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Review Article

Enhancement of solubility of poorly soluble drugs by solid dispersion: An Overview

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ABSTRACT

Most of the newly invented chemical drug moieties are poorly water soluble. According to BCS classification, class II and IV drugs are considered as poorly water soluble. So enhancement of oral absorption and bioavailability of solid dosage forms remains a challenge to formulation scientists due to their solubility criteria. Therefore many techniques are being explored to enhance the solubility of poor soluble drugs. Solid dispersion is one of the most important method for enhance the solubility (dissolution rate) and hence oral bioavailability of poorly soluble drugs. In solid dispersion the particle size of drug is reduced or a crystalline pure drug is converted into amorphous form and hence the solubility is increased. Polymer incorporating in solid dispersion technology is usually hydrophilic in nature and also showing compatibility with the drug to enhance the drug solubility. This review mainly discus about solid dispersion, preparation methods, and finally characterization.

Introduction

The solubility of drug is one of the most important criteria in formulation development. Oral bioavailability of drugs depends on its solubility and dissolution rate, these drugs having very low solubility in biological fluids, which results into poor bioavailability after oral administration[1]. Solid dispersion is one of the techniques to improve solubility and hence bioavailability of poorly water soluble drugs. Solid dispersion methodologies are have attracted considerable interest of enhancing the dissolution rate of highly lipophilic drugs thereby increasing their solubility by reducing drug particle size, improving wettability and forming the amorphous particles.[2] The term solid dispersion defined to a group of solid products consisting of at least two different components, generally a hydrophilic inert carrier and a hydrophobic drug[3]. Bioavailability refers as the rate and extent to which the active substance or therapeutic moiety is absorbed from a pharmaceutical dosage form and becomes available at the site of action.[4] An orally administered drug of its bioavailability depends on its solubility in aqueous media over the pH range of 1.0–7.5 and the rate of mass transfer into biological membranes. [5-7]. In the oral bioavailability of poorly water soluble compounds, the insufficient dissolution rate is the limiting factor[8]. in the biopharmaceutical classification system (BCS) drugs with low aqueous solubility and high membrane permeability are categorized as Class II drugs. Therefore, solid dispersion technologies are particularly promising for improving the oral absorption and bioavailability of BCS Class II drugs. (9). In case of solid dispersion, drug is dispersed in the matrix generally a hydrophilic matrix and a hydrophobic drug, thereby forming a solid dispersion[10].

Solubility: Solubility can be defined as qualitatively as well as quantitatively. Quantitatively solubility can be defined as the solute concentration in a saturated solution at a particular temperature. Whereas qualitative it can be defined as the spontaneous interaction of two substances to produces a homogenous molecular dispersion[11].The amount of substance that passes into solution in order to establish the equilibrium at constant pressure and temperature and so produced a saturated solution is known as the ‘solubility[12]. Solubility is of the Consideration of the modified Noyes-Whitney equation provides some hints as to how improve the dissolution rate of even very poorly soluble compounds and to minimize the limitations to oral bioavailability of substance[13].

$$dC/dt = AD (Cs - C)/h$$

Where,

dC/dt is the rate of dissolution, A is the surface area available for dissolution, D is the diffusion coefficient of the compound, Cs is the solubility of the compound in a

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dissolution medium, C is the concentration of drug present in the medium at a time t and h is the thickness of the diffusion boundary layer adjacent to the surface of the dissolving compound[14].

Solid Dispersion: In 1961, Sekiguchi and Obi first proposed the utilization of solid dispersions to enhance the dissolution and oral absorption of poorly water-soluble drugs. They first proposed the formation of a eutectic mixture of a poorly water-soluble drug is physiologically inert, easily soluble carriers and the carriers are introduced in the year 1969 by Chiou and Riegelman.

Definition: The term 'solid dispersion' has been defined as the technique whereby the drug is dispersed in a biologically inert matrix, to improving oral bioavailability.

Solid dispersion was firstly introduced to overcome the low bioavailability of lipophilic drugs by forming of eutectic mixtures of drugs with water-soluble carriers. In the Biopharmaceutical Classification System (BCS) Class II drugs are those are having low aqueous solubility and high membrane permeability (Amidon et al., 1995) and therefore, solid dispersion technologies are particularly promising for enhancing the oral absorption and bioavailability of BCS Class II drugs. According to the BCS, drug substances are classified in four groups as shown in Table 1 (FDA 2000). The table is adopted from Lindenberg et al., 2004, only for the BCS Class II drugs [15].

Table 1: Biopharmaceutical Classification System (BCS)

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

Merits of solid dispersion

- Increased wettability during solid dispersion, results in enhancing the solubility. Here the carriers play the key role to improve the wettability of the solid particles.
- In solid dispersion method, the particles are having high degree of porosity. Increase in porosity influence carrier properties and increase drug release profile.[17]
- Amorphous state of drug leads to enhancement in drug release. By using solid dispersion method, drugs are presented as supersaturated solutions, which are considered to be metastable Polymorphic form.
- Particle size reduction in solid dispersion leads to increase surface area which cause increase in dissolution rate hence improved bioavailability.[18]

Demerits of Solid Dispersions:

- Stability problem of vehicle and drug.
- Physicochemical properties reproducibility**.**
- Method of preparation is expensive.
- Difficult to prepare solid dispersions in a dosage form.[19]

Types of Solid Dispersions

Based on their molecular arrangement, four different types of solid dispersions can be distinguished.

They are described below.

1. Eutectics
2. Amorphous precipitations in crystalline matrix
3. Solid solutions

a. Continuous solid solutions
b. Discontinuous solid solutions
c. Substitutional solid solutions
d. Interstitial solid solutions

4. Glass suspensions and solutions

Eutectic Mixtures

Eutectic mixtures are formed by the drug and polymer is miscible in their molten state, but on cooling, they crystallize as two distinct components with negligible miscibility. In this type of solid dispersion a drug (A) and a carrier (B) are co-melted at their eutectic composition defined by point 'e'. [20]

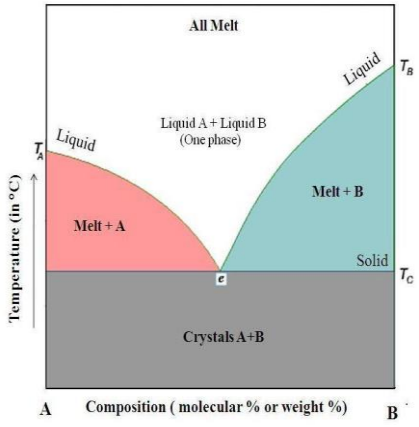

Figure 1: Eutectics system phase diagram

Amorphous precipitation in crystalline matrix: In this type within the amorphous solvent the solute molecules are dispersed irregularly and molecularly[21]. In earlier studies other carriers were used in this type of dispersion such as urea and sugars (sucrose, galactose and dextrose). But now a day's cellulose derivatives and organic polymers are used (PVP, PEG etc). To plasticize the polymer various solute molecules are used. The reduction in glass transition temperature is due to solutes which are used to mould the polymer[22].

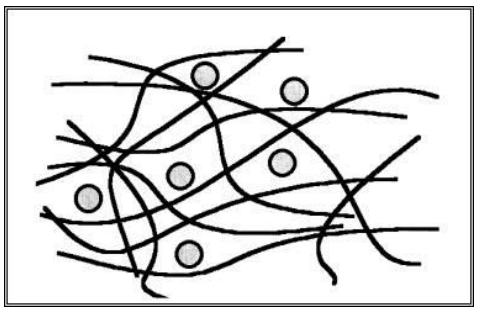

Figure 2: Amorphous solutions

Solid solutions: In a solid solution the two components are crystallize together in a homogeneous one phase system. The particle size of the drug in the solid solutions is reduced to its molecular size. Thus, a solid solution can achieve a faster dissolution rate than the corresponding eutectic mixture. Solid solutions can be classified by two methods. According to the extent of miscibility of the two components, the solid solutions may be classified as continuous or discontinuous[23]

- Continuous solid solutions - In continuous solid solutions, the components are miscible in all proportions i.e. the bonding strength between the two components is stronger than the bonding between the individual component.

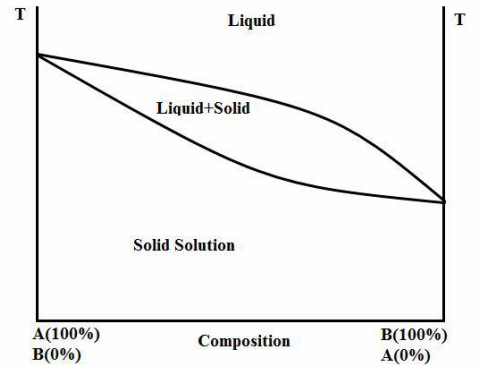

Figure 3: Continuous solid solution phase diagram

- Discontinuous solid solutions - In discontinuous solid solutions, the solubility of each of the component in the other component is limited in nature[24].

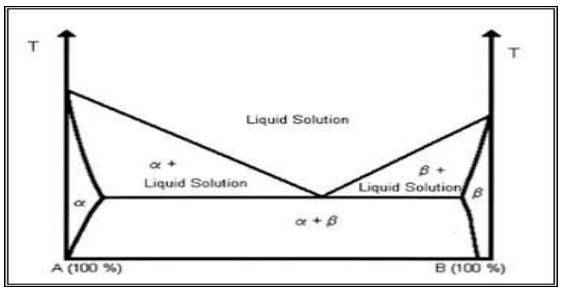

Figure 4: Discontinuous solid solutions phase diagram

- **Substitutional solid solutions:** In this solution system the solvent molecules are within the crystal lattice of the solid solvent molecules are substituted by the solid molecules by substitutional solid solutions.

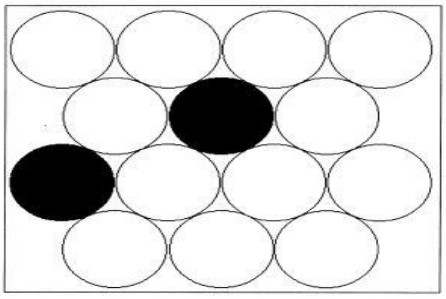

Figure 5: Substitutional solid solutions

- **Interstitial solid solutions**

In the crystal lattice the dissolved molecules are occupies the interstitial spaces between the solvent molecules. The molecular diameter of the solute molecules in case of interstitial solid solutions should not be greater than solvent molecules diameter i.e 0.59 and solvent molecules have more than 20% diameter than solute molecules[25].

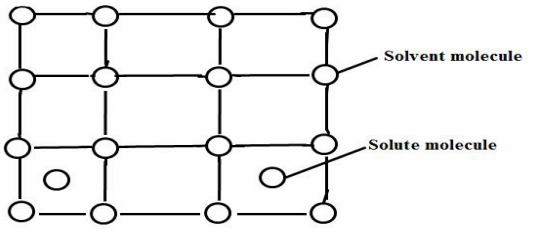

Figure 6: Interstitial solid solutions

Glass Solutions and Glass Suspensions

A glass solution or glass suspensions are a homogenous, in 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 [26]

Table 2: Mechanisms to Increase Dissolution Rate [28]

MECHANISM	CHARACTERISTICS
1. Reduction of particle size:	1. Particle size is reduced to a low level in case of glass, either solid solution or amorphous dispersions. 2. This lead to an enhancing dissolution rate by an increase in both the surface area.
2. Solubilization effect	1. When the carrier material dissolves it has solubilization effect on the drug. 2. Drugs with increase solubilization effect of like acetaminophen and chlorpropamide in urea.
3. Metastable Forms	Reduced lattice energy due to formation of metastable dispersions results in faster dissolution rate.
4.Wettability and dispersibility	Carrier used has enhancing effect on wettability and dispersibility.

Selection of Carrier

A carrier should have the following suitable characteristics for enhance the solubility and dissolution rate of a drug.

1. Freely water-soluble with having the intrinsic rapid dissolution properties.
2. Pharmacologically inert and Non-toxic to drug molecules.
3. Should have thermo 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. Capable to preferably improve the aqueous solubility of the drug and
6. Chemically compatible with the drug and should not form a strongly bonded complex with the drug[26].

Classification of Solid Dispersion

First generation: The first generation solid dispersions can be developed by using crystalline carriers like urea and sugar, which were the first carriers to be imparted

in solid dispersion. They are having the disadvantage of forming crystalline solid dispersion, which were thermodynamically more stable and cannot release the drug as quickly as amorphous ones.

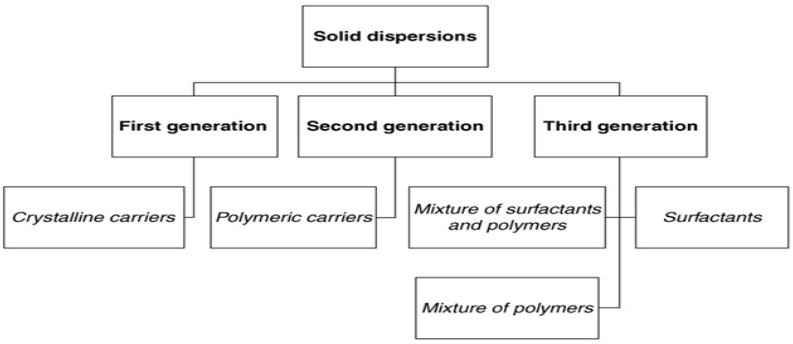

Figure 7: Generations of carriers of solid dispersion

Second generation: In second generation solid dispersions, amorphous carriers are used instead of crystalline carriers, which are usually polymers. These polymers are include synthetic polymers such as poly vinyl pyrolidone (PVP), polyethylene glycols (PEG), ethyl cellulosepolymethacrylates, natural product based polymers such as hydroxylpropylmethyl-cellulose (HPMC) and hydroxypropyl cellulose or starch derivatives like cyclodextrins.

Third generation: Recently, it has been observed that the dissolution profile can be improved further, if the carrier has surface activity or self-emulsifying properties. Therefore, third generation solid dispersions were developed. The use of surfactant such as inutec SP1, inulin, compritol 888 ATO, gelucire 44/14 and poloxamer 407 as carriers were shown to be effective in originating high polymorphic purity and enhanced in vivo bioavailability.[27]

Preparation Methods of Solid Dispersion

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
10. Direct Capsule Filling
11. Co-precipitation method
12. Dropping method

Melting Method: Accurately weighed drug and carrier are mixed by using glass mortar and pestle. The mixture is heated at or above the melting point of all the components to achieve a homogenous dispersion. It is then cooled to obtain a congealed mass. It is pulverized and sieved[28].

Solvent evaporation method: The solvent-based process uses the organic solvent to dissolve and intimately disperse the drug and carrier molecule. Large volumes of solvents are generally required which can give rise to toxicological problems. Many investigators studied SD of meloxicam, naproxen, rofecoxib, felodipine using solvent evaporation technique. These findings suggest that the above-mentioned technique can be employed successfully for improvement and stability of solid dispersions of poor water drugs[28].

Hot melt extrusion: Hot-stage extrusion (HME) consists of the extrusion. The extraction is processed at high rotational speed of the drug and carrier, previously mixed, at melting temperature for a small period of time. The resulting product is then collected after cooling at room temperature and milled. A reduction in processing temperature can be achieved by the association of hot-stage extrusion with the use of carbon dioxide as a plasticizer, which broadens the application of hot-stage extrusion to thermally labile compounds. HME also offers several advantages over traditional pharmaceutical processing techniques including the absence of solvents, few processing steps, continuous operation, more possibility of the formation of solid dispersions and improved bioavailability. [29]

Melting –solvent method: A drug is first dissolved in a suitable liquid solvent and then this solution is incorporated into the melt of polyethylene glycol, obtainable below 70^{o}C without removing the liquid solvent. The selected solvent or dissolved drug may not be miscible with the melt of the polyethylene glycol. Also polymorphic form of the drug precipitated in the solid dispersion may get affected by the liquid solvent used. [27]

Lyophillization Technique: Freeze-drying involves transfer of heat and mass to and from the product under preparation. This technique was proposed as an alternative technique to solvent evaporation. Lyophillization 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.

Melt Agglomeration technique: In this technique binders are used as carriers. There are two methods of preparations of solid dispersing, first is by spraying the drug on melted binder plus excipients. Other one is melting of binder drug and excipients above the melting temperature of binders 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.

The use of surfactant: The utility of the surfactant systems in solubilization is well known. Surfactant reduces

hydrophobicity of drug by reducing interfacial or surface tension. Because of this unique property of surfactants have attracting the attention of investigators for preparation of solid dispersions. Recently a new class of surfactant known as gelucires are introduced which identify by melting points and HLB values. Gelucire is widely used in the formulation of semi solid dispersions. Gelucires with low HLB can be employed to decrease the dissolution rate of drugs and higher HLB ones for fast release. Hemant et al and Sheen et al studied that polysorbate 80, a commonly used surfactant, results in improvement of dissolution and bioavailability of poorly water soluble drug attributed to solubilization effect of surface active agent. Polysorbate 80 also ensures complete release of drug in metastable finely dispersed state having large surface area.

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. 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. Upon increasing the electrostatic field strength up to formation of charged species, but not exceed a critical value. The charged species are accumulated on the surface of a pendant drop; destabilize the hemispherical shape into a conical shape (commonly known as Taylor's cone). Beyond the critical value, a charged polymer jet is ejected from the apex of the cone (as a way of relieving the charge built-up on the surface of the pendant drop). The ejected charged jet is then carried to the collection screen via the electrostatic force. The thinning down of the charged jet is limited. If the viscosity increases, the charged jet is dried. This technique has tremendous potential for the preparation of nanofibres and controlling the release of biomedicine, as it is simplest, the cheapest this technique can be utilized for the preparation of solid dispersions in future.

Supercritical Fluid Method: Supercritical fluid technology is important because it operates at high temperature and pressure. Above critical temperature and pressure supercritical fluid exists as single phase. The most commonly used SCF is CO2 due to its low temperature (31.3 degree C) and low pressure (73.8 bar). It is used because it non toxic, non inflammable, inexpensive and for processing heat labile molecules. In this drug and inert carrier are dissolved in carbon dioxide solvent and are sprayed by nozzle with low pressure on expansion vessel and particles are formed. And then the expansion of mixture is rapidly cooled. Another name of this technique is Rapid Expansion of supercritical solution.

Direct Capsule Filling: In this technique large scale manufacturing equipment and laboratory scale semiautomatic equipment is used. Liquid melt of solid dispersion is directly filled in to hard gelatin capsule due to this it overcomes the problem due to grinding which cause change in crystalline behaviour of drug. Eg. Molten dispersion of triamterene-PEG 1500 can be filled in hard gelatine capsule by the use of Zanasi LZ 64 capsule filling machine.

Co-precipitation method: Co-precipitation is a recognized technique for increasing the dissolution of poorly water soluble drugs, so as to consequently improve bioavailability. In this method non solvent is added drop wise to the drug and carrier solution, under constant stirring. In the course of the non solvent addition, the drug and carrier are co-precipitated to form micro particles. At the end, the resulted micro particle suspension is filtered and dried. The required quantity of polymer and the drug were mixed and then solvent was added to obtain clear solution. The Solution was first dried under vacuum at room temperature and kept inside incubator (370c) for 12 hrs. Finally it was passed through sieves.

Dropping method: This technique may overcome some of the difficulties inherent in the other method and developed by Ulrich et al.12 to facilitate the crystallization of different chemicals, is a new procedure for producing round particles from melted solid dispersions. A solid dispersion of a melted drug carrier mixture is pipette and then dropped onto a plate, where it solidifies into round particles. The size and shape of the particles can be influenced by factors such as the viscosity of the melt and the size of the pipette. The dropping method does not use organic solvents and, therefore, has none of the problems associated with solvent evaporation. This method also avoids the pulverization, sifting and compressibility difficulties.

Characterization of solid dispersions:

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

• Polarized 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[27-29]

Conclusion

Now days so many techniques and methods are there to improve the solubility and oral bioavailability of solid dosage forms of having poorly water soluble drugs. Solid dispersion is one of the approaches to achieve the goal of enhancing the solubility of poorly soluble drugs. In this review some methods of solid dispersion techniques were explained briefly. Manufacturing of solid dispersions requires a suitable combination of drug and carriers. Whatever this technology is also highly potential to formulate controlled release dosage forms as the carriers may enhance or delay drug release.

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