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Review Article

Self-emulsifying drug delivery systems: An Overview

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ABSTRACT
Solubility of orally administered drug is major challenge of pharmaceutical industry as nearly 35-40% of newly launched drugs possess low aqueous solubility that results in their poor dissolution and low bioavailability, leading to high intra subject variability & lack of dose proportionality. This can be increased by totally different ways like salt formation, solid dispersion and complex formation. Self Emulsifying Drug Delivery System & 40; SEDDS & 41; is gaining popularity for improving the solubility of lipophilic drugs. SEDDS are defined as identical mixtures of one or more hydrophilic solvents and cosolvents/surfactants that have a unique ability of forming fine oil-in-water (o/w) small emulsions upon mild agitation followed by dilution in aqueous media, such as GI fluids. Present review provides an updated account of advancements in SEDDS with regard to its composition, evaluation, different dosage forms and newer techniques to convert liquid SEDDS to solid and also various applications.

KEYWORDS
Self emulsification system, emulsion, solubility.

1. INTRODUCTION

Oral route has been the major route of drug delivery for the chronic treatment of many diseases. However, oral delivery of the drug compounds is hampered because of the high lipophilicity of the drug itself. Nearly 40% of new drug candidates exhibit low solubility in water, which leads to poor oral bioavailability, high intra-and inter-subject variability and lack of dose proportionality [1]. Thus, for such compounds, the absorption rate from the gastrointestinal (GI) lumen is controlled by dissolution [2]. Modification of the physicochemical properties, such as salt formation and particle size reduction of the compound may be one approach to improve the dissolution rate of the drug [3]. However, these methods have their own limitations. For instance, salt formation of neutral compounds is not feasible and the synthesis of weak acid and weak base salts may not always be practical [4]. Moreover, the salts that are formed may convert back to their original acid or base forms and lead to aggregation in the gastrointestinal tract [4]. Particle size reduction may not be desirable in situations where handling difficulties and poor wettability are experienced for very fine powders [4].To overcome these drawbacks, various other formulation strategies have been adopted including the use of cyclodextrins, nanoparticles, solid dispersions and permeation enhancers [1,5]. Indeed, in some selected cases, these approaches have been successful. In recent years, much attention has focused on lipid−based formulations to improve the oral bioavailability of poorly water soluble drug compounds. In fact, the most popular approach is the incorporation of the drug compound into inert lipid vehicles such as oils [6], surfactant dispersions [7,8], self-emulsifying formulations [9−12], emulsions [13−17] and liposomes [18] with particular emphasis on self-emulsifying drug delivery systems (SEDDS).

1.1. Advantages of SEEDS[19,20]

- **(a)** Quick Onset of Action.
- **(b)** Reduction in the Drug Dose.
- **(c)** Ease of Manufacture & Scale-up.
- **(d)** Improvement in oral bioavailability.
- **(e)** Inter-subject and Intra-subject variability and food effects.
- **(f)** Ability to deliver peptides that are prone to enzymatic hydrolysis in GIT.
- **(g)** No influence of lipid digestion process.
- **(h)** Increased drug loading capacity.

1.2. Disadvantages of SEDDS[20]

1. Traditional dissolution methods do not work, because these formulations potentially are dependent on digestion prior to release of the drug.
2. 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.
3. The drawbacks of this system include chemical instabilities of drugs and high surfactant concentrations in formulations (approximately 30-60%) which GIT.

1.3. Properties of SEDDS[21]

(1) They are able to self-emulsify rapidly in gastro-intestinal fluids & under the influence of gentle agitation provided by peristaltic and other movements of gastro intestinal tract, they form a fine o/w emulsion.

(2) They can effectively incorporate drug (hydrophobic or hydrophilic) within the oil surfactant mixture.

(3) They can be used for liquid as well as solid dosage forms.

(4) They require lower dose of drug with respect to conventional dosage forms. Window in the GI tract, and drug protection from the hostile environment in the gut. Thus, for lipophilic drug compounds that exhibit dissolution rate limited absorption, these systems may offer an improvement in the rate and extent of absorption and result in more reproducible blood time profiles.

(5) 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, liposome, nanoparticles, etc., as they 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 pharmaceutical industry in the SMEDDS.

1.4. Composition of Self Emulsifying Drug Delivery System

A. Active Pharmaceutical Ingredient (API)

As, SEDDS are used to increase the solubility of poor water-soluble drugs, BCS class II drugs are preferred e.g. itraconazole, nifedipine, vitamin E, simvastatin, danazol, ketoconazole, mefanimic acid, naproxen, carbamazepine [22,23]

B. Excipients used in SEDDS

Considering, pharmaceutical acceptability and the toxicity issues the selection of excipients is really critical. So there is a great restriction as to which excipients should be used. The self emulsification process is specific to the concentration and nature of the oil/surfactant ratio, surfactant/co-surfactant ratio and the temperature at which self-emulsification occurs. So, this entire issue must be thought of during selection of excipients in SEDDS.

C. Oils

Oils can solubilize the required dose of the lipophilic drug and facilitate self emulsification and also they 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[24]. Both long and medium chain acylglycerol (LCT and MCT) oils with different degrees of saturation have been used for the design of self-emulsifying formulations. Novel semisynthetic MCT, which can be defined as amphiphilic compounds with surfactant properties, are progressively and effectively replacing the regular MCT oils in the SMEDDS MCT are more soluble and

have a higher mobility in the lipid/water interfaces than LCT associated with a more rapid hydrolysis of MCT.

In general, when using LCT, a higher concentration of cremophor RH40 is required to form microemulsions compared with MCT. Edible oils are not oft selected due to their poor ability to dissolve large amounts of lipophilic drugs. Modified or hydrolyzed vegetable oils are widely used since these excipients form good emulsification systems with a large number of surfactants approved for oral administration and exhibit better drug solubility properties[25]. They offer formulative and physiological advantages and their degradation products resemble the natural finish products of intestinal digestion. Table 1, given bellow gives a list of different oils used to solubilised different drugs.

Table 1. Type of oils used in marketed SEDDS.

Types of oil	Drug	Marketed product
Corn oil	Valproic acid	Depakene capsules
Seasame oil	Dronabonol	Marinol soft gelatine capsule
Soya bean oil	Isotretinoin	Accutane soft gelatin capsule
Peanut oil	Progesterone	Prometrium soft gelatin capsule
Hydrogenated soya bean oil	Isotretinoin	Accutane soft gelatin capsule

D. Surfactants

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) and less toxicity than ionic surfactants but they may lead to reversible changes in the permeability of the intestinal lumen. Safety is a major determining factor in choosing a surfactant. Hence emulsifiers of natural origin are preferred than the synthetic surfactant, but they have a limited self-emulsification capacity. There is a relationship between the droplet size and the concentration of the surfactants being used. In some cases, increasing the surfactant concentration could lead to decreasing mean droplet size (SMEDDS), 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. On the other hand, the mean droplet size may increase with increasing surfactant concentrations. 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. 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. A list of surfactant used in marketed SEDDS is given in table 2.

Table 2. Type of surfactant used in marketed SEDDS.

Surfactant	Drug	Marketed product
Span 80, tween 80,	Cyclosporine	Gengraf soft gelatin capsule
Tween 20	Bexarotone	Targretin hard gelatin capsule
Cremophor RH 40	Carmustine	BCNU self emulsifying implant
D-alpha Tocopheryl	Amprenavir	agenerase soft gelatin capsule
Poly ethylene glycol		Agenerase oral solution

E. Co-surfactants

The production of an optimum SMEDDS requires relatively high concentrations (generally more than 30% w/w) of surfactants but it causes GI irritation. So co surfactant is used to reduce concentration of surfactant. Role of the cosurfactant together with the surfactant is to lower the interfacial tension to a very small even transient negative value. 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.

This process known as 'spontaneous emulsification' forms the micro emulsions. Organic solvents, suitable for oral administration {ethanol, propylene glycol (PG), polyethylene glycol (PEG), etc} 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, although alcohol- free self-emulsifying micro emulsions have also been described in the literature 3. Such systems may exhibit some advantages over the other formulations when incorporated in capsule dosage forms, since alcohol and other volatile co-solvents in the conventional self-emulsifying formulations are known to migrate into the shells of soft gelatin or hard sealed gelatin capsules resulting in the precipitation of the lipophilic drug.
On the other hand, the lipophilic drug dissolution ability of the alcohol free formulation may be limited. Hence, proper choice has to be made during selection of components. A list of surfactant used in marketed SEDDS is given in table 3.

Table 3. Types of co surfactant used in marketed SEDDS.

Co surfactant	Marketed preparation
Glycerin	Sandimmune soft gelatin capsule
Propylene glycol	Neural soft gekatin,neural oral solution,gengraf hard gelatin ,lamprene soft

	gelatin capsule
Ethnol	Neural soft gelatin& neural oral,sandimmune soft gelatin& oral sol, fengraf hard gelatin capsule

F. Viscosity Enhancers

The viscosity of the emulsions can be altered by the use of additional material such as acetyl alcohol, tragacanth, beeswax and stearic acids etc.

G. Polymers

Polymer matrix (inert) present in 5 to 40% w/w, which is not ionizable at physiological pH are able to form matrix. Examples are hydroxyl propyl methyl cellulose, ethyl cellulose, etc.

H. Antioxidant Agents

Lipophilic antioxidants (E.g. α tocopherol, propyl gallate, ascorbic palmitate) stabilize the oily content of SEDDS formulations.

1.5. Method of preparation

1.5.1. Solidification techniques for transforming liquid/semisolid[26]

Various solidification techniques are as listed below;

1.5.2. Capsule filling with liquid and solid self-emulsifying formulations

Capsule filling is the simplest and the most common technology for the encapsulation of liquid or solid 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 melt 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.

1.5.3. 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 associate degree emulsion) vapour prepared into pill pattern and the drying chamber design are selected according to the drying characteristic the product and powder specification.

1.5.4. 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 On to carriers by mixing in a blender.

1.5.5. Soften granulation

Melt granulation could be a process in which powder agglomeration is obtained through the addition of a binder that melts or softens at comparatively low temperatures.

1.5.6. Melt extrusion/extrusion spheronization

Melt extrusion is a solvent-free process that allows high drug loading (60%), as well as content uniformity[27]. Extrusion may be a procedure of product of uniform shape and density, by forcing it through a die underneath controlled temperature, product flow, and pressure conditions [28].

1.6. The Emulsification Process

1.6.1. Mechanism of Self-emulsification

Self emulsification occurs, when the entropy (energy) change occurs. 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.

$\Delta G == \Sigma N \pi r2 \sigma$ **---Equation 1**

Where, Δ G 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[29]. In case of self-emulsifying system, the free energy requires to form the emulsion is either very low or positive or negative then, the emulsion process occurs spontaneously [30].

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 [31]. Emulsification can be associated with the ease by which water penetrates into the various liquid crystals or phases get formed on the surface of the droplet. 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 [30].

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.

1.6.2. Construction of Ternary Phase Diagrams

This is the first step before starting the formulation. It 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 [31]. The methods are used to plot ternary phase diagrams are namely Dilution method and Water Titration method.

1.6.2.1. Dilution method

Ternary mixtures with varying compositions of surfactant, cosurfactant and oil were prepared. The percentage of surfactant, co-surfactant and oil decided on the basis of the requirements. Compositions are evaluated for nanoemulsion formation by diluting appropriate amount of mixtures with appropriate double distilled water. Globule size of the resulting dispersions was determined by using spectroscopy. The area of nanoemulsion formation in Ternary phase diagram(as shown in figure 2a) was identified for the respective system in which nanoemulsions with desire globule size were obtain.

1.6.2.2. 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 figure 2b). Oil phase, Surfactant and the co-surfactant, at Km 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 [33]. 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 micro-emulsion 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.

1.7. Factors affecting SMEDDS

1.7.1. Nature and dose of the drug

Drugs which are administered at very high dose are not suitable for SMEDDS 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 2 are most difficult to deliver by SMEDDS[34]. The ability of SMEDDS to maintain the drug in solubilised form is greatly influenced by the solubility of the drug in oil phase.

1.7.2. Concentration of Surfactant or Cosurfactant

If surfactant or co-surfactant is contributing to the greater extent in drug solubilization then there could be a risk of precipitation, as dilution of SMEDDS will lead to lowering of solvent capacity of the surfactant or co-surfactant.

1.7.3. Polarity of the lipophilic phase

The polarity of the lipid phase is one of the factors that govern the drug release from the microemulsions. 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 drug.

1.8. Evaluation[35-37]

1.8.1. 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.

1.8.2. 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.

1.8.3. 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. 7.1.3 Freeze thaw cycle: Three freeze for the formulations. Those formulations passed this test showed good stability with no phase separation, creaming, or cracking.

1.8.4. 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 0C. 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, gray 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.

1.8.5. Turbidimetric Evaluation

Nepheloturbidimetric evaluation is done to monitor the growth of emulsification. Fixed quantity of Self emulsifying 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 turbidimeters. 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),

1.8.6. 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.

1.8.7. 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.

1.9. 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). 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.
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. 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.

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 of ketoprofen include preparation of matrix pellets of nanocrystalline 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 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.

2. 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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