

## Lipid-based systems as a promising approach for enhancing the bioavailability of poorly water-soluble drugs

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Low oral bioavailability as a consequence of low water solubility of drugs is a growing challenge to the development of new pharmaceutical products. One of the most popular approaches of oral bioavailability and solubility enhancement is the utilization of lipid-based drug delivery systems. Their use in product development is growing due to the versatility of pharmaceutical lipid excipients and drug formulations, and their compatibility with liquid, semi-solid, and solid dosage forms. Lipid formulations, such as self-emulsifying (SEDDS), self-microemulsifying SMEDDS) and self-nanoemulsifying drug delivery systems (SNEDDS) were explored in many studies as an efficient approach for improving the bioavailability and dissolution rate of poorly water-soluble drugs. One of the greatest advantages of incorporating poorly soluble drugs into such formulations is their spontaneous emulsification and formation of an emulsion, microemulsion or nanoemulsion in aqueous media. This review article focuses on the following topics. First, it presents a classification overview of lipid-based drug delivery systems and mechanisms involved in improving the solubility and bioavailability of poorly water-soluble drugs. Second, the article reviews components of lipid-based drug delivery systems for oral use with their characteristics. Third, it brings a detailed description of SEDDS, SMEDDS and SNEDDS, which are very often misused in literature, with special emphasis on the comparison between microemulsions and nanoemulsions.

**Keywords:** lipid-based drug delivery systems (LBDDS), self-emulsifying drug delivery systems (SEDDS), self-microemulsifying drug delivery systems (SMEDDS), self-nanoemulsifying drug delivery systems (SNEDDS), microemulsions, nanoemulsions

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Most of the newly developed drugs are hydrophobic and therefore poorly water-soluble, which causes difficulties in selecting the proper delivery system to achieve sufficient bioavailability of such drugs. Poor water solubility and dissolution rate are restrictive factors with respect to their absorption rate and bioavailability. Undoubtedly, the majority of drugs marketed worldwide are administered orally. The efficacy of these drugs is dependent on their oral bioavailability, which, in turn, depends on several factors; the most important being drug solubility in an aqueous environment and drug permeability through lipophilic membranes (1–3). Orally administered drugs are completely absorbed only when they show good solubility in the gastric medium. According to the solubility factor (low/high) and permeability through biological membranes (low/high), these drugs are commonly classified as Class 2 (low solubility, high permeability) or Class 4 (low solubility, low permeability) drugs according to the biopharmaceutical classification system (BCS), both of which identify solubility as a challenge. Due to the essential influence of solubility on drug bioavailability, numerous strategies have been developed to improve the solubility, and consequently absorption and bioavailability of poorly water-soluble drugs. Among the most promising approaches are lipid-based delivery systems (LBDDS) (4, 5), which have gained considerable research attention in the last 15 years after recognition that the oral bioavailability of poorly water-soluble drugs may be enhanced when they are co-administered with meals rich in fat, and after the commercial success of Sandimmune Neoral<sup>®</sup> (Cyclosporine A), Fortovase<sup>®</sup> (Saquinavir) and Norvir<sup>®</sup> (Ritonavir) (4–7).

Some of the commercially available pharmaceutical products formulated as self-emulsifying delivery systems are presented in Table I.

Various types of LBDDS are known; from simple oil solutions or oily suspensions to coarse, multiple and dry emulsions, and more complex self-emulsifying, microemulsifying or nanoemulsifying drug delivery systems (SEDDS/SMEDDS/SNEDDS) (9). The

Table I. Examples of LBDDS on the market (3, 7, 8)

Product name	Drug	Dosage form	Company
Sandimmune Neoral <sup>®</sup>	cyclosporine A/I	soft gelatine capsule	Novartis
Gengraf <sup>®</sup>	cyclosporine A/III	hard gelatine capsule	Abbott
Norvir <sup>®</sup>	ritonavir	soft gelatine capsule	Abbott
Fortovase <sup>®</sup>	saquinavir	soft gelatine capsule	Roche
Agenerase <sup>®</sup>	amprenavir	soft gelatine capsule	GlaxoSmithKline
Lipirex <sup>®</sup>	fenofibrate	hard gelatine capsule	Sanofi-Aventis
Convulex <sup>®</sup>	valproic acid	soft gelatine capsule	Pharmacia
Rocaltrol <sup>®</sup>	calcitriol	soft gelatine capsule	Roche
Targretin <sup>®</sup>	bexarotene	soft gelatine capsule	Novartis
Vesanoid <sup>®</sup>	tretinoine	soft gelatine capsule	Roche
Accutane <sup>®</sup>	isotretionine	soft gelatine capsule	Roche
Kaletra <sup>®</sup>	lopinavir and ritonavir	oral solution	Abbott
Aptivus <sup>®</sup>	tipranavite	soft gelatine capsule	Boehringer Ingelheim

last three have a fairly similar composition, which comprises a mixture of oils, surfactants, and possibly co-solvents that has the ability to form fine oil-in-water (O/W) emulsions, microemulsions or nanoemulsions upon mild agitation following dilution with an aqueous medium.

This review focuses on the presentation and differentiation of various lipid based drug delivery systems for oral application, and their mechanisms for improving the solubility and bioavailability of poorly water soluble drugs. Special attention will be paid to differentiation of SEDDS, SMEDDS and SNEDDS.

### *Lipid-based drug delivery systems (LBDDS)*

There are increasing demands to develop suitable drug-carrier systems in order to control, localize, and improve drug delivery. LBDDS can reduce the inherent limitation of slow and incomplete dissolution of poorly soluble drugs and facilitate formation of solubilized structures after digestion in the gastrointestinal tract (GIT), from which absorption may occur (10).

A LBDDS is typically composed of lipids and surfactants, and may also contain a hydrophilic co-solvent. According to the lipid formulation classification system (LFCS) introduced by Pouton (11, 12), these systems are divided into four groups (I–IV), depending on their composition and the possible influence of dilution and digestion on their ability to prevent drug precipitation. This classification system enables differentiation among various systems hiding behind the term »lipid-based delivery systems« and also offers a better explanation and comparison of reported data (9–12). The composition, properties, advantages, and disadvantages of systems from each group of LFCS are presented in Table II.

Class I systems include simple oil solutions without surfactants, containing only mono-, di-, and/or tri-glycerides. Systems of Class II contain lipophilic surfactants in addition to the oil phase in order to increase the solubilization capacity of the systems for incorporated drugs, and to facilitate the stability of the emulsion formed upon dilution. These LBDDS are known as SEDDS. The addition of hydrophilic components (surfactants and/or co-solvents) to the oil phase creates SMEDDS, which belong to Class III systems. Representatives of the most hydrophilic group, Class IV, are systems that are only composed of hydrophilic surfactants and hydrophilic co-solvents, which form a colloidal micellar dispersion upon dilution with aqueous media (11).

### *Strategies to enhance the bioavailability of orally administered poorly water-soluble drugs*

The effectiveness of LBDDS to improve the gastrointestinal absorption of poorly water-soluble drugs is well documented. It is suggested that improved absorption is predominantly due to their higher solubilization capacity, being a prerequisite for absorption from the GIT. The lipid droplets formed upon dispersion of self-emulsifying LBDDS may directly facilitate drug absorption, regardless of the bile salt-mediated mixed micelle transport system. Other mechanisms proposed include protection of the drug inside the lipid droplets from chemical and enzymatic degradation, localized in the aqueous environment, changes in gastrointestinal membrane permeability, and promo-

Table II. Lipid formulation classification system by Pouton: structure, characteristics, advantages, and disadvantages of lipid-based systems (11, 12)

Classes	I	II	IIIa	IIIb	IV	
Composition (%)	Glycerides (mono-, di-, tri-glycerides)	100	40–80	40–80	< 20	0
	Lipophilic surfactants (HLB < 12)	0	20–60	20–40	0	0–20
	Hydrophilic surfactants (HLB > 12)	0	0	0	20–50	20–80
	Co-solvents	0	0	0–40	20–50	0–80
Characteristic features	Simple oil solution	Self-emulsifying ability	Self-emulsifying ability	Self-micro-mulsifying ability	Spontaneous formation of micellar dispersion	
Advantages	GRAS (generally recognized as safe) status Capsule compatibility	Unlikely to lose solvent capacity on dispersion	Formation of clear / opalescent dispersion; droplet size < 250 nm No digestion needed for drug absorption	Transparent dispersion No digestion needed for drug absorption	Good solvent capacity for many drugs	
Disadvantages	Poor solvent capacity for the drug with intermediate log P values Suitable only for lipophilic drugs limited or no dispersion requires digestion	Coarser emulsion (droplet size: 0.25– 2 μm)	Likely to lose solvent capacity on dispersion Less easily digested	May cause partial drug precipitation Less easily digested	Risk of drug precipitation upon dispersion May not be digestible	

tion of lymphatic drug transport (10, 13). Strategies for increasing the absorption of hydrophobic drugs with LBDDS are presented in Table III.

It is widely accepted that the performance of LBDDS is governed by their fate in the GIT, where dilution with aqueous media and digestion of LBDDS take place. Due to composition diversity, formulations belonging to different classes according to LFCS behave differently in the GIT. Type III and IV formulations may, for example, lose their sol-

Table III. Strategies of LBDDS for increasing bioavailability of incorporated drugs

Strategy	Brief explanation
Extended retention in the stomach	Introduction of lipids into the GIT results in slower peristaltic action and gastric emptying, and consequently increased the retention time of its content and possibly the co-administered drug in the upper intestine, where absorption occurs. This contributes to more efficient dissolution in the upper intestine and positively influences drug absorption (9, 14).
Increased solubilization	The presence of lipids in the GIT stimulates increased excretion of bile salts and endogenous bile lipids (including cholesterol and phospholipids), which facilitates emulsification of the lipids present and drug solubilization. This leads to the formation of intestinal mixed micelles of endogenous origin and increased solubilization capacity of the GIT for the drug (9, 14, 16).
Changes in the biochemical barrier	Some lipids and surfactants can reduce the activity of intestinal secretion vectors in the gastrointestinal wall (such as P-glycoprotein) and inhibit metabolic activity in the enterocytes and lumen of the GIT ( <i>e.g.</i> , cytochromes), which contributes to enhanced absorption of drugs that are substrates for these enzymes or transporters (9, 14–16).
Changes in the physical barrier	Various combinations of lipids and/or surfactants and their digestion products may act as promoters of intestinal absorption due to increased membrane permeability. Surfactants can cause fluidization of the intestinal cell membrane and opening of tight junctions, which results in increased membrane permeability (9, 14, 16).
Stimulation of intestinal lymphatic transport	Lipids composed of LCT or MCT are differently transported in the body; whereas MCT is directly transported by the portal blood to systemic circulation, LCT stimulates the formation of lipoproteins, which facilitates their lymphatic transport. LBDDS containing LCT are therefore likely to enhance the lymphatic transport of a lipophilic drug substance, and thus they can also affect the extent of the first-pass metabolism as the intestinal lymph circulation bypasses the liver (9, 14–16).

vent capacity on dispersion due to diffusion of water-soluble components into the bulk aqueous phase, leading to drug precipitation (13, 16, 17). Digestion of some formulation components in the GIT can also contribute to decreased solvent capacity. Besides solubilization capacity and droplet size of dispersions formed, the self-emulsifying ability also depends on the functionality of excipients, which thus influences the drug absorption process. The formulation-related factors affecting the bioavailability of drugs that are delivered in LBDDS are presented in Table IV.

### *Excipients for lipid-based formulations*

*Common selection criteria.* – When formulating LBDDS, drugs have to be incorporated into an appropriate mixture of oil(s) and surfactant(s); therefore formulation development commonly starts with excipient selection. As there are many lipid-based substances that can be used for formulating LBDDS, some general criteria for excipient

Table IV. Formulation parameters affecting bioavailability of drugs from LBDDS

Factor	Explanation
Lipid digestion	<p>If the drug possesses high affinity to the lipid vehicle, it can be assumed that it moves through the GIT incorporated into lipid droplets indicating that the digestibility of the lipid would be as important as its gastric emptying rate. Thus, careful selection of the lipid excipient can control the absorption rate of the drug (10).</p>
Mean emulsion droplet size	<p>This parameter indicates the type and, according to some researchers, also the quality of LBDDS. Droplet size of the dispersion formed upon dilution of SEDDS and SMEDDS with aqueous media is primarily influenced by the type and concentration of surfactant(s): the higher the surfactant concentration, the smaller is the emulsion droplet and faster drug release (10, 18).</p> <p>Spontaneous formation of emulsion advantageously presents the drug in a dissolved form, and the resultant small droplet size provides a large interfacial surface area. These characteristics result in faster drug release from the emulsion in a reproducible manner, which can be designed further to make the release characteristics independent of the gastrointestinal physiology and the fed/fasted state of the patient (19).</p> <p>The emulsion droplets formed are positively or negatively charged. As the mucosal lining is charged negatively, positively charged emulsion droplets can penetrate deeper into the ileum and cationic emulsions and thus exhibit greater bioavailability than anionic emulsions (20, 21).</p>
Lipophilicity of the API	<p>Highly hydrophobic drugs (<math>\log P &gt; 5</math>) can be taken up into the lymphatic system by partitioning into chylomicrons and avoiding the first-pass metabolism (10, 20).</p>
Chemism of lipids	<p>The nature of lipids is important, since digestible lipids may influence absorption in a manner differing from that of non-digestible lipids (10). Enhanced drug absorption was reported when using LCT (long chain triglycerides) compared to MCT (medium chain triglycerides) in SMEDDS (22, 23); however, this cannot be taken as a rule.</p>

selection were introduced in order to save time and cut costs. During preliminary selection studies, a few excipients are identified as possibly appropriate for further research owing to their safety, drug solubility and stability in excipients, and some other characteristics presented in Fig. 1. Initial selection of promising excipients is then followed by construction of phase diagrams to identify suitable mixing ratios for homogeneous formulations, being just as crucial as sufficient solubilization capacity for the drug to be incorporated. Once candidate formulations are proposed, the drug-loaded systems are subjected to *in vitro* dispersion and digestion tests to predict the fate of the drug in the GIT.

*Oil phase.* – The oil phase used to prepare LBDDS can be formulated from various non-polar components. The formation, stability and properties of dispersions formed from LBDDS often depend on the bulk physicochemical characteristics of the oil phase, *e.g.*, polarity, water-solubility, interfacial tension with the water phase, viscosity, density, phase behavior and chemical stability (24). From a practical point of view, the oil phase

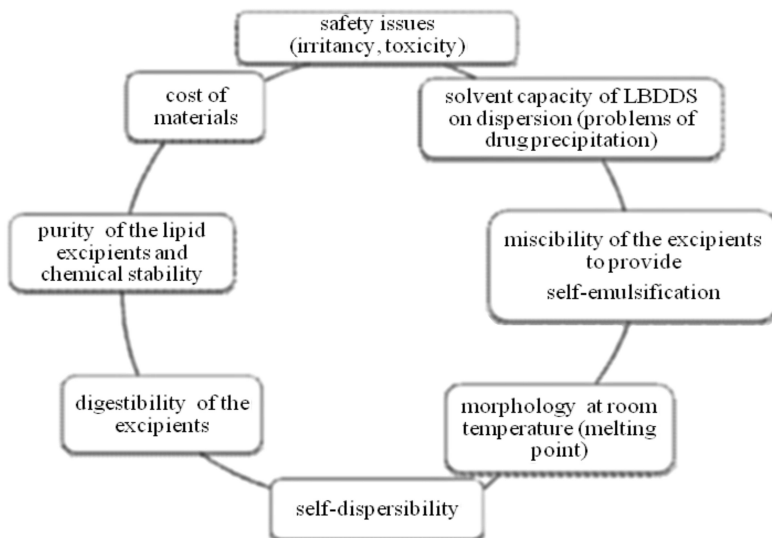


Fig. 1. General selection criteria for excipients in LBDDS (16).

highly influences dissolution of hydrophobic drugs and may contribute to their lymphatic transport. It also influences the self-emulsifying ability of the formulation and drug precipitation in the GIT.

The oil phase is usually composed of triglycerides or mixed glycerides (a mixture of mono-, di- and triglycerides) consisting of long-chain and/or medium-chain fatty acids. Some authors also report the use of hydrophobic surface-active agents named »polar oils« (16, 22, 25–27). It is often desirable to prepare LBDDS using glycerides due to their safety status and low cost; therefore various types and properties of different mono-, di- and triglycerides are presented in Table V. The majority of LBDDS described in the literature are composed of single lipid components. Lately, a growing interest in a more rational approach to excipient selection for lipid-based systems can be seen.

According to literature data, medium chain triglycerides (MCT) have been preferred for LBDDS due to their better solubilization properties, self-emulsification ability, and better chemical stability of active ingredients compared to long chain triglycerides (LCT). Grove *et al.* made a direct comparison of two seocalcitol II loaded SMEDDS containing either MCT or LCT. The study was performed on monophasic systems with the same lipid/surfactant/co-surfactant ratio, which formed dispersions with the same droplet size distribution upon dilution with the aqueous phase. Cremophor® RH40 was used as surfactant in both cases, whereas the co-surfactant was chosen to resemble the lipid component in chain length. Reportedly, a larger microemulsion area was achieved in the phase diagram when MCT was used instead of LCT due to the difference in polarity between the lipids. As the more hydrophobic LCT is more difficult to emulsify, higher concentration of Cremophor® RH 40 was generally required to form microemulsions when using LCT compared to MCT. Nevertheless, no significant differences were observed in the absorption and bioavailability of seocalcitol between the two aforemen-

Table V. Classification of glycerides according to the number and length of fatty acids esterified with glycerol

Class	Example	Characteristics
Triglycerides	Long-chain (LCT) Corn oil, soybean oil, olive oil, peanut oil, sesame oil, sunflower oil, castor oil, <i>etc.</i>	GRAS status, easily ingested, digested, and absorbed, poor self-dispersing properties of LCT and generally lower loading capacity for drugs with intermediate log P values. Their advantage is generally a higher solubilizing capacity after dispersion and digestion of the formulation (25, 26, 32).
	Medium-chain (MCT) Fractionated coconut oil, palm seed oil, triglycerides of caprylic/ capric acid Miglyol® 812, Captex® 355	
Mixed mono-, di- and tri-glycerides	Imwitor® 988, Imwitor® 308, Maisine® 35-1, Peceol® Plurol Oleique® CC49, Capryol®, Myrj®	They possess surface active properties because of their amphiphilic nature and are effective in replacing conventionally used oils owing to their better self-dispersing ability and higher solubilizing capacity for poorly water-soluble drugs (25, 26).

tioned SMEDDS upon their oral administration to male rats (28). This is contrary to previous studies, where the bioavailability of danazol and halofantrine from SMEDDS containing LCT was found to be superior to SMEDDS containing MCT (22, 29). However, SMEDDS compared in these studies consisted of different amounts of lipid and surfactant, whereas Grove *et al.* used quantitatively comparable systems. Considering the mentioned data, one can conclude that the extent of influence of MCT and LCT on the bioavailability of drugs is drug specific.

Besides the chain length of glycerides, solubility properties and self-emulsification ability of the formulation are further influenced by the type of glycerides used, since mono- and diglycerides possess amphiphilic properties whereas triglycerides do not. Hetal N. Prajapati *et al.* carried out a comparative evaluation of mixed glycerides of medium-chain fatty acids to develop a pharmaceutical dosage form with the model drug danazol. Phase diagrams were prepared using a monoglyceride (glycerol monocaprylocaprate: Capmul® MCM), a diglyceride (glycerol dicaprylate) and two triglycerides (glycerol tricaprylate: Captex® 8000; caprylic/capric triglycerides: Captex® 355 EP/NF) as the oil phase in combination with common surfactants (PEG-35 castor oil: Cremophor® EL) and water as the hydrophilic phase. They revealed that the use of the monoglyceride resulted in the formation of clear or translucent microemulsions, whereas the formation of an additional gel phase was observed when the oil phase consisted of di- and triglycerides. Among individual mono-, di- and triglycerides, the largest oil-in-water microemulsion region was that for the diglyceride. By adding the monoglyceride to di- or triglycerides (1:1), the region of this gel phase region formation could be practically eliminated. The oil phase composed of mixed glycerides further resulted in an expanded region of microemulsion formation in the phase diagram (30).



Bolko *et al.* made a direct comparison between SMEDDS composed of the mixed lipid phase (containing castor oil as long-chain triglycerides, and Capmul<sup>®</sup> MCM as medium-chain mono- and diglycerides) and the corresponding single lipid systems. They investigated whether the heterogeneous oil phase composed of medium- and long-chain mixed glycerides had a beneficial impact on SMEDDS self-emulsifying properties in comparison with a single lipid phase. According to their study, SMEDDS containing mixed glycerides showed the best self-emulsifying ability with regard to self-emulsifying time as well as droplet size and homogeneity of microemulsions obtained upon SMEDDS dilution with the aqueous phase (31).

Small (33) developed a physicochemical system to classify lipids (including surfactants) into non-polar and polar lipids based on their interaction with bulk water and their behavior at the water-air interface. This classification is presented in Table VI. Non-polar lipids do not spread to form a monolayer on water surface and are insoluble in bulk water (examples: alkanes, liquid paraffin, cholesterol esters, and fatty-acid esters, including waxes). Polar lipids are divided into four different classes and are described as insoluble non-swelling, insoluble swelling, and soluble. Soluble polar lipids are fur-

Table VI. Classification of polar lipids by Small (33)

Class of polar lipids	Characteristics
I	Insoluble non-swelling – Insoluble in water – Cannot swell by taking up water – Form stable monolayers at interfaces Examples: triglycerides, diglycerides, cholesterol, long-chain fatty acids
II	Insoluble swelling – Form stable monolayers at interfaces – Insoluble in water – Can incorporate water between their polar head groups, creating a swollen lipid structure (liquid crystalline state) Examples: phospholipids, 2-monoacylglycerides
III	Soluble – Soluble amphiphiles with lyotropic mesomorphic behavior at higher lipid concentration in water – Form unstable monolayers at interfaces – Form micelles above CMC (critical micellar concentration) – Form liquid crystalline structures at higher lipid concentrations Examples: lyso-phospholipids, sodium and potassium salts of long-chain fatty acids, amphiphiles, lipophilic surfactants with low HLB: Cremophor <sup>®</sup> RH 40, Labrasol <sup>®</sup>
IIIb	Soluble – Form micelles – Form unstable monolayers at interfaces – Do not form liquid crystalline structures at higher lipid concentrations Examples: conjugated and free bile salts, saponins, surfactants with high HLB

ther divided into two sub-classes depending on whether or not they show formation of liquid crystalline structures at higher lipid concentration in bulk (33).

While Small's classification is focused on lipid excipients, the LCFS introduced by Pouton emphasized the differences among various types of lipid formulations. In addition, Small's classification also includes highly hydrophilic surfactants with high HLB values (*e.g.*, Cremophor® RH 40, which has a HLB value around 15). Nevertheless, surfactants cannot be compared to lipids and cannot replace them due to their physicochemical characteristics and irritation potential.

Therefore the aforementioned classifications cannot be used as alternatives but are supplementary since they can both contribute useful information to formulators.

*Surfactants.* – Selection of an appropriate emulsifier is one of the most important factors to consider for the proper design of LBDDS. The stability of dispersions formed from LBDDS to environmental stresses such as pH, ionic strength, and temperature variation is often predominantly determined by the type of emulsifier used. It is generally acceptable that most stable emulsions are formed in the presence of surfactant combinations, in which one acts as an emulsifier and the other as a co-emulsifier, depending on their HLB values.

Table VII. Surfactants classified according to their HLB number (36, 37)

HLB value	Type of surfactant
Low HLB (< 10)	Phosphatidylcholine and phosphatidylcholine mixtures Phosphatidylcholine, mixtures in propylene glycol / MCT, ethanol
	Unsaturated polyglycolized glycerides (macroglycerides) Labrafil® M1944 CS, Labrafil® M2125CS
	Sorbitan esters Capmul®, Capmul® S, Span® 20, Span® 40
	Polyethoxylated alkyl ethers Brijs® 30,52,72
	Polyoxyethylene sorbitan esters (polysorbates) Tweens® 20, 40, 60, 80
High HLB (> 10)	Polyethoxylated fatty acid ester Myrj® 52, Solutol® HS15
	Polyethoxylated alkyl ethers Brijs® 35, 56, 78
	Polyethoxylated glycerides Caprylo/caproil macroglyceride: Labrasol®
	Polyoxyl castor oil derivatives Polyoxyl 35 castor oil: Cremophor® EL, Polyoxyl 40 hydrogenated castor oil: Cremophor® RH40
	Polyoxyethylene polyoxypropylene block copolymer Poloxamer® 188, Poloxamer® 407
	Saturated polyglycolized glycerides Lauroyl macroglycerides: Gelucire® 44/14, Stearoyl macroglycerides: Gelucire® 50/13

An emulsifier is a surface-active molecule that partitions at the oil-water interface and stabilizes the internal phase of emulsion delivery systems by lowering the interfacial tension and protecting droplets against aggregation. According to their HLB value, they are categorized as lipophilic ( $HLB \leq 10$ ) or hydrophilic ( $HLB > 10$ ) surfactants, as presented in Table VII. Nonionic hydrophilic surfactants are generally required for SEDDS and SMEDDS formulation, with HLB values above 12 (Gelucire® 44/14, Gelucire® 50/13, Labrasol®, Cremophor® EL, Cremophor® RH 40, etc.) needed to obtain systems that spontaneously form oil-in-water dispersions with droplet size below 100 nm upon dilution with digestive fluids in GIT (34).

The choice of surfactants is limited since very few are acceptable for oral administration. Safety is a major determining factor when choosing a surfactant. In keeping with this, the nonionic surfactants, such as polyethoxylated lipid derivatives, are the most widely recommended and used ones (16, 35). These surfactants can consist of fatty acids, alcohols, or glycerides, which are linked to a certain number of repeating polyethylene oxide units through ester linkage (fatty acids and glycerides) and ether linkage (alcohols). Polyethylene groups provide hydrophilic characteristics (36, 37). In addition, emulsifiers of natural origin are preferred since they are considered to be safer than synthetic surfactants (27).

Besides the lower toxicity of nonionic surfactants compared to anionic and cationic ones, they also enable good stabilization of emulsions over a wider range of ionic strength and pH. On the other hand, a possible disadvantage is their influence on the permeability of intestinal lumen with a reversible effect. Once again, this impact is generally less problematic than in the case of ionic surfactants. The surfactant concentration required to form a stable SMEDDS ranges from 30 to 60 % (*m/m*) (34, 38). The lowest possible surfactant concentration should be used in order to prevent gastric irritation. The extremely small droplet size produced in the case of SMEDDS promotes rapid gastric emptying and low local concentration of the surfactant, thereby reducing gastric irritation. Surfactant concentration has been shown to have varying effects on the droplet size of emulsion. Increase in surfactant concentration causes a decrease in droplet size associated with stabilization of surfactant molecules at the oil-water interface, although the reverse is possible due to enhanced water penetration into oil droplets leading to their breakdown (39–41).

*Co-solvents.* – Co-solvents in LBDDS are used in order to increase the solubilization capacity of incorporated drugs and to enhance dispersibility of hydrophilic surfactants in the oil phase, thus promoting formulation homogeneity and stability. In general, medium-chain-length alcohols (8 to 12 C atoms) are adequate. Otherwise, derivatives of ethylene-glycol, glycerol, and propylene glycol can be also included (11, 16, 34). When choosing between co-solvent and co-surfactant, one should consider lower solubilization capacity for hydrophobic drugs observed upon diluting co-solvent-containing formulations with the aqueous phase (28). This is related to the large amount of co-solvent usually needed to improve the drug solubilization capacity, which in turn increases the risk of drug precipitation when the formulation is dispersed in aqueous media. While in the presence of co-surfactants the co-administered drug is solubilized in micellar structures, systems containing co-solvents lose their solvent capacity faster due to solvent diffusion into aqueous media.

Furthermore, use of a co-solvent increases the complexity of the LBDDS production process. LBDDS can interact with primary packaging (*e.g.*, gelatin capsules), and therefore LBDDS without alcohols and other volatile solvents are preferred (38).

*Influence of the drug on the selection of excipients.* – Poor water-soluble drugs are a broad class of compounds differing considerably in their properties. Although there is an endless number of possible combinations for LBDDS, knowing the structure and physicochemical properties of the drug candidate may make it possible to narrow the search, and identify the most appropriate formulation for specific drugs. For example, if the drug is an amine, it may be soluble in oleic acid through formation of an ion pair, as exhibited by commercial formulations of ritonavir and ritonavir/lopinavir (37). Further, it is useful to acknowledge that poorly water-soluble drugs are hydrophobic but not necessarily lipophilic, and can therefore be poorly soluble in glycerides. Nevertheless, hydrophobic non-ionizable drugs (generally characterized by a  $\log P_{\text{oct/wat}} \geq 3$ ) may be solubilized by LCT or MCT and/or by a combination of a lipid with a low HLB surfactant such as phosphatidylcholine/MCT or oleoyl macrogolglycerides. Less hydrophobic drugs ( $\log P_{\text{oct/wat}} \leq 3$ ) may be solubilized by monoglycerides or propylene glycol monoesters, or by combinations of these lipids with high HLB surfactants or hydrophilic co-solvents (37). In any case, a systematic approach is needed to select the optimal formulation, since there are still insufficient comparative literature data available, which would enable formulators to make the most appropriate choices.

### *Types of lipid-based drug delivery systems*

There are various types of LBDDS; from simple drug in lipid solutions or suspensions, to emulsions and more complex self-emulsifying, self-microemulsifying, or self-nanoemulsifying (SEDDS/SMEDDS/SNEDDS) systems.

Type II and IIIa formulations according to LBCS are generally named SEDDS. They are formulated with mixtures of lipid vehicles, non-ionic surfactants and drug in the absence of water, and are assumed to exist as transparent isotropic solutions. These systems have a unique property: they are able to self-emulsify rapidly in the gastrointestinal fluids, forming fine oil-in-water emulsions (droplet size diameter < 300 nm) under gentle agitation provided by gastrointestinal motion. SEDDS are commonly suitable for oral delivery in soft and hard gelatin or hard hydroxypropyl methylcellulose (HPMC) capsules (14, 39, 40).

Type IIIb formulations according to LBCS are commonly called SMEDDS and are defined as isotropic mixtures of an oil, surfactant, co-surfactant (or solubilizer) and drug. Such systems form fine oil-in-water microemulsions under gentle agitation provided by digestive motility of the stomach and intestine following dilution by the aqueous phase *in vivo*. SMEDDS are distinguished from SEDDS by smaller emulsion droplets produced on dilution, resulting in a transparent or translucent stable dispersion. Mean droplet size after dilution is < 100 nm in the case of SMEDDS or < 300 nm in the case of SEDDS. SMEDDS generally contain relatively high concentrations of surfactant (typically 30 to 60 %, *m/m*), and optionally also hydrophilic co-solvents (*e.g.*, propylene glycol, polyethylene glycols). They are often described as microemulsion pre-concentrates because the microemulsion is formed on dilution in aqueous media (37, 42–44).

It must be pointed out that it may not be appropriate to describe dispersions that are produced from SMEDDS routinely as microemulsions, although this terminology is widely used. Namely, according to the definition, microemulsions are thermodynamically stable systems that form spontaneously, whereas »microemulsions« formed upon diluting SMEDDS are not necessarily thermodynamically stable and may need some energy input (such as stirring or gastrointestinal motility) to be formed. Some authors therefore prefer to refer to the type IIIb formulations according to LBCS as self-nanoemulsifying drug delivery systems (SNEDDS) (26, 35, 46, 47). According to the scientific definition, this may be a more accurate terminology, as pointed out in a recent expert review by Anton and Vandamme (47). However, this also resulted in even bigger confusion regarding the terminology used, which is sometimes misleading. In concordance to type IIIb systems, SNEDDS spontaneously form transparent to opalescent oil-in-water dispersions of approximately 200 nm in size upon dilution with water under gentle stirring. The problem arises when some define SNEDDS as isotropic mixtures of oils, surfactants or, alternatively, one or more hydrophilic solvents and co-solvents/co-surfactants, and a drug, which are capable of forming thermodynamically stable oil-in-water nanoemulsions (48, 49). First, if SNEDDS consist of one or more hydrophilic solvents and co-solvents/co-surfactants, then such a formulation should be classified as type IV system according to LBCS, which is composed only of surfactants and co-solvents (no oil phase) and form a colloidal micellar dispersion upon dilution with aqueous phase. Even more problematic is defining nanoemulsions that are formed from SNEDDS in the presence of water as thermodynamically stable. Namely, nanoemulsions are thermodynamically unstable systems that will tend to break down over time. It is therefore important to note that the only emulsion-type system that is thermodynamically stable under particular environmental conditions (*e.g.*, composition, pressure and temperature) is microemulsion (50). However, dispersion systems formed from type IIIb formulations are usually not thermodynamically stable and are more likely to be nanoemulsions than microemulsions. In keeping with this, it would be more accurate in most cases to name those systems SNEDDS instead of SMEDDS.

The characteristics differentiating SEDDS, SMEDDS and SNEDDS are presented in Table VIII; however, this terminology certainly needs clarification, as recently pointed out in an expert review by Anton and Vandamme, 2011.

In general, water-free systems (SEDDS, SMEDDS, SNEDDS) are preferred for oral preparation to the regular (micro-/nano-) emulsion system due to their lower volume and increased drug stability.

On the other hand, the advantage of microemulsions as potential therapeutic systems for oral delivery is their specific structure, which enables incorporation of hydrophilic, amphiphilic and lipophilic drugs to increase their solubility, rate and extent of absorption, to protect labile agents from the gastrointestinal environment, to reduce inter- and intrasubjective variability and to mask unpleasant odor and taste. Nevertheless, the therapeutic use of microemulsions as an oral dosage form is negligible. The main limiting factors are large volumes and composition requirements, namely, a high ratio of surfactants that are potentially toxic (26, 32, 54, 55).

Table VIII. Characteristics of SEDDS, SMEDDS, and SNEDDS and dispersions obtained upon their dilution with the aqueous phase (14, 19, 48, 51)

System/ characteristic	SEDDS	SMEDDS	SNEDDS
Composition	Can be simple binary formulations with the drug and lipid excipient able to self-emulsify in contact with gastrointestinal fluids or a system comprising a drug, surfactant, and oil (lipid phase)  SEDDS, SMEDDS, and SNEDDS form a fine oil-in-water dispersion (emulsion, microemulsion, nanoemulsion) in contact with gastrointestinal fluids.	Composed of the drug compound, surfactant, co-surfactant, oil (lipid phase) and optionally hydrophilic co-solvent	Composed of the drug compound, oils, surfactant/co-surfactant and hydrophilic solvents
Lipid droplet size in dispersion	From 200 nm to 5 $\mu$ m (14, 48) or more commonly 100–300 nm (19), providing a large surface area for absorption. The dispersion has a turbid appearance.	< 50 nm (19) or more commonly < 100 nm (52), or < 140 nm (53) providing a large surface area for absorption. The dispersion has an optically clear to translucent appearance.	< 200 nm (14, 48) or more commonly < 100 nm (52). The dispersion has an optically clear appearance.
Solubilizing capacity	SEDDS, SMEDDS, and SNEDDS have high solubilizing capacity and high dispersibility.		
Stability of dispersions	Thermodynamically unstable	Thermodynamically stable	Kinetically stable formulations.
Formulation technique	Development/optimization of SEDDS may require the development of ternary phase diagrams.	Pseudo-ternary phase diagrams are required to optimize SMEDDS, whereas the order of mixing preselected components is not important.	Techniques for preparing SNEDDS are not completely defined, but the order of mixing preselected combinations of components is defined.
	SEDDS, SMEDDS, and SNEDDS formulations can be prepared as liquids and semi-solids for capsule dosage forms and solid forms for tableting.		

Nanoemulsions are transparent or translucent dispersions with the droplet size in the same length-scale as microemulsions (52). They possess a relatively high kinetic stability and cannot form spontaneously and consequently energy input is required.

As discussed earlier, microemulsions and nanoemulsions are different types of colloidal dispersions also from the physicochemical point of view. It is therefore important to distinguish between them because this affects the methods used to fabricate them, the strategies used to stabilize them and the approaches used to design their functional attributes (43, 47). An expanded comparison of nanoemulsions and microemulsions is presented in Table IX.

Table IX. Comparison of the characteristics of nanoemulsions and microemulsions (32, 35, 43, 47, 52, 53, 55-57)

System/ Characteristics	Nanoemulsions	Microemulsions
Stability	Thermodynamically unstable but kinetically stable systems	Thermodynamically stable systems
Composition	Water, oil, surfactants	Water, oil, surfactants, co-solvent if needed
Order of mixing	Surfactants should be first mixed with the oily phase, followed by titration of the obtained mixture with the aqueous phase.	The order of mixing the components does not affect formation.
Droplet size	50–200 nm (58, 59) 50–500 nm (60, 61) generally accepted < 100 (10–100) nm (52)	Droplet size < 140 nm (53) or more commonly 2–100 nm (52).
Formulation technique	High-energy methods of preparation use specific devices (ultrasound generators, high pressure homogenizers) to supply enough energy to increase the interfacial area (35, 57)	Spontaneous formation They exhibit a large range of structures: bicontinuous, hexagonal, spherical, liquid crystalline

To distinguish whether the system formed is a microemulsion or nanoemulsion, one should first test if the order of mixing compounds during formulation affects the droplet size. If there is no influence, the system is most probably a microemulsion. They further differ considerably in their behavior during dilution with the aqueous phase. While microemulsions are strongly affected and even break down by dilution, nanoemulsion droplets will remain stable with unchanged droplet size distribution. Furthermore, varying the temperature can strongly affect the structures and droplet size in the case of microemulsions whereas it has no immediate effect on the structure of nanoemulsions; nevertheless, an effect is evident after some time because the temperature has influence on the structure of surfactants.

An increase in temperature causes a decrease in the critical micelle concentration (CMC; concentration above which micelles are formed in solutions) due to destruction of hydrogen bonds between water molecules and hydrophilic groups of surfactants (62). The presented approaches can be also useful in distinguishing between SMEDDS and SNEDDS by testing dispersions formed upon their dilution with the aqueous phase.

## CONCLUSIONS

Low water solubility is widely recognized as the main reason for the poor oral absorption of many drugs. Conventional solubilization approaches which include the use of surfactants, cyclodextrin complexes, salt formations, nanoparticles, solid dispersions,



lipids, and permeation enhancers are employed in enhancing the oral absorption of drugs. However, one of the most promising novel approaches for enhancing solubility are undoubtedly LBDDS. They can be made as solutions, emulsions, suspensions, microemulsions, solid lipid nanoparticles, liposomes, SEDDS, SMEDDS, SNEDDS, dry emulsions, dry microemulsions, melted microemulsions, and solid dosage forms containing a LBDDS.

LBDDS are a successful strategy for increasing solubility and improving the bioavailability of poorly soluble drugs (BCS Classes II and IV). They attain increased absorption of poorly soluble drugs with specific mechanisms: extended time of retention in the stomach, an increase in solubilization, stimulation of gastrointestinal lymphatic transport and impact on the biochemical and physical barrier of the GIT. Their effectiveness, however, also depends on the composition and proportion of the components. Different aspect ratios and different types of excipients determine a particular delivery system. It is necessary to determine experimentally the appropriate composition of the selected delivery system for each individual drug and thus ensure maximum effectiveness of the selected LBDDS.

This review article will direct researchers' attention to understanding the role of individual components used for formulating LBDDS and to the critical distinction between SMEDDS and SNEDDS. It also offers inspiration and courage to introduce more LBDDS at pilot and industrial scales.

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