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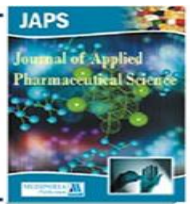

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Enhancement of Oral Bioavailability and Solid Dispersion: A Review

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ABSTRACT

Improving oral bioavailability of drugs those given as solid dosage forms remains a challenge for the formulation scientists due to solubility problems. Most of the newly invented chemical entities are poorly water soluble. As a result formulating them as oral solid dosage forms is a hurdle to the specialists. Many techniques have been exercised to improve oral bioavailability of drugs. Among several methods, solid dispersion has attracted attention of the researchers for previous 50 years. Different formulation strategies have been taken to prepare solid dispersions. It is evident that solid dispersions improve solubility of drug particles thus enhancing dissolution characteristics of drugs they increase the oral bioavailability. This review paper will focus on different aspects of solid dispersion preparation; their advantages, major challenges and preparation methods.

Key words: Bioavailability; Solubility; Hot melt extrusion; Carrier; Biopharmaceutical classification; Hot-spin-melting.

INTRODUCTION

Clinicians have generally agreed that the best way to accomplish rapid onset of drug action is to create an instant therapeutic blood level by administering the drug IV (MacGregor and Graziani, 1997). But rapid onset of action is not required always. It is required in critically ill and hospitalized patients. In general the oral route of drug administration is the most common and preferred method of delivery (Dhirendra et al., 2009) as it is the simplest and easiest way of administering drugs (Vasconcelos et al., 2007). The rout offers ease of drug administration in a convenient manner and patients are more familiar with this rout. So, patient compliance and thus drug treatment is typically more effective with orally given medications when compared with other routes of administration, for example, parenteral (Dhirendra et al., 2009). There are strong evidences that oral administration produces equally good clinical results, has fewer complications, is less costly and causes less patient inconvenience (MacGregor and Graziani, 1997). Most of the new chemical entities (NCE) under development now-a-days are intended to be used as a solid dosage form that originates an effective and reproducible *in vivo* plasma concentration after oral administration due to many advantageous features of this rout like, greater stability, smaller bulk, accurate dosage and easy production (Vasconcelos et al., 2007). But the fact is most NCEs are poorly water soluble drugs, not well-absorbed after oral administration and the oral delivery of such drugs is frequently associated with low bioavailability, high intra- and inter-subject variability, and a lack of dose proportionality (Tang et al., 2007). It has been estimated that 40% of new chemical entities currently being discovered are poorly water-soluble (Lipinski, 2001). To overcome the problems associated with oral absorption and bioavailability issue, various strategies have been utilized including prodrug formation (Murtha and Ando, 1994) complexation (Ghorab

and Adeyeye, 2001), microcapsulation (Adeyeye and Price, 1994), the use of surfactants, lipids, permeation enhancers, micronization, salt formation, cyclodextrines, nanoparticles, solid dispersions, self emulsifying drug delivery system (Shakhtshneider et al., 1996; Craig, 2002; Gao and Morozowich, 2006; Tang et al., 2007) etc. However ahead of all, solid dispersion is the most promising method to the scientists due to the ease of preparation, ease of optimization and reproducibility of the manufacturing method (Chiou and Reigelman, 1971; Ford, 1986; Law et al., 1992; Leuner and Dressman, 2000; Uddin et al., 2010).

SOLID DISPERSION: DEFINITION

In 1961, Sekiguchi and Obi first proposed the utilization of solid dispersions to increase the dissolution and oral absorption of poorly water-soluble drugs. They proposed the formation of a eutectic mixture of a poorly water-soluble drug with a physiologically inert, easily soluble carrier (Chiou and Riegelman, 1969). In 1971 Chiou and Riegelman defined solid dispersion 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" (Chiou and Riegelman, 1971). The solid dispersions may also be called solid-state dispersions, as first used by Mayersohn and Gibaldi (1966). Corrigan defined the term as "product formed by converting a fluid drug-carrier combination to the solid state" (Corrigan 1985). In a recent review work by Dhirendra et al. adopted the definition given by Chiou and Riegelman "a group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug. The matrix can be either crystalline or amorphous. The drug can be dispersed molecularly, in amorphous particles (clusters) or in crystalline particles" (Dhirendra et al., 2009). But if the drug is converted to amorphous form and forms one phase system with polymer, it can be classified as a solid solution, whereas if the drug exists as microcrystalline dispersion, i.e., forms two-phase system, it is generally referred to as a solid dispersion (Goldberg et al., 1965; Sekiguchi and Obi 1961; Chokshi et al., 2007).

IDEAL CANDIDATES FOR SOLID DISPERSION

Much of the research that has been reported on solid dispersion technologies involves drugs that are poorly water-soluble and highly permeable to biological membranes as with these drugs dissolution is the rate limiting step to absorption. Hence, the hypothesis has been that the rate of absorption *in vivo* will be concurrently accelerated with an increase in the rate of drug dissolution (Dhirendra et al., 2009). In the Biopharmaceutical Classification System (BCS) Class II drugs are those with low aqueous solubility and high membrane permeability (Amidon et al., 1995) and therefore, solid dispersion technologies are particularly promising for improving 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). Table 2 represents some BCS Class II drugs on the WHO model list of Essential Medicines. The table is adopted from Lindenberg et al., 2004, only for the BCS Class II drugs.

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

Table 2. Some BCS class II drugs on the WHO model list of Essential Medicines.

Drug	Used as
Classification of orally administered drugs on the WHO model list of Essential Medicines according to the BCS: Drugs with reliable solubility and permeability	
Carbamazepin	Antiepileptic
Dapsone	Antirheumatic/leprosy
Griseofulvin	Antifungal
Ibuprofen	Pain relief
Nifedipine*	Ca-channel blocker
Nitrofurantoin	Antibacterial
Phenytoin	Antiepileptic
Sulfamethoxazole	Antibiotic
Trimethoprim	Antibiotic
Valproic acid	Antiepileptic
Classification of orally administered drugs on the WHO model list of Essential Medicines according to the BCS: Drugs for which complete solubility and/or permeability data are lacking	
Iopanoic acid	Contrast medium
Nalidixic acid	Antibacterial agent
Nevirapine	Antiviral
Praziquantel *	Antihelmentic
Rifampicin*	Antituberculotic
Classification of orally administered drugs on the WHO model list of Essential Medicines according to the BCS: drugs with inconclusive data	
Albendazole*#	Antiparasitic
Amitriptyline*¶	Antidepressive
Artemether + Lumefantrine*#	Antimalarial agents
Chlorpromazine*#	Antidepressive
Ciprofloxacin*#	Antibiotic
Clofazimine#	Antibacterial agent
Diloxanide**#	Antiprotozoal agent
Efavirenz#	Antiviral
Folic acid#	Vitamin
Glibenclamide#	Antidiabetic
Haloperidol*#	Neuroleptic
Ivermectin#	Anthelmentic
Lopinavir*#	Antiviral
Mebendazole#	Antihelmentic
Mefloquine#	Antimalarial
Niclosamide#	Anthelmentic
Pyrantel#	Anthelmentic
Pyrimethamine#	Toxoplasmose
Retinol*#	Vitamin
Spironolactone*#	Diuretic
Sulfadiazine#	Antibacterial agent
Sulfasalazine#	Colitis ulcerosa/morbus crohn
Triclabendazole#	Anthelmentic
Verapamil hydrochloride*¶	Ca-channel blocker
Warfarin Sodium¶	Anticoagulant

* First pass effect; ** Degradation in the GI-Tract; ¶also considered as Class I drug; # also considered as Class IV drug.

SOLID DISPERSION: CLASSIFICATION

Chiou and Riegelman (1971) in their review article classified solid dispersions into six categories on the basis of their major fast-release mechanisms. This classification was adopted by

Dhirendra et al. (2009) based on the molecular arrangement and they tabulated six different types of solid dispersions as shown in the following table (Table 3).

Table 3. Types of solid dispersion as mentioned by Dhirendra et al. (2009).

Solid dispersion type		Matrix*	Drug**	Remarks	No. of phases
I	Eutectics	C	C	The first type of solid dispersion prepared	2
II	Amorphous precipitations in crystalline matrix	C	A	Rarely encountered	2
III	Solid solutions				
	Continuous solid solutions	C	M	Miscible at all composition, never prepared	1
	Discontinuous solid solutions	C	M	Partially miscible, 2 phases even though drug is molecularly dispersed.	2
	Substitutional solid solutions	C	M	Molecular diameter of drug (solute) differs less than 15% from the matrix (solvent) diameter. In that case the drug and matrix are substitutional. Can be continuous or discontinuous. When discontinuous: 2 phases even though drug is molecularly dispersed.	1 or 2
	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
IV	Glass suspension	A	C	Particle size of dispersed phase dependent on cooling/evaporation rate. Obtained after crystallization of drug in amorphous matrix	2
V	Glass suspension	A	A	Particle size of dispersed phase dependent on cooling/evaporation rate many solid dispersions are of this type	2
VI	Glass solution	A	M	Requires miscibility OR solid solubility, complex formation or upon fast cooling OR evaporation during preparation, many (recent) examples especially with PVP	1

* 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

According to the classification of Chiou and Riegelman (1971) and Dhirendra et al. (2009) solid solutions like continuous solid solutions are classified under the term solid dispersion. But as mentioned earlier if the drug is converted to amorphous form and forms one phase system with polymer (as in continuous solid solutions) , it can be classified as a solid solution not as solid dispersion. Vasconcelo et al. (2007) in their review article classified solid dispersions in three generations; i) first generation, ii) second generation and iii) third generation solid dispersions.

The first generation solid dispersions includes eutectic mixtures of sulphathiazole (Sekiguchi and Obi, 1961), fused conglomerates of Chloramphenicol and urea (Sekiguchi and Obi, 1964), as prepared by Levy (1963) and Kanig (1964) using mannitol as carrier and using chloramphenicol-urea system (Goldberg et al., 1966a). All these solid dispersions were prepared using crystalline carriers like urea and sugars. But 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 (Vasconcelos et al., 2007).

Second generation of solid dispersion appeared as it was observed that solid dispersions, where the drug was maintained in the crystalline state, might not be as effective as the amorphous, because the former were more thermodynamically strong (Vippagunta et al., 2007; Simonelli 1969; Urbanetz, 2006). In second generation solid dispersions drugs are molecularly dispersed in an irregular form within an amorphous carrier which is usually polymers (Vilhelmsen et al., 2005). The most common solid dispersions do not use crystalline carriers but amorphous one. According to molecular interaction of drug and carriers amorphous solid dispersions can be of three types; solid solutions (van Drooge et al., 2006a; Leuner and Dressman 2000; Van den Mooter et al., 2006), solid suspensions (van Drooge et al., 2006a; Chiou and Riegelman, 1971; Goldberg et al., 1966b) or a mixture of both (van Drooge et al., 2006a; van Drooge et al., 2006b). Second generation solid dispersions use fully synthetic polymers and natural product based polymers as carriers. Different kinds of polymers used in second generation solid dispersions are shown in Table 4.

Table 4. Different kinds of polymers used in second generation solid dispersions.

Polymer type	Polymer	Reference(s)
Fully synthetic polymers	Polyvinylpyrrolidone (povidone)	van Drooge et al., 2006a; Simonelli et al., 1969; Karavas et al., 2006; van Drooge et al., 2006b; Pokharkar et al., 2006; Hasegawa et al., 2005; Lloyd et al., 1999; Yoshihashi et al., 2006; Chokshi et al., 2007; Sun et al., 2008; Ito et al., 2010; Kubo et al., 2011; Kaewnopparat et al., 2009; Bikiaris et al., 2005; Shinde et al., 2008
	Polyethylene glycols	Prabhu et al., 2005; Urbanetz, 2006; Guyot et al., 1995; Yao 2005; Chiou and Riegelman 1970; Newa et al., 2008a; Yao et al., 2011; Bikiaris et al., 2005; Khoo et al., 2000; Dhumal et al., 2009; Newa et al., 2008b; Preetham and Satish, 2011; Shinde et al., 2008; Corrigan, 1986
	Polymethacrylates	Ceballos et al., 2005; Huang et al., 2006; Nollenberger et al., 2009; Goddeeris et al., 2008; Wiranidchapong et al., 2008; Sriamornsak et al., 2011; Sahoo et al., 2009
Natural product based polymers (cellulose derivatives, starch derivatives)	Hydroxypropyl-methylcellulose	Won et al., 2005; Konno and Taylor, 2006; Ohara et al., 2005; Engers et al., 2010; Dobaria et al., 2009; Papageorgiou et al., 2008
	Ethylcellulose	Desai et al., 2006; Ohara et al., 2005; Verreck et al., 2006; Ying et al., 2011
	Hydroxypropyl-cellulose	Tanaka et al., 2005; Tanaka et al., 2006; Tiwari et al., 2008; Park et al., 2009
	Cyclodextrines	Garcia-Zubiri et al., 2006; Rodier et al., 2005; Rahman et al., 2010; Srinarong et al., 2009; Preetham and Satish, 2011

Third generation solid dispersions are those which are prepared by using carriers having surface activity or self emulsifying properties. These solid dispersions contain a surfactant carrier, mixtures of amorphous polymers and surfactants as carriers. Examples of carriers in third generation solid dispersions include inulin (van Drooge et al., 2006a), inutec SP1 (Van den Mooter et al., 2006), compritol 888 ATO (Li et al., 2006), gelucire

44/14 (Karata et al., 2005; Chauhan et al., 2005; Yüksel et al., 2003), poloxamer 188 (Chokshi et al., 2007; Tran et al., 2011), poloxamer 407 (Majerik et al., 2007; Newa et al., 2008c), PEG and polysorbate 80 mixture (Dannenfelser et al., 2004), HPMC-poloxomer and HPMC-polyoxyethylene hydrogenated castor oil (Won et al., 2005) polyethylene glycol-HPMC (Mesnukul et al., 2008; Janssens et al., 2008). 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 (Vasconcelos et al., 2007).

Leuner and Dressman (2000) reviewed some carriers (polyethylene glycol, polyvinylpyrrolidone, Polyvinylalcohol, crospovidone, polvinylpyrrolidone-polyvinylacetate copolymer, hydroxypropylmethylcellulose, hydroxypropylcellulose, carboxymethylethylcellulose, hydroxypropylmethylcellulose phthalate, polyacrylates and polymethacrylates, urea, sugar, polyols and their polymers like mannitol, sorbitol, chitosan, Emulsifers including sodium lauryl sulphate, Tween 80, alkali dodecylsulphate surfactants, bile salts and their derivatives, cholesterol and various cholesterol esters, organic acids and their derivatives , a hydrolysis product of collagen, Gelita Collagel, pentaerythritol and phospholipids) used in the preparation of solid dispersions.

ADVANTAGES OF SOLID DISPERSIONS

Vasconcelos et al. (2007) identified four advantageous features of producing solid dispersions. The features are summarized below:

1. Preparation of solid dispersions results in particles with reduced particle size and thus the surface area is improved and increased dissolution rate is attained. The ultimate result is improved bioavailability.

2. Wettability is improved during solid dispersion production. Improved wettability results in increased solubility. Here the carriers play the major role to improve the wettability of the particles.

3. Particles in solid dispersions have been found to have a higher degree of porosity. The increased porosity of solid dispersion particles accelerates the drug release profile. Increased porosity also depends on the carrier properties.

4. In solid dispersions drugs are presented as supersaturated solutions which are considered to be metastable polymorphic form. Thus presenting drugs in amorphous form increase the solubility of the particles.

DISADVANTAGES OF SOLID DISPERSIONS

Serajuddin (1999) identified some 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. Solid dispersions are not broadly used in commercial products due to mainly the problem of crystallization of the components from amorphous state during processing (mechanical stress) or storage (temperature and humidity stress) (Pokharkar et al., 2006; Chauhan et al., 2005; Vasanthavada et al., 2004; Vasconcelos et al., 2007). Moisture may increase drug mobility and promote drug crystallization and thus may hamper storage stability of amorphous pharmaceuticals (Johari et al., 2005; Vasanthavada et al., 2004). Phase separation, crystal growth or conversion of a product to more stable structure from metastable crystalline form during storage are also considered to be major hurdles to commercialize solid dispersions as they result in decreased solubility and thus dissolution rate (Wang et al., 2005; Vasconcelos et al., 2007).

MANUFACTURING PROCESSES FOR PREPARATION OF SOLID DISPERSIONS

There are two major methods of preparing solid dispersions; melting method and solvent evaporation method (Dhirendra et al., 2009; Vasconcelos et al., 2007). Fusion method is synonymous to melt method (Dhirendra et al., 2009).

Melting method

Melting method was first used to prepare simple eutectic mixtures by Sekiguchi and Obi (Vasconcelos et al., 2007; Leuner and Dressman, 2000). Leuner and Dressman (2000) used to describe melting method as hot melt method. This method consists of melting the drug within the carrier followed by cooling and pulverization of the obtained product. The process has got some limitations like, use of high temperature and chance of degradation of drug during melting (Serajuddin 1999), incomplete miscibility between drug and carrier (Taylor and Zografi, 1997). To avoid these limitations several modifications were introduced to the original process; i.e. hot stage extrusion (Henrist et al., 1999; Verreck et al., 2005), Meltrex® (Roth et al., 2009; Breitenbach and Lewis, 2003), melt agglomeration (Johansen et al., 1999; Gupta et al., 2002; Seo et al., 2003), injection molding (Wacker et al., 1991), hot-spin-melting (Dittgen et al., 1995a; 1995b; 1995c). Though hot melt extrusion was a common processing method in polymer industry it was first adapted for the pharmaceutical purposes by Speiser (El-Egakey et al., 1971) and Hüttenrach (Leuner and Dressman 2000).

Solvent evaporation method

Solvent evaporation method is a simple way to produce solid dispersions where the drug and carrier is solubilized in a volatile solvent. The solvent is later evaporated. Tachibani and Nakumara (1965) 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. The method was then taken up by Mayersohn and Gibaldi (1966). With the discovery of the solvent method, many of the problems associated with the melting method were solved and for many years the solvent method was the method of choice for polymer-based systems. With time, however, the ecological and subsequent economic problems associated with the use of organic polymers began to make solvent-based methods more and more problematic. For these reasons, hot melt extrusion is the current method of choice for the manufacture of solid dispersions (Leuner and Dressman 2000).

CONCLUSION

Due to the advantageous features of solid dispersions formulation scientists consider it as one of the most potential method of improving oral bioavailability. But changes in crystal behavior of drug and/or carrier particles during processing and storage limits the method to be commercially applicable. Manufacturing of solid dispersions requires a perfect combination of drug to carrier(s). Carrier molecules play the most important role in enhancing solubility of the resultant dispersion and hence improvement in oral bioavailability. Whatever this technology is also highly potential to formulate controlled release dosage forms as the carriers may enhance or delay drug release.

Conflict of Interest: Nadia Saffoon is a Product Executive in the Medical Services Department of Ziska Pharmaceuticals Ltd. But she declares no conflict of interest regarding the manuscript. The other authors declare no conflict of interest.

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