

**SELF MICRO EMULSIFYING DRUG DELIVERY SYSTEM FOR IMPROVED
ORAL DELIVERY OF LIPOPHILIC DRUGS****JILL B. SHUKLA***

PhD Research Scholar, Departments of Pharmaceutics, Gujarat Technological University, Ahmedabad, Gujarat, India. 382424.

ABSTRACT

Oral route has always been preferred route for formulators and has dominated over other routes of administrations. This route is limited to those drugs molecule that are permeable across the gastric mucosa and are at least sparingly soluble. Approximately 40% of new chemical entities exhibit poor aqueous solubility and present a major challenge to modern drug delivery system, because of their low bioavailability. Some examples of marketed lipid based formulations are Sand immune Neoral (Cyclosporine A), Novartis Pvt. Ltd. and Fortovase (Saquinavir), Roche Laboratories Inc. with much attention focused on self micro-emulsifying drug delivery systems (SMEDDS). Self microemulsifying drug delivery systems are isotropic mixtures of oil, surfactant, co-surfactant and drug with a unique ability to form fine oil in water microemulsion upon mild agitation following dilution with aqueous phase. This article gives a complete overview of SMEDDS as a promising approach to effectively tackle the problem of poorly soluble molecules.

KEYWORDS: Self microemulsifying drug delivery system, Oral bioavailability, Lipid based formulations, Poorly water soluble drugs

**JILL B. SHUKLA**PhD Research Scholar, Departments of Pharmaceutics, Gujarat Technological University,
Ahmedabad, Gujarat, India. 382424.

* Corresponding author

INTRODUCTION

Self microemulsifying drug delivery system (SMEDDS) are defined as isotropic mixtures of natural or synthetic oils, solid or liquid surfactants, or alternatively, one or more hydrophilic solvents and co-solvents/surfactants that have a unique ability of forming fine oil-in-water (o/w) micro emulsions upon mild agitation followed by dilution in aqueous media, such as GI fluids. ¹ SMEDDS spread readily in the GI tract, and the digestive motility of the stomach and the intestine provide the agitation necessary for self-emulsification. The basic difference between self emulsifying drug delivery systems (SEDDS) also called as self emulsifying oil formulation (SEOF) and SMEDDS is SEDDS typically produce opaque emulsions with a droplet size between 100 and 300 nm while SMEDDS form transparent micro emulsions with a droplet size of less than 50 nm also the concentration of oil in SMEDDS is less than 20 % as compared to 40-80% in SEDDS. When compared with emulsions, which are sensitive and metastable dispersed forms, SMEDDS are physically stable formulations that are easy to manufacture. 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. SMEDDS formulation is in theory, comparatively simple. The key step is to find a suitable oil surfactant mixture that can dissolve the drug within the required therapeutic concentration. The SMEDDS mixture can be filled in either soft or hard gelatin capsules. A typical SMEDDS formulation contains oils, surfactants and if required an antioxidants. Often co-surfactants and co-solvents are added to improve the formulation characteristics.

ADVANTAGES OF SMEDDS

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, liposome, 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 when compared with conventional lipid solution as the solubility of poorly water soluble drugs with intermediate partition coefficient ($2 < \log P < 4$) are typically low in natural lipids and much greater in amphiphilic surfactants, co surfactants and co-solvents.

ADVANTAGES OF SMEDDS OVER EMULSION

SMEDDS not only offer the same advantages of emulsions of facilitating the solubility of hydrophobic drugs, but also overcomes the drawback of the layering of emulsions after sitting for a long time. SMEDDS can be easily stored since it belongs to a thermodynamically stable system. Microemulsions formed by the SMEDDS exhibit good thermodynamic stability and optical transparency. The major difference between the above microemulsions and common emulsions lies in the particle size of droplets. The size of the droplets of common emulsion ranges between 0.2 and 10 μm , and that of the droplets of microemulsion formed by the SMEDDS generally ranges between 2 and 100 nm (such droplets are called droplets of nano particles). Since the particle size is small, the total surface area for absorption and dispersion is significantly larger than that of solid dosage form and it can easily penetrate the gastrointestinal tract and be absorbed. The bioavailability of the drug is therefore improved. SMEDDS

offer numerous delivery options like filled hard gelatin capsules or soft gelatin capsules or can be formulated in to tablets whereas emulsions can only be given as an oral solutions.

DISADVANTAGES OF SMEDDS

- One of the obstacles for the development of SMEDDS and other 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-micro emulsifying 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.

EXCIPIENTS USED IN SMEDDS

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-microemulsification 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-microemulsification occurs. These important discoveries were further supported by the fact that only very specific combinations of pharmaceutical excipients led to efficient self-microemulsifying systems.

OILS

The oil represents one of the most important excipients in the SMEDDS 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.⁶ 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. Furthermore, edible oils which could represent the logical and preferred lipid excipients

choice for the development of SMEDDS are not frequently selected due to their poor ability to dissolve large amounts of lipophilic drugs. Modified or hydrolyzed vegetable oils have been 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.⁷ They offer formulative and physiological advantages and their degradative products resemble the natural end products of intestinal digestion. Novel semisynthetic medium chain derivatives, which can be defined as amphiphilic compounds with surfactant properties, are progressively and effectively replacing the regular medium chain triglyceride oils in the SMEDDS.⁸ This is in accordance with findings of Deckelbaum (1990) showing that MCT is 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 was required to form microemulsions compared with MCT.

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). The commonly used emulsifiers are various solid or liquid ethoxylated polyglycolized glycerides and polyoxyethylene 20 oleate. Safety is a major determining factor in choosing a surfactant. Emulsifiers of natural origin are preferred since they are considered to be safer than the synthetic surfactants.⁶ However, these surfactants have a limited self-emulsification capacity. Non-ionic surfactants are less toxic than ionic surfactants but they may lead to reversible changes in the permeability of the intestinal lumen.⁸ The lipid mixtures with higher surfactant and co-surfactant/oil ratios lead to the formation of SMEDDS.⁹ There is a relationship between the droplet size and the concentration of the surfactant being used. In some cases, increasing the surfactant concentration could lead to droplets with smaller mean droplet size, this could be explained by the stabilization of the oil droplets as a result of the localization of the surfactant molecules at the oil-water interface.¹⁰ On the other hand, in some cases the mean droplet size may increase with increasing surfactant concentrations.¹¹ 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. Formulation effect and surfactant concentration on gastrointestinal mucosa should ideally

be investigated in each case. Surfactant molecules may be classified based on the nature of the hydrophilic group within the molecule. The four main groups of surfactants are defined as follows,

1. Anionic surfactants
2. Cationic surfactants
3. Ampholytic surfactants
4. Nonionic surfactants

1. Anionic Surfactants: where the hydrophilic group carries a negative charge such as carboxyl (RCOO^-), sulphonate (RSO_3^-) or sulphate (ROSO_3^-). Examples: Potassium laurate, sodium lauryl sulphate.
2. Cationic surfactants: where the hydrophilic group carries a positive charge. Example: quaternary ammonium halide.
3. Ampholytic surfactants (also called zwitterionic surfactants) contain both a negative and a positive charge. Example: sulfobetaines.
4. Nonionic surfactants, where the hydrophilic group carries no charge but derives its water solubility from highly polar groups such as hydroxyl or polyoxyethylene ($\text{OCH}_2\text{CH}_2\text{O}$). Examples: Sorbitan esters (Spans), polysorbates (Tweens).

CO-SOLVENTS

The production of an optimum SMEDDS 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. 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 microemulsion. 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 SMEDDS, but also to solubilization of the drug in the SMEDDS. 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 microemulsions have also been described in the literature. Indeed, such systems may exhibit some advantages over the previous 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.

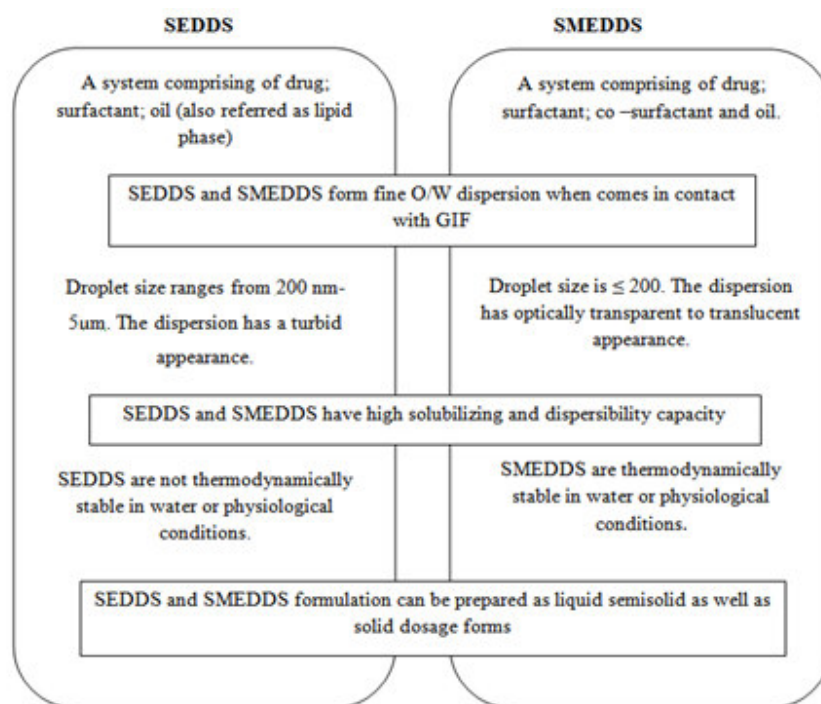


Figure 1
Schematic diagram of SEDDS and SMEDDS formulation

Table: 1
Relative bioavailability of lipid based formulation of hydrophobic drugs

Drug name	Species tested	Test product Formulation	Reference Product Formulation	Increase in bioavailability
Vitamin E	Human	Tween 80, Span 80 and Vitamin E dissolved in palm oil in the proportion 4:2:4 to form SEDDS	Natophenol soft gelatin capsules	2 fold
Cyclosporin	Human	SMEDDS, Nerol soft gelatin Capsules	SEDDS, Sand immune soft gelatin capsules	6.5 fold
Ontazolast	Rats	SEDDS, 8:2 mix of Gelucire 44/14 and Peceol	Aqueous suspension, Tween 80 + HPMC	13 fold
Atorvastatin	Dogs	SMEDDS, Labrafil, Camphor RH 40, Propylene glycol	Lipitor tablets 10 mg	1.5 fold

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.

(a) Mechanism of Self Emulsification

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

$$\Delta G = \sum N_i \pi r_i$$

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) in n-hexane. 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 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 self-emulsification. 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.

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.

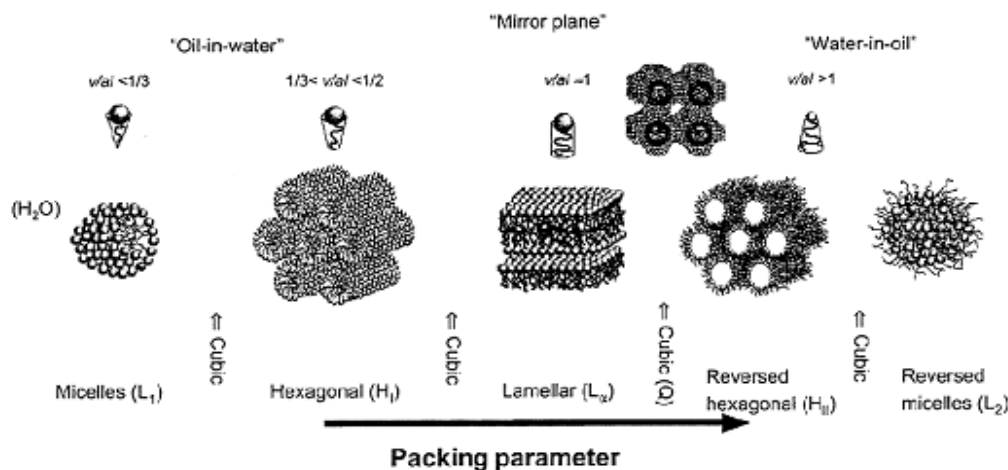


Figure 2

Representation of the most commonly encountered phases upon addition of water to an oil-surfactant combination (from Jonsson 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 times¹³. 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 release¹³. This can be explained by the fact that a layer of liquid crystalline material surrounds the oil droplets, affecting drug dissolution and formulation digestion. Some examples are shown in table 2;

Table 2
Examples of SEDDS for oral delivery of lipophilic drugs

Type of delivery system	Oil	Surfactant(s)	%w/w	Solvent(s)	Drug compound	Drug content
SEDDS (Sandimmune)	Olive oil	Polyglycolized glycerides	30	Ethanol	CsA	10
SEDDS (positively charged)	Ethyl oleate	Tween 80	25	Ethanol	CsA	10
SEDDS (Norvir)	Oleic acid	Polyoxyl 35 castor oil	NA	Ethanol	Ritonavir	8
SEDDS (Fortovase)	dl-alpha tocopherol	Medium chain mono-and diglycerides	NA	-	Saquinavir	16

➤ FACTORS AFFECTING SMEDDS

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. The ability of SMEDDS to maintain the drug in solubilised form is greatly influenced by the solubility of the drug in oil phase. As mentioned above 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. Equilibrium solubility measurements can be carried out to anticipate potential cases of precipitation in the gut. However, crystallization could be slow in the solubilising and colloidal stabilizing environment of the gut. Pouton's study reveal that such formulations can take up to five days to

reach equilibrium and that the drug can remain in a supersaturated state for up to 24 hours after the initial emulsification event. It could thus be argued that such products are not likely to cause precipitation of the drug in the gut before the drug is absorbed, and indeed that super-saturation could actually enhance absorption by increasing the thermodynamic activity of the drug. There is a clear need for practical methods to predict the fate of drugs after the dispersion of lipid systems in the gastrointestinal tract.

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 for their propensity to inhibit crystallization and, thereby, generate and maintain the supersaturated state for prolonged time periods.¹⁴ A supersaturable self-microemulsifying drug delivery system

(S-SMEDDS) of paclitaxel was developed employing HPMC as a precipitation inhibitor with a conventional SMEDDS formulation. *In-vitro* dilution of the S-SMEDDS formulation resulted in formation of a microemulsion, followed by slow crystallization of paclitaxel on standing. This result indicated that the system was supersaturated with respect to crystalline paclitaxel, and the supersaturated state was prolonged by HPMC in the formulation. In the absence of HPMC, the SMEDDS formulation underwent rapid precipitation, yielding a low paclitaxel solution concentration. A pharmacokinetic study showed that the paclitaxel S-SMEDDS formulation produced approximately a 10-fold higher maximum concentration (C_{max}) and a 5-fold higher oral bioavailability ($F \sim 9.5\%$) compared with that of the orally administered Taxol formulation ($F \sim 2.0\%$) and the SMEDDS formulation without HPMC ($F \sim 1\%$). Applying the supersaturable SMEDDS approach, a reduced amount of surfactant can be used with HPMC in order to produce a temporarily supersaturated state with reduced solubilization. Thus a high free drug concentration would be obtained through generating and maintaining a supersaturated state *in vivo* and to increase the driving force for absorption.¹⁴ It is worth emphasizing that the significantly reduced amount of surfactant used in the S-SMEDDS formulation approach provides a better toxicity/safety profile than the conventional SMEDDS formulations. However, the underlying mechanism of the inhibited crystal growth and stabilized super saturation by means of these polymers is poorly understood even although several studies have been carried out to investigate this.¹⁴

BIOPHARMACEUTICAL ASPECTS

The ability of lipids and/or food to enhance the bioavailability of poorly water-soluble drugs is well known. Although incompletely understood, the currently accepted view is that lipids may enhance bioavailability via a number of potential mechanisms, including.^{14,31}

- a) Alterations (reduction) in gastric transit, thereby slowing delivery to the absorption site and increasing the time available for dissolution.¹⁵
- b) 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 solubilization 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 solubilization capacity.¹⁵
- c) 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. A hydrophilic drug is less likely to be absorbed through the lymphatic (chylomicron) and instead may diffuse directly in to the portal supply. Hence in this case,

increased dissolution from the large surface area afforded by emulsion may be a contributing factor to enhanced absorption of drugs.¹⁶

- d) 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 thus reduce the extent of enterocyte-based metabolism.¹⁶
- e) 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.¹⁶ 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.

➤ INFLUENCE OF SELF-MICROEMULSIFYING LIPID-BASED FORMULATIONS ON FOOD EFFECT

Increased drug exposure, relative to the fasted state, following postprandial administration of poorly water-soluble drugs in conventional solid formulations is well documented in the literature [e.g., isotretinoin¹⁷; danazol (43, 52, and 53); L- 683,453 (54); DPC 961¹⁸; halofantrine¹⁹. It has been postulated that the magnitude of the exposure increase may indicate the maximum extent of absorption possible when the drug is administered in a lipid-based formulation²⁰. The effect of food on the bioavailability of poorly water-soluble, hydrophobic drugs is determined by multiple factors, including the physicochemical properties of the drug substance, the dose, the nature of the formulation and the amount and composition of the ingested food²¹. Postprandial changes in the GIT that can increase drug absorption, relative to the fasted state, include: (i) increased drug solubilization by bile salt mixed micelles and (ii) increased intestinal membrane permeability secondary to the presence of bile and lipid digestion products. Since food effect can lead to exaggerated pharmacologic responses or unexpected toxicity²¹, clinical trial guidelines routinely require studies comparing drug exposure in fed and fasted subjects. Although limited in number, studies showing the efficacy of self-emulsifying lipid-based formulations for mitigating food effect have been described in the literature. Grove et al.²² studied the influence of food on the bioavailability of seocalcitol in minipigs following administration as either a solution in MCT, a MC-SMEDDS, or a solution in propylene glycol (PG). The fasted state bioavailability of seocalcitol was 15%, 21% and 28% for the PG, MCT and MC-SMEDDS formulations, respectively. In the postprandial state, the seocalcitol bioavailability from the PG solution nearly doubled to 29%, but was unchanged, relative to the fasted state, for both the MCT and MC-SMEDDS formulations. These results suggest a common mechanism by which food and lipid-based formulations improve the absorption of poorly soluble drugs. Other poorly soluble drugs for which lipid-based formulations have reduced the effect of food on drug absorption include danazol²³ and L-683,453 and cyclosporine.²⁴

➤ **Some examples of marketed Pharmaceutical SEDDS formulations are as shown below**

Table 3
Examples of marketed SEDDS formulations²⁵

Drug Name	Compound	Dosage form	Company	Indication
Norvir®	Ritonavir	Soft gelatin capsule	Abbott Laboratories	HIV antiviral
Fortovase®	Saquinavir	Soft gelatin capsule	Hoffmann-La Roche inc.	HIV antiviral
Agenerase®	Amprenavir	Soft gelatin capsule	Glaxo Smithkline	HIV antiviral
Gengraf®	Cyclosporine A/III	Hard gelatin Capsule	Abbott Laboratories	Immuno suppressant

Various patents for SEDDS and SMEDDS formulations are as shown in table below;

Table 4
Patents for SEDDS and SMEDDS

Sr. no.	Approaches	Patent Number	Claim
1.	Self microemulsions As Solid Dosage Forms For Oral Administration. ²⁹	US2000009093 Assignee: Cima Labs Inc, USA	To form a free flowing and compressible powder comprising an admixture of drug containing SMEDDS and solid particle adsorbents.
2.	Self-Microemulsifying Drug Delivery Systems. ³⁰	US2008077823 Assignee: Lek Pharmaceuticals D.D	To enhance the solubility of pharmaceutical ingredients comprising a polyoxyethylene sorbitan fatty acid ester emulsifier; a fatty acid ester co-emulsifier and an oil.

➤ **SOLID SELF-MICROEMULSIFYING DRUG DELIVERY SYSTEM (S-SMEDDS)**

SMEDDS can exist in either liquid or solid states. SMEDDS are usually, limited to liquid dosage forms, because many excipients used in SMEDDS are not solids at room temperature. Given the advantages of solid dosage forms, S-SMEDDS have been extensively exploited in recent years, as they frequently represent more effective alternatives to conventional liquid SMEDDS. From the perspective of dosage forms, S-SMEDDS mean solid dosage forms with self-emulsification properties. S-SMEDDS focus on the incorporation of liquid/semisolid SE ingredients into powders/ nanoparticles by different solidification techniques (e.g. adsorptions to solid carriers, spray drying, melt extrusion, nanoparticles technology, and so on). Such powders/nanoparticles, which refer to SE nanoparticles/dry emulsions/solid dispersions are usually further processed into other solid SE dosage forms, or, alternatively, filled into capsules (i.e. SE capsules). SE capsules also include those capsules into which liquid/semisolid SEDDS are directly filled without any solidifying excipient.^{31, 32, 35} To some extent, S-SMEDDS are combinations of SMEDDS and solid dosage forms, so many properties of S-SMEDDS (e.g. excipients selection, specificity, and characterization) are the sum of the corresponding properties of both SMEDDS and solid dosage forms. For instance, the characterizations of SE pellets contain not only the assessment of self-emulsification, but also friability, surface roughness, and so on.

➤ **SOLIDIFICATION TECHNIQUES FOR TRANSFORMING LIQUID/SEMISOLID SMEDDS TO S-SMEDDS**

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.²⁷ 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.³⁵

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.³³

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 'one-step' 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.

DOSAGE FORM DEVELOPMENT OF S-SMEDDS

Various dosage forms of S-SMEDDS are as listed below;

- Dry emulsions
- Self-emulsifying capsules
- Self-emulsifying sustained/controlled-release tablets
- Self-emulsifying sustained/controlled-release pellets
- Self-emulsifying solid dispersions
- Self-emulsifying beads
- Self-emulsifying sustained-release microspheres
- Self-emulsifying nanoparticles
- Self-emulsifying suppositories
- Self-emulsifying implant

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