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

[1]D.S. Rajput, [1]Amit Alexander, [2]Vishal Jain, [1]T.K. Giri, [1]D.K. Tripathi and [1]Ajazuddin
[1]Rungta College of Pharmaceutical Sciences and Research,
Kokha-kurud Road, Bhilai, Chhattisgarh, India
[2]University Institute of Pharmacy, Pt. Ravishankar Shukla University,
Raipur, Chhattisgarh, India

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; Aungst, 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 (SEOF) 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).

Corresponding Author: Ajazuddin, Rungta College of Pharmaceutical Science and Research Institute, Kokha-kurud Road, Bhilai, Chhattisgarh, India Tel: +91-9827199441

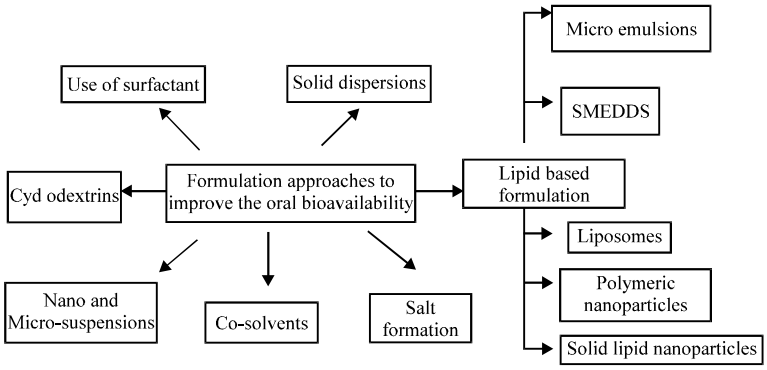

Fig. 1: Some of the formulation approaches to improve the oral bioavailability of poorly water soluble drugs

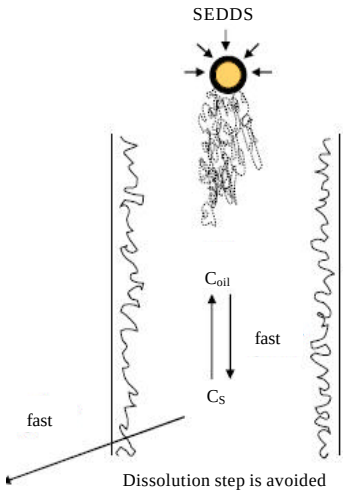

Fig. 2: Self Emulsifying drug Delivery System

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; Gursoy 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

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

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

Oil	Surfactants	Co-Surfactant/cosolvent
Cotton seed oil	Polysorbate 20(Tween 20)	Span 20
Soybean oil	Polysorbate 80(Tween 80)	Span 80
Corn oil	D-alpha Tocopheryl polyethylene	Capryol 90
Sunflower oil	glycol 1000 succinate (TPGS)	Lauroglycol
Castor oil	Polyoxy-35-castor oil	Transcutol
Sesame oil	(Cremophore RH40)	Capmul
Peanut oil	Polyoxy-40-	Ethanol
Labrafac	hydrogenated castor oil	Propylene glycol
Labrafil	Labrasol	

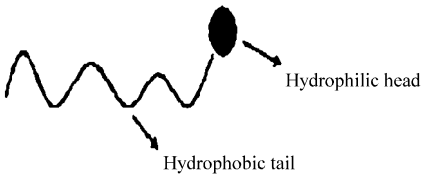

Fig. 3: Surfactant molecule containing hydrophilic head and hydrophobic tail group

used emulsifiers are a variety of solid or liquid ethoxylated polyglycolyzed glycerides and Tween 80 (Patel *et al*., 2011a; Kyatanwar *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 Glycol (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; Solanki *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 SES (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.

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) use solid self emulsifying system in the delivery of diclofenac 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 he was concluded that Itraconazole is a representative poorly water-soluble drug. Thus, the marketed formulation Sporanox\ 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

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).

Setthacheewakul *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 SMEDDS 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 selfemulsification 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 selfemulsification region. From these studies, an optimized formulation is selected and its bioavailability is compared with a reference formulation (Saifuddin 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

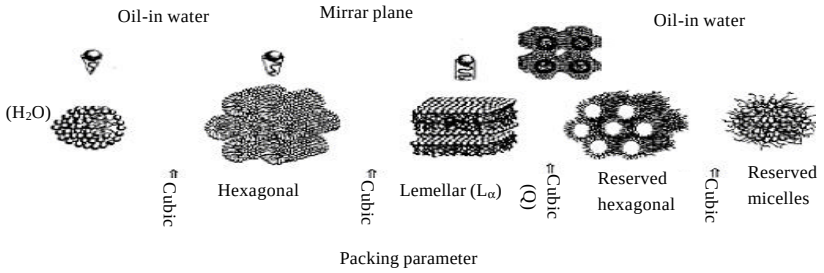

Fig. 4: Representation of the most commonly encountered phases upon addition of water to an oil surfactant combination

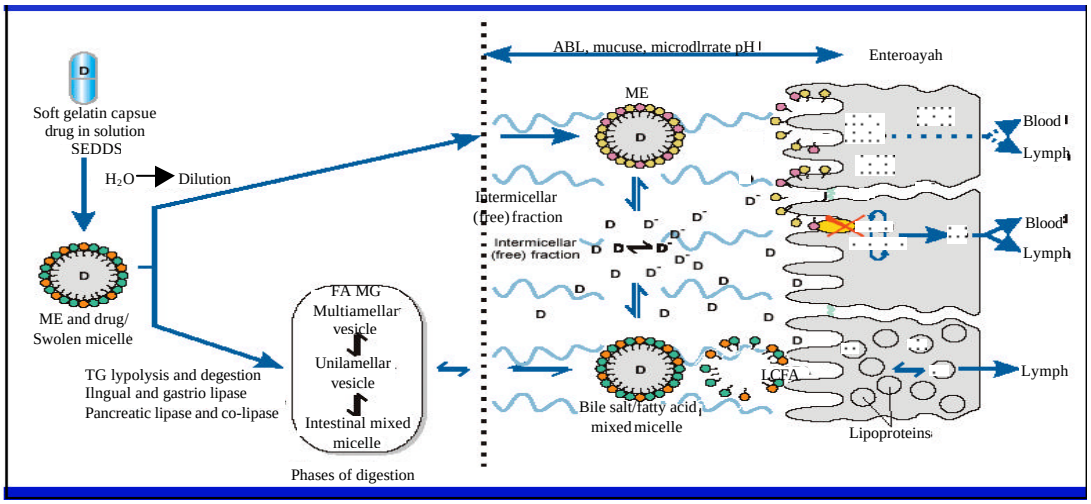

Fig. 5: Potential mechanism for absorption enhancement

Table 3: Various examples of SEDDS

Bioactives	Category	Objective	Application	Key-ingredients	Route	Reference
Diclofenac	NSAID	Better release rate	Solubility and bioavailability increases	Tween 65 goat fat	Oral	Attama (2003)
Indomethacin	NSAID	Increase bioavailability	AUC_{0-12h} increased	Ethyl oleate	Oral	Kim and Ku (2000)
Ketoprofen	NSAID	Influence of cryogenic grinding on SEDDS	Solubility and Bioavailability increases	Gelucire	Oral	Patil *et al.* (2004)
Nimesulide	NSAID	Influence of formulation variables on the *in vitro* absorption	Improved drug solubility and permeability	Oils lactose	Oral	Franceschinis *et al.* (2005)
Celecoxib	NSAID	Increase bioavailability	Solubility and bioavailability increases	Labrafil Labrasol	Oral	Shaji and Lodha (2011)
Etodolac	NSAID	Enhancement of dissolution and oral absorption	SEDDS formulation reduced edema by 69%	Labrafac 1349 Capryol 90 Labrasol	Oral	Barakat (2010)
Piroxica	NSAID	Determine particle size, absolute drug content.	Higher dissolution profile than pure drug	Tween 65 goat fat homolipid	Oral	Attama and Mpamaugo (2006)
Aceclofenac	NSAID	Increase solubility and oral bioavailability	*In vitro* release of pellets was higher than pure drug	Oleic acid lemon oil Tween 80	Oral	Reddy *et al.* (2011)
Artemether	Antimalarial	Novel indigenous natural lipophilic as an oily phase	Self emulsification efficiency and release increases	Oil-(N-LCT) Capryol-90	Oral	Mandawgade *et al.* (2008)
Halofantrine	Antimalarial	Increase solubility and oral bioavailability	6 to 8 fold improvement in absolute oral bioavailability	Captex, maisine Capmul MCM	Oral	Khoo *et al.* (1998)
Amlodipine	Anti-hypertensive	Enhance the solubility and oral bioavailability	Drug Release ($p \leq 0.01$) Higher than marketed tablet	Labrafil M Tween 80 Ethanol	Oral	Chhabra *et al.* (2011)
Glyburide	Anti-diabetic	Improve the dissolution properties	Improvement of drug dissolution	Transcutol Tween 20	Oral	Mura *et al.* (2010)
Carvedilol	Anti -hypertensive	Increase solubility, dissolution rate and oral bioavailability	Dissolution rate of SEEDS and SMEDDS was more than 2 fold faster than tablets	Labrafil Transcutol P Labrasol	Oral	Wei *et al.* (2005)
Acyclovir	Anti-viral	Enhancement of bioavailability	3.5 fold increases in bioavailability	Tween 60 glycerol sunflower oil	Oral	Patel and Vavia (2007)
Irbesartan	Anti-hypertensive	Enhance the oral bioavailability	7.5 fold increases in the oral bio availability	Cremophore EL Carbitol	Oral	Patel *et al.* (2011b)
Nimodipine	Anti-hypertensive	A controlled release system based SMEDDS mixture	Combining the character of controlled release and SEDDS	Ethyl-oleate cremophore	Oral	Kale and Patravale (2008)
Metronidazole	Anti-microbial	Preliminary studies on two vegetable oil based SEDDS	Reduction in the number of formulation that maintain isotropicity and stability after 72 h	Tween 65 palm oil	Oral	Obitte *et al.* (2008)

Table 3: Continue

Bioactives	Category	Objective	Application	Key-ingredients	Route	Reference
Vinpocetine	Anti-inflammatory	Evaluated pharmacokinetic and bioavailability	Oral bioavailability was 1.72 fold higher than tablet	Solutol	Oral	Cui *et al.* (2009)
Curcumin	Anti-inflammatory	Improve solubility dissolution and *in vivo* oral absorption	10-14 fold increased absorption	Cremophore EL labrasol labrafac PG	Oral	Setthacheewakul *et al.* (2010)
Nobiletin	Anti-inflammatory	Improve the solubility and oral absorption	SMEDDS dilution was higher	Castor oil Tween 80	Oral	Yao *et al.* (2008)
Vitamin E	Anti-Oxidant	Improve bioavailability	Absorption was increased by almost 3 fold	Tween-80 Span-80	Oral	Julianto *et al.* (2000)
Pueraria lobata isoflavone	Anti-oxidant	Improve *in vitro* dissolution and oral absorption in beagal dogs	2.5 fold increases in the relative bioavailability	Ethyl-oleate Tween 80 transcutol P	Oral	Cui *et al.* (2005)
Tocotrienol	Anti-oxidant	Influence of lipolysis and droplet size on absorption	Bioavailability increase up to 2 to 3 times	Soybean oil Tween 80	Oral	Yap and Yuen (2004)
Buparvaquone	Antiprotozoal	Prepare a lipid based SMEDDS	Oral bioavailability for BPQ was found to be 40.10%.	Capryol 90 Cremophore EL	Oral	Gantala *et al.* (2010)
Loratadine	Antihistamine	Porous polystyrene beads act as carrier for SES.	PPB are potential carriers for solidification	Captex 200 Cremophore EC	Oral	Patil and Paradkar (2006)
Exemestane	Aromatase inhibitor	Improve the solubility and Bioavailability.	2-9 fold increases in bioavailability	Labrasol Labrafil	Oral	Singh *et al.* (2009)
Lutein	Carotenoids	Improve the bioavailability	Bioavailability increases 16.1 folds	Leutin Tween 80	Oral	Shanmugam *et al.* (2011)
Atorvastatin	Hypolipidemic	To improve oral Bioavailability	Bioavailability increases	Oleic acid Tween 20 Carbitol	Oral	Chouksey *et al.* (2011)
Simvastatin	Hypolipidemic	Improve biopharmaceuticals performance	Significant reduction in plasma CH and TG	Captex 355 Lauroglycol Cremophore EL	Oral	Kang *et al.* (2004)
Fenofibrate	Hypolipidemic	Develop and evaluate an optimal SMEDDS	Higher pharmacodynamic potential as compared with plain	PEG400 Labrafac Tween 80	Oral	Patel and Sawant (2007)
Lovastatin	Hypolipidemic	Evaluation of SEDDS	Bioavailability increases	Transcutol Lauroglycol Labrasol	Oral	Singh *et al.* (2010)
Torcetrapib	Hypolipidemic	Reduces the food effect for torcetrapib	Absorption was rapid and the food effect was reduced	Olive oil Oleic acid Labrafil	Oral	Perlman *et al.* (2008)
Pidotimod	Immunostimulant	Improve the oral absorption	2.56- fold (p=0.05)increased absorption	Span 80 Oleic acid	Oral	Qi *et al.* (2011)
Oridonin	Ditrepenoid	Enhance the oral bioavailability of the poorly water soluble drug	2.2 fold increase in relative bioavailability	Maisine Labrafac Cremophore EL	Oral	Zhang *et al.* (2008)
Docetaxel	Anticancer	improvement of stability of Dtx in aqueous media	More effective in inhibition of $B_{16}F_{10}$ cell proliferation	Tetraglycol Cremophore	Oral	Kim *et al.* (2011)
Itraconazole	Anti-mycotic agent	Evaluated physicochemical properties and pharmacokinetic parameter	Bioavailability and permeability increases	Transcutol Pluronic Tocopherol	Oral	Hong *et al.* (2006)
Phenytoin	Anti-epileptic	Develop and characterize a selfemulsifying drug delivery system	After SEDDS administration AUC increased by 2:3 times	Labrasol Transcutol Plurol	Oral	Atef and Belmonte (2008)
Xibornol	Anti-biotic	Developing a stable liquid formulation of the drug	Dissolution and bioavailability increases	Labrafac Labrasol Transcutol	Oral	Cirri *et al.* (2007)
Cefpodoxime	Anti-biotic	Overcome the problems associated with the delivery of cefpodoxime proxetil (CPF)	Completely dissolved within 20 min irrespective of the ph of dissolution medium.	Cremophore EL Transcutol Plurol oleique	Oral	Date and Nagarsenker (2007)
Silymarin	Flavonolignans	Develop new solid self emulsifying pellets to deliver milk.	100 times bioavailability increases.	Miglyol 812 Tween 80	Oral	Iosio *et al.* (2011)

Table 3: Continue

Bioactives	Category	Objective	Application	Key-ingredients	Route	Reference
Tacrolimus	Immunosuppressive	Formulate SMEDDS	Higher in immunosuppressant activity and superior *in vitro* dissolution profile	Carbitol Cremophore EL Capmul	Oral	Borhade *et al.* (2008)
Rapamycin	Immunosuppressive	Influence of different content of co-solvent on stability and bioavailability	Increased bioavailability	MCT cremophore RH40 transcutol	Oral	Sun *et al.* (2011)
Prednisolone	Immunosuppressive	Formulation of SME and micro emulsion	Excellent radiation protection	Span 20 Span 80 Ethyl oleate	Oral	El Maghraby and Bosela (2011)
Cyclosporine	Immunosuppressive	Characteristic for self drug delivery system based on natural lipid	Solubility and bioavailability increases	Galactolipids	Oral	Odeberg *et al.* (2003)
Danazol	Steroid	Evaluate bioavailability after administration to dogs	Improved dispersion and good oral bioavailability	Soya bean oil Polyoxyl 35	Oral	Cuine *et al.* (2008)
Progesterone	Steroid	Improve oral bioavailability of progesterone	No toxic effect when the dose was the 30 times the potential dose	Tween 80 Ethyl oleate Oleylamine	Oral	Gershanik and Benita (1996)
Furosemide	Diuretics	Enhance the solubility and permeability	Improve bioavailability	Plurol oleique Miglyol	Oral	Zvonar *et al.* (2010)
Amphotericin B	Antifungal	Enhanced drug solubility stability and anti fungal activity	Significantly decreases kidney fungal CFU concentration	Medium chain triglycerides fatty acid	Oral	Wasan *et al.* (2009)
Griseofulvin	Antifungal	Study dissolution and powder flow characterization	SEDDS dependent on pore length and nucleation interface	Labrasol captex Tween 80	Oral	Agarwal *et al.* (2009)

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 explanation has 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, intercalation 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; Muranishi, 1991; Benet and Cummins, 2001; Dintaman and Silverman, 1999).

Effect of oils on the absorption: Such formulations form a fine oil-in-water emulsion with gentile agitation, which may be provided by gastrointestinal motility. A SES also improves the reproducibility of the plasma level-time profile (Kommuru *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 Rasedee, 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 Hach 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 (Wangcharoenrung and Warisnocharoen, 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 (Bajaj *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 dispersed 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±18°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; Gershanik 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 Yunus, 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 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 too thick to create a problem. The rheological properties of the micro emulsion are evaluated by Brookfield viscometer. This viscosities determination conform 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 formulation have percent transmittance >99%, then formulation have transparent nature (Strickley, 1998; Lowell, 2008; Wang *et al*., 2009).

Electro conductivity study: The SEDD 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 degradating 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

Active ingredients	Trade name	Indication	Dose form	Company
Cyclosporine A/l	Neoral	Immune suppressant	Soft gelatin capsule	Novartis
Ritonavir	Norvir	HIV antiviral	Soft gelatin capsule	Abbott laboratories
Saquinavir	Fortovase	HIV antiviral	Soft gelatin capsule	Hoffmann-la Roche inc.
Amprenavir	Agenerase	HIV antiviral	Soft gelatin capsule	GalaxoSmithKline
Valproic acid	Convulex	Anti-epileptic	Soft gelatin capsule	Pharmacia
Fenofibrate	LipRex	Anti-hyperlipoproteinemic	Hard gelatin capsule	Genus
Cyclosporine A/ll	Sandimmune	Immunosuppressant	Soft gelatin capsule	Novartis
Bexarotene	Targretin	Antineoplastic	Soft gelatin capsule	Ligand
Calcitriol	Rocaltrol	Calcium regulator	Soft gelatin capsule	Roche
Cyclosporine A/lll	Gengraf	Immunosuppressant	Hard gelatin capsule	Abbott laboratories
Tocopherol nicotinate	Juvela	Hypertension hyperlipidemia	Soft gelatin capsule	Eisai Co.
Teprenone	Selvex	Acute gastritis	Hard gelatin capsule	Eisai Co.
Testosterone undecanoate	Restandol	Hormone replacement therapy	Soft gelatin capsule	Organon labs
Indometacin farnesil	Infree	Anti-inflammatory and analgesic	Hard gelatin capsule	Eisai Co.
Ethyl icosapentate	Epadel	Hyperlipidemia	Soft gelatin capsule	Mochida Pharmaceuticals
Menatetrenone	Glakay	Osteoporosis	Hard gelatin capsule	Eisai Co.
Morphine sulphate	MXL	Analgesic	Hard gelatin capsule	Napp pharmaceuticals

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

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

Supersaturable SEDDS (S-SEDDS): The high surfactant level in SEDDS formulations can cause GI side-effect. So that, a new class of supersaturable formulations, as well as the supersaturable 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; Kararli *et al*., 1992). It is shows that the significantly reduced amount of surfactant used in the S-SEDDS formulation approach provides a better toxicity/safety profile than the traditional SEDDS formulations (Raghavan *et al*., 1986; Pellett *et al*., 1997; Hasegawa *et al*., 1988) (Table 4).

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