SELF-MICRO EMULSIFYING DRUG DELIVERY SYSTEM (SMEDDS): A REVIEW

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ABSTRACT

The oral delivery of lipophilic drugs has a major challenge because of low aqueous solubility of drugs. Improving oral bioavailability of poorly water soluble drugs using self-micro emulsifying drug delivery systems (SMEDDS) is also a challenge. Nearly 40% new chemical substances exhibit poor water solubility, oral delivery of BCS class II and BCS class IV drugs presents a major challenge to developing formulations for such active pharmaceutical ingredients (API). Self-microemulsifying drug delivery systems (SMEDDS) have the ability to increase solubility and bioavailability of poorly soluble drugs. Self-micro emulsifying drug delivery systems are isotropic mixtures of oil, surfactant, co-surfactant of co-solvents can be used for the design of formulations in order to improve the oral absorption of highly lipophilic drugs. It can be converted into solid by suitable means can be orally administered in hard or soft gelatin capsule. These solid SMEDDS are considered more stable over liquid SEDDS, also solid forms improve handling, packaging and storage. The hydrophobic nature of drug which are studies with SMEDDS will continue and more drug compounds formulated as SMEDDS will reach pharmaceutical market.

INTRODUCTION

Nearly 40% new chemical substances exhibit poor water solubility, oral delivery of such drugs shows a major challenge to pharmaceutical scientist when developing formulations for such active pharmaceutical ingredients (API). This is because when they are administered orally the dissolution rate in gastrointestinal tract becomes the rate limiting step in the absorption and hence bioavailability from gastro intestine. Low aqueous solubility will lead to poor oral absorption, high intra-inter subject variability and lack of dose proportionality[1]. According to the Biopharmaceutical Classification System (BCS), two classes of drugs show poor aqueous solubility namely BCS II and BCS IV. BCS II drugs possess low aqueous solubility but have high permeation properties. BCS class IV drugs are plow water soluble and low permeable. Developing a formulation for a class IV drug is nearly impossible unless the dose necessary is very small. Most of the times, such drugs are withdrawn at its lead optimization stage of drug discovery and reworked to improve its physic -chemical properties. Developing a formulation for a drug belonging to BCS IV is often challenging as it requires improved dissolution characteristics[2].

Biopharmaceutical Classification System (BCS)

Table 1. The Lipid Formulation classification system[3, 4]

<table>
<thead>
<tr>
<th>Formulation Type</th>
<th>Materials</th>
<th>Characteristics</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type I</td>
<td>Oils without surfactants (e.g. tri-, di- and Monoglyceride)</td>
<td>Non dispersing, requires digestion</td>
<td>GRAS status; simple; excellent capsule Compatibility</td>
<td>Formulation has Low solvent capacity unless drug is highly lipophilic</td>
</tr>
<tr>
<td>Type II</td>
<td>Oils and water insoluble surfactants</td>
<td>SEDDS formed without water - soluble component</td>
<td>Unlikely to lose solvent capacity on dispersion</td>
<td>Turbid o/w Dispersion (particle size 0.25-2μm)</td>
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</tr>
<tr>
<td>Type III</td>
<td>Oils, surfactant, Co-solvents/Co-surfactant (both water insoluble and water soluble excipients)</td>
<td>SEDDS/SMEDDS are formed with water soluble components</td>
<td>Clear or almost clear dispersion; drug absorption without digestion</td>
<td>Possible loss of solvent capacity on dispersion</td>
</tr>
<tr>
<td>Type III</td>
<td>Water-soluble surfactants and cosolvents / cosurfactants (no oils)</td>
<td>Formulation disperses typically to form a micellar solution.</td>
<td>Formulation has good solvent capacity for many drugs</td>
<td>Likely loss of solvent capacity on dispersion; may not be digestible</td>
</tr>
</tbody>
</table>

**Self Microemulsifying drug delivery systems (SMEDDS) –^[4, 5, 6]^[**

Self Microemulsifying drug delivery systems (SMEDDS) are isotropic mixtures of oil, hydrophilic surfactant, cosurfactant, and a solubilized drug. They can be encapsulated in hard or soft gelatin capsules or can be converted to solid state (Solid SMEDDS). These formulations form a fine oil-in-water emulsion upon dilution with water. In the GI tract, they are readily dispersed, where the motility of the stomach and small intestine provides the gentle agitation necessary for emulsification. SEDDS produces coarse emulsions while SMEDDS produces droplets of size between 50 to 250nm.^[2]\

This property of SMEDDS makes them a natural choice for delivery of hydrophobic drugs that have adequate solubility in oil-surfactant blends.^[4] SMEDDS improves the rate and extent of absorption of hydrophobic drugs, whose absorption is considered to be dissolution rate-limited. Upon aqueous dilution the drug remains in the oil droplets or as a micellar solution since the surfactant concentration is very high in such formulations.^[7] The drug in the oil droplet may partition out in the intestinal fluid as shown in figure-1.
Figure 1: Mechanism of drug partitioning in SMEDDS

Figure 2: Schematic diagram of SEDDS and SMEDDS:
Advantages of SMEDDS\textsuperscript{[8, 9-11]}

1. Improve the dissolution rate and oral bioavailability of the poorly water soluble drugs.
2. Reduces inter and intra-subject variability.
3. Reduces the dose of drug.
4. Ease of formulation technique
5. Bypass the first-pass metabolism of drugs through lymphatic absorption
6. Ability to deliver peptides that are prone to enzymatic hydrolysis in GIT.
8. Selective targeting of drug toward specific absorption window in GIT.
9. Protection of drug from the hostile environment in gut

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 phase separation of emulsion. SMEDDS can be easily stored since it belongs to a thermodynamics stable system. The size of the droplets of common emulsion ranges between 0.2 and 10 μm, and that of the droplets of microemulsion formed by the SMEDDS generally ranges between 50 and 250 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 hard gelatin capsules or soft gelatin capsules or can be formulated in to tablets whereas emulsions can only be given as oral solutions.

Excipients used in SMEDDS

SMEDDS consists of oil, a surfactant and a co-surfactant.

I) Oil

Various natural oils are available and suitable for use in encapsulated oral formulation products. Naturally occurring oils and fats are composed of mixtures of triglycerides which contain fatty acids. Triglycerides are classified as short (< 5 carbons), medium (6–12 carbons), or long chain (< 12 carbons). Oils may be synthetically hydrogenated to decrease the degree of unsaturation, thereby conferring resistance to oxidative degradation. The use of newer synthetic oils that are amphiphilic in nature can dissolve large quantities of the drug when compared to conventionally used pure vegetable oils or its derivatives.\textsuperscript{[2, 12]}
II) Surfactants
The most widely recommended surfactants are the non-ionic surfactants with a relatively high hydrophilic-lipophilic balance (HLB). Emulsifiers of natural origin are preferred since they are considered to be safer than the synthetic surfactants.

However, these surfactants have a limited self-emulsification capacity. Non-ionic surfactants are less toxic than ionic surfactants and they may lead to reversible changes in the permeability of the intestinal lumen. 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.[3,13]

The lipid mixtures with higher surfactant and co-surfactant ratios lead to the formation of SMEDDS.

III) Co-surfactants / Co-solvents
The production of SMEDDS requires relatively high concentrations (generally more than 30% w/w) of surfactants, thus the concentration of surfactant can be reduced by incorporation of cosurfactant. Role of the co-surfactant together with the surfactant is to lower the interfacial tension to a very small even transient negative value. At this value the interface expand to form fine dispersed droplets, and subsequently adsorb more surfactant to make interfacial tension positive again. This process known as ‘spontaneous emulsification’ forms the microemulsion. The selection of surfactant and co-surfactant is crucial not only to the formation of SMEDDS, but also to solubilisation of the drug in the SMEDDS. Organic solvents, suitable for oral administration may help to dissolve large amounts of either the hydrophilic surfactant or the drug in the lipid base and can act as co-surfactant in the self-emulsifying drug delivery systems.[14,15]

Formulation of SMEDDS
1) Formulation Composition
SMEDDS are composed of oil, hydrophilic surfactant, and a Cosurfactants/Cosolvent. The process of self-emulsification is only specific to certain combinations of pharmaceutical excipients. It depends on the type of oil and surfactant pair, their ratios, the surfactant concentration and the temperature at which self-emulsification occurs. The primary step
during formulation of a SMEDDS is the identification of these specific combinations of excipients and construct a phase diagram which shows various concentrations of excipients that possess self-emulsification. Mutual miscibility of these excipients is also important for producing a stable liquid formulation. Long chain triglycerides (LCT) are usually immiscible with hydrophilic surfactants and cosolvents. Polar oils such as mixed glycerides show an affinity towards hydrophilic surfactants and thus are miscible with the surfactant and also aids in self-dispersion of the formulation. \[^{16,17}\]

2) Drug Incorporation

Poorly water soluble drugs are often a choice for SMEDDS. It is essential that the therapeutic dose of the drug be soluble in an acceptable volume of self microemulsifying mixture. Surfactants also provide good solvency for the drug.

Although, the cosolvent is capable of dissolving a large quantity of the drug, they may cause drug precipitation on aqueous dilution due to loss of solvent capacity. This necessitates performing equilibrium solubility measurements of the drug in the excipients under use. The drug may affect the self-emulsification efficiency by changing optimal oil/surfactant ratio. The incorporated drug may increase or decrease the self-emulsifying efficiency or may not affect it at all. Hence SMEDDS should also be evaluated for its self-emulsification efficiency in the presence of the drug.

SMEDDS are known to be more sensitive towards any changes in the ratio of excipients. Because of these reasons, pre-formulation solubility and phase diagrams should be thoroughly evaluated when choosing the optimized formulation. \[^{15,18}\]

Mechanism of self-emulsification

Self-emulsification occurs when the entropy change, that favours dispersion, is greater than the energy required to increase the surface area of the dispersion. In addition, the free energy of a 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 equation.

\[
\Delta G = \sum_i N_i \pi r_i^2 \sigma
\]

Where, \( G \) is the free energy associated with the process (ignoring the free energy of mixing), \( N \) is the number of droplets of radius, \( r \), and \( \sigma \) represents the 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 systems.

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. In the case of self-emulsifying systems, the free energy required to form the emulsion is either very low and positive, or negative (then, the emulsification process occurs spontaneously). Emulsification requiring very little input energy involves destabilization through contraction of local interfacial regions. In earlier work. The addition of a binary mixture (oil/nonionic surfactant) to water results in 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. This will occur until the solubilization limit is reached close to the interface. Further, aqueous penetration will result in the formation of the dispersed liquid crystal phase. As the aqueous penetration proceeds, eventually small oil droplets are 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 stability of these self-emulsified systems to coalescence is considered to be due to the LC interface surrounding the oil droplets. The correlation between the spontaneous emulsification and LC formation is still not definitely established.\textsuperscript{2,15,18}

**FACTOR AFFECTING OF SEDDS**

**A) Nature and dose of the drug:** Drugs which are administered at very high dose are not suitable for unless they exhibit extremely good solubility in at least one of the components of SMEDDS, preferably lipophilic phase. The drugs which exhibit limited solubility in water and lipids (typically with log P values of approximately are most difficult to deliver by SMEDD.

**B) Polarity of the lipophilic phase:** The polarity of the lipid phase is one of the factors that govern the drug release from the micro emulsions. 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 micronized for their propensity to inhibit crystallization and, thereby, generate and maintain the supersaturated state for prolonged time period.
DOSAGE FORM OF SEDDS

(1) Oral delivery

(A) Self emulsifying capsule: After administration of capsules containing conventional liquids SE formulations, microemulsion droplets form and subsequently disperse in the GIT to reach site of absorption. For handling this problem, sodium dodecyl sulfate was added into the SE formulation\textsuperscript{43,19,20,21}.

(B) Self--Emulsifying sustained / controlled release: Combination of lipids and surfactant has presented great potential preparing SE tablets. SE tablets are of great utility in obviating adverse effect. Inclusion of indomethacin (or other hydrophobic NSAID) for example, into SE tablets may increase its penetration efficacy through GI mucosal membrane, potentially reducing GI bleeding\textsuperscript{22,23}.

(C) Self emulsifying sustained / controlled release pellets: Pellets, as a multiple unit dosage form, possess many advantages over conventional solid dosage form, such as flexiability of manufacture, reducing intra subject and inter subject variability of plasma profile and minimizing GI irritation without lowering drug bioavailability.

(D) Self emulsifying solid dispersions: Solid dispersions can increase the dissolution rate and bioavailability of low water soluble drugs but still some manufacturing difficulties and stability problems existed\textsuperscript{24}.

(2) Topical Delivery: Topical administration of drugs is good method have advantages over other methods for several reasons, one of which is the avoidance of hepatic first pass metabolism of the drugs and related toxicity effects\textsuperscript{24}.

(3) Oculars and Pulmonary delivery: For the treatment of eye disease, drugs are essentially delivered topically o/w microemulsion have been investigated for ocular administration, to dissolve poorly soluble drugs, to increase absorption and to attain prolong release profile.

(4) Parenteral delivery: Parenteral administration of drugs with limited solubility is a major problem in industry because of the extremely low amount of drug actually delivered as target site.

Solid SMEDDS (S-SMEDDS)

SMEDDS can exist in either liquid or solid states. However, 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, SSMEDDS have been extensively
used in recent years as they are frequently more effective alternatives to conventional liquid SMEDDS. In the 1990s, SSMEEDDS were usually in the form of self emulsifying (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 beads, microspheres/nanoparticle and SE suppositories/implants.[25,26,27].

Techniques for transforming liquid/semisolid SEDDS to S-SEDDS
1) Capsule filling with liquid and semisolid self-emulsifying formulations
2) Spray drying
3) Freeze drying
4) Adsorption to solid carriers
5) Melt granulation
6) Melt extrusion/extrusion spheronization

1) Capsule filling with liquid and semisolid self-emulsifying formulations
Capsule filling is the simplest and the most common technology for the encapsulation of liquid or semisolid SE formulations for the oral route. A primary consideration in capsule filling is the compatibility of the excipients with the capsule shell. The advantages of capsule filling are simplicity of manufacturing; suitability for low-dose highly potent drugs and high drug loading (up to 50% (w/w)) potential.[25]

2) Spray drying
This technique involves the preparation of a formulation by mixing lipids, surfactants, drug, solid carriers, and solubilization of the mixture before spray drying. The solubilised liquid formulation is then atomized into a spray of droplets. The droplets are introduced into a drying chamber, where the volatile phase (e.g. the water contained in an emulsion) evaporates, forming dry particles under controlled temperature and airflow conditions. Such particles can be further prepared into tablets or capsules.[25,26]

3) Freeze-drying
Dry emulsions are powders from which emulsion spontaneously occurs in vivo or when exposed to an aqueous solution. Dry emulsions can be useful for further preparation of tablets and capsules. Dry emulsion formulations are typically prepared from oil/water (O/W) emulsions containing a solid carrier (lactose, maltodextrin, and so on) in the aqueous phase by rotary evaporation, freeze-drying.[28]
4) Adsorption to solid carriers
Free flowing powders may be obtained from liquid SE formulations by adsorption to solid carriers. The adsorption process is simple and just involves addition of the liquid formulation onto carriers by mixing in a blender. The resulting powder may then be filled directly into capsules or, alternatively, mixed with suitable excipients before compression into tablets. A significant benefit of the adsorption technique is good content uniformity. SEDDS can be adsorbed at high levels (up to 70% (w/w) on to suitable carriers. Solid carriers can be microporous inorganic substances, high surface area colloidal inorganic adsorbent substances, cross-linked polymers or nanoparticle adsorbents, for example, silica, silicates, magnesium trisilicate, magnesium hydroxide, talcum, crospovidone, cross-linked sodium carboxymethyl cellulose and crosslinked polymethyl methacrylate.[28,29]

5) Melt granulation
Melt granulation is a process in which powder agglomeration is obtained through the addition of a binder that melts or softens at relatively low temperatures. As a ‘onestep’ operation, melt granulation offers several advantages compared with conventional wet granulation, since the liquid addition and the subsequent drying phase are omitted. Moreover, it is also a good alternative to the use of solvent. The main parameters that control the granulation process are impeller speed, mixing time, binder particle size, and the viscosity of the binder. A wide range of solid and semisolid lipids can be applied as meltable binders.[25] Gelucire, a family of vehicles derived from the mixtures of mono/di/tri-glycerides and poly-ethylene glycols (PEG) esters of fatty acids, is able to further increase the dissolution rate compared with PEGs, probably owing to its SE property.

6) Melt extrusion/extrusion spheronization
Melt extrusion is a solvent-free process that allows high drug loading (60%), as well as content uniformity. The extrusion–spheronization process requires the following steps: dry mixing of the active ingredients and excipients to achieve ahomogeneous powder; wet massing with binder; extrusion into a spaghetti-like extrudate; spheronization from the extrudate to spheroids of uniform size; drying; sifting to achieve the desired size distribution and coating (optional). Applying extrusion–spheronization, SE pellets of diazepam and progesterone and bi-layered cohesive SE pellets have been prepared.[26]

Dosage form development of S-SMEDDS[10]:
• Dry emulsions
• Self-emulsifying capsules
• Self-emulsifying sustained/controlled release tablets
• Self-emulsifying beads
• Self-emulsifying sustained-release microspheres
• Self-emulsifying nanoparticles
• Self-emulsifying suppositories
• Self-emulsifying implant

EVALUATION

Thermodynamic stability studies: The physical stability of a lipid–based formulation is also crucial to its performance, which can be adversely affected by precipitation of the drug in the excipient matrix. In addition, poor formulation physical stability can lead to phase separation of the excipient, affecting not only formulation performance, but visual appearance as well. In addition, incompatibilities between the formulation and the gelatin capsules shell can lead to brittleness or deformation, delayed disintegration, or incomplete release of drug.

Heating cooling cycle: Six cycles between refrigerator temperature (40°C) and 450°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.

Freeze thaw cycle: Three freeze for the formulations. Those formulations passed this test showed good stability with no phase separation, creaming, or cracking.

Dispersibility test
The efficiency of self-emulsification of oral nano or micro emulsion 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.

Grade E: Formulation, exhibiting either poor or minimal emulsification with large oil globules present on the surface. Grade A and Grade B formulation will remain as nanoemulsion when dispersed in GIT. While formulation falling in Grade C could be recommend for SEDDS formulation.\[30\]

Turbidimetric Evaluation
Nephelometric evaluation is done to monitor the growth of emulsification. Fixed quantity of Selfemulsifying system is added to fixed quantity of suitable medium (0.1N hydrochloric acid) under continuous stirring (50 rpm) 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 rate of emulsification.\[31\][32]

Viscosity Determination
The SEDDS system is generally administered in soft gelatin or hard gelatin capsules. So, it can 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 a high viscosity then it is w/o type of the system.\[31,33\]

Droplet Size Analysis Particle Size Measurements
The droplet size of the emulsions is determined by photon correlation spectroscopy (which analyses the fluctuations in light scattering due to Brownian motion of the particles) using a Zeta sizer able to measure sizes between 10 and 5000 nm. Light scattering is monitored at 25°C at a 90° angle, after external standardization with spherical polystyrene beads. The
nanometric size range of the particle is retained even after 100 times dilution with water which proves the system’s compatibility with excess water.\cite{31,33}

**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 (1.333). 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 (1.333) and formulation have percent transmittance > 99 percent,

**Grade D**: Dull, grayish white emulsion having slightly oily appearance that is slow to emulsify (longer than 2 min).

**APPLICATIONS**

1) **Improvement in Solubility and bioavailability**

If drug is incorporated in SEDDS, it increases the solubility because it circumvents the dissolution step in of Class-II drug (Low solubility/high permeability).

This formulation enhanced bioavailability due to increase the solubility of drug and minimizes the gastric irritation. Also incorporation of gelling agent in SEDDS sustained the release In SEDDS, the lipid matrix interacts readily with water, forming a fine particulate Oil in-water (o/w) emulsion. The emulsion droplets will deliver the drug to the gastrointestinal mucosa in the dissolved state readily accessible for absorption. Therefore increase in AUC i.e. bioavailability and Cmax is observed with many drugs when presented in SEDDS.

2) **Protection against Biodegradation**

The ability of self-emulsifying drug delivery system to reduce degradation as well as improve absorption may be especially useful for drugs, for which both low solubility and degradation in the GI tract contribute to a low oral bioavailability. Many drugs are degraded in physiological system, may be because of acidic PH in stomach, enzymatic degradation or hydrolyte. Such drugs when presented in the form of SEDDS can be well protected against these degradation processes as liquid crystalline phase in SEDDS might be an act as barrier between degradating environment and the drug.
3) Controlling the release of drug

Different formulation approaches that have been sought to achieve sustained release, increase the bioavailability, and decrease the gastric irritation. Preparation and stabilization of nano-crystalline or improved solubility forms of drug may pose processing, stability, and economic problems. This formulation enhanced bioavailability due to increase the solubility of drug and minimizes the gastric irritation.

CONCLUSION

SMEDDS formulation can be optimized for the delivery of hydrophobic compounds with drug loading; minimum surfactant concentration and proper infinite dilution can be achieved without drug precipitation. Self-emulsifying drug delivery system can be use for the formulations of drugs compounds with poor aqueous stability. Development of this technology SEDDS will continue to enable novel applications in drug delivery system. SEDDS have been shown to be reasonably successful in improving the oral bioavailability of poorly water-soluble and Traditional preparation of SEDDS involves dissolution of drugs in oils and their blending with suitable solubilizing agents.

REFERENCE

