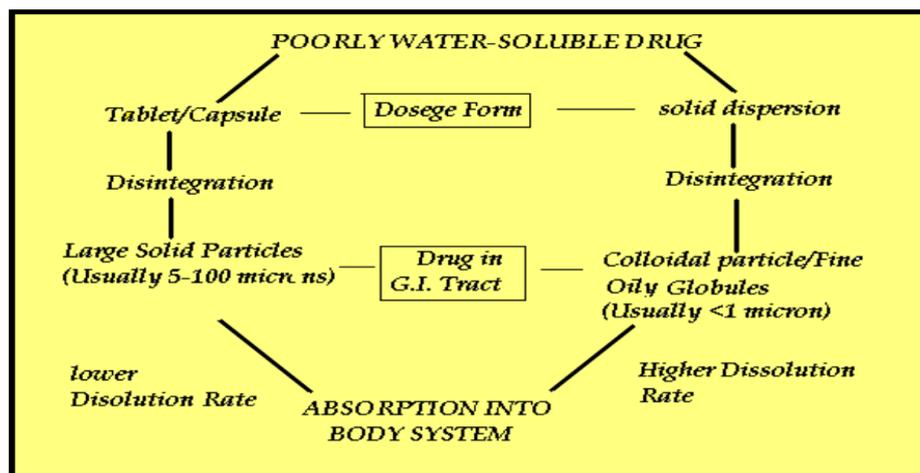
containing a polymer solution or melt and a conductive collection screen.

9. Super Critical Fluid (Scf) Technology^[29]

The supercritical fluid antisolvent techniques, carbon dioxide are used as an antisolvent for the solute but as a solvent with respect to the organic solvent. Different acronyms were used by various authors to denote micronization processes: aerosol solvent extraction system, precipitation with a compressed fluid antisolvent, gas anti-solvent, solution enhanced dispersion by supercritical fluids and supercritical antisolvent.^[30]

Future prospects of solid dispersions

Despite many advantages of solid dispersions, issues related to preparation, reproducibility, formulation, scale-up and stability limited its use in commercial dosage forms for poorly water soluble drugs.^[31] However, successful development has been feasible in recent years due to availability of surface-active and self-emulsifying carriers with relatively low melting points. The drug along with carrier are filled into hard gelatin capsules because of easy manufacturing process and improved bioavailability and enhanced dissolution rate.^[32] One of the major focuses for research would be the identification of new surface-active and self-emulsifying carriers for solid dispersion.^[33] The other focus would be on identification of vehicles or excipients that would retard or prevent crystallization of drugs from super-saturated systems along with development of extended release dosage forms and physical and chemical stability of both drug and carrier in solid dispersion.



Application of Solid Dispersion

1. To increase the solubility, dissolution rate, absorption and bioavailability.
2. Improved the solubility & stability.
3. To formulate a fast released dosage form.
4. To reduce side effect of certain drugs.
5. Masking of unpleasant taste and smell of drugs
6. Improvement of drug release from ointment, creams.

Future Prospects

1. Develop new method of preparation.
2. Development of controlled release preparation.
3. Identification of newer carrier.
4. Identification of vehicle or excipient that retard or prevent crystallization

CONCLUSION

The solid dispersion method is one of the effective approaches to achieve the goal of solubility enhancement of poorly water-soluble drugs. In developing a new solid dispersion system for a given drug, it is important to understand the physicochemical properties of the drug and carrier that best match the properties and find a solid dispersion method. The preparation method and the amount of the carrier also play a vital role in the enhancement of drug dissolution rate. With future development of this technology, solid dispersions will continue to enable novel applications in drug delivery and solve problems associated with the delivery of poorly soluble drugs.

Types of Solid Dispersions

Eutectic mixtures

A simple eutectic mixture consists of two compounds which are completely miscible in the liquid state but only to a very limited extent in the solid state. It is prepared by rapid solidification of fused melt of two components that show complete liquid miscibility but negligible solid-solid solution.

Amorphous precipitation in crystalline matrix

Solid solution

Solid solutions are comparable to liquid solutions, consisting of just one phase irrespective of the number of components. In the case of solid solutions, the drug's particle size has been reduced to its absolute minimum viz. the molecular dimensions¹⁴ and the dissolution rate is determined by the dissolution rate of the carrier. Classified according to their miscibility (continuous versus discontinuous solid solutions) or second, according to the way in which the solvate molecules are distributed in the solvent (substitutional, interstitial or amorphous).

Continuous solid solutions

In a continuous solid solution, the components are miscible in all proportions. Theoretically, this means that the bonding strength between the two components is stronger than the bonding strength between the molecules of each of the individual components. Solid solutions of this type have not been reported in the pharmaceutical world till date.

Discontinuous solid solutions

In the case of discontinuous solid solutions, the solubility of each of the components in the other component is limited. Due to practical considerations it has been suggested by Goldberg *et al.*¹⁴ that the term 'solid solution' should only be applied when the mutual solubility of the two components exceeds 5%.

Substitutional solid dispersions

Substitution is only possible when the size of the solute molecules differs by less than 15% or so from that of the solvent molecules.¹⁵ Classical solid solutions have crystalline structure, in which the solute molecules can

either substitute for solvent molecules in the crystal lattice or fit into the intrsticies between the solvent molecule.

Interstitial solid solutions

In interstitial solid solutions, the dissolved molecules occupy the interstitial spaces between the solvent molecules in the crystal lattice. Solute molecule diameter should be less than 0.59 times than that of solvent molecular diameter.¹⁶

Glass solution and suspensions

Glass solutions are homogeneous glassy system in which solute dissolves in glass carrier. Glass suspensions are mixture in which precipitated particles are suspended in glass solvent. Lattice energy is much lower in glass solution and suspension.¹³

Selection of Solvents³³

Solvent to be included for the formulation of solid dispersion should have the following criteria:

Both drug and carrier must be dissolved. Toxic solvents to be avoided due to the risk of residual levels after preparation e.g. chloroform and dichloromethane Ethanol can be used as alternative as it is less toxic. Water based systems are preferred. Surfactants are used to create carrier drug solutions but as they can reduce glass transition temperature, so care must be taken in to consideration.

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