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IJPBS |Volume 2| Issue 2 |APRIL-JUNE |2012|42-52

SELF EMULSIFYING DRUG DELIVERY SYSTEM (SEDDS): A Review

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PHARMACEUTICAL SCIENCES REVIEW ARTICLE

ABSTRACT

Self-emulsifying drug delivery systems (SEDDS), 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. It can be orally administered in soft or hard gelatin capsules. These systems form fine emulsions (or micro-emulsions) in gastro-intestinal tract (GIT) with mild agitation provided by gastric mobility.
Many parameters like surfactant concentration, oil/surfactant ratio, polarity of the emulsion, droplet size and charge plays a critical role in oral absorption of drug from SEEDS. This formulation enhanced bioavailability due to increase the solubility of drug and minimizes the gastric irritation. The fact that almost 40% of the new drug compounds are hydrophobic in nature implies that studies with SEDDS will continue, and more drug compounds formulated as SEDDS will reach the pharmaceutical market in the future.

KEYWORDS: *Self-emulsifying drug delivery systems, isotropic, emulsions, bioavailability*

INTRODUCTION [1]

SEDDS formulations can be simple binary systems: lipophilic phase and drug, or lipophilic phase, surfactant and drug. The formation of a SEDDS requires the use of a co-surfactant to generate a micro emulsion. SEDDS formulations are characterized by in vitro lipid droplet sizes of 200 nm–5 mm and the dispersion has a turbid appearance.

Self-emulsifying drug delivery systems (SEDDS) are mixtures of oils and surfactants, ideally isotropic, and sometimes containing co-solvents, which emulsify spontaneously to produce fine oil-in-water emulsions when introduced into aqueous phase under gentle agitation[4-8,]. Recently, SEDDS have been formulated using medium chain tri-glyceride oils and non-ionic surfactants, the latter being less toxic. Upon per oral administration, these systems form fine emulsions (or micro-emulsions) in gastro-intestinal tract (GIT) with mild agitation provided by gastric mobility[2,4,9].

ADVANTAGES OF SEEDS:[10,11]

- ✓ 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

DISADVANTAGES OF SEDDS [11]

- ✓ 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 GIT.

FORMULATION OF SEDDS:

The following points should be considered in the formulation of a SEDDS:

Selection of oils, surfactant and co-solvent based on the solubility of the drug .The preparation of SEDDS formulation by dissolving the drug in mixture of oil, surfactant, co-solvents .The addition of drug to SEDDS is critical because the drug interferes with the self emulsifying process to certain extent, which leads to a change in optimal oil-surfactant ratio so design of optimal SEDDS require pre-formulation solubility and phase diagram study. Recently synthesized drug that are being discovered are lipophilic in nature and have poor aqueous solubility, thereby posing problems in their formulation into delivery systems. Because of their low aqueous solubility and low permeability, dissolution and/or release rate from the delivery system forms the rate limiting step in their absorption and systemic availability.

More than 60% of potential drug products suffer from poor water solubility. For the therapeutic delivery of lipophilic active moieties (BCS class II drugs), lipid based formulations are inviting increasing attention[12, 13]. Currently a number of technologies are available to deal with the poor solubility, dissolution rate and bioavailability of insoluble drugs. The Self-Dispersing Lipid Formulations (SDLFs) is one of the promising approaches to overcome the formulation difficulties of various hydrophobic/lipophilic drugs and to improve the oral bioavailability of poorly absorbed drugs[11, 33]. The SDLFs contain oil and a surfactant mixture into which the drug is incorporated. They emulsify when mixed with aqueous environment. The self-emulsification process is specific to the particular pair of oil and surfactant, surfactant concentration, oil/surfactant ratio, and the temperature at which self-emulsification occurs. After self-dispersion, the drug is rapidly distributed throughout the gastrointestinal tract as fine droplets. The SDLFs are of two kinds namely, Self-Emulsifying Drug Delivery Systems (SEDDS) formed using surfactants of HLB < 12 and Self-Micro Emulsifying Drug Delivery Systems (SMEDDS) formed surfactants of HLB > 12. Both SEDDS and SMEDDS are stable preparations and improve the dissolution of the drug due to increased surface area on dispersion. Many researchers have reported applications of SEDDS for delivering and targeting lipophilic drugs,

e.g.: Coenzyme Q10[14], Vitamin E[15], Halofantrine[16] and Cyclosporine A[17].

THE EMULSIFICATION PROCESS:

Self-emulsification is a phenomenon which has been widely exploited commercially in formulations of emulsifiable concentrates of herbicides and pesticides[18]. 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.

(a) Mechanism of Self Emulsification[19]:

In emulsification process the free energy (ΔG) associated is given by the equation:

$$\Delta G = \Sigma N i \pi r i \quad \text{---------- (1)}$$

In which 'N' is Number of droplets with radius 'r' and 'σ' is interfacial energy. It is apparent from equation that the spontaneous formation

of the interface between the oil and water phases is energetically not favored. The system commonly classified as SEDDS have not yet been shown to emulsify spontaneously in the thermodynamic sense.

The emulsification process may be associated with the ease with which water penetrates the oil-water interface with the formation of liquid crystalline phases resulting in swelling at the interface thereby resulting in greater ease of emulsification[20-22]. However, for system containing co- surfactant, significant partitioning of components between the oil and aqueous phases may take place leading to a mechanism described as "diffusion and stranding", where by the oil is solubilized, leading to migration in to the aqueous phase.

b) Dilution phases:

Upon dilution of a SMEDDS formulation, the spontaneous curvature of the surfactant layer changes via a number of possible liquid crystalline phases. The droplet structure can pass from a reversed spherical droplet to a reversed rod-shaped droplet, hexagonal phase, lamellar phase, cubic phase and various other structures until, after appropriate dilution, a spherical droplet will be formed again dilution.

EXCIPIENTS USED IN SEDDS[23-25]:

Pharmaceutical acceptability of excipients and the toxicity issues of the components used makes the selection of excipients really critical. There is a great restriction as which excipients to be used. Early studies revealed that the self emulsification process is specific to the nature of the oil/surfactant pair, the surfactant concentration and oil/surfactant ratio, the concentration and nature of co-surfactant and surfactant/co-surfactant ratio and the temperature at which self emulsification occurs.

Important parameter for excipient-to sedds:

• The solubility of drug in the formulation as such and upon dispersion (for SEDDS),

• The rate of digestion (for formulations susceptible to digestion) and possibly

• The solubilization capacity of the digested Formulation.

EXCIPIENTS:

A) OILS [11, 26, 27]:-

The oil represents one of the most important excipients in the SEDDS 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 triglyceride [28-30]. Both long and medium chain triglyceride (LCT and MCT) oils with different degrees of saturation have been used for the design of self-emulsifying formulations.

B) SURFACTANTS [31, 32]:

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) [34]. Safety is a major determining factor in choosing a surfactant

The four main groups of surfactants are defined as following-

A) Anionic surfactants

B) Cationic surfactant

C) Ampholytic surfactants

D) Nonionic surfactants

A) **Anionic Surfactants**:- where the hydrophilic group carries a negative charge such as carboxyl (RCOO-), sulphonate (RSO3 -) or sulphate (ROSO3 -).

Examples: Potassium laurate, sodium lauryl sulphate.

B) Cationic surfactants: - where the hydrophilic group carries a positive charge.
Example: quaternary ammonium halide.

C) Ampholytic surfactants: - (also called zwitterionic surfactants) contain both a negative and a positive charge. Example: sulfobetaines.

D) Nonionic surfactants: - where the hydrophilic group carries no charge but derives its water solubility from highly polar groups such as hydroxyl or polyoxyethylene.

Examples: Sorbitan esters (Spans), poly - sorbates (Tweens).

C) CO-SOLVENTS[35]:-

The production of an optimum SEDDS requires relatively high concentrations (generally more than 30% w/w) of surfactants, thus the concentration of surfactant can be reduced by incorporation of co surfactant.Role of the co-surfactant together with the surfactant is to lower the interfacial tension to a very small even transient negative value[36].

.At this value the interface would expand to form fine dispersed droplets, and subsequently adsorb more surfactant and surfactant/co-surfactant until their bulk condition is depleted enough to make interfacial tension positive again. However, the use of co-surfactant in self emulsifying systems is not mandatory for many non-ionic surfactants. The selection of surfactant and co-surfactant is crucial not only to the formation of SEDDS, but also to solubilization of the drug in the SEDDS.

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.

CRITERIA OF DRUG PROPERTIES: [12-13]

BCS (Bio-pharmaceutical classification system) classifies the drug based on solubility and permeability of a drug. Mainly Class 2 (Low Solubility, High Permeability) is used for SEDDS.

Ex. Azithromycin Carbamazepine Carvedilol Chlorpromazine Cisapride Ciprofloxacin.

DOSAGE FORM OF SEDDS:

(1) Oral delivery:

(A) Self emulsifying capsule [39-42]:

After administration of capsules containing conventional liquids SE formulations, microemulsion droplets form and subsequently disperse in the GIT to reach site of absorption. If irreversible phase separation of microemulsion occurs an improvement of drugs absorption can't be expected. For handling this problem, sodium dodecyl sulfate was added into the SE formulation[43].

(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[37, 38].

(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 could increase the dissolution rate and bioavailability of poorly water soluble drugs but still some manufacturing difficulties and stability problems existed. Serajuddin pointed out that these difficulties could be surmounted by the use of se excipients[31].

(2) Topical Delivery:

Topical administration of drugs can 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.

(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 industrybecause of the extremely low amount of drug actually delivered as target site.

BIOPHARMACEUTICAL ASPECTS:

The ability of lipids and/or food to enhance the bioavailability of poorly watersoluble drugs is well known. Although incompletely understood, the currently accepted view is that lipids may enhance bioavailability via a number of potential mechanisms, including.

a) Alterations (reduction) in gastric transit.

b) Increases in effective luminal drug solubility.

c) Stimulation of intestinal lymphatic transport

d) Changes in the biochemical barrier function

e) Changes in the physical barrier function of the GI tract.

f) The polarity of lipid phase is one of the factors that govern the release from the micro-emulsion.

METHOD OF PREPARATION:

A) Solidification techniques for transforming liquid/semisolid[44]:

Various solidification techniques are as listed below;

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. For semisolid formulations, it is a four-step process:

A) Heating of the semisolid excipient to at least 20˚C above its melting point.

B) Incorporation of the active substances (with stirring).

C) Capsule filling with the molt cooling to room temperature. For liquid formulations, it involves a two-step process.

D) Filling of the formulation into the capsules followed by sealing of the body and cap of the capsule, either by banding or by micro spray sealing.

B) Spray drying:

Essentially, this technique involves the preparation of a formulation by mixing lipids, surfactants, drug, solid carriers, and solubilization of the mixture before spray drying. The solubilized 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) evaporprepared into tablet pattern and the drying chamber design are selected according to the drying characteristic the product and powder specification.

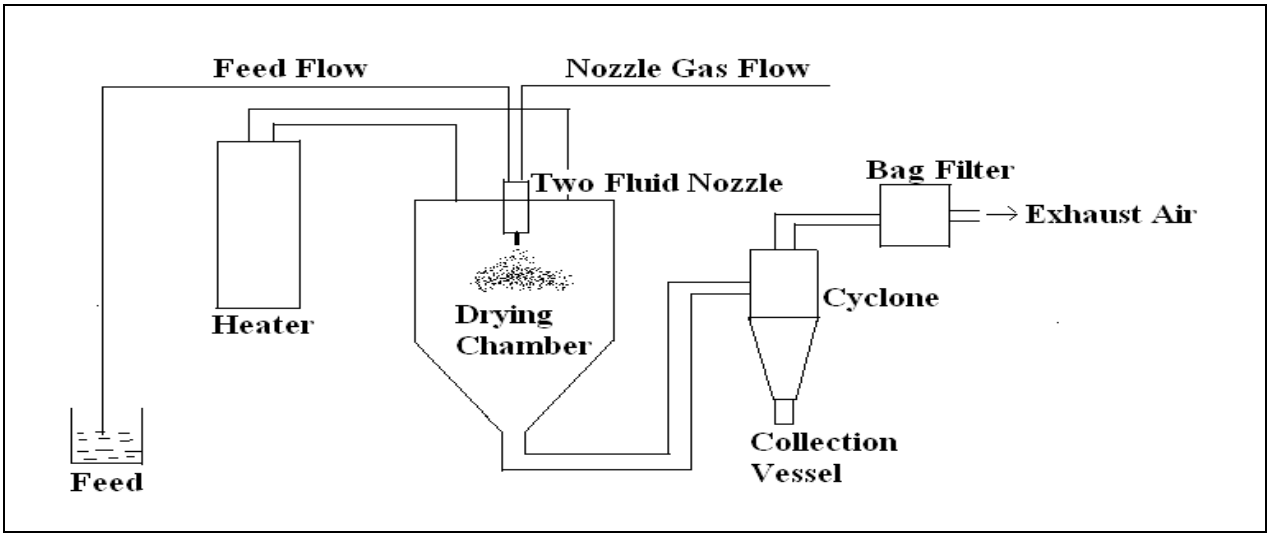

Fig 1 -Spray Drying.

C) 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 On to carriers by mixing in a blender.

D) 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.

E) Melt extrusion/extrusion spheronization:

Melt extrusion is a solvent-free process that allows high drug loading (60%), as well as content uniformity[45]. Extrusion is a procedure of product of uniform shape and density, by forcing it through a die under controlled temperature, product flow, and pressure conditions[46].

EVALUATION[47-49]:-

A) 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.

a) **Heating cooling cycle:** Six cycles between refrigerator temperature (40ºC) and 45ºC with storage at each temperature of not less than 48 hr is studied. Those formulations, which are stable at these temperatures, are subjected to centrifugation test.

b) Centrifugation: Passed formulations are centrifuged thaw cycles between 21 ºC and +25 ºC with storage at temperature for not less than 48 hr 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.

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

B) 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 ^{0}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 D: Dull, grayish white emulsion having slightly oily appearance that is slow to emulsify (longer than 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.

C) Turbidimetric Evaluation:

Nepheloturbidimetric 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),

D) 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 high viscosities then it are w/o type of the system.

E) 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 Zetasizer able to measure sizes between 10 and 5000 nm.

APPLICATIONS:

- ✓ **Improvement in Solubility and bioavailability:**

If drug is incorporated in SEDDS, it increases the solubility because it circumvents the dissolution step in of Class-П drug (Low solubility/high permeability). Ketoprofen, a moderately hydrophobic (log P 0.979) nonsteroidal anti-inflammatory drug (NSAID), is a drug of choice for sustained release formulation has high potential for gastric irritation during chronic therapy. Also because of its low solubility, ketoprofen shows incomplete release from sustained release formulations.

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 of Ketoprofen. 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.

✓ **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 ebarrier between degradating environment and the drug.

Ex: - Acetylsalicylic acid (Log P = 1.2, Mw=180), a drug that degrades in the GI tract because it is readily hydrolyzed to salicylic acid in an acid environment. The oral bioavailability of undegraded acetylsalicylic acid is improved by 73% by the Galacticles Oral Lipid Matrix

✓ **Controlling the release of drug:**

Different formulation approaches that have been sought to achieve sustained release, increase thebioavailability, and decrease the gastric irritation of ketoprofen include preparation of matrix pellets of nano-crystalline ketoprofen, sustained release ketoprofen microparticles and floating oral ketoprofen systems and transdermal systems of ketoprofen. Preparation and stabilization of nano-crystalline or improved solubility forms of drug may pose processing, stability, and economic problems.

This problem can be successfully overcome when Ketoprofen is presented in SEDDS formulation. This formulation enhanced bioavilability due to increase the solubility of drug and minimizes the gastric irritation. Also incorporation of gelling agent in SEDDS sustained the release of Ketoprofen.

FUTURE TREND:

In relation to formulation development of poorly soluble drugs in the future, there are now techniques being used to convert liquid/semi-solid SEDDS and SMEDDS formulations into powders and granules, which can then be further processed into conventional 'powder-fill' capsules or even compressed into tablets.

Hot melt granulation is a technique for producing granules or pellets, and by using a waxy solubilising agent as a binding agent, up to 25% solubilising agent can be incorporated in a formulation. There is also increasing interest in using inert adsorbents, such as the Neusilin products for converting liquids into powders – which can then be processed into powder fill capsules or tablet.

Oral delivery of poorly water-soluble compounds is to pre-dissolve the compound in a suitable solvent and fill the formulation into capsules.

The main benefit of this approach is that pre-dissolving the compound overcomes the initial rate limiting step of particulate dissolution in the aqueous environment within the GI tract. However, a potential problem is that the drug may precipitate out of solution when the formulation disperses in the GI tract.

Table 1: MARKETED SEDDS FORMULATION [40, 49-52]:

Brand name	Drug used	Dosage form	Company
Neoral	Cyclosporine	SGC	Novartis
Norvir	Ritonavir	SGC	Abott laboraties
Fortovase	Saquinavir	SGC	Hoffmann roche
Agenerase	Amprenavir	SGC	GSK
Convulex	Volporic acid	SGC	Pharmacia

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.

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