



Self micro-emulsifying drug delivery system (SMEDDS) : Review

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ABSTRACT

Oral route has always been preferred route for formulators and has dominated over other routes of administrations. However this preferred 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. 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. Also Lipid-based drug delivery systems have gained considerable interest after the commercial success of Sandimmune Neoral™ (Cyclosporine A), Novartis Pvt. Ltd. and Fortovase (Saquinavir), Roche Laboratories Inc. with much attention focused on self micro-emulsifying drug delivery systems (SMEDDS). SMEDDS 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. The hypothesis behind dissolution rate enhancement with SMEDDS is the spontaneous formation of the emulsion in the gastrointestinal tract which presents the drug in solubilized form, and the small size of the formed droplet provides a large interfacial surface area for drug absorption. This article gives a complete overview of SMEDDS as a promising approach to effectively tackle the problem of poorly soluble molecules.

Keywords: SMEDDS, Excipients used in SMEDDS, Biopharmaceutical Aspects.

INTRODUCTION

Oral route is the easiest and most convenient way of non-invasive administration. Oral drug delivery systems being the most cost-effective have always lead the worldwide drug delivery market. This oral route may be a problem route for drug molecules which exhibit poor aqueous solubility. When a drug is administered by oral route the first step for it to get absorbed is its solubilization followed by permeation. Approximately 40% of new chemical entities exhibit poor aqueous solubility and present a major challenge to modern drug delivery system. A rate limiting step for the absorption of these drugs is often their solubilization in the gastrointestinal tract. These drugs are classified as class II drug by Biopharmaceutical classification system (BCS), drugs with poor aqueous solubility and high permeability. Different formulation approaches like micronization, solid dispersion, and complexation with cyclodextrins have come up. [1] 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 drug may degrade and lose bioactivity when they are micronized by conventional method. For solid dispersion the amount 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-microemulsifying drug delivery systems (SMEDDS). Being hydrophobic i.e. more lipophilic a lipid-based drug delivery system would ideally work for a poorly water soluble drug. Lipid-based drug delivery systems have gained considerable interest after the commercial success of Sandimmune Neoral™ (Cyclosporine A), [2] Fortovase (Saquinavir) and Norvir (Ritonavir). [3]

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Table 1. Lipid Formulation Classification System (LFCS) as described by Pouton showing typical compositions and properties of lipid-based formulations

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
Significance of aqueous dilution	Ltd. importance	Solvent capacity unaffected	Some loss of solvent capacity	Significant phase changes and potential loss of solvent capacity	Significant phase changes and potential loss of solvent capacity
Significance of digestibility	Crucial need	Not crucial but likely to occur	Not crucial but may be inhibited	Not required	Not required

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 systems 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 (2006). [5] 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.

Type I systems consist of formulations which comprise drug in solution in triglycerides and/or mixed glycerides or in an oil-in-water emulsion stabilized by low concentrations of emulsifiers such as 1% (w/v) polysorbate 60 [6] and 1.2% (w/v) lecithin. [7] 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).

Type II lipid formulations constitute SEDDS. [8] 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. [9, 10] 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. [11, 12]

Type III lipid-based formulations, commonly referred to as self-microemulsifying 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.

Type IV: In order to capture the recent trend towards formulations which contain predominantly hydrophilic surfactants and co-solvents, this category was recently added [5] 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 solubilisation 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. [15]

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

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). [16]

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). [16]

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) micro emulsions upon mild agitation followed by dilution in aqueous media, such as GI fluids. [4] 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. [17]

• **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.

• **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. [18]

• **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. [19] These systems are formed spontaneously without aid of energy or heating [20] thus suitable for thermo labile drugs such as peptides.

• **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 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.
- Emulsion can not be autoclaved as they have phase inversion temperature, [21] while SMEDDS can be autoclaved.

EXCIPIENTS USED IN SEDDS:

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. [23] 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. [20] 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. [21] 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 (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. [23] 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. [24] 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. [25]

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. [26] On the other hand, in some cases the mean droplet size may increase with increasing surfactant concentrations [27] 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. [28] 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 cosurfactant. 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 solubilisation 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.

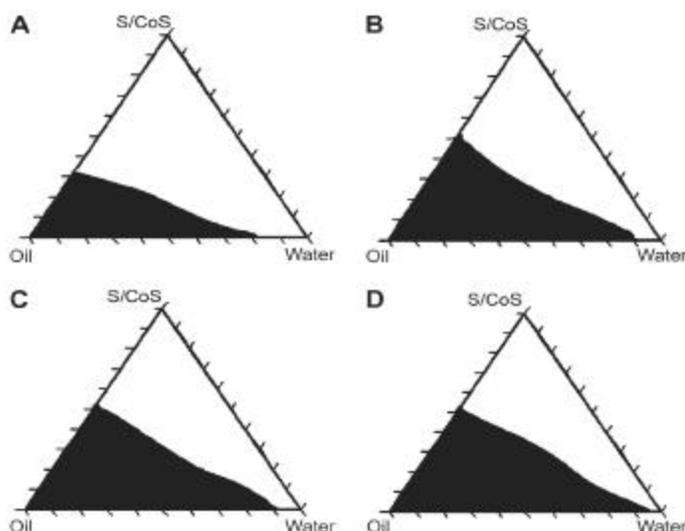
Fig 1. Shows phase micro-emulsion existence area for Fenofibrate SMEDDS

FIGURE 1.1 Pseudoternary phase diagram of system with the following components: oil = Labrafac CM10, surfactant = Tween 80, and cosurfactant = polyethylene glycol 400. S/CoS ratio of A is 1:1, B is 2:1, C is 3:1, and D is 5:1. S/CoS indicates surfactant/cosurfactant.

PSEUDO TERNARY PHASE DIAGRAMS:

Phase diagrams are useful tools to determine the number and types of phases, the wt% of each phase and the composition of each phase at a given temperature and composition of the system. These diagrams are three-dimensional but are illustrated in two-dimensions for ease of drawing and interpretation. Fig. 1 shows phase micro-emulsion /existence area for Fenofibrate SMEDDS. [22]

CHARACTERIZATION OF SMEDDS:

Particle size: The droplet size of the emulsion is a crucial factor in self-emulsification performance because it determines the rate and extent of drug release as well as absorption. [39] Photon correlation spectroscopy (PCS) is a useful method for determination of emulsion droplet size [40] especially when the emulsion properties do not change upon infinite aqueous dilution, a necessary step in this method. However, microscopic techniques should be employed at relatively low dilutions for accurate droplet size evaluation. [41]

Polarity: Emulsion droplet polarity is also a very important factor in characterizing emulsification efficiency. [39] The HLB, chain length and degree of unsaturation of the fatty acid, molecular weight of the hydrophilic portion and concentration of the emulsifier have an impact on the polarity of the oil droplets. Polarity represents the affinity of the drug compound for oil and/or water and the type of forces formed. Rapid release of the drug into the aqueous phase is promoted by polarity.

Zeta potential: The charge of the oil droplets of SMEDDS is another property that should be assessed. [41] The charge of the oil droplets in conventional SMEDDS is negative due to the presence of free fatty acids; however, incorporation of a cationic lipid, such as oleylamine at a concentration range of 1.0-3%, will yield cationic SMEDDS. Thus, such systems have a positive z-potential value of about 35-45 mV. [41] This positive z-potential value is preserved following the incorporation of the drug compounds.

Drug precipitation /stability on dilution: The ability of SMEDDS to maintain the drug in solubilised form is greatly influenced by the solubility of the drug in oil phase. If the surfactant or co-surfactant is contributing to the greater extent in drug solubilisation 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, hence it is very important to determine stability of the system after dilution. This is usually done by diluting a single dose of SMEDDS in 250ml of 0.1N HCl solution. This solution is observed for drug precipitation if any. Ideally SMEDDS should keep the drug solubilized for four to six hours assuming the gastric retention time of two hours.

BIOPHARMACEUTICAL ASPECTS:

The ability of lipids and/or food to enhance the bioavailability of poorly water-soluble drugs is well known. [28] Although incompletely

understood, the currently accepted view is that lipids may enhance bioavailability *via* a number of potential mechanisms, including. [28]

a) Alterations (reduction) in gastric transit, thereby slowing delivery to the absorption site and increasing the time available for dissolution. [28]

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 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. [28, 29]

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. [30] 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. [31]

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. [32]

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. [33] 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.

ENHANCED DRUG ABSORPTION BY LYMPHATIC DELIVERY

Drug candidates for lymphatic transport should have a log $P > 5$ and, in addition, a triglyceride solubility > 50 mg/ml. The importance of lipid solubility was illustrated by a comparing the lymphatic transport of DDT (log P 6.19) with hexachlorobenzene (HCB, log P 6.53). While both compounds have similar log P values, the difference in lymphatic transport on administration in oleic acid, 33.5% of the dose in the case of DDT and 2.3% with HCB, was attributed to the 13-fold difference in triglyceride solubility. [34] However, combination of a high log P and high triglyceride solubility does not always guarantee significant lymphatic transport. Penclomedine, an experimental cytotoxic agent with a log P of 5.48 and a triglyceride solubility of 175 mg/ml, was poorly transported in the intestinal lymph, ~3% of the dose. [35] Although enhanced lymphatic transport has been suggested as a potential mechanism of enhanced bioavailability, few studies have investigated the lymphotropic potential of SMEDDS.

However, one such study investigated the effects of a range of lipid-based formulations on the bioavailability and lymphatic transport of ontazolast, following oral administration to conscious rats. This drug undergoes extensive hepatic first-pass metabolism and it has solubility in soybean oil of 55 mg/ml, and a log P of 4. The formulations of ontazolast investigated included a suspension (lipid-free control), a 20% soybean o/w emulsion, and two SMEDDS containing Gelucire44/14 and Peceol in the ratios 50:50 and 80:20, respectively, and a solution of the drug in Peceol alone. All the lipid formulations increased the bioavailability of ontazolast relative to the control suspension, while the SMEDDS promoted more rapid absorption. Maximum lymphatic transport occurred with the emulsion and the Peceol solution. The emulsion prolonged lymphatic transport and this may be related to the need for preabsorptive lipolysis of the triglyceride vehicle and an associated slower gastric emptying time. The Peceol solution provided the highest rate of lymphatic triglyceride transport thus resulting in greater partitioning of the drug into the lymph. The SMEDDS formulations resulted in the highest concentration of ontazolast in the chylomicron triglyceride. The authors suggest that SMEDDS, which promote more rapid absorption of ontazolast, could produce higher concentrations of the drug in the enterocytes during absorption and hence improve lymphatic drug transport by a concentration-partitioning phenomenon. [36]

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 solubilisation 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, crystallisation could be slow in the solubilising and colloidal stabilising 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.

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

the hydrophilic portion and the concentration of the emulsifier. In fact, the polarity reflects the affinity of the drug for oil and/or water, and the type of forces formed. The high polarity will promote a rapid rate of release of the drug into the aqueous phase. This is confirmed by the observations of Sang-Cheol Chi, who observed that the rate of release of idebenone from SMEDDS is dependant upon the polarity of the oil phase used. The highest release was obtained with the formulation that had oil phase with highest polarity.

PHARMACEUTICAL APPLICATIONS:

The potential for lipidic self-emulsifying drug delivery systems(SMEDDS) to improve the oral bioavailability of a poorly absorbed, antimalarial drug (Halofantrine, HF) has been investigated in fasted beagles in 1998. The lipid based formulations of HF-base afforded a 6-8 fold improvement in absolute oral bioavailability relative to previous data of the solid HF. [6] The study evaluating the effects of combined use of two non-ionic surfactants on the characteristics of oil-in-water microemulsions generated from flurbiprofen-loaded preconcentrate was performed. The combined use of surfactants in preconcentrate showed the promise in generating desired self-emulsifying implications in future dosage development for poor water soluble drugs in using self-emulsifying microemulsions drug delivery systems (SMEDDS) [7]. An optimal paclitaxel microemulsion prepared by SMEDDS which is a mixture of paclitaxel, tetraglycol, cremophore ELP, and labrafill 1944 and a paclitaxel microemulsion containing poly(D,L-lactide-co-glycolide) (PLGA) in order to offer controlled release of paclitaxel was developed. It was observed that the droplet size of microemulsion without PLGA was smaller than that of microemulsion containing PLGA by transmission electron microscopy (TEM). The droplet of microemulsion containing PLGA was almost of spherical shape with smooth surface and there was no aggregation and adhesion among droplet of microemulsion containing PLGA by atomic force microscopy(AFM). The formulation enhanced the anti-tumor activity in-vivo compared with microemulsion without PLGA against SKOV-3 human ovarian cancer cells bearing nude mice model. [9] To study the effect of two SMEDDS containing labrasol with different dilutions on tight junctions was conducted. Changes in barrier properties of Caco-2 cell monolayers, including transepithelial electrical resistance (TEER) and permeability to the paracellular marker, i.e. mannitol, were assessed in response to dilutions and surfactant contents within formulations. The results demonstrated that the negatively charged SMEDDS with different dilutions had no effect on TEER, but significantly increased the permeability of mannitol. The

mechanism of opening of tight junctions was found to involve F-actin related changes and redistribution of ZO-1. [10] Another study involved formulation of gentamicin SMEDDS. Gentamicin was dispersed with a surfactant used for SMEDDS, labrasol, and the mixture was solidified with several kinds of adsorbents [microporous calcium silicate (florite RE), magnesium alumino meta silicate (Neusilin US₂), and silicon dioxide (Sylysia 320)]. High plasma gentamicin levels were obtained the results suggest that an adsorbent system is useful as an oral solid delivery system of poorly adsorbate drugs such as gentamicin. [10] Yet another study involved HPLC determination of anethole trithione (ATT). After administration of SMEDDS and tablets to rabbits, significant differences were found in main pharmacokinetic parameters of T_{max}, C_{max} and AUC₀₋₈ between these two formulations, and a 2.5-fold enhancement of relative bioavailability of ATT was observed from the SMEDDS compared with tablets. [13] Low molecular weight heparin (LMWH) was dispersed with a surfactant used for the self-microemulsifying drug delivery system (SMEDDS), PEG-8 caprylic/capric glycerides (Labrasol), and the mixture was solidified with three kinds of adsorbents. Florite RE system was evaluated in dogs after oral administration in an enteric capsule made of Eudragit S100 at the LMWH dose of 200 IU/kg. The results suggest that adsorbent system is useful as an oral solid delivery system of poorly absorbable drugs such as LMWH. [14, 16] Table 2 shows examples of SMEDDS designed for the oral delivery of lipophilic drugs.

FUTURE ASPECTS:

Supersaturable SMEDDS (S-SMEDDS): The toxic effects of surfactant are well known and to use these surfactants at such a high level as typically used in SMEDDS formulations can lead to GI side-effects, thus to overcome this problem and to minimize the GI side-effects a new class of supersaturable formulations, called as supersaturable SMEDDS (S-SMEDDS) formulations, have been designed and developed. [42] The S-SMEDDS approach is to generate a protracted supersaturated solution of the drug when the formulation is released from an appropriate dosage form into an aqueous medium. Supersaturation is intended to increase the thermodynamic activity to the drug beyond its solubility limit and, therefore, to result in an increased driving force for transit into and across the biological barrier. [42] The S-SMEDDS formulations contain a reduced level of surfactant and a polymeric precipitation inhibitor to yield and stabilize a drug in a temporarily supersaturated state. Hydroxypropyl methylcellulose (HPMC) and related cellulose polymers are well recog-

Table 2. Examples of SMEDDS designed for the oral delivery of lipophilic drugs

Delivery systems	Oil	Surfactant(s)	% w/w	Solvent(s)	Drug compound	Drug content(%)
SMEDDS	-	Polyglycolized glycerides (HLB: 1-14)	96	-	Indomethacin	4
SMEDDS (Sandimmun Neoral)	Hydrolyzed corn oil	Polyglycolized glycerides, POE-castor oil derivative	NA	Glycerol	CsA	10
SMEDDS (Sandimmun Neoral)	Hydrolyzed corn oil	Polyglycolized glycerides, POE-castor oil derivative	NA	Ethanol	CsA	10
SMEDDS	Triglyceride (LLL, LML, MLM)	Maisine 35-1, CremophorEL	58	Ethanol	Halofantrine	5
SMEDDS (supersaturable)	Glyceryl dioleate	Cremophor EL, PEG400	55-58	Ethanol	Paclitaxel (± CsA)	5.7-6.25
SMEDDS	dl-alpha tocopherol	TPGS, tyloxapol, DOC-Na	62	Ethanol	Paclitaxel	3

NA, not available

nized for their propensity to inhibit crystallization and, thereby, generate and maintain the supersaturated state for prolonged time periods. [43] 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 ($F \sim 1\%$). [42] 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 solubilisation. 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. [42] 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 supersaturation by means of these polymers is poorly understood even although several studies have been carried out to investigate this. [42, 44, 45]

Solid SMEDDS: SMEDDS are normally prepared as liquid dosage forms that can be administered in soft or hard gelatin capsules, which have some disadvantages especially in manufacturing process for soft and leakage problem with hard gelatin capsules. An alternative method is the incorporation of liquid self-emulsifying ingredients into a powder in order to create a solid dosage form (tablets, capsules). A pellet formulation of progesterone in SEDDS has been prepared by the process of extrusion/spheronization to provide a good *in vitro* drug release (100% within 30 min, T50% at 13 min). The same dose of progesterone (16 mg) in pellets and in the SEDDS liquid formulation resulted in similar AUC, C_{max} and T_{max} values. [46] A method of producing self-emulsifying pellets by wet granulation of a powder mixture composed of microcrystalline cellulose, lactose and nimesulide as model drug with a mixture containing mono- and diglycerides, polysorbate 80 and water has been investigated. The pellets produced with oil to surfactant ratio of 1:4 (w/w) showed improved performance in permeation experiments. [47]

CONCLUSION:

SMEDDS are a promising approach for the formulation of drug compounds with poor aqueous solubility. The oral delivery of hydrophobic drugs is now possible by SMEDDS, which have been shown to improve oral bioavailability substantially. The efficiency of the SMEDDS formulation is case specific in most instances thus,

composition of the SMEDDS formulation should be determined very carefully. Since a relatively high concentration of surfactants is generally employed in the SMEDDS formulation, toxicity of the surfactant being used should be taken into account. In fact, a compromise must be reached between the toxicity and self-emulsification ability of the surfactant that is considered for use. The size and charge of the oil droplet in the emulsion formed are two other important factors that affect GI absorption efficiency. Versatility of SMEDDS could be proved if issues like method to predict solubilisation state of the drug *in vivo*, interaction of lipid systems with components of capsule shell and basic mechanism of transport of SMEDDS through GIT are adequately addressed. Despite the proven ability of these systems relatively few lipid based product have been commercialized. The reasons underlying the lack of application of these technologies is not clear, but likely reflects the limited knowledge of the formulation parameters that are responsible for good *in vivo* performance and the fact that relatively few *in vivo* studies in human have been reported in literature when compared with conventional dosage forms. Perhaps more importantly the lack of effective *in vitro* tests that are predictive of *in vivo* performance has significantly hindered successful development of these self emulsifying drug delivery systems.

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