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**Review article**

# Self-Micro Emulsifying Drug Delivery Systems: An Oral Bioavailability Enhancing Lipid-Based Drug Delivery System

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**ABSTRACT:**
The fact that around 40% of novel drug candidates have partial solubility in water presents a task in finding the suitable oral solid dosage form. Various approaches, including varying the solubility or maintaining the medication dissolved during the gastrointestinal transit time, have been used to address these problems. There are number of technologies that can improve less solubility, dissolving rate, and bioavailability of unsolvable medicines. One of the possible methods is SMEDDS, or self-microemulsifying drug delivery systems. Owing to their capacity to upsurge the solubility and bioavailability of poorly soluble medicines, SMEDDS have attracted interest. Formulations that increase the oral absorption of highly lipophilic medicinal substances can be made using SMEDDS, which remain isotropic combinations of oils, surfactants, solvents, and co-solvents/surfactants. The most recognizable SMEDDS are formed like liquids, which can have some very serious disadvantages. SMEDDS are available as soft or hard gelatin capsules for oral administration and produce fine, mostly stable oil-in-water emulsions. The usage of solid-SMEDDS, which are formed by turning liquid or semi-solid components into powders, has augmented. This article covers the complete SMEDDS system, although it pays particular attention to the development, design and evaluation

**Keywords:** Self-microemulsifying drug delivery system, Surfactant, Oil, Co-surfactant, Bioavailability, Lipophilic.

## 1. INTRODUCTION

Formulations can be created using SMEDDS, which are isotropic mixtures of oils, surfactants, solvents, and co-solvents/surfactants, to increase the oral absorption of extremely lipophilic pharmaceutical compounds. The majority of conventional SMEDDS take the form of liquids, which can have some significant drawbacks. SMEDDS are available as soft or hard gelatin capsules for oral administration and produce fine, largely stable oil-in-water emulsions. There has been an increase in the use of solid-SMEDDS, which are made by powdering components that are liquid or semi-solid. This article covers the full SMEDDS system, but it gives special focus to the formulation, design, assessment, and application of SMEDDS. By changing a medicine's physicochemical properties, such as producing more salt or reducing the size of its particles, the rate at which it dissolves can be enhanced. However, these procedures are not always feasible; for example, it is impossible to produce salt from neutral chemicals [3]. Weak acid and basic salts may also go back to their unique acid or base forms, aggregating in the digestive tract. When very tiny particles are poorly wettable, particle size reduction is not desirable since it might lead to the accumulation of static charges, make handling more difficult, and result in handling issues. Other formulation options, with the use of cyclodextrins, nanoparticles, solid dispersions, and permeation enhancers, have been used in an effort to get around these restrictions. These procedures have, in fact, worked in a few carefully chosen instances [4, 5].

Recent research has demonstrated that oral bioavailability of medications with inadequate water solubility can be improved by lipid-based formulations [6]. The preferable approach is, in fact, to include lipophilic drugs into inert lipid carriers [7, 8]. This might enhance their solubilization while also changing their pharmacokinetic properties, boosting therapeutic effectiveness.

Lipid-based formulations come in a variability of forms, including solutions, suspensions, solid dispersions, and self-micro emulsifying drug delivery systems (SMEDDS). After the commercial success of the HIV protease inhibitors ritonavir (Norvir®) and saquinavir (Fortovase®), as well as

the immunosuppressive drug cyclosporine A (Neoral®), the SMEDDS have garnered a lot of attention. When uncovered to the fluids of the gastrointestinal tract (GIT), self-emulsifying formulations emulsify to create oil-in-water emulsion or micro emulsion [9, 10].

**Principle**

The basic characteristic of this system is its capability to produce fine oil-in-water microemulsions with only minimal agitation followed by an aqueous phase [11]. SMEDDS can promote drug absorption by better drug solubility and diffusion, increased intestinal lymphatic drug transport, defence against enzymatic hydrolysis, and P-glycoprotein-inhibited efflux. This strategy has been revealed to be effective for Biopharmaceutical Classification System (BCS) II drugs such silymarin, oridonin, and curcumin [12]. While SMEDDS has remained to upsurge the water solubility of several medicines, this increase in water solubility takes a limited outcome on the bioavailability of BCS IV substances.

## 2. CLASSIFICATION SYSTEM FOR LIPID FORMULATIONS

The classification system was initially familiarized in 2000 and the additional formulation 'type' was added in 2006.

**Type I** - These systems have meagre initial aqueous dispersion and need pancreatic lipase/co-lipase digestion in the GIT in order to yield more amphiphilic lipid digestion products and aid medicine transfer into the colloidal aqueous phase. These are a viable alternative for medications with adequate oil solubility [13]. Soft gelatin capsules incorporating maize oil as a lipidic component have been developed for valproic acid.

**Type II** - SEDDS are formulations of type II lipids. Self-emulsification often occurs when the surfactant level is greater than 25% (w/w). These formulations have the benefit of avoiding the slow dissolution step that solid dosage forms typically experience, and as was mentioned earlier, they produce bulky interfacial areas that let for effective drug partitioning amid oil droplets and the aqueous phase, from which absorption arises [14].

**Type III** -Type III lipid-based formulations, also known as self-micro emulsifying drug delivery systems (SMEDDS), can be recognized by the presence of a hydrophilic surfactant (HLB > 12) and a co-solvent like ethanol, polyethylene glycol, or propylene glycol [15].

Type III formulations can be further separated into type IIIA and type IIIB formulations [16]. Type IIIB formulations frequently have quicker dispersion rates than type IIIA formulations, but because the formulation has less lipid, there is a greater chance of drug precipitation during dispersion.

**Type IV**- These formulations frequently offer improved drug payloads when related to those made up of simple glycerides lipids, and they also induce very fine dispersion when added to aqueous [17,18]. The existing capsule version of the HIV protease inhibitor Amprenavir (Agenerase®), which contains TGPS as a surfactant and PEG 400 and PG as a cosolvent, is an example of a type IV formulation.

Advantages of SMEDDS [18, 19]

- Enhanced oral bioavailability by improved medication solubility and transport.
- Simple production related to other lipid dosage forms; easy to scale up.
- Lessening of dietary effects and intra- and inter-subject variability.
- SMEDDS has no effect on the lipid digestion process and can transport peptides that are susceptible to enzymatic hydrolysis in the gastrointestinal tract.
- The inclusion of polymer in the SMEDDS composition causes a delayed release of the medication.

Disadvantages of SMEDDS [20, 21]

- There aren't any reliable projecting in vitro models for evaluating the formulations; therefore, the model needs to be improved and validated before its potency can be assessed.
- Because additional development will be dependent on correlations amid in vitro and in vivo tests, numerous prototype lipid-based formulations must be created and put to the test in vivo in an appropriate animal model.
- In addition, it has been observed that volatile cosolvents in conventional self-micro emulsifying formulations can travel into the gelatin capsules' soft or hard shells, precipitating the lipophilic medicines.
- The hydrophilic solvent's dilution action may cause the drug's tendency to precipitate on dilution to be higher.

Mechanism of SMEDDS

The surfactant molecules that surround the internal phase droplet in a film stabilise the emulsion. Due to the extremely little, positive, or even negative free energy of formation for SMEDDS, thermodynamic spontaneous emulsification occurs. One theory state that water can get into the liquid crystalline (LC) phase that forms at the oil/surfactant/water interface and causes it to self-emulsify. Mild agitation makes this penetration easier. Once water has penetrated the interface to a certain point, it will break and produce droplets. This LC phase is responsible for the resultant microemulsion's excellent stability against coalescence [22, 23].

## 3. FORMULATION COMPONENTS OF SMEDDS

- **Active Pharmaceutical Ingredient**

Lipid-based formulations provide a likely platform for enhancing the oral bioavailability of medications, particularly those falling under BCSII and IV. Analyzing the drug's lipophilicity (log P) and its solubility in pharmaceutically acceptable lipid excipients, which must be adequate to let the administration of the entire dose of the medicine in a single dosage unit, can provide a primary indication of the probable utility of lipid-based formulation [24, 25].

SMEDDS can increase the degree and amount of absorption for lipophilic pharmaceutical mixes that exhibit dissolution-rate-limited absorption, resulting in a predictable blood time profile [26].When compared to lipid solutions, SMEDDS systems typically have a higher drug loading capacity because amphiphilic surfactants, co-surfactants, and co-solvents have much higher solubilities of poorly water-soluble drugs 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. For the development of lipidic systems, low melting points and low doses are preferred [27].

- **Lipids (Oils)**

Lipids are a key component of SMEDDS because the category and concentration of oil used in the formulation determines how well-watered-down medications are soluble and can reach the lymphatic system [28, 29]. In comparison to non-digestible lipids, which may have lower bioavailability owing to diminishing in absorption produced by retention of the fraction of directed drug in the formulation itself, digestible lipids like triglycerides, diglycerides, fatty acids, phospholipids, cholesterol, and other lipids based on synthetic origin offer improved bioavailability of the drug. The composition of fatty acids, melting point, Hydrophilic-Lipophilic Balance (HLB), and solubility in non-polar chemical solvents are widely used to identify lipids. Lipids are typically insoluble in water. For continuous release, lipids with low HLB and high melting points are best [30]. Excipients for immediate release and bioavailability enhancement are semi-solid and have a high HLB. Dietary oils made of medium- or long-chain triglycerides (corn, olive, peanut, or sesame oil) are examples of lipid-based excipients.

- **Surfactants**

HLB and safety are the two primary deciding considerations when choosing a surfactant. The emulsifier used in SMEDDS formulation should have high HLB and hydrophilicity in order to achieve high emulsifying property [31]. As a result, oil-in-water droplets are immediately formed, and the formulation is quickly dispersed in aqueous media (such as digestive fluid). For effective absorption, the medication disseminated in the SMEDDS formulation would stay solubilized for a long time at the site of absorption, preventing the drug molecule from precipitating within the GI lumen. Since non-ionic surfactants have a comparatively more HLB value, they are utmost frequently advised. Stable SMEDDS are produced when surfactant concentrations between 30% and 60% w/w are used [32]. Cremophor® EL, Cremophor® RH40, Cremophor® RH60, polysorbate 80, various grades of gelucires, etc. are surfactants that are approved for use in pharmaceuticals.

- **Co-surfactants**

Co-surfactants that are approved for use in pharmaceuticals include propylene glycol, ethanol, and polyethylene glycol 400. In order to softenhuge amounts of hydrophilic surfactants, lipid soluble solvents are utilised in the formulation of SMEDDS [33,34]. Lipid mixtures with higher surfactant and co-surfactant to oil ratios make it easier to produce stable SMEDDS.

- **Co-solvents**

Hugequantities of the hydrophilic surfactant or the medication can be dissolved in oil phase thanks to organic solvents. Examples include alcohols like ethanol, butanol, and propylene glycol as well as esters like tributyl citrate and ethyl propionate, as well as amides like 2-pyrolidine, caprolactum, and polyvinyl pyrolidine [35].

- **Other components**

pH adjusters, tastes, antioxidants, consistency builders, enzyme inhibitors, polymers, and others are additional ingredients. [36]

## 4. SMEDDS FORMULATION DESIGN

**Screening of Oil**

Choosing oil with the maximum level of solubility for the medication and a surfactant or cosurfactant with the highest solubility potential are the standard objectives of solubility research. The most common approach for determining a medication's solubility is the shake flask method, which involves adding an excessive amount of the drug to the solvent and shaking the mixture for 48 hours at room temperature [37]. The samples should then be centrifuged, filtered through 0.45-micron filters, and the drug concentration was directly assessed using the high-performance liquid chromatography (HPLC) technique [38].

Screening of Surfactant and co-surfactant

It is likely to assess the capacity of surfactants to emulsify by homogenising the mixture after combining the chosen oil and the surfactant in equal quantities. Once this combination is introduced to double-distilled water, the numeral flask inversions necessary to create a homogeneous emulsion is noted, and this shows how quickly the emulsion will come together. The following step is to measure the microemulsion's clarity, turbidity, and transmittance percentage. The best surfactants to use are those with the highest percentage transmittance or those with the lowest requirements for flask inversion [39, 40]. The cosurfactants should be screened in the same way after adding a chosen surfactant and oil phase to the mixture [41].

**Construction of pseudoternary Phase Diagram**

These diagrams demonstrate how the behaviour of the system varies depending on its make-up. A ternary phase diagram is castoff to study the phase behaviour of three components [42]. This is the SEDDS representation of a system consisting of three components: oil, water, and surfactant. However, the addition of a cosurfactant or cosolvent is the component that is added to SMEDDS the

most frequently. On a ternary diagram, three of the corners correspond to the entire given component. When a quarter components is present, the ternary diagram can be thought of as a pseudoternary phase diagram because one of the corners parallels to the mixing of dual components, such as surfactant and cosurfactant [43].

To create a pseudoternary phase diagram, blends with dissimilar ratios of microemulsion components must have their emulsification efficiency evaluated [44]. Phase diagrams can be used to visualize how different structures, including emulsions, microemulsions, micelles, inverted micellar forms, and others, are formed at various compositions. This phase diagram details the numerous compositions that produce monophasic clear solutions and helps determine the formulation's dilutability [45].

The ratio of any two of the four components is kept continuous when producing pseudoternary diagrams, and this ratio, along with the other two components, typically forms three corners of the phase diagram. It is common practice to combine a cosurfactant and a surfactant to produce this fixed (mixed) ratio, though it is occasionally possible to combine an oil and a surfactant [46, 47]. This is varied with the essential quantity of the third phase [48, 49], and then the fourth part, usually water, is added in small amounts. Testing the solution for clarity, flowability, time for self-emulsification, and dispersibility should be done after each addition of the fourth component [50]. A 100% percent concentration should be achieved across all components in each mixture [51]. Then, using the appropriate software, a pseudoternary diagram needs to be plotted. The suitable symbols in the phase diagram should be used to represent the samples that produced clear solutions [52]. A large area shows good emulsification efficiency, and the area created when these points are linked specifies the monophasic microemulsion current area.

How Should a Ternary Diagram Be Read?

The following details might make ternary diagrams easier to read and understand. A, B, and C, the trio components, are characterized by the three corners of a typical ternary diagram [53, 54]. The proportion of C, A, and B increases from 0% concentration at point B to 100% concentration at point A, as shown by the arrows pointing towards BA, AC, and CB, respectively, just as it does for the arrows pointing towards BA, AC, and CB. The data below can be used to calculate the composition at point "O" as seen in Figure 1.

i. From point X towards AB, draw a line parallel to CB. This line's intersection with AB at point X signifies the % composition of A at that location (A%).

ii. Next, the % composition of B at point X can be found by drawing a line parallel to AC and pointing towards BC. The point at which this line traverses BC represents the percent composition of B at point X (B%).

iii. In a like manner, the percent composition of C at point X can be found by drawing a line parallel to AB and pointing in the direction of AC (C%).

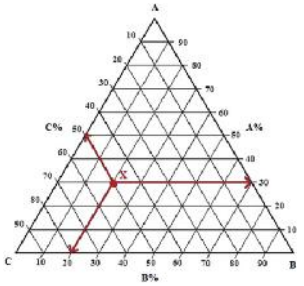


**Fig 1: A common ternary diagram display the association between A, B, and C at point X**

### Preparation of SMEDDS

The procedure entails adding the medication to the blend of oil, surfactant, and co surfactant before vortexing it [55]. Sometimes, only one excipient is used to dissolve the medication before the other excipients are added [56]. The mixture of the solution should then be thoroughly inspected for turbidity. The solution should then equilibrate for 48 hours at room temperature before, if required, being boiled to produce a transparent solution. Dependent on the final volume, the formulation must be stored in appropriate-sized capsules.

## 5. CHARACTERIZATION OF SMEDDS

### Macroscopic evaluation

The homogeneity of formulations is observed using a macroscopic evaluation study [57]. The optimized formulation shows any colour and transparency changes or phase separation that takes place under standard storage conditions (37°C). The uniformity of globule size guarantees the formulation's ability to distribute drugs effectively.

### Visual assessment

100 ml of water were added, and the mixture was gently stirred by hand in a glass Erlenmeyer flask at 25°C to test the formulation's capacity to self-emulsify. When there is weak or no emulsion formation, the tendency to impulsively produce a transparent emulsion is considered bad. The ideal self-emulsifying zone is identified using a phase diagram [58]. The production of a transparent product may be considered the point at which preparation is said to have been successful.

### Zeta-potential and droplet size/distribution determination

With a measurement range of 10-5000 nm, a zetasizer is one tool for determining droplet size. This technique examines variations in light scattering brought on by particle Brownian moments. Only at relatively low dilutions can this method be castoff to accurately regulate droplet size. Oil droplets have a surface charge because certain groups are present, such as traditional SMEDDS, which is negative as free fatty acids are present. However, cationic SMEDDS will be produced if cationic lipids are added in amounts between 1% and 3%. These systems consequently show a positive potential of about 35–45 mV and is maintained after the incorporation of the therapeutic molecules [59].

**Rheological determination**

Rheological qualities of a microemulsion can be assessed using a rotational viscometer like the Brookfield Rheomat 108. Whether the system is o/w or w/o is confirmed by this study. It should be carried out in three copies [60].

**Polarity**

How polar an oil droplet depends on a number of variables, such as the HLB, chain length and degree of fatty acid unsaturation, hydrophilic part molecular weight, and emulsifier content. Polarity affects both the types of forces produced and the drug's affinity for water and/or oil. The formulation that produces the highest release has an oil phase with the highest polarity [61].

**Dispersibility test**

The effectiveness of self-emulsification of an oral nano- or microemulsion is assessed using a conventional USP XXII dissolution apparatus 2. At a temperature of 37-10°C, 500 ml of water were added with one millilitre of each formulation. Mild agitation is provided by a simple stainless steel dissolution paddle rotating at 50 rpm. [62,63] The in vitro performance of the formulations is graded by means of the following grading scale:

- Grade A: A nanoemulsion that forms rapidly (within one minute) and appears clear or bluish.
- Grade B: An emulsion that forms fast, is significantly less transparent, and looks bluish-white. Grade C: Within two minutes, a fine milky emulsion formed.
- Grade D: Slow to emulsify (more than 2 minutes), dull, grayish-white emulsion with a faintly greasy look.
- Grade E: Formulation with either insufficient or limited emulsification and observable surface oil globules.

When distributed in GIT, Grade A and Grade B formulations will still be Nano-emulsions. While SEDDS formulations could be advised to use Grade C formulations.

**Turbidimetric evaluation**

The development of an emulsion can be checked using nephelo turbidimetric analysis. A fixed quantity of self-emulsifying system is added along with a fixed amount of acceptable medium (0.1 N hydrochloric acid). On a magnetic plate, constant stirring (50 rpm) is carried out at room temperature while a turbidimeter measures the rise in turbidity [64]. But, owing to the short amount of time essential for complete emulsification, it is impossible to screen the rate of change in turbidity (rate of emulsification).

**Refractive index and percent transmittance**

The refractive index and percent transmittance of the formula assist as indicator of its transparency. By pouring a solution onto a slide and comparing the result to distilled water (1.333), refractive index is measured. A formulation is considered transparent when it's percent transmittance is >99% and the system's refractive index is near to that of water [65].

**Electro conductivity test**

To ascertain whether the system is conductive, this test is performed. It is measured using an electro-conductometer. Oil droplets in typical SMEDDSs have a negative charge because there are free fatty acids there [66].

**Time for Emulsification**

The USP type II dissolution apparatus can be used to estimate the amount of time needed for self-emulsification for many preparations. In this device, the formulation is added dropwise to a basket containing water, and the development of a clear solution is detected while the paddle is being rotated at 50 rpm [67].Self-emulsification is used to evaluate how well the formulation self-emulsifies. The category of oil phase and the oil/surfactant ratio have been found to influence the rate of emulsification. Because water enters the interface more quickly at higher surfactant concentrations, oil droplets are ejected more quickly. The emulsification time can also be estimated visually by putting the formulation in 0.1 N HCl and stirring it at body temperature to simulate GI conditions [68].

**Cloud Point Determination**

The formula is typically measured spectrophotometrically in a water bath whereas the temperature is slowly improved to regulate the cloud point. The point at which transmittance percentages start to decline serves as a proxy for the cloud point, or the temperature above which clear solution becomes cloudy. Formulations must be warmer than the body temperature, which is 37 °C, in order to uphold their ability to self-emulsify. Phase separation and a decline in drug solubilization are often detected at temperatures higher than the cloud point because surfactant is prone to dehydration [69]. The cloud point is influenced by formulation variables such as drug lipophilicity.

**Dilution Studies**

The impact of dilution on microemulsion clarity may be studied by diluting microemulsion preconcentrate to different concentrations that imitate stomach circumstances and in different diluents such double distilled water, simulated gastric fluid (SGF), and simulated intestinal fluid (SIF) [70]. Drug precipitation is not present if clarity endures with increasing dilution as well as when changing the type of diluents. To mimic in vivo conditions, SMEDDS can be diluted up to 100 times with all of the aforesaid diluents [71]. The impact of the dilution medium's pH can be examined by dilution SMEDDS with various solvents like buffer pH 1.2, buffer pH 6.8, and so forth along with distilled water. It is possible to assess transparency and self-emulsification efficiency [72].

**Differential Scanning Calorimetry**

This is used to define the water-corresponding peaks in micro emulsions made by dilution of SMEDDS. The peaks reveal data about the water's condition, such as whether it is bound or free [73]. When using pure water as a reference, the freezing point can be seen as a huge, abrupt peak at about 17 °C. The discovered peaks that corresponded to the water at lower temperatures than the pure water, indicate that water is present in the bound state and is preferably bound to surfactants. A concentration of water greater than this,

results in a change in temperature and to the conclusion that large concentrations of water formed O/W micro emulsions [74].

**NMR Technique**

It is used to evaluate the structural steadiness of the microemulsions following SMEDDS dilution. The diffusing behaviour of microemulsion components can be investigated using the Fourier transforms pulsed gradient spin-echo method (PGSE). Self-diffusion NMR experiments are used to regulate the type of microemulsion that develops after SMEDDS are diluted. These experiments are also used to determine transitions such as W/O to bicontinuous and bicontinuous to O/W type after incremental dilution [75]. The self-diffusion coefficients of various microemulsion components are related to those of pure components using this technique. If the diffusion of one of the components is lower than that of the pure component, O/W or W/O droplets are present. A bicontinuous type microemulsion is present when the diffusion coefficients of the oil and aqueous phases are high and equivalent to those of the pure components [76].

**Small Angle X-Ray and Neutron Scattering Methods**

The structures created by SMEDDS dilution may be described using small angle X-ray scattering techniques. It is vital to evaluate the liquid crystalline structures shaped by the dilution of SMEDDS since they influence the formulation's stability, ability to self-emulsify, and degree of drug release. Small angle neutron scattering techniques, transitions in microemulsion structures upon dilution, and droplet size and shape can all be used to regulate the size and shape of the droplets [77].

**Thermodynamic Stability Studies**

These studies are beneficial in understanding how temperature variation impacts formulation. Before being centrifuged at 15,000 or 3500 rpm for 15 or 30 minutes, respectively, the formulation is diluted with aqueous phase [46, 59]. Phase separation-free samples are subjected to freeze-thaw cycles (at 20 and 40 °C, respectively), and the outcomes are evaluated visually. The visual description of formulations that are thermodynamically stable won't alter [78].

**In-vitro Dissolution Profile**

The drug release from the formulation can be measured using the USP apparatus I at 100 rpm or USP apparatus II at 50 rpm, or using the dialysis method at 37 ±0.5° C, after the formulation has been placed in a hard gelatin capsule. At regular intervals, the medium should be taken out of samples so that the drug content can be calculated and related to the control. The polarity of the oil droplet has an influence on the medicine release from the diluted SMEDDS. The higher the polarity, the quicker the drug is released from the oil droplet into the aqueous phase [79].

**Stability Assessment**

Stability tests are carried out on the formulation that is placed inside gelatin capsules in accordance with ICH requirements. At regular intervals, samples must be collected and examined for appearance, colour, drug content, pH of the diluted formulation, and dissolving profile. If no one of these features change although the formulation is being stored, it can be thought to be stable [80].

## 6. CONCLUSION

Self-microemulsifying drug delivery devices are a cutting-edge and efficient way to increase the oral bioavailability of several pharmaceuticals that are poorly water soluble, only if that the medication is potent and has a high lipid solubility. SMEDDS has been demonstrated to make very hydrophobic medications with good solubility (>50 mg/mL in triglycerides) and a high octanol:water partition coefficient more easily transported through the lymphatic system. Smaller droplets enable more rapid and efficient drug release, which boosts bioavailability. The current review focused on the development of pseudoternary phase diagrams, and numerous tests necessary to produce a trustworthy and stable dosage form. By leading added research to develop SMEDDS with low-toxic surfactants and to develop in vitro methodologies to better realize the in vivo fate of these formulations, it is possible to increase the marketability of SMEEDS.

## 7. REFERENCES

1. Bhatt V, Rathore RP, Tanwar YS. Self miro emulsifying drug delivery system, A review. ARPB 2014;4(2):664-9.
2. Kyatanwar AU, Jadva KR. Self micro-emulsifying drug delivery system. J Pharm Res 2010;3(1):75-83.
3. Mandawgade SD, Sharma S, Pathak S, Patravale VB. Development of SMEDDS using natural lipophile: Application to beta-artemether delivery. Int J Pharm 2008;362(1-2):179-83.
4. Khedekar K, Mittal S. Self emulsifying drug delivery system: A review. IJPSR 2013;4(12):4494-507.
5. Gugulothu D, Pathak S, Suryavanshi S, Sharma S, Patravale V. Selfmicroemulsifiyng suppository formulation of ß-artemether. AAPS Pharm Sci Tech 2010;11(3):1179-84.
6. McConville C, Friend D. Development and characterisation of a selfmicroemulsifying drug delivery systems (SMEDDSs) for the vaginal administration of the antiretroviral UC-781. Eur J Pharm Biopharm 2013;83(3):322-9.
7. Woo JS, Kim TS. Formulation and evaluation of silymarin using SMEDDS. Arch Pharm Res 2007;30(1):82-9.
8. Pimple SS, Yeole SE, Chaudhari PD. Self-micro drug delivery system for poorly water soluble drug. Int J Pharm Sci Res 2013;23(1):155-62.
9. Laddha P, Suthar V, Butani S. Development and optimization of self miro Asian J Pharm Clin Res, Vol 9, Suppl. 2, 2016, 33-38

10. Li L, Yi T, Lam CW. Effects of spray-drying and choice of solid carriers on concentrations of Labrasol® and Transcutol® in solid self-microemulsifying drug delivery systems (SMEDDS). Molecules 2013;18(1):545-60.
11. Zhu JX, Tang D, Feng L, Zheng ZG, Wang RS, Wu AG, et al. Development of self-microemulsifying drug delivery system for oral bioavailability enhancement of berberine hydrochloride. Drug Dev Ind Pharm 2013;39(3):499-506.
12. Sharma B, Sharma A, Arora S. Formulation, and evaluation of calcium loaded microemulsion. J Pharm Drug Res 2012;1:1-7.
13. Nisha GS, Geeta R, Vaishali P. Formulation and evaluation of SMEDDS. Int J Res Pharm Sci 2011;2(2):162-9.
14. Khan BA, Bakhsh S, Khan H. Basics of self-micro emulsifying drug delivery system. J Pharm Altern Med 2012;1:13-20.
15. Nekkannti V, Kalepu S. Novel lipid based drug delivery system. IRJP 2012;3(9):166-73.
16. Bhagwat DA, D'Souza JI. Formulation, and evaluation of solid self miro emulsifying drug delivery system. Int Curr Pharm J 2012;1(12):414-9.
17. Patel RN, Rajput AP. In-vivo chariterization of SMEDDS. Int J Pharm Pharm Sci 2013;5(3):793-800
18. Manoharui PJ, Kunchithapatham J. Development of SMEDDS. Der Pharm 2013;4(6):48-58.
19. Harshal DM, Rajendra DW, Tanvvir S. Design and development of self-micro emulsifying drug delivery system. Int J Curr Pharm Res 2011;5(4):163-5.
20. Sha X, Wu J, Chen Y, Fang X. Self-microemulsifying drug-delivery system for improved oral bioavailability of probucol: Preparation and evaluation. Int J Nanomedicine 2012;7:705-12.
21. Cai S, Yang L, Suo H. Self-micro emulsifying drug delivery system for improved oral bioavailability. Int J Nanomedicine 2014;9:913-20.
22. Wei JD, Ho HO, Chen CH, Ke WT, Chen ET, Sheu MT. Characterisation of fenofibrate dissolution delivered by a self-microemulsifyingdrugdelivery system. J Pharm Pharmacol 2010;62(12):1685-96.
23. Dahan A and Hoffman A. Rationalizing the selection of oral lipid based drug delivery systems by an in vitro dynamic lipolysis model for improved oral bioavailability of poorly water soluble drugs," Journal of Controlled Release, 2008; 12:1–10.
24. Chakraborty S, Shukla D, Mishra B, Singh S. Lipid—an emerging platform for oral delivery of drugs with poor bioavailability," European Journal of Pharmaceutics and Biopharmaceutics, 2009; 73(1):1–15.
25. Gursoy RN and Benita S. Self-emulsifying drug delivery systems (SEDDS) for improved oral delivery of lipophilic drugs," Biomedicine and Pharmacotherapy, 2004; 58(3):173–82.
26. di Maio S and Carrier RL. Gastrointestinal contents in fasted state and post-lipid ingestion: in vivo measurements and in vitro models for studying oral drug delivery. Journal of Controlled Release 2011; 151: 110–22.
27. Jannin V, Musakhanian J, and Marchaud D. Approaches for the development of solid and semi-solid lipid-based formulations. Advanced Drug Delivery Reviews, 2008; 60(6): 734– 46.
28. Tang JL, Sun J, He J. Self-emulsifying drug delivery systems: strategy for improving oral delivery of poorly soluble drugs. Current Drug Therapy, 2007; 2: 85–93.
29. Stegemann S, Leveiller F, Franchi D, de Jong H, Linden H. When poor solubility becomes an issue: from early ´ stage to proof of concept," European Journal of Pharmaceutical Sciences, 2007;31:249–61.
30. Alex MRA, Chacko AJ, Jose S, Souto EB. Lopinavir loaded solid lipid nanoparticles (SLN) for intestinal lymphatic targeting. European Journal of Pharmaceutical Sciences, 2011; 42: 11–8.
31. Gohel MC, Parikh RK, Modi SC, Vyas KG, Sheth KM. Novel drug delivery approaches to bypass Pglycoprotein efflux pump. Pharmainfo.net,2011; 9.
32. Constantinides PP, Scalart JP, Lancaster C et al. Formulation and intestinal absorption enhancement evaluation of water-in-oil microemulsions incorporating medium-chain glycerides. Pharmaceutical Research, 1994; 11(10): 1385– 90.
33. Narang AS, Delmarre D, Gao D. Stable drug encapsulation in micelles and microemulsions. International Journal of Pharmaceutics, 2007; 345: 9–25.
34. Bansal T, Akhtar N, Jaggi M, Khar RK, and Talegaonkar S. Novel formulation approaches for optimising delivery of anticancer drugs based on P-glycoprotein modulation. Drug Discovery Today, 2009; 14: 1067–74.
35. Dwibhashyam VSNM and Vijayaralna J. The permeability glycoprotein (P-GP)—a threat to effective drug therapy?. Indian Drugs 2006; 43(8): 609–15.
36. Ke WT, Lin SY, Ho HO, and Sheu MT. Physical characterizations of microemulsion systems using tocopheryl polyethylene glycol 1000 succinate (TPGS) as a surfactant for the oral delivery of protein drugs. Journal of Controlled Release, 2005; 102 (2):489–507.
37. Nornoo AO, Zheng H, Lopes LB, Johnson-Restrepo B, Kannan K, and Reed R. Oral microemulsions of paclitaxel: in situ and pharmacokinetic studies. European Journal of Pharmaceutics and Biopharmaceutics, 2009; 71(2):310–7.
38. Kim HJ, Yoon KA, Hahn M, Park ES, and Chi SC. Preparation and in vitro evaluation of self-microemulsifying drug delivery systems containing

idebenone. Drug Development and Industrial Pharmacy, 2000; 26(5):523–9.
39. Jadhav KR, Shaikh IM, Ambade KW, and Kadam VJ. Applications of microemulsion based drug delivery system. Current Drug Delivery, 2006; 3(3):267–73.
40. Buyukozturk F, Benneyan JC, Carrier RL. Impact of emulsion-based drug delivery systems on intestinal permeability and drug release kinetics. Journal of Controlled Release 2010; 142(1): 22–30.
41. Djekic L and Primorac M. The influence of cosurfactants and oils on the formation of pharmaceutical microemulsions based on PEG-8 caprylic/capric glycerides. International Journal of Pharmaceutics, 2008; 352: 231–9.
42. Gershanik T and Benita S. Self-dispersing lipid formulations for improving oral absorption of lipophilic drugs. European Journal of Pharmaceutics and Biopharmaceutics, 2000; 50: 179–88.
43. Porter CJH, Pouton CW, Cuine JF, and Charman WN. Enhancing intestinal drug solubilisation using lipid-based delivery systems," Advanced Drug Delivery Reviews, 2008;60(6): 673–91.
44. Pouton CW, Porter CJH. Formulation of lipid-based delivery systems for oral administration: materials, methods and strategies. Advanced Drug Delivery Reviews,2008;60(6): 625–37.
45. H. N. Prajapati, D. M. Dalrymple, and A. T. M. Serajuddin, "A comparative evaluation of mono-, di- and triglyceride of medium chain fatty acids by lipid/surfactant/water phase diagram, solubility determination and dispersion testing for application in pharmaceutical dosage form development," Pharmaceutical Research, 2012; 29: 285–305.
46. Ya´nez JA, Wang SWJ, Knemeyer IW, Wirth MA, and ˜ Alton KB. Intestinal lymphatic transport for drug delivery. Advanced Drug Delivery Reviews 2011;63: 923–42.
47. Sun M, Zhai X, Xue K et al., "Intestinal absorption and intestinal lymphatic transport of sirolimus from self-microemulsifying drug delivery systems assessed using the single-pass intestinal perfusion (SPIP) technique and a chylomicron flow blocking approach: linear correlation with oral bioavailabilities in rats," European Journal of Pharmaceutical Sciences, 2011; 43(3):132–40.
48. Hauss DJ. Oral lipid-based formulations. Advanced Drug Delivery Reviews, 2007; 59(7): 667–76.
49. Kohli K, Chopra S, Dhar D, Arora S, and Khar RK,. Selfemulsifying drug delivery systems: an approach to enhance oral bioavailability. Drug Discovery Today, 2010; 15: 958–65.
50. Sha X, Yan G, Wu Y, Li J, and Fang X. Effect of selfmicroemulsifying drug delivery systems containing Labrasol on tight junctions in Caco-2 cells. European Journal of Pharmaceutical Sciences, 2005; 24(5):477–86.
51. Bagwe RP, Kanicky JR, Palla BJ, Patanjali PK, and Shah DO. Improved drug delivery using microemulsions: rationale, recent progress, and new horizons. Critical Reviews in Therapeutic Drug Carrier Systems 2001; 18(1):77–140.
52. Pouton WJ. Lipid formulations for oral administration of drugs: non-emulsifying, self-emulsifying and "self-microemulsifying" drug delivery systems. European Journal of Pharmaceutical Sciences 2000; 11: S93–S98.
53. Li Y and McClements DJ. Inhibition of lipase-catalyzed hydrolysis of emulsified triglyceride oils by low-molecular weight surfactants under simulated gastrointestinal conditions. European Journal of Pharmaceutics and Biopharmaceutics 2011;79: 423–31.
54. Mullertz A, Ogbonna A, Ren S, and Rades T. New perspec- ¨ tives on lipid and surfactant based drug delivery systems for oral delivery of poorly soluble drugs. Journal of Pharmacy and Pharmacology, 2010; 62(11):1622–36.
55. Bandivadeka MM, Pancholi EE, Kaul-Ghanekar R, Choudhari A, and Koppikar S. Self-microemulsifying smaller molecular volume oil (Capmul MCM) using non-ionic surfactants: a delivery system for poorly water-soluble drug. Drug Development and Industrial Pharmacy, 2012; 38(7): 883– 92.
56. V. Borhade, H. Nair, and D. Hegde, "Design and evaluation of self-microemulsifying drug delivery system (SMEDDS) of tacrolimus. AAPS PharmSciTech 2008; 9: 13–21.
57. Wang Y, Sun Y, Zhang T, Liu H, He F, and He Z. Enhanced oral bioavailability of tacrolimus in rats by self-microemulsifying drug delivery systems. Drug Development and Industrial Pharmacy 2011; 37(10): 1225–30.
58. Singh AK, Chaurasiya A, Awasthi A et al., "Oral bioavailability enhancement of exemestane from self-microemulsifying drug delivery system (SMEDDS)," AAPS PharmSciTech, 2009; 10(3), 906–16.
59. Basalious EB, Shawky N, and Badr-Eldin EN. SNEDDS containing bioenhancers for improvement of dissolution and oral absorption of lacidipine. I. Development and optimization. International Journal of Pharmaceutics, 2010; 391:203– 11.
60. Elnaggar YSR, El-Massik MA, and Abdallah OY. Selfnanoemulsifying drug delivery systems of tamoxifen citrate: design and optimization," International Journal of Pharmaceutics, 2009; 380: 133–41.
61. Lawrence MJ and Rees GD. Microemulsion-based media as novel drug delivery systems. Advanced Drug Delivery Reviews, 2000; 45: 89–121.
62. Cui SX, Nie SF, Li L, Wang CG, Pan G, and Sun J. Preparation and evaluation of self-microemulsifying

drug delivery system containing vinpocetine. Drug Development and Industrial Pharmacy, 2009; 35: 603–11.
63. Hu L, Wu H, Niu F, Yan C, Yang X, and Jia Y. Design of fenofibrate microemulsion for improved bioavailability. International Journal of Pharmaceutics, 2011; 420: 251–255.
64. Singh AK, Chaurasiya A, Singh M, Upadhyay SC, Mukherjee R, and Khar RK. Exemestane loaded self-microemulsifying drug delivery system (SMEDDS): development and optimization. AAPS PharmSciTech, 2008; 9: 628–34.
65. Zhang H, Cui Y, Zhu S, Feng F, and Zheng X. Characterization and antimicrobial activity of a pharmaceutical microemulsion. International Journal of Pharmaceutics, 2010; 395: 154–60.
66. Ghosh PH, Majithiya RH, Umrethia ML, and Murthy RSR, "Design and development of microemulsion drug delivery system of acyclovir for improvement of oral bioavailability. AAPS PharmSciTech, 2006; 7(3):E1–E11.
67. Balakrishnan P, Lee BJ, Oh DH et al. Enhanced oral bioavailability of Coenzyme Q10 by self-emulsifying drug delivery systems. International Journal of Pharmaceutics, 2009; 374: 66–72.
68. Parveen R, Baboota S, Ali J, Ahuja A, Vasudev SS, and Ahmad S. Oil based nanocarrier for improved oral delivery of silymarin: In vitro & In vivo studies. International Journal of Pharmaceutics, 2011; 411: 245–253.
69. Patel AR and Vavia PR. Preparation and in vivo evaluation of SMEDDS (self-microemulsifying drug delivery system) containing fenofibrate. The AAPS Journal, 2007; 9: E344– 52.
70. Sharma G, Wilson K, van der Walle CF, Sattar N, Petrie JR, and Kumar MN. Microemulsions for oral delivery of insulin: design, development and evaluation in streptozotocin induced diabetic rats. European Journal of Pharmaceutics and Biopharmaceutics, 2010;76:159–69.
71. Bali V, Ali M, and Ali J. Nanocarrier for the enhanced bioavailability of a cardiovascular agent: in vitro, pharmacodynamic, pharmacokinetic and stability assessment. International Journal of Pharmaceutics 2011; 403: 45–56.
72. Atef T and Belmonte AA. Formulation and in vitro and in vivo characterization of a phenytoin self-emulsifying drug delivery system (SEDDS). European Journal of Pharmaceutical Sciences. 2008; 35(4): 257–263.
73. Boonme P, Krauel K, Graf A, Rades T, and Junyaprasert TB. Characterization of microemulsion structures in the pseudoternary phase diagram of isopropyl palmitate/water/Brij 97:1- butanol. AAPS PharmSciTech, 2006; 7(2): E45.
74. Karamustafa F and Celebi N. Development of an oral ´ microemulsion formulation of alendronate: Effects of oil & cosurfactant type on phase behaviour. Journal of Microencapsulation, 2008; 25(5): 315–23.
75. de Campos Araujo LMP, Thomazine JA, and. Lopez RFV. Development of microemulsions to topically deliver 5-aminolevulinic acid in photodynamic therapy. European Journal of Pharmaceutics and Biopharmaceutics 2010; 75: 48–55.
76. Shafiq S, Shakeel F, Talegaonkar S, Ahmad SF, Khar SK, and Ali M. Development and bioavailability assessment of ramipril nanoemulsion formulation," European Journal of Pharmaceutics and Biopharmaceutics, v 2007; 66: 227–243.
77. Shafiq-un-Nabi S, Shakeel F, Talegaonkar S et al. Formulation development and optimization using nanoemulsion technique: a technical note. AAPS Pharm SciTech, 2007;8: E12–E17.
78. Gradzielski M. Recent developments in the characterisation of microemulsions. Current Opinion in Colloid and Interface Science 2008; 13 (4): 263–69.
79. Goddeeris C, Goderis B, and van den Mooter G. Lyotropic, liquid crystalline nanostructures of aqueous dilutions of SMEDDS revealed by small-angle X-ray scattering: impact on International Scholarly Research Notices 11 solubility and drug release," European Journal of Pharmaceutical Sciences 2010; 40(2): 110–17.
80. Bachhav YG and Patravale VB. SMEDDS of glyburide: formulation, in vitro evaluation, and stability studies," AAPS PharmSciTech, 2009;10( 2): 482–7.

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