Review Article

Solid Dispersion Technique for Solubility Enhancement and its Characterization: A Review

Abstract:
Among the newly discovered chemical entities approximate 30% drugs are lipophillic and fail to reach market due to their poor aqueous solubility. For orally administered drugs solubility is one of the rate limiting parameter to achieve their desired concentration in systemic circulation for pharmacological response. Problem of solubility is a major challenge for formulation scientist, which can be solved by different technological approaches during the pharmaceutical product development. Solid dispersion, Micronization, Salt formation, are some of the vital approaches routinely employed to enhance the solubility of poorly soluble drugs but each approach has some limitation and advantages. Novel techniques like Nano-suspension, Supercritical processing, Cryogenic technology may allow greater opportunities in the delivery of poorly soluble drugs. The solubility behavior of drugs remains one of the most challenging aspects in formulation development. The present review is devoted to solid dispersion technique for the solubility enhancement of drug, a novel technique for enhancing drug solubility to reduce the percentage of poorly soluble drug candidates eliminated from the development and its characterization.

Keywords: Solid dispersion, Bioavaliability, Solid dispersion generation, Carrier Selection, Amorphous, Crystalline

Introduction:

Sekiguchi and Obi first proposed the use of solid dispersion in the reduction of particle size and hence enhance the rate of dissolution and absorption in 1961. [1].Solid dosage form have many advantages over other types of oral dosage forms due to greater stability, smaller bulk, accurate dosage and easy production [2].Although the oral route of administration is having many advantages, for many drugs it can be a problematic and inefficient mode of delivery for a number of reasons. The attributes include, poor

absorption, rapid degradation and lamination (peptides and proteins) resulting in insufficient concentration, dug distribution to other tissues with high drug toxicities, poor solubility of drugs and fluctuations in plasma levels owing to unpredictable bioavailability [3,4].

Salient Features and Advantages of Amorphous Solid Dispersion (ASD)

1. ASD is broadly applicable to acidic, basic, neutral and zwitterionic drugs.
2. Minimize API (active drug) requirements necessary to evaluate efficacy and safety.
3. Minimize resources required to manufacture preclinical supply.
4. Investigate alternate pathways to improve bioavailability.
5. Rapid dissolution and absorption of drug, which may produce quick onset of action.
6. Improve exposure (increase bioavailability, more rapid onset and decrease dose).

Various factors causing poor solubility are, the high crystallinity/high melting point , Zwitterion formation , Insoluble salts, H-bonding network, Hydrophobicity/High log P , Lack of ionisable group , High molecular weight [5]

Solid dispersions Generations: Based on the advancement in the solid dispersion technologies it is categorized into three generations:

First Generation Solid Dispersions:

The solid dispersions, which could be designed as first generation solid dispersions were prepared using crystalline carriers. Crystalline carriers include urea and sugars which were the first carriers to be employed in solid dispersion. They have the disadvantage of forming crystalline solid dispersions, which were more thermodynamically stable and did not release the drug as quickly as amorphous ones.

Second Generation Solid Dispersions:

Second generation of solid dispersions containins amorphous carriers instead of crystalline. They are divided into fully synthetic polymers and natural product-based polymers. Fully synthetic polymers include povidone (PVP), polyethyleneglycols (PEG) and polymethacrylates. Natural product based polymers are mainly composed by cellulose derivatives, such as hydroxypropylmethylcellulose(HPMC), ethylcellulose or

hydroxypropylcellulose or starch derivates like cyclodextrins. In second generation solid dispersions, the drug is in its supersaturated state because of forced solubilization in the carrier. These systems are able to reduce the drug particle size to nearly a molecular level, to solubilize or co-dissolve the drug by the water soluble carrier, to provide better wettability and dispersibility of the drug by the carrier material and to produce amorphous forms of the drug and carriers.

Third Generation Solid Dispersions:

Recently, it has been shown that the dissolution profile can be improved if the carrier has surface activity or self-emulsifying properties, therefore third generation solid dispersions appeared. These contain a surfactant carrier or a mixture of amorphous polymers and surfactants as carriers. These third generation solid dispersions are intended to achieve the highest degree of bioavailability for poorly soluble drugs and to stabilize the solid dispersion, avoiding drug recrystallization. The use of surfactants such as inulin, inutec SP1, compritol 888 ATO, gelucire 44/14 and poloxamer 407 as carriers was shown to be effective in originating high polymorphic purity and enhanced *in vivo* bioavailability [6, 7]

Types of Solid Dispersion:

Eutectic Mixtures: Solid eutectic mixtures are usually prepared by rapid cooling of a co-melt of the two compounds in order to obtain a physical mixture of very fine crystals of the two components. [9]

Solid Solutions: In solid solutions, the two components crystallize together in homogeneous one-phase system. The particle size of drug in a solid solution is reduced to its molecular size. Thus, a solid solution can achieve a faster dissolution rate than corresponding eutectic mixtures [8].

Discontinuous Solid Solutions: In the case of discontinuous solid solutions, the solubility of each of the components in the other component is limited. A typical phase diagram, show the regions of true solid solutions. In these regions, one of the solid components is completely dissolved in the other solid component. Below a certain temperature, the mutual solubilities of the two components start to decrease [8].

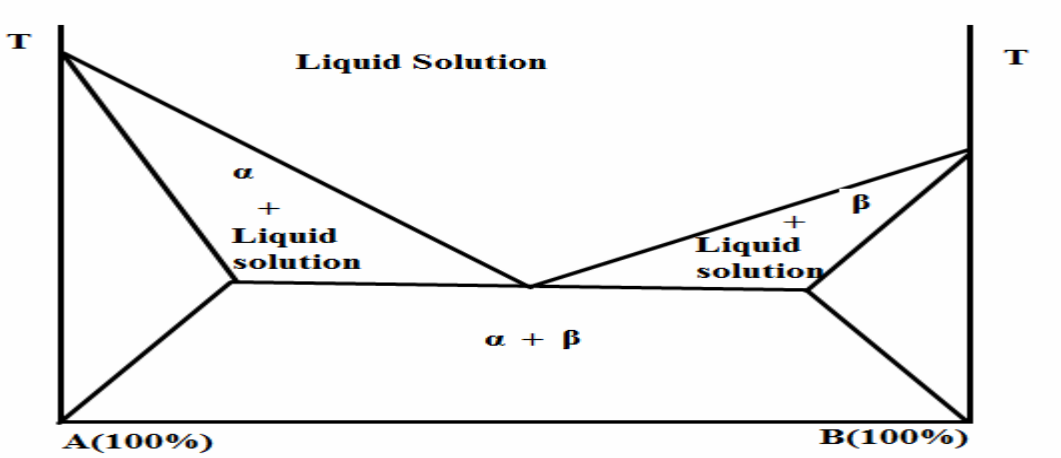

Figure 1: Hypothetical phase diagram of a discontinuous solid solution

According to the way in which the solvate molecules are distributed in the solvendum the two type of solid solution are:

Substitutional Crystalline Solutions: In this type of solid solution the solute molecules act as substitutes (in crystal lattice of solid solvent) for the solvent molecule continuous and discontinuous solid solutions can be prepared by this method. As possible the size of solute and solvent are of similar dimension (9).

Interstitial Crystalline Solid Solutions: In interstitial solid solution dissolved molecules occupy the interstitial spaces between the solvent molecules in the crystal lattice. It usually forms only a discontinuous solid state. [10]. The volume of the solute molecules should be less than 20% of the solvent. [11].

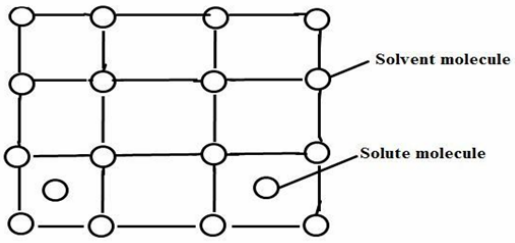

Figure 2 Phase diagram of Interstitial Crystalline Solid Solutions

Amorphous Solid Solutions: In an amorphous solid solution, the solute molecules are dispersed molecularly but irregularly within the amorphous solvent. This method is similar to simple eutectic mixtures but the only difference is that the drug is precipitated in

amorphous form [11]. Using griseofulvin in citric acid, Chiou and Riegelman were the first to report the formation of an amorphous solid solution to improve a drug's dissolution properties.

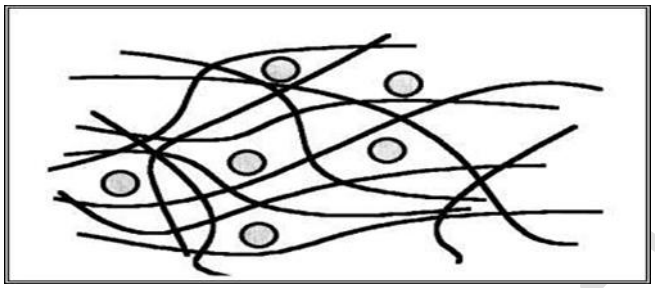

Figure 3 Phase diagram of amorphous Solutions

Glass Solutions and Glass Suspensions: A glass solution is a homogenous, glassy system in which a solute dissolves in a glassy solvent. The term glass can be used to describe either a pure chemical or a mixture of chemicals in a glassy or vitreous state. The glassy or vitreous state is usually obtained by an abrupt quenching of the melt. It is characterized by transparency & brittleness below the glass transition temperature. Glassy solid solution is a multi-ingredient, glassy system, which consist of one phase only. At the molecular level it is homogeneous and uniform. The carrier in this system occurs in amorphous state, while the dissolved molecules are molecularly dispersed.

Selection of a Carrier:

A carrier should meet the following criteria to be suitable for increasing the dissolution rate of a drug.

1. Freely water-soluble with intrinsic rapid dissolution properties.\
2. Non-toxic and pharmacologically inert.
3. Heat stable with a low melting point for the melt method.
4. Soluble in a variety of solvents and pass through a vitreous state upon solvent evaporation for the solvent method.
5. Able to preferably increase the aqueous solubility of the drug.
6. Chemically compatible with the drug and not form a strongly bonded complex with the drug. [12]

The excipients employed as carriers in solid dispersions and their nature has been summarized in table:

Table 1: Carriers used in solid dispersion

Sr No.	Carriers	Nature
1	Dextrose, Sucrose, Lactose, Sorbitol, Maltose, Mannitol, Galactose	Sugar
2	Citric acids, Succinic acids	Acids
3	Povidone, Polyethylene Glycol, Hydroxyl Propyl Methyl Cellulose, Methyl Cellulose, Hydroxy Ethyl Cellulose, Pectine, Galactomannan	Polymeric material
4	Hydroxy Propyl Methyl Cellulose, Pthalate, Eudragit RS	Insoluble or Enteric Polymers

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

1. Both drug and carrier must be dissolved.
2. Toxic solvents to be avoided due to the risk of residual levels after preparation e.g. chloroform and dichloromethane.
3. Ethanol can be used as alternative as it is less toxic.
4. Water based systems are preferred.
5. Surfactants are used to create carrier drug solutions but as they can reduce glass transition temperature, so care must be taken in to consideration [13,14].

Methods of Solid Dispersion Preparation:

Melting and solvent evaporation methods are the two major processes of preparing solid dispersions.

Melting Method: Sekiguchi et al. were the first to use a melting method consisting of melting the drug within the carrier followed by cooling and pulverization of the obtained product [15,16]. In general, heating all components above their melting or glass transition temperatures, followed by mixing and cooling is 'melting method [17]. The uniformly mixed melted mass is allowed to cool at room temperature or under cool conditions. The cooling rate may have great impact on characteristics and stability of solid dispersions. For cooling and solidification process, ice bath agitation [18], solidification on petridishes at room temperature inside a desiccator [19] spreading on plates placed over dry ice [20],

immersion in liquid nitrogen [21] or stored in desiccator were used . The most important requirement of this method is that drug and carrier should be stable at room temperature. Carrier should have low melting point (Tm) or (Tg) to obtain more processing temperature and decrease potential of drug degradation.

Hot Stage Extrusion: 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 [22] .The process involves embedding a drug in a polymer while shaping the composite material to form a pharmaceutical product. The concentration of drug in the dispersions is always 40% (w/w) [23]. This technique is same as the fusion method. The only difference is that in this method, intense mixing of the components is induced by the extruder. High shear forces results in to the high local temperature in the extruder and that can be problematic for the heat sensitive materials.

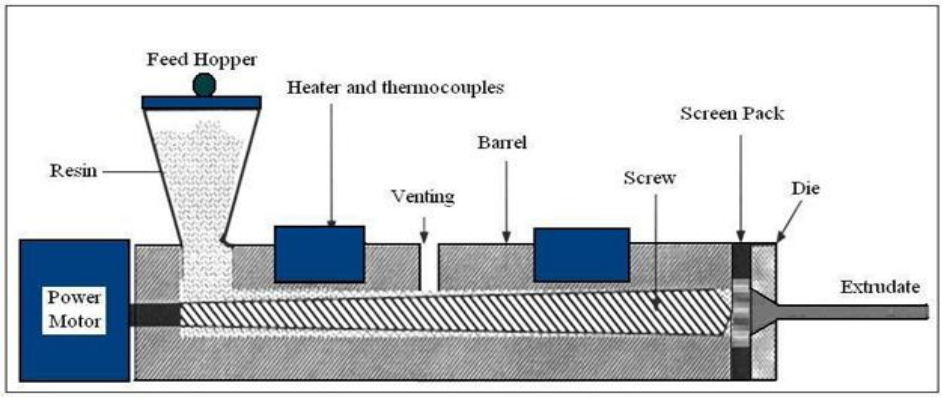

Figure 4 Schematic diagram showing components of a single screw melt extruder

Melt Agglomeration: This technique has been used to prepare solid dispersion, wherein the binder acts as a carrier. In addition, solid dispersion are prepared either by heating binder, drug and excipient to temperature above melting point of binder .The rotary processer might be preferable to melt agglomeration because it is easier to control the temperature and a higher binder content can be incorporated in the agglomerates. [24].

Solvent Evaporation Method: The first step in the solvent method is the preparation of a solution containing both matrix material and drug. The second step involves the removal of solvent resulting in formation of a solid dispersion. Mixing at the molecular level is

preferred, because this leads to optimal dissolution properties .The product is crushed, pulverized & sieved through a suitable mesh. [25]

Spray-drying: Spray-drying is one of the most commonly used solvent evaporation procedures in the production of solid dispersions. It consists of dissolving or suspending the drug and carrier, then spraying it into a stream of heated air flow to remove the solvent. Due to the large specific surface area offered by the droplets, the solvent rapidly evaporates and solid dispersion is formed within seconds, which may be fast enough to phase separation. The drying medium is typically air and the product is then separated after completion of drying [26].

Freeze-drying: This process consists of dissolving the drug and carrier in a common solvent, which is immersed in liquid nitrogen until it is fully frozen. Then, the frozen solution is further lyophilized. Spray the solution through nozzle in to liquid nitrogen. Set the liquid feed rate and atomizing air flow. Position the outlet of nozzle at about 10 cm above the liquid nitrogen. Hot water is pumped through the jacket of the nozzle in order to avoid freezing of the solution inside the nozzle. Transfer the resulting suspension (frozen droplets of the solution in liquid nitrogen) to the lyophilizer. Lyophilization procedure is started as soon as all liquid nitrogen is evaporated [27].

Kneading Method: A mixture of accurately weighed drug and carrier is wetted with solvent, kneaded thoroughly for some time in a glass mortar, the paste formed is dried and sieved. [28]

Characterization:

A number of techniques can be employed to identify the physical nature of the solid dispersions. No single method however, can furnish the complete information and hence a rational combination of the methods is preferred.

Thermal Analysis:

(a) Thermo-microscopic Methods*:* The technique has been used to support DTA or DSC measurement. It gives information about the phase diagram of binary systems. The physical mixture or dispersion on a slide is heated at rate of 1-5˚C per minute. Then observations are recorded. [29].

(b) Differential Thermal Analysis (DTA): This is an effective thermal method for studying the phase equilibria of pure substance or solid mixture. Differential heat changes

that accompany physical and chemical changes are recorded as a function of temperature as the substance is heated at uniform rate. The greatest advantage of using this technique is in constructing phase diagram of high reproducibility; a higher temperature range is permitted, greater resolution realest. In DTA, the temperature difference that develops between a sample and an inert reference material is measured, at identical heat treatments. [30].

(c) Differential Scanning Colorimetry (DSC): In DSC, both the sample and reference materials are subjected to linear heating, but both are maintained at the same temperature. Here change in temperature is not recorded, but the heat flow into the system is recorded which is required to maintain isothermal conditions. The method is useful to study the behavior of crystallization and melting and deriving phase diagrams of solid dispersions .It is a thermal process to find out the heat flow and temperature related with substance transitions as a function of time and temperature [31].

X-ray diffraction (XRD): The detection of crystalline phases in mixed systems can be analyzed by powder X-ray diffraction. However, too much crystallinity causes brittleness. The crystallinity parts give sharp narrow diffraction peaks and the amorphous component gives a very broad peak. The ratio between these intensities can be used to calculate the amount of crystallinity in the material. Single crystal x-ray crystallography dealing with the determination of bond angle and inter atomic distances. Power x-ray diffraction deals with the study of crystal lattice parameter, where the x-ray diffraction intensity from a sample is measured as a function of diffraction angles. Thus, changes in diffraction pattern indicate changes in crystal structure. The relationship between wavelength of the x-ray, the angle of diffraction θ, and the distance between each set of atomic planes of crystal lattice d, is given by equation: $M\lambda=2d \sin \theta$, where M represent the order of diffraction. [31]

FT-IR Spectroscopy: FT-IR spectroscopy used to study the possibility of an interaction between drug and polymer in solid state .Appearance and disappearance of peak indicate interaction between two compound and degradation of drug. Infrared spectroscopy (IR) can be used to detect the variation in the energy distribution of interactions between drug and matrix .IR can be used to detect the variation in the energy distribution of interactions between drug and matrix. Sharp vibrational bands indicate crystallinity. Fourier Transformed Infrared Spectroscopy (FTIR) was used to accurately detect crystallinity

ranging from 1 to 99% in pure material. It can be applied to follow changes in bonding between functional groups. [32]

Advantages of Solid Dispersion:

1. Molecular dispersions, as solid dispersions, represent the last state on particle size reduction, and after carrier dissolution the drug is molecularly dispersed in the dissolution medium.

2. Solid dispersions apply this principle to drug release by creating a mixture of a poorly water soluble drug and highly soluble carriers.

3. A strong contribution to the enhancement of drug solubility is related to the drug wettability improvement verified in solid dispersions.. Carriers with surface activity, such as cholic acid and bile salts, when used, can significantly increase the wettability property of drug. Moreover, carriers can influence the drug dissolution profile by direct dissolution or co-solvent effects.

4. Particles in solid dispersions have been found to have a higher degree of porosity. The increase in porosity also depends on the carrier properties.

5. Bioavailability of anticancer drugs has been improved by incorporating them in solid dispersions

6. They reduce the effect of food on drug absorption thus making it convenient to take the drug on empty stomach [33].

Disadvantages of Solid Dispersions:

The major disadvantages of solid dispersion are related to their instability

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.

2. 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. This may result in decreased solubility and dissolution rate. [33, 34]

Application of Solid Dispersion:

Solid dispersion systems can provide numerous additional benefits; some of them are as following:

1. In improving immunosuppressive therapy in lung transplant patients, dry powder formulation consisting of a solid dispersion for inhalation is prepared. It can avoid many problems like use of local anesthesia and irritating solvents.

2. Solid dispersion formulations were demonstrated to accelerate the onset of action for drugs such as non-steroidal anti-inflammatory drugs (NSAIDS) where immediacy of action is crucial in relieving acute pain and inflammation.

3. Solid dispersion systems were shown to provide bioavailable oral dosage forms for anti-cancer drugs, which could be substituted for standard injections to improve patient comfort and compliance. [14, 19, 27, 34]

Conclusion: For orally administered drugs solubility is one of the rate limiting parameter to achieve their desired concentration in systemic circulation for pharmacological response. Problem of solubility is a major challenge for formulation scientists. Solid dispersion techniques, described in this review alone or in combination can be successfully used to enhance the solubility of hydrophobic drugs for improving their oral bioavailability, but successful improvement is mainly depends on selection of method. Among all the solubility enhancement techniques solid dispersion technique is most acceptable and most commonly used technique for solubility enhancement because of its easiness, cost effectiveness and maximum solubility enhancement over other technique.

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