**Novel Integrated Approach for the Strategic Delivery of Hydrophobic Drugs by the Use of Self Emulsifying Drug Delivery System**

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**Abstract:** The oral delivery of hydrophobic drugs faces a major challenge because of the low aqueous solubility of such compounds. Approximately, 40% of new chemical entities exhibit poor aqueous solubility and present a major challenge to modern drug delivery system because of their low bioavailability. The availability of the drug for absorption can be enhanced by presentation of the drug as a solubilizer within a colloidal dispersion. Self-emulsifying Drug Delivery Systems (SEDDS), which are isotropic mixtures of oils, surfactants, solvents and co-solvents/surfactants, can be used for the design of formulations in order to improve the oral absorption of highly lipophilic drug compounds. The principal characteristic of these systems is their ability to form fine oil-in-water (o/w) emulsions or microemulsions upon mild agitation following dilution by an aqueous phase through the gastrointestinal tract for lipophilic drugs, which display dissolution rate-limited absorption. SEDDS may be a promising strategy to improve the rate and extent of oral absorption. This article gives an overview of the recent advances in the study of SEDDS and improvement of pharmacokinetic parameters of bioactives through SEDDS.

**Key words:** Self emulsifying drug delivery system, surfactants, co solvent, bioavailability

**INTRODUCTION**

Oral route has been the major route of drug delivery for the chronic treatment of many diseases (Gursoy and Benita, 2004; Katteboina et al., 2009). Since, most of the orally delivered drugs (40-50%) either synthetic or herbal are vulnerable because of the poor water solubility of the drug itself, which results in poor oral bioavailability, high intra- and inter-subject variability and lack of dose proportionality (Ajazuddin, 2010; Gursoy and Benita, 2004; Robinson, 1996).

To bypass the associated problems as discussed above, a number of technologies have been applied, such as the use of surfactants, lipids, permeation enhancers, micronization, salt formulation, cyclodextrins, nanoparticles and solid dispersions (Fig. 1) (Giri et al., 2010a; 2008; Kohli et al., 2010; Pouton, 2000; Angst, 1993; Stegemann et al., 2007). Hence, producing suitable formulations is essential to improve the solubility and bioavailability of such drugs. SEDDS is being used by the formulation scientists as a reliable method for increasing oral bioavailability of poorly soluble drugs. So, we have prepared this review to describe a number of aspects of self-emulsifying drug delivery systems (Wakerly et al., 1987; Charman et al., 1992; Shah et al., 1994; Constantinides, 1995). Self-emulsifying Drug Delivery Systems (SEDDS) (Fig. 2) or self-emulsifying oil formulations (SEOIF) are defined as, isotropic mixtures of natural or synthetic oils, Solid or liquid surfactants or alternatively, one or more hydrophilic solvent and cosolvent (Craig, 1993; Hussain et al., 2004; Shukla et al., 2010; Patel et al., 2010a).

SEDDS emulsify spontaneously to produce, fine oil in-water emulsions when introduced into an aqueous phase under gentle agitation in GIT (Mahesh et al., 2011; Patel et al., 2010b; Tang et al., 2007; Kommuru et al., 2001).

**Potential advantages of these systems include:** Protection of sensitive drug substances, more steady drug absorption, selective targeting of drug(s) toward specific absorption window in GIT, safety of drug(s) from the gut environment, manage of delivery profiles, reduced changeability including food effects and better oral bioavailability enabling reduction in dose (Patel et al., 2008; Amidon et al., 1995; Giri and Tripathi, 2010).

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Fig. 1: Some of the formulation approaches to improve the oral bioavailability of poorly water soluble drugs

Fig. 2: Self-Emulsifying drug Delivery System

**Advantages of SEDDS over conventional drug delivery system (DDS):** Emulsions are sensitive and metastable dispersed forms while SEDDS are physically stable formulation that are easy to manufacture, as compared with oily solutions, they provide a large interfacial area for partitioning of the drug between oil and water (Oviawe et al., 2006; Nidhi and Srivastava, 2009; Ousroy and Benita, 2004).

**Need of SEDDS:** Poor water solubility sometimes become a constraint for required absorption of a drug from its oral delivery system. Particulate dissolution is observed as rate limiting step. For this the drug is predissolved in a suitable solvent and dispersed in the form of capsule (Obitte et al., 2008; Bajaj et al., 2011).

**Lipid formulation classification system (LFCS):** Lipid Formulation Classification System (LFCS). Table 1 showing typical compositions and properties of lipid-based drug delivery systems.

**Components of SEDDS:** There is large variety of liquid or waxy excipients existing, ranging from oils through biological lipids, lipophilic and hydrophilic surfactants, water soluble cosolvents, or many different combinations which could be used for encapsulation in hard or soft gelatin (Shanmugam et al., 2011). List of various components which are used for the formulation of SEDDS are listed into Table 2. The self-emulsifying process is depends on the nature of the oil-surfactant pair, the surfactant concentration, the temperature at which self-emulsification occurs (Reddy et al., 2011; Mallikarjun and Rajesh Babu, 2011).

**Oils:** For development of a SEDDS formulation oil play an important role because lipophilic drug are dissolved in oil, it facilitate the emulsification and it can transport a fraction of dissolved drug through the intestinal lymphatic system, thereby can improve the absorption of drug depending on the nature of triglyceride. In general long to medium chain triglycerides with variable degree of unsaturation are used for preparation of SEDDS (Lindmark et al., 1995; Charman and Stella, 1991; Holm et al., 2002; Gupta et al., 2009). Unmodified edible oils provide the most 'natural' basis for lipid vehicles, but having poor capacity to dissolve large amounts of hydrophobic drugs and comparatively not produce efficient self-emulsification markedly diminish their use in SEDDS (Kimura et al., 1994; Hauss et al., 1998; Farah et al., 1994; Tripathi et al., 1994).

**Surfactants:** A number of compounds exhibiting surfactant properties may be employed for the design of self-emulsifying systems, the most widely suggested ones being the non-ionic surfactants with a relatively high Hydrophilic Lipophilic Balance (HLB). The frequently
Table 1: Lipid formulation and classification system

<table>
<thead>
<tr>
<th>Formulation type</th>
<th>Composition</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type I</td>
<td>Oils without surfactants</td>
<td>Non-dispersing, poor solvent capacity</td>
</tr>
<tr>
<td>Type II</td>
<td>Oils and water-insoluble surfactants</td>
<td>Turbid w/o dispersion (particle size 0.25-2 μm), loss of solvent capacity on digestion</td>
</tr>
<tr>
<td>Type III</td>
<td>Oils-water-soluble surfactants and co-solvent</td>
<td>Bushy to clear dispersion, possible loss of solvent capacity on dispersion</td>
</tr>
<tr>
<td>Type IV</td>
<td>Water-soluble surfactants and co-solvents (oil-free)</td>
<td>Form a clear micellar solution on dispersion</td>
</tr>
</tbody>
</table>

Table 2: Examples of oils, surfactants, co-surfactant and co-solvents used

<table>
<thead>
<tr>
<th>Oil</th>
<th>Surfactants</th>
<th>Co-Surfactant/co-solvent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cotton seed oil</td>
<td>Polysorbate 20 (Tween 20)</td>
<td>Span 20</td>
</tr>
<tr>
<td>Soybean oil</td>
<td>Polysorbate 80 (Tween 80)</td>
<td>Span 80</td>
</tr>
<tr>
<td>Corn oil</td>
<td>D-alpha Tocopheryl polyethylene glycol 1000 succinate (TPGS)</td>
<td>Capryol 90</td>
</tr>
<tr>
<td>Sunflower oil</td>
<td></td>
<td>Lauroglycol</td>
</tr>
<tr>
<td>Castor oil</td>
<td>Polyoxy-35-castor oil</td>
<td>Transcutol</td>
</tr>
<tr>
<td>Sesame oil</td>
<td>(Cremophore RH40)</td>
<td></td>
</tr>
<tr>
<td>Peanut oil</td>
<td>Polyoxy-40</td>
<td>Ethanol</td>
</tr>
<tr>
<td>Labrafac</td>
<td>hydrogenated castor oil</td>
<td>Propylene glycol</td>
</tr>
<tr>
<td>Labrasol</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Fig. 3: Surfactant molecule containing hydrophilic head and hydrophobic tail group

Julianto et al. (2000) work on improved bioavailability of vitamin E with a self-emulsifying formulation and on the basis of the result obtained, he was concluded that it is apparent that the self-emulsifying preparation achieved a higher rate and extent of absorption compared to the soft gelatin capsule under fasted condition.

Attama (2003) is using solid self-emulsifying system in the delivery of digitoxigenin and he concluded that the tablets showed good release profile, as well as acceptable tablet properties the batches with higher tween 65: goat fat content ratios gave better release rate.

Hong et al. (2006) formed a new self-emulsifying formulation of Itraconazole with improved dissolution and oral absorption and it was considered that Itraconazole is a representative poorly water-soluble drug. Thus, the marketed formulation Spronar® capsule showed great differences between post and pre-prandial state in human.

Self-emulsifying formulation developed in this study, shows constant absorption after oral administration with no effect of dietary condition. Since SEDDS rapidly formed fine particles sized 100-1000 nm, the dissolution problems were solved and the absorption was improved.

Agarwal et al. (2009) studied dissolution and powder flow characterization of solid self-emulsifying drug delivery system (SEDDS) of griseofulvin could be readily adsorbed on silica and silicates. He was found that the effect of SEDDS on the flow behavior of the adsorbent is similar to that observed in wet granulation process. Adsorption of SEDDS, however, exhibits a lag or critical phase during which no change in flow is observed. During this phase, the SEDDS formulation is embedded within the carrier and entrapped in the intraparticular pores. Therefore, the duration of the lag phase depends on the adsorbing capacity, size and specific surface area

used emulsifiers are a variety of solid or liquid ethoxylated polyglycolyzed glycerides and Tween 80 (Patel et al., 2011a; Kyanwar et al., 2010a). Emulsifiers of natural origin are selected since they are better than the synthetic surfactants (Yuasa et al., 1994; Georgakopoulos et al., 1992; Crison and Amidon, 1999; Reiss, 1975) (Fig. 3).

Surfactants are amphiphilic in nature and they can dissolve or solubilize relatively high amounts of hydrophobic drug compounds (Sen et al., 2011). The precipitation of drug in the lumen of GI tract can be arrested by the surfactant present. Surfactant can also increase the residence time in GI tract. However, due to excess of surfactant permeability of intestinal wall can reversibly change to a moderate extent. Thus, it is very necessary and important to optimize the concentration of surfactant (Gupta et al., 2009; Belur et al., 2011).

Co-solvents: Generally high surfactant concentrations (more than 30% w/w) are used in order to produce an effective self-emulsifying formulation. Organic solvents are suitable for oral administration Propylene Glycerol (PG), ethanol, polyethylene glycol (PEG), etc. may be help to dissolve large quantity of the hydrophilic surfactant in the drug which is the lipid base and can act as co-surfactant in the self-emulsifying drug system (Panesar et al., 2011; Alexander et al., 2011; Scianki et al., 2011).

Recent researches and rationales of SEDDS in various category of drug: Kim and Ku (2000) enhanced absorption of indomethacin after oral or rectal administration in rats by self-emulsifying system and he was observed that, the SEDDS (30% of Tween 85 and 70% of Ethyl Oleate) was selected as an optimized formulation (high drug loading, low surfactant concentration and small particle size) for IDM, a poorly water-soluble drug.
of the adsorbent. This phase could be used as a guide in formulation development to determine the extent of SEDDS addition without impacting flow. In addition, it could be used as a measure of the critical point after which further SEDDS addition would cause particle agglomeration.

Zvonar et al. (2010) formed microencapsulation of self-microemulsifying system for improving solubility and permeability of furosemide. At last, he was explained that the permeability of furosemide was enhanced by its implementing into SMES, most probably by altering apical membrane fluidity, opening tight junctions and inhibiting efflux transporters involved in the intestinal secretion of furosemide (Soliman et al., 2007). Also the dissolution rate of furosemide from microcapsules was considerably faster than from reference microsphere (Zvonar et al., 2010).

Setthachowakul et al. (2010) work on development and evaluation of self-microemulsifying liquid and pellet formulations of curcumin and absorption study on rats, he concluded that the optimal formulations of the curcumin-SMEDDS liquid (F6) and curcumin-SMEDDS pellets (P3) were successfully developed in this study. The SMEDD and SMEDDS pellets readily released the lipid phase to form a fine oil-in-water micro emulsion, with a narrow distribution size. The release of about 80% of curcumin from curcumin-SMEDDS in liquid and pellet forms was considerably greater compared to only 5% in aqueous solution from the unformulated curcumin. Pharmacokinetic studies in rats revealed that both liquid and pellet SMEDDS showed 14- and 10-fold greater absorption, respectively, of curcumin, compared to the same oral dose (50 mg kg⁻¹) of the curcumin aqueous suspension. The capsules filled with SMEDDS liquid and pellets were found to be stable over a period of 6 months under intermediate and accelerated conditions. Our studies illustrated the potential use of new self-microemulsifying systems in liquid and pellet forms for oral delivery of poorly water-soluble drug such as curcumin.

Iosio et al. (2011) formulated self-emulsifying pellets for increase oral bioavailability of silymarin. At last he concluded that, extrusion/spheronization is a viable technology to produce self-emulsifying pellets of good quality and able to improve in vivo oral bioavailability of main components of a phytotherapeutic extract of more than 100 times by enhancing the lymphatic route of absorption (Iosio et al., 2011; Amarji et al., 2007). Similarly, various categories of drugs that are formulated as SEDDS are discussed in the given Table 3 with their purpose of making, excipient use, route and advances. (Fig. 4, 5).

**Formulation:** Various studies are performed for choice of oil, which is an important and important requisite for development of SEDDS and SMEDDS. It is mixture of oil, a surfactant and a co-surfactant. Solubility of drug is determined in various oils and surfactants. A series of SEDDS and SMEDDS system containing drug, various oil and surfactants are prepared. Then, studied in vitro self-emulsification properties and droplet size analysis of these formulations upon their addition to water under mild agitation conditions. Pseudo-ternary phase diagram is constructed, identifying the efficient self-emulsification region. From these studies, an optimized formulation is selected and its bioavailability is compared with a reference formulation (Sarfuddin and Chua, 2006; Giri et al., 2010b).

The process of making self-emulsion drug delivery system for increasing the bioavailability of a drug and/or pharmaceutical ingredient by emulsifying the drug with the self-emulsifying excipient consists of various steps as Solubilizing a poorly water-soluble drug and/or pharmaceutical ingredient in a mixture of surfactant, cosurfactant and solvent (Craig et al., 1995; Dabros et al., 1999; Venkatesh et al., 2010). Now mix the oil phase if necessary, by heating or other elementary means, to the solubilized drug formulation and thoroughly mixed. The formed emulsion can then be poured to a suitable dosage form such as soft or hard-filled gelatin capsules and allowed to cool (Porter and Charman, 2001a; Kyatanwar et al., 2010b). The addition of a drug to a

![Image](image.png)

Fig. 4: Representation of the most commonly encountered phases upon addition of water to an oil surfactant combination.
Fig. 5: Potential mechanism for absorption enhancement

Table 3: Various examples of SEDDS

<table>
<thead>
<tr>
<th>Bioactives</th>
<th>Category</th>
<th>Objective</th>
<th>Application</th>
<th>Key-ingredients</th>
<th>Route</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diclofenac</td>
<td>NSAID</td>
<td>Better release rate</td>
<td>Solubility and bioavailability increases</td>
<td>Tween 65, Praditin</td>
<td>Oral</td>
<td>Attaran et al. (2002)</td>
</tr>
<tr>
<td>Ketoprofen</td>
<td>NSAID</td>
<td>Increased bioavailability</td>
<td>AUC$_{0-24h}$ increased</td>
<td>Oils, lactose</td>
<td>Oral</td>
<td>Patil et al. (2004)</td>
</tr>
<tr>
<td>Nimesulide</td>
<td>NSAID</td>
<td>Influence of cryogenic grinding on SEDDS</td>
<td>Improved drug solubility and permeability</td>
<td>Labrafac, Labrasol</td>
<td>Oral</td>
<td>Franceschini et al. (2005)</td>
</tr>
<tr>
<td>Celecoxib</td>
<td>NSAID</td>
<td>Increase bioavailability</td>
<td>Solubility and bioavailability increases SEDDS formulation</td>
<td>Labrafac 1349, 90</td>
<td>Oral</td>
<td>Saji and Lohia (2011)</td>
</tr>
<tr>
<td>Etodolac</td>
<td>NSAID</td>
<td>Enhancement of digestion and oral absorption</td>
<td>SEDDS formulation: reduced efflux by 60%</td>
<td>Capryol 90</td>
<td>Oral</td>
<td>Barakat (2010)</td>
</tr>
<tr>
<td>Piroxicam</td>
<td>NSAID</td>
<td>Determine particle size, absolute drug content</td>
<td>In vivo release of pellets was higher than oral drug</td>
<td>Tween 65, fat homolipid</td>
<td>Oral</td>
<td>Attaran et al. (2006)</td>
</tr>
<tr>
<td>Aceclofenac</td>
<td>NSAID</td>
<td>Increase solubility and bioavailability</td>
<td>In vitro release of pellets was higher than pure drug</td>
<td>Oleic acid, lecithin, oil</td>
<td>Oral</td>
<td>Reddy et al. (2011)</td>
</tr>
<tr>
<td>Artemether</td>
<td>Antimalarial</td>
<td>Novel indigenous natural lipophiles as an oil phase</td>
<td>Self emulsification efficiency and release increases</td>
<td>Oil-in-NLCs, Tween 80</td>
<td>Oral</td>
<td>Mandaogade et al. (2008)</td>
</tr>
<tr>
<td>Halofantrine</td>
<td>Antimalarial</td>
<td>Novel indigenous natural lipophiles as an oil phase</td>
<td>6 to 8 fold improvement in absolute oral bioavailability</td>
<td>Captopril, masine</td>
<td>Oral</td>
<td>Kho et al. (1998)</td>
</tr>
<tr>
<td>Amiodipine</td>
<td>Anti-hypertensive</td>
<td>Increase solubility and oral bioavailability</td>
<td>Drug Release (p&lt;0.01) Higher than marketed tablet</td>
<td>Labrafac M, Tween 80, Ethanol</td>
<td>Oral</td>
<td>Chhabra et al. (2011)</td>
</tr>
<tr>
<td>Glyburide</td>
<td>Anti-diabetic</td>
<td>Improve the dissolution properties</td>
<td>Improvement of drug dissolution</td>
<td>Transcutol, Tween 20</td>
<td>Oral</td>
<td>Muru et al. (2010)</td>
</tr>
<tr>
<td>Carvedilol</td>
<td>Anti-hypertensive</td>
<td>Increase solubility, dissolution rate and oral bioavailability</td>
<td>Dissolution rate of SEEDSS and SMEDDS was more than 2 fold faster than tablets</td>
<td>Labrafac, Transcutol P</td>
<td>Oral</td>
<td>Wei et al. (2005)</td>
</tr>
<tr>
<td>Acyclovir</td>
<td>Anti-viral</td>
<td>Enhancement of bioavailability</td>
<td>3.5 fold increases in bioavailability</td>
<td>Tween 60, glycerol, sunflower oil</td>
<td>Oral</td>
<td>Patel and Vavia (2007)</td>
</tr>
<tr>
<td>Irbesartan</td>
<td>Anti-hypertensive</td>
<td>Enhance the oral bioavailability</td>
<td>7.5 fold increases in the oral bioavailability</td>
<td>Cremophore EL, Carbopol</td>
<td>Oral</td>
<td>Patel et al. (2011b)</td>
</tr>
<tr>
<td>Nimodipine</td>
<td>Anti-hypertensive</td>
<td>A controlled release system based SMEDDS mixture</td>
<td>Combining the character of controlled release and SEDDS</td>
<td>Ethyl-oleate, cremophore</td>
<td>Oral</td>
<td>Hafez et al. (2008)</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>Anti-microbial</td>
<td>Preliminary studies on two vegetable oil based SEDDS</td>
<td>Reduction in the number of formulation that maintain isotropicity and stability after 72 h</td>
<td>Tween 65, palm oil</td>
<td>Oral</td>
<td>Obeme et al. (2008)</td>
</tr>
</tbody>
</table>
Table 3: Continue

<table>
<thead>
<tr>
<th>Bioactives</th>
<th>Category</th>
<th>Objective</th>
<th>Application</th>
<th>Key-ingredients</th>
<th>Route</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vinpocetine</td>
<td>Anti-inflammtory</td>
<td>Evaluated pharmacokinetic and bioavailability</td>
<td>Oral bioavailability was 1.72 fold higher than tablet</td>
<td>Solutol</td>
<td>Oral</td>
<td>Cui et al. (2009)</td>
</tr>
<tr>
<td>Curcumin</td>
<td>Anti-inflammtory</td>
<td>Improve solubility and bioavailability in vivo and oral absorption</td>
<td>10-14 fold increased absorption</td>
<td>Cremophore EL</td>
<td>Oral</td>
<td>Sethacheewakul et al. (2010)</td>
</tr>
<tr>
<td>Nobiletin</td>
<td>Anti-inflammtory</td>
<td>Improve the solubility and oral absorption</td>
<td>SMEDDS dilution was higher</td>
<td>Castor oil</td>
<td>Oral</td>
<td>Yao et al. (2008)</td>
</tr>
<tr>
<td>Vitamin E</td>
<td>Anti-Oxidant</td>
<td>Improve bioavailability</td>
<td>Absorption was increased by almost 3 fold</td>
<td>Tween 80</td>
<td>Oral</td>
<td>Julianto et al. (2006)</td>
</tr>
<tr>
<td>Paenarumia</td>
<td>Anti-oxidant</td>
<td>Improve in vitro dissolution and oral absorption in beagle dogs</td>
<td>2.5 fold increases in the relative bioavailability</td>
<td>Tween 80</td>
<td>Oral</td>
<td>Cui et al. (2005)</td>
</tr>
<tr>
<td>Tocotrienol</td>
<td>Anti-oxidant</td>
<td>Influence of lipolysis and droplet size on absorption</td>
<td>Bioavailability increase up to 2 times</td>
<td>Soybean oil</td>
<td>Oral</td>
<td>Yap and Yuen (2004)</td>
</tr>
<tr>
<td>Buparvaquone</td>
<td>Antiprotozoal</td>
<td>Prepare a liquid based SMEDDS</td>
<td>Oral bioavailability for BPQ was found to be 40.10%</td>
<td>Cetyl alcohol</td>
<td>Oral</td>
<td>Gentala et al. (2010)</td>
</tr>
<tr>
<td>Loratadine</td>
<td>Antihistamine</td>
<td>Porous polystyrene beads act as carrier for SES.</td>
<td>PFPs are potential carriers for solidification</td>
<td>Cremophore EL</td>
<td>Oral</td>
<td>Patil and Pandiar (2006)</td>
</tr>
<tr>
<td>Exemestane</td>
<td>Aromatase inhibitor</td>
<td>Improve the solubility and bioavailability</td>
<td>2-9 fold increases in bioavailability</td>
<td>Labraofin</td>
<td>Oral</td>
<td>Singh et al. (2009)</td>
</tr>
<tr>
<td>Lutein</td>
<td>Carotenoids</td>
<td>Improve the bioavailability</td>
<td>Bioavailability increases 16.1 fold</td>
<td>Oleic acid</td>
<td>Oral</td>
<td>Shammugam et al. (2011)</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>Hypolipidemic</td>
<td>Improve oral biochemical performance</td>
<td>Bioavailability increases</td>
<td>HCL</td>
<td>Oral</td>
<td>Chouksey et al. (2011)</td>
</tr>
<tr>
<td>Fenofibrate</td>
<td>Hypolipidemic</td>
<td>Develop and evaluate an optimal SMEDDS</td>
<td>Higher pharmacodynamic potential than compared with plain</td>
<td>Cremophore EL</td>
<td>Oral</td>
<td>Patel and Sawant (2007)</td>
</tr>
<tr>
<td>Lovastatin</td>
<td>Hypolipidemic</td>
<td>Evaluation of SEDDS</td>
<td>Bioavailability increases</td>
<td>Cremophore EL</td>
<td>Oral</td>
<td>Singh et al. (2010)</td>
</tr>
<tr>
<td>Torcetrapib</td>
<td>Hypolipidemic</td>
<td>Reduces the food effect for torcetrapib</td>
<td>Absorption was rapid and the food effect was reduced</td>
<td>Labraofin</td>
<td>Oral</td>
<td>Perlman et al. (2008)</td>
</tr>
<tr>
<td>Pidotimod</td>
<td>Immunostimulant</td>
<td>Improve the oral absorption</td>
<td>2.56-fold (p=0.05) increased absorption</td>
<td>Oleic acid</td>
<td>Oral</td>
<td>Qi et al. (2011)</td>
</tr>
<tr>
<td>Orudonin</td>
<td>Diterpenoid</td>
<td>Enhance the oral bioavailability of the poorly water soluble drug</td>
<td>2.2 fold increase in relative bioavailability</td>
<td>Oleic acid</td>
<td>Oral</td>
<td>Zhang et al. (2008)</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>Anticancer</td>
<td>Improvement of stability of DOX in aqueous media</td>
<td>More effective in inhibition of E, F, cell proliferation</td>
<td>Tetraglycol</td>
<td>Oral</td>
<td>Kim et al. (2011)</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>Anti-mycotic agent</td>
<td>Evaluated physicochemical properties and pharmacokinetic parameter</td>
<td>Bioavailability and permeability increases</td>
<td>Transcutol</td>
<td>Oral</td>
<td>Hoog et al. (2006)</td>
</tr>
<tr>
<td>Phenytin</td>
<td>Anti-epileptic</td>
<td>Develop and characterize self-mobilizing drug delivery system</td>
<td>After SEDDS administration AUC increased by 2.3 times</td>
<td>Labraofin</td>
<td>Oral</td>
<td>Atef and Belmonte (2008)</td>
</tr>
<tr>
<td>Xibromol</td>
<td>Anti-biotic</td>
<td>Developing a stable liquid formulation of the drug</td>
<td>Dissolution and bioavailability increases</td>
<td>Labraofin</td>
<td>Oral</td>
<td>Cirri et al. (2007)</td>
</tr>
<tr>
<td>Cefodoxime</td>
<td>Anti-biotic</td>
<td>Overcome the problem associated with the delivery of cefodoxime</td>
<td>Completely dissolved within 20 min irrespective of the pH of dissolution medium.</td>
<td>Labraofin</td>
<td>Oral</td>
<td>Date and Nagarsenker (2007)</td>
</tr>
<tr>
<td>Silymarin</td>
<td>Flavonolignans</td>
<td>Develop novel solid self-emulsifying pellets to deliver milk</td>
<td>100 times bioavailability increases</td>
<td>Miglylol 812</td>
<td>Oral</td>
<td>Iosio et al. (2011)</td>
</tr>
</tbody>
</table>

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Table 3: Continue

<table>
<thead>
<tr>
<th>Bioactive</th>
<th>Category</th>
<th>Objective</th>
<th>Application</th>
<th>Key-Ingredients</th>
<th>Route</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tacrolimus</td>
<td>Immunosuppressive</td>
<td>Formulate SMEDDS</td>
<td>Higher in immunosuppressant activity and superior in vitro dissolution profile</td>
<td>Carbitol</td>
<td>Oral</td>
<td>Borha et al. (2008)</td>
</tr>
<tr>
<td>Rapamycin</td>
<td>Immunosuppressive</td>
<td>Influence of different content of co-solvent on stability and bioavailability</td>
<td>Increased bioavailability</td>
<td>MCT capmul</td>
<td>Oral</td>
<td>Sun et al. (2011)</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>Immunosuppressive</td>
<td>Formulation of SME and micro emulsion</td>
<td>Excellent radiation protection</td>
<td>Span 20 Span 80 Elvax 1700, galactolipids</td>
<td>Oral</td>
<td>El Madzra and Bosella (2011)</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>Immunosuppressive</td>
<td>Characteristic for self drug delivery system based on natural lipid</td>
<td>Solubility and bioavailability increases</td>
<td>Galactolipids</td>
<td>Oral</td>
<td>Odberg et al. (2003)</td>
</tr>
<tr>
<td>Danazol</td>
<td>Steroid</td>
<td>Evaluate bioavailability after administration to dogs</td>
<td>Improved dispersion and good oral bioavailability</td>
<td>Soya bean oil Polyox 1150 Tween 80 Elvax 1700, oleylamine</td>
<td>Oral</td>
<td>Quine et al. (2008)</td>
</tr>
<tr>
<td>Progesterone</td>
<td>Steroid</td>
<td>Improve oral bioavailability of progesterone</td>
<td>No toxic effect when the dose was 30 times the potential dose</td>
<td>Tween 80, Elvax 1700, oleylamine</td>
<td>Oral</td>
<td>Genbani and Benita (1996)</td>
</tr>
<tr>
<td>Furosemide</td>
<td>Diuretics</td>
<td>Enhance the solubility and permeability</td>
<td>Improve bioavailability</td>
<td>Pterol oleique, Miglyol</td>
<td>Oral</td>
<td>Zverov et al. (2010)</td>
</tr>
<tr>
<td>Amphotericin B</td>
<td>Antifungal</td>
<td>Enhanced drug solubility stability and anti fungal activity</td>
<td>Significantly decreases kidney fungal CFU concentration</td>
<td>Medium chain triglycerides, fatty acid, Labrasol capex, Tween 80</td>
<td>Oral</td>
<td>Wassef et al. (2009)</td>
</tr>
<tr>
<td>Griseofulvin</td>
<td>Antifungal</td>
<td>Study dissolution and powder flow characterization and nucleation interface</td>
<td>SEDDS dependent on pore length and nucleation interface</td>
<td>Labrasol capex, Tween 80</td>
<td>Oral</td>
<td>Agarwal et al. (2009)</td>
</tr>
</tbody>
</table>

SEDDS is vital because the drug obstructs with the self-emulsification process to a certain extent, which leads to a change in the optimal oil-surfactant ratio. So, the design of an optimal SEDDS requires Preformulation-solubility and phase-diagram studies (Crison and Amidon, 1999; Farah et al., 1994).

**Biopharmaceutical aspects:** According to some reviewers certain poorly soluble drug becomes more bioavailable due to the presence of some lipids either alone or in combination with food. The reason is not completely known. Currently certain possible explanations have been given:

**Alterations (reduction) in gastric transit:** the lipid and/or food reduce the transit time of the drug and thus, increase the time available for dissolution and there by absorption (Karthikeyan et al., 2007).

**Increase in effective luminal drug solubility:** The presence of lipids in the GI tract stimulates an increase in the secretion of bile salts (BS) and endogenous biliary lipids including phospholipid (PL) and cholesterol (CH), leading to the formation of BS/PL/CH intestinal mixed micelles and an increase in the solubilization capacity of the GI tract. The cholesterol content was expressed as mg g⁻¹ (Farvin et al., 2009).

However, interaction of administered (exogenous) lipids into these BS structures either directly (if sufficiently polar), or secondary to digestion, leads to swelling of the micellar structures and a further increase in solubilization capacity.

**Changes in the biochemical barrier function of the GI tract:** It is understood that the activity of intestinal efflux transporters may be reduced by the lipids and surfactants this may be indicated by the glycoprotein’s efflux pump. Thus lipids and surfactants can diminish the enterocyte-base metabolism.

**Changes in the physical barrier function of the GI tract:** This has been observed that the permeability of drug can be increased by some lipids, lipid metabolism and surfactants. Although, the bioavailability of most of the poorly soluble drugs do not find problem with passive intestine permeability (Humberstone and Charman, 1997; Munari, 1991; Benet and Cummins, 2001; Dintzian and Silverman, 1999).

**Effect of oils on the absorption:** Such formulations form a fine oil-in-water emulsion with gentle agitation, which may be provided by gastrointestinal motility. A SES also improves the reproducibility of the plasma level-time profile (Kommuk et al., 2001; Porter and Charman, 1997; Nerurkar et al., 1996). Various physiological mechanisms have been planned to explain the effect of oils on the absorption of water-insoluble compounds, including altered gastrointestinal motility, increased bile flow and drug solubilization (Aungst, 2000; Mistry and Sheth, 2011).

**Characterization of SEDDS:** The primary means of self-emulsification assessment is visual evaluation. The efficiency of self-emulsification could be estimated by determining the rate of emulsification, droplet-size distribution and turbidity measurements.
Visual assessment: This may provide important information about the self-emulsifying and micro emulsifying property of the mixture and about the resulting dispersion.

Thermodynamic stability studies: Stability factor like physical stability of a lipid based formulation can be hindered in various ways, precipitation of drug in excipient matrix can be on of them (Al-Haj and Raseedee, 2009). In addition, poor formulation physical stability can lead to phase separation of the excipient, affecting not only formulation performance, but visual appearance as well (Prasong, 2010). The primary packaging material e.g., Capsule shell can affect the stability of the formulation. Incompatibility between the product and gelatin capsule shell make the shell can make the shell brittle deformed resulting delayed disintegration or incomplete release of drug. The stability of the formulation can be assessed by expressing it to heating cooling cycles of 4 and 45°C for six times and storing for 48 h at each temperature If the formulation does not indicated any sign of instability it is subjected to centrifugation at 3500 rpm for 30 min (Uchegbu and Florence, 1995, Rajesh et al., 2010).

Freeze thaw test: Three freeze for the formulations. Those formulations passed this test showed good stability with no phase separation, creaming or cracking (Shafiq et al., 2007; Patil et al., 2007; Patel et al., 2011b).

Turbidity measurement: This identifies efficient self-emulsification by establishing whether the dispersion reaches equilibrium rapidly and in a reproducible time (Paul and Maulik, 1997; Venkatesh et al., 2010). These measurements are performed on turbidity meters, most commonly the Hash turbidity meter and the Orbeco-Helle turbidity meter. Nepheloturbidimetric evaluation is done to monitor the growth of emulsification. A definite amount of the formulation is added to fixed quantity of suitable medium (0.1 N HCL) under continuous stirring (50 rpm) using magnetic stirrer at ambient temperature. Any change in turbidity is measured using a turbidity meter (Maulik and Paul, 1998).

Droplet size analysis particle size measurements: This determines the rate and extent of drug release along with the stability of the emulsion. Photon correlation spectroscopy using Zetasizer (which analyses the fluctuations in light scattering due to Brownian motion of the particles) is generally used to determine the droplet size of emulsion in the size range between 10 and 5000 nm (Wangeharonrungrung and Warisonnocharoen, 2011). Scattering of light is monitored at 90° angle at 25°C, after external standardization with spherical polystyrene beads. The nanometric size range of the particle is also observed even after 100 times dilution with water which proves the system’s compatibility with excess water (Serajuddin et al., 1988; Wakerly et al., 1986).

Drug content: Drug from pre-weighed SEDDS is extracted by dissolving in suitable solvent. Drug content in the solvent extract was analyzed by suitable analytical method against the standard solvent solution drug (Reddy et al., 2011; Wasan, 2001).

Emulsification time: Porter and Charman (2001b) measured the emulsification time by using a rotating paddle to promote emulsification in a crude nephelometer. This enabled an estimation of the time taken for emulsification (Bujaj et al., 2011; Pouton, 1997; Kamble et al., 2010).

Emulsification rate: The rate of self-emulsification system is usually determined by adding a dose of the SEDDS pre-concentrate, preferably in a capsule, to a relevant amount of water or biorelevant media. Rate of dispersion is determined by visual observation or by monitoring the change of turbidity of dispersion using a UV spectrophotometer or nephelometer (Sarpal et al., 2010).

Dispersibility test: The efficiency of self-emulsification of oral nano or micro emulsion can be assessed using a standard USP XXII dissolution apparatus 2. One millilitre of each formulation to be added to 500 mL of water at 37±0.5°C. A standard stainless steel dissolution paddle rotating at 50 rpm can be used to provide. The emulsion can be graded as follows on the basis of their Dispersibility.

Grade A: Rapidly forming (within 1 min) nanoemulsion, having a clear or bluish appearance.

Grade B: Rapidly forming, slightly less clear emulsion, having a bluish white appearance.

Grade C: Fine milky emulsion that formed within 2 min.

Grade D: Dull, greyish white emulsion having slightly oily appearance that is slow to emulsify (longer than 2 min)

Grade E: Formulation, exhibiting either poor or minimal emulsification with large oil globules present on the surface. Grade A and Grade B formulation will remain as
nanoemulsion when dispensed in GIT. While formulation falling in Grade C could be recommend for SEDDS formulation (Sachan et al., 2010; Shafiq et al., 2007).

Liquefaction time: This test is designed to estimate the time required by solid SEDDS to melt in vivo in the absence of agitation to simulated GI conditions. One dosage form is covered in a transparent polyethylene film and tied to the bulb of a thermometer by means of a thread. The thermometer with attached tablets is placed in a round bottom flask containing 250 mL of simulated gastric fluid without pepsin maintained at 37±1°C. The time taken for liquefaction is subsequently noted (Bajaj et al., 2011; Attama, 2003; Kohli et al., 2010).

Zeta potential measurement: This is used to identify the charge of the droplets. In conventional SEDDS, the charge on an oil droplet is negative because of the presence of free fatty acids (Bajaj et al., 2011; Gershank and Benita, 1996).

Equilibrium phase diagram: Although self-emulsification is a dynamic no equilibrium process involving interfacial phenomena, information can be obtained about self-emulsification using equilibrium phase behavior (Nour and Yusuf, 2006). There seems to be a correlation between emulsification efficiency and region of enhanced water solubilization and phase inversion region, formation of lamellar liquid crystalline dispersion phase on further incorporation of water (Anisa et al., 2010). An equilibrium phase diagram enables comparison of different surfactants and their synergy with co solvent or co surfactant. The boundaries of one phase region can easily be assessed visually. The phase behavior of a three component system can be represented by a ternary phase diagram (Pouton, 1987).

Viscosity determination: The SEDDS system is generally administered in soft gelatin or hard gelatin capsules. So, it can be easily pourable into capsules and such system should not be too thick to create a problem. The rheological properties of the micro emulsion are evaluated by Brookfield viscometer. This viscosities determination confirm whether the system is w/o or o/w. If system has low viscosity then it is o/w type of the system and if high viscosities then it is w/o type of the system (Patel et al., 2011c).

Refractive index and percent transmittance: Refractive index and percent transmittance proved the transparency of formulation. The refractive index of the system is measured by refractometer by placing drop of solution on slide and it compare with water (1.333). The percent transmittance of the system is measured at particular wavelength using UV-spectrophotometer keeping distilled water as blank. If refractive index of system is similar to the refractive index of water (1.333) and formuation have percent transmittance >99%, then formulation have transparent nature (Strickley, 1998; Lowell, 2008; Wang et al., 2009).

Electro conductivity study: The SEDDS system contains ionic or non-ionic surfactant, oil and water. So this test is used to measure the electro conductive nature of system. The electro conductivity of resultant system is measured by electro-conductometer.

In vitro diffusion study: In vitro diffusion studies is performed to study the release behavior of formulation from liquid crystal-line phase around the droplet using dialysis technique (Reddy et al., 2011; Patil et al., 2004).

Application

Improvement in solubility and bioavailability: If drug is added in SEDDS, it increases the solubility because it by passes the dissolution step in case of Class-II drug (Low solubility/high permeability) e.g. Ketoprofen, a moderately hydrophobic (log P 0.979) Nonsteroidal anti-inflammatory drug (El-Kamel et al., 2001; Vergote et al., 2001), is also a drug of choice for SEDDS, but it has high potential for gastric irritation during chronic therapy. Because of its low solubility, ketoprofen shows incomplete release characteristic from different formulations (Kreuter, 1994; Patel et al., 2008). By formulating ketoprofen in form of SEDDS these problem can be overcome rather increased bioavailability of the drug can be achieved. (Daud et al., 2011; Ymada et al., 2001; Roda et al., 2002).

Protection against biodegradation: Many drugs are degraded in physiological system, may be because of acidic pH in stomach, enzymatic degradation or hydrolytic degradation etc. Such drugs when presented in the form of SEDDS can be well protected against these degradation processes as liquid crystalline phase in SEDDS might be an act as barrier between degrading environment and the drug (Rhee et al., 2001; Patel et al., 2010a, 2011c, 2008).

Controlling the release of drug: Preparation and stabilization of nano-crystalline or improved solubility forms of drug may pose processing, stability and economic problems. This problem can be successfully overcome when Ketoprofen is presented in SEDDS.
Table 4: Some example of marketed pharmaceutical SEDDS formulation are as shown below

<table>
<thead>
<tr>
<th>Active ingredients</th>
<th>Trade name</th>
<th>Indication</th>
<th>Dose form</th>
<th>Company</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclosporine A/l</td>
<td>Neoral</td>
<td>Immune suppressant</td>
<td>Soft gelatin capsule</td>
<td>Novartis</td>
</tr>
<tr>
<td>Ritonavir</td>
<td>Norvir</td>
<td>HIV antiviral</td>
<td>Soft gelatin capsule</td>
<td>Abbott laboratories</td>
</tr>
<tr>
<td>Saquinavir</td>
<td>Fortovase</td>
<td>HIV antiviral</td>
<td>Soft gelatin capsule</td>
<td>Hoffmann-La Roche inc.</td>
</tr>
<tr>
<td>Amprenavir</td>
<td>Agenerase</td>
<td>HIV antiviral</td>
<td>Soft gelatin capsule</td>
<td>GalapagosPharmaceuticals</td>
</tr>
<tr>
<td>Valprox acid</td>
<td>Convulex</td>
<td>Anti-epileptic</td>
<td>Soft gelatin capsule</td>
<td>Pharmacia</td>
</tr>
<tr>
<td>Fenofibrate</td>
<td>LipRefex</td>
<td>Anti-hyperlipoproteic</td>
<td>Hard gelatin capsule</td>
<td>Geras</td>
</tr>
<tr>
<td>Cyclosporine A/l</td>
<td>Sandimmune</td>
<td>Immunosuppressant</td>
<td>Soft gelatin capsule</td>
<td>Novartis</td>
</tr>
<tr>
<td>Baclofenol</td>
<td>Targretin</td>
<td>Anticonvulstic</td>
<td>Soft gelatin capsule</td>
<td>Ligand</td>
</tr>
<tr>
<td>Calcitrol</td>
<td>Calcitrol</td>
<td>Calcium regulator</td>
<td>Soft gelatin capsule</td>
<td>Roche</td>
</tr>
<tr>
<td>Cyclosporine A/l</td>
<td>Genotropin</td>
<td>Immunosuppressant</td>
<td>Hard gelatin capsule</td>
<td>Abbott laboratories</td>
</tr>
<tr>
<td>Tocopherol nicotinate</td>
<td>Juvela</td>
<td>Hypertension hyperlipidemia</td>
<td>Soft gelatin capsule</td>
<td>Essai Co.</td>
</tr>
<tr>
<td>Teprenone</td>
<td>Selvax</td>
<td>Acute gastritis</td>
<td>Hard gelatin capsule</td>
<td>Essai Co.</td>
</tr>
<tr>
<td>Testosterone undecanoate</td>
<td>Restandol</td>
<td>Hormone replacement therapy</td>
<td>Soft gelatin capsule</td>
<td>Organon labs</td>
</tr>
<tr>
<td>Indomethacin farnesil</td>
<td>Infree</td>
<td>Anti-inflammatory and analgesic</td>
<td>Hard gelatin capsule</td>
<td>Essai Co.</td>
</tr>
<tr>
<td>Ethyl iodocaprate</td>
<td>Epadel</td>
<td>Hyperlipidemia</td>
<td>Soft gelatin capsule</td>
<td>MozhinaPharmaceuticals</td>
</tr>
<tr>
<td>Minocycline</td>
<td>Glibay</td>
<td>Osteoporosis</td>
<td>Hard gelatin capsule</td>
<td>Essai Co.</td>
</tr>
<tr>
<td>Morphine sulphate</td>
<td>MXL</td>
<td>Analgesic</td>
<td>Hard gelatin capsule</td>
<td>Napp pharmaceuticals</td>
</tr>
</tbody>
</table>

The formulation enhanced bioavailability due to the increase in the solubility of drug and minimizes the gastric irritation. (Vergote et al., 2001; El-Kamel et al., 2001; Roy et al., 2001).

**Solid SEDDS:** SEDDS are usually a liquid dosage form packed in a soft gelatin capsule which have certain limitations. Do combat these short coming solid SEDDS in the form of tablet, capsule and powders have also been prepared (Woo and Suh, 2001; Bajaj et al., 2011).

**Supersaturatable SEDDS (S-SEDDS):** The high surfactant level in SEDDS formulations can cause GI side-effect. So that, a new class of supersaturatable formulations, as well as the supersaturatable SEDDS (S-SEDDS) formulations, have been introduced and developed to overcome the surfactant side-effects and reach rapid absorption of poorly soluble drugs. (Gao et al., 2003, 2004, Kararl et al., 1992). It is shown that the significantly reduced amount of surfactant used in the S-SEDDS formulation approach provides better toxicity/safety profile than the traditional SEDDS formulations (Raghavan et al., 1986; Pellet et al., 1997; Hasegawa et al., 1988) (Table 4).

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**REFERENCES**


