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SMEDDS: A NOVEL APPROACH FOR LIPOPHILIC DRUGS

Vikas Sharma, Jatinder Singh, Bhawandeep Gill* and S.L. Harikumar

Rayat and Bahra Institute of Pharmacy, Sahauran, Mohali- 140 103, Panjab, India

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Correspondence to Author:

Bhawandeep Gill

Assistant Professor, Rayat and Bahra Institute of Pharmacy, Sahauran, Mohali-140 103, Panjab, India

E-mail:gillbhawan84@gmail.com

ABSTRACT

The oral delivery of lipophilic drugs presents a major challenge because of the low aqueous solubility and less bioavailability. Self-micro emulsifying drug delivery systems (SMEDDSs) have gained exposure for their ability to increase solubility and bioavailability. SMEDDS, which are isotropic mixtures of oils, surfactants, solvents and co-solvents/surfactants, can be used for the design of formulations in order to improve the oral absorption of highly lipophilic drug compounds. SMEDDS can be orally administered in soft or hard gelatin capsules and form fine relatively stable oil-in-water (o/w) emulsions upon aqueous dilution owing to the gentle agitation of the gastrointestinal fluids. The efficiency of oral absorption of the drug compound from the SMEDDS depends on many formulation-related parameters, such as surfactant concentration, oil/surfactant ratio, polarity of the emulsion, droplet size and charge, all of which in essence determine the self-emulsification ability. Thus, only very specific pharmaceutical excipient combinations will lead to efficient self-microemulsifying systems. The fact that almost 40% of the new drug compounds are hydrophobic in nature implies that studies with SMEDDS will continue, and more drug compounds formulated as SMEDDS will reach the pharmaceutical market in the future. Further this review highlights various components of SMEDDS. This review gives an overview of SMEDDS as a promising approach to effectively tackle the problems of poorly soluble molecules.

INTRODUCTION: The fact that a large majority of the newly discovered chemical entities and many existing drugs molecules are poorly water soluble presents a serious challenge to the successful formulation and marketing of new drugs in the pharmaceutical industry [1]. Since in many cases the dissolution step is the rate limiting step, formulation design can be a useful approach to improve the absorption and thus the oral bioavailability of such drug candidates [2].

As oral route has always been preferred and has dominated over other routes of administration due to its convenience, non-invasiveness, and cost effectiveness thus it become necessary that drug should have some aqueous as well as some lipid solubility for better absorption through this route. The oral route is not suitable for those chemical entities which exhibit poor aqueous solubility.

Approximately 40% of new chemical entities exhibit poor aqueous solubility is often poor candidates for development of formulation. These drugs are classified as class 2 drugs according to Biopharmaceutical classification system (BCS), drugs with poor aqueous solubility a high permeability.

Different formulation approaches like micronization, solid dispersion and complexation with cyclodextrins have been used but they have some disadvantages [3]. The problem with micronization is chemical/thermal stability; many drugs may degrade and lose bioactivity when they are micronized by conventional method. For solid dispersion the amount of carriers used is often large, and thus if the dose of active ingredient is high, the tablets or capsules formed will be large in volume and difficult to swallow.

Moreover, since the carriers used are usually expensive and freeze-drying or spray-drying method requires particular facilities and processes, leading to high production cost. Though traditional solvent method can be adopted instead, it is difficult to deal with co-precipitates with high viscosity. Complexation with cyclodextrin techniques is not applicable for drug substances which are not soluble in both aqueous and organic solvents [4].

Lipid suspension, solutions and emulsions have all been used to enhance the oral bioavailability but due to this, in stability there have been much focus on the utility of self-microemulsifying drug delivery systems (SMEDDS). Being hydrophobic i.e. more lipophilic a lipid-based drug delivery system would ideally work for a poorly water soluble drug [5].

SMEDDS is one of the most widely used approaches for enhancing the bioavailability of poorly aqueous soluble drugs, improvement in bioavailability through this system due to increased solubilization and modification of pharmacokinetic profile of hydrophobic drugs. SMEDDS is isotropic mixture of an oil, surfactant, co-surfactant (or solubilizer), and drug. The basic principle of this system is its ability to form fine oil-in-water (o/w) microemulsions under gentle agitation following dilution by aqueous phases. That is the digestive motility of the stomach and intestine providing the agitation required for self-emulsification in vivo [6, 8].

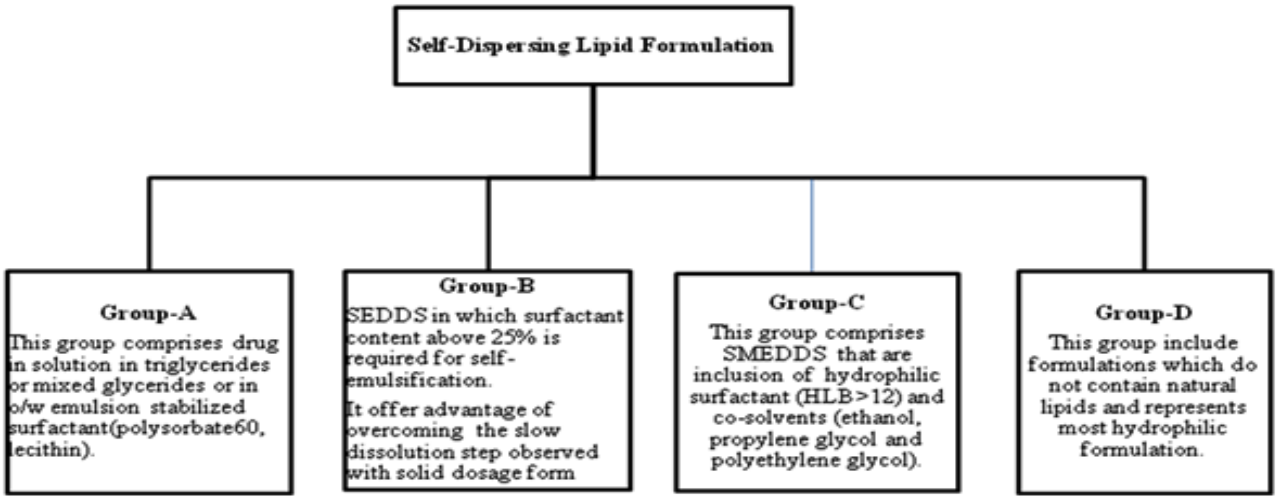
The spontaneous formation of an emulsion upon drug release in the GI tract advantageously presents the drug in a dissolved form and the small droplet size provides a large interfacial surface area for drug absorption [7, 8]. For selecting a suitable self-emulsifying vehicle, it is important to assess:

(a) The drug solubility in various components,

(b) The area of self-emulsifying region in the phase diagram, and

(c) Droplet size distribution following self-emulsification [9].

Self Dispersing Lipid Formulation System: Various delivery systems for the lipophilic drugs are available such as, microemulsion, lipid solution, lipid emulsion, dry emulsion, whose formulation involve large number of possible combination of excipients, further to understand these lipid based formulation and to get a clear picture of all these different systems a particular classification system have been established called as 'lipid formulation classification system' have been introduced [2]. The classification helps to better understand the fate of different lipid formulation *in vivo*. According to the composition and the effect of dilution and digestion on the ability to prevent precipitation of drug, lipid based formulations are classified into four groups:



Self-Dispersing Lipid Formulation:

1. **Group-A:** This group include formulations which comprises drug in solution in triglycerides or in mixed glycerides or in o/w emulsion then stabilized by surfactants like polysorbate 60 (1%), lecithin (1.2%) [10]. To promote drug transfer into the colloidal aqueous phase this system requires digestion by pancreatic lipase/co-lipase in the GIT to generate more amphiphilic lipid digestion products because these system exhibit poor initial aqueous dispersion. Group-A lipid formulations thus represents relatively simple formulation potent and highly lipophilic compounds.

2. **Group-B:** Self-Emulsifying Drug Delivery System (SEDDS) in which surfactant content above 25% is required for self-emulsification. However, at higher concentration of surfactants (greater than 50-60% (w/w) depending on the materials) formation of viscous liquid crystalline gels occur at the interface leading interruption in progress of self-emulsification [11, 29]. Group-B lipid based formulation provide the advantage of overcoming the slow dissolution step typically observed with solid forms and as described above generate large interfacial areas which is in turns allows efficient partitioning of drug between the oil droplets and the aqueous phase from where absorption occurs [6, 12].

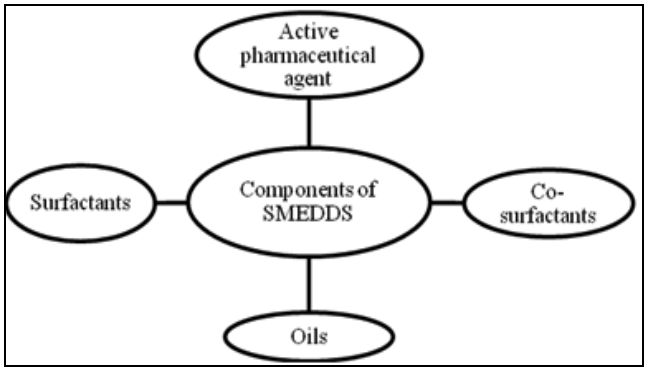
3. **Group-C:** SMEDDS are defined by inclusion of hydrophilic surfactants (HLB>12) and co- solvents (ethanol, propylene glycol and polyethylene glycol). Group-C formulations can be further divided into A and B type respectively to identify more hydrophilic system where the content of hydrophilic surfactants and co-solvents increases and the lipid content reduces.

4. **Group-D:** This group include formulations which do not contain natural lipids and represents most hydrophilic formulations [2]. These formulations commonly offer increased drug payloads when compared to formulations containing simple glyceride lipids and also produce very fine dispersions when introduced in aqueous media [13].

SMEDDS is the type of self dispersing lipid formulations (SDLFs) which contain mixture of oils and surfactants, ideally isotropic. Sometime it also contains co-surfactants. Drug is incorporated into this mixture. 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* [14].

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 increase in bioavailability is observed. 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 excipients used in formulation is very important.

Formulation Design of SMEDDS: Preformulation 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 system containing drug in various oils and surfactants/co-surfactants. These formulations are analysed for self-emulsification properties and droplet size upon addition to water under mild agitation (*in-vitro*) studied. By contracting 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.



Various components of SMEDDS:

Active Pharmaceutical Ingredient (API):

Properties of drug suitable for loading in SMEDDS: Active pharmaceutical agent should be soluble in oil phase as this influence the ability of SMEDDS to maintain the API in solubilised form. Drugs which have low solubility in water or lipids are difficult to deliver through SMEDDS. Drugs which are administered in very high dose are not suitable for formulation unless they have extremely good solubility in at least one of the components of SMEDDS, preferably oil phase. Ideal log p value of drug candidate suitable for SMEDDS should be above 2 (log p>2).

Oil: Oil is the most important excipient in the formulation of SMEDDS as it solubilises the lipophilic drug in a required quantity or facilitates self-emulsification and also enhances the absorption through the GIT by increasing fraction of lipophilic drug transported through it. The main criterion for selecting the oil is that the drug should have high solubility in it so this will minimize the volume of the formulation for the delivery of effective dose.

Lipid part of SMEDDS formulation forms the core of emulsion particle and is typically composed of non-polar lipids. Long chain triglycerides (LCTs) and Medium chain triglyceride (MCTs) oils with different degree of saturation have been used as oil phase in the formulation of SMEDDS [15]. Unmodified edible oils are the most biocompatible lipid vehicles but they are enable to dissolve large dose of lipophilic drug and less efficient self-emulsification limits their use in formulation of SMEDDS, whereas modified and hydrolysed vegetable oils are successful in these formulations as they shows formulative and physiological advantages.

MCTs were preferred over LCTs because according to Deckelbaum (1990) MCT is more soluble and have a higher mobility at the lipid/water interfaces than LCT associated with a more rapid hydrolysis of MCT and more concentration of surfactant (Cremophore RH40) is required when LCTs were used as oil phase as compared to MCTs. Now the novel approach includes use of semi-synthetic medium chain derivatives which exhibit surfactant properties and also known as amphiphilic compounds.

In such type of cases more lipophilic surfactants may play the role of hydrophilic oil in the formulation. By blending the triglycerides with mono- and di-glycerides solvent capacity for hydrophobic drugs can be improved [16].

Surfactant: Several compounds exhibiting surfactant properties may be employed for the design of self-emulsifying systems, but the choice is limited as very few surfactants are orally acceptable. The most widely recommended ones being the non-ionic surfactants with a relatively high hydrophilic-lipophilic balance (HLB). Safety is a major determining factor in choosing a surfactant. Emulsifiers of natural origin are preferred since they are considered to be safer than the synthetic surfactants [17].

However, these surfactants have a limited self-emulsification capacity. Non-ionic surfactants are less toxic than ionic surfactants but they may lead to reversible changes in the permeability of the intestinal lumen [18]. Usually the surfactant concentration ranges between 30 and 60% w/w in order to form stable SMEDDS. It is very important to determine the surfactant concentration properly as large amounts of surfactants may cause GI irritation. Surfactants are amphiphilic in nature and they can dissolve or solubilize relatively high amounts of hydrophobic drug compounds. The lipid mixtures with higher surfactant and co-surfactant/oil ratios lead to the formation of SMEDDS [19].

There is a relationship between the droplet size and the concentration of the surfactant being used. In some cases, increasing the surfactant concentration could lead to droplets with smaller mean droplet size, this could be explained by the stabilization of the oil droplets as a result of the localization of the surfactant molecules at the oil-water interface [20].

On the other hand, in some cases the mean droplet size may increase with increasing surfactant concentrations [21]. This phenomenon could be attributed to the interfacial disruption elicited by enhanced water penetration into the oil droplets mediated by the increased surfactant concentration and leading to ejection of oil droplets into the aqueous phase [22]. 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. However, the large quantity of surfactant may cause moderate reversible changes in intestinal wall permeability or may irritate the GI tract. Formulation effect and surfactant concentration on gastrointestinal mucosa should ideally be investigated in each case.

Co-surfactant: 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.

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 [23]. 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. 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 Microemulsion [24]. Here, **Table 1** contains some examples of SMEDDS along with Active pharmaceutical agent, Oil, Surfactant, Co-surfactants used in the formulations.

TABLE 1: LITERATURE SURVEY OF SOME SMEDDS COMBINATIONS

API	Oil phase	Surfactant	Cosurfactant	Researcher
Xibornol	Labrafil M1944, Labrafil M2125 and Labrafac CC	Labrasol and Labrafac PG	Transcutol	Cirri M. *et al*
Furosemide	Mygliol 812	Caprylocaproyl macrogo lglycerides, Labrasol	Polyglyceryl-6 dioleate plurol oleique	Zvonar A. *et al*
Candesartan cilexetil	Transcutol P	Capryol 90	Plurol Oleque	Shukla J.B. *et al*
Nobiletin	Mixture of polyoxyethylene 35 castor oil and polysorbate 80 oil	Mixture of polyoxyethylene 35 castor oil and polysorbate 80	Polyethylene glycol 400	Yao J. *et al*
9-Nitrocamptothecin	Ethyloleat	Tween-80 and CremophoL EL	PEG-400	Wang J.C. *et al*
Fenofibrate	Labrafac CM10	Tween 80	PEG 400	Patel A.R. *et al*
Atorvastatin	Labrafil, Labrafac, Estol and IPM(Isopropyl myristate)	Cremophor EL, Cremophor RH40, Tween 80 and Labrasol	Ethanol, propylene glycol, PEG 400 and Transcutol	Shen H.R. *et al*
Oridonin	Labrafac CC	Cremopher EL	Transcutol P	Zhang P. *et al*
Fexofinadine	Lauroglycol 90	Labrasol	Plurol Oleique CC497 or the mixture of Plurol Oleique CC497 and PEG 400 at 1:1 ratio	Piao H.M. *et al*
Valproic acid	castor oil	Cremaphor RH 40	PEG 400	PatroM.N. *et al*
Curcumin	Isopropyl myristate, Aethylis oleas, Soybean oil	Tween 80, Cremophor RH40, Cremophor EL	Ethanol, PEG 400, 1,2-propylene glycol	Wu X. *et al*
Cefpodoxime proxetil	Capryol 90	Cremophore-EL	Akoline-MCM	Abhijit A. Date
Lacidipine	Labrafil	Cremophore-EL	Transcutol	Emad B. Basalious
Tamoxifen citrate	Capryol	Cremophore RH40	propylene glycol	Yosra S.R. Elnaggar
Coenzyme-Q	Capryol-90	Labrafac CC	Plurol	Prabagar Balakrishnan. *et al*

Advantages:

- **Oral Bioavailability Improvement:** Dissolution rate dependant absorption is a major factor that limits the bioavailability of various 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 [25].

- **Ease of manufacture and scale-up:** Ease of manufacture and scale-up is one of the most important advantage that makes SMEDDS unique when compared to other drug delivery systems like solid dispersions, liposomes, nanoparticles, etc., dealing with improvement of bio-availability. SMEDDS require very simple and economical manufacturing facilities like simple mixer with agitator and volumetric liquid filling equipment for large-scale manufacturing. This explains the interest of industry in the SMEDDS.

- **Inter-subject and intra-subject variability and food effects are reduced:** 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 [26]. Food is a major factor affecting the therapeutic performance of the drug in the body. SMEDDS are a beneficial for such drugs. Several studies specifying that, the performance of SMEDDS is independent of food and, SMEDDS offer reproducibility of plasma profile are available [27].

- **Ability to deliver peptides:** 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 as they offer protection from enzymatic hydrolysis. The intestinal hydrolysis of prodrug by cholinesterase can be protected if polysorbate 20 is emulsifier in micro emulsion formulation [28]. These systems are formed spontaneously without aid of energy or heating [15] thus, suitable for thermo labile drugs such as peptides.

- **Not effected by lipid digestion process**: Unlike the other lipid-based drug delivery systems, the performance of SMEDDS is not influenced by the lipolysis, emulsification by the bile salts, action of pancreatic lipases and mixed micelle formation. SMEDDS are not necessarily digested before the drug is absorbed as they present the drug in micro-emulsified form which can easily penetrate the mucin and water unstirred layer**.**

- **Increased Drug Loading Capacity**: SMEDDS also provide the advantage of increased drug loading capacity when compared with conventional lipid solution as the solubility of poorly water soluble drugs with intermediate partition coefficient (2<log P<4) are typically low in natural lipids and much greater in amphiphilic surfactants, co surfactants and co-solvents.

- This system provides High stability and longer Self life to drug [29].

Mechanism of self-emulsification: Self emulsification occurs, when the entropy change occurs**,** dispersion is greater than the energy required to increase the energy required to increase the surface area of the dispersion [30]. The free energy of conventional emulsion formation is a direct function of the energy required to create a new surface between the two phases and can be described by the equation.

$$\delta G=\sum Nir_i^2\sigma \quad \text{..... (i)}$$

Where, δG is the free energy associated with the process (ignoring the free energy of mixing), N is the number of droplets of radius r, σ is interfacial energy with time.

The two phases of the emulsion will tend to separate, in order to reduce the interfacial area and subsequently, the free energy of the system. Therefore, the emulsions resulting from aqueous dilution are stabilized by conventional emulsifying agents, which form a monolayer around the emulsion

droplets and hence, reduce the interfacial energy, as well as providing a barrier to coalescence [31]. In case of self-emulsifying system, the free energy required to form the emulsion is either very low or positive or negative then, the emulsion process occurs spontaneously [32]. Emulsification require very little input energy, involves destabilization through contraction of local interfacial regions. For emulsification to occur, it is necessary for the interfacial structure to have no resistance to surface shearing [33].

In earlier work, it was suggested that the case of emulsification could be associated with the ease by which water penetrates into the various liquid crystal or phases get formed on the surface of the droplet [34]. The addition of a binary mixture (oil/non-ionic surfactant) to the water results in the interface formation between the oil and aqueous continuous phases, followed by the solubilization of water within the oil phase owing to aqueous penetration through the interface, which occurs until the solubilization limit is reached close to the interface [35].

Further, aqueous penetration will result in the formation of the dispersed liquid crystalline phase. As the aqueous penetration proceeds, eventually all materials close to the interface will be liquid crystal, the actual amount depending on the surfactant concentration in the binary mixture once formed, rapid penetration of water into the aqueous cores, aided by the gentle agitation of the self emulsification process causes interface disruption and droplet formation. The high solubility of these self-emulsified systems to coalescence is considered to be due to liquid crystal interface surrounding the oil droplets.

A combination of particle size analysis and low frequency dielectric spectroscopy was used to examine self-emulsifying properties of a series of Imwitor 742 (a mixture of mono-and di-glycerides of Caprylic acids/Tween 80) systems, which provided evidence that the formation of the emulsion may be associated with liquid crystal formation, although the relationship was clearly complex [32]. The presence of the drug may alter the emulsion characteristics, possibly by interacting with the liquid crystal phase.

Construction of Ternary Phase Diagrams: Ternary phase diagram 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 [9]. The methods are used to plot Ternary phase diagrams are namely Dilution method and Water Titration method.

Dilution Method: Ternary mixtures with varying compositions of surfactant, co-surfactant and oil will be prepared. The surfactant concentration will vary from 30 to 75% (w/w), oil concentration will vary from 25 to 75% and co-surfactant concentration will vary from 0 to 30% (w/w) (as shown in **fig. 1a**). For any mixture, the total of surfactant, co-surfactant and oil concentrations always added to 100%. For example, in the experiment, first mixture consisted of 75% of surfactant, 25% of the oily phase and 0% of co-surfactant.

Further, the co-surfactant was increased by 5% for each composition, oily phase concentration will keep constant and the surfactant concentration will adjust to make a total of 100%. Forty-two such mixtures with varying surfactant, co-surfactant and oil concentrations will prepare. The percentage of surfactant, co-surfactant and oil used herein will decide on the basis of the requirements [2]. Compositions are evaluated for nanoemulsion formation by diluting appropriate amount of 42 mixtures with appropriate double distilled water.

Globule size of the resulting dispersions will be determined by using spectroscopy technique. Dispersions, having globule size 200 nm or below will consider desirable. The area of nanoemulsion formation in Ternary phase diagram will identified for the respective system in which nanoemulsions with desire globule size were obtain.

Water Titration Method: The pseudo-ternary phase diagrams were also constructed by titration of homogenous liquid mixtures of oil, surfactant and cosurfactant with water at room temperature (as shown in **fig. 1b**). Oil phase, Surfactant and the co-surfactant, at *K*m values 1.5 and 1 (surfactant: co-surfactant ratio), oily mixtures of oil, surfactant and co-surfactant were prepared varied from 9:1 to 1:9 and

weighed in the same screw-cap glass tubes and were vortexed. Each mixture was then slowly titrated with aliquots of distilled water and stirred at room temperature to attain equilibrium. The mixture was visually examined for transparency. After equilibrium was reached, the mixtures were further titrated with aliquots of distilled water until they showed the turbidity.

Clear and isotropic samples were deemed to be within the microemulsion region. No attempts were made to completely identify the other regions of the phase diagrams. Based on the results, appropriate percentage of oil, surfactant and co-surfactant was selected, correlated in the phase diagram and were used for preparation of SMEDDS [36].

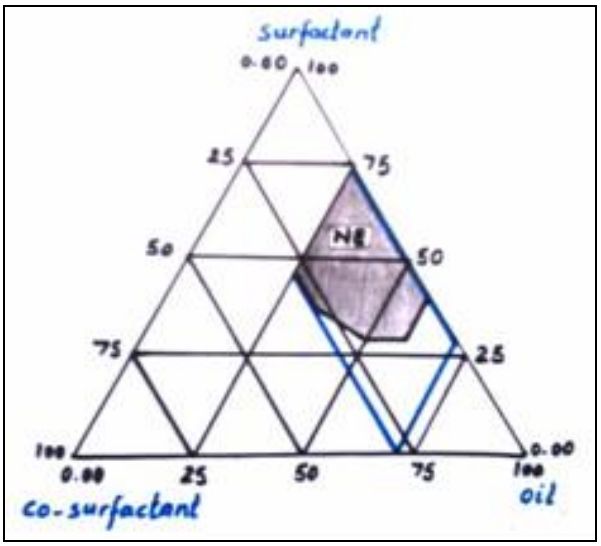


FIG. 1A: TERNARY PHASE DIAGRAM BY DILUTION METHOD

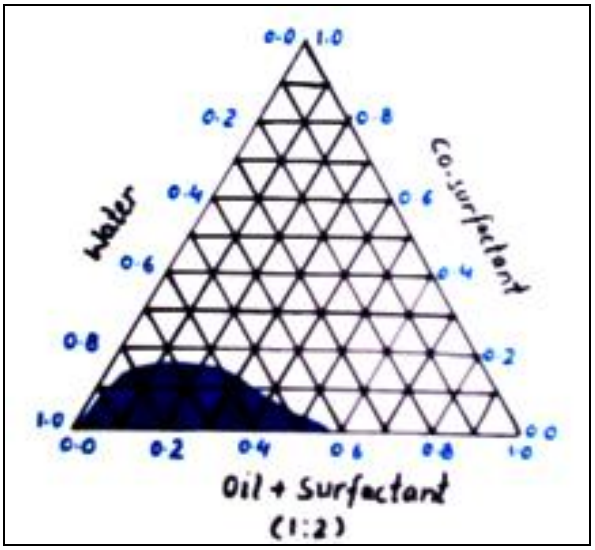


FIG. 1B: TERNARY PHASE DIAGRAM BY TITRATION METHOD

Preparations of SMEDDS formulations: SMEDDS was prepared according to recently reported methods [37, 38]. 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 [39, 40], 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.

Future Aspects:

Supersaturable SMEDDS (S-SMEDDS): These are the kind of the formulation which supersaturates the solution of drug from the dosage form into an aqueous medium. S-SMEDDS is the advance approach to SMEDDS use to overcome the problem associate with the toxic effect of surfactants used in the SMEDDS. Toxic effect of surfactants in SMEDDS at higher concentration can lead to GI side effect in such cases S-SMEDDS is boon or beneficial as a formulation [41].

Supersaturation intended to increase thermodynamic activity to the drug beyond its solubility limit and therefore, to result in an increased driving force for transit into and across the biological barrier.

In S-SMEDDS a reduce amount of surfactant will be use with Hydroxypropylmethylcellulose (HPMC) in order to produce a temporarily supersaturable state with reduced solubilization. Thus a high free drug concentration will be obtain through generating and maintaining a supersaturate state *in-vivo* and to increase a driving force in absorption. HPMC and related cellulose polymers are well known to use to maintain supersaturated state for prolong time period [42].

A study shows that S-SMEDDS approach shows approximately 10-folds higher maximum concentration (Cmax) and 5-folds higher oral bioavailability compare with orally administered formulation and SMEDDS without HPMC.

Solid SMEDDS: SMEDDS are mostly prepared in liquid dosage form in soft and hard gelatin capsules which have some manufacturing and leakage problems. The Solid SMEDDS are new approach to overcome above mention problems. In this formulation the liquid self-emulsifying ingredients are incorporated into powder to make solid dosage form such as-tablets, capsules by using different techniques such as spheronization, extrusion, etc [43].

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