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SELF MICROEMULSIFYING DRUG DELIVERY SYSTEM: A LIPID BASED DRUG DELIVERY SYSTEM

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ABSTRACT: Administration of drug by oral route is the most effective and acceptable route as it has better therapeutic efficacy, low cost and good patient compliance. More than 40% of new drugs are poorly water soluble. These drugs present development challenges and also have poor bioavailability. Although many formulation approaches like solid dispersions, complexation, pH modification exist, novel lipid based drug delivery system is best approach to design formulation with increased therapeutic benefit for poorly water soluble drug. This review provides recent updates on lipid based drug delivery system with main focus on self micro-emulsifying drug delivery system. Self-microemulsifying formulations are evident to improve the oral bioavailability of hydrophobic drugs due to their efficiency in presenting the hydrophobic drug in solubilized form whereby dissolution process can be circumvented. Oil, surfactant and co-surfactant also contribute to the overall improvement in oral bioavailability via promoting the lymphatic transport; thereby hepatic first pass metabolism can be surmounted.

INTRODUCTION: Today, one of the major problems to drug formulation development is poor water solubility of new drug. More than 40% of all new drugs are poorly water soluble. ¹ Poor solubility and ultimately low dissolution rate of these drugs in the gastro-intestinal fluids cause poor bioavailability. For BCS class II drugs, the bioavailability may be enhanced by increasing the solubility and dissolution rate of these drugs in the gastro-intestinal fluids.

The efficacy of these can be improved by increasing its gastrointestinal solubilization with modification of pharmacokinetic profiles. ² Oral route is the preferred route as it is non invasive, economic, and does not give pain at site of injection. ³ It is the most convenient method for chronic treatment. Oral route is limited by problems related to physicochemical properties of the drug, including poor solubility, low permeability, instability, and rapid metabolism, all of which decrease oral bioavailability. ⁴

Lipid-based drug delivery systems play an important role in the delivery of hydrophobic drugs with low bioavailability by using lipids as carriers. ⁵ Lipid-based drug delivery systems have gained considerable interest after the commercial success of Sandimmune Neoral, Novartis Pvt. Ltd. and

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Fortovase, Roche Laboratories Inc. with much attention focused on self micro-emulsifying drug delivery systems (SMEDDS). Lipid-based drug delivery system (LBDDS) is a well-tolerated system. LBDDS is used to deliver many drugs such as proteins and peptides, nucleic acids. LBDDS are administered through different routes such as oral, parenteral, ocular, intranasal, dermal, transdermal,

vaginal.^{6,7} Vegetable oils and their derivatives are the primary source for formulation of lipid-based excipient.⁸

Table 1 shows Lipid formulation classification system (LFCS) with typical proportions of lipid formulations.

TABLE 1: LIPID FORMULATION CLASSIFICATION SYSTEM (LFCS) SHOWING TYPICAL PROPORTIONS OF LIPID FORMULATIONS

Excipient in formulation	Content of formulation (%w/w)				
	Type I	Type II	Type III A	Type III B	Type IV
Oils: triglyceride or mixed mono and diglyceride	100	40-80	40-80	<20	-
Water insoluble surfactants (HLB*<12)	-	20-60	-	-	0-20
Water soluble surfactants (HLB*>12)	-	-	20-40	20-50	30-80
Hydrophilic cosolvents (eg.PEG, transcitol)	-	-	0-40	20-50	0-50

*HLB: Hydrophilic Lipophilic Balance.

Type I formulations are simply oil based,

Type II systems are water-insoluble self emulsifying drug delivery systems (SEDDS),

Type III systems are SEDDS or self-microemulsifying drug delivery systems (SMEDDS) and

Type IV systems are oil-free formulations.⁹

Self-Microemulsifying Drug Delivery Systems (SMEDDS):

SMEDDS (Type III B systems) are defined as isotropic mixtures of natural or synthetic oils, solid or liquid surfactants, or one or more hydrophilic solvents and co-solvents/surfactants that have ability to form fine oil -in-water (o/w) microemulsions upon mild agitation followed by dilution in aqueous media, such as GI fluids. SMEDDS spread readily in the GI tract, and the

digestive motility of the stomach and the intestine provide the agitation necessary for self-emulsification. SMEDDS have large quantities of co-solvents but contain less quantity of oil. These formulations have high risk of drug precipitation. Most of the marketed lipid formulations belong to Type III.¹⁰ SMEDDS have gained lots of importance due to clarity, high solubilisation capacity, thermodynamic stability, simple preparation method and ability to be filter.¹¹ They can increase oral bioavailability and eliminate food effects.¹² Some authors refer to the type IIIB formulations as self-nanoemulsifying drug delivery systems (SNEDDS). SNEDDS spontaneously form transparent oil-in-water emulsion of approximately less than 100 nm in size upon dilution with water.¹³

Table 2 shows characteristics of SEDDS, SMEDDS, and dispersions obtained upon their dilution with the aqueous phase.^{13,14}

TABLE 2: CHARACTERISTICS OF SEDDS, SMEDDS, SNEDDS.

System/characteristic	SEDDS	SMEDDS	SNEDDS
Composition	A system with a drug, oil, surfactant.	A system with drug, oil, surfactant, co-surfactant/ hydrophilic co-solvent.	A system with drug, oil, surfactant, co-surfactant/ hydrophilic co-solvent.
Lipid droplet size in dispersion	SEDDS, SMEDDS, SNEDDS form a fine oil-in-water microemulsion in contact with GI fluids. From 200 nm to 5 µm. providing a large surface area for absorption. The emulsion has a turbid appearance.	Less than 200nm, giving a large surface area for absorption. These are clear to translucent in appearance.	Less than 100 nm (small polydispersity index). These are clear in appearance.

Solubilizing capacity	SEDDS, SMEDDS, SNEDDS have high drug solubilizing capacity.		
Stability of dispersions	Thermodynamically unstable.	Thermodynamically stable	Thermodynamically stable
Formulation technique	Optimization of SEDDS may require the development of ternary phase diagrams.	Pseudo-ternary phase diagrams are required to optimize SMEDDS, whereas the order of mixing of preselected components is not important	Pseudo-ternary phase diagrams are required to optimize SMEDDS, whereas the order of mixing of preselected components is not important
Concentration of oil	SEDDS, SMEDDS, formulations can be prepared as liquids and semi-solids for capsule dosage forms and solid forms for tableting.	The oil concentration in SMEDDS is less than 20%	The oil concentration in SNEDDS should be less as possible.
Surfactant used with HLB	The oil concentration in SEDDS is 40 – 80%	Surfactants of HLB > 12.	Surfactants of HLB > 12.

Drug Selection for SMEDDS:

Lipid based formulation are useful for Biopharmaceutical classification system BCS Class II and IV. Drug lipophilicity (logP) is useful for design of lipidic system. High logP of drug (greater than 4) is desirable. Low melting point and low dose of drug is desirable for formulation of SMEDDS.

Biopharmaceutical aspects of SMEDDS: Mechanism for increase in absorption of drug by SMEDDS:

- **In vivo solubilization of drug** - Presence of lipid in gastrointestinal tract (GIT) stimulates secretion of bile salt and biliary lipid such as phospholipids and cholesterol, leads to formation of intestinal mixed micelles. This causes enhancement in solubilization capacity of GIT. Addition to lipid from formulation causes further increase in solubilization capacity.
- **Increase in gastric residence time of drug** – Lipid in the GIT causes delay in gastric emptying. This enables better dissolution of drug and improves drug absorption.
- **Promotion of intestinal lymphatic transport of drug** – Lipid enhances the lymphatic transport of lipophilic drug and enhances bioavailability via reduction in first pass metabolism.
- **Affecting intestinal permeability** – Lipid can change the physical barrier function of

gut wall. Thus increase in permeability of drug.

- **Reduced metabolism and efflux activity of drug**- Certain surfactant and lipid show reduction in activity of efflux transporters in the gut wall thus increase in absorption of drug. eg. Labrasol, Cremophore EL.

Lipid digestion and drug solubilization in GIT:

Gastric lipase helps in digestion of lipid. Peristalsis and gastric emptying aids in emulsification before it enters in duodenum. In the small intestine pancreatic lipase converts dietary glycerides to diglycerides, monoglycerides and fatty acid. The presence of exogenous lipid in small intestine stimulates secretion of bile salt, phospholipid and cholesterol. This leads to formation of intestinal mixed micelle. It causes increase in drug solubilization.

Circulatory uptake of drug:

Fatty acid and monoglycerides digestion products are resynthesized into triglycerides and assembled into colloidal lipoprotein within endoplasmic reticulum. These lipoproteins are exocytosed across the basolateral membrane of the enterocytes and enter the mesenteric lymph vessel due to their size which causes easy diffusion through vascular endothelium. Highly lipophilic drug therefore access intestinal lymph via association with developing lipoprotein.¹⁵

Advantages of SMEDDS:

1. Improvement in oral bioavailability- SMEDDS present the drug to GIT in solubilized and micro emulsified form and increase in specific surface

area enable more efficient drug transport through the intestine leading to improved bioavailability. Oil phase can work not only as a carrier but also a 'shield' to protect the attack and degradation from enzymes.

P-glycoprotein is a type of combined protein existing in normal cells. It expels the drugs out of the cells as a self-biological defense and can reduce the drugs absorption. A drug incorporated in SMEDDS can inhibit the activity of P-glycoprotein which results in an enhancement of oral absorption.

2. Ease of manufacture and scale-up- SMEDDS require very simple and economical equipments like simple mixer with agitator and volumetric liquid filling equipment.

3. Reduction in inter-subject and intra-subject variability in absorption and food effects- The performance of SMEDDS is independent of food.

4. Ability to deliver peptides that are prone to enzymatic hydrolysis in GIT- SMEDDS deliver peptides, hormones, enzyme substrates and inhibitors and gives protection from enzymatic hydrolysis.

Disadvantages of SMEDDS:

1. *In vitro* model needs further development and validation before its strength can be evaluated.

2. Chemical instabilities of drugs and high % of surfactant may irritate GIT.

3. Co solvents can migrate into the shells of soft or hard gelatin capsules, resulting in the precipitation of drugs.

4. The precipitation tendency of the drug on dilution may be high due to the dilution effect of the hydrophilic solvent.

5. Formulations containing several excipients become more challenging to validate.¹⁶

Excipient for SMEDDS Formulations:

Oils:

Oil solubilizes the hydrophobic drug and aids in self-emulsification. Lipid has a tendency to increase the fraction of drug transported via the intestinal lymphatic system and thus increasing lipophilic drug absorption from the GI tract. The

molecular structure of oil is responsible for emulsification property of oil.¹⁷ **Table 3** gives an idea about commonly used oil in SMEDDS.^{18, 19, 20}

TABLE 3: LIST OF OILS THAT CAN BE USED IN SMEDDS

Class	Examples
Triglyceride vegetable oils-	
1) Triglycerides of long chain fatty acids	Soybean oil, peanut oil, corn oil
2) Triglycerides of medium chain fatty acids	Miglyol 812, Captex 355, Labrafac
Vegetable oils derivatives	
1) Hydrogenated vegetable oil	Hydrogenated cottonseed oil
2) Mixed Partial Glycerides	Capmul MCM
3) Polyoxylglycerides/ Macroglycerides	Labrafil 1944CS, Labrafil M 2125CS, Labrasol, Gelucire 44/14.
4) Ethoxylated glycerides	Cremophor EL, Cremophor RH40, Cremophor RH60.
5) Polyalcohol esters of fatty acids	Plurol Oleique CC497, Capryol, Mirj.
Fatty acids	Oleic acid, Myristic acid, Caprylic acid, Capric acid.
Ethanol ester	Ethyl oleate.

Surfactants:

Surfactants are important components of SMEDDS systems as they are responsible for forming a stable emulsion upon dilution and stabilize the internal phase in an emulsion. A surfactant with an HLB value of more than 12 is necessary in SMEDDS. Surfactants used in lipid based drug delivery are usually polyethoxylated lipid derivatives.¹⁴ Emulsifiers of natural origin are not widely used because of their poor self-emulsification property.²⁰ Nonionic surfactants are less toxic than ionic surfactants and possess good emulsion stability.^{21, 22} Usually the surfactant concentration ranges between 30 and 60% w/w to form stable SMEDDS. Extremely small droplet size produced in case of SMEDDS promotes rapid gastric emptying and low local concentration of surfactant, thereby reducing the gastric irritation.²³ Increase in surfactant concentration causes a decrease in droplet size thus surfactant molecules stabilize at the oil-water interface²⁴ and if surfactant concentration is less then it causes enhanced water penetration into oil droplets leading to breakdown of oil droplets.²⁵

Thus surfactant is also responsible for total solubility of the drug in SMEDDS, preventing drug precipitation upon aqueous dilution and keep the drug in solubilized form in GI tract.²⁴ **Table 4** gives an idea about commonly used surfactants in SMEDDS.

TABLE 4: LIST OF SURFACTANTS THAT CAN BE USED IN SMEDDS

Chemical or Common Name	Trade name	HLB
Polyoxyethylene 20 sorbitan monolaurate	Polysorbate 20	16.7
PEG 1500	lauric glycerides Gelucire 44/14	14
PEG 400 capric/caprylic glycerides	Labrasol	14
Polyoxyethylene 20 sorbitan monooleate	Polysorbate 80	15
Polyoxyl 35 castor oil	CremophorEL	12-14
Polyoxyl 40 hydrogenated castor oil	Cremophor RH40	14-16
Polyoxyl 40 hydrogenated castor oil	Cremophor RH 40	14 -16
Polyoxyl 60 hydrogenated castor oil	Cremophor RH 60	14 – 18
Polyoxyethylene lauryl ether	Brij 35	13.7
Unsaturated polyglycolized glycerides	Labrafil MI 2125, M1944	4
Saturated polyglycolized glycerides	Gelucire44/14, 50/13	13-14
PEG-8 Caprylic/Capric glycerides	Labrasol	14
PEG-8 Caprylic/Capric glycerides	Labrafac®CM10	10
Polyoxyl 40 stearate	Myrij 52	16.9

Co-surfactant:

Co-surfactant is added to lower the interfacial tension between the oil and water phase, fluidize the hydrocarbon region of the interfacial-film, and to influence the film curvature.²⁶ The role of a Co-surfactant is to:

- 1) Increase the fluidity of the interface.
- 2) Destroy liquid crystalline or gel structure which would prevent the formation of micro emulsion.
- 3) Adjust HLB value and spontaneous curvature of the interface by changing surfactant partitioning characteristic.^{27, 28} **Table 5** gives idea about commonly used co-surfactant in SMEDDS.

TABLE 5: LIST OF CO-SURFACTANTS THAT CAN BE USED IN SMEDDS

Co-surfactant
PEG 200,400,600
Propylene glycol
Ethanol
Transcutol P
Lauroglycol FCC
Lutrol E400

Other components:

Other components might be pH adjusters, flavors, and antioxidant agents. Lipid peroxides may be formed due to auto-oxidation, which increases with unsaturation level of the lipid. So lipophilic antioxidants may be required. eg. α -tocopherol, propyl gallate, ascorbyl palmitate or BHT.

Formulation of SMEDDS:

The synthetic hydrophilic oils and surfactants provides good solubility to hydrophobic drugs than conventional vegetable oils. Ethanol, PG and PEG also contribute for the improvement of drug solubility in lipid vehicle.⁹

The following points should be considered in the formulation of a SMEDDS -

Find solubility of the drug in different oil, surfactants and cosurfactant:

Determine solubility by adding excess amount of drug in small vials containing 2 ml of selected oil, surfactant and cosurfactant separately. The drug was mixed with glass rod for 30 min, and then the vials kept for sonication about 2 hours. The vials are tightly stopper and continuously stirred for 72 hours in orbital shaking incubator at 25°C. Then centrifuged at 3500 rpm for 20 min. The 1ml supernatants are separated and dissolve in methanol or alcohol and solubility is quantified by UV-spectrophotometer at specific wavelength after appropriate dilution with methanol or alcohol. But after dilution the solutions are not clear. So oils should be diluted with 66% v/v chloroform in methanol and surfactant should be diluted with 7% v/v chloroform in methanol.²⁹

Select oil, surfactant and co solvent based on the solubility of the drug.

Select ratio of surfactant to cosurfactant:

The emulsifying effect is good if the ratio of the surfactant to the co-surfactant is higher than 1:2.5 but stability properties are inferior at this ratio. Fixing the surfactant/co-surfactant ratio at 1:1 is a better choice for the stability of SMEDDS.³⁰

Construction of Phase Diagram:

Phase diagrams were constructed to obtain the proportion of components that can result in

maximum microemulsion existence area.¹² Chemix software can be used for this. These diagrams were constructed with oil, surfactant/co-surfactant (Smix) and water (pseudo-ternary phase diagram) by using water titration method at room temperature. The procedure consists of preparing solutions of different ratio of surfactant to cosurfactant by weight such as 1:1, 2:1, 3:1 etc. These solutions then vortexed for 5 min and placed at 50°C for 1 hour so that an isotropic mixture can be obtained. Each of these solutions was then used for preparing a mixture containing oil and Smix (mixture of surfactant and co-surfactant) in the following ratios by weight: 1:9, 2:8, 3:7, 4:6, 5:5, 6:4, 7:3, 8:2, 9:1 and after preparation vortexed for 5 min followed by placing in oven at 50°C for 1 hour.

All the mixtures then placed at room temperature for 24 hour. Water from 5% to 95% of the mixture added at 10-15 min interval to each of the mixture under stirring on magnetic stirrer. After each addition the mixtures were observed for their appearance (turbid or clear). Turbidity of the samples would indicate formation of a coarse emulsion^{31, 32} whereas a clear isotropic solution, would indicate the formation of a microemulsion. The formation of microemulsion regions was monitored visually for turbidity–transparency–turbidity.

Preparation of SMEDDS:

From the ternary phase diagram ratio of surfactant to co-surfactant was optimized.¹¹ Then by varying ratio of oil to Smix, different formulations were prepared with and without drug. Formulations were prepared by preparing optimized ratio of Smix first, for this surfactant and co-surfactant were accurately weighed and then vortexed for 5-10 min. After that Smix was placed in oven at 50°C for 1 h. Oil with different ratio was added to Smix then these formulations were vortexed for 5-10 min and placed in oven at 50°C for 1 h so that an isotropic mixture was formed. Drug was loaded to these isotropic formulations at the end and vortexed by vortex shaker until clear solution was obtained.^{31, 32}

Mechanism of self-emulsification:

When the entropy change is greater than the energy required to increase the surface area, then self-

emulsification takes place. Free energy of formation is very low and positive or even negative which results in spontaneous emulsification in case of SMEDDS. For emulsification to take place, it is important for the interfacial structure to no resistance against surface shearing. The interface between the oil and aqueous continuous phases is formed upon addition of a binary mixture (oil/non-ionic surfactant) to water. This is followed by solubilization within the oil phase, as a result of aqueous penetration through the interface. This occur upto the solubilization limit attained close to the interphase. Aqueous penetration will lead to the formation of the dispersed liquid crystal (LC) phase.

Lastly, everything that is near with the interface will be liquid crystal, the actual amount of which depends upon the emulsifier concentration in the binary mixture. Hence, following gentle agitation of the self-emulsifying system, water rapidly penetrates into the aqueous cores leading to interface disruption and droplet formation. This LC phase is considered to be responsible for the high stability of the resulting microemulsion against coalescence.³³

Evaluation of SMEDD:

Thermodynamic stability studies:

Freeze thawing is employed to evaluate the stability of formulations. The formulations are subjected to 3 to 4 freeze -thaw cycles, which include 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.³⁴

Dispersibility test:

The efficiency of self-emulsification SMEDDSs checked using a standard USP dissolution apparatus. 1ml of each formulation added to 500 ml of water 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 using the following grading system: Grade A: Rapidly forming (within 1 min) nanoemulsion, having a clear or bluish appearance. Grade B: Rapidly

forming, slightly less clear emulsion, having a bluish white appearance. Grade C: Fine milky emulsion that is formed within 2 min.

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

Grade E: Formulation, exhibiting either poor or minimal emulsification with large oil globules present on the surface.

Grade A and Grade B formulation will remain as nanoemulsion when dispersed in GIT, while formulation falling in Grade C could be recommend for SMEDDS formulation.³⁵

Turbidimetric evaluation:

Nepheloturbidimetric evaluation is done to monitor the growth of emulsification. Fixed quantity of self emulsifying system is added to fixed quantity of suitable medium (generally 0.1 M HCl) under continuous stirring (50 rpm) on magnetic plate at ambient temperature, and the increase in turbidity is measured using a turbidimeter. However, since the time required for complete emulsification is too short, it is not possible to monitor the rate of change of turbidity.

Droplet Size:

This is a crucial factor in self emulsification performance because it determines the rate and extent of drug release as well as the stability of the emulsion. Photon correlation spectroscopy, microscopic techniques or a Coulter Nanosizer are mainly used for determination of the emulsion droplet size.

Viscosity Measurement:

The Rheological properties of the micro emulsion are evaluated by Brookfield viscometer. This viscosities determination conform whether the system is w/o or o/w. If system has low viscosity then it is o/w type of emulsion and if a high viscosity then it is w/o emulsion.³⁶

Zeta potential measurement:

In conventional SMEDDS, the charge on an oil droplet is negative because of the presence of free fatty acids.³⁷ The SMEDDS diluted with a ratio

1:2500 (v/v) with distilled water and mixed with magnetic stirrer. Zeta-potential of the resulting microemulsion was determined using the Zetasizer (Malvern instrument, Australia).³⁸

In vitro release:

The quantitative *in vitro* release test is performed in 900 ml purified distilled water, which is based on USP XXIV dissolution method. SMEDDS is placed in dialysis bag during the release period to compare the release profile with conventional tablet. 10 ml of sample solution is withdrawn at predetermined time intervals, filtered through a 0.45 μ membrane filter, dilute suitably and analyzed spectrophotometrically. Equal amount of fresh dissolution medium is replaced immediately after withdrawal of the test sample. Percent drug dissolved at different time intervals was calculated using the Beer Lamberts equation.³⁹

Applications:

Improvement in Solubility and bioavailability: SMEDDS have the ability to present the drug to GIT in 1 - 100 nm globule size improves dissolution and bioavailability of drug for which water is a rate limiting step. Because of the fine oil droplets empty rapidly from the stomach and causes wide distribution of the drug through the intestinal tract and thereby reducing irritation due to drugs. SMEDDS enhance the bioavailability enabling reduction in dose of the drug.⁴⁰

Protection against Biodegradation:

Many drugs are degraded in physiological system, may be because of acidic PH in stomach, enzymatic degradation. Such drugs when presented in the form of SMEDDS can be well protected from these degradation processes as liquid crystalline phase might be act as a barrier.

Recent trends in SMEDDS:

- Self-emulsifying sustained/controlled -release tablets.
- Self-emulsifying capsule.
- Self-emulsifying suppositories.
- Self-emulsifying sustained/controlled release pellets.

- Self-emulsifying beads.
 - Self-emulsifying sustained-release microspheres.
 - Positively charged self-emulsifying drug delivery system.
 - Self-double-emulsifying drug delivery system (SDEDDS).
 - Supersaturatable self-emulsifying drug delivery system (S-SEDDS).
 - Self-micro emulsifying floating dosage form.
 - Self-micro emulsifying mouth dissolving films (SMMDF)
- Table 6** gives idea about SEDDS/ SMEDDS/ SNEDDS formulation composition.

TABLE 6: SOME EXAMPLES OF SEDDS/ SMEDDS/ SNEDDS FORMULATION COMPOSITION.

Type	Drug	Formulation composition				Reference
		Oil	Surfactant	Co-surfactant /cosolvent	Surfactant :Co-surfactant	
SNEDDS	celecoxib	capryol 90	Cremophor RH 40	propylene glycol	1.6:1	[41]
SEDDS	Artemether	Peceol	Labrasol	Transcutol	3:1	[42]
SMEDDS	Curcumin	Isopropyl Myristate 20%	Cremophor RH40 60%	Ethanol 20%	3:1	[43]
SNEDDS	Nateglinide	Capmul MCM C-8 20.23%	Cremophor EL 55.77%	Transcutol HP 23%	3:1	[44]
SEDDS	Lornoxicam	Capmul MCM	Tween 20	PEG 400	1:1	[45]
SNEDDS	Atorvastatin	Oleic acid 20%	Tween 80 60%	Brij 20%	3:1	[46]
SNEDDS	Telmisartan	Acrysol 32%	Tween 20 43.33%	Carbitol 23.3%	2:1	[47]
SEDDS	Valsartan	Castor oil	Tween 80	PEG-600	1:1	[48]
SMEDDS	fenofi brate	Labrafac CM10 31.5%	Tween 80 47.3%	PEG 400 12.7%	3.7:1	[49]
SMEDDS	Cefuroxime axetil	Capryol 90	Labrasol	Lutrol E400	2:1	[50]
SMEDDS	Acyclovir	Oleic acid 25%	Tween 80 56.25%	Transcutol 18.75%	3:1	[51]
SMEDDS	Mebendazole	Oleic acid	Tween 80	polypropylene glycol	2:1	[52]
SNEDDS	Rosuvastatin calcium	Capmul MCM 20%	Tween 20 40%	PEG 200 40%	1:1	[13]

CONCLUSION: SMEDDS is used to improve dissolution characteristics of a poorly water soluble drug as it maintains the drug in a solubilized form in the GI tract. SMEDDS enhance the bioavailability enabling reduction of dose of the drug. Thus SMEDDS can be potentially used for delivering a BCS Class II and IV drugs.

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