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Self-emulsifying drug delivery systems: an approach to enhance oral bioavailability

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Self-emulsifying drug delivery systems are a vital tool in solving low bioavailability issues of poorly soluble drugs. Hydrophobic drugs can be dissolved in these systems, enabling them to be administered as a unit dosage form for per-oral administration. When such a system is released in the lumen of the gastrointestinal tract, it disperses to form a fine emulsion (micro/nano) with the aid of GI fluid. This leads to *in situ* solubilization of drug that can subsequently be absorbed by lymphatic pathways, bypassing the hepatic first-pass effect. This article presents an exhaustive account of various literature reports on diverse types of self-emulsifying formulations with emphasis on their formulation, characterization and *in vitro* analysis, with examples of currently marketed preparations.

Nearly half of the new drug candidates that reach formulation scientists have poor water solubility, and oral delivery of such drugs is frequently associated with low bioavailability [1,2]. To overcome these problems, various formulation strategies have been exploited, such as the use of surfactants, lipids, permeation enhancers, micronization, salt formulation, cyclodextrins, nanoparticles and solid dispersions. The availability of the drug for absorption can be enhanced by presentation of the drug as a solubilizate within a colloidal dispersion [3].

Much attention has focused on lipid solutions, emulsions and emulsion preconcentrates, which can be prepared as physically stable formulations suitable for encapsulation of such poorly soluble drugs. Emulsion systems are associated with their own set of complexities, including stability and manufacturing problems associated with their commercial production. Self-emulsification systems are one formulation technique that can be a fitting answer to such problems [4].

Self-emulsifying drug delivery systems (SEDDS) are isotropic mixtures of drug, lipids and surfactants, usually with one or more hydrophilic cosolvents or coemulsifiers [5]. Upon mild agitation followed by dilution with aqueous media, these systems can form fine (oil in water) emulsion instantaneously. 'SEDDS' is a broad term, typically producing emulsions with a droplet size ranging from a few nanometers to several microns. 'Self-microemulsifying drug delivery systems' (SMEDDS) indicates the formulations forming transparent microemulsions with oil droplets ranging between 100 and 250 nm. 'Self-nano-emulsifying drug delivery systems' is a recent term construing the globule size range less than 100 nm [6].

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Suitable drug candidate identification for SEDDS

One of the primary challenges to any oral formulation design program is maintaining drug solubility within the gastrointestinal tract and, in particular, maximizing drug solubility within the prime absorptive site of the gut [7]. For lipophilic drug compounds that exhibit dissolution-rate-limited absorption, SEDDS can offer an improvement in rate and extent of absorption, resulting in reproducible blood time profiles. Logically speaking, however, use of SEDDS can be extended to all four categories of biopharmaceutical classification system (BCS) class drugs [6]. These systems can help in solving the under-mentioned problems of all the categories of BCS class drugs, as depicted in Table 1.

Lipinski's rule of five has been widely proposed as a qualitative predictive model for oral absorption trends. In the discovery setting, the 'rule of five' predicts that poor absorption or poor permeation is more likely when there are more than five H-bond donors, there are more than ten H-bond acceptors, the molecular weight >500 and the calculated log $P > 5$.

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TABLE 1

Application of SEDDS in various BCS category drugs

BCS class	Problems
Class I	Enzymatic degradation, gut wall efflux
Class II	Solubilization and bioavailability
Class III	Enzymatic degradation, gut wall efflux and bioavailability
Class IV	Solubilization, enzymatic degradation, gut wall efflux and bioavailability

The question arising is whether solubility and log *P* are sufficient to identify potential drug candidates for such formulations. Although classification systems such as the BCS and Lipinski's rule of five are useful, particularly at the initial screening stage, they have limitations. It is considered that the rule of five only holds for compounds that are not substrates for active transporters, and with increasing evidence suggesting that most drugs are substrates for some efflux or uptake transporters, this limitation might be notable. Aqueous solubility and/or log *P* alone are unlikely to be sufficient for identifying the suitability of a lipid-based formulation approach because they do not adequately predict potential *in vivo* (i.e. physiological) effects.

It has been found that individually, these poorly water-soluble compounds, which are generally classified as 'lipophilic', behave differently in similar vehicles, thus highlighting the need to assess candidate compounds on an individual basis.

Lipid Formulation Classification System

The Lipid Formulation Classification System was introduced as a working model in 2000 [3], and an extra 'type' of formulation was added in 2006. The main purpose of the Lipid Formulation Classification System is to enable *in vivo* studies to be interpreted more readily and, subsequently, to facilitate the identification of the most appropriate formulations for specific drugs (i.e. with reference to their physicochemical properties) [8]. Table 2 indicates the fundamental differences between types I, II, III and IV formulations [9].

Regulatory aspects of lipid excipients

Initially excipients were considered inert substances that would be used mainly as diluents, fillers, binders, lubricants, coatings, solvents and dyes in the manufacture of drug products. Over the years, however, advances in pharmaceutical science and technology have facilitated the availability of a wide range of novel excipients. It is now recognized that not all excipients are inert substances and some might be potential toxicants [10].

In the United States, the Food and Drug Administration (FDA) has published listings in the Code of Federal Regulations for Generally Recommended as Safe (GRAS) substances that are generally recognized as safe (http://www.fda.gov/Food/FoodIngredientsPackaging/GenerallyRecognizedasSafeGRAS/default.htm). Over the years, the Agency has also maintained a list entitled 'Inactive Ingredient Guide' for excipients that have been approved and incorporated in marketed products (http://www.accessdata.fda.gov/scripts/cder/iig/index.cfm). This guide is helpful in that it provides the database of allowed excipients with the maximum dosage level by route of administration or dosage form for each excipient. For new drug development purposes, once an inactive ingredient has appeared in an approved drug product for a particular route of administration, the inactive ingredient is not considered new and might require a less extensive review the next time it is included in a new drug product. In this context, the FDA has published a guidance document for industry on the conduct of nonclinical studies for the safety evaluation of new pharmaceutical excipients [11].

Existing human data for some excipients can substitute for certain nonclinical safety data. In addition, an excipient with documented prior human exposure under circumstances relevant to the proposed use might not require evaluation with a full battery of toxicology studies. There is no process or mechanism currently in place within the FDA to independently evaluate the safety of an excipient.

For a drug or biological product subject to premarketing approval, their excipients are reviewed and approved as 'components' of the drug or biological product in the application. This is particularly true for lipid excipients, in view of their distinct physicochemical properties and the potential complex interactions with other ingredients or the physiological environment that might occur *in vivo*. In addition, oils can turn into severe cytotoxic agents when reduced to nano range *in situ* (as in the case of self-nano-emulsifying drug delivery systems), so scientists must be very careful while using oils in such systems. Surfactants can also be a source of severe gastrointestinal tract (GIT) irritation if used in higher concentrations.

TABLE 2

The Lipid Formulation Classification System: characteristic features, pros and cons of the four essential types of 'lipid' formulations

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

Formulation of SEDDS

The SEDDS formulation should instantaneously form a clear dispersion, which should remain stable on dilution. The hydrophobic agent remains solubilized until the time that is relevant for its absorption [12]. Silva *et al.* [13] found that two main factors, small particle size and polarity of resulting oil droplets, determine the efficient release of the drug compounds from SEDDS. In o/w microemulsions, however, the impact of polarity of oil droplets is not considerable because the drug compound incorporated within the oil droplets reaches the capillaries. Isotropic liquids are preferable to waxy pastes because if one or more excipient(s) crystallize(s) on cooling to form a waxy mixture, it is very difficult to determine the morphology of the materials and, most importantly, the polymorphism properties of the drug within the wax. As a general rule, it is sensible to use the simplest effective formulation, restricting the number of excipients used to a minimum.

Screening of excipients for SEDDS

With a large variety of liquid or waxy excipients available, ranging from oils through biological lipids and hydrophobic and hydrophilic surfactants to water-soluble cosolvents, there are many different combinations that could be formulated for encapsulation in hard or soft gelatin or mixtures that disperse to give fine colloidal emulsions. The following points should be considered in the formulation of a SEDDS: (i) the solubility of the drug in different oil, surfactants and cosolvents and (ii) the selection of oil, surfactant and cosolvent based on the solubility of the drug and the preparation of the phase diagram. The backbone of SEDDS formulation comprises lipids, surfactants and cosolvents. The right concentration of the above three decides the self-emulsification and particle size of the oil phase in the emulsion formed. These ingredients are discussed below.

Lipids. Lipid is a vital ingredient of the SEDDS formulation. It can not only solubilize large amount of lipophilic drugs or facilitate self-emulsification but also enhance the fraction of lipophilic drug transported via intestinal lymphatic system, thereby increasing its absorption from the GIT [14,15].

Natural edible oils, comprising medium-chain triglycerides, are not frequently preferred in this regard owing to their poor ability to dissolve large amounts of lipophilic drugs [16]. Modified long- and medium-chain triglyceride oils, with varying degrees of saturation or hydrolysis, have been used widely for the design of SEDDS [17]. These semisynthetic derivatives form good emulsification systems when used with a large number of solubility-enhancing surfactants approved for oral administration [18,19].

Surfactants. A surfactant is obligatory to provide the essential emulsifying characteristics to SEDDS. Surfactants, being ampiphilic in nature, invariably dissolve (or solubilize) high amounts of hydrophobic drug compounds. The two issues that govern the selection of a surfactant encompass its hydrophilic–lipophilic balance (HLB) and safety. The HLB of a surfactant provides vital information on its potential utility in formulation of SEDDS. For attaining high emulsifying performance, the emulsifier involved in formulation of SEDDS should have high HLB and high hydrophilicity for immediate formation of o/w droplets and rapid spreading of formulation in aqueous media in this context. It would keep drug solubilized for a prolonged period of time at the site of absorption for effective absorption, so precipitation of drug compound within GI lumen is prevented [20,21].

A range of industrial nonionic surfactants were screened for their ability to form SEDDS with medium-chain and long-chain triglycerides by Pouton and Porter [8] and Werkley *et al.* [22], using subjective visual assessment.

Cosolvents. Usually, the formulation of an effective SEDDS requires high concentrations of surfactant. Accordingly, cosolvents such as ethanol, propylene glycol and polyethylene glycol are required to enable the dissolution of large quantities of hydrophilic surfactant. The lipid mixture with higher surfactant and cosurfactant:oil ratios leads to the formation of SMEDDS [23,24]. Alcohol and other volatile cosolvents have the disadvantage of evaporating into the shell of soft or hard gelatin capsules, leading to precipitation of drug.

Mechanism of self-emulsification

According to Reiss [25], self-emulsification occurs when the entropy change that favors dispersion is greater than the energy required to increase the surface area of the dispersion. The free energy of the conventional emulsion is a direct function of the energy required to create a new surface between the oil and water phases and can be described by the equation:

$$\mathrm{DG} = SN_{\mathrm{i}}\, pr_{\mathrm{i}}2S \qquad (1)$$

where DG is the free energy associated with the process (ignoring the free energy of mixing), N is the number of droplets of radius r and S represents the interfacial energy. The two phases of emulsion tend to separate with time to reduce the interfacial area and, subsequently, the emulsion is stabilized by emulsifying agents, which form a monolayer of emulsion droplets, and hence reduces the interfacial energy, as well as providing a barrier to prevent coalescence [17,26].

In vitro dissolution problems for poorly water-soluble drugs

Traditionally, dissolution testing has fulfilled two principal functions. As a mechanism to control quality, dissolution is a sensitive, reproducible and straightforward test that can be used to effectively monitor batch-to-batch variability and ensure bioequivalence once bioavailability has been established [27]. In some circumstances, *in vitro* dissolution can be used as a surrogate indicator of the likely *in vivo* dissolution profile and, therefore, as a tool to predict the extent of absorption where dissolution is limiting [28,29]. The principal determinants of the dissolution rate of a poorly water-soluble compound, however, are the degree of wetting and extent of drug solubility in the intestinal contents.

The use of simple aqueous media to assess the dissolution profile of poorly water-soluble drugs is often limited by the low intrinsic aqueous solubility of the drug (and, therefore, difficulty in maintaining sink conditions), which – when coupled with analytical sensitivity and logistical issues such as drug binding to filters – can make reproducible dissolution assessment difficult. These problems can be overcome, especially for dissolution tests principally designed to perform a quality control function, by using nonaqueous dissolution media or simple surfactant solutions. Similarities between these media and the likely gastrointestinal environment,

however, are limited. To improve the accuracy of *in vivo* dissolution prediction using *in vitro* dissolution, several studies have developed and defined modified dissolution media that more accurately reflect the solubilization power of the *in vivo* GI tract. The components of these various dissolution media have been modeled primarily on the likely levels of endogenous bile salts and phospholipids in the fasted and postprandial intestine [30,31].

Although for many poorly water-soluble compounds, solubility in the stomach is not sufficient for appreciable dissolution to occur before gastric emptying, for some compounds (and particularly for weak bases), the stomach is the principal site of dissolution. In these circumstances, simulated gastric fluid, as described in the United States Pharmacopoeia (USP) (2 g NaCl, 3.2 g pepsin, 7 ml HCl, H_2O to 1000 ml, pH 1.2), can be used to simulate fasted gastric conditions, and homogenized long-life milk (3.5% fat, pH 6.5) has been suggested to simulate fed gastric conditions [32].

Dressman and colleagues have compared the dissolution profiles of several poorly water-soluble compounds using different dissolution media [33,34]. For nonionizable drugs, good correlations were found between the difference in dissolution profiles in simulated fasted-state intestinal media and simulated fed-state media and the difference in plasma profiles obtained after fasted and postprandial administration.

For compounds with appreciable ionization over the likely physiological pH range, the situation is complicated by the impact of both ionization and solubilization on solubility. The increased solubilizing power of the postprandial intestine is, at least in part, sufficient to overcome the low solubility of the unionized species, and the dissolution rate of such drugs under simulated fed-state intestinal conditions is only slightly lower than under fasted-state gastric (i.e. acidic) conditions [33].

Assessment of lipid-based formulations using *in vitro* lipolysis

The design of self-emulsifying lipid-based formulations has focused on optimizing the solubility of the drug in the formulation and on the *in vitro* emulsification efficiency and particle size of the dispersion obtained on dilution in aqueous media [35]. In recent years, however, *in vitro* dispersion tests and *in vitro* lipid digestion models that are more reflective of the gastrointestinal environment have been developed to better predict the *in vivo* dissolution profile of poorly water-soluble drugs. Pictorial representation of this can be seen in Fig. 1.

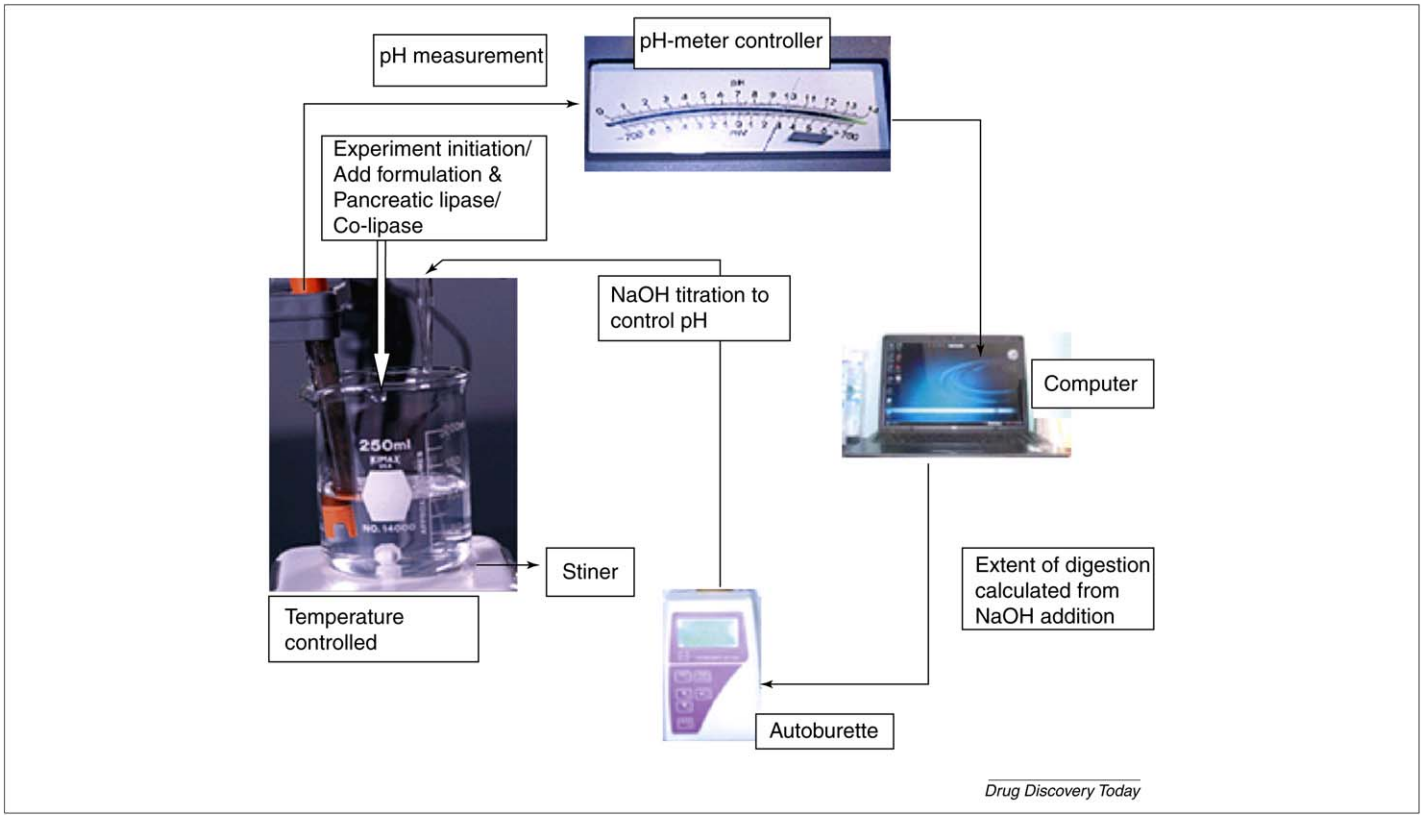

FIGURE 1

Lipid digestion models for *in vitro* assessment of lipidic formulations. **(a)** The vessel contains digestion buffer, bile salts and phospholipids (to represent a model intestinal fluid), into which lipid-based formulations are introduced and digestion initiated by the addition of pancreatic lipase or colipase. The onset of lipid digestion results in the liberation of fatty acids (FA), which, in turn, causes a transient drop in pH. **(b)** The drop in pH is quantified by a pH electrode that is coupled to a pH-stat controller and autoburette, which, together, automatically titrate the liberated FA via the addition of an equimolar quantity of sodium hydroxide. This maintains the pH at a set point (thereby enabling the pH-sensitive process of digestion to continue) and facilitates indirect quantification of the extent of digestion (via quantification of the rate of sodium hydroxide addition and assumption of stoichiometric reaction between FA and sodium hydroxide). **(c)** Throughout the digestion process, samples can be taken and ultra-centrifuged to separate the digest into a poorly dispersed oil phase, a highly dispersed aqueous phase and a precipitated pellet phase. Quantification of the mass of drug that is subsequently trafficked through to the highly dispersed aqueous phase and which does not precipitate provides an indication of the relative proclivity of the formulation with respect to *in vivo* precipitation and, therefore, a mechanism to (at least) rank order the likely *in vivo* performance of a series of lipidic formulations [54].

In contrast to traditional dissolution testing, in which the dissolution of drug from the solid state into both simple and biorelevant dissolution media is measured, assessment of the utility of lipid-based formulations is more appropriately based on evaluation of the rate and extent of drug precipitation with respect to time (rather than solubilization) because drug is usually already dissolved in the formulation. In this case, *in vitro* 'dispersion' testing seems to be a more accurate description of the process of monitoring the ability of a formulation to maintain the drug in a solubilized state during dispersion in the stomach and subsequent processing of the formulation in the presence of pancreatic and biliary fluids.

Evaluation of self-emulsifying formulations using in vitro lipolysis

In vitro lipid digestion models have been used to examine the potential *in vivo* performance of self-emulsifying and self-microemulsifying formulations [36,37]. A reasonable rank-order correlation was described between the patterns of solubilization obtained on *in vitro* digestion and the plasma profile of Danazol after oral administration of SMEDDS formulations containing long-chain lipid SMEDDS and medium-chain lipid SMEDDS to fasted beagle dogs. Sek *et al.* [38] examined the impact of a range of surfactants on the *in vitro* solubilization behavior and oral bioavailability of lipid-based formulations of Atovaquone. They observed no difference in the solubilization behavior of two SEDDS formulations comprising long-chain glycerides, ethanol and either Cremophor EL or Pluronic L121 on *in vitro* digestion, despite both formulations displaying different self-emulsifying properties. In agreement with the lipolysis data, drug bioavailability after oral administration of the Cremophor EL- and Pluronic L121-containing formulations to beagle dogs was indistinguishable, confirming the importance of consideration of the impact of formulation digestion on solubilization behavior when assessing the likely *in vivo* performance of lipid-based formulations.

It seems, therefore, that reasonable correlation between differences in drug solubilization profiles during *in vitro* lipolysis and differences in *in vivo* exposure are evident for typical lipid-based self-emulsifying formulations.

Characterization of SEDDS

The primary means of self-emulsification assessment is visual evaluation [39,40]. The various ways to characterize SEDDS are compiled below.

Equilibrium phase diagram

Although self-emulsification is a dynamic nonequilibrium process involving interfacial phenomena, information can be obtained about self-emulsification using equilibrium phase behavior. There seems to be a correlation between emulsification efficiency and region of enhanced water solubilization and phase inversion region, formation of lamellar liquid crystalline dispersion phase on further incorporation of water.

An equilibrium phase diagram enables comparison of different of different surfactants and their synergy with cosolvent or cosurfactant [41]. The boundaries of one phase region can easily be assessed visually. The phase behavior of a three-component system can be represented by a ternary phase diagram.

Turbidity measurement

This identifies efficient self-emulsification by establishing whether the dispersion reaches equilibrium rapidly and in a reproducible time [42]. These measurements are carried out on turbidity meters, most commonly the Hach turbidity meter and the Orbeco-Helle turbidity meter [43,44]. This apparatus is connected to a dissolution apparatus and optical clarity of formulation is taken every 15 s to determine clarity of nano or micro emulsion formed and emulsification time. Turbidity can also be observed in terms of spectroscopic characterization of optical clarity (i.e. absorbance of suitably diluted aqueous dispersion at 400 nm) [45].

Droplet size

This is a crucial factor in self-emulsification performance because it determines the rate and extent of drug release, as well as the stability of the emulsion. Photon correlation spectroscopy, microscopic techniques or a Coulter Nanosizer are mainly used for the determination of the emulsion droplet size [46,47].

Electron microscopic studies

Freeze-fracture electron microscopy has been used to study surface characteristics of such dispersed systems [48]. Because of the high lability of the samples and the possibility of artifacts, electron microscopy is considered a somewhat misleading technique. Particle size analysis and low-frequency dielectric spectroscopy have been used to examine the self-emulsifying properties of Imwitor 742 (a mixture of mono- and diglycerides of capric and caprylic aciss) and Tween 80 systems [49].

Zeta potential measurement

This is used to identify the charge of the droplets. In conventional SEDDS, the charge on an oil droplet is negative because of the presence of free fatty acids [50].

Determination of emulsification time

Pouton *et al.* [51] quantified the efficiency of emulsification of various compositions of the Tween 85 and medium-chain triglyceride systems using a rotating paddle to promote emulsification in a crude nephelometer. This enabled an estimation of the time taken for emulsification. Once emulsification was complete, samples were taken for particle sizing by photon correlation spectroscopy, and self-emulsified systems were compared with homogenized systems. The process of self-emulsification was observed using light microscopy. It was clear that the mechanism of emulsification involved erosion of a fine cloud of small particles from the surface of large droplets, rather than a progressive reduction in droplet size.

Cryo-TEM studies

For Cryo-Transmission Electron Microscopy (TEM), samples were prepared in a controlled environment verification system. A small amount of sample is put on carbon film supported by a copper grid and blotted by filter paper to obtain thin liquid film on the grid. The grid is quenched in liquid ethane at −180°C and transferred to liquid nitrogen at −196°C. The samples were characterized with a TEM microscope.

Liquefaction time

This test is designed to estimate the time required by solid SEDDS to melt *in vivo* in the absence of agitation to simulated GI conditions. One dosage form is covered in a transparent polyethylene film and tied to the bulb of a thermometer by means of a thread. The thermometer with attached tablets is placed in a round-bottom flask containing 250 ml of simulated gastric fluid without pepsin maintained at $37 \pm 1^{\circ}C$ [52]. The time taken for liquefaction is subsequently noted.

Small-angle neutron scattering

Small-angle neutron scattering can be used to obtain information on the size and shape of the droplets. The term 'droplet' is used to describe micelles, mixed micelles and oil-swollen micelles throughout the present work. Small-angle neutron scattering experiments use the interference effect of wavelets scattered from different materials in a sample (different scattering-length densities).

Small-angle X-ray scattering

This a small-angle scattering technique in which the elastic scattering of X-rays by a sample that has inhomogeneities in the nm range is recorded at very low angles (typically 0.1–10°). This angular range contains information about the shape and size of macromolecules, characteristic distances of partially ordered materials, pore sizes and other data. Small-angle X-ray scattering is capable of delivering structural information of macromolecules between 5 and 25 nm, of repeat distances in partially ordered systems of up to 150 nm. Small-angle X-ray scattering is used for the determination of the microscale or nanoscale structure of particle systems in terms of such parameters as averaged particle sizes, shapes, distribution and surface-to-volume ratio. The materials can be solid or liquid and they can contain solid, liquid or gaseous domains (so-called 'particles') of the same or another material in any combination.

In addition to these tools, others – such as nuclear magnetic resonance and differential scanning colorimetry – have also been exploited to characterize these self-emulsifying systems for a better insight.

Biological aspects in selection of SEDDS

Very few biopharmaceutical studies have been performed with SEDDS [2], and there is a need for more comparative studies, particularly against simple oils and solid dosage forms. At this stage, however, it is worth speculating on the issues that will influence the absorption from SEDDS [53]. The rate of gastric emptying of SEDDS is similar to solutions, so they are particularly useful where rapid onset of action is desirable. Conversely, if the therapeutic index of the drug is low, the rapid onset and accompanying high T_{half} might lead to undesirable side-effects. With regard to bioavailability, there are differences between formulations that contain water-soluble surfactants or cosolvents and those that do not. The former systems can produce emulsions or micellar solutions with a lower capacity for solubilization of drugs, which might result in precipitation of drugs in the gut. SEDDS formed with relatively hydrophobic surfactants (HLB < 12), such as Tween 85 or Tagat TO, which do not migrate into the aqueous phase, tend to have lower solvent capacities for drugs unless $\log P$ (drug) > 4. These SEDDS should be preferable, however, if the drug can be dissolved to an adequate extent. Highly potent but poorly water-soluble drug candidates are a common outcome of contemporary drug discovery programs and present several challenges to drug development – most notably, the issue of reduced systemic exposure after oral administration [54].

Application

SEDDSs present drugs in a small droplet size and well-proportioned distribution and increase the dissolution and permeability. Furthermore, because drugs can be loaded in the inner phase and delivered by lymphatic bypass share, SEDDSs protect drugs against hydrolysis by enzymes in the GI tract and reduce the presystemic clearance in the GI mucosa and hepatic first-pass metabolism.

Solid self-emulsifying drug systems

This approach enables the development of tablets using a liquid SEDDS for a poorly water-soluble drug. A high content of liquid SEDDS can be loaded (up to 70%) onto a carrier, which not only maintains good flowability but also enables the production of tablets with good cohesive properties and good content uniformity in both capsules and tablets. This clearly expands the options available to the formulator.

In addition to providing the obvious *in vivo* benefits of a SEDDS system in tablet dosage form (improved drug absorption, and so on), the benefits of developing a solid SEDDS system are that a high content of liquid SEDDS can be loaded onto a carrier and the

TABLE 3

Marketed formulations of SEDDS

Active moiety	Trade name	Dosage forms
Tretinoin	Vesanoid (Roche)	Soft gelatin capsule, 10 mg
Isotretinoin	Accutane (Roche)	Soft gelatin capsule, 10, 20 and 40 mg
Cyclosporine	Panimum bioral (Panacea Biotec)	Capsule, 50 and 100 mg
Cyclosporin A	Gengraf (Abbott)	Hard gelatin capsule, 25 and 100 mg
Cyclosporin A	Sandimmune (Novartis)	Soft gelatin capsule, 25, 50 and 100 mg
Lopinavir and Ritonavir	Kaletra (Abbott)	Soft gelatin capsule, Lopinavir 133.33 mg and Ritonavir 33.3 mg
Sanquinavir	Fortovase (Roche)	Soft gelatin capsule, 200 mg
Tipranavir	Aptivus (Boehringer Ingelheim)	Soft gelatin capsule, 250 mg
Amprenavir	Agenerase (GSK)	Soft gelatin capsule

process gives good content (granule) uniformity. In terms of functionality and performance, the solubilizing properties of the final solid dosage form should remain unaffected by both the adsorption of the liquid SEDDS onto a carrier and the state of the drug in the lipid formulation (solubilized versus suspended). The formulation and process is remarkably straightforward and few challenges can be envisaged at the industrial scale. This technique offers formulators an additional option in the quest to achieve product performance, product design and manufacturability.

Some examples of bioavailability enhancement achieved with various drugs using SEDDS are Indomethacin [55], Coenzyme Q 10 [56], Ontazolast [19], Simvastatin [57], Celecoxib [45], Carvedilol [40], Paclitaxel [58], Ramipril [59], Ibuprofen, Ketoprofen [60] and PNU-91325 [61]. Table 3 shows some of the marketed formulations of SEDDSs available for oral delivery of various drugs.

Concluding remarks

For poorly soluble drug candidates, SEDDS provide an effective and practical solution to the problem of formulating drugs where low solubility in the fluids of the GIT limits drug exposure. Although the potential utility of SEDDS has been known for some time, it is only in recent years that a mechanistic understanding of their impact on drug disposition has emerged. To this end, the use of a combination of *in vitro* dispersion and digestion methodologies has enabled a much improved understanding of the role of intestinal lipid processing on the solubilization behavior of lipid-based formulations. This *in situ* emulsion-forming system can be taken as an emulsion premix with high stability as such in the formulation. With future developments in this novel technology, SEDDS will remove deficiencies associated with delivery of poorly soluble drugs. Thus, this field requires further exploration and research to bring out a wide range of commercially available self-emulsifying formulations. To conclude, we can say that this system is not only about lipids and surfactants but also about their selection and the ratio in which they are used.

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