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## ADVANCED DELIVERY OF POORLY WATER SOLUBLE DRUGS BY LIPID BASED FORMULATION AS SMEDDS

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### ABSTRACT

Oral route has always been preferred route for formulators and has dominated over other routes of administrations. But major problem encountered in oral formulations, is low bioavailability, giving rise to further problems like, high inter and intra subject variability, lack of dose uniformity and finally leading to therapeutic failure. 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. Particularly for BCS class II substances, the bioavailability may be enhanced by increasing the solubility and dissolution rate of the drug in the gastro-intestinal fluids. The newer and novel technologies developed in recent year for troubleshooting such above problems. This review article gives a complete overview of SMEDDS as a capable approach to effectively capture the problem of poorly soluble molecules and give the novel approaches for evaluation of the SMEDDS.

### KEYWORDS

SMEDDS, Solubility enhancement, Oil, Surfactant and Co-surfactant.

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### INTRODUCTION

Solubility is one of the important parameter to achieve desired concentration of drug in systemic circulation for pharmacological response<sup>1</sup>. Poor aqueous solubility of lipophilic drugs creates problems in formulation as well as in oral administration. Various approaches have been developed to resolve poor aqueous solubility of lipophilic drugs. As oral route for drug administration is most commonly used among all the routes of administration due to its convenience, non-invasiveness and cost effectiveness it become

necessary that drug should have some aqueous as well as some lipid solubility for their absorption<sup>2</sup>. The most popular approach is the incorporation of the active lipophilic component into inert lipid vehicles, such as oils, surfactant dispersions, self-emulsifying formulations, emulsions and liposomes, with every formulation approach having its special advantages and limitations. Efficacy of lipophilic drug is often hindered due to their poor aqueous solubility leading to low absorption after *in vivo* administration<sup>3</sup>. Self-micro emulsifying drug delivery system (SMEDDS) are defined as an 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<sup>4</sup>. These systems form homogeneous, transparent/translucent, isotropic and thermodynamically stable microemulsion upon dispersion in aqueous media with oil droplet sizes of less than 50 nm<sup>5</sup>. When the mixture of drug, oil and a surfactant comes in contact with the aqueous environment in GIT they form an emulsion under gentle agitation provided by digestive motility of stomach and intestine which is necessary for self-emulsification *in-vivo*. Once an emulsion is formed then the drug is quickly distributed throughout the GIT as fine droplets, due to this dispersion and large surface area of fine droplets the bioavailability of drug enhanced. Presence of surfactant also influences absorption due to membrane induced permeation changes. The mechanism of self-emulsification is specific for parameters like, pair of oil and surfactant, type and concentration of surfactant, oil/surfactant ratio, and temperature at which self-emulsification occur. Since the drug delivery should be biocompatible so the selection of excipient used in formulation is very important<sup>6</sup>.

#### **BIOPHARMACEUTICAL CLASSIFICATION SYSTEM**

The BCS is a scientific framework for classifying a drug substance based on its aqueous solubility and

intestinal permeability. When combined with the *in vitro* dissolution characteristics of the drug product, the BCS takes into account three major factors: solubility, intestinal permeability, and dissolution rate, all of which govern the rate and extent of oral drug absorption from IR solid oral-dosage forms. It classifies drugs into four classes<sup>7,8</sup> as shown in Figure No.1.

#### **SELF MICRO EMULSIFYING DRUG DELIVERY SYSTEM (SMEDDS)**

In recent years, much attention has been focused on oral dosage forms using a self-micro emulsifying drug delivery system (SMEDDS) for the purpose of improving the solubility and absorption of poorly water-soluble drugs.<sup>[9]</sup> Self micro emulsifying drug delivery system (SMEDDS) are defined as an isotropic mixtures of natural or synthetic oils, solid or liquid surfactants, or alternatively, one or more hydrophilic solvents and co-solvents/co-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<sup>4</sup>.

#### **ADVANTAGES OF SMEDDS**

##### **Enhancement in oral bioavailability**

Dissolution rate dependent 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 solubilized 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.

##### **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 is available.

#### **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. These systems are formed spontaneously without aid of energy or heating 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 microemulsified 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 ( $2 < \log P < 4$ ) are typically low in natural lipids and much greater in amphilic surfactants, co surfactants and co-solvents.

#### **Ease of manufacture and scale-up**

Ease of manufacture and scale up is one of the most important advantages that make 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.

#### **SMEDDS are suitable for both liquid and solid dosage forms<sup>10,11</sup>**

#### **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. It can be easily stored since it belongs to a thermodynamics stable system.

Microemulsions formed by the SMEDDS exhibit good thermodynamics stability and optical transparency.

Droplets of microemulsion formed by the SMEDDS generally ranges between 2 and 100 nm. 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 can be filled in hard gelatin capsules or soft gelatin capsules or can be formulated into tablets whereas emulsions can only be given as oral solutions.

Emulsion cannot be autoclaved as they have phase inversion temperature, while SMEDDS can be autoclaved<sup>12</sup>.

#### **DISADVANTAGES OF SMEDDS**

- One of the obstacles for the development of SMEDDS and other lipid-based formulations is the lack of good predicative *in vitro* models for assessment of the formulations.
- Traditional dissolution methods do not work, because these formulations potentially are dependent on digestion prior to release of the drug.
- This *in vitro* model needs further development and validation before its strength can be evaluated.
- Further development will be based on *in vitro* - *in vivo* correlations and therefore different prototype lipid based formulations needs to be developed and tested *in vivo* in a suitable animal model.
- The drawbacks of this system include chemical instabilities of drugs and high surfactant

concentrations in formulations (approximately 30-60%) which irritate GIT.

- Moreover, volatile co solvents in the conventional self-microemulsifying formulations are known to transfer into the shells of soft or hard gelatin capsules, resulting in the precipitation of the lipophilic drugs.
- The precipitation tendency of the drug on dilution may be higher due to the dilution effect of the hydrophilic solvent.
- Formulations containing several components become more challenging to validate<sup>4,5</sup>.

### FORMULATION DESIGN OF SMEDDS

Pre-formulation studies are carried out for the selection of oil, surfactant and co-surfactant as these are specific for a particular SMEDDS. First we determine solubility of drug in various oils and surfactant/co-surfactant then prepare a series of SMEDDS containing drug in various oil and surfactant/co-surfactant. These formulations are analysed for self-emulsification properties and droplet size upon addition to water under mild agitation (*in-vitro*) studied. By constructing the pseudo-ternary phase diagram we identify the efficient self-emulsification region. So by doing such studies an optimized formulation is selected and its bioavailability also compared with a reference formulation.

Parameters taken into consideration while formulating SMEDDS

- Solubility of drug in formulation as such and upon dispersion
- The rate of digestion (for digestion susceptible formulation)
- The solubilization capacity of the digested formulation<sup>13</sup>.

### FORMULATION COMPONENTS OF SMEDDS

- Drug
- Oil
- Surfactant
- Co-surfactant
- Co-solvent

The components are selected with objectives, such as:

- To achieve maximal drug loading.
- To achieve minimal self-emulsification time and droplet size in the gastric milieu for maximal absorption.
- To reduce variation in the emulsion droplet size as a function of pH and electrolyte content of the aqueous medium.
- To prevent/minimize drug degradation/metabolism in physiological milieu.

The components of the SMEDDS are as follows:

#### Drug

Poorly water soluble drugs are a broad class of drugs that differ significantly in physicochemical properties, so it would be useful if there were practical guidelines to help identify the most appropriate formulation for specific drugs. High melting point drugs with log P values of about 2 are poorly suited to SMEDDS. At the other end of the spectrum, lipophilic drugs, such as cinnarizine with log P values greater than 5, are good candidate for SMEDDS.

#### Oil

Long chain triglyceride and medium chain triglyceride oils with different degree of saturation have been used in the design of SMEDDS. Unmodified edible oils provide the most natural basis for lipid vehicles, but their poor ability to dissolve large amounts of hydrophobic drugs and their relative difficulty in efficient self-micro emulsification markedly reduces their use in SMEDDS. Recently medium chain triglycerides are replaced by novel semi synthetic medium chain triglycerides containing compound such as gelucire, other suitable oil phases are digestible or non-digestible oils and fats such as olive oil, corn oil, soya bean oil, palm oil and animal fats etc.

#### Surfactants

Nonionic surfactants with high Hydrophilic Lipophilic Balance (HLB) values are used in formulation of SMEDDS (e.g., Tween, Labrasol, Labrafac CM 10, Cremophore, etc.). The usual surfactant strength ranges between 30–60% w/w of the formulation in order to form a stable SEDDS.

Surfactants have a high HLB and hydrophilicity, which assists the immediate formation of o/w droplets and/or rapid spreading of the formulation in the aqueous media. Surfactants are amphiphilic in nature and they can dissolve or solubilize relatively high amounts of hydrophobic drug compounds. This can prevent precipitation of the drug within the GI lumen and for prolonged existence of drug molecules.

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:

**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 zwitterionic 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).

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 p-glycoprotein drug efflux.

**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.

**Co-Solvent:** Organic solvents are suitable for oral administration. Examples are ethanol, propylene glycol, and polyethylene glycol, which may help to

dissolve large amounts of hydrophilic surfactant or drug in liquid base. Addition of an aqueous solvent such as Triacetin, (an acetylated derivative of glycerol) for example glyceryl triacetate or other suitable solvents that act as co-solvents<sup>14-18</sup>.

## THE EMULSIFICATION PROCESS

Self-emulsification is a phenomenon which has been widely exploited commercially in formulations of emulsifiable concentrates of herbicides and pesticides. Concentrates of crop-sprays are to be diluted by the user, such as farmers or house-hold gardeners, allowing very hydrophobic compounds to be transported efficiently. In contrast, SMEDDS, using excipients acceptable for oral administration to humans, have not been widely exploited and knowledge about their physicochemical principles is therefore limited<sup>4</sup>.

### Mechanism of Self-Emulsification

The theory of formation of microemulsion shows that emulsification occurs when the entropy change for dispersion, is greater than energy required to increase the surface area of the dispersion and the free energy ( $\Delta G$ ) is negative. The free energy in the microemulsion formation, is directly proportional to the energy required to create new surface between the two desired phases and can be described by the equation (1)

$$\Delta G = \Sigma N \pi r^2 \sigma \dots\dots\dots (1)$$

Where,  $\Delta G$  is the free energy associated with the process,  $N$  is the number of droplets of radius  $r$  and  $\sigma$  represents the interfacial energy. After a certain time, the two phases of the emulsion tend to separate to reduce the interfacial area, and subsequently, the free energy of the system decreases. To stabilize emulsions, emulsifying agents are added which reduces the interfacial energy, as well as provide a barrier to prevent coalescence<sup>19</sup>.

## RECENT TRENDS IN SMEDDS AS S-SMEDDS

SMEDDS can exist in either liquid or solid states. SMEDDS are usually, limited to liquid dosage forms, because many excipients used in SMEDDS are not solids at room temperature. Given the advantages of solid dosage forms, S-SMEDDS have

been extensively exploited in recent years, as they frequently represent more effective alternatives to conventional liquid SMEDDS. From the perspective of dosage forms, S-SMEDDS mean solid dosage forms with self-emulsification properties. S-SMEDDS focus on the incorporation of liquid/semisolid SE ingredients into powders/nanoparticles by different solidification techniques (e.g. adsorptions to solid carriers, spray drying, melt extrusion, nanoparticles technology, and so on). Such powders/nanoparticles, which refer to SE nanoparticles/dry emulsions/solid dispersions are usually further processed into other solid SE dosage forms, or, alternatively, filled into capsules (i.e. SE capsules). SE capsules also include those capsules into which liquid/semisolid SEDDS are directly filled without any solidifying excipient. To some extent, S-SMEDDS are combinations of SMEDDS and solid dosage forms, so many properties of S-SMEDDS (e.g. excipients selection, specificity, and characterization) are the sum of the corresponding properties of both SMEDDS and solid dosage forms. For instance, the characterizations of SE pellets contain not only the assessment of self-emulsification, but also friability, surface roughness, and so on. In the 1990s, S-SEDDS were usually in the form of SE capsules, SE solid dispersions and dry emulsions, but other solid SE dosage forms have emerged in recent years, such as SE pellets/tablets, SE microspheres/nanoparticles and SE suppositories/implants<sup>20,21</sup>.

#### ADVANTAGES OF S-SMEDDS

- Ease of manufacture and scale-up
- High stability and reproducibility
- Improvement in oral bioavailability
- Better patient compliance
- Thermodynamic stability
- Improved solubilization of bioactive materials
- More consistent sequential profiles of drug absorption
- Less drug need to be used
- Increased drug loading capacity
- For many drugs taken by mouth

- Faster release rates and it improve the drug acceptance by consumers
- Selective drug targeting toward a specific absorption window in the GI tract and Drug protection from the hostile environment in the gut
- Reduction in inter-subject and intra-subject variability and food effects
- Thus, for lipophilic drug compounds that exhibit dissolution rate limited absorption<sup>3,4</sup>.

#### SOLIDIFICATION TECHNIQUES FOR TRANSFORMING LIQUID/ SEMISOLID SMEDDS TO S-SMEDDS

1. Capsule filling with liquid and semisolid self-emulsifying formulations
2. Spray drying
3. Adsorption to solid carriers
4. Melt granulation
5. Melt extrusion/extrusion spheronization<sup>3,4, 22, 23</sup>.

#### DOSAGE FORM DEVELOPMENT OF S-SMEDDS

1. Dry emulsions
2. Self- micro emulsifying capsules
3. Self-emulsifying tablet
4. Self- micro emulsifying sustained/controlled-release tablets
5. Self- micro emulsifying sustained/controlled-release pellets
6. Self- micro emulsifying solid dispersions
7. Self- micro emulsifying suppositories
8. Self- micro emulsifying implants
9. Self-Emulsifying Beads
10. Supersaturable Self-Emulsifying System
11. Gelled Self-Emulsifying System For Extended Release
12. Self-Emulsifying Microsphere
13. Self-Emulsifying Liposphere
14. Self-Emulsifying Nanoparticles<sup>2-4,24-26</sup>.

#### CONSTRUCTION OF TERNARY PHASE DIAGRAMS

The relationship between the phase behavior of a mixture and its composition can be captured with the

aid of a phase diagram. Compositional variables can also be studied as a function of temperature and, pressure, although with the exception of microemulsions prepared using supercritical or near critical solvents, or with liquified chlorofluorocarbon and HFA propellants, the large majority of systems are studied under conditions of ambient pressure. The phase behavior of simple microemulsion systems comprising oil, water and surfactant can be studied with the aid of ternary phase diagram in which each corner of the diagram represents 100% of that particular component<sup>14</sup>. Ternary phase diagram as shown in Figure No.2 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. The methods are used to plot Ternary phase diagrams are namely Dilution method and Water Titration method.

#### **PREPARATION OF LIQUID SELF MICRO-EMULSIFYING DRUG DELIVERY SYSTEM (LIQUID SMEDDS)**

Based on the pilot studies (equilibrium solubility, phase diagram at different surfactant: co-surfactant ratio), the surfactant: co-surfactant ratio at which maximum microemulsion region obtained was selected for formulation of liquid SMEDDS. Liquid SMEDDS formulation which shows maximum microemulsion region in the pseudoternary phase diagram is selected for the further study.

SMEDDS was prepared according to recently reported method. Variable proportions of oil, surfactant and co-surfactant were added into a 10 ml screw capped glass tube, and the components were mixed by gentle stirring. After complete dissolution, SMEDDS, a clear and transparent solution, was obtained. Based on the results of above experiment and the reported concentration scope of three ingredients forming SMEDDS, the contents of surfactant, co-surfactant and oil were chosen at the range of 30-65%, 30-65% and 5-40%, respectively, in order to obtain the optimal formulation of SMEDDS. Now a days for optimization and design

of SMEDDS the surface methodology, modified simplex method and box-behnken design optimization techniques use<sup>27-29</sup>.

#### **CHARACTERIZATION OF LIQUID SMEDDS**

##### **Emulsification efficiency**

Various compositions were categorized on the basis of clarity and apparent stability of the resultant emulsion. 1 mL of Liquid SMEDDS was added drop wise to 200 ml of distilled water in the beaker during constant stirring on a magnetic stirrer at low speed, at temperature 37°C. SMEDDS assessed visually according to the rate of emulsification and final appearance of the emulsion<sup>29-32</sup>.

##### **Precipitation assessment**

Liquid SMEDDS formulation was diluted upto 100 times with distilled water with continuous stirring on magnetic stirrer to form emulsion. Precipitation was evaluated by visual inspection of the resultant emulsion after 24 hours. The formulations were then categorized as clear (transparent or transparent with bluish tinge), non-clear (turbid), stable (no precipitation at the end of 24 hours), or unstable (showing precipitation within 24 hours)<sup>31,33</sup>.

##### **Drug content determination**

Amount of drug present in the liquid SMEDDS formulation was determined by UV Spectrometric method. Weighed accurate quantity of liquid SMEDDS formulation equivalent to 10 mg of drug in 100 ml volumetric flask and diluted with methanol to make up volume upto 100 ml. Further 1 ml of the solution was diluted to 10 ml using methanol to make 10 µg/ml solution. The drug content was analyzed by taking UV absorbance<sup>34-35</sup>.

##### **Self-emulsification time**

Few ml of prototype formulation (approximately 1 ml) was added to 250 ml of purified water, stirred gently and checked for clarity of solution. Self-emulsification time of formulation was determined using USP II dissolution apparatus. 1 ml of formulation was added drop wise to 250 ml of purified water at 37°C, gentle agitation was provided by dissolution paddle rotating at 75 rpm. Time taken for formation of clear solution was noted as self-emulsification time<sup>36</sup>.

**Refractive Index**

Refractive Index proved the transparency of formulation. The refractive index of the system is measured by Abbe refractometer by placing drop of solution on slide and it compare with water (Refractive index of water 1.333). If refractive index of system is similar to the refractive index of water, then formulation has transparent nature<sup>18</sup>.

**Measurement of mean globule size**

It has been reported that the smaller particle size of the micro emulsion droplets may lead to more rapid absorption and improve the bioavailability<sup>35</sup>. Prepared SMEDDS (1 mL) was diluted 100 times with distilled water and 0.1N HCl in beaker with constant stirring on a magnetic stirrer to form a microemulsion. The droplet size of microemulsion was allowed to equilibrate for 1 h and distributions of resultant microemulsion were determined by laser

scattering technique using. All measurements were performed at a  $25 \pm 2^\circ\text{C}$ <sup>37</sup>.

**Zeta potential measurement**

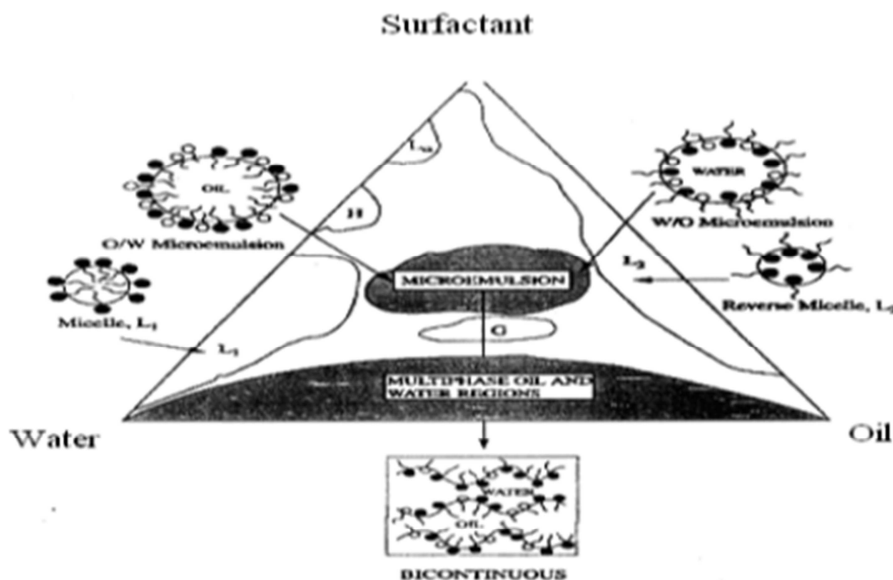
SMEDDS formulation containing 10 mg of drug was diluted to 20 mL with distilled water in a flask and was mixed gently by inverting the flask. The particle size so formed was determined by dynamic light scattering (DLS) technique using Zetasizer<sup>35</sup>.

**Drug release study**

The *in-vitro* dissolution study of liquid SMEDDS and plain drug were carried out using dissolution test apparatus. Quantity equivalent to dose of liquid SMEDDS formulation was added to dissolution media. The dissolution media and the process parameters were used that as per drugs specifications in Pharmacopoeia<sup>18,38</sup>.

Permeability	High	I	II
	Low	III	IV
		High	Low
		Solubility	

**Figure No. 1: Biopharmaceutical classification system**



**Figure No.2: Ternary Phase Diagram**



## CONCLUSION

This review article gives a complete overview of SMEDDS as a capable approach to effectively capture the problem of poorly soluble molecules and give the novel approaches for evaluation of the SMEDDS.

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## CONFLICT OF INTEREST

None declared.

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