Development of supersaturatable self-emulsifying drug delivery system formulations for improving the oral absorption of poorly soluble drugs

Ping Gao & Walter Morozowich

PGRD, Pfizer, Inc., 301 H enrrietta Street, Kalamazoo, MI 49007, USA

The supersaturatable self-emulsifying drug delivery system (S-SEDDS) represents a new thermodynamically stable formulation approach wherein it is designed to contain a reduced amount of a surfactant and a water-soluble cellulose polymer (or other polymers) to prevent precipitation of the drug by generating and maintaining a supersaturated state in vivo. The S-SEDDS formulations can result in enhanced oral absorption as compared with the related self-emulsifying drug delivery systems (SEDDS) formulation and the reduced surfactant levels may minimise gastrointestinal surfactant side effects.

Keywords: bioavailability, lipid-based formulations, microemulsion, oral delivery, poorly soluble drugs, self-emulsifying drug delivery systems, supersaturation, surfactant

1. Introduction

1.1 Conventional SEDDS formulations

The development of formulations of highly lipophilic, poorly soluble drugs is often associated with serious challenges with respect to oral absorption. Lipophilic drugs usually have low water solubility and this can result in incomplete oral absorption, low bioavailability and high variability following oral administration. One of the most popular approaches for formulating poorly soluble drugs is the incorporation of the drug into a lipid vehicle containing a surfactant. These formulations represent a unique class of formulations, commonly referred to as self-emulsifying drug delivery systems (SEDDS), and these have been widely explored over the last decade [1-8]. Typically, the SEDDS formulation contains a drug dissolved in a vehicle that is encapsulated in a soft gelatin capsule (softgel), wherein the composition of the vehicle is designed to emulsify rapidly on contact with water and yield a fine oil/water emulsion or microemulsion in the stomach.

SEDDS formulations are commonly developed by an empirical, trial-and-error approach, although some useful guidelines have emerged from the characterisation of successful formulations, such as the cyclosporin A (CsA; Neoral®, Sandoz-Novartis) softgel formulation [9-10]. In general, formulation scientists are presented with a series of challenging decisions in the development of SEDDS formulations, beginning with the formulation strategy, excipient selection, solubility and stability assessment, prototype formulation finding and optimisation, scale up and, finally, production of the drug product. The key consideration in the development of a SEDDS formulation of poorly soluble drug is preventing precipitation of the drug following dilution with water. Thus, the drug must remain partitioned within the oil/water emulsion droplets following dilution of the SEDDS formulation with the aqueous medium in the intestine. If the partition coefficient of the drug for the SEDDS emulsion or microemulsion particle is such that the solubility of the drug is...
Development of S-SEDDS formulations for improving the oral absorption of poorly soluble drugs

exceeded in the aqueous phase, the drug could precipitate following dilution with water, and this could result in poor in vivo performance.

1.2 Supersaturatable SEDDS formulations

Supersaturatable SEDDS (S-SEDDS) formulations differ from the conventional SEDDS formulations as they contain a reduced amount of surfactant and a polymeric precipitation inhibitor (e.g., water-soluble cellulose polymers, such as hydroxypropylmethylcellulose [HPMC]), in order to generate and maintain a supersaturated state of the drug following mixing with water.

A high surfactant level is normally employed in conventional SEDDS formulations in order to prevent precipitation of the drug following dilution with water in the gastrointestinal (GI) tract and, in some cases, the surfactants can lead to an increased incidence of GI side effects [11-15].

Increasing the thermodynamic activity of drug formulations and, thereby, increasing the bioavailability of poorly soluble drugs, through supersaturation was recognised by Higuchi more than four decades ago [16]. Since then a number of publications have appeared in the literature employing supersaturated formulations as a means of enhancing bioavailability. Most of the work on supersaturation reported in the literature deals with topical delivery [16-27] with less attention to the use of supersaturation for improving the oral delivery of poorly soluble drugs [28-34].

Polyvinylpyrrolidone (PVP) was found to be useful in generating a supersaturated state with a number of poorly soluble drugs [17-21,28,29,35]. Other studies reported the use of the water-soluble cellulose polymers, such as HPMC [22-25,27,30,31,36], methylcellulose [25], hydroxypropyl methylcellulose phthalate [33,34] and sodium carboxymethylcellulose [37]. The cellulose polymers are excellent crystal growth inhibitors and are effective in prolonging the supersaturated state of the drugs as shown by a number of in vitro studies [21,22,36,37].

Based on the above-cited literature, a promising approach for enhancing the oral bioavailability of poorly soluble drugs is the use of the principle of supersaturation in the development of supersaturatable formulations [38,39]. Supersaturatable formulations differ from supersaturated formulations as they are not thermodynamically stable and, in some cases, the drug can crystallise on storage [40]. In contrast, supersaturatable formulations are thermodynamically stable dosage forms as they yield a supersaturated state only following dilution with water.

2. Design and development of S-SEDDS formulations

S-SEDDS formulations of three poorly soluble drugs (paclitaxel, PNU-91325 and Drug X) were developed and their in vitro behaviour was characterised, and the oral bioavailability was determined. The in vitro test methodology employing biorelevant conditions is useful in guiding the development of the S-SEDDS formulations, as well as in the development of in vitro/in vivo relationships.

Prompted by the biorelevant dissolution system reported by Tang et al. [41] and the importance of GI physiology and dosage form performance, a small-scale in vitro release/precipitation test was developed for evaluating and optimising the S-SEDDS formulations of the three poorly soluble drugs. The biorelevant in vitro release/precipitation test method consisted of simulated gastric fluid (SGF) containing 0.01 M HCl and 0.15 M NaCl (pH 2) stirred at 50 rpm at 37°C [38,39]. The total volume of the medium is 50 – 100 ml, which is the approximate volume of the stomach fluid when swallowing a tablet or capsule dosage form with 2 – 3 oz of water.

The in vitro release/precipitation test is conducted by placing a unit dose of the prototype S-SEDDS formulation or related formulation in the stirred test medium at 37°C and withdrawing samples from the test medium as a function of time followed by filtration (0.8 µm), and the determination of the total drug concentration in the filtrate using high-performance liquid chromatography. The apparent drug concentration following filtration of the S-SEDDS formulation during the test provides the total concentration of the drug in the filtrate, which consists of free drug along with some emulsion, micelle or solid drug particles with a particle size < 0.8 µm generated within in the release/precipitation test medium [38,39]. The in vitro release/precipitation test and the resulting apparent drug concentration versus time plots were employed in guiding the development of the S-SEDDS formulations, as illustrated by the three case studies described below.

3. Case studies on the development of S-SEDDS formulations

3.1 Paclitaxel

Paclitaxel is an antitumour agent that is widely used in the treatment of advanced breast and ovarian cancer. Paclitaxel has a molecular weight of 853 Da and a low solubility in water (< 1 µg/ml), as well as a low solubility in common pharmaceutical vehicles [42,43]. The currently marketed intravenous formulation of paclitaxel (Taxol®, Bristol-Miers Squibb) contains paclitaxel 6 mg/ml, Cremophor EL 527 mg/ml (polyoxyethylene castor oil) and 49.7% (v/v) of dehydrated ethanol [44]. Intravenous administration of paclitaxel using this formulation is associated with side effects that are attributed to the surfactant Cremophor EL and these side effects can be controlled by the coadministration of antihistamine [43,45-47].

The oral bioavailability of paclitaxel using the Taxol IV formulation is extremely low (< 2%) when administered orally to animals and humans [48-50]. Oral coadministration of the Taxol IV formulation along with CSA, an inhibitor of P-glycoprotein and cytochrome P450 3A enzymes, resulted in a sevenfold increase in the plasma area under the curve (AUC) value for paclitaxel in humans [48-51].

The mean plasma concentration of paclitaxel obtained in rats with the SEDDS and S-SEDDS formulations and
of precipitation of the drug on dilution of this formulation after dilution of the formulation with water. The inhibition and no precipitation of paclitaxel is observed for several days (10-fold increase in the oral bioavailability; namely 9.5% formulation containing only HPMC. As discussed in [39], the increase in the oral bioavailability over that of the S-SEDDS ever, the slower elimination kinetics, resulted in a twofold S-SEDDS + CsA whereas the S-SEDDS formulation (with HPMC) resulted in PFUND WP paclitaxel with improved oral bioavailability.

Taxol are plotted in Figure 1 [39]. The pharmacokinetic parameters corresponding to these treatment groups are summarised in [39]. The rank order of the mean total exposure as given by the AUC$_{0-\infty}$ for the four formulations is S-SEDDS + CsA > S-SEDDS > > Taxol ~ SEDDS.

The difference in the pharmacokinetic profiles exhibited by the SEDDS and S-SEDDS formulations is intriguing because these two formulations differ only in the content of HPMC; 0 and 5%, respectively. Thus, the SEDDS formulation (without HPMC) showed a very low maximum concentration (C$_{max}$) of only 13.1 ng/ml and an oral bioavailability of 0.9%, whereas the S-SEDDS formulation (with HPMC) resulted in an impressive 20-fold increase in C$_{max}$ (~ 277 ng/ml) and a 10-fold increase in the oral bioavailability; namely 9.5% (Figure 1). The S-SEDDS formulation with the addition of CsA and HPMC showed similar absorption kinetics; however, the slower elimination kinetics, resulted in a twofold increase in the oral bioavailability over that of the S-EDDS formulation containing only HPMC. As discussed in [39], the rat bioavailability results indicate that the higher paclitaxel solution concentration generated by the S-SEDDS formulation in the in vitro release/precipitation test as a result of supersaturation is responsible for the enhanced oral bioavailability of paclitaxel.

The Taxol formulation generates a nearly transparent solution (particle size < 30 nm) following dilution with water, and no precipitation of paclitaxel is observed for several days after dilution of the formulation with water. The inhibition of precipitation of the drug on dilution of this formulation with water is due to the high Cremophor EL content in the formulation (weight ratio of Cremophor EL:paclitaxel was 88:1) and this results in complete solubilisation of paclitaxel by the Cremophor micelles. Apparently, the free-drug concentration does not exceed the solubility of paclitaxel in water [39]. It is noteworthy that the Taxol formulation (Figure 1) produced a low mean C$_{max}$ (~ 30 ng/ml) and a low oral bioavailability (~ 2%). Thus, the poor oral exposure of paclitaxel from the Taxol formulation in rats is probably due to the excess Cremophor, resulting in sequestration of the paclitaxel within the micelle and reducing the free-drug concentration in the formulation [39], which is consistent with similar reports in the literature [52,53].

3.2 PNU-91325

PNU-U-91325 is a lipophilic drug with a calculated Log P partition coefficient (CLogP) of 2.8 [38]. This molecule shows a U-shaped pH-solubility dependency, indicating two $\log_{10}$ dissociation constant for an acid (pK$_a$) values (a basic pK$_a$ of 2.61 and an acidic pK$_a$ of 6.85). PNU-U-91325 shows an almost constant solubility of ~ 6 µg/ml within the physiological pH range of 2 - 7.

The difference in the in vitro release/precipitation profile between the two formulations, with and without HPMC, clearly indicates that a small amount of HPMC plays a critical role in achieving a supersaturated state with PNU-U-91325 by retarding drug precipitation and, in addition, sustaining the high supersaturated drug concentration. As shown in Figure 2A, in the absence of HPMC the PNU-U-91325 concentrations were low following administration of a propylene glycol (PG) formulation, whereas a much higher concentration was observed when 2% HPMC was incorporated in the same PG formulation. Similarly, the PNU-U-91325 concentrations from an S-SEDDS formulation with HPMC increased by approximately fivefold as compared with those of the same SEDDS formulation without HPMC during the time course of 0 - 3 h.

The mean oral plasma concentrations of PNU-U-91325 in beagle dogs (n = 4, crossover) are plotted in Figure 3 as obtained with the Tween 80 formulation, the polyethylene glycol (PEG) 400 formulation, the S-SEDDS formulation and the PG plus 2% HPMC (S-cosolvent) formulation [38]. The mean dose, mean AUC$_{0-\infty}$, C$_{max}$ and the estimated absolute bioavailability values observed with each of the formulations are reported in [38]. The low oral bioavailability observed with the PEG 400 solution of PNU-U-91325 is probably due to the rapid precipitation of the drug in vivo. As indicated by the above in vitro release/precipitation test data, the PG plus 2% HPMC (S-cosolvent) formulation of PNU-U-91325 yielded a significantly higher apparent drug concentration (Figure 2B). This formulation resulted in an approximately sevenfold higher C$_{max}$ (6.04 µg/ml) and a five-fold higher oral bioavailability (~ 60%) as compared with the PEG 400 formulation that showed a lower C$_{max}$ (0.88 µg/ml) and a lower oral bioavailability (~ 12%).
Development of S-SEDDS formulations for improving the oral absorption of poorly soluble drugs

The PNU-91325 S-SEDDS formulation showed an oral bioavailability of ~76%, which is higher than the bioavailability of ~68% observed with the Tween 80 formulation. As the formulation compositions were reported in Table 1 in [38], the weight ratio of drug:Cremophor EL is 1:7.5 in the S-SEDDS formulation, whereas the weight ratio of drug:Tween 80 is 1:39 in the Tween 80 formulation. Clearly, the surfactant level is about fivefold higher in the Tween 80 formulation as compared with the S-SEDDS formulation. The S-SEDDS formulation yielded a supersaturated state following dilution as evidenced by the decline in the apparent drug concentration with respect to time (Figure 2B) and by the observation of crystal formation in the in vitro release/precipitation test medium [38].

3.3 Drug X

Formulations of Drug X were under development for preclinical and clinical evaluation. Drug X has a log P of ~3.5, a water solubility of only ~5 µg/ml in the physiological pH range of 2 – 7 and it is nonionisable in this pH range. A human oral pharmacokinetic study using Drug X showed slow and incomplete oral absorption using the drug powder in a gelatin capsule, whereas rapid and more complete absorption was found with a small particle size aqueous suspension of Drug X.

3.3.1 S-SEDDS formulations containing suspended HPMC powder

The in vitro release/precipitation test used 1 g of the S-SEDDS formulations containing 200 mg of Drug X filled into two hard gelatin capsules (0.5 g/capsule) and 50 ml of SGF to yield a theoretical concentration of Drug X in the test medium of 4 mg/ml. The apparent Drug X concentration found with the SEDDS formulation (without HPMC) in the
in vitro release/precipitation test is plotted in Figure 4A. The concentration of Drug X in the medium was ∼ 0.3 mg/ml at the first time point (0.5 h) and this remained unchanged over the entire 6-h test period. A white precipitate of Drug X was observed with the SEDDS formulation in the release/precipitation test medium at 0.5 h and the precipitate was found to be crystalline as shown by polarised light microscopy. The formation of drug crystals in the test medium indicates that the solution was supersaturated with respect to the crystalline form of Drug X. In contrast, a markedly higher concentration of Drug X (∼ 2.7 – 3.5 mg/ml) was observed with the same SEDDS formulation in SGF containing 0.025% HPMC. The presence of HPMC at the remarkably low concentration of only 0.25 mg/ml (0.025%) in the test medium is sufficient to generate and maintain the supersaturated state with Drug X for at least 6 h under the conditions of the release/precipitation test.

Figure 4.

Figure 4A. Apparent concentration-time profiles of Drug X observed in the in vitro release/precipitation test using the same SEDDS formulation with and without HPMC. All formulations were filled into hard gelatin capsules. B. Mean plasma concentration profiles of Drug X in the dogs in vivo (n = 6, crossover) using the SEDDS and S-SEDDS formulations as compared with an aqueous suspension formulation [54].

A) In vitro
- S-SEDDS with HPMC
- SEDDS in the in vitro test medium containing 0.025% HPMC
- SEDDS without HPMC

B) In vivo
- Aqueous suspension
- S-SEDDS containing HPMC
- SEDDS without HPMC

3.3.2 S-SEDDS formulations in a HPMC capsule
The use of a HPMC capsule shell was explored as an alternate approach for incorporating HPMC into the S-SEDDS formulation. The same SEDDS liquid fill that was used in the above studies was filled into HPMC capsules (Quali-V capsules, Shionogi; capsule shell weight ∼ 90 mg). Three dosage forms were selected for comparison in the in vitro release/precipitation test; a SEDDS liquid formulation corresponding to 1 mg/ml (of HPMC, w/w) was about threefold higher in the Cmax value, and the AUC is 2.5-fold larger as compared with that of the same SEDDS formulation without HPMC. This clearly indicates that the S-SEDDS formulation containing HPMC results in an increase in both the Cmax and the extent of absorption of Drug X. The aqueous suspension and the S-SEDDS formulation showed a similar pharmacokinetics profile in dogs with slightly higher Cmax and AUC values for the S-SEDDS formulation.
Development of S-SEDDS formulations for improving the oral absorption of poorly soluble drugs

An oral bioavailability study was conducted in dogs (n = 6, crossover) with the three SEDDS formulations. The mean plasma concentration–time profiles of Drug X are plotted in Figure 5B. As expected, the SEDDS formulation of Drug X in the gelatin capsule showed a low C_max and a low AUC. However, the plasma concentration–time profiles observed with the two S-SEDDS formulations, consisting of the SEDDS formulation containing HPMC, and the SEDDS formulation filled into HPMC capsules, were almost superimposable and the resulting C_max and AUC values were approximately twofold higher than that of the SEDDS liquid without HPMC in the gelatin capsule. The in vivo behaviour of the three formulations is in accord with the in vitro release/precipitation test results.

In summary, Drug X in S-SEDDS formulations containing HPMC either as suspended powder or as HPMC in the capsule shell results in achieving and maintaining a supersaturated Drug X solution following contact with water, and this results in higher in vivo oral bioavailability in dogs. Further evaluation in the clinic is discussed in the following section.

3.3.3 Clinical evaluation of the S-SEDDS formulation

S-SEDDS softgel formulations of Drug X were evaluated in fasted humans in comparison with two other formulations, namely a bulk drug powder formulated in a gelatin capsule and an aqueous suspension of Drug X (23 subjects, crossover).

The clinical study results obtained with the three dosage forms of Drug X are shown in Figure 6 where the mean C_max maximum time (T_max) and AUC values are taken from [54]. The bulk drug powder formulation in the gelatin capsule showed the lowest C_max (621 ng/ml) and the aqueous suspension of the drug showed a slightly higher C_max (804 ng/ml). In contrast, the S-SEDDS softgel containing suspended HPMC showed the highest C_max (2061 ng/ml), which is an impressive 331% increase in C_max and a 40% increase in the AUC as compared with the Drug X powder formulation in the gelatin capsule. The highest C_max and the largest AUC along with the shortest T_max (∼ 1 h) were observed with the S-SEDDS softgel containing suspended HPMC indicating more rapid and more complete absorption.

4. Possible drug absorption mechanism from SEDDS and S-SEDDS formulations, and significance of supersaturation-based drug delivery

4.1 Drug absorption from the SEDDS and S-SEDDS formulations

Drugs with water solubilities < ∼ 1 – 50 µg/ml frequently show incomplete oral absorption when the dose is ≥ 50 mg [55-59]. However, there are a number of other extremely insoluble and highly lipophilic compounds that have solubilities that are orders of magnitude < 1 – 50 µg/ml and yet, they are absorbed orally [60-62]. The early work of Börgström et al. [63,64] and later Carey et al. [65-67], as well as many others [68-99], showed that it is the bile acid mixed micelle (BAMM)...
in the fed state and the bile acid (BA) micelle in the fasted state that constitute the endogenous surfactant system that is responsible for the presentation of extremely lipophilic compounds and drugs to the surface of the enterocyte brush border region where transfer of the compound from the BA/BAMM particle to the glycocalyx can occur by collisional contact [100-103]. Cholesterol with a ClogP of 12 and a water solubility of ~10 ng/ml is efficiently absorbed from the intestine by initial presentation of cholesterol in the BAMM particles to the enterocyte brush border mucosa with subsequent collisional transfer to the glycocalyx [63-68]. Many other extremely insoluble and lipophilic compounds are absorbed more efficiently in the fed state due to the high concentration of BAMM in the intestine in this state [55]. The BAMM system in the fed state is more effective in solubilising drugs than the BA system in the fasted state because of the higher total micellar concentration of BAMM as compared with that of BA in the fasted state.

Lipophilic drugs are known to partition into BA/BAMM systems [99,104-106] and predictive relationships have been reported [106]. Highly lipophilic compounds can equilibrate between populations of liposomes by collisional contact, whereas less lipophilic compounds can equilibrate between populations of liposomes via the compound that is dissolved in the aqueous medium [107].

Based on the above, it appears that drugs can be delivered to the intestinal enterocyte brush border region by the aqueous diffusion pathway, as well as by the BA/BAMM pathway. The delivery of cholesterol from the BAMM to the enterocyte surface occurs via collisional transfer [88-90,93,94,96-98,108-113,201].

Figure 7 shows a possible scheme for the presentation of poorly soluble lipophilic drugs from SEDDS and S-SEDDS formulations to the intestinal enterocyte brush border by three possible pathways; the aqueous pathway; by mimicking the BA/BAMM pathway; or by equilibrating with the BA/BAMM pathway.

Figure 7 shows that the emulsion or microemulsion generated in the intestinal lumen from a SEDDS/S-SEDDS softgel formulation can undergo lipolysis or transfer of the excipients to the enterocyte (path A). The drug in the remnant emulsion/microemulsion or the resulting micelle that is generated from the SEDDS/S-SEDDS formulation can undergo collisional transfer to the glycocalyx (path B). Alternatively, the drug in the aqueous medium can become absorbed directly by the well-known passive diffusion aqueous pathway (path C). The free drug in the aqueous medium could equilibrate with the BAMM or remnant BAMM with collisional transfer of the drug to the glycocalyx (path D) without requiring water solubility.

After absorption into the enterocyte, the drug could diffuse across the enterocyte or, if the drug is highly lipophilic, the drug could partition into the chylomicrons in the fed state with subsequent transfer to the lymphatics and ultimately to the systemic venous circulation [5,8,114,115]. Moderately lipophilic drugs could escape from the chylomicrons by partitioning or collisional transfer with subsequent entry into the venous system.

Lipid digestion can be important in the absorption of highly lipophilic drugs because of their probable high partition affinity for the emulsion/microemulsion particle. Lipids, such as long-chain fatty acid triglycerides, must undergo lipolysis before absorption of the resulting fatty acids can occur. The lipid digestion process and the subsequent absorption of some lipophilic drugs can be adversely affected by the presence of surfactants in the formulation [58], and by a large droplet size for the emulsion/microemulsion particle formed following exposure to GI fluids.

### 4.2 Significance of supersaturation in enhancing drug absorption

 supersaturation was shown to occur in the authors' in vitro release/precipitation test, wherein the drug filtrate concentration of a S-SEDDS formulation of PNU-91325 showed a maximum value of ~420 µg/ml at 30 min (figure 28, S-SEDDS with HPM C). However, the SEDDS formulation of PNU-91325, without HPM C, yielded a drug filtrate concentration of only ~30 µg/ml at 3 h in the release/precipitation test and, thus, the approximate degree of apparent supersaturation with the S-SEDDS formulation of PNU-91325 is 420/30 or about 14. The ~14-fold degree of apparent supersaturation observed with the SEDDS formulation of PNU-91325 suggests that intestinal absorption should be markedly increased as a result of the supersaturated state. Initially, the test medium did not show evidence of drug crystals under the microscope; however, on long standing, crystals were readily seen, thus indicating that the medium was supersaturated.

The failure to provide high oral exposure of paclitaxel with the Taxol formulation is significant in that the common

---

**Figure 6.** Human bioavailability study (subject number = 23, cross-over) with three formulations of Drug X: formulated Drug X powder/hard gelatin capsule, an aqueous suspension, and a S-SEDDS formulation/softgel [54]. S-SEDDS: Supersaturatable self-emulsifying drug delivery system.
Development of S-SEDDS formulations for improving the oral absorption of poorly soluble drugs

practice of formulating poorly soluble drugs with high concentrations of surfactants inevitably results in the reduction in the free-drug concentration or the thermodynamic activity. It is well known that micelle solubilisation of poorly soluble, lipophilic drugs can result in a low free-drug concentration, as given by the partition coefficient, and the low free-drug level can result in a reduced rate and extent of absorption [13-15]. The work by Poelma et al. [13,14] is noteworthy in that the kinetics of the intestinal absorption of griseofulvin in rats was found to be directly related to the concentration of the free griseofulvin level found in the aqueous solutions containing Tween 80 (a surfactant) [13]. These workers also showed a reduction in the rate of absorption of griseofulvin from the small intestine of rats in the presence of 10 - 20 mM taurocholate, and reduction was directly related to the reduced free drug level [14]. Likewise, Chiu et al. [15] showed that the presence of surfactants (Cremophor EL, RH 40 and VE-TPGS with surfactant concentrations at 0.02% weight/volume or higher) significantly decreased the apparent permeability of CsA in Caco-2 cells, and the magnitude of the decrease in permeability (2- to 12-fold) was directly related to the surfactant concentration. Reduction in the apparent permeability of CsA in the presence of surfactants decreased the free drug levels of CsA in the solution as a result of micellar solubilisation.

In conclusion, the mechanism responsible for the enhanced intestinal absorption of poorly soluble drugs from S-SEDDS formulations containing HPMC is probably due to enhanced presentation of the drug to the enterocyte brush border region by the aqueous pathway due to the increased free-drug levels achieved by supersaturation, in addition to presentation of the drug to the enterocyte brush border by mimicking, or equilibrating with, the BA/BAMM pathway.

5. Drug-polymer interaction in sustaining the supersaturated state

Although there have been many reports in the literature on inhibition of crystallisation by HPMC and other polymeric
materials [16-37] with pharmaceutical substances, the underlying mechanism of inhibition is complex and is rarely illustrated or studied.

The ability to generate a supersaturated state with HPMC with the S-SEDDS formulations may be due to the formation of a widely spaced cellulosic-polymer network that is created by the HPMC chains in water. According to the literature, solutions of HPMC consist of cellulosic bundles resulting in a tenuous network of swollen clusters with hydrophobic substituents surrounded by sheaths of structured water [116,117]. Studies on the mechanism responsible for inhibiting crystallisation of drugs in aqueous solutions containing HPMC suggest that the HPMC polymer chain may inhibit nucleation, as well as crystal growth by adsorption of the HPMC molecules onto the surface of the nuclei, or onto the surface of crystals [20,28,118]. The general applicability of cellulosic polymers in inhibiting crystallisation of many pharmaceutical substances is widely reported [21-23,25,27,31,33,34,36].

Simonelli et al. [28] suggested that the polymer at the crystal surface forms a net-like structure, which allows the drug to grow out in finger-like protrusions leading to a growth with a rough surface. Ziller et al. [118] suggests that the polymer inhibits the introduction of drug molecules from solution into the crystal lattice by occupying adsorption sites and, thus, the adsorbed polymer forms a mechanical barrier that inhibits crystallisation. Raghavan et al. [20] proposed that the mechanism of nucleation and growth is based on the interaction between the drug and the polymer molecules through hydrogen bonding. In their work, they pointed out that the adsorption of the polymer substance on the nuclei surface of hydrocortisone acetate occurs through hydrogen bonding. The hydrodynamic boundary layer surrounding the crystal, resulting from adsorption of the polymer molecules onto the crystal surface, leads to crystal growth inhibition as well as habit modification of the crystals.

The general applicability of HPMC polymer in inhibiting crystallisation of many pharmaceutical substances is widely reported [22-25,27,30,31,36], suggesting that a non-specific mechanism may be involved in the inhibition of crystallisation. Understanding the mechanism for inhibition of crystallisation could aid the selection of other effective precipitation inhibitors and this could enhance the application of supersaturatable formulations.

6. Expert opinion and conclusions

The S-SEDDS formulation is designed to contain both a reduced amount of surfactant(s) and a polymeric precipitation inhibitor (e.g., water-soluble cellulosic polymers, such as HPMC), and generate and maintain a supersaturated state of the drug following mixing with water. The three case studies with paclitaxel, PNU-91325 and the exploratory drug Drug X, clearly show that the new S-SEDDS formulation approach provides higher oral bioavailability as compared with that of the conventional SEDDS formulations. Increasing the free-drug concentration by generating and maintaining a supersaturated state in the intestine is a means of overcoming the solubility limited absorption problems typical of poorly soluble drugs.

In addition to the potential for enhanced oral bioavailability, the S-SEDDS formulations could provide rapid onset such as in acute pain relief, migraine and other therapies. Rapid onset is difficult to achieve with poorly soluble drugs because of their low solubility and slow dissolution of the crystalline solids. Another advantage of S-SEDDS formulations is their potential for reducing the extent of GI side effects typically seen with SEDDS formulations due to the reduced surfactant levels in the S-SEDDS formulations.

Further exploration of the S-SEDDS formulation technology including an understanding of the precipitation kinetics and the mechanism for inhibiting drug precipitation with polymeric substances could lead to improved supersaturatable formulation strategies with enhanced oral absorption of poorly soluble drugs.
Development of S-SEDDS formulations for improving the oral absorption of poorly soluble drugs


** The reduction in the absorption kinetics of griseofulvin in the presence of taurocholate correlated well with the reduction of the drug-free fraction in solution due to micellar solubilisation.


** First theoretical basis for enhancing skin absorption of drugs by supersaturated solutions.


• Evaluation of HPMC, methyl cellulose, PVP and PEG 400 on crystallisation of hydrocortisone acetate from supersaturated solutions, showing HPMC was most effective in delaying crystallisation.


• HPMC and hydroxypropyl methylcellulose acet phthalate inhibited the crystallisation of abendazole from supersaturated solutions.


** The rate of crystallisation of nifedipine, griseofulvin and spironolactone was remarkably inhibited by the presence of carboxymethyl ethyl cellulose. The inhibition was not due to solubilisation of the drugs, and it was suggested that crystal growth was inhibited due to adsorption of...
Biorelevant dissolution media were developed and used in formulation development.


57. An in vitro dissolution system is described for the prediction of pH-dependent solubility drug absorption using the physiological conditions in the GI tract.


62. Excellent review of the absorption of lipids and the role of the bile acid mixed micelle.
Development of S-SEDDS formulations for improving the oral absorption of poorly soluble drugs

In the intestinal lumen, triglycerides are hydrolysed to monoglycerides and free fatty acids. These fatty acids are absorbed as free acids. However, in the presence of bile, the fatty acids are re-esterified to triglycerides. In the presence of micellar solutions, the fatty acids are absorbed as mixed micelles, which are then transported across the unstirred water layer and brush border of the small intestine. The absorption of fatty acids and cholesterol occurs via both the micellar saturated and nonmicellar supersaturated phases.

**References**


**Development of S-SEDDS formulations for improving the oral absorption of poorly soluble drugs**
**Collisonal transfer of cholesterol occurs with the enterocyte brush border.**


**Comprehensive review of lipid absorption.**


**Excellent review.**


**Evidence supports a protein-mediated mechanism for cholesterol uptake into the intestinal mucosal cell.**


**Plant sterols in the diet reduces intestinal uptake of cholesterol by reducing the intestinal micellar solubility and, hence, its transport towards the intestinal brush border membrane decreases.**


**Low intestinal pH can reduce uptake of oleic acid.**


**The glycolipid on the luminal surface of the intestinal villi covered the top of the microvilli of the epithelial cells and the glycolipid is observed as filamentous structures, 7 – 15 nm in diameter.**


**Drug are solubilised by bile salts in a predictive fashion.**


**Increased solubility of mefenamic acid in simulated fed-state media.**


**Poorly water soluble drugs can have high solubility in bile acid micelles.**


**Collisonal transfer with different size populations of vesicles. Shorter chain fatty acids can equilibrate via the aequous phase.**


**The transepithelial transport of poorly soluble moderately lipophilic benzophenones (ClogP 2.6 – 4.1) is attributed to the passive diffusion of available free-drug molecules rather than the collision complex transfer at the enterocyte cell surface.**


**The mechanism of the hexadecylglycerol absorption involves mainly monomer diffusion and probably collision-induced transfer.**


**These data strongly suggest that fatty acid transfer from intestinal fatty acid-binding proteins but not liver fatty acid-binding proteins to membranes occurs by direct collisional interaction of the protein with the phospholipid bilayer.**


114. CONSTANTINIDES PP, SCALART JP: Formulation and physical characterization of water-in-oil microemulsions containing...
Development of S-SEDDS formulations for improving the oral absorption of poorly soluble drugs

- See statement: ‘As the ingesta is mixed, the bile salt mixed micelles bump into the brush border and the lipids, including monoglyceride and fatty acids, are absorbed.’

Affiliation
Ping Gao† PhD & Walter Morozowich PhD
†Author for correspondence
PGRD, Pfizer, Inc., 301 Henrietta Street, Kalamazoo, MI 49007, USA
Tel: +1 269 833 6474; Fax: +1 269 833 2325;
E-mail: ping.gao@pfizer.com; pgaous@yahoo.com

Website
201. http://arbl.cvmbs.colostate.edu/hbooks/contrib.html

AUSTGEN L, BOWEN RA, ROUGE M: Pathophysiology of the digestive system.
Colorado State University, CO, USA (2004)