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SELF–MICROEMULSIFYING DRUG DELIVERY SYSTEM: SPECIAL EMPHASIS ON VARIOUS SURFACTANTS USED IN SMEDDS

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ABSTRACT: The majority of novel chemical entities getting discovered are having low water solubility and it must be addressed to distribute the drug more effectively. SMEDDS, a lipid-based drug delivery approach, is thought to boost oral absorption of less hydrophilic drugs. Surfactants are the major excipients used in SMEDDS as they are responsible for the emulsification process. The two main criteria while choosing a surfactant should be HLB and safety. A high emulsifying property is what the emulsifier employed in SMEDDS formulation is ought to have. The high hydrophilicity and HLB value of a surfactant guarantees instant oil-in-water droplet production and fast dispersion of formulation in aqueous fluids. The most frequently advised and preferred surfactant type used in SMEDDS are non-ionic surfactants with a rather high HLB value. A high concentration of surfactant is required for a stable self – micro-emulsifying drug delivery systems and they usually contain surfactant concentrations in the range of 30% to 60% w/w. Surfactants that are suitable for use in pharmaceuticals include kolliphor RH40, Cremophor® RH40, Polysorbate 80, different grades of glaciers, labrasol, *etc*. This article reviews SMEDDS and their medicinal usage in drug delivery with a focus on numerous surfactants used in SMEDDS.

INTRODUCTION: Given that more than 40% of novel medication candidates are poorly soluble in water, successful oral drug delivery has remained a difficulty. In the drug delivery sector because of the implications of low bioavailability, oral administration is commonly mentioned. Reduction in Particle size (micronization or nanosizing), cyclodextrins complexation, salt formation and solubilization of cosolvents, usage of surfactants, and other methods have all been carefully investigated to elevate the oral bioavailability of such medications.

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Lipid-based formulations have garnered significant attention recently as a means of augmenting the oral bioavailability of medications with low solubility. In reality, the preferred method is to include lipophilic medications in innocuous lipid carriers such as oils, surfactant dispersions, and microemulsion [1]. In actuality, "lipid" formulations represent a wide range of formulations with different characteristics which are the outcomes of combining up to five different excipient classes, ranging from mixed glycerides to pure triglyceride oils, lipophilic surfactants, hydrophilic surfactants, and water-soluble cosolvents [2].

Lately, self-microemulsifying drug delivery systems (SMEDDS) have drawn increased attention, due to the reports that they can help patients take inadequately soluble medications by reducing the inherent restriction of slow and

incomplete dissolution and also by facilitating the formation of a microemulsion in the intestine that can keep otherwise poorly soluble medications in solution. SMEDDS are isotropic blends of hydrophilic cosolvents/co-surfactants, solid or liquid surfactants, and natural/synthetic oils that have the special capacity to create an oil-in-water (o/w) fine microemulsions after gentle agitation and dilution in aqueous media, such as GI fluids [3].

Importance of SMEDDS [4, 5]: SMEDDS's benefits include an increase in oral bioavailability through improved solubility and drug transport.

1. Ease of production compared to other lipid dosage formulations; easy to scale up.
2. Reduction of intra- and inter-subject variability as well as dietary influences.
3. The ability to distribute peptides in the GIT that are susceptible to enzyme hydrolysis.
4. Unlike other drug delivery systems, SMEDDS do notaffect the lipid digestion process.
5. When a precipitation inhibitor polymer is added to the composition of SMEDDS, the medication is released over a longer period.

Improvement of Oral Absorption by SMEDDS: The medicinal molecule is released from SMEDDS after partitioning into the intestinal fluids along the GI tract, by droplet breakdown and transportation.

Having a Small particle size along with the resulting oil droplet's polarity were said to be the two main parameters that govern how effectively the therapeutic ingredient is released from SMEDDS and in o/w microemulsions the polarity of the oil droplets, however, has no impact because the medicinal component enters the capillaries.

Mechanism of Self-Emulsification [6, 7]: It has been proposed that self-emulsification occurs when the dispersion-promoting entropy shift is more than the energy needed to expand the dispersion's surface area. The energy needed to produce a new interface between the oil and water phases directly determines the free energy of a standard emulsion formulation. Over time, the emulsion's two phases have a tendency to separate, reducing the system's free energy and interfacial area. The traditional emulsifying ingredient lowers the interfacial energy and creates a barrier to coalescence around the emulsion droplets to stabilize the emulsion produced by aqueous dilution.

Previous research has proposed a possible correlation between the ease of emulsification and the ease of water penetration into the different Liquid crystalline or gel phases that develop on the droplet surface. Water is added to a binary mixture (oil and non-ionic surfactant) and this causes the oil and aqueous-continuous phases to create an interface. Water is then solubilized within the oil phase as a result of aqueous penetration *via* the interface. This will continue until the solubilization limit near the interface is reached.

Subsequent aqueous penetration will cause the scattered Liquid crystalline phase to develop. The actual amount of Liquid crystals that eventually form near the interface will depend on the concentration of surfactant in the binary mixture as the aqueous penetration continues.

Once created, interface rupture and droplet formation are brought about by the fast penetration of water into the aqueous cores, which is facilitated by the mild agitation of the self-emulsification process.

These self-emulsified systems are thought to be highly stable to coalescence because of the Liquid crystalline interface that envelops the oil droplets.

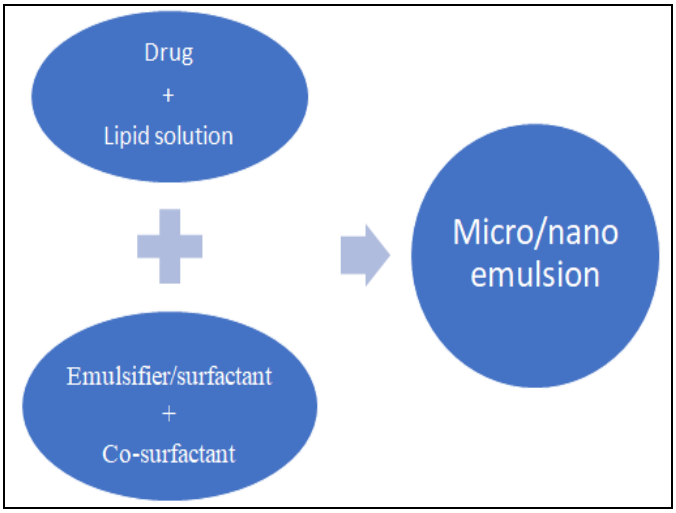

FIG. 1: DIAGRAMMATIC FLOWCHART ILLUSTRATING THE GENERAL APPROACH FOR CREATING SELF-EMULSIFYING SYSTEMS AND TURNING THEM INTO MICRO/NANOEMULSIONS

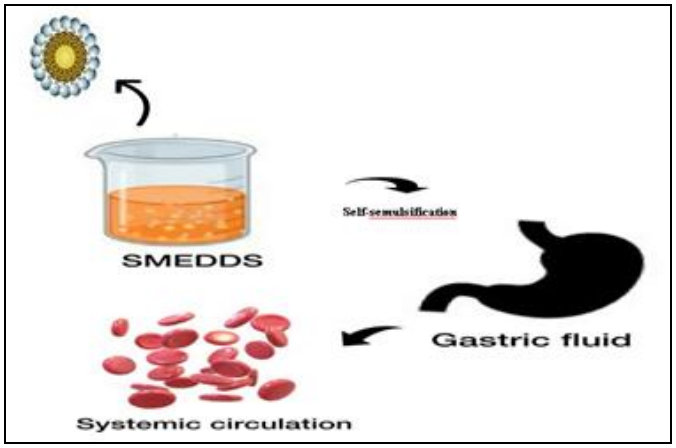

FIG. 2: DIAGRAMATIC REPRESENTATION OF SELF-EMULSIFICATION PROCESS INSIDE THE BODY

Components of SMEDDS:

API: The BCS classification system primarily recognizes four categories, with BCS class II medicines having low permeability and high solubility, hence these classes are used in the SMEDDS preparation. Unless they exhibit significant solubility any one component in SMEDDS medicines with any dosage is typically not a good choice for the system. Additionally, medications shouldn't have log P values that are close to 5 [8].

Oils: A triglyceride is an ester in which the glycerol is joined to three fatty acid molecules. Triglycerides can be entirely absorbed and digested following oral delivery, which reduces the potential for adverse effects on future pharmacological development. The majority of the triglycerides currently used and approved by the US Food and Drug Administration (FDA) come from plants. Triglycerides can be classified as medium-chain (MCT) or long-chain (LCT) triglycerides based on the length of the fatty acid chain. In general, MCT is the preferred oil phase for creating lipid formulations because it is thought to have less oxidative damage and a higher solvent capacity than LCT [8].

Co-solvents: A successful SMEDDS formulation often calls for high surfactant concentrations (up to 50%), and the addition of co-surfactants promotes self-emulsification. In order to increase drug loading to SMEDDS, fluidize the hydrocarbon component of the interfacial layer, decrease the oil-water interfacial tension, and enable spontaneous microemulsion formation, co-surfactants with HLB values of 10 to 14 are typically utilized with surfactants. Therefore, amphiphilic solubilizers and or surfactants (hydrophilic or lipophilic) are employed in this process [9].

Co-surfactant: Micro-emulsion production from SMEDDS is dynamic, and its equilibrium is maintained by the continual exchange of substances/molecules between scattered phases. Water exchange between bound and free states, co-surfactant exchange from the interfacial film to continuous and dispersed phases, and surfactant exchange between the interfacial film and water are all included in the dynamic process [9].

Bio-surfactants: Surfactants have varying concentrations, which decrease the medication availability at the site of absorption, they may have an impact on the therapeutic efficacy of the drug moiety. It may potentially cause toxicity at different concentrations, but this can be avoided by using biosurfactants instead of conventional surfactants. Biosurfactants improve safety and reduce the toxicity that is related to surfactant-induced gastrointestinal irritation.

Biosurfactants are classified into two classes depending on their chemical structures, lipopeptides and glycolipids. Microemulsions generated with biosurfactants are stable thermodynamically, and their isotropic systems are thought to be particularly promising in the development of DDS [10].

Surfactants: The term surfactant is an abbreviation for surface active agents, which have both hydrophilicity and hydrophobicity, and it implies the surface-active nature of certain kinds of chemicals and their proclivity to adsorb at surfaces. A polar component is known as a hydrophobic part or lipophile because it is attracted to oil, and the polar component is known as the hydrophilic part or hydrophile because it has a strong affinity or attraction to polar solvents [11].

Surfactants play a significant role in a variety of industrial processes, including those involving lubricants, foaming and wetting agents, corrosion inhibitors, antistatic agents, and viscosity modifiers. In recent times, there has been a significant push to develop a wide range of beneficial products, including detergents, soaps,

emulsifiers, disinfectants, and dispersants, with a focus on functional and structural diversity [12]. The minimal surfactant concentration at which micelles form is known as the "critical micelle concentration" (CMC), and it is one of the most essential chemical-physical parameters to measure for these amphiphilic compounds [13].

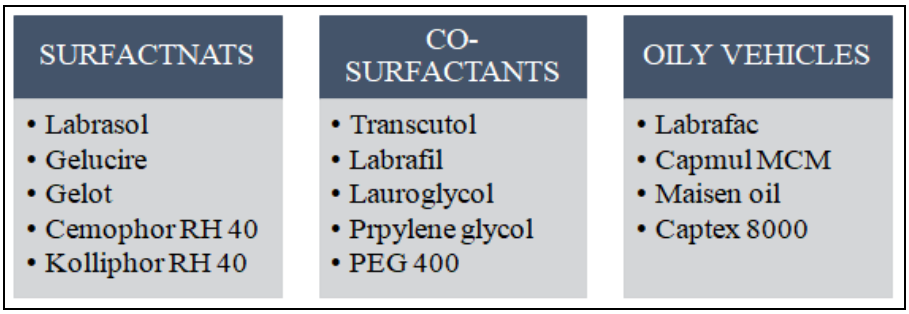

FIG. 3: LIST OF VARIOUS EXCIPIENTS USED IN SMEDDS

Principle for Use of Surfactants: In the ternary systems such as microemulsions, the surface-active agent molecules could form a monolayer at the oil-water interface, with a hydrophobic tail of the surface-active agent molecules dissolved in the oil section, and thus the hydrophilic head teams in the liquid section. Self-assembled structures of many forms, including (inverted) spherical micelles and cylindrical micelles, lamellar phases, and bi-continuous microemulsions, will form in binary systems (water/surfactant or oil/surfactant), just as in those systems, with oil or liquid phases predominating.

The three primary elements determining transcutaneous permeation are drug within the vehicle, drug release from the vehicle, and drug permeation into the skin. These variables affect the drug itself or the thermodynamic activity that powers the medicine [14]. The size of the droplets is not significantly influenced by the type of surfactant, although microemulsions including co-surfactant have the largest droplets and maximum viscosity. Particle size will likewise rise proportionately with an increase in the oil phase ratio.

The addition of surfactants to these systems is known to induce the interfacial film to stabilize and condense, whereas the addition of the co-surfactants causes the film to expand. As a result, the globule size is affected differently depending on the relative proportion of the surfactant to that of the co-surfactant. Additionally, it has been suggested that the emulsion globules with lower particle size may promote faster absorption and increased bioavailability [15].

TABLE 1: AN ILLUSTRATION OF HOW SURFACTANTS ARE EMPLOYED IN COMMERCIAL FORMULATIONS

Tween 80 (Polysorbate 80).	Hard gelatin capsules by Gengraf
Tween 20 (Polysorbate 20)	Soft gelatin capsules for Targretin
Span 80 (sorbitan monooleate).	Hard gelatin capsules by Gengraf
(Cremophor RH40) Polyoxy-35 castor oil	Ritonavir soft gelatin pills, Nerol soft gelatin capsules,
Castor oil with a polyoxy-35 hydrogenation (Cremophor RH40)	Ritonavir soft gelatin pills, Nerol soft gelatin capsules,

Physicochemical Properties of Surfactants: A fundamental characteristic of surface active agents is their propensity for aggregating into micelles, or to put it in another way, the tendency for molecules with both polar and non-polar areas to aggregate into micelles in aqueous solutions but the Polar heads in a micelle form an outer shell when it comes in contact with water, whereas the non-polar tails are restricted to the core. The concentration at which the micelles start to form is known as the critical micelle concentration (CMC). This phenomenon is significant because of the surfactant molecules where they exhibit drastically diverse behaviors based on whether they are present as free monomers or micelles.

The solubility of the organic hydrocarbons and oils in aqueous solutions as well as viscosity, a critical property, are both influenced by the micelles [16].

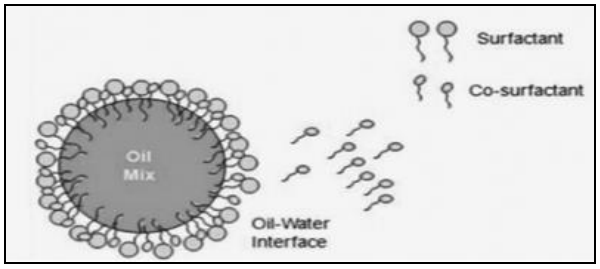

FIG. 4: THE STABILIZING EFFECT OF THE SURFACTANT AND CO-SURFACTANT ON THE O/W INTERFACE

Types of Surfactants (Classes) [17]:

Nonionic Surfactants: They are usually hydrophilic, whereas nonionic surfactants can be either way depending on how the hydrophilic and lipophilic groups are balanced. Stated differently, the solubility of nonionic surfactants is determined by the ratio of the hydrophilic group's ability to attract water to that of the lipophilic group's ability to attract oil. The hydrophilic-lipophilic balance (HLB) is a metric that measures this relative balance. Griffin proposed HLB first and other formulas for calculating HLB have since been published. HLB reveals the properties of nonionic surfactants, it is frequently used as a surfactant selection indicator for particular uses, like cleansers or emulsifiers. HLB can, however, be used as a guide when choosing a surfactant for a particular application because it is merely a signal based on experience however, this is insufficient in the formulation development, which can lead to numerous issues and knowing the properties of surfactants quickly and effectively is critical in formulation creation. In addition to the HLB, there are two indicators that show these features subjectively, the cloud point for nonionic surfactants and the Krafft point for ionic surfactants [18].

Anionic Surfactants: The particle's surface dynamic segment is negatively charged. The most often used class of surfactants in mechanical applications is anionic. They are used in virtually every type of cleanser due to how simple they can assemble.

Examples: Laurate sodium $CH_3(CH_2)_{10}COO$

Sodium dodecylbenzenesulfonate $CH_3(CH_2)_{11}C_6H_4SO_3Na$.

Cationic Surfactants: Alkyl halides and the primary, secondary, or tertiary fatty amines can react to create cationic surfactants. Because the water-soluble portion of the molecule is negatively charged and the water-insoluble portion is positively charged, this substance is referred to as a cationic surface-active agent in this instance. Surface tension with cationic surface-active substances in acid media are employed as a wetting agent. However, when incorporated into an alkaline solution, such as quaternary ammonium salts, cationic surface-active agents have no detergent function [19]. Cremophor® EL, Cremophor® RH40, Cremophor® RH60, polysorbate 80, various grades of gelucires, *etc*. are surfactants that are approved for use in pharmaceuticals.

TABLE 2: LIST OF VARIOUS SURFACTANTS AVAILABLE COMMERCIALLY

Name	Description
Emulcire™ 61 WL 2659	Mixture of Cetylalcohol and eteth-20/Steareth-20
Gelot™ 64	Mixture of glycerol monostearate and PEG-75 stearate (type I)
Transcutol® HP	Highly purified diethylene glycol monoethyl ether
Gelucire® 44/14	Lauroyl macrogol-32 glycerides Lauroyl polyoxyl-32glyceridesLauroylmacrogolglycerides (32)
Labrafil® M 1944 CS	Oleoyl macrogol-6 glycerides, Oleoyl polyoxyl-6 glycerides
Labrasol®	Caprylocaproyl macrogol-8 glycerides, Carlocaproyl polyoxyl-8 glycerides
Labrasol® ALF	Caprylocaproyl macrogol-8 glycerides, Caprylocaproyl polyoxyl-8 glycerides
LauroglycolT™ 90	Propyleneglycolmonolaurate (Type I)
Ovucire® WL 3264	Mixture of Hard fat with additives
Plurol® Diisostearique	Triglyceroldiisostearate Polyglyceryl-3 diisostearate
Sedefos™ 75	Mixture of tricetearеth-4 phosphate and ethylene glycol stearate (and) diethylene glycol stearate
Tefose® 1500	Mixture of PEG-6 stearate (type I) and PEG-32 stearate (type I)

Surfactants Suitable for SMEDDS [20, 21]:

Labrafil: Oleoyl polyoxyl-6 glycerides known as labrafilis a liquid emulsifier having HLB value of 9. It is a nonionic water-dispersible surfactant for lipid-based formulations to solubilize and increase the oral bioavailability of poorly water-soluble APIs. Labrafil can self-emulsify in aqueous media forming a coarse dispersion, *i.e*., emulsion

(SEDDS) & as a Co-emulsifier in topical formulations to improve the stability of emulsions.

Labrasol: Caprylocaproyl Polyoxyl-8 glycerides known as labrasol is a nonionic oil-in-water surfactant used as solubilizer in topical formulations having an HLB value of 12. It is a Solubilizer and skin penetration enhancerin O/W surfactant for microemulsion.

Gelot 64: Gelot 64 is a Glyceryl monostearate Polyoxylethylene stearates that has an HLB range of 10. It is a nonionic oil-in-water emulsifier for topical emulsions. It provides excellent emulsion stability with difficult-to-formulate and combination APIs. Provides heat stability and high tolerance over a wide pH range.

Transcutol p: It is a high-purity solvent and powerful solubilizer associated with skin penetration enhancement in topical dosage forms. Transcutolis a Diethylene glycol monoethyl ether produced by the condensation of ethylene oxide and ethanol by distillation.

It consists of an ether and has an alcohol function which is the reason for its exceptional solubilizing capacity as a solvent.

Gelucire: There are various hydrophilic grades of gelucire such as 50/13, 44/14, 48/16, 55/18, 35/10, 48/09.

Gelucire 44/14: It is a lauroyl peg-32 glycerides and Consists of a small fraction of mono, di- and triglycerides and mainly PEG-32 (MW 1500) mono- and diesters of lauric acid (C12).

Gelucire 48/16: It is a PEG-32 STEARATE Consists of PEG-32 (MW 1500) esters of palmitic (C16) and stearic (C18) acids.

Lauroglycol FCC: Lauroglycol FCC is a Propylene glycol monolaurate that consists of propylene glycol mono- and di-esters of lauric (C12) acid and has an HLB value of 5.

It is a Solubilizer for poorly soluble APIs and a bioavailability enhancer and it can be a Co-surfactant in LFCS Type II (SEDDS) and Type III (SMEDDS) formulations.

Cremophor RH 40: Cremophor RH 40 is a PEG-40 hydrogenated castor which is a non-ionic solubilizers and emulsifying agents that is obtained by reacting hydrogenated castor oil with ethylene oxide. The main constituents of this product are glyceryl polyethylene glycol oxy stearate, which together with fatty acid glyceryl polyglyceryl esters, form the hydrophobic part of the product.

Kolliphor RH 40: Kolliphor RH 40 is a nonionic solubilizer and emulsifying agent obtained by reacting1 mole of hydrogenated castor oil with 40 moles of ethylene oxide.

The main constituent of Kolliphor RH 40 is glycerol polyethylene glycol hydroxystearate, which, together with fatty acid glycerol polyglycol esters, forms the hydrophobic part of the product. The hydrophilic part consists of polyethylene glycols and glycerol ethox.

Lansurf SMO: It is an Amber coloured viscous liquid composed of Sorbitan mono oleate having a HLB value of 4.3.

Lansurf SMO can be used singularly or in combination with ester ethoxylates such as Lansurf SMO80.Lansurf SMO is an excellent emulsifier for emulsion polymerization for systems such as Acrylamide.

TABLE 3: CHARACTERISTICS OF SURFACTANTS

S. no.	Name	Physical nature	Melting point (ºC)	HLB
1	Gelucire 44/14	Waxy solid	42.5-47.5	11
2	labrasol	Liquid	80-110(20)	12
3	Lauroglycol 90	Liquid	-	3
4	Lauroglycol FCC	Liquid	-	5
5	Gelucire 48/16	pellets	46-50	12
6	Transcutol	Liquid	196-200	Not applicable
7	Gelot 64	Pellets	55.5-62.5	10
8	Labrafil M 1944 CS	Liquid	-	9

Surfactants Used for Various Drugs:

TABLE 4: SURFACTANTS UTILIZED IN FORMULATING DIFFERENT DRUGS

S. no.	Formulation	Author	Drug	Name of Surfactant Used	Route of Administration	Ref.
1	Supersaturable SMEDDS of Telmisartan	Sun-young Park, *et al.*	Telmisartan	Cremophor	Oral route	22
2	SNEDDS loaded with Lipophenol	Maxime Vincent, *et al.*	Lipophenol	Labrasol	Oral route	23
3	Supersaturable SMEDDS tablets of Astaxanthin	Wai thet Aung, *et al.*	Astaxanthin	Kolliphor RH 40	Oral route	24
4	Lovastatin solid SMEDDS &liquisolid formulation	Dinesh suram, Kishan Veera Brahma	Lovastatin	Labrasol	Oral route	25
5	SNEDDS of Resveratrol	Shadab Md, *et al.*	Resveratrol	Cremophor RH	Oral route	26
6	SNEDDS tablets of Sertraline	Anroop B nair, *et al.*	Sertraline	Tween 80	Oral route	27
7	Solid SNEDDS of Quetiapine fumarate	Prateek uttreja, *et al.*	Quetiapine fumarate	Gelucire 48/16	Oral route	28
8	SMEDDS OF Sertraline hydrochloride	Sanjay Sharma, *et al.*	Sertraline hydrochloride	Tween 80	Oral route	29
9	Solid SMEDDS of Agomelatine	Priyanka tomar, *et al.*	Agomelatine	Kolliphor EL	Oral route	30
10	SNEDDS of repaglinide	Pathuri Raghuveer, a. prameela rani	repaglinide	Cremophor RH 40	Oral route	31
11	Solid supersaturable SMEDDS of canagliflozin	Dilpreet singh,amrit pal singh,etal.	canagliflozin	Lauroglycol FCC	Oral route	32
12	Supersaturable SMEDDS of benzimidazole	Annalisa rosso, eyadalmouazen, *et al*.	Benzimidazole	Kolliphor RH40	Oral route	33
13	Solid SNEDDS of dabigatran	Sanke manasa, k. anievijetha	dabigatran	Labrasol ALF	Oral route	34
14	SMEDDS of Raloxifene	Muhhamad Mohsin Ansari, *et al.*	Raloxifene	Tween 80/labrasol ALF	Oral route	35
15	S-SNEDDS of glimepiride	Abdul barimohd, krishnasanka, *et al.*	glimepiride	Tween 80	Oral route	36
16	Ultra fine solid Supersaturated bio-SNEDDS of linagliptin	Hend mohammed Mansour, *et al.*	Linagliptin	Cremphor CO 40	Oral route	37
17	SMEDDS of venlafaxine HCI	Sanjeevani Shekhar deshkar, *et al.*	venlafaxine HCI	Tween 20	Oral route	38

CONCLUSION: The novel drug delivery system claims that SMEDDS is a potential technique for the formulation of medicinal compounds with a poor aqueous solubility. SMEDDS, which have been demonstrated to have significantly improve the oral bioavailability, which can enable the oral delivery of hydrophobic medicines that are part of BCS Class II as a result, the dose of the drug can be decreased .A surfactant is necessary for SMEDDS, the main technique for making microemulsions, to acquire self-emulsification property and be effective in solubilizing hydrophobic medicines, the disintegration rate can be raised as a result. Oleates, polysorbates, polyoxyls, and other nonionic surfactants provide less toxicity than ionic surfactants, making them more frequently used in the development of SMEDDS. This study therefore focused on the foundations of the SMEDDS and other surfactants used in lipid-based drug delivery systems, as well as their interaction with the Surfactants used in line with the various administration routes.

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CONFLICTS OF INTEREST: Nil

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