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Review article

# Self-dispersing lipid formulations for improving oral absorption of lipophilic drugs

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**Abstract**

The main purpose of this review is to provide a current and general overview of the existing self-dispersing formulations resulting from dilution into emulsions, microemulsions and surfactant dispersions. The systematic approach used and the presentation of the various physico-chemical and biopharmaceutical aspects should facilitate the comprehension of this interesting field and clarify the main considerations involved in designing and characterizing a specific self-dispersing drug delivery system. Studies have shown that the self-emulsification process is specific to the nature of the oil/surfactant pair, surfactant concentration, oil/surfactant ratio and temperature at which self-emulsification occurs. It was suggested that the ease of emulsification could be associated with the ease by which water penetrates into the various liquid crystalline (LC) or gel phases formed on the surface of the droplet. Numerous bioavailability studies carried out in animals and humans, reviewed in the present study, suggest that hydrophobic drugs are better absorbed when administered in self-dispersing lipid formulations (SDLFs). Examples which illustrate the beneficial use of SDLFs for drug absorption enhancement are presented. This review outlines SDLFs as one of the most promising approaches to overcome the formulation difficulties of these hydrophobic/lipophilic drugs.
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*Keywords*: Self-emulsifying; Emulsion; Microemulsion; Dispersion; Oral bioavailability; Lipophilic drugs; Positive charge

## 1. Introduction

The oral route is the preferred route for chronic drug therapy. Numerous potent lipophilic drugs exhibit low oral bioavailability due to their poor aqueous solubility properties. For this class of compounds, defined by Amidon et al. as 'low solubility/high permeability class', dissolution in the environmental lumen is the rate-controlling step in the absorption process [1]. Efforts are ongoing to enhance the oral bioavailability of lipophilic drugs in order to increase their clinical efficacy. The most popular approach is the incorporation of the active lipophilic component into inert lipid vehicles [2], such as oils [3], surfactant dispersions [4,5], self-emulsifying formulations [6–9], emulsions [10–14] and liposomes [15], with every formulation approach having its specific advantages and limitations.

Self-emulsifying drug delivery systems (SEDDS) have been previously described in the literature as homogeneous mixtures of natural or synthetic oils, solid or liquid surfactants, or alternatively, one or more hydrophilic solvents and co-solvents [6–9,16,17]. The principal characteristic of these systems is their ability to form fine oil-in-water (o/w) emulsions or microemulsions upon mild agitation following dilution by aqueous phases. This property renders SEDDS as good candidates for the oral delivery of hydrophobic drugs with adequate solubility in oil or oil/surfactant blends.

The extensive research of SEDDS led to the design of other original lipid self-dispersing pharmaceutical vehicles capable of forming drug-loaded fine lipid particles in the gastrointestinal (GI) lumen. Therefore, self-microemulsion formulations [16,18,19], surfactant dispersions [4,5], pre-formulated freeze-dried [20], or microencapsulated [21] emulsions and lipid/cross-linked polymeric matrices [22] have been recently proposed as alternatives to conventional SEDDS. All these formulations can be administered in soft or hard gelatin capsules, and will produce fine oil droplets/micelle dispersion upon capsule disintegration and aqueous dilution. Self-emulsifying/dispersing formulations spread readily in the GI tract, while the digestive motility of the stomach and intestine provide the agitation necessary for

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self-emulsification/dispersion. For lipophilic drugs which display dissolution rate-limited absorption, these lipid self-dispersing lipid formulations (SDLFs) may offer an improvement in the rate and extent of absorption, while yielding more reproducible blood–time profiles.

The present work reviews the use of lipid self-emulsifying/dispersing formulations for the oral absorption enhancement of lipophilic drugs, and discusses their main physicochemical and biopharmaceutical aspects.

## 2. Physico-chemical aspects of SDLFs

### *2.1. SDLF composition*

Early studies [6,23,24] revealed that the self-emulsification process is specific to: (1), the nature of the oil/surfactant pair; (2), the surfactant concentration and oil/surfactant ratio; and (3), the temperature at which self-emulsification occurs. These important discoveries were further supported by the fact that only very specific combinations of pharmaceutical excipients led to efficient self-emulsifying systems [7,8,25–28].

#### *2.1.1. Oils*

Both long- and medium-chain triglyceride (MCT) oils with different degrees of saturation have been used for the design of self-dispersing formulations (Table 1). Unmodified edible oils provide the most 'natural' basis for lipid vehicles, but their poor ability to dissolve large amounts of hydrophobic drugs and their relative difficulty in efficient self-emulsification markedly reduce their use in SDLFs. In contrast, modified or hydrolyzed vegetable oils have contributed widely to the success of the above systems [16,26,27] since they exhibit formulative and physiological advantages. These excipients form good emulsification systems, with a large number of non-ionic surfactants approved for oral administration, while their degradation products resemble the end products of intestinal digestion. MCTs were preferred in the earlier self-emulsifying formulations [7,8,29] because of higher fluidity, better solubility properties and self-emulsification ability, but evidently, they are considered less attractive compared to the novel semi-synthetic medium-chain derivatives [16] which can be defined rather as amphiphilic compounds exhibiting surfactant properties. In such cases, the more lipophilic surfactant may play the role of the hydrophilic oil in the formulation [16,30].

#### *2.1.2. Surfactants*

Non-ionic surfactants with a relatively high hydrophilic–lipophilic balance (HLB) were advocated for the design of self-dispersing systems, where the various liquid or solid ethoxylated polyglycolyzed glycerides and polyoxyethylene 20 oleate (Tween 80) are the most frequently used excipients (Table 1). Emulsifiers derived from natural sources are expected to be safer than synthetic ones and are recommended for SDLF use [16,27,31,32], despite their limited ability to self-emulsify. Non-ionic surfactants are known to be less toxic compared to ionic surface-active agents, but they may cause moderate reversible changes in intestinal wall permeability [6,33]. Amemiya et al. proposed a new vehicle based on a fine emulsion using minimal surfactant content (3%) to avoid the potential toxicological problems associated with high surfactant concentration [34]. The usual surfactant concentration in self-emulsifying formulations required to form and maintain an emulsion state in the GI tract ranged from 30 to 60% w/w of the formulation. A large quantity of surfactant may irritate the GI tract. Thus, the safety aspect of the surfactant vehicle should be carefully considered in each case.

The high HLB and subsequent hydrophilicity of surfactants is necessary for the immediate formation of o/w droplets and/or rapid spreading of the formulation in the aqueous environment, providing a good dispersing/self-emulsifying performance. The surface-active agents are amphiphilic by nature, and they are therefore usually able to dissolve and even solubilize relatively high quantities of the hydrophobic drug. The latter is of prime importance for preventing precipitation within the GI lumen and for the prolonged existence of the drug molecules in soluble form, which is vital for effective absorption [4,8]. The lipid mixtures with higher surfactant and co-surfactant/oil ratios lead to the formation of self-microemulsifying formulations (SMEDDS) [16,18,19,28]. Formulations consisting only of the surfactant mixture may form emulsions or microemulsions (when surfactants exhibit different low and high HLB) [30], micelle solution [5] or, in some particular cases, niosomes, which are non-ionic, surfactant-based bilayer vehicles [35].

#### *2.1.3. Co-solvents*

Relatively high surfactant concentrations (usually more than 30% w/w) are needed in order to produce an effective self-emulsifying system (Table 1). Organic solvents, suitable for oral administration (ethanol, propylene glycol (PG), polyethylene glycol (PEG), etc.) may help to dissolve large amounts of either the hydrophilic surfactant or the drug in the lipid base. These solvents sometimes play the role of the co-surfactant in the microemulsion systems, although alcohol-free self-emulsifying microemulsions have also been described in the literature [16]. Indeed, such systems may exhibit some advantages over the previous formulations when incorporated in capsule dosage forms, since alcohol and other volatile co-solvents comprised in the conventional self-emulsifying formulations are known to migrate into the shells of soft gelatin, or hard, sealed gelatin capsules, resulting in the precipitation of the lipophilic drug. On the other hand, the lipophilic drug dissolution ability of the alcohol-free formulation may be limited.

#### *2.1.4. Drug incorporation*

SDLFs are normally designed to be administered in a

Table 1
Composition of SDLFs that led to oral bioavailability enhancement of lipophilic drugs in in-vivo models[a]

| Delivery system type | Oil | Surfactant(s) | %w/w | Solvent(s) | Model drug | Drug content (%) | Reference |
|---|---|---|---|---|---|---|---|
| SEDDS | A mixture of mono- and di-glycerides of oleic acid | Solid, polyglycolyzed mono-, di- and tri-glycerides (HLB = 14) | 80 or 20 | – | Ontazolast | 7.5 | [27] |
| Surfactant/solvent dispersion | – | Tween 80 (HLB = 15) | NA | Ethanol, PG | Retinol (vitamin A), riboflavine (vitamin B2) | NA | [60] |
| Surfactant dispersion | – | Solid, polyglycolyzed mono-, di- and tri-glycerides (HLB = 14) | 81 | – | α-pentyl-3-(2-quinolinyl-methoxy)-benzenemethanol | 19 | [4] |
| Sandimmune® formulation, SEDDS | Olive oil | Polyglycolyzed glycerides (HLB = 3/4) | 30 | Ethanol | CsA | 10 | [61] |
| Lipid dispersion | Medium-chain monoacyl glycerol | Soybean phosphatidyl choline | 30 | – | Hexarelin | 11.8 | [62] |
| SEDDS | Medium-chain saturated fatty acids, peanut oil | Medium-chain mono- and di-glycerides, Tween 80, PEG-25 glyceryl trioleate, polyglycolyzed glycerides (HLB = 6–14) | 5–60 | – | Ro 15-0778, a naphthalene derivative | 5 | [8] |
| SEDDS | Medium-chain saturated fatty acids | PEG-25 glyceryl trioleate | 25 | – | WIN 54954 (5-(5-(2,6-dichloro-4-(dihydro-2-oxazolyl)phentoxy)pentyl)-3-methylisoxazole) | 35 | [7] |
| SMEDDS | – | Polyglycolyzed glycerides (HLB = 1–14) | 96 | – | Indomethacin | 4 | [30] |
| Surfactant dispersion | – | Polyglycolyzed glycerides (HLB = 14) | 79.5 | PEG 400 | DMP 323 (HIV protease inhibitor) | 7.5 or 12.5 | [5] |
| Neoral® formulation, SMEDDS | Hydrolyzed corn oil | Polyglycolyzed glycerides, POE–castor oil derivative | NA | Glycerol | CsA | 10 | [16] |
| Neoral® formulation, SMEDDS | Hydrolyzed corn oil | Polyglycolyzed glycerides, POE–castor oil derivative | NA | Ethanol | CsA | 10 | [19] |
| Positively charged SEDDS | Ethyl oleate | Tween 80 | 25 | Ethanol | CsA | 10 | [41] |
| Positively charged SEDDS | Ethyl oleate | Tween 80 | 25 | Ethanol | Progesterone | 2.5 | [44] |

[a] NA, not available.

small unidose form which can be dispensed in gelatin capsules. In some particular cases, like solid surfactant dispersions [4,5], the drug is dispersed within the formulation, but as a rule, a relatively high (therapeutic) quantity of drug has to be dissolved in SDLFs. The novel synthetic hydrophilic oils and surfactants usually dissolve hydrophobic drugs to a greater extent than conventional vegetable oils. The addition of solvents, such as PEGs, PG, ethanol, etc., may also improve the drug solubility in the lipid vehicle.

From the overall results published in the literature, it can be deduced that the outcome of drug addition to SEDDS is specific to every case, and depends on the drug/system physico-chemical compatibility. Generally, the drug interferes with the process of self-emulsification to some extent, probably by changing the optimal oil/surfactant ratio. It was suggested that SEDDS performance alteration can be caused either by blocking charge movement through the system, via the direct complexation of the drug with some mixture components through its interaction with the liquid crystalline (LC) phase [9,17], or by penetration into the surfactant interfacial monolayer [7,9,36]. Craig et al. [7] have shown that the incorporation of a poorly water-soluble benzodiazepine derivative within self-emulsifying formulations decreased the emulsification effici ency. The authors have observed that the drug interacted with one or more components of the self-emulsifying systems, leading to a change in the droplet size distribution which varied as a function of drug concentration. However, it was shown that the incorporation of up to 40% of the investigation compound (5-5-(2,6-dichloro-4(dihydro-2-oxazolyl) pentyl)-3-methylisoxazole (WIN 54954) into the MCT/polyoxyethylene [25] glycerol trioleate (Tagat TO) system did not alter the efficiency of emulsification [7]. Moreover, the self-emulsifying properties were even improved by the incorporation of a model drug, benzoic acid, to the MCT/polyoxyethylene 20 sorbitan trioleate (Tween 85) mixture [24]. However, it should be pointed out that the above early developed systems formed relatively coarse emulsions with a droplet size of up to a few microns. The more complex formulations, resulting in emulsions with smaller oil droplets and microns, are more sensitive to composition changes caused by drug addition [16,18]. In any case, pre-formulation solubility and phase diagram studies are required in order to design an optimal self-emulsifying drug vehicle.

### 2.2. The mechanism of self-emulsification

The process by which self-emulsification takes place is not yet well understood. However, according to Reiss [37], self-emulsification occurs when the entropy change that favors dispersion is greater than the energy required to increase the surface area of the dispersion. In addition, the free energy of a conventional emulsion formation is a direct function of the energy required to create a new surface between the two phases and can be described by Eq. (1) [37]

$$\Delta G = \sum_{i} N_i \pi r_i^2 \sigma \quad (1)$$

Where $\Delta G$ is the free energy associated with the process (ignoring the free energy of mixing), $N$ is the number of droplets of radius, $r$, and $\sigma$ represents the interfacial energy. With time, the two phases of the emulsion will tend to separate, in order to reduce the interfacial area, and subsequently, the free energy of the systems. Therefore, the emulsions resulting from aqueous dilution are stabilized by conventional emulsifying agents, which form a monolayer around the emulsion droplets, and hence, reduce the interfacial energy, as well as providing a barrier to coalescence. In the case of self-emulsifying systems, the free energy required to form the emulsion is either very low and positive, or negative (then, the emulsification process occurs spontaneously) [38]. Emulsification requiring very little input energy involves destabilization through contraction of local interfacial regions. For emulsification to occur, it is necessary for the interfacial structure to have no resistance to surface shearing [39]. In earlier work, it was suggested that the ease of emulsification could be associated with the ease by which water penetrates into the various LC or gel phases formed on the surface of the droplet [6,40,41]. According to Wakerly et al. [6], the addition of a binary mixture (oil/non-ionic surfactant) to water results in interface formation between the oil and aqueous-continuous phases, followed by the solubilization of water within the oil phase owing to aqueous penetration through the interface. This will occur until the solubilization limit is reached close to the interface. Further aqueous penetration will result in the formation of the dispersed LC phase. As the aqueous penetration proceeds, eventually all material close to the interface will be LC, the actual amount depending on the surfactant concentration in the binary mixture. Once formed, rapid penetration of water into the aqueous cores, aided by the gentle agitation of the self-emulsification process, causes interface disruption and droplet formation. The high stability of these self-emulsified systems to coalescence is considered to be due to the LC interface surrounding the oil droplets. The involvement of the LC phase in the emulsion formation process was extensively studied by Pouton et al. [6,23,29,41]. Later, Craig et al. used the combination of particle size analysis and low frequency dielectric spectroscopy (LFDS) to examine the self-emulsifying properties of a series of Imwitor 742 (a mixture of mono- and diglycerides of capric and caprylic acids)/Tween 80 systems [9,17,38]. The dielectric studies provided evidence that the formation of the emulsions may be associated with LC formation, although the relationship was clearly complex [38]. The above technique also pointed out that the presence of the drug may alter the emulsion characteristics, possibly by interacting with the LC phase [17]. However, the correlation between the spontaneous emulsification and LC formation is still not definitely established [17,42].

### 2.3. SDLF evaluation

Few methods have been proposed in the literature to characterize the self-emulsifying performance. Visual assessment may provide important information about the self-emulsifying properties of the mixture and about the resulting dispersion system [38,42,43], although more objective criteria are required for efficient SDLF evaluation and comparison. Pouton proposed estimating the efficiency of self-emulsification by evaluating the rate of emulsification and the particle size distribution. He used turbidity measurements to identify efficient self-emulsifying systems by establishing whether the dispersion reached equilibrium rapidly and in a reproducible time [42]. Shah et al. pointed out the role of emulsion droplet polarity, in addition to droplet size, as an important emulsion characteristic [8]. The polarity of the oil droplets is governed by the HLB, the chain length and degree of unsaturation of the fatty acid, the molecular weight of the hydrophilic portion and the concentration of the emulsifier. In fact, the polarity reflects the affinity of the drug for oil and/or water, and the type of forces formed. The polarity will promote a rapid rate of release of the drug into the aqueous phase. More recently, Craig et al. investigated the physico-chemical properties of SEDDS with and without drugs using LFDS in order to investigate the effects of drug inclusion. The corresponding emulsions were checked for their surface tension, particle size and short-term stability [9,38]. The effect of drug incorporation on the emulsification efficiency has already been reported above.

Emulsion droplet size is considered to be a decisive factor in self-emulsification/dispersion performance, since it determines the rate and extent of drug release and absorption [8,44]. Droplet/particle size is usually established by the photon correlation spectroscopy method (PCS) [8,23,38,43,45]. The PCS technique is very useful when the emulsion properties are not changed following the infinite aqueous dilutions necessary for applying this method, although at relatively low dilutions, various microscope visualization techniques are recommended for reliable droplet size characterization [43,45].

Efficient emulsification was arbitrarily defined by Shah et al. as a system which produces mean emulsion droplet diameter values of less than 5 μm [8]. Further reduction of droplet size led to the development of SMEDDS capable of forming thermodynamically stable, isotropic, clear o/w dispersions [16,18,19,28,32]. These systems can be best described by pseudo-ternary diagrams, where a constant ratio of two of the components is used, and the other two are varied [16]. Simple tests, such as dye solubilization, dilutability by dispersed phase excess and conductance measurements, are employed to characterize the microemulsion system [16].

Positively charged self-emulsifying oil formulations (SEOF), recently developed by Gershanik and Benita, introduced a new parameter for SEDDS characterization: the charge of resulting droplets [43,45]. The emulsion droplets, resulting from the aqueous dilution of conventional self-emulsifying formulations formed by traditional oil/non-ionic surfactant blend, in practice, carry some negative charge, possibly provided by free fatty acids present in the mixture [9]. Incorporation of a small amount of cationic lipid (2.5–3%), oleylamine, into such an oil/surfactant system reversed the charge nature, leading to the formation of emulsion droplets which exhibit a positive $\zeta$-potential value of about 35–45 mV [43,45,46]. This positive $\zeta$-potential value was also preserved after the incorporation of the model drugs.

## 3. Biopharmaceutical aspects of SDLFs

### 3.1. Drug absorption from SDLFs

Numerous bioavailability studies carried out in animals suggested that hydrophobic drugs are better absorbed when administered as o/w emulsions [10–14,17,47–50]. However, the poor physical stability and large volumes of these o/w dispersion systems markedly limited their use in routine oral drug administration. It was shown that SDLFs may represent an attractive alternative to orally administered emulsions, since they are physically stable lipid solutions or dispersions incorporated in standard soft gelatin capsules. The following examples illustrate the beneficial use of SDLFs for drug absorption enhancement.

The improvement of the plasma profile reproducibility of WIN 54954 following administration in SEDDS compared to PEG solution was emphasized by Charman et al. [7], while other authors reported a higher bioavailability of the hydrophobic drugs after administration as SEDDS [8,27,51]. In in-vivo absorption studies in non-fasting dogs for a lipophilic drug, RO15-0778, which is a naphthalene derivative [8], SEDDS gave at least a three-fold greater $C_{max}$ and AUC than the drug in any other liquid or solid oral dosage form (Table 2). The absorption in rats of ontazolast, a poorly water-soluble, lipophilic anti-inflammatory compound (a potent calcium ionophore A23187-stimulated leukotriene B4 inhibitor), as a function of lipid-based delivery system composition was investigated by Hauss et al. [27]. The bioavailability of this drug was significantly enhanced by all lipid-based formulations: the emulsion, glyceryl oleate (Peceol) solution and both semisolid SEDDS, containing either 20/80 or 50/50 Peceol/Gelucire 44/14 (PEG-32 glyceryl laurate) compared to suspension formulation. The absorption of the poorly water-soluble experimental drugs REV 5901 (α-pentyl-3-(2-quinolinylmethoxy)-benzenemethanol) and DMP 323 (HIV protease inhibitor) in dogs from capsules containing solid dispersion with Gelucire 44/14 was higher than that from PEG-based formulations [4,5]. In multiple dosage studies carried out in HIV-infected patients, the administration of SEDDS formu-

Table 2
Pharmacokinetic parameters of a lipophilic naphthalene derivative (Ro 15-0778) from different formulations in non-fasting dogs[a]

| Formulation | $C_{max}$ (mg/ml) | $T_{max}$ (h) | AUC (μg/h per ml) | Relative bioavailability (%) |
|---|---|---|---|---|
| Self-emulsifying solution (SEDDS) | 5.57 | 2.50 | 29.77 | 389.0 |
| Drug solution in PEG 400 (control) | 1.44 | 2.00 | 7.64 | 100.0 |
| Capsule formulation of wet-milled spray dried powder | 0.78 | 3.00 | 2.69 | 35.3 |
| Tablet of micronized drug | 0.58 | 2.00 | 1.32 | 17.2 |

[a] From reference [8].

lation resulted in a larger AUC, and a higher $C_{min}$ and $C_{max}$, of the HIV protease inhibitor SC-52151 (a urea-based peptidomimetic compound) than the corresponding elixir formulation [28,51]. A recently designed freeze-dried formulation, consisting of olive oil and egg albumin, was shown to markedly enhance the oral bioavailability of several hydrophobic drugs [20].

### 3.2. Influence of the lipid vehicle

The effect of the oil vehicle on lipophilic drug pharmacokinetic parameters may be discussed with respect to the effect of lipid composition and the efficiency of the carrier system.

The effect of lipids on the bioavailability of orally administered drugs is highly complex due to numerous mechanisms by which the lipids can alter the biopharmaceutical characteristics of the drug. They include a decreased rate of gastric emptying, an increased dissolution rate of the drug and solubility in the intestinal fluid, and the formation of lipoproteins promoting the lymphatic transport of highly lipophilic drugs [17,27,49,50]. Factors such as the acid chain length of triglyceride, the saturation degree and the volume of lipid administered may affect the drug absorption profile and its blood/lymph distribution.

Three major processes occur in the intestine: large fat droplets are further emulsified by bile salts, monoglycerides, cholesterol, lecithin and lysolecithin to produce droplets with a mean diameter of 0.5–1 μm. These droplets are then metabolized by pancreatic lipase, an enzyme with a molecular weight of about 40 000 Da [17,49]. The dispersed oil droplet fragments form mixed micelles with bile salts [16,32].

Although it is known from the literature that intact micro- and nano-particles can penetrate through GI mucosa [47,52], there is no evidence that undigested oil droplets can permeate into the bloodstream. Oil emulsion droplets entering the GI tract undergo structural changes; they may be broken and restructured [2,32]. However, mixed micelles and microemulsions can penetrate through the aqueous layer and the mucin, and are absorbed by one of the following different ways: pinocytosis, diffusion, or endocytosis [32]. The active drug will reach the systemic blood circulation via the portal vein or through the lymphatic system.

### 3.3. Lymphatic absorption pathway

Partitioning of the absorbed drug into the lymph is hindered by the low rate of lymph fluid transport relative to that of blood, which is approximately 500-fold greater in the rat. Nevertheless, this way may be contributive for highly lipophilic drugs with a log$P$ of more than 5, and high triglyceride solubility [10,27,50]. The extent of lymphatic absorption may be altered by the lipid vehicle [10,27,50,53]. The rank order effect of the vehicles for the promotion of the lymphatic transport of halofantrine hydrochloride, a highly lipophilic anti-malarial agent, was micelles > emulsion > lipid solution [53]. In another study, the soybean-based emulsion formulation produced significantly greater drug (ontazolast) transport into the lymph than Peceol/Tween 80 SEDDS formulations [27]. Evidently, the lipid composition of the vehicle, more so than the vehicle type, is the decisive factor for lymphatic transport promotion. It was shown that enhanced lymphatic transport is not necessarily reflected by proportionally elevated plasma AUC [27,50]. The amount of ontazolast transported by the lymph with only Peceol solution was as high as that for the emulsion formulation, but the overall drug bioavailability from oil was lower than that with SEDDS or emulsion formulations. In the other study, the total quantity of CI-976 (2,2-dimethyl-*N*-(2,4,6-trimethoxyphenyl) dodecanamide), a poorly water-soluble lipid regulator, transported in the lymph and accumulated in the peripheral fat as a percentage of the dose administered, was much greater for the emulsion compared to the surfactant dispersion formulation, although the plasma AUC was higher for the dispersion formulation [50].

### 3.4. Drug release

The release of a drug occurs following its partitioning to aqueous intestinal fluids during droplet transport and disintegration along the GI tract. Shah et al. proposed that the effective delivery of a drug from SEDDS is governed by two main factors: small particle size and the polarity of the resulting oil droplets, which permits a faster rate of drug release into the aqueous phase [8]. The optimal polarity of the formulation is achieved by the appropriate combination of oil and surfactants. In o/w microemulsion formulations, the polarity of the oil phase is a less dominant factor, since

the drug can reach the capillaries while still incorporated within the microemulsion droplets [16,18,19,32]. Excess surfactant in a formulation may also promote the effective dispersion of drug in the lumen by the solubilization process, in addition to drug spreading in oil droplets [48,54]. The solubilized drug does not precipitate in the lumen, and undergoes rapid absorption which is independent of the lipid digestion process. The presence of the lipid core in the dispersed system is not a prerequisite for achieving the best solubilization effect. In some cases, therefore, the surfactant-based vehicle may be preferable, due to relative ease of formulation design compared to SEDDS/microemulsion formulations [4,5]. It was shown that the drug-loading improvement of an o/w microemulsion over a micellar system appears to depend on the solubility of the drug in the dispersed oil phase, and is significant only for very lipophilic drugs [36,55]. The effect of droplet size on the oral bioavailability of lipophilic drugs was best demonstrated with a hydrophobic endecapeptide, cyclosporine A (CsA), the bioavailability of which, from the marketed formulation Sandimmune®, was significantly increased by pre-administration droplet size reduction [43]. Later, cyclosporine was formulated in a new pre-concentrate microemulsion formulation, Sandimmune Neoral®, which resulted in a much higher and much more reproducible cyclosporine blood profile [18,19]. Along with beneficial solubility/dissolution rate properties, the above formulation has the advantage of avoiding an oil digestion process which might hinder drug absorption. Raymond et al. showed that the digestion of lipid droplets containing CsA results in three phases: a calcium soap precipitate, an oily phase from undigested lipids, and an aqueous mixed micellar phase. A large concentration of dissolved cyclosporine was found in the undigested lipid phase following Sandimmune® administration, while in the case of the microemulsion formulation, a mixed micellar phase was most often obtained due to 'in vitro pre-digestion' of the oily solution [18], although administration of CsA in another type of dispersed lipid carrier, a LC formulation, the composition of which was reported to be monoglyceride/water/CsA (62:34:4), gave much greater variability than self-emulsifying formulations. This is in conflict with the hypothesis that small aggregates give better and more predictable absorption [56].

### 3.5. Positively charged SEDDS

Multiple physiological studies proved that the apical potential of absorptive cells, as well as that of all other cells in the body, is negatively charged with respect to the mucosal solution in the lumen [57–59]. It was recently shown by Gershanik and Benita [45,46] that positively charged emulsion droplets formed by appropriate SEDDS dilution undergo electrostatic interaction with the Caco-2 monolayer and the mucosal surface of the everted rat intestine. This formulation enhanced the oral bioavailability of progesterone in young female rats [43] and exhibited higher blood levels of CsA in perfused rats in comparison to the corresponding negatively charged formulation. Many aspects of these formulations are still unclear. Positively charged formulations differ from negatively charged formulations with respect to their interaction with biological components in the GI environment. Positively charged droplets should be attracted to the negatively charged physiological compounds naturally occurring in lumen [45]. It was already shown by these authors that larger droplets (a few microns in size range) are less neutralized by mucin solutions of different concentrations than smaller droplets (submicron size range) formed by the same formulation [45]. A similar behavior was also observed in different SEOFs, which, upon aqueous dilution, resulted in positively charged coarse or fine emulsions, or microemulsions, as depicted in Fig. 1. Thus, the droplet size/bioavailability correlation is much more complex in positively charged formulations. This was further confirmed in a rat oral bioavailability study, where groups of six rats were given different emulsion formulations of CsA resulting from SEOF dilutions. It can be noted from Fig. 2B that CsA blood levels, as determined by radioimmunoassay and AUC, were significantly higher from the positively charged Arachis oil/Labrafil 2609/oleylamine (OA) SEOF compared to the same, but negatively charged (without oleylamine), respective formulation. In these formulations, the mean droplet size of the emulsion resulting from SEOF dilution was in the range of a few microns, whereas no difference in blood level profiles was noted as a function of droplet surface charge when the mean droplet size of the emulsions resulting from SEOF dilution (Tween 80, ethyl alcohol/ethyl oleate with and without OA) was in the range of 200–500 nm (Fig. 2A). However, irrespective of the surface charge nature, the AUC and the relative bioavailability reached by these latter fine emulsion-producing

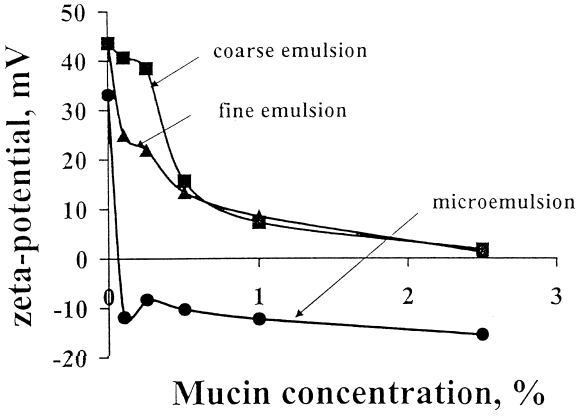


Fig. 1. Neutralization of SEOF positive charge by increasing mucin concentration as a function of droplet size. Coarse emulsion (mean droplet size of a few microns) composition (%w/w), Labrafil 2609 25/OA 3/arachis oil to 100. Fine emulsion (mean droplet size, 200–500 nm) composition (%w/w), Tween 80 25/ethyl alcohol 30/OA 3/ethyl oleate to 100. Microemulsion composition, Tween 80 70/OA 3/ethyl alcohol 10/ethyl oleate to 100.

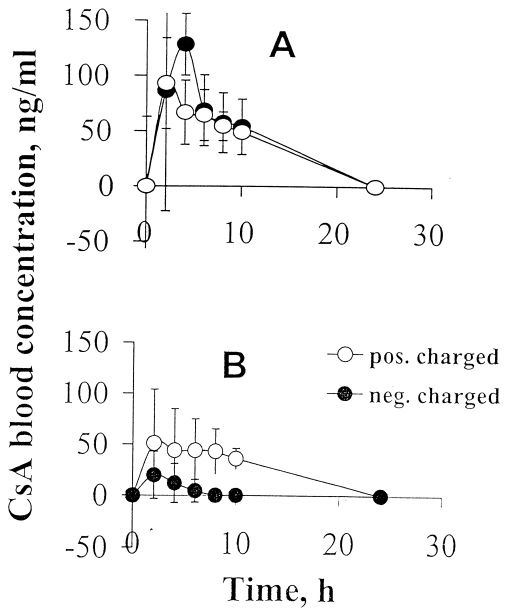


Fig. 2. CsA blood levels as a function of droplet size and surface charge. (A) Fine emulsion (mean droplet size, 200–500 nm) composition (%w/w), Tween 80 25/ethyl alcohol 30/OA 0 or 3/ethyl oleate to 100. (B) Coarse emulsion (mean droplet size of a few microns) composition (%w/w), Labrafil 2609 25/OA 0 or 3/arachis oil to 100.

formulations were higher than those achieved with the former formulations, including the positively charged coarse emulsion (Fig. 2).

## 4. Conclusions

More than 40% of the new chemical entities exhibit poor aqueous solubility and complex technical formulation problems. They represent a real challenge for the design of appropriate formulations aimed at enhancing oral bioavailability. This review outlined SDLFs as one of the most promising approaches towards overcoming the formulation difficulties of these hydrophobic/lipophilic drugs.

SDLFs are versatile and offer numerous possibilities to the formulation designers for developing suitable dosage forms to meet the requirements of specific molecules. SDLFs are likely to have an increasing application in the design of innovative delivery systems for lipophilic drugs. However, the role of formulation variables, such as particle structure and size, and droplet surface charge, in the determination of in-vivo performance is still unclear and requires further investigation.

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