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A CONCISE REVIEW ON NOVEL APPROACH FOR CHALLENGING PHARMACEUTICALS THROUGH SELF – MICRO EMULSIFYING DRUG DELIVERY SYSTEM (SMEDDS)

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Keywords:

Bioavailability, Surfactants, Absorption, Self-micro emulsifying drug delivery system (SMEDDS), Lipophilic drugs, HLB value

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ABSTRACT: SMEDDS are formulated to improve the oral bioavailability of lipophilic drugs. It is an isotropic mixture of compounds like oil, surfactant, co-surfactant, and drug having the unique ability to form fine o/w micro-emulsion by agitation and diluted with GI fluid. Its liquid formulation technique enhanced the absorption and bioavailability of poorly water-soluble drugs but also had a few drawbacks like long time period stability issues and storage conditions. Some special techniques convert the liquid form into solid dosage form to overcome these problems. The present paper gives exhaustive information about formulation design by screening excipients. We study the selection and solubility of excipients, its preparation and characterization, and the mechanism by which bioavailability can be improved. This discussion is useful for a better understanding of SMEDDS for its recent advancements, marketed formulation, and patents on SMEDDS. The poorly water-soluble drugs having dissolution rate absorption limited can be effectively formulated in the form of SMEDDS causing a stable plasma profile. The plasma levels of the poorly aqueous soluble medicament show the critical passage of drug absorption, *i.e.*, dissolution. Surfactants with a high HLB value, such as Tween 80 are said to increase the permeability of active ingredients when administered in conjunction with the formulation due to their loosening effect on tight junctions.

INTRODUCTION: The oral route of administration is preferred for persistent drug therapy. Scientists were facing many problems in finding the techniques to improve the bioavailability of poorly aqueous soluble drugs. Since a drug has to be dissolved in gastrointestinal tract (GIT) before passing through gastrointestinal mucosa, poor water solubility can lead to incomplete and irregular absorption [1].

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The issues of low oral bioavailability afflict several therapeutic molecules including lipophilic drugs. Improvement in their bio-availability and simultaneous prevention of the oral degradation of the susceptible molecules seems to be challenging [2]. Approximately 40 % of modern drug applicants have poor water solubility and hurdles to their successful oral delivery due to a complex web of physical, chemical, physiological, and anatomical factors that act independently and in concert to limit drug bioavailability [3].

Numerous techniques are suggested to elucidate these problems, such as the use of surfactants, cyclodextrin, nanoparticles, strong dispersions, lipids complexes, and permeation enhancers. Particulate drug transport systems, consisting of nanoparticles and microspheres, were studied

considerably for 10 years. But the toxicity of the synthetic polymeric substances consisting of alkyl cyno-acrylate, poly (lactic acid), Methyl methacrylate, *etc*. have been regularly used. The feasible accumulation and their poisonous metabolite product have also been studied [4].

Microemulsions are being investigated as a capable new colloidal provider for lipophilic drugs. Microemulsions provide benefits like amazing thermodynamic stability, excessive drug solubilization capacity, progressed oral bioavailability and safety in opposition to enzymatic hydrolysis. The best hassle with microemulsion is terrible palatability because of the excessive lipid content which affect patient compliance. Moreover, because of their water-content material, microemulsions can't be encapsulated in hard gelatin and soft gelatin drugs subsequently, there may be a need for anhydrous Self Emulsifying Drug Delivery system [5]. Thus, Self-Micro emulsifying Drug Delivery System (SMEDDS) is a lipid-based system designed to enhance oral bioavailability of lipophilic drugs. Few researchers have stated enhancement in bioavailability of poorly soluble capsules while formulated as SMEDDS. Researchers have tried lipid-based delivery of lipophilic drugs like cyclosporine and concluded that cyclosporine is capable for such delivery [6].

Self- micro emulsifying drug delivery systems (SMEDDS) are described as isotropic combinations of natural or synthetic oils, surfactants, and co-surfactants which have a completely unique capacity of forming splendid oil-in-water (o/w) micro emulsions upon slight agitation observed through dilution in aqueous media, together with GI fluids. Droplet sizes of SMEDDS ranging from 300-500 nm, even much less than 500 nm can also form. Lipophilic drugs showing dissolution rate-limited absorption might additionally provide growth in rate and volume of absorption and reproducible blood-time profiles [7, 8]. The SMEDDS can enhance the solubility and dissolution rate of the interfacial site for partitioning the medication among the oil and aqueous GI fluids. Generally, the conventional liquid SMEDDS (L-SMEDDS) are encapsulated in hard or soft gelatin capsules. However, the lipid technique may also interact with the capsules, ensuing both hardness and softness of the shell [9, 10, 11, 12]. L-SMEDDS promotes drug absorption via intestinal lymph by passing the first-pass impact of drugs. Moreover, drug added with the aid of using L-SMEDDS can spontaneously shape micro-emulsion with a droplet size of dozens of nanometers inside the gastrointestinal tract after oral administration [13, 14, 15, 16] and, therefore, enhances the absorption and bioavailability of poorly waters soluble drugs [17].

Despite many advantages, L-SMEDDS also have some significant drawbacks, including long-time stability issues, storage, transportation incon-venience, and irreversible drug precipitation [18]. Liquid formulations may be converted to solid dosage forms through appropriate techniques to conquer these drawbacks. A form of therapeutic solidification techniques have been explored, extrusion roll technique [19], spray drying technique [20, 21] solid carrier adsorption technique [22,] and so on [23]. Nevertheless, those therapeutic techniques require harsh preparation conditions. For example, extrusion roll and spray drying techniques contain high temperatures, which can be infeasible for heat-sensitive drugs. Also, high temperature impacts the drug loading capacity because of a low range of volatile surfactants in L-SMEDDS. On the other hand, solid carrier adsorption requires a massive quantity of adsorbent, which may cause high viscosity and low drug loading capacity. Thus, a more efficient technique for curing L-SMEDDS is urgently demanded [24].

Liquid-solid compacts (LSC) are amongst the novel formulations for BCS category II medicine to extend the drug dissolution [25, 26]. In liquid-solid formulation, a non-volatile solvent may be used for solubilizing the drug. Therefore the resultant mixture adsorbs onto a carrier system to make dry and free-flowing powder [27]. Liquid-solid compacts are non-adherent, free-flowing powders formed by exploitation drugs, non-volatile solvents, and fine-grained excipients like carrier and coating material [28]. Compared to the other dissolution enhancement techniques, the liquid-solid technique is convenient [29, 30]. In the SMEDDS technique, the drug is present in the soluble form inside the oil and ends up in fine globules when administered orally because of self -emulsification. The surfactant and co-surfactant reduce the interfacial surface tension of the system. In LSC technique, the drug is

solubilized within the non-volatilizable solvent. Hence, these developed systems may improve the solubility of aqueous insoluble drugs. But, the development of good oral bioavailability and better pharmacodynamic effects are important. Out of those two systems, *in-vivo* performance should be superior (PK and PD effects) [31]. Therefore, there is a tendency to work on developing an efficient tablet dosage form by concurrent works exploiting the approaches of each SMEDDS-associated liquid-solid formulation technique [32]. Incorporating liquid SMEDDS into a solid dosage form provides the benefit of SMEDDS with those of solid formulations and overcomes the drawbacks associated with this system. With this aim, an experimental design strategy to optimize a SMEDDS formulation of the tablet can be adopted, and the simplest composition in terms of drug dissolution properties can be selected [33].

Advantages:

- ✓ The irritation caused by prolonged contact between the drug and the stomach wall can be overcome with the SMEDDS formulation, as the micro-size droplets support the broad distribution of the drug along the GIT and are quickly transported through GIT [34, 35].
- ✓ When dispersed in water, these formulations produce fine droplets with a large interface, as the active ingredient can easily be distributed from the oil phase to the aqueous phase, which is not to be expected with oily solutions having lipophilic active ingredients [35].
- ✓ Compared to emulsions, SMEDDS are advantageous in terms of stability due to their low energy consumption and simple manufacturing process. Simple mixing devices are sufficient for the formulation of SMEDDS, and the time required for preparation is lower than emulsions [36, 38].
- ✓ The poor water-soluble drugs having dissolution rate absorption limited can be effectively formulated in the form of SMEDDS causing a stable plasma profile [36]. The constant plasma levels of the poorly aqueous soluble medicament show the critical passage of drug absorption, *i. e.* dissolution [39].
- ✓ Along with lipids, surfactants commonly used in SMEDDS formulations, such as Tween 80, Spans, Cremophors (EL and RH40), and Pluronic's, are reported to have an inhibitory effect on efflux transporters that help in improving the bioavailability of the drugs [30, 32, 33, 34]. The surfactant Tocopheryl polyethylene glycol succinate 1000 (TPGS), which is produced by esterifying vitamin E succinate and polyethylene glycol 1000, has an inhibitory effect on efflux transporters such as P-glycoprotein [42]. Paclitaxel from the GIT is inhibited with a formulation containing a surfactant called polysorbate 80 [43].
- ✓ Drugs that tend to be chemically and enzymatically degraded in the GIT can be protected by the formulation of SMEDDS, as the drug is presented to the body in oil droplets [36].
- ✓ Microemulsion pre-concentrate is advantageous over microemulsions dispensed as liquid-filled soft gelatin capsules [44].
- ✓ SMEDDS are advantageous over SEDDS, as the former are less dependent on bile salts for droplet formation, so better active substance absorption is expected compared to SEDDS [45].
- ✓ Surfactants with a high HLB value, such as Tween 80, are said to increase the permeability of active ingredients when administered in conjunction with the formulation due to their loosening effect on tight junctions [46].

Disadvantages [47, 48, 49]:

1. One of the barriers to the development of SMEDDS and other lipid-based formulations is the lack of good in vitro predictive models for evaluating formulations.
2. Conventional dissolution methods do not work as these formulations may depend on digestion before drug release.
3. The drawback of this system includes chemical instabilities of the drugs and high surfactant concentrations in the formulations (approx. 30–60%), which can irritate the gastrointestinal tract.

4. It is known that volatile co-solvents in conventional SMEDDS formulations migrate into the shells of soft or hard gelatin capsules and cause precipitation of lipophilic drugs.
5. Formulations with several components become more difficult to validate.
6. High Production cost.
7. Low drug compatibility.
8. Due to drug leakage, it may allow fewer drug loading.

Composition of SMEDDS: The self-emulsification process is reported to be specific to the nature of the oil surfactant pair. The procedure is based on [50, 51, 52]:

1. Oils.
2. The surfactant concentration and the oil / surfactant ratio.
3. The temperature at which self-emulsification occurs.

Some of the components used in SMEDDS are:

Oils: Long-chain triglycerides (*e. g.* soybean oil) and medium-chain triglycerides (*e. g.* Capmul MCM) were used in the development of SMEDDS with different degrees of saturation. Due to their biocompatibility, oils significantly contributed to the success of the SMEDDS [53]. Recently, medium-chain triglycerides have been replaced with new medium-chain semi-synthetic triglycerides containing compounds like Gelucire. Other suitable oils and fats for SMEEDS formulation include olive oil, corn oil, soybean oil, and animal fats [54].

Surfactants: A surfactant is required to take the property of self-emulsification by SMEDDS, which is the main method of forming a micro-emulsion and is also useful for solubilizing the hydrophobic drug; in turn, the dissolution rate can be improved [34]. The solubilization behavior of surfactants containing active ingredients gained popularity due to its inhibitory effect on the precipitation of *actives in-vivo* [59]. The permeability barrier, i. e. the intestinal cell membrane, which consists of lipids, can be modified by the distribution of the surfactant; therefore, the potency can be improved [36]. The opening of tight junctions by surfactants helps in improved permeability, as shown in the study by Sha *et al.* a greater permeability of the drug with the Labrasol surfactant was observed due to the opening of tight junctions [60]. The inhibitory effect of surfactants on the p-glycoprotein helps to improve the overall bioavailability of many drug substrates for the p-glycoprotein transporter [33]. Although natural surfactants are less toxic, the effectiveness of self-emulsification is limited [36]. Surfactants must be carefully selected for spontaneous emulsification to achieve an extremely low interfacial tension [60].

The surfactant selection is based on HLB value. Surfactants with a high HLB value facilitate the formation of o/w microemulsions [59]. Surfactants with a hydrophilic nature, *i. e.* HLB greater than 12, along with water-soluble co-solvents having relatively low octanol: water partition coefficient therefore to increase the solvent capacity of the formulation and the systems, very fine droplets size smaller than 100 nm at high surfactant concentrations is required [61]. The lower toxicity of non-ionic surfactants, such as oleates, polysorbates, polyoxyl, *etc*. compared to ionic surfactants enables them to be used more frequently in the formulation of SMEDDS [58]. Lipids commonly used in SMEDDS formulations, such as medium and long-chain triglycerides and non-ionic surfactants such as HLB-11 oleates with unsaturated acyl side chains are more suitable excipients for effective self-emulsification [57].

Co-Solvents: Co-solvent facilitates the dissolution of the surfactant and hydrophobic drug in the oil phase due to their ability to enable water to enter the formulation [34]. These excipients play the role of co-surfactants in the micro-emulsion system. Short-chain alcohols such as ethanol, n-butanol, propylene glycol, and polyethylene glycol are used as co-solvents [36, 59]. The addition of co-solvents such as short-chain alcohols gives flexibility to the interface, which is useful for the free movement of the hydrophobic tails of the surfactant at the interface, which in turn gives micro-emulsions dynamic behavior [60]. Alcoholic co-solvents with low molecular weight can cause drug precipitation when the formulation is filled into gelatin capsules, as they are absorbed into the capsule shells [57]. In addition to nature, the co-surfactant concentration also influences drug precipitation. Due to their high polarity, they tend to migrate into the aqueous

phase when dispersed in aqueous media, leading to the drug's precipitation. It is, therefore, advisable to formulate SMEDDS in minimal concentration [62]. The selection of the suitable surfactant and co-surfactant should consider the effectiveness, irritation, changes in effect due to repeated administration of the formulation, the interaction with mucosal proteins and lipids, and the metabolic pathway followed [56].

Active Agent: The lipid-based formulations are mostly preferred when poor solubility is the main reason for insufficient drug absorption [58].

The maximum bioavailability of SMEDDS can be achieved at very low doses, especially for drugs with high octanol: water partition coefficient. The absorption of the drug from SMEDDS depends mainly on its solubility in water and lipid phase [61]. The compounds having poor bioavailability due to the pre-systemic metabolism can be formulated as SMEDDS as long as the drug has a high solubility in long-chain triglycerides (> 50 mg/ml) octanol: water partition coefficient of more than five [55]. Some excipients used in different preparations are shown in **Table 1.**

TABLE 1: EXCIPIENTS USED IN DIFFERENT SMEDDS FORMULATIONS

S. no.	Drug	Oil	Surfactant	Co-Surfactant	Co-Solvent	Use
1	Atorvastatin	Labrafil, estol, isopropyl, myristate	Cremophor RH40, Cremophor EL	PG, PEG 400, Transcutol	_	Cardio-vascular
2	Acyclovir	Crodamol GTCC	Labrasol	Plurololeque CC 497	Macrogol 400	Anti-viral
3	Danazol	Capmul MCM	Tween 80	Transcutol HP	_	Endometerosis
4	Simvastatin	Capryol 90	Cremophor EL	Carbitol	_	HMG CoA Inhibitors (statin)

Mechanism of Self-Emulsification: The free energy of the emulsion can be described by the following equation:

$$\Delta G = \sum N \Pi r 2 \sigma \qquad (1)$$

Where ΔG is the free energy is the number of droplets, r is the radius of the droplets, σ is the Interfacial energy. The mechanism is explained diagrammatically.

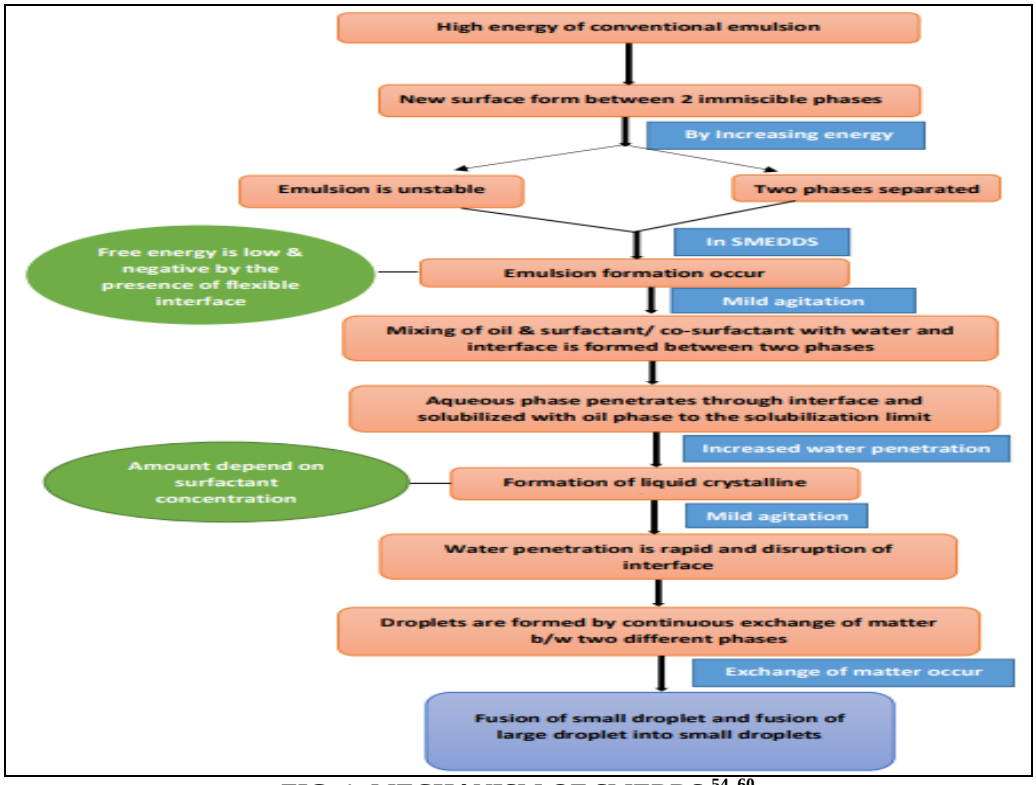

FIG. 1: MECHANISM OF SMEDDS [54, 60]

This equation shows that the lower the interfacial energy, the lower the free energy. Self-emulsification occurs when the energy involved in dispersion is greater than the energy required for droplet formation [34, 36].

Factor Affecting of SMEDDS:

1. **Drug Dosage:** Drugs that are administered in very high doses are not suitable for SMEDDS unless they show extremely good solubility in at least one of the SMEDDS components; preferably in lipophilic phases, drugs show limited solubility in water and lipids (typically with log P values of about 2) are the most difficult to administer as SMEDDS.

2. **Solubility of the Drug in the Oil Phase:** The ability of SMEDDS to keep the drug in solution is generally influenced by the solubility of the drug in the oil phase.

   Suppose the surfactant or co-surfactant contributes more to the solubilization of the drug. In that case, there is a risk of precipitation as the dilution of SMEDDS leads to a decrease in the solvent capacity of the surfactant or co-surfactant [1].

3. **Equilibrium Solubility:** The equilibrium solubility measurement can be performed to anticipate possible precipitations in the intestine. However, crystallization could be slow in the intestine's colloidal stabilization and solubilization environment [52].

4. **Polarity of the Oil Droplets:** The polarity of the lipid phase is one of the factors determining the microemulsion's release. The length of the HLB chain and the degree of unsaturation of the fatty acid, the molecular weight of the hydrophilic component and the concentration of the emulsifier determines the polarity of the droplets. In fact, the polarity reflects the affinity of the drug for oil and water and the nature of the process involved. The high polarity promotes rapid release of the drug into the aqueous phase [63].

Bioavailability Enhancement of SMEDDS: After oral administration, when SMEDDS comes into contact with aqueous intestinal components, it emulsifies spontaneously, which is further emulsified by the bile salt, resulting in the formation of small oil droplets about 0.5 µm in size.

To understand the mechanism by which the subsequent absorption of the drug from the emulsion system occurs, it is necessary to consider the *in-vivo* behavior of the constituent components [1].

Several reports point to improved absorption of active substances from the emulsified dosage form and SMEDDS [64, 65].

Different Modes of Enhanced Drug Absorption can be assumed as follows:

1. Digestible oil phase of the emulsion can synthesis chylomicrons from the fat components due to which the drugs can be absorbed through the lymphatic vessels.

   A lipophilic active ingredient, which preferably remains in the oil droplets, can mainly be absorbed together with the metabolite of the lipid carrier via bile salt micelles [66, 67].

2. The inhibition of gastric motility caused by the presence of the lipid phase of the emulsion could allow more time for the drug to dissolve and be absorbed from the lipid phase.

3. Increased mucosal permeability due to lipid storage from mixed micelles and increased mesenteric lymph flow can be responsible for improved drug absorption.

4. A hydrophilic agent is less likely to be absorbed via the lymphatic vessels (chylomicrons) and instead diffuses directly into the portal vein [63, 66, 68].

   Therefore, in this case, increasing the dissolution of the large surface area provided by the emulsion can contribute to improving drug absorption.

5. A relatively less focused consideration is the presence of surfactants in the formulation, which can also increase drug uptake [69, 70].

Formulation Design: The design is depicted as shown below:

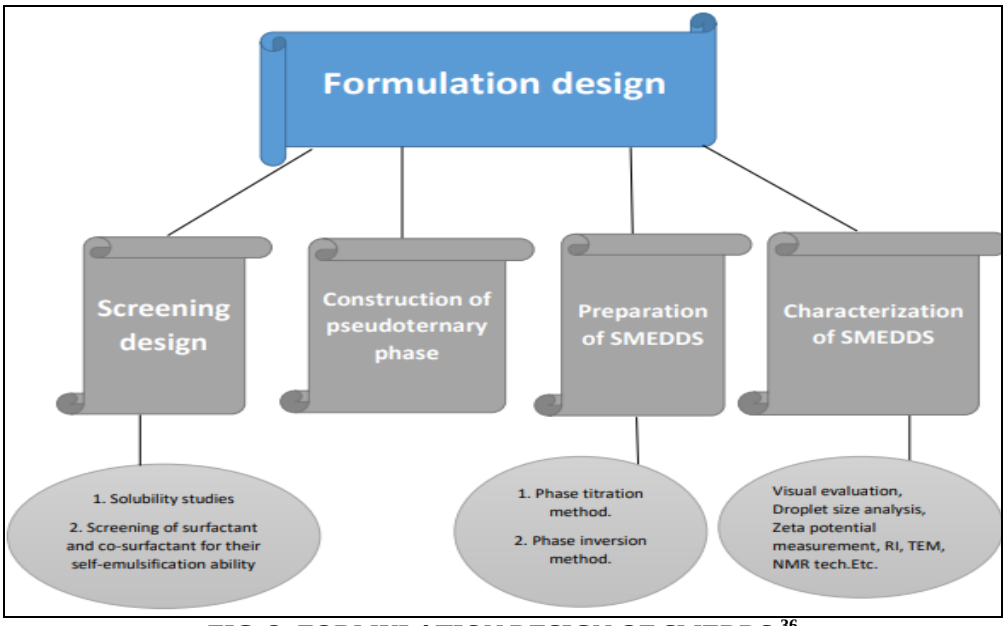

FIG. 2: FORMULATION DESIGN OF SMEDDS [36]

1. Screening of Excipients:

- **Solubility Studies:** These are mainly useful for selecting the most suitable excipients that can be used in the manufacture of the SMEDDS and in predicting the precipitation of live drugs. The solubility of the drug in different oils, surfactants, and co-surfactant should be tested. These investigations are usually carried out using the shake flask method, in which the active ingredient is usually added to the excipient in excess and then stirred for 48 hours in a water bath shaker or an air oscillator at room temperature [73, 74]. The samples should then be centrifuged and filtered through a 0.45 µm filter, with the active ingredient content determined. These solubility studies are generally conducted to select the oil that shows the maximum solubility of the drug and the surfactant / co-surfactant that has the maximum ability to solubilize the drug. The other goal is to achieve optimal drug loading with a minimal total formulation volume. Drug precipitation can occur from diluted SMEDDS, which depends on the drug's octanol: water distribution coefficient and the degree of surfactant participation in drug solubilization drug[75].

- **Selection of Surfactants and Co-surfactants to determine their Self-emulsifying Ability:** The emulsifying ability of surfactants can be determined by mixing equal proportions of selected oil and surfactant with subsequent homogenization. When this mixture is added to double distilled water, the number of revolutions of the piston required to form a homogeneous emulsion is recorded, indicating the ease of emulsification. The resulting microemulsion must be tested for clarity, turbidity, and percentage permeability, require low piston inversions should be chosen [76, 77]. Similarly, co-surfactants should be screened using the same procedure by mixing the selected surfactant and the oil phase with the co-surfactant [78].

2. Construction of Pseudo-ternary Phase Diagram: The ternary phase diagram is used to study the phase behavior of three components *i. e.* oil, water, and surfactant, but in the case of SMEDDS, the additional component, such as the addition of co-surfactant / solvent is the most common. The ternary diagram has three corners that correspond 100% to each component. If the fourth component is added, the ternary diagram can be referred to as a pseudo-ternary phase diagram since one of the corners corresponds to the mixture of two components, such as surfactant and surfactant[78].

- To construct the pseudo-ternary phase diagram, mixtures with different compositions of

microemulsion components have to be evaluated for their emulsification efficiency [79]. Different structures, such as emulsions, microemulsions, micelles, inverted micelle shapes, *etc*., can be formed in different compositions. The formation of these structures can be known by constructing a phase diagram. This phase diagram helps to determine the formulation's dilution capacity and obtain information about the different compositions that form transparent single-phase solutions [39].

- Pseudo-ternary diagrams are constructed by keeping the ratio of two of the four components constant. This ratio, along with the remaining two components, generally forms three corners of the phase diagram. This fixed ratio (mixture) is usually formed by the combination of surfactant and cosurfactant [75, 80,] and can sometimes be a mixture of oil and surfactant. This is mixed with the required volume of the third phase as an oil[80, 81] or cosurfactant [38]; then the other component, which is generally water, is added in incremental amounts, and for each addition of the fourth component, the solution must be tested for clarity, flowability, self-emulsification time and dispersibility [75].

The total percentage concentration of all components in each mixture should be 100% [79]. The pseudo-ternary diagram must then be drawn with the aid of suitable software. Samples that form a clear solution are to be identified by appropriate symbols in the phase diagram [82]. The area that forms when these points are connected shows the existing area of the monophasic microemulsion[83] and the broad area shows good emulsification efficiency [75].

3. Preparation of SMEDDS: Preparation involves adding the drug to the mixture of oil, surfactant, and cosurfactant, followed by vortexing. In some case the drug dissolve in one of the excipients and the remaining excipients are added to the drug solution [81].

The solution must then be properly mixed and inspected for signs of cloudiness. After equilibrating for 48 hours at room temperature, the solution should be heated to a clear solution if necessary. Volume, the formulation should be stored in capsules of the appropriate size [74].

Method of Preparation:

1. **Phase Titration Method:** Microemulsions are produced using the spontaneous emulsification method (phase titration method) and can be represented with the help of phase diagrams. Creating a phase diagram is useful for studying the complex series of interactions that can occur when different components are mixed. Formed along with various association structures (including emulsion, micelles, laminar, hexagonal, cubic, and various gel and oil dispersions) depending on each component's chemical composition and concentration. Understanding the phase equilibrium and delineating the phase boundaries is essential, with each corner of the diagram representing 100% of the component in question. The region can be divided into w / o or o / w microemulsion simply by considering the composition, that is, whether it is rich in oil or water. To rule out metastable systems, careful monitoring is required [71].

2. **Phase Inversion Method:** The phase inversion of micro-emulsions takes place by adding an excess of the dispersed phase or as a reaction to the temperature. Drastic physical changes occur during phase inversion, including changes in particle size that can affect drug release both *in-vivo* and *in-vitro*. These methods make use of changing the spontaneous curvature of the surfactant. In the case of non-ionic surfactants, this can be achieved by changing the system's temperature, which forces a transition from a low-temperature O / W micro-emulsion to a W / O micro-emulsion at higher temperatures (transition phase inversion). As the system cools, it passes through a point with no spontaneous curvature and minimal surface tension, encouraging the formation of finely divided oil droplets. This process is known as the phase inversion temperature (PIT) process. Instead of temperature, other parameters such as salt concentration or pH value can be taken into account instead of temperature alone. In addition, a transition of the spontaneous radius of curvature can be achieved by changing the volume fraction of water. By gradually adding water to the oil, water droplets are initially formed in a continuous oil phase. An increase in the volume fraction of water changes the

spontaneous curvature of the surfactant of water/oil micro-emulsion, which initially stabilizes an O / W micro-emulsion at the point of inversion. Short-chain surfactants form flexible monolayers at the o / w interface, which leads to a discontinuous micro-emulsion at the point of inversion[72].

4. Characterization of SMEDDS

1. **Visual Evaluation:** The self-emulsification can be assessed by visual assessment. After dilution of SMEDDS with water, an opaque and milky-white appearance indicates the formation of a microemulsion. In contrast, a clear, isotropic, clear solution indicates the formation of a micro-emulsion. Precipitation of the drug in diluted SMEDDS is also possible by visual evaluation. Formulations can be considered stable if no precipitation of the drug is evident. Precipitation is common when the formulation contains water-soluble co-solvents and can be avoided by increasing the surfactant concentration [36, 84, 86].

2. **Droplet Size Analysis:** The droplet size depends mainly on the type and concentration of the surfactant [87]. The micro-emulsion formed on dilution with water creates droplets of very narrow size and size distribution for efficient drug release, in vivo absorption, and stability. For droplet size analysis, spectroscopic techniques such as photon correlation spectroscopy and microscopic techniques are used [36, 84]. Dynamic light scattering techniques with the zeta meter can also be used for droplet size analysis [88]. Samples must be sufficiently diluted before size determination [73, 74]. Determining the polydispersity index (PDI) provides reasonable information about the size distribution [89].

3. **Zeta Potential Measurement:** The zeta potential is generally measured with a zeta potential analyzer or a zeta meter system. The zeta potential value indicates the stability of the emulsion after sufficient dilution. A higher zeta potential indicates good formulation stability [90]. In general, the zeta potential value is negative due to free fatty acids [84], but when cationic lipids such as oleyl-amine are used, the positive charge develops. Positively charged droplets have the property of efficiently interacting with the mucosal surface of the GIT. These interactions are electrostatic in nature, so strong adhesion with increased absorption can be expected.

4. **Time for Emulsification:** The time required for self-emulsion for the various formulations can generally be assessed using a USP Type II dissolution device by adding the formulation drop-wise to the water-containing basket, and the formation of a clear solution with stirring is observed while agitation provided by paddle at 50 rpm. Self-emulsification helps to determine the self-emulsification efficiency of the formulation [57]. It was found that the emulsification rate depends on the type of oil phase and the oil/surfactant ratio. A rapid rate of emulsification is observed at a higher surfactant concentration due to the rapid expulsion of oil droplets by penetration of water at the interface. Visual assessment can also determine the emulsification time after the formulation has been placed in 0.1 N HCl with shaking at body temperature, whereby GI conditions can be simulated [76].

5. **Cloud Point Determination:** The cloud point is generally determined by gradually increasing the temperature of the water bath into which the formulation is placed and measured spectrophotometrically. The point, at which the permeability in% decreases means the cloud point, which is the temperature above which the clear solution changes to a cloudy solution. The temperature is 37 °C; formulations must have a cloud point higher than body temperature to retain their self-emulsifying properties. Due to the susceptibility of the surfactant to dehydration, phase separation and reduced solubilization of the drug are often observed at temperatures above the cloud point. The cloud point is influenced by the drug's lipophilicity and other formulation components [57, 77].

6. **Viscosity Measurements:** The viscosity of the diluted SMEDDS formulation, which is a micro-emulsion, is generally determined with rheometers such as the Brookfield cone-plate rheometer with conical spindle or a Brookfield rotating spindle viscometer [91, 92]. During the

titration, the initial increase in viscosity followed by a decrease, whereby the increase in water volume is due to the water percolation threshold, indicates the formation of an O / W micro-emulsion from a W / O micro-emulsion with an intermediate bi-continuous phase. The rheology of the micro-emulsion can be determined from the diagram between shear stress and shear rate. The behavior indicates the presence of small, spherical droplets [93].

7. **Dilution Studies:** The effect of dilution on the clarity of the micro-emulsion can be assessed by diluting the micro-emulsion preconcentrate in various dilutions that simulate gastric conditions and in various diluents such as double distilled water, simulated gastric juice (SGF), and simulated intestinal juice (SIF) [94]. If the clarity is maintained with increasing dilution and a change in the type of diluent, this indicates the absence of drug precipitation [81]. The 100-time dilution of SMEDDS with all the diluents mentioned above can simulate in-vivo conditions [95]. The influence of the pH value of the dilution medium can be examined by diluting SMEDDS with various solvents such as buffer pH 1.2, buffer pH 6.8, etc., together with distilled water, and the transparency and efficiency of the self-emulsification should be observed [73].

8. **Refractive Index*:*** The index of refraction is the property by which the isotropic nature of dilute SMEDDS, a micro-emulsion, can be determined. Karamustafa and Celebi' performed refractive index measurements of the optimized formulation at 4 °C and 25 °C for up to 6 hours at different time intervals and concluded that there was no significant change in the refractive index, indicating the constant microemulsion structure [92]. The constant refractive index also indicates the thermodynamic stability of the formulation. Refractive index measurements are usually carried out with refractometers [93]. The refractive index depends mainly on two factors, namely the amount of co-surfactant and the size of the beads. The refractive index decreases with increasing cosurfactant concentration, which is due to the decrease in the rigidity of the micro-emulsion structure and increases with increasing bead size [89].

9. **Percentage Transmittance:** This test indicates the transparency of the diluted SMEDDS formulation. It is determined spectrophotometrically after diluting the formulation with water; the water is kept as a blank value. The percentage transmission value close to 100% indicates a clear and transparent micro-emulsion formation [75].

10. **Transmission Electron Microscopy (TEM) Study:** It is mainly used to study the structure and morphology of micro-emulsions formed by diluting SMEDDS. These studies are carried out by combining bright-field images with increasing magnification and diffraction modes [96, 97]. The grid and the morphology of the perforated film can be determined. Basalious *et al.* and Elnaggar *et al.* carried out TEM examinations by staining the samples. In both experiments, the drop of the diluted formulation was placed on a copper grid and, after staining with suitable dyes such as uranyl acetate, dried. Then the droplets were visualized for morphology detection, such as droplet size and shape. Some other colorants can also be used, such as B. 1% phosphotungstic acid solution and 1% methylamine vanadate [88]. TEM examinations can also be used to determine the uniformity of the droplet sizes [75, 76].

11. **Differential Scanning Colorimetry:** It is mainly used to characterize micro-emulsions formed by diluting SMEDDS with peaks corresponding to water. The peaks provide information about the state of the water as a bound or Free State. Pure water is used as a reference, showing a large, sharp peak at around -17 ° C, indicating the freezing point. Podlogar et al. DSC experiments carried out on water micro-emulsions, isopropyl myristate system Tween 40 / Imwitor 308 and identified peaks which correspond to water at a lower temperature than pure water (approx. -45'C at 15% W/W) shows the presence of the bound state in micro-emulsions preferably bound to surfactants. A higher water concentration than this leads to a change in temperature. From the observations of thermal water behavior, they concluded that the high-water concentration (> 35% p / w) generated micro-emulsions O / W [77, 98].

12. **NMR Techniques:** These are used to evaluate the structure of the micro-emulsions formed after diluting SMEDDS. The diffusion behavior of the components of the micro-emulsion can be investigated with the help of the pulsed gradient spin echo (PGSE) method of Fourier transform. Examined with the PGSE-NMR method. The droplet size of the micro-emulsion can be determined with 129xe NMR by observing the shift of the signal to a higher field with the corresponding increase in the droplet size. Self-diffusion NMR studies are used to determine the type of micro-emulsion that forms upon dilution of SMEDDS and also to determine transitions such as W / O to bi-continuous and bi-continuous to O / W type in incremental dilution. This technique compares the self-diffusion coefficients of the micro-emulsion components with those of the pure components. Suppose the diffusion of any of the components is less than that of the pure component. In that case, this indicates the presence of droplets, that is, O / W or W / O, and cosurfactant also diffuses slowly through these components due to the formation of a film around the droplets. If the oil and aqueous phases have high diffusion coefficients and are of the same size as the neat components, this indicates the presence of a bi-continuous micro-emulsion. [91,99].

13. **Small-Angle X-Ray and Neutron Scattering Methods:** Small-angle X-ray scattering techniques are useful for characterizing structures formed by thinning SMEDDS. Assessment of the liquid crystal structures formed by dilution of SMEDDS is important as they determine formulation stability, self-emulsion and the degree of drug release. Goddeeris *et al.* performed small-angle X-ray scattering studies on formulations containing different proportions of water. A random lamellar or periodic structure was observed at 10% w / w (lower) water concentration, and lamellar structures were observed at 20% w / w water concentration. It showed hexagonal or lamellar structures at a water concentration of 40% w / w. The temperature increase from 25 ° C to 37 ° C did not significantly change the liquid-crystalline structures formed [100]. Methods of small-angle neutron scattering are useful for determining transitions in micro-emulsion structures after dilution and for determining droplet size and shape [84, 99].

14. **Thermodynamic Stability Studies:** These studies are useful to assess the consequences of a temperature change in the formulation. The formulation is diluted with an aqueous phase and centrifuged for 15 min at 15,000 rpm [81] or 30 min at 3,500 rpm. The sample in which phase separation is not observed is subjected to freezing and thawing cycles (-20 ° C and 40 °C temperature, respectively) and observed visually. Thermodynamically stable formulations show no change in the visual description [81, 96].

15. ***In-vitro* Dissolution Profile:** The release of the drug from the formulation can be assessed after placing the formulation in a hard gelatin capsule with Apparatus I of USP XXIII at 100 rpm or Apparatus II of USP XXIII at 50 rpm or with the dialysis method. at 37 ± 0.5 °C [101, 102]. Samples should be taken from the medium at regular intervals and the active substance content estimated and compared with the control. The polarity of the oil droplet influences the active ingredient release from diluted SMEDDS. The higher the polarity, the faster the drug will be released from the oil droplet into the aqueous phase. The polarity depends mainly on the HLB of the surfactant, the molecular weight of the hydrophilic part of the surfactant, and its concentration, together with the degree of unsaturation of the fatty acid of the lipid phase. In a study performed by Jantratid *et al.*, a comparison is made between the drug release profile using paddle-type apparatus and the reciprocating cylinder using USP apparatus 3. The active ingredient release from liquid lipid dosage forms such as SMEDDS is more suitable than the paddle method and provided reproducible results compared to the paddle method and concluded that this behavior is due to the even breakdown of the oil layer by the movement of the inner cylinder can be attributed to net inserts compared to the paddling method [103,104].

16. **Stability Assessment:** Stability studies are performed on the formulation packaged in

gelatin capsules according to ICH guidelines. Samples should be taken at regular intervals and analyzed for appearance, color, active ingredient content, pH value of the diluted formulation, and dissolution profile. If all these properties change during storage conditions, the formulation can be closed as a stable formulation [90, 102]. The various marketed formulations of SMEDDS are shown in **Table 2.**

TABLE 2: VARIOUS MARKETED FORMULATIONS OF SMEDDS [126, 127, 128]

S. no.	Drug	Indication	Brand name	Manufacturer	Dosage form
1.	Paclitaxel	Anticancer	Paclitax	Cipla Ltd	Intravenous injection
2.	Fenofibrate	Antihyperlipidemic	Lipired	Square pharmaceutical Ltd	Hard gelatin capsule
3.	Cyclosporine	Immunosuppressive	Genraf	AbbVie	Hard gelatin Capsule
4.	Naproxen	Analgesic	Arthopan	Crescent therapeutics Ltd	Tablet
5.	Tipranavir	Anti –HIV	Aptivus	Boehringer Ingelheim	Soft gelatin Capsule
6.	Acyclovir	Antiviral	Ocuvir	FDC Ltd	Tablet

Application [106, 107, 108]: Various applications of SMEDDS are discussed below:

1. **Improving the Solubility and Bioavailability:** Increasing the bioavailability of BCS class II drugs several times by improving drug solubility and rate of dissolution.

2. **Protection of the Drug from Biodegradation:** Many drug formulations degrade in physiological fluids/systems due to the change in pH around the drug. Since the acidic pH value in the stomach leads to enzymatic or hydrolytic degradation, an obstacle between the drug and the degrading environment is formed due to the LC phase.

3. **No Effect of Lipid Digestion Process:** This drug delivery system is not affected by lipolysis as this system is not broken down by the action of pancreatic lipases and bile salts, as this only help in self-emulsification of the formulation.

4. **Drug Loading Capacity Improvement:** Formulation excipients provide high drug solubility, resulting in the formulation's high drug loading capacity.

5. **SMEDDS for Herbal Medicines and Traditional Medicines:** A large number of herbal and traditional medicines are used to develop SMEDDS because most contain volatile and solid oils [109].

6. **Peptide Delivery:** This drug delivery system offers protection against enzymatic degradation in the GIT, as this system is suitable for the delivery of peptides, hormones, substrates/enzyme inhibitors.

7. **Controlled Release Formulation:** The addition of polymer into the SMEDDS composition provides a sustained/controlled release of the drug. [110-112]

Recent Trends in Smedds [113, 125]:

1. Self-micro Emulsifying Mouth Dissolving Film (SMMDF): SMMDF was developed for water-soluble drugs. Indomethacin was made by fusing self-emulsifying segments to a solid support (microcrystalline cellulose [MCC], low-substituted HPMC, and hypromellose). SMMDFs breakdown in 20 seconds, and the active ingredient was completely released into the disintegration medium with a bead size of 28.81 ± 3.26 nm within 5 minutes. The units of measure complied with the 2010 Chinese Pharmacopoeia criteria for consistency parameters. Pharmacokinetic parameters such as T-max, C-max, and area under the curve (AUC) were measured compared to liquid SMMDF and SMEDDS. The C-max and AUC for SMMDF have been found to be significantly higher than those for normal, mouth-dissolving films or tablets with poor water solubility.

2. Sponges Carrying SMEDDS: Sponges wear SMEDDS to improve the solubility of lipophilic drugs, but their liquid nature has been a limitation to their wide use. Its sponge expansion, created using a common hydrophilic polymer, is another system for the SMEDDS scheme. Its nanosponge structure focused on inspecting in electron microscopy and little Edge x-pillar diffuse. The oil globules were dried, and 9 nm SMEDDS were found on the dry sponge. The sponge was rehydrated and the presence of SMEDDS was determined on the rehydrated sponge.

SMEDDS containing Nile Red (soluble in all dry and rehydrated sponges) are discharged drop by drop from the nanosponge at a rate that depends on the drying method used. The drying schedule was found to have an incredible impact on the nanosponge water absorption. SMEDDS could be a way of providing a solid framework for SMEDDS that can cope with the use of hydrophobic drug delivery.

3. Herbal SMEDDS [117]: The SMEDDs delivered fluids that filled hard gelatin capsules that have been considered to formulate safe and stable dose forms for herbal extracts. The formulation's development and selection were based on the solubility and phase diagram results. Warke *et al.* used the improved preparation for in vitro dissolution consisting of Cremophor RH 40 (40%), Plurol Oleique (30%), and herbal extract (30%) and showed a complete discharge in 10 minutes. SMEDDS successfully passed its solubility testing in storage conditions as per ICH guidelines for 3 months. Improved dissolution profiles of herbal extracts were created from SMEDDS. SMEDDS turned out to be an amazing approach to increasing the bioavailability and solubility of herbal medicines.

4. Self-micro Emulsifying Floating Dosage form [118]: The drug, which is poor in solubility, subject to pre-systemic metabolism and irregular absorption of the drug throughout the gastrointestinal tract, is faced with poor oral bioavailability. The floating system increases the residence time of the drugs in the stomach, which leads to a prolonged release of the drugs. Adsorption on a mixture of highly functional excipients, matrix-forming polymers such as HPMC E50 LV, HPMC K4M, and $NaHCO_3$ (a gas-generating agent) to achieve a floating matrix with a controlled release drug profile. In another experiment, floating alginate beads containing tetra-hydrocurcumin (SEDDS) were developed to improve the solubility of drugs and to increase the residence time in the stomach. Using different levels of calcium chloride, a water-soluble pore former, and sodium alginate in the bead formulation resulted in different effects on their ability to float and drug release rates in vitro.

5. SE Capsules: In the case of conventional SE formulations, no improvement in drug absorption can be expected with permanent phase separation of the micro-emulsion. To solve this problem, sodium dodecyl sulfate was used in the SE preparations. Supersaturated SEDDS was developed for a parallel purpose by using small amounts of HPMC (and / or other polymers) in the formulation to prevent drug precipitation from creating a supersaturated state *in-vivo* and to maintain side effects on GIT Liquid self-emulsifiable materials can also be filled in the solid or semi-solid state in capsule shells, which are obtained by adding solid carriers such as polymers and adsorbents. For example, the presence of a solid PEG matrix did not interfere with the self-micro-emulsification process or the solubility of the drug. These are typically made in liquid form or encapsulated in soft gelatin capsules.

Conventional liquid SMEDDS had some drawbacks in the manufacturing process, which caused high production costs, were difficult to use, and also gave rise to problems of physical incompatibility with the shells of soft gelatin capsules, they also gave rise to storage problems. Liquid SMEDDS can be prevented by filling the capsules with S-SMEDSS. In the case of semi-solid materials, the excipients materials are first melted and then packed in capsules. The contents of the capsule are solidified to room temperature [119,120].

Solid SMEDDS (S-SMEDDS): This new technology provides an effective replacement for traditional liquid SMEDDS for low solubility drugs. SMEDDS is produced by adding semi-solid / liquid SE components in powders or nanoparticles. Different solidification technique like spray drying, absorption onto solid carriers and melt extrusion techniques are used by which it is converted into solid nanoparticles of SE, which can be processed into other solid pharmaceutical forms of SE such as capsules, solid dispersions, dry emulsions, microspheres, nanoparticles, suppositories, implants, beads, granules and tablets [115].

Future Perspective: SMEDDS could be an effective way to overcome the problem of drug solubility with relatively poor solubility in GIT fluids. The role of gut lipids in solubilizing lipid-based formulations could be better understood through the combination of dispersion and *in-vitro*

digestion. In the future, the development of SMEDDS eliminates all complications associated with administering low-solubility drugs. Have a long way to cover, before more SMEDDS products are brought to market as more SMEDDS needs to be used, including bioavailability research and the development of *in-vitro* and *in-vivo* correlation (IVIVC) and other dosage dosage forms [119]. Patents

Over the past few decades, self-micro emulsifying drug delivery systems have been investigated for a variety of potential applications in diagnostic and drug delivery technologies. Pharmaceutical industries have granted various patents for self-micro emulsifying drug delivery devices. A couple of these issued patents are shown in **Table 3.**

TABLE 3: PATENTED SMEDDS FORMULATIONS [130-134]

S. no.	Approaches	Application	Patent no.	Inventor
1.	SMEDDS of mitotane.	Method was developed to enhance the bioavailability of a poorly water-soluble drug using a surfactant and a polar-lipids.	US14/802,837	Hassan (2017)
2.	Self-micro emulsifying formulation consisting of poorly soluble drugs, vitamin E, co-solvent, bile salts and surfactant.	Increases bioavailability of poorly soluble drugs Paclitaxel and Docetaxel.	EP2062571A1	Hao WH, Hsu CS, Wang JJ (2012)
3.	SMEDDS of Imwitor 308	Enhanced solubility of formulation, containing oil, surfactant, co-surfactant and co-solvent.	US20100331356	Legen and Igor (2010)
4.	Self-micro emulsifying formulation containing taxoid, surfactant and co-surfactant.	Taxoid are poorly water-soluble compounds having high molecular weight and slightly lipophilic. It enhances oral bioavailability of toxoids through self-emusification.	EP1498143A1	Cote S, Goudel G, Peracchia MT (2005)
5.	SMEDDS of simvastatin	Method of reducing effect of intestinal metabolism on drug using other excipient in formulation.	US6652865	Benomeur *et al.* (2003)

CONCLUSION: Self-micro emulsifying drug delivery systems are a novel and efficient approach for enhancing the oral bioavailability of many poorly water-soluble drugs, provided the drug is potent and has a high lipid solubility.

SMEDDS has been shown to promote lymphatic delivery of extremely hydrophobic drugs with good triglyceride solubility. The current review emphasized the developmental steps involved in obtaining a consistent and stable dosage form, such as solubility studies, the construction of pseudo ternary phase diagrams and various evaluation tests. Further research into developing SMEDDS with low-toxicity surfactants and developing *in-vitro* methods to better understand the *in-vivo* fate of these formulations can increase the market availability of SMEEDS.

From Literature survey it is revealed that SMEDDS considered being very stable formulation, very good alternative of microemulsion.

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