Solid Dispersions for Solubility and Bioavailability Enhancement of Poorly Aqueous Soluble Drugs: A Review

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Abstract- Solid dispersions are considered as the one of the most emerging technologies for improving the practically water insoluble drugs dissolution profile thereby increasing the bioavailability of hydrophobic drugs. This article review provides the information about different types of solid dispersions based on their molecular arrangement and type of matrix material employed. Different methods of preparations of solid dispersions and recent advances in preparation methods have been highlighted. Various analytical tools employed in the characterization of solid dispersions are discussed.

Key words: Solid dispersions, dissolution profile, bioavailability, matrix material, characterization.

I. INTRODUCTION

Oral drug delivery is the simplest and easiest way of administering drugs [1, 2]. The augment of oral bioavailability of poorly water soluble drugs remains one of the most challenging aspects of drug development [3-5]. Although many techniques like salt formation, solubilization, and particle size reduction have commonly been used to enhance dissolution rate. The oral absorption and bioavailability of such drugs there are practical limitations of these techniques. The salt formation is not feasible for neutral compounds and the synthesis of appropriate salt forms of drugs that are weakly acidic or weakly basic may often not be practical. Even when salts can be prepared, an increased dissolution rate in the gastrointestinal tract may not be achieved in many cases because of the reconversion of salts into aggregates of their respective acid or base forms. The solubilization of drugs in organic solvents or in aqueous media by the use of surfactants and co-solvents leads to liquid formulations that are usually undesirable from the view points of patient acceptability and commercialization. Although particle size reduction is commonly used to increase dissolution rate, there is a practical limit to how much size reduction can be achieved by such commonly used methods as controlled crystallization, grinding, etc. The use of very fine powders in a dosage form may also be problematic because of handling difficulties and poor wettability [6, 7].

Drug release is a critical and limiting step for oral drug bioavailability. By improving the drug release profile of these drugs, it is possible to enhance their bioavailability. Solid dispersions are one of the most doing well strategies to improve drug release of poorly soluble drugs [8-10]. In 1961, Sekiguchi and Obi observed that the formulation of eutectic mixtures enhances the drug release rate there by increasing the bioavailability of poor aqueous soluble drugs. They suggested that the drug present in eutectic mixture is in the form of microcrystalline state [11]. Goldberg et al. showed that the drug in solid dispersion may not be essentially present in microcrystalline state but a certain fraction of the drug might be molecularly dispersed in the carrier, thereby forming a solid solution [12].

Solid dispersions

Solid dispersions are material comprising more than one or more active ingredients where they are dispersed throughout a carrier or matrix material. Solid dispersion, as implied in its name, refers to the solid state where one substance is dispersed into another material. The substances can be mixed completely or partially, containing several phases. In general, solid dispersion is defined as the dispersion of one or more active ingredients in a carrier or matrix at solid state [13, 14]. In most of the cases, since the drug is a practically insoluble, drug solid dispersions may be considered as the mixture of hydrophilic matrix or carrier and the hydrophobic drug [15, 16].

II METHODS

The Classification of Solid Dispersions

Based on the type of carriers or matrix material employed solid dispersions may be grouped in to three generations as shown in figure. 1and can be called as

first generation SDs, second generation SDs and third generation SDs [17, 18].

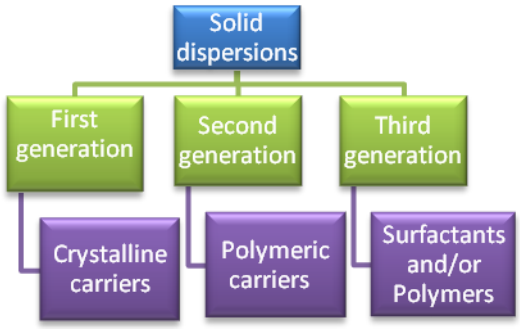

Fig. 1. Classification of solid dispersions.

First generation solid dispersions

The First generation solid dispersions consist of crystalline carriers such as urea and sugars. These carriers are the first to be employed by researchers in the production of solid dispersions [19-21]. Polyethylene glycols (PEG) and polyoxyethylene-polyoxypropylene also can be used as an excellent pharmaceutical-property eutectic mixture [22]. Sekiguchi and Obi in 1961 reported the solid dispersions by eutectic mixtures which are formed when the drug and carrier are homogeneously mixed in melted state [23]. When eutectic solid dispersions are dissolved in an aqueous medium, the carrier part will dissolve quickly and, the drug part is released in the form of fine crystals. The fast release gives eutectic solid dispersion a rapid dissolution rate of drug. The large surface area of these small size particles results in better wettability, based on which eutectic solid dispersions improve bioavailability [18]. The main disadvantage of forming crystalline solid dispersions is that they do not release the drug as quickly as amorphous solid dispersions because of they are thermodynamically more stable.

Second generation solid dispersions

Second generation solid dispersions contain amorphous carriers which are mostly polymers. Because of more thermodynamic stability of crystalline solid dispersions, amorphous solid dispersions were considered to be more effective in terms of drug release characteristics [24-26]. The polymeric carriers are divided in to two types i.e. synthetic polymers and natural product based polymers. Synthetic polymers include povidone (PVP) [27- 29], polyethyleneglycols (PEG) [30- 32] and polymethacrylates [33]. The natural product based polymers is mainly composed of cellulose derivatives like hydroxypropylmethylcellulose (HPMC), ethylcellulose, hydroxypropylcellulose and starch derivates, like cyclodextrins [34- 37]. Based on the molecular interaction of drug and carriers the amorphous solid dispersions can be divided into solid solutions, solid suspensions or a mixture of both [38]. In amorphous solid solutions, the drug and carrier are completely soluble with each other, making a homogeneous mixture. Amorphous solid suspensions are made when the drug has limited carrier solubility or are of very high melting points [15].

Third generation solid dispersions

The third generation solid dispersions consist of surface active carriers which improve dissolution profile because of its self emulsifying property. The surface activity which prevents nucleation and agglomeration may improve stability physically and chemically [39]. Few commonly used surfactants are compritol 888 ATO, gelucire 44/14 and poloxamer 407 [40- 42]. The inclusion of surfactants in the formulation containing a polymeric carrier may help to prevent precipitation and/or protect a fine crystalline precipitate from agglomeration into much larger hydrophobic particles [43].

The drug can be dispersed molecularly. In amorphous particles (clusters) or in crystalline particles, based on their molecular arrangement six different types of solid dispersions can be distinguished. They are described in Table 1.

Table 1. Six subtypes of solid dispersions

Solid dispersion type		Matrix (*)	Drug (**)	Remarks	No. of Phases	Literature References
I	Eutectics	C	C	The first type of solid dispersions prepared.	2	[15]
II	amorphous precipitations in crystalline matrix	C	A	Rarely encountered	2	[44]
III	Solid solutions					
	Continuous solid solutions	C	M	Miscible at all compositions, never prepared.	1	[45]
	Discontinuous solid solutions	C	M	Partially miscible, 2 phases even though drug is molecularly dispersed.	2	[11]
	substitutional solid solutions	C	M	Molecular diameter of drug (solute) differs less than 15% from matrix (solvent) diameter. In that	1or 2	[46]

				case the drug and matrix are substitutional. It can be continuous or discontinuous. If discontinuous, 2 phases are present even though drug is molecularly dispersed.		
	Interstitial solid solutions	C	M	Drug (solute) molecular diameter less than 59% of matrix (solvent) diameter. Usually limited miscibility, discontinuous. Example: Drug in helical interstitial spaces of PEG.	2	[15], [25]
IV	Glass suspension	A	C	Particle size of dispersed phase dependent on cooling/evaporation rate. Obtained after crystallization of drug in amorphous matrix.	2	[15]
V	Glass suspension	A	A	Particle size of dispersed phase dependent on cooling/evaporation rate many solid dispersions are of this type	2	[15]
VI	Glass solution	A	M	Requires miscibility/solid solubility, complex formation or upon fast cooling/evaporation during preparation, many (recent) examples especially with PVP.	1	[26]

*: A: matrix in the amorphous state

C: matrix in the crystalline state

**: A: drug dispersed as amorphous clusters in the matrix

C: drug dispersed as crystalline particles in the matrix

M: drug molecularly dispersed throughout the matrix

Methods to obtain solid dispersions

Various preparation methods for solid dispersions have been reported in literature. These methods deal with the challenge of mixing a matrix and a drug, preferably on a molecular level, while matrix and drug are generally poorly miscible. During many of the preparation techniques, partially or complete demixing, and formation of different phases are observed. During the solid dispersion preparation partial or total separation of phases mixed and formation of new ones are observed.

Fusion method (Melting method)

Melting method is also referred to as a fusion method. For the first time, this method was employed to form solid dispersions by Sekiguchi and Obi, who obtained physical mixture consisting of sulfathiazole and urea [11]. The dispersion consisted of sulfathiazole and urea as a matrix which were melted using a physical mixture at the eutectic composition, followed by a cooling step. The eutectic composition was chosen to obtain simultaneous crystallization of drug and matrix during cooling. The melting point of a binary system is dependent upon its composition, i.e., the weight fraction of drug and the carrier present in the system. By proper selection and control, the melting point of a binary system may be made to be much lower than the melting points of its two components. Under such conditions, this melting method can be used to prepare solid dispersions, even if the pure drug may undergo decomposition at or near its melting point [15]. The main advantages of this method are its simplicity and economy. In addition, melting under vacuum or blanket of an inert gas such as nitrogen may be used to prevent oxidation of drug or carrier material.

There are few limitations of fusion method. Firstly, a major disadvantage is that the method can only be applied when drug and matrix are compatible and when they mix well at the heating temperature. When drug and matrix are incompatible two liquid phases or a suspension can be observed in the heated mixture which results in an inhomogeneous solid dispersion. Secondly, a problem can arise during cooling when the drug-matrix miscibility changes. In this case phase separation can occur. Indeed, it was observed that when the mixture was slowly cooled, crystalline drug occurred, whereas fast cooling yielded amorphous solid dispersions. Thirdly, degradation of the drug and or matrix can occur during heating to temperatures necessary to fuse matrix and drug [16].

Solvent method

Tachibana and Nakamura were the two researchers who firstly applied solvent evaporation method for the preparation of solid dispersions. Drug (b-carotene) and carrier (PVP) were dissolved in a common solvent (chloroform) and solvent was evaporated to form the solid mass [47]. 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(s) resulting in formation of a solid dispersion

[48]. Mixing at the molecular level is preferred, because this leads to optimal dissolution properties. Nature of the solvent used and the rate and temperature of evaporation of the solvent are the critical factors which can affect the formed mass [49]. The main advantage of the described solid dispersion preparation method is preventing degradation of the drug substance or carrier by maintenance of low temperature needed to vaporize the organic solvent. The disadvantages include high cost of production, difficulties with selection of an easily volatile solvent and its complete removal, possible side effects caused by solvent residues affecting chemical stability of the substance, as well as problem with reconstruction of the crystalline form [50]. Manimaran et al., in 2010, prepared the solid dispersion of glibenclamide by the solvent evaporation method using PVP, PEG6000 and Poloxamer as hydrophilic carrier. In this study, they observed that the solid dispersion prepared by using various hydrophilic carriers enhanced the solubility of glibenclamide to a varying degree. All SDs showed increased dissolution rate as compared to pure glibenclamide and PVP was found better than PEG and Poloxamer [51].

Melt evaporation method

Solid dispersions are created also by dissolving drug in relevant solvent and incorporating this solution in polyethylene glycol (PEG) melt below 70^{o}C. After combining the two solutions, the solvent is evaporated leaving the product layer. The resulting film is then dried until a fixed weight is achieved. The difficulty in preparing solid dispersion using this method is limited mixing of the used solvents or of the dissolved drug with the molten PEG. In addition, liquid solvent used in this method is capable of initiating formation of polymorphic drug forms which then, as precipitates, appear in the resulting solid dispersion [52].

Hot melt extrusion method

This technology was first utilized predominantly in the plastic industry and to lesser extent in the food industry since 1930's. Many advantages of hot melt extrusion over conventional solid dosage from manufacturing picked the interest of pharmaceutical industry and researchers for the useful technology to prepare novel drug delivery system [52]. Melt extrusion method to prepare solid dispersions was introduced relatively recently. It is considered particularly useful to obtain dispersions of drug substances occurring in various polymorphic forms of different bioavailability .In the process of solid dispersion formation with the use of this technique drug substances dissolve in polymer and remain in form of molecular dispersion even as the polymer solidifies. Melt extrusion method is a variation of the previously discussed melting method [53, 54].

Some examples of pharmaceutically approved polymeric materials which are used in hot-melt extrusion include vinyl polymers (polyvinylpyrrolidone (PVP), PVP-vinyl acetate (PVP-VA)), polyethylene oxide (PEO), Eudragit® (acrylates), Polyethylene glycol (PEG) and cellulose derivatives [55]

Spray Drying

Spray drying method consists of dissolving or suspending the drug and polymer in a common solvent or solvent mixture and then drying it into a stream of heated air flow to remove the solvent [56]. Due to the large surface area of the droplets, the solvent rapidly evaporates and solid dispersion is formed within seconds, which may be fast enough to phase separation. Spray drying usually yields drugs in the amorphous state, but sometimes the drug may be partially crystallized during processing [57, 58].

Lyophilisation technique

Lyophilisation technique has been proposed as an alternative to solvent method of solid dispersion preparation. The difference is that the carrier and the drug are dissolved in a solvent and then, frozen in an atmosphere over, e.g. liquid nitrogen. This stage lasts a few minutes and is conducted in lyophilizer, which ensures that low pressure and sublimation temperature of –53°C are maintained. Sample introduced into the device sublimates to form a molecular dispersion, which is then placed in a vacuum desiccator over silica gel at room temperature for at least one day [50, 59]. An important advantage of lyophilisation is reduction in time of sample exposure to thermal stress during formation of solid dispersion and minimal risk of phase separation. A more promising drying method than classic lyophilisation is spray drying at temperature of freezing. The solution is sprayed into liquid nitrogen or cold, dry air, and then the frozen droplets are lyophilised. A large surface and direct contact with the refrigerant accelerate process of glass transition and reduce the risk of phase separation to a minimum [60].

Electro Spinning Method

Electro-spinning is a technique that enables production of long polymer fibres of 40–2000 nm in diameter in the presence of electric field. Formation of solid dispersion fibres occurs when the liquid, or molten polymer with the drug substance, is pressed through a one millimeter nozzle and injected toward a focusing screen. The charged fibers dry or solidify on /their way to collector. They may be directed or accelerated by electric forces. This method is limited to a few matrices because only a few high molecular weight materials are fibre forming materials [61].

Coating on sugar beads using fluidized bed-coating system

This method involves a fluidized bed-coating system, wherein a drug-carrier solution is sprayed onto the granular surface of excipients or sugar spheres to produce either granule ready for tableting or drug-coated pellets for encapsulation in one step. The method can be applied for both controlled- and immediate-release solid dispersions [62].

Supercritical Fluid Technology – SCF

Supercritical fluid (SCF) technology offers tremendous potential and the low operating conditions (temperature and pressure) make the method more attractive for pharmaceutical research. In the pharmaceutical field, the supercritical fluid technology was industrially applied in the early 1980's. A supercritical fluid exists as a single phase above its critical temperature and pressure [63]. In SCF method, the role of a carrier and a solvent for the drug is played most often by carbon dioxide. Use of carbon dioxide is determined by the physical parameters, i.e. low critical temperature (Tc = 31.1°C) and low critical pressure (Pc = 73.8 bar). This gas may be present in supercritical state, where temperature and pressure are greater than the pressure and temperature of its critical point. Apart from being nontoxic, non-flammable, and inexpensive, the low critical temperature of CO_2 makes it attractive for processing heat-labile molecules [64].

Characterization of solid dispersions

The crystallinity content in any powder solid dosage form, here in the solid dispersions can be determined quantitatively by X-ray powder diffraction technique [65, 66]. Interaction of solid dispersion with water at different temperatures and relative humidity can be determined by vapour sorption techniques like gravimetric vapour sorption analysis [67]. Other techniques such as differential scanning calorimetry, infrared spectroscopy, isothermal microcalorimetry, dissolution calorimetry and macroscopic techniques etc. can be employed for the characterization of various physical properties of solid dispersions.

III CONCLUSION

Solid dispersions are considered to be one of the very important tools since many years to promote the enhancement of aqueous solubility, dissolution profile and bio availability of poorly water soluble drugs. Even though many techniques are available for the preparation of solid dispersions, their commercial application is very limited. Many technologies have been evolved to overcome the practical applicability of methods of preparation of solid dispersions which have been discussed in this review. With solid dispersion technology there lies a great promise that accelerates the release profiles of poorly water soluble drugs.

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