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Research

Self-Micro Emulsifying Drug Delivery System (SMEDDS): An Innovative Tool To Improve Bioavailability

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Abstract

Self-microemulsifying drug delivery systems (SMEDDS) have emerged as a promising approach to enhance the oral bioavailability of poorly water-soluble drugs. SMEDDS is composed of an oil phase, surfactant, co-surfactant, and drug, which spontaneously form a fine oil-in-water microemulsion when exposed to gastrointestinal fluids. This microemulsion enhances drug solubilization and absorption by increasing the drug's surface area and promoting rapid gastrointestinal epithelium permeation. The formulation of SMEDDS involves careful selection and optimization of components to achieve desired drug solubility, stability, and emulsification efficiency. SMEDDS offers numerous advantages, including improved drug bioavailability, reduced variability in pharmacokinetic parameters, and the potential for reduced dosing frequency. They can effectively deliver a wide range of drugs, including lipophilic and poorly water-soluble compounds. This review provides an overview of SMEDDS, its advantages, and disadvantages, drug delivery mechanism, formulation design, excipients used for formulation, and evaluation techniques as well as their potential applications in drug delivery.

Keywords: SMEDDS, Co-surfactant, Microemulsion, Solubilization

INTRODUCTION

Various techniques enhance oral bioavailability of poorly water-soluble drugs [1, 2]. The oral route has been the major route of drug delivery for the chronic treatment of many diseases as it offers a high degree of patient compliance. However, oral delivery of 50% of the drug compounds is hampered because of the high lipophilicity of the drug itself. Nearly 40% of new drug candidates exhibit low solubility in water, which is a challenge in developing optimum oral solid dosage forms regarding formulation design and bioavailability of new pharmaceutical products. Many strategies have been used to overcome these problems either through modifying

the solubility or maintaining the drug in dissolved form throughout gastric transit time [4,5]. These strategies may include the use of surfactants, cyclodextrins, micronization, liquisolid techniques[6], salt formation, pH change, nano size delivery [7], solid dispersions [8, 9], and permeation enhancers [10,11]. Indeed, in some selected cases, these approaches have been successful but they offer many other disadvantages. The main problem with micronization is chemical / thermal stability. Many drugs may degrade and lose bioactivity when they are micronized by conventional methods. For solid dispersion, the number of carriers used is often large, and thus if the dose of active ingredient is high, the tablets or capsules formed will be large in volume and difficult to swallow. Moreover, since the carriers used are usually expensive and freeze-drying or spray-drying methods require particular facilities and processes, leading to high production costs. Though the traditional solvent method can be adopted instead, it is difficult to deal with co-precipitates with high viscosity. Complexation with cyclodextrins techniques is not applicable for drug substances that are not soluble in both aqueous and organic solvents. The realization that the oral bioavailability of poorly water-soluble drugs may be enhanced when co-administered with meals rich in fat has led to increasing recent interest in the formulation of poorly water-soluble drugs in lipids. Lipid suspension, solutions, and emulsions have all been used to enhance oral bioavailability but, more recently there has been much focus on the utility of self-micro emulsifying drug delivery systems (SMEDDS) [12]. 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 [13]. Among the lipid-based systems, Self-emulsifying drug delivery systems (SEDDS) are a promising strategy to improve the bioavailability of poorly water-soluble compounds. SEDDS are isotropic mixtures of drugs, lipids, and surfactants, usually with one or more hydrophilic co-solvents or co-emulsifiers [14]. Upon mild agitation followed by dilution with aqueous media, these systems can form fine (oil in water) emulsion instantaneously. The size of the droplet formed is between 100 and 300 nm while self-micro-emulsifying drug delivery systems (SMEDDS) form transparent micro-emulsions with a droplet size of less than 50 nm [15]. In self-emulsifying formulations, the formed emulsion increases membrane permeability as a result of surfactant presence and enhances lymphatic absorption (lymphatic transport) due to medium and long-chain oils. These factors may contribute significantly to the better performance of the formulations [16,17]. Recently, SMEDDS especially have attracted increasing interest primarily because SMEDDS is physically stable, easy to manufacture, can be filled in soft gelatin capsules, and then will generate a drug-containing micro-emulsion with a large surface area upon dispersion in the gastrointestinal tract. The emulsions will further facilitate the absorption of the drug due to a faster digestion by gastrointestinal enzymes and subsequent transfer to mixed micelles or possible absorption directly from the emulsion particle, by partitioning of drug into the aqueous phase of intestinal fluids [18]. Herein, an overview of SMEDDS as a key technology for formulating lipophilic drugs and increasing their oral bioavailability is presented.

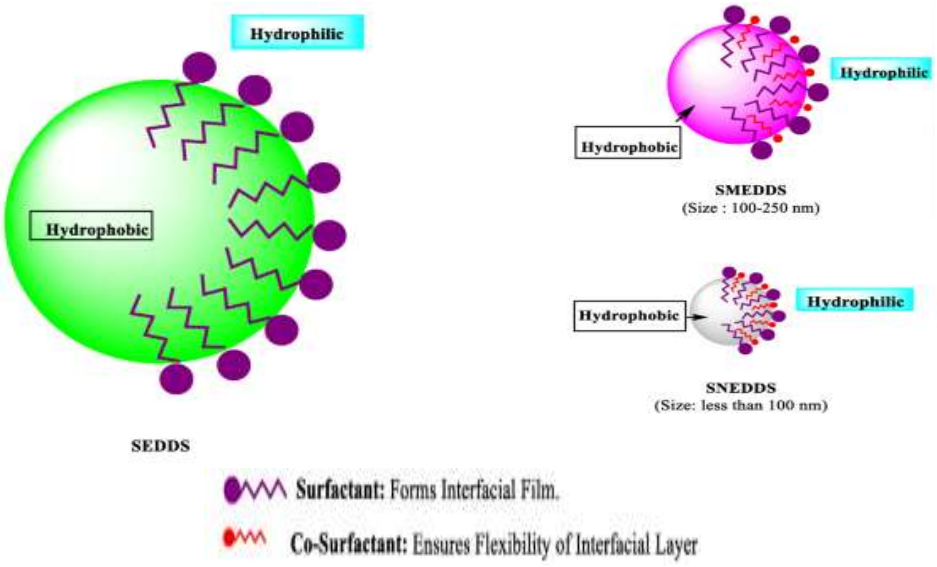

Fig 1: Diagrammatic representation of SEDDS (self-emulsifying drug delivery system), SMEDDS (self-micro-emulsifying drug delivery system), and SNEDDS (self-nano-emulsifying drug delivery system) [19].

Lipid Formulation Classification System

Various lipid-based drug delivery systems exist, including lipid solution, lipid emulsion, microemulsion, and dry emulsion. To facilitate understanding and streamline formulation development due to the multitude of excipient combinations, a classification system known as the Lipid Formulation Classification System (LFCS) was established. LFCS, introduced by Pouton in 2000 and updated recently [20], categorizes lipid formulations into four types based on composition and their resilience against dilution and digestion, aiding in predicting their fate in vivo. This classification system promotes a systematic and rational approach to formulation, reducing the need for trial-and-error methods and providing a framework for regulatory guidance as shown in Table 1.

Table 1: Compositions of lipid-based formulation [21]

Types	Type I	Type II	Type III		Type IV
Composition	**OIL**	**SEDDS**	**III A SEDDS**	**III B SMEDDS**	**OIL-FREE**
Glycerides (TG, DG, MG)	100%	40-80%	40-80%	<20%	-
Surfactants (HLB < 12)	-	20-60%	-	-	0-20%
(HLB > 12)	-	-	20-40%	20-50%	20-80%
Hydrophilic co-solvents	-	-	0-40%	20-50%	0-80%
Particle size of dispersion(nm)	Coarse	100-250	100-250	50-100	<50

***Type I** Systems* comprise drug formulations dissolved in triglycerides and/or mixed glycerides or in oil-in-water emulsions stabilized by low concentrations of emulsifiers like 1% (w/v) polysorbate 60 and 1.2% (w/v) lecithin. These systems typically exhibit poor initial aqueous dispersion and rely on pancreatic lipase/co-lipase digestion in the gastrointestinal tract (GIT) to generate more amphiphilic lipid digestion products, facilitating drug transfer into the colloidal aqueous phase. Type I lipid formulations offer a straightforward option for potent drugs or highly lipophilic compounds, where drug solubility in oil suffices for incorporating the required payload (dose) as shown in Table 2.

***Type II** Systems* encompass Self-Emulsifying Drug Delivery Systems (SEDDS), where self-emulsification occurs typically with surfactant contents surpassing 25% (w/w). However, at higher surfactant levels (exceeding 50–60% (w/w), depending on materials), emulsification progress might be hindered by the formation of viscous liquid crystalline gels at the oil/water interface. These lipid-based formulations, Type II, offer the advantage of circumventing the slow dissolution often associated with solid dosage forms. Moreover, they generate extensive interfacial areas, facilitating efficient drug partitioning between oil droplets and the aqueous phase, thereby enhancing absorption [22].

Table 2: Typical properties of Type I, II, III and IV lipid formulations [23, 24]

Formulation Type	Materials	Characteristics	Advantages	Disadvantages
Type I	Oils without surfactants (e.g., tri-, di-and monoglycerides)	Non-dispersing requires digestion	Generally recognized as safe (GRAS) status; simple; excellent capsule Compatibility	The formulation has poor solvent capacity unless a drug is highly lipophilic
Type II	Oils and water-insoluble surfactants	SEDDS formed without water-soluble Components	Unlikely to lose solvent capacity on dispersion	Turbid o/w dispersion (particle size 0.25–2 μm)
Type III	Oils, surfactants, cosolvents (both water-insoluble and water-soluble excipients)	SEDDS/SMEDDS formed with water-soluble components	Clear or almost clear dispersion; drug Absorption without digestion	Possible loss of solvent capacity on dispersion. less easily digested
Type IV	Water-soluble surfactants and cosolvents (no oils)	Formulation disperses typically to form a micellar solution	Formulation has a good solvent capacity for many drugs	Likely loss of solvent capacity on dispersion; may not be digestible

***Type III** Systems,* known as self-microemulsifying drug delivery systems (SMEDDS), include hydrophilic surfactants (HLB>12) and co-solvents like ethanol, propylene glycol, and polyethylene glycol. Within Type III formulations, there's a subdivision into Type IIIA and Type IIIB, with Type IIIB being more hydrophilic due to

increased hydrophilic surfactants and co-solvents and decreased lipid content. Type IIIB formulations generally achieve faster dispersion rates than Type IIIA, albeit with a higher risk of drug precipitation due to lower lipid content [25].

***Type IV** Systems,* a recent addition to lipid-based formulations, primarily consists of hydrophilic surfactants and co-solvents, reflecting a shift in formulation trends. These formulations lack natural lipids, making them the most hydrophilic among lipid-based options. They often accommodate increased drug payloads compared to those containing simple glyceride lipids and yield very fine dispersions in aqueous media. However, *in vivo,* solubilization capacity, especially in maintaining poorly water-soluble drugs in solution along the gastrointestinal tract (GIT), remains poorly understood compared to formulations with natural oils (Type II and Type III). An example is the capsule formulation of the HIV protease inhibitor amprenavir (Agenerase), featuring TPGS as a surfactant, and PEG 400 and propylene glycol as co-solvents [26].

Biopharmaceutical classification system (BCS)

Biopharmaceutics Classification System (BCS) was introduced in 1995 as a basis for predicting the likelihood of *in vitro-in vivo* correlations for immediate release dosage forms,

Table 3: Application of SMEDDS in various BCS class drugs [27]

BCS class	Aqueous Solubility	Membrane Permeability	Problems
Class I	High	High	Enzymatic degradation, gut wall efflux
Class II	Low	High	Solubilization and bioavailability
Class III	High	Low	Enzymatic degradation, gut wall efflux, and bioavailability
Class IV	Low	Low	Solubilization, enzymatic degradation, gut wall efflux and bioavailability

based on the recognition that drug solubility/dissolution properties and gastrointestinal permeability are the fundamental parameters controlling the rate and extent of drug absorption. According to BCS, drug substances are classified along with their problems, as shown in Table 3. The FDA has set specifications regarding the solubility and permeability class boundaries used for this BCS classification.

Solubility

A drug substance is considered highly soluble when the highest dose strength is soluble in 250 ml or less of aqueous media over a pH range of 1 to 7.5 (equilibrium solubility at 37°C).

Permeability

In the absence of evidence suggesting instability in the gastrointestinal tract, a drug substance is considered highly permeable when the extent of absorption in humans is determined to be 90% or more of an administered dose based on mass balance determination or in comparison to an intravenous reference dose (absolute bioavailability study).

Advantages of SMEDDS over other emulsions

1. Storage*:* SMEDDS has the same advantage as emulsions, of facilitating the solubility of hydrophobic drugs. Macroemulsions undergo creaming over a while, whereas SMEDDS being thermodynamically stable can be stored easily [28].
2. Stability: Unlike micro/Nano emulsions, SMEDDS do not contain water; hence, they have improved physical and chemical stability in long-term storage. Self-nanoemulsifying tablets of carvedilol showed successful incorporation of carvedilol within the SNEDDS. This improved the stability of carvedilol on dilution with aqueous media in the presence of cellulosic polymers [29].
3. Compliance: Most of the SMEDDS formulations are in capsule or tablet dosage forms, thus occupying smaller volumes, easy to administer and hence improving patient compliance [30, 31].
4. Palatability: SMEDDS formulation can be easily filled into capsules resolving the palatability issues associated with lipid formulations [32].
5. Effect of food: Absorption of drug from SMEDDS formulation is not affected by food. The lipophilic contents of a fatty diet aid, aids in the absorption of drugs from these systems. It was observed that food had a marked effect on the absorption of itraconazole from the marketed formulation (Sporanox capsule), whereas the influence was less pronounced for the self-emulsifying formulation of itraconazole (ITRA-GSMP capsule) in human volunteers [33].

6. Quick onset of action: SMEDDS can facilitate rapid oral absorption of the drug, which results in a quick onset of action. It was found that the tmax of vitamin A was reduced and bioavailability was increased when administered as a SNEDDS capsule and SNEDDS tablet as compared to vitamin A oily solution-filled capsules without any additives [34].
7. Ease of manufacture and scale-up: SMEDDS can be easily manufactured at a large scale as it requires simple and economical manufacturing facilities, such as a simple mixer with an agitator and volumetric liquid filling equipment [35].

Limitations of SMEDDS

Although SMEDDS formulation has several advantages, there are certain limitations associated with this system are given below: -

- The precipitation tendency of the drug on dilution is higher due to the dilution effect of the hydrophilic solvent. It thereby requires the incorporation of polymers to minimize drug precipitation in vivo [36].
- Most SMEDDS are in gelatin capsules, but they face issues like cost, TSE, and religious concerns. Volatile solvents in SMEDDS may precipitate drugs in gelatin shells, prompting the search for alternatives like HPMC capsules, particularly for super-saturable formulations. [37].
- Storage and handling: Liquid SMEDDS exhibit problems in handling, storage, and stability. Thus, formulating solid SMEDDS seems to be a logical solution to address these problems [38].
- Lymphatic targeting offers advantages over portal blood absorption, bypassing hepatic metabolism and enabling site-specific delivery to lymphatic organs. Typically, drugs with high triglyceride solubility and log P are favoured for lymphatic transport. However, drug variability necessitates a deeper understanding of lipophilicity and triglyceride solubility correlation for effective predictive models and consistent lymphatic transport [39].
- The dearth of predictive in vitro models poses a challenge to SMEDDS and other lipid-based formulation development. Traditional dissolution methods are ineffective as these formulations rely on gut lipid digestion before drug release. An in vitro duodenal digestion model has been developed but requires refinement and validation for reliable assessment. Additionally, *in vitro–in vivo* correlations and animal model studies are necessary for prototype formulation development [40].
- Oxidation and polymorphism of the lipids used in formulating *SEDDS/SMEDDS*: Lipid excipients containing unsaturated fatty acids and their derivatives are prone to lipid oxidation [41]. This requires the inclusion of Lipid-soluble antioxidants in capsule formulation[32]. Polymorphism associated with thermo-softening lipid excipients requires specific process control in their application, to minimize polymorphic changes in the excipient matrix [42].

Composition of SMEDDS

Literature surveys commonly explore different oil/surfactant and co-surfactant mixtures at various ratios for SMEDDS formulations. These studies typically involve blending surfactant and co-surfactant with oil to prepare SMEDDS. Multiple components are utilized in SMEDDS formulation. As shown in table 3.

Table 4: Excipients used in the formulation of SMEDDS

S. No	Oil	Surfactant	Co-Surfactant	Reference
1.	Capmul MCM C8	Cremophor EL	Transcutol HP	[43]
2.	Castor Oil	Tween-20	Propylene Glycol	[44]
3.	Triacetin	Triton-X 100	Carbitol	[45]
4.	Castor oil	Capmul MCM, Kolliphor EL	Kolliphor RH 40	[46]
5.	Capryol 90	Gelucire 44/14	Tween 80	[47]
6.	Isopropyl Myristate (IPM)	Tween 80	Propylene Glycol	[48]

Components of SMEDDS components

Oils: The oil refers to the most significant excipient in the SMEDDS formulation. Without a doubt, it will solubilize the important measure of the poor soluble dug [49]. Both medium-chain triglyceride (MCT) and long-chain triglyceride (LCT) oils with various degrees of immersion have been utilized in the design of SMEDDS [50]. For example, corn oil, olive oil, soybean oil, hydrolyzed corn oil, castor oil, sesame oil, and soyabean oil isopropyl myristate [50, 51].

Surfactant: Surfactant molecules may be classified based on the nature of the hydrophilic group within the molecule [50]. The surfactants are defined as four main categories as follows [49].

a. Anionic surfactants: The anionic surfactant is a water-loving group that conveys a negative charge [60]. For example, carboxyl (RCOO-), sulphonate (RSO3-) or sulfate (ROSO3-). Potassium laurate, Sodium lauryl Sulphate (SLS) [49].
b. Cationic surfactants: The cationic surfactant is a hydrophilic component that passes on a positive charge. For example, quaternary ammonium halide [49].
c. Zwitterionic surfactants (also called Ampholytic surfactants): The ampholytic surfactant contains both a positive charge (+ve) and a negative charge (-ve.) Such as sulfobetaine [49,50].
d. Non-ionic surfactants: Non-ionic surfactants, like Tween, possess polar groups conferring water solubility without carrying a charge. In SMEDDS, high HLB value non-ionic surfactants, constituting 30–60% w/w, yield stable formulations. Their high HLB and polar groups facilitate rapid oil/water droplet formation, aiding dispersion. These amphiphilic surfactants efficiently solubilize hydrophobic drugs [49, 50].

Co-solvents
Co-surfactant is an organic solvent, for example, ethanol, propylene glycol, and polyethylene glycol (PEG) are suitable for oral conveyance and they accelerate the dissolution of huge amounts of either the water-loving or the lipid-soluble drug surfactants [50]. These solvents will even work as co-surfactants in microemulsion preparation. Then again, liquor and other co-surfactants have the burden of dissipating into the shells of the delicately wrapped gelatine or hard gelatine case unmistakable [52, 53].

Consistency builder
Additional material can be added to adjust the consistency of the emulsion; for instance, stearic corrosive, cetyl liquor, tragacanth, beeswax, etc. [49].
Polymers: Inert polymer matrix denoting from 5-40 % of ingredient comparative to the weight, which is not ionizable at physiological pH, and being able of developing matrix. Examples are HPMC, ethyl cellulose, etc [49].

Other components
SMEDDS may contain flavours, antioxidants, and pH adjusters. Lipid products, particularly unsaturated ones, form peroxides through oxidation, generating harmful free radicals like Peroxyl (ROO), Alkoxide (RO), and Hydroxyl (OH), leading to drug toxicity. Auto-oxidation increases lipid peroxide formation with unsaturation. High-speed lipid hydrolysis due to pH or processing energy requires lipophilic antioxidants (e.g., α-tocopherol, propyl gallate, BHT) to preserve SMEDDS oily content. [49].

Mechanism of SMEDDS
The Self-Emulsification Process
Self-emulsification is a phenomenon that has been widely exploited commercially in formulations of emulsifiable concentrates of herbicides and pesticides. Concentrates of crop sprays are to be diluted by the user, such as farmers or household gardeners, allowing very hydrophobic compounds to be transported efficiently. In contrast, SMEDDS, using excipients acceptable for oral administration to humans, have not been widely exploited and knowledge about their physicochemical principles is therefore limited.

Mechanism of Self Emulsification
In the emulsification process the free energy (ΔG) associated is given by the equation: [54]
$\Delta G = \sum Ni\pi ri$
In which N 'is the Number of droplets with radius r 'and σ 'is interfacial energy. It is apparent from the equation that the spontaneous formation of the interface between the oil and water phases is energetically not favoured. The system commonly classified as SEDDS has not yet been shown to emulsify spontaneously in the thermodynamic sense. The process of self-emulsification was observed using light microscopy. Fig 2 explains the mechanism of action of oral administration of SMEDDS on oral administration of drug [55].

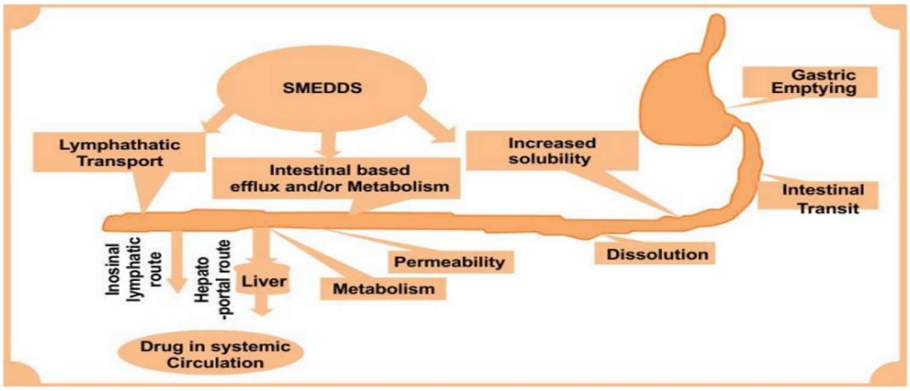

Fig 2: Mechanism of action of self-micro-emulsifying drug delivery system on oral administration of the drug

Groves and Mustafa devised a quantitative method to assess emulsification ease by monitoring oil-surfactant turbidity in a water stream with phosphated nonylphenoloxylate (PNE) and phosphated fatty alcohol ethoxylate (PFE) in n-hexane. Pouton linked emulsification to phase inversion, where an increase in oil-water temperature triggers surfactant cloud point, leading to phase inversion. At this temperature, surfactant mobility peaks, reducing interfacial energy and easing emulsification. Specific surfactant combinations may minimize phase inversion temperature, enhancing emulsion ease. Phase studies indicate optimal formulations operate near phase inversion, promoting aqueous solubilization. A phase diagram of the system (30% w/w tween and 85/70% w/w MCT oil) reveals a phase inversion region at around 40°C, crucial for emulsion stability.

The method functions effectively within ambient temperatures up to 60°C, beyond which water-in-oil emulsions tend to develop [56]. The emulsification process is linked to water penetrating the oil-water interface, forming liquid crystalline phases that swell the interface, enhancing emulsification. However, in systems with co-surfactants, substantial partitioning between oil and water phases occurs, termed "diffusion and stranding," where solubilized oil migrates into the aqueous phase [56].

Dilution Phases

Upon dilution of a SMEDDS formulation, the spontaneous curvature of the surfactant layer changes via some possible liquid crystalline phases. The droplet structure can pass from a reversed spherical droplet to a reversed rod-shaped droplet, hexagonal phase, lamellar phase, cubic phase, and various other structures until, after appropriate dilution, a spherical droplet will be formed again (Fig. 3) [56].

Liquid crystalline phases, occurring upon aqueous dilution of lipid formulations, play various roles. Early research by Groves and Mustafa linked emulsification behaviour to surfactant-oil phase behaviour, showing shorter emulsification times in systems forming liquid crystals. They suggested water penetration into droplets, facilitated by solvent movement through liquid crystalline phases, influences emulsification ease [57].

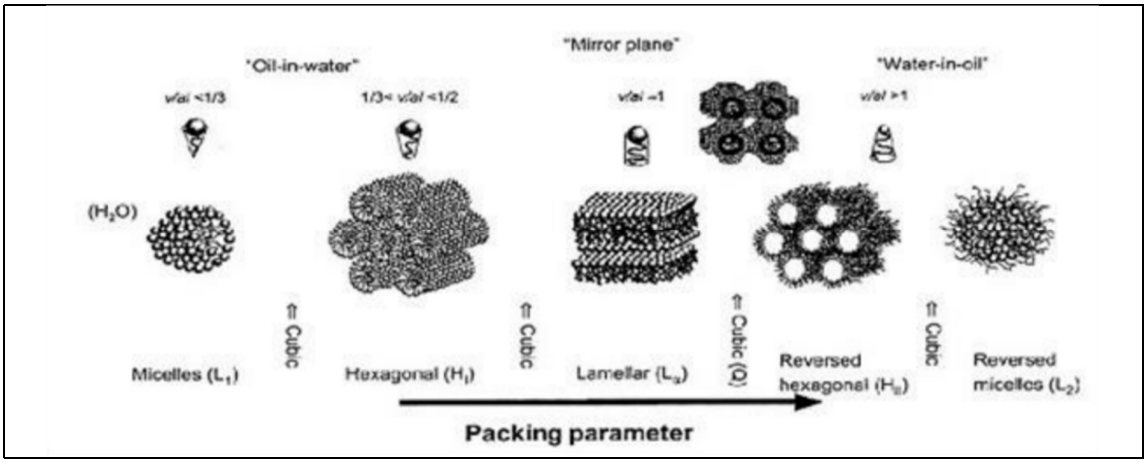

Fig 3: Representation of the most commonly encountered phases upon addition of water to an oil-surfactant combination [56]

These structures affect diluted microemulsion stability and drug release rates. A surrounding layer of liquid crystalline material around oil droplets impacts drug dissolution and formulation digestion, emphasizing their significance in formulation performance. Some examples are shown in Table 4.

Table 5: Examples of SEDDS for Oral Delivery of Lipophilic Drugs [16]

Type of delivery system	Oil	Surfactants	%w/w	Solvent(s)	Drug compound	Drug content
SEDDS	A mixture of mono and diglycerides of oleic acid	Solid, polyglycoled mono-di and triglycerides, Tween 80	80 or 20	-	Ontazolast	7.5
SEDDS (Sand immune)	Olive oil	Polyglycoled glycerides	30	Ethanol	CsA	10
SEDDS (positively charged)	Ethyl oleate	Tween 80	25	Ethanol	CsA	10
SEDDS (positively charged)	Ethyl oleate	Tween 80	25	Ethanol	Progesterone	2.5
SEDDS	Myvacet 9-45 or captex 200	Labrasol or Labrafac CM10	5-30 0-25	-	coQ10	5.66
SEDDS(Norvir)	Oleic acid	Polyoxyl 35, castor oil	NA	Ethanol	Ritonavir	8
SEDDS (Fortovase)	dl-alpha tocopherol	Medium chain mono- and diglycerides	NA	-	Saquinqvir	16

Formulation design

The formulation of SMEDDS involves the following steps.

(1) Selection of active pharmaceutical ingredient (API) for self-micro-emulsifying drug delivery system (SMEDDS).

(2) Screening of surfactant for emulsifying ability.

(3) Choice of excipients for self-micro emulsifying drug delivery system (SMEDDS).

(4) The solubility of a drug in oils, surfactants, and co-surfactants.

(5) Construction of pseudo ternary phase diagram.

(6) Preparation of self-micro-emulsifying drug delivery system (SMEDDS).

(7) Factor influencing self-micro-emulsifying drug delivery

Selection of active pharmaceutical ingredient for *SMEDDS*

The choice of active pharmaceutical ingredient (API) significantly impacts various aspects of self-micro emulsifying drug delivery systems (SMEDDS), including phase behavior and micro-emulsion particle size. Physicochemical properties such as pKa, log P, molecular structure, ionizability, and dosage affect SMEDDS functionality. Drugs with low therapeutic doses are commonly suitable for SMEDDS. Solubility within the gastrointestinal tract (GIT) is challenging, particularly for drugs requiring high doses. Successful SMEDDS candidates should demonstrate solubility in at least one lipophilic excipient. Additionally, API stability within the preparation and consistent drug release throughout its shelf life is crucial for effective SMEDDS formulations [58].

Screening of surfactants for emulsifying ability

The different surfactants are screened for their emulsification capacity. Surfactants can be added to the particular oil in a 1:1 ratio. The admixture is homogenized. A fixed quantity of isotropic admixture is diluted with double purified water to yield a clear emulsion [59, 60]. The resulting emulsions can be inspected outwardly for their relative polluting influence and their transmittance can be evaluated in a UV-visible spectrophotometer with the help of double purified water as the blank [61,62].

Selection of excipients

The excipients should be preferred from the record of generally regarded as safe "GRAS" excipients printed by USFDA [59, 63]. Good consideration of the physical appearance of excipients and their performance in preparation is the essential desire for effective preparation development [64]. To prepare an effective SMEDDS for the highest therapeutic outcomes, outstanding thought must be given to the following components;

- physicochemical characteristics of the API as well as excipients;
- Development for drug excipients collaboration;
- Physiological aspects that stimulate or restrain the bioavailability;
- Biopharmaceutical features such as solubilization capacity, physical state regulatory status, and miscibility, of the excipients at 25 °C;
- Regulatory features of excipients;
- The temperature at which self-emulsification occurs.

The solubility of a drug in oils, surfactants, and co-surfactants

The dissolvability of medication in oils, surfactants, and co-surfactant: the aggregate of the oil's surfactants, and co-surfactants were screened for their attributes to dissolve a tremendous amount of pure drug [66]. An additional quantity of the drug is taken in clear screw cap glass vials that confine oil/surfactant/co-surfactant followed by blending on cyclomixer (vortex mixture). The admixture is shaken and centrifuged [67]. An aliquant part from the supernatant is withdrawn and further analyzed by UV–UV-visible spectrophotometer at required nm [68, 69].

Construction of pseudo ternary phase diagram

Different proportions of oil, surfactant, and cosurfactant is agitated to formulate various techniques [70, 71]. A fixed quantity of each system is added in a beaker containing 0.1 N HCl at 37°C and the substances are mixed using the magnetic stirrer [72, 73]. The clearness of the designed dispersion was visually examined with the help of the following grading techniques;

A. Denoting the clear microemulsion formation with bluish ting.
B. Denoting a translucent micro emulsion formation had a bluish appearance.
C. Denoting a little less clear emulsion preparation.
D. Indicating a clear white emulsion development.
E. Signifying the details that had either poor emulsification with huge oil droplets superficially or the emulsion was not developed. A phase diagram is developed to distinguish the results. Type A and B systems are most preferred because of the lower particle size. The following pyramid-like structure shows the construction of a pseudo-ternary phase diagram. The following Fig. 4 demonstrates a sample of a pseudo ternary phase diagram [68, 74, 75]

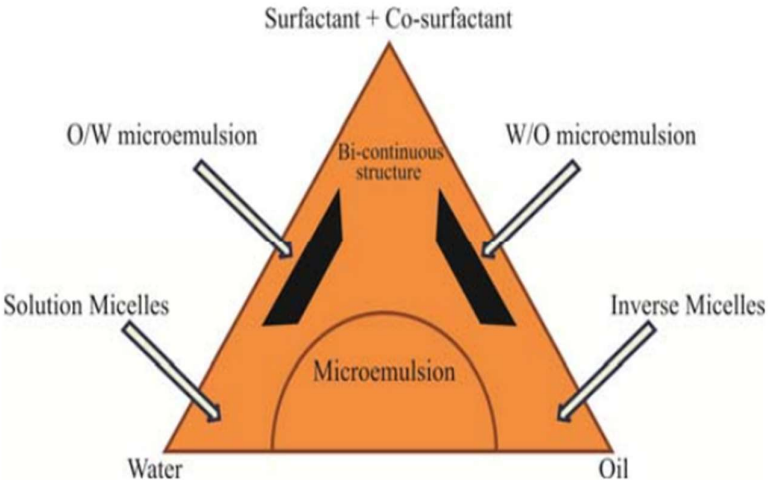

Fig 4: Construction of pseudo ternary phase diagram

Preparation of SMEDDS

The formulation contains the addition of the drug to the admixture of oil, surfactant, and co-surfactant and then it must be exposed to vertexing [76]. At that time, the drug is solubilized in any of the excipients and the remaining excipients are added to the drug solution [77, 78]. At that point, the solution must be appropriately admixture and tested for the indication of impurity [79, 80]. After equilibration at atmospheric temperature for 48 hours, the solution must be heated for the development of a fine solution, whenever required [81, 82]. Contingent on the final volume, the preparation must be put away in capsules of appropriate size. The general technique of preparation of a self-micro-emulsifying drug delivery system and their resulting from microemulsion/nano-emulsion is shown in Fig.5 [77, 83].

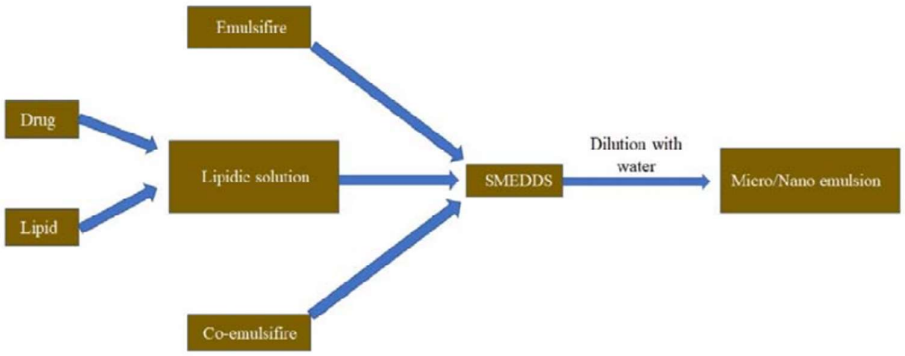

Fig 5: The general technique of preparation of a self-micro-emulsifying drug delivery system and their resulting form to micro emulsion /nano-emulsion.

Factor affecting SMEDDS

API dose: Generally, drugs having a low therapeutic dose are preferred for the formulation of SMEDDS. However, such drugs are highly soluble in any constituents of SMEDDS specifically in the lipid phase. The drug which is not well dissolvable both in oil and water and has low Log P-value (around 2) is not an appropriate contender for SMEDDS [47].

Drug solubility in the oil phase*:* The solubility of drugs in the oil phase influenced the capacity of the SMEDDS system to keep the medication in the solution state. Right when the medication is solvent with the assistance of surfactant and co-surfactant the weakening of SMEDDS can bring about diminishing the dissolvable ability of surfactant, thereby causing precipitation [47].

The polarity of the lipid phase: Variables such as HLB, chain length, degree of unsaturation of unsaturated fats, molecular weight of the hydrophilic segment, and emulsifier concentration influence micro-emulsion release. Globule polarity, determined by these factors, dictates drug affinity for oil and water, impacting release kinetics. Higher polarity enhances drug release into the aqueous phase, with maximum release achieved in formulations exhibiting maximal polarity. Stability assessments predict potential precipitation in the gut, although delayed crystallization can stabilize colloidal systems. Studies suggest formulations may take up to 5 days to reach equilibrium, with medication remaining supersaturated for up to 24 hours post-emulsification. [47].

Characterization of SMEDDS

Turbid metric evaluation: Nepheloturbidimetric evaluation was done to monitor the growth of emulsification. Self-emulsifying system was added to 0.1N hydrochloric acids under continuous stirring on the magnetic plate at ambient temperature, and the increase in turbidity was measured using a turbid meter [84, 85].

Viscosity determination: Viscosities of the systems as such and after dilution with 5% v/v water were determined using a Brookfield rheometer at ambient temperature. Under varying shear rates, viscosities were measured and the data obtained were further analyzed by regression treatments [84, 85].

Droplet size analysis or particle size measurements: The droplet size of the emulsions is determined by microscopic techniques or Coulter Nanosizer or photon correlation spectroscopy. The nanometric size range of the particle is retained even after 100 times dilution with water which proves the system ‘s compatibility with excess water [84, 85].

Droplet polarity: The polarity of oil droplets is governed by the HLB value of oil, chain length and degree of unsaturation of the fatty acids, the molecular weight of the hydrophilic portion, and concentration of the emulsifier. The polarity of the oil droplets is also estimated by the oil/water partition coefficient of the lipophilic drug [84, 85].

Electrical Conductivity Measurement: The electrical conductivity of the samples was measured using a conductivity meter. The electrical conductivity of the formulations was determined to check the stability and assert the nature of the formulation [86].

Refractive index and percent transmission: Refractive index and percent transmittance prove the transparency of formulation. The refractive index of the system is measured by a refractometer by placing a drop of solution on a slide and it is compared with water. If the refractive index of the system is similar to the refractive index of

water and the formulation has a percent transmittance > 99 percent then the formulation has a transparent nature [86].

Centrifugation*:* Microemulsion systems were subjected to centrifugation at 3000 rpm for 30 minutes and then examined for any phase separation this technique helps to determine the behavior of small particles in a gravitational field [87].

Differential scanning calorimetry (DSC): The physical state of the drug in lipid carrier was analyzed by DSC studies. Thermal analysis of the drug, the physical mixture of the drug, and the Lipid carrier were carried out using the differential scanning calorimetric method [87].

X-ray diffraction studies: X-ray diffraction studies analyze the crystalline nature of the drug in the mixture. X-ray diffraction was performed using a diffractometer, with monochromatic radiation having suitable voltage and current at an angle of 2θ over a range of 5º 40º. Diffraction patterns of pure drug and Lipid carrier were prepared at the suitable drug-to-lipid ratio for the determination [87].
In-vitro diffusion study: In vitro diffusion studies were performed using dialysis technique/Dissolution apparatus [88].

Drug content: A drug from pre-weighed SMEDDS is extracted by dissolving in a suitable solvent. Drug content in the solvent extract was analyzed by a suitable analytical method against the standard solvent solution of the drug [88].

In-vivo Characterization includes Nonclinical Evaluation, Choice of nonhuman Test Species, and Lymphatic Transport [88].

Table 6: Marketed formulations of SEDDS [89]

Drug name	Compound	Dosage form	Company	Indication
Neoral	Cyclosporine A/I	Soft gelatin capsule	Novartis	Immune suppressant
Norvir	Ritonavir	Soft gelatin capsule	Abbott Laboratories	HIV antiviral
Convulex	Valproic acid	Soft gelatin capsule	Pharmacia	Antiepileptic
Lipirex	Fenofibrate	Hard gelatin capsule	Genus	Antihyper- Lipo proteinemic
Sand immune	Cyclosporine A/II	Soft gelatin capsule	Novartis	Immune suppressant

Applications

1. **Solubilization in SMEDDS**
   SMEDDS are usually efficient solubilizers of substances of a wide range of lipophilicity.
2. **Sustain release from SMEDDS**
   Microemulsion composition is important for the drug sustain release rate.
3. **Increase the bioavailability of drug**
   Many lipophilic drugs are having low solubility and bioavailability, there bioavailability increased by SMEDDS formulation.
4. **Super-saturable SMEDDS (S-SMEDDS)**
   S-SMEDDS was designed and developed to reduce surfactant side effects and achieve rapid absorption of poorly soluble drugs.
5. **Solid SMEDDS**
   An alternative approach for liquid SMEDDS to improve stability.

CONCLUSION

Self-microemulsifying Drug Delivery Systems (SMEDDS) offer a breakthrough in delivering hydrophobic/lipophilic drugs orally, with the potential for further extension pending the resolution of certain challenges. However, the formulation efficiency of SMEDDS varies case by case, necessitating meticulous composition determination. Given the prevalent use of relatively high surfactant concentrations in SMEDDS, the surfactant's toxicity becomes a crucial consideration, requiring a balance between toxicity and self-emulsification ability. Additionally, the particle size and charge of the oil droplets formed in the emulsion significantly impact gastrointestinal (GI) absorption efficiency. Validating SMEDDS efficiency relies on addressing key issues such as predicting the drug's solubilization state in vivo, and elucidating the basic mechanism of SMEDDS transport

through the GI tract. Despite their proven efficacy, the commercialization of lipid-based products remains limited. This scarcity may stem from insufficient understanding of the formulation parameters crucial for optimal in vivo performance and the relatively sparse human in vivo studies compared to conventional dosage forms. Furthermore, the absence of reliable in vitro tests predictive of in vivo performance significantly impedes the successful development of SMEDDS. In conclusion, SMEDDS offer a promising avenue for enhancing the oral delivery of challenging drug molecules. However, further research is imperative to optimize formulation parameters and explore their diverse applications in various therapeutic areas.

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Conflicts of interest

There are no conflicts of interest regarding the publication of this article to disclose.

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