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Solid Dispersion as a Strategy to Enhance Solubility: A Review Article

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ABSTRACT

Improving oral bioavailability of drugs remains most challenging aspects in formulation development due to solubility problems of poorly water soluble drugs. Most of the new chemical entities (NCEs) are poorly water soluble as well as not well-absorbed after oral administration. Solid dispersion technologies are promising task for improving solubility and hence oral bioavailability of Biopharmaceutical Classification System (BCS) class II drugs. Solid dispersion techniques have attracted due to improving the dissolution rate of highly lipophilic drugs and hence their bioavailability. This article reviews on classification, various preparation methods, advantages and disadvantages of solid dispersion.

KEYWORDS

Solubility enhancement, Bioavailability Enhancement, Biopharmaceutical Classification, Carrier, Poorly water soluble drug.

INTRODUCTION

For a drug to enter systemic circulation and to produce its therapeutic effect, it must be in solution form but relatively insoluble and poorly water soluble drugs create problems. So improving solubility and hence oral bioavailability remains challenging aspects for formulation scientists.

In general oral route of drug administration is most common and preferable route for drug delivery. Most of the new chemical entities (NCEs) which are intended to be used as a solid dosage form shows an effective and reproducible in vivo plasma concentration after oral administration that is because of beneficial features of oral route like easy production, smaller bulk, accurate dosage and greater stability[1,2]. After oral administration of drug, it firstly dissolves in gastric and or intestinal fluids before it, and then permeates the membranes of the GI tract to enter systemic circulation.

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Therefore, a drug which is having poor aqueous solubility will show dissolution rate limited absorption and a drug which is having poor membrane permeability will show permeation rate limited absorption. Hence, pharmaceutical research area focus on two aspects to improve oral bioavailability of active pharmaceutical ingredient (API) include: (i) enhancement of solubility and dissolution rate of poorly water-soluble drugs and (ii) enhancement of permeability of poorly permeable drugs[3]. Most of the research reported on solid dispersion involves BCS class II drugs. In the Biopharmaceutical Classification System (BCS) drugs having low aqueous solubility and high membrane permeability are classified as Class II drugs[4]. By improving the drug release profile of these drugs, it is possible to enhance their bioavailability and reduce side effects[5-10]. Modified Noyes-Whitney equation provides some information as to how the dissolution rate of even very poorly soluble compounds might

be improved to minimize the limitations to oral bioavailability[5,11].

$$dC / dt = AD (Cs – C) / h$$

Where,

dC/dt = the rate of dissolution of drug,

A = the surface area available for dissolution,

D = the diffusion coefficient of the compound,

Cs = the solubility of the compound in the dissolution medium,

C = the concentration of drug in the medium at time t,

h = the thickness of the diffusion boundary layer adjacent to the surface of the dissolving compound.

Class	Solubility	Permeability
Class I	High	High
Class II	Low	High
Class III	High	Low
Class IV	Low	Low

Solid Dispersion

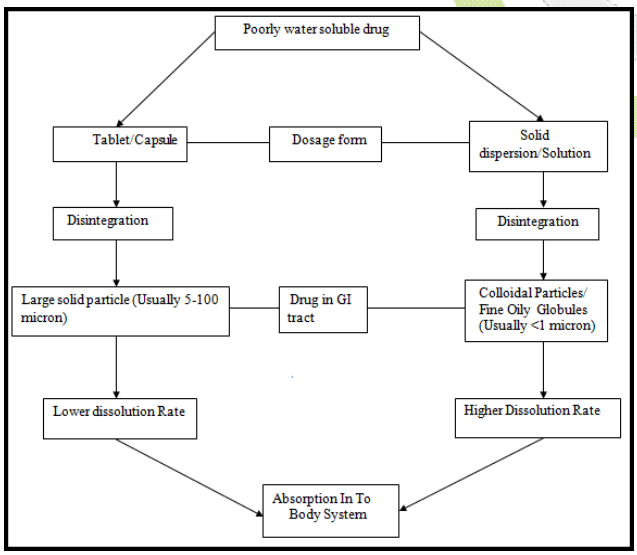


Figure 1: A schematic Representation of the Bioavailability Enhancement of a Poorly Water-Soluble Drug by Solid Dispersion Compared with Conventional Tablet or Capsule

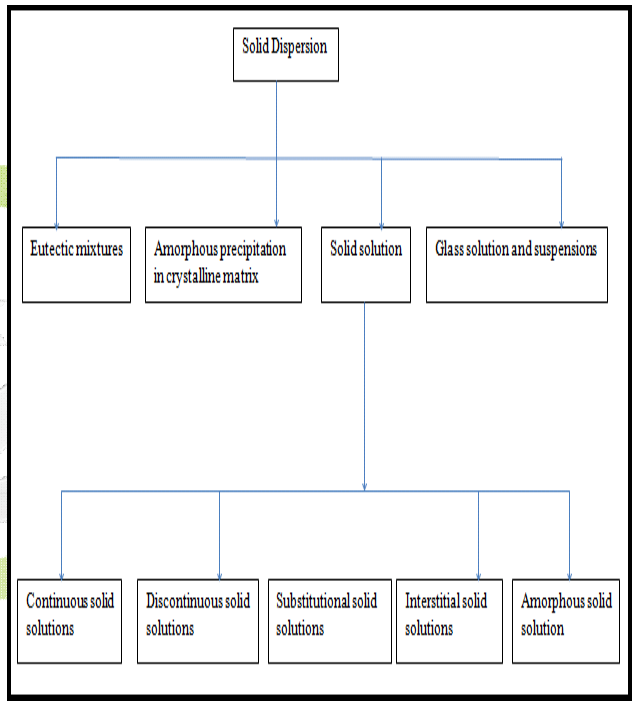
The term "solid dispersions" first described by Sekiguchi and Obi in 1961. The drug can be dispersed molecularly, in amorphous particles (clusters) or in crystalline particles.

"A dispersion of one or more active ingredients in an inert carrier or matrix at solid state prepared by the melting (fusion), solvent or melting-solvent method."

"A product formed by converting a fluid drug-carrier combination to the solid state."

Types of Solid Dispersion

Based on their molecular arrangement, different types of solid dispersions can be distinguished as shown below.



Eutectic Mixtures

Review of solid dispersions would not be complete without a brief description of 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 (Fig. 2). Solid eutectic mixtures are usually prepared by rapid cooling of a fused melt of the two compounds that show complete liquid miscibility but negligible solid-solid solution in order to obtain a physical mixture of very fine crystals of the two components[12,13].

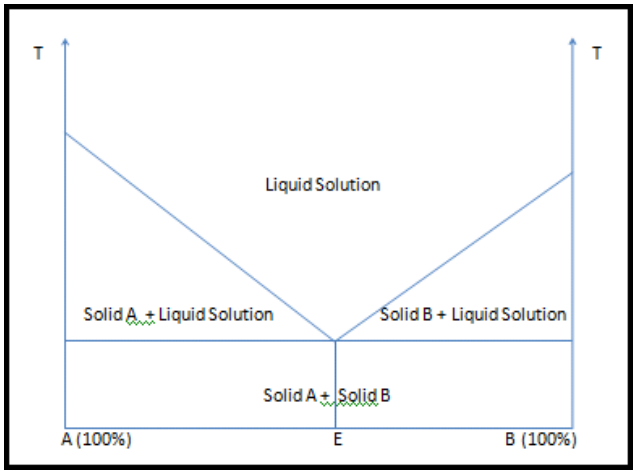


Figure: 2 Phase Diagram for a Eutectic System[14]

Amorphous Precipitation in Crystalline Matrix

It is similar to that of simple eutectic mixtures but it is only differ from simple eutectic mixtures in the case that drug is precipitated out in an amorphous form[15].

Solid Solution

Solid solutions are comparable to liquid solutions, consisting of just one phase irrespective of the number of components. Drug's particle size has been reduced to its absolute minimum viz. the molecular dimensions[16] and the dissolution rate is determined by the dissolution rate of the carrier. They are classified based on their miscibility (continuous versus discontinuous solid solutions) or according to the way in which the solvate molecules are distributed in the solvendum (substitutional, interstitial or amorphous).

Continuous Solid Solutions

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

Discontinuous Solid Solutions

In this type of solid solutions, the solubility of each of the components in the other component is limited. The term `solid solution' should only be applied when the mutual solubility of the two components exceeds 5%[16].

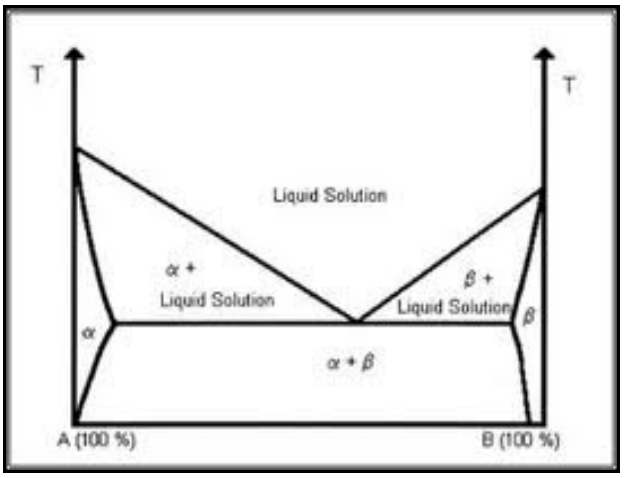


Figure: 3 Phase Diagram for a Discontinuous Solid Solution[14]

Substitutional Solid Solutions

A substitutional crystalline solid dispersion is showed in Fig. 4. In classical solid solutions the solute molecules can either substitute for solvent molecules in the crystal lattice or fit into the interstices between the solvent molecules. Substitution is only possible when the size of the solute molecules differs by less than 15% or so from that of the solvent molecules[17].

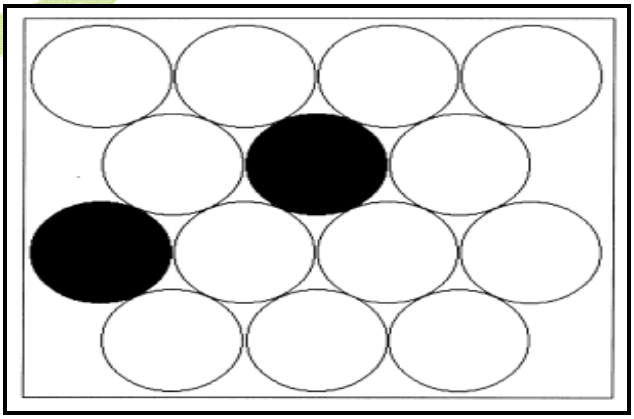


Figure: 4 Substitutional Crystalline Solid Solution[18]

Interstitial Solid Solutions

In interstitial solid solutions, the dissolved molecules occupy the interstitial spaces between

the solvent molecules in the crystal lattice (Fig.5).

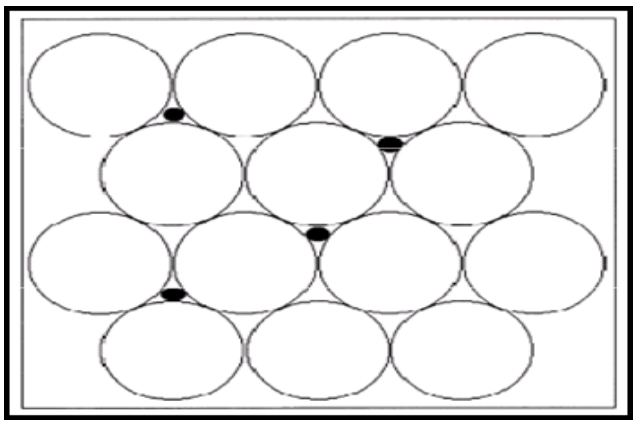


Figure: 5 Interstitial Crystalline Solid Solution[18]

The solute molecules should have a molecular diameter that is no greater than 0.59 times of the solvent molecule's molecular diameter[19]. The volume of the solute molecules should be less than 20% of the solvent.

Amorphous Solid Solutions

In an amorphous solid solution, the solute molecules are dispersed molecularly but irregularly within the amorphous solvent (Fig. 6). Polymer carriers are particularly likely to form amorphous solid solutions. Chiou and Riegelman[20] were the first to report the formation of an amorphous solid solution using griseofulvin in citric acid.

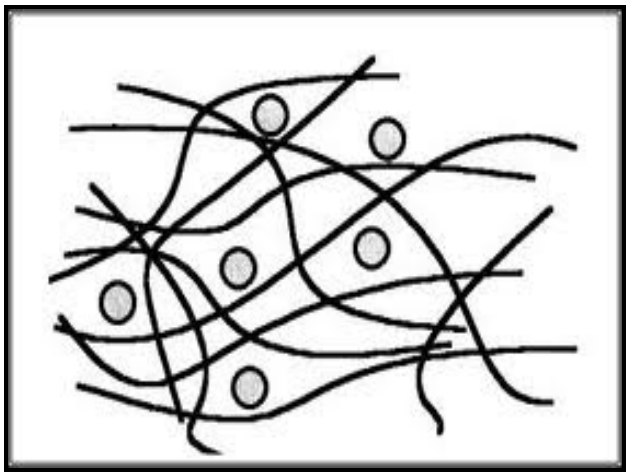


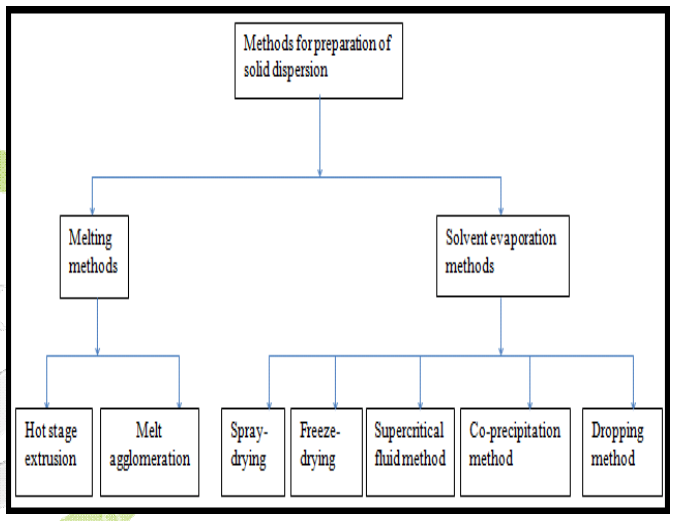
Figure: 6 Amorphous Solid Solution[21]

Glass Solution and Suspensions

Glass solutions are homogeneous glassy system in which solute dissolves in glass carrier. Particle size of dispersed phase dependent on cooling/evaporation rate. Glass solutions requires miscibility or solid solubility, complex formation or upon fast cooling or evaporation during preparation. Glass suspensions are mixture in which precipitated particles are suspended in glass solvent. In case of glass solution and suspension, lattice energy is much lower[15].

Methods for Preparation of Solid Dispersion

Melting and solvent evaporation methods are the two major methods for preparation of solid dispersions[22-25].



Melting Method

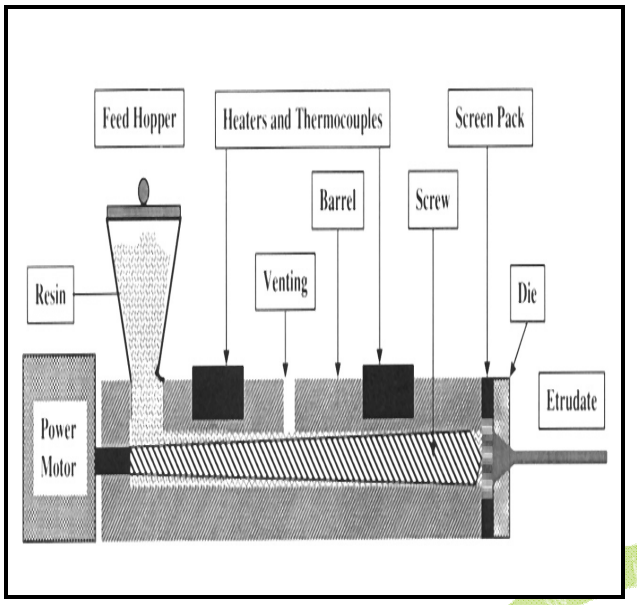
In this method the drug is melted within the carrier followed by cooling and pulverization of the obtained product. The use of high temperatures and degradation of several drugs by the melting process can be a limitation of this method[26].

Hot Stage Extrusion

Extrusion of moistened powders has been well known in the pharmaceutical sciences for many years[27]. The hot stage extrusion process is highly dependent on the physicochemical properties of the compounds and their miscibility in the molten form. Hot stage extrusion consists of the hot melt extruder at high rotational speed, the drug and carrier which is previously mixed at melting temperature for a small period of time. After cooling at room

temperature extrusion is collected and milled[23,28,29].

Hot stage extrusion



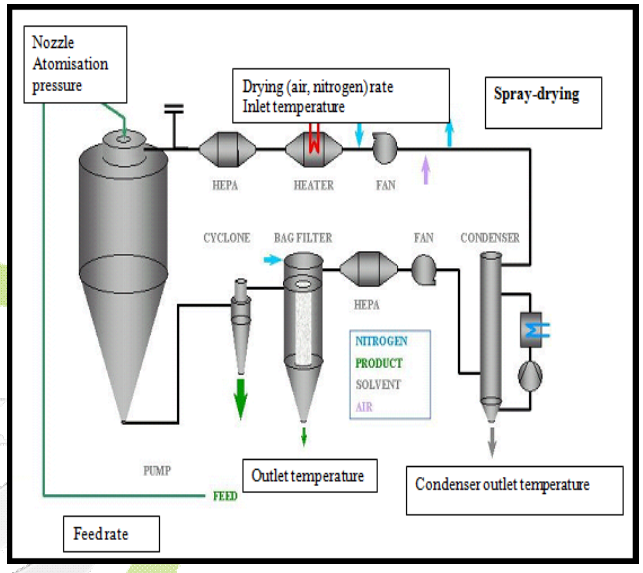
Melt Agglomeration

In this method the carrier which contain drug is melted and then this molten mass is added to heated excipients[30].

This method allows the preparation of solid dispersions in conventional high shear mixers. Processing temperature is within or above the melting range of the carrier[31].

Solvent Evaporation Method

Tachibani and Nakumara were the first to dissolve both the drug and the carrier in a common solvent and then evaporate the solvent under vacuum to produce a solid solution[35]. In solvent evaporation method the drug and carrier is solubilized in common volatile solvent which is then evaporated[32-34]. An important prerequisite for the manufacture of a solid dispersion using the solvent method is that both the drug and the carrier are sufficiently soluble in the solvent. The thermal decomposition of drugs or carriers can be prevented since organic solvent evaporated at lower temperature[24].Temperatures used for solvent evaporation usually lie in the range 23-65°C[36,37].



Spray-Drying

In this method the drug and carrier is dissolved or suspended[23,38,39] and then spraying it into a stream of hot air flow to evaporate the solvent[23,39].Van Drooge et al.[41] prepared an alternative solid dispersion by spraying a povidone and diazepam solution into liquid nitrogen, forming a suspension that was then lyophilized.

Freeze-Drying

Freeze – drying process consists of dissolving the drug and carrier in a common solvent, which is immersed in liquid nitrogen until it is fully frozen. After that the frozen solution is further lyophilized[40,41]. Important advantages of freeze drying are that the drug is subjected to minimal thermal stress during the formation of the solid dispersion and the risk of phase separation is minimized.

Supercritical Fluid Method

This technique consists of dissolving the drug and the carrier in a common solvent that is introduced into a particle formation vessel through a nozzle, simultaneously with CO_2. During spraying the solvent is rapidly extracted by the SCF, resulting in the precipitation of solid dispersion particles[42].

Co-Precipitation Method

In this method non solvent is added drop wise to the drug and carrier solution, under constant stirring. So that the drug and carrier are co-precipitated to form micro particles. After that this micro particle suspension is filtered and dried[43].

Dropping Method

It is a new procedure in that a solid dispersion of a melted drug carrier mixture is pipetted and then dropped onto a plate, where it solidifies into round particles. This method also avoids the pulverization, sifting and compressibility difficulties[44].

Advantages of Solid Dispersions

Carriers with surface activity, such as cholic acid and bile salts, when used, can significantly increase the wettability properties of drugs.

A high surface area is formed, resulting in an increased dissolution rate and, consequently, improved bioavailability[45,46].

Solid dispersions containing linear polymers produce larger and more porous particles than those containing reticular polymers and, therefore, result in a higher dissolution rate[47].

Presenting drugs in amorphous form increase the solubility of the particles.

Disadvantages of Solid Dispersions

Problems limiting the commercial application of solid dispersion which involved (a) its method of preparation, (b) reproducibility of its physicochemical properties, (c) its formulation into dosage forms, (d) the scale up of manufacturing processes, and (e) the physical and chemical stability of drug and vehicle. Phase separation, crystal growth or conversion of a product to more stable structure from metastable crystalline form during storage are major disadvantages as they result in decreased solubility and thus dissolution rate.

CONCLUSION

Solid dispersion is useful tool to enhance solubility and oral bioavailability of poorly water soluble drugs. When the solid dispersion is exposed to aqueous media, the carrier dissolves and the drug releases as fine colloidal particles. This technology is also highly potential to formulate controlled release dosage forms as the carriers may enhance or delay drug releases.

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