Pharmaceutical Technologies for Enhancing Oral Bioavailability of Poorly Soluble Drugs

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Abstract

The oral bioavailability of BCS (biopharmaceutics classification system) class II drugs with poor solubility and reasonable permeability is limited by the drug dissolution step from drug products. Though prodrug approach is an exciting way of improving the oral bioavailability, it requires extensive studies to establish the safety profile of prodrugs in humans. In view of the increasing market share of oral drug products, a variety of technologies are developed to enhance the oral bioavailability of poorly soluble drugs using the excipients with approved or GRAS (generally regarded as safe) status. The present review describes the main technologies such as micronization, nanosizing, crystal engineering, solid dispersions, cyclodextrins, solid lipid nanoparticles and other colloidal drug delivery systems with a few relevant research reports.

Keywords: Bioavailability; Oral drug products; Enhancement; Technologies; Dissolution; Micronization; Crystal engineering; Nanosizing; Solid dispersion; Cyclodextrins; Microemulsions; Liposomes

Introduction

Oral ingestion is the most convenient and commonly employed route of drug delivery due to its ease of administration, high patient compliance, cost-effectiveness, least sterility constraints and flexibility in the design of dosage form. As a result, many of the generic drug companies are inclined more to produce bioequivalent oral drug products. The high costs and time involved in new drug development, expiry of patents for a significant number of drug molecules, ease of manufacturing and ready availability of technology for the production of oral drug products are also driving the generic pharmaceutical companies towards the development of bioequivalent oral dosage forms. However, the major challenge with the design of oral dosage forms lies with their poor bioavailability. The oral bioavailability depends on several factors including aqueous solubility, drug permeability, dissolution rate, first-pass metabolism, pre-systemic metabolism and susceptibility to efflux mechanisms (Sakaeda et al., 2001; Vieth et al., 2004; Wenlock et al., 2003). The most frequent causes of low oral bioavailability is attributed to poor solubility and low permeability (Vieth et al., 2004). The tremendous pharmaceutical research in understanding the causes of low oral bioavailability has led to the development of novel technologies to address these challenges. One of the technologies is to design a prodrug with the required physico-chemical properties to improve the oral bioavailability (Ettmayer et al., 2004). For example, the prodrug approach resulted in improved bioavailability of etilevodopa, capecitabine, oseltamivir, docarpamine and simvastatin (Djaldetti et al., 2003; Hayden et al., 2000; Mauro, 1993; Milano et al., 2004; Yoshikawa et al., 1995). For BCS class IV drugs with poor solubility and poor membrane permeability and BCS class III drugs with high solubility and low permeability, prodrug approach is the best option to enhance their bioavailability (Gomez-Orellana, 2005). Though prodrug approach is an exciting way of improving the oral bioavailability of BCS class II drugs, it requires extensive studies to establish the safety profile of prodrugs in humans, which ultimately may result in failure. Furthermore, the potential drawback of this approach is the reduced solubility of the prodrug. In today’s market, more than 40% of oral drug products contain poorly soluble drugs, and among the pharmacopoeia, this share is more than 30% (Giliyar et al., 2006; Lipinski et al., 2001). For these BCS class II drugs with low solubility and reasonable permeability, drug dissolution step is the rate-limiting process of drug absorption. When administered as oral dosage forms, the pharmaceutical formulation plays a critical role in the absorption of such drugs from gastrointestinal tract.

A variety of pharmaceutical formulation technologies are used to enhance oral bioavailability of BCS class II drugs. They use already approved excipients and GRAS materials. This in turn reduces the cost and development time. The main technologies to achieve the enhanced oral bioavailability of drugs with poor aqueous solubility include the use of micronization, nanosizing, crystal engineering, solid dispersions, cyclodextrins, solid lipid nanoparticles and other colloidal drug delivery systems such as microemulsions, self-emulsifying drug delivery systems, self-microemulsifying drug delivery systems and liposomes (Fahr and Liu, 2007; Gomez-Orellana, 2005). A brief review of the technologies along with a few reports is presented to emphasize their importance in enhancing the oral bioavailability of poorly soluble drugs.

Micronization

The oral bioavailability of drugs presented in a solid dosage form depends mainly on size, size distribution and morphology of particles. This is due to enhanced surface area of drug particles available for dissolution. Hence, a variety of micronization technologies such as spray-drying, freeze-drying, crystalization

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Received January 29, 2010; Accepted March 30, 2010; Published March 30, 2010

Citation: Krishnaiah YSR (2010) Pharmaceutical Technologies for Enhancing Oral Bioavailability of Poorly Soluble Drugs. J Bioequiv Availab 2: 028-036. doi:10.4172/jbb.1000027

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and milling processes were developed to decrease the particle size. However, the disadvantages associated with these traditional technologies are production of coarse particles with broad size distribution, degradation of the particle due to thermal or mechanical stress and contamination of the particles with toxic solvents. In the recent times, supercritical fluid (SCF) technologies are developed to overcome these disadvantages so as to produce a solvent-free drug product with improved dissolution, bioavailability and stability (Kompella and Koushik, 2001; Vemavarapu et al., 2005; York, 1999). These greener SCF technologies have been demonstrated to produce particles with residual solvent content below the FDA-permitted levels (Steckel et al., 1997). Furthermore, control over the morphology and crystallographic purity of the particles is shown to be better than several other conventionally used processes (Beach et al., 1999).

The various SCF processes are Supercritical Antisolvent System (SAS), Rapid Expansion of Supercritical Solutions (RESS), Particles from Gas–Saturated Systems (PGSS), Gas Antisolvent System (GAS), Precipitation using Compressed Antisolvent (PCA), Solution Enhanced Dispersion by Supercritical fluids (SEDS) etc. In all these processes, SCF basically acts as a precipitation agent producing solvent-free drug particles. In RESS, it acts like a solvent whereas in SAS, PCA and SEDS it acts like an antisolvent. Typically, in an SAS process, a mixture of drug and carrier are dissolved in a solvent, and then sprayed through a nozzle into a high pressure chamber filled with SCF. As each droplet is formed in the high pressure vessel, the SCF extracts the solvent leaving behind a solvent-free drug powder. By manipulating the temperature, pressure and concentration of supercritical fluids, and nozzle design one can produce a variety of powder sizes. A good number of reports appear in the literature wherein SCF technologies are used for improving the dissolution rate of drugs such as nifedipine, felodipine, fenofibrate, atorvastatin,itraconazole, budesonide and carbamazepine (Kere et al., 1999; Kim et al., 2008; Lee et al., 2005; Liu et al., 2007; Salmaso et al., 2009; SencarBozic et al., 1997; Sethia and Squillante, 2002; Yamanaka and Leong, 2008). The scale-up of these novel SCF technologies is on its way for industrial production of micronized particles in drug delivery.

Nanosizing

This involves the reduction of drug particle size to the sub-micron range. The advances in milling technologies made it possible to produce drug particles in the range of 100 to 200 nm in a reproducible manner. While reduction of particle size has been employed in pharmaceutical industry for several decades, nanosizing can provide a further enhancement of dissolution rate. Nanosizing involves mechanical attrition to render large crystalline particles into nanoparticles. Elian’s NanoCrystal® wet-milling technology and SkyPharma’s Dissocubes® high-pressure homogenization technology utilize these principles for producing nanoparticles (Keck and Muller, 2006; Merisko-Liversidge et al., 2003; Muller et al., 2001). An important requirement is that the nanoparticles are to be stabilized and formulated rigorously to retain their nature and properties (Merisko-Liversidge et al., 2003). This is achieved with surfactants or polymers in nanosuspensions which can be further processed into standard dosage forms such as capsules or tablets suitable for oral administration. These nanof ormulations offer increased dissolution rates for drug compounds and complement other technologies used to enhance bioavailability of insoluble compounds (BCS Class II and IV drugs) such as solubility enhancers (i.e. surfactants), liquid-filled capsules or solid dispersions of drugs in their amorphous state (Kesisoglou et al., 2007).

Elian’s NanoCrystal® technology can reduce crystalline particle size to < 100-250 nm. The drawback of this technique is that the milling process often requires grinding for hours to days in order to reach the desired size range. In high-pressure homogenization method, a jet-milled product is dispersed in an aqueous surfactant solution by high-speed stirring. The obtained macro-suspension is passed through a high-pressure homogenizer applying typically 1500 bar and three to ten homogenization cycles. The suspension passes a very small gap in the homogenizer. Due to the narrowness of the gap, the streaming velocity of the suspension increases tremendously, which means the dynamic fluid pressure increases. Simultaneously, the static pressure on the fluid decreases below the boiling point of water at room temperature. Consequently, water starts boiling at room temperature due to the high pressure, and gas bubbles are formed, which implode when the fluid leaves the homogenization gap. These cavitation forces are strong enough to break drug microparticles into drug nanoparticles (Muller et al., 2001).

Many reports in the literature have demonstrated the advantage of nanof ormulations over micronized drugs in improving oral bioavailability (Dai et al., 2007; Fakes et al., 2009; Yang et al., 2010). The success of the nanosizing technologies is exemplified by the marketability of drugs such as sirolimus, fenofibrate, aprepitant and megestrol acetate (Kesisoglou et al., 2007). Before considering the application of nanosizing to enhance the oral bioavailability, the biopharmaceutical properties of the drug are to be carefully evaluated. Drugs exhibiting dissolution rate-limited absorption are the best candidates for nanosizing. It is anticipated that nanosizing will attract increased attention in formulating fast dissolving oral dosage forms.

Crystal engineering

The surface area of drug available for dissolution is dependent on its particle size and ability to be wetted by luminal fluids. This particle size, which is critical to drug dissolution rate, is dependent on the conditions of crystallization or on methods of comminution such as impact milling and fluid energy milling. The comminution techniques can produce particles which are highly heterogeneous, charged and cohesive, with the potential to cause problems in downstream processing and product performance. Hence, crystal engineering techniques are developed for the controlled crystallization of drugs to produce high purity powders with well defined particle size distribution, crystal habit, crystal form (crystalline or amorphous), surface nature and surface energy (Blagden et al., 2007). By manipulating the crystallization conditions (use of different solvents or change in the stirring or adding other components to crystallizing drug solution), it is possible to prepare crystals with different packing arrangement; such crystals are called polymorphs. As a result, polymorphs for the same drug may differ in their physico-chemical properties such as solubility, dissolution rate, melting point and stability. Most drugs exhibit structural polymorphism and it is preferable to develop the most thermodynamically stable polymorph of the drug to assure reproducible
bioavailability of the product over its shelf-life under a variety of real-world storage conditions. A classic example of the importance of polymorphism on bioavailability is that of chloramphenicol palmitate suspensions. It was shown that the stable α-polymorph of chloramphenicol palmitate produced low serum levels, whereas the metastable β-polymorph yielded much higher serum levels when the same dose was administered (Aguiar et al., 1967). In another study, it was found that tablets prepared from the form A polymorph of oxytetracycline dissolved significantly more slowly than the tablets with form B polymorph of the same drug (Liebenberg et al., 1999). The tablets with form A polymorph exhibited about 55% dissolution at 30 min, while the tablets with form B polymorph exhibited almost complete (95%) dissolution at the same time (30 min).

Crystal engineering approach also involves the preparation of hydrates and solvates for enhancing the dissolution rate. During the crystallization process, it is possible to trap molecules of the solvent within the lattice. If the solvent used is water, the material is described as hydrate. If solvents other than water are present in a crystal lattice, the material is called a solvate. The dissolution rate and solubility of a drug can differ significantly for different solvates. For example, glibenclamide has been isolated as pentanol and toluene solvates, and these solvates exhibited higher solubility and dissolution rate than two non-solvated polymorphs (Suleiman and Najib, 1989). It is possible for the hydrates to have either a faster or slower dissolution rate than the anhydrous form. The most usual situation is for the anhydrous form to have a faster dissolution rate than the hydrate. For example, the dissolution rate of theophylline anhydrate was faster than its hydrate form (Shetter and Higuchi, 1963). In certain cases, hydrate form of the drug may show rapid dissolution rate than its anhydrous form. Erythromycin dihydrate was found to exhibit significant differences in the dissolution rate when compared to monohydrate and anhydrate form (Allen et al., 1978). In general, it is undesirable to use solvates for drugs and pharmaceuticals as the presence of organic solvent residues may be toxic.

Crystal engineering offers a number of routes to improved solubility and dissolution rate, which can be adopted through an in-depth knowledge of crystallization processes and the molecular properties of active pharmaceutical ingredients. The process involves dissolving the drug in a solvent and precipitating it in a controlled manner to produce nanoparticles through addition of an anti-solvent (usually, water) (Blagden et al., 2007). This technology is available from DowPharma (Midland, MI, USA) and BASF Pharma Solutions (Florham Park, NJ, USA).

Pharmaceutical co-crystals open a new avenue to address the problems of poorly soluble drugs. They contain two or more distinct molecules arranged to create a new crystal form whose properties are often superior to those of each of the separate entities. The pharmaceutical co-crystals are formed between a mutual volatile solvent followed by evaporation. Sometimes, drug is dissolved in a solvent such as propylene glycol and the resulting solution is added to the molten carrier. Solid dispersions of spironolactone, itraconazole and prednisolone, prepared by solvent evaporation method, were shown to enhance their dissolution rate (Leonardi et al., 2007; Uchino et al., 2007; Wang et al., 2004). The solvent evaporation method has several advantages (Bloch and Speiser, 1987). It is time-consuming and expensive because of long processing and drying times. Moreover, it is not environment-friendly due to the use of organic solvents, and may have toxic residual solvent(s) in the final product.

As described under micronization approach, the SCF technologies involving mild processing conditions of low temperatures (~30°C) and minimal or no organic solvents are considered the most promising to overcome the disadvantages associated with the melt and solvent evaporation methods of preparation.
Cyclodextrins

These starch derivatives are the most widely investigated excipients for enhancing the solubility and dissolution rate of poorly soluble drugs. The interior of these molecules is relatively lipophilic and the exterior relatively hydrophilic. Cyclodextrins and their commercially available derivatives are able to incorporate apolar molecules or parts of molecules inside their hydrophobic cavity resulting in better stability, high water solubility, increased bioavailability or decreased undesirable side effects (Duchene et al., 1999). The mechanism for the enhanced solubilization is entrenched in the ability of cyclodextrin to form non-covalent dynamic inclusion complexes in solution. Other solubilizing attribute may include the ability to form non-inclusion based complexes, the formation of aggregates and related domains and the ability of cyclodextrins to form and stabilize supersaturated drug solutions (Brewster and Loftsson, 2007). Though β-cyclodextrin was the first cyclodextrin used to enhance the dissolution rate of poorly soluble drugs, its low aqueous solubility together with its nephrotoxicity prompted the development of high water soluble and less toxic derivatives such as 2-hydroxypropyl-β-cyclodextrin, methyl-β-cyclodextrin and sulfobutyl ether-β-cyclodextrin (Fahr and Liu, 2007; Stella and Rajewski, 1997; Szente and Szejtli, 1999). The increase in solubility also can increase dissolution rate and thus improve the oral bioavailability of BCS Class II drugs. The success rate of cyclodextrins for enhancing the dissolution rate of poorly soluble drugs is witnessed by the presence of over 35 marketed drug products incorporating them as excipients. The examples include itraconazole-hydroxypropyl-β-cyclodextrin, piroxicam-β-cyclodextrin and benexate-β-cyclodextrin (Fahr and Liu, 2007). The inclusion complexes of acelofenac with hydroxypropyl-β-cyclodextrin prepared by spray drying process were shown to provide enhanced dissolution rate as well as improved anti-inflammatory activity (Ranpise et al., 2010).

The solubilizing ability of cyclodextrins can be further enhanced by incorporating other water-soluble excipients. For example, the association of water-soluble polymer PEG4000 with glimepiride-2-hydroxypropyl-β-cyclodextrin systems has shown a greatly enhanced dissolution rate, increased duration of action and improvement of therapeutic efficacy of the drug (Ammar et al., 2006). The drug-cyclodextrin complexes are prepared by freeze-drying, spray-drying, and co-precipitation of a cyclodextrin/drug solution or simple grinding the slurry of drug and cyclodextrin (Carrier et al., 2007). These methods may involve one or more organic solvent and thus the final product may contain residual toxic solvents. The difference in complex formation methodology can affect the dissolution kinetics and subsequently the bioavailability. This may be due to the differences in the extent of complex formation, changes in the particle size and degree of amorphous nature of the resulting material. Hence, it is essential to carefully control the processing variables while preparing the drug-cyclodextrin complexes (Miller et al., 2007). This could be achieved using the latest technologies such as SCF processing methods (Al-Marzouqi et al., 2009; Hassan et al., 2007; Hussein et al., 2007).

Solid lipid nanoparticles

Solid lipid nanoparticles (SLN) represent an alternative carrier system to traditional colloidal carriers (emulsions, liposomes and polymeric micro- and nanoparticles) in enhancing the oral bioavailability of poorly soluble drugs. These particulate systems contain solid lipids as matrix material which possesses adhesive properties that make them adhere to the gut wall and release the drug exactly where it should be absorbed (Muller and Keck, 2004). In addition, the lipids are known to have properties that promote the oral absorption of lipophilic drugs and drugs in general (Charman, 2000). Thus, SLN can improve the oral bioavailability of the poorly soluble drugs. Of the available methods, high-pressure homogenization and microemulsion technology are considered as the most feasible methods for large scale production of SLN (Muchow et al., 2008; Muller et al., 2000). Lipid matrix of solid lipid nanoparticles is made from physiologically tolerated lipid components, which decreases the potential for acute and chronic toxicity (Mehnert and Mader, 2001). Another significant advantage of SLN formulations is that they have the ability to be stable for 3 years, which is of paramount importance with respect to colloidal drug carriers (Freitas and Muller, 1998). There are a number of reports indicating the enhanced oral bioavailability of drugs including praziquantel, quercetin, lovastatin, nitrrendipine, vinpocetine and cyclosporine (Kumar et al., 2007; Li et al., 2009; Luo et al., 2009).
Microemulsions

The emulsions are cloudy, thermodynamically unstable and re-lated and administered to beagle dogs (Hansen et al., 2005). Let and capsule) when a model drug (Lu 28-179) was formu-lated as tablets or capsules. Comparable bioavailability were obtained from dry emulsion powder and oral dosage form (tablet and/or hydrophobic tail region of the surfactant and the hydro-

**Other colloidal drug delivery systems**

These include the emulsified systems as well as liposomes. Traditional emulsions, microemulsions, self-emulsified drug delivery systems and self-microemulsifying drug delivery systems belong to emulsified systems. The formulation of emulsions involves the use of digestible oils such as cottonseed oil and soybean oil. The enhanced drug absorption from an emulsion is a widely known concept. For example, the oral bioavailability of griseofulvin from a corn oil emulsion formulation was found to be twofold in humans when compared with either an aqueous suspension or commercial tablet formulation (Bates and Sequeria, 1975). However, emulsions are known for their thermodynamic instability. This drawback can be elimi-nated by converting the liquid emulsions into solid emulsion powder by means of a suitable technique such as spray drying. These dry emulsions are cohesive and bulky, and hence formulated as tablets or capsules. Comparable bioavailability were obtained from dry emulsion powder and oral dosage form (tablet and capsule) when a model drug (Lu 28-179) was formulated and administered to beagle dogs (Hansen et al., 2005).

Microemulsions are novel pharmaceutical formulations designed to overcome the above disadvantages. They are thermodynamically unstable and requires high amount of energy for producing them. Microemulsions are novel pharmaceutical formulations designed to overcome the above disadvantages. They are thermodynamically stable, transparent, low viscosity, easy to prepare and iso-tropic dispersions consisting of oil and water stabilized by an interfacial film of surfactant molecules, typically in conjunction with a cosurfactant. It is possible to incorporate water-soluble, oil-soluble and amphiphilic drugs into microemulsions. For example, while formulating a microemulsion, water-insoluble lipophilic drugs can be incorporated into the disperse oil phase and/ or hydrophobic tail region of the surfactant and the hydro-philic drug can be incorporated into disperse aqueous phase of water-in-oil droplet.

For enhancing the solubility and dissolution rate of poorly soluble drugs, it is preferable to formulate them as oil-in-water microemulsions instead of water-in-oil microemulsions (Lawrence and Rees, 2000). This is because the droplet structure of oil-in-water microemulsions is often retained on dilu-tion by aqueous biological fluid thereby enhances oral bioavailability. In contrast, if formulated as water-in-oil microemulsions, the droplet size increases on dilution in GI tract, and ultimately results in dose dumping due to phase separation. Microemulsion systems are widely used to improve the solubility and absorption of poorly water-soluble drugs. In one of the studies, microemulsions with varying weight ratios of surfac-tant to cosurfactant were prepared using caprylic/capric triglyce-ride as oil, polyoxyethylated castor oil as a surfactant, Transcutol® as a cosurfactant and saline (Gao et al., 1998). The absolute bioavailability of cyclosporine loaded in this microemulsion system was increased about 3.3 and 1.25 fold compared with Sandimmun® and Sandimmun Neoral®. The enhanced bioavailability of cyclosporine loaded in this microemulsion system were considered due to the reduced droplet size of microemulsion systems (Gao et al., 1998). A microemulsion system of docetaxel was prepared and evaluated for its solubilization capacity and oral bioavailability improve-ment (Yin et al., 2009). The oil-in-water microemulsion formula-tion composed of Capryol 90 (oil), Cremophor EL (surf-ac-tant) and Transcutol (co-surfactant) enhanced the solubility of docetaxel up to 30 mg/mL, which maintained solubilization capacity for 24 h even after it was diluted 20 times with normal saline. The oral bioavailability of the microemulsion formula-tion in rats (34.42%) rose dramatically compared to that of the orally administered Taxotere® (6.63%). The studies showed that combined effect of the enhancement in solubility, the inhibition of P-gp efflux system and the increase in permeability might have increased the bioavailability of docetaxel (Yin et al., 2009). In another study, microemulsion formulation of puerarin, prepared with soybean oil, soybean lecithin/ethyl lactate (1:1) and 1,2-propanediol/water, was shown to be stable with enhanced oral bioavailability when compared to suspension formulation (Wu et al., 2009).

**Self-emulsifying drug delivery systems (SEDDS) and self-microemulsifying drug delivery systems (SMEDDS)**

SEDDS and SMEDDS are isotropic solutions of oil and surfactant which form oil-in-water microemulsions on mild agitation in the presence of water (Shah et al., 1994). The poorly soluble drug can be dissolved in a mixture of surfactant and oil which is widely known as preconcentrate. These novel colloidal formulations on oral administra-tion behave like oil-in-water microemulsions. Compared with ready-to-use microemulsions, the SEDDS and SMEDDS have been shown to improve physical stability profile in long-term storage. SEDDS have been reported to enhance the oral bioavailability of paclitaxel, griseofulvin and dexibuprofen (Arida et al., 2007; Balakrishnan et al., 2009; Gao et al., 2003). Similarly, SMEDDS were shown to enhance the oral bioavailability of poorly soluble drugs such as simvastatin, acyclovir and exemestane (Kang et al., 2004; Patel and Sawant, 2007; Singh et al., 2009). Solid SEDDS are the advanced for-mulations that can be filled directly into soft or hard gelatin capsules for conventional drug delivery (Tang et al., 2008). For example, solid SEDDS of dexibuprofen, prepared by spray drying of liquid SEDDS with an inert solid carrier Aerosil 200, showed twofold increase in the oral bioavailability when compared to the powder form (Balakrishnan et al., 2009).

One of the challenges in formulating microemulsions, SEDDS or SMEDDS is the limited availability of formulation compo-nents with GRAS status. In this context, liposomal formula-tions may be preferred over the above colloidal drug delivery systems for solubilizing the drugs and thereby to enhance oral bioavailability (Fahr et al., 2005). This is because of the GRAS status of phospholipid constituents used in liposomal formula-tions. Liposomes are phospholipid vesicles, comprising a phos-pholipid bilayer surrounding an aqueous compartment. In the lipid domain of the bilayer membrane, lipophilic drugs can be dissolved. Due to their biphasic characteristic and diversity in design, composition and construction, liposomes offer a dynamic and adaptable technology for enhancing drug solubility (Fahr and Liu, 2007). It has been reported that the liposome encapsu-lation efficiency of lipophilic drugs depends on both the
physicochemical properties of the drug, such as its lipophilicity, and on factors including bilayer composition and the method of preparation (Fresta et al., 1993). Liposomes are shown to be promising carriers for enhancing the bioavailability of poorly soluble drugs such as ibuprofen, amphotericin B, cyclosporine, and griseofulvin (Dupont, 2002; Fahr and Seelig, 2001; Mohammed et al., 2004; Stocek and Borysiewicz, 1991). A fenofibrate liposomal formulation was prepared by a dry-film dispersing method coupled with sonication and homogenization using soybean phosphatidylcholine and sodium deoxycholate or cholesterol (Chen et al., 2009). In vivo measurements of pharmacokinetics and bioavailability demonstrated higher rates of fenofibrate absorption from the liposomal formulations than micronized fenofibrate.

Conclusions

In view of the increasing market share of oral drug products, pharmaceutical companies are focusing their research to resolve the issue of poor drug solubility through the development of novel technologies. Though prodrug approach is an exciting way of improving the oral bioavailability of BCS class II drugs with low solubility and reasonable permeability, it requires extensive studies to establish the safety profile of prodrugs in humans. The traditional methods of micronization are likely to be replaced with greener SCF technologies that can have a precise control over the particle size and distribution and product quality (solvent-free) with improved dissolution, bioavailability and stability. The scale-up of SCF technologies is on its way for industrial production of micronized particles for enhancing the bioavailability of poorly soluble drugs. The advancements in milling technologies (e.g. Elan’s NanoCrystal® technology) could result in the production of nanosized drug particles in the range of 100 to 200 nm in a reproducible manner. The success of the nanosizing technologies is exemplified by the marketability of drugs such as sirolimus, fenofibrate, aprepitant and megestrol acetate. Crystal engineering techniques (e.g. SCF technologies) are developed for the controlled crystallization of drugs to produce polymorphs, hydrates, solvates, nanoparticles and pharmaceutical co-crystals with enhanced oral bioavailability. Melt sonocrystallization is another emerging technology that uses ultrasonic energy to produce porous fast dissolving particles for BCS class II drugs.

The vast amount of research on the use of solid dispersion technique for enhancing the dissolution rate of poorly soluble drugs has paved the way for the development of novel technologies such as melt extrusion technology and SCF technologies. These technologies are able to overcome the disadvantages associated with traditional methods of preparing solid dispersions (melt method and solvent evaporation method). Cyclodextrins and their commercially available derivatives are able to incorporate poorly soluble drugs or parts of molecules inside their hydrophobic cavity resulting in high water solubility and increased bioavailability. The solubilizing ability of these cyclodextrins can be further enhanced by incorporating other water-soluble excipients. Like solid dispersions, the traditional methods of preparing drug-cyclodextrin complexes involve the use of one or more organic solvents, and thus the final product may contain residual toxic solvents. The SCF technologies appear to be the most promising to eliminate the use of organic solvents in preparing drug-cyclodextrin complexes. The solid lipid nanoparticles are able to entrap lipophilic drugs and stick to the gut wall resulting in enhanced oral bioavailability. Of the available methods, high-pressure homogenization and microemulsion technology are considered as the most feasible methods for large scale production of SLN. The potential of these SLN is indicated by the efforts of pharmaceutical companies (SkyePharma AG, Muttenz, Switzerland and Vectorpharma, Trieste, Italy) to produce commercially feasible products through their own technologies.

Microemulsions are novel pharmaceutical formulations that are thermodynamically stable, transparent, low viscosity, easy to prepare and isotropic dispersions designed to enhance the oral bioavailability of poorly soluble drugs. SEDDS and SMEDDS are isotropic solutions of oil and surfactant which form oil-in-water microemulsions in GI tract after mixing with biological fluids. The poorly soluble drugs can be incorporated in the oil phase to enhance their oral bioavailability. One of the challenges in formulating microemulsions, SEDDS or SMEDDS is the limited availability of formulation components with GRAS status. In this context, liposomal formulations may be preferred over the SEDDS and SMEDDS for solubilizing the drugs and thereby to enhance oral bioavailability. This is because of the GRAS status of phospholipid constituents used in liposomal formulations. The excellent research reports from academia and pharmaceutical industry are continuously encouraging the development of industrially feasible technologies for producing quality products with enhanced oral bioavailability of poorly soluble drugs.

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