

CONVENTIONAL AND ALTERNATIVE PHARMACEUTICAL METHODS TO IMPROVE ORAL BIOAVAILABILITY OF LIPOPHILIC DRUGS

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ABSTRACT

Out of newly discovered drugs more than 40 % drugs are lipophilic and out of which up to 40 % of pharmacologically active new molecules failed to reach to market only due to little or no water solubility; a serious challenge for the successful development and commercialization of new drugs in the pharmaceutical industry. Therefore various formulation strategies have been investigated to improve the solubility and the rate of dissolution to enhance the oral bioavailability of lipophilic drugs. In the present review the different approaches discussed to overcome this problem, and successfully deliver the lipophilic drug for mankind.

Keywords: Lipophilic, bioavailability, dissolution, solubility

INTRODUCTION

It is one of the major challenges to synthesize any new molecule, which is pharmacologically active for the researchers and pharmaceutical companies. It not only takes a long time but also consumes a lot of money. Out of this research around 40% of lipophilic drug candidates fail to reach market although exhibiting potential pharmacodynamic activities.^{1, 2} No matter how active or potentially active a new molecular entity (NME) is against a particular molecular target, if the NME is not available in solution at the site of action, it is not a viable development candidate. As a result, the development of many exciting NMEs is stopped before their potential is realized or confirmed because pharmaceutical companies cannot afford to conduct rigorous pre-clinical and clinical studies on a molecule that does not have a sufficient pharmacokinetic profile due to poor water solubility. Even some of the lipophilic drugs on the market have to be administered at high doses. More than 90% of drugs approved since 1995 have poor solubility, poor permeability, or both³. A marketed drug with poor water solubility can still show performance limitations, such as incomplete or erratic absorption, poor bioavailability, and slow onset of action. Effectiveness can vary from patient to patient, and there can be a strong effect of food on drug absorption. Finally, it may be necessary to increase the dose of a poorly soluble drug to obtain the efficacy required.

Although pharmaceutical companies have been able to overcome difficulties with very slightly soluble drugs, those with aqueous solubility of less than 0.1 mg/ml present some unique challenges. These drugs are particularly good candidates for advanced solubilization technologies developed by companies specializing in drug delivery. These strategies include the solubilization and surfactants, the use of different polymorphic/amorphous drug forms, the reduction of drug particle size, the complexation (e.g., cyclodextrins) and the formation of solid drug solutions/dispersions.^{4, 5}

Solubilization and Surfactants

One approach to increase the bioavailability of lipophilic drugs is the solubilization of the drugs by means of pH adjustment, cosolvent, microemulsification, self-emulsification, micelles, liposomes and emulsions.⁶ Each has its advantages and limitations.

pH adjustment

pH adjustment is the simplest and most commonly used method to increase water solubility of ionizable compounds. However, this salt formation is infeasible for unionized compounds. The formed salts may also converse to respective acid or base forms in gastrointestinal-tract (GIT).

Cosolvent

Cosolvents are the mixtures of miscible solvents often

used to solubilize lipophilic drugs. The solubilizing excipients used in commercially available oral and injectable formulations are listed in Table 1. Currently, the water-soluble organic solvents are polyethylene glycol 400 (PEG 400), ethanol, propylene glycol, and glycerin. For example, Procardia® (nifedipine) was developed by Pfizer contains glycerin, peppermint oil, PEG 400 and sodium saccharin in soft gelatin capsules. The water-insoluble solvents include long-chain triglycerides (i.e. peanut oil, corn oil, soybean oil, sesame oil, olive oil, peppermint oil, hydrogenated vegetable oil and hydrogenated soybean oil), medium-chain triglycerides (Miglyol 812), beeswax, d- α -tocopherol (vitamin E) and oleic acid. Progesterone is a water-insoluble steroid and is solubilized in peanut oil (Prometrium®).

Microemulsion

Microemulsion is a thermodynamically stable iso-tropical dispersion composed of a polar solvent, oil, a surfactant and a cosurfactant. The formation of microemulsions is spontaneous and does not involve the input of external energy. One theory considers negative interfacial tension while another considers swollen micelles. The surfactant and the cosurfactant alternate each other forming a mixed film at the interface contributing to the stability of the microemulsion. Microemulsions are potential drug delivery systems for poorly water-soluble drugs due to their ability to solubilize the drugs in the oil phase, thus increasing their dissolution rate.⁷ Even if the microemulsions are diluted after oral administration below the critical micelles concentration (CMC), the resultant drug precipitates have a fine particle size allowing enhanced absorption.⁸

Self Emulsification

In the absence of external phase (water), the mixture of oil, surfactant, cosurfactant, one or more hydrophilic solvents and cosolvent forms a transparent isotropic solution that is known as the self-emulsifying drug delivery system (SEDDS). This forms fine O/W emulsions or microemulsions spontaneously upon dilution in the aqueous phase and is used for improving lipophilic drug dissolution and absorption.^{9, 10} The self-emulsification process is specific to the nature of the oil/surfactant pair, surfactant concentration, oil/surfactant ratio and temperature at which self-emulsification occurs. The ease of emulsification could be associated with the ease of water penetrating into the various liquids crystalline or gel phases formed on the surface of the droplet. A

few parameters have been proposed to characterize the self-emulsifying performance including the rate of emulsification, the emulsion size distribution and the charge of resulting droplets. Among them, emulsion droplet size is considered to be a decisive factor in self-emulsification/ dispersion performance, since it determines the rate and extent of drug release and absorption.¹¹ In addition, positively charged emulsion droplets could be obtained by incorporation of a small amount of cationic lipid (oleylamine) into such system.^{10, 12} The oral bioavailability of progesterone was significantly enhanced in rats by forming positively charged emulsion in comparison to the corresponding negatively charged formulation.¹²

One of the advantages of SEDDS in relation to scale-up and manufacture is that they form spontaneously upon mixing their components under mild agitation and they are thermodynamically stable. The drawbacks of this system include chemical instabilities of drugs and high surfactant concentrations. The large quantity of surfactant in self-emulsifying formulations (30-60%) irritates GIT. Consequently, the safety aspect of the surfactant vehicle had to be considered. Moreover, volatile cosolvents in the conventional self-emulsifying formulations are known to migrate into the shells of soft or hard gelatin capsules, resulting in the precipitation of the lipophilic drugs. As an example of self-emulsification, Neoral® is composed of ethanol, corn oil-monodiglycerides, Cremophor RH 40 and propylene glycol. It exhibits less variability and better drug uptake compared to Sandimmune®. There is a long list of water soluble, insoluble and surfactants, which can use as solubilizing excipients.¹³

Polymeric Modification (Polymorphs)

Polymorphs are different crystalline forms of a drug that may have different physicochemical properties and biological activities, such as shelf-life, melting point, vapor pressure, solubility, morphology, density and bioavailability.^{14, 15} Metastable forms are associated with higher energy with increased surface area, subsequently solubility, bioavailability and efficacy.^{15, 16} With regard to bioavailability, it is preferable to change drug from crystal forms into metastable or amorphous forms. However, the possibility of a conversion of the high energy amorphous or metastable polymorph into a low energy crystal form having low solubility cannot be ruled out

during manufacture and storage. 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. For instance, ritonavir is the active ingredient in Norvir®, a protease inhibitor used to treat HIV/AIDS. It was launched by Abbott Laboratories in 1996 as an amorphous semisolid dispersion consisting of medium chain triglycerides, polyoxyl 35 castor oil, citric acid, ethanol, polyglycolized glycerides, polysorbate 80, propylene glycol and 100 mg of ritonavir. The dissolution and the oral bioavailability were decreased due to crystallization of amorphous ritonavir into an insoluble crystal form during storage. This polymorph (form II) was 50% less soluble than the original form in the market, and caused the drug to fail its regulatory dissolution specifications. Finally, the drug was relaunched with the form II polymorph in a soft gelatin formulation that required refrigeration. Therefore, it is important to note that the selection of a polymorph of a drug should balance between solubility and stability to maintain its potency over the shelf-life period.

Particle Size Reduction

Micronization or nanonization is one of the most promising approaches to improve the bioavailability of lipophilic drugs by an increase in surface area and saturation solubility via reduction of the particle size to less than 1μ .¹⁰ Such size reduction cannot be achieved by the conventional milling techniques. Patented engineering processes have come up based on the principles of pearl milling (NanoCrystals®), high-pressure homogenization (DissoCubes®), solution enhanced dispersion by supercritical fluids (SEDS), rapid expansion from supercritical to aqueous solution (RESAS), spray freezing into liquid (SFL) and evaporative precipitation into aqueous solution (EPAS).¹⁷

Pearl milling

Based on pearl milling the drug microparticles are ground to nanoparticles (< 400 nm) in between the moving milling pearls. The milling efficiency is dependent on the properties of the drug, the medium and the stabilizer. Rapamune®, an immune suppressant agent, is the first FDA approved nanoparticle drug using NanoCrystals® technology developed by Elan Drug Delivery. Emend® is another product containing 80 or 125 mg aprepitant formulated by this technique.

Overall in general the limitation of the pearl milling process is the introduction of contamination to the product from the grinding material, batch-to-batch variations and the risk of microbiological problems after milling in an aqueous environment.

High-pressure homogenization

DissoCubes® manufacture involves dispersing a drug powder in an aqueous surfactant solution and passing through a high-pressure homogenizer, subsequently nanosuspensions are obtained. The cavitation force experienced is sufficient to disintegrate drug from microparticles to nanoparticles. The particle size is dependent on the hardness of the drug substance, the processing pressure and the number of cycles applied. The possible interesting features of nanosuspensions are,¹⁸:

- Increase in saturation solubility and dissolution rate of drug
- Increase in adhesive nature, thus resulting in enhanced bioavailability
- Increase the amorphous fraction in the particles, leading to a potential change in the crystalline structure and higher solubility
- Possibility of surface modification of nanosuspensions for site-specific delivery
- Possibility of large-scale production, the prerequisite for the introduction of a delivery system to the market

However, only brittle drug candidates might be broken up into nanoparticles by this technique. A few points has to be considered, such as chemical instability of fragile drugs under the harsh production conditions, Ostwald ripening in long-term storage, toxicity of surfactants, redispersibility of the dried powder, batch-to-batch variation in crystallinity level and finally the difficulty of quality control and the stability of the partially amorphous nanosuspensions.

Solution enhanced dispersion by the supercritical fluids (SEDS)

The SEDS process was developed and patented by the

University of Bradford.¹⁹ The use of a coaxial nozzle provides a means whereby the drug in the organic solvent solution mixes with the compressed fluid CO₂ (antisolvent) in the mixing chamber of the nozzle prior to dispersion, and flows into a particle-formation vessel via a restricted orifice. Such nozzle achieves solution breakup through the impaction of the solution by a higher velocity fluid. The high velocity fluid creates high frictional surface forces, causing the solution to disintegrate into droplets. A wide range of materials has been prepared as carriers of microparticles and nanoparticles using the SEDS process¹⁹. A key step in the formation of nanoparticles is to enhance the mass transfer rate between the droplets and the antisolvent before the droplets coalesce to form bigger droplets. In another study, a significant decrease in the particle size is achieved by using the ultrasonic nozzle-based supercritical antisolvent process.^{20, 21}

Rapid expansion from supercritical to aqueous solution (RESAS)

This process induces rapid nucleation of the supercritical fluid dissolved drugs and surfactants resulting in particle formation with a desirable size distribution in a very short time. The surfactants in the supercritical fluid stabilize the newly formed small particles and suppress any tendency of particle agglomeration or particle growth when spraying this solution (drug + surfactant + CO₂) into an aqueous solution containing a second surface modifier.^{22, 23} The low solubility of poorly water soluble drugs and surfactants in supercritical CO₂ and the high pressure required for these processes restrict the utility of this technology in pharmaceutical industry.

Spray freezing into liquid (SFL)

The SFL technology was developed and patented by the University of Texas at Austin in 2003 and commercialized by the Dow Chemical Company. This technique involves atomizing an aqueous, organic, aqueous-organic cosolvent solution, aqueous-organic emulsion or suspension containing a drug and pharmaceutical excipients directly into a compressed gas (i.e. CO₂, helium, propane, ethane), or the cryogenic liquids (i.e. nitrogen, argon, or hydrofluoroethers). The frozen particles are then lyophilized to obtain dry and free-flowing micronized powders²⁴. Using of acetonitrile as the solvent increased the drug loading and decreased the drying time for lyophilization. The dissolution rate was remarkably enhanced from the SFL powder contained

amorphous nanostructured aggregates with high surface area and excellent wettability.²⁵

Evaporative precipitation into aqueous solution (EPAS)

The EPAS process utilizes rapid phase separation to nucleate and grow nanoparticles and microparticles of lipophilic drugs. The drug is first dissolved in a low boiling point organic solvent. This solution is pumped through a tube where it is heated under pressure to a temperature above the solvent's boiling point and then sprayed through a fine atomizing nozzle into a heated aqueous solution. Surfactants are added to the organic solution and the aqueous solution to optimize particle formation and stabilization. In EPAS, the surfactant migrates to the drug-water interface during particle formation, and the hydrophilic segment is oriented towards the aqueous continuous phase.⁴ The hydrophilic stabilizer on the surface inhibits crystallization of the growing particles and therefore facilitates dissolution rates.

Complexation

Cyclodextrins and their derivatives have been employed as complexing agents to increase water solubility, dissolution rate and bioavailability of lipophilic drugs for oral or parenteral delivery.²⁶ The solubility enhancement factors of pancratistatin, hydrocortisone, and paclitaxel are 7.5, 72.7 and 99000 by forming complexes with cyclodextrin derivatives.²⁷ The lower the aqueous solubility of the pure drug, the greater the relative solubility enhancement obtained through cyclodextrin complexation. Pharmaceutical applications of cyclodextrins in drug solubilization and stabilization²⁷, in vivo drug delivery²⁸, toxicological issues and safety evaluation and mechanisms of cyclodextrins modifying drug release from polymeric drug delivery systems have been previously reviewed. Commercially available cyclodextrin based pharmaceutical products enumerated in Table 1 and many are waiting for approval.²⁹ Cyclodextrins are a group of cyclic oligosaccharides obtained from enzymatic degradation of starch. The three major cyclodextrins α -, β -, and γ - (CD) are composed of six, seven, and eight D-(+)-glucopyranose units. These agents have a torus structure with primary and secondary hydroxyl groups orientated outwards. Consequently, cyclodextrins have a hydrophilic exterior and a hydrophobic internal cavity. This cavity enables cyclodextrins to complex 'guest' drug molecules and hence alters the properties of the drugs such as solubility, stability, bioavailability and toxicity

profiles.³⁰ The forces driving complexation were attributed to (i) the exclusion of high energy water from the cavity, (ii) the release of ring strain particularly in the case of α -CD, (iii) Vanderwall's interactions, and (iv) hydrogen and hydrophobic bindings (Ross and Rekharsky, 1996). β -CD, the most widely used native cyclodextrins, is limited in its pharmaceutical application by its low aqueous solubility (1.85 g/100 ml, 25°C), toxicity profile and low aqueous solubility of the formed complexes. Accordingly, derivatives such as hydroxypropyl- β -CD (HP- β -CD; Enapsin®) and sulphobutylether- β -CD (SE- β -CD; Captisol®) have been developed to produce more water-soluble and less toxic entities.

Solid solutions/dispersions

Solid dispersion was firstly introduced to overcome the low bioavailability of lipophilic drugs by forming of eutectic mixtures of drugs with water-soluble carriers. It was defined as the dispersion of one or more active ingredients in an inert carrier matrix in solid-state prepared by melting (fusion), solvent or melting-solvent method. More than 500 papers have been published on the subject and various materials are employed as drug carriers. Despite an active research interest, the number of marketed products arising from this approach is disappointing mainly caused by the physical and chemical instability and scale-up problems.³¹ Only two commercial products, a griseofulvin in polyethylene glycol 8000 solid dispersion (Gris-PEG, Novartis) and a nabilone in povidone solid dispersion (Cesamet, Lilly) were marketed during the last four decades following the initial work of Sekiguchi and Obi.³²

Carriers

Many water-soluble excipients were employed as carriers of solid solutions/dispersions. Among them, polyethylene glycols (PEG, Mw 1500-20000) were the most commonly used due to their good solubility in water and in many organic solvents, low melting points (under 65°C), ability to solubilize some compounds and improvement of compound wettability. The marketed Gris-PEG is the solid dispersion of griseofulvin in PEG 8000. The others carriers include polyvinyl pyrrolidone (PVP), polyvinylalcohol (PVA), polyvinylpyrrolidone polyvinylacetate copolymer (PVP-PVA), hydroxypropyl methylcellulose (HPMC), hydroxypropyl cellulose (HPC), urea, Poloxamer 407, sugars, emulsifiers (SDS, Tween 80) and organic acids (succinic acid and citric acid). Because of the rapid dissolution of the water-soluble car-

riers than the drugs, drug-rich layers were formed over the surfaces of dissolving plugs, which prevented further dissolution of drug from solid dispersions. Therefore, surface-active or self-emulsifying agents including bile salts, lecithin, lipid mixtures, Gelucire 44/14³³ and Vitamin E TPGS NF³⁴ were used as additional additives, acting as dispersing or emulsifying carriers for the liberated drug to prevent the formation of any water-insoluble surface layer. In addition, the release behaviors of many drugs are also improved by using water-insoluble polymers such as crospovidone^{35, 36} and enteric polymers such as hydroxypropyl methylcellulose phthalate (HPMCP), cellulose acetate phthalate (CAP), Eudragit® L100 and S100 (Takada et al., 1989) and Eudragit® E.³⁷

Controlled Precipitation

Controlled precipitation is a particle engineering technology that creates crystalline nanostructured drug particles with rapid dissolution rates. With this technology, the drug is dissolved in a suitable solvent then precipitated into an aqueous solution in the presence of crystal growth inhibitors to form drug nanoparticles. Particles prepared by controlled precipitation have the advantage of a narrower particle size distribution as compared to particle size reduction technologies, such as wet milling. The process is fast, continuous, and scalable with conventional process equipment. Levels of residual solvents are low, and the excipients used are pharmaceutically acceptable. The danazol powder prepared by controlled precipitation shows substantially improved bioavailability compared to the drug as-received (micronized danazol). Tablets prepared on a Carver press from precipitated danazol (equivalent to 200 mg danazol) formulated with microcrystalline cellulose and carboxymethylcellulose (47.5:47.5:5) show further enhancement in bioavailability. The increased bioavailability observed with the control is due to an excipient effect that enhances wettability of the powder.³⁸

Ultra-Rapid Freezing

Ultra-rapid freezing is a novel, cryogenic technology that creates nanostructured drug particles with greatly enhanced surface area. The technology has the flexibility to produce particles of varying particle morphologies, based on control of the solvent system and process conditions.

The technology involves dissolving a drug in a water-miscible or anhydrous solvent along with a stabilizer acting as a crystal growth inhibitor. The drug/stabilizer solution is then applied to a cryogenic substrate. The solvent is removed by lyophilization or atmospheric freeze-drying, resulting in highly porous, agglomerated

particles. As with controlled precipitation, this process uses pharmaceutically acceptable solvents, excipients and conventional process equipment making it fast and scalable. An additional feature is that polymer absorption on the crystal surface upon freezing aids reduction of Ostwald ripening, e.g. Ketoconazole.³⁸

Table 1: Cyclodextrin based commercially available products

Cyclodextrin/Drug	Route	Market	Trade names
SE7- β -CD (CAPTISOL)/ Zipradidone Voriconazole	IM IV	Europe, USA Europe, USA	Zeldox, Geodon Vfend
α -CD			
PG1, Alprostadil	IV	Europe, Japan, USA	Prostanding, Prostavasin, Edex
OP-1206 Cefotiam hexetil HCl	Oral Oral	Japan Japan	Opalmon Pansporin T
β -CD			
Piroxicam PGE2 Benexate Iodine Dexamethasone Glyteer Nitroglycerin Nimesulide Tiaprofenic acid Omeprazole ME 1207 Cephalosporin	Oral, Rectal Buccal Oral Topical Dermal Buccal Oral Oral Oral Oral	Europe Japan Japan Japan Japan Japan Europe Europe Europe Japan	Brexin, Cycladol, Brexidol Prostarmon E Ulgut, Lonmiel Mena-Galgle Glymesason Nitropen Nimedex, Mesulid Fast Surgamyl Ombeta Meiact
γ -CD			
HP- β -CD (Encapsin) Itraconazole Cisapride Mitomycin	Oral, IV Rectal IV	Europe, USA Europe USA	SporanoxPrepusid Mitozytrex

CONCLUSION

By using one of the above techniques many lipophilic drugs were utilized successfully and will continue to be many more in the future. The success ratio may depend on many factors from pilotization of techniques to uniformity of the product, as well as characterization. However, in the future it may be possible to utilize all the NMEs, no matter what their properties are, if they are pharmacologically active.

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