



A Systemic Review on the Self Micro Emulsifying Drug Delivery System

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ABSTRACT

Comfort direction and painless method made oral route the most favored. Mainstream of recent active constituents have less oral bioavailability because of dissolution rate limited absorption. While many inventive methods like complexation, cocrystals exist, solid dispersions, pH modification and, lipid-based delivery systems conclusively improved appliance with the seeming rise in drug absorption. Among lipid-based formulations, self-micro emulsifying formulations (SMEDDS) (droplet size < 100 nm) are evident to enhance permeation across intestinal membrane, protection of drug against gastric effect, unit dosage is possible, increased bioavailability of drug, reduces the dose of drug etc. Numerous components are used to formulate these dosage forms like Oil, surfactants, Co-surfactant and lipids mixture contribute to the enhancement in oral bioavailability through promoting the lymphatic passage; thus, hepatic first pass metabolism can be overcoming. The present review highlights comprehensive information on the formulation design, probable mechanisms and characterization of SMEDDS.

Keywords: Self Microemulsion, Bioavailability, Solubility, Lipid based formulation.

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INTRODUCTION

Approximately 40% of new drug candidates have poor water solubility and the oral delivery of such drugs is frequently associated with low bioavailability, high intra- and inter- subject variability, and a lack of dose proportionality.¹ To overcome these problems, various formulation strategies are exploited including the use of surfactants, lipids, permeation enhancers, micronization, salt formation, cyclodextrins, nanoparticles and solid dispersions¹. Recently, much attention has been paid to lipid-based formulations with particular emphasis on self-emulsifying drug delivery systems (SEDDS) to improve the oral bioavailability of lipophilic drugs.^{2,3} SEDDS or self-emulsifying oil formulations (SEOF) 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.⁴ Upon mild agitation followed by dilution in aqueous media, such as gastrointestinal (GI) fluids, these systems can form fine oil-in-water (o/w) emulsions or microemulsions or Self-micro emulsifying drug delivery system (SMEDDS). Fine oil droplets would pass rapidly from the stomach and promote wide distribution of the drug throughout the GI tract, thereby

minimizing the irritation frequently encountered during extended contact between bulk drug substances and the gut wall. When compared with emulsions, which are sensitive and metastable dispersed forms, SMEDDS are physically stable formulations that are easy to manufacture. An additional advantage of SMEDDS over simple oily solutions is that they provide a large interfacial area for partitioning of the drug between oil and water. Different formulation approaches like micronization, solid dispersion, and complexation with cyclodextrins have come up for the poorly water-soluble drugs.⁵ Indeed, in some selected cases, these approaches have been successful but they offer many other disadvantages. The main problem with micronization is chemical / thermal stability. Many drugs may degrade and lose bioactivity when they are micronized by conventional method. For solid dispersion the number of carriers used is often large, and thus if the dose of active ingredient is high, the tablets or capsules formed will be large in volume and difficult to swallow. Moreover, since the carriers used are usually expensive and freeze-drying or spray- drying method requires particular facilities and processes, leading to high production cost. Though, traditional solvent method can be adopted instead, it is difficult to deal with co-precipitates with high viscosity. Complexation with cyclodextrins techniques is not applicable for drug substances which are not soluble in both aqueous and organic solvents. Realization that the oral bioavailability of poor water-soluble drugs may be enhanced when co-administered with meal rich in fat has led to increasing recent interest in the formulation of poorly water-soluble drugs in lipids. Lipid suspension, solutions and emulsions have all been used to enhance the oral bioavailability but,



more recently there have been much focus on the utility of self-micro emulsifying drug delivery systems (SMEDDS).⁶

Lipid Formulation Classification System

The different lipid drug delivery systems available include lipid solution, lipid emulsion, microemulsion, dry emulsion. To get a clear picture of all these different systems and due to large number of possible excipient combinations that may be used to assemble these lipid-based formulations, self-emulsifying systems in particular a classification system have been established called as lipid formulation

classification system (LFCS). This classification helps to better understand the fate of different lipid formulation *in vivo*, it also helps to use a systematic & rational formulation approach avoid —trial-and-error|| iterations and provide framework to guide regulatory agencies. LFCS was established by Pouton in 2000 and recently updated.⁷ The LFCS briefly classifies lipid-based formulations into four types according to their composition and the possible effect of dilution and digestion on their ability to prevent drug precipitation, as shown in Table 1.

Table 1: Compositions of lipid-based formulation

Composition	Type I	Type II	Type III		Type IV
	Oil	SEDDS	III A SEDDS	III B SMEDDS	Oil-Free
Glycerides (TG, DG, MG)	100%	40-80%	40-80%	< 20%	-
Surfactants (HLB < 12)	-	20-60%	-	-	0-20%
(HLB > 12)	-	-	20-40%	20-50%	20- 80%
Hydrophilic co-solvents	-	-	0-40%	20-50%	0-80%
Particle size of dispersion(nm)	Coarse	100-250	100-250	50-100	< 50

Type I Systems consist of formulations which comprise drug in solution in triglycerides and/or mixed glycerides or in oil-in-water emulsion stabilized by low concentrations of emulsifiers such as 1% (w/v) polysorbate 60 and 1.2% (w/v) lecithin. Generally, these systems exhibit poor initial aqueous dispersion and require digestion by pancreatic lipase/ co - lipase in the GIT to generate more

amphiphilic lipid digestion products and promote drug transfer into the colloidal aqueous phase. Type I lipid formulations therefore represent a relatively simple formulation option for potent drugs or highly lipophilic compounds where drug solubility in oil is sufficient to allow incorporation of the required payload (dose).

Table 2: Typical properties of Type I, II, III and IV lipid formulations

Formulation Type	Materials	Characteristics	Advantages	Disadvantages
Type I	Oils without surfactants (e.g. tri-, di-and monoglycerides)	Non-dispersing, requires digestion	Generally recognized as safe (GRAS) status; simple; excellent capsule Compatibility	Formulation has poor solvent capacity unless drug is highly lipophilic
Type II	Oils and water-insoluble surfactants	SEDDS formed without water-soluble Components	Unlikely to lose solvent capacity on dispersion	Turbid o/w dispersion (particle size 0.25–2 μm)
Type III	Oils, surfactants, cosolvents (both water-insoluble and water-soluble excipients)	SEDDS/SMEDDS formed with water-soluble components	Clear or almost clear dispersion; drug Absorption without digestion	Possible loss of solvent capacity on dispersion. less easily digested
Type IV	Water-soluble surfactants and cosolvents (no oils)	Formulation disperses typically to form a micellar solution	Formulation has good solvent capacity for many drugs	Likely loss of solvent capacity on dispersion; may not be digestible

Type II lipid formulations constitute SEDDS. Self-emulsification is generally obtained at surfactant contents above 25% (w/w). However, at higher surfactant contents (greater than 50–60% (w/w) depending on the materials) the progress of emulsification may be compromised by the formation of viscous liquid crystalline gels at the oil/water interface. Type II lipid-based formulations provide the

advantage of overcoming the slow dissolution step typically observed with solid dosage forms and as described above generate large interfacial areas which in turn allows efficient partitioning of drug between the oil droplets and the aqueous phase from where absorption occurs.^{8,9}



Type III lipid-based formulations, commonly referred to as self-micro emulsifying drug delivery systems (SMEDDS), are defined by the inclusion of hydrophilic surfactants (HLB>12) and co-solvents such as ethanol, propylene glycol and polyethylene glycol. Type III formulations can be further segregated (somewhat arbitrarily) into Type IIIA and Type IIIB formulations in order to identify more hydrophilic systems (Type IIIB) where the content of hydrophilic surfactants and co-solvents increases and the lipid content reduces. Type IIIB formulations typically achieve greater dispersion rates when compared with Type IIIA although the risk of drug precipitation on dispersion of the formulation is higher given the lower lipid content.¹⁰

Type IV

In order to capture the recent trend towards formulations which contain predominantly hydrophilic surfactants and co-solvents, this category was recently added. Type IV formulations do not contain natural lipids and represent the most hydrophilic formulations. These formulations commonly offer increased drug payloads when compared to formulations containing simple glyceride lipids and also produce very fine dispersions when introduced in aqueous media. Little is known however, as to the solubilization capacity of these systems *in vivo* and in particular whether they are equally capable of maintaining poorly water-soluble drug in solution during passage along the GIT when compared with formulations comprising natural oils (Type II and Type III). An example of a Type IV formulation is the current capsule formulation of the HIV protease inhibitor amprenavir (Agenerase) which contains TPGS as a surfactant and PEG 400 and propylene glycol as co-solvents.¹¹

Biopharmaceutical Classification System (BCS)

Biopharmaceutics Classification System (BCS) was introduced in 1995 as a basis for predicting the likelihood of *In vitro-In vivo* correlations for immediate release dosage forms, based on the recognition that drug solubility/dissolution properties and gastrointestinal permeability are the fundamental parameters controlling the rate and extent of drug absorption. According to BCS, drug substances are classified as, shown in Table 3.

Table 3: BCS classification

Class I	High solubility High permeability
Class II	Low solubility High permeability
Class III	High solubility Low permeability
Class IV	Low solubility Low permeability

The FDA has set specifications regarding the solubility and permeability class boundaries used for this BCS classification.

Solubility

A drug substance is considered highly soluble when the highest dose strength is soluble in 250 ml or less of aqueous media over a pH range of 1 to 7.5 (equilibrium solubility at 37°C).

Permeability

In the absence of evidence suggesting instability in the gastrointestinal tract, a drug substance is considered highly permeable when the extent of absorption in humans is determined to be 90% or more of an administered dose based on mass balance determination or in comparison to an intravenous reference dose (absolute bioavailability study).

Self-Micro Emulsifying Drug Delivery Systems

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) microemulsions upon mild agitation followed by dilution in aqueous media, such as GI fluids.¹¹ 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 100 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 which 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. 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 dependent 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 solubilized 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 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.¹²

Ease of manufacture and scale-up

Ease of manufacture and scale-up is one of the most important advantage that makes 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.¹³

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.¹³

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.¹⁴ These systems are formed spontaneously without aid of energy or heating thus suitable for thermolabile drugs such as peptides.¹⁵

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.¹⁵

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.¹⁵

Advantages of SMEDDS over Emulsion¹⁵

SMEDDS not only offers the same advantages of emulsions of facilitating the solubility of hydrophobic drugs, but also overcomes the drawback of the creaming of emulsions after long time. SMEDDS can be easily stored since it belongs to a thermodynamically stable system.

Microemulsions formed by the SMEDDS exhibit good thermodynamics 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.

Excipients Used In SMEDDS^{16,17}

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-micro emulsification process is specific to the nature of the oil/surfactant pair, the surfactant concentration and oil/surfactant ratio, the concentration and nature of co-surfactant and surfactant/co-surfactant ratio and the temperature at which self-micro emulsification occurs. These important discoveries were further supported by the fact that only very specific combinations of pharmaceutical excipients led to efficient self-micro emulsifying 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 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. 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 excipient 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. They offer formulative and physiological advantages and their degradation 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. This is in accordance with findings of Deckelbaum 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 (Tween 80). 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. 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. Usually the surfactant concentration ranges between 30 and 60% w/w in order to form stable SMEDDS. It is very important to determine the surfactant concentration properly as large amounts of surfactants may cause GI irritation. Surfactants are amphiphilic in nature and they can dissolve or solubilize relatively high amounts of hydrophobic drug compounds. The lipid mixtures with higher surfactant and co-surfactant/oil ratios lead to the formation of SMEDDS. 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 on the other hand, in some cases 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. Formulation effect and surfactant concentration on gastrointestinal mucosa should ideally be investigated in each case.

Co-Solvents

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

Mechanism of SMEDDS

The Self 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

In emulsification process the free energy (ΔG) associated is given by the equation: $\Delta G = \sum N_i \pi r_i^2$, In which N_i is Number of droplets with radius r_i and π 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 ethoxylate (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.¹⁸ 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.¹⁸

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 (Fig. 1).¹⁸

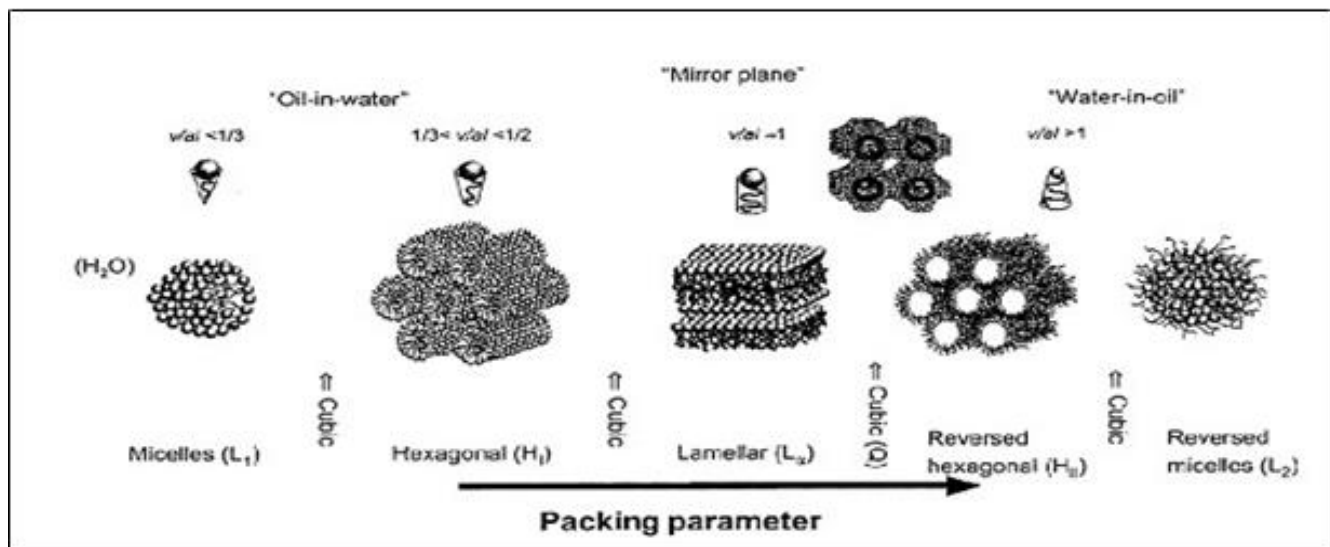


Figure 1: Representation of the most commonly encountered phases upon addition of water to an oil-surfactant combination

Many roles have been described 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.¹⁹ 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. 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 4;

Table 4: 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	A mixture of mono- and di- glycerides of oleic acid	Solid, polyglycolyzed mono-di and triglycerides, Tween 80	80 or 20	-	Ontazolast	7.5
SEDDS (Sandimmune)	Olive oil	Polyglycolyzed glycerides	30	Ethanol	CsA	10
SEDDS (positively charged)	Ethyl oleate	Tween 80	25	Ethanol	CsA	10
SEDDS (positively charged)	Ethyl oleate	Tween 80	25	Ethanol	Progesterone	2.5
SEDDS	Myvacet 9- 45 or captex 200	Labrasol or Labrafac CM10	5-30 0-25	-	CoQ10	5.66
SEDDS(Norvir)	Oleic acid	Polyoxyl 35, castor oil	NA	Ethanol	Ritonavir	8
SEDDS (Fortovase)	dl-alpha tocopherol	Medium chain mono-and diglycerides	NA	-	Saquinquir	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 super-saturated 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 gastro-intestinal tract.²⁰

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.²⁰ 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 ~ 9.5%) compared with that of the orally administered Taxol formulation (F~2.0%) and the SMEDDS formulation without HPMC (F ~ 1%).²⁰

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. a) Alterations (reduction) in gastric transit, thereby slowing delivery to the absorption site and increasing the time available for dissolution.²¹ 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.²¹ 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. [20] 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. 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. 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.²⁰

Susceptibility to Digestion

The well-known positive effect of food on the bioavailability of many poorly water-soluble drugs is often ascribed to the ingested lipid and points to the beneficial role of lipids on drug absorption. Although the form, content and volume of dietary lipids is markedly different to oil phases included in a pharmaceutical formulation, possible food effects on drug bioavailability can be a starting point for the design of lipid self-emulsifying formulations for such drugs. The presence of lipids in the GI tract increases drug solubilization and thus drug

dissolution via a number of potential mechanisms. SMEDDS increased secretion of bile salts and endogenous biliary lipids, intercalation of administered lipids into bile salt structures, directly or after digestion, reduced gastric transit time, resulting in an increased dissolution time, Changes of the physical and biochemical barrier function of the intestinal tract. Various lipid digestion products and surfactants show permeability enhancing properties and/or alternate the activity of intestinal efflux transporters. The co-administration of drugs with lipids can also have an effect on their absorption path.

In-Vitro Characterization of SEDDS/SMEDDS

Pouton classified lipid-based formulations into three categories based on the polarity of the excipient blends (Table 5). Due to their relative simplicity Type I formulations, which are simple solutions of the drug in triglycerides and/or mixed glycerides, are a reasonable starting point in the search for a lipid-based formulation. Type II formulations that add a lipophilic surfactant (HLB 12), are employed when SEDDS and greater drug solubilizing capacity is desired in a formulation. Type III formulations include the further addition of hydrophilic surfactants (HLB -12) and co solvents to further improve the self-emulsification process in the GIT, thereby yielding a SMEDDS formulation. Type III formulations are further subdivided into Types IIIA and IIIB, where Type IIIB contains a greater ratio of hydrophilic to lipophilic components than the former. While Type IIIB formulations are associated with more facile self-emulsification and smaller lipid droplet size than Type IIIA, they carry a greater risk of drug precipitation as the hydrophilic components may separate from the oil phase during dispersion in the GIT leading to a loss of drug-solubilizing capacity.²²

Table 5: Classification of Lipid Based Formulations

INCREASING HYDROPHILIC CONTENT				
Composition (%)	Type I	Type II	Type III	Type IV
Triglycerides or mixed glycerides	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
<i>In vivo</i> performance Particle size of dispersion (nm)	Coarse	100–250	100–250	50–100
Significance of aqueous dilution	Limited importance	Solvent capacity unaffected	Some loss of solvent capacity	Significant phase changes and potential loss of solvent capacity
Significance of digestibility	Crucial requirement	Not crucial but likely to occur	Not crucial but likely to inhibited	Not required and not likely occur

Excipient combinations yielding SEDDS/SMEDDS formulations are identified by construction of ternary phase diagrams. Each point in the phase diagram represents a given combination of oil, surfactant, and co

surfactant. In instances where combinations of more than three excipients must be tested, a fixed ratio between two of the excipients (e.g., the surfactant and co surfactant) is selected and treated as a single component. As a practical



example, mixtures consisting of different amounts of the selected excipients are evaluated for their self-emulsifying properties by the addition of pharmaceutically relevant amounts of the formulation to 250mL of water or a biorelevant, simulated physiological fluid. The resulting dispersion is examined by direct visualization and by dynamic light scattering to accurately determine the lipid droplet size, thereby allowing classification of the formulation as a SEDDS or SMEDDS. The number of combinations of drug and excipients resulting in a microemulsion, which is typically small, defines the microemulsion existence field on the ternary phase diagram: the area enclosed in the broken line in Figure 1.3 represents the microemulsion existence field for various combinations of medium chain triglycerides (MCT) or LCT, Cremophor RH40 and Akoline MCM or Peceol.²³

Influence of Emulsion Droplet Size on Drug Absorption

Although improved drug absorption is generally assumed to be associated with smaller lipid droplet size, many examples exist in which drug absorption is not influenced by droplet size. Khoo et al evaluated the bioavailability of the poorly soluble antimalarial drug, halofantrine, in dogs following administration of either MC-SEDDS (mean lipid droplet size of 119nm) or MC-SMEDDS (mean lipid droplet size of 52nm) formulations; both yielded comparable bioavailability.²⁴ Studies conducted in humans comparing the Sand immune® formulation of cyclosporine, which forms a crude emulsion in the GIT, to that of the self-micro emulsifying Neoral® formulation demonstrated improved performance of the latter with regard to the rate, extent, uniformity and linearity of cyclosporine exposure as a function of dose. In addition, absorption of cyclosporine from the Neoral formulation was relatively unaffected by food as compared to the Sand immune formulation.²⁴ From the foregoing discussion, it is difficult to determine the impact of lipid droplet size on drug absorption. It should be noted, however, that the cited studies utilized different lipid and surfactant systems, which can also influence drug absorption and confound the experimental results, thus making it difficult to draw conclusions. However, these findings collectively suggest that lipid droplet size may be less likely to impact formulation performance unless the normal lipid digestion process, which inherently produces a fine emulsion from ingested lipid, is compromised.²⁴

In-Vivo Studies with SEDDS/SMEDDS

Several published studies describing modest to substantial increases in drug bioavailability from SEDDS and SMEDDS formulations, relative to conventional solid dosage forms, water- miscible glycol solutions [e.g., PEG and propylene glycol (PG)] or simple oil solutions are summarized in Table 1.1. Relative to conventional solid dosage forms, increases in drug bioavailability from self-emulsifying formulations ranged from 1.5-fold for simvastatin to approximately seven-fold for L-365,260 (cholecystokinin antagonist). The results of these studies suggest that the physicochemical properties of the drug substance, as well as the excipients selected for the formulation, appear to determine the bioavailability enhancing potential of a particular formulation for a given drug substance.²⁴

Effect of Dispersion on Bioavailability

Compared to simple oil solutions of the drug, only modest improvements in drug bioavailability were generally observed from self-emulsifying formulations. However, it is important to note that these studies were conducted in different species, with different formulations and with different lipid and surfactant doses, which sometimes differed within an individual study. It should also be noted that only healthy test subjects, with fully functioning GI lipid handling pathways, were studied. Self-emulsifying formulations appear to provide better absorption enhancement, when the normal physiological processes enabling lipid digestion and dispersion are compromised. Studies conducted by Porter et al. demonstrated a significant increase in the bioavailability of danazol, administered as either a LCT solution or a LC-SMEDDS formulation, relative to either a conventional solid dosage form or a MC-SEDDS formulation. The presence of a high concentration of surfactant in the SMEDDS containing long chain triglycerides (LC-SMEDDS) formulation did not improve danazol absorption over that seen from the simple LCT solution, which supported the findings of who demonstrated similar bioavailability of seocalcitol, when administered to rats as simple MCT or LCT solutions or following addition of high concentrations of surfactant to yield MC-SMEDDS or LC- SMEDDS formulations, respectively. It should be noted that the SMEDDS formulations of danazol were not controlled for the ratio amounts of oil, surfactant or cosurfactant, which makes it difficult to accurately assess the impact of dispersion on drug absorption.²⁵ Some examples of marketed Pharmaceutical SEDDS formulations are as shown below Table 6:^{26,27}

Table 6: Examples of Marketed SEDDS Formulations

Drug Name	Compound	Dosage form	Company	Indication
Neoral	Cyclosporine A/I	Soft gelatin capsule	Novartis	Immune suppressant
Norvir	Ritonavir	Soft gelatin capsule	Abbott Laboratories	HIV antiviral
Convulex	Valproic acid	Soft gelatin capsule	Pharmacia	Antiepileptic
Lipirex	Fenofibrate	Hard gelatin Capsule	Genus	Antihyper- Lipo proteinemic
Sand immune	Cyclosporine A/II	Soft gelatin capsule	Novartis	Immuno Suppressant



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