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SELF-MICROEMULSIFYING DRUG DELIVERY SYSTEM: SPECIAL EMPHASIS ON VARIOUS OILS USED IN SMEDDS

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ABSTRACT: In pharmaceuticals formulation, poorly aqueous soluble medications are becoming more difficult to administer into dosage form as 40-50% of new chemical entities discovered are reported to be poorly aqueous soluble, preventing appropriate absorption from the GI tract. Oral administration is preferred over other forms of administration due to its ease of administration & painless approach. The main problem in the oral dosage form is poor bioavailability due to aqueous solubility. As a result, formulation scientists are employing several ways to improve the absorption and bioavailability of poorly aqueous soluble medication, which is difficult. The different strategies used are nano-suspensions, complexation, pH modification, solid dispersion, liposome, solid lipid nanoparticle (SLN), Self-Emulsifying Drug Delivery systems (SMEDDS) and other techniques are used. In the last few decades, pharmaceutical research has been highly diversified for self-emulsifying systems: from micrometer to nanometer size. Therefore, (SMEDDS) has gained much attention as it requires a minimum dose, and the API can be protected into the hostile environment in the gut. It also forms the droplet size <100 nm. This article aims to review (SMEDDS) and their pharmaceutical application in drug delivery, with special emphasis on various oils, used.

INTRODUCTION: As much as 40% of new chemical entities discovered are poorly water soluble, resulting in low bioavailability. So for the therapeutic drug delivery of those drugs in recent years, SMEDDS is considered reliable. In 1943 T. P. Hoar & J. H. Shulman chemistry professors at Cambridge University, coined the term microemulsion [1]. Oral administration is the most favored and convenient route, although it has drawbacks as poor solubility and bioavailability of medication as well as quick metabolism and a lack of consistent blood plasma level [2].

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SMEDDS are mixtures of oil, surfactant, co. surfactant & co-solvents that forms isotropic mixture. When SMEDDS is administered orally upon mild agitation it undergoes spontaneous emulsification & forms a fine O/W emulsion. Where this emulsified oil stimulates digestive juices secretion, and bile salts further emulsify drug-containing oil droplets. Lipases, which are released by the secretion gland, stomach mucosa, pancreas, metabolise the lipid droplets, which further hydrolyze the oil (triglycerides) into mono/di glycerides & free fatty acids. Upon further solubilization of these molecules during GIT passage, emulsion droplets, vesicular structure, and micelles containing phospholipids and cholesterol are formed [3].

Advantages:

1. It improves the oral bioavailability of poorly soluble drugs while lowering the drug dose.

2. It reduces the irritation caused by the prolonged contact between the drug & wall of GIT.
3. SMEDDS protect the drugs from the hostile environment in the GI tract.
4. Excipients utilized in SMEDDS primarily have an inhibitory effect on outflow transporters, leading to the increase in the bioavailability of the drug. *E.g.* - tween-80, spans, cremophor (EL & RH) [1].
5. It delivers protein delivery that is prone to enzymatic hydrolysis in the GIT.
6. It reduces variability, including food effects.

Types of Self Emulsifying Systems: These are of the following types: Self-emulsifying System, Self-micro emulsifying Systems, Self-nano emulsifying Systems (SEDDS, SMEDDS and SNEDDS). These are stable isotropic mixture of (natural/synthetic) oil, (solid /liquid) surfactant & co. surfactant that forms the fine O/W emulsion, micro-emulsion, and nano-emulsion, respectively, when introduced to aqueous medium under gentle agitation. As a result, these formulations dispersed easily into the GIT, where the stomach's motility provides the essential agitation for self-emulsification.

SEDDS are the thermodynamically unstable (in aqueous or physiological conditions) simple binary composition of (lipophilic phase & drug) or (lipophilic phase, surfactant & drug). SEDDS formulations provide lipid droplets 200 nm- 5 um, providing a larger surface area for absorption. Dispersion appears turbid, and the development of SEDDS is mainly done using a ternary phase diagram. The surfactant used in SEDDS has an HLB value below 12. SMEDDS needs the use of a co-surfactant to create a microemulsion and is defined as the isotropic mixture if the oil, surfactant & co. surfactant, which forms O/W emulsion upon gentle agitation and forms the size of the droplets in between 100-300 nm. This droplet provides a larger surface area for the absorption of the drugs. Formed dispersion has an appearance that is optically clear to translucent and the development is mainly done by using the pseudo ternary phase diagram. The surfactant used in SEDDS has an HLB value above 12 [4]. SNEDDS are an isotropous mixture of oil, surfactant &co. surfactant which forms O/W emulsion with gentle agitation and forms droplets smaller than 50 nm. SNEDDS involves the digestion of the excipients, which form nanodroplets. Due to decreased interfacial tension, these droplets produced larger surface areas, which are available for the absorption of poorly aqueous soluble drugs. Research also reveals that SNEDDS facilitates transcellular and Paracellular absorption; thereby, the drug is absorbed through the lymphatics *via* chylomicron synthesis of components of the oil phase of the emulsion, thus inhibiting the first pass metabolism of the drug. Besides that, SMEDDS/SEDDS require higher conc. of the surfactant, while SNEDDS requires the (3-10%) of the surfactant, which having HLB value above 12 [5, 6].

Lipid-Based Formulation Classification System: The lipid-based formulation system was proposed by Pouton in 2000 and newly revised in 2006 to distinguish the formulation with similar components due to a large number of excipients combinations. The different lipid drug delivery systems include lipid emulsion, lipid solution, lipid microemulsion, *etc*. The LFCS divided lipid-based formulation into four main key components based on their composition, dilution effect, and digesting ability to prevent drug precipitation [7].

Type I: This system consists of formulations comprising drugs in triglycerides or mixed glycerides solution or in oil water emulsion, which are further stabilized by low emulsifiers as 1% w/v polysorbate 60 and 1.2% w/v lecithin. This system possesses a coarse dispersion particle. This approach generally has poor initial aqueous dispersion, which requires digestion in GIT by pancreatic lipase/co-lipase for more amphiphilic lipid digestion products. Then the transfer of the drug into the colloidal aqueous phase is promoted. This system is represented for the formulation of potent and highly lipophilic drugs where the drug solubility in oil is sufficient for incorporating the required dose [8].

Type II: This lipid formulation system is a non-water soluble component system. Self-emulsification is achieved in this system at a surfactant concentration of above 20-25% w/w, but higher surfactant content of 50-60% w/w results in the formation of viscous liquid crystalline gels at oil/water interface. The type II approach can

overcome the slow dissolution step typically observed with solid dosage forms.

Type III: SMEDDS is a lipid-based formulation characterized by the presence of hydrophilic surfactant having HLB>12 and co-solvent such as PEG. These systems are additionally apart as type III A and type III B formulations to know specific hydrophilic systems. In contrast, III B content of hydrophilic surfactant & co-surfactant increases, and lipid content decreases.

Type IV: System is recently added to LFCS which excludes natural lipid from the formulation and represents hydrophilic formulation. Due to the maximum solvability of medicament in surfactant and co-solvent, the drug payload is increased in these formulations. These systems produce very fine dispersion in aqueous media compared to simple glycerides containing formulation [4].

Self-emulsification Mechanism: The actual mechanism of SMEDDS is still not well understood. However, some scientists believe that when the entropy increases, the energy necessary to raise the surface area is greater than the energy required to raise the dispersion's surface area [9]. Furthermore, the traditional surface free energy is proportional to the energy necessary to build a new surface between the two phases, which is given by the following equation:

$$\Delta G = \Sigma N\pi r2\sigma$$

Where:

ΔG = free associated with the method (ignoring the free energy of the mixing)

N = no. of droplets with the radius 'r'

σ = interfacial energy associated with the process.

With time, the 2 phases of the emulsion can tend to separate to decrease the interfacial energy and, consequently, free energy related to the method. Thus, the emulsion from the aqueous dilution is stabilized by the emulsifying agent. This agent's form monolayer of the emulsion droplets lowers the interfacial energy and functions as a barrier to prevent coalescence [10].

Composition of SMEDDS:

1. **API:** According to the BCS classification system, there are mainly four types; among them, BCS grade II drugs have low solubility and high permeability. Therefore, these classes are employed in the preparation of the SMEDDS. Mainly drugs having dose are aren't an appropriate candidate for SMEDDS unless they are showing high solubility into one of the components of the SMEDDS. Also, drugs should not have a log P value near about 2. BCS grade II Examples: ketoconazole, glibenclamide, cyclosporine-A, Itraconazole *etc*.

2. **Lipids (Oils):** Because the kind and concentration of oil employed in formulation affect Solubilisation and access to a lymphatic circulation of poorly water-soluble drugs, oil is a significant component of SMEDDS. The selection of oil regulatory guidelines should be considered depending on the route of administration.

3. **Surfactant:** Mainly to adopt the self-emulsification process by SMEDDS, the surfactant must be added, which is the primary technique for forming microemulsion and solubilizing hydrophobic drug, which improves the amount of dissolution of the drug. A surfactant is an amphiphilic substance with both hydrophilic (polar) and lipophilic (non-polar) groups. By selecting a suitable surfactant, low ultra-tension at the oil-water interface can be attained. The surfactant is chosen based on the following criteria:

a) The selection of surfactant depends on the HLB value; the surfactant having high HLB forms the O/W microemulsion.

b) Potency and quickness to micro emulsify the selected oil.

c) Type of emulsion to be formulated.

d) Safety (depends upon the route of administration).

e) Solubilizing capacity of the drug.

f) Ability to inhibit p-gp (if API is p-gp substrate) which leads to improving the oral biological availability of the medication that are p-gp substrate transporters due to which surfactant

gained so much attention to be used in Smedds [11].

Also, surfactants also helpful for the enhancement of the permeability of as it disrupt the intestinal cell membrane which is comprised of the lipid [12]. Surfactant also enhances the permeability by opening the tight junctions; and the permeability of the drug was increased with surfactant labrasol the permeability of the drug was increased & observed with surfactant labrasol due to opening of tight junctions [13]. Utility range of surfactants used in the Smedds is about 30-60%, but using too much (% of the surfactant) causes GI irritation due to tissue damage also reduces self-emulsification effectiveness.

TABLE 1: COMMONLY USED POLYOXYETHYLENE SURFACTANTS

Chemical name	Commercial name	HLB
POE Sorbitanmonolaurate	Tween 20	17
POE Sorbitanmonopalmitate	Tween 40	15.6
POE Sorbitanmonostearate	Tween 60	15.0
POE Sorbitanmonooleate	Tween 80	15.0
POE glycerol trioleate	Tagat TO	11.5
POE-40-Hydrogenated castor oil	Cremophor RH 40 (solid)	14.0-16.0
POE-35-Castor oil	Cremophor EL (liquid)	12.0-14.0

4. Co-surfactant: Along with required conc. of surfactant (>30%) co-surfactant aids into self-emulsification. The co-surfactant's presence decreases the interface's bending stress, which provides flexibility to form a microemulsion. If nonionic surfactant is used into SMEDDS, then co. surfactant is not used. Both surfactant & co. surfactant are to be used into SMEDDS not only for formulation but also for the solubilization of drugs into SMEDDS. Some of the organic solvents such as (propylene glycol) PG, (polyethylene glycol) PEG, ethanol also Transcutol P is helpful to dissolve the large amounts of drug / hydrophilic surfactants into the lipid base and acts as co. surfactant. Due to the partitioning of co-surfactant into aqueous phase, a higher concentration of co. surfactant resulted in drug precipitation.

Oils used in SMEDDS: In SMEDDS, oil is primarily utilized to solubilize the hydrophobic /lipophilic drug to increase the bioavailability of the drug. Lipids are naturally occurring oil /fats composed of triglycerides and fatty acids of varying chain lengths of the degree of unsaturation. The oil choice is critical in SMEDDS because it controls the amount of the drug that dissolves in the system [14]. Generally, lipids are classified based on their structure, polarity, degree of interaction with water. The lipid's polarity highly influences the drug's release as lipid having higher polarity indicates quick release of the drug into the aqueous state. According to a study, the rate of idebenone release from SMEDDS formulation is determined by the polarity of the oil used in the formulation, with the highest polarity with (labrafil 2609 HLB > 4) [15]. In SMEDDS, a lipoid molecule with highhydrophobic portion is preferred in the SMEDDS as it maximizes amount of the drug that can be solubilized in SMEDDS compared to the hydrophilic portion. The lipid a part of the SMEDDS, mainly creates the basis of the emulsion particle which are composed of the non-polar/polar lipids according to the Class-I lipid classification system [16]. The most common lipid excipient used in the SMEDDS is triglycerides vegetable oils derivative because they are safe, fully digested, and absorbed [17].

Triglycerides are mainly divided into long chain triglycerides **(**LCT), and medium chain triglycerides (MCT). The solvent capacity is mostly determined by the effective concentration of the ester groups [16]. The emulsion's stability mainly depends upon the rheological behavior of the oils as non-digestible lipids (mineral oil), e.g., liquid paraffin & sucrose polyesters, mainly remain unabsorbed into the intestinal lumen and reduce the absorption of the drug by retaining a certain amount of co. administered drug. Triglycerides, diglycerides, fatty acids, phospholipids, cholesterol, and other lipid-based synthetic derivatives improve the drug's bioavailability. Edible oils derived from natural sources are favored, but they do not possess the high solubilization property for the lipophilic drug and also do not have the sufficient capacity for self-emulsification, and also possess a large

molecular volume. As a result, instead of edible oils mostly hydrolyzed or modified vegetable oils are employed because they have better self-emulsification.

Various Types of Oils used are:

Fixed Oils (Long-chain Triglycerides): Soybean oil, arachis oil, cottonseed oil, maize (corn) oil, hydrolyzed corn oil, olive oil, sesame oil, sunflower oil, palm oil, peanut oil, triolein *etc*.

Medium-chain Triglycerides and Related Esters: Caprylic/capric triglycerides (Akomed E, Akomed R, Miglyol 810 and Captex 355, Crodamol GTCC), fractionated coconut oil (Miglyol 812), Captex 300, Labrafac CC, Triacetin.

Medium-chain Mono and Di-glycerides: Mono and diglycerides of capric/caprylic acid. (Capmul MCM and Imwitor).

Long-chain Mono Glycerides: Glyceryl-monooleate (Peceol, Capmul GMO), glyceryl mono linoleate (Maisine -35).

Propylene Glycol (PG) Fatty Acid Esters: PG Diester of caprylic/capric acid (Labrafac PG), PG monocaprylic ester (Sefsol-218), PG monolaurate (Lauroglycol FCC, Lauroglycol 90, Capmul PG-12) PG dicaprylate (Miglyol 840).

Caprylic / Capric/diglyceryl Succinate: Miglyol 829.

Fatty Acids: Caprylic acid, oleic acid (crossential 094).

Fatty Acid Esters: Ethyl butyrate, Isopropyl myristate, Isopropyl palmitate, ethyl oleate (crodamol EO).

Vitamins: Vitamin E Mineral oil: Liquid paraffin

Long-chain Triglycerides: Fixed oils that is vegetable oils containing the mixture of the esters of the unsaturated long chain fatty acids [18]. Fixed oils are considered safe for digestion and available into daily food. Long chain triglycerides are lipids which are consisting of the 14-20 long fatty acid chain of the carbon atoms [19]. The large hydrophobic portion of triglycerides mainly has a high solvent capacity of the lipophilic molecule. Some of the marketed formulations consist of the LCT, *e.g.* (Neoral® consists of olive oil, which shows improved bioavailability) & Topicaine® gel (which consists of Jojoba oil for transdermal application) have been successfully adopted in the synthesis of microemulsion using LCT [20]. Long chain triglycerides like cottonseed and soybean are reported to enhance the bioavailability by stimulation of lymphatic transport of the drug [21]. When drugs like Mepitiostane (pro-drug of the epitiostanol) and Mepitiostaneolefin with octanol: water partition coefficients of 6 and 5.1 respectively, when given with the LCT are proved to be undergoing the significant lymphatic transport of drug [22].

Long hydrocarbon chains (high molecular volume) such as soybean oil, castor oil are more difficult to micro emulsify than MCT (low molecular volume) such as capmul MCM and Miglyol. With the oil's increasing chain length (hydrophobic portion), the solubilizing capacity for the lipophilic moiety increases. Hence the selection of oil is a compromise between the solubilizing potential and the ability to facilitate the formation of microemulsion [21]. Drug substances should possess minimum solubility of 50 mg/ml in LCTs for lymphatic absorption [16].

Medium Chain Triglycerides and Related Esters: MCT stands for medium chain triglycerides and associated esters with a fatty acid chain of 6-12 carbon [19]. Because of their highly effective concentration of ester group, MCT is the most widely used oil for SMEDDS because they are resistant to oxidation and have a higher solvent capacity than LCT. MCT produced from coconut oil distillation is known as glyceryl tricaprylate and comprises saturated C8 and C10 fatty acids in the liquid state [23]. (Labrafac CM 10), is an MCT that has improved fenofibrate solubility and produced a wide microemulsion area in all surfactant/co-surfactant combinations compared to Maisine 35, which is an LCT.

Oils used in Various Routes of Administration: The different oils are to be used in the SMEDDS/ SNEDDS formulation mainly belonging to the various categories like LCT, MCT, *etc*. A new trend is coming up, which involves the formulation of microemulsion-based drug delivery. For example it comprises microemulsion based topical

gel, microemulsion-based *in-situ* gel, microemulsion-based nasal drug delivery or microemulsion also incorporated into vaginal route *etc*. So the selection of oil is mainly getting important as they will be used for the different routes of administration.

1. **Oils used in Oral Drug Delivery:** Examples are: Capmul® MCM), Castor Oil, Capryol 90, Triacetin (SCT), Glycerol Mono Oleate, Sunflower Oil, Ethyl Oleate, Capmul PG 8 NF, Gelucire (44/14), Labrafil WL 2609, Sesame Oil, Triethyl Citrate Benzyl Alcohol, Captex 355, Caprylic Acid: Labrafil, Mixture Of Labrafil®/Capmul, Capmul MCM C8, Propylene Glycol Monocaprylate, Cremophor RH40, Maisine 35-1 *etc*.
2. **Oils used in Topical Drug Delivery:** Example: Isopropyl myristate, Oleic Acid, Isopropyl Palmitate, Transcutol P *etc*.
3. **Oils used in Ocular Drug Delivery:** Example: Capryol 90, oleic acid, olive oil, Castor Oil, soybean oil *etc*.
4. **Oils used in Vaginal Drug Delivery:** Example: Capryol 90, Linseed oil, Oleic Acid, lauric acid, myristic acid, capric acid, oleic acid, linoleic acid, linolenic acid *etc*.

Oils used for Various Drugs:

TABLE 2: OILS USED IN THE FORMULATION OF MICROEMULSION OF VARIOUS DRUGS

S. no.	Name of Article	Journal	Drug	Oils Used	Route of Administration	Ref.
1	Development of a solidified self-micro emulsifying drug delivery system (S-SMEDDS) for atorvastatin calcium with improved dissolution and bioavailability	International Journal of Pharmaceutics	Atrovastatin Calcium	Capmul (MCM)	Oral Route	24
2	Formulation and evaluation of solid-emulsifying drug delivery system of Bambuterol Hydrochloride	Indian Journal of Pharmaceutical Sciences	Bambuterol Hydrochloride	Triacetin	Oral Route	25
3	Novel Solid Self-Nanoemulsifying Drug Delivery System (S-SNEDDS) for Oral Delivery of OlmesartanMedoxomil: Design, Formulation, Pharmacokinetic and Bioavailability Evaluation.	Pharmaceutics	OlmesartanMedoxomil	Capryol 90	Oral Route	26
4	Preparation and Evaluation of Self-micro Emulsifying Drug Delivery Systems of LercanidipineHcl using Medium and Short Chain Glycerides: A Comparative Study	Asian Journal of Pharmaceutics	Lercanidipine Hcl	Triacetin (SCT)	Oral Route	27
5	Microemulsion-loaded hydrogel formulation of butenafine hydrochloride for improved topical delivery	Arch Dermatol Res	Butenafine	Isopropyl Palmitate	Topical Route	28
6	Preparation and evaluation of novel microemulsion-based hydrogels for dermal delivery of benzocaine	Pharmaceutical Development And Technology	Benzocaine	Isopropyl myristate	Topical Route	29
7	Micro-emulsion-based hydrogel of Tacrolimus for the treatment of Atopic Dermatitis.	Pharmaceutical nanotechnology	Tacrolimus	Lauroglycol	Topical Route	30
8	Preparation and Pharmacokinetics Evaluation of Solid Self-Micro emulsifying Drug Delivery System (S-SMEDDS) of Osthole	AAPS Pharm Sci Tech	Osthole	Castor Oil	Oral Route	31
9	Novel bicephalousheterolipid based self-microemulsifying drug delivery system for solubility and bioavailability enhancement	International Journal of Pharmaceutics	Efavirenz	Bicephalous hetero lipid	Oral Route	32

11	Novel drug delivery approach via self-microemulsifying drug delivery system for enhancing oral bioavailability of Asenapine Maleate	American Association of Pharmaceutical Scientists	Asenapine Maleate	Capryol 90	Oral Route	34
12	Development of a solid self-microemulsifying drug delivery system (SMEDDS) for solubility enhancement of naproxen	Drug Development And Industrial Pharmacy	Naproxen	Miglyol 812/Peceol (1:1)	Oral Route	35
13	Quality-by-design based development of a self-microemulsifying drug delivery system to reduce the food effect of Nelfinavir mesylate	International Journal Of Pharmaceutics	Nelfinavir Mesylate	Maisine 35-1	Oral Route	36
14	Spontaneous Emulsification of Nifedipine-Loaded Self-Nanoemulsifying Drug Delivery System	American Association Of Pharmaceutical Scientists	Nifedipine	Cremophor RH40	Oral Route	37
15	Oral solid self-nanoemulsifying drug delivery systems of candesartan citexetil:formulation, characterization and in vitro drug release studies	American Association Of Pharmaceutical Scientists	Candesartan Citexetil	Cinnamon Oil	Oral Route	38
16	Fabrication and characterization of selfmicroemulsifying mouth dissolving flim for effective delivery of Piroxicam	Indian Journal Of Pharmaceutical Sciences	Piroxicam	Capmul MCM	Oral Route	39
17	Formulation Optimization and pharmacokinetics evaluation of oral self-microemulsifying drug delivery system for poorly water-soluble drug cinacalcet and no food effect	Drug Development And Industrial Pharmacy	Cinacalcet	Ethyl Oleate	Oral Route	40
18	A-Tocopherol as functional excipient for Resveratrol and Coenzyme Q10 loaded SNEDDS for improved bioavailability and prophylaxis of breast cancer	Journal Of Drug Targeting	Resveratrol	Capmul MCM EP	Oral Route	41
19	Self-microemulsifying drug-delivery system for improved oral bioavailability of pranlukast hemihydrate: preparation and evaluation	International Journal Of Nanomedicine	Pranlukast Hemihydrate	Triethyl Citrate Benzyl Alcohol	Oral Route	42
20	In vivo Evaluation of Self Emulsifying Drug Delivery System for Oral Delivery of Nevirapine	Indian Journal Of Pharmaceutical Sciences	Nevirapine	Caprylic Acid	Oral Route	43
21	Ultra-fine super self-nanoemulsifying drug delivery system (SNEDDS) enhanced solubility and dissolution of Indomethacin	Journal Of Molecular Liquids	Indomethacin	Labrafil	Oral Route	44
22	SNEDDS contain bio enhancers for improvement of dissolution and oral absorption of lacidipine. I: Development and optimization	International Journal Of Pharmaceutics	Lacidipine	Mixture Of Labrafil®/Capmul	Oral Route	45
23	Statistical modeling, optimization and characterization of solid self-nanoemulsifying drug delivery system of lopinavir using design of experiment	Drug Delivery	Lopinavir	Lopinavir	Oral Route	46
24	Design, optimization and evaluation of glipizide solid self-nanoemulsifying drug delivery for enhanced solubility and dissolution	Saudi Pharmaceutical Journal	Glipizide	Captex 355	Oral Route	47
25	Solid self-microemulsifying dispersible tablets of celastrol: Formulation development, characterization and	International Journal Of Pharmaceutics	Celastrol	Masine-1, Ethyl Oleate And Olive	Oral Route	48

	bioavailability evaluation			Oil		
26	Solid super saturated self-nanoemulsifying drug delivery system (sat-SNEDDS) as a promising alternative to conventional SNEDDS for improving rosuvastatin calcium oral bioavailability	Expert Opinion On Drug Delivery	Rosuvastatin Calcium	Garlic /Olive Oil	Oral Route	49
27	Improved pharmacodynamic potential by SMEDDS: In-vitro and in-vivo evaluation	International Journal of Nanomedicine	Rosuvastatin	Capmul MCM	Oral Route	50
28	Formulation and evaluation of Oral self-microemulsifying drug delivery system of Candesartan cilexetil.	Internatinal journal of Pharmacy and Pharmaceutical sciences.	Candesartan cilexetil	Capryol 90	Oral Route	51
29	Development of Self-microemulsifying Drug Delivery System for Oral Delivery of Poorly Water-soluble Nutraceuticals	Drug Development And Industrial Pharmacy	Vitamin A, Vitamin K2, Coenzyme Q10, Quercetin And Trans-Resveratrol	CapmulMcm Nf:Captex 355 Ep/Nf (1:1)	Oral Route	52
30	Anticancer efficacy of self-nanoemulsifying drug delivery system of Sunitinib Malate	American association of Pharmaceutical scientist	Sunitinib Malate	Lauroglycol-90	Oral Route	53
31	Design and Evaluation of Self-Nanoemulsifying Drug Delivery System of Flutamide	Journal Of Young Pharmacists	Flutamide	Sesame Oil	Oral Route	54
32	Design, development and optimization of self-microemulsifying drug delivery system of an anti-obesity drug	Journal Of Pharmacy And Bio allied Sciences	Orlistat	Propylene Glycol Monocaprylate	Oral Route	55
33	Formulation and evaluation of SNEDDS derived tablet of Sertraline	Pharmaceutics	Sertraline	Glycerol Triacetate	Oral Route	56
34	Food grade microemulsion systems: Canola oil/ lecithin: n-propanol/ water	Food Chemistry	-	Canola oil	Oral Route	57
35	Formation and Investigation of Microemulsions based on Jojoba Oil and Nonionic Surfactants	Journal of American Oil Chemists Society	-	Jojoba Oil	-	58
36	Rats given linseed oil in micro emulsion forms enriches the brain synaptic membrane with docosahexaenoic acid and enhances the neurotransmitter levels in the brain	Nutritional Neuroscience	Docosahexaenoic acid	Linseed oil	Oral Route	59
37	Hollow pessary loaded with lawsone via self- micro emulsifying drug delivery system for vaginal candidiasis	Journal of Drug Delivery Science and Technology	Lawsone	Capryol 90	Vaginal Route	60
38	A vaginal Nano-formulation of a SphK inhibitor attenuates lipopolysaccharide-induced preterm birth in mice	Nanomedicine	SphK inhibitor	Captex 300	Vaginal Route	61
39	17- alpha Hydroxyprogesterone Nano-emulsifying Preconcentrate-Loaded Vaginal Tablet: A Novel Invasive Approach for the prevention of Preterm Birth.	Pharmaceutics	17- alpha Hydroxy progesterone	Medium chain triglyceride Captex 300	Vaginal Route	62
40	Efavirenz Self-Nano-Emulsifying Drug Delivery: In Vitro In2Vivo Evaluation	AAPS Pharma Sci.Tech	Efavirenz	Labrafil M 2125	Oral Route	63
41	Self-emulsifying drug delivery system: Design of a novel vaginal delivery	European Journal of Pharmaceutics	Curcumin	Medium chain	Vaginal Route	64

	system for curcumin.	and Biopharmaceutics		triglyceride		
42	Development and characterization of a self-micro emulsifying drug delivery system(SMEDDSs) for the vaginal administration of the anti-retroviral UC-781	European Journal of Pharmaceutics and Biopharmaceutics	UC-781	Mono and di glyceride of caprylic acid	Vaginal Route	65
43	A Solid Ultra fine Self-Microemulsifying Drug Delivery System (S-SNEEDS) of Deferasirox for Improved Solubility, Optimization, Characterization and In vitro Cytotoxicity studies	Pharmaceuticals	Deferasirox	Peceol	Oral Route	66
44	The use of orange peel essential oil microemulsion and Nanoemulsion in pectin-based coating to extend the shelf life of fresh-cut orange	Journal of Food Processing and preservation	-	Orange oil	Oral Route	67

CONCLUSION: Lipid-based drug delivery systems are a viable option for enhancing drug bioavailability and solubility. The impact of the lipoids on the orally administered drug is very complicated because of the varied mechanism through which lipids will alter the biopharmaceutical aspects of the given drug.

So, understanding the role of various components used in a lipid-based formulation is very important. As a result, the focus of the review was on the basics of the SMEDDS and various oils used in the lipid-based drug delivery system, as well as their mechanism and interaction with the oils used according to the varied routes of administration.

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