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REVIEW ON SOLUBILITY ENHANCEMENT APPROACH: SELF MICRON EMULSIFYING DRUG DELIVERY SYSTEM

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Abstract: Solubility is one of the most important parameter to achieve desired concentration of drug in systemic circulation for therapeutic response. As a consequence of modern drug discovery techniques, there has been a steady increase in the number of new pharmacologically active lipophilic compounds that are poorly water soluble. It is a great challenge for pharmaceutical scientist to convert those molecules into orally administered formulation with sufficient bioavailability. Among the several approaches to improve oral bioavailability of these molecules, Self- micron emulsifying drug delivery system (SMEDDS) is one of the approaches usually used to improve the bioavailability of hydrophobic drugs.

Keywords: Solubility, Self Micron Emulsifying Drug Delivery System, Hydrophobic drugs

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INTRODUCTION

Nearly half of the new drug candidates that reach formulation have poor water solubility, and oral delivery of such drugs is frequently associated with low bioavailability.[1,2] To overcome these problems, various formulation strategies have been exploited, such as the use of surfactants, lipids, permeation enhancers, micronization, salt formulation, cyclodextrins, nanoparticles and solid dispersions. The availability of the drug for absorption can be enhanced by presentation of the drug as a solubilizate within a colloidal dispersion.[3]

Much attention has focused on lipid solutions, emulsions and emulsion preconcentrates, which can be prepared as physically stable formulations suitable for encapsulation of such poorly soluble drugs. Emulsion systems are associated with their own set of complexities, including stability and manufacturing problems associated with their commercial production. Self-emulsification systems are one formulation technique that can be a fitting answer to such problems. Self-emulsifying drug delivery systems (SEDDS) are isotropic mixtures of drug, lipids and surfactants, usually with one or more hydrophilic co- solvents or co-emulsifiers.[4]

Upon mild agitation followed by dilution with aqueous media, these systems can form fine (oil in water) emulsion instantaneously. 'SEDDS' is a broad term, typically producing emulsions with a droplet size ranging from a few nanometers to several microns. 'Self-microemulsifying drug delivery systems' (SMEDDS) indicates the formulations forming transparent microemulsions with oil droplets ranging between 100 and 250 nm. 'Self-nano-emulsifying drug delivery systems (SNEDDS)' is a recent term construing the globule size range less than 100 nm.[5]

Figure 1 gives the schematic diagram of intestinal drug transport from lipid-based

formulations via the portal and the mesenteric lymphatic routesof the formulation in vivo will determine both the uptake of the drug in the GIT as well as the degree of participation of the portal venous and mesenteric lymphatic pathways in overall drug absorption.[6]

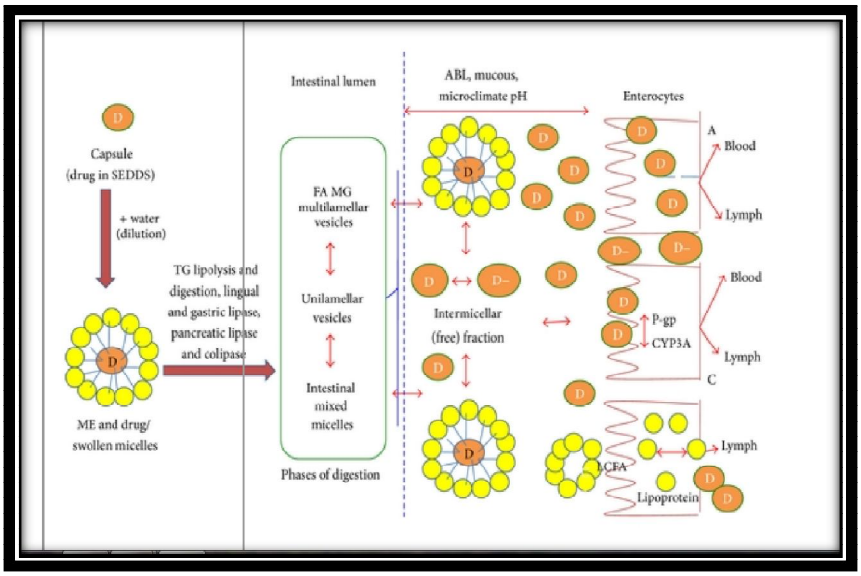

Figure 1.1 Schematic diagram of intestinal drug transport from lipid-based formulations via the portal and the mesenteric lymphatic routes. (A) Increased membrane fluidity facilitating transcellular absorption. (B) Opening of tight junctions to allow paracellular transport. (C) Inhibition of P-gp and/or CYP450 to increase intracellular concentration and residence time. (D) Stimulation of lipoprotein/chylomicron production. ABL: aqueous boundary layer; D: drug; D−: ionized drug substance; FA: fatty acid; LCFA: long chain fatty acid; ME: microemulsion; MG: monoglyceride; SEDDS: self-emulsifying drug delivery system; TG, triglyceride; TJ, tight junction.[6]

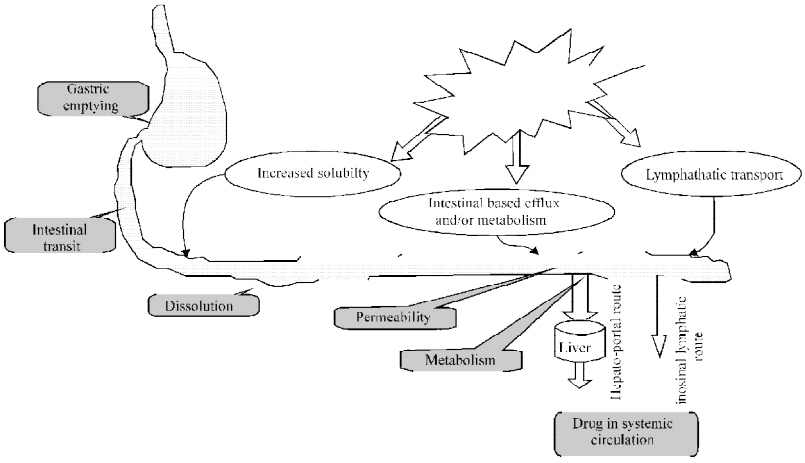

Fig. 1.2 Self-emulsifying formulations enhancing the Bioavailability of drugs through oral absorption[7]

Table 1.1: Application of SEDDS in Various BCS category Drugs[8]

BCS class	Problems
Class I	Enzymatic degradation, gut wall efflux
Class II	Solubilization and bioavailability
Class III	Enzymatic degradation, gut wall efflux, Bioavailability
Class IV	Solubilization, enzymatic degradation, gut wall efflux and bioavailability

1.1.1 CLASSIFICATION OF SEDDS

The simplest lipid products are those in which the drug is dissolved in digestible oil, usually a vegetable oil or medium chain triglyceride (fractionated coconut oil). These are safe food substances, classed as GRAS (generally regarded as safe) by regulatory agencies, and do not present a toxicological risk to formulators. Although few drugs have been formulated in this way, oil solution has been the standard way of administering oil-soluble vitamins (A and D) for many years.

Table 1.2 Typical Properties of type I, II, IIIA and IIIB lipid formulation

	Type I	Type II	Type IIIA	Type IIIB
Typical composition (%)				
Triglycerides or Mixed glycerides	100	40-80	40-80	20
surfactant	-	20-60(HLB-12)	20-40(HLB-11)	20-50(HLB-11)
Hydrophilic Cosolvents	-	-	0-40	20-50
Particle size of dispersion (nm)	Coarse	100-250	100-250	50-100
Significance of	Limited	Solvent capacity	Some loss of	Significant Phase

aqueous dilution	importance	unaffected	solvent capacity	changes and potential loss of solvent capacity
Significant of digestibility	Crucial requirement	Not Crucial but likely to occur	Not Crucial but may be inhibited	Not required and not likely to occur

Bioavailability from oil solutions is likely to be very good because the triglycerides are rapidly digested to free fatty acids and 2-monoglycerides, and these products are solubilized to form a colloidal dispersion within bile salt-lecithin mixed micelles. A hydrophobic drug is also likely to be sol in mixed micelles resulting in a reservoir of drug in colloidal solution from which it can partition, allowing efficient, passive (transcellular) absorption. The bioavailability and plasma profile of a lipophilic 5a-reductase inhibitor from an oil solution were equivalent to those achieved using a self-emulsifying system. Formulations which comprise drug in solution in triglycerides and / or mixed glycerides are classified here as 'Type I' (Table 1.2).[2] When an appropriate dose of the drug can be dissolved, a Type I formulation may well be the system of choice, in view of its simplicity and biocompatibility. SEDDS which emulsifies in aqueous solutions under very gentle conditions of agitation, to result in a dispersion of colloidal dimensions. If the surfactant is insufficiently hydrophilic to dissolve and form micelles in aqueous solution, then it exists itself as a dispersed phase, either with or separated from the oily components. This type of formulation is likely to retain its solvent capacity for the drug after dispersion and is referred to as Type II (Table 1.2). The extent of precipitation will depend on the physical chemistry of the drug and how hydrophilic is the formulation. Formulations which include water-soluble components are referred to in Table 1.2 as Type III formulations, and have been referred to as 'self-micro emulsifying' systems, due to the optical clarity which can be achieved with Type III systems. As the risk of precipitation is greater when the formulation contains a higher proportion of hydrophilic components, Type III formulations can be arbitrarily split into Type IIIA and Type IIIB, to help identify very hydrophilic (Type IIIB) Type IIIB, to help identify very hydrophilic (Type IIIB).

1.1.2 FORMULATION OF SEDDS

The SEDDS formulation should instantaneously form a clear dispersion, which should remain stable on dilution. The hydrophobic agent remains solubilized until the time that is relevant for its absorption. Silva et al.[9] found that two main factors, small particle size and polarity of resulting oil droplets, determine the efficient release of the drug compounds from SEDDS. In o/w microemulsions, however, the impact of polarity of oil droplets is not considerable because the drug compound incorporated within the oil droplets reaches the capillaries. Isotropic liquids

are preferable to waxy pastes because if one or more excipient(s) crystallize(s) on cooling to form a waxy mixture, it is very difficult to determine the morphology of the materials and, most importantly, the polymorphism properties of the drug within the wax. As a general rule, it is sensible to use the simplest effective formulation, restricting the number of excipients used to a minimum.

1.1.2.1 Screening of excipients for SEDDS

With a large variety of liquid or waxy excipients available, ranging from oils through biological lipids and hydrophobic and hydrophilic surfactants to water-soluble co-solvents, there are many different combinations that could be formulated for encapsulation in hard or soft gelatin or mixtures that disperse to give fine colloidal emulsions. The following points should be considered in the formulation of a SEDDS:

(i) The solubility of the drug in different oil, surfactants and co-solvents and

(ii) The selection of oil, surfactant and co-solvent based on the solubility of the drug and the preparation of the phase diagram.

The backbone of SEDDS formulation comprises lipids, surfactants and co-solvents. The right concentration of the above three decides the self-emulsification and particle size of the oil phase in the emulsion formed. These ingredients are discussed below.

Lipids

Lipid is a vital ingredient of the SEDDS formulation. It can not only solubilize large amount of lipophilic drugs or facilitate self-emulsification but also enhance the fraction of lipophilic drug transported via intestinal lymphatic system, thereby increasing its absorption from the GIT.[10] Natural edible oils, comprising medium-chain triglycerides, are not frequently preferred in this regard owing to their poor ability to dissolve large amounts of lipophilic drugs.[11] Modified long and medium- chain triglyceride oils, with varying degrees of saturation or hydrolysis, have been used widely for the design of SEDDS. These semi-synthetic derivatives form good emulsification systems when used with a large number of solubility enhancing surfactants approved for oral administration.

Table 1.3 Type of oils used in marketed SEDDS

Type of oil	Marketed Product	Drug
Corn oil	Depakene Capsule	Valproic acid
Olive oil	Sandimmune oral solution	Cyclosporine
Seasame oil	Marinol soft gelation Capsule	Dronabinol
Soya bean oil	Accurate soft gelatin capsule	Isotretinoin
Peanut oil	Prometrium soft gelatin capsule	Progesterone
Bees wax	Vesanoid soft gelatin capsule	Tretinoin
Hydrogenated soya	Accutane soft gelatin Capsule	Isotretinoin

Table 1.4 Type of oil used with Different Drug in SEDDS

Oil	Drug
Soya bean oil	Probucol, Ibuprofen
Ethyl oleate	Vinpocetine
Oleic Acid	Puerarin
Maisine oil	Lercanidipine
Polyoxy Castor oil	Simvastatin
Peanut oil	Griseofulvin

Surfactants

A surfactant is obligatory to provide the essential emulsifying characteristics to SEDDS. Surfactants, being ampiphilic in nature, invariably dissolve (or solubilize) high amounts of hydrophobic drug compounds. The two issues that govern the selection of a surfactant encompass its hydrophilic–lipophilic balance (HLB) and safety. The HLB of a surfactant provides vital information on its potential utility in formulation of SEDDS. For attaining high emulsifying performance, the emulsifier involved in formulation of SEDDS should have high HLB and high

hydrophilicity for immediate formation of o/w droplets and rapid spreading of formulation in aqueous media in this context.

Table 1.5 Type of Surfactant used in marketed SEDDS

Surfactant	Marketed Product	Drug
Span 80, Tween 80	Gengraf soft gelatin capsule	Cyclosporine
Tween 20	Targretin Hard gelatin Capsule	Bexarotene
Cremophore RH 40	BCNU self-emulsifying implant	Carmustine
Labrafil M 1944 CS	Sandimmune oral solution	Cyclosporine

It would keep drug solubilized for a prolonged period of time at the site of absorption for effective absorption, so precipitation of drug compound within GI lumen is prevented. A range of industrial nonionic surfactants were screened for their ability to form SEDDS with medium-chain and long-chain triglycerides by Pouton and Porter.[3] using subjective visual assessment.

Co-solvents

Usually, the formulation of an effective SEDDS requires high concentrations of surfactant. Accordingly, co-solvents such as ethanol, propylene glycol and polyethylene glycol are required to enable the dissolution of large quantities of hydrophilic surfactant. The lipid mixture with higher surfactant and co-surfactant: oil ratios leads to the formation of SMEDDS. Alcohol and other volatile co-solvents have the disadvantage of evaporating into the shell of soft or hard gelatin capsules, leading to precipitation of drug.

Table 1.6 Types of Co-solvent used in SEDDS

Co-Surfactant
Poly Ethylene Glycol
Glycerin
Propylene Glycol
Ethanol

1.1.3 MECHANISM OF SELF-EMULSIFICATION

According to Reiss[12], self-emulsification occurs when the entropy change that favors dispersion is greater than the energy required to increase the surface area of the dispersion. The free energy of the conventional emulsion is a direct function of the energy required to create a new surface between the oil and water phases and can be described by the equation:

DG ¼ SNi pri2S (1)

Where, DG is the free energy associated with the process (ignoring the free energy of mixing), N is the number of droplets of radius r and S represents the interfacial energy. The two phases of emulsion tend to separate with time to reduce the interfacial area and, subsequently, the emulsion is stabilized by emulsifying agents, which form a monolayer of emulsion droplets, and hence reduces the interfacial energy, as well as providing a barrier to prevent coalescence.

1.1.4 ADVANTAGES OF SEDDS

- Poor water-soluble drugs give poor dissolution and bioavailability. SEDDS is novel approach to improve water solubility and ultimate bioavailability of lipophilic drugs. The ability of SEDDS to present the drug to GIT in globule size between 1-100 nm and subsequent increase in specific area enables more efficient drug transport through the intestinal aqueous boundary layer leading to improvement in bioavailability.
- Many drugs show large inter-subject and intra-subject variation in absorption leading to fluctuation in plasma profile. Food is the major factor affecting therapeutic performance of the drug in the body. SEDDS produce reproducible plasma profile.
- Fine oil droplets empty rapidly from the stomach and promote wide distribution of the drug throughout the intestinal tract and thereby minimizing irritation frequently encountered with extended contact of drugs and gut wall.
- Ease of manufacture and scale up is one of the most important advantages that makes SEDDS unique, when compared to other drug delivery systems like solid dispersions, liposomes, nanoparticles, etc., and dealing with improved bioavailability. SMEDDS require very simple and economical manufacturing facility like simple mixing with agitator and liquid filling equipment for large scale manufacturing. This is hence of interest to the pharmaceutical industry.
- SEDDS has potential to deliver peptides that are prone to enzymatic hydrolysis in GIT.

- When polymer is incorporated in the composition of SEDDS, it gives prolonged release of medicaments.

1.1.5 BIOPHARMACEUTICAL ISSUES AND CHOICE OF FORMULATION[2]

Dose of drug

The optimum formulation for each drug will depend on a number of considerations on the required dose, on which types of formulation have sufficient solvent capacity to allow for formulation of a unit dose, and in particular on the fate of the drug after these formulations have been administered to the gut. In many instances the choice of formulation will be limited by solvent capacity, and in others the drug will not be sufficiently soluble in any lipid formulations. Generally the most difficult drugs are those which have limited solubility in both water and lipids (typically with log P values of approximately 2). It is unlikely that lipid formulation will be of value for such drugs. In contrast, more hydrophobic drugs may permeate lipid bilayers freely but dissolve very slowly in the lumen of the gut. It has been common in the past for formulators to be presented with the challenge of formulating a high-dose oral product for a new hydrophobic drug, in circumstances when the dose has been estimated using the results of early pre-clinical animal studies. Such studies may have been conducted with an inadequate formulation, such as a crude aqueous suspension, from which bioavailability is poor. It these circumstances it is wise to anticipate that bioavailability may be much greater from a lipid system, which may allow pharmacological activity to be achieved with a lower dose. This is particularly important for drugs with high log P, when in the first instance the solvent capacity of lipid formulations appear to fall short of the required dose.

If the drug is potent and is sufficiently soluble in Type I, Type II or Type III systems then a choice will need to be made between these options. The most important consideration should be to avoid precipitation of the drug (see below), but a secondary consideration is whether or not rapid absorption is desirable. Typically Type II or Type III systems will undergo gastric emptying earlier and will be in a colloidal state earlier than Type I systems. An emulsifying system is likely to result in more rapid absorption and higher peak concentrations of drug. If the drug has a low therapeutic index this may be undesirable, which argues in favour of a Type I formulation.

Significance of droplet size

Tarr and Yalkowsky (1989) were able to demonstrate in a gut perfusion experiment that emulsion droplet size affected the rate of absorption of cyclosporin A. Absorption was more rapid from the finer of two emulsions, though the emulsions compared were both relatively coarse. The situation is very different when a small volume of a lipid formulation is administered in a capsule. The contents of the capsule will be emptied into the digestive

environment of the upper small intestine, so that the most important factor may not be the size of the particles in the initial dispersion, but rather their susceptibility to digestion and/or solubilization by mixed micelles of bile salts and phospholipids. One consequence of reducing the oil con tent and including surfactants and cosolvents is that the droplets become less susceptible to digestion (see below). This means that self-emulsifying systems are dependent on the initial emulsification process to produce a colloidal dispersion. It is assumed that the droplet size should be as fine as possible, and there is some evidence that this assumption holds in the case of cyclosporin A. The drug was more available from the 'Neoral' formulation than the

The risk of precipitation

Consider the example of a hydrophobic drug dissolved in a pure co solvent such as polyethylene glycol or propylene glycol. When the formulation is added to water the solvent capacity of the mixture falls approximately logarithmically as the formulation is diluted into water. The result is precipitation of the drug. It is much more difficult to predict the fate of the drug on dispersion of a typical Type IIIA lipid formulation; perhaps consisting of a drug dissolved in 30% medium chain triglycerides, 40% mixed partial glycerides, and 30% hydrophilic surfactant. The hydrophilic surfactant will be substantially separated from the oily components, forming a micellar solution in the continuous phase. The question is does this lower the overall solvent capacity for the drug. That will depend on the log P of the drug, and to what extent the surfactant was contributing to its solubilization within the formulation. At present there are no established techniques available to help formulators assess the risk of precipitation. Equilibrium solubility measurements can be carried out and this will help anticipate potential cases of precipitation in the gut. However crystallisation could be slow in the solubilizing and colloidal, stabilizing environment of the gut. Our preliminary studies at Bath have shown that crystallisation from some Type III formulations can take up to 5 days to reach equilibrium, and that the drug can remain in a super-saturated state for up to 24 h after the initial emulsification event (Hasan and Pouton, unpublished results). It could be argued that such products are not likely to cause precipitation of the drug in the gut before the drug is absorbed, and indeed that super-saturation could actually enhance absorption by increasing the thermodynamic activity of the drug. There is a clear need for practical methods to predict the fate of drugs after the dispersion of lipid systems in the gastro-intestinal tract.

1.1.6 FACTORS AFFECTING SEDDS

- **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.

- **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.

1.1.7 DOSAGE FORM OF SEDDS[13]

(1) Oral delivery:

(A) Self emulsifying capsule: After administration of capsules containing conventional liquids SE formulations, microemulsion droplets form and subsequently disperse in the GIT to reach site of absorption. If irreversible phase separation of microemulsion occurs an improvement of drugs absorption can't be expected. For handling this problem, sodium dodecyl sulfate was added into the SE formulation.

(B) Self--Emulsifying sustained / controlled release: Combination of lipids and surfactant has presented great potential preparing SE tablets. SE tablets are of great utility in obviating adverse effect. Inclusion of indomethacin (or other hydrophobic NSAID) for example, into SE tablets may increase its penetration efficacy through GI mucosal membrane, potentially reducing GI bleeding.

(C) Self emulsifying sustained / controlled release pellets: Pellets, as a multiple unit dosage form, possess many advantages over conventional solid dosage form, such as flexibility of

manufacture, reducing intra subject and inter subject variability of plasma profile and minimizing GI irritation without lowering drug bioavailability.

(D) Self emulsifying solid dispersions: Solid dispersions could increase the dissolution rate and bioavailability of poorly water soluble drugs but still some manufacturing difficulties and stability problems existed. Serajuddin pointed out that these difficulties could be surmounted by the use of se excipients.

(2) Topical Delivery: Topical administration of drugs can have advantages over other methods for several reasons, one of which is the avoidance of hepatic first pass metabolism of the drugs and related toxicity effects.

(3) Oculars and Pulmonary delivery: For the treatment of eye disease, drugs are essentially delivered topically o/w microemulsion have been investigated for ocular administration, to dissolve poorly soluble drugs, to increase absorption and to attain prolong release profile.

(4) Parenteral delivery: Parenteral administration of drugs with limited solubility is a major problem in industry because of the extremely low amount of drug actually delivered as target site.

1.1.8 EXAMPLES OF MARKETED PRODUCTS[14]

Table 1.7 marketed product of SEDDS

Dosage Form	Example
Soft Gelatin Capsule	Targretin soft gelatin capsule
	Ritonavir soft gelatin capsule
	Sandimmune soft gelatin capsule
	Nerol soft gelatin capsule
	Norvir soft gelatin capsule
	Vesanoid soft gelatin capsule
	Prometrium soft gelatin capsule
Hard Gelatin Capsule	Gengraf hard gelatin capsule
	Depakene hard gelatin capsule

Oral Solution	Ritonavir oral solution Sandimmune oral solution Rocaltrol oral solution

CONCLUSION:

SMEDDS are a promising approach for the formulation of drugs with poor aqueous solubility. The oral delivery of hydrophobic drugs can be made possible by SMEDDS, which have been shown to substantially improve oral

Bioavailability. As mentioned above, numerous studies have confirmed that SMEDDS substantially improved solubility/dissolution, absorption and bioavailability of poorly water-soluble drugs. There are reduced the particle size upto nanometer range. So, increase the solubility of lipopihilic drug.

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