ABSTRACT
Oral route is the easiest and most convenient route of drug administration, but major problem encountered in oral formulations estimated 60-70% of new chemical entities exhibit poor aqueous solubility, because of their low bioavailability. The challenges task is to increase the bioavailability of drugs. Various strategies are reported in the literature including micronization, solid dispersions, cyclodextrines complex formation. Self micro-emulsifying drug delivery systems are usually used to improve the bioavailability of hydrophobic drugs. SMEDDS isotropic mixtures of oils, surfactants and co-surfactants and administered orally which on mild agitation with GI fluids forms o/w microemulsion. SMEDDS have enhanced bioavailability of drugs with reduction in dose and also drugs are protected from hostile environment in gut.

KEYWORDS: Self microemulsifying drug delivery system (SMEDDS), surfactant, co-surfactant.

INTRODUCTION
The oral route is most commonly route for chronic drug therapy, majority of drugs are frequently administered through oral route, but approximately 40% of new drug candidates have poor water solubility and the oral delivery of such drugs is complicated for the reason that of their low bioavailability high intra and inter subject variability, and not have dose linearity. One of the most popular and commercially viable formulation approaches for solving these problems is self emulsifying drug delivery systems. SEDDS have been shown to be reasonably successful in improving the oral bioavailability of poorly water soluble and
lipophilic drugs. Traditional preparation of SEDDS involves dissolution of drugs in oils and their blending with suitable solubilizing agents. However SE formulation are normally prepared as liquids that produce some disadvantages, for example, high production costs, low stability and portability, low drug loading and few choices of dosage forms. Irreversible drugs/excipient precipitation may also be problematic. More importantly, the large quantity of surfactants in the formulations can induce GI irritation. SMEDDS are mostly prepared in liquid dosage form in soft and hard gelatin capsules which have some manufacturing and gelatin capsules which have some manufacturing and leakage problems.\[^{1}\]

**Lipid Formulation Classification System**

<table>
<thead>
<tr>
<th>LFCSType</th>
<th>Characteristics</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Oils without surfactants non-dispersing; requires digestion</td>
<td>GRAS status; simple; excellent capsule compatibility</td>
<td>Formulation has poor solvent capacity unless drug is highly lipophilic</td>
</tr>
<tr>
<td>II</td>
<td>SEDDS without water-soluble components</td>
<td>Unlikely to lose solvent capacity on dispersion</td>
<td>Turbid o/w dispersion</td>
</tr>
<tr>
<td>IIIA</td>
<td>SEDDS/SMEDDS with water soluble components</td>
<td>Clear or almost clear dispersion; absorption without digestion</td>
<td>Possible loss of solvent capacity on dispersion; less easily digested</td>
</tr>
<tr>
<td>IIIB</td>
<td>SMEDDS with water soluble components and low oil content</td>
<td>Clear dispersion; drug absorption without digestion</td>
<td>Likely loss of solvent capacity on dispersion</td>
</tr>
<tr>
<td>IV</td>
<td>Oil-free formulation based on surfactants and co-solvents</td>
<td>Good solvent capacity for many drugs; disperses to micellar solution</td>
<td>Loss of solvent capacity on dispersion; may not be digestible[^{6}]</td>
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**Self Micro Emulsifying Drug Delivery System (Smedds)**

SMEDDS are physically stable, isotropic mixtures of oil, surfactant, co-surfactant and solubilize drug substance which emulsify spontaneously to produce fine oil-in-water emulsions when introduced into aqueous phase under gentle agitation. SMEDDS are suitable for oral delivery in soft and hard gelatin capsules. Depending on the excipient selection and relative composition of the formulation, aqueous dilution will result in spontaneous formation of lipid droplets ranging in size from approximately 100 nm (SEDDS) to less than 50 nm (SMEDDS). The optimum concentrations or concentration ranges of oil, surfactant and co-surfactant necessary to promote self-emulsification are determined by construction of a pseudo-ternary phase diagram, which should also assess the effect of drug loading on the efficiency of self-emulsification.\[^{7}\]
Advantages of SMEDDS
Quick Onset of Action
Reduction in the Drug Dose
Ease of Manufacture & Scale-up
Improvement in oral bioavailability
Inter-subject and Intra-subject variability and food effects
Ability to deliver peptides that are prone to enzymatic hydrolysis in GIT
No influence of lipid digestion process
Increased drug loading capacity

Formulation Design of SMEDDS
Preformulation studies carried out for the solubility of different oil, surfactants and co-surfactant in drug. The selection of oil, surfactants and co-surfactant based on the solubility of the drug are preparation of phase diagram. Preparation of SMEDDS dissolved the drug in a mixture in different oil, surfactants and co-surfactants. Drug added in the SMEDDS is very difficult because process to certain extent, which leads to a change in the maximum oil-surfactant ratio.

Excipient used in SMEDDS
Oils
The oil represents one of the most important excipient 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 triglycerides. Both long and medium chain triglyceride oils with different degrees of saturation have been used for the design of self-emulsifying formulations.

Edible oils 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 excipient form good emulsification systems with a large number of surfactants approved for oral administration and exhibit better drug solubility properties.
Surfactants

Surfactant molecules consist of two part, polar head group region and non polar tail region. They are classified into four categories according to the nature of hydrophilic group within the molecule.

- Anionic surfactant
- Cationic surfactant
- Non ionic surfactant
- Ampholytic surfactant

Surfactant reduces the interfacial tension between two immiscible liquids and makes them miscible. When surfactants are incorporated in oil and water mixture then their polar heads is self associated towards water phase and non polar tails towards oil phase or they can locate at the interface, which is thermodynamically very favorable. Some of the possible self-association structures that surfactant can form in the presence of oil, water or combination.

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 p-glycoprotein drug efflux. However, the large quantity of surfactant may cause moderate reversible changes in intestinal wall permeability or may irritate the GIT. The effect of formulation and surfactant concentration on GI mucosa should ideally be investigated in each case2.

Co-surfactants

For the production of an optimum SMEDDS, high concentration of surfactant is required in order to reduce interfacial tension sufficiently, which can be harmful, so co-surfactants are used to reduce the concentration of surfactants. Co-surfactants together with the surfactants provide the sufficient flexibility to interfacial film to take up different curvatures required to form micro-emulsion over a wide range of composition. Selection of proper surfactant and co-surfactant is necessary for the efficient design of SMEDDS and for the solubilization of drug in the SMEDDS.

Generally co-surfactant of HLB value 10-14 is used. Organic solvents like ethanol, propylene glycol, polyethylene glycol are able to dissolve large amount of either drug or hydrophilic surfactant in lipid base and are suitable for oral delivery, so they can be used as co-surfactant for SMEDDS. Alternately alcohols and other volatile co-solvents show a disadvantage that
by evaporation they get entered into soft/hard gelatin capsule shells resulting in precipitation of drug. On the other hand formulations which are free from alcohols have limited lipophilic drug dissolution ability. Hence, proper choice of components has to be made for formulation of efficient SMEDDS.

**Mechanism of self emulsification**[5]

Self emulsifying process are related to the free energy, $\Delta G$ given by

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

$N$ = number of droplet

$r$ = radius

$\sigma$ = interfacial energy

It is apparent from the equation that the spontaneous formation of interface between the oil and water phase is energetically not favorable. The system commonly classified as SEDDS have not yet been shown to emulsify spontaneously in the thermodynamic sense. Pouton has argued that the emulsification properties of the surfactant may be related to phase inversion behavior of the system. For example, if one increases the temperature of the oil in the water system stabilized by using non ionic surfactants, the cloud point of the surfactant will be reached followed by phase inversion. The surfactant is highly mobile at the phase inversion temperature; hence the o/w interfacial energy is minimized, leading to a reduction in energy required to bring about emulsification. Pouton has suggested that the specificity of surfactant combination required to allow spontaneous emulsification is associated with a minimization of phase inversion temperature, thereby increasing the ease of emulsification.
Method of preparation

(A) Phase Titration Method

Microemulsion is prepared by the spontaneous emulsification method and can be depicted with the help of phase diagrams. Construction phase diagram is a useful approach to study the complex series of interactions that can occur when different components are mixed. Microemulsion is formed along with various association structures like emulsion, micelles, lamellar depending on the chemical composition and concentration of each component.

Pseudo ternary phase diagram

The understanding of their phase equilibrium and demarcation of the phase boundaries are essential aspects of the study. As quaternary phase diagram is time consuming and difficult to
interpret, pseudo ternary phase diagram is often constructed to find different zones including Microemulsion zone, in which each corner of the diagram represents 100% of the particular component. The region can be separated into w/o or o/w Microemulsion by simply considering the compositions.

Approches of Delevery of Smedds
A. Super saturable self emulsifying drug delivery system
This formulation have been designed and developed to reduce the surfactant effects, here high surfactant concentration in SEDDS formulation can direct to GI side effect. This approach can provide a better toxicity/safety profile. Including the S-SEDDS approach is designed to make an extended supersaturated solution of the drug while the formulation is released from aqueous medium.

B. Solid self emulsifying drug delivery system
This system is initially developed due to problems. That’s SEDDS are normally prepared as liquid dosage form that can be administered in soft gelatin capsules, some disadvantages particularly in the manufacturing process. An alternative method in the inclusion of liquid self emulsifying ingredients into a powder in order to create a solid dosage form tablets, capsules.

Method of Preparation
Solidification Technique for transforming Liquid/semisolid SMEDDS to SOLID-SMEDDS
Capsule filling with liquid and semisolid self emulsifying formulations: This technique is simple and most common technology for the encapsulation of liquid or semisolid self emulsifying formulations for oral route. (A). For semisolid formulations, it is a four step (1) incorporation of the active substances, (2) heating of the semisolid excipient to at least 200c above its melting point, (3) capsule filling with the molten mixture (4) cooling to room temperature. (B) For liquid formulation, it involves two step processes: filling of the formulation into the capsule followed by sealing of the body and cap of the capsule, either by banding or by micro spray sealing.

Spray drying: In this technique first the preparation formulation by mixing lipids, surfactants, drug, solid carriers and solubilization of the mixture before spray drying. The solubilization liquid formulation is then atomized into a spray of droplets. The droplets are
introduced into a drying chamber, where the volatile phase evaporates, and forming dry particles under controlled temperature and airflow conditions. Such particles can be further prepared into tablets or capsules. The atomizer, the temperature the most suitable airflow pattern and the drying chamber design are selected according to the drying characteristics of the product and powder specification.

**Melt granulation:** This process in which powder agglomeration is obtained through the addition of a binder that melts or softens at relatively low temperatures as a one step operation. Advantages compared with conventional wet granulation. The liquid addition and the subsequent drying phase are omitted. Control the granulation process are impeller speed, mixing time, binder particle size, viscosity of binder.

**Adsorption to solid carriers:** Solid carriers are used for the adsorption of liquid formulation to get final solid product and it will be free flowing so that it can be compressed and directly filled in hard gelatin capsules. A significant of the adsorption technique is good content uniformly as well as the possibility for the high lipid exposure.

**Factors Influencing Formulation of Smedds**

**Solubility of drug:** The ability of SMEDDS to maintain the drug in solubilised form is greatly influenced by the solubility of the drug in oil phase. If surfactant or co-surfactant is contributing to the greater extent in drug solubilization 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.

**Polarity of lipid phase:** The polarity of the lipid phase is another factor that influences the drug release from the micro emulsion. 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. Polarity indicates the affinity of drug towards solvent, oil or water and type of forces involved. The high polarity promotes rapid release of the drug towards solvent, oil or water and type of forces involved. The high polarity promotes rapid release of the drug into the aqueous phase. It was observed that the rate of release of idebenone from SMEDDS is dependent upon the polarity of the oil phase used. The highest release was obtained with the formulation that had oil phase with highest polarity.
**Charge of emulsion droplets:** Multiple physiological studies apical potentials of absorptive cells, ands of other cells in the body, are negatively charged compared to the mucosal solution in the lumen. Gershanik and Benita have shown that positively charged emulsion droplets formed by adding oleylamine to SMEDDS undergo electrostatic interaction with the caco2 monolayer and the mucosal surface of the exerted rat intestine. The formulation enhanced the oral bioavailability of progesterone in young rats. Benzoic acid had a dual function on the SEDDS; it could improve the self emulsifying performance of oily phase and self micro emulsifying oily formulations in 0.1 HCL due to formation of a positively charged emulsion.

**Equilibrium solubility:** for assessment of possibilities of precipitation in the gut equilibrium solubility measurement can be employed. Poutons study reveals that such formulation can take up to 5 days reach equilibrium and that the drug can remain in a super saturated state up to 24 h after the initial emulsification event.

**Nature and dose of the drug:** High dose are not suitable for SMEEDS formulation. Lipophilic phase they are good solubility in at least one of the best components of SMEEDS. Limited less solubility of drug in water and lipid are most problematic to deliver by SMEDDS to maintained the drug solubilize form is influenced by the drug in oil phase solubility. Dilution of SMEDDS will lead to lowering of solvent capacity of surfactant is contributing to the drug solubilize be a risk of precipitation. Slow solubility and colloidal stability of gut environment in crystallization.

**Evaluation of Smedds[^4]**

1) **Thermodynamic stability studies**

**Heating cooling cycle:** Six cycles between Refrigerator temperature (4°C) and 45°C with storage at each temperature of not less than 48 h is studied. Those formulations, which are stable at these temperatures, are subjected to centrifugation test.

**Centrifugation:** Passed formulations are centrifuged Thaw cycles between 21°C and 25°C with storage at each temperature for not less than 48 h is done at 3500 rpm for 30 min. Those formulations that does not show any phase separation are taken for the freeze thaw stress test.
Dispersibility test
The efficiency of self-emulsification of oral nano or microemulsion is assessed using a standard USP XXII dissolution apparatus 2. One milliliter of each formulation was added to 500 mL of water at 37 ± 0.5 °C. A standard stainless steel dissolution paddle rotating at 50 rpm provided gentle agitation. The in vitro performance of the formulations is visually assessed using the following grading system:

Grade A: Rapidly forming (within 1 min) nanoemulsion, having a clear or bluish appearance.
Grade B: Rapidly forming, slightly less clear emulsion, having a bluish white appearance.
Grade C: Fine milky emulsion that formed within 2 min.

Turbidimetric Evaluation
Nepheloturbidimetric evaluation is done to monitor the growth of emulsification. Fixed quantity of self microemulsifying system is added to fixed quantity of suitable medium under continuous stirring on magnetic plate at ambient temperature, and the increase in turbidity is measured using a turbidimeter. However, since the time required for complete emulsification is too short, it is not possible to monitor the rate of change of turbidity.

Viscosity Determination
The SMEDDS system is generally administered in soft gelatin or hard gelatin capsules. So, it should be easily pourable into capsules and such system should not too thick to create a problem. The rheological properties of the micro emulsion are evaluated by Brookfield viscometer. This viscosities determination conform whether the system is w/o or o/w. if system has low viscosity then it is o/w type of the system and if high viscosities then it is w/o type of the system.

Droplet size determination
It is a precise method for evaluation of stability. Size of droplet is measured by photon correlation spectroscopy with zetasizer. All measurements are carried out at scattering angle of 90° and 25° temperatures. Prior to measurement, microemulsion is diluted in two-steps with pure water then it is filtered through a 0.22μm filter just before it is added to cuvette. In first step it is diluted with equal amount of water. In second step the mixture is further diluted to appropriate concentration for the measurement. That depends on droplet size.
Zeta potential measurement
Zeta potential for microemulsion is determined using zetasizer HAS 3000. Samples are placed in clear disposable zeta cells and results were recorded. Before putting the fresh sample, cuvettes were washed with the methanol and rinsed using the sample to be measured before each experiment.

Refractive index and percent Transmittance
Refractive index and percent transmittance proved the transparency of formulation. The refractive index of the system is measured by refractometer by placing drop of solution on slide and it compare with water. The percent transmittance of the system is measured at particular wavelength using UV-spectrophotometer keeping distilled water as blank. If refractive index of system is similar to the refractive index of water and formulation have percent transmittance > 99% percent, then formulation have transparent nature.

In vitro release study: It was performed in USP XXIP, dissolution apparatus. Invitro test was performed in 900 ml purified distilled water. SMEEDS was placed in dialysis bag. 10 ml of sample solution was withdrawing at predetermined time intervals, filter and dilute suitably and analyzed spectrophotometer.

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

Polydispersibility index (PDI): Determines size range of particles. SMEDDS should be widely distributed with particles less than 100nm and so PDI should be less than 0.3 or in other words particles having size more than 100nm should be maximum up to 23%.

\[
PDI = \frac{\text{No. of particles having size greater than 100nm}}{\text{No. of particles having size less than 100nm}}
\]

Differential scanning calorimetry: Thermal properties of drug, placebo and granulated lipid formulation were investigated using DSC Q-1000. Weighed samples of 3-5 mg were taken in an open aluminum DSC pans and then sealed and crimped. These samples were scanned at a ramp of 100c/min over a range of 10-3000c under an inert environment using Nitrogen.

Determination of self emulsification time: The emulsification time SMEDDS was determined according to USP type 2 dissolution apparatus 300 mg of each formulation added
drop wise to 500ml purified water at 37°C. Gentle agitation was provided by standard stainless steel dissolution paddle rotating at 50 rpm. Emulsification time was assessed visually.

**FTIR spectroscopy:** Fourier transform infrared for SMEEDS can be determined using FT-IR. Liquid sample should be placed in the liquid sample holder and result can be recorded. Any type of chemical interaction should be determined using FT-IR.

**Disadvantages of Smedds**
1. One of the obstacles for the development of SMEDDS and other lipid-based formulations is the lack of good predictive in vitro models for assessment of the formulations.
2. Traditional dissolution methods do not work, because these formulations potentially are dependent on digestion prior to release of the drug.
3. This in vitro model needs further development and validation before its strength can be evaluated.
4. Further development will be based on in vitro - in vivo correlations and therefore different prototype lipid based formulations need to be developed and tested in vivo in a suitable animal model.
5. The drawbacks of this system include chemical instabilities of drugs and high surfactant concentrations in formulations (approximately 30-60%) which irritate GIT.

**Application of Smedds**
**Supersaturable SEDDS**
The high surfactants level typically present in SEDDS formulations can lead to GI side effects and a new class of Supersaturable formulations, including Supersaturable SEDDS formulations, have been designed and developed to reduce the surfactant side effects and achieve rapid absorption of poorly soluble drugs. The s-SEDDS approach is to generate a protracted supersaturated solution of the drug when the formulation is released from an appropriate dosage form into an aqueous medium. Super saturation is intended to increase the thermodynamic activity to the drug beyond its solubility limit and, therefore, to results in an increased driving force for transit into and across the biological barrier.
Protection from Biodegradation
Drugs for which both solubility and degradation is low in the GI tract contribute to a low oral bioavailability, SMEDDS is useful for such drugs due to ability to reduce degradation as well as improve absorption.

Enhancement in solubility and Bioavailability
SMEDDS formulation enhances the bioavailability by increasing solubility of drug and also decreasing the gastric irritation. Also incorporation of gelling agent in SMEDDS sustains the release drug.

CONCLUSION

REFERENCES
7. Shukla Prachi, Prajapati SK, Sharma UK. A review on self microemulsifying drug delivery system: an approach to enhance the oral bioavailability of poorly water soluble drugs, 2012; 3(9).