

# A REVIEW ON SELF-MICROEMULSIFYING DRUG DELIVERY SYSTEMS

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**Abstract:** Oral route has always been preferred route for formulators and has dominated over other routes of administrations. However this preferred route is limited to those drugs molecule that are permeable across the gastric mucosa and are at least sparingly soluble. Approximately 40% of new chemical entities exhibit poor aqueous solubility and present a major challenge to modern drug delivery system, because of their low bioavailability. Improving oral bioavailability of low poorly water soluble drugs using self-emulsifying drug delivery systems (SEDSS) possess significant potential. Oral bioavailability of hydrophobic drugs can be improved using SEDSS, and appears most promising. Their dispersion in gastro intestinal (GI) fluid after administration forms micro or nano emulsified drug which gets easily absorbed through lymphatic pathways bypassing the hepatic first pass metabolism. SMEDDS are isotropic mixtures of oil, surfactant, co-surfactant and drug with a unique ability to form fine oil in water microemulsion upon mild agitation following dilution with aqueous phase. This article gives an overview of SMEDDS as a promising approach to effectively tackle the problem of poorly soluble drugs.

**Keywords:** SEDSS, SMEDDS, low bioavailability and microemulsions

## 1. Introduction:

Oral route is the easiest and most convenient way of noninvasive administration. Oral drug delivery systems being the most cost-effective have always lead the worldwide drug delivery market. This oral route may be a problem route for drug molecules which exhibit poor aqueous solubility. When a drug is administered by oral route the first step for it to get absorbed is its solubilization followed by permeation. Approximately 40% of new chemical entities exhibit poor aqueous solubility and present a major challenge to modern drug delivery system. A rate limiting step for the absorption of these drugs is often their solubilization in the gastrointestinal tract. These drugs are classified as class II drug by Biopharmaceutical classification system (BCS), drugs with poor aqueous solubility and high permeability. Different formulation approaches like micronization, solid dispersion, and complexation with cyclodextrins have come up. [1] Indeed, in some selected cases, these approaches have been successful but they offer many other disadvantages. The main problem with micronization is chemical / thermal stability, many drug may degrade and lose bioactivity when they are micronized by conventional method. For solid dispersion the amount of carriers used is often large, and thus if the dose of active ingredient is high, the tablets or capsules formed will be large in volume and difficult to swallow. Moreover, since the carriers used are usually expensive and freeze-drying or spray-drying method requires particular facilities and processes, leading to high production cost. Though traditional solvent method can be adopted instead, it is difficult to deal with co-precipitates with high viscosity. Complexation with cyclodextrins techniques is not applicable for drug substances which are not soluble in both aqueous and organic solvents. Realization that the oral bioavailability of poor water soluble drugs may be enhanced when co-administered with meal rich in fat has led to increasing recent interest in the formulation of poorly water soluble drugs in lipids. Lipid suspension, solutions and emulsions have all been used to enhance the oral bioavailability but, more recently there have been much focus on the utility of self-microemulsifying drug delivery systems (SMEDDS). Being hydrophobic i.e. more lipophilic a lipid-based drug delivery system would ideally work for a poorly water soluble drug. Lipidbased drug delivery systems have gained considerable interest after the commercial success of Sandimmune Neoral™ (Cyclosporine A), [2] Fortovase (Saquinavir) and Norvir (Ritonavir). [3]

Self emulsifying drug delivery system (SEDSS) is defined as isotropic mixture of oil and surfactants or alternatively one or more hydrophilic solvents and co-solvents. Upon mild agitation followed by dilution in aqueous media such as the gastrointestinal (GI) fluid, these systems can form fine oil in water (o/w) emulsions or micro emulsions. Self micro emulsifying formulations spread readily in the GI tract and the digestive motility of the stomach and the intestine provide the agitation necessary for self-emulsification (SEDSS) typically produce emulsion with a droplet size between 100 and 300 nm while SMEDDS form transparent

micro emulsion with a droplet size of less than 50 nm. When compared with emulsions which are sensitive and metastable dispersed forms, SEDDS and SMEDDS are physically stable formulations that are easy to manufacture. SMEDDS can be formulated to give sustained release dosage form by adding polymeric matrix, which is not ionizable at physiological pH and after ingestion in contact with GI fluid forms a gelled polymer making it possible to release the micro emulsified active agent in a continuous and sustained manner by diffusion.

## 2. BIOPHARMACEUTICAL CLASSIFICATION SYSTEM (BCS):

Biopharmaceutics Classification System (BCS) was introduced in 1995 as a basis for predicting the likelihood of in vitro-in vivo correlations for immediate release dosage forms, based on the recognition that drug solubility/dissolution properties and gastrointestinal permeability are the fundamental parameters controlling the rate and extent of drug absorption. According to BCS, drug substances are classified as Class I High solubility High permeability Class II Low solubility High permeability Class III High solubility Low permeability Class IV Low solubility Low permeability The FDA has set specifications regarding the solubility and permeability class boundaries used for this BCS classification. Solubility: A drug substance is considered highly soluble when the highest dose strength is soluble in 250 ml or less of aqueous media over a pH range of 1 to 7.5 (equilibrium solubility at 37°C). [4] Permeability: In the absence of evidence suggesting instability in the gastrointestinal tract, a drug substance is considered highly permeable when the extent of absorption in humans is determined to be 90% or more of an administered dose based on mass balance determination or in comparison to an intravenous reference dose (absolute bioavailability study). [4]

## 3. Self-emulsifying drug delivery systems (SEDDS):

SEDDS belong to lipid-based formulations. Lipid formulations can be oils, surfactant dispersions, emulsions, solid lipid nanoparticles and liposomes. SEDDS are isotropic mixtures of drug, lipids and surfactants, usually with one or more hydrophilic co-solvents or co-emulsifiers. Upon mild agitation followed by dilution with aqueous media, these systems can form fine (oil in water) emulsion instantaneously. 'SEDDS' is a broad term, typically producing emulsions with a droplet size ranging from a few nanometers to several-microns. "Self micro- emulsifying drug delivery systems" (SMEDDS) indicates the formulations forming transparent microemulsions with oil droplets ranging between 100 and 250 nm. "Self-nano-emulsifying drug delivery systems" (SNEDDS) is a recent term with the globule size ranges less than 100 nm.[5] A schematic about self-micro-emulsifying drug delivery systems" (SMEDDS) is shown in Figure1.

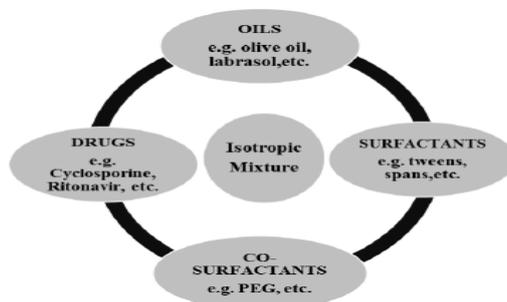
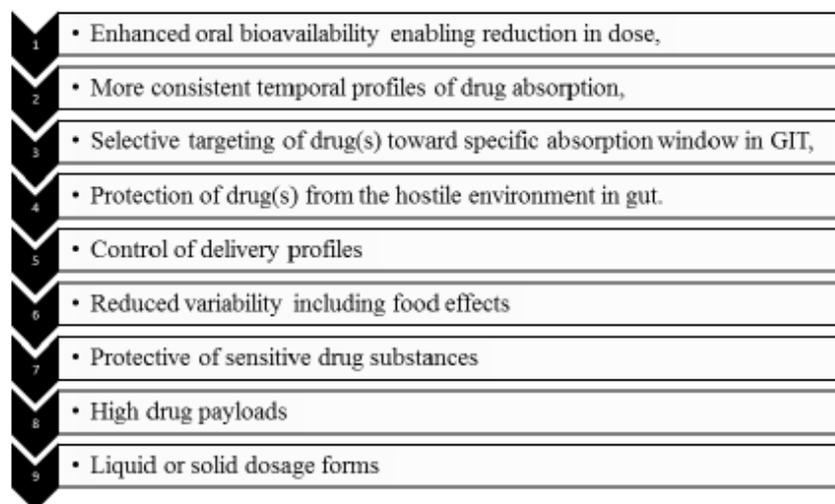


Figure 1: components of SMEDDS

### 3.1. Need of SEDDS

Oral delivery of poorly water-soluble compounds is to pre-dissolve the compound in a suitable solvent and fill the formulation into capsules. The main benefit of this approach is that predissolving the compound overcomes the initial rate limiting step of particulate dissolution in the aqueous environment within the GI tract. However, a potential problem is that the drug may precipitate out of solution when the formulation disperses in the GI tract, particularly if a hydrophilic solvent is used (e.g. polyethylene glycol). If the drug can be dissolved in a lipid vehicle there is less potential for precipitation on dilution in the GI tract, as partitioning kinetics will favor the drug remaining in the lipid droplets. Another strategy for poorly soluble drugs is to formulate in a solid solution using a water-soluble polymer to aid solubility of the drug compound. For example, polyvinyl pyrrolidone (PVP) and polyethylene glycol (PEG 6000) have been used for preparing solid solutions with poorly soluble drugs. One potential problem with this type of formulation is that the drug may favor a more thermodynamically stable state, which can result in the compound crystallizing in the polymer matrix. Therefore the physical stability of such formulations needs to be assessed using techniques such as differential scanning calorimetry or X-ray crystallography. In this type of case SEDD system is a good option.[6-8]. Figure No:2 summarises the advantages of SEDDS.



**Figure 2: Potential advantages of SEDDS**

### 3.2. Limitations of SEDDS

1. Chemical instabilities of drug and high surfactant concentrations
2. The large amount of surfactant in self-emulsifying formulations (30-60%) irritates GIT
3. Moreover, volatile co-solvent in the conventional self-emulsifying formulations are known to migrate into the shells of soft or hard gelatin capsule, resulting in the precipitation of the lipophilic drug.[9]

### 3.3. Mechanism of SEDDS:

Different approaches have been reported in the literature. No single theory explains all aspects of micro emulsion formation. Schulman et al. considered that the spontaneous formation of micro emulsion droplets was due to the formation of a complex film at the oil-water interface by the surfactant and co-surfactant. Thermodynamic theory of formation of micro emulsion explains that emulsification occurs, when the entropy change that favour dispersion is greater than the energy required to increase the surface area of the dispersion and the free energy ( $\Delta G$ ) is negative. The free energy in the micro emulsion formation is a direct function of the energy required to create a new surface between the two phases and can be described by the equation:

$$\Delta G = \sum N \pi r^2 \sigma$$

Where,  $\Delta G$  is the free energy associated with the process (ignoring the free energy of the mixing).  $N$  is the number of droplets of radius  $r$  and  $\sigma$  are presents the interfacial energy. With time, the two phases of the emulsion tend to separate to reduce the interfacial area, and subsequently, the free energy of the system decreases. Therefore, the emulsion resulting from aqueous dilution are stabilized by conventional emulsifying agents, which forms a mono layer around the emulsion droplets, and hence, reduce the interfacial energy, as well as providing a barrier to prevent coalescence.[10]

### 4. Lipid formulation classification system (LFCS)

LFCS was established by Pouton in 2000 and recently updated (2006) to help stratify formulations into those with similar component parts.[11] The LFCS briefly classifies lipid-based formulations into four types according to their composition and the possible effect of dilution and digestion on their ability to prevent drug precipitation.

#### 4.1. Type I lipid formulations:

It consist of formulations which comprise drug in solution in triglycerides and/or mixed glycerides or in an oil in water emulsion stabilized by low concentrations of emulsifiers such as 1% (w/v) polysorbate 60 and 1.2% (w/v) lecithin.[12] Generally, these systems exhibit poor initial aqueous dispersion and require digestion by pancreatic lipase/ co-lipase in the GIT to generate more amphiphilic lipid digestion products and promote drug transfer into the colloidal aqueous phase. Type I lipid formulations therefore represent a relatively simple formulation option for potent drugs or highly lipophilic compounds where drug solubility in oil is sufficient to allow incorporation of the required payload (dose).[13]

#### 4.2. Type II lipid formulations:

Self-emulsification is generally obtained at surfactant contents above 25% (w/w). However, at higher surfactant contents (greater than 50–60% (w/w) depending on the materials) the progress of emulsification may be compromised by the formation of viscous liquid crystalline gels at the oil/water interface.[14,15] Type II lipid-based formulations provide the advantage of overcoming the slow dissolution step typically observed with solid dosage forms and as described above generate large interfacial areas which in turn allows efficient partitioning of drug between the oil droplets and the aqueous phase from where absorption occurs.[16,17]

#### 4.3. Type III lipid formulation:

Commonly referred to as self-microemulsifying drug delivery systems (SMEDDS), are defined by the inclusion of hydrophilic surfactants (HLB>12) and co-solvents such as ethanol, propylene glycol and polyethylene glycol. Type III formulations can be further segregated (somewhat arbitrarily) into Type IIIA and Type IIIB formulations in order to identify more hydrophilic systems (Type IIIB) where the content of hydrophilic surfactants and co-solvents increases and the lipid content reduces. Type IIIB formulations typically achieve greater dispersion rates when compared with Type IIIA although the risk of drug precipitation on dispersion of the formulation is higher given the lower lipid content.

#### 4.4. Type IV lipid formulation :

In order to capture the recent trend towards formulations which contain predominantly hydrophilic surfactants and cosolvents, this category was recently added.[11] Type IV formulations do not contain natural lipids and represent the most hydrophilic formulations. These formulations commonly offer increased drug payloads when compared to formulations containing simple glyceride lipids and also produce very fine dispersions when introduced in aqueous media. Little is known however, as to the solubilisation capacity of these systems in vivo and in particular whether they are equally capable of maintaining poorly water soluble drug in solution during passage along the GIT when compared with formulations comprising natural oils (Type II and Type III). An example of a Type IV formulation is the current capsule formulation of the HIV protease inhibitor amprenavir (Agenerase) which contains TPGS as a surfactant and PEG 400 and propylene glycol as co-solvents.[18]

### 5. SELF MICRO EMULSIFYING DRUG DELIVERY SYSTEMS:

SMEDDS are defined as isotropic mixtures of natural or synthetic oils, solid or liquid surfactants, or alternatively, one or more hydrophilic solvents and co-solvents/surfactants that have a unique ability of forming fine oil-in-water (o/w) micro emulsions upon mild agitation followed by dilution in aqueous media, such as GI fluids. [19] SMEDDS spread readily in the GI tract, and the digestive motility of the stomach and the intestine provide the agitation necessary for self-emulsification. The basic difference between self emulsifying drug delivery systems (SEDDS) also called as self emulsifying oil formulation (SEOF) and SMEDDS is SEDDS typically produce opaque emulsions with a droplet size between 100 and 300 nm while SMEDDS form transparent micro emulsions with a droplet size of less than 50 nm also the concentration of oil in SMEDDS is less than 20 % as compared to 40-80% in SEDDS. When compared with emulsions, which are sensitive and metastable dispersed forms, SMEDDS are physically stable formulations that are easy to manufacture. Thus, for lipophilic drug compounds that exhibit dissolution rate-limited absorption, these systems may offer an improvement in the rate and extent of absorption and result in more reproducible blood-time profiles. SMEDDS formulation is in theory, comparatively simple. The key step is to find a suitable oil surfactant mixture that can dissolve the drug within the required therapeutic concentration. The SMEDDS mixture can be filled in either soft or hard gelatin capsules. A typical SMEDDS formulation contains oils, surfactants and if required an antioxidants. Often co-surfactants and co-solvents are added to improve the formulation characteristics.

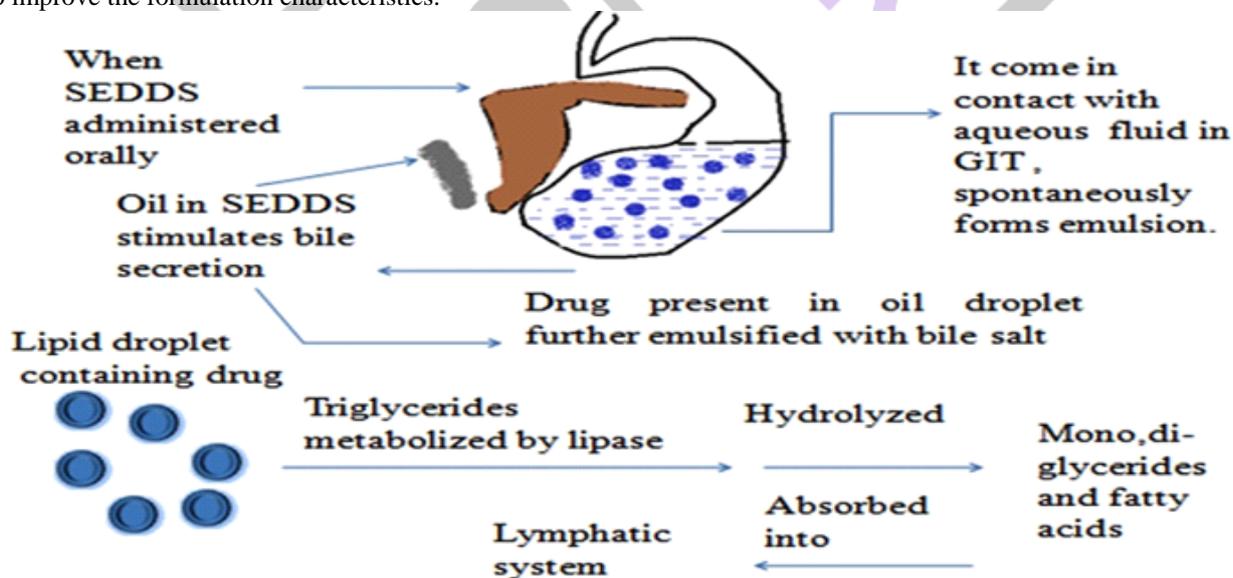


Figure No: 3 Process of self-emulsification

#### 5.1. ADVANTAGES OF SMEDDS:

**Improvement in oral bioavailability:** Dissolution rate dependant absorption is a major factor that limits the bioavailability of numerous poorly water soluble drugs. The ability of SMEDDS to present the drug to GIT in solubilised and micro emulsified form (globule size between 1-100 nm) and subsequent increase in specific surface area enable more efficient drug transport through the intestinal aqueous boundary layer and through the absorptive brush border membrane leading to improved bioavailability. E.g. In case of halofantrine approximately 6-8 fold increase in bioavailability of drug was reported in comparison to tablet formulation. [20] · **Ease of manufacture and scale-up:** Ease of manufacture and scaleup is one of the most important advantage that makes SMEDDS unique when compared to other drug delivery systems like solid dispersions, liposomes, nanoparticles, etc., dealing with improvement of bio-availability. SMEDDS require very simple and economical manufacturing facilities like simple mixer with

agitator and volumetric liquid filling equipment for large-scale manufacturing. This explains the interest of industry in the SMEDDS. · Reduction in inter-subject and intra-subject variability and food effects: There are several drugs which show large inter-subject and intra-subject variation in absorption leading to decreased performance of drug and patient non-compliance. Food is a major factor affecting the therapeutic performance of the drug in the body. SMEDDS are a boon for such drugs. Several research papers specifying that, the performance of SMEDDS is independent of food and, SMEDDS offer reproducibility of plasma profile are available. [21]

Ability to deliver peptides that are prone to enzymatic hydrolysis in GIT: One unique property that makes SMEDDS superior as compared to the other drug delivery systems is their ability to deliver macromolecules like peptides, hormones, enzyme substrates and inhibitors and their ability to offer protection from enzymatic hydrolysis. The intestinal hydrolysis of prodrug by cholinesterase can be protected if polysorbate 20 is emulsifier in micro emulsion formulation. [22] These systems are formed spontaneously without aid of energy or heating [23] thus suitable for thermo labile drugs such as peptides. · No influence of lipid digestion process: Unlike the other lipid-based drug delivery systems, the performance of SMEDDS is not influenced by the lipolysis, emulsification by the bile salts, action of pancreatic lipases and mixed micelle formation. SMEDDS are not necessarily digested before the drug is absorbed as they present the drug in micro-emulsified form which can easily penetrate the mucin and water unstirred layer. · Increased drug loading capacity: SMEDDS also provide the advantage of increased drug loading capacity when compared with conventional lipid solution as the solubility of poorly water soluble drugs with intermediate partition coefficient (24) are typically low in natural lipids and much greater in amphiphilic surfactants, co surfactants and co-solvents. Advantages of SMEDDS over emulsion: · SMEDDS not only offer the same advantages of emulsions of facilitating the solubility of hydrophobic drugs, but also overcomes the drawback of the layering of emulsions after sitting for a long time. SMEDDS can be easily stored since it belongs to a thermodynamically stable system. · Microemulsions formed by the SMEDDS exhibit good thermodynamic stability and optical transparency. The major difference between the above microemulsions and common emulsions lies in the particle size of droplets. The size of the droplets of common emulsion ranges between 0.2 and 10  $\mu\text{m}$ , and that of the droplets of microemulsion formed by the SMEDDS generally ranges between 2 and 100 nm (such droplets are called droplets of nano particles). Since the particle size is small, the total surface area for absorption and dispersion is significantly larger than that of solid dosage form and it can easily penetrate the gastrointestinal tract and be absorbed. The bioavailability of the drug is therefore improved. · SMEDDS offer numerous delivery options like filled hard gelatin capsules or soft gelatin capsules or can be formulated in to tablets whereas emulsions can only be given as an oral solutions. · Emulsion can not be autoclaved as they have phase inversion temperature, [25] while SMEDDS can be autoclaved

## 5.2. Excipients used in SMEDDS:

Pharmaceutical acceptability of excipients and the toxicity issues of the components used makes the selection of excipients really critical. There is a great restriction as which excipients to be used. Early studies revealed that the self-microemulsification process is specific to the nature of the oil/surfactant pair, the surfactant concentration and oil/surfactant ratio, the concentration and nature of co-surfactant and surfactant/co-surfactant ratio and the temperature at which self-microemulsification occurs. These important discoveries were further supported by the fact that only very specific combinations of pharmaceutical excipients led to efficient self-microemulsifying systems.

### 5.2.1. Oils

The oil represents one of the most important excipients in the SMEDDS formulation not only because it can solubilize the required dose of the lipophilic drug or facilitate self emulsification but also and mainly because it can increase the fraction of lipophilic drug transported via the intestinal lymphatic system, thereby increasing absorption from the GI tract depending on the molecular nature of the triglyceride.[26] Both long and medium chain triglyceride (LCT and MCT) oils with different degrees of saturation have been used for the design of self-emulsifying formulations. Furthermore, edible oils which could represent the logical and preferred lipid excipients choice for the development of SMEDDS are not frequently selected due to their poor ability to dissolve large amounts of lipophilic drugs. Modified or hydrolyzed vegetable oils have been widely used since these excipients form good emulsification systems with a large number of surfactants approved for oral administration and exhibit better drug solubility properties.[27] They offer formulative and physiological advantages and their degradation products resemble the natural end products of intestinal digestion. Novel semisynthetic medium chain derivatives, which can be defined as amphiphilic compounds with surfactant properties, are progressively and effectively replacing the regular medium chain triglyceride oils in the SMEDDS.[25] This is in accordance with findings of Deckelbaum (1990) showing that MCT is more soluble and have a higher mobility in the lipid/water interfaces than LCT associated with a more rapid hydrolysis of MCT. In general, when using LCT, a higher concentration of cremophor RH40 was required to form microemulsions compared with MCT.

E.g.: Cotton seed oil, Soybean oil, Corn oil, Sunflower oil, Castor oil etc.

### 5.2.2. Surfactants

Several compounds exhibiting surfactant properties may be employed for the design of self-emulsifying systems, but the choice is limited as very few surfactants are orally acceptable. The most widely recommended ones being the non-ionic surfactants with a relatively high hydrophilic-lipophilic balance (HLB). The commonly used emulsifiers are various solid or liquid ethoxylated polyglycolized glycerides and polyoxyethylene oleate. Safety is a major determining factor in choosing a surfactant. Emulsifiers of natural origin are preferred since they are considered to be safer than the synthetic surfactants. However, these surfactants have a limited self-emulsification capacity. Non-ionic surfactants are less toxic than ionic surfactants but they may lead to reversible

changes in the permeability of the intestinal lumen.[24] The lipid mixtures with higher surfactant and co-surfactant/oil ratios lead to the formation of SMEDDS.

There is a relationship between the droplet size and the concentration of the surfactant being used. In some cases, increasing the surfactant concentration could lead to droplets with smaller mean droplet size, this could be explained by the stabilization of the oil droplets as a result of the localization of the surfactant molecules at the oil-water interface. On the other hand, in some cases the mean droplet size may increase with increasing surfactant concentrations.[28] This phenomenon could be attributed to the interfacial disruption elicited by enhanced water penetration into the oil droplets mediated by the increased surfactant concentration and leading to ejection of oil droplets into the aqueous phase.[29] The surfactants used in these formulations are known to improve the bioavailability by various mechanisms including: improved drug dissolution, increased intestinal epithelial permeability, increased tight junction permeability and decreased/inhibited glycoprotein drug efflux. However, the large quantity of surfactant may cause moderate reversible changes in intestinal wall permeability or may irritate the GI tract. Formulation effect and surfactant concentration on gastrointestinal mucosa should ideally be investigated in each case. Surfactant molecules may be classified based on the nature of the hydrophilic group within the molecule. The four main groups of surfactants are defined as follows,

1. Anionic surfactants
2. Cationic surfactants
3. Ampholytic surfactants
4. Nonionic surfactants

**Anionic Surfactants:** where the hydrophilic group carries a negative charge such as carboxyl (RCOO<sup>-</sup>), sulphonate (RSO<sub>3</sub><sup>-</sup>) or sulphate (ROSO<sub>3</sub><sup>-</sup>).

Examples: Potassium laurate, sodium lauryl sulphate.

**Cationic surfactants:** where the hydrophilic group carries a positive charge.

Example: quaternary ammonium halide.

**Ampholytic surfactants:** (also called zwitter ionic surfactants) contain both a negative and a positive charge. Example: sulfobetaines.

**Nonionic surfactants:** where the hydrophilic group carries no charge but derives its water solubility from highly polar groups such as hydroxyl or polyoxyethylene (OCH<sub>2</sub>CH<sub>2</sub>O). Examples: Sorbitan esters (Spans), polysorbates (Tweens).

### 5.2.3. Co-solvents

The production of an optimum SEDDS requires relatively high concentrations (generally more than 30% w/w) of surfactants, thus the concentration of surfactant can be reduced by incorporation of co surfactant. Role of the co-surfactant together with the surfactant is to lower the interfacial tension to a very small even transient negative value. At this value the interface would expand to form fine dispersed droplets, and subsequently adsorb more surfactant and surfactant/co-surfactant until their bulk condition is depleted enough to make interfacial tension positive again. This process known as 'spontaneous emulsification' forms the microemulsion. However, the use of co-surfactant in self emulsifying systems is not mandatory for many non-ionic surfactants. The selection of surfactant and co-surfactant is crucial not only to the formation of SEDDS, but also to solubilization of the drug in the SEDDS. Organic solvents, suitable for oral administration (ethanol, propylene glycol (PG), polyethylene glycol (PEG), etc.) may help to dissolve large amounts of either the hydrophilic surfactant or the drug in the lipid base and can act as co-surfactant in the self emulsifying drug delivery systems, although alcohol-free self-emulsifying microemulsions have also been described in the literature. Indeed, such systems may exhibit some advantages over the previous formulations when incorporated in capsule dosage forms, since alcohol and other volatile co-solvents in the conventional self-emulsifying formulations are known to migrate into the shells of soft gelatin or hard sealed gelatin capsules resulting in the precipitation of the lipophilic drug. On the other hand, the lipophilic drug dissolution ability of the alcohol free formulation may be limited. Hence, proper choice has to be made during selection of components.[30]

### 5.2.4. Co-surfactant

In SMEDDS, generally co-surfactant of HLB value 10-14 is used. Hydrophilic co-surfactants are preferably alcohols of intermediate chain length such as hexanol, pentanol and octanol which are known to reduce the oil water interface and allow the spontaneous formulation of micro emulsion. E.g. span, capryol 90, capmul.[31,32]

## 6. PSEUDO TERNARY PHASE DIAGRAMS:

Phase diagrams are useful tools to determine the number and types of phases, the wt% of each phase and the composition of each phase at a given temperature and composition of the system. These diagrams are three-dimensional but are illustrated in two-dimensions for ease of drawing and interpretation

**Construction of Ternary Phase Diagrams:** This is the first step before starting the formulation. It is useful to identify best emulsification region of oil, surfactant and co-surfactant combinations. Ternary phase diagram of surfactant, co-surfactant and oil will plot; each of them, representing an apex of the triangle.[33] The methods are used to plot ternary phase diagrams are namely Dilution method and Water Titration method are shown in **figure 2**.

- **Dilution method:** Ternary mixtures with varying compositions of surfactant, co-surfactant and oil were prepared. The percentage of surfactant, co-surfactant and oil decided on the basis of the requirements. Compositions are evaluated for nanoemulsion formation by diluting appropriate amount of mixtures with appropriate double distilled water. Globule size of the resulting dispersions was determined by using spectroscopy. The area of nanoemulsion formation in Ternary phase diagram(as shown in **figure 2a**) was identified for the respective system in which nanoemulsions with desire globule size were obtain.

• **Water Titration method:** The pseudo-ternary phase diagrams were also constructed by titration of homogenous liquid mixtures of oil, surfactant and co-surfactant with water at room temperature (as shown in figure 2b). Oil phase, Surfactant and the co-surfactant, at Km values 1.5 and 1 (surfactant: co-surfactant ratio), oily mixtures of oil, surfactant and co-surfactant were prepared varied from 9:1 to 1:9 and weighed in the same screw-cap glass tubes and were vortexed.[34] Each mixture was then slowly titrated with aliquots of distilled water and stirred at room temperature to attain equilibrium. The mixture was visually examined for transparency. After equilibrium was reached, the mixtures were further titrated with aliquots of distilled water until they showed the turbidity. Clear and isotropic samples were deemed to be within the micro-emulsion region. No attempts were made to completely identify the other regions of the phase diagrams. Based on the results, appropriate percentage of oil, surfactant and co-surfactant was selected, correlated in the phase diagram and were used for preparation of SMEDDS.

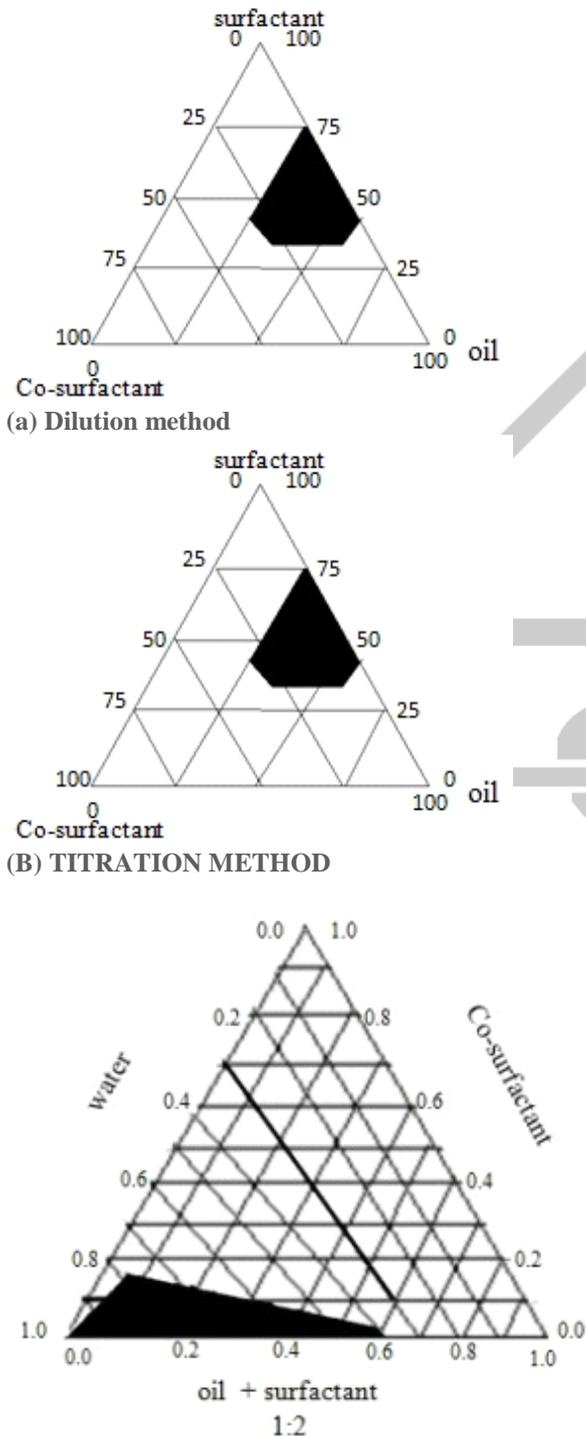


FIGURE 4: TERNARY PHASE DIAGRAM

**7. CHARACTERIZATION OF SMEDDS:**

**Particle size:** The droplet size of the emulsion is a crucial factor in self-emulsification performance because it determines the rate and extent of drug release as well as absorption. [35] Photon correlation spectroscopy (PCS) is a useful method for determination

of emulsion droplet size [36] especially when the emulsion properties do not change upon infinite aqueous dilution, a necessary step in this method. However, microscopic techniques should be employed at relatively low dilutions for accurate droplet size evaluation. [37]

**Polarity:** Emulsion droplet polarity is also a very important factor in characterizing emulsification efficiency. [38] The HLB, chain length and degree of unsaturation of the fatty acid, molecular weight of the hydrophilic portion and concentration of the emulsifier have an impact on the polarity of the oil droplets. Polarity represents the affinity of the drug compound for oil and/or water and the type of forces formed. Rapid release of the drug into the aqueous phase is promoted by polarity. **Zeta potential:** The charge of the oil droplets of SMEDDS is another property that should be assessed. [37] The charge of the oil droplets in conventional SMEDDS is negative due to the presence of free fatty acids; however, incorporation of a cationic lipid, such as oleylamine at a concentration range of 1.0-3%, will yield cationic SMEDDS. Thus, such systems have a positive  $\zeta$ -potential value of about 35-45 mV. [37] This positive  $\zeta$ -potential value is preserved following the incorporation of the drug compounds. **Drug precipitation /stability on dilution:** The ability of SMEDDS to maintain the drug in solubilised form is greatly influenced by the solubility of the drug in oil phase. If the surfactant or co-surfactant is contributing to the greater extent in drug solubilisation then there could be a risk of precipitation, as dilution of SMEDDS will lead to lowering of solvent capacity of the surfactant or co-surfactant, hence it is very important to determine stability of the system after dilution. This is usually done by diluting a single dose of SMEDDS in 250ml of 0.1N HCl solution. This solution is observed for drug precipitation if any. Ideally SMEDDS should keep the drug solubilized for four to six hours assuming the gastric retention time of two hours.

### 8. FACTORS AFFECTING SMEDDS:

**Nature and dose of the drug:** Drugs which are administered at very high dose are not suitable for SMEDDS unless they exhibit extremely good solubility in at least one of the components of SMEDDS, preferably lipophilic phase. The drugs which exhibit limited solubility in water and lipids (typically with log P values of approximately 2) are most difficult to deliver by SMEDDS. The ability of SMEDDS to maintain the drug in solubilised form is greatly influenced by the solubility of the drug in oil phase. As mentioned above if surfactant or co-surfactant is contributing to the greater extent in drug solubilisation then there could be a risk of precipitation, as dilution of SMEDDS will lead to lowering of solvent capacity of the surfactant or co-surfactant. Equilibrium solubility measurements can be carried out to anticipate potential cases of precipitation in the gut. However, crystallisation could be slow in the solubilising and colloidal stabilizing environment of the gut. Pouton's study reveal that such formulations can take up to five days to reach equilibrium and that the drug can remain in a super-saturated state for up to 24 hours after the initial emulsification event. It could thus be argued that such products are not likely to cause precipitation of the drug in the gut before the drug is absorbed, and indeed that super-saturation could actually enhance absorption by increasing the thermodynamic activity of the drug. There is a clear need for practical methods to predict the fate of drugs after the dispersion of lipid systems in the gastrointestinal tract. **Polarity of the lipophilic phase:** The polarity of the lipid phase is one of the factors that govern the drug release from the microemulsions. The polarity of the droplet is governed by the HLB, the chain length and degree of unsaturation of the fatty acid, the molecular weight of the hydrophilic portion and the concentration of the emulsifier. In fact, the polarity reflects the affinity of the drug for oil and/or water, and the type of forces formed. The high polarity will promote a rapid rate of release of the drug into the aqueous phase. This is confirmed by the observations of Sang-Cheol Chi, who observed that the rate of release of idebenone from SMEDDS is dependant upon the polarity of the oil phase used. The highest release was obtained with the formulation that had oil phase with highest polarity.

### 9. PHARMACEUTICAL APPLICATIONS:

The potential for lipidic self-emulsifying drug delivery systems (SMEDDS) to improve the oral bioavailability of a poorly absorbed, antimalarial drug (Halofantrine, HF) has been investigated in fasted beagles in 1998. The lipid based formulations of HF-base afforded a 6-8 fold improvement in absolute oral bioavailability relative to previous data of the solid HF. [39] The study evaluating the effects of combined use of two non-ionic surfactants on the characteristics of oil-in-water microemulsions generated from flurbiprofen loaded concentrate was performed. The combined use of surfactants in concentrate showed the promise in generating desired self-emulsifying implications in future dosage development for poor water soluble drugs in using self-emulsifying microemulsions drug delivery systems (SMEDDS) [40]. An optimal paclitaxel microemulsion prepared by SMEDDS which is a mixture of paclitaxel, tetraglycol, cremophore ELP, and labrafill 1944 and a paclitaxel microemulsion containing poly(D,L-lactide-co-glycolide) (PLGA) in order to offer controlled release of paclitaxel was developed. It was observed that the droplet size of microemulsion without PLGA was smaller than that of microemulsion containing PLGA by transmission electron microscopy (TEM). The droplet of microemulsion containing PLGA was almost of spherical shape with smooth surface and there was no aggregation and adhesion among droplet of microemulsion containing PLGA by atomic force microscopy (AFM). The formulation enhanced the anti-tumor activity in-vivo compared with microemulsion without PLGA against SKOV-3 human ovarian cancer cells bearing nude mice model. [41] To study the effect of two SMEDDS containing labrasol with different dilutions on tight junctions was conducted. Changes in barrier properties of Caco-2 cell monolayers, including transepithelial electrical resistance (TEER) and permeability to the paracellular marker, i.e. mannitol, were assessed in response to dilutions and surfactant contents within formulations. The results demonstrated that the negatively charged SMEDDS with different dilutions had no effect on TEER, but significantly increased the permeability of mannitol. The mechanism of opening of tight junctions was found to involve F-actin related changes and redistribution of ZO-1. [42] Another study involved formulation of gentamicin SMEDDS. Gentamicin was dispersed with a surfactant used for SMEDDS, labrasol, and the mixture was solidified with several kinds of adsorbents [microporous calcium silicate (florite RE), magnesium alumino meta silicate (Neusilin US2), and silicon dioxide (Sylsilia 320)]. High plasma gentamicin levels were obtained the results suggest that an adsorbent system is useful as an oral solid delivery system of poorly adsorbate drugs such as gentamicin. [42] Yet another study involved HPLC determination of anethole trithione (ATT).

After administration of SMEDDS and tablets to rabbits, significant differences were found in main pharmacokinetic parameters of  $T_{max}$ ,  $C_{max}$  and  $AUC_{0-8}$  between these two formulations, and a 2.5-fold enhancement of relative bioavailability of ATT was observed from the SMEDDS compared with tablets. [43] Low molecular weight heparin (LMWH) was dispersed with a surfactant used for the self-microemulsifying drug delivery system (SMEDDS), PEG-8 caprylic/capric glycerides (Labrasol), and the mixture was solidified with three kinds of adsorbents. Florite RE system was evaluated in dogs after oral administration in an enteric capsule made of Eudragit S100 at the LMWH dose of 200 IU/kg. The results suggest that adsorbent system is useful as an oral solid delivery system of poorly absorbable drugs such as LMWH. [44, 45].

**TABLE 1: APPLICATION OF SELF-EMULSIFYING DRUG DELIVERY SYSTEMS**

Type of delivery system	Drug	Oil: Surfactant: Cosolvent	Improvement
SEDSS (gelled)	Ketoprofen	Captex 200: Tween80: Capmul MCM	Silicon dioxide was used for gelling agent. As the Conc. of Silicon dioxide increases it causes an increase in the droplet size of emulsion and slows the drug diffusion.[46]
SEDSS	Carvedilol	Labrasol: Labrafil M: Transcutol P	It improves the oral bioavailability of Carvedilol upto 413% when compared to convectional tablet.[47]
SMEDDS	Simvastatin	Caproyl:Cremophor EL: Carbitol	The release rate was higher and oral bioavailability is about 1.5 fold higher than convectional tablet.[48]
Self-emulsifying tablet	Diclofenac sodium	Goat fat: Tween 65	SEDSS tablet were formulated by pour molding using plastic mould the tablet containing higher tween 65: goat fat ratio gives better release rate.[49]
Self-emulsifying pellet	Methyl and propyl perabens	Mono and diglycerides of capric and caprylic acids: Tween 80	The self-emulsifying formulation improve the rate of drug release from the pellets by applying a water insoluble polymer containing a water soluble plasticizer, it reduces the rate of drug release.[50]

### CONCLUSION:

SMEDDS are a promising approach for the formulation of drug compounds with poor aqueous solubility. The oral delivery of hydrophobic drugs is now possible by SMEDDS, which have been shown to improve oral bioavailability substantially. The efficiency of the SMEDDS formulation is case specific in most instances thus, composition of the SMEDDS formulation should be determined very carefully. Since a relatively high concentration of surfactants is generally employed in the SMEDDS formulation, toxicity of the surfactant being used should be taken into account. In fact, a compromise must be reached between the toxicity and self-emulsification ability of the surfactant that is considered for use. The size and charge of the oil droplet in the emulsion formed are two other important factors that affect GI absorption efficiency. Versatility of SMEDDS could be proved if issues like method to predict solubilisation state of the drug in vivo, interaction of lipid systems with components of capsule shell and basic mechanism of transport of SMEDDS through GIT are adequately addressed. Despite the proven ability of these systems relatively few lipid based product have been commercialized. The reasons underlying the lack of application of these technologies is not clear, but likely reflects the limited knowledge of the formulation parameters that are responsible for good in vivo performance and the fact that relatively few in vivo studies in human have been reported in literature when compared with conventional dosage forms. Perhaps more importantly the lack of effective in vitro tests that are predictive of in vivo performance has significantly hindered successful development of these self emulsifying drug delivery systems.

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