SOLID SELF-EMULSIFYING DRUG DELIVERY SYSTEM: PREPARATION TECHNIQUES AND DOSAGE FORMS

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ABSTRACT
Drugs are most often administered by the oral route. However, more than 40% of new chemical entities exhibit poor aqueous solubility, resulting in unsatisfactory oral drug delivery. Recently, much attention has been focused on Self-emulsifying drug delivery systems (SEDDS) which are usually used to improve the bioavailability of hydrophobic drugs. Conventional SEDDS, however, are mostly prepared in a liquid form, which can produce some disadvantages. Accordingly, solid SEDDS (S-SEDDS), prepared by solidification of liquid/semisolid self-emulsifying (SE) ingredients into powders, have gained popularity. This article gives an overview of the recent advances in the study of S-SEDDS, especially the related solidification techniques and the development of solid SE dosage forms. Finally, the existing problems and the possible future research directions in this field are pointed out.

Key words: Self-emulsifying drug delivery systems, Solid self-emulsifying drug delivery systems, Multifunctional excipient, Biopharmaceutical aspect.

INTRODUCTION
The oral route is most commonly route for chronic drug therapy, majority of drugs are frequently administered through oral route, but approximately 40% of new drug candidates have poor-water solubility and the oral delivery of such drugs is complicated for the reason that of their low bioavailability, high intra- and inter-subject variability, and not have dose linearity (Sunitha R et al., 2011). One of the most popular and commercially viable formulation approaches for solving these problems is self-emulsifying drug delivery systems (SEDDS). SEDDS have been shown to be reasonably successful in improving the oral bioavailability of poorly water-soluble and lipophilic drugs. Traditional preparation of SEDDS involves dissolution of drugs in oils and their blending with suitable solubilizing agents. However, SE formulations are normally prepared as liquids that produce some disadvantages, for example, high production costs, low stability and portability, low drug loading and few choices of dosage forms. Irreversible drugs/excipients precipitation may also be problematic. More importantly, the large quantity (30–60%) of surfactants in the formulations can induce gastrointestinal (GI) irritation. SMEDDS are mostly prepared in liquid dosage form in soft and hard gelatine capsules which have some manufacturing and leakage problems. The Solid SMEDDS are new approach to overcome above mention problems. In this formulation the liquid self-emulsifying ingredients are incorporated into powder to make solid dosage form such as tablets, capsules by using different techniques such as spheronization, extrusion, etc. To date, there have been some studies that mainly focus on the preparation and
characterization of a single, solid SE dosage form, yet relatively few that introduce S-SEDDS in a systemic way, especially with respect to dosage form development and preparation techniques (Tang B et al., 2008; Sharma V et al., 2012).

**Self-emulsifying drug delivery systems**

Self-emulsifying drug delivery systems (SEDDS) or self-emulsifying oil formulations (SEOF) are defined as isotropic mixtures of natural or synthetic oils, solid or liquid surfactants, or alternatively, one or more hydrophilic solvents and co-solvents/surfactants. Upon mild agitation followed by dilution in aqueous media, such as GI fluids, these systems can form fine oil-in-water (o/w) emulsions or microemulsions (SMEDDS). Self-emulsifying formulations spread readily in the GI tract, and the digestive motility of the stomach and the intestine provide the agitation necessary for self-emulsification. SEDDS typically produce emulsions with a droplet size between 100 and 300 nm while SMEDDS form transparent microemulsions with a droplet size of less than 50 nm. When compared with emulsions, which are sensitive and metastable dispersed forms, SEDDS are physically stable formulations that are easy to manufacture. Thus, for lipophilic drug compounds that exhibit dissolution rate-limited absorption, these systems may offer an improvement in the rate and extent of absorption and result in more reproducible blood–time profiles (Neslihan Gursoy R et al., 2004). The difference between SEDDS and SMEDDS, as depicted in table 1 (Pujara ND, 2012).

**Multifunctional excipient used in SEDDS/SMEDDS**

Rice germ oil (RGO) as a multifunctional excipient in SEDDS. The RGO is obtained from Oryza sativa family Gramineae. RGO is an edible oil having 2.35:1.36:1 proportion of monounsaturated, polyunsaturated, and saturated fatty acids. It consists of triglycerides, mainly C16–C18 fatty acids (81.3–84.3% w/w). RGO is one of the richest sources of potent antioxidant gammaoryzanol (4–5% w/w). Gammaoryzanol is ferulic acid ester derivatives such as 10-phytosteryl ferulates, cycloartenyl ferulate, 24-methylenecycloartanyl ferulate, and campesteryl ferulate. It has various medicinal applications such as prevention of cancer, maintenance of plasma lipid level, and prevention of platelet aggregation. Accelerated oxidation study demonstrated the capability of gamma-oryzanol in preventing lipid peroxidation of oil. Tacrolimus (TAC) is a macrolide antibiotic having potent immunosuppressant activity with very low and variable bioavailability due to its poor solubility, first pass metabolism, and intersubject variability. Hence, Pawar et al. 2012 prepared the SMEDDS of TAC using gamma-oryzanol-enriched RGO as a multifunctional excipient having inherent antioxidant potential as well as higher solubilization capacity for lipophilic drugs like TAC (Pawar SK et al., 2012). Some typical excipients used in SEDDS or SMEDDS as depicted in table 2 (Sarpal K et al., 2010).

**Biopharmaceutical aspect**

It is important to note that lipids (e.g. triglycerides) affect the oral bioavailability of drugs by changing biopharmaceutical properties, such as increasing dissolution rate and solubility in the intestinal fluid, protecting the drug from chemical as well as enzymatic degradation in the oil droplets and the formation of lipoproteins promoting lymphatic transport of highly lipophilic drugs. The absorption profile and the blood/lymph distribution of the drug depend on the chain length of the triglyceride, saturation degree, and volume of the lipid administered. Logically speaking, however, use of SEDDS can be extended to all four categories of biopharmaceutical classification system (BCS) class drugs. These systems can help in solving the undermentioned problems of all the categories of BCS class drugs, as depicted in table 3 (Tang B et al., 2008; Kohli K et al., 2010).

**Biological aspects in selection of SEDDS**

Very few biopharmaceutical studies have been performed with SEDDS, and there is a need for more comparative studies, particularly against simple oils and solid dosage forms. At this stage, however, it is worth speculating on the issues that will influence the absorption from SEDDS. The rate of gastric emptying of SEDDS is similar to solutions, so they are particularly useful where rapid onset of action is desirable. Conversely, if the therapeutic index of the drug is low, the rapid onset and accompanying high T half might lead to undesirable side-effects. With regard to bioavailability, there are differences between formulations that contain water-soluble surfactants or co-solvents and those that do not. The former systems can produce emulsions or micellar solutions with a lower capacity for solubilization of drugs, which might result in precipitation of drugs in the gut. SEDDS formed with relatively hydrophobic surfactants (HLB < 12), such as Tween 85 or Tagat TO, which do not migrate into the aqueous phase, tend to have lower solvent capacities for drugs unless log P (drug) > 4. These SEDDS should be preferable, however, if the drug can be dissolved to an adequate extent. Highly potent but poorly water-soluble drug candidates are a common outcome of contemporary drug discovery programs and present several challenges to drug development – most notably, the issue of reduced systemic exposure after oral administration (Kohli K et al., 2010).

**Solid self-emulsifying drug delivery systems**

SMEDDS can exist in either liquid or solid states. SMEDDS are usually, limited to liquid dosage...
forms, because many excipients used in SMEDDS are not solids at room temperature. Given the advantages of solid dosage forms, S-SMEDDS have been extensively exploited in recent years, as they frequently represent more effective alternatives to conventional liquid SMEDDS. From the perspective of dosage forms, S-SMEDDS mean solid dosage forms with self-emulsification properties. S-SMEDDS focus on the incorporation of liquid/semisolid SE ingredients into powders/ nanoparticles by different solidification techniques (e.g. adsorptions to solid carriers, spray drying, melt extrusion, nanoparticles technology, and so on). Such powders/nanoparticles, which refer to SE nanoparticles/dry emulsions/solid dispersions are usually further processed into other solid SE dosage forms, or, alternatively, filled into capsules (i.e. SE capsules). SE capsules also include those capsules into which liquid/semisolid SEDDS are directly filled without any solidifying excipient. To some extent, S-SMEDDS are combinations of SMEDDS and solid dosage forms, so many properties of S-SMEDDS (e.g. excipients selection, specificity, and characterization) are the sum of the corresponding properties of both SMEDDS and solid dosage forms. For instance, the characterizations of SE pellets contain not only the assessment of self-emulsification, but also friability, surface roughness, and so on. In the 1990s, S-SEDDS were usually in the form of SE capsules, SE solid dispersions and dry emulsions, but other solid SE dosage forms have emerged in recent years, such as SE pellets/tablets, SE microspheres/nanoparticles and SE suppositories/implants (Patel MB et al., 2012).

**Advantage of S-SMEDDS over Liquid SMEDDS**
- Low production cost.
- Convenience of process control.
- High stability and reproducibility.
- Better patient compliance etc.

**Solidification techniques for transforming liquid/semisolid SEDDS to S-SEDDS** (Tang B et al., 2008; Ravichandiran et al., 2011)

**Capsule filling with liquid and semisolid self-emulsifying formulations**

Capsule filling is the simplest and the most common technology for the encapsulation of liquid or semisolid SE formulations for the oral route. For semisolid formulations, it is a four step process:

1. Heating of the semisolid excipient to at least 20°C above its melting point;
2. Incorporation of the active substances (with stirring);
3. Capsule filling with the molten mixture
4. Cooling to room temperature.

For liquid formulations, it involves a two-step process: filling of the formulation into the capsules followed by sealing of the body and cap of the capsule, either by banding or by microspray sealing. The advantages of capsule filling are simplicity of manufacturing; suitability for low dose highly potent drugs and high drug loading potential (up to 50% (w/w)) (Patel MB et al., 2012).

**Spray drying**

Essentially, this technique involves the preparation of a formulation by mixing lipids, surfactants, drug, solid carriers, and solubilization of the mixture before spray drying. The solubilised liquid formulation is then atomized into a spray of droplets. The droplets are introduced into a drying chamber, where the volatile phase (e.g. the water contained in an emulsion) evaporates, forming dry particles under controlled temperature and airflow conditions. Such particles can be further prepared into tablets or capsules. The atomizer, the temperature, the most suitable airflow pattern and the drying chamber design are selected according to the drying characteristics of the product and powder specification.

**Adsorption to solid carriers**

Free flowing powders may be obtained from liquid SE formulations by adsorption to solid carriers. The adsorption process is simple and just involves addition of the liquid formulation onto carriers by mixing in a blender. The resulting powder may then be filled directly into capsules or, alternatively, mixed with suitable excipients before compression into tablets. A significant benefit of the adsorption technique is good content uniformity. SEDDS can be adsorbed at high levels (up to 70% (w/w) onto suitable carriers Solid carriers can be microporous inorganic substances, high surface- area colloidal inorganic adsorbent substances, cross-linked polymers or nanoparticle adsorbents, for example, Neusilin TM US2, Dextran40, silica, silicates, magnesium trisilicate, magnesium hydroxide, talcum, crospovidone and cross-linked sodium carboxymethyl cellulose. Cross-linked polymers create a favorable environment to sustain drug dissolution and also assist in slowing down drug reprecipitation. Nanoparticle adsorbents comprise porous silicon dioxide (Sylysia 550), carbon nanotubes, carbon nanohorns, fullerene, charcoal and bamboo charcoal.

**Melt granulation**

Melt granulation is a process in which granulation is obtained through the addition of a binder that melts at relatively low temperatures. As a ‘one-step’ operation, melt granulation offers several advantages compared with conventional wet granulation, since the liquid addition and the subsequent drying phase are omitted. Moreover, it is also a good alternative to the use of solvent. The notable advantage of this technique includes no use of solvent. The main parameters that
control the granulation process are impeller speed, mixing time, binder particle size, and the viscosity of the binder. A wide range of solid and semisolid lipids can be applied as meltable binders. Thereinto, Gelucire®1, a family of vehicles derived from the mixtures of mono-/di-/tri-glycerides and polyethylene glycols (PEG) esters of fatty acids, is able to further increase the dissolution rate compared with PEG usually used before, probably owing to its SE property.

Melt extrusion/extrusion spheronization

Melt extrusion is a solvent-free process that allows high drug loading (60%), as well as content uniformity. Extrusion is a procedure of converting a raw material with plastic properties into a product of uniform shape and density, by forcing it through a die under controlled temperature, product flow, and pressure conditions. The size of the extruder aperture will determine the approximate size of the resulting spheroids. The extrusion–spheronization process is commonly used in the pharmaceutical industry to make uniformly sized spheroids (pellets). The extrusion–spheronization process requires the following steps: dry mixing of the active ingredients and excipients to achieve a homogenous powder; wet massing with binder; extrusion into a spaghetti-like extrudate; spheronization from the extrudate to spheroids of uniform size; drying; sifting to achieve the desired size distribution and coating (optional). In the wet masses comprising SES (polysorbate 80 and mono-/di-glycerides), lactose, water and MCC, the relative quantities of SES and water had a significant effect on the extrusion force, size spread, disintegration time, and surface roughness of pellets. Studies suggested that the maximum quantity of this SES that can be solidified by extrusion spheronization occupies 42% of the dry pellet weight. Generally, the higher the water level, the longer the disintegration time. The rheological properties of wet masses may be measured by an extrusion capillary. It has been shown that SES containing wet mass with a wide range of rheological characteristics can be processed, but a single rheological parameter cannot be used to provide complete characterization of how well it can be processed by extrusion–spheronization. Applying extrusion–spheronization, SE pellets of diazepam and progesterone and bi-layered cohesive SE pellets have been prepared.

Dosage form development of S-SEDDS

Dry emulsions

Dry emulsions are powders dosage form, in which emulsion spontaneously occurs in vivo or after exposure to an aqueous solution dry emulsion technology solves the stability problems associated with classic emulsions (e.g. phase separation, and contamination by microorganisms) during storage and also helps avoid the use of harmful or toxic organic solvents. Dry emulsions may be redispersed in water before use. Medium chain triglycerides are commonly used as the oil phase for these emulsions. Dry emulsion formulations are typically prepared from oil/ water (O/W) emulsions containing a solid carrier (such as lactose or maltodextrin) in the aqueous phase by rotary evaporation (Myers SL et al., 1992), freeze-drying or spray drying (Christensen KL et al., 2001). Dry emulsions can be used for further preparation of tablets and capsules. To promote the bioavailability of the poorly soluble drug, amlopidine, oleyl polyoxylglycerides (Labrafil® M 1944 CS) were used as the lipophilic phase of the dry emulsion. Most recently, nimodipine dry emulsions have been prepared using Dextran 40 as a water-soluble solid carrier. The most exciting finding in this field is the newly developed enteric-coated dry emulsion formulations, which are potentially applicable for the oral delivery of peptide and protein drugs. These formulations consist of a surfactant, a vegetable oil, and a pH-responsive polymer, and lyophilization is used (Toorisaka E et al., 2005).

Self-emulsifying capsules

After administration of capsules containing conventional liquid SE formulations, microemulsion droplets form and subsequently disperse in the GI tract to reach sites of absorption. However, if irreversible phase separation of the microemulsion occurs, an improvement in drug absorption can be expected. Hence, sodium dodecyl sulfate has been added to SE formulations: Itch et al., 2001 and supersaturatatable SEDDS has been designed, using a small quantity of HPMC (or other polymers) in the formulations to prevent drug precipitation by generating and maintaining a supersaturated state in vivo. These contain a reduced amount of surfactant, thereby minimizing any GI side effects: Gao and Morozowich, 2006; Gao et al., 2003 (Agrawal S et al., 2012). Oral administration of SE capsules has been found to enhance patient compliance compared with the previously used parenteral route. For instance, low molecular weight heparin (LMWH) used for the treatment of venous thrombo-embolism was clinically available only via the parenteral route. So, oral LMWH therapy was investigated by formulating it in hard capsules. LMWH was dispersed in SMEDDS and thereafter the mixture was solidified to powders using three kinds of adsorbents: microporous calcium silicate (FloriteTM RE); magnesium aluminum silicate (NeusilinTM US2) and silicon dioxide (SylsiaTM 320). Eventually these solids were filled into hard capsules. In another study, such adsorbents were also applied to prepare SE tablets of gentamicin that, in clinical use, was limited to administration as injectable or topical dosage forms (Ito Y. et al., 2005).

Self-emulsifying tablet

Combinations of oil and surfactants have offered
great prospective of preparing self emulsifying tablets that have been widely researched. It consists of solidified liquid SES either compressed or moulded into tablet. These preparation offers advantages like tablet melt at body temperature without agitation and in GIT; agitation as peristaltic movements lowers the melting time, resulting in faster emulsification with increased plasma concentration. The resultant SE tablets consistently maintain a higher drug concentration in blood plasma over the same time frame compared with a non emulsifying tablet. Self nano-emulsified tablet dosage form of Ubiquinone was developed by S. Nazzal et al. 2002. SES was absorbed by granular materials and then compressed into tablet (Taksande JB et al., 2011).

Self-emulsifying sustained/controlled-release tablets

SE tablets are mainly prepared as they are stable than the available dosage forms. Sustained action can be produced by using polymeric approach. The latest research in SE tablets is self emulsifying OROS, in which elementary osmotic pump serves as the carrier for the drug. Self emulsifying OROS have some advantages like providing stable plasma concentration and controllable release rate, and increased bioavailability. Solid self emulsifying tablet of diclofenac were prepared by using goat fat and tween 65. Carvedilol prepared as SEDDS tablets is used for treatment of hypertension and cardiac heart failure with controlled release (Ravichandiran V et al., 2011). In order to reduce significantly the amount of solidifying excipients required for transformation of SEDDS into solid dosage forms, a gelled SEDDS has been developed by Patil et al. In their study, colloidal silicon dioxide (Aerosil 200) was selected as a gelling agent for the oil-based systems, which served the dual purpose of reducing the amount of required solidifying excipients and aiding in slowing down of the drug release (Patil P et al., 2004).

Self-emulsifying sustained/controlled-release pellets

Serratoni et al., prepared SE controlled-release pellets by incorporating drugs into SES, thereby improved their rate of release, and then by coating pellets with a water-insoluble polymer that reduces the rate of drug release. To formulate and prepare SEDDS, there were some basic guidelines are considered: safety, compatibility, drug solubility, efficient self-emulsification efficiency and droplet size, etc. Pellets are multiple unit dosage forms, they may provide many advantages than conventional solid dosage forms, due to some factors like flexibility of manufacture, reducing intra subject and inter subject variability of plasma profiles and minimizing GI irritation without lowering drug bioavailability. Thus, it is very interesting to combine the advantages of pellets with those of SEDDS by SE pellets. They were prepared by extrusion/spheronization and contained two water-insoluble model drugs (methyl and propyl parabens); SES contained monoglycerides and Polysorbate 80 (Sunitha R et al., 2011). SE sustained-release matrix pellets could be successfully formulated with glycercyl palmito-stearate (Gelucire 54/02) and glycercyl behenate (Gelucire 70/02) (Hamdani J. et al., 2003).

Self-emulsifying solid dispersions

Although solid dispersions can increase the dissolution rate and bioavailability of poorly water-soluble drugs, some manufacturing problems involving stability are continuing targets for pharmaceutical research. Serajuddin pointed out that these difficulties could be overcome by the use of SE excipients. SE excipients, like Gelucire1 44/14, Gelucire 50/02, Labrasol, Transcutol and TPGS (tocopheryl polyethylene glycol 1000 succinate), have been widely used to solve the same problem (Serajuddin ATM, 1999). Gupta et al. prepared SE solid dispersion granules using the hot-melt granulation method for seven drugs, including four carboxylic acid containing drugs, a hydroxyl-containing drug, an amide containing drug (phenacetin) and a drug with no propondonating groups (progesterone) in which Gelucire 50/13 was used as the dispersion carrier, while Neusilin US2 was used as the surface adsorbent (Patel MB et al., 2012).

Self-emulsifying beads

In an attempt to transform SES into a solid form with minimum amounts of solidifying excipients, Patil and Paradkar investigated loading SES into the microchannels of porous polystyrene beads (PPB) using the solvent evaporation method. PPB with complex internal void structures is typically produced by copolymerizing styrene and divinyl benzene. They are inert, stable over a wide pH range and to extreme conditions of temperature and humidity. This research concluded that PPB was potential carriers for solidification of SES, with sufficiently high SES to PPB ratios required to obtain solid form. Geometrical features, such as bead size and pore architecture of PPB, were found to govern the loading efficiency and In vitro drug release from SES-loaded PPB (Patil P et al., 2006).

Self-emulsifying suppositories

Kim and Ku 2002; investigated the solid-SEDDS could increase not only GI absorption but also rectal/vaginal absorption. Glycyrrhizin which by the oral route, barely achieves therapeutic plasma concentration, can obtain satisfactory therapeutic levels foe chronic hepatic diseases by either vaginal or rectal SE suppositories. The formulation included glycyrrhizin and a mixture of a C6- C18 fatty acid glycerol ester and a C6-C18 fatty acid macrogol ester (Takada and murakami, 2005; Wanwimolruk et al., 1999).
Self-emulsifying nanoparticles

Nanoparticles techniques have been useful in the production of SE nanoparticles. Solvent injection is one of these techniques. In these methods, the lipid, surfactant and drugs were melted together and injected wise into a stirred non-solvent. The resulting self emulsifying nanoparticles were thereafter filtered out and dried. This approach yielded nanoparticles (about 100 nm) with a high drug loading efficiency of 74% (Attama and Nkemnele, 2005). More recently a novel nanoparticles drug delivery system consisting of chitosan and Glyceryl Monooleate (GMO) for the delivery of paclitaxel (PTX) has been developed. The SE property of GMO enhanced the solubility of PTX and provided a formulation for chitosan aggregation, meanwhile causing near 100% loading and entrapment efficiencies (Attama et al, 2005). More recently a novel nanoparticles drug delivery system consisting of chitosan aggregation, meanwhile causing near 100% loading and entrapment efficiencies of PTX: Trickler, 2008 (Agrawal S, 2013).

Self-emulsifying sustained release microspheres

Zedoary turmeric oil (ZTO; a traditional Chinese medicine) shows effective pharmacological actions like tumour suppressive, antibacterial, and antithrombotic activity. You et al, prepared solid SE sustained release microspheres using the quasiemulsion-Solvent diffusion method of the spherical crystallization technique, in this technique ZTO used as oil phase. ZTO release activities might be controlled by the ratio of hydroxyl propyl methylcellulose acetate succinate to Aerosil 200 in the formulation. After oral administration of such microspheres to rabbits, the plasma concentrations were achieved with increased bioavailability of 135.6% with respect to the conventional liquid SEDDS (Sunitha R et al., 2011).

Self-emulsifying implants

SE implants have very much improved efficacy under application of SSEDDS, since they have short half-life. As an example, 1, 3-bis (2 chloroethyl)-1-nitrosourea (carmustine, BCNU) is a chemotherapeutic agent used to treat malignant brain tumors. In order to enhance its stability compared with that released from poly (d,1-lactide-coglycolide)(PLGA) wafer implants, SES was formulated with tributyrin, Cremophor RH 40 (polyoxy140 hydrogenated castor oil) and Labrafal 1944 (polyglycolyzed glycercide). Therefore SES increased In vitro half-life of BCNU up to 130 min compared with 45 min of intact BCNU. In vitro release of BCNU from SE PLGA wafers were extended up to 7days. Such wafers had higher In vitro antitumor activity and were less prone to hydrolysis than those wafers without of SES (Serratoni M, 2012). Table 4 shows some of the marketed formulations of SEEDSs available for oral delivery of various drugs (Kohli K et al., 2010).

### Table 1. Difference between SEEDS and SMEDDS

<table>
<thead>
<tr>
<th>S.No.</th>
<th>SEDDS</th>
<th>SMEDDS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Can be a simple binary formulation with the drug and lipidic excipients able to self emulsify in contact with Gastrointestinal fluids(GIF) Or A system comprising Drug, surfactant, oil (also referred to as lipid phase).</td>
<td>Are composed of the Drug compound, Surfactant, Co-surfactant, and Oil(or lipid phase)</td>
</tr>
<tr>
<td>2</td>
<td>Lipid droplets size in the dispersion ranges from 200nm- 5μm providing a large surface area for absorption.</td>
<td>Lipid droplets size in the dispersion is&lt; 200nm Providing a large surface area for absorption.</td>
</tr>
<tr>
<td>3</td>
<td>The dispersion has a turbid appearance.</td>
<td>The dispersion has an optically clear to translucent appearance.</td>
</tr>
<tr>
<td>4</td>
<td>SEEDS systems are not Thermodynamically stable in water or physiologic conditions.</td>
<td>SEEDS systems are Thermodynamically stable in water or physiologic conditions.</td>
</tr>
</tbody>
</table>

### Table 2. Examples of typical excipients used in SEEDS/SMEDDS

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Trade name</th>
<th>Chemical name</th>
<th>HLB</th>
<th>Regulatory status</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Vegetable oil</td>
<td>Long- chain TAG</td>
<td>-</td>
<td>Oral product, GRAS, FDA IIG</td>
</tr>
<tr>
<td>2</td>
<td>Miglyol 812</td>
<td>Medium-chain TAG caprylic/capric TAG</td>
<td>-</td>
<td>Oral product, GRAS, FDA IIG</td>
</tr>
<tr>
<td>3</td>
<td>Tricaprylin</td>
<td>Medium-chain TAG</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>Labrafac CC</td>
<td>caprylic/capric TG</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>Ethyl oleate</td>
<td>Ethyl ester of C18:1 omega FA</td>
<td>-</td>
<td>FDA IIG</td>
</tr>
<tr>
<td>6</td>
<td>Captex 355</td>
<td>Glyceryl caprylate caprate</td>
<td>-</td>
<td>GRAS, FDA IIG</td>
</tr>
<tr>
<td>7</td>
<td>Isopropyl myristate</td>
<td>FA ester</td>
<td>-</td>
<td>FDA IIG</td>
</tr>
<tr>
<td>8</td>
<td>Labrafac PG</td>
<td>PG dicaprylocaprate</td>
<td>-</td>
<td>USFA, JSFA, EP</td>
</tr>
</tbody>
</table>
Table 3. Application of SEDDS in various BCS category drugs

<table>
<thead>
<tr>
<th>BCS Class</th>
<th>Problems</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I</td>
<td>Enzymatic degradation, gut wall efflux</td>
</tr>
<tr>
<td>Class II</td>
<td>Solubilization and bioavailability</td>
</tr>
<tr>
<td>Class III</td>
<td>Enzymatic degradation, gut wall efflux and bioavailability</td>
</tr>
<tr>
<td>Class IV</td>
<td>Solubilization, enzymatic degradation, gut wall efflux and bioavailability</td>
</tr>
</tbody>
</table>

Table 4. Marketed formulations of SEDDS

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Active moiety</th>
<th>Trade name</th>
<th>Dosage forms</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Tretinoin</td>
<td>Vesanoid (Roche)</td>
<td>Soft gelatin capsule, 10 mg</td>
</tr>
<tr>
<td>2</td>
<td>Isotretinoin</td>
<td>Accutane (Roche)</td>
<td>Soft gelatin capsule, 10, 20 and 40 mg</td>
</tr>
<tr>
<td>3</td>
<td>Cyclosporine</td>
<td>Panimum bioral (Panacea Biotec)</td>
<td>Capsule, 50 and 100 mg</td>
</tr>
<tr>
<td>4</td>
<td>Cyclosporin A</td>
<td>Gengraf (Abbott)</td>
<td>Hard gelatin capsule, 25 and 100 mg</td>
</tr>
<tr>
<td>5</td>
<td>Cyclosporin A</td>
<td>Sandimmune (Novartis)</td>
<td>Soft gelatin capsule, 25, 50 and 100 mg</td>
</tr>
<tr>
<td>6</td>
<td>Lopinavir and Ritonavir</td>
<td>Kaletra (Abbott)</td>
<td>Soft gelatin capsule, Lopinavir 133.33 mg and Ritonavir 33.3 mg</td>
</tr>
<tr>
<td>7</td>
<td>Sanquinavir</td>
<td>Fortovase (Roche)</td>
<td>Soft gelatin capsule, 200 mg</td>
</tr>
<tr>
<td>8</td>
<td>Tipranavir</td>
<td>Aptivus (Boehringer Ingelheim)</td>
<td>Soft gelatin capsule, 250 mg</td>
</tr>
<tr>
<td>9</td>
<td>Amprenavir</td>
<td>Agenerase (GSK)</td>
<td>Soft gelatin capsule</td>
</tr>
</tbody>
</table>
CONCLUSION

S-SEDDS are a promising approach for the formulation of drug compounds with poor aqueous solubility. As improvements or alternatives of conventional liquid SEDDS, S-SEDDS are superior in reducing production cost, simplifying industrial manufacture, and improving stability as well as patient compliance. Most importantly, S-SEDDS are very flexible to develop various solid dosage forms for oral and parenteral administration. Moreover, GI irritation is avoidable and controlled/sustained release of drug is achievable.

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