Self-Emulsifying Drug Delivery Systems (SEDDS) in Pharmaceutical Development

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Abstract

Lipid-based formulations, such as Self-Emulsifying Drug Delivery Systems (SEDDS), are an important tool for lipophilic drugs and offer the potential for enhancing drug absorption and oral bioavailability. SEDDS are a promising approach for the formulation of drug compounds with poor aqueous solubility. These systems are easily manufactured and physically stable mixtures of oil, surfactants, co-surfactants and solubilized drug substances that are administered orally in soft or hard gelatin capsules. In the gastrointestinal tract environment, these systems spontaneously emulsify. This review focuses on SEDDS formulations, describes their different types and presents case studies in which enhanced bioavailability were demonstrated in vivo using this formulation system.

Keywords: Lipid-based drug delivery system; Self-emulsifying drug delivery systems; SMEDDS; SNEDDS; Poorly water-soluble drugs; Bioavailability

Introduction

In pharmaceutical drug discovery, various new chemical entities suffer from poor water solubility. Solubility is considered one of the prerequisites for intestinal absorption; therefore, drugs with low water solubility are predisposed to low and variable oral bioavailability [1,2]. Thus, an increasingly important area of pharmaceutical research is finding safe and effective methods of solubilizing Poorly Water-Soluble Drugs (PWSDD) [3]. Many approaches to improving oral bioavailability have been investigated by enhancing drug solubility or increasing the surface area available for dissolution [4].

In fact, many PWSDD candidates are currently in development, which leads to an increase in the approaches that can be taken to promote the apparent solubility in the gastrointestinal tract and support drug exposure after oral administration [2]. Salt formulation [5], micronization [6], inclusion in cyclodextrins [7], encapsulation in micro/nanoparticles [8-10], preparation of solid dispersions [11], solubility in lipid-based systems [12], mixed micelles [13,14] and the use of silica-based mesoporous materials [15-19] have been the main approaches studied. Lipid-based formulations include lipid solutions, lipid nanoparticles, emulsions, microemulsions or Self-Emulsifying Drug Delivery Systems (SEDDS), as seen in Figure 1 [20-22]. Although the exact mechanisms responsible for this enhanced absorption are not fully known, it is believed that various factors, including improved drug solubilization, increase the particle diffusion in the gastrointestinal tract.

Lipid-based formulations, including self-emulsifying formulations, are the most promising technologies for PWSDD delivery and have been shown to enhance the oral absorption of these drugs [20]. In self-emulsifying formulations, the formed emulsion increases membrane permeability as a result of surfactant presence and enhances lymphatic absorption (lymphatic transport) due to medium and long chain oils. These factors may contribute significantly to the better performance of the formulations [23-25].

Among the lipid-based systems, SEDDS has been selected as a promising strategy to improve the bioavailability of PWSDD. Herein, an overview of SEDDS as a key technology for formulating lipophilic compounds and increasing their oral bioavailability is presented. The emphasis is on SEDDS formulation, characterization and increases in drug bioavailability.

Self-Emulsifying Drug Delivery Systems (SEDDS)

SEDDS are defined as a pre-concentrate containing a mixture of drug, oil, surfactant, co-surfactant and, sometimes, co-solvent [18,26-30]. SEDDS is a broad term associated with the production of emulsions with a droplet size ranging from a few nanometers to several microns, which can be classified as Self-MicroEmulsifying Drug Delivery Systems (SMEDDS) and Self-NanoEmulsifying Drug Delivery Systems (SNEDDS). SMEDDS form transparent microemulsions with oil droplets ranging between 100 and 200 nm, while SNEDDS are more recent, with droplet sizes smaller than 100 nm [31].

SEDDS are usually packed in hard or soft gelatin capsules as pre-concentrate formulations, which form the emulsions when they are dispersed in the gastric and/or intestinal fluids. The dispersions are clear (transparent or at least translucent) and should remain stable on dilution. The hydrophobic agent remains solubilized until the time that is relevant for its absorption [30].

The digestive motility of the stomach and intestine provides the agitation required for self-emulsification in vivo [28]. The advantages of these systems include not only improved drug solubilization but also enhanced release and absorption properties due to the already dissolved form of the drug in the formulation and the resulting small droplet size, which provides a large interfacial surface area [17,32].

As the SEDDS self-emulsifies in the stomach and presents the drug in fine emulsion droplets, it improves drug dissolution by providing a large interfacial area for drug release and absorption. In addition,
SMEDDS was found to depend on the solubility of the drugs in the excipients. The optimal solubility parameter (log P) of the compounds was found to be in the range of 2 to 4.

Date and Nagarsenker [41] prepared SEDDS to overcome problems associated with the delivery of Cefpodoxime Proxetil (CFP), a poorly bioavailable high dose antibiotic with a pH-dependent solubility. The solubility of CFP was determined, and ternary phase diagrams were constructed. The influences of CFP and the pH of the dilution medium on the phase behavior of the selected system were assessed. The globule sizes of optimized CFP-SNEDDS in various dissolution media were determined to investigate the effect of pH on their behavior. In this case, the SEDDS was composed of Capryol 90, Cremophor EL or Solutol HS15 and Akoline-MCM as the oil phase, surfactant and co-surfactant, respectively. The optimized CFP SEDDS needed a surfactant content of less than 40% to form nanoemulsions, and the droplet size was not affected by the pH of the dilution medium. The SNEDDS of CFP could accommodate a high dose of CFP (130 mg) and exhibited a rapid release (20 min.), independent of the pH of the dissolution medium.

In another study, El-Naggar et al. [42] evaluated the possibility of the development of tamoxifen citrate (TAMC) in SNEDDS in an attempt to circumvent the problems of poor water solubility and vulnerability to enzymatic degradation. An optimum system composed of TAMC (1.6%), Maisine 35-1 (16.4%), Capryol 90 (32.8%), Cremophor RH40 (32.8%) and propylene glycol (16.4%) was selected. The system was robust to different dilution volumes and types, and transmission electron microscopy revealed a spherical particle morphology. Additionally, the drug release from the selected formulation was significantly higher than that from other SNEDDS and the drug suspension.

Optimized SNEDDS formulations containing Lacidipine (LCPD) were developed by Basalious et al. [43] in an attempt to improve dissolution and oral absorption. A preliminary screening was carried out to select the proper component combination, and an experimental design was applied to optimize a SNEDDS that contains a minimum amount of surfactant. The optimized formulation of LCPD (4 mg/g), composed of 34.20% oil phase (mixture of Labrafil/Capmul), 40.41% surfactant (mixture of Cremophor/Tween 80) and 25.39% co-surfactant (Transcutol), showed a significant increase in dissolution rate compared to the drug suspension under the same conditions.

**SEDDS bioavailability**

SEDDS improve the oral bioavailability of PWSD by enhancing the solubility and maintaining the drug in a dissolved state, in small droplets of oil, during its transit through the gastrointestinal tract [20]. The improvement of the oral bioavailability has been attributed to dissolution increase of drug, larger surface area provided by the fine emulsion droplets, improved diffusion across the unstirred aqueous layer, and increased mucosal permeability due to high content of surfactants and also by the long chain oil that promotes lipoprotein synthesis with subsequent lymphatic absorption [21,44-50]. The mechanisms by which these factors act are closely linked to the formulation components and properties of the formed emulsions such as fast emulsification, mean size of the droplets and zeta potential. Figure 2 summarizes the main factors acting on the bioavailability of hydrophobic drugs formulated as SEDDS.

Typical case studies from the literature are briefly described here, focusing on formulation components, properties of the dispersions and bioavailability improvements of the drugs in SEEDS.

Attivi et al. [46] studied the bioavailability of mitotane (o,p′-DDD) formulated in SMEDDS. Optimized formulation was composed by
of Capryol®, Tween®, and Cremophor® EL (33:33:33). The intestinal permeation of mitotane in SMEDDS was around 4-fold higher than the marketed formulation Lysodren®. The bioavailability after oral administration in rabbits increased 3.4 times.

Optimal formulation of valsartan drug in SMEDDS was prepared using Capmul MCM oil, Tween 80, and polyethylene glycol 400 (cosurfactant) in a proportion 10:45:45 [47]. SMEDDS preparations were characterized by particle size (12.3 nm), polydispersity (0.138) and zeta potential (-0.746). In vitro release was increased more than 90% when compared with marketed formulation, while drug absorption was 1.78-fold compared to conventional capsule formulation. The authors attribute the gains with SMEDDS mainly to increased permeability of intestinal membrane due to high content of surfactants. Other contributing mechanisms are the lymphatic transport of SMEDDS through transcellular pathway, and also by synthesis of lipoprotein that is promoted by the long-chain oil.

Nielsen et al. [48] studied the influence of SNEDDS and SEDDS and also the dietary state (fasted or fed) of mini pigs on the bioavailability of probucol drug. The formulations were composed of Cremophor RH40; Maisine 35-1:Sesame oil 1:1 w/w and ethanol. The quantities of lipid and surfactant were the same in both formulations. However, they differed in the size of the drops (approx. 100-fold) and twice the ethanol content in SEDDS. Despite these differences, SNEDDS and SEDDS formulations showed no significant difference in drug bioavailability or with the diet condition of the animals. Formulations containing oil or surfactant only had mild decrease in bioavailability. The dietary state of the animals only influenced drug bioavailability in powder formulation. This is a case where drug bioavailability was controlled by the dispersion quality of lipid and surfactant based formulations.

The oral absorption of curcumin-loaded SMEDDS was investigated in mice [49,50].

The formulations comprised 12.5% ethyl oleate, 57.5% of OP:Cremophor, 30.0% co-surfactant (PEG 400), and 20% isopropyl myristate, 60% Cremophor RH40®, 20% ethanol respectively. In both cases the size of the particles ranged between 20-30 nm. The curcumin-loaded SMEDDS absorption was 3.86 times [50] or 12.73 times [51] compared with a curcumin suspension. In both studies, the improved bioavailability was attributed to the increase of dissolution rate of curcumin in SMEDDS, drug protection from chemical and enzymatic degradation, as well as the increasing of the residence time in vivo.

Kommuru et al. [51] developed and characterized SEDDS containing Coenzyme Q10 (CoQ10) and a polyglycolyzed glyceride as cosurfactant. An optimized formulation consisted of Myvacet 9-45 (40%), Labrasol (50%) and lauroglycol (10%). SEDDS improved the bioavailability of CoQ10 two-fold compared to a powder formulation, as evaluated in dogs. The superior performance of SEDDS formulation was attributed to the increase of dissolution rate of curcumin in SMEDDS, drug protection from chemical and enzymatic degradation, as well as the increasing of the residence time in vivo.

Zhao et al. [52] investigated SNEDDS in formulating Zedoary Turmeric Oil (ZTO). In this case, ZTO itself served as a partial lipid phase with the dual advantages of increasing drug loading and
minimizing the amount of the inert oil. An optimized formulation consisted of ZTO, ethyl oleate, Tween 80, transcutol P (30.8:7.7:40.5:21, w/w) and 30% drug loading. Upon dispersion in water, the formulation was rapidly formed fine droplets with a mean size of 68.3 +/- 1.6 nm and zeta-potential of -41.2 +/- 1.3 mV, thereby ensuring physical stability. Following oral administration of ZTO-SNEDDS in rats, both AUC and C_{max} of germacrone, a bioactive marker of ZTO, increased by 1.7-fold and 2.5-fold respectively compared with the unformulated ZTO.

Although the studies are not always reporting the properties of emulsions, such as average diameter, polydispersity and zeta potential, certainly dispersions of finer droplets are most promising. In addition, a zeta potential with high absolute value provides physical stability to the particles in storage and should improve their interaction with the intestinal membrane. Furthermore, optimal coverage of the particles by surfactant / cosurfactant protects drugs from degradation and also maintains the integrity of the particles thus benefiting the intestinal permeation.

**Self-Double-Emulsifying Drug Delivery Systems (SDEDDS)**

Water-in-Oil-in-Water (w/o/w) double emulsions have the potential to enhance the oral bioavailability of drugs with high solubility and low permeability, but their industrial application is limited due to their instability. Self-Double-Emulsifying Drug Delivery Systems (SDEDDS) are formulated by mixing hydrophobic surfactants and water-in-oil emulsions, which are easier to stabilize through formulation optimization.

SDEDDS can spontaneously emulsify to water-in-oil-in-water (w/o/w) double emulsions in the mixed aqueous gastrointestinal environment, with drugs encapsulated in the internal water phase of the double emulsions.

In a study conducted by Qi et al. [53], the potential use of novel SDEDDS for oral drug delivery was described. The authors employed SDEDDS to improve the oral absorption of Pidotimod (PTD), a peptide-like drug with high solubility and low permeability. The PTD-SDEDDS formulation was typical prepared with phospholipids, Span 80, oleic acid, medium chain triglycerides, and Tween 80. Pharmacokinetic studies in rats revealed that the absorption of PTD from SDEDDS showed a 2.56-fold increase in bioavailability compared to a PTD solution. These studies demonstrated the potential use of SDEDDS for formulating PTD and improving the oral bioavailability in vivo.

**Solid Self-Emulsifying Drug Delivery Systems (Solid SEDDS)**

Solid SNEDDS are technological innovations that incorporate liquid or semisolid ingredients into powders, employing diverse solidification techniques such as spray drying [54], melt granulation [55], extrusion–spherization [56], eutectic mixing and nanoparticle technology [57]. The solid SNEDDS are relatively more robust formulations with high stability, improved patient compliance and simple manufacturing [31,54,57].

Solid SEDDS should be used as an alternative for overcoming problems associated with precipitation of the active ingredient and/or the excipients. Kang et al. [58] investigated the effects of solid carriers on the crystalline properties, dissolution and bioavailability of Flurbiprofen (FBP) in a solid SNEDDS. The liquid SNEDDS, composed of Labrafial M 1944 CS, Labrasol and Transcutol HP with 2% FBP, gave a z-average diameter of approximately 100 nm. Different solid SNEDDS formulations were prepared by spray drying the solutions containing liquid SNEDDS and various carriers. Silicon dioxide produced an excellent conventional solid SNEDDS, and it greatly improved the dissolution rate and oral bioavailability of FBP in rats. Magnesium stearate produced a solid SNEDDS with the largest diameter, and it greatly enhanced the dissolution rate and oral bioavailability due to the formation of a simple eutectic mixture. The selection of the carrier is an important factor in the development of solid SNEDDS because the carriers had significant effects on the dissolution and oral bioavailability of FBP and on the formation of solid SNEDDS.

Solid SEDDS can be further formulated into free-flowing powders, granules, pellets, tablets, solid dispersions, microspheres and nanoparticles [53,59,60]. In addition, a limited volume of literature is available describing the use of porous carriers, such as cross-linked porous silicon dioxide (Sylysia 320,350,550,750), magnesium aluminum silicate (Neusilin US2) and microporous calcium silicate (Florite RE), for the adsorption of liquid self-emulsifying formulations and for transforming them into solid SEDDS [61-63].

Beg et al. [64] reported that bioavailability was increased by using porous carriers for the production of solid SNEDDS granules. This investigation demonstrated the potential use of solid SNEDDS granules of Ondansetron Hydrochloride (ONH) to enhance its oral bioavailability by improving its aqueous solubility and facilitating its absorption through lymphatic pathways. Preformulation studies included the screening of excipients for solubility, and pseudo-ternary phase diagrams suggested the suitability of Capmul MCM as the lipid, Labrasol as the surfactant, and Tween 20 as the co-surfactant for the preparation of self-emulsifying formulations. The liquid SNEDDS transformed into free flowing granules by adsorption onto porous carriers such as Sylysia (350,350, and 730) and Neusilin US2. The porous carriers (Sylysia 350,550,730) were found to be suitable for transforming the SNEDDS into solid SNEDDS granules, ostensibly due to their oil adsorption property. The optimized solid SNEDDS granule formulation exhibited a 3.01-fold increase in the oral bioavailability of ONH in rats compared to the pure drug.

**Supersaturated Self-Emulsifying Drug Delivery Systems (super-SEDDS)**

Super-SEDDS formulations contain a reduced amount of surfactant and a water-soluble Polymeric Precipitation Inhibitor (PPI) for generating and maintaining a supersaturated state in vivo by preventing or minimizing the precipitation of the drug [29]. Many research groups have demonstrated that supersaturable formulations are a promising alternative to improve the oral bioavailability of PWSD [29,34,65].

Thomas et al. [65-67] reported a novel super-SEDDS, in which they compared super-SEDDS containing Halofantrine (HAL) above the equilibrium solubility (150% Seq) with conventional SNEDDS containing the drug below the equilibrium solubility (75% Seq). Pre-concentrates comprising either medium chain lipids (Captor 300/Capmul MCM) or long chain lipids (soybean oil/Maisine), Cremophor RH40 and ethanol were formulated, maintaining the lipid-to-surfactant-to-co-solvent ratio constant (55:35:10%). The ability of super-SEDDS to increase the absorption of HAL in dogs, as well as the predictability of the dynamic in vitro lipolysis model, was studied. During in vitro lipolysis, the rapid precipitation of HAL from super-SNEDDS occurred, resulting in an amorphous precipitate of HAL that demonstrated enhanced dissolution characteristics. The enhanced dissolution of the amorphous HAL was also reflected in vivo because
two capsules of conventional SNEDDS were needed to achieve similar AUC and Cmax as those obtained after dosing of a single capsule of super-SNEDDS. The study demonstrated that the absorption of HAL was not hampered by drug precipitation.

In another study, Wei et al. [29] explored super-SEDDS to improve the oral bioavailability of Silybin (SLB) and employed hydroxypropyl methylcellulose (HPMC) as a precipitation inhibitor. The super-SEDDS formulation consisted of SLB, Labrafac CC, Cremophor RH40, Labrasol, and 5% HPMC. In vitro dilution of the super-SEDDS formulation resulted in the formation of a microemulsion, followed by a slow precipitation of SLB, while the conventional SEDDS formulation underwent rapid precipitation, yielding a low SLB solution concentration. The results showed that the presence of HPMC effectively sustained the supersaturated state by retarding the precipitation kinetics. The in vivo study indicated that the AUC-time curve (AUC0→12 h) of the SLB super-SEDDS increased by nearly 3-fold more than that of the conventional SEDDS without the presence of HPMC.

**Perspectives and Future Trends in SEDDS Development**

Lipid formulations such as self-emulsifying/ microemulsifying/nanoemulsifying drug delivery systems have been attempted in many researches to improve the bioavailability and dissolution rate for their better dispersion properties. The performance and ongoing advances in manufacturing technologies has rapidly introduced lipid-based drug formulations as commercial products into the marketplace with several others in clinical development [66]. Some medicines are already commercially available and many research works were published using SEDDS as an alternative to improve lipophilic drugs solubility and therefore bioavailability. Table 1 shows a list of commercially available SEDDS products.

<table>
<thead>
<tr>
<th>Trade name</th>
<th>Year of Approval</th>
<th>Molecule</th>
<th>Composition</th>
<th>Therapeutic use</th>
<th>Company</th>
</tr>
</thead>
<tbody>
<tr>
<td>Accutane</td>
<td>1982</td>
<td>Isotretinoin</td>
<td>beeswax, butylated hydroxyanisole, edetate disodium, hydrogenated soybean oil flakes, hydrogenated vegetable oil, soybean oil, glycerine, parabens (methyl and propyl), iron oxide (red), titanium dioxide, FD&amp;C Red No. 3, FD&amp;C Blue No. 1, FD&amp;C Yellow No. 6, and D&amp;C Yellow No. 10, and</td>
<td>Retinoid (acne)</td>
<td>Hoffmann La Roche</td>
</tr>
<tr>
<td>Sandimmune</td>
<td>1990</td>
<td>Cyclosporine A</td>
<td>corn oil, gelatin, iron oxide red, linoleyl macrogolglycerides, sorbitol, titanium dioxide, and iron oxide yellow</td>
<td>Immunosuppressive Agent</td>
<td>Novartis</td>
</tr>
<tr>
<td>Vesanoid</td>
<td>1995</td>
<td>Tretinoin</td>
<td>beeswax, butylated hydroxyanisole, edetate disodium, hydrogenated soybean oil flakes, hydrogenated vegetable oils, soybean oil, glycerin, yellow iron oxide, red iron oxide, titanium dioxide, methylparaben, and propylparaben</td>
<td>Retinoid (leukemia)</td>
<td>Hoffmann La Roche</td>
</tr>
<tr>
<td>Neoral</td>
<td>1995</td>
<td>Cyclosporine A</td>
<td>corn oil-mono-di-triglycerides, polyoxy 40 hydrogenated castor oil NF, DL-α-tocopherol USP, gelatin NF, glycerol, iron oxide black, propylene glycol USP, titanium dioxide USP, carmine</td>
<td>Immunosuppressive Agent</td>
<td>Novartis</td>
</tr>
<tr>
<td>Norvir</td>
<td>1996</td>
<td>Ritonavir</td>
<td>butylated hydroxytoluene, ethanol, gelatin, iron oxide, oleic acid, polyoxy 35 castor oil, and titanium dioxide</td>
<td>Antiretroviral Agent</td>
<td>Abbott</td>
</tr>
<tr>
<td>Fortovase</td>
<td>1997</td>
<td>Saquinavir</td>
<td>medium chain mono- and diglycerides, povidone, dl-α-tocopherol, gelatin, glycerol, red iron oxide, yellow iron oxide, and titanium dioxide</td>
<td>Antiretroviral Agent</td>
<td>Hoffmann La Roche</td>
</tr>
<tr>
<td>Gengraf</td>
<td>2000</td>
<td>Cyclosporine A</td>
<td>alcohol USP absolute, FD&amp;C Blue No. 2, gelatin NF, polyethylene glycol NF, polyoxy 35 castor oil NF, polysorbate 80 NF, propylene glycol USP, sorbitan monooctade NF, and titanium dioxide</td>
<td>Immunosuppressive Agent</td>
<td>Abbott</td>
</tr>
<tr>
<td>Kaletra</td>
<td>2000</td>
<td>Lopinavir + Ritonavir</td>
<td>FD&amp;C Yellow No. 6, gelatin, glycerin, oleic acid, polyoxy 35 castor oil, propylene glycol, sorbitol special, titanium dioxide, water</td>
<td>Antiretroviral Agent</td>
<td>Abbott</td>
</tr>
<tr>
<td>Aptivus</td>
<td>2005</td>
<td>Tipranavir</td>
<td>polyethylene glycol 400, vitamin E polyethylene glycol succinate, purified water, and propylene glycol</td>
<td>Antiretroviral Agent</td>
<td>Boehringer</td>
</tr>
</tbody>
</table>

*Source: www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm
*Label informations

**Table 1:** Commercially available pharmaceutical products formulated as SEDDS for oral administration.

The fact that almost 50% or more than of the new drugs are hydrophobic by nature implies that SEDDS studies should continue, where more SEDDS formulations should be released at the pharmaceutical market [40]. Formulating these compounds using lipid based systems is one of the growing interest and suitable drug delivery strategies are applied to this class of molecules [68]. Recent advances in these formulation technologies have led to the successful commercialization of lipid-based formulations [67].

Still there is low uptake of lipid-based formulations due to the large empirical development strategies, which include only few commercially successful drug products in the market [68]. There are a number of issues in relation to lipid-based systems which require further investigation including; an understanding of physicochemical properties of lipids and how lipids reduce the variability in plasma profile, lipid drug interactions and formulation classification systems, a better understanding of the versatility of lipid systems and standard methodologies by which the best formulation can be selected for each drug [69].

**Conclusion**

Lipid-based formulations are a key technology to formulating lipophilic compounds and represent an alternative for improving the oral absorption of PWSD. SEDDS are usually explored to improve the bioavailability of hydrophobic drugs. Currently, several formulations have been developed to produce modified emulsified formulations as alternatives to conventional SEDDS. The vast amount of research on the use of SEDDS for enhancing the bioavailability of PWSD has paved the way for the development of novel commercial drugs. SEDDS formulations are a promising pharmaceutical form for the oral administration of PWSD to improve their solubility as well as their bioavailability profile.
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