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Self-nano-emulsifying drug delivery systems: an update of the biopharmaceutical aspects

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Introduction: Thirty percent of top marketed drugs in the USA and 70% of all new drug candidates are lipophilic and exhibit poor water solubility. With such physicochemical properties, the oral bioavailability of these compounds lacks dose proportionality, is very limited and extremely erratic. Different lipid-based formulations have been explored in the past few decades to improve the oral delivery of such compounds. In recent years, the most popular approach is their incorporation into self-emulsifying drug delivery systems (SEDDS), with particular emphasis on self-nano-emulsifying drug delivery systems (SNEDDS).

Areas covered: This review offers an updated overview of SNEDDS application from the biopharmaceutical point of view. The focus of this review deals with the potential of SNEDDS utilization to overcome absorption barriers following oral administration of lipophilic drugs. This includes a comprehensive description of the primary mechanisms by which lipids and lipophilic excipients, used to formulate SNEDDS, could affect drug absorption, bioavailability and disposition following oral administration.

Expert opinion: The utilization of SNEDDS to augment the oral bioavailability of poorly water-soluble drugs goes beyond improvement in drug’s solubility, as was initially presumed. In fact, SNEDDS have a potential to increase oral bioavailability by multi-concerted mechanisms such as reduced intra-enterocyte metabolism by CYP P450 enzymes, reduced P-glycoprotein (P-gp) efflux activity and hepatic first-pass metabolism bypass via lymphatic absorption. This unique biopharmaceutical point of view, presented in this review, contributes to the understanding of proper drug candidate selection and of the approach in SNEDDS formulation design.

Keywords: intra-enterocyte metabolism, lymphatic delivery, oral bioavailability, P-gp efflux, poorly water-soluble drugs, self-emulsifying drug delivery systems, solubilization

1. Introduction

The oral route is the preferred mode of drug administration due to its safety, comfort, low cost and improved patient compliance. The drug’s presence in a solution at the absorptive site of the gastro intestinal (GI) tract is a prerequisite for oral absorption. Poor drug solubility is a significant and frequently encountered problem for pharmaceutical scientists. The introduction of combinatorial chemistry accompanied by advances in in-vitro high-throughput screening methods has resulted in the rapid identification of many highly potent but poorly water-soluble drug candidates. In fact, to date > 30% of top marketed drugs in the USA and 70% of all new drug candidates are lipophilic and exhibit poor water solubility [1,2]. In addition, many other promising active compounds do not reach clinical phases in their development process due to their poor oral bioavailability.
The Biopharmaceutics Classification System (BCS) divides these drugs into two categories called Class II and Class IV. Class II drugs are defined as being poorly water soluble and highly permeable through biological membranes. Class IV drugs have poor water solubility and are poorly permeable through biological membranes.

Having such physicochemical properties, the oral bioavailability of these drugs is very limited and is extremely erratic, in some cases, ranging from 2 to 90%. Moreover, in addition to poor water solubility, certain lipophilic drugs have been reported to be substrates for different membrane transporters and for metabolism via CYP P450 enzymes, as detailed in this review.

A promising strategy to overcome these obstacles is the development of suitable DDS. As the in-vivo behavior of a drug is dictated not only by the drug itself, but also by its mode of administration and the carrier system, which should enable an optimal release profile according to therapy requirements. Different lipid-based formulations were explored in the past few decades to improve the oral delivery of lipophilic drugs. In recent years, the most popular approach is their incorporation into self-emulsifying drug delivery systems (SEDDS) with particular emphasis on self-nano-emulsifying drug delivery systems (SNEDDS).

SEDDS are isotropic homogenous mixtures of an active compound in a combination of natural or synthetic lipids, surfactants and co-solvents. These anhydrous liquid mixtures are commonly termed pre-concentrates. Upon gentle agitation in an aqueous phase, such as the upper GI lumen content, these pre-concentrates spontaneously form drug-encapsulated O/W nano-emulsions with a particle diameter of 200 nm or less. Contrary to emulsions and suspensions, SNEDDS are highly thermodynamically stable formulations. SNEDDS can be filled into soft/hard gelatin capsules or hydroxypropyl-methylcellulose capsules, which results in attractive commercial viability and patient compliance. A key factor is that the dose volume can be restricted to meet the maximal 1 g of formulated liquid that soft gelatin capsule can contain.

During the past decade several reviews covered the formulation design process and the physico-chemical characterization of SNEDDS; however, the biopharmaceutical aspects with emphasis on oral drug absorption from SNEDDS were only briefly addressed.

In 2012 Khan et al. have published an excellent review covering a summary of the lipid formulation classification system proposed by Pouton in 2000, advantages of SNEDDS over micro/nano-emulsions and a detailed discussion concerning the selection of excipients for SNEDDS development. Additionally, an overview of phase behavior diagrams, mechanism of self-emulsification and in-vitro SNEDDS characterization was also provided in great detail. Thus, these physicochemical aspects of SNEDDS are not addressed in the current review.

This review offers a comprehensive and updated overview of SNEDDS utilization from the biopharmaceutical point of view. The focus of this review is on the potential in SNEDDS utilization to overcome absorption barriers following the oral administration mainly of BCS Class II compounds. This includes an inclusive description of the primary mechanisms by which lipids and lipophilic excipients, used to formulate SNEDDS, can affect drug absorption, bioavailability and disposition following oral administration. Current reports on SNEDDS effects on: i) pre-enterocyte level (alteration of the composition and character of the intestinal milieu and increased solubilization); ii) intra-enterocyte level (interaction with enterocyte-based transport processes such as permeability through the cell membrane and effects on intra-enterocyte metabolism and drug transporters); and iii) post-enterocyte level (recruitment of intestinal lymphatic drug transport) are broadly detailed.

2. The impact of the physicochemical properties of SNEDDS on its in-vivo performance

2.1 Particle size

In the case of peroral administration the accurate estimation of the particle size of SEDDS is extremely important as it can have a direct impact not only on the in-vitro evaluated parameters (e.g., stability and release kinetics) but also on in-vivo performance. It has been reported that smaller droplet size measured in-vitro has a favorable effect on the bioavailability of the drug incorporated into SEDDS. Tarr and Yalkowsky assessed the bioavailability of cyclosporine...
A (CsA) in rats by administrating the drug in micro-emulsions, forming particles of different sizes. Upon reduction of the size of the droplets, enhanced oral absorption of CsA was observed [8]. It should be noted that in that study the formulations were prepared using the same ingredients and differed only by the method of preparation. Thus, other influences on the bioavailability of the drug can be ruled out; the sole applicable factor is the effect of the size of the particles [9]. Findings of a study published in 2004 by Bekerman et al. corroborate the results described by Tarr and Yalkowsky. This study evaluates several SNEDDS formulations incorporating CsA in healthy volunteers. The range of the particle size formed upon introduction of these SNEDDS into aqueous phase varied between 25 and 400 nm. This study result demonstrates an inverse correlation between the particle size of the studied SNEDDS and the oral bioavailability of the incorporated CsA [10]. A similar trend was observed and reported by several other researches investigating versatile lipid-based formulations [11-13].

Thus, it is reasonable to deduce that particle size distribution can be of great importance on the oral bioavailability of a drug incorporated into SNEDDS.

2.2 Zeta potential
High values of zeta potential (± 30 mV) exhibit strong electrostatic repulsive forces, thus ruling out the possibility of flocculation indicating formation of stable SNEDDS [14]. However, as SNEDDS are administered as a pre-concentrate formulation, which forms nano-dispersion only upon exposure to the fluids of the GI milieu, this characteristic is not of crucial importance. Therefore, the long-term stability of the obtained nano-emulsion in-vitro is less relevant.

Nonetheless, the charge of the particles formed can have an influence on the oral bioavailability of the drug incorporated into SNEDDS. Charge-dependent interactions with human intestinal cells with respect to absorption enhancement have been reported [15].

The apical surface of the intestinal epithelial cells is negatively charged with respect to the mucosal solution in the lumen [16]. Gershmanik et al. developed SEDDS incorporating progesterone, which form positively charged particles upon dilution with the aqueous phase. They hypothesized that the positively charged particles can interact with the negatively charged mucosal surface of the GI tract and increase the cellular uptake of the incorporated drug. Indeed, oral administration of this formulation results in an increased bioavailability of progesterone in female rats [17]. This hypothesis is further confirmed by the administration of SEDDS incorporating CsA in the perfused rat model. Higher blood concentrations following administration of positively charged SEDDS compared to corresponding negatively charged SEDDS are observed [18]. Though, the impact of the differences in the excipients may cause this effect via (yet) unknown mechanism(s).

It can thus be concluded that the size and the charge of the particles formed, following introduction of SNEDDS to the water phase, can affect not only stability and release kinetics, but may also dictate the extent of absorption of the incorporated drug.

3. SNEDDS effect on solubility
Only after the drug molecule is presented in its dissolved state can it partition into the enterocyte and finally cross it. The bioavailability of BCS class II compounds is significantly hampered due to their poor water solubility. The primary mechanism by which lipid-based formulations enhance drug solubilization is by delivering the entire dose as a solution. Thus, the limiting step in drug absorption, that is, the slow dissolution from the crystalline state is avoided [19].

The digestion of lipid-based formulations including SNEDDS induces changes in lipid composition within the GI tract. Thus, the solubilized phase is not obtained directly from the administered lipid-based formulation, but most likely from the intra-luminal processing to which lipids are subjected prior to absorption [20]. A review of the physiology of the GI lipid absorption is, therefore, a key to understanding the role of lipids and the mechanism by which lipid-based formulations enhance drug solubilization.

The presence of lipid and lipid-digestion products in the duodenum stimulates secretion of endogenous biliary-derived solubilizing components such as bile salts and biliary lipids (cholesterol and phospholipids). Bile increases the solubility of lipid digestion products (i.e., 2-monoglyceride and fatty acids) in the aqueous intestinal lumen by their incorporation into micellar and mixed-micellar structures. The polar group of micelles projects into the aqueous phase, whereas the nonpolar hydrocarbon chain forms the center [21,19]. The formation of the aqueous mixed micellar phase significantly expands the solubilization capacity of the small intestine. When a poorly water-soluble drug is administered with dietary lipids or with lipids present in the formulation, the drug is distributed between these colloidal species. This process prevents drug precipitation and leads to an increase in effective aqueous solubility of the co-administered poorly water-soluble compound. Moreover, SNEDDS utilization provides a large interfacial area for partitioning of the incorporated lipophilic drug between oil and the GI fluid [22].

Numerous studies report increased dissolution of various poorly water-soluble compounds by their incorporation into SNEDDS. For example, incorporation of a poorly water-soluble lacidipine into SNEDDS significantly increases its in-vitro solubility [23]. It should be kept in mind, however, that promising results observed in in-vitro models are often not corroborated by in-vivo studies. Thus, further in-vivo evaluation is necessary to investigate whether SNEDDS formulations, which successfully increase drug’s in-vitro solubility, can promote enhanced oral bioavailability.
The micellar solubilization has another important role in overcoming a further barrier to effective uptake of lipophilic compounds. This is diffusion across the unstirred water layer (UWL). UWL separates the brush-border membrane of the enterocyte from the bulk fluid phase in the intestinal lumen [24]. The UWL, as the name implies, mixes poorly with the bulk phase in the intestinal lumen. As the solubility of lipophilic compounds in an aqueous medium is extremely low, very few molecules gain access to the brush-border membrane [25]. Solubilization of fatty acids, monoglycerides and lipophilic drugs in micellar and mixed-micellar structures, however, can greatly enhance their transport across the UWL, thereby enhancing lipid and drug absorption [19].

4. SNEDDS effect on permeability through biological membranes and on transporters

It was proposed that increased transcellular permeability could be a possible cause of improved oral bioavailability by SNEDDS utilization. One of the proposed mechanisms behind this phenomenon is attributed to the association of SNEDDS components with the enterocyte membrane, leading to an increase in its fluidity and thus enhanced passive permeability [26-28].

Other studies have pointed out that the alteration in the membrane fluidity by SNEDDS components can alter the conformation of membrane-bound transporters and promote the inhibition of membrane-bound efflux transporters. Thus, the increase in drug permeability is a result of a reduced efflux [29,30].

These may be two different and isolated mechanisms independent from one another. It is also possible that the enhanced permeability of the drug by SNEDDS utilization could result from the combination of the mechanisms described above, that is, increased passive transcellular transport together with efflux inhibition.

4.1 SNEDDS effect on efflux transporters

An increasing body of evidence has shown that certain non-ionic surfactants used to formulate SNEDDS can reduce drug efflux pumps activity. An efflux transporter of particular interest in regard to drug absorption is the MDR1 gene product P-glycoprotein (P-gp). This plasma membrane-bound protein is mainly distributed in drug-eliminating organs [31,32]. In the apical membrane of the intestinal epithelial cells, its role is to efflux compounds back into the intestinal lumen. It can, therefore, act as a barrier to the oral absorption of P-gp substrates.

Tweens, Spans, Cremophors (EL and RH40) and vitamin E TPGS are examples of non-ionic surfactants, which have been reported to inhibit the P-gp efflux activity [33-36]. Zhang et al. report an increased maximal concentration of drug in plasma (Cmax) and area under the curve (AUC) of a well-known P-gp substrate digoxin when it was orally administered with Tween 80 to rats. Moreover, their findings indicate that P-gp efflux inhibition is produced in a dose-dependent manner [37].

P-gp and intra-enterocyte metabolizing enzymes (mainly CYP3A4, which are elaborated in great detail in the next section) share numerous substrates and inhibitors; they probably work coordinately as a protective mechanism and are responsible for the poor bioavailability mainly of class II drugs [38]. Thus, when conducting studies to investigate the SNEDDS mechanism of action responsible for enhanced oral bioavailability, it is difficult to distinguish between these two absorption barriers. Bearing this in mind, the authors have incorporated into SNEDDS an exclusive P-gp substrate talinolol, which is not subjected to intra-enterocyte metabolism [39]. The results of this study demonstrate a threefold increase in talinolol relative oral bioavailability following administration of talinolol-SNEDDS compared to a free drug (Figure 1) [40]. Once finding an exclusive P-gp substrate, the authors were able to isolate the effect of their SNEDDS on the P-gp activity.

It is worth noting that for BCS Class II compounds, which are commonly formulated into SNEDDS, poor permeability is not a limiting factor in their absorption pathway [3]. However, the effect of efflux transport by P-gp can significantly limit their oral bioavailability [41]. Thus, the increased permeability of BCS Class II compounds by SNEDDS should be attributed to diminished efflux of the compound, rather than to the increased passive transcellular transport.

4.2 SNEDDS effect on uptake transporters

Usually, when investigating SNEDDS effects on intestinal transporters, the research is focused on the efflux transport, as described above. Recently a surprising issue was raised. It was reported that surfactants could also affect uptake intestinal transporters. This new insight implies that surfactant oral administration may lead to reduced or increased permeability, depending on the contribution of the individual event [36].

Several uptake transporters including organic anion transporting polypeptide (OATP) are expressed in the apical membrane of enterocytes. These transporters were reported to be involved in the oral absorption of many endogenic compounds and xenobiotics [42,43]. Dresser et al. report that grapefruit, orange and apple juices’ administration to human volunteers significantly reduces the uptake of an OATP substrate fexofenadine and decreases its AUC and Cmax [44]. Additionally, in-vitro studies conducted by Engel et al. indicate that polyethylene glycol, Solutol HS and Cremophor EL inhibit some of the OATP family transporters [45].

To date, there is a significant lack in comprehensive understanding of the possible SNEDDS effect on uptake transporters and its clinical relevance to drug bioavailability. Thus, this subject should be further evaluated.

It should be pointed out, though, that in the case of BCS class II drugs, which are highly permeable compounds, intestinal uptake transporters most probably do not have an important influence on their absorption. Some drugs, however, especially low permeable compounds depend on uptake transporters in the intestine to achieve effective systemic concentrations. In this case, the administration of surfactants...
alone or by SNEDDS utilization could have an unfavorable effect on their oral bioavailability.

5. SNEDDS effect on first-pass metabolism

It was generally assumed that the liver exerted the dominant effect in the first-pass metabolism process, whereas the intestinal wall was presumed to function as a physical barrier to drug permeability. This traditional point of view was based on the observation that the protein levels of drug-metabolizing enzymes in the small intestine were found to be generally significantly lower than those in the liver [46,47]. Nonetheless, enzymes of the CYP3A sub-family were found to be highly expressed in the mature villus tip enterocytes of the small intestine [48,49]. The CYP3A sub-family of enzymes is considered to have a major role in Phase I metabolism in human beings. In fact, the CYP3A sub-family is responsible for the oxidative metabolism of ~ 50% of currently marketed drugs [50]. It was shown that enzymes of the CYP3A family constitute > 70% of the small intestinal CYP P450s, whereas CYP3A constitute only 30% of total human hepatic CYP [47,51]. Thus, the perception that the liver is the only major organ responsible for the first-pass effect was replaced by the realization that the intestinal wall can also significantly contribute to the drug metabolism process.

Research conducted in the past two decades confirms this hypothesis. The most prominent example of intestinal Phase I metabolism was reported by Benet et al. Their clinical pharmacokinetic studies demonstrate the substantial role of the intestinal metabolism on the oral bioavailability of CsA in healthy volunteers. The study results reveal that 14% of the orally administered CsA is unabsorbed, due to either irreversible efflux by P-gp or degradation in the GI, 51% (of the absorbed dose) is metabolized in the enterocytes and only 8% is lost due to hepatic first-pass metabolism [52]. Moreover, intestinal Phase I first-pass metabolism has been shown to be clinically relevant for several other drugs, among them are midazolam, tacrolimus, nifedipine, felodipine and verapamil [53,54]. Thus, these observations of the past two decades led to greater credence to the preeminence of intestinal enzymes in the first-pass metabolism process. Therefore, the impact of intestinal, Phase I first-pass metabolism on oral drug bioavailability, should not be overlooked or underestimated.

It is worth noting that intestinal first-pass metabolism and hepatic first-pass metabolism are two different processes. This fact is sometimes overlooked, which can lead to some misconceptions in the drug development process. These metabolic routes should be distinguished, because for some drugs hepatic first-pass metabolism is the main barrier in the absorption process, whereas for others intestinal first-pass metabolism predominates. This is important to realize, because the means to bypass hepatic first-pass metabolism are different from those that can be applied to evade metabolism by the intestinal wall.

5.1 Reduced intra-enterocyte metabolism by SNEDDS

An increasing body of evidence has shown that certain components used to formulate SNEDDS can affect the disposition of drugs by inhibiting CYP enzymes in cellular microsomes of the enterocytes. Shen et al. report that the oral bioavailability of a CYP3A4 substrate atorvastatin is significantly increased upon incorporation into SEDDS containing Cremophore [55]. In the study by Ren et al., 22 pharmaceutical excipients were tested for their ability to inhibit the activity of CYP3A4 enzymes [56]. Fifteen of the tested excipients, amongst which are Tween 20, Cremophore 35, lecithin and Cremophor RH40, inhibit the activity of CYP3A4 by at least 50% in-vitro. Similar results were obtained in their in-vivo midazolam (a CYP3A4 substrate) study. Ren et al. [57] also indicate that non-ionic surfactants inhibit midazolam metabolism in a concentration-dependent manner and meet the criteria for a mixed competitive inhibitory model.

5.2 Stimulation of intestinal lymphatic drug transport to avoid hepatic FPM

The intestinal lymphatic system is a physiological pathway for the absorption of dietary lipid digestion products, for example, long chain fatty acids (LCFA), triglycerides (TG) and cholesterol esters [58]. Within intestinal cells the LCFA and monoglycerides are re-esterified into TG in the endoplasmic reticulum. Before these TGs leave the enterocytes they are incorporated into chylomicrons. Chylomicrons are the largest lipoproteins found [59]; thus, they cannot enter blood capillaries. Instead they enter the lymphatic capillaries termed lacteals, which are located in the villi of the enterocyte (Figure 2) [19]. This way post prandial lipids, which enter the lymph, bypass the liver at first passage. Eventually the lymph reunites with the blood at the junction of the left jugular and the left subclavian veins [60].

The pharmaceutical community hypothesized that this unique physiological route of lipid absorption can be exploited...
as a potential means of DDS to circumvent hepatic first-pass metabolism. It was presumed that some lipophilic drugs may associate with TG of the chylomicrons in the enterocyte and enter the systemic circulation via the lymphatic route [61].

Indeed, it has been reported that lipid-based delivery systems such as SNEDDS can be utilized to promote lymphatic drug transport. The oil phase used in SNEDDS formulations is a component of great importance. Not only can it facilitate the solubilization of a lipophilic compound; but it can also affect the absorption pathway of the incorporated drug [62]. Several researchers report that the biological fate of the drug is primarily influenced by long-chain triglycerides (LCTs), thus indicating that lipid-based delivery systems containing LCTs, such as SNEDDS, can promote the lymphatic transport of lipophilic drugs, while bypassing the hepatic portal vein route and enhancing the oral bioavailability of the drug [19,63].

Recently it has been reported that not only the oil component of SNEDDS can promote lymphatic transport, but certain surfactants can also produce the same effect [64,65]. As the concentration of surfactants in SNEDDS formulations is high and can reach up to 60% [66], their contribution to the lymphatic transport needs to be further explored.

It should be noted that the fluid flow rate in portal blood is ~500-fold higher than that of intestinal lymph. Thus, most low-molecular-mass drugs are absorbed through the portal vein [19]. Therefore, to enter the lymph the targeted drug should exhibit an intrinsic capacity for intestinal lymphatic transport. There are a number of in-vivo models to investigate drug presence in the lymph [67-69]. For example, an in-vivo model used is the lymphatic venous shunt. Using this model drug concentration in lymph can be measured for a long period of time by collecting a sample of the lymphatic fluid [70]. However, these models are very difficult to perform, time consuming and require high surgical skills. For this reason, an ex-vivo model for studying intestinal lymphatic transport was developed. This model is based on the finding that there is a linear correlation between the degree of uptake of lipophilic molecules by plasma-derived chylomicrons and the extent of lymphatic transport measured in-vivo (Figure 3) [71]. Thereafter, these researchers took this approach even further, to provide in-silico estimation of the expected lymphatic bioavailability impact of TG formulation on molecules prior to their synthesis [72].

Although the observed enhanced oral bioavailability is sometimes hypothesized to be a result of enhanced lymphatic transport of the lipophilic drug by SNEDDS utilization, only a limited number of studies have investigated the direct lymphophotrophic potential of SNEDDS using the models described above. An example is a study conducted by Hauss et al. [73] and a study conducted by Wu et al. [74].

It should be emphasized that drugs that are trafficked to the systemic circulation via the intestinal lymphatic system effectively bypass the liver, consequently reducing the opportunity for hepatic first-pass metabolism. However, it should be kept in mind that the intestinal metabolism is not bypassed and can provide significant first-pass effect prior to the entering of the drug into the lymphatic system.

6. SNEDDS effect on oral bioavailability

The previous sections of this review focuses on the different barriers in the absorption process of mainly Class II compounds in the isolated manner. The current chapter provides an insight into the overall SNEDDS effect using oral bioavailability as the end point of the investigation.

Diverse liquid SNEDDS have been developed and have shown superior in-vivo characteristics in terms of improved oral bioavailability (Table 1).

Aside from enhanced oral bioavailability, SNEDDS have been reported to decrease the influence of food effect [75], and bile secretion on oral bioavailability. Moreover, reduced intra- and inter-patient variability in the plasma concentration profile by SNEDDS was reported [75,76].
The SNEDDS effect on the oral bioavailability of tacrolimus has been examined. Tacrolimus is a potent immunosuppressant [77,78]; however, its clinical use is hampered by its poor oral bioavailability and extremely high inter- and intra-patient variability. This is due to extensive pre-systemic metabolism by intra-enterocyte CYP3A enzymes and efflux by P-gp pumps [79]. Study results indicate that the relative oral bioavailability of tacrolimus upon incorporation into SNEDDS was significantly greater in comparison to free drug [80]. Moreover, reduced variability in tacrolimus plasma concentrations is obtained following tacrolimus-SNEDDS administration. The ability of SNEDDS to increase oral bioavailability and reduce variability was further corroborated in recently performed studies. An antiarrhythmic BCS Class II [81] compound amiodarone (AM) has been incorporated into SNEDDS [40]. AM is characterized by erratic, unpredictable absorption and low oral bioavailability (20 – 80%), which is mainly mediated by intra-enterocyte metabolism via CYP3A4 [82]. The oral administration of AM-SNEDDS to rats results in a 1.65 and 1.54-fold increase in Cmax and AUC, respectively (Figure 4). In addition, incorporation of AM into SNEDDS results in reduced variability in the AUC and Cmax values [40].

These findings emphasize the added value of SNEDDS, that is, reduced plasma fluctuations or a more predictive absorption in addition to enhanced oral bioavailability.

7. Candidate compound selection

SNEDDS have been stated by many scientists to be suitable formulations for improving the oral bioavailability, mainly of BCS Class II drugs. BCS is a drug classification scheme for correlating in-vitro drug product dissolution and in-vivo bioavailability, based on the recognition that drug dissolution and GI permeability are the fundamental parameters controlling rate and extent of drug absorption [5]. The BCS divides drugs and drug candidates into four principal categories based on these parameters: Class I – High solubility-high permeability; Class II – Low solubility-high permeability; Class III – High solubility-low permeability; and Class IV – Low solubility-low permeability drugs. To date, > 30% of top marketed drugs in the USA and 70% of all new drug candidates are lipophilic and consequently have poor aqueous solubility, combined with high permeability through the enterocyte membrane; thus they frequently fall into Class II as defined by the BCS [2].

It was traditionally believed that the extremely low and erratic bioavailability of Class II compounds is hampered mainly due to their poor water solubility. The use of lipid-based DDS such as SNEDDS for improving the bioavailability of Class II drugs was based on the observation that co-administration of poorly water-soluble drugs with a high-fat meal can improve their bioavailability [83]. The prevailing view was that SNEDDS is an effective and practical solution in improving the oral bioavailability of a lipophilic compound by its presentation and maintenance in a dissolved state. This way the drug is introduced in fine oil droplets at the molecular level, throughout the transit in the GI tract. However, there are compounds for which poor water solubility is not the main hurdle in their oral absorption process. The case of cyclosporine is the most prominent example demonstrated by Wu et al. For example, CsA, a BCS Class II compound, is a P-gp and CYP3A substrate. It had no permeability difficulty and is absorbed at least 86% when solubilized with corn oil in a commercially available lipid-based formulation. Its oral bioavailability, however, is low due to a marked intra-enterocyte first-pass extraction and P-gp efflux of 60% or more [84].

In light of these data, Wu and Benet examined the BCS from a biopharmaceutical perspective and developed a modified classification system that may be useful in predicting routes of elimination, effects of efflux and absorptive transporters as well as effects of transporter-enzyme interplay on oral absorption. They suggest that it may be more useful to replace the permeability criterion with the major route of drug elimination and metabolism and proposed designation of the major route of drug elimination as a part of or instead of permeability criteria used in the BCS classifications. According to this model termed Biopharmaceutical Drug Disposition Classification System (BDDCS), drugs classified as Class II compounds are those for which the influence of pre-systemic metabolism by CYP 450 enzymes and efflux by P-gp on oral drug bioavailability predominates. This is because their low solubility does not enable us to facilitate adequate drug concentrations at the absorption site to produce the inhibition of those barriers [85].

It is reasonable to attribute the increased bioavailability of griseofulvin [86,87], vitamin A [88] and other solubility-limited compounds to improved solubilization. However, for extensive...
pre-systemic (and especially intestinal) metabolism substrates, such as for CsA [10,89], tacrolimus [90], simvastatin and most of the drugs and herbal remedies as those listed in (Table 1), enhancement of solubility by SNEDDS utilization is probably not the only mechanism responsible for their improved bioavailability. Moreover, several recent studies demonstrated that the solubilization capacity of SNEDDS decreases following the lipolysis process in the GI tract, mainly as the nano-vesicle structures do not remain intact following lipolysis, but rather become a part of mixed micelles formed by bile salts, phospholipids and other GI composites [91]. Furthermore, some of the excipients that compose SNEDDS undergo digestion in the GI tract, which leads to significant loss of solubilization capacity [92].

As elaborated in the previous sections of this review, SNEDDS have demonstrated potential to increase oral bioavailability by multi-concerted mechanisms such as reduced intra-enterocyte metabolism by CYP P450 enzymes, reduced P-gp efflux activity and by promoting hepatic first-pass bypass via lymphatic absorption. It is, therefore, more than reasonable to conclude that enhancement of solubility is obviously not the only mechanism responsible for improved oral bioavailability by SNEDDS. Thus, in the author’s opinion a more accurate statement is that SNEDDS can serve as a drug delivery platform for poorly soluble and highly metabolized drugs, that is, Class II drugs as defined by the BDDCS.

Here are some examples from the literature to support the stated hypothesis. For instance, it was generally agreed that poor water solubility was the main reason for the low oral bioavailability of glyburide. Liu et al. developed SNEDDS incorporating this poorly soluble drug [95]. Their in-vitro studies indicate that SNEDDS increases the solubility of glyburide and eliminates the influence of pH on its dissolution. Additionally, oral administration of this formulation results in a 1.53-fold increase in the relative bioavailability. The increased oral bioavailability was judged to be mainly a result of the increased drug solubilization. Poor water solubility, however, is probably not the only barrier to its oral absorption. A study published by Zhou et al. reveals that glyburide undergoes metabolism mainly by CYP3A4 enzymes [93]. As elaborated above in Section 5.1, some components used to produce SNEDDS (such as Cremophore RH-40 used in the study by Liu et al.) reportedly inhibit the activity of metabolizing enzymes [35]. Thus, there is a possibility that in addition to increased solubility, the oral bioavailability of this antiglycemic agent is also augmented due to the

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<tr>
<td>Amiodarone</td>
<td>Trilaurin, Tween 20, Span 80, Cremophore RH 40, lecithin, ethyl lactate</td>
<td>1.8 and twofold increase in Cmax and AUC</td>
<td>Rats</td>
<td>Increased solubility, reduced metabolism</td>
<td>[40]</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>Labrafil, Tween 80, and Transcutol</td>
<td>1.55 and 1.5-fold increase in Cmax and AUC</td>
<td>Human volunteers</td>
<td>Increased solubility</td>
<td>[100]</td>
</tr>
</tbody>
</table>

SNEDDS: Self-nano-emulsifying drug delivery systems.
amino acids, 12.5 mg/kg (n = 6 for each group). The utilization of lipid-based drug delivery systems in general and of SNEDDS in particular shows great potential in improving the solubility, enhancing bioavailability and reducing inter/intra subject variability. Although this potential has been recognized for nearly two decades, the full impact on drug disposition by SNEDDS and its components has been recognized only in the recent years. This review summarizes the current comprehension of the biopharmaceutical aspects of SNEDDS. Recent mechanistic research conducted by our group and by other researchers implies that SNEDDS ability to augment the oral bioavailability of poorly water-soluble drugs goes beyond improvement in the solubility of a drug as it was initially presumed. The summarized data in the current review indicates that SNEDDS have a potential to increase oral bioavailability by multi-concerted mechanisms such as reduced intra-enterocyte metabolism by CYP P450 enzymes, reduced P-gp efflux activity and by bypassing hepatic first-pass metabolism via lymphatic absorption.

It should be however noted that there is a phenomenon of ‘negative results bias’, meaning that in many cases there were no enhancement in bioavailability despite the SNEDDS utilization. Such negative results are rarely published; thereby mask the fact that the optimized properties of the pharmaceutical compounding are rather specific, and need further investigational efforts to uncover. Thus, critical comparison between negative results (which are only known to the specific laboratory where the studies were conducted) and successful formulations may provide important information that is beyond the available published data.

Nevertheless, in light of the information presented in the current review, it is evident that SNEDDS have attracted increasing attention as a means to enhance the oral bioavailability of poorly soluble and highly metabolized drugs. Although many studies have been conducted there are only few approved commercial self-emulsifying products available on the pharmaceutical market. There are several reasons for this phenomenon. One of them is the difficulty in incorporation of a lipophilic compound into SNEDDS. Additionally, it has been reported that the fate of the drug incorporated into SNEDDS may be altered throughout its transit in the GI tract. Some poorly water-soluble drugs are successfully solubilized by SNEDDS; however, they fail to reach the site of absorption in their molecular state. This is because precipitation occurs following dispersion of SNEDDS in aqueous media of the GI tract milieu [94]. As described in the third section of this review, upon dispersing SNEDDS pre-concentrates in the GI milieu, fine emulsions are formed, which facilitates lipid hydrolysis by lipase on the o/w interface. Following this process, micelles together with other colloidal structures composed of the lipophilic products, bile salts and phospholipids are formed. In case the solubilization capacity of these micelles is lower as compared to the initial fine emulsion formed, the incorporated drug might precipitate in the GI tract. *In-vitro* drug solubility in the formulation is indeed an important characteristic in lipid-based formulation design; however, solubilization capacity following lipid digestion is also required to estimate *in-vivo* performance. The absence of proper guidelines for lipid-based formulations on formulation design represents difficulty in developing new products, as well.
This review summarizes the recent advances in the understanding of the versatile biopharmaceutical effects of SNEDDS. This unique biopharmaceutical point of view contributes to the understanding of proper drug candidate selection and of the approach in SNEDDS formulation design. The selection of candidates to be formulated into SNEDDS to achieve improved oral bioavailability and reduced variability should be based on the intelligent recognition of the absorption barriers of a drug. The understanding of the role of certain transporters or intestinal CYP P450 enzymes on the absorption and disposition characteristics of a specific drug must be investigated. This knowledge will enable intelligent excipient selection in the SNEDDS formulation process. Optimal SNEDDS composition per individual physicochemical properties and absorption processes of a drug will enable the modulation of the relevant absorption barriers for each drug candidate. In opinion of the authors, SNEDDS utilization can offer the most beneficial outcome in augmenting the bioavailability of poorly soluble and highly metabolized drugs, that is, BDDCS Class II drugs.

Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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