19.1 INTRODUCTION

SEDDS and S-SEDDS are self-emulsifying formulations of poorly soluble drugs that contain both a surfactant and lipid, along with a co-solvent, and they are usually formulated in gelatin capsules. Dilution of SEDDS or S-SEDDS formulations with water results in the generation of a microemulsion with a particle size from $<150\text{nm}$ to as low as $10-20\text{nm}$, when properly optimized. SEDDS/S-SEDDS formulations are useful in improving the animal or human oral bioavailability of poorly soluble drugs. S-SEDDS formulations contain less surfactant (and lipid) than the related SEDDS formulations and they create a supersaturated state upon contact with water, when properly optimized. The supersaturated state is maintained for a minimum of $\sim 1-2\text{hrs}$ and, as a result, S-SEDDS formulations can provide more rapid drug absorption, as evidenced by high $C_{\text{max}}$ and shortened $T_{\text{max}}$ values, as discussed in the case studies in this chapter, and they have potential for reducing surfactant-induced GI side-effects.

Four poorly soluble drugs are now marketed in lipid–surfactant formulations that are self-emulsifying or SEDDS formulations, with improved oral absorption, and these are: Sandimmune® (cyclosporine), Neoral® (cyclosporine), Norvir® (ritonavir), Fortavase® (saquinavir), and Aptivus® (tipranavir). The design, development strategy, and improved oral absorption achieved with SEDDS/S-SEDDS formulations of other poorly soluble drugs are described in detail in the case studies, which include paclitaxel and two experimental drugs.

The proposed pathways for the intestinal absorption of poorly soluble drugs via SEDDS/S-SEDDS formulations involves presentation of the drug–microemulsion to the intestinal glycocalyx, with uptake by either the aqueous pathway or equilibrating with or mimicking, the intestinal BA/BAMM (bile acid/bile acid mixed micelle) system.

19.2 OVERVIEW OF SEDDS AND S-SEDDS FORMULATIONS

A SEDDS formulation is defined as a Self-Emulsifying Drug Delivery System that contains a surfactant and usually, but not always, an oil, and a drug. By optimization with various additives, a SEDDS formulation results. Upon contact with water, the SEDDS formulation spontaneously generates an oil-in-water
drug microemulsion with a particle size <~150 nm and, preferably, as low as 10–20 nm. By this definition the term SEDDS includes all other self-emulsifying formulations that contain a surfactant and a lipid, such as SNEDDS or SMEDDS. The term, SEDDS, based on the above definition includes “self-emulsifying formulations” or “self-emulsifying,” abbreviated as SEF or SE, respectively, and this would also include all self-emulsifying formulations reported in the literature, including various particle sizes (micro-, nano-). This proposal would eliminate the proliferation of alternate labels for “self-emulsifying formulations,” and it would centralize the literature.

S-SEDDS (supersaturatable) formulations of poorly soluble drugs (PSDs) are simply SEDDS formulations with a reduced amount of surfactant, with an addition of a crystal growth inhibitor, such as HPMC, other cellulosic polymers or other polymers. S-SEDDS formulations generate a supersaturated drug state upon dispersion with water within the GI tract. The resulting oral bioavailability of a poorly soluble drug in an S-SEDDS formulation can be increased, if formulated properly, and the $T_{max}$ can be shorter than that of the poorly soluble drug in a conventional SEDDS formulation that contains a higher amount of surfactant. In addition to the ability to improve absorption of PSDs, the S-SEDDS formulation with reduced surfactant levels has the potential to reduce the incidence of surfactant induced diarrhea and colitis that can occur with the surfactant-laden SEDDS formulation.

The most common excipients used in a SEDDS/S-SEDDS formulation are:

1. solvents such as ethanol, propylene glycol, and polyethylene glycol 400 (PEG 400);
2. surfactants such as polysorbate 80, polyoxyl 35 castor oil (Cremophor EL), and polyoxyl hydrogenated 40 castor oil (Cremophor RH40); and
3. lipids such as mono-/di-/tri-olein, Masine, safflower oil, corn oil, MCT, and LCT.

SEDDS/S-SEDDS formulations are usually liquids that can be formulated or encased within a soft gelatin capsule or alternatively, encased in a hard gelatin or an HPMC capsule. Alternate solid SEDDS/S-SEDDS formulations are possible. SEDDS and S-SEDDS formulations can improve the oral bioavailability of poorly soluble drugs (PSDs) by improving the presentation of the drug in the microemulsion to the intestinal mucosal surface glycocalyx, by a process of either simulating the behavior of or equilibrating with the intestinal bile acid mixed micellar (BAMM) system or the bile acid (BA) micellar system in the fed and fasted states, respectively, within the intestine.

The objectives of this chapter are:

1. to review scientific literature on the topic of SEDDS and S-SEDDS formulations published from 1998 to 2008, with a few other relevant publications;
2. to provide a detailed summary of the development of the SEDDS and S-SEDDS formulations of poorly soluble drugs, along with the oral bioavailability of the SEDDS/S-SEDDS formulations by us; and
3. to review the underlying mechanism responsible for the improved absorption of poorly soluble lipophilic drugs via SEDDS and S-SEDDS formulations.

**19.2.1 Growth in the Number of SEDDS/ S-SEDDS Publications**

The first publication containing the words “SEDDS” or “S-SEDDS” was reported in 1992, and by 2007 there were a total of 34 publications with the words SEDDS or S-SEDDS in the title or abstract. Figure 19.1 shows that the cumulative number of SEDDS/S-SEDDS publications dealing with poorly soluble drugs is increasing exponentially.
19.2.2 Marketed SEDDS Formulations

The SEDDS formulation approach has proven the potential of improving the oral absorption of poorly soluble drugs, and it is a new and rapidly expanding area. Four poorly soluble drugs have been marketed in SEDDS formulations, and these are shown below along with their solubility and lipophilicity values, obtained from either the SciFinder (Am. Chem. Soc.), the Drug Bank (NIH) databases or the RxMed database at: http://www.rxmed.com/b.main/b2.pharmaceutical/b2.1.monographs/CPS-%20Monographs/CPS-%20(General%20Monographs-%20S)/SANDIMMUNE%20(CYCLOSPORINE).html

**Sandimmune® (Cyclosporine)**

Cyclosporine
Immunosuppressant for organ transplantation:
MW = 1202.61
log P = 2.92 Exp.
pKa = non-ionizable
calcS = 9 μg/mL H₂O
Dose = 25–700 mg (2–10 mg/kg).
Marketed Sandimmune formulation and ingredients:
Softgel: 25–100 mg cyclosporine in EtOH, corn oil, Labrafil M 2125 CS, gelatin, glycerol.
Oral Solution: 100 mg/mL in 12.5% EtOH, olive oil, Labrafil M 1944.

**Norvir® (Ritonavir)**

AIDS drug:
MW = 720.9
clog P = 5.28
pKa = 3.48 (basic)
calcS = 0.37 μg/mL at pH 6, 25°C
Dose = 1200 mg (600 mg BID)
Marketed formulation and ingredients:
Softgel: 100 mg ritonavir, ethanol, oleic acid, polyoxyl 35 castor oil, butylated hydroxytoluene.
Oral Solution: 80 mg/mL drug in ethanol (43% w/v), polyoxyl 35 castor oil, propylene glycol, citric acid.

**Fortavase® (Saquinavir)**

AIDS drug:
MW = 670.84
clog P = 4.40
pKa = 7.6
calcS = 5 μg/mL at pH 7, 25°C
Dose = 1200 mg
Marketed formulation and ingredients:
Softgel: 200 mg drug in medium chain mono- and di-glycerides, and povidone.

**Aptivus® (Tipranavir)**

AIDS drug:
MW = 602.66
clog P = 7.2
pKa = 6.7, 10.2
calcS = 5 μg/mL at pH 6, 25°C
Dose = 1000 mg (with 400 mg Ritonavir) (500 mg BID)
Marketed formulation and ingredients:
Softgel: 250 mg tipranavir. Major inactive ingredients in formulation are 7% dehydrated alcohol, polyoxyl 35 castor oil, propylene glycol, mono-/di-glycerides of caprylic/capric acid.

19.3 REVIEW OF SCIENTIFIC LITERATURE DEALING WITH BOTH THE DEVELOPMENT OF SEDDS/S-SEDDS FORMULATIONS, AND ORAL BIOAVAILABILITY

This section reviews the scientific literature on SEDDS/S-SEDDS formulations over the past ten years from 1998 to 2008, and summarizes the key publications dealing with both:

1. the development and characterization of SEDDS/S-SEDDS formulations; and
2. the determination of the oral bioavailability of the resulting SEDDS/S-SEDDS formulations of poorly soluble drugs in preclinical and clinical studies.

The first citation in PubMed occurred in 1992, and by the end of 2007 the cumulative number of citations was 34 for the search terms “SEDDS” or “S-SEDDS.” Most of these citations were also found in a PubMed search for “self-emulsifying formulations,” where the total number of citations was 101. However, these search results included many publications that did not deal with both the development of SEDDS/S-SEDDS formulations and oral bioavailability. The 34 citations in the PubMed search for “SEDDS or S-SEDDS” are briefly reviewed chronologically in the following text.

19.3.1 Year 2008: Key Publications on SEDDS Formulations in the PubMed Database, and Related Articles

Using danazol as a model compound, SEDDS formulations were prepared with Cremophor RH40 or Cremophor EL, and a long chain triglyceride. It was concluded that the key design parameters for efficient oral absorption of danazol from lipid based formulations were: (a) rapid dispersibility of the formulation upon dilution with water; and (b) rapid intestinal digestion or hydrolysis of the triglyceride excipients by pancreatic enzymes.1

Self-emulsifying delivery systems are useful for improving the absorption of poorly soluble lipophilic drugs. The mechanism for drug absorption was reviewed, and the in vitro test methods found useful in formulation design are formulation dispersibility and digestibility of the surfactant and lipid excipients.2 SEDDS formulations of alpha-tocopherol containing polysorbate 80, labrasol, EtOH, and Captex 355 were subjected to lipase-catalyzed hydrolysis in biorelevant media to determine the effect of the excipients on the rate and extent of hydrolysis. The authors found that:

“the excipients influenced each response differently and, therefore, each method can only reveal distinctive characteristics of the SEDDS formulation, and may not be used interchangeably”3

Two SEDDS formulations of probucol with the same composition, but with a 100-fold difference in particle size, gave comparable oral bioavailability in fed or fasted minipigs.4

19.3.2 Year 2007: Key Publications on SEDDS Formulations in the PubMed Database, and Related Articles

Table 19.1 shows the key surfactant–lipid formulations reported in the literature with poorly soluble drugs.5 The table shows that many of the drug–lipid formulations, such as the SEDDS formulations, enhance the absorption of a variety of poorly water soluble drugs.

The literature on SEDDS formulations of poorly soluble drugs and oral bioavailability was surveyed, and it was concluded that improved oral bioavailability is best achieved with the aid of screens for dispersibility, lipolysis of triglycerides, and digestion of surfactants.5

In a comprehensive review of lipid formulations containing surfactants, such as SEDDS/S-SEDDS, it was stated that the key role of these formulations was to enhance the solubility of the drug in the formulation and in the GI tract.5a Figure 19.2 shows that dispersion of a lipid–surfactant SEDDS formulation occurs in the stomach, and this dispersion can equilibrate with the bile salt/phospholipid micelle. Lipid and surfactant hydrolysis products are formed in the intestine by lipolytic pancreatic enzymes.

A decision support tool was developed for orally active poorly soluble compounds, based on the proposed formulation selection process,6 as shown in Figure 19.3.
### TABLE 19.1
Survey of SEDDS formulations and their reported bioavailabilities. Examples of studies describing the bioavailability enhancement of PWSD after administration of SEDDS and SMEDDS formulations

<table>
<thead>
<tr>
<th>Compound</th>
<th>Formulation(s)</th>
<th>Study design</th>
<th>Observations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Win 54954</td>
<td>SEDDS (35% drug, 40% Neobee M5 (MCT), and 25% Tagat (TO) or PEG 600 solution)</td>
<td>Relative BA in dogs</td>
<td>No difference in BA but improved reproducibility, increased $C_{\text{max}}$</td>
</tr>
<tr>
<td>Cyclosporin</td>
<td>Sandimmum (SEDDS: corn oil and ethanol) or Neoral (SMEDDS: corn oil glycerides, Cremophor RH40, PG, DL-$\alpha$-tocopherol and ethanol)</td>
<td>Relative BA in humans</td>
<td>Increased BA and $C_{\text{max}}$ and reduced $T_{\text{max}}$ from SMEDDS</td>
</tr>
<tr>
<td></td>
<td>Sandimmum (SEDDS) or Neoral (SMEDDS)</td>
<td>Relative BA in humans</td>
<td>Increased $C_{\text{max}}$, AUC and dose linearity and reduced food effect from SMEDDS</td>
</tr>
<tr>
<td></td>
<td>Sandimmum (SEDDS) or Neoral (SMEDDS)</td>
<td>Relative BA in humans</td>
<td>Reduced intra- and inter-subject variability from SMEDDS</td>
</tr>
<tr>
<td>Halofantrine</td>
<td>5% drug in MCT SEDDS (47% Captex 355, 23% Capmul MCM, 15% Cremophor EL and ethanol), MCT SMEDDS (33% Captex 355, 17% Capmul MCM, 33% Cremophor EL, and ethanol), or LCT SMEDDS (29% Soybean oil, 29% Maisine 35-1, 30% Cremophor EL, and 7% ethanol)</td>
<td>Relative BA in dogs</td>
<td>Trend to higher BA from LCT SMEDDS</td>
</tr>
<tr>
<td>Ontazolast</td>
<td>Soybean oil emulsion, drug solution in Pecelol, drug suspension or two semi-solid SEDDS comprising Gelucr€ 44/14 and Pecelol in the ratios 50:50, and 80:20</td>
<td>Absolute BA in rats</td>
<td>BA increases of at least 10-fold from all lipid-based formulations</td>
</tr>
<tr>
<td>Vitamin E</td>
<td>SEDDS (Twee 80:Span 80:palm oil (LCT) in a 4:2:4 ratio) or soybean oil (LCT) in solution</td>
<td>Relative BA in humans</td>
<td>BA 3-fold higher from SEDDS</td>
</tr>
<tr>
<td>Coenzyme Q10</td>
<td>SMEDDS (40% Myvacet 9–45, 50% Labrasol, and 10% luaroglycol) or powder formulation</td>
<td>Relative BA in dogs</td>
<td>BA 2-fold higher from SEDDS</td>
</tr>
<tr>
<td>Ro-15-0778</td>
<td>SEDDS (polyglycolyzed glycerides and peanut oil), PEG 400 solution, wet-milled spray dried powder or tablet of micronized drug</td>
<td>Relative BA in dogs</td>
<td>BA 3-fold higher from SEDDS when compared with other formulations</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>SMEDDS (37% Capryol 90, 28% Cremophor EL, 28% Carbitol) or tablet</td>
<td>Relative BA in dogs</td>
<td>BA 1.5-fold higher from SMEDDS</td>
</tr>
<tr>
<td>Biphenyl dimethyl dicarboxylate</td>
<td>SEDDS (43% Twee 80, 35% triacetin, and 22% Neobee M-5 (MCT)) or powder formulation</td>
<td>Relative BA in rats</td>
<td>BA 5-fold higher from SEDDS</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>SEDDS (70% ethyl oleate and 30% Tween 85) or powder formulation</td>
<td>Relative BA in rats</td>
<td>BA significantly increased from SEDDS</td>
</tr>
<tr>
<td>Progesterone</td>
<td>SEDDS (mono-di-glycerides:polysorbate 80, 50/50 w/w) or aqueous suspension</td>
<td>Relative BA in dogs</td>
<td>BA 9-fold higher from SEDDS</td>
</tr>
<tr>
<td>Tocotrienols</td>
<td>Two SEDDS (Twee 80 and labrasol) or LCT solution</td>
<td>Relative BA in humans</td>
<td>BA 2- to 3-fold higher from SEDDS</td>
</tr>
<tr>
<td>Danazol</td>
<td>LC-SMEDDS (long chain lipids, Cremophor EL, and ethanol), MC-SMEDDS (medium chain lipids, Cremophor EL, and ethanol) or LCT solution</td>
<td>Relative BA in dogs</td>
<td>BA from LCT solution and LC-SMEDDS 7-fold and 6-fold higher than that from MC-SEDDS</td>
</tr>
<tr>
<td>Carvedilol</td>
<td>SEDDS (labrafil M1944CS, Twee 80 and transcutol), and tablet</td>
<td>Relative BA in dogs</td>
<td>BA 4-fold higher from SEDDS</td>
</tr>
<tr>
<td>Solvent green 3</td>
<td>Semi-solid SMEDDS (Gelucr€ 44/14) or soybean oil emulsion</td>
<td>Relative BA in rats</td>
<td>BA 1.7-fold higher from SMEDDS</td>
</tr>
<tr>
<td>Silymarin</td>
<td>SMEDDS (Twee 80, ethyl alcohol, and ethyl linoleate), PEG 400 solution</td>
<td>Relative BA in rabbits</td>
<td>BA approximately 2- and 50-fold higher from SMEDDS than that of PEG 400 solution and suspension</td>
</tr>
</tbody>
</table>

(Continued)
III. DESIGN, DEVELOPMENT, AND SCALE-UP OF FORMULATION AND PROCESS

19 IMPROVING THE ORAL ABSORPTION OF POORLY SOLUBLE DRUGS USING SEDDS AND S-SEDDS FORMULATIONS

FIGURE 19.2 Cartoon depicting the major physiological and biochemical events occurring with a lipid–surfactant–drug formulation such as a gelatin softgel formulation of a poorly water soluble drug. The lipolytic enzymes (pancreatic lipase) stored in the gall bladder enter the duodenum and they hydrolyze the long chain triglycerides (LCT) to give 2-mono-acyl glycerides. The resulting BA and BAMM particles can equilibrate with the drug–SEDDS microemulsion followed by intestinal absorption of the drug.5

TABLE 19.1 (Continued)

<table>
<thead>
<tr>
<th>Compound</th>
<th>Formulation(s)</th>
<th>Study design</th>
<th>Observations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin</td>
<td>Three SMEDDS (Cremophor RH40, propylene glycol, and labrafil, estol or labrafac) or tablet</td>
<td>Relative BA in dogs</td>
<td>BA significantly increased from all SMEDDS formulations</td>
</tr>
<tr>
<td>Itroconazole</td>
<td>SEDDS (Transcutol, pluronic L64, andtocopherol acetate) or conventional capsule</td>
<td>Relative BA in rats</td>
<td>Increased BA and reduced food effect from SEDDS</td>
</tr>
<tr>
<td>Atovaquone</td>
<td>Two SMEDDS (long chain lipids, ethanol, and Cremophor EL or Pluronic L121) or aqueous suspension</td>
<td>Relative BA in dogs</td>
<td>BA 3-fold higher from SMEDDS</td>
</tr>
<tr>
<td>Seocalcitol</td>
<td>LC-SMEDDS (sesame oil, Peecol, Cremophor RH40) versus MC-SMEDDS (Viscoleo MCT), Alkiline MCM (medium chain mono- and di-glyceride) and Cremophor RH40</td>
<td>Absolute BA in rats</td>
<td>BA LC-SMEDDS = MC-SMEDDS</td>
</tr>
<tr>
<td>PNU-91325</td>
<td>Supersaturable co-solvent (S-co-solvent) and supersaturable SEDDS (S-SEDDS comprising 20% HMPC, 30% Cremophor EL, 18% Pluronic L44, 9% PEG, 6% long chain glyceride lipid, 5% DMA) formulations compared to co-solvent (PG) or Tween 80 solutions</td>
<td>Relative BA in rats</td>
<td>5–6-fold enhancement in oral bioavailability for S-co-solvent, S-SEDDS, and Tween 80 formulations relative to co-solvent</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>SEDDS formulation comprising Transcutol, Pluronic L64, and tocopherol acetate versus commercial Sporanox formulation</td>
<td>Relative BA in rats</td>
<td>Increased BA and reduced food effect from SEDDS</td>
</tr>
<tr>
<td>7 model compounds</td>
<td>Comparison of PEG 200 solution and suspension formulations to SEDDS (comprising 25% MCT, 5% diglycerylmonoooleate, 45% Cremophor RH40, 25% Ethanol), and liquid microemulsion (comprising 5% MCT, 1% diglycerylmonoooleate, 9% Cremophor RH40, 5% Ethanol, and 80% phosphate buffered saline)</td>
<td>Relative BA in rats and dogs</td>
<td>Improved BA relative to the suspension formulations for either or both of the liquid microemulsion and SEDDS formulation in all cases</td>
</tr>
</tbody>
</table>
Formulation Selection Process

**DECISION 1**
Conventional Formulations
Non-Conventional Formulations

**DECISION 2**
Crystalline Nanoparticles
Solid Dispersions
Lipidic/Surfactant. Systems
Other Formulations

**DECISION 3**
Stabilizer selection
Carrier selection
Excipient selection

**FIGURE 19.3** Decision tree for guiding formulation decisions (Branchu, 2007)

**FIGURE 19.4** The effect of lipolytic digestion of the Cremophor RH40 and Cremophor EL formulations of danazol. Left: (a)—the aqueous phase levels of the danazol formulations and right: (b)—the danazol plasma levels of these formulations in the dog. Formulation 1: The Cremophor RH 40 SMEDDS contains 55% w/w Cremophor RH, 37.5% w/w soybean oil/Maisine, 7.5% w/w ethanol. Formulation 2: The Cremophor EL SMEDDS contains 55% w/w Cremophor EL, 37.5% w/w soybean oil/Maisine, 7.5% w/w ethanol. The lower digestibility of Cremophor RH40 results in higher bioavailability.5

Figure 19.3 shows the three major decision points in formulation development. The authors concluded that the decision support tool has great potential for improving the efficiency and the predictability of the formulation development process. Figure 19.4 shows that the reported increase in the aqueous solubility of danazol (a) in Cremophor RH40, however, does not result in enhanced oral bioavailability of danazol (b).5

In a previous study, increasing the surfactant-to-lipid ratio was found to reduce the oral bioavailability of danazol in dogs.8 The increase in drug solubilization observed during in vitro digestion resulted in increased oral bioavailability of danazol. Interestingly, the oral bioavailability (in beagle dogs) was highest with a soybean–Maisine–Cremophor EL microemulsion generating formulation, and the lowest with a formulation containing Cremophor without soybean–Maisine.

A study of the effect of small amounts of lipids on gastric emptying and biliary secretion showed that oral administration of as little as 2 gm of glycerol monooleate (GMO) (in healthy males) resulted in stimulation of biliary secretion of bile and bile acids. The same amount of medium-chain triglyceride (MCT) (Miglyol 810) failed
to cause contraction of the gall bladder, and did not result in secretion of bile. The authors pointed out that the amount of lipid, namely, 2 gm of GMO/MCT, is a quantity that “might be realistically expected on administration of $2 \times 1$ g soft gelatin capsules.” Furthermore, this suggests that administration of $2 \times 1$ g of GMO in soft gelatin capsules containing a drug in a clinical study in the fasted state could result in drug absorption that mimics the fed state. The development of lipid-based formulations was reviewed with respect to:

1. major excipient classes (natural product oils, semi-synthetic lipid excipients, fully synthetic excipients, and surfactants);
2. formulation types and modalities (single component lipid solutions, self-emulsifying formulations, and melt pelletization);
3. formulation development and characterization, including drug candidate selection, excipient compatibility, selection of a formulation modality, physico-chemical consideration, biopharmaceutical consideration, in vitro characterization, in vitro dissolution testing, and role of lipolysis in release testing.

The authors admits that “due to the complex and incompletely understood dynamics of the interaction of formulations with the gastrointestinal milieu,” animal bioavailability studies should precede clinical studies. The key advantages of lipid-based formulations are:

1. reduced variability;
2. reduction in the number of formulation-based processing steps;
3. reduction in positive food effect; and
4. the ease of formulation manufacture and scale-up.

The use of lipid-based formulations for enhancing drug absorption was reviewed with respect to the mechanisms responsible for improved oral absorption. The concentration of bile salts in the fasted state in the duodenum/jejunum is ~3–4 mM, while in the fed state the bile salt concentration is ~10–16 mM. This increased concentration of bile salts in the fed state is responsible for increased drug solubilization. With poorly soluble drugs, improved oral bioavailability is often observed in the fed state. The solubilizing property in the fed state is due to the presence of the bile acid mixed micelle (BAMM). The review of the lipid

FIGURE 19.5 Cartoon showing that lipid-based drug formulations can improve drug absorption by drug solubilization in the resulting micellar phases, principally the bile acid mixed micelle that arises from bile. Highly lipophilic drugs can undergo lymphatic uptake, thereby, bypassing first pass liver metabolism.
absorption pathway.\(^5\) indicated that highly lipophilic drugs can show significant lymphatics.

The use of surfactants as enterocyte P-gp pump inhibitors (Table 19.2) was reviewed, and improved oral absorption was documented with a number of drugs using this strategy.\(^1^1\)

The reservation with the use of P-gp inhibitors is that intestinal absorption of undesirable compounds could occur, along with improved absorption of the drug in question.\(^1^1\) In addition, P-gp inhibitors have pharmacological activity of their own and, therefore, P-gp–drug combinations could result in enhanced side-effects.

The effect of administering a high fat meal (peanut oil) or plain water on the plasma levels of DDT in rats was studied.\(^1^2\) The resulting plasma profiles for DDT (oral) or plain water on the plasma levels of DDT in rats side-effects. P-gp–drug combinations could result in enhanced pharmacological activity of their own and, therefore, drug in question.\(^1^1\) In addition, P-gp inhibitors have the reservation with the use of P-gp inhibitors is that intestinal absorption of undesirable compounds could occur, along with improved absorption of the drug in question.\(^1^1\) In addition, P-gp inhibitors have pharmacological activity of their own and, therefore, P-gp–drug combinations could result in enhanced side-effects.

The utility of microemulsion-generating formulations in enhancing the oral absorption of poorly soluble drugs was reviewed. The key considerations in the development of SEDDS formulations capable of generating a microemulsion upon contact with water are: (1) surfactant; (2) co-surfactant; and (3) oils. Using nitrendipine formulations consisting of: (a) medium-chain triglycerides; (b) triglyceride suspension (c) long-chain triglyceride solution, and (d) Tween 80, it was shown that the resulting \(T_{\text{max}}\) values in a fasted human clinical study were 8, 4, 1.3, and \(\geq 8\) hours, respectively. The \(T_{\text{max}}\) values in the fed state in the same clinical study resulted in \(T_{\text{max}}\) values of 1.5, 3.5, 1.3, and \(\geq 7\)hrs.\(^1^3\) These data are significant, in that the \(T_{\text{max}}\) of nitrendipine was reduced to 1.5 hours in the fed state, compared to 8 hours in the fasted state.

### Table 19.2 Surfactants with P-gp inhibitor activity\(^1^1\)

<table>
<thead>
<tr>
<th>Surfactants</th>
</tr>
</thead>
<tbody>
<tr>
<td>C8/C10 Glycerol and PEG Esters, Cremophor, Solutol HS-15, Labrasol, Softigen 767, Aconnon E</td>
</tr>
<tr>
<td>Sucrose Esters, Sucrose Monolaurate</td>
</tr>
<tr>
<td>Polysorbates, Tween 80, Tween 20</td>
</tr>
<tr>
<td>Tocopherol Esters, (\alpha)-Tocopheryl PEG 100 Succinate (TPGS)</td>
</tr>
</tbody>
</table>

A nanoemulsion-generating formulation of paclitaxel was developed using 1920mg of Labrasol plus vitamin E-TPGS (3:1), 80mg of Labrafil M1944CS, and 20mg of paclitaxel.\(^1^4\) Dilution of the formulation with water resulted in formation of a nanoemulsion with a particle (globule) size of 21.58nm, which is in the range of many microemulsion-generating formations. The rat oral bioavailability (absolute) of paclitaxel from this nanoemulsion formulation was reported to be 70.25%. The absolute rat oral bioavailability of paclitaxel from the Taxol\(^5\) IV formulation was only 10.62% and <30% for a S-SEDDS formulation of paclitaxel.

The effect of the fasted (FaSSIF) and fed (FeSSIF-Mod6.5) state (Table 19.3) on the absorption (in dogs) of danazol from a self-emulsifying formulation was found to be in excellent agreement with the higher solubility of danazol in the FeSSIF, as compared to the FaSSIF.\(^1^5\)

The oral bioavailability of itraconazole in a SEDDS formulation containing transcutol, pluronic, and tocopherol acetate was found to give an AUC (oral) similar to that of the marketed Sporanox\(^5\) product, however, the \(T_{\text{max}}\) was 1.3 hours for the SEDDS formulation, and 8 hours for the Sporanox\(^5\) product.\(^1^6\)

The oral bioavailability of the naphthalene analog, Ro 15-9778, either in a SEDDS formulation, a PEG 400

### Table 19.3 Composition of simulated intestinal fluids\(^1^7\)

<table>
<thead>
<tr>
<th>Simulated intestinal fluid</th>
<th>pH</th>
<th>Taurocholate</th>
<th>Lecithin</th>
<th>mOsm</th>
</tr>
</thead>
<tbody>
<tr>
<td>FaSSIF(^a)</td>
<td>6.5</td>
<td>3 mM</td>
<td>0.75 mM</td>
<td>270 + 10</td>
</tr>
<tr>
<td>FeSSIF(^b)</td>
<td>5.0</td>
<td>15 mM</td>
<td>3.75 mM</td>
<td>635 + 10</td>
</tr>
<tr>
<td>Simulated intestinal fluid</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FaSSIF-Mod(^c)</td>
<td>6.5</td>
<td>3 mM</td>
<td>0.75</td>
<td>311.7 + 0.6</td>
</tr>
<tr>
<td>FeSSIF-Mod5.0(^d)</td>
<td>5.0</td>
<td>15 mM</td>
<td>3.75 mM</td>
<td>327.0 + 1.0</td>
</tr>
<tr>
<td>FeSSIF-Mod6.5(^e)</td>
<td>6.5</td>
<td>15 mM</td>
<td>3.75 mM</td>
<td>325.7 + 0.6</td>
</tr>
</tbody>
</table>

\(^a\)FaSSIF: 3.9 gm KH\(_2\)PO\(_4\), 3 mM Na TC, 0.75 gm lecithin, 7.7 gm KCl, pH adj. with NaOH to 6.50

\(^b\)FeSSIF: 8.65 gm acetic acid, 15 mM NaTC, 3.75 mM lecithin, 15.2 gm KCl, pH adj. with NaOH to 5.00

\(^c\)FaSSIF-Mod: 3.9 gm KH\(_2\)PO\(_4\), 3 mM Na TC, 0.75 gm lecithin, 7.7 gm KCl, pH adj. with HEPES to 6.50

\(^d\)FaSSIF-Mod5.0: 3.9 gm KH\(_2\)PO\(_4\), 3 mM Na TC, 0.75 gm lecithin, 7.7 gm KCl, pH adj. with HEPES to 5.00

\(^e\)FaSSIF-Mod6.5: 3.9 gm KH\(_2\)PO\(_4\), 3 mM Na TC, 0.75 gm lecithin, 7.7 gm KCl, pH adj. with HEPES to 6.50
solution, a spray dried powder or a tablet formulation, showed a relative oral bioavailability (in dog) of 389, 100, 35, and 17%, respectively. The self-dispersing SEDDS formulation gave superior oral bioavailability, as compared to the alternate conventional formulations. 18

In a review of the oral absorption of drugs in SEDDS formulations, it was noted that bioavailability was dependent on the surfactant concentration, and the polarity of the resulting emulsion/microemulsion formed on dilution with water, the droplet size, and the charge.

The rat oral bioavailability of the highly-lipophilic compound seocalcitol was roughly the same in SEDDS formulations and in simple triglyceride solutions, indicating that highly lipophilic drugs may not require SEDDS formulation for maximizing oral bioavailability. 19

19.3.3 Year 2005–2003: Key Publications on SEDDS Formulations in the PubMed Database, and Related Articles

The mechanism of intestinal uptake of drugs and drug formulations was addressed in a large number of papers by Charman, Porter and coworkers. These publications included the solubilization of poorly soluble drugs in the GI tract after administration of lipid-based drug delivery systems, wherein it was concluded that the digestion and dispersion of the lipidic vehicle provides a solubilization sink that can prevent precipitation of the poorly soluble drug. 20 A study on the factors that dictate lymphatic absorption of poorly soluble drugs showed that the “lymph-lipid pool” is a key determinant of intestinal lymphatic drug transport. 21,22 The physico-chemical properties of halofantrine, such as log D versus pH dependency, were found to explain the extensive lymphatic transport of halofantrine in the fed state. At a pH below 2, the log D of halofantrine is <0, but as the pH is increased to ~7, the log D is increased to ~3 in aqueous Na taurocholate-lecithin (4:1). The high lipophilicity of halofantrine at pH ~7 suggests high affinity for the lymphatic system. 23

In a review of the lymphatic delivery of drugs, the exceptionally high log P values of itretinate (7.8), and isotretinoin (6.8), are responsible for the extensive lymphatic delivery. 24 The effect of the fatty acid binding protein (FABP) on the enterocyte uptake of fatty acids showed that the FABP can be a determinant of lymphatic drug transport. 22

A microemulsion-generating formulation was prepared using MCT, DGMOC-C, HCO-40, and EtOH, in the ratio of 5:1:9:5 (v/v), and this SEDDS formulation was found to improve the oral absorption of 10 drugs, including ibuprofen, ketoprofen, tamoxifen, testosterone, and tolbutamide, in addition to other new drugs. 25

An emulsion generating formulation of cyclosporine was developed with an oat galactolipid and MCM (1:1). 26 Dilution of the formulation with water gave a particle size ~3μm (an emulsion), whereas dilution of the Neoral formulation of cyclosporine gave a particle size of 10–20nm (a microemulsion). A clinical study showed that the oral bioavailability of the galactolipid cyclosporine formulation, compared to the Neoral® formulation, was virtually the same, as evidenced by the T_{\text{max}} and AUC values. Both formulations showed a T_{\text{max}} of ~1.5 hours.

19.3.4 Year 2003–2000: Key Publications on SEDDS Formulations in the PubMed Database, and Related Articles

The Neoral® SEDDS formulation of cyclosporine was the first marketed microemulsion-generating formulation in the pharmaceutical industry. Dilution of the Neoral® formulation with water results in rapid formation of a transparent solution, typical of a microemulsion, with a bluish cast, and a particle size of ~20nm. Figure 19.6 shows the oral bioavailability of the Sandimmune® emulsion-generating formulation, along with the improved Neoral microemulsion-generating formulation of cyclosporine in a renal transplant patient. 27,28 The Sandimmune® SEDDS formulation contains a long-chain triglyceride, with a surfactant and the lipophilic compound, cyclosporine. The absorption of cyclosporine from the Sandimmune® formulation occurs after partial hydrolysis of the long-chain triglyceride, and this can be a slow process, as shown by the evening dosing blood level curve (SIM p.m.), which shows a peak at 8 hours. The peak blood levels of cyclosporine after morning dosing (SIM a.m.) show a somewhat shorter peak at 4 hours. The Neoral® formulation, however, shows a peak in the blood level curve for cyclosporine at ~1.5 hours in the fasted state, and 1.2 hours in the fed state. The resulting AUC for the Neoral® formulation is larger than that of the Sandimmune® SEDDS formulation, as shown in Figure 19.6. There is virtually no food effect (AUC = 997, fasting, and AUC = 892, fed) with the Neoral® formulation. The superiority of the new microemulsion-generating Neoral formulation of cyclosporine has been confirmed in expanded clinical studies. 29,30

It was pointed out that the absorption of poorly soluble drugs can be enhanced in SEDDS formulations
with formulation designed to give a submicron-sized colloidal state upon dilution with water.\(^2\) Knowledge of the efficiency of self-emulsification on contact with water, the susceptibility to digestion of the surfactant excipients, as well as the lipid triglyceride excipients, and the subsequent fate of the drug is useful in optimization of the formulation.\(^2\)

19.3.5 Year 1999–1992: Key Publications on SEDDS Formulations in the PubMed Database, and Related Articles

Studies on intestinal absorption of lipids and, especially, cholesterol, established the key role of the bile acid mixed micelle (BAMM) in the oral absorption of lipophilic compounds.\(^31\)–\(^34\),\(^7\)

There were four papers dealing with SEDDS/S-SEDDS formulations in 1997. The requirements for lymphatic transport were developed, and it was concluded that the log \(P\) of the drug should be high (>6), and the drug should be soluble in triglycerides, in order to achieve efficient lymphatic absorption.

The development of SEDDS formulations was reviewed in detail with respect to the factors that influenced ease of emulsification.\(^35\) SEDDS formulations usually contain triglycerides, along with PEG surfactants, with surfactant concentrations greater than 15%.

The first paper found in the PubMed search on “SEDDS or S-SEDDS” was published in 1992, dealing with a SEDDS formulation of the poorly soluble drug, WIN 54954.\(^35\) The particle size of the formulation on dilution with water was <3\(\mu\)m. The SEDDS formulation showed higher AUC in the dog than a PEG 400 solution.

19.4 CASE STUDIES ON THE DEVELOPMENT OF SEDDS AND S-SEDDS FORMULATIONS

The case studies dealing with the development of new SEDDS and S-SEDDS formulations of the poorly soluble drugs, paclitaxel and two experimental drugs, are described in detail in this section, along with emphasis on the key screening tests that were employed in optimizing the SEDDS/S-SEDDS formulations, and the resulting oral bioavailability data. The key \(\textit{in vitro}\) screening tests that were applied are:

1. ease of dispersibility of the SEDDS/S-SEDDS formulation in an aqueous medium;
2. particle size upon dispersion; and
3. the free drug concentration in the aqueous medium upon dispersion.

The case studies discussed herein are taken from previous publications.\(^37\)–\(^43\)

![FIGURE 19.6](image_url) Representative cyclosporine blood concentration profiles from a renal transplant patient given the currently marketed formulation Sandimmune® (SIM) or the new Neoral® formulation without food (a.m.) or with food (p.m.).\(^27\)
19.4.1 Case Study on the Development of a SEDDS Formulation of Drug X

### PHYSICO-CHEMICAL PROPERTIES OF DRUG X

The experimental drug is a free acid with two acidic pKas (~6 and ~9), it is highly lipophilic (clogP of ~7), it has a molecular weight of ~600, and it is a poorly soluble drug with an intrinsic aqueous solubility of only ~5 μg/mL. A high daily dose of experimental drugs was desired for oral administration in AIDS patients and, as a result, SEDDS formulations with 300 mg of the experimental drug per gm of the formulation were explored. The solubility of the experimental drug in various pharmaceutically acceptable excipients is shown in Table 19.4.

The solubility of the drug in surfactants Cremophor EL and Polysorbate 80 was found to be high (~500 mg/mL), but the solubility in glycerolipids Capmul MCM and GDO/GMO (glycerol di-olein/glycerol mono-olein) was ~10–20 times lower, suggesting that development of a high dose of the Experimental Drug–SEDDS formulation might be a challenging task.

The SEDDS formulations of Drug X were evaluated and optimized with respect to the key variable, namely, in vitro dispersibility and spontaneity of emulsification, particle size upon dilution with water, and the nature of the lipid excipients.

### Influence of Dispersibility on Absorption of Drug X–SEDDS Formulation

The effect of the dispersion property (e.g., particle size, dispersion spontaneity) of the 300 mg/gm Drug X–SEDDS formulation on oral bioavailability was evaluated in preclinical studies (rat, dog). These results collectively revealed that the particle size of the 300 mg/gm Drug X–SEDDS formulation upon dilution with water is a key factor that dictates the oral absorption of Drug X with a smaller particle size, resulting in improved oral bioavailability.

The ability to generate a microemulsion with the 300 mg/g Drug X–SEDDS formulation was explored by adding a small amount of an organic amine. As shown in Figure 19.7, the mean droplet size of the microemulsion/emulsion generated upon dilution of 300 mg/gm Drug X formulation with water showed a rapid reduction in particle size as the percentage of diethanolamine (DEA) was increased from 0 to 3%. The presence of a small amount of DEA (~1%) dramatically reduced the particle size of the 300 mg/gm Drug X–SEDDS formulation to about 150 nm or less.

The relative oral bioavailability of Drug X in a 300 mg/gm SEDDS formulation with the same composition, but differing only with respect to the presence or absence of DEA, was evaluated orally in rats, dogs, and in humans. The in vivo pharmacokinetic results are shown in Figure 19.8.

The relative oral bioavailability of Drug X in rats (non-crossover), dogs (crossover), and humans (crossover) showed that the bioavailability was improved by ~2–3 fold.

---

**TABLE 19.4** Solubility of the experimental drug in various formulation excipients

<table>
<thead>
<tr>
<th>Excipient</th>
<th>Solubility of the experimental drug (mg/gm of excipient)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethanol</td>
<td>1950</td>
</tr>
<tr>
<td>Propylene glycol</td>
<td>710</td>
</tr>
<tr>
<td>PEG 400</td>
<td>670</td>
</tr>
<tr>
<td>Glycerol</td>
<td>&lt;10</td>
</tr>
<tr>
<td>Polysorbate 80</td>
<td>500</td>
</tr>
<tr>
<td>Cremophor EL</td>
<td>430</td>
</tr>
<tr>
<td>Capmul MCM</td>
<td>20</td>
</tr>
<tr>
<td>GDO/GMO (8:2)</td>
<td>11</td>
</tr>
<tr>
<td>Soybean oil</td>
<td>&lt;20</td>
</tr>
<tr>
<td>Miglyol 812</td>
<td>20</td>
</tr>
</tbody>
</table>

*Values are the means with the %CV in parenthesis

**FIGURE 19.7** The mean particle size of the 300 mg/gm Drug X SEDDS formulations upon dilution with SIF (dilution factor: 100X) vs. the % diethanolamine (DEA) (w/w) in the formulation. The addition of a small amount of DEA (0.1%) results in a dramatic reduction in particle size from ~950 nm to ~200 nm.
by the simple addition of 1.5–5.0% of an amine (DEA or Tris) to the corresponding SEDDS formulation of Drug X.

**Influence of Lipid Excipients on Absorption of Drug X**

To evaluate the effect of the amount of lipid on the oral absorption of Drug X, three SEDDS formulations containing 300 mg/gm of Drug X were evaluated. Drug X–SEDDS formulations were identical in composition (see insert in Figure 19.9), with the exception of the amount of the glycerolipid (an 8:2 mixture of GDO:GMO), which ranged from 50 to 180 mg/gm of formulation.

A similar SEDDS formulation without GDO/GMO was also administered as a control. In the presence of 45 mg/gm of DEA, the dispersibility of all SEDDS formulations with a wide range of glycerolipid content (0 to 180 mg/gm) was similar, and the dispersion was a microemulsion with a particle size of ~120–150 nm. This observation indicates that: (a) the dispersibility of the formulation is primarily dictated by the presence of an organic amine; and (b) the presence of a substantial amount of glycerolipid in the formulation does not alter the particle size upon dispersing the SEDDS formulation with water.

These formulations were dosed orally as a predispersed emulsion in fasted rats at a dose level of 20 mg/kg. The normalized AUC/dose values for Drug X in four SEDDS formulations containing 0 to 180 mg/g GDO/GMO are plotted in Figure 19.9. A positive dependency is seen for the amount of GDO/GMO in the formula. There is virtually no difference in the AUC/dose ratio when the GDO/GMO concentrations in the SEDDS formulation are low (about 0–50 mg/gm). Both GDO/GMO and Capmul MCM are mixtures of mono- and di-glycerides, but they differ in the chain length of the fatty acids. GDO and GMO consist mainly of oleic acid (C18) glyceride esters, whereas Capmul MCM consists of C8–C10 fatty acid mono- and di-glyceride esters. Three SEDDS formulations with variable amounts of a glycerolipid (Capmul MCM) were similarly evaluated in rats. Their AUC/dose obtained is plotted against the amount of Capmul MCM in the formulation in Figure 19.9, and a positive dependency is seen for the exposure on the amount of Capmul MCM. The AUC/dose values with Drug X–SEDDS formulations containing 180 mg/gm of either GDO/GMO or Capmul MCM are essentially the same, indicating that the fatty acid chain length in the glycerolipids does not affect the oral bioavailability of Drug X–SEDDS formulations in rats.

The small difference in the AUC/dose ratio for Drug X between the SEDDS formulations containing 100 and 180 mg/gm of either GDO/GMO or Capmul MCM (Figure 19.13) indicates that approximately 100 mg/gm of the mono-/di-glycerides is the minimum quantity required to enhance oral absorption. This implies that a minimum amount of the mono-/di-glyceride of ~100 mg/gm in Drug X–SEDDS formulation is required, in order to increase the oral bioavailability of Drug X.

**Influence of Solvent Level on the Emulsification of SEDDS Formulations**

The release profiles of Drug X–SEDDS formulations with various ethanol concentrations ranging from...
0 to 100 mg/gm, while keeping the PG level constant at 73 mg/gm, are shown in Figure 19.10. These in vitro drug release profiles indicate little change in the initial percentage of drug released as the PG concentration in the formulation is increased.

The difference in the amount of Drug X released from the SEDDS formulations with varying amounts of PG, from 0 to 75 mg/g (Figure 19.11), is small as compared to the SEDDS formulations with varying amounts of ethanol (0 to 100 mg/gm, Figure 19.10). Thus, the release profile of Drug X from the SEDDS formulations is indicative of the spontaneous emulsification, and it shows a higher sensitivity to the ethanol level than to the PG level.

**Preliminary In Vitro and In Vivo Relationship (IVIVR) with SEDDS Formulations**

Three prototype SEDDS formulations of Drug X were evaluated in clinical trial (n = 15, crossover, fasted) at a single dose of 1200 mg with the di-sodium salt of Drug X (filled in hard filled capsules) as a control. The

**FIGURE 19.10** Effect of EtOH concentration (0–100 mg/g) on the drug release profile from Drug X SEDDS formulations containing 73 mg/g propylene glycol (PG).\(^{37}\)

**FIGURE 19.11** Effect of propylene glycol (PG) concentration (0–75 mg/g) on the drug release profile from Drug X SEDDS formulation containing 100 mg/g EtOH.\(^{37}\) The initial slope and the shape of the drug release profiles indicate that an increase in the ethanol concentration in the formulation improves the emulsification spontaneity and the subsequent extent of release. Similarly, the release profiles of Drug X SEDDS formulations with various propylene glycol (PG) concentrations from 0 to 75 mg/gm and a constant EtOH level of 100 mg/gm are shown in Figure 19.10.
pharmacokinetic profiles observed in humans are shown in Figure 19.12.\textsuperscript{37} The “No Tris” SEDDS softgels showed a lower AUC and $C_{\text{max}}$ value, compared to the Tris/MCM SEDDS formulation in gelatin HFC. The di-sodium salt of Drug X was administered as the bulk drug in a capsule and the oral bioavailability was somewhat higher than the No Tris SEDDS softgel. The “Tris/GDO/GMO” SEDDS softgel showed a two-fold higher $C_{\text{max}}$ and AUC value, compared to that of the “No Tris” SEDDS softgel formulation.

As described above, the enhanced absorption of Drug X from the Tris-containing SEDDS formulations appears to be due to the combined effect of better emulsification spontaneity and the smaller particle size upon dilution. Although the Tris/GDO/GMO SEDDS and the Tris/MCM SEDDS formulations of Drug X are very similar in composition, there is a noticeable difference between the release profiles of these two dosage forms (Figure 19.13), as well as their particle size upon dilution with water.

Further investigation indicated that the poor release of Drug X from the Tris/GDO/GMO SEDDS softgel, as compared to the Tris/MCM SEDDS filled in hard gelatin capsule is due to the reduction of the solvent (ethanol and PG) levels in the softgel fill. This was attributed to the solvent migration from the fill material into the gelatin shell, and subsequent evaporation of the ethanol during the softgel drying process. Figure 19.14 shows an IVIVR plot of the $in\text{ vivo}$ AUC values with the three SEDDS dosage forms of Drug X observed in the clinical trial on the percentage of drug released at 60 minutes in the $in\text{ vitro}$ test.

A rank-order correlation was observed between the $in\text{ vitro}$ release and the oral exposure of Drug X among the three SEDDS dosage forms. In addition, there was a rank-order correlation between the oral bioavailability and the population of large particles with a size $>1\text{ m}$ for the three SEDDS dosage forms evaluated in the clinical trial, as shown by the following results. The $in\text{ vitro}$ dispersibility test showed that the “Tris/MCM” SEDDS HFC yielded the smallest amount ($<2.3\%$) of large particles ($>1\text{ m}$), while the “No Tris” SEDDS softgel showed the highest amount of large particles ($<70\% >1\text{ m}$) upon dilution with water. The “Tris/GDO/GMO” SEDDS softgel had an intermediate amount of large particles ($<12\% >1\text{ m}$). These results are in accordance with...
19.4.2 Development of Supersaturatable S-SEDDS Formulations

Background on Supersaturated Formulations and the Advantages of Supersaturatable Formulations

The potential for supersaturated drug formulations in improving drug absorption was first proposed by T. Higuchi. Since then, a number of publications have appeared employing supersaturated drug formulations as a means of enhancing the flux (or bioavailability) of drugs in topical formulations, however, the development of supersaturatable drug formulations for improving the oral absorption of poorly soluble drugs has received limited attention. Supersaturated drug formulations can undergo spontaneous crystallization during storage. Supersaturatable drug formulations, on the other hand, become supersaturated only upon contact with water.

Polyvinylpyrrolidone (PVP) and the water soluble cellulosic polymers such as HPMC, methylcellulose, hydroxypropylmethylcellulose phthalate, and sodium carboxymethylcellulose, are useful in generating a supersaturated state with a number of poorly soluble drugs. The cellulosic polymers are excellent crystal growth inhibitors, and they are effective in maintaining the supersaturated state of the drugs at surprisingly low concentrations (<2%).

In the initial studies on the development of S-SEDDS formulations, it was found that reducing the amount of surfactant and lipid in a SEDDS formulation, in order to generate a supersaturated state upon dilution of the formulation with an aqueous medium, invariably resulted in rapid precipitation of the poorly soluble drug. However, incorporation of a surprisingly small amount (e.g., ~50 mg/g) of a water soluble cellulosic polymer (e.g., HPMC) into a SEDDS formulation was found to stabilize a supersaturated state, either by preventing or retarding drug precipitation upon dilution with water. These supersaturatable SEDDS (referred as S-SEDDS), formulations are described in further detail in the following text.

In Vitro Evaluation of the S-SEDDS Formulations

An in vitro dissolution/precipitation test was designed to evaluate various prototype S-SEDDS formulations containing poorly soluble drugs with respect to:

1. the kinetics of formulation dispersion, and drug release upon contact with water; and
2. the ability to generate and maintain the supersaturated state under physiologically relevant conditions.

The “biorelevant in vitro dissolution/precipitation test” that was developed in our laboratory consisted of simulated gastric fluid (SGF) containing 0.01M HCl and 0.15M NaCl (pH 2.0), stirred at 50–100 RPM at 37°C using a VanKel 7010 dissolution apparatus. The total volume of the biorelevant in vitro dissolution medium was 50–100 mL. This volume approached the combined volume of the residual stomach fluid (~20–50 mL) in a fasted state, plus the amount of water (~30–60 mL) administered in either an animal (e.g., dog, monkey) or clinical study in the fasted state.

A unit dose of the S-SEDDS formulation (or related formulation for comparison) was placed into the dissolution fluid, and solution samples were withdrawn from the medium and filtered through a 0.8 μm filter, followed by determination of the drug concentration in the filtrate by an HPLC assay. The concentration of drug in the filtrate represented the amount of drug in the aqueous phase plus the amount of drug in the microemulsion/emulsion state with solid particle size <0.8 μm. This in vitro dissolution/precipitation test and the resulting drug concentration upon filtration versus time plots were used to guide the development of the S-SEDDS formulations.
CASE STUDY WITH PACILITAXEL

Properties of Paclitaxel and the Marketed Formulations

Paclitaxel (Figure 19.15) is an antitumor agent used in the treatment of advanced breast and ovarian cancer. Paclitaxel has a molecular weight of 853, with a low solubility in water (<1 μg/mL) and in common pharmaceutical vehicles. The currently marketed intravenous (IV) formulation of paclitaxel (Taxol®, Bristol-Meyers Squibb, BMS) contains 6 mg/mL of paclitaxel, 527 mg/mL of Cremophor EL (polyoxyethylenated castor oil), and 49.7% (v/v) of dehydrated ethanol.

The oral bioavailability of paclitaxel using the Taxol® formulation is extremely low (<2%) in rats, and even in humans. The following section describes the development, and the evaluation, of the oral bioavailability of a paclitaxel S-SEDDS formulation in rats.

In Vitro and In Vivo Evaluation of a S-SEDDS Formulation of Paclitaxel

In order to examine the applicability of the S-SEDDS technology, paclitaxel was selected as a model drug and prototype S-SEDDS formulations were developed. The in vitro and in vivo performance of the paclitaxel SEDDS formulations without HPMC, and the resulting S-SEDDS formulations of paclitaxel, prepared with a suspension of powdered HPMC in the SEDDS formulation, were evaluated in comparison with the commercial Taxol® formulation. The in vivo oral bioavailability of paclitaxel in the S-SEDDS formulation co-administered with CsA was also assessed in rats, in order to determine the maximal exposure possible, as well as the role of P-gp inhibition when the transporter is exposed to the supersaturated concentration of paclitaxel using an S-SEDDS formulation.

A prototype S-SEDDS solution formulation containing ~60 mg/g of paclitaxel and 5% (w/w) HPMC (Formulation A) was prepared. The apparent paclitaxel solution concentrations in SGF (e.g., 0.01 M HCl + 0.15 M NaCl, pH 2.0) after dilution of the SEDDS formulation without HPMC (Formulation C) and the S-SEDDS formulation containing 5% HPMC (Formulation A) are shown in Figure 19.16a.

The theoretical concentration of paclitaxel in the test medium with these formulations, differing only in the presence or absence of HPMC, was 1.2 mg/mL based on the dilution factor of 50. Immediately upon dilution of the SEDDS formulation in the SGF medium, an opalescent solution characteristic of a microemulsion was formed. However, turbidity developed by the first sampling time (10 minutes) and crystalline paclitaxel was formed, as determined by microscopy and XPRD, indicating that the dispersion was supersaturated. The apparent paclitaxel concentration in the in vitro dissolution test (Figure 19.16a) was...
S-SEDDS Formulations of Drug Y

Drug Y was a candidate under development for preclinical and clinical evaluation. Drug Y has a log p of ~3.5, a water solubility of only ~310 μg/mL in the physiological pH range of 2–7, and it is nonionizable in this pH range. A human oral pharmacokinetic study using Drug Y showed slow and incomplete oral absorption using a powder formulation of the bulk drug in a gelatin capsule. In order to improve the rate and the extent of the oral absorption of Drug Y, an S-SEDDS formulation was developed and evaluated in the clinic.

S-SEDDS Formulations of Drug Y with HPMC

The in vitro dissolution/precipitation test using 50 mL of SGF fluid (0.01 M HCl + 0.15 M NaCl, pH 2) was employed in evaluating the performance of 1 gm of the S-SEDDS formulations containing 200 mg of Drug Y filled into two hard gelatin capsules (0.5 g/capsule). Based on a dilution factor of 50, the theoretical concentration of Drug Y in the test medium is 4 mg/mL.

The apparent Drug Y concentration found with the SEDDS formulation (without HPMC) in the in vitro dissolution/precipitation test is plotted in Figure 19.17a. The concentration of Drug Y in the medium was about 0.3 mg/mL at the first time point (0.5 hour), and this remained unchanged over the 6 hour test period. In contrast, a markedly higher concentration of Drug Y (~2.7 to 3.5 mg/mL) was observed with the same SEDDS formulation in the same test medium by adding 0.025% w/v of HPMC (Figure 19.17a).

The S-SEDDS formulation of Drug Y containing 40 mg/g HPMC was evaluated. The apparent Drug Y concentration observed is plotted versus time in Figure 19.17a. Little precipitation of Drug Y was observed over the 6-hour test period, and the Drug Y concentration was sustained at ~3–3.5 mg/mL, comparable to the concentrations of Drug Y that were observed in the test medium with HPMC. The apparent Drug Y concentration from the S-SEDDS formulation in the test medium was about 10-fold higher than the SEDDS formulation without HPMC in the dissolution medium. The in vitro test
III. DESIGN, DEVELOPMENT, AND SCALE-UP OF FORMULATION AND PROCESS

19.4 CASE STUDIES ON THE DEVELOPMENT OF SEDDS AND S-SEDDS FORMULATIONS

CASE STUDY (CONTINUED)

![FIGURE 19.17](a) Apparent concentration–time profiles of Drug Y observed in vitro dissolution/precipitation test using the same SEDDS formulation with and without HPMC. All formulations were filled into gelatin hard capsules; (b) Mean plasma concentration profiles of Drug Y in the dogs (n = 6, crossover) using the two SEDDS formulations with and without HPMC as compared to an aqueous suspension formulation.

![FIGURE 19.18](a) Apparent concentration Drug Y concentration (obtained by filtration through a 0.8 μm filter) versus time profiles of Drug Y observed in the in vitro dissolution/precipitation test using the three formulations with different capsule shells as indicated; (b) Mean plasma concentration profiles of Drug Y in the dogs using the three formulations (n = 6, crossover).

Clearly revealed that the presence of a small amount of HPMC could effectively maintain a supersaturated state of Drug Y for at least 6 hours.

The *in vivo* pharmacokinetics of both the SEDDS and the S-SEDDS formulations of Drug Y were evaluated after oral administration in dogs, as compared to an aqueous suspension. Figure 19.17b shows that the mean plasma concentration profile of Drug Y obtained after dosing the S-SEDDS formulation (with 4.4% HPMC) is about threefold higher in the $C_{\text{max}}$ and the AUC is two and a half times larger, as compared to the same SEDDS formulation without HPMC. This clearly indicates that the S-SEDDS formulation containing HPMC results in an increase in both the $C_{\text{max}}$ and the extent of absorption of Drug Y. The aqueous suspension and the S-SEDDS formulation showed a similar pharmacokinetics profile in dogs.

**S-SEDDS of Drug Y in HPMC Capsule**

The use of an HPMC capsule was explored as an alternative approach for incorporating HPMC into an S-SEDDS formulation. Three dosage forms were selected for comparison in the *in vitro* dissolution/precipitation test. The formulations consisted of:

1. the SEDDS liquid formula filled in hard gelatin capsules;
2. the SEDDS liquid formula containing 44 mg of HPMC powder suspended in a hard gelatin capsule; and
3. the SEDDS liquid formula filled into an HPMC capsule.

The SEDDS liquid formula in all three formulations was identical, however, HPMC or an HPMC capsule were employed in 2 and 3. Figure 19.18a shows the apparent drug concentrations of Drug Y as a function of time, obtained with these three dosage forms in the *in vitro* dissolution/precipitation test.

A 1 gm SEDDS formulation of Drug Y containing a suspension of 44 mg of powdered HPMC in hard gelatin capsules showed an almost constant drug concentration of $\sim$1 mg/mL over the entire 4 hour period in the dispersibility test, whereas the concentration obtained with SEDDS...
formulation of Drug Y without HPMC declined rapidly (Figure 19.18a). The SEDDS liquid filled into an HPMC capsule showed essentially the same Drug Y concentration–time profile as the SEDDS formulation containing suspended HPMC powder filled into gelatin capsules, but the levels of Drug Y were approximately five-fold higher.

The oral bioavailability study was determined in dogs (n = 6, crossover) with the three SEDDS formulations described above. The mean plasma concentration–time profiles of Drug Y are plotted in Figure 19.18b. As expected, the SEDDS formulation in the gelatin capsule showed a low $C_{\text{max}}$ and a low AUC. However, the plasma concentration–time profiles observed for the S-SEDDS formulation (containing HPMC), and the SEDDS formulation filled into HPMC capsules, were almost superimposable, and the resulting $C_{\text{max}}$ and AUC values were approximately two-fold higher than that of the SEDDS liquid without HPMC in the gelatin capsule. The in vivo behavior of the three formulations is in accord with the in vitro test results.

**Clinical Evaluation of Drug Y S-SEDDS Formulation**

A human clinical trial was designed to evaluate the oral bioavailability of an S-SEDDS softgel of Drug Y, in comparison with two other formulations, namely, the Drug Y powder in a gelatin capsule and an aqueous suspension of Drug Y fine particles. An S-SEDDS formulation of Drug Y containing suspended HPMC was encapsulated in softgels, and these softgels were orally administered to fasted healthy volunteers (n = 23, crossover).

The plasma concentration versus time profiles for Drug Y administered in each of these formulations are shown in Figure 19.19, and the mean $C_{\text{max}}$, $T_{\text{max}}$, and AUC values are reported in Table 19.5. The conventional Drug Y powder formulation in the gelatin capsule showed the lowest mean $C_{\text{max}}$ (621 ng/mL), and the aqueous suspension showed a slightly higher mean

<table>
<thead>
<tr>
<th>Pharmacokinetic parameters</th>
<th>Drug powder in gelatin capsule</th>
<th>Aqueous suspension</th>
<th>S-SEDDS softgel</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$ (ng/mL)</td>
<td>621 (45)</td>
<td>804 (45)</td>
<td>2061 (34)</td>
</tr>
<tr>
<td>$T_{\text{max}}$ (hr)</td>
<td>2.15 (42)</td>
<td>0.97 (43)</td>
<td>1.03 (36)</td>
</tr>
<tr>
<td>AUC ((ng/mL)*hr)</td>
<td>5060 (45)</td>
<td>4892 (45)</td>
<td>7004 (41)</td>
</tr>
</tbody>
</table>

$C_{\text{max}}$ (804 ng/mL). In contrast, the S-SEDDS softgel showed the highest $C_{\text{max}}$, and the largest AUC, along with the shortest $T_{\text{max}}$ (~1 hour), indicating a more rapid and complete absorption than Drug Y in a capsule or the aqueous suspension.

**PROPOSED PATHWAYS FOR ENHANCED ORAL ABSORPTION OF POORLY SOLUBLE DRUGS WITH SEDDS AND S-SEDDS APPROACH**

### 19.5.1 Drug Absorption Pathway

The enhanced oral bioavailability observed with SEDDS and S-SEDDS formulations of poorly soluble lipophilic drugs, as compared to that of simple aqueous suspension of the drug or the bulk drug powder in a capsule, indicates that SEDDS formulations appear to present the drug more efficiently to the intestinal enterocyte brush border glycopaxyl. The enhanced oral bioavailability often seen with the SEDDS and S-SEDDS formulations appears to be due to improved presentation of the poorly soluble drug to the enterocyte brush border membrane.
Studies on the mechanism responsible for inhibiting crystal growth by adsorption of the HPMC chains could inhibit nucleation of the drug or it could inhibit crystal growth by adsorption of the HPMC polymeric chains onto the surface of the drug nuclei.56 The cellulosic polymers are useful in inhibiting crystallization in topical and transdermal formulations. Based on this background, Figure 19.20 shows a cartoon of a possible scheme for the presentation of poorly soluble lipophilic drugs in SEDDS formulations to the intestinal enterocyte brush border, followed by uptake by the aqueous pathway or equilibration of the drug with the BA/BAMM pathway or by mimicking the behavior of the BA/BAMM pathway.

The enhanced intestinal absorption and shortened $T_{\text{max}}$ values of poorly soluble drugs administered in S-SEDDS formulations is consistent with enhanced uptake by the aqueous pathway in Figure 19.20, due to the higher free drug concentration that is generated by the supersaturated state in the GI tract with the S-SEDDS microemulsion. The shortened $T_{\text{max}}$ values seen with the optimized supersaturatable S-SEDDS formulations are consistent with an enhanced uptake by the aqueous pathway, and the enhanced bioavailability seen by the optimized S-SEDDS microemulsion is consistent with enhanced uptake by equilibration with the BAMM pathway or by mimicking the BAMM.
FIGURE 19.20 Cartoon showing proposed pathways for presentation of drugs in SEDDS/S-SEDDS formulations to the enterocyte glycocalyx on apical membrane and uptake of drugs (D) by: (a) the aqueous pathway; (b) the BAMM pathway; and (c) the microemulsion pathway. However, the drug in the emulsion/microemulsion remnant can equilibrate with the free drug in aqueous solution or, in turn, the drug can partition into the BAMM particle. Collisional transfer of the drug to the glycocalyx can occur from the drug–BAMM particle and from the remnant microemulsion particle. The drug in the aqueous media can be taken up by the aqueous pathway. The enterocyte intracellular processing can lead to venous or lymphatic delivery of the drug.

FIGURE 19.21 Cartoon showing the pathway for the uptake of extremely lipophilic drugs (D) by the intestinal enterocyte. Extremely lipophilic compounds with log $P > -8$ with very few polar functional groups could be absorbed by diffusion of the compound via the bilayer, through the tight junction and into the basolateral region where the drug could be removed from the basolateral membrane by association.

FIGURE 19.22 Scanning electron micrograph (SEM) showing the tightly formed glycocalyx consisting of glycoproteins and glycolipids that are attached to the surface of the columnar microvilli on the lumenal or apical surface of the intestinal enterocyte. The microvilli are seen at the bottom of the SEM with an M scribed on one of the microvilli.
apical (lumenal) surface of the intestinal enterocyte. The glycocalyx functions as a physical barrier that prevents direct contact of food particles and microparticulates (including microemulsions) in the intestinal lumen from direct contact with the intestinal microvilli. The cartoon in Figure 19.20 shows that the proposed presentation of a drug in a SEDDS/SEDDS microemulsion particle or remnant thereof, to the glycocalyx, could lead to uptake:

1. by the classical aqueous pathway;
2. by the BA/BAMM pathway; or
3. by simulating the behavior of the BAMM pathway.

The S-SEDDS remnant particles could promote drug uptake by the aqueous pathway through the higher free drug concentration.

19.6 CONCLUSIONS

Table 19.6 shows the water solubility of the compounds in the marketed SEDDS formulations, and the experiment drugs in the SEDDS and S-SEDDS formulations discussed in the case studies. From the data in Table 19.6, the lowest water solubility of 10 drugs formulated in marketed or experimental SEDDS/SEDDS formulations with reasonable oral bioavailability is 0.04 μg/mL, as given by PNU-74006F. The solubility of PNU074006F was determined experimentally in water at pH 6.5 at room temperature. This is somewhat lower than the publication of another group of 11 marketed and experimental poorly soluble drugs, where the lowest solubility consistent with good oral bioavailability in rats and dogs was reported as “<3 μg/mL”. The solubilities of drugs in a biorelevant fluid that simulates the intestinal fluids would be a better choice than those in water. However, information on the solubilities of drugs in biorelevant fluids is not readily available for the drugs in Table 19.6.

In general, the SEDDS and S-SEDDS formulations are not very useful with drugs with low lipophilicities (e.g., log P or log D <2) to improve their absorption. This is because these drugs would not be retained in the resulting microemulsion upon contact with water and the dilution occurring in the stomach and in the small intestine.

We consider that the SEDDS and S-SEDDS approaches are potentially useful for those drugs with key attributes listed below:

1. \( MW \leq 600 \);
2. \( clog P \geq 2 \);
3. do not possess extensive first-pass metabolism;
4. the number of \(-NH-CO-\) amide groups \( \leq 3 \);
5. its intrinsic aqueous solubility \( \geq 5-10 \mu g/mL \) (corresponding to a dose of 50–200 mg in human); and
6. shows substantial solubility in pharmaceutically acceptable co-solvents, surfactants, and lipids.

The recognition of the potential of SEDDS and S-SEDDS formulations for improving the gastrointestinal absorption of poorly water soluble drugs has been a major driver of these technologies. Properly designed SEDDS and S-SEDDS formulations provide the formulation scientists with a unique opportunity to the drug absorption profile design the absorption profile of poorly soluble drugs.

**TABLE 19.6** Aqueous solubilities of marketed and experimental drugs in SEDDS formulations

<table>
<thead>
<tr>
<th>No</th>
<th>Drug</th>
<th>Names of Marketed and Experimental SEDDS/S-SEDDS Formulations described in this review</th>
<th>Calc. or Exp. Water Sol. of Drug* (μg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cyclosporine</td>
<td>Sandimmune®. Forms a coarse emulsion with H₂O.</td>
<td>9 Calc.</td>
</tr>
<tr>
<td>2</td>
<td>Cyclosporine</td>
<td>Neoral®. Forms a microemulsion with H₂O.</td>
<td>9 Calc.</td>
</tr>
<tr>
<td>3</td>
<td>Ritanovir</td>
<td>Norvir®.</td>
<td>0.37 Exp.</td>
</tr>
<tr>
<td>4</td>
<td>Saquinavir</td>
<td>Fortavase®.</td>
<td>2 Calc.</td>
</tr>
<tr>
<td>5</td>
<td>Tipranavir</td>
<td>Aptivus®. Forms a microemulsion with H₂O.</td>
<td>5 Calc.</td>
</tr>
<tr>
<td>6</td>
<td>Paclitaxel</td>
<td>Experimental S-SEDDS Formulation.</td>
<td>&lt;0.3 Exp.</td>
</tr>
<tr>
<td>7</td>
<td>PNU-74006 F</td>
<td>Experimental SEDDS Formulation.</td>
<td>0.04 Exp.</td>
</tr>
<tr>
<td>8</td>
<td>PNU-91325</td>
<td>Experimental S-SEDDS Formulation.</td>
<td>6 Exp.</td>
</tr>
<tr>
<td>9</td>
<td>Drug X</td>
<td>Experimental SEDDS Formulation.</td>
<td>5 EXP</td>
</tr>
<tr>
<td>10</td>
<td>Drug Y</td>
<td>Experimental S-SEDDS Formulation.</td>
<td>3 Exp.</td>
</tr>
<tr>
<td>11</td>
<td>Danazol</td>
<td>Experimental Formulation. (Charman, 2005)</td>
<td>0.59 Exp.</td>
</tr>
</tbody>
</table>

*Calc. = Calculated water solubility using ALogPS in the DrugBank Database ([www.drugbank.com](http://www.drugbank.com))
ACKNOWLEDGEMENTS


References


III. DESIGN, DEVELOPMENT, AND SCALE-UP OF FORMULATION AND PROCESS
