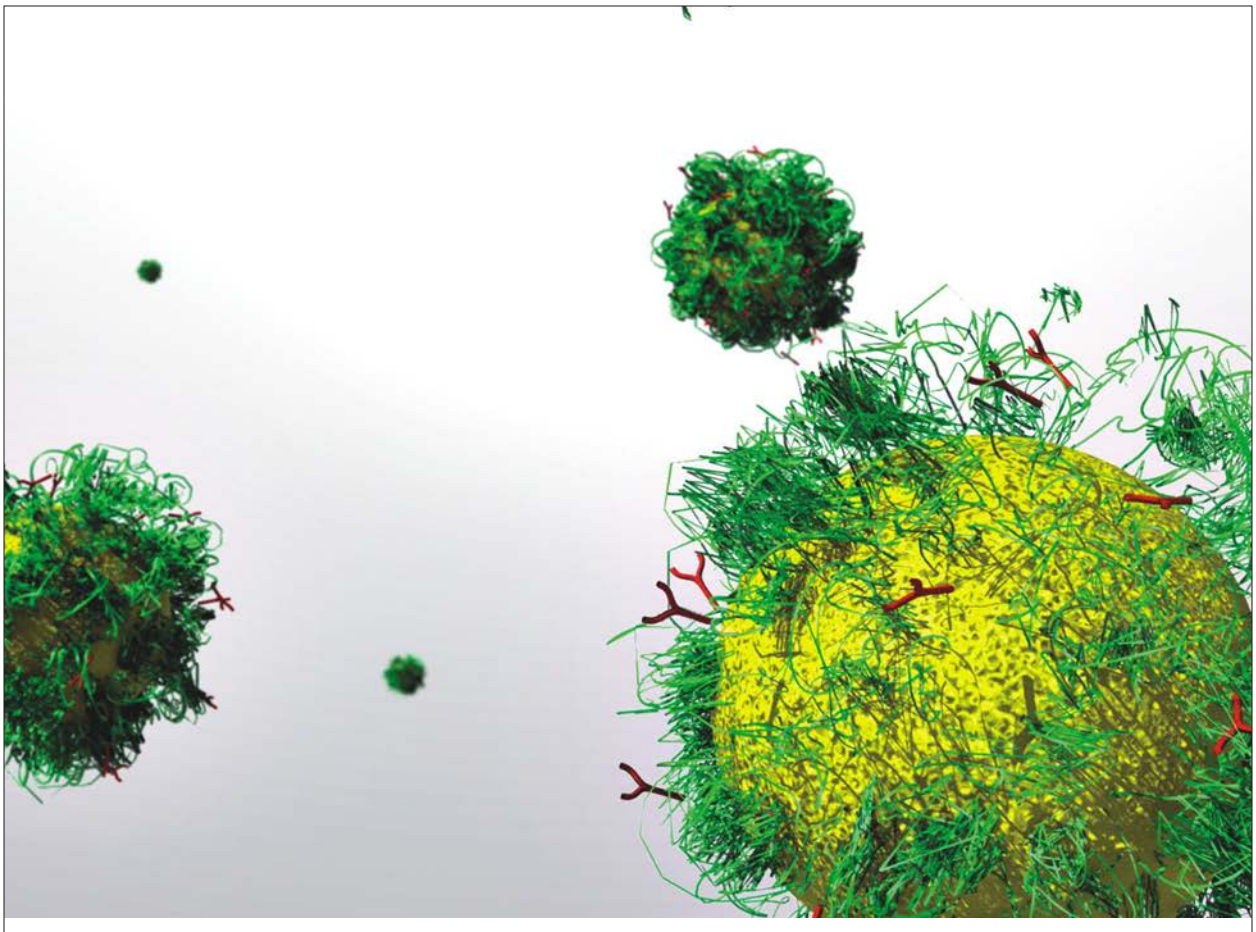

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A Review on Novel Therapeutic Strategies for the Enhancement of Solubility for Hydrophobic Drugs through Lipid and Surfactant Based Self Micro Emulsifying Drug Delivery System: A Novel Approach

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ABSTRACT

Self micro-emulsifying drug delivery systems (SMEDDS) are vital tool for enhancement of oral bioavailability of hydrophobic drugs. These systems are currently of interest to the researchers because of their significant capability to act as drug delivery vehicles by incorporating a extensive range of drug molecules. The present communication embodies approaches in the design of lipid based formulation, evaluation processes, mechanism involved there in, updated with latest findings from literature reports and patents. Also, this comprehensive review offers an explicit discussion on vital possibilities of the SMEDDS in bioavailability improvement of various drugs. A pseudo ternary phase diagram is used for identifying the micro-emulsification region. Thus, this current article provides an updated compilation of extensive information and result on all the unexplored areas of the self micro emulsifying drug delivery systems, thus encouraging the researchers to accelerate their research work in this direction for the development and enhancement of dissolution profile of hydrophobic drugs and pay a novel approach to pharmaceutical research.

Key words: SMEDDS, self-emulsification, solubility enhancement, bioavailability, cosolvent, lipophilic

INTRODUCTION

Oral route is the easiest, most convenient route for non invasive administration and the major route of drug delivery for the chronic treatment of many diseases (Reddy and Murthy, 2002). In current years, new chemical entities exhibit poor aqueous solubility which in turn leads to low oral bioavailability (Robinson, 1996). Formulation of poorly aqueous soluble drugs is a challenging job to the pharmaceutical scientists as result of modern drug discovery technique and oral delivery of such drugs is frequently associated with low bioavailability, high inter subject variability and lack of dose proportionality (Dey *et al*., 2009; Kanika *et al*., 2010; Giri *et al*., 2010b). The formulation technique plays an important role in overcoming this shortcoming of poorly water soluble drugs, to encountered these problems, various formulation strategies are reported including use of surfactants, pulverization, crystal polymorphism selection, salt formation, solid dispersion, mixed pulverization, complex formation agent like cyclodextrin, emulsion, micro emulsion, liposome, particle size, nanoparticles, micro and nano spheres, lipids carriers, use of prodrug, drug

derivatization, solution phase studies and permeation enhancers to improve the dissolution rate of the drug (Mandal and Mandal, 2011; Badawi *et al*., 2011; Seedher and Sharma, 2007; Wanwimolruk *et al*., 1992; Amarji *et al*., 2007). In recent years, a lot interest has given on lipid-based formulations to enhance the oral bioavailability of poorly aqueous soluble drug compounds (Burcham *et al*., 1997; Patel *et al*., 2011). Lipid formulations for oral administration of drugs generally consist of a drug dissolved in oils, partial glycerides, surfactants or co-surfactants. The principal mechanism of action which leads to improved bioavailability is usually avoid the slow dissolution process which limits the bioavailability of hydrophobic drugs from solid dosage forms (Pouton, 2000; Tang *et al*., 2007). The Self-Dispersing Lipid Formulations (SDLFs) is one of approaches to overcome the formulation difficulties of various hydrophobic drugs and to improve the oral bioavailability of poorly absorbed drugs. The SDLFs are mainly two type's i.e., Self Emulsifying Drug Delivery System (SEDDS) and Self Micro Emulsifying Drug Delivery System (SMEDDS) (Gershanik and Benita, 2000). SMEDDS are isotropic and thermodynamically transparent stable solutions consisting of an oil, surfactant, co-surfactant and drug mixtures which form oil-in-water microemulsions when mixed with aqueous phase under mild stirring. Potential advantages of these systems include not only enhanced drug solubilization but also improved release and absorption properties due to the already dissolved form of the drug in the formulation and the resulting small droplets size, providing a large interfacial surface area for drug absorption (Farah *et al*., 1994; Craig *et al*., 1995). To the improved dissolution of drugs by SMEDDS, one more factor contributing to the increasing bioavailability is that lymphatic transport is responsible for a portion of the complete drug uptake as well (Porter *et al*., 2007). Figure 1 illustrates the oral drug absorption of self-emulsifying formulations from the GI mucosa to systemic circulation. It can also be changed into granules, pellets, powders for dry filled capsules or tablet preparations and also include into Ca-alginate microcapsules (Nazzal and Khan, 2006; Abdalla *et al*., 2008; Serratoni *et al*., 2007; Tan *et al*., 2009).

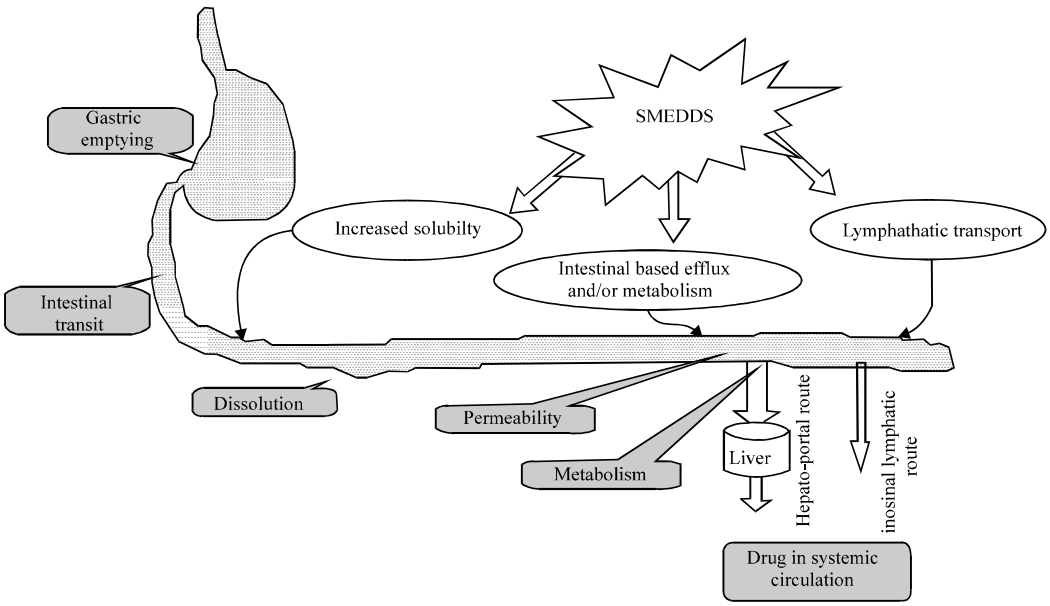

Fig. 1: Self-emulsifying formulations enhancing the bioavailability of drugs through oral absorption

MICROEMULSION

The concept of microemulsion was first introduced by Hoar and Schulman in 1943 (Hoar and Schulman, 1943). Microemulsion is a system of water, oil and amphiphilic compounds (surfactant and co-surfactant) which is a transparent, optically isotropic and thermodynamically stable liquid (Lawrence and Rees, 2000). In practice 'micro emulsions' are frequently identified by equilibrium phase studies as systems which are optically transparent to the eye, however, contain a extensive mass of both oil and water (Pouton, 1997). Micro emulsions were prepared by mixing a suitable quantity of aqueous solution with the organic phase containing the surfactant solution (Yadav *et al.*, 2008). They help in the improvement of drug bioavailability, protection against enzymatic hydrolysis and decrease toxicity. The only problem with microemulsion is poor palatability and moreover due to their water content, microemulsions cannot be encapsulated in soft and hard gelatin (Shinde *et al.*, 2011). Hence, there is a need for delivery of hydrophobic drug is Self-Micro emulsifying Drug Delivery System (SMEDDS).

SMEDDS

Self Micro Emulsifying Drug Delivery System (SMEDDS) are defined as isotropic mixtures of oils, surfactants, along with co-solvents/surfactants that have a unique ability of forming fine oil-in-water (o/w) micro emulsions upon moderate mixing of these ingredients in aqueous media, such as GI (Gastrointestinal) fluids (Patravale *et al.*, 2003). Self emulsifying drug delivery systems (SEDDS) SEDDS produce not clear emulsions with a droplet size between 100 and 300 nm while SMEDDS form clear micro emulsions with a droplet size of less than 50 nm also the concentration of oil in SMEDDS is less than 20% as compared to 40-80% in SEDDS. According to the studies of Self-Emulsifying Drug Delivery Systems (SEDDS) formed using surfactants of HLB<12 and Self-Micro Emulsifying Drug Delivery Systems (SMEDDS) formed with surfactants of HLB>12. 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 (Gursoy and Benita, 2004; Pouton, 2000). The key step is to find a suitable oil surfactant mixture that can dissolve the drug within the required therapeutic concentration. The SMEDDS mixture can be filled in either soft or hard gelatin capsules. A typical SMEDDS formulation contains oils, surfactants and if required an antioxidants. Often co-surfactants and co-solvents are added to improve the formulation characteristics (Khoo *et al.*, 1998; Aqil *et al.*, 2011).

Benefits of SMEDDS:

- Enhancement in oral bioavailability e.g., ketoprofen
- Reduction in inter-subject and intra-subject variability and food effects e.g., cyclosporine
- SMEDDS has capability to deliver peptides that are prone to enzymatic hydrolysis in GIT
- For both liquid and solid dosage forms. e.g., Progesterone
- Ease of manufacture and scale- up (Patel and Sawant, 2009)

Limitations of SMEDDS:

- Chemical instabilities of drugs and high surfactant concentrations
- The large amount of surfactant in self-emulsifying formulations (30-60%) irritates GIT
- Moreover, volatile co solvents in the conventional self-emulsifying formulations are known to migrate into the shells of soft or hard gelatin capsules, resulting in the precipitation of the lipophilic drug

MECHANISM OF SELF EMULSIFICATION

The exact mechanism of self-emulsification is not yet well explained. When the energy required for increasing the surface area of dispersion is less than the change in entropy required for dispersion, self emulsion takes place. Moreover, the free energy of a traditional emulsion formation and the energy required for increasing surface area are directly related as shown below:

$$\Delta G = \Sigma N_i \pi r_i^2 \sigma$$

where, ΔG is the free energy associated with the process (ignoring the free energy of mixing), N is the number of droplets having radius, r and s is the interfacial energy. The above equation shows that spontaneous formation of interface between oil and aqueous phase is thermodynamically stable (Reiss, 1975). Gershanik and Benita (2000) explained the spontaneous formation of emulsion, i.e., self-emulsification, in terms of the free energy required to form the emulsion which is either very low and positive, or negative.

The ease of emulsification has been quantitatively measured by Mustafa and Groves. The turbidity of the oil-surfactant system in a water stream was monitored by using Phosphated nonyl phenoloxylate (PNE) and Phosphated Fatty alcohol Ethoxylate (PFE) in n-hexane. They proposed the relation between emulsification process and (i) how easily water can penetrates into the oil-water interface (ii) formation of liquid crystalline phase that results swelling at the interface.

Pouton has proposed a relationship between the emulsification properties of the surfactant and phase inversion behavior of the system. For example, the temperature of the oil in water system, stabilized by using non-ionic surfactant(s) is increased; the cloud point of the surfactant would be attained followed by phase inversion. The surfactant is highly mobile at the phase inversion temperature; hence, the o/w interfacial energy is minimized, leading to a reduction in energy required to bring about emulsification.

CLASSIFICATION OF LIPID FORMULATION

The main purpose of the lipid formulation classification system is to enable in vivo studies to be interpreted more readily and, subsequently, to facilitate the identification of the most appropriate formulations for specific drugs with reference to their physicochemical properties (Pouton and Porter, 2008). Each lipid formulation type has specific features as described in Table 1 by Pouton (2006).

Table 1: Characteristics, advantages and disadvantages of lipid formulations

LCFS type	Characteristics	Advantages	Disadvantages
Type I	Non-dispersing, require digestion	GRAS status, simple, excellent capsule compatibility	Poor solvent capacity unless the drug is highly lipophilic
Type II	SEDDS without water soluble components	Unlikely to lose solvent capacity on dispersion	Turbid o/w emulsion (0.25-2 μm)
Type IIIA	SEDDS/SMEDDS with water soluble components	Clear or almost clear dispersion, drug absorption without digestion	Possible loss of solvent capacity on dispersion, less easily digested
Type IIIB	SMEDDS with water-soluble components and low oil content	Clear dispersion, drug absorption without digestion	Likely loss of solvent capacity on dispersion
Type IV	Oil-free formulation based on surfactant and cosolvents	Good solvent capacity for many drugs, disperses to micellar solution	Loss of solvent capacity on dispersion, may not be digestible LCFS-Lipid classification formulation system

Source: Pouton (2006)

Types of lipid formulations: Type I formulations consist of formulations solubilized drug in triglycerides and/or mixed glycerides or in an oil-in-water emulsion stabilized by little concentration of emulsifiers such as 1% (w/v) polysorbate 60 and 1.2% (w/v) lecithin. Generally, these systems show poor initial aqueous dispersion and require digestion by pancreatic lipase/co-lipase in the GIT to produce more amphiphilic lipid digestion products and promote drug transfer into the colloidal aqueous phase. Type 1 formulations therefore are a good option for drugs having sufficient solubility in oils. Valproic acid has been formulated in soft gelatin capsule containing corn oil as lipidic component.

Type II formulations are referred to as SEDDS. SEDDS are isotropic mixtures of lipids, surfactants (HLB<12), co-surfactant and the drug which form oil-in water emulsions under gentle agitation subsequent dilution with aqueous phases. Self-emulsification is usually obtained at surfactants contents above 25% (w/w). However, at higher surfactants concentration (greater than 50-60% (w/w)), the progress of emulsification may be hindered by the formation of viscous crystalline, gels at the oil/water interface. A Type II system has received limited attention and no marketed products have emerged. One reason may be that the most effective surfactants for Type II formulation do not appear on the FDA list of inactive ingredients.

Type III formulations are generally referred as self microemulsifying drug delivery systems (SMEDDS). It consist of oils, hydrophilic surfactants (HLB>12) and co-solvents. Type III formulations are further divided into Type IIIA and Type IIIB formulations. Later comprises of higher amount of hydrophilic surfactants and co-solvents and lesser lipid content, as compared to Type IIIA. Type IIIB formulations cause greater risk of drug precipitation on dispersions given their high content of hydrophilic surfactants and co-solvents. An example of marketed Type III formulation is Neoral® (Novartis) cyclosporine formulation. This formulation comprises of corn oil glycerides, cremophor RH40, glycerol, propylene glycol and ethanol.

Type IV systems are basically pure surfactants or mixtures of surfactants and co-solvents. Formulation of poorly water-soluble drugs in pure co-solvents is likely to result in precipitation of the drug. An example of a commercial Type IV formulation is Agenerase® (GlaxoSmithKline), a capsule formulation of the HIV protease inhibitor amprenavir containing tocopherol polyethylene glycosuccinate (TPGS) as a surfactant and PEG 400 and propylene glycol as co-solvents (Porter *et al.*, 2008; Carrigan and Bates, 1973; Myers and Stella, 1992; Patel *et al.*, 2011; Wanwimolruk and Levy, 1987; Arif *et al.*, 1996). Table 2 provides a list of various lipid formulations in commercial circulation available.

SELECTION OF COMPONENTS FOR SMEDDS

The crucial challenges to any oral formulation design program is maintaining drug solubility within the gastrointestinal tract and, in particular, maximizing drug solubility within the primary absorptive site of the gut (O'Driscoll and Griffin, 2008). Lipid based formulations offer a potential platform for improving oral bioavailability of drugs especially those belonging to biopharmaceutical Classification System (BCS) class II and class IV. Class II drugs are poorly water soluble drugs with high permeability but once they are dissolved; they absorbed over the gastro- intestinal membrane, and Class IV compounds are poorly soluble with poor permeability, respectively (Tapas *et al.*, 2011). The basic criteria for selection of components of lipid formulation are; the lipophilicity of the drug, with solubility in pharmaceutically-acceptable lipid excipients which should be sufficient to allow the entire dose of the drug to be administered in a single dosage unit. Another reason for achieving success of a lipid based formulation by use of a strong positive food effect. The presence of fatty

Table 2: List of marketed product of lipid formulation

Brand	Drug	Dose	Company	Dosage form
Neoral®	Cyclosporin A	25 g, 100 mg	Novartis	Soft gelatin capsule
Norvir®	Ritonavir	100 mg	Abbott Laboratories	Soft gelatin capsule
Fortovase®	Saquinavir	200 mg	Hoffmann-La Roche	Soft gelatin capsule
Agenerase®	Amprenavir	50,150 mg	GlaxoSmithKline	Soft gelatin capsule
Convulex®	Valproic acid	100, 200 mg	Pharmacia	Soft gelatin capsule
Lipirex®	Fenofibrate	200 mg	Genus	Hard gelatin capsule
Targretin®	Bexarotene	75 mg	Ligand	Soft gelatin capsule
Rocaltrol®	Calcitriol	0.25, 0.5 µg	Roche	Soft gelatin capsule
Gengraf®	Cyclosporin	25, 100 mg	Abbott Laboratories	Hard gelatin capsule
Solufen®	Ibuprofen	200 mg	Sanofi- Aventis	Hard gelatin capsule
Sandimmune®	Cyclosporin A	25 mg	Novartis	Soft gelatin capsule
Marinol®	Dronabinol	2.5, 5, or 10 mg	Roxane and Unimed	Soft gelatin capsule
Accutane®	Isotretinoin	10, 20 and 40 mg	Roche	Soft gelatin capsule
Prometrium®	Progesterone	100 or 200 mg		
Vesanoid®	Tretinoin	10 mg	Roche	Soft gelatin capsule
Avodart®	Dutasteride	0.4, 0.5 mg	GlaxoSmithKline	Soft gelatin capsule
Hectorol®	Doxercalciferol	0.5, 1 and 2.5 mcg	Genzyme	Soft gelatin capsule
Coreg CR®	Carvedilol phosphate	10, 20, 40 and 80 mg	GlaxoSmithKline	Controlled release Soft gelatin capsule
Lovaza®	Omega-3-acid ester	2, 4 g	GlaxoSmithKline	Hard gelatin capsule
Rapamune®	Sirolimus	0.5, 1, 2 mg	Wyeth-Ayerst	Oral Solution
Detrol LA®	Tolterodine tartrate	2 or 4 mg	Pharmacia	Extended release Hard gelatin capsule
Pentasa®	Mesalamine	250, 500 mg	Shire US inc.	Controlled release capsule
Zemplar®	Paricalcitol	1, 2 and 4 mcg	Abbott Laboratories	Soft gelatin capsule

Source: Chakraborty *et al*. (2009)

Table 3: Application of SMEDDS in various BCS category drugs

BCS class	Aqueous solubility	Membrane permeability	Hurdles overcome by SMEDDS	e.g.
Class I	High	High	Enzymatic degradation, Gut wall efflux	Metoprolol, Paracetamol
Class II	Low	High	Solubilization and bioavailability	Nifedipine, phenytoin
Class III	High	Low	Enzymatic degradation, gut wall efflux and bioavailability	Atenolol, Cimetidine
Class IV	Low	Low	Solubilization, enzymatic degradation, gut wall efflux and bioavailability	Ritonavir, Cyclosporin A

Source: Kanika *et al*. (2010)

meal in stomach instead of empty stomach favors the absorption of drug from the lipid based formulation because the absorption of lipophilic drug usually exhibit dissolution-rate-limited. SMEDDS can improve the rate and extent of absorption resulting in reproducible blood time profiles (Hauss, 2007). These systems can help in solving the under-mentioned problems of all the categories of BCS class drugs, as depicted in Table 3. To explain the trends for oral absorption Lipinski's rule of five has been widely used as a qualitative predictive model. The rule of five explains poor absorption or poor permeation in terms of situation where there are more than five H-bond donors, there are more than ten H-bond acceptors, the molecular weight >500 and the calculated log p >5. Both BCS and Lipinski's rule of five are useful, mainly at the primary screening stage but they have limitations. It is considered that the rule of five only applicable to compounds

which are not substrates for active transporters, and with increasing evidence suggesting that most drugs are substrates for some efflux or uptake transporters, this limitation might be notable (Kohli *et al*., 2010). For design a lipidic systems Log P can be consider as the prime characteristics. For lipidic systems higher log P (more than 4) values are desirous. For e.g., cinnarizine, a lipophilic drug, having log P values greater than 5 is strong candidate for SMEDDS. Among physicochemical characteristics melting point and dose play a major role. Low melting point and low dose are desirable for development of lipidic systems. Drugs high melting point having with low log P values (around 2) is not suitable for SMEDDS.

EXCIPIENTS USED IN SMEDDS

As described, a SMEDDS pre-concentrate can contain four categories of components: drug, lipids, surfactants and co solvents. Commonly used lipids, surfactants and co-solvents are listed in Table 4.

Oil: The oil represents one of the most essential excipients in the SMEDDS formulation not only because it can solubilize the necessary dose of the lipophilic drug or assist self emulsification but also and mainly because it can improve the fraction of lipophilic drug transported via the intestinal lymphatic system, thereby increasing absorption from the GI tract depending on the molecular nature of the triglyceride (Kimura *et al*., 1994). As a result, triglycerides such as medium chain and long chain with different degree of saturation have been used for the solvation of hydrophobic therapeutic agent in the design of SMEDDS (Constantinides, 1995). Long-chain triglycerides are derived from vegetable sources such as soybean or safflower oil, whereas MCTs are obtained by the re-esterification of fractionated coconut oil fatty acids with glycerin (Angare *et al*., 2012). Semisynthetic derivatives form good emulsification systems when used with a large amount of solubility enhancing surfactants approved for oral administration (Gershanik and Benita, 2000; Devani *et al*., 2004). Patravale *et al*. (2003) demonstrated that because of high fluidity, improved solubilizing potential and self-microemulsification potential these excipients form good emulsification systems. The stability of emulsion also depends on the rheology and characteristics of the oil (Anisa *et al*., 2010). Vegetables oil like Olive oil, Peanut oil, Safflower oil, Sesame oil, Soybean oil, Wheat germ oil, rice bran oil etc. (Pogori *et al*., 2008).

Surfactants: A surfactant is an amphiphilic agent formed by two parts with different affinities for the solvents. One of them has affinity for water (polar solvents) and the other has for oil (non-polar solvents) widely used for industrial, agricultural, food, cosmetics and pharmaceutical application such as emulsifying, solubilizing agent and enhancer (Gharaei-Fathabad, 2011; Noudeh *et al*., 2008). Surfactants used to stabilize microemulsion system may be: (i) non-ionic, (ii) zwitterionic, (iii) cationic, or (iv) anionic surfactants. Combinations of these, particularly ionic and non-ionic, can be very effective at increasing the degree of the microemulsion region (De Gennes and Taupin, 1982; Ajazuddinm, 2010). Surfactant also play vital role in the structure of colloidal sized cluster in solution, known as Micelles (Gokturk and Var, 2011). Anionic and nonionic surfactant mixtures are responsible for possible synergism (combined effect) in Critical Micelle Concentration (CMC) thus; Synergism of both surfactants was sought in presence of oil phase (Muherei and Junin, 2009; Tripathi *et al*., 1994). Non-ionic surfactants are identified to be less toxic compared to ionic surfactants. Various non-ionic surfactants such as the polysorbates like Tween 40, 60, 80 and polyoxyls which cover the HLB range from 2 to 18, may be used in

Table 4: List of excipients

Trade name	Chemical name	Composition	HLB
Lipid			
Vegetable oil	Long-chain TAG	TAG of C18, C16 and C14 FA	
Labrafac CC	Caprylic/capric triglyceride	TAG of C8-12 FA	1
Captex 355	Glycerol caprylate caprate	TAG of C8 and C10	
Isopropyl myristate	FA ester	Isopropyl ester of C14 FA (myristic acid)	11.5
Capmul MCM	Caprylic/capric glycerides	MAG and DAG of C8 and C10 FA and 2%free glycerol	5–6
Maisine 35-1	Glyceryl monolinoleate	MAG and DAG of C18 and C16 FA with small quantities of TAG	4
Akoline MCM	Caprylic/capric glycerides	MAG and DAG of C8 and C10 with small quantity of TAG	5–6
Miglyol 812	Medium-chain TAG		
Caprylic/capric TAG	TAG of C8 and C10 FA		
Viscoleo	Fractionated coconut oil	TAG of C8-12 FA	
Surfactant			
Tween 85	Polyoxyethylene (20) sorbitan trioleate	Partial triesters of sorbitol and its mono-and di-anhydrides with oleic acid	11
Span 20	Sorbitan monolaurate	Plain (non-PEGylated) sorbitan with C20 FA	8.6
Capryol 90	PG monocaprylate	C8 FA mono-esters of PG	6
Lauroglycol 90	PG monolaurate	C12 FA mono-esters of propylene glycol	5
Labrafil M1944CS	Oleoyl macrogolglycerides (polyoxylglycerides)	Mainly C18:1 mono- and diesters of PEG 300 and MAG, DAG and TAG	4
Cremophor EL	Polyoxyl 35 castor oil	Glycerol-PEG ricinoleate, FA esters of PEG	12-14
Cremophor RH40	Polyoxyl 40 hydrogenated castor oil	FA esters of glycerol-PEG, FA esters of PEG, free PEG and ethoxylate glycerol	14-16
Acconon MC-8	Caprylocaproyl macrogolglycerides (polyoxylglycerides) and C10:0 and some free PEG 400	FA C8:0/C10:0 mono- and diesters of PEG 400 and MAG, DAG and TAG with mainly C8:0	14-15
Tween 20	Polyoxyethylene (20) sorbitan monolaurate	PEGylated sorbitan (a derivative of sorbitol) esterified with C12 FA	16.5
Labrasol	Caprylocaproyl macrogolglycerides (polyoxylglycerides)	FA C8:0/C10:0 mono- and diesters of PEG 400 and MAG, DAG and TAG with mainly C8:0 and C10:0 and some free PEG 400	14
Tween 80	Polyoxyethylene (20) sorbitan mono-oleate	PEGylated sorbitan (a derivative of sorbitol) esterified with 80 C18:1 FA	15
Co-solvents			
Ethanol	Ethyl alcohol		7.9
PEG	Polyethylene Glycol		15.5
Carbitol	Diglycol monoethyl ether		
Transcutol P	Diethylene glycol monoethyl ether		4.2
Propylene glycol			11.6

Source: Mullertz *et al*. (2010)

combination with lipid excipients to facilitate self-emulsification or micro-emulsification (Hauss, 2007; Chen *et al*., 2011). The surfactant used to enhance the bioavailability by various mechanisms

including: improved drug dissolution in the gastrointestinal fluids, especially in the presence of bile salts, lecithin and lipid digestion mixtures, increased intestinal epithelial permeability, increased tight junction permeability and decreased/inhibited p-glycoprotein drug efflux (Patel and Sawant, 2009; Giri *et al.*, 2010a). Emulsifier, a subset of surfactants which improves in machinability, strengthening and shelf life extension (Hoque *et al.*, 2009). This can avoid precipitation of the drug within the GI lumen and for prolonged existence of drug molecules. In self-emulsifying formulations the usual surfactant concentration ranged from 30 to 60% w/w of the formulation. A large quantity of surfactant may irritate the GI tract (Tang *et al.*, 2007).

Co-surfactant: In SMEDDS, usually co-surfactant of HLB value 10-14 is used with surfactants together to diminish the oil water interface, fluidize the hydrocarbon region of the interfacial film and allow the spontaneous formation of micro emulsion. The choice of co-surfactant and surfactant is critical not only to form the formation of microemulsion but also to solubilization in microemulsions (Patravale *et al.*, 2003; Ozawa *et al.*, 1986).

Co-solvent: The role of co-solvents in lipid based formulations mainly in SMEDDS is to assist the dispersion process and in earlier dispersion rates (Gursoy and Benita, 2004). Gershanik and Benita (2000) mentioned in their review about alcohol and other volatile co-solvent free self emulsifying micro emulsion formulations are known to migrate into the shells of soft gelatin, or hard, sealed gelatin capsules, resulting in the precipitation of the lipophilic drug.

Consistency builder: Tragacanth, cetyl alcohol, stearic acid or beeswax can be added to modify the stability of the emulsion (Osol, 1975).

Polymer: Inert polymer matrix representing from 5 to 40% of composition relative to the weight, which is not ionizable at physiological pH and being capable of forming matrix are used for the formulation of sustained release SMEDDS. Examples are hydroxypropylmethyl cellulose and ethyl cellulose (Barthelemy and Benameur, 2001; Alexander *et al.*, 2011).

Table 5 shows list of various drug with their respective solubility in different vehicles like oil, surfactant and co-surfactant.

PSEUDO-TERNARY PHASE DIAGRAM STUDY

Pseudo-ternary phase diagrams are useful tools to determine the composition of an aqueous phase, oil phase and surfactant: co-surfactant phase that will yield a Micro Emulsion (ME), Liquid Crystal (LC) and coarse emulsion (EM). Each corner of diagram typically represents 100% of the particular component. It is constructed to define the extent and nature of micro emulsion region. The different phases are mix in different proportion to constructed the phase diagram and identify micro emulsion region. Since, four chemical species were incorporated in micro emulsion, one of the components (co-surfactant) is in fixed ratio with surfactant. Each of the three components for a system is titrated with the aqueous phase until a phase changes between micro emulsion and two phases of mixture was observed. Further addition of water it form the LC were detected under gentle stirring. By continuing the addition of water LC disappeared. However, unlike the first situation the mixture was somewhat cloudy and opaque which form the coarse emulsion (Li *et al.*, 2005; Zadeh *et al.*, 2010). An optimized formula for finding out region of microemulsion with the help of titration shows in Table 6. After optimization of microemulsion region we can draw the

Table 5: Drugs with their respective solubility in various vehicles

	Vehicles			Solubility			
Drug	Oil	Surfactant:Cosurfactant	Ratio	Oil	Surfactant	Co-Surfactant	References
Tacrolimus	Capmul MCM C_8	Cremophore EL :Carbitol	2:1	32.19±1.02 mg mL^{-1}	25.02±1.16 mg mL^{-1}	58.69±3.94 mg mL^{-1}	Borhade *et al.* (2008)
Lovastatin	Sunflower oil	Acrysol K 140: Campul MCM	2:1	83.56±1.96 mg g^{-1}	78.5±1.89 mg g^{-1}	78.5±1.89 mg g^{-1}	Patel *et al.* (2010a)
Simvastatin	Caproyl 90	Cremophor EL: Carbitol	1:1	144.44±4.89 mg mL^{-1}	70.53±4.60 mg mL^{-1}	194.35±8.95 mg mL^{-1}	Kang *et al.* (2004a)
Flutamide	Sesame oil	Tween 80: PEG 400	_	0.912±0.008 mg mL^{-1}	0.905±0.035 mg mL^{-1}	0.747±0.041 mg mL^{-1}	
Celecoxib	CCG	Tween 20: MPG	3:1	300.9±1.35 mg mL^{-1}	315.4±2.07 mg mL^{-1}	52±1.09 mg mL^{-1}	Natesan *et al.* (2004)
Oridonin	Labrafac CC & Maisine 35-1	Cremophor EL: Transcutol P	2:1	0.41±0.08 mg mL^{-1} 7.00+0.93 mg mL^{-1}	9.46±0.17 mg mL^{-1}	54.10±1.32 mg mL^{-1}	Zhang *et al.* (2008)
Glyburide	Caproyl 90	Tween 20: Transcutol P	_	5.85±0.45 ng mL^{-1}	6.3±6.5 ng mL^{-1}	15±1.2 ng mL^{-1}	Bachhav and Patravale (2009)
Etodolac	Labrafac WL 1349	Labrasol: Lauroglycol 90 Caproyl 90	_	97.3±4.2 mg mL^{-1}	147.4±8.3 mg mL^{-1}	87.3±3.8 mg mL^{-1} 98.5±4.3 mg mL^{-1}	Barakat (2010)
Itraconazole	Tocopherol Acetate	Pluronic L64 : Transcutol	4:1	5.22 mg g^{-1}	5.20±1.57 mg g^{-1}	4.60±0.48 mg g^{-1}	Hong *et al.* (2006)
Cefpodoxime proxetil	Capryol 90	Cremophore-EL: Akoline-MCM	_	512.1 mg g^{-1}	15.45 mg g^{-1}	457.5 mg g^{-1}	Date and Nagarsenker (2007)
Curcumin	Ethyl oleate	Cremorphor EL:PEG 400 Emulsifier OP	1:1	0.357±0.032 mg g^{-1} 1.924±0.232 mg g^{-1}	1.145±0.115 mg g^{-1}	1.924 mg g^{-1}	Cui *et al.* (2009a)
Buparvaquone	Capryol 90	Cremophor EL: Labrasol	4:1	15.58± 0.57 mg mL^{-1}	15.70± 0.52 mg mL^{-1}	17.00±0.28 mg mL^{-1}	Venkatesh *et al.* (2010)
Acyclovir	Sunflower oil	Tween 60: Glycerol	1:0.5	4.333±0.028 mg mL^{-1}	_	152.9± 0.556 mg mL^{-1}	Patel and Sawant (2007)
Vinpocetine	Ethyl oleate	Solutol HS 15: Transcutol P	3:2	7.10± 1.4 mg mL^{-1}	10.41±2.9 mg mL^{-1}	24.08±4.8 mg mL^{-1}	Cui *et al.* (2009b)

Table 6: Titration chart to find out microemulsion region

Ratio Oil:Smix	Oil (mL)	Surfactant (Smix) (mL)	Water (mL)	Water added (mL)	Total (mL)	Oil (%)	Surfactant (Smix) (%)	Water (%)
1:9	0.1	0.9	0.10	0.10	1.10	9.09	81.82	9.09
	0.1	0.9	0.20	0.10	1.20	8.33	75.00	16.67
	0.1	0.9	0.25	0.05	1.25	8.00	72.00	20.00
	0.1	0.9	0.35	0.10	1.35	7.41	66.67	25.93
	0.1	0.9	0.45	0.10	1.45	6.90	62.07	31.03
	0.1	0.9	0.55	0.10	1.55	6.45	58.06	35.48
	0.1	0.9	0.65	0.10	1.65	6.06	54.55	39.39
	0.1	0.9	0.80	0.15	1.80	5.56	50.00	44.44
	0.1	0.9	1.00	0.20	2.00	5.00	45.00	50.00
	0.1	0.9	1.20	0.20	2.20	4.55	40.91	54.55
	0.1	0.9	1.50	0.30	2.50	4.00	36.00	60.00
	0.1	0.9	1.85	0.35	2.85	3.51	31.58	64.91
	0.1	0.9	2.35	0.50	3.35	2.99	26.87	70.15
	0.1	0.9	3.00	0.65	4.00	3.00	23.00	75.00
	0.1	0.9	4.00	1.00	5.00	2.00	18.00	80.00
	0.1	0.9	5.50	1.50	6.50	2.00	14.00	85.00
	0.1	0.9	9.00	3.50	10.00	1.00	9.00	90.00
	0.1	0.9	20.00	11.00	21.00	0.48	4.29	95.24
2:8 (1:4)	0.2	0.8	0.10	0.10	1.10	18.18	72.73	9.09
	0.2	0.8	0.20	0.10	1.20	16.67	66.67	16.67
	0.2	0.8	0.25	0.05	1.25	16.00	64.00	20.00
	0.2	0.8	0.35	0.10	1.35	14.81	59.26	25.93
	0.2	0.8	0.45	0.10	1.45	13.79	55.17	31.03
	0.2	0.8	0.55	0.10	1.55	12.90	51.61	35.48
	0.2	0.8	0.65	0.10	1.65	12.12	48.48	39.39
	0.2	0.8	0.80	0.15	1.80	11.11	44.44	44.44
	0.2	0.8	1.00	0.20	2.00	10.00	40.00	50.00
	0.2	0.8	1.20	0.20	2.20	9.09	36.36	54.55
	0.2	0.8	1.50	0.30	2.50	8.00	32.00	60.00
	0.2	0.8	1.85	0.35	2.85	7.02	28.07	64.91
	0.2	0.8	2.35	0.50	3.35	5.97	23.88	70.15
	0.2	0.8	3.00	0.65	4.00	5.00	20.00	75.00
	0.2	0.8	4.00	1.00	5.00	4.00	16.00	80.00
	0.2	0.8	5.50	1.50	6.50	3.08	12.31	84.62
	0.2	0.8	9.00	3.50	10.00	2.00	8.00	90.00
	0.2	0.8	20.00	11.00	21.00	0.95	3.81	95.24
3:7 (1:2.3)	0.3	0.7	0.10	0.10	1.10	27.27	63.64	9.09
	0.3	0.7	0.20	0.10	1.20	25.00	58.33	16.67
	0.3	0.7	0.25	0.05	1.25	24.00	56.00	20.00
	0.3	0.7	0.35	0.10	1.35	22.22	51.85	25.93
	0.3	0.7	0.45	0.10	1.45	20.69	48.28	31.03
	0.3	0.7	0.55	0.10	1.55	19.35	45.16	35.48
	0.3	0.7	0.65	0.10	1.65	18.18	42.42	39.39
	0.3	0.7	0.80	0.15	1.80	16.67	38.89	44.44
	0.3	0.7	1.00	0.20	2.00	15.00	35.00	50.00
	0.3	0.7	1.20	0.20	2.20	13.64	31.82	54.55
	0.3	0.7	1.50	0.30	2.50	12.00	28.00	60.00

Table 6: Continue

Ratio Oil:Smix	Oil (mL)	Surfactant (Smix) (mL)	Water (mL)	Water added (mL)	Total (mL)	Oil (%)	Surfactant (Smix) (%)	Water (%)
	0.3	0.7	1.85	0.35	2.85	10.53	24.56	64.91
	0.3	0.7	2.35	0.50	3.35	8.96	20.90	70.15
	0.3	0.7	3.00	0.65	4.00	7.50	17.50	75.00
	0.3	0.7	4.00	1.00	5.00	6.00	14.00	80.00
	0.3	0.7	5.50	1.50	6.50	4.62	10.77	84.62
	0.3	0.7	9.00	3.50	10.00	3.00	7.00	90.00
	0.3	0.7	20.00	11.00	21.00	1.43	3.33	95.24
4:6 (1:1.5)	0.4	0.6	0.10	0.10	1.10	36.36	54.55	9.09
	0.4	0.6	0.20	0.10	1.20	33.33	50.00	16.67
	0.4	0.6	0.25	0.05	1.25	32.00	48.00	20.00
	0.4	0.6	0.35	0.10	1.35	29.63	44.44	25.93
	0.4	0.6	0.45	0.10	1.45	27.59	41.38	31.03
	0.4	0.6	0.55	0.10	1.55	25.81	38.71	35.48
	0.4	0.6	0.65	0.10	1.65	24.24	36.36	39.39
	0.4	0.6	0.80	0.15	1.80	22.22	33.33	44.44
	0.4	0.6	1.00	0.20	2.00	20.00	30.00	50.00
	0.4	0.6	1.20	0.20	2.20	18.18	27.27	54.55
	0.4	0.6	1.50	0.30	2.50	16.00	24.00	60.00
	0.4	0.6	1.85	0.35	2.85	14.04	21.05	64.91
	0.4	0.6	2.35	0.50	3.35	11.94	17.91	70.15
	0.4	0.6	3.00	0.65	4.00	10.00	15.00	75.00
	0.4	0.6	4.00	1.00	5.00	8.00	12.00	80.00
	0.4	0.6	5.50	1.50	6.50	6.15	9.23	84.62
	0.4	0.6	9.00	3.50	10.00	4.00	6.00	90.00
	0.4	0.6	20.00	11.00	21.00	1.90	2.86	95.24
5:5 (1:1)	0.5	0.5	0.10	0.10	1.10	45.45	45.45	9.09
	0.5	0.5	0.20	0.10	1.20	41.67	41.67	16.67
	0.5	0.5	0.25	0.05	1.25	40.00	40.00	20.00
	0.5	0.5	0.35	0.10	1.35	37.04	37.04	25.93
	0.5	0.5	0.45	0.10	1.45	34.48	34.48	31.03
	0.5	0.5	0.55	0.10	1.55	32.26	32.26	35.48
	0.5	0.5	0.65	0.10	1.65	30.30	30.30	39.39
	0.5	0.5	0.80	0.15	1.80	27.78	27.78	44.44
	0.5	0.5	1.00	0.20	2.00	25.00	25.00	50.00
	0.5	0.5	1.20	0.20	2.20	22.73	22.73	54.55
	0.5	0.5	1.50	0.30	2.50	20.00	20.00	60.00
	0.5	0.5	1.85	0.35	2.85	17.54	17.54	64.91
	0.5	0.5	2.35	0.50	3.35	14.93	14.93	70.15
	0.5	0.5	3.00	0.65	4.00	12.50	12.50	75.00
	0.5	0.5	4.00	1.00	5.00	10.00	10.00	80.00
	0.5	0.5	5.50	1.50	6.50	7.69	7.69	84.62
	0.5	0.5	9.00	3.50	10.00	5.00	5.00	90.00
	0.5	0.5	20.00	11.00	21.00	2.38	2.38	95.24
6:4 (1:0.7)	0.6	0.4	0.10	0.10	1.10	54.55	36.36	9.09
	0.6	0.4	0.20	0.10	1.20	50.00	33.33	16.67
	0.6	0.4	0.25	0.05	1.25	48.00	32.00	20.00
	0.6	0.4	0.35	0.10	1.35	44.44	29.63	25.93

Table 6: Continue

Ratio Oil:Smix	Oil (mL)	Surfactant (Smix) (mL)	Water (mL)	Water added (mL)	Total (mL)	Oil (%)	Surfactant (Smix) (%)	Water (%)
	0.6	0.4	0.45	0.10	1.45	41.38	27.59	31.03
	0.6	0.4	0.55	0.10	1.55	38.71	25.81	35.48
	0.6	0.4	0.65	0.10	1.65	36.36	24.24	39.39
	0.6	0.4	0.80	0.15	1.80	33.33	22.22	44.44
	0.6	0.4	1.00	0.20	2.00	30.00	20.00	50.00
	0.6	0.4	1.20	0.20	2.20	27.27	18.18	54.55
	0.6	0.4	1.50	0.30	2.50	24.00	16.00	60.00
	0.6	0.4	1.85	0.35	2.85	21.05	14.04	64.91
	0.6	0.4	2.35	0.50	3.35	17.91	11.94	70.15
	0.6	0.4	3.00	0.65	4.00	15.00	10.00	75.00
	0.6	0.4	4.00	1.00	5.00	12.00	8.00	80.00
	0.6	0.4	5.50	1.50	6.50	9.23	6.15	84.62
	0.6	0.4	9.00	3.50	10.00	6.00	4.00	90.00
	0.6	0.4	20.00	11.00	21.00	2.86	1.90	95.24
7:3 (1:0.43)	0.7	0.3	0.10	0.10	1.10	63.64	27.27	9.09
	0.7	0.3	0.20	0.10	1.20	58.33	25.00	16.67
	0.7	0.3	0.25	0.05	1.25	56.00	24.00	20.00
	0.7	0.3	0.35	0.10	1.35	51.85	22.22	25.93
	0.7	0.3	0.45	0.10	1.45	48.28	20.69	31.03
	0.7	0.3	0.55	0.10	1.55	45.16	19.35	35.48
	0.7	0.3	0.65	0.10	1.65	42.42	18.18	39.39
	0.7	0.3	0.80	0.15	1.80	38.89	16.67	44.44
	0.7	0.3	1.00	0.20	2.00	35.00	15.00	50.00
	0.7	0.3	1.20	0.20	2.20	31.82	13.64	54.55
	0.7	0.3	1.50	0.30	2.50	28.00	12.00	60.00
	0.7	0.3	1.85	0.35	2.85	24.56	10.53	64.91
	0.7	0.3	2.35	0.50	3.35	20.90	8.96	70.15
	0.7	0.3	3.00	0.65	4.00	17.50	7.50	75.00
	0.7	0.3	4.00	1.00	5.00	14.00	6.00	80.00
	0.7	0.3	5.50	1.50	6.50	10.77	4.62	84.62
	0.7	0.3	9.00	3.50	10.00	7.00	3.00	90.00
	0.7	0.3	20.00	11.00	21.00	3.33	1.43	95.24
8:2(1:0.25)	0.8	0.2	0.10	0.10	1.10	72.73	18.18	9.09
	0.8	0.2	0.20	0.10	1.20	66.67	16.67	16.67
	0.8	0.2	0.25	0.05	1.25	64.00	16.00	20.00
	0.8	0.2	0.35	0.10	1.35	59.26	14.81	25.93
	0.8	0.2	0.45	0.10	1.45	55.17	13.79	31.03
	0.8	0.2	0.55	0.10	1.55	51.61	12.90	35.48
	0.8	0.2	0.65	0.10	1.65	48.48	12.12	39.39
	0.8	0.2	0.80	0.15	1.80	44.44	11.11	44.44
	0.8	0.2	1.00	0.20	2.00	40.00	10.00	50.00
	0.8	0.2	1.20	0.20	2.20	36.36	9.09	54.55
	0.8	0.2	1.50	0.30	2.50	32.00	8.00	60.00
	0.8	0.2	1.85	0.35	2.85	28.07	7.02	64.91
	0.8	0.2	2.35	0.50	3.35	23.88	5.97	70.15
	0.8	0.2	3.00	0.65	4.00	20.00	5.00	75.00
	0.8	0.2	4.00	1.00	5.00	16.00	4.00	80.00

Table 6: Continue

Ratio Oil:Smix	Oil (mL)	Surfactant (Smix) (mL)	Water (mL)	Water added (mL)	Total (mL)	Oil (%)	Surfactant (Smix) (%)	Water (%)
	0.8	0.2	5.50	1.50	6.50	12.31	3.08	84.62
	0.8	0.2	9.00	3.50	10.00	8.00	2.00	90.00
	0.8	0.2	20.00	11.00	21.00	3.81	0.95	95.24
9:1 (1:0.1)	0.9	0.1	0.10	0.10	1.10	81.82	9.09	9.09
	0.9	0.1	0.20	0.10	1.20	75.00	8.33	16.67
	0.9	0.1	0.25	0.05	1.25	72.00	8.00	20.00
	0.9	0.1	0.35	0.10	1.35	66.67	7.41	25.93
	0.9	0.1	0.45	0.10	1.45	62.07	6.90	31.03
	0.9	0.1	0.55	0.10	1.55	58.06	6.45	35.48
	0.9	0.1	0.65	0.10	1.65	54.55	6.06	39.39
	0.9	0.1	0.80	0.15	1.80	50.00	5.56	44.44
	0.9	0.1	1.00	0.20	2.00	45.00	5.00	50.00
	0.9	0.1	1.20	0.20	2.20	40.91	4.55	54.55
	0.9	0.1	1.50	0.30	2.50	36.00	4.00	60.00
	0.9	0.1	1.85	0.35	2.85	31.58	3.51	64.91
	0.9	0.1	2.35	0.50	3.35	26.87	2.99	70.15
	0.9	0.1	3.00	0.65	4.00	22.50	2.50	75.00
	0.9	0.1	4.00	1.00	5.00	18.00	2.00	80.00
	0.9	0.1	5.50	1.50	6.50	13.85	1.54	84.62
	0.9	0.1	9.00	3.50	10.00	9.00	1.00	90.00
	0.9	0.1	20.00	11.00	21.00	4.29	0.48	95.24
1:2	0.2	0.4	0.06	0.06	0.66	30.30	60.61	9.09
	0.2	0.4	0.11	0.05	0.71	28.17	56.34	15.49
	0.2	0.4	0.15	0.04	0.75	26.67	53.33	20.00
	0.2	0.4	0.20	0.05	0.80	25.00	50.00	25.00
	0.2	0.4	0.26	0.06	0.86	23.26	46.51	30.23
	0.2	0.4	0.33	0.07	0.93	21.51	43.01	35.48
	0.2	0.4	0.40	0.07	1.00	20.00	40.00	40.00
	0.2	0.4	0.50	0.10	1.10	18.18	36.36	45.45
	0.2	0.4	0.60	0.10	1.20	16.67	33.33	50.00
	0.2	0.4	0.75	0.15	1.35	14.81	29.63	55.56
	0.2	0.4	0.90	0.15	1.50	13.33	26.67	60.00
	0.2	0.4	1.12	0.22	1.72	11.63	23.26	65.12
	0.2	0.4	1.40	0.28	2.00	10.00	20.00	70.00
	0.2	0.4	1.80	0.40	2.40	8.33	16.67	75.00
	0.2	0.4	2.40	0.60	3.00	6.67	13.33	80.00
	0.2	0.4	3.40	1.00	4.00	5.00	10.00	85.00
	0.2	0.4	5.40	2.00	6.00	3.33	6.67	90.00
	0.2	0.4	11.40	6.00	12.00	1.67	3.33	95.00
1:3	0.2	0.6	0.10	0.10	0.90	22.22	66.67	11.11
	0.2	0.6	0.14	0.04	0.94	21.28	63.83	14.89
	0.2	0.6	0.20	0.06	1.00	20.00	60.00	20.00
	0.2	0.6	0.27	0.07	1.07	18.69	56.07	25.23
	0.2	0.6	0.35	0.08	1.15	17.39	52.17	30.43
	0.2	0.6	0.43	0.08	1.23	16.26	48.78	34.96
	0.2	0.6	0.54	0.11	1.34	14.93	44.78	40.30
	0.2	0.6	0.66	0.12	1.46	13.70	41.10	45.21

Table 6: Continue

Ratio Oil:Smix	Oil (mL)	Surfactant (Smix) (mL)	Water (mL)	Water added (mL)	Total (mL)	Oil (%)	Surfactant (Smix) (%)	Water (%)
	0.2	0.6	0.80	0.14	1.60	12.50	37.50	50.00
	0.2	0.6	0.98	0.18	1.78	11.24	33.71	55.06
	0.2	0.6	1.20	0.22	2.00	10.00	30.00	60.00
	0.2	0.6	1.49	0.29	2.29	8.73	26.20	65.07
	0.2	0.6	1.87	0.38	2.67	7.49	22.47	70.04
	0.2	0.6	2.40	0.53	3.20	6.25	18.75	75.00
	0.2	0.6	3.20	0.80	4.00	5.00	15.00	80.00
	0.2	0.6	4.55	1.35	5.35	3.74	11.21	85.05
	0.2	0.6	7.00	2.45	7.80	3.00	8.00	90.00
	0.2	0.6	15.20	8.20	16.00	1.25	3.75	95.00
1:3.5	0.2	0.7	0.10	0.10	100.00	20.00	70.00	10.00
	0.2	0.7	0.16	0.06	106.00	18.87	66.04	15.09
	0.2	0.7	0.23	0.07	113.00	17.70	61.95	20.35
	0.2	0.7	0.30	0.07	120.00	16.67	58.33	25.00
	0.2	0.7	0.39	0.09	129.00	15.50	54.26	30.23
	0.2	0.7	0.49	0.10	139.00	14.39	50.36	35.25
	0.2	0.7	0.60	0.11	150.00	13.33	46.67	40.00
	0.2	0.7	0.74	0.14	164.00	12.20	42.68	45.12
	0.2	0.7	0.90	0.16	180.00	11.11	38.89	50.00
	0.2	0.7	1.10	0.20	200.00	10.00	35.00	55.00
	0.2	0.7	1.35	0.25	225.00	8.89	31.11	60.00
	0.2	0.7	1.68	0.33	258.00	7.75	27.13	65.12
	0.2	0.7	2.10	0.42	300.00	6.67	23.33	70.00
	0.2	0.7	2.70	0.60	360.00	5.56	19.44	75.00
	0.2	0.7	3.60	0.90	450.00	4.44	15.56	80.00
	0.2	0.7	5.10	1.50	600.00	3.33	11.67	85.00
	0.2	0.7	8.10	3.00	900.00	2.22	7.78	90.00
	0.2	0.7	17.10	9.00	1800.00	1.11	3.89	95.00
1:5	0.2	1	0.14	0.14	1.34	14.93	74.63	10.45
	0.2	1	0.22	0.08	1.42	14.08	70.42	15.49
	0.2	1	0.30	0.08	1.50	13.33	66.67	20.00
	0.2	1	0.40	0.10	1.60	12.50	62.50	25.00
	0.2	1	0.53	0.13	1.73	11.56	57.80	30.64
	0.2	1	0.65	0.12	1.85	10.81	54.05	35.14
	0.2	1	0.80	0.15	2.00	10.00	50.00	40.00
	0.2	1	1.00	0.20	2.20	9.09	45.45	45.45
	0.2	1	1.20	0.20	2.40	8.33	41.67	50.00
	0.2	1	1.47	0.27	2.67	7.49	37.45	55.06
	0.2	1	1.80	0.33	3.00	6.67	33.33	60.00
	0.2	1	2.25	0.45	3.45	5.80	28.99	65.22
	0.2	1	2.80	0.55	4.00	5.00	25.00	70.00
	0.2	1	3.60	0.80	4.80	4.17	20.83	75.00
	0.2	1	4.80	1.20	6.00	3.33	16.67	80.00
	0.2	1	6.80	2.00	8.00	2.50	12.50	85.00
	0.2	1	11.00	4.20	12.20	1.64	8.20	90.16
	0.2	1	23.00	12.00	24.20	0.83	4.13	95.04
1:6	0.2	1.2	0.16	0.16	1.56	12.82	76.92	10.26

Table 6: Continue

Ratio Oil:Smix	Oil (mL)	Surfactant (Smix) (mL)	Water (mL)	Water added (mL)	Total (mL)	Oil (%)	Surfactant (Smix) (%)	Water (%)
	0.2	1.2	0.25	0.09	1.65	12.12	72.73	15.15
	0.2	1.2	0.35	0.10	1.75	11.43	68.57	20.00
	0.2	1.2	0.47	0.12	1.87	10.70	64.17	25.13
	0.2	1.2	0.60	0.13	2.00	10.00	60.00	30.00
	0.2	1.2	0.76	0.16	2.16	9.26	55.56	35.19
	0.2	1.2	0.93	0.17	2.33	8.58	51.50	39.91
	0.2	1.2	1.15	0.22	2.55	7.84	47.06	45.10
	0.2	1.2	1.40	0.25	2.80	7.14	42.86	50.00
	0.2	1.2	1.72	0.32	3.12	6.41	38.46	55.13
	0.2	1.2	2.10	0.38	3.50	5.71	34.29	60.00
	0.2	1.2	2.60	0.50	4.00	5.00	30.00	65.00
	0.2	1.2	3.30	0.70	4.70	4.26	25.53	70.21
	0.2	1.2	4.20	0.90	5.60	3.57	21.43	75.00
	0.2	1.2	5.60	1.40	7.00	2.86	17.14	80.00
	0.2	1.2	8.00	2.40	9.40	2.13	12.77	85.11
	0.2	1.2	12.60	4.60	14.00	1.43	8.57	90.00
	0.2	1.2	27.00	14.40	28.40	0.70	4.23	95.07
1:7	0.2	1.4	0.18	0.18	1.78	11.24	78.65	10.11
	0.2	1.4	0.30	0.12	1.90	10.53	73.68	15.79
	0.2	1.4	0.40	0.10	2.00	10.00	70.00	20.00
	0.2	1.4	0.54	0.14	2.14	9.35	65.42	25.23
	0.2	1.4	0.70	0.16	2.30	8.70	60.87	30.43
	0.2	1.4	0.86	0.16	2.46	8.13	56.91	34.96
	0.2	1.4	1.07	0.21	2.67	7.49	52.43	40.07
	0.2	1.4	1.35	0.28	2.95	6.78	47.46	45.76
	0.2	1.4	1.60	0.25	3.20	6.25	43.75	50.00
	0.2	1.4	1.96	0.36	3.56	5.62	39.33	55.06
	0.2	1.4	2.40	0.44	4.00	5.00	35.00	60.00
	0.2	1.4	3.00	0.60	4.60	4.35	30.43	65.22
	0.2	1.4	3.75	0.75	5.35	3.74	26.17	70.09
	0.2	1.4	4.80	1.05	6.40	3.13	21.88	75.00
	0.2	1.4	6.40	1.60	8.00	2.50	17.50	80.00
	0.2	1.4	9.07	2.67	10.67	1.87	13.12	85.00
	0.2	1.4	14.40	5.33	16.00	1.25	8.75	90.00
	0.2	1.4	30.50	16.10	32.10	0.62	4.36	95.02
1:8	0.2	1.6	0.20	0.20	2.00	10.00	80.00	10.00
	0.2	1.6	0.32	0.12	2.12	9.43	75.47	15.09
	0.2	1.6	0.45	0.13	2.25	8.89	71.11	20.00
	0.2	1.6	0.60	0.15	2.40	8.33	66.67	25.00
	0.2	1.6	0.78	0.18	2.58	7.75	62.02	30.23
	0.2	1.6	0.97	0.19	2.77	7.22	57.76	35.02
	0.2	1.6	1.20	0.23	3.00	6.67	53.33	40.00
	0.2	1.6	1.47	0.27	3.27	6.12	48.93	44.95
	0.2	1.6	1.80	0.33	3.60	5.56	44.44	50.00
	0.2	1.6	2.20	0.40	4.00	5.00	40.00	55.00
	0.2	1.6	3.35	1.15	5.15	3.88	31.07	65.05
	0.2	1.6	4.20	0.85	6.00	3.33	26.67	70.00

Table 6: Continue

Ratio Oil:Smix	Oil (mL)	Surfactant (Smix) (mL)	Water (mL)	Water added (mL)	Total (mL)	Oil (%)	Surfactant (Smix) (%)	Water (%)
	0.2	1.6	5.40	1.20	7.20	2.78	22.22	75.00
	0.2	1.6	7.20	1.80	9.00	2.22	17.78	80.00
	0.2	1.6	10.20	3.00	12.00	1.67	13.33	85.00
	0.2	1.6	16.20	6.00	18.00	1.11	8.89	90.00
	0.2	1.6	34.20	18.00	36.00	0.56	4.44	95.00

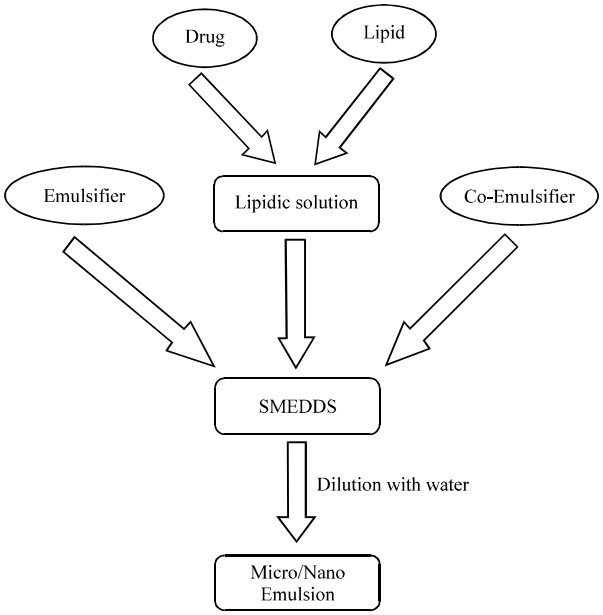

Fig. 2: The general strategy of formulating self micro-emulsifying systems and their subsequent conversion to micro/nano emulsions

phase diagram with the help of software like Tri-plot 4.1.2, Chemix. For down loading the software please refer the given link home.c2i.net/astandne/help-htm/dwnload1.htm,mypage.iu.edu/~tthomps/programs/.

GENERAL METHOD FOR PREPARATION OF SMEDDS

Figure 2 illustrates the usual methodology pathways to prepare SMEDDS formulations and the formation of the micro-/nanoemulsions following their dilution.

- The solubility of the drug in different oil, surfactants and co solvents
- The selection of oil, surfactant and co solvent based on the solubility of the drug
- Preparation of the phase diagram
- The formulations were prepared by initially mixing oil with surfactant at 50-60°C. Drug compounds were then dissolved into the mixture of surfactant and oil by constant stirring and kept at 50°C until a clear solution was obtained. All mixtures stayed clear at room temperature (Thia *et al.*, 2009)

Table 7: Literature Updates on various reports of Type II & III LFCS designed for the oral delivery of lipophilic drugs

Types	Drugs	Lipid	Surfactant: Cosurfactant	Route	Dose	Log p	Improvement	References
SMEDDS	Pueraria lobata	Ethyl oleate	Tween 80: Transcutol P	Oral	20%W/W		BA 2.5 fold higher than yufengningxin tablets	Cui *et al*. (2005)
SMEDDS	Docetaxel	Tetraglycol	Cremophor ELP: Labrasol	Oral	0.003 gm	2.4	Dtx-loaded SMES showed an inhibitory effect on B16F10 melanoma proliferation.	Kim *et al*. (2011)
SMEDDS	Sulpiride	Oleic acid	Tween 80: Propylene glycol	Oral	20 mg	0.6	The permeability coefficient was higher with the SMEDDS and micellar solutions containing sulpiride across all the intestinal segmentscompared to the drug solution.	Chitneni *et al*. (2011)
SMEDDS	β- Artemether	N-LCT	Cremophor EL: Gelucire	Oral	40 mg		Resulted in significant improvement in the anti-malarial activity as compared to that of Larither®	Mandawgade *et al*. (2008)
SMEDDS	Halofantrine	Captex	Cremophor EL: Ethanol	Oral	50 mg	8.9	BA 6-8 fold higher than solid Hf.HCl tablet formulation.	Khoo *et al*. (1998)
SMEDDS	Furosemide	Miglyol	Labrasol: Plurol oleique	Oral	_	1.4	Core of microcapsules resulted in improved permeability and drug release characteristics in comparison to microspheres.	Zvonar *et al*. (2010)
SMEDDS	Bicalutamide	Caproyl PGMC	Polyethylene: Cremophore RH Glycol 300 40	Oral		2.5	BA 2 folds higher than suspension formulation.	Singh *et al*. (2009a)
SMEDDS	Tacrolimus	Capmul MCM C8	Cremophore EL: Carbitol	Oral	5 mg		It was superior to marketed Pangraf capsules formulation with respect to *in vitro* dissolution profile and *in vivo* immunosuppressant activity.	Borhade *et al*. (2008)
SMEDDS	Lovastatin	Sunflower oil	Acrysol K 140: Campul MCM	Oral	40 mg	4.5	It provide excellent drug solubilization, drug stability in water and 0.1 mol/l Hcl and improved in vitro release of lovastatin compare to marked product.	Patel *et al*. (2010a)
SMEDDS	N-442	L-ascrobic acid	Gelucire®: HCO 60®	Oral	1.5 mg		Rapid self-microemulsification in various aqueous media, and formed stable microemulsion droplets with a mean droplet size of about 20 nm.	Itoh *et al*. (2002)
SMEDDS	Siymarin	Ethyl linoleate	Tween 80: Ethyl alcohol	Oral	100 mg		Relative bioavailability of SMEDDS was enhanced in an average of 1.88- and 48.82-fold that of silymarin PEG 400 solution and suspension, respectively.	Wu *et al*. (2006)

Table 7: Continue

Types	Drugs	Lipid	Surfactant: Cosurfactant	Route	Dose	Log p	Improvement	References
SMEDDS	Exemestane	Caproyl 90	Cremophor ELP: Transcutol HP	Oral	25 mg	2.7	It enhance dissolution of exemestane.	Singh *et al.* (2008)
SMEDDS	Xibornal	Labrafil M 1944	Labrasol: Transcutol P	Liquid spary	3%W/V		Stable liquid SMEDDS which allowed the introduction of relatively high concentration (3%w/v) of xibornol in the form of solution.	Cirri *et al.* (2007)
SMEDDS	Nimodipine	Ethyl oleate	Cremophor®RH 40: Labrasol®	Oral	0.4 gm	3.7	HPMC used as controlled release and enhance the bioavilability	Yi *et al.* (2008)
SMEDDS	Simvastatin	Caproyl 90	Cremophor EL: Carbitol	Oral	6.98%w/w	4.7	BA1.5 fold higher than conventional tablets	Kang *et al.* (2004a)
SMEDDS	Fenofibrate	Labrafac CM 10	Tween 80: PEG 400	Oral	8.5%w/w	5.3	SMEDDS formulation higher oral bioavailability as compared with plain fenofi brate.	Patel and Vavia (2007)
SMEDDS	Celecoxib	Acconon MC-8	Tween 20: Capmul PG-8	Oral	10%	3.9	Relative bioavailability of the SMEDDS formulation to the conventional capsule was 132%.	Natesan *et al.* (2004)
SMEDDS	Oridonin	Labrafac Ccand Maisine 35-1	Cremophor EL: Transcutol P	Oral	1.5%w/v		BA2.2 fold higher than suspension	Zhang *et al.* (2008)
SMEDDS	Glyburide	Caproyl 90	Tween 20: Transcutol P	Oral	5 mg	4.7	It improve the dissolution rate of GLY compared to the marketed formulation and pure GLY powder.	Bachhav and Patravale (2009)
SMEDDS	Nifedipine	Sesame oil	Span 80/ Tween 80: n-butanol	Oral	2 mg	2	BA 4 and 5.5 fold higher than pure drug	Kumar *et al.* (2011)
SMEDDS	Sorafenib	Ethyl oleate	Cremophor EL: PEG 400	Oral	_	3.8	BA 25 times higher than suspension	Liu *et al.* (2011)
SMEDDS	Silybin	Ethyl linoleate	Cremophor EL: PEG 400	Oral	_		BA 2.3 fold higher than hard capsule	Li *et al.* (2009)
SMEDDS	Valsartan	Campul MCM	Tween 80: PEG 400	Oral	5%w/w	5.8	BA 1.78-fold times higher than conventional capsule formulation.	Dixit *et al.* (2010)
SMEDDS	Rapamycin	MCT	CremophorRH 40: Transcutol P Glycerol	Oral	4 mg		BA 1.5- 2.5-fold higher than oral solution Rapamune®.	Sun *et al.* (2011)
SMEDDS	Bufalin	Maisine 35-1 Miglycol 812M	Cremophor EL: Transcutol	Oral	0.5%w/w		BA 2.38 fold higher than bufalin suspension	Liu *et al.* (2010)

Table 7: Continue

Types	Drugs	Lipid	Surfactant: Cosurfactant	Route	Dose	Log p	Improvement	References
SMEDDS	Carvediol	Gelucire 44/14	Lauroglycol 90: Oleylamine Tween 20	Oral	12.5 mg		Enhance its absorption and without interaction or incompatibility between the ingredients	Singh *et al*. (2009c)
SMEDDS	Paclitaxel	Vit E	Cremophor EL: Ethanol	Oral	1.5%w/v	3	BA 5 fold & Cmax 10 fold higher oral bioavailability than orallyTaxol® formulation	Oostendorp *et al*. (2011)
SMEDDS	Curcumin	Ethyl oleate	Cremorphor EL: PEG 400 Emulsifier OP	Oral	_		BA 3.86 times higher than the curcumin *in vivo* in mice was enhanced by SMEDDS compared with curcumin suspension.	Cui *et al*. (2009a)
SMEDDS	Buparvaquone	Capryol 90	Cremophor EL: Labrasol	Oral	1.78%		Increases the rate and extent of absorption.	Venkatesh *et al*. (2010)
SMEDDS	Acyclovir	Sunflower oil	Tween 60: Glycerol	Oral	50 mg		BA 3.5 fold higher than the pure drug solution.	Patel and Sawant (2007)
SMEDDS	Vinpocetine	Ethyl oleate	Solutol HS 15: Transcutol® P,	Oral	5 mg		BA 1.72-fold higher than the commercial tablet.	Cui *et al*. (2009b)
SMEDDS	Seocalcitol	Viscoleo	Cremophor RH40: AkolineMCM	Oral	_			Grove *et al*. (2006)
SMEDDS	Ligusticum chuanxiong oil	chuanxiong oil	Tween-80 : propylene glycol	Oral	_		The absorption rate was 2.13 & 1.59 times higher than that of VOC & VOC/â-CD.	Yao and Li (2010)
SMEDDS	Oridonin	Labrafac CC and Maisine 35-1	Cremophor EL: Transcutol P	Oral	_		A rapid release with approximately 26% released at the first 10 min.	Liu *et al*. (2009)
SNEDDS	Clotrimazole	Oleic acid	Tween 20: PEG 200 n-butanol	Oral	_	6.1	It Produced acceptable properties in terms of immediate drug release and could increase the bioavailability of CT.	Kassem *et al*. (2010)
SNEDDS	Cefpodoxime proxetil	Capryol 90	Cremophore-EL: Akoline- MCM	Oral	130 mg		BA 98% higher than cefpodoxime proxetil tablet i.e. 50%.	Date and Nagarsenker (2007)
SNEDDS	Zedoary turmeric oil	Ethyl Oleate	Tween 80, Transcutol P	Oral	30%		BA 1.7-fold & Cmax 2.5-fold than the unformulated ZTO.	Zhao *et al*. (2010)
SEDDS	Dexibuprofen	Labrafil M 1944	Labrasol: Caproyl 90	Oral	20%W/V		BA 2 folds higher than dexibuprofen powder.	Balakrishnan *et al*. (2009)
SEDDS	Ibuprofen	Soyabean oil	Tween 80 : Span 80	Oral	6%	3.6	Enhance the absoption.	Mercuri *et al*. (2011)

Table 7: Continue

Types	Drugs	Lipid	Surfactant: Cosurfactant	Route	Dose	Log p	Improvement	References
SEDDS	Etodolac	Labrafac WL 1349	Labrasol: Lauroglycol 90 Caproyl 90	Oral	20%w/w	2.5	BA 2.3 times & 1.5 times higher than pure drug and suspension form.	Barakat (2010)
SEDDS	Atrovastatin	Captex 355	Campul MCM : Tween 80 PEG 400	Oral	1.9%w/w		It also shows better *in vivo* hypolipidimic activity than pure ATR.	Kadu *et al.* (2011)
SEDDS	Diclofenac	Goat fat	Tween 65	Oral	5 mg	3.9	Diclofenac could be comfortably administered in the form of selfemulsifying tablets using goat fat and Tween 65 admixtures and better release rates than conventional tablets.	Attama (2003)
SEDDS	AmphotericinB	Captex 355	Tween 80: Capmul MCM	Oral	0.8		Enhance the bioavilability.	Wasan *et al.* (2009)
SEDDS	Tocotrienol	Soyabean oil	Tween 80: Labrasol	Oral	148.7 mg		BA 2-3 times higher than NSES-C.	Yap and Yuen (2004)
SEDDS	Griseofulvin	Captex 355	Tween 80 : Labrasol	Oral	1%		Increase in dissolution rate	Agarwal *et al.* (2009)
SEDDS	Halofantrine	Captex	Cremophor EL: Ethanol	Oral	50 mg		BA 6-8 fold higher than solid Hf.HCl tablet formulation.	Khoo *et al.* (1998)
SEDDS	Itraconazole	Tocopherol acetate	Pluronic L64: Transcutol	Oral	_	6.5`	BA 3.7 fold and Cmax 2.8-fold higher than Sporanox® capsule	Hong *et al.* (2006)
SEDDS	Torcetrapib	MTPC	Cremophor RH40	Oral	90 mg		Absorption did increase with Cremophor RH40 content, and at 50% Cremophor RH40 there was no food effect.	Perlman *et al.* (2008)
SEDDS	Phenytoin	Labrafac	Labrasol:Plurol oleique Transcutol P	Oral	3%w/w	2.2	BA 2.3 times higher than Dilantin®	Atef and Belmonte (2008)
S-SEDDS	Paclitaxel	Glycerol dioleate	Cremorphor EL: PEG 400	Oral	6.8 mg/gm	3	BA 5 fold & Cmax 10 fold higher oral bioavailability than orally Taxol® formulation	Gao *et al.* (2003)
S-SEDDS	Candesartan cilexetil	Labrasol	Cremophor EL: Transcutol P	Oral	16 mg	6.1	Enhanced solubility & dissolution.	Nekkanti *et al.* (2010)
SES	Loratadine	Captex 200	Cremophor EL: Campul MCM	Oral	5% wt/wt	3.8	Porous Polystyrene Beads (PPB) used as controlled release.	Patil and Paradkar (2006)
SES	Indomethacin	Ethyl oleate	Tween 85	Oral	_	3.4	BA 57% & 46% greater than Indomethacin suspension & powder, respectively.	Kim and Ku (2000)

Table 7: Continue

Types	Drugs	Lipid	Surfactant: Cosurfactant	Route	Dose	Log p	Improvement	References
SEF	Ketoprofen	Captex 200	Tween 80: Campul MCM	Oral	100 mg	3.2	Silicon dioxide was used as a gelling agent, which increased the liquid crystal phase viscosity, which led to the formation of coarser droplets and slower drug diffusion	Patil *et al.* (2005)
SEF	Vitamin E	Palm oil	Tween 80, span 80	Oral		10	BA 3 fold higher than commercial product, Natopherol®	Julianto *et al.* (2000)

SMEDDS: Self micro emulsifying drug delivery system, S-SMEDDS: Solid self micro emulsifying drug delivery system, SEDDS: Self emulsifying drug delivery system, SNEDDS: Self nano emulsifying drug delivery system, SES: Self emulsifying system, SEF: Self emulsifying formulation, S-SEDDS: Solid self emulsifying drug delivery system, N-LCT: Natural lipophile, HCO: Hydrogenated castor oil, PEG: Polyethylene glycol, NSAID: Non steroidal anti inflammatory drug, MTPC: MCT/triacetin/polysorbate 80/capmulMCM, MCT: Medium chain triglyceride, PPB: Porous polystyrene beads, GLY: Glyburide, BA: Bioavilability, Dtx: Docetaxel

A Literature Updates on various reports of Type II and III LFCS designed for the oral delivery of lipophilic drugs for bioavailability enhancement as shown in Table 7.

FACTOR AFFECTING SMEDDS

Drug dose: Usually drugs having high dose are not preferred for developing SMEDDS. However, such drug if extremely soluble in any components of SMEDDS particularly in lipid phase. The drug which are not well soluble both in water and oil, and also posses low Log P value (around 2) are not suitable candidates for SMEDDS.

Drug solubility in oil phase: Solubility of the drug in oil phase greatly influenced the ability of SMEDDS in maintaining the drug in solution state. When the drug is solubilized by the use of surfactant and co surfactant the dilution of SMEDDS can lead to lowering the solvent capacity of surfactant or co surfactant, their by resulting precipitation.

Equilibrium solubility: For assessment of possibilities of precipitation in the gut equilibrium solubility measurement can be employed. Poutons study reveals that such formulation can take up to 5 days to reach equilibrium and that the drug can remain in a super saturated state up to 24 h after the initial emulsification event (Patel *et al*., 2010b).

Polarity of lipid phase: The polarity of lipid phase is one of the factors influencing the release of drug from the microemulsion. HLB, chain length and degree of unsaturation of fatty acid, molecular weight of the lipophilic portion and concentration of the emulsifier are factors for the polarity of droplets. The polarity indicates the affinity of the drug towards solvent, oil or water and the type of forces involved. The high polarity will promote rapid rate of release of the drug into the aqueous phase. Sang-Cheol *et al*. observed that the rate of release of Idebenone from SMEDDS is dependent upon the polarity of oil phase used. The highest release was obtained with the formulation that had oily phase with highest polarity (Kim *et al*., 2000).

Charge of emulsion droplets: Multiple physiological studies have shown the apical potentials of absorptive cells, ands of other cells in the body, are negatively charged compared to the mucosal solution in the lumen. Gershanik and Benita have shown that positively charged emulsion droplets formed by adding oleylamine (OA) to appropriate SEDDS undergo electrostatic interaction with the Caco-2 monolayer and the mucosal surface of the everted rat intestine (Gershanik *et al*., 2000). This formulation enhanced the oral bioavailability of progesterone in young rats. Benzoic acid had a dual function on the SEDDS; it could improve the self-emulsifying performance of Self-Emulsifying Oily Formulations (SEOFs) and Self-Microemulsifying Oily Formulations (SMEOFs) in 0.1 N HCl due to formation of a positively charged emulsion (Gershanik and Benita, 1996).

BIOPHARMACEUTICAL ASPECTS

Comprehensive literature survey reveals that certain lipids alone or with food can increase the bioavailability of some drugs. With incompleteness few explanations in support have been placed:

Alterations (reduction) in gastric transit: Increase in gastric resistance time shows the delivery of the drug of it site of absorption. There by the time for dissolution visa vis absorption is increased.

Increases 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 phospholipids (PL) and Cholesterol (CH), leading to the formation of BS/PL/CH intestinal mixed micelles and an increase in the solubilisation capacity of the GI tract. 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 solubilisation capacity (Porter and Charman, 2001a).

Stimulation of intestinal lymphatic transport: For highly lipophilic drugs, lipids may enhance the extent of lymphatic transport and increase bioavailability directly or indirectly via a reduction in first-pass metabolism (Porter and Charman, 2001b).

Changes in the biochemical barrier function of the GI tract: It is evident some lipids and surfactants have ability to minimize the activity of intestinal efflux transporters, as sign of p-glycoprotein efflux pump. Similarly, the extent of enterocyte-based metabolism diminished (Benet and Cummins, 2001; Dintaman and Silverman, 1999; Nerurkar *et al*., 1996).

Changes in the physical barrier function of the GI tract: Although the passive intestinal permeability does not affect the bioavailability of majority of lipophilic, poorly soluble drugs, their permeability may be increased by certain mixtures of lipids, lipid digestion products and surfactants (Aungst, 2000; Muranishi, 1990).

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. The effect of lipids on the bioavailability of orally administered drugs is highly complex due to numerous mechanisms by which the lipids can alter the biopharmaceutical characteristics of the drug. They include a decreased rate of gastric emptying, an increased dissolution rate of the drug and solubility in the intestinal fluid and the formation of lipoproteins promoting the lymphatic transport of highly lipophilic drugs (Craig, 1993; Hauss *et al*., 1998, 2007).

MECHANISM OF BIOAVAILABILITY ENHANCEMENT FROM SMEDDS

Most SMEDDs are based on triglycerides; it is helpful to consider the mechanisms by which SMEDDs are absorbed from the GI tract (Fig. 3a, b).

The absorption of fats from the GIT: Constantinides (1995) demonstrated that triglyceride molecules are fatty acid esters of glycerol. The ester groups of the triglycerides are prone to hydrolysis and this represents the major initial route of metabolism within the GI tact. On ingestion of the triglycerides, the lipids enter the stomach. Some hydrolysis may occur in the stomach due to the presence of gastric lipase. On entering the upper section of the small intestine, two processes occur. The fat droplets are further emulsified by the bile salts, monoglycerides, cholesterol, lecithin and lysolecithin to produce droplets with a diameter of approximately 0.5-1 μm. The triglyceride droplets are then metabolized by pancreatic lipase, to free fatty acids and 2-monoglycerides, the last two contributing to the digestion process as they themselves are emulsifying agents. The fatty acids are distributed between the aqueous solution, the emulsion droplet and the micelles, while the

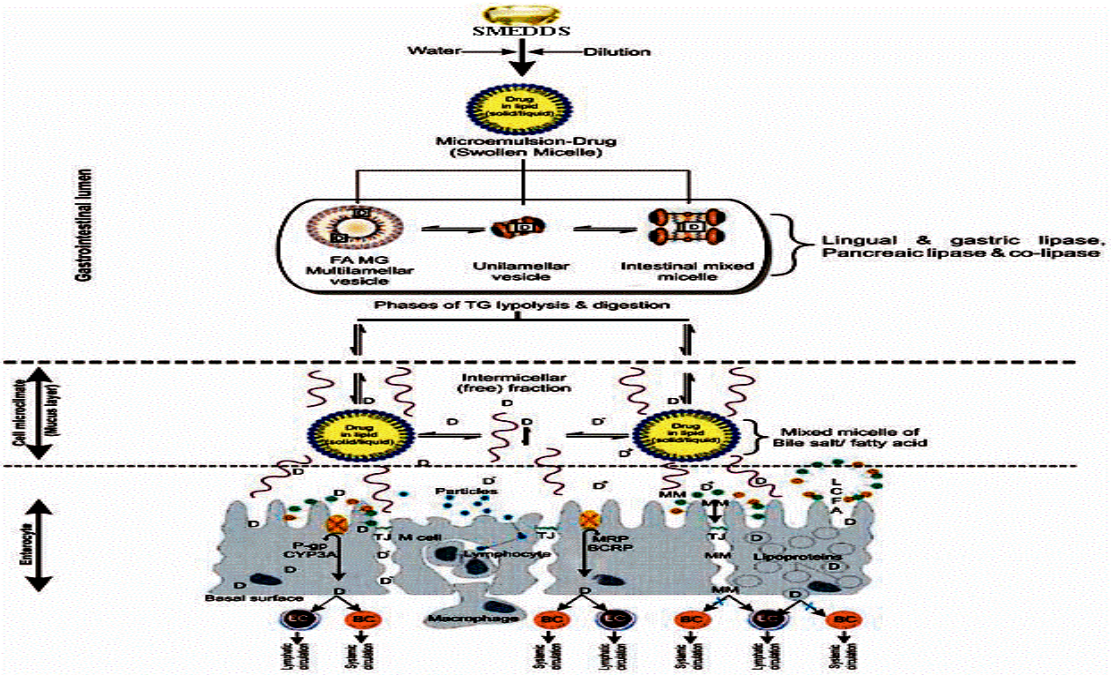

Fig. 3a: Diagrammatic representation mechanistic pathways for transportation of drugs across the GI lumen using SMEDDS

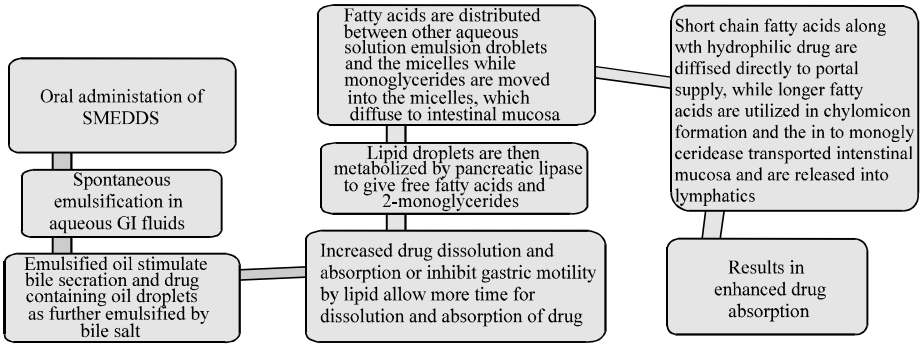

Fig. 3b: Mechanisms proposed for bioavailability enhancement of drugs

monoglycerides are incorporated into the micelles and are believed to swell the structure, allowing incorporation of other water insoluble components. The micelles then diffuse through the gut contents to the intestinal mucosa. Once in the intestinal mucosa, the monoglycerides are resynthesized into triglycerides and covered with a layer of lipoprotein, cholesterol and phospholipids. The resulting particles are released into lymphatic system. Short chain fatty acids may diffuse directly into the portal supply.

Bioavailability of drugs from oily vehicles: According to studies of (Benet and Cummins, 2001) compared the absorption of griseofulvin from commercial tablets, a corn oil emulsion

(equivalent to 12 g oil) and an aqueous suspension in humans. The authors found that emulsion gave a much more rapid excretion of griseofulvin metabolite, desmethylgriseofulvin. The authors suggested that factors such as the inhibition of gastric motility caused by the presence of the lipid might have allowed more time for dissolution and absorption of drug. Alternatively, the presence of the emulsified oil may have stimulated bile secretion, which may have improved bioavailability. Later hypothesis have included increased mucosal permeability via incorporation of lipids from mixed micelles and enhanced mesenteric lymph flow.

Drug absorption from SMEDDs: The authors suggested that as the oil phase was a medium chain triglyceride, lymphatic uptake was unlikely to be enhanced; hence, the drug absorption may be a function of the increased surface area for dissolution provided by the emulsion. The authors also suggested that the presence of the surfactant in the formulation might play a role in increasing the absorption of the drug (Charman *et al*., 1992).

EVALUATION OF SMEDDS

The primary means of self micro emulsification assessment is visual evaluation. The efficiency of self micro emulsification could be estimated by determining the rate of micro emulsification, droplet size distribution and turbidity measurement.

Droplet size and particle size measurement: The particle size of the micro emulsion is determined by photon correlation spectroscopy or SEM (Scanning Electron Microscopy) which can measure sizes between 10 and 5000 nm. The nanometric size range of the particle is retained even after 100 or 1000 times diluted with distill water, which proves the system's compatible with excess water (Rad, 2010; Ramachandran *et al*., 2011).

Refractive index and percent transmission: Refractive index and percent transmittance proves the clearness of formulation. The refractive index of the SMEDDS is measured by refractometer and compared with that of water. The percent transmittance of the system is measured at particular wavelength using UV-Vis spectrophotometer keeping distilled water as blank. If refractive index of system should be similar to that of water. Formulation showing transmittance >99 percent is transparent in nature (Patil *et al*., 2004; Patil *et al*., 2007).

Determination of percentage drug content: One capsule of each formulation was taken in a 100 mL volumetric flask, and added 100 mL of extracting solvent. Then mixture was shaken for 1 h in mechanical shaker and kept a side for 24 h. After 24 h, filtered the solution through Whatman filter paper (0.45 μm) to collect the filtrate. The filtrate was then analyzed in UV-spectrophotometer at. The concentration of drug in solution was calculated from absorbance and standard graph (Patil *et al*., 2007).

Phase separation study: One milliliter SMEDDS was added to glass test tube containing 5 mL of 0.1 N HCl, buffer pH 6.8 and distilled water. After inverting the test tube for 3-4 times, each mixture was stored for a period of 2 h and phase separation was observed visually (Kim and Ku, 2000).

Dispersibility test: The efficiency of self-emulsification of oral micro-/nano-emulsions is measured by using a standard USP dissolution apparatus. To 500 mL of water 1 mL of the formulation is to

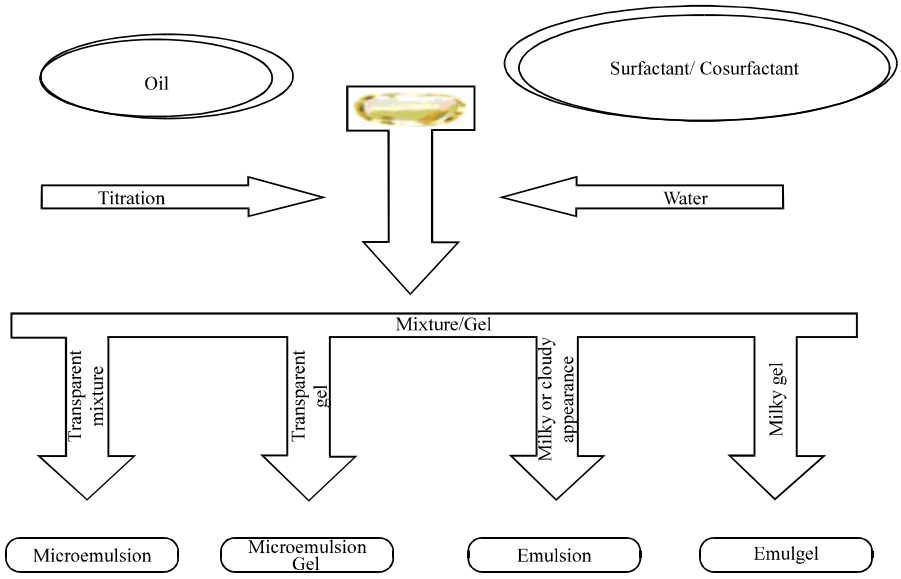

Fig. 4: Dispersibility test of microemulsion, microgel, emulsion and emulgel in decreasing order of emulsion stability

be added at 37±0.5°C. A standard stainless steel dissolution paddle rotating at 50 rpm provides gentle agitation. The *in vitro* performance of the formulations is visually assessed from such a dispersion using a suitable grading system. Grading systems can be based upon the formation of a microemulsion (o/w or w/o), microemulsion gel, emulsion, or emulgel. The schematic flow chart in Fig. 4 illustrates the mode to characterize the type of formulation on the basis of this grading system and the type of dispersion formed on water dilution (Singh *et al*., 2009b).

Zeta potential measurement: Zeta potential for microemulsion can be determined using a suitable Zetasizer, in triplicate samples (Abbasalipourkabir *et al*., 2011).

Stability: SMEDDS was diluted with distilled water and to check the temperature stability of samples, they were kept at two different temperature range (2-8°C (refrigerator), room temperature) and observed for any evidences of phase separation, flocculation or drug precipitation.

In order to estimate metastable systems, the optimized SMEDDS formulation was diluted with distilled water. Then microemulsion was centrifuged at 1000 r min^{-1} for 15 min at 37°C and observed for any alteration in homogeneity of microemulsions (Ghosh *et al*., 2004).

***In vitro* release study:** *In vitro* drug release study of SMEDDs formulation was performed by dialysis method, dissolution apparatus 2 and diffusion cell. Study of drug release was done by modified diffusion cell in 200 mL buffer solution 6.8 pH. One gram SMEDDs formulation was placed in boiling tube, both side of boiling tube was opened and one side of tube was tied with cellophane membrane and dipped in buffer solution kept in a beaker below. Upper side of the cylinder was clamped to hold. The beaker was continuously stirred by magnetic stirrer and sample was withdrawn after different time intervals it in straight position and analyzed by UV-Spectrophotometer Percent drug dissolved at different time intervals was calculated using the beer Lambert's equation (Kang *et al*., 2004b).

Bioavailability study: Based on the self emulsification properties, particle size data and stability of micro emulsion the formulation is selected for bioavailability studies. The *in vivo* study is performed to quantify the drug after administration of the formulation. Some of the drugs used in different *in vivo* models shows in Table 8. The plasma profiles of the drug in experimental animals following oral administration of the conventional tablet and SMEDDS form are compared. Pharmacokinetic parameters of the maximum plasma concentration (Cmax) and the corresponding time (Tmax) for the drug following oral administration are calculated. The area under the concentration-time curve (AUC0→24 h) is estimated according to the linear trapezoidal rule. The relative Bioavailability (BA) of SMEDDS form to the conventional table is calculated using the following Equation Relative BA (%) = (AUC test/AUC reference) X (Dose reference/Dose test).

RECENT ADVANCEMENTS IN SMEDDS

Some of the patents publication on diverse type of lipid formulation shows in Table 9.

Self-emulsifying capsules: After administration of capsules containing conventional liquid SE formulations, micro emulsion droplets form and subsequently disperse in the GI tract to reach sites of absorption. However, if irreversible phase separation of the micro emulsion occurs, an improvement of drug absorption cannot be expected. For handling this problem, sodium dodecyl sulfate was added into the SE formulation (Itoh *et al*., 2002). With the similar purpose, the super saturable SEDDS was designed, using a small quantity of hydroxyl propyl methyl cellulose (or other polymers) in the formulation to prevent precipitation of the drug by generating and maintaining a supersaturated state *in vivo*. This system contains a reduced amount of a surfactant, thereby minimizing GI side effect (Gao and Morozowich, 2006; Gao *et al*., 2003).

Table 8: Drug used in different *in vivo* models

Drug	Category	Model	AUC	References
Dexibuprofen	NSAID	Rats	120.75±29.38 (µg h/mL)	Balakrishnan *et al*. (2009)
Pueraria lobata	Antihypertensive	Beagle dogs	154.93±44.05 (µg mL/min)	Cui *et al*. (2005)
Bicalutamide	Anti-androgen	Rats	AUC_{0-8} 464±69.22 (µg h/mL)	(Singh *et al*. (2009a)
Silymarin	Antihepatotoxic	Rabbit	AUC_{0-8} 3.17± 1.63 (µg h/mL)	Wu *et al*. (2006)
Simvastatin	Hypolipidemic	Beagle dogs	$AUC_{0-24\,h}$ 123.75±25.40 (ng h/mL)	Kang *et al*, (2004a)
Celecoxib	NSAID	Human	AUC_{0-8} 13371.82±931.5 (ng h/mL)	Natesan *et al*. (2004)
Oridonin	Antitumor	Rats	AUC_{0-8} 639.21± 53.62 (ng mL/min)	Zhang *et al*. (2008)
Nifedipine	C_a blocking agent	Rats	$AUC_{0-24\,h}$ 214.11±3.38 and 1146.8±16.25 (ng h/mL)	Kumar *et al*. (2011)
Ketoprofen	NSAID	Human	$AUC_{0-8\,h}$ 37.9718 (µg/mL/h)	Patil *et al*. (2005)
Sorafenib	Anticancer	Rats	$AUC_{0-72\,h}$ 28118.7±4619.1 (ng h/mL)	Liu *et al*. (2011)
Indomethacin	NSAID	Rats	Oral $AUC_{0-12\,h}$ 375±41.1 (µg h/mL) Rectal $AUC_{0-12\,h}$ 362±86.6 (µg h/mL)	Kim and Ku (2000)
Silybin	Antihepatotoxic	Rats	AUC_{0-8} 305.30 (µg h/mL)	Li *et al*. (2009)
Etodolac	NSAID	Rabbits	AUC_{0-8} 58.0±1.5 (µg min/mL)	Barakat (2010)
Valsartan	Angiotensin II receptor antagonist	Rabbits	AUC_{0-8} 1,124.57±79.66 (ng h/mL)	Dixit *et al*. (2010)
Bufalin	Anticancer	Rats	AUC_{0-8} 6468.30±13125.71 (ng min^{-1} mL^{-1})	Liu *et al*. (2010)
Paclitaxel	Anticancer	Mice	1841±166 (ng mL/h)	Oostendorp *et al*. (2011)
Acyclovir	Antiviral	Rats	14.4969 (µg h/mL)	Patel and Sawant (2007)
Vinpocetine	Anti-inflammatory	Beagle dogs	564.91±3.29 (ng /mL h)	Cui *et al*. (2009b)

NSAID- Non Steroidal Anti Inflammatory Drug

Table 9: Some Patented formulation

U.S. Patent No.	Inventors	Types	Active ingredient	Information
20110160168	Dhingra (2011)	SMEDDS	Testosterone	A formulation for drug delivery, as long as improved modulation of solubility, stability, absorption, metabolism, and/or pharmacokinetic profile of a lipophilic therapeutic agent by formulation with sterols and/or sterol esters, resulting in higher bioavailability of a therapeutic agent administered to a subject in need of such therapeutic agent
20100331356	Legen and Igor (2010)	SMEDDS	Imwitor 308	Self-microemulsifying drug delivery systems and microemulsions used to increase the solubility of pharmaceutical excipients comprising surfactant, co surfactant and an oil
7588786	Khan *et al.* (2009)	SNEDDS	Coenzyme Q_{10} (CoQ_{10})	A eutectic-based SNEDDS is formulated from essential oils, and a pharmacologically effective drug. The drug is poorly water soluble, such as ubiquinone (CoQ_{10}). The SNEDDS can be further incorporated into a powder to produce a solid dosage form. The solid dosage form contains the SNEDDS, a copolymer of vinylpyrrolidone and vinyl acetate, maltodextrin, and microcrystalline cellulose
20080319056	Liu *et al.* (2008)	SEDDS	Butylphthalide	It composed of essential ingredients 1% to 65% of butylphthalide and 10% to 65% of a emulsifying agent, together with various ingredients as required for dosage forms. It increases the contact area between butylphthalide and the mucous membrane of the gastrointestinal tract, and hence improves the absorptivity of the drug
20070190080	Friedman (2007)	SMEDDS		The present invention provides a composition of poor water soluble drug, dispersed low crystalline form in an emulsion type composition of oily-solvent and water soluble solvent, whereas emulsifying stabilizer comprises low fraction of the composition, and emulsions of mean droplets size below one micron is obtained upon dilution with physiological fluids, particularly to facilitating biological availability performance or improving clinical
20060275358	Lin and Jing (2006)	SMEDDS	Co-enzyme Q_{10}	The present invention composed of a hydrophilic surfactant and a lipophilic co-surfactant (forming a surfactant pair). The HLB (Hydrophile-Lipophile Balance) values of surfactant should be more than 12 and less than 8 respectively
20050032878	Deboeck (2005)	SEDDS	Fenofibrate	Oral pharmaceutical composition containing, effective amounts of a HMG-CoA reductase inhibitor derivative and of a PPARα, especially fenofibrate. The use of some inactive ingredients which allow to improve the dissolution and/or bioavailability of the drugs

Table 9: Continue

U.S. Patent No.	Inventors	Types	Active ingredient	Information
20040248901	Lee and Jin (2004)	SMEDDS	Itraconazole	The present invention relates to itraconazole which is a sparingly-soluble drug, oil, and surfactant. Where itraconazole which is a sparingly-soluble drug is dissolved to form a mocoidal phase, and the mocoidal phase is dissolved in water to form microemulsion & greatly improved bioavailability
6652865	Benameur *et al.* (2003)	SMEDDS	Simvastatin	The carrier includes: effective amount of the active principle; a lipophilic phase, a surfactant phase, a co-surfactant phase. A method of decreasing the effect of intestinal metabolism on a drug using the composition is also disclosed
6436430	Mulye and Nirmal (2002)	SEDDS	Cyclosporin	The present invention includes an amount of a lipophilic drug, in association with a pharmaceutical carrier, i.e. effective amount of a propylene glycol monoester of C.sub.6 -C.sub.18 fatty acid having at least 60% by weight monoester based on the total weight of the propylene glycol ester and a non-ionic surfactant
6312704	Farah and Denis (2001)	SMEDDS		It comprising a lipophilic phase consists of a mixture of C_8 to C_{18} polyglycolized glycerides having hydrophilic-lipophilic balance (HLB) of less than 16, this lipophilic phase representing from 32 to 75% of the total weight of the composition. The cosurfactant (CoSA) is chosen from the group comprising lauric esters of propylene glycol, oleic esters of polyglycerol and ethyl diglycol
6057289	Mulye and Nirmal (2000)	SEDDS	Cyclosporin	The present invention is comprising of lipophilic drug i.e. cyclosporin in association with effective amount of a fatty acid having 6-22 carbon atoms and a non-ionic surfactant

Self-emulsifying suppositories: Kim and Ku (2000) investigated the Solid-SEDDS could increase not only GI adsorption but also rectal/vaginal adsorption. Glycyrrhizin which by the oral route, barely achieves therapeutic plasma concentrations, can obtain satisfactory therapeutic levels for 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: Nanoparticle techniques have been useful in the production of SE nanoparticles. Solvent injection is one of these techniques. In this method, the lipid, surfactant and drugs were melted together and injected drop wise into a stirred non-solvent. The resulting SE 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 nanoparticle 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 foundation for chitosan aggregation, meanwhile causing near 100% loading and entrapment efficiencies of PTX (Trickler, 2008).

Self-emulsifying sustained/controlled-release pellets: Formulation of SE controlled-release pellets by incorporating drugs into SES that enhanced their rate of release and then by coating pellets with a water-insoluble polymer that reduced the rate of drug release are also very useful. Pellets were prepared by extrusion/spheronization and contained two water-insoluble model drugs (methyl and propyl parabens); SES contained mono-diglycerides and Polysorbate 80 (Abdalla and Mader, 2007). Figure 5 shows the functioning of the polymer matrix dispersed in a SMEDDS formulation, the composition obtained being in the form of gel capsule. Serratoni *et al.* (2007) have been developing the combinations of coating and SES could control in vitro drug release by providing a range of release rates and the presence of the SEDDS did not influence the ability of the polymer film to control drug dissolution.

FUTURE PERSPECTIVE

SMEDDS can be an effective solution to the problem of formulating poorly soluble drugs with low solubility in the fluids of the GIT. Although for some time the potential utility of SMEDDS has been known, it is being widely developed and in use only in recent years. The use of a combination of *in vitro* dispersion and digestion methodologies has enabled a much improved understanding of the role of intestinal lipid processing on the solubilization behavior of lipid based formulations. This *in-situ* emulsion-forming system with high stability can be taken as an emulsion premix as a formulation. As on date formulation of SMEDDS with drugs having low solubility both in water and in oil is difficult to be developed. With future developments in this novel technology, SMEDDS will remove deficiencies associated with delivery of poorly soluble drugs.

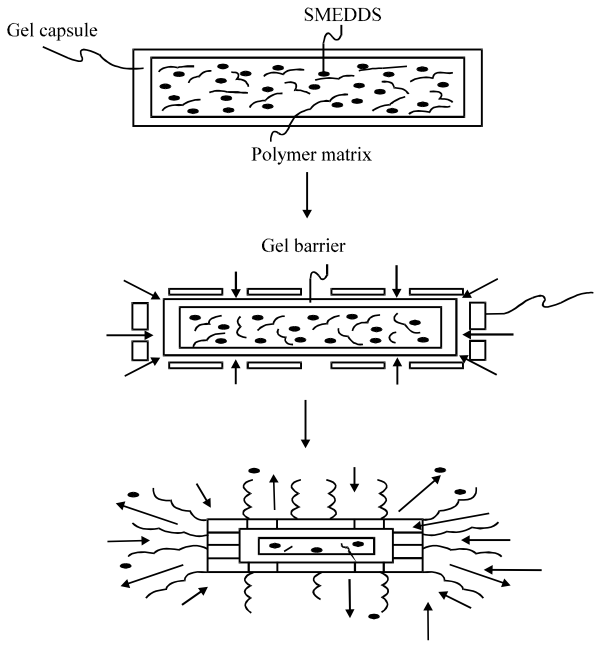

Fig. 5: Functioning of the polymer matrix dispersed in a SMEDDS formulation

CONCLUSION

Some of the concealed features of Self micro emulsifying drug delivery systems (SMEDDS) have been revealed by the literature review. SMEDDS is a promising drug delivery system for the enhancement and improvement of bioavailability for a hydrophobic drug. This review article will definitely drag the attention of the young researchers to understand the role of individual lipids and surfactants used for the formulation of SMEDDS as lipid based formulations are still not very widespread as commercial formulations. Also this study explores the possibilities of loading a wide variety of hydrophobic drugs and plant actives as their scale up is convenient as well as economical too.

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