ISSN 0975 - 6299 Vol 2 / Issue 4 / Oct - Dec 2011

International Journal of Pharma and Bio Sciences

REVIEW ARTICLE

NOVEL DRUG DELIVERY SYSTEM

SELF-EMULSIFYING DRUG DELIVERY SYSTEM: FORMULATION AND EVALUATION

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ABSTRACT

The major problem in oral drug formulations is low and erratic bioavailability, which mainly results from poor aqueous solubility. This may lead to high inter- and intra subject variability, lack of dose proportionality and therapeutic failure. Due to this fact, many drug candidates fail to reach the market, although they exhibit potential pharmacodynamic activity or otherwise administered in higher doses, leading to the rise of toxicity problems. Self-emulsifying drug delivery systems (SEDDS) are usually used to improve the bioavailability of hydrophobic drugs. These are defined as isotropic mixtures of natural or synthetic oils, solid or liquid surfactants or, alternatively, one or more hydrophilic solvents and co-solvents/ surfactants. The system being thermodynamically stable requires low energy emulsification which will be provided by GI fluid agitation. The basic evaluation parameters studied for these systems are droplet size & morphology determination, emulsification time, zeta potential measurement, stability studies, *in vivo* and *in vitro* absorption studies.

ISSN 0975 - 6299 Vol 2 / Issue 4 / Oct - Dec 2011

KEYWORDS

Self emulsifying, Microemulsion, Zeta potential, Photon Correlation Spectroscopy, Phase diagram

INTRODUCTION

A large number of drugs being discovered today are highly lipophilic and poorly water soluble. They show poor and erratic bioavailability[1]. Lipid-based drug delivery systems have been demonstrated to be useful in enhancing the bioavailability of highly lipophilic compounds because they can keep the drug in the dissolved state until it is absorbed, thus overcoming the barrier of slow dissolution rates[2]. In practice, lipid formulations range from pure oils to formulations containing some proportions of surfactants, cosurfactants or cosolvents[3]. Recently a number of studies related to lipid formulations focused attention on microemulsion formulations with particular emphasis on self-microemulsifying or self-emulsifying drug delivery systems to improve oral bioavailability of poorly water-soluble drugs[4]. SEDDS or self-emulsifying oil formulations (SEOF) are defined as isotropic mixtures of natural or synthetic oils, solid or liquid surfactants or, alternatively, one or more hydrophilic solvents and co-solvents/ surfactants. Upon mild agitation followed by dilution in aqueous media, such as GI fluids, these systems can form fine oil-in-water (o/w) emulsions or microemulsions (SMEDDS)[5]. Self-emulsifying drug delivery systems (SEDDS) are a vital tool in solving low bioavailability issues of poorly soluble drugs. Hydrophobic drugs can be dissolved in theses systems, enabling them to be administered as a unit dosage form for per-oral administration[6].

As SEDDS self-emulsifies in the stomach and presents the drug in small droplets of oil, it improves drug dissolution through providing a large interfacial area for partitioning of the drug between the oil and GIT fluid. Self-microemulsifying drug delivery systems (SMEDDS) easily form microemulsions with mild agitation, and have been identified as a promising technology for drug delivery (independent of the delivery mode) because they have a large solubilization capacity, small particle size, and excellent stability, and they can enhance permeation across the intestinal membrane, provide reproducible and increased bioavailability, and eliminate or reduce food effects[2].

Oral absorption of several drugs has been reported to be enhanced by SEDDS by one of the several mechanisms. Main mechanisms include increasing membrane fluidity to facilitate transcellular absorption, opening tight junction to allow paracellular transport, inhibiting P-gp and/or Cytochrome P450 (CYP450) enzymes to increase intracellular concentration and residence time by surfactants, and stimulating lipoprotein/chylomicron production by lipid. Also specific components of SEDDS promote the intestinal lymphatic transport of drugs which would be very useful in reducing the first pass of the drugs[7]. An example of commercially available SEDDS is cyclosporine. Cyclosporine SEDDS formulation, Neoral, resulted in a twofold increase in its bioavailability in humans

compared to other cyclosporine formulations[8]. The commercial success of the SEDDS formulation Sandimmune Neoral (cyclosporine), as well as the commercialization of novel self-emulsifying formulations such as Norvir (ritonavir) and Fortovase (saquinavir), has raised the interest in such promising emulsion based drug delivery system[9]. The SEDDS formulation has been well accepted for drugs with poor aqueous solubility and high permeability, classified as Class II drugs by BCS system[10]. The rate and extent of absorption of class II compounds is highly dependent on the performance of the formulated product. (Figure 1) These drugs can be successfully formulated for oral administration, but care needs to be taken with formulation design to ensure consistent bioavailability. Essentially the options available involve either reduction of particle size (of crystalline drug) or formulation of the drug in solution, as an amorphous system or lipid formulation[11].

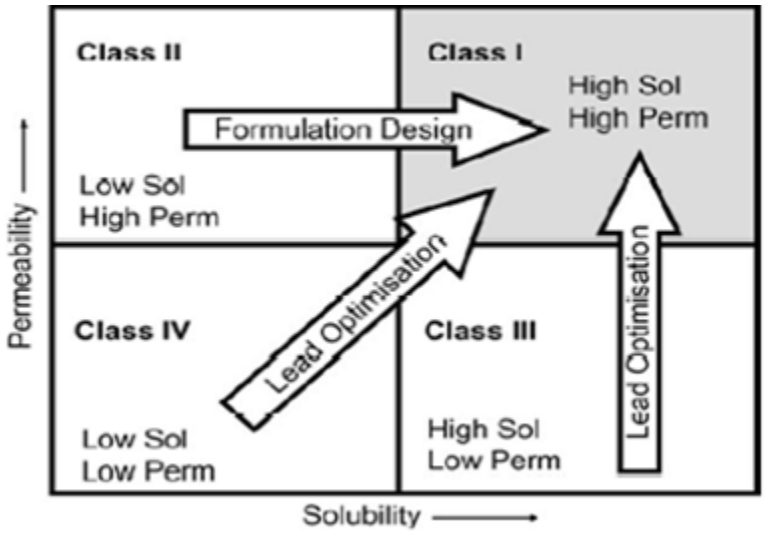

Figure 1
A typical representation of biopharmaceutical classification system

The SEDDS properties strongly depend on the selected lipids and emulsifiers and their mixing ratios. In addition, the characteristics and load of the incorporated drug are critical parameters. The use of lipid mixture with different polarities and emulsifiers give the possibility to optimize the SEDDS for a particular drug[12]. The digestion of lipid based formulations, in the presence of endogenous materials (bile salts, phospholipids and cholesterol), induces a change in lipid composition and result in the formation of different colloidal phases (micelles, vesicles, and liquid crystalline phases) in the intestinal lumen. The changes in lipid composition, induced by digestion, play a major role in the solubilization capacity and consequently the absorption of co-administered drugs. Recent research studies showed that not only the chemical composition but also the digestion dynamics of the SEDDS constituents plays an important role in the drug's absorption and thus its bioavailability.[13] In recent years, lipid

microemulsions incorporating medium-chain glycerides have attracted much interest as oral dosage forms to improve drug dissolution and/or intestinal absorption because (1) they are stable food grade products and generally recognized as safe by the US Food and Drug Administration; (2) microemulsions incorporating these excipients can be formulated at ambient temperature over a wide range of compositions; and (3) early studies have shown that medium-chain glycerides and fatty acids improve intestinal absorption of many drug molecules. In the small intestine, they are hydrolyzed by intestinal lipases to generate monoglycerides and free fatty acids that can be directly absorbed through the portal route and detected in the plasma[13].

The distinction between SEDDS and SMEDDS formulations is also commonly made based on the particle size and optical clarity of the resultant dispersion. Thus, SEDDS formulations typically provide opaque dispersions with particle sizes > 100 nm whereas SMEDDS formulations (which contain higher concentrations of hydrophilic surfactants and co-solvents) disperse to give smaller droplets with particle sizes < 100 nm, and provide optically clear or slightly opalescent dispersions, more consistent with the presence of a microemulsion[14]. Conventionally, SEDDS is contained in hard or soft gelatin capsules for ease of administration. However, certain problems such as leaking, leaching of components from the capsule shell, and interaction of SEDDS with capsule shell components are often observed for such liquid-filled capsules. Solidification of liquid systems has been a challenge that has attracted wide attention due to handling difficulties and machinability and stability problems that are often encountered with liquids. Various attempts have been reported in literature to transform liquids into solids. Many reports on producing liquisolids based on the concept of blending liquid systems with selected powder excipients to produce free-flowing, readily compressible powders have been documented in the literature[15].

EXCIPIENT SELECTION:

Oils can solubilize the lipophilic drug in a specific amount. It is the most important excipient because it can facilitate self-emulsification and increase the fraction of lipophilic drug transported via the intestinal lymphatic system, thereby increasing absorption from the GI tract[16]. The self-emulsification process is specific to the nature of the oil/ surfactant pair, surfactant concentration, oil/surfactant ratio and temperature at which self-emulsification occurs[17].

The self-emulsifying formulations consisted of oil, surfactants, cosurfactant, and drug should be a clear and monophasic liquid at ambient temperature when introduced to aqueous phase and should have good solvent properties to allow presentation of the drug in solution[18]. The oily/lipid component is generally a fatty acid ester or a medium/long chain saturated, partially unsaturated or unsaturated hydrocarbon, in liquid, semisolid or solid form at room temperature. Examples include mineral oil, vegetable oil, silicon oil, lanolin, refined animal oil, fatty acids, fatty alcohols, and mono-/di-/tri-glycerides[9]. Unmodified edible oils provide the most `natural' basis for lipid vehicles, but their poor ability to dissolve large amounts of hydrophobic drugs and their relative difficulty in efficient self-

emulsification markedly reduce their use in SEDDS. In contrast, modified or hydrolyzed vegetable oils have contributed widely to the success of the above systems[19].

Lipophilic surfactants with hydrophilic lipophilic balance (HLB) < 10 are capable of promoting some emulsification of the oil, but the resulting emulsions are normally too crude (in terms of size) to be useful. Hydrophilic surfactants with HLB >10 are much superior at this providing fine, uniform emulsion droplets which are more likely to empty rapidly from the stomach[20]. Furthermore, the large surface area facilitates faster and more complete absorption. However, in most cases it is the right blend of low and high HLB surfactants that leads to the formation of a stable microemulsion upon exposure to water[21]. The usual surfactant strength ranges between 30–60% w/w of the formulation in order to form a stable SEDDS[22]. Cosolvents like diethyl glycol monoethyl ether (transcutol), propylene glycol, polyethylene glycol, polyoxyethylene, propylene carbonate, tetrahydrofurfuryl alcohol polyethylene glycol ether (Glycofurol), etc., may help to dissolve large amounts of hydrophilic surfactants or the hydrophobic drug in the lipid base. These solvents sometimes play the role of the cosurfactant in the microemulsion systems[23].

Table 1
Example of surfactants, co-surfactant, and co-solvent used in commercial formulations

Sr. No.	Excipient Name	Commercial Products
1. Surfactant/Cosurfactant	Span 80	Gengraf hard gelatin capsule
	Tween 20	Targretin soft gelatin capsule
	Cremophor RH40	Nerol soft gelatin capsule, Ritonavir oral solution
	Labrafil M 2125 Cs	Sandimmune soft gelatin capsules
2. Co solvents	Polypylene glycol	Nerol soft gelatin Capsule, Lamprene soft gelatin capsule
	Glycerin	Sandimmune soft gelatin Capsules, Nerol soft gelatin Capsule
	Ethanol	Gengraf Hard gelatin Capsule, Sandimmune soft gelatin Capsule
	Polyethylene glycol	Targretin soft gelatin capsule, Agenerase soft capsule, Agenerase oral solution
3. Lipid Ingredients	Corn oil mono,di, tri-glycerides	Nerol soft gelatin Capsule
	Fractionated triglyceride of palm seed oil	Rocatrol oral solution
	Fractionated triglyceride of coconut oil	Rocaltrol soft gelatin capsule, Hectrol soft gelatin capsule
	Corn oil	Sandimmune soft gelatin capsule
	Mixture of mono-and di-glycerides of caprylic/capric acid	Avodat soft gelatin capsule
	Soyabean oil	Accutane soft gelatin capsule
	Oleic acid	Ritonavir soft gelatin capsule, Norvir soft gelatin capsule
	Peanut oil	Prometrium soft gelatin capsule
	Sesame oil	Marinol soft gelatin capsule
	Beeswax	Vesanoid soft gelatin capsule

FORMULATION OF SEDDS:

A series of SEDDS formulations are generally prepared using different Surfactant/Cosurfactant combinations and the oil. In all the formulations, the level of active moiety is kept constant according to the required dose. Accurately weighed drug is placed in a glass vial, and oil, surfactant, and cosurfactant are added. Then the components are mixed by gentle stirring and vortex mixing and are heated at 40-50ºC on a magnetic stirrer if required until the drug is perfectly dissolved. The mixture is stored at room temperature until further use.

***CHARACTERIZATION AND OPTIMIZATION OF SEDDS*:**

SMEDDS forms fine o/w microemulsions with only gentle agitation, upon its introduction into aqueous media. Since the Gibbs energy required to form microemulsion is very low, the formation is thermodynamically spontaneous. Surfactants (emulsifiers) form a layer around the emulsion droplets and reduce the interfacial energy as well as provide a mechanical barrier to coalescence. For selecting a suitable self-emulsifying vehicle, it is important to assess (a) the drug solubility in various components, (b) the area of self emulsifying region in the phase diagram, and (c) droplet size distribution following self-emulsification[24].

1) *Solubility Studies*

The solubility of drug in various oils, surfactants and cosurfactants is determined by using shake flask method. An excess amount of drug is added to each vial containing 1 mL of the selected vehicle i.e. oil, surfactant or solubilizer. After sealing, the mixture is vortexed using a cyclomixer for 10 min in order to facilitate proper mixing of drug with the vehicles. Mixtures are then shaken for 72 h in an isothermal shaker maintained at 37±1°C for equilibration. Equilibrated samples are centrifuged at 5,000 rpm for 15 min, followed by filtration through membrane filter (0.22 µm). The concentrations of drug are then determined by high-performance liquid chromatography (HPLC) method[7].

Balakrishan et al[18] determined the solubility of Coenzyme Q10 in various oils and surfactants. After preformulation solubility studies only, oils (Labrafil M 1944 and Labrafil M 2125), surfactant (Labrasol) and cosurfactant (Lauroglycol FCC and Capryol 90 were chosen. In all the formulations, the level of Coenzyme Q 10 was fixed at 6% (w/v) of the vehicle.

2) *Construction of Pseudoternary Phase Diagrams*

Pseudo-ternary phase diagrams are constructed to identify the self-emulsifying regions and to optimize emulsifier to coemulsifier ratio and the concentration of oil. The microemulsion regions in the diagrams are plotted, and the wider region indicated the better self-emulsification efficiency. Pseudo-ternary phase diagrams of oil, surfactant/ co surfactant, and water are developed using the water titration method. The mixtures of oil and S/CoS at certain weight ratios are diluted with water in a dropwise manner[24]. For each phase diagram at a specific ratio of S/CoS, transparent and homogenous mixture of oil and S/CoS is formed by vortexing for 5 minutes. Then each mixture is titrated with water and visually observed for phase clarity and flowability. The concentration of water at which turbidity-to-transparency and

transparency-to-turbidity transitions occurred is derived from the weight measurements. These values are then used to determine the boundaries of the self emulsifying domain corresponding to the chosen values of oils, as well as the S/CoS mixing ratio[25].

Xinru Li et al[26] assessed visually the equilibrated samples after titration with saline under magnetic stirring or vortexing. The phase state was classified into three, that is, clear one-phase with low viscosity, clear one-phase with high viscosity, and multiple phases. The one-phase with low viscosity was separated further into water-in-oil (w/o) or o/w microemulsion phase by simply considering the composition, that is, whether it was oil-rich or water-rich. The clear one-phase with high viscosity was separated further into gel or liquid crystalline by using polarized light microscope and multiple phases were considered as crude emulsion. The influence of weight ratio of emulsifier to coemulsifier on the area of o/w microemulsion region was investigated on the pseudo-ternary phase diagram.

Singh et al[27] prepared eight potential different combinations of surfactant, co-surfactant, and oil based on the results of solubility studies which were used for the phase diagram study for Exemestane SMEDDS. No distinct conversion from water-in-oil (w/o) to (o/w) microemulsion was observed. The translucent and low viscosity microemulsion area was presented in the phase diagram marked as microemulsion.

3) *Droplet Size Measurement*

Properly diluted samples of self-emulsifying systems are used for droplet size analysis using Photon Correlation Spectroscopy. Average droplet size and polydispersity index are determined and the data obtained are further treated with regression analysis[28]. Measurements are obtained in duplicate at an angle of 90°. The diluted emulsions are also allowed to stand for 12 h at room temperature to assess dilution stability[7].

4) *Transmission Electron Microscopy*

Transmission electron microscope is used as a visualizing aid for the observation of morphology of droplets. SMEDDS is diluted with water (1/100). A drop of the diluted emulsion is directly deposited on the holey film grid to observe the morphology of formulations.

Xinru Li et al[26] observed the morphology of microemulsion by transmission electron microscopy. To improve the contrast, the samples were treated with a 1 wt % phosphotungstic acid solution for 2 h, deposited on copper grids, and allowed to dry for 48 h before TEM examination. The homogeneous and spherical droplets in microemulsion were observed.

Singh et al[27] examined the morphology of microemulsion with a transmission electron microscope. The droplet on the microemulsion appeared dark with the bright surroundings. TEM photographs further conformed that the globules were spherical in shape.

5) *Turbidimetric Evaluation*

Nepheloturbidimetric evaluation is done to monitor the growth of emulsification. Patil et al[15] worked on Loratadine SES which was added to 0.1N hydrochloric acid (150 mL) under continuous stirring (50 rpm) on magnetic plate at ambient temperature, and the increase in turbidity was measured using a turbidimeter. Time required to disperse the system completely and uniformly was determined by observing change in turbidity as a function of time. Time point beyond which there was no increase in the turbidity

was recorded as emulsification time which was found to be 1.75 minutes.
Patil et al[28] reported the emulsification time for gelled SEDDS of Ketoprofen as 30 seconds with turbidity 82 NTU. However, since the time required for complete emulsification was too short, it was not possible to monitor the rate of change of turbidity (rate of emulsification).

6) *Zeta Potential Measurement*

In disperse systems, electrical charges are developed by several mechanisms at the interface between the dispersed phase and the aqueous medium. The two most common mechanisms are the ionization of surface functional groups and the specific adsorption of ions. Theses electrical charges play an important role in determining the interaction between the particles of the dispersed phase and the resultant physical stability of the system, particularly for those in the colloidal size range. The potential between the tightly bound surface liquid layer (shear plane) of the particle and the bulk phase of the solution is called as zeta potential. The measurement of the zeta potential tells about the stability[29]**.** For o/w emulsions with low electrolyte content in the aqueous phase, a zeta potential of 30 mV is found to be sufficient to establish an energy maximum to ensure emulsion stability.

7) *Refractive Index and Percent Transmittance*

The refractive index of the system was measured by an Abbe refractometer by placing 1 drop of solution on the slide. The percent transmittance of the system was measured at 650 nm using UV spectrophotometer keeping distilled water as a blank. Ghosh et al[30] measured the refractive index of acyclovir system and it was found similar to the water (1.333). In addition, the developed system showed percent transmittance > 99%. The refractive index and percent transmittance data prove the transparency of the system.

8) *Thermodynamic Stability Study*

In thermodynamic stability studies, formulations selected are subjected to different stress tests like centrifugation and freeze– thaw test. In Freeze thawing, the formulations are subjected to 3 to 4 freeze-thaw cycles, which included freezing at –4°C for 24 hours followed by thawing at 40°C for 24 hours. Centrifugation is performed at 3000 rpm for 5 minutes. The formulations are then observed for phase separation. Only formulations that are stable to phase separation are selected for further studies. Samples of SMEDDS are also charged on accelerated and long term stability conditions.
Patel et al[31] conducted evaluation tests on stability samples of Fenofibrate SMEDDS. The formulation was found to be stable for 6 months at intermediate and accelerated conditions and 12 months at long-term conditions. There was no significant change in the appearance, drug content, drug release, microemulsifying property or particle size of the resultant emulsion. Furthermore, the formulation was found to show no phase separation, drug precipitation, or capsule leaks.

9) In Vitro Intestinal Permeability Studies

Male Sprague- Dawley rats (250-300 g) are killed by overdose with pentobarbitone administered by intravenous injection. To check the intraduodenal permeability, the duodenal part of the small intestine is isolated and taken for the in vitro diffusion study. Then this tissue is thoroughly washed

with cold Ringer's solution to remove the mucous and lumen contents. The SEDDS sample is diluted with 1 mL of distilled water (outside mixing for 1 minute by vortex mixer). The resultant sample (2 mg/mL) is injected into the lumen of the duodenum using a syringe, and the 2 sides of the intestine are tightly closed. Then the tissue is placed in a chamber of organ bath with continuous aeration and a constant temperature of 37^0C. The receiver compartment is filled with 30 mL of phosphate-buffered saline (pH 5.5). The absorbance is measured using a UV-VIS spectrophotometer at the specific wavelength, keeping the respective blank. The percent diffusion of drug is calculated against time and plotted on a graph[7].

10) ***Absorption Studies***

Male rats weighing 300 ± 20 g are used. The animals are divided into 3 groups, the first group is fasted for 12h before drug administration; the second and third groups are continuously fed with normal diet and lipid diet for 12 h before drug administration, respectively. After anesthesia, the femoral artery is cannulated and cannula is flushed with heparin saline solution to prevent blood clotting. After rats recovered from anesthesia, SEDDS after dilution with distilled water is administered orally to rats using oral sonde. Blood samples are withdrawn at regular time intervals and frozen until analysis. The pharmacokinetic parameters like AUC, T_{max} and C_{max} are calculated from the plasma data.

APPLICATIONS OF SEDDS:

Improvement in Solubility:

If drug is incorporated in SEDDS, it increases the solubility because it circumvents the dissolution step in case of Class-Π drug (Low solubility/high permeability). A SMEDDS formulation of a poorly water soluble drug, candesartan cilexetil was formulated for directly filling in hard gelatin capsules for oral administartaion. The results from the study show the utility of SMEDDS to enhance solubility and dissolution of sparingly soluble compounds like candesartan[32].

Enhanced Bioavailability:

Ketoprofen, a moderately hydrophobic (log P 0.979) nonsteroidal anti-inflammatory drug (NSAID), is a drug of choice for sustained release formulation has high potential for gastric irritation during chronic therapy. Also because of its low solubility, ketoprofen shows incomplete release from sustained release formulations. Ketoprofen is presented in SEDDS formulation. This formulation has enhanced bioavilability due to increase in the solubility of drug which minimizes the gastric irritation. Also incorporation of gelling agent in SEDDS has sustained the release of Ketoprofen[33]. In SEDDS, the lipid matrix interacts readily with water, forming a fine particulate oil-in-water (o/w) emulsion. The emulsion droplets will deliver the drug to the gastrointestinal mucosa in the dissolved state readily accessible for absorption. Therefore, increase in AUC i.e. bioavailability and Cmax is observed with many drugs when presented in SEDDS. These drugs are listed in Table 2. The successful marketed SEDDS preparations are given in Table 3.

Protection against Biodegradation:

The ability of self emulsifying drug delivery system to reduce degradation as well as improve absorption may be especially useful for drugs, for which both low solubility and degradation in the GI tract contribute to a

low oral bioavailability. Many drugs are degraded in physiological system, 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. Acetylsalicylic acid (Log P = 1.2, Mw=180), a drug that degrades in the GI tract because it is readily hydrolyzed to salicylic acid in an acid environment. When the drug was formulated in a Galacticles™ Oral Lipid Matrix System (SEDDS formulation) and compared to a commercial formulation, it showed the good plasma profile. The oral bioavailability of undegraded acetylsalicylic acid is improved by 73% by the Galacticles™ Oral Lipid Matrix System formulation compared to the reference formulation. This suggests that the SEDDS formulation has a capacity to protect drugs from degradation in the GI tract.

Table 2
Examples of bioavailability enhancement of poorly soluble drug after administration of SEDDS and SMEDDS formulations

Compound	Observation after Study	Reference
Cyclosporin	Increased bioavailability and C_{max} and reduced T_{max} from SMEDDS	34
	Increased C_{max}, AUC and dose linearity and reduced food effect from SMEDDS	35
	Reduced intra- and inter-subject variability from SMEDDS	36
Ontazolast	Bioavailability increase of at least 10- fold from all lipid based formulations	37
Win 54954	No difference in bioavailability but improved reproducibility, increased C_{max}	38
Vitamin E	Bioavailability 3- fold higher from SEDDS	39
Coenzyme Q10	Bioavailability 2- fold higher from SEDDS	40
Simvastatin	Bioavailability 1.5 fold higher from SMEDDS	41
Progesterone	Bioavailability 9- fold higher from SEDDS	42

Indomethacin	Bioavailability significantly increased from SEDDS	43
Tocotrienols	Bioavailability 2-3 fold higher from SEDDS	44

Table 3
Examples of marketed products with SEDDS formulation

Active moiety	Trade name	Dosage forms
Tretinoin	Vesanoid	Soft gelatin capsule, Roche
Cyclosporine	Neoral	Soft gelatin capsule, Novartis
Cyclosporine	Panimum bioral	Capsule, Panacea Biotec
Ibuprofen	Solufen	Hard gelatin capsule, Sanofi-Aventis
Fenofibrate	Lipirex	Hard gelatin capsule, Sanofi-Aventis
Ritonavir	Norvir	Soft gelatin capsule, Abbott laboratories
Isotretinoin	Accutane	Soft gelatin capsule, Roche
Cyclosporin A	Gengraf	Hard gelatin capsule, Abbott
Cyclosporin A	Sandimmune	Soft gelatin capsule, Novartis
Lopinavir and Ritonavir	Kaletra	Soft gelatin capsule, Abbott
Sanquinavir	Fortovase	Soft gelatin capsule, Hoffmann-La Roche Inc.
Tipranavir	Aptivus	Soft gelatin capsule, Boehringer Ingelheim

FUTURE TREND AND SCOPE:

SEDDS are a promising approach for the formulation of drug compounds with poor aqueous solubility. The oral delivery of hydrophobic drugs can be made possible by SEDDS, which have been shown to substantially improve oral bioavailability. The efficiency of the SEDDS formulation is case-specific in most instances, thus, composition of SEDDS formulation should be determined very carefully. As a relatively high concentration of surfactant is generally

employed in the SEDDS formulation, toxicity of the surfactant being used should be taken into account. In fact, a compromise must be reached between the toxicity and self-emulsification ability of the surfactant that is considered for use. The size and charge of the oil droplet in the emulsion formed are two other important factors that affect GI absorption efficiency. Renaissances in the use of self-emulsifying system over the past two decades are inviting increasing attention. Recent trends are focused on the development of modified self-emulsifying solid or semi-solid formulations as an alternative to the conventional liquid self-emulsifying system. Hot melt granulation is a technique for producing granules or pellets, and by using a waxy solubilising agent as a binding agent, up to 25% solubilising agent can be incorporated in a formulation. There is also an increasing interest in using inert adsorbents, such as the Neusilin (Fuji Chemicals) and Zeopharm (Huber) products for converting liquids into powders – which can then be processed into powder fill capsules or tablets.

At present, drug products including Cyclosporin A, Ritonavir and Saquinavir, which are designed as SEDDS, are readily available on the market. In future, SEDDS will continue to enable novel applications in drug delivery and solve deficiency associated with the delivery of poorly soluble drugs. Thus this field requires further exploration and research so as to bring out commercially available self emulsifying formulation.

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ACKNOWLEDGMENT

The author extends gratitude to Dr. K.G. Bothara, Principal, Sinhgad Institute of Pharmacy, Pune, Maharashtra, India for inspiration and support

REFERENCES

1. Ma¨der K and Abdalla A, Preparation and characterization of a self-emulsifying pellet formulation. Eur. J. Pharm. Biopharm., 66: 220–226, (2007).
2. Rane SS and Anderson BD, What determines drug solubility in lipid vehicle: Is it predictable? Adv. Drug Del. Rev., 60: 638-656, (2008).
3. Pouton CW, Lipid formulations for oral administration of drugs: non-emulsifying, self-emulsifying and 'self-microemulsifying' drug delivery systems. Eur. J. Pharm. Sci., 11 (2): S93-S98, (2000).
4. Tang JI, Sun J and He ZG, Self-Emulsifying Drug Delivery Systems: Strategy for Improving Oral Delivery of Poorly Soluble Drugs. Curr. Drug Ther., 2: 85-93, (2007).
5. Kumar A, Sharma S and Kamble R, Self Emulsifying Drug Delivery System (SEDDS): Future Aspects. Int. J. Pharm. Pharm. Sci., 2(4), (2010).
6. Kohli K, Chopra S, Dhar D, Arora S and Khar RK, Self-emulsifying drug delivery systems: an approach to enhance oral bioavailability. Drug Discov. Today, 15 (21, 22): 958-965, (2010).
7. Kale AA and Patravale VB, Design and Evaluation of Self-Emulsifying Drug Delivery Systems (SEDDS) of

Nimodipine. AAPS PharmSciTech, 9(1), (2008).

8. Jeevana JB and Sreelakshmi K, Design and Evaluation of Self-Nanoemulsifying Drug Delivery System of Flutamide. J Young Pharm., 3(1): 4–8, (2011).
9. Friedman D. Non-aqueous compositions for oral delivery of insoluble bioactive agents, U.S. Patent US 20070190080, 2007.
10. Driscoll CM and Griffin BT, Biopharmaceutical challenges associated with drugs with low aqueous solubility—The potential impact of lipid-based formulations. Adv. Drug Del. Rev., 60: 617-624, (2008).
11. Pouton CW, Formulation of poorly water-soluble drugs for oral administration: Physicochemical and physiological issues and the lipid formulation classification system. Eur. J. Pharm. Sci., 29(3-4): 278-287, (2006).
12. Abdalla A, Klein S and Mäder K, A new self-emulsifying drug delivery system (SEDDS) for poorly soluble drugs: Characterization, dissolution, *in vitro* digestion and incorporation into solid pellets. Eur. J. Pharm. Sci., 35(5): 457-464, (2008).
13. El-Laithy HM, Preparation and Physicochemical Characterization of Dioctyl Sodium Sulfosuccinate (Aerosol OT) Microemulsion for Oral Drug Delivery. AAPS PharmSciTech, 4 (1) : Article 11, (2003).
14. Katteboina S, Chandrasekhar V S R and Balaji S, Approaches for the development of solid self-emulsifying drug delivery systems and dosage forms. Asian J. Pharm. Sci., 4(4): 240-253, (2009).
15. Patil P and Paradkar A, Porous Polystyrene Beads as Carriers for Self-Emulsifying System Containing Loratadine. AAPS Pharm Sci. Tech. 7(1): Article 28, (2006).
16. Kommuru TR, Gurley B, Khan MA and Reddy IK, Self-emulsifying drug delivery systems (SEDDS) of coenzyme Q10: formulation development and bioavailability assessment. Int. J. Pharm., 212: 233–246, (2001).
17. Franceschinis E, Bortoletto C, Perissutti B, Dal Zotto M, Voinovich D and Realdon N, Self-emulsifying pellets in a lab-scale high shear mixer: Formulation and production design. Powder Technol., 207: 113–118, (2011).
18. Balakrishnana P, Leeb BJ, Oha D H, Kima J O, Leea YI and Kimc DD, Enhanced oral bioavailability of Coenzyme Q10 by self-emulsifying drug delivery systems. Int. J. Pharm., 374: 66–72, (2009).
19. Constantinides PP, Lipid microemulsions for improving drug dissolution and oral absorption: physical and biopharmaceutical aspects. Pharm. Res., 12: 1561-1572, (1995).
20. Lacy JE and Embleton JK. Delivery systems for hydrophobic drugs, U.S. Patent US 5645856, 1997.
21. Khoo SM, Humberstone AJ, Christopher JH, Edwards GA and Charman WN, Formulation design and bioavailability assessment of lipidic self-emulsifying formulation of halofanitrine. Int. J. Pharm., 167 (1-2): 155-164, (1998).
22. Pathak A, Jain V, Nagariya AK, Singh R, Nayak S and Bansal P, Recent

advances in self emulsifying drug delivery system - A review. Drug Invention Today, 2(2): 123-129, (2010).

23. Patel VP, Desai TR, Kapupara PP, Atara SA and Keraliya RA, Self Emulsifying Drug Delivery System: a conventional and alternative approach to improve oral bioavailability of lipophilic drugs. Int. J. Drug Dev. & Res., 2(4), (2010).
24. Boonme P, Krauel K, Graf A, Rades T and Junyaprasert VB, Characterization of Microemulsion Structures in the Pseudoternary Phase Diagram of Isopropyl Palmitate/Water/Brij 97:1-Butanol. AAPS PharmSciTech, 7(2): Article 45, (2006).
25. Shukla JB and Patel SJ, Formulation and evaluation of self micro emulsifying system of Candesaratan cilexetil. Int. J. Pharm. Pharm. Sci; 2(4), (2010).
26. Xinru L, Quan Y, Yanqing H, Yanxia Z and Yan L, Development of Silymarin Self-Microemulsifying Drug Delivery System with Enhanced Oral Bioavailability. AAPS PharmSciTech, 11(2), (2010).
27. Singh AK, Chaurasiya A, Awasthi A, Mishra G, Asati D and Khar RK, Oral Bioavailability Enhancement of Exemestane from Self-Microemulsifying Drug Delivery System (SMEDDS). AAPS PharmSciTech, 10(3), (2009).
28. Patil P, Prasad Joshi and Paradkar A, Effect of Formulation Variables on Preparation and Evaluation of Gelled Self-emulsifying Drug Delivery System (SEDDS) of Ketoprofen. AAPS PharmSciTech, 5 (3) : Article 42, (2004).
29. L.C. Li and Y. Tian. Zeta Potential. In: J. Swarbrick (eds.), Encyclopedia of Pharmaceutical Technology, Informa Healthcare USA, Inc., New York, 2007, pp. 4117-4127.
30. Ghosh PK, Majithiya RJ, Umrethia ML and Murthy RSR, Design and Development of Microemulsion Drug Delivery System of Acyclovir for Improvement of Oral Bioavailability. AAPS PharmSciTech, 7 (3): Article 77, (2006).
31. Patel AR and Vavia PR, Preparation and In Vivo Evaluation of SMEDDS (Self-Microemulsifying Drug Delivery System) Containing Fenofibrate. The AAPS Journal, 9 (3) Article 41, (2007).
32. Shukla JB and Patel SJ, Formulation and Evaluation of Self micro Emulsifying System of Candesartan cilexetil. Int. J. Pharm. Pharm. Sci., 2(4), (2010).
33. Patil P, Joshi J and Paradkar P, Effect of Formulation Variables on Preparation and Evaluation of Gelled Self-emulsifying Drug Delivery System (SEDDS) of Ketoprofen. AAPS PharmSciTech., 5(3): article 42, (2004).
34. Trull AK, Tan KKC and Tan L, Enhanced absorption of new oral cyclosporin microemulsion formulation, Neoral, in liver, transplant recipients with external biliary diversion. Transplant. Proc., 26: 2977–2978, (1994).
35. Mueller EA, Kovarik JM and Van Bree JB, Improved dose linearity of cyclosporine pharmacokinetics from a microemulsion formulation. Pharm. Res., 11: 301–304, (1994).
36. Kovarik JM, Mueller EA, Van Bree JB, Tetzloff W and Kutz K, Reduced inter- and intraindividual variability in cyclosporine pharmacokinetics from a microemulsion formulation. J. Pharm. Sci, 83: 444–446, (1994).

37. Hauss DJ, Fogal SE and Ficorilli JV, Lipid-based delivery systems for improving the bioavailability and lymphatic transport of a poorly water-soluble LTB4 inhibitor. J. Pharm. Sci., 87: 164-169, (1998).

38. Charman SA, Charman WN and Rogge MC, Self emulsifying drug delivery systems: formulation and biopharmaceutical evaluation of an investigational lipophilic compound. Pharm Res., 9:87-93, (1992).

39. Julianto T, Yuen KH and Mohammad Noor A, Improved bioavailability of vitamin E with a self emulsifying formulation. Int. J. Pharm., 200: 53–57, (2000).

40. Kommuru TR, Gurley B, Khan MA and Reddy IK, Self-emulsifying drug delivery systems (SEDDS) of coenzymeQ10: formulation development and bioavailability assessment. Int. J. Pharm., 212: 233–246, (2001).

41. Kang BK, Lee JS and Chona SK, Development of self-microemulsifying drug delivery systems (SMEDDS) for oral bioavailability enhancement of simvastatin in beagle dogs. Int. J. Pharm., 274: 65–73, (2004).

42. Tuleu C, Newton JM, Rose J, Euler D, Saklatvala R, Clarke A and Booth SW, Comparative bioavailability study in dogs of a self-emulsifying formulation of progesterone presented in a pellet and liquid form compared with an aqueous suspension of progesterone. J. Pharm. Sci., 93: 1495– 1502, (2004).

43. Kim JY and Ku YS, Enhanced absorption of indomethacin after oral or rectal administration of a self-emulsifying system containing indomethacin to rats. Int. J. Pharm., 174: 81–89, (2000).

44. Yap SP and Yuen KH, Influence of lipolysis and droplet size on tocotrienol absorption from self-emulsifying formulations. Int. J. Pharm., 281: 67–78, (2004).