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**Review Article**

# SOLUBILITY ENHANCEMENT OF POORLY WATER SOLUBLE DRUGS

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## ABSTRACT

Aqueous solubility is a limiting factor in the oral bioavailability of a certain class of poorly water soluble drugs. A consequence of low aqueous solubility is a slow dissolution rate. For the drugs with low aqueous solubility and high permeability the dissolution rate will be the rate limiting step for absorption. The most successful techniques that are employed for dissolution enhancement are micronization, formulation of amorphous systems and cyclodextrins containing dosage forms. This combined approaches to improve the dissolution of some poorly soluble drugs. Micronization increases the dissolution rate of drugs through increased surface area. The high surface area of drug micro/nano particles renders them thermodynamically unstable, promoting agglomeration and crystal growth. Microparticles of the poorly water soluble drugs were produced by the supercritical antisolvent method and simultaneously mixed with pharmaceutical excipients in a single step to prevent the drug agglomeration of drug particles. In the third approach cyclodextrins (CDs) were used as pharmaceutical solubilizers and inclusion complexes of drugs with β-CD.

**Key words**: micronization, supercritical antisolvent, cyclodextrins

## INTRODUCTION

Poor aqueous solubility of drugs is an industry wide issue for pharmaceutical scientists. Because of their low aqueous solubility, up to 40% of new chemical entities fail to reach market despite exhibiting potential pharmacodynamic activities (Lipinski 2005). In addition, up to 50% of orally administered drugs suffer from formulation problems related to their high lipophilicity (Gursoy and Benita 2004). Poorly aqueous soluble drugs are associated with slow drug absorption leading eventually to inadequate and variable bioavailability (Amidon *et al.,* 1995; Leuner and Dressman, 2000). Oral absorption of a drug can be influenced by variety of factors, such as the physicochemical properties (e.g., pKa, solubility, stability, diffusivity, lipophilicity, polar-nonpolar surface area, presence of hydrogen bond functionalities, particle size and crystal form), physiological conditions (e.g., gastrointestinal pH, blood flow, gastric emptying, small intestinal transit time, colonic transit time and absorption mechanisms) and type of dosage form (e.g., tablet, capsule, solution, suspension and emulsion). Despite this complexity, the work revealed that permeability of drug through the gastro-intestinal (GI) membrane and solubility/ dissolution of drug dose in the GI environment are the fundamental events in successful drug absorption (Dahan *et al.,* 2009). The Biopharmaceutics Classification System (BCS) classifies drugs into four categories (Table I) based on their solubility and permeability characteristics. According to BCS, the oral bioavailability of class-II (poorly soluble and highly permeable) drugs is limited by their solubility and dissolution rate (Yu *et al.,* 2002).

Table I. Biopharmaceutics classification system

| | |
|---|---|
| Class-I<br>High Solubility,<br>High Permeability | Class-II<br>Low Solubility,<br>High Permeability |
| Class-III<br>High Solubility,<br>Low Permeability | Class-IV<br>Low Solubility,<br>Low Permeability |

If the ratio of the drug dose to the lowest drug saturation solubility in the pH range of 1-8 is greater than 250 then the drug is

called poorly soluble. So regardless of other factors, it is reasonable to conclude that a compound must be in solution form or solubilized in the GI tract to diffuse into and across the enterocytes lining the intestinal lumen for absorption (Gullapalli, 2001). The complete oral absorption of a drug depends on the events depicted in Equation 1, their importance relative to one another and the rate at which they occur (Dressman and Reppas, 2000). Drug release (dissolution) and absorption must occur within the available transit time i.e., the time the drug spends in GI tract and at the site of absorption. The dissolution rate of the drug is given by the Noyes-Whitney equation.

$$\text{Dissolution rate} = \frac{dX}{dt} = \frac{A.D}{h}\frac{[Cs - Xd]}{V}$$

Where *A* is the surface area of the drug; *D* is the diffusion coefficient of the drug; *h* is the effective boundary layer thickness; *C*s is the saturation concentration of the drug under the local GI conditions; *V* is the volume of the fluid available to dissolve the drug, and *Xd* is the amount of drug already dissolved.

The diffusion coefficient (D) and diffusion layer thickness (h) are less suitable targets for dissolution rate enhancement/ bioavailability optimization. *D* depends on the molecular weight of the drug and the viscosity of the gastro intestinal fluids, which varies in the fed and fasted state and is subject to large intra- and inter-subject variability. *h* also largely depends on the hydrodynamics during GI transit. Therefore, based on the equation 1, the possibilities for increasing the dissolution/ bioavailability are to increase the effective surface area or to improve the apparent solubility of the drug. Different approaches to enhance the dissolution rate of poorly soluble drugs include, but are not limited to, particle size reduction (Rasenack and Mueller, 2002; Jounela *et al.,* 1985; Liversidge and Cundy, 1995; Vogt *et al.,* 2008), inclusion complexation with cyclodextrins (Brewster, *et al.,* 1992; Badr-Eldin, *et al.,* 2008; Sathigari *et al.,* 2009),solid dispersion (Joshi *et al.,* 2004; Dannenfelser, *et al.,* 2004; Kennedy *et al.,* 2008), salt formation (Han, *et al.,* 2007; O'Connor and Corrigan, 2001), use of surfactants (Balakrishnan *et al.,* 2004; Chiou, *et al.,* 1976), cosolvency (Kawakami *et al.,* 2004; Viernstein *et al.,* 2003), and various particle engineering techniques (Blagden, *et al.,* 2007; Jung and Perrut, 2001; Loth and Hemgesberg, 1986). Among, the different approaches, they are the most successful technologies in terms of the number of commercial products which are on the market (Tables II, III and IV).

## Micro/Nano particle production

This is one of the most efficient and reliable methods used commercially to improve the bioavailability of poorly soluble drugs that is limited by poor dissolution rates (Jonghwi, 2003). Improvement in bioavailability after micronization of drugs has been well documented for numerous drugs (Farinha, *et al.,* 2000). Micronization increases the dissolution rate of drugs through increased surface area (Barrett, *et al.,* 2008). Reduction of the particle size to micron or nano size can be achieved by precipitation from a solution (built-up) or milling (sized–down). Milling is a well established technique which is relatively cheap, fast and is easy to scale-up, but it has several disadvantages (Wong, *et al.,* 2006). This method has limited opportunity to control the final particle size, shape, morphology, surface properties and electrostatic charge and it is difficult to reduce the particle size below 1 μm because of the cohesiveness of the particles. In addition, milling is a high energy process which causes disruptions in the drugs crystal lattice, resulting in the presence of disordered or amorphous regions in the final product (Saleki-Gerhardt, *et al.,* 1996). Wet milling techniques (bead milling and high pressure homogenization) can produce submicron particles without any concern for particle cohesiveness. However, these techniques often require a long time, introduce impurities, can also cause disruptions in the drug crystal lattice, and limits flexibility in controlling particle morphology. These methods also require further pharmaceutical operations such as lyophilization or spray drying to produce solids for use in oral solid dosage forms. Supercritical fluids are involved in numerous industrial processes and offer considerable advantages as solvents or anti solvents for crystallization and precipitation processes (Matteucci, 2006).

Table II. List of nano/ micro particle based drugs that are commercialized

| Description | Drug | Technology | Brand name | Company |
|---|---|---|---|---|
| Downsizing | | | | |
| 1.Milling | Aprepitant | NanoCrystal (Elan) | Emend® | Merck |
| | Sirolimus | NanoCrystal (Elan) | Rapamune® | Pfizer |
| | Fenofibrate | Nanocrystal (Elan) | Tricor® | Abbott |
| | Paliperidone Palmitate | Nanocrystal (Elan) | Invege Sustenna® | Janseen |
| | Megestrol Acetate | Nanocrystal (Elan) | Megace ES® | Par Pharmaceuticals |
| 2.Homogenization | Fenofibrate | IDD™ | Triglide® | Skyepharma |

Table III. Commercially available solid dispersion

| Drug | Brand name | Company |
|---|---|---|
| Griseofulvin | Gris-PEG® | Pedinol Pharmcal Inc. |
| Nabilone | Cesamet® | Valent Pharmaceutical |
| Lopinavir,Ritonavir | Kaletra® | Abbot |
| Itraconazole | Sporanox® | Janseen pharmaceutical |
| Etravirin | Intelence® | Tibotec |
| Everolimus | Certican® | Novartis |
| Verapamil | Isoptin SR-E® | Abbott |
| Nivaldipine | Nivadil® | Fujisawa Pharmaceutical Co.Ltd. |
| Tacrolimus | Prograf® | Fujisawa Pharmaceutical Co.Ltd. |
| Troglitazone | Rezulin® | Developed by Sankyo,manufactured by Parke-Davis |

Among different methods using supercritical fluids, precipitation using supercritical carbon dioxide ($CO_2$) as an antisolvent is well known and has been used to micronize several kinds of compounds (Jung and Perrut, 2001). Carbon dioxide is an ideal supercritical fluid because of its low critical temperature (31.18$^{o}$C) and pressure (73.8 Pa), low cost, non-toxicity and inert nature. In addition, $CO_2$ is recyclable and environmentally safe (Rogers, *et al.,* 2004). The driving force for particle formation using supercritical fluids is super saturation which is same as that of traditional crystallization. In the supercritical anti-solvent process the solubilization power of a solvent is decreased by addition of a supercritical fluid as an antisolvent in which the solute is insoluble (Figure 1). The nucleation and consequent growth of the crystals from the solute-organic solvent-antisolvent are governed by the diffusion of the antisolvent into the organic phase and the evaporation of the organic solvent into the antisolvent phase (Reverchon and Della 2001). The rapid diffusion of antisolvent into the organic solvent produces the supersaturation of the solute that leads to nucleation and particle formation.

## Complexation with Cyclodextrins

Cyclodextrins (CDs) have been used extensively in pharmaceutical research and development, and there are currently over 30 marketed cyclodextrins containing pharmaceutical products world wide (Pasquali, *et al.,* 2008). Some of the cyclodextrins based marketed products world wide are given in Table IV (Lengsfeld, *et al.,* 2000). Most commonly, CDs are used in drug formulations as solubility enhancers because of their ability to form water soluble inclusion complexes with poorly soluble drugs. The complexation with

Table IV. List of marketed pharmaceutical containing cyclodextrins

| Drug | Brand name | Company | Formulation |
|---|---|---|---|
| αcyclodextrin(αCD) | | | |
| Cefotiam-hexetil HCL | Pansporin | Takeda | Tablet |
| OP-1206 | Opalmon | Ono | Tablet |
| βCyclodextrin(βCD) | | | |
| Benexate Hcl | Ulget | Teikoku | Capsule |
| | Lonmiel | Shionogi | Capsule |
| Cephalosporin | Meiact | Meiji Seika | Tablet |
| Nicotine | Nicorette | Pfizer | Tablet |
| Nimesulide | Nimedex | Novartis | Tablet |
| 2-Hydroxy propyl-β-cyclodextrin(HPβCD) | | | |
| Itraconazole | Sporanox | Janssen | Oral and IV solution |
| Sulfabutyl ether-β-cyclodextrin sodium salt | | | |
| Voriconazole | Vfend | Pfizer | IV solution |
| Ziprasidone Mesylate | Geodon Zeldox | Pfizer | IM solution |
| Aripiprazole | Abilify | BMS | IM solution |

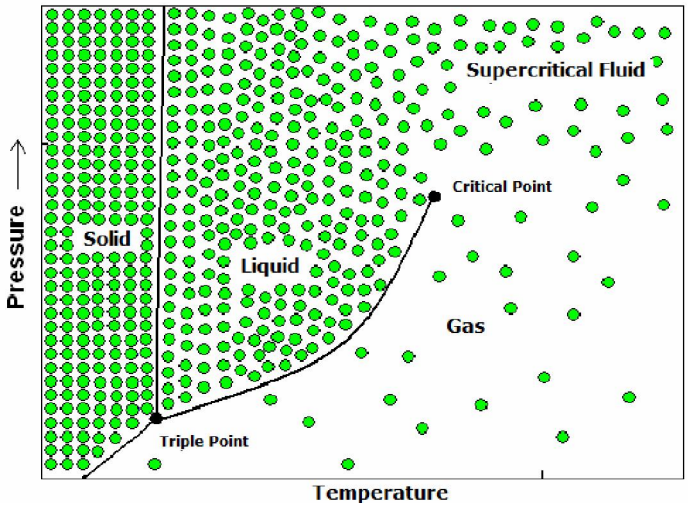


Figure 1 Phase diagram showing supercritical fluid region.

CDs enhances the solubility, dissolution rate, and bioavailability of poorly soluble drugs. In addition, CDs are used to enhance stability, to mask drug taste, to aid pharmaceutical processes by serving as filler, binder and channeling agents, etc., and as an osmogen in controlled release osmotic pump dosage forms. CDs are cyclic (α-1,4)-linked oligosaccharides of α-D-glucopyranose containing a relatively hydrophobic central cavity and hydrophilic outer surface. The central cavity provides a lipophillic microenvironment into which suitably sized lipophilic drug molecules can be accommodated due to hydrophobic interactions. No covalent bonds are formed in the drug/cyclodextrin (CD) complexation and the complexes are readily dissociated. The three natural CDs are α-CD, β-CD, and γ-CD which are made up of 6, 7 or 8 glucopyranose units respectively. Several chemically modified CD derivatives have been reported in the literature to enhance the

aqueous solubility, physical and microbiological stability and to reduce toxicity of the parent CDs. The majority of drugs form apparent 1:1 complexes with CDs although the formation of higher order complexes is not uncommon (Gupta, 2007).

### Amorphous system

Amorphization is one of the techniques to enhance the dissolution rate and bioavailability of poorly water soluble drugs (Pasquali and Bettini, 2008). Delivering the pharmaceutical active ingredient in the amorphous form is very attractive due to the potentially large increases in drug solubility, dissolution rate, and bioavailability (Baldyga, 2010). The amorphous form of drugs can have as much as a 10-1600 fold higher solubility than their crystalline forms (Yasuji, 2008). The improvement in dissolution of amorphous systems can be attributed to improved wetting of the drug, deagglomeration and micellization of the drug with hydrophilic polymers and the high energy amorphous state of the drug (Ito, 2006).

However, the amorphous forms of drugs are physically unstable due to their higher energy state and may recrystallize over pharmaceutically relevant time scales, negating any solubility advantage. The most typically used approach to stabilize an amorphous system is to combine it with pharmaceutically acceptable polymers, such as polyvinylprrolidone, polyvinylpyrrolidone vinyl acetate, polyethylene glycol and various hydroxypropylmethyl cellulose and polyacrylic acid derivatives (Hancock, 1997). Thermodynamically the drug has a lower chemical potential when mixed with a polymer, resulting in a change of crystallization driving force (Yu, 2001). The long polymeric chains can sterically hinder the association between drug molecules and, thereby, inhibit the recrystallization of drug. In addition, the interaction between the drug and polymer provides an increased energy barrier for nucleation and, consequently, enhances the physical stability (Hancock and Parks 2000). Amorphous drug-polymer systems are commonly characterized in terms of physical properties such as the glass transition temperature (*Tg*), heat capacity and miscibility. Although it is still not completely clear as to how the polymer stabilizes.

The amorphous drug in the mixture, drug polymer miscibility is generally considered as one of the critical attributes that affect the stability of the amorphous systems, which in turn is dictated by the thermodynamics of mixing (Chokshi *et al.,* 2007). The entropy of mixing is always favorable (an increase on mixing) providing one driving force facilitating mixing. The enthalpic component of the Gibbs function of mixing is controlled by the relative strength of the cohesive drug - drug, polymer - polymer and the drug - intercomponent interactions (Konno and Taylor 2006).

## CONCLUSION

Microparticles of the poorly water soluble drugs were produced by the supercritical antisolvent method and simultaneously mixed with pharmaceutical excipients in a single step to prevent the drug agglomeration of drug particles. In the third approach cyclodextrins (CDs) were used as pharmaceutical solubilizers and inclusion complexes of drugs with β-CD

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