

Solid Dispersion: Methods and Polymers to increase the solubility of poorly soluble drugs

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ABSTRACT

The solubility behaviour of drugs remains one of the most exigent aspects in formulation development. These days, the number of new chemical entities has dramatically increased having hiccups of poor solubility and poor permeability. Solid dispersion as a dosage form has been established a superior option for the drugs having poor aqueous solubility. Solid dispersions in water-soluble carriers have engrossed considerable interest as a means of improving the dissolution rate and bioavailability of hydrophobic drugs. Although solid dispersions have tremendous potential for improving drug solubility and only a few marketed products using this approach. There are various methods available to improve the solubility of the new drug in which solid dispersion emerged promising. A Solid dispersion generally composed of two components- the drug and the polymer matrix. Numerous methods are existing to prepare the solid dispersions such as melting method, solvent evaporation method, fusion method, kneading method, melting method, spray drying method, co-grinding method, lyophilization technique, hot melt extrusion, melt agglomeration, supercritical fluid (SCF) technology etc. A variety of hydrophilic carriers have been investigated for enhancement of dissolution characteristics and bioavailability of poorly aqueous-soluble drugs. In this review an endeavour is made to discuss about the comprehensive methods of preparation and numerous carriers are used for solid dispersions.

INTRODUCTION

Solubility is a significant physicochemical factor affecting absorption of drug and its therapeutic effectiveness. Formulation development would lead to be failure if drug having poor aqueous solubility. The low dissolution rate and low solubility of drug substances in water in aqueous G.I.T fluid frequently leads to inadequate bioavailability. The venture to improve the solubility and dissolution of hydrophobic drugs remain one of the trickiest tasks in drug development. Several methods have been introduced to triumph over this problem (Ford, 1986; Dressman *et al.*, 2000).

For enhancement of solubility and dissolution rate of poorly soluble drugs, abundant commercially viable methods are

available such as liquisolid, in which drug in solution state or dissolved drug is adsorbed over insoluble carriers (Nokhodchi *et al.*, 2005; Spireas *et al.*, 1992; Javadzadeh *et al.*, 2005). To improve wettability and solubility of various lipophilic substances surfactants can also be used in formulations (Bakatselou *et al.*, 1991). Micronization of drug is not ideal because micronized product has the propensity of agglomeration, which leads to reduced effective surface area for dissolution. But solid dispersion is the mainly promising method to formulators because of its simplicity of preparation, ease of optimization, and reproducibility (Chiou *et al.*, 1971; Goldberg *et al.*, 1966; Leuner *et al.*, 2000). The term 'solid dispersion' has been employed 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 (Noyes *et al.*, 1997; Nernst, 1994).

The mechanism by which the solubility and dissolution rate of the drug is augmented includes: the particle size of the drug is abridged to submicron size or to the molecular size in the case

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where solid solution is achieved. The particle size reduction usually enhances the rate of dissolution; the changed from crystalline to amorphous form, the high energetic state which is very soluble; finally the wettability of the drug particle is enhanced by the dissolution carrier. Regardless of these promising advantages, the application of solid dispersion in pharmaceutical industry has certain boundaries (Ford, 1986; Dressman *et al.*, 2000).

With the recent dawn of high throughput screening of potential therapeutic agents, the number of poorly soluble drug candidates has increased sharply and the formulation of poorly soluble compounds for oral delivery currently presents one of the most frequent and utmost challenges to formulation scientists in the pharmaceutical industry (Noyes *et al.*, 1997; Nernst, 1994). Only small amounts of solid dispersion products are commercially exist. This is due to their poor physical characteristic for dosage form formulation. The solid dispersions prepared by employing water soluble carrier are soft and tacky mass which is hard to handle, particularly in the capsule-filling and tablet making development e.g, pulverization, sieving and mixing.

Consideration of the modified Noyes-Whitney equation gives some hints as to how the dissolution rate of even very poorly soluble compounds might be improved to diminish the limitations to oral availability:

$$\frac{dC}{dt} = \frac{AD(C_s - C)}{h}$$

where dC/dt is the rate of dissolution, A is the surface area available for dissolution, D is the diffusion coefficient of the compound, C_s is the solubility of the compound in the dissolution medium, C is the concentration of drug in the medium at time t and h is the thickness of the diffusion boundary layer adjacent to the surface of the dissolving compound.

More particularly, Chiou and Riegelman, 1971 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', while Corrigan (1985) suggested the definition as being a 'product formed by converting a fluid drug-carrier combination to the solid state' (Corrigan, 1985). In practice, these dosage forms have been conventionally considered as being indistinguishable with systems whereby the *in vitro* release of the drug is enhanced compared to conventional dosage forms, with allied implications for *in vivo* release.

The main possibilities for improving dissolution according to this analysis are to increase the surface area available for dissolution by decreasing the particle size of the solid dispersion. However, the most attractive option for increasing the release rate is improvement of the solubility through formulation approaches like Polymorphs, Nanosuspensions, Pseudopolymorphs (including solvates), Use of cyclodextrines, Eutectic mixtures, Solid dispersions (non-molecular), Soluble prodrugs and salts (Leuner *et al.*, 2000).

Various formulation parameters that play a crucial role for successful formulation are aqueous solubility, stability at ambient temperature and humidity, photo stability, compatibility with solvents and excipients etc. Of these, solubility is the most important property for developing formulations. As per recent report, 46% of the total NDAs filed between 1995 to 2002 were BCS class IV, while only 9% were BCS class I drugs, revealing that a majority of approved new drugs were water insoluble (Kumar *et al.*, 2009).

Various hydrophilic carriers such as polyethylene glycol [PEG], polyvinylpyrrolidone [PVP], hydroxypropyl cellulose, hydroxypropylmethyl cellulose, gums, sugar, mannitol, urea, hydroxypropylmethyl cellulose phthalate, gelucires, eudragits (Singh *et al.*, 2011) and chitosan have been investigated for improvement of dissolution characteristics and bioavailability of poorly aqueous soluble drugs (Prajapati *et al.*, 2007). Hydrophilic swellable polymers *viz.*, sodium carboxymethyl cellulose, sodium starch glycolate and pregelatinized starch are also used (Modi *et al.*, 2006).

METHODS FOR PREPARING SOLID SOLUTIONS

Kneading Technique

In this method, carrier is permeated with water and transformed to paste. Drug is then added and kneaded for particular time. The kneaded mixture is then dried and passed through sieve if necessary.

Solvent evaporation method

In this method, both drug and carrier are dissolved in organic solvent. After entire dissolution, the solvent is evaporated. The solid mass is ground, sieved and dried. Ex. Solid dispersion of furosemide with eudragits was prepared by solvent evaporation method (Rasenack *et al.*, 2003).

Co-precipitation method

Required amount of drug is added to the solution of carrier. The system is kept under magnetic agitation and protected from the light. The formed precipitate is separated by vacuum filtration and dried at room temperature in order to avoid the loss of the structure water from the inclusion complex (Moyano *et al.*, 1997).

Melting method

Drug and carrier are mixed using mortar and pestle. To accomplish a homogenous dispersion the mixture is heated at or above the melting point of all the components. It is then cooled to acquire a congealed mass. It is crushed and sieved. Ex. albendazole and urea solid dispersion was prepared by this method (Kalaiselvan *et al.*, 2006).

Co-grinding method

Physical mixture of drug and carrier is mixed for some time employing a blender at a particular speed. The mixture is then charged into the chamber of a vibration ball mill steel balls are

added. The powder mixture is pulverized. Then the sample is collected and kept at room temperature in a screw capped glass vial until use. Ex. chlordiazepoxide and mannitol solid dispersion was prepared by this method (Nokhodchi *et al.*, 2007).

Gel entrapment technique

Hydroxyl propyl methyl cellulose is dissolved in organic solvent to form a clear and transparent gel. Then drug for example is dissolved in gel by sonication for few minutes. Organic solvent is evaporated under vacuum. Solid dispersions are reduced in size by mortar and sieved (Bhise *et al.*, 2008).

Spray-Drying Method

Drug is dissolved in suitable solvent and the required amount of carrier is dissolved in water. Solutions are then mixed by sonication or other suitable method to produce a clear solution, which is then spray dried using spray dryer (Bakatselou *et al.*, 1991).

Lyophilization Technique

Freeze-drying involves transfer of heat and mass to and from the product under preparation. This technique was proposed as an alternative method to solvent evaporation. 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 (Betageri *et al.*, 1995).

Electrospinning Method

The electrospinning technology used in the polymer industry combines solid solution/dispersion technology with nanotechnology. In this procedure, a liquid stream of a drug/polymer solution is subjected to a potential between 5 and 30 kV. When electrical forces prevail over the surface tension of the drug/polymer solution at the air interface, fibers of submicron diameters are produced. As the solvent evaporates, the formed fibers can be collected on a screen to give a nonwoven fabric, or they can be collected on a spinning mandrel (Deitzel *et al.*, 2001). This technique has tremendous potential for the preparation of nanofibres and controlling the release of biomedicine, as it is simplest and the cheapest this technique can be utilized for the preparation of solid dispersions in future (Zhang *et al.*, 2007).

Dropping method solution

The dropping method, developed by Ulrich *et al.* (1997) to facilitate the crystallization of different chemicals, is a new procedure for producing round particles from melted solid dispersions. This technique may overcome some of the difficulties inherent in the other methods. For laboratory-scale preparation, a solid dispersion of a melted drug-carrier mixture is pipette and then dropped onto a plate, where it solidifies into round particles. The use of carriers that solidify at room temperature may aid the dropping process. The dropping method not only simplifies the manufacturing process, but also gives a higher dissolution rate. It does not use organic solvents and, therefore, has none of the

problems associated with solvent evaporation (Bashiri *et al.*, 2003).

Melt Extrusion Method

Solid dispersion by this method is composed of active ingredient and carrier, and prepare by hot-stage extrusion using a co-rotating twin-screw extruder. The concentration of drug in the dispersions is always 40% (w/w). Melt extrusion technique is used in the preparation of diverse dosage forms in the pharmaceutical industry e.g. sustained-release pellets (Karanth *et al.*, 2006).

Melt Agglomeration Process

This technique has been used to prepare Solid Dispersion where the binder acts as a carrier. SD(s) are prepared either by heating the binder, drug and excipient to a temperature above the melting point of the binder or by spraying a dispersion of drug in molten binder on the heated excipient by using a high shear mixer (Tsinontides *et al.*, 2004). A rotary processor has been shown to be alternative equipment for melt agglomeration because of easier control of the temperature and because higher binder content can be incorporated in the agglomerates (Vilhelmsen *et al.*, 2005).

CARRIERS

Polyethylene glycol (PEG)

Polyethylene glycols (PEG) are polymers of ethylene oxide, with a molecular weight (MW) usually falling in the range 200-300000. For the manufacture of solid dispersions and solutions, PEGs with molecular weights of 1500-20 000 are usually employed. As the MW rises, so does the viscosity of the PEG. At MW of up to 600, PEGs are fluid, in the range 800 -1500 they have a consistency that is best described as vaseline-like, from 2000 to 6000 they are waxy and those with MW of 20 000 and above form hard, brittle crystals at room temperature. Their solubility in water is generally good, but reduces with MW. A meticulous advantage of PEGs for the solid dispersions is that they have good solubility in numerous organic solvents. The melting point of the PEGs of interest lies under 65 °C in every case (e.g. the m.p. of PEG 1000 is 30-40°C, the m.p. of PEG 4000 is 50-58°C and the m.p. of PEG 20 000 is 60-63°C) (Price JC *et al.*, 1994). Additional attractive features of the PEGs include their ability to solubilise some compounds (Betageri *et al.*, 1995) and also to improve compound wettability. Even the dissolution rate of a relatively soluble drug like aspirin can be improved by formulating it as a solid dispersion in PEG 6000 (Asker *et al.*, 1975).

Problems with PEGs

In general, there are few toxicity concerns associated with the PEGs and they are approved for many purposes as excipients. The low molecular weights PEGs do, however, tend to show slightly greater toxicity than those of higher molecular weight (Price *et al.*, 1994). In addition, a vast number of drugs are attuned with the PEGs. A hardly any cases have been observed in

which the PEG confirmed to have stability problems during manufacture by the hot melt method.

Polyvinylpyrrolidone (PVP)

Polymerization of vinylpyrrolidone leads to polyvinylpyrrolidone (PVP) of molecular weights ranging from 2500 to 3000 000. These can be classified according to the K value, which is calculated using Fikentscher's equation (Walking *et al.*, 1994). The temperature of a given PVP is dependent not only on its MW but also on the moisture content. In general, the glass transition temperature (T_g) is high; for example, PVP K25 has a T_g of 1558C (Buèhler *et al.*, 1993). For this reason PVPs have only restricted application for the preparation of solid dispersions by the hot melt method. Due to their excellent solubility in an ample variety of organic solvents, they are mostly suitable for the preparation of solid dispersions by the solvent method. Improved wetting and thereby an improved dissolution rate from a solid dispersion in PVP has been demonstrated for fufenamic acid (Itai *et al.*, 1985). The aqueous solubility of the PVPs becomes poorer with increasing chain length and a further disadvantage of the high MW PVPs is their much higher viscosity at a given concentration (Walking *et al.*, 1994). Similarly, the slower dissolution was observed of indomethacin from PVP K90 compared to PVP K12 was attributed to the higher viscosity generated by PVP K90 in the diffusion boundary layer adjacent to the dissolving surface of the dispersion (Hilton *et al.*, 1986).

Cellulose Derivatives

1. Hydroxypropylmethylcellulose (HPMC)

HPMCs are mixed ethers of cellulose, in which 16.5-30% of the hydroxyl groups are methylated and 4-32% are derivatized with hydroxypropyl groups. For example, Type 2910 has an average methoxy content of 29% and an hydroxypropyl content of 10%. The molecular weight of the HPMCs ranges from about 10 000 to 1 500 000 and they are soluble in water and mixtures of ethanol with dichloromethane and methanol with dichloromethane (Hilton *et al.*, 1986). Other drugs which exhibit faster release from solid dispersion in HPMC include the poorly soluble weak acids nilvadipine (Hilton *et al.*, 1986; Harwood *et al.*, 1994) and benidipine (Kohri *et al.*, 1999).

2. Hydroxypropylcellulose (HPC)

Hydroxypropylcellulose (HPC) exhibits good solubility in a range of solvents, including water (up till 40°C), ethanol, methanol and chloroform. The average MW of the HPCs ranges from 37 000 (Type SSL) to 1 150 000 (Type H) (Okimoto *et al.*, 1997; Suzuki *et al.*, 1996). Yuasa *et al.* carried out extensive studies of the influence of the chain length and proportion of HPC in the solid dispersion on the release behaviour of flurbiprofen. The release rate enhanced as the ratio of HPC was amplified and when lower MW HPCs were used as the carrier.

3. Carboxymethylethylcellulose (CMEC)

CMEC also belongs to the cellulose ethers, but unlike

many of the others it is resistant to dissolution under gastric (acidic) conditions. It dissolves readily at pH values above 5-6, with lowest dissolution pH being dependent on the grade of the CMEC. CMECs also dissolve readily in acetone, isopropanol 70%, ethanol 60% and 1:1 mixtures of dichloromethane and ethanol. Amorphous solid dispersions of nifedipine and spironolactone show enormous increases in the dissolution rate of the drug at pH values of 6.8 (Okimoto *et al.*, 1997).

4. Hydroxypropylmethylcellulose phthalate (HPMCP)

HPMCPs are cellulose esters which are often used as enteric coatings. Depending on the grade, they dissolve first at pH 5 (HP 50) or pH 5.5 (HP 55). They are having a type-dependent solubility in organic solvents. Their MWs ranges from 20,000 to 2 000,000 (Itai *et al.*, 1985). The dissolution rate of griseofulvin at pH 6.8 could be greatly enhanced by incorporating it in a coevaporate of HPMCP (Hilton *et al.*, 1986). Using a spray-drying technique to form a solid dispersion in HP 55, the dissolution rate of the anti-fungal drug MFB-1041 could be increased by a factor of 12.5 as compared to the best possible dissolution achievable by micronizing the drug (Harwood *et al.*, 1994).

Polyacrylates and polymethacrylates

Polyacrylates and polymethacrylates are glassy substances that are produced by the polymerization of acrylic and methacrylic acid, and derivatives of these polymers such as esters amides and nitriles. In pharmaceuticals they are mainly used as coatings to change the release of the drug from the dosage form. Commonly they are referred to by the trade name Eudragit drug (Harwood *et al.*, 1994). Among the Eudragits, Eudragit E is often used to improve the release rate since it is soluble in buffer solutions at pH values up to 5 and swells at higher pHs, while Eudragit L can be used when it is desirable to avoid release in the stomach. When benidipine was formulated as a coevaporate with Eudragit E, the rate of dissolution was much higher than from the pure drug powder (Hasegawa *et al.*, 1985; Asker *et al.*, 1975). On the other hand, Eudragit L has been successfully used to increase the dissolution of griseofulvin and spironolactone at a pH value of 6.8. (Okimoto *et al.*, 1997).

Urea

Urea is the end product of human protein metabolism, has a light diuretic effect and is regarded as non-toxic. Its solubility in water is greater than 1 and it also reveals good solubility in several common organic solvents. In one of the first bioavailability studies of solid dispersions, it was shown that sulphathiazole was better absorbed in rabbits when given as a eutectic with urea (Okimoto *et al.*, 1997).

In the case of ursodeoxycholic acid the release rate from urea dispersions prepared by the hot melt method was faster than from other carriers studied, including PEG 6000 (Hilton *et al.*, 1986). A two-fold increase in the dissolution rate of phenytoin has also been achieved with urea; however, in this case PEG 6000 was far more efficient (Kohri *et al.*, 1999).

Sugar, polyols and their polymers

Although sugars and related compounds are highly water soluble and have few, if any, toxicity issues, they are less suitable than other carriers for the manufacture of solid dispersions. The melting point of most sugars is high, making preparation by the hot melt method problematic, and their solubility in most organic solvents is poor, making it difficult to prepare co-evaporates. Even with these drawbacks, several attempts have been reported to prepare solid dispersions using sugars and their derivatives. Mannitol, which has a melting point of 165-168 °C and decomposes only above 250°C, can be employed in some cases to prepare dispersions by the hot melt method (Kai *et al.*, 1996; Shukla, 1994).

Organic acids and their derivatives

Organic acids such as succinic acid and citric acid have also been used as carriers in solid dispersions, originally to enhance the release rate of griseofulvin method (Kai *et al.*, 1996; Shukla, 1994).

Other carriers

Many other substances have been tested as carriers for solid dispersions. A hydrolysis product of collagen, Gelita Collagel, was reported to improve the release rate of oxazepam by a factor of six when prepared as a solid dispersion by spray drying (Hasegawa *et al.*, 1985; Lee *et al.*, 1994).

Characterization of solid dispersions

Methods for the characterization of solid dispersions

- Dissolution testing
- Thermoanalytical methods: differential thermoanalysis and hot stage microscopy.
- X-Ray diffraction (XRD) and Differential scanning calorimetry (DSC)
- Spectroscopic methods, e.g. IR spectroscopy
- Microscopic methods including polarization microscopy and scanning electron microscopy

CONCLUSION

Knowledge with solid dispersions over the last few decades indicates that this is a very lucrative approach to improving the release rate and oral bioavailability of hydrophobic drugs. Two trends powerfully favour an increasing role for solid dispersions in pharmaceutical development: the growing number of drug candidates which are poorly soluble, and the considerable improvements in the manufacturing techniques for solid dispersions that have been made in the last few years. Another advantage of solid dispersions over other approaches is that many of the carriers that can be applied are already extensively used in the pharmaceutical industry as excipients, no toxicity studies are required. This article provided the plenty of information to the use of solid dispersions for the development of the release rate and oral bioavailability of poorly water soluble drugs, by careful

choice of the carrier it is also feasible to delay or slow down the release pattern of a drug by formulating it into solid dispersion.

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