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Review

New perspectives on lipid and surfactant based drug delivery systems for oral delivery of poorly soluble drugs

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Abstract

Objectives The aim of this review is to highlight relevant considerations when implementing a rational strategy for the development of lipid and surfactant based drug delivery system and to discuss shortcomings and challenges to the current classification of these delivery systems. We also aim to offer suggestions for an improved classification system that will accommodate lipid based formulations that are not currently accommodated in the lipid formulation classification system.

Key findings When categorising lipid and surfactant based drug delivery systems, the current Lipid Formulations Classifications System is a useful tool. However, it does not apply to all marketed lipid and surfactant systems or those reported in research papers. A more profound understanding of the functionalities of lipids and surfactants and their role in emulsion formation will enable a rational development strategy and will create the basis for a revised classification system encompassing all employed lipid and surfactant drug delivery systems.

Summary The ever-increasing number of poorly soluble compounds in drug discovery and development calls for the serious need for effective and affordable drug delivery strategies that will enhance bioavailability and decrease variability. Lipid and surfactant based drug delivery systems offer these advantages; however, the development of these systems requires proper understanding of the physicochemical nature of the compound as well as the lipid excipients and gastrointestinal digestion. One major challenge of lipid excipients and delivery systems is the varying range of compounds they contain. This has contributed to the challenge of proper characterisation and evaluation of these delivery systems, their stability, classification and regulatory issues, which consequently have affected the number of these formulations that eventually reach the market. Suggestions as to proper classification of these delivery systems based on their main lipid component and recommended use are put forward. The prospect of these delivery systems looks promising.

Keywords lipid and surfactant based drug delivery systems; lipolysis; poorly soluble drug

Introduction

The increasing number of poorly water soluble drug candidates in development in the pharmaceutical industry calls for advanced drug delivery systems that are able to increase bioavailability and at the same time decrease day-to-day and food-intake-dependent variation in the bioavailability.[1–4] Many of these drug candidates are class 2 drugs according to the Biopharmaceutics Classification System (BCS)[5,6] (low solubility, high permeability), and thus the solubility or dissolution rate in the gastrointestinal tract are the limiting steps for their absorption. BCS class 4 drugs (low solubility, low permeability) also constitute a significant proportion of drug candidates, meaning that the intestinal permeability is the rate limiting step. However, these drugs still need to dissolve in the gastrointestinal tract before absorption.

In general, two principles are available to increase bioavailability of BCS class 2 and 4 compounds: solid dosage forms developed to increase dissolution rate and liquid dosage forms containing the compound in solution. The first principle includes solid dosage forms where dissolution rate is enhanced by either increasing the surface area (e.g. nanoparticles) or by stabilising an amorphous or molecular form of the compound in polymers[7,8] (e.g. solid

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dispersions or solid solutions). The second principle covers formulation approaches using lipid and surfactant excipients to create formulations where the compound is in solution.[9,10]

These lipid and surfactant based drug delivery systems (LSBDDS) cover a large array of different drug delivery systems (e.g. oil solutions, emulsions, micellar systems and self (micro)emulsifying drug delivery systems (S(M)EDDS) and are being increasingly used in the pharmaceutical industry.[3] LSBDDS circumvent the dissolution step in the gastrointestinal tract, but complex processes, often involving digestion of the excipients, formation of different colloid phases and transfer of the drug between these colloid phases, are involved. The drug will be transferred from being in solution in the formulation to partition into lamellar or hexagonal phases formed during digestion and then into mixed micelles.[11,12] Recently, S(M)EDDS especially have attracted increasing interest primarily because these systems are dosed as pre-concentrates in a capsule and then will generate a drug containing (micro)-emulsion with a large surface area upon dispersion in the gastrointestinal tract. The emulsions will further facilitate the absorption of the drug due to a faster digestion by gastrointestinal enzymes and subsequent transfer to mixed micelles or possible absorption directly from the emulsion particle, by partitioning of drug into the aqueous phase of intestinal fluids.[13]

SEDDS produce crude, milky, emulsions upon dispersion in water. The terminology around S(M)EDDS is more unclear and identical systems have been called both SMEDDS and selfnano-emulsifying drug delivery systems (SNEDDS). The confusion is due to the fact that both SMEDDS and SNEDDS form dispersions with an emulsion particle size in the nanometre range. Microemulsions are by definition thermodynamically stable and will thus be in equilibrium, while nano-emulsions are non-equilibrium systems that over time spontaneously will exhibit coalescence of the dispersed droplets. However, nano-emulsions can have a high kinetic stability, and in this case it will be difficult to separate micro and nano-emulsions. In any case for both SMEDDS and SNEDDS the emulsion will be formed in the gastrointestinal tract and its long-term stability is of minor concern. In the following, we will use the term SMEDDS to describe these systems.

Even though BCS class 2 and 4 drugs are hydrophobic with high logP values and low solubility and dissolution rate, they can still have very different properties. In general they can be divided into two groups depending on their lipophilicity. Non-lipophilic hydrophobic drugs ('brick dust') have a tight crystal lattice and are not very soluble in lipids such as triacylglycerides; instead they can have considerable solubility in surfactants or co-solvents, and can therefore often be formulated in delivery systems also containing surfactants or co-solvents. The second group includes lipophilic hydrophobic drugs ('grease balls'), which are soluble in lipids and are well suited for being formulated in lipid based drug delivery systems.

LSBDDS offer great potential for increasing bioavailability of BCS class 2 and 4 compounds. However, development of these delivery systems is not trivial and requires fundamental knowledge of physical chemistry, thermodynamics and gastrointestinal digestion. This paper will review aspects that need to be taken into consideration when trying to implement a rational strategy for the development of lipid and surfactant based drug delivery systems, with specific emphasis on SMEDDS.

In-vivo lipid digestion process

One important aspect to consider when developing oral LSBDDS is the environment that the delivery system will meet upon ingestion. This includes both the gastrointestinal juices and the digestion processes. LSBDDS will be dispersed in the gastric fluids, unless the dosage form is enteric coated, in which case they will be dispersed in the intestine. The environment that the LSBDDS are subjected to will also depend on the nutritional state of the gastrointestinal tract; in the following both the fasted and the fed state will be reviewed.

The volume of the fasted stomach is around 50 ml[14] and since patients are encouraged to take dosage forms with 250 ml of water, the average volume available for dispersion of the LSBDDS is 300 ml. However, water is continuously emptied from the stomach, thus the actual volume available for dispersion could be considerably less.

In the fasted intestine the dispersed LSBDDS encounters a relatively small concentration of bile salt (see other publication in this issue)[15] and presumably a low level of enzymes. It has, however, been observed that as little as 2 ml of long-chain fatty acids are able to induce gall bladder contraction in humans and thus increase the level of bile salt/phospholipid (BS/PL) micelles in the small intestine.[16] To our knowledge no studies on enzyme activity in the fasted small intestine have been performed.

Food intake induces secretion of gastric lipase in the stomach. Thus in addition to dispersion and emulsification, lipid digestion also takes place. The gastric lipase is responsible for 10–20% of the digestion of ingested triacylglycerides.[17] Gastric lipase catalyses the formation of one free fatty acid and a diacylglyceride from a triacylglyceride molecule. Both free fatty acids and diacylglycerides have surface-active properties and facilitate the emulsification of lipids from food or from an LSBDDS, before it enters the duodenum.

Gastric lipase also has specificity towards several surfactants typically used in LSBDDS. These are surfactants that contain an ester bond and typically the activity of gastric lipase results in the formation of free fatty acids.[18,19] However, not much is known about the impact of gastric digestion upon the bioavailability of drug dosed in LSBDDS.

The digestion of the major part of the ingested triacylglycerides happens in the small intestine and is catalysed by pancreatic lipase. However, other pancreatic enzymes, such as carboxyl ester hydrolase and pancreatic lipase like protein 2, are also involved in the intestinal hydrolysis of lipids and surfactants.[18,19]

The activity of pancreatic lipase is dependent on its interaction with colipase on the surface of the triacylglyceride droplets. It hydrolyses the fatty acids in positions 1 and 3 of the triacylglyceride, generating two free fatty acid and one 2-monoacylglyceride. The free fatty acids and 2-monoacylglyceride accumulate as multilamellar liquid crystalline phases on the surface of the triacylglyceride droplet, and are then

gradually 'detached' from the surface and produce either multior unilamellar vesicles.[20] In addition, recent studies have identified the formation of hexagonal phases during in-vitro lipolysis of SMEDDS.[21] The increased level of BS/PL micelles in the fed intestine further helps remove free fatty acids and 2-monoacylglycerides that otherwise would accumulate on the surface of triacylglyceride droplets and hinder the activity of pancreatic lipase. The formed mixed micelles are then believed to diffuse to the unstirred water layer lining the intestine and here the mixed micelles dissociate due to a pH gradient. Here the 2-monoacylglycerides, free fatty acids and lyso-phospholipids are absorbed, while the bile salt will be reused in the digestive processes until it is absorbed by the bile salt transporter in the terminal ileum.

Poorly soluble drug compounds will follow the colloid phases during digestion and will finally end up in mixed micelles. When the mixed micelles dissociate in the unstirred water layer, the drug will be released and be absorbed as a free molecule.[22,23] However, many of the mechanisms involved in the absorption processes of poorly soluble drug compounds are not very well understood.

Classification of excipients used in lipid and surfactant based drug delivery systems

Over the years lipids have been defined in many ways but so far there is not one generally accepted definition. Christie[24] defined lipids as fatty acids and their derivatives and substances related biosynthetically or functionally to these compounds and this definition will be used in the present review.

Small[25] has developed a physicochemical-based system to classify lipids (including surfactants) into non-polar and polar lipids based on their interaction with bulk water and their behaviour in the water–air interface.

Non-polar lipids do not spread to form a monolayer on the surface of water and are insoluble in the bulk. Examples of non-polar lipids include alkanes, paraffin oil, 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*. The soluble polar lipids are further divided into two sub-classes depending on whether or not they show formation of liquid crystalline structures at higher lipid concentration in the bulk.

Class I lipids are the most hydrophobic of the polar lipids, and are described as *insoluble non-swelling* lipids. Triacylglycerides, diacylglycerides, cholesterol and protonated long-chain fatty acids belong to this group. They are insoluble in water and cannot swell by taking up water. In contrast to non-polar lipids, however, they do form stable monolayers at interfaces.

Among the insoluble swelling polar lipids (Class II) are phospholipids and 2-monoacylglycerides.[21] Like the Class I lipids they form stable monolayers at interfaces and are insoluble in water. However, above their phase transition temperature, they can incorporate water between their polar head groups creating a swollen lipid structure (liquid crystalline state).

The group of Class IIIA lipids contains soluble amphiphiles that show lyotropic mesomorphic behaviour at higher lipid concentrations in water. They form an unstable monolayer in the interface and form micelles when their concentration is above their respective critical micellar concentration (CMC). Examples of this class of polar lipids include lyso-phospholipids, sodium and potassium salts of long-chain fatty acids and other anionic surfactants, as well as cationic and non-ionic amphiphiles. This group contains both hydrophilic and lipophilic surfactants as described by the HLB system (see below).

Both conjugated and free bile salts, saponins and other water soluble compounds with bulky aromatic moieties belong to the Class IIIB group. Members of this subclass of polar lipids are also able to form micelles on their own, as well as unstable monolayers. In contrast to Class IIIA lipids, however, they do not form liquid crystalline structures at higher lipid concentrations. Both Class IIIA and IIIB lipids possess a high capacity to solubilise non-polar and insoluble non-swelling (Class I) and swelling (Class II) polar lipids.

An empirical classification system of polar lipids is the hydrophilic–lipophilic balance (HLB) system, which has originally been used for the design of emulsions. The HLB number takes into account the relative contributions of the hydrophilic and hydrophobic fragments of the surfactant molecule. The HLB scale ranges from 1 to 20, with hydrophilic surfactants having high HLB numbers and hydrophobic ones having low HLB numbers.

One inherent problem with classifying pharmaceutical excipients is that they often contain a range of compounds (e.g. the macrogol glycerides Labrasol and Labrafil contain both triacylglycerides and 2-monoacylglycerides as well as the macrogol glycerides).[26,27] In this review we will classify the excipients according to the main component and their recommended use.

Classifications of lipid and surfactant based drug delivery systems

As mentioned above, the term 'lipid and surfactant based drug delivery system' covers a broad range of different formulations, spanning from simple lipid solutions to self-emulsifying drug delivery systems (SEDDS), self-microemulsifying drug delivery systems (SMEDDS) and micellar systems that form emulsions/micelles with different droplet sizes upon dispersion in the gastrointestinal tract. The Lipid Formulations Classification System (LFCS) proposed by Pouton[28,29] categorises lipid-based formulations into four different types, according to their composition and the possible effect of dilution and digestion on their ability to prevent drug precipitation, as described in Table 1. The LFCS is a useful tool when trying to classify LSBDDS for oral administration. Table 2 summarises the commercially available LSBDDS and their excipients, and attempts to classify the formulations according to the LFCS. As can be seen from Table 1, the LFCS does not cover all commercially available LSBDDS. In addition some of the underlying assumptions in the LFCS would benefit from further consideration, as will be outlined in the following section.

Table 1 The lipid formulation classification scheme according to Pouton[29]

Excipients in formulation	Content of formulation (%, w/w)				
	Type I	Type II	Type IIIA	Type IIIB	Type IV
Oils: triglycerides or mixed mono and diglycerides	100	40–80	40–80	<20	–
Water-insoluble surfactants (HLB < 12)	–	20–60	–	–	0–20
Water-soluble surfactants (HLB > 12)	–	–	20–40	20–50	30–80
Hydrophilic co-solvents (e.g. PEG, propylene glycol, transcutol)	–	–	0–40	20–50	0–50

The Type I formulations consist of oils, which are required to be digested. Type I formulations are defined to contain triacylglycerides, diacylglycerides and 2-monoacylglycerides. However, 2-monoacylglyceride is not required to be digested before absorption, and thus does not fit into this category. Further, triacylglycerides and diacylglycerides are insoluble non-swelling lipids (Class I, according to Small[25]), forming a separate phase in water with no internal structure. In contrast 2-monoacylglycerides spontaneously can form liquid crystalline structures when mixed with water,[21] and therefore belong to Class II. Thus there still remains an argument if 2-monoacylglycerides should be included in the Type I formulations, and we propose that Class II lipids like 2-monoacylglycerides and phospholipids are added as a separate group in the LFCS. This will enable the elucidation of the function of these lipids in LSBDDS.

When an appropriate dose of the drug can be dissolved, a triacylglyceride solution as described in Type I formulations may well be the delivery system of choice, in view of its simplicity and biocompatibility. As described above, triacylglycerides are not miscible with water and require digestion by pancreatic lipase/co-lipase in the gastrointestinal tract to generate more amphiphilic lipid digestion products and promote drug transfer into the colloidal aqueous phase. Valproic acid has been formulated as an oil solution (Table 1) but, other than that, oil solution dosage forms are primarily known from fat soluble vitamins; vitamin A, D and E are often dosed in oil.

The Type II formulations, defined as SEDDS, are isotropic mixtures of lipids and lipophilic surfactants (HLB < 12) that self-emulsify to form crude oil-in-water emulsions when introduced in aqueous media. However, several limitations are valid here. First of all, from the very limited number of publications[32,33] dealing with Type II systems, it appears that predominantly medium-chain triacylglycerides were able to be self dispersed. Further, the hydrophobic surfactants used in these studies are in fact borderline hydrophilic (HLB approx. 11). It therefore seems premature to specify Type II systems generally as mixtures of triacylglycerides with surfactants of HLB below 12. While the Type II formulations may lead to systems that can be emulsified with energy input, it is unlikely that many of these systems indeed can form SEDDS. It therefore appears that Type II systems should be classified more strictly, to serve as a useful tool to prepare these systems. No marketed product, to our knowledge, has been reported during the past decade using the Type II formulation.

The Type III formulations (referred to as SEDDS or 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 separated into Type IIIA and Type IIIB formulations in order to include more hydrophilic systems (Type IIIB) where the content of hydrophilic surfactants and co-solvents is increased and the lipid content reduced. The self-emulsification process is specific to the particular pair of oil and surfactant, surfactant concentration, oil/surfactant ratio and the temperature at which self-emulsification occurs. Type IIIB formulations typically achieve faster dispersion rates when compared with Type IIIA, due to a higher level of water soluble co-solvents. SEDDS formulations typically provide opaque dispersions with particle sizes >200 nm whereas SMEDDS formulations disperse to give smaller droplets with particle sizes <200 nm and provide optically clear or slightly opalescent dispersions, more consistent with the presence of a microemulsion. According to the LFCS, drugs can be absorbed from Type IIIA and IIIB without digestion, although it should be considered that both the Class I polar lipids as well as some of the Class IIIA surfactants (examples; Cremophor RH40[34] and Labrasol[18]) present in the formulation can be digested, therefore it has not yet been verified that drugs are absorbed without excipient digestion from Type III formulations.

Type III formulations show much promise to overcome the formulation difficulties of various hydrophobic/lipophilic drugs to improve their absorption.[23,35] Type III formulations have contributed to the improvement of oral bioavailability of numerous poorly water-soluble drugs,[36–39] and, as demonstrated in Table 2, a number of products based on Type III formulations have been marketed. Perhaps the best-known example of a successfully marketed SMEDDS formulation is the Neoral ciclosporin formulation (corn oil glycerides, Cremophor RH40, glycerol, propylene glycol and ethanol). In contrast to the earlier ciclosporin formulation Sandimmune (corn oil, Labrafil M-2125CS, glycerol and ethanol), which formed a coarse emulsion on dispersion into water, Neoral spontaneously forms a transparent and thermodynamically stable dispersion with a droplet size around 30 nm when introduced into an aqueous medium.[40–43] Other drugs marketed as Type III formulation include antibacterial (ciprofloxacin) and anti-retroviral drugs (lopinavir, ritonavir and tipranavir) (Table 2).

Considering Small's classification of polar lipids,[25] Type IIIA and IIIB systems contain Class I polar lipids, Class II polar lipids (e.g. 2-monoacylglycerides) and Class IIIA polar lipids (surfactants). Considering the HLB system, 2-monoacylglycerides indeed should be considered as a special group of lipids and, thus, this group of polar lipids should also be labelled as present in Type IIIA and Type IIIB systems. This also raises the question of whether SMEDDS

Table 2 Selected commercially available LSBDDS, their excipients categorised according to the present suggestions and the LSBDDS classified according to the LFCS proposed by Pouton[28–31]

Drug	Trade name	Non-polar lipids & Class I polar lipids	Class II polar lipids	Water-insoluble surfactants (HLB < 12)	Water-soluble surfactants (HLB > 12)	Hydrophilic co-solvents	LFCS
Alfacalcidol	One-Alpha	Sesame oil	–	–	–	–	I
Amprenavir	Agenerase	–	–	–	TPGS	PEG 400, PG	IV
Bexarotene	Targretin	–	–	–	Tween 20	PEG 400	IV
Calcitriol	Rocaltrol	Fractionated TAG of	–	–	–	–	I
Calcitriol	Rocaltrol	Fractionated TAG of palm seed oil	–	–	–	–	I
Ciprofloxacin	Cipro	Medium-chain TAG	Lecithin	–	Tween 20	–	III
Clofazimine	Lamprene	Rapeseed oil, wax blend (beeswax, hydrogenated soybean oil, partially hydrogenated plant oils)	–	–	–	PG	–
Clomethiazole edisilate	Heminevrin	Fractionated TAG of coconut oil	–	–	–	–	I
Ciclosporin	Neoral	MAG, DAG and TAG of corn oil	–	–	Cremophor RH 40	Ethanol, glycerol, PG	III[a]
Ciclosporin	Sandimmune	Corn oil	–	Labrafil M-2125CS	–	Ethanol, glycerol	–
Ciclosporin	Sandimmune	Olive oil	–	Labrafil M-1944CS	–	Ethanol	–
Ciclosporin	Gengraf	–	–	–	Cremophor EL, Tween 80	Ethanol, PG	IV
Ciclosporin	Sidmark	Labrafac	Glyceryl caprylate	–	Labrasol, Cremophor EL	–	–
Doxercalciferol	Hectorol	Fractionated TAG of coconut oil	–	–	–	Ethanol	–
Dronabirol	Marinol	Sesame oil	–	–	–	–	I
Dutasteride	Avodart	–	MAG and DAG of caprylic/capric acid	–	–	–	I[a]
Efavirenz	Sustiva	Medium-chain TAG	–	–	–	–	I
Ethyl icosapentate	Epadel	α-Tocopherol	–	–	–	–	–
Fenofibrate	Fenogal	–	–	–	Gelucire 44/14	–	IV
Ibudilast	Ketas	–	–	–	Cremophor RH 60	–	IV
Indometacin farnesil	Infree	α-tocopherol	–	–	–	–	–
Indometacin farnesil	Infree	–	–	–	Cremophor RH 60	–	IV
Isotretinoin	Accutane	Beeswax, hydrogenated soybean oil, soybean oil	–	–	–	–	–
Lopinavir and ritonavir	Kaletra	–	–	Span 20	–	–	–
Lopinavir and ritonavir	Kaletra	Oleic acid	–	–	Cremophor EL	PG	–
Lopinavir and ritonavir	Kaletra	–	–	–	Cremophor RH40	Ethanol, glycerin, PG	IV
Menatetrenone	Glakay	Carnauba wax, hydrogenated oil	Glyceryl monooleate	PG esters of FA	–	Glycerin	–
Paricalcitol	Zemplar	Medium-chain TAG	–	–	–	Ethanol	–
Morphine sulfate	MXL	Hydrogenated vegetable oil	–	–	–	–	I
Progesterone	Prometrium	Peanut oil	–	–	–	–	I
Ritonavir	Norvir	Oleic acid	–	–	Cremophor EL	Ethanol	–
Ritonavir	Norvir	–	–	–	Cremophor EL	Ethanol, PG	IV
Saquinavir	Fortovase	–	Medium-chain MAG and DAG	–	–	–	I[a]

(Continued)

Table 2 *(Continued)*

Drug	Trade name	Non-polar lipids & Class I polar lipids	Class II polar lipids	Water-insoluble surfactants (HLB < 12)	Water-soluble surfactants (HLB > 12)	Hydrophilic co-solvents	LFCS
Sirolimus	Rapamune	Soy fatty acids	Phosphatidyl choline, sunflower MAG and DAG	–	Tween 80	Ethanol, PG	
Teprenone	Selbex	α-Tocopherol	–	–	–	–	–
Testosterone undecanoate	Restandol	Oleic acid	–	–	–	–	–
Tipranavir	Aptivus	–	Medium-chain MAG and DAG	–	Cremophor EL	Ethanol, PG	III[a]
Tipranavir	Aptivus	–	–	–	TPGS	PEG 400 and PG	IV
Tocopherol nicotinate	Juvela	Carnauba wax, medium chain TAG	–	Glycol esters of FA	–	Glycerin	–
Tolterodine tartrate	Detro	Medium-chain TAG, oleic acid	–	–	–	–	I
Tretinoin	Vesanoid	Beeswax, hydrogenated soybean oil, soybean oil	–	–	–	–	–
Valproic acid	Depakene	Corn oil	–	–	–	–	I
Valproic acid	Convulex	Medium-chain TAG	–	–	–	–	I

LSBDDS, lipid and surfactant based drug delivery systems; LFCS, Lipid Formulations Classification System; HLB, hydrophilic–lipophilic balance; TPGS, tocopherol polyethylene glycosuccinate; PEG, polyethylene glycol; PG, propylene glycol; TAG, triacylglyceride; MAG, 2-monoacylglyceride; DAG, diacylglyceride; FA, fatty acid. The classification is based only on the category of formulated excipients, not on their quantity. [a]Formulations containing Class II polar lipids and thus not complying with the suggested LSBDDS classification.

(which are the most likely type of structure formed form Type IIIA and Type IIIB systems) can generally be formed from formulations containing a mixture of surfactants with HLB values higher and lower than 12. Since the HLB systems does not differentiate between Class II and Class III polar lipids, further work seems to be required to establish the role of Class II polar lipids (such as phospholipids and 2-monoacylglycerides) versus low HLB Class III polar lipids (such as Spans) in the formation of SMEDDS.

The Type IV formulations are oil-free and based on surfactant and co-solvent mixtures; this type was recently added to the LFCS. These formulations represent the most hydrophilic type of lipid formulation and commonly offer increased drug payloads when compared with Type I formulations. They also produce very fine dispersions when introduced into aqueous media. This in turn has been suggested to lead to rapid drug release and increased drug absorption. Little is known, however, about the solubilisation capacity of these systems *in vivo* and in particular whether they are equally capable of maintaining drug substances in solution during passage along the gastrointestinal tract when compared with formulations comprising natural oils (Type II and Type III).[44] In general, however, when the active substance is hydrophobic but not lipophilic, co-solvents or co-solvent–surfactant mixtures could be used to solubilise the active substance. A recent study showed that PEG 400 and polysorbate 80 mixtures increased the bioavailability of halofantrine in rats, compared with pure polyethylene glycol (PEG) solutions.[45] An example of a commercial Type IV formulation is Agenerase (Glaxo-SmithKline), a capsule formulation of the HIV protease inhibitor amprenavir containing tocopherol polyethylene glycosuccinate (TPGS) as a surfactant and PEG 400 and propylene glycol as co-solvents.[46,47]

To summarise this section, we conclude that the LFCS is a practical and, by and large, useful attempt to order the plethora of lipid and surfactant based systems for oral delivery of poorly soluble drugs. We have, however, also highlighted some conceptional shortcomings of this system. We propose to modify the system to reconcile it with both Small's lipid classification systems, based on the fundamental difference in surface and bulk behaviour of lipids, as well as with the empirical HLB system. Instead of using the excipient type oils, low HLB surfactants, high HLB surfactants and cosolvents, we propose to use non-polar lipids and Class I polar lipids; Class II polar lipids; Class IIIA polar lipids (low HLB); Class IIIA (high HLB) and co-solvents. This way the role of phospholipids and 2-monoacylglycerides could be clarified, as they have an HLB < 12, but show fundamentally different behaviour compared with Class IIIA (low HLB).

Rational formulation strategy for self-emulsifying drug delivery systems

As described, a SMEDDS pre-concentrate can contain four categories of components: drug, lipids, surfactants and co-solvents. Frequently used lipids, surfactants and co-solvents are listed in Table 3.

Development of SMEDDS typically entails a two-step process. First, homogeneous pre-concentrates containing the

Table 3 Examples of typical excipients used in SMEDDS

Trade name	Chemical name	Composition	HLB	Regulatory status
Lipid phase – Non polar lipids and Class 1 polar lipids				
Vegetable oil	Long-chain TAG	TAG of C18, C16 and C14 FA	–	Oral product, GRAS, FDA IIG
Miglyol 812	Medium-chain TAG Caprylic/capric TAG	TAG of C8 and C10 FA	–	Oral product, GRAS, FDA IIG
Tricaprylin	Medium-chain TAG	TAG of C8 FA	–	–
Viscoleo	Fractionated coconut oil	TAG of C8-12 FA	–	–
Labrafac CC	Caprylic/capric triglyceride	TAG of C8-12 FA	–	–
Oleic acid	FA (*cis*-9-octadecanoic acid)	–	–	GRAS, FDA IIG
Ethyl oleate	Ethyl ester of C18:1(ω9) FA	–	–	FDA IIG
Captex 355	Glycerol caprylate caprate	TAG of C8 and C10	–	GRAS, FDA IIG
Isopropyl myristate	FA ester	Isopropyl ester of C14 FA (myristic acid)	–	FDA IIG
Labrafac PG	PG dicaprylocaprate	C8-C10 di-esters of propylene glycol	–	USFA, JSFA, EP, USP-NF pending
Class II polar lipids				
Peceol	Glyceryl mono-oleate	MAG and DAG of C18 and C16 FA with smaller quantities of TAG	3.3	GRAS, E471, EP, USP-NF, FDA IIG
Maisine 35-1	Glyceryl mono-linoleate	MAG and DAG of C18 and C16 FA with small quantities of TAG	4	Oral product, GRAS, E471, EP, USP-NF
Myvacet 9-45	Acetylated MAG	Acetylated MAG from hydrogenated soy bean oil	3.8	–
Imwitor 988	Caprylic/capric glycerides	MAG and DAG of C10 and C8 FA with traces of TAG	3.8	USP, Ph.Eur
Akoline MCM	Caprylic/capric glycerides	MAG and DAG of C8 and C10 with small quantity of TAG	5–6	–
Lipoid E80	Egg phosphatidylcholine	–	4	GRAS, FDA IIG
Capmul MCM	Caprylic/capric glycerides	MAG and DAG of C8 and C10 FA and 2% free glycerol	5–6	GRAS, FDA IIG
Capmul GMO 50	Glyceryl oleate	Mainly MAG with small amount of DAG and TAG of oleic acid	3–4	GRAS, EP, USP-NF
Class III surfactants, HLB < 12				
Span 20	Sorbitan monolaurate	Plain (non-PEGylated) sorbitan with C20 FA	8.6	EP, USP-NF
Polysorbate 85/Tween 85	Polyoxyethylene (20) sorbitan trioleate	Partial triesters of sorbitol and its mono-and di-anhydrides with oleic acid	11	UK
Tagat TO	Polyoxyethylene glycerol trioleate	Polyethoxylated glyceryl trioleate	11.5	–
Labrafil M1944CS	Oleoyl macrogolglycerides (polyoxylglycerides)	Mainly C18:1 mono- and diesters of PEG 300 and MAG, DAG and TAG from apricot kernel oil	4	EP, FDA IIG, USP NF
Labrafil M 2125 CS	Linoleoyl macrogolglycerides (polyoxylglycerides)	Mainly C18:1 mono- and diesters of PEG 300 and MAG, DAG and TAG from corn oil	4	EP, FDA IIG, USP NF
Lauroglycol 90	PG monolaurate	C12 FA mono-esters of propylene glycol	5	USFA, FCC, EFA, JSFA, UFA, USP-NF pending, IIF, EP, JPED
Lauroglycol FCC	PG laurate	C12 FA mono- and diesters of PG	4	USFA, FCC, EFA, JSFA, UFA, USP-NF pending, IIF, EP, JPED
Capryol 90	PG monocaprylate	C8 FA mono-esters of PG	6	USFA, FCC, JSFA, IFA, JPED
Capmul PG8	PG caprylate	C8 FA mono- and di-esters of PG	5–6	USP-NF
Poloxamer 331	Polyoxypropylene/ polyoxyethylene copolymer	–	1	–
Class III surfactants, HLB > 12				
Poloxamer 185	Polyethylene-polypropylene glycol	Polyoxyethylene, polyoxypropylene block polymers	15	USP XXII
Vitamin E TPGS	D-Alpha-tocopheryl PEG 1000 succinate	Alpha-tocopheryl PEG esters	13	Oral product

(Continued)

Table 3 *(Continued)*

Trade name	Chemical name	Composition	HLB	Regulatory status
Cremophor EL	Polyoxyl 35 castor oil	Glycerol-PEG ricinoleate, FA esters of PEG, free PEG and ethoxylate glycerol	12–14	Oral product, USP-NF, FDA IIG
Cremophor RH40	Polyoxyl 40 hydrogenated castor oil	FA esters of glycerol-PEG, FA esters of PEG, free PEG and ethoxylate glycerol	14–16	Oral product, EP, USP-NF, FDA IIG
Gelucire 44/14	Lauroyl macrogolglycerides (polyoxylglycerides)	FA C12:0 mono- and diesters of PEG 1500 and MAG, DAG and TAG with mainly C12:0 and some free PEG 1500 and glycerol	14	EP, USP-NF, FDA IIG
Labrasol	Caprylocaproyl macrogolglycerides (polyoxylglycerides)	FA C8:0/C10:0 mono- and diesters of PEG 400 and MAG, DAG and TAG with mainly C8:0 and C10:0 and some free PEG 400	14	EP, USP-NF, FDA IIG
Acconon MC-8	Caprylocaproyl macrogolglycerides (polyoxylglycerides) and C10:0 and some free PEG 400	FA C8:0/C10:0 mono- and diesters of PEG 400 and MAG, DAG and TAG with mainly C8:0	14–15	EP, USP-NF
Polysorbate 80/Tween	Polyoxyethylene (20) sorbitan mono-oleate	PEGylated sorbitan (a derivative of sorbitol) esterified with 80 C18:1 FA	15.0	Oral product, GRAS, EP, USP-NF, FDA IIG
Polysorbate 20/Tween 20	Polyoxyethylene (20) sorbitan monolaurate	PEGylated sorbitan (a derivative of sorbitol) esterified with C12 FA	16.7	Oral product, GRAS, EP, USP-NF, FDA IIG
Emulsifier OP	Nonyl phenol polyethenoxy ether	–	14.5	–
Tagat V20	Polyoxyethylene (20) glycerol monooleate	–	15	Oral product, FDA IIG
Co-solvents				
Ethanol	–	–	–	Oral product, EP, USP-NF
PEG	e.g. PEG 300 and PEG 400	–	–	Oral product, EP, USP-NF
PG	–	–	–	Oral product, EP, USP-NF
Carbitol	Diglycol monoethyl ether	–	–	–
Transcutol P	Diethylene glycol monoethyl ether	–	–	EP, US-NF, FDA IIG
Croderol	Glycerol	–	–	Oral product, GRAS, FDA IIG

PEG, polyethylene glycol; PG, propylene glycol; TAG, triacylglyceride; MAG, 2-monoacylglyceride; DAG, diacylglyceride; FA, fatty acid. Regulatory status: Oral product, excipient used in commercially available oral formulation(s); GRAS, generally recognised as safe; E471, European Food Additive; EP, European Pharmacopoeia; USP-NF, United States Pharmacopeia – National Formulary; FDA IIG, FDA Inactive Ingredient Guide; Ph.Eur., Pharmacopoeia Europea.

drug in solution are developed. Second, the homogenous preconcentrates that form an emulsion with the desired appearance and characteristics upon gentle agitation in an aqueous medium, with no precipitation of drug, are selected.

Lipids

The lipid part of the SMEDDS forms the core of the emulsion particle and is typically composed of non-polar lipids or Class I polar lipids in Small's Lipid Classification system.[48] Examples of lipids utilised in SMEDDS include long-chain and medium-chain triacylglycerides, diacylglycerides and fatty acid esters, as well as protonated long-chain fatty acids.

Surfactants

The role of surfactants in SMEDDS is to reduce the interfacial tension and adjust the spontaneous curvature of the interface so as to enable the dispersion process and provide a flexible film that can easily cover the lipid core of the emulsion droplets and lead to the spontaneous formation of a nano- or microemulsion. Basically, the increase of surfactant activity at the water–oil interface would result in a decrease of interfacial tension. Moreover, the addition of a second surfactant to the system would usually cause a further decrease in interfacial tension down to a very small, even transient negative value, at which the interface would expand to form fine dispersed droplets. For the formation of SMEDDS the presence of water-soluble surfactants, often in a concentration higher than 20%, is necessary. The surfactants used in SMEDDS are typically classified as Class IIIA in Small's Lipid Classification system. The use of non-ionic surfactants is preferred as these have proven to be safer than ionic surfactants.

Class II polar lipids, like 2-monoacylglycerides, are also often employed in SMEDDS. 2-Monoacylglycerides are not able to make SMEDDS alone, but used together with Class III

polar lipids they will ease the emulsification process and often reduce the emulsion particle size. Most likely 2-monoacylglycerides will orient themselves with their polar head group on the surface of the emulsion particle. Taking this into consideration Class II polar lipids can be referred to as co-surfactants. One issue in this regard is that 2-monoacylglyceride is often present in pharmaceutical excipients together with Class I polar lipids, like diacylglycerides (see Table 3), thus complicating the separation of the functional components in a self-emulsifying drug delivery system.

Co-solvents

The function of co-solvents in SMEDDS is to facilitate the dispersion process and often addition of co-solvents to SMEDDS results in faster dispersion rate. Co-solvents frequently used in SMEDDS for oral administration include polyethylene glycols, ethanol, propylene glycol and glycerol. Co-solvents often improve the solubility of the drug in the SMEDDs pre-concentrate, although this can constitute a problem upon dispersion of the SMEDDS, since the polar cosolvent will partition into the aqueous phase, and that way reduce the solubilisation capacity of the dispersed system, resulting in precipitation of the drug compound. It is therefore advisable to use a smaller quantity of co-solvents in SMEDDS and also to select the ones that can remain at the interface of the emulsion particle.

Development and characterisation of self-emulsifying drug delivery systems

Construction of ternary or pseudo-ternary phase diagrams is often employed in the development of SMEDDS. The diagram helps to determine the optimum concentration ranges of different excipients necessary to obtain, for example, homogenous pre-concentrates, self-emulsification ability and drug loading. In a pseudo-ternary diagram, each corner represents 100% of a particular component and when more than three components are used, closely related ones are grouped together as one component and treated as such in the diagram.

A pseudo-ternary phase diagram can be utilised in many ways. For development of SMEDDS, the first pseudo-ternary diagram produced (Figure 1) typically identifies the area covering homogenous pre-concentrates. When this area has been defined, the next step will be to elucidate which preconcentrates form nano- or micro-emulsions with the desired characteristics (Figure 1). The emulsification capacity of a pre-concentrate can be determined by creation of a specific dilution of the pre-concentrate in water or buffer. Alternatively, biorelevant media simulating either gastric or intestinal fluids can be applied. Typically, dilutions of 1 : 50, 1 : 100 or 1 : 250 have been employed. When deciding the dilution to be used, the in-vivo relevant dilution should be considered, as the volume of the fasted stomach is, on average, 50 ml, as mentioned above. Another method is to titrate the aqueous phase drop-wise into the pre-concentrate. When water is incorporated to the SMEDDS pre-concentrates, complex systems begin to form, ranging from gels to systems containing lamellar, hexagonal or cubic phases to microemulsions.[11,12,21] The changes can be assessed visually or by the method mentioned below and described in ternary-phase diagrams.

The water absorption and emulsification process during addition of an aqueous phase to the pre-concentrate can be characterised by *viscosity* and *conductivity*. When a

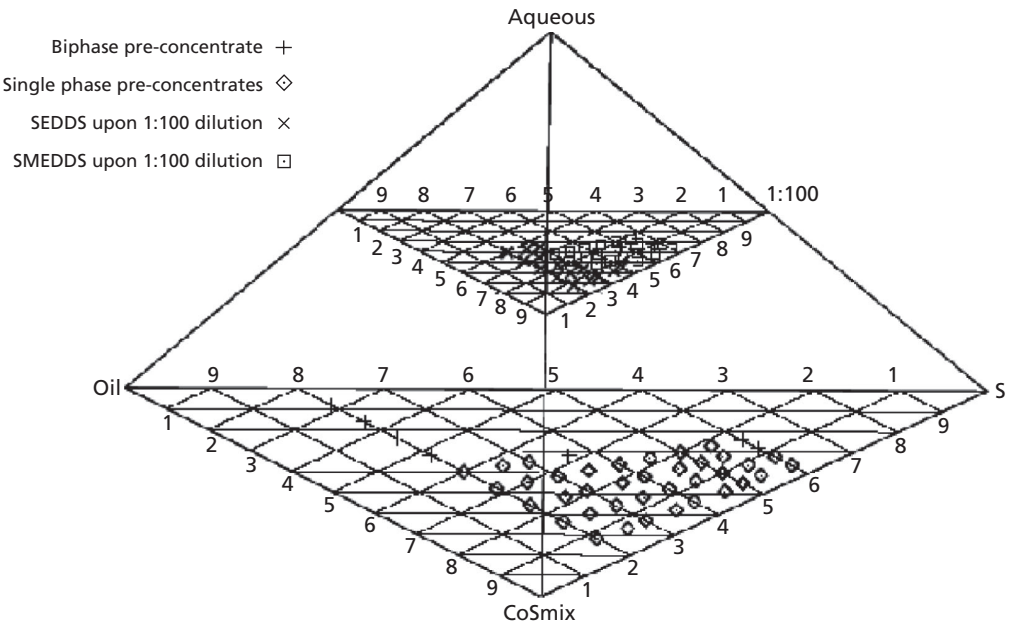

Figure 1 3D *pseudo*-ternary phase diagrams indicating regions of single phase and biphase of pre-concentrates (bottom) as well as demonstrating o/w microemulsion (ME) region (upper) on titration with 100-fold water (unpublished data). S, surfactant; CoSmix, mixture of co-surfactant and co-solven.

SMEDDS pre-concentrate is diluted with water, different mesomorphic phases are formed, which exhibit different rheological properties. Upon introduction of water to the system, often an increase in viscosity is observed until enough water has been added to form a continuous water phase, then the viscosity decreases and is close to that of water in a dispersed SMEDDS. Viscosity measurement helps to determine the transition between mesomorphic structures.[49]

Conductivity measurements are able to determine the point of aqueous phase addition where the system changes from having oil continuous to a water continuous phase. It also helps in monitoring percolation or phase inversion phenomena.[50,51]

The *rate of self emulsification* is usually determined by adding a dose of the SMEDDS pre-concentrate, preferably in a capsule, to a relevant amount of water or biorelevant media. By visual observation or by monitoring the change of turbidity of dispersion using a UV spectrophotometer or nephlometer, the rate of dispersion is determined.

Particle size distribution in the formed nano- or microemulsion is measured by dynamic light scattering techniques. This utilises the fluctuation in scattered light intensity to measure the velocity of the Brownian diffusion and consequently the dispersed droplets. It is ideal for measuring particles in the range of 3 nm to 3 μm. Particle size distributions can be further verified by cryogenic transmission electron microscopy (cryo-TEM). Cryo-TEMoffers the advantage of vizualising the particle sizes and shapes.[11] By picture-analysis the particle size distribution can be determined.

Another way to characterise the formed emulsion particles is by determining their *zeta potential*. When a SMEDDS is immersed in a liquid, a range of processes causes the interface to become electrically charged. The charge cannot be measured directly, but only through the electrical field it creates around the particle. Zeta potential measures the velocity of particles using the Doppler shift of light scattered from the moving particles. Consequently zeta potential can be determined by measuring the drift velocity of the particle in an electrical field of known strength. It helps to predict the stability and flocculation effect in emulsion systems. If the zeta potential falls below a certain level, the colloid will aggregate due to the attractive forces. Conversely, a high (absolute) zeta potential maintains a stable system, and can be used to identify stable emulsions with long shelf life.[52]

In-vitro lipolysis models

In addition to the methods for development of SMEDDS mentioned above, another very important factor to examine is the digestibility of SMEDDS in the gastrointestinal tract. When excipients in SMEDDS are digested the solubilisation capacity may be compromised, leading to precipitation of drug, which can have implications for the bioavailability. The digestibility of SMEDDS can be assessed by the use of in-vitro lipolysis models.[53–55]

The existing in-vitro lipolysis models are simulating lipid digestion in the upper small intestine. Bile salts, phospholipids, buffer and SMEDDS containing drug are mixed and incubated at 37°C in a pH-stat using NaOH as titrant. The levels of bile salt and phospholipid are selected to simulate either the fasted or the fed state, depending on the purpose of the study. The lipolysis is initiated by the addition of pancreatic extract, containing all pancreatic enzymes. The action of pancreatic lipase and other esterases present in the pancreatic extract will induce the hydrolysis of triacylglycerides and other excipients, releasing free fatty acids and causing a drop in the pH. The pH drop will be immediately corrected by NaOH addition by the pH-stat. The moles of NaOH added will correspond to the moles of fatty acid formed. During lipolysis, free fatty acids will accumulate on the surface of the lipid droplet and inhibit the activity of pancreatic lipase; however, addition of calcium ions will remove the free fatty acid by forming insoluble

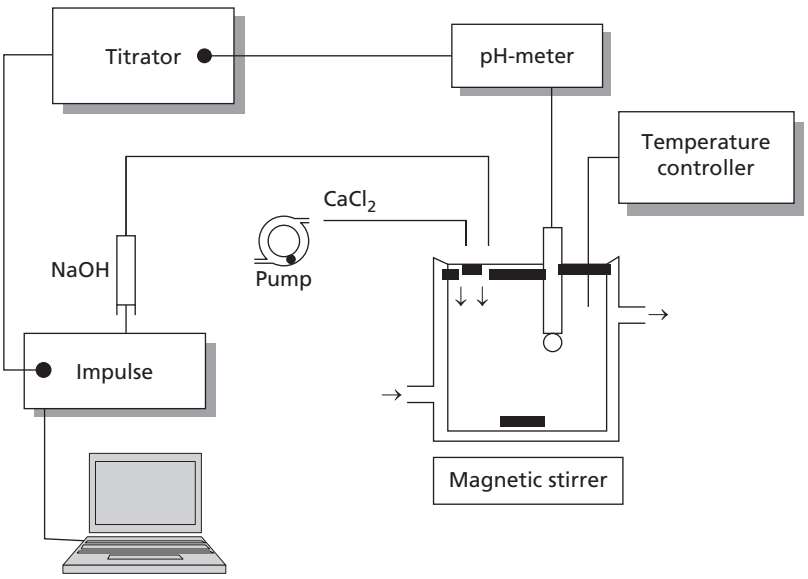

Figure 2 Schematic set-up of the dynamic in-vitro lipolysis model.[56]

calcium fatty acid soaps, which precipitate, thereby removing free fatty acid from the system.

Basically two different in-vitro lipolysis models have been described: a model where calcium chloride (Ca^{2+}) is added at the initiation of the lipolysis[53] and a model where Ca^{2+} is added continuously during the lipolysis[54,55] (the dynamic lipolysis model). However, other differences also apply between the two different models.

The first model employs pure taurocholate as a source of bile salt, has a total volume of 9 ml and is operated at pH 7.5. A fixed amount of Ca^{2+} (typically 5 mM) is added at the beginning of the lipolysis and the reaction will stop when all the added calcium has been complexed with the generated free fatty acid. Usually this takes less than 5 min and the lipolysis is stopped at 30 min.

The dynamic lipolysis model (Figure 2) employs crude bile extract as a source of bile. This is done not only to reduce cost but also to render the model closer to the in-vivo situation. Upon initiation of the lipolysis, a continuous addition of Ca^{2+} is also started. The Ca^{2+} addition enables the control of the lipolysis rate in such a way that samples can be taken out at desired time points. Due to the sampling during lipolysis the dynamic lipolysis model is often run using a larger volume (e.g. 300 ml). For the dynamic lipolysis model, a pH of 6.5 has been chosen as a compromise between the average pH in the upper small intestine, the pH optimum of the pancreatic lipase and esterases and the pKa of free fatty acids.[54,55]

In both models samples are collected at different time points and lipolysis is inhibited immediately by using

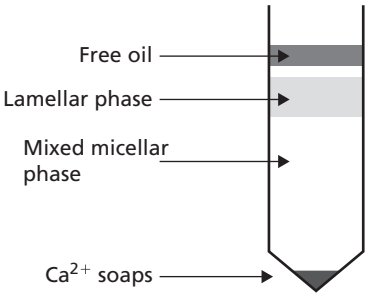

Figure 3 Different phases of lipid-based formulation after digestion and ultracentrifugation.[28]

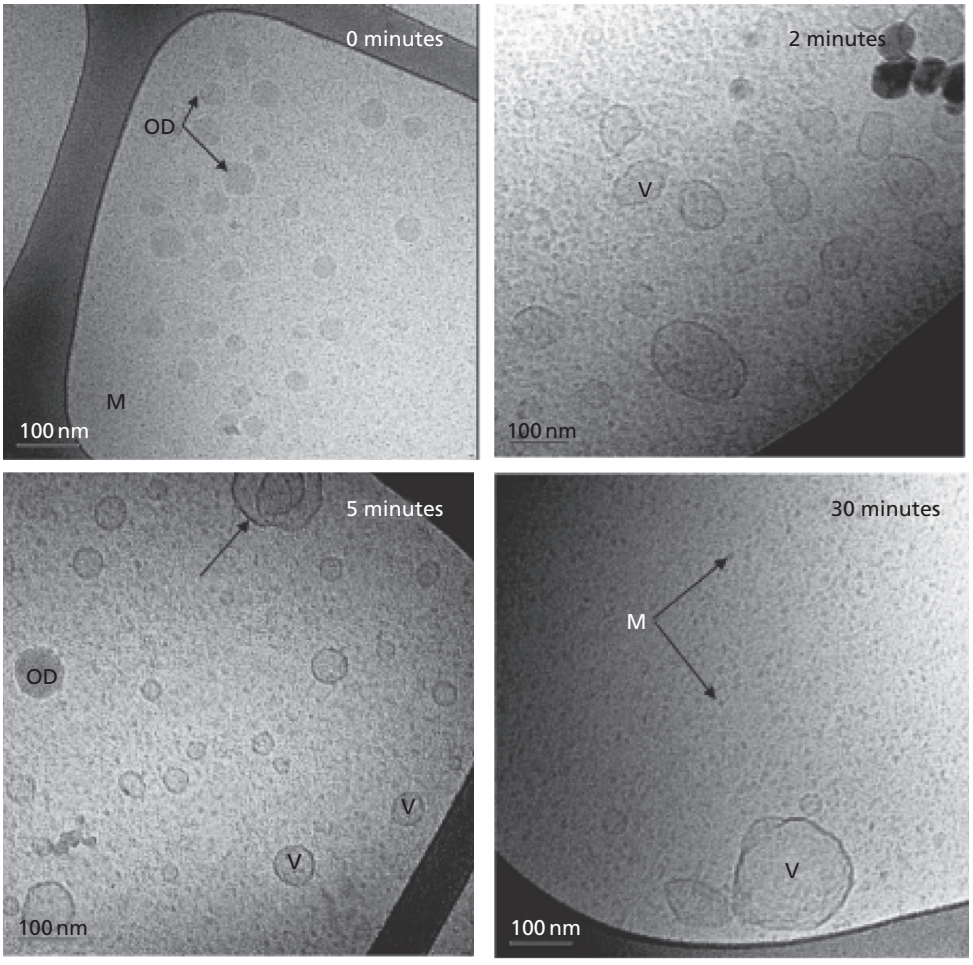

Figure 4 Cryo-transmission electron microscopy micrographs of colloid structures present during in-vitro lipolysis of a SMEDDS. In 5 : 1 mM bile salt : phospholipid; before addition of lipase, and at 2, 5 and 30 min after initiation of lipolysis.[11] OD, oil droplets; V, vesicles; M, micelles.

4-bromobenzeneboronic acid solution. The samples are separated by ultracentrifugation into three different phases (oil, micellar and pellet phase) (Figure 3). The oil phase on the top of the tube is generally only seen at the beginning of the experiment, and originates from non-lipolysed formulation. The pellet phase consists of calcium soap of free fatty acid and precipitated drug, while the micellar phase contains the part of the drug that is supposedly available for absorption. For this reason the drug content in the micellar phase has been used to correlate with the bioavailability of drug from the formulation.[57,58]

In-vitro lipolysis is a very important tool in the evaluation of LSBDDS containing digestible excipients, even for formulations containing only surfactants and co-solvents (LFCS Type IV).[59] Several studies have shown that many surfactants are subject to digestion in the gastrointestinal tract.[34,60,61] Studies on the digestion of LSBDDS have proved that solvent capacity can be lost during this process, leading to precipitation of the drug[38,59,62] in the lumen and possibly reduced bioavailability. More studies are needed in this area to enhance the understanding of digestion of these formulations, the formed digestion products and their interaction with bile salts.

Morphology

Cryo-TEM has been used[63,64] to study the colloid phases such as vesicles and micelles. Cryo-TEM operates on the same basic principles as the light microscope but uses electrons instead of light. It has the advantage of not utilising fixation of the sample on the copper grids, which normally causes artefacts due to staining, thereby keeping the sample close to original state. Cryo-TEM has been used to study the morphological changes of SMEDDS during digestion in the dynamic lipolysis model.[11] It was possible to demonstrate gradual formation of different mesomorphic structures over time (Figure 4); initially intact oil droplets were seen, but gradually unilamellar vesicles were formed as a consequence of the lipolysis. At 5 min, unilamellar vesicles and micelles dominated, but these had disappeared after 30 min of in-vitro lipolysis, leaving primarily micelles.

SEDDS and SMEDDS recently used in research

Table 4 depicts some of the SEDDS and SMEDDS that have been developed and used in recent publications. As can be

Table 4 Representative formulations of SEDDS and SMEDDS in research

Drug	Non-polar lipids & Class I polar lipids (HLB < 12)	Class II Polar lipids	Class III lipids, hydrophobic surfactant HLB > 12)	Class III lipids, hydrophilic surfactant	Co-solvent	LCFS
Celecoxib	Capmul PG8	–	–	Tween 20 Acconon MC-8	–	III[65]
Clonixic acid	Castor oil	–	Tween 85	Tween 80	–	–[66]
Curcumim	Ethyl oleate	–	–	Cremophor EL Emulsifier OP	PEG 400	III[67]
Danazol	Sesame oil	Maisine 35-1	–	Cremophor RH40	Ethanol	III[a][34,68]
Danazol	Captex 355	Capmul MCM	–	Cremophor EL	Ethanol	III[a][69]
Danazol	Soybean oil	Maisine 35-1	–	Cremophor EL	Ethanol	III[a][69]
Fenofibrate	Miglyol 812	–	Tween 85	–	–	II[37,58]
Fenofibrate	Miglyol 812	Imwitor 988	Tween 85	–	–	II[a][59]
Fenofibrate	–	–	–	Tween 80	PG	IV[59]
Fenofibrate	–	–	Labrafac CM-10	Tween 80	PEG 400	–[70]
Griseofulvin	–	Myvacet 9-45 Capmul GMO-50	–	Poloxamer	–	III[a][71]
Halofantrine	Captex 355	Capmul MCM	–	Cremophor EL	Ethanol	III[a][72]
Halofantrine	Soybean oil	Maisine 35-1	–	Cremophor EL	Ethanol	III[a][72]
Oridonin	Labrafac CC	Maisine 35-1	–	Cremophor EL	Transcutol P	III[a][73]
Puerarin	Oleic acid	–	–	Tween 80	PG	III[74]
Probucol	Sesame oil	Maisine 35-1	–	Cremophor RH40	Ethanol	III[a][62]
Seocalcitol	Viscoleo	Akoline MCM	–	Cremophor RH40	–	III[75]
	Sesame oil	Maisine 35-1		Cremophor RH40	–	III[a]
Simvastatin	–	–	Capryol 90	Cremophor EL	Carbitol	–[37]
Simvastatin	–	–	Capryol 90	Cremophor EL	PEG 400	–[37]
Simvastatin	–	–	Lauroglycol 90	Cremophor EL	Carbitol	–[37]
Tamoxifen citrate	–	Maisine 35-1	Capryol 90	Cremophor RH40	PG	–[76]
Zedoary essential oil	Ethyl oleate	–	–	Tween 80	Transcutol P	III[52]
Zedoary essential oil	Miglyol 812	–	Tween 85	–	Transcutol P	–[52]

PEG, polyethylene glycol; PG, propylene glycol. The classification is based only on the category of formulated excipients and not on their quantity.
[a]Formulations containing Class II polar lipids and thus not complying with the suggested LSBDDS classification

seen, many of the formulations do not fit into the LFCS. Excipients in SMEDDS are usually selected according to their capability of forming SMEDDS, and also according to their solubilising capacity towards the used drug, both in the pre-concentrate and in the dispersed SMEDDS.

Most of the SMEDDS listed in Table 4 that do not fit into the LFCS contain a mixture of high and low HLB surfactants,[36,52,56,63,68,70,76] which is not described in the current LFCS.

Frequently the SMEDDS contain Class II polar lipids, typically from excipients that are mixtures of Class I and Class II polar lipids[2,34,62,73,75], like Maisine 32-1 or Capmul MCM. The Class II polar lipids ease the emulsification process and can be regarded as co-surfactants in SMEDDS as described above. In addition some drugs will display a higher solubility in Class II polar lipids.

Further medium-chain triacylglycerides are widely used in SMEDDS Type III, due to their higher polarity compared with long-chain triacylglycerides, which facilitates the emulsification process.[37,52,64,66,72,74,75] Other lipid phases that have been employed are ethyl oleate[52] and oleic acid.[74]

In conclusion the LFCS does not encompass all the SEDDS and SMEDDS that have recently been used in research and thus would benefit from being updated as suggested in the present review.

Conclusions

Lipid- and surfactant-based drug delivery systems, especially SMEDDS, are a promising approach for improving the bioavailability of poorly soluble drug compounds. The mechanisms behind this improvement have been attributed to a number of factors, including delivery of the drug in solution to the gastrointestinal tract, increased bile secretion, easier partition of the drug into the mixed micelles that are believed to facilitate drug absorption, stimulation of lymphatic transport, modulation of enterocyte-based enzyme and transporters systems and increased intestinal permeability.

Despite their great success in bioavailability enhancement, and the large number of poorly soluble compounds on the market, LSBDDS are still not very widespread as commercial formulations. Explanations for this range from lack of knowledge and understanding of the development and manufacturing process to physical and chemical stability issues, as well as the preconceived notion that tablets are the preferred dosage form.

In the present review we have, for the first time, applied basic physicochemical properties of lipid and surfactant excipients to the classification of LSBDDS. Knowledge of the behaviour of non-polar and polar lipids in bulk water and in the water–air interface will enable a more rational and strategic development of LSBDDS.

Future focus should be on obtaining a better understanding of the role of individual lipids and surfactants in the formation of SMEDDS, with regard to the dispersion process, the structure of the formed emulsion particle and drug solubilisation. In addition the digestibility of SMEDDS and the implication of digestion for drug solubilisation should also be studied so as to achieve a better understanding. All in all this will enable a more rational development strategy for LSBDDS.

Finally, based on a better knowledge and understanding of non-polar and polar lipids and their functionality, it should be possible to improve the current LFCS to accommodate all the LSBDDS currently in the market and used in research.

Declarations

Conflict of interest

The Author(s) declare(s) that they have no conflicts of interest to disclose.

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