

# Self-Micro emulsifying Drug Delivery System: A Review

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**Abstract-** Self-micro emulsifying drug delivery systems are designed for drugs having pre-systemic first-pass effects, high molecular weights, gastric irritability, enzymatic degradation, slow rates of dissolution, and lower bioavailability. Due to the drug's solubilization in lipidic excipients, which skips the dissolving stage, the generated emulsion delivers faster absorption, faster dissolution rates, and excellent bioavailability, making this method ideal for practically all drugs. SMEDDS, or self-micro emulsifying drug delivery systems, are isotropic blends of natural or synthetic oils, solid or liquid surfactants, or alternatively one or more hydrophilic solvents and co-solvents/surfactants.

The review covered the mechanism of self-emulsification in detail as well as the construction of a pseudo ternary phase diagram, the formulation of SMEDDS, its solidification techniques, its characterization, the advantages of SMEDDS over emulsion, and the limitations as well as applications of SMEDDS. This review article will provide as a starting point for researchers studying SMEDDS, methods for improving bioavailability, and drug solubility in water.

**Keywords:** Self-Micro emulsifying drug delivery system, Surfactant, Co-surfactant, Pseudo-ternary phase diagram.

## INTRODUCTION:

Most novel chemical entities (NCEs) of today are poorly water-soluble, which makes it difficult to create the best solid oral dosage form for them. For the treatment of many chronic diseases, including cancer, the oral route has been the predominant medication delivery method. The low aqueous solubility of about 40% of the drug compounds, which results in low oral bioavailability, high intra- and inter-subject variability, and a lack of dose proportionality, restricts oral delivery. Different formulation strategies have been used, such as the use of cyclodextrins, nanoparticles, solid dispersions, and permeability enhancers, to solve the above mentioned limitations [1]. The integration of the active lipophilic component into inert lipid carriers, such as oils, surfactant dispersions, self-emulsifying formulations, emulsions, and liposomes, is one of the most often used strategies [2]. Self-emulsifying and self-microemulsifying drug delivery systems (SEDDS and SMEDDS) have demonstrated some effectiveness in recent years in increasing the oral bioavailability of lipophilic and weakly water soluble medicines [3]. Typically, SEDDS and SMEDDS are made as liquids or encapsulated in soft gelatin capsules, both of which have drawbacks, particularly in the manufacturing process, which drives up production costs [4]. SEDDS is an isotropic blend of natural or synthetic oils, one or more hydrophilic solvents, solid or liquid surfactants, and cosolvents/cosurfactants. Due to the agitation caused by the stomach and intestinal motility during digestion, which is required for self-emulsification, they cause the development of o/w type emulsion or microemulsion in the digestive tract (GIT) [5].

Self-microemulsifying drug delivery systems (SMEDDS) have gained more attention recently as a potential method for delivering medicines with poor water solubility. Due to their high effectiveness in enhancing drug solubility, speeding up the dissolution process, enhancing oral absorption for medications with weak water solubility, and ease of preparation, SMEDDS have grown in popularity [6]. SMEDDS are isotropic compositions of drug ingredient, oil, surfactant, and co-surfactant. In order to dissolve the weakly water-soluble medicine and create fine microemulsion droplets after being added to the aqueous media with gentle agitation, oil, surfactant, and co-surfactant are crucial components. Basically, solubility studies and phase behaviour analysis can be used to determine the type of each ingredient in the SMEDDS formulation [7]. The Biopharmaceutical Classification System (BCS II) drug difficulties of high molecular weight, low solubility, stomach irritability, enzymatic degradation, pre-systemic first pass-effect, limited bioavailability, and drug stability are all resolved by SMEDDS. To identify the optimal emulsifying zone, a ternary phase diagram is plotted using water titration and dilution procedures. The resulting microemulsions particle size is less than 100 nm, and the hydrophobic drug's rising solubility can improve intestinal absorption [8].

As a novel and adaptable method for increasing the water solubility and ultimate bioavailability of lipophilic drugs, SMEDDS has a number of benefits, including safe and simple composition, more consistent temporal profiles of drug absorption, ease of manufacture and scale up, prolonged release of medications when a polymer is used, selective drug targeting toward a particular absorption window in the GI tract, and drug protection from the hostile environment in the gut. Greater bioavailability results in a reduction in the amount of medication needed, which not only decreases the overall cost of medications but also minimizes the toxicity of drugs taken orally. Thus, the overall advantages suggest that SMEDDS research will proceed and that new medicines molecules made using SMEDDS will soon be available on the pharmaceutical market [9].

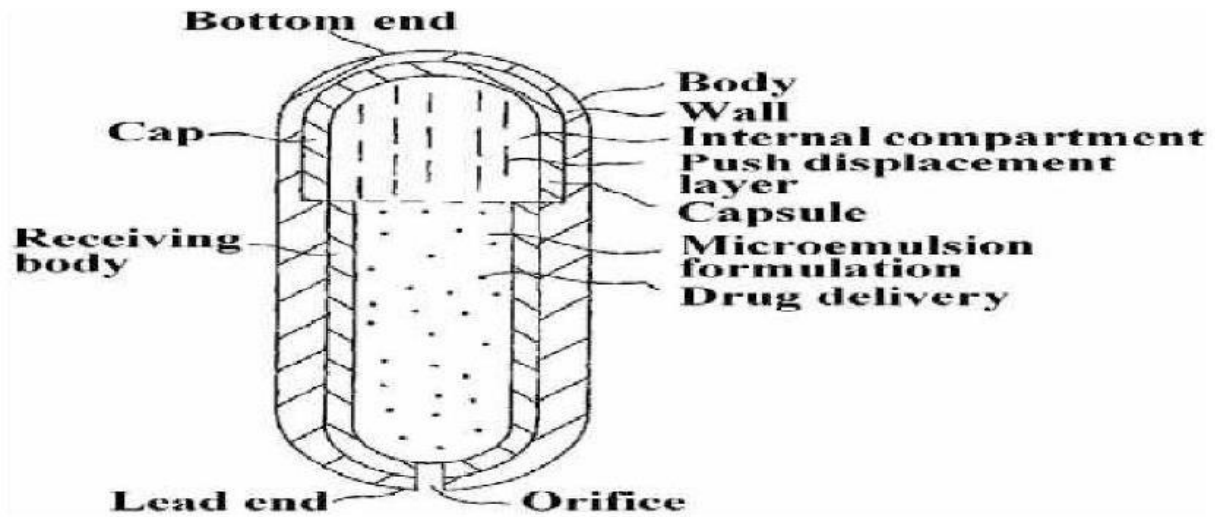


Figure 1: Capsule dosage form containing Micro emulsions

### MECHANISM OF SELF-EMULSIFICATION:

Reiss' research indicates that self-emulsification takes place when an increase in entropy occurs when dispersion is larger than the energy needed to increase its surface area. Equation can be used to describe the free energy of traditional emulsion formation, which is a direct function of the energy needed to establish a new surface between the two phases [10]

$$\Delta G = \Sigma N i \pi r^2 \sigma$$

Where,

$\Delta G$  – free energy accompanying the process (apart from the free energy of mixing),  $N$  – Total number of droplets,

$r$  – Radius of the droplets,  $\sigma$  – Energy at the interface.

To decrease the interfacial area and, thus, the system's free energy, the two phases of the emulsion will tend to separate. As a result, typical emulsifying agents stabilise the emulsions produced by aqueous dilution by forming a monolayer surrounding the emulsion droplets, which lowers the interfacial energy and acts as a barrier to coalescence. The interfacial structure must not be resistant to surface shearing for emulsification to take place. Since the free energy created in SMEDDS can be either positive, extremely low, or even negative, spontaneous thermodynamic emulsification occurs as a result. When a binary mixture (non-ionic surfactant/oil) is added to water, the interface between the continuous aqueous phase and oil is created. According to research, self-emulsification occurs when water enters the liquid crystal phase that forms at the water-oil/surfactant interface, where water can easily enter with the help of gentle agitation. When water reaches a specific point of penetration, the contact is disrupted and droplet production occurs [11].

### FORMULATION OF SMEDDS:

There are many oils and surfactants that can be utilized as microemulsion system components, but their use is restricted due to their toxicity, potential for irritability, and unknown mode of action. In order to produce mild and non-aggressive microemulsions, one must select materials that are biocompatible, non-toxic, and clinically acceptable. Emulsifiers must also be used in the proper concentration range. The nature of the oil/surfactant pair, the surfactant concentration and oil/surfactant ratio, the concentration and nature of the co-surfactant, the surfactant/co-surfactant ratio, and the temperature at which self-microemulsification takes place were all found to be important factors in early studies. The fact that only highly precise combinations of pharmaceutical excipients produced effective self-microemulsifying systems further validated these significant discoveries [12]. The SMEDDS formulation instantly creates a clear dispersion after diluting and keeps its stability. The hydrophobic medication that is distributed in the SMEDDS formulation is still soluble after absorption. The size of the globules and the polarity of the droplets play major roles in the efficient release of the drug from the formulation. Since the medicine included in the oil globules reaches the capillaries, the polarities of oil droplets are not significant in oil-in-water microemulsions [13].

When developing SMEDDS, the following factors must be taken into account:

1. The drug's ability to dissolve in a variety of oils, surfactants, and cosolvents.
2. Choosing the oil, surfactant, and cosolvent depending on the drug's solubility and creating the phase diagram [14].

### Selection of suitable drug candidate:

Lipid-based formulations provide a possible platform for enhancing the oral bioavailability of medications, particularly those falling under classes II and IV of the Biopharmaceutical Classification System (BCS). By evaluating the drug's lipophilicity ( $\log P$ ) and its solubility in pharmaceutically acceptable lipid excipients, which should be sufficient to allow the entire dose of the drug to be administered in a single dosage unit, a primary indication of the potential utility of lipid-based formulation can be obtained. When compared to lipid solutions, SMEDDS systems often have a higher drug loading capacity because amphiphilic surfactants, co-surfactants, and co-solvents have substantially higher solubilities of poorly water soluble medicines with intermediate partition coefficients ( $2 < \log P < 4$ ). The primary factor to consider while building lipid-based systems is the partition coefficient ( $\log P$ ). For

lipidic systems, a high log P (higher than 4) is preferred. Melting point and dosage are the following physicochemical characteristics that are crucial. To build lipidic systems, it is preferable to have low melting points and low doses. [15].

The components of SMEDDS formulation are as follows:

1. Oils
2. Surfactant
3. Co-surfactant/ Co-Solvent
4. Other excipients

### 1. Oils

Depending on the molecular structure of the triglyceride, oils can solubilize the required dose of the lipophilic drug, facilitate self-emulsification, and increase the percentage of lipophilic drug delivered by the intestinal lymphatic system, hence improving absorption from the GI tract. For the creation of self-emulsifying formulations, long and medium chain triglyceride (LCT and MCT) oils with various saturation levels have been employed. In the SMEDDS, novel semi-synthetic MCT, which are amphiphilic molecules with surfactant characteristics, are gradually and successfully replacing the conventional MCT oils. MCT hydrolyze more quickly than LCT because they are more soluble and active in the lipid/water interfaces. In comparison to MCT, creating microemulsions with LCT often requires a larger concentration of cremophor RH40. Due to their low ability to dissolve significant doses of lipophilic drugs, edible oils are not usually chosen. Since these excipients form effective emulsification systems with a large variety of surfactants approved for oral administration and exhibit enhanced drug solubility qualities, modified or hydrolyzed vegetable oils have been widely employed. They have physiological and formulative benefits, and the breakdown products they produce resemble the natural byproducts of intestine digestion [16].

Example of oils: - Corn oil, Sesame oil, Soya bean oil, Peanut oil, Hydrogenated soya bean oil, olive oil, peanut oil, palm seed oil, coconut oil [16].

### 2. Surfactants

Surfactants help to facilitate the dispersion process by forming the interfacial film and reducing the interfacial tension to a low value. When choosing a surfactant, it is crucial to take into account the HLB value and surfactant concentration. The emulsifier used in the formulation of SMEDDS should have a high HLB larger than 12, which aids in the creation of small o/w droplets and the quick spreading of formulation in aqueous media, in order to achieve strong emulsifying performance. For the design of self-dispersing systems, non-ionic surfactants with HLB values larger than 12 are typically recommended since they are less hazardous than ionic surfactants. The type of hydrophilic group that exists within a surfactant molecule can be used to categorize the molecule. The four major categories of surfactants are as follows: [17]

- a. Anionic surfactants:** An anionic surfactant is a group that prefers water and has a negative charge. For instance, sulphate (RSO<sub>3</sub><sup>-</sup>), carboxyl (RCOO<sup>-</sup>), or Sulphate (ROSO<sub>3</sub><sup>-</sup>). Sodium lauryl Sulphate with potassium laurate (SLS).
- b. Cationic surfactants:** A hydrophilic substance that transmits a positive charge is a cationic surfactant. Quaternary ammonium halide, as an illustration.
- c. Zwitterionic surfactants (also called Ampholytic surfactants):** include substances like sulfobetaine that have both a positive (+ve) and a negative (-ve) electrical charge.
- d. Non-ionic surfactants:** Non-ionic surfactants are polar groups that do not transfer any charge, but they still gain their water solubility from extremely hydrophilic groups, like polyoxyethylene or hydroxyl, for instance, in tween [17].

### 3. Co-surfactants/ Co-Solvent:

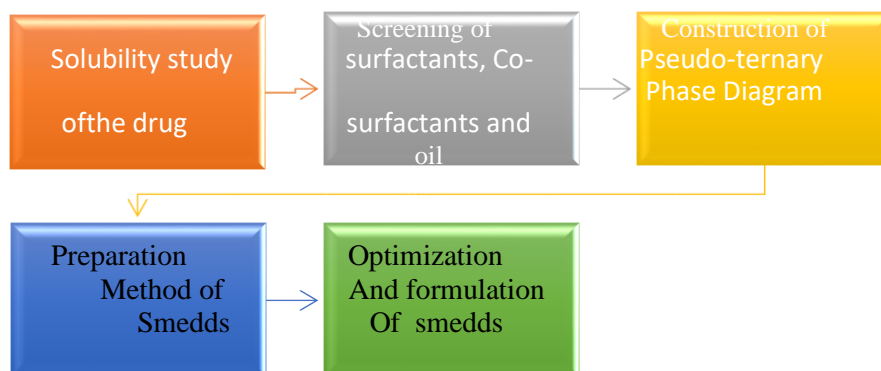
The ideal SMEDDS is typically prepared with more than 30% w/w of surfactant; therefore, other co-surfactants are used to lower the surfactant concentration. When used in formulations, co-surfactants have the tendency to reduce interfacial tension to very low transitory values. A finely distributed droplet causes the interface to expand at this stage, and it then continues to absorb additional surfactants and surfactant/co-surfactants until its bulk condition is sufficiently depleted to restore positive interfacial tension. Large volumes of hydrophilic surfactant or drug in lipid base are typically dissolved with the aid of short-chained alcohols, such as methanol and ethanol, propylene glycol (PG), polyethylene glycol (PEG), etc [18].

### 4. Other excipients:

To enhance the stability and compliance of the SMEDDS formulation, several pH adjusters, flavouring agents, and antioxidants agents were used. A small number of free radicals (ROO<sup>-</sup>, RO<sup>-</sup>, and -OH) produced during the formulation process may harm the drug and cause toxicity. Lipids self-oxidize and produce peroxide ions; the pH of the solution may also increase lipid breakdown. Thus, lipophilic antioxidants such as tocopherol, propyl gallate, or BHT are utilised to preserve the stability [17].

## FORMULATION APPROACH:

The steps below can be used to prepare SMEDDS:



#### a. Solubility study of the drug:

A study on the drug's solubility in different food oils is being conducted. A vial is filled with extra drug (300–500 mg), 2 gm of a chosen oil, and a seal. The combination is then mixed for 48 hours in a controlled setting with a temperature of around  $30 \pm 0.5^\circ\text{C}$ . The mixture is then transferred to a centrifuge and mixed for 5 minutes at 3000 rpm before being filtered using a 0.45mm membrane filter. Chloroform is used to dilute the filtrate and as a blank for spectrophotometric quantification. In triplicate, each experiment is being conducted [19].

#### b. Screening of Surfactants:

Out of the category of surfactants that can be used orally, screening is done to see how well they can emulsify. The ratio of oil to surfactant is the same. The mixture is heated to  $40^\circ\text{C}$  and stirred for a while to achieve homogeneity. Various types of surfactants are used in the addition of distilled water to the mixture to create a homogeneous and transparent combination. After two hours of storage, the created transparent emulsion is used to calculate the percentage transmittance at an appropriate wavelength using a UV spectrophotometer and distilled water as a standard. Visual observation is used to detect any changes in the stability, phase separation, or physical appearance [20].

#### c. Drug-excipient compatibility:

Using a Fourier transform infrared spectrophotometer using the diffuse reflectance concept, the FTIR spectra of pure drug, a physical mixture containing drug and oily excipients, and all components of SMEDDS were captured over the frequency range of  $4000 - 400 \text{ cm}^{-1}$ . The compatibility of the excipient is investigated, and any spectrum changes in the latter are detected and compared with those of the pure medication [20].

#### d. Construction of pseudo-ternary Phase Diagram:

The process of creating ternary-phase diagrams is typically used to describe the microemulsion region. A microemulsion must have three elements in order to form: an oil phase, an aqueous phase, and a surfactant. When a co-surfactant is utilised, it may occasionally be represented as a single component and handled as a single "pseudo-component" at a fixed ratio to the surfactant. A ternary phase diagram can show how much of each of these three components is present in various amounts [21]. Phase diagrams can be used to represent micro emulsions, which are created using the spontaneous emulsification technique (also known as the phase titration technique). Building phase diagrams is a helpful method for examining the elaborate system of interactions that might develop when several components are combined. Depending on the chemical content and concentration of each component, microemulsions are created along with a variety of association structures (including emulsion, micelles, lamellar, hexagonal, cubic, and different gels and oily dispersion). The investigation must include understanding their phase equilibrium and defining their phase limits. In order to find the various zones, including the microemulsion zone, where each corner of the diagram represents 100% of the specific component, pseudo ternary phase diagrams, which are quicker to construct and easier to understand, are frequently used instead of quaternary phase diagrams (four component systems). Pseudo-ternary phase diagrams are employed when four or more components are being studied, and a corner often represents a binary mixture of two components, such as surfactant and co-surfactant, water and drug, or oil and drug. Visual analysis can determine how many different phases are present in a given mixture. It is important to keep in mind that not all conceivable combinations of components result in microemulsions; in certain cases, the extent of microemulsion generation may be quite small. The phase diagram is constructed using the titration method. Various ratios of oil to surfactant are made and put into different vials, such as 10:0, 9:1, 8:2, 7:3, 6:4, 5:5, 4:6, 3:7, 2:8, 1:9, and 0:10. The vials are filled with a little water, which is added in 5% (w/w) increments. The mixture in the vials is gently shaken for 48 hours at  $25^\circ\text{C}$  after each addition of water and centrifuged for 2 to 3 minutes. Both optical and microscopic examination are used to assess the final mixture. The micro emulsion in a phase diagram is an area of clear, isotropic solution. The area of hazy dispersion is called the coarse emulsion [22].

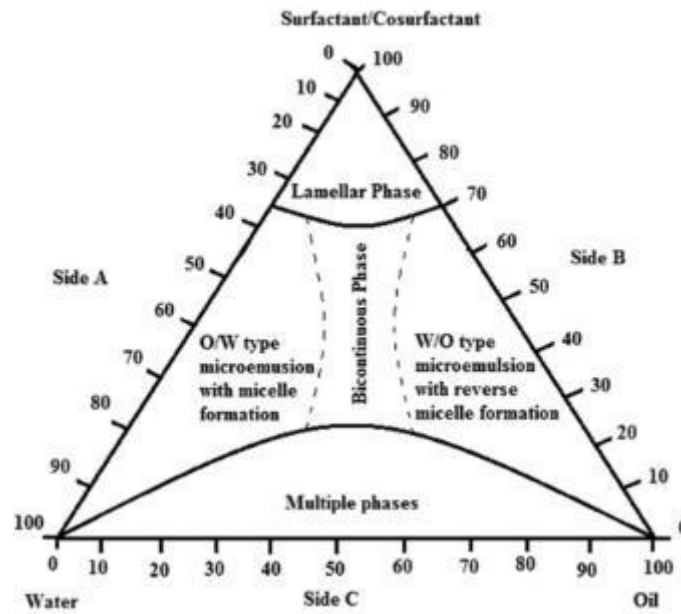
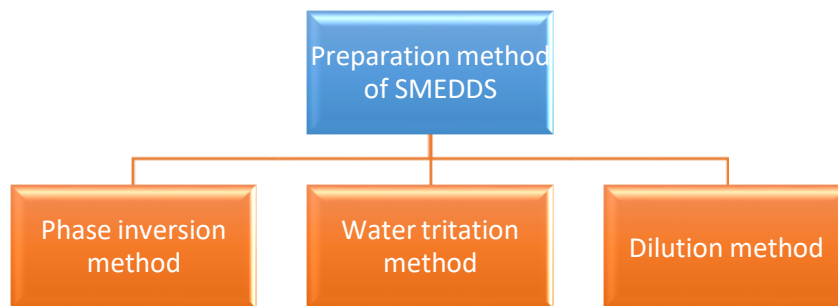


Fig. Pseudo-ternary phase diagram

**METHOD OF PREPARATION:**



**1. Phase inversion Method:**

Microemulsions experience phase inversion when too much of the dispersed phase is added or when the temperature changes. Significant physical changes, such as variations in particle size, take place during phase inversion and may influence drug release both in vivo and in vitro. These techniques work by altering the surfactant's natural curvature. This can be accomplished for non-ionic surfactants by altering the system's temperature, causing a change from an o/w microemulsion at low temperatures to a w/o microemulsion at higher temperatures (transitional phase inversion). The development of finely distributed oil droplets is encouraged by the system crossing a point of zero spontaneous curvature and negligible surface tension as it cools. The phase inversion temperature (PIT) method is the name of this technique.

Other factors, such as salt concentration or pH value, may be taken into account in addition to or instead of temperature. Additionally, by altering the water volume fraction, a transition in the spontaneous radius of curvature can be obtained. Water droplets are initially created in a continuous oil phase by adding water to it in stages. The spontaneous curvature of the surfactant shifts from initially stabilising a w/o microemulsion to an o/w microemulsion at the inversion locus as the water volume fraction increases. At the o/w interface, short-chain surfactants create flexible monolayers that cause a discontinuous microemulsion at the inversion point [24].

**2. Water Titration method:**

By titrating homogenous liquid mixes of oil, surfactant, and cosurfactant with water at room temperature, the pseudo ternary phase diagrams were also created. Oil phase, Surfactant, and Co-surfactant were created in oily combinations ranging from 9:1 to 1:9 and weighed in the same screw-cap glass tubes before being vortexed at Km values of 1.5 and 1 (surfactant: co-surfactant ratio). To achieve equilibrium, each mixture was gradually titrated with aliquots of distilled water and agitated at room temperature. The mixture's transparency was visually assessed. The mixtures were further titrated with aliquots of distilled water once equilibrium was established until they displayed the turbidity. The micro-emulsion zone was determined to include samples that were clear and isotropic. The other areas of the phase diagrams were not completely identified. Using the findings as a guide, the proper ratio of oil, surfactant, and co-surfactant was chosen, correlated in the phase diagram, and used to make SMEDDS [25].



### 3. Dilution method:

Ternary mixes were created using different ratios of surfactant, cosurfactant, and oil. Based on the needs, the amounts of oil, co-surfactant, and surfactant were chosen. By diluting the required amount of mixes with suitable double-distilled water, compositions are assessed for nanoemulsion production. Spectroscopy was used to determine the resulting dispersions' globule size. For each system, the region of the ternary phase diagram where nanoemulsions with the desired globule size were produced was identified [16].

### f. Formulation and optimization:

Oil, surfactant, and co-surfactant will be added to a precisely weighed dose of drug in a glass vial in the proportions determined by the phase diagram's micro-emulsion area. The components are combined using gentle stirring, followed by vortex mixing, then heated at 40°C on a magnetic stirrer to produce a transparent and isotropic solution, which helps to completely dissolve the medication [23].

### TECHNIQUES FOR SOLIDIFICATION TO CONVERT LIQUID SMEDDS TO SOLID SMEDDS:

SMEDDS can be found in both liquid and solid forms. However, because many of the excipients used in SMEDDS are not solid at normal temperature, SMEDDS are typically restricted to liquid dosage forms. Given the benefits of solid dose forms, S-SMEDDS have received a lot of attention lately because they frequently serve as more potent substitutes for traditional liquid SMEDDS. S-SMEDDS stands for solid dosage forms with self-emulsification capabilities in the context of dosage forms [25]. Here are a few SMEDDS solidification processes-

#### 1. Encapsulation of liquid and semisolid Self-emulsifying formulation:

One of the most popular and straightforward techniques for converting a liquid and semisolid formulation into capsules works for both high dose drug loading (up to 50%) for low dose strong drugs and vice versa. For a liquid formulation, direct filling and sealing of the capsule is possible, however for a semisolid formulation, they must be heated to at least 20°C above the melting point before the active component may be included into the capsule with continuous agitation and sealed [26].

#### 2. Spray drying:

Oil phase, aqueous phase, surfactants, co-surfactants, and drug are mixed to create the liquid or semisolid SMEDDS formulation, which is then ready for spray drying. The volatile phase (in this case, the water present in the system) vaporises to generate dry particles, which can subsequently be formed into tablet or capsule formulation, after being delivered into a spray of droplets in a drying chamber under regulated temperature and airflow conditions. The drying properties of the medication product and the powder specification are used to select the overall design of temperature and airflow parameters [9].

#### 3. Adsorption to a solid carrier:

Using a blender, the liquid formulation is poured onto the adsorbent carrier and blended to produce a free-flowing powder. The choice of carrier should be based on its capacity to adsorb liquid excipients, which favours higher drug loading and more exposure to lipids (i.e., 70% w/w of liquid SMEDDS), as well as on the method's ability to produce powder with good flow properties. Good content homogeneity is another important benefit of this approach. However, reducing the drug load in the final dosage form is a drawback of this approach. The adsorbents used are calcium silicate, magnesium trisilicate, magnesium aluminometasilicate (Neusilin US), silicon dioxide, talc, crosslinked povidone, crosslinked sodium carboxymethylcellulose, crosslinked polymethyl methacrylate. This process requires minimal equipment costs and allows for the conversion to tablets. Colloidal silicon dioxide has been widely reported as an adsorbent carrier for various drugs such as ezetimibe, ketoprofen and siramesine hydrochloride; Porous polystyrene granules have been reported as carriers for self-emulsifying formulations containing loratadine [27].

#### 4. Melt granulation:

By adding a binder that melts or softens at relatively low temperatures, melt granulation is a method that produces powder agglomeration. Melt granulation, which is a "one-step" process compared to traditional wet granulation, has a number of advantages. This is because the liquid addition and subsequent drying phase are skipped. Additionally, it offers a superior substitute for the usage of solvent. Impeller speed, mixing duration, binder particle size, and binder viscosity are the primary factors that govern the granulation process [21].

#### 5. Spray Cooling:

Another name for it is spray congealing. The objective is to spray molten mass into a cooling chamber, where the molten droplets further solidify as they come in contact with the cold air and re-crystallize into spherical solid particles. After that, the bottom of the container started to accumulate solid particles as a fine powdered product. The liquid combination has been atomized into droplets using a variety of atomizers, including rotary, ultrasonic, and pressure atomizers. Spray cooling using lipid-based excipients has been accomplished utilising ultrasonic atomizers. The melting points of the excipients (50°C and 80°C), the viscosity of the SMEDDS formulation during atomization, and the temperature of the cooling air inside the atomizer are the process variables that determine how quickly and completely the droplets crystallize. Depending on the composition of the lipid matrix and how the drug interacts with it, spray cooling may be

utilised to enhance prolonged release and bioavailability (solution or dispersion). Due to the formulation's high viscosity—dispersions are typically more viscous than solutions—this approach has limited drug loading potential. It has been claimed that this method uses polyoxyglycerides, in particular stearyl polyoxyglycerides (Gelucire® 50/13) to produce microparticles with narrow particle size distributions that display dramatically enhanced drug release [28].

#### 6. Melt extrusion/extrusion Spheronization:

The process of adding binders to a formulation that relatively melts at a low temperature and forms granules known as melt granulation. Given that the drying phase is skipped and granulation is accomplished in a single step, this procedure is more comparable to spray drying. The mixture is put through an impeller with a predetermined impeller speed, viscosity, and total mixing duration. Gelucire 1 is a typical binder made from mixtures of fatty acid esters of polyethylene glycols (PEG) and mono-, di-, and tri-glycerides [9].

#### Dosage forms of Solid SMEDDS:

- **Dry emulsions:** Powdered solid dose forms known as dry emulsions spontaneously emulsify when water is added. Rotary evaporation, freeze drying, and spray drying are methods for producing dry emulsions. When making dry emulsions, the spray drying process is more usually employed. The aqueous phase is eliminated by spray-drying the o/w emulsion once it has been created.
- **Capsules:** Filling capsule shells with solid SMEDDS manufactured using a variety of methods, including spray drying, adsorption to solid carriers, etc. This avoids physical compatibility issues between liquid SMEDDS and the capsule shell.
- **Tablets:** Different ratios of liquid SMEDDS could be adsorbed on to porous carriers. The liquid SMEDDS with surface adsorbed is then combined with other appropriate excipients. After that, a compression machine is used to compress the mixture. Self-emulsifying tablets based on eutectic prevented the medication from precipitating in an irreversible manner within the formulation [29].
- **Self- micro emulsifying sustained/controlled-release pellets:** As a multiple unit dosage form, it has various benefits over traditional solid dosage forms, including manufacturing flexibility, a decrease in intra- and inter-subject variability of plasma profiles, and a reduction in GI irritation without compromising drug absorption. Therefore, combining the benefits of pellets with those of SMEDDS by SME pellets is highly enticing.
- **Self- micron emulsifying solid dispersions:** Although poorly water-soluble drugs bioavailability and dissolution rate may be increased by solid dispersions, there were several production challenges and stability issues. Excipients may be placed directly into hard gelatin capsules in the molten state, eliminating the need for milling and blending prior to filling, and they have the potential to boost further absorption of weakly water-soluble medicines compared to previously utilised PEG solid dispersions. This field has seen extensive usage of SME excipients including Gelucire 144/14, Gelucire 150/02, Labrasol 1, Transcutol 1, and TPGS (tocopheryl polyethylene glycol 1000 succinate).
- **Self- micron emulsifying suppositories:** Some researchers shown that S-SMEDDS could improve rectal/vaginal adsorption in addition to GI adsorption. For instance, Glycyrrhizin, which is administered orally, barely reaches therapeutic plasma concentrations, but can acquire adequate therapeutic levels by using either vaginal or rectal SME suppositories for chronic liver disorders.
- **Self- micron emulsifying implants:** SME implant research has significantly improved the use of S-SMEDDS. One such chemotherapeutic drug is 1,3-bis (2-chloroethyl)-1-nitrosourea, which is used to treat malignant brain tumours. However, due to its brief half-life, it was less effective. SMEDDS was created to improve stability compared to that released from poly (D, L-lactide-co-glycolide) wafer implants. These wafers were more effective against tumours in vitro and less prone to hydrolysis [21].

#### Factors affecting SMEDDS:

1. It is ideal for a drug to dissolve in every formulation component. Therefore, a bigger drug proportion can be provided with the expected bioavailability, solubility must be at least higher in oil.
2. To prevent drug and component interactions, all excipients utilised must be compatible with one another and the drug.
3. Using more surfactants and co-surfactants than necessary can result in precipitation during formulation and GI irritation after in vivo micro-emulsion production.
4. The drug release profile is higher the more polar the lipid base.
5. Smaller droplet sizes result in more surface area, which promotes absorption.
6. The use of cationic surfactants may give the droplets a positive charge, increasing membrane penetration and bioavailability [30].

#### Characterization and evaluation of SMEDDS:

##### 1. Visual evaluation:

The formulation was added to 100 ml of water in a glass Erlenmeyer flask at 25°C, and the mixture was then gently swirled by hand to evaluate the self-emulsification capabilities. When there was weak or no emulsion formation, the tendency to spontaneously produce a transparent emulsion was deemed unfavourable. A phase diagram was created to show the ideal self-emulsifying area [12]. While the fine, isotropic, transparent solution demonstrates the development of micro emulsion, the impermeable and milky white occurrence demonstrates the development of macro emulsion. When drug precipitation is not distinguishable, the preparation might be thought of as continuous. If the preparation comprises water soluble co-solvents, precipitation is expected and can be avoided by enhancing the concentration of surfactant [31].

##### 2. Droplet size and particle size measurement:

PCS (photon correlation spectroscopy) or SEM (scanning electron microscopy), which can detect sizes between 10-5000 nm, are used to determine the globule size of the microemulsion. The molecule's nanometric size range remains largely unchanged after being diluted with distilled water 100 or 1000 times, demonstrating the system's compatibility with more water. Because it affects the rate and amount of drug release as well as the stability of the micro-emulsion, globule size is an important aspect in SMEDDS. The PCS method, which can measure sizes between 10 – 5000 nm, is used to estimate the globule size of the micro-emulsion. PCS estimates the variations in light scattering caused by Brownian motion of the particles. Light scattering is observed at an angle of 90° after external standardisation with spherical polystyrene droplets at room temperature [32].

### 3. Refractive index and percent transmission:

Refractive index and % transmittance demonstrate the formulation's clarity. A refractometer is used to calculate the SMEDDS's refractive index and compare it to water's. If the system's refractive index is expected to be close to that of water, the UV-visible spectrophotometer is used to measure the system's percent transmittance at a specific wavelength while using distilled water as a reference. Transparent formulation is one that has a transmittance of greater than 99 percent [33].

### 4. Zeta potential measurement:

The surface charge of the droplets in the dispersion media can be estimated using the zeta potential, which is the potential between the droplet surface and the dispersing liquid medium. Zeta potential is frequently used as a measure of droplet stability; values more than +30 mV and less than -30 mV signify strong stability against coalescence, respectively. Zetasizer was used to examine the formulation (0.1 ml), which had been diluted 100 times in double-distilled water [34].

### 5. Differential scanning calorimetry:

DSC 60 can be used to calculate differential scanning calorimetry for SMEDDS. In an aluminium pan, a liquid sample and a solid sample should be placed so that the results may be recorded. DSC could be used to identify the departure from expected thermal behaviour. This could help by giving an idea of potential drug-excipient interactions [21].

### 6. Thermodynamic stability studies:

As precipitation of the drug in the excipient matrix can negatively impact a formulation's performance, physical stability is crucial. The bioavailability and therapeutic efficacy of a formulation might be impacted by excipient phase separation caused by poor physical stability. Additionally, if the formulation is poured into the capsule, the incompatibilities between the formulation and the gelatin shell of the capsule may result in brittleness, softness, delayed disintegration, or insufficient drug release. The cycles that are used for these investigations are as follows:

- a. **Heating cooling cycle:** Six cooling and heating cycles are carried out between the low (4°C) and high (45°C) temperatures, with exposure at each temperature lasting at least 48 hours. Centrifugation testing is then performed on those formulations that pass the stability test.
- b. **Centrifugation:** Centrifuging is done at 3500 rpm for 30 min on formulations that make it through the heating and cooling stage. For the freeze-thaw stress test, formulations that do not exhibit any phase separation are chosen.
- c. **Freeze thaw stress cycle:** Those formulations that pass this test demonstrate good stability with no phase separation, cracking, or creaming after three freeze-thaw cycles between -21° C and 25° C with storage at each temperature for at least that long. The formulations that pass this test are next submitted for a dispersibility test to determine their ability to self-emulsify [16].

### 7. Dispersibility test:

Using a type II standard USP dissolution apparatus, the self-emulsification effectiveness of prepared SMEDDS is tested. 500 mL of water are mixed with 1 ml of each formulation at a temperature of  $37 \pm 5^\circ\text{C}$ . 50 rpm of mild agitation is given to the formulation being used. Utilizing the following grading system, visual observation is used to assess the formulations' in vitro performance:

- Grade A: Rapidly developing (within 1 minute), clear or bluish nanoemulsion.
- Grade B: An emulsion that forms quickly, is significantly less transparent, and appears bluish- white.
- Grade C: Within two minutes, a fine milky emulsion formed.
- Grade D: Slow-emulsifying, dull, grayish-white emulsion with a faint greasy look (longer than 2min).
- Grade E: Formulation with significant oil globules on the surface and either weak or limited emulsification [9].

### 8. Turbidimetric Evaluation:

Monitoring the development of emulsification is done by Nepheloturbidimetric analysis. On a magnetic plate at room temperature, a fixed amount of self-emulsifying system is introduced to a fixed amount of a suitable medium (0.1N hydrochloric acid), while stirring continuously (50 rpm). The increase in turbidity is then measured using a turbidimeter. However, it is impossible to measure the rate of change of turbidity because the time needed for complete emulsification is too short [35].

### 9. Viscosity Determination:

Typically, capsules made of either soft gelatin or hard gelatin are used to deliver the SMEDDS system. Therefore, it should be simple to pour into capsules and shouldn't be too thick to be a difficulty. The Brookfield viscometer is used to assess the microemulsions rheological characteristics [35].

### 10. Drug Content:

Drug is extracted from pre-weighed SMEDDS by dissolving in an appropriate solvent. A suitable analytical approach was used to compare the drug content of the solvent extract to the drug's standard solvent solution [35].

### 11. Determination of Self emulsification time:

The USP II dissolving apparatus was used to measure the SMEDDS emulsification time. At a temperature of 37°C and with paddles revolving at 50 rpm to give gentle agitation, each formulation is added dropwise to 500ml of filtered water. Visual emulsification evaluation and timing were done [21].

### 12. In vitro drug release:

To assess the in-vitro drug release, a USP dissolving testing mechanical assembly type-II (paddle type) assembly should be used.



A reasonable dissolution media is used in the dissolution test at a temperature of 37.5 °C. The paddle should continue to rotate at 75 rpm for one hour. The study was carried out in accordance with USP protocol. The corresponding weight of the preparation is added to the dissolving vessel. The right amount of samples are taken from the centre of vessels at regular intervals. After removing the sample, a new amount of dissolving media is added to maintain the sink state. The sample is then removed, filtered, and viewed in a UV-spectrophotometer against a blank in its appropriate range of maximum. The amount of drug that has dissolved from the formulation is calculated. For each preparation, the above techniques were repeated three times [36].

#### CHARACTERIZATION OF SOLID SMEDDS:

- a. Morphological analysis:** By using scanning electron microscopy, the surface morphology of the solid SMEDDS is investigated. The powder was slightly dispersed on a double adhesive tape that was attached to an aluminium stub to create the SEM samples, which were then put inside the scanning electron microscopy chamber. Following a random scan of the samples, photomicrographs are taken, and the SEM findings are acquired.
- b. Flow properties:**
  - **Angle of repose:** The funnel method is used to determine the angle of repose of S-SMEDDS. A predetermined sample amount is weighed and passed through a funnel. The tip of a funnel is positioned vertically so that it barely touches the pile of powder. The height of the pile and the diameter of the powder particles are measured after passing the S-SMEDDS. The angle of repose is calculated using the formula below:  
 $\tan\theta = \text{height of pile} / \text{radius of pile base}$ .
  - **Bulk density:** The tapped bulk density (TBD) and the loose bulk density (LBD) are both calculated. 2 g of S-SMEDDS were added to a measuring cylinder with a capacity of 10 ml. After measuring the initial volume, the cylinder is permitted to drop from a height of 2.5 cm onto a hard surface at intervals of 2 seconds. Until there is no longer any intensity change, the tapping is kept up. The following equations were used to determine LBD and TBD:  
 $\text{LBD} = \text{weight of powder} / \text{initial volume (before tapping)}$   
 $\text{TBD} = \text{weight of powder} / \text{volume after tapping}$ .
  - **Compressibility Index:** Carr's Compressibility Index is used to determine the granules' compressibility.  
 $\text{Carr's compressibility index (\%)} = (\text{TBD} - \text{LBD}) / \text{TBD} \times 100$
  - **Hausner ratio:** This formula can be used to determine the Hausner ratio: Hausner ratio = TBD/LBD.
- c. Differential Scanning Calorimetry (DSC):** Using a differential scanning calorimeter, the DSC thermograms for drugs and SSMEDDS are recorded. Each sample is heated to a temperature between 30 and 300 degrees Celsius in an aluminium pan (Al- Crucibles, 40 Al) at a rate of 10 degrees Celsius per minute while being sprayed with nitrogen at a flow rate of 50ml/min.
- d. X-ray powder diffraction (XRD):** The X-ray diffractometer scans the X-ray diffraction patterns of the powdered drug and formulation samples from diffraction angle (2θ) 5 to 500. S-SMEDDS and drug Diffraction patterns were obtained [30].

#### ADVANTAGES:

**Enhanced oral bioavailability:** A significant aspect that restricts the bioavailability of many drugs that are poorly water soluble is dissolution rate-dependent absorption. A more effective drug transport through the intestinal aqueous boundary layer and the absorptive brush border membrane is made possible by SMEDDS's ability to present the drug to the GIT in solubilized and microemulsified form (globule size between 1-100 nm). This results in improved bioavailability [12].

**Ease of Manufacture and Scale-Up:** For large-scale manufacturing, SMEDDS require relatively basic and affordable manufacturing facilities, such as a straightforward mixer with agitator and volumetric liquid filling machinery. This explains why business is interested in SMEDDS [12].

**Reduction in Inter-Subject and Intra-Subject Variability and Food Effects:** Numerous medications have significant intra- and inter-subject variation in absorption, which reduces their effectiveness and increases patient non-compliance. Food has a significant impact on how well a medicine works therapeutically in the body. SMEDDS are helpful for such medications. There are numerous research publications stating that SMEDDS performance is independent of food and that SMEDDS offers reproducibility of plasma profile [12].

**Ability to deliver peptides that are prone to enzymatic hydrolysis in GIT:** The ability of SMEDDS to carry macromolecules such peptides, hormones, enzyme substrates and inhibitors and their capacity to provide protection from enzymatic hydrolysis are two distinctive qualities that set them apart from other drug delivery systems. If Polysorbate 20 is used as an emulsifier in the formulation of the micro emulsion, the intestinal hydrolysis of the prodrug by cholinesterase can be prevented. These systems spontaneously develop without the use of energy or heating, making them suited for thermolabile medications like peptides [35].

**No influence of lipid digestion process:** SMEDDS's performance is unaffected by pancreatic lipase activity, mixed micelle production, bile salt emulsification, or lipolysis, in contrast to other lipid-based drug delivery systems. SMEDDS present the drug in a micro-emulsified form, which can easily permeate the mucin and water unstirred layer, hence the drug need not be digested before being absorbed [35].

**Increased Drug Loading Capacity:** SMEDDS also have the benefit of having a higher drug loading capacity when compared to conventional lipid solutions because amphiphilic surfactants, co-surfactants, and co-solvents have much higher solubility than natural lipids for poorly water soluble drugs with an intermediate partition coefficient ( $2 < \log p < 4$ ) [35].

#### ADVANTAGES OF SMEDDS OVER EMULSION:

- SMEDDS not only eliminates the disadvantage of emulsion layering after prolonged sitting but also provides the same benefits of emulsions in enhancing the solubility of hydrophobic medicines. It belongs to a thermodynamically stable system, making storage simple.
- The SMEDDS-created microemulsions have excellent thermodynamic stability and optical transparency.

- In contrast to emulsions, which can only be administered as oral solutions, SMEDDS offer a variety of delivery choices, including the ability to be placed inside of either hard or soft gelatin capsules or to be made into tablets.
- SMEDDS can be autoclaved, whereas emulsions cannot because of their phase inversion temperature [37].

#### LIMITATIONS OF SMEDDS:

- 1. Drug precipitation on dilution:** SMEDDS that have been diluted go through drug precipitation in gastrointestinal fluid. The ability to maintain the medication in the gastrointestinal tract in its solubilized state is a typical requirement for lipid formulations. The benefit provided by the lipid-based formulation technique is lost when the drug precipitates out of the system.
- 2.** As a result of the hydrophilic solvent's dilution action, the drug has a higher potential to precipitate when diluted. Polymers must therefore be used to reduce drug precipitation in vivo [38].
- 3. Encapsulation in gelatin capsules:** Certain drawbacks associated with gelatin capsules include the tendency for volatile co-solvents to move to shells, which causes lipophilic drugs to precipitate.
- 4. Storage and handling:** SMEDDS that are liquids have issues with handling, stability, and storage. Consequently, developing strong SMEDDS appears to be a rational option to address these issues.
- 5. Limited targeting to lymphatics:** The use of lymphatics as a target offers two key benefits over traditional absorption by the portal circulation. First, oral medication concentration that reaches the systemic circulation is increased because transport by the intestinal lymph avoids pre-systemic hepatic processing. Second, it might be possible to administer drugs to lymphatic organs at specific sites. Normal requirements for lymphatic transport include high log P and high triglyceride solubility. The amount of a drug that enters lymphatics varies depending on the drug. Therefore, a deeper understanding of medication lipophilicity and triglyceride solubility in connection to lymphatic transport is necessary, and a more suitable predictive model is required [39].
- 6.** The lack of meaningful in vitro prediction models for defining formulation systems.
- 7.** Because lipid excipients contain unsaturated fatty acids, they can oxidise [40].

#### APPLICATIONS:

##### 1. Super Saturable SMEDDS (SS-SMEDDS):

A novel type of supersaturable formulations, including supersaturable SMEDDS, can result from the high surfactant content generally found in SMEDDS formulations, which can cause GI side effects. (S-SMEDDS) formulations have been created and developed to speed up the absorption of drugs that are poorly soluble in surfactants and lessen their negative effects [41].

##### 2. Solid SMEDDS:

SMEDDS are typically made as liquid dosage forms that can be taken orally in soft gelatin capsules, however this has significant drawbacks, particularly during production. Incorporating liquid chemicals that self-emulsify into a powder to create a solid dosage form is an alternate technique (tablets, capsules). Progesterone in SMEDDS has been created as a pellet formulation by the extrusion/spheronization process to offer a good in vitro drug release (100% within 30 min, T50% at 13 min) [42].

##### 3. Sustain release from SMEDDS:

SMEDDS have a rich behaviour when it comes to the release of solubilized material because of the diverse variety of structures that may be found in them. Because of this, hydrophobic medicines in O/W micro emulsions that are mostly soluble in oil droplets encounter impeded diffusion and release relatively slowly (depending on the substance's oil/water partitioning). Conversely, drugs that are water soluble diffuse almost completely unhindered and release quickly (depending on the volume percentage of the dispersed phase). Due to the bicontinuous nature of the micro emulsion "structure," both water- and oil-soluble drugs diffuse and release very quickly in balanced micro emulsions. The micro emulsion composition is crucial for the drug release rate in addition to the micro emulsion structure [41].

##### Some marketed formulations of SMEDDS [12, 43]:

Drug Name	Compound	Company	Indication	Dosage form
Gengraf®	Cyclosporine A/III	Abbott Laboratories	Immuno suppressant	Hard gelatin Capsule
Rocaltrol®	Calcitriol	Roche	Calcium regulator	Soft gelatin capsule
Targretin®	Bexarotene	Ligand	Antineoplastic	Soft gelatin capsule
Sandimmune®	Cyclosporine A/II	Novartis	Immuno Suppressant	Soft gelatin capsule
Lipirex®	Fenofibrate	Genus	Anti hyperlipoproteinemic	Hard gelatin Capsule
Convulex®	Valproic acid	Pharmacia	Antiepileptic	Soft gelatin capsule
Agenerase®	Amprenavir	Glaxo Smithkline	HIV antiviral	Soft gelatin capsule

Fortovase®	Saquinavir	Hoffmann-La Roche Inc.	HIV antiviral	Soft gelatin capsule
Norvir®	Ritonavir	Abbott Laboratories	HIV antiviral	Soft gelatin capsule
Neoral®	Cyclosporine A/I	Novartis	Immune suppressant	Soft gelatin capsule
Vesanoid®	tretinoine	Roche	Retinoid	soft gelatin capsule
Kaletra®	lopinavir and ritonavir	Abbott	HIV antiviral	oral solution
Aptivus®	tipranavire	Boehringer Ingelheim	HIV antiviral	soft gelatin capsule

### Some patents on SMEDDS:

Sr. No.	Patent no.	Active ingredients	Excipients
1.	US005993858A	Nifedipine	Labrafac CM10, Lauroglycol, Gelucire 44/14
2.	9278070	Cyclosporin A (8.0–12.0%)	2 (2ethoxyethoxy) ethanol (15.0–19.0%) ; polyethoxylated castor oil (8.0– 12.0%) ; caprylic/capric triglyceride (2.0–6.0%) ; Sodium dodecyl sulfate (1.0–4.5%) ; Dsorbitol (3.0–8.0%) ; and gelatin (45.0–55.0%)
3.	20060275358	Coenzyme Q1	-
4.	WO2004002414 A2	Fenofibrate	Transcutol P, Captex 200, Labrasol, Span 80
5.	WO2012032415 A2	Atorvastatin	Polysorbate 20, polyoxyl 15 hydroxystearate, sesame oil
6.	US006309665B2, 2001	Indomethacin	Labrafil WL2609BS, Labrasol, Plurololeic
7.	WO2009130225 A2	Celecoxib	Labrasol, Plurololeique, Miglyol 812
8.	6652865	Simvastatin	-
9.	US6555558 B2	Tipranavir	Capmul MCM, Cremophore EL, Propylene glycol
10.	WO 02/07712 A2	Indolinone derivatives	Cremophore, Capmul MCM, Gelucire 44/14
11.	WO2008073731 A2	Valsartan	Lauroglycol, Propylene glycol, tween 20, Cremophore, Spearmint oil, PEG400, Labrafil M2125, Capmul, Maisine 35-1
12.	US 2002/0119198 A1	3-[(2,4-dimethylpyrrol-5-yl)methylene]-2-indolinone	Polyvinylpyrrolidone polymer, fatty acid and surfactant
13.	WO201001043 A1	Curcumin	Gelucire, Labrasol, Vitamin E TPGS
14.	US007815933B2	NO releasing NSAID	Phosphotidylcholine, Propylene Glycol, Ethanol
15.	WO2014009434A1	Abiraterone	Captex 355/Capmul MCM, Cremophore EL

### Conclusion:

SMEDDS and other lipid-based drug delivery systems offer a promising means of increasing the bioavailability of drugs that are not readily soluble. The formation of SMEDDS might be a successful strategy to address the problem of medication solubility of significantly reduced solubility in the fluids of GIT. SMEDDSs, which have been proven to significantly improve oral bioavailability and hence allow for the reduction of the drug's dose, can enable the oral delivery of hydrophobic medicines. S-SMEDDS are

superior to conventional liquid SMEDDS as upgrades or substitutes because they lower production costs, simplify industrial manufacturing, increase stability, and boost patient compliance. Most significantly, S- SMEDDS are particularly adaptable in creating several solid dosage forms for parenteral and oral administration. SMEDDS is able to get around the difficulties of marketing numerous drugs in the future. Before releasing more SMEDDS goods on the market, however, there is still a long way to go because SMEDDS requires further exploitation, which includes bioavailability research and the creation of in-vitro, in-vivo correlation (IVIVC), and other dosage forms. This review article will provide as a starting point for researchers studying SMEDDS, methods for improving bioavailability, and drug solubility in water.

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