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A Review on Self-Emulsifying Drug Delivery Systems: Strategy for Improving Oral Delivery of Poorly Soluble Drugs

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Abstract

Oral route is the easiest and most convenient route for drug administration. Oral drug delivery systems being the most cost-effective and leads the worldwide drug delivery market. The major problem in oral drug formulations is low and erratic bioavailability, which mainly results from poor aqueous solubility. This may lead to high inter- and intra subject variability, lack of dose proportionality and therapeutic failure. It is estimated that 40% of active substances are poorly water soluble. For the improvement of bio-availability of drugs with such properties presents one of the greatest challenges in drug formulations. Various technological strategies are reported in the literature including solid dispersions, cyclodextrins complex formation, or micronisation, and different technologies of drug delivery systems. Including these approaches self-emulsifying drug delivery system (SEDDS) has gained more attention for enhancement of oral bio-availability with reduction in dose. SEDDS are isotropic mixtures of oil, surfactants, solvents and cosolvents/surfactants. The principal characteristic of these systems is their ability to form fine oil-in-water (o/w) emulsions or micro-emulsions upon mild agitation following dilution by an aqueous phase. For lipophilic drugs, which have dissolution rate-limited absorption, SEDDS may be a promising strategy to improve the rate and extent of oral absorption. This review article explains how self-emulsifying drug delivery systems can increase the solubility and bioavailability of poorly soluble drug.

Key words: Self emulsifying drug delivery system (SEDDS), oil, co-surfactant, surfactant, self-micro-emulsifying drug delivery systems (SMEDDS).

Introduction

The oral route is one of the preferred routes for chronic drug therapy. Approximately 35-40% of new drug candidates has poor water solubility. The oral delivery of such drugs is frequently associated with low bioavailability, high inter and intra subject variability and lack of dose proportionality. Efforts are going on to enhance the oral bioavailability of lipophilic drugs in order to increase their clinical efficacy. To overcome these problems, new strategies were reported to increase solubility and bioavailability including complexation with cyclodextrins, solid dispersion (suspension), co-precipitation, micronisation, salt formation, emulsion, use of micelles, and cogrinding [1].

Emulsions are used as vehicles for the administration of drugs, especially due to its potential of enhancing the oral bioavailability of poorly absorbed drugs. Microemulsion has got advantage like excellent thermodynamic stability, high drug solubilisation capacity, improvement in oral bioavailability and protection against enzymatic hydrolysis. The only problem with microemulsion is poor palatability due to the lipid content leading to poor patient compliance, more over due to their water content, micro-emulsions cannot be encapsulated into soft gelatin or hard gelatin capsule. There is a need for converting it into an alternative formulation like anhydrous self emulsifying drug delivery system (SEDDS) etc., because of its low loading dose. The primary mechanism by which lipid-based formulations enhance bioavailability is through solubilization of the drug, although other mechanisms of absorption enhancement have been implicated and include reduction of P-glycoprotein-mediated efflux, mitigation of hepatic first pass metabolism through enhanced lymphatic transport[1,2], prolongation of gastrointestinal (GI) transit time, or protection from degradation in the GI tract. The Lipid Formulation Classification System (LFCS) was introduced as a working model in 2000. Typical properties of Type I, II, IIIA and IIIB lipid formulations are shown in Table 1. The main purpose of the LFCS is to enable in vivo studies to be interpreted more readily, and subsequently to facilitate the identification of the most appropriate formulations for specific drugs, i.e. with reference to their

physicochemical properties [3,4]. The SEDDS formulation typically produce emulsions with a droplet size between 100 and 300 nm, while SMEDDS form transparent microemulsions with a droplet size that is less than 50 nm. Hence microemulsions are thermodynamically stable, transparent (or translucent), isotropic, low viscosity colloidal dispersions of oil and water stabilized by an interfacial film of alternating surfactant and cosurfactant molecules.

Table 1. Classification and typical properties of Type I, II, III A and III B lipid formulations

Parameter	Type I	Type II	Type III A	Type III B
Triglyceride or mix glycerieds **(%)**	100	40-80	40-80	<20
Surfactants **(%)**	-	20-60 (HLB>12)	20-40 (HLB<11)	20-50 (HLB<11)
Hydrophilic cosolvents **(%)**	-	-	0-40	20-50
Particle size (nm) **(%)**	Coarse	100-250	100-250	50-100

Self-emulsifying drug delivery (SEDDS) systems are isotropic mixtures of oils, surfactants, cosurfactants and drug that form fine oil-in-water micro/submicron emulsion when introduced into aqueous phase under conditions of gentle agitation. When the resultant emulsion is a microemulsion, it is called as self-microemulsifying drug delivery system (SMEDDS) and when it is a submicron emulsion then self-nano emulsifying drug delivery system (SNEDDS). It has unique property, that is they are able to self emulsify rapidly into fine O/W emulsion in the gastrointestinal fluids, under gentle agitation provided by the gastrointestinal tract. This fine O/W emulsion results in small droplets of oil dispersed in the gastrointestinal fluids that provide a large interfacial area enhancing the activity and minimizing the irritation due to contact of drug in the gut wall[5]. Self Emulsifying System (SES) can be formulated with little energy input and the shelf life is longer than conventional emulsions. Therefore, an SES can be an efficient vehicle for class II to IV molecules of the Biopharmaceutical Classification System (BCS) drugs.

Biopharmaceutical Drug Classification System[6]

Biopharmaceutical drug classification is a fundamental guideline classifying drugs based on the solubility and permeability, as shown in Table.2

Table 2: - Biopharmaceutical drug classification

Class	Solubility	Permeability
I	High	High
II	Low	High
III	High	Low
IV	Low	Low

Class I includes drugs that are water soluble and gastrointestinal tract permeable. This class does not suffer from absorption or permeation problems that may affect oral drug bioavailability. While classes II, III and IV contain drugs having problems in solubility and/or permeability that may reflect on their bioavailability in the blood after the drug is taken orally. Classes II, III and IV form approximately 80% of the drugs available in the market.

Formulation type	Composition	Characteristics
Type-I	Oils without surfactants	Non-dispersing, poor solvent capacity except for highly lipophilic drugs requires digestion to release drug.
Type-II	Oils and water insoluble surfactants	SEDDS, turbid o/w dispersion (particle size 0.25-2 µm), unlikely to lose solvent capacity on digestion.
Type-III	Oils, water-soluble surfactants and co-solvent	SEDDS/SMEDDS, slightly bluish to clear dispersion, possible loss of solvent capacity on dispersion, less easily digested, possible loss of solvent capacity on digestion.
Type-IV	Water-soluble surfactant and co-solvents(oil free)	Forms a clear micellar solution on dispersion, likely loss of solvent capacity on dispersion, unlikely to be digested.

Biopharmaceutical Aspects:

The ability of lipids and/or food to enhance the bioavailability of poorly water-soluble drugs has been comprehensively reviewed Although incompletely understood, the currently accepted view is that lipids may enhance bioavailability via a number of potential mechanisms, including:

Alterations (reduction) in gastric transit: Thereby slowing delivery to the absorption site and increasing the time available for dissolution.

Increases in effective luminal drug solubility: The presence of lipids in the GI tract stimulates an increase in the secretion of bile salts (BS) and endogenous biliary lipids including phospholipids (PL) and cholesterol (CH), leading to the formation of BS/PL/CH intestinal mixed micelles and an increase in the solubilisation capacity of the GI tract. However, intercalation of administered (exogenous) lipids into these BS structures either directly (if sufficiently polar), or secondary to digestion, leads to swelling of the micellar structures and a further increase in solubilisation capacity.

Stimulation of intestinal lymphatic transport: For highly lipophilic drugs, lipids may enhance the extent of lymphatic transport and increase bioavailability directly or indirectly via a reduction in first-pass metabolism

Changes in the biochemical barrier function of the GI tract: It is clear that certain lipids and surfactants may attenuate the activity of intestinal efflux transporters, as indicated by the p-glycoprotein efflux pump, and may also reduce the extent of enterocyte-based metabolism

Changes in the physical barrier function of the GI tract: Various combinations of lipids, lipid digestion products and surfactants have been shown to have permeability enhancing properties. For the most part, however, passive intestinal permeability is not thought to be a major barrier to the bioavailability of the majority of poorly water-soluble, and in particular, lipophilic drugs [26, 27]

Need of Sedds[47]

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, particularly if a hydrophilic solvent is used (e.g. polyethylene glycol). If the drug can be dissolved in a lipid vehicle there is less potential for precipitation on dilution in the GI tract, as partitioning kinetics will favor the drug remaining in the lipid droplet.[47]Another strategy for poorly soluble drugs is to formulate in a solid solution using a water-soluble polymer to aid solubility of the drug compound. For example, poly-vinyl-pyrrolidone (PVP) and polyethylene glycol (PEG 6000) have been used for preparing solid solutions with poorly soluble drugs. One potential problem with this type of formulation is that the drug may favor a more thermodynamically stable state, which can result in the compound crystallizing in the polymer matrix. Therefore the physical stability of such formulations needs to be assessed using techniques such as differential scanning calorimetry or X-ray crystallography. In this type of case SEDD system is a good option.

The Emulsification Process

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

Mechanism of Self Emulsification [7]

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

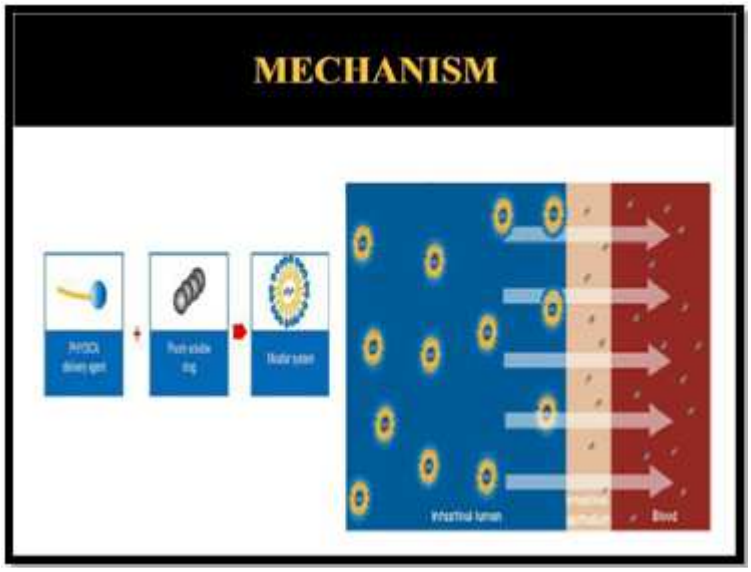
$$\Delta G = \Sigma N i \pi r i \text{ ------ ---------- (1)}$$

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 process of self-emulsification was observed using light microscopy. Groves and Mustafa developed a method of quantitatively assessing the ease of emulsification by monitoring the turbidity of the oil-surfactant in a water stream using phosphated nonylphenoloxylate (PNE) and phosphated fatty alcohol ethoxlate (PFE) Inhexane.

Pouton has argued that the emulsification properties of the surfactant may be related to phase inversion behavior of the system. For example, on increase the temperature of an oil in water system stabilized using nonionic surfactant, the cloud point of the surfactant will be reached followed by phase inversion. The surfactant is highly mobile at the phase inversion temperature; hence the o/w interfacial energy is minimized leading to a reduction in energy required to cause emulsification. The specificity of surfactant combination required to allow spontaneous emulsification may

be associated with a minimization of the phase inversion temperature, thereby increasing the ease of emulsion. Phase studies are also necessary for liquid crystal formation in selfemulsification. These indicate that good formulations are usually operating close to a phase inversion region and in a region of enhanced close to a phase inversion region and in a region of enhanced aqueous solubilization. In the phase diagram of the system (30 % w/w tween and 85/70 % w/w MCT oil) for dilution in water over a range of temperature shows that the phase inversion region is at approximately 40° C and the system works well at ambient temperature up to 60°C above which water in oil emulsion tend to form. [12]



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. 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.

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 (figure 1).

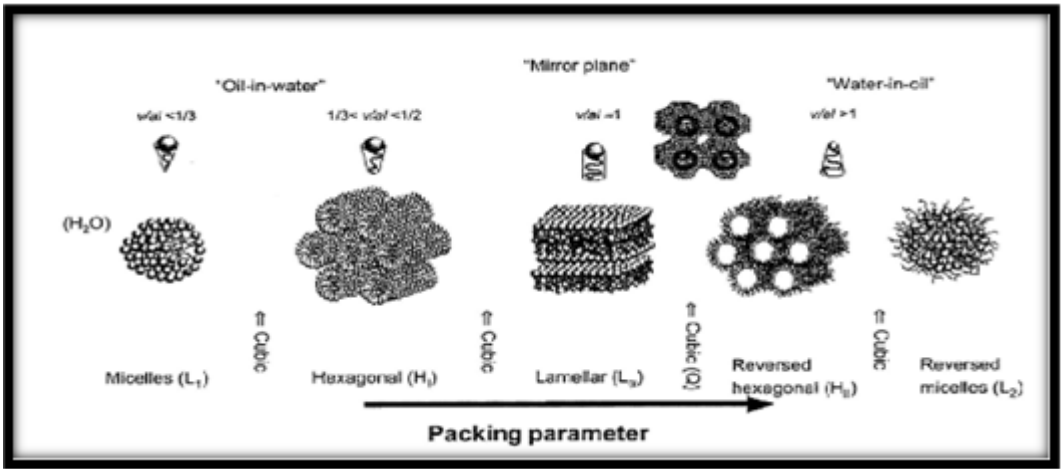


Figure: -Representation of them most commonly encountered phases upon addition of water to an oil surfactant combination (from jonson et al., Surfactants and Polymers in aqueous Solution.Wiley,1998.)

Many roles have been ascribed to the occurrence of liquid crystalline phases upon aqueous dilution of a lipid formulation. Early work of Groves and Mustafa related the emulsification behaviour to the phase behaviour of the surfactant-oil mixtures with systems forming liquid crystals showing shorter emulsification times [13]. The authors suggested that the ease of emulsification could be associated with the passage of water into the droplet, more

precisely the ease with which the solvent may penetrate into the liquid crystalline phases formed on the surface of the droplet. The structures formed upon dilution have been ascribed an important role in the stability of the diluted microemulsion and the rate of drug release [13]. This can be explained by the fact that a layer of liquid crystalline material surrounds the oil droplets, affecting drug dissolution and formulation digestion.

Dosage Forms From Self Emulsifying System [8]

Self Emulsifying Capsule: It is a capsule containing liquid or semisolid form of self emulsifying system. In the GIT, the capsules get dispersed to self emulsifying system (SES) uniformly in the fluid to micron size, enhancing bioavailability. Second type of self emulsifying capsule is solid SES filled into capsule.

Self Emulsifying Tablets: S.Nazzal et al developed self-nanoemulsified tablet dosage form of Ubiquinone. The main objectives of this study were to study effect of formulation ingredients on the release rate of Ubiquinone and to evaluate an optimized self-nano-emulsified tablets formulation. The first prepared self nano-emulsion system containing Ubiquinone was prepared as nano-emulsion; this nano-emulsion was adsorbed by granular materials and then compressed to form tablets. The optimized formulation of coenzyme Q10 self-nano-emulsified tablet dissolution profile showed that 80-90% drug release took place in 45 minute. A.A. Attama et al formulated the solid self-emulsifying systems in the delivery of Diclofenac. This solid self emulsifying system was developed using goat fat and tween 65. The fatty material and surfactant were heated together to melt and added to weighed quantity of drug and drug was dissolved in the melt, this molten mass was then poured into plastic mould and cooled. These tablets will liquify at body temperature without agitation and at gastrointestinal conditions, agitation as peristaltic movement will lower the liquification time, resulting in faster emulsification with increased plasma concentration. Different formulation ratio shows varing dissolution profile at constant speed/agitation. These tablets showed good release profiles with acceptable tablet properties.

Self Emulsifying Pellets: C. Tuleu et al presented comparative bioavailability study in dogs of a self – emulsifying formulation of progesterone presented as in pellets and the liquid form was compared with an aqueous suspension of progesterone. The in vitro dissolution tests showed that nearly 100% of progesterone dissolved within 30 min and within 5 min from capsules containing the progesterone dissolved in self emulsifying system. From the aqueous suspension, 50% of the dose was released within 60 min. They also showed that pellets administered orally to dogs were tested versus the same dose of progesterone dissolved in liquid SES in capsules or a suspension of micronized progesterone. In that SES pellets and SES solution had higher plasma levels of progesterone at each time point as compared to the aqueous suspension of progesterone. E. Franceschinis et al developed a method of producing self-emulsifying pellets by wet granulation. Here they first developed a binder solution containing an oil (mono and diglycerides), polysorbate 80 and model drug nimesulide in different proportion. This oil surfactant mixture was stirred then added to water to form Self- emulsifying system. Second step was to prepare granules from microcrystalline cellulose and lactose in a granulator. These binder solutions were sprayed on to the granules and pellets were formed by increasing the speed of the granulator. Pellets were able to generate significantly smaller droplets with respect to corresponding emulsions. M. Serratoni et al presented controlled drug release from self-emulsifying pellets. The prepared self emulsifying systems were formed by mixing oil surfactant within solublised drug in appropriate concentrations, because higher quantity of drug incorporated into SES, could be precipitated when diluted with water. This SES was added into damp mass of microcrystalline cellulose and lactose monohydrate, water was then added to the prepared wet mass for extrusion-spheronization to form pellets. These pellets were coated by hydrophilic polymers namely ethyl cellulose then coated by aqueous.

Self Emulsifying Bead: Self emulsifying system can be formulated as a solid dosage form by using less excipient. Patil and Paradkar discovered that deposition of SES into microporous polystyrene beads was done by solvent evaporation. Porous polystyrene beads with complex internal void structures were typically produced by copolymerising styrene and divinyl benzene. It is inert and stable over a wide range of pH, temperature and humidity. Geometrical features, such as bead size and pore architecture of PPB, were found to govern the loading efficiency and in vitro drug release from SES-loaded PPB.

Self Emulsifying Microspheres: You et al. formulated solid SE sustained-release microspheres using the quasi-emulsion solvent diffusion method for the spherical crystallization technique. Zedoary turmeric oil release behaviour could be controlled by the ratio of hydroxypropyl methylcellulose acetate succinate to Aerosil 200 in the formulation. The plasma concentration time profiles were achieved after oral administration of such microspheres into rabbits, with a bioavailability of 135.6% with respect to the conventional liquid SEDDS.

Self Emulsifying Nanoparticle: Nanoparticle technology can be applied to the formulation of self emulsifying nanoparticle. One of the solvent was injection, in this method the prepared molten lipid mass contained lipid, surfactant and drug. This lipid molten mass was injected drop wise into a non solvent system. This is filtered and dried to get nanoparticles. By these method 100 nm size particles with 70-75% drug loading efficiency was obtained. Second technique is sonication emulsion diffusion evaporation; by this method co-load 5-flurouracil and antisense EGFR (epidermal growth factor receptor) plasmids into biodegradable PLGA/O-CMC nanoparticles. The mixture of PLGA (poly-lactide-coglycolide) and O-CMC (O-carboxmethyl-chitosan) had a self emulsifying effect, with no additional surfactant required.

Composition of Sedds [9]

SEDDS are composed of the following components-

Drug
Oil
Surfactant
Co-surfactant

A. Drug

For formulation into SEDDS the drug should have following characteristics:
It should have low dose.
It should have moderate half-life.
Bioavailability of the drug should be low.
Drugs undergoing extensive hepatic metabolism are good candidates.
Drug should have low water solubility (Preferably belongs to BCS Class II).
Drug should have sufficient lipophilicity & solubility in oil (i.e., higher log P value).

B. **Oils:**

It is the most important excipient because it can facilitate self-emulsification and increase the fraction of lipophillic drug transported via the intestinal lymphatic system, thereby increasing absorption from gastrointestinal tract. Medium chain triglycerides (Table1.3) like caprylic/capric di/triglycerides (Capryol, Capryol90, Labrafac, Capmer etc), Miglyol-812 are most often used. Long chain glycerides like castor oil, soyabean oil, olive oil, sesame oil, corn oil, peanut oil, hydrogenated vegetable oils can also be used. But they are not preferred due to their poor solubility for large number of lipophilic drugs. Novel semi-synthetic medium chain triglycerides have surfactant properties and are widely replacing regular medium chain triglycerides.

Table 3: List of various medium chain triglycerides with their chemical name

Sr. No	Medium chain triglyceride	Chemical Name
1	Capryol 90	Polyethylene glycol monocaprylate
2	Capryol PGMC	Polyethylene glycol caprylate
3	Labrafac PG	Polyethylene glycol dicaprylocaprate

C. Surfactants

Most commonly used surfactants for formulation of SEDDS or SMEDDS are water soluble, though by definition these materials can be used in type III or Type IV formulation HLB value of these surfactants is approximately 12 or higher. Several compounds exhibiting surfactant properties are employed for the design of self-emulsifying systems. The most widely recommended ones are being the non-ionic surfactants (Table 1.4) with a relatively high HLB value, which assists the immediate formation of o/w droplets and/or rapid spreading of formulation in the aqueous media and have relatively low toxicity. Emulsifiers from natural origin are not preferred as they have limited self-emulsification capacity. Polyethylene glycol ethers can also be used.

Table 4: List of various surfactants/Co-surfactants and their chemical names

S.No.	Surfactant/ Co-surfactant	Chemical Name
1	Cremophore EL	Polyoxyl 35 castor oil
2	Cremophore RH 40	Polyoxyl 40 hydrogenated castor oil
3	Cremophore RH 60	Polyoxyl 60 hydrogenated castor oil
4	Tween 20	Polysorbate 20
5	Tween 80	Polysorbate 80
6	Span 20	Sorbitan monooleate
7	Labrafil M 2125 CS	Polyoxyethylated linoleic glyceride
8	Labrafil M 1944 CS	Polyoxyethylated oleic glyceride
9	PEG 400 monostearate	Polyoxyl 8 stearate
10	PEG 1750 monostearate	Polyoxyl 40 stearate
11	Labrasol	Caprylocaproylmacrogol glyceride
12	Transcutol P	Diethylene glycol monoethyl ether

D. **Cosolvents**

The production of optimum SEDDS requires relatively high concentrations of surfactants. Organic solvents such as ethanol, propylene glycol, PEG400, glycerol etc, are suitable for oral delivery, and they enable the dissolution of large quantities of either the hydrophilic surfactant or the drug in the lipid base. These solvents can even act as cosurfactants.

Selection of Excipients [4]

Wide varieties of excipients are available by which a self-emulsifying system can be formulated, but selection of proper excipients is of paramount importance for development of an effective formulation. As a general rule the simplest effective formulation should be used, restricting the number of excipients used to a minimum[8].

Some of the factors which should be considered while selecting excipients are-

1. Self-dispersibility
2. Digestibility and fate of digested products
3. Capsule shell compatibility
4. Purity
5. Regulatory issues- irritancy, toxicity, etc.
6. Solvent capacity
7. Miscibility
8. Chemical stability
9. Cost

Advantages of Sedds

Improvement in oral bioavailability:

Dissolution rate dependant absorption is a major factor that limits the bioavailability of numerous poorly water soluble drugs. The ability of SMEDDS to present the drug to GIT in solubilised 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.[2]

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

Reduction in inter-subject and intra-subject variability and food effects: There are several drugs which show large inter-subject and intra-subject variation in absorption leading to decreased performance of drug and patient non-compliance. Food is a major factor affecting the therapeutic performance of the drug in the body. SMEDDS are a boon for such drugs. Several research papers specifying that, the performance of SMEDDS is independent of food and, SMEDDS offer reproducibility of plasma profile are available. [3]

Ability to deliver peptides that are prone to enzymatic hydrolysis in GIT : One unique property that makes SMEDDS superior as compared to the other drug delivery systems is their ability to deliver macromolecules like peptides, hormones, enzyme substrates and inhibitors and their ability to offer protection from enzymatic hydrolysis. The intestinal hydrolysis of prodrug by cholinesterase can be protected if Polysorbate 20 is emulsifier in micro emulsion formulation. [4] These systems are formed spontaneously without aid of energy or heating thus suitable for thermo labile drugs such as peptides. [5]

No influence of lipid digestion process: Unlike the other lipid-based drug delivery systems, the performance of SMEDDS is not influenced by the lipolysis, emulsification by the bile salts, action of pancreatic lipases and mixed micelle formation. SMEDDS are not necessarily digested before the drug is absorbed as they present the drug in 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 whencompared with conventional lipid solution as the solubility of poorly water soluble drugs with intermediate partition coefficient (2<log P>4) are typically low in natural lipids and much greater in amphilic surfactants, co surfactants and co-solvents.

Advantages of Sedds over Conventional DDS: [16]

- Upon mild agitation followed by dilution in aqueous media, such as gastrointestinal (GI) fluids, this system can form fine oil in water (o/w) emulsion or microemulsion (SMEDDS). Fine oil droplets would pass rapidly and promote wide distribution of the drug throughout the GI tract, thereby minimizing the irritation frequently encountered during extended contact between bulk drug substance and the gut wall.
- Emulsion are sensitive and metastable dispersed forms while S(M)EDDS are physically stable formulation that are easy to manufacture.
- As compared with oily solutions, they provide a large interfacial area for partitioning of the drug between oil and water.
- Thus for lipophilic drug compounds that exhibit dissolution rate limited absorption, this system may offer an improvement in the rate and extent of absorption and result in more reproducible blood time profiles.

Disadvantages of Smedds [14]

- Lipid-based formulations is the lack of good predicative *in vitro* models for assessment of the formulations.

- Traditional dissolution methods do not work, because these formulations potentially are dependent on digestion prior to release of the drug.
- This *in vitro* model needs further development and validation before its strength can be evaluated.
- Further development will be based on *in vitro - in vivo* correlations and therefore different prototype lipid based formulations needs to be developed and tested *in vivo* in a suitable animal model.
- The drawbacks of this system include chemical instabilities of drugs and high surfactant concentrations in formulations (approximately 30-60%) which irritate GIT.
- Moreover, volatile co-solvents in the conventional self-microemulsifying formulations are known to migrate into the shells of soft or hard gelatin capsules, resulting in the precipitation of the lipophilic drugs.
- The precipitation tendency of the drug on dilution may be higher due to the dilution effect of the hydrophilic solvent.
- Formulations containing several components become more challenging to validate.

Solidification Techniques For Transforming Liquid/Semisolid Smedds To S-Smedds [15]

Various solidification techniques are as listed below:

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: (i) heating of the semisolid excipient to at least 20˚C above its melting point; (ii) incorporation of the active substances (with stirring); (iii) capsule filling with the molten mixture and (iv) cooling to room temperature. For liquid formulations, it involves a two-step process: 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. The advantages of capsule filling are simplicity of manufacturing; suitability for low-dose highly potent drugs and high drug loading potential (up to 50% (w/w).

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) evaporates, forming dry particles under controlled temperature and airflow conditions. Such particles can be further prepared into tablets or capsules. The atomizer, the temperature, the most suitable airflow pattern and the drying chamber design are selected according to the drying characteristics of the product and powder specification.

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/SMEDDS can be adsorbed at high levels (up to 70% (w/w)) onto suitable carriers.

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.

Melt extrusion/extrusion spheronization

Melt extrusion is a solvent-free process that allows high drug loading (60%), as well as content uniformity. Extrusion is a procedure of converting a raw material with plastic properties into a product of uniform shape and density, by forcing it through a die under controlled temperature, product flow, and pressure conditions.

Routes of Administration

There are various potential routes for delivery of SEDDS which includes

- Oral Route
- Transdermal Route
- Parenteral Route
- Topical Route
- Intranasal Route
- Rectal Route

Characterization of Sedds [1,10]

The primary means of evaluating a SEDDS is the visual assessment. The efficiency of a self-emulsifying formulation can be estimated by determining the rate of emulsification and droplet size. Construction of phase diagrams help in identifying the self-emulsifying region and in determining the concentrations of various components. Zeta potential estimates the charge on oil droplets and is usually negative due to presence of free fatty acids.

The droplet size is a crucial factor in self-emulsification performance as it determines the rate and extent of drug release as well as absorption. Photon correlation spectroscopy is a useful method for determination of droplet size of an emulsion. It works on the principle that droplets in an emulsion undergo Brownian motion. This is the motion induced by bombardment by solvent molecules. If the molecules are illuminated with a laser light, the intensity of the scattered light fluctuates at a rate that is dependent upon the size of the particles. Analysis of these intensity fluctuations yields the velocity of the Brownian motion and hence, the particle size using the Stokes-Einstein relationship.

Evaluation [28]

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 (4^0C) and 45^0C 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 21^0C 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 millilitre 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, greyish 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.

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 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).

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.

Droplet Size Analysis Particle Size Measurements:

The droplet size of the emulsions is determined by photo 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. 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

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, then formulation have transparent nature.

Electro conductivity Study: The SEDD system contains ionic or non-ionic surfactant, oil, and water. So, this test is used to measure the electoconductive nature of system. The electro conductivity of resultant system is measured by electoconductometer.

In Vitro Diffusion Study: In vitro diffusion studies are performed to study the release behaviour of formulation from liquid crystalline phase around the droplet using dialysis technique

Drug content: Drug from pre-weighed SEDDS is extracted by dissolving in suitable solvent. Drug content in the solvent extract was analyzed by suitable analytical method against the standard solvent solution of drug.

Marketed Formulations of Sedds:

The successful commercialization of Sandimmune Neoral® generated a considerable interest in self-emulsifying drug delivery system. At present following products are available in market.

Table 5: List of marketed formulations of SEDDS

S. No.	Product Name	API	Dosage Form	Company
1	Gengraf®	Cyclosporine	Hardgelatin capsule	Abott Laboratories
2	Convulex®	Valproic acid	Soft gelatin capsule	Pharmacia
3	Targretin®	Bexarotene	Soft gelatin capsule	Ligand
4	Sandimmune Neoral®	Cyclosporine	Soft gelatin capsule	Novartis
5	Sandimmune®	Cyclosporine	Soft gelatin capsule	Novartis
6	Juvela®	Tocopherol nicotinate	Soft gelatin capsule	Eisai Co.
7	Fortovase®	Saquinavir	Soft gelatin capsule	Hoffman-La Roche
8	Agenerase®	Amprenavir	Soft gelatin capsule	Glaxosmithkline
9	Solufen®	Ibuprofen	Hard gelatin capsule	Sanofi-Aventis
10	Lipirex®	Fenofibrate	Hard gelatin capsule	Sanofi-Aventis

Future Trend[29]

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 (Fuji Chemicals) and Zeopharm (Huber) products for converting liquids into powders – which can then be processed into powder fill capsules or tablets. But to obtain solids with suitable processing properties, the ratio of SEDDS to solidifying excipients must be very high, which seems to be practically non-feasible for drugs having limited solubility in oil phase. In this regard, it was hypothesized that the amount of solidifying excipients required for transformation of SEDDS in solid dosage forms will be significantly reduced if SEDDS is gelled. Colloidal silicon dioxide (Aerosil 200) is selected as a gelling agent for the oil based systems, which may serve the dual purpose of reducing the amount of solidifying excipients required and aiding in slowing drug release.

Conclusion

Self-emulsifying drug delivery systems are substantially improved solubility/dissolution, absorption and bioavailability of poorly water-soluble compounds. Most importantly, Solid- SEDDS are very flexible to develop various solid dosage forms for oral and parenteral administration and GI irritation is avoidable and controlled and sustained release of drug of drug release is achievable.

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