This installment of “Eye on Excipients” provides some DOs and DON’Ts for developing successful SEDDS formulations to enhance API bioavailability.

The self-emulsifying drug delivery system (SEDDS) is one of the most viable options for enhancing the bioavailability of poorly soluble active pharmaceutical ingredients (APIs). SEDDS consist of digestible components, so they can provide a product with optimized pharmacokinetic properties while minimizing variability and food effect. They maintain API solubility during gastrointestinal dilution and transit by processes that govern the digestion of dietary lipids. The enhanced bioavailability and performance of SEDDS formulations can also be attributed to increased intestinal absorption via supersaturation, tight junction modulation, and reduced first-pass effect via lymphatic transport with long-chain fatty acid esters.

SEDDS can be simple formulations to develop and process. A typical formulation is composed of an oily vehicle (lipid), a surfactant, and a co-surfactant, or else a single excipient with self-emulsifying properties. Depending on the formulation, SEDDS can be manufactured as either liquid-filled softgels or liquid-filled two-piece capsules.

**Developing a successful SEDDS formulation**

As shown in Figure 1, API solubility screening is the first step in developing a SEDDS formulation. Solubility is an indication of a formulation’s expected drug load and performance. After obtaining solubility data at ambient conditions in a broad range of oily vehicles, surfactants, and co-surfactants, you can select the best delivery vehicle based on the targeted dosage form (softgel or two-piece capsule) and the API’s biopharmaceutics (such as efflux system and first-pass effect). Solubility screening for SEDDS formula-

**Figure 1**

SEDDS formulation development steps

<table>
<thead>
<tr>
<th>Step 1</th>
<th>API solubility screening</th>
</tr>
</thead>
<tbody>
<tr>
<td>• API solubility limit in liquid and solid excipients</td>
<td></td>
</tr>
<tr>
<td>• Excipient selection based on dose and type of dosage form</td>
<td></td>
</tr>
<tr>
<td>• Eventual role of excipient in formulation and <em>in vivo</em></td>
<td></td>
</tr>
</tbody>
</table>

**Step 2**

Miscibility testing to rule out immiscible formula

**Step 3**

*In vitro* lipolysis testing
Formulation maintains the dose in solution (≥75% at 60 minutes)

**In vivo** testing
Pre-clinical study

---

Inayet Ellis
Gattefossé USA
tions requires in vitro lipolysis testing, which assesses the formulation’s performance upon dilution in the presence of lipolytic enzymes.

While performing these screening steps, it’s important to strike a balance between bioavailability, stability, and manufacturability. The following are some DOs and DON’ Ts to help you optimize the screening and development process for a SEDDS formulation.

Optimizing screening for solubility and bioavailability

DO determine equilibrium solubility at ambient conditions, even in solid vehicles. DON’T use kinetic solubility to determine the API concentration or dosage in the lipid vehicle(s).

Saturation solubility in liquid vehicles can be determined by equilibrium the API at room temperature and assaying using high-performance liquid chromatography (HPLC). In solid lipids, equilibration can be first achieved at elevated temperature. Then, the solidified mixture (after 24 hours of repose) can be examined by differential scanning calorimetry (DSC) and/or hot-stage microscopy (HSM) to determine its saturation concentration at room temperature. The melting enthalpy depression of the solid lipid at various concentrations is observed by the DSC method.

When the concentration is at the saturation point, a break will be observed in the slope of melting enthalpy versus concentration. HSM provides visual observation of any undissolved API crystals under cross-polarized light upon rapid heating (30°C/min) of the solid excipient. For effective results using HSM, the API’s melting point should be 10°C higher than the excipient’s melting point.

DO screen API solubility in a wide range of excipients, and DON’T limit selections to liquid vehicles only.

Depending on the API, some solid excipients can provide sufficient solubility results and enhanced bioavailability. For solid vehicles that become molten at or above their melting points (40°-65°C) before adding the API, DO consider the effect of the short heating and cooling rate on the API-formulation stability.

DO select an API dose below 80 percent of the saturation concentration to avoid nearing the saturation point.

A supersaturated solution might be beneficial for bioavailability enhancement. However, supersaturation can also jeopardize the formulation’s physical stability and lead to potential API crystallization during the product’s shelf life.

DON’T expect lymphatic uptake if the API isn’t highly lipophilic or if your formulation consists of short-chain fatty acids.

Excipients containing long-chain fatty acids such as oleate and linoleate help boost the lymphatic absorption of highly lipophilic APIs that have logP values of 5 or higher. This strategy can be used to avoid the first-pass effect. However, the API needs to have enough lipophilicity and affinity to the oily vehicle (solubility 50 mg/g) to be absorbed and circulated in the lymphatic system.

DO evaluate the dispersion size in an aqueous medium or conventional dissolution test as a characterization tool only, not as an in vitro screening tool. DO test the formulation under lipolysis conditions.

Lipid digestion in the gut is the main physiological event that enhances the bioavailability of poorly soluble compounds. Lipolysis begins in the stomach with gastric lipase and continues in the duodenum with pancreatic lipase and colipase. A SEDDS formulation containing an oily vehicle in a capsule first disperses then emulsifies in the gastrointestinal fluids spontaneously. Lipolysis in the presence of lipases and bile salts creates colloidal structures such as unilamellar and multi-lamellar vesicles and mixed micelles. The initial larger colloidal structures are ultimately converted into smaller micelles, which significantly increase the API’s solubilization capacity in the gastrointestinal milieu.

For these reasons, any in vitro dispersion testing in the absence of gastric and lipolytic media is not representative of a lipid formulation’s in vitro API solubilization capacity and should be used as a characterization tool only. Instead, monitor API solubility under in vitro lipolysis conditions, where the SEDDS formulation is dispersed into a buffer with bile salts, and the API in the water phase is monitored with addition of pancreatic lipase using a pH-stat.

DON’T expect enhanced bioavailability if the API isn’t solubilized in any of the SEDDS components.

If a poorly soluble API is dispersed but not solubilized in any lipid vehicle in a SEDDS, the API can precipitate out upon dilution. As a result, it won’t be able to participate in the lipolysis process with the lipid vehicle as described previously.

Optimizing screening for stability and manufacturability

DO perform API-excipient compatibility studies and also consider capsule-shell compatibility.

As with any other formulation development, API-excipient compatibility studies should be part of a SEDDS formulation screening. These studies can be performed by assaying the API in the mixture under forced conditions. Capsule-shell compatibility can be assessed by consulting both the excipient and capsule suppliers.

DO consider processing the formulations under vacuum.

Manufacturing a SEDDS formulation includes a mixing process that occurs either at ambient conditions for liquid formulations or at an elevated temperature for solid formulations. Processing under vacuum prevents air from incorporating into the liquid during mixing.

DON’T select two-piece capsules for liquid formulations
Copyright CSC Publishing

The capsule-filling temperature should be high enough to maintain the formulation’s free-flowing liquid state but low enough to minimize any potential harmful effects of elevated temperature on the formulation or capsules. An evaluation of the formulation’s viscosity at various temperatures can be useful for finding the optimal filling temperature, as shown in the example thermo-rheogram chart in Figure 2.

**Figure 2**

Example thermo-rheogram showing the optimal filling temperature for a solid excipient (Gelucire 48/16)

![Thermo-rheogram chart](image)

The capsule-filling temperature should be high enough to maintain the formulation’s free-flowing liquid state but low enough to minimize any potential harmful effects of elevated temperature on the formulation or capsules. An evaluation of the formulation’s viscosity at various temperatures can be useful for finding the optimal filling temperature, as shown in the example thermo-rheogram chart in Figure 2.

**DO add antioxidant(s)!**

As previously stated, lipids should be stored under nitrogen. However, it may also be necessary to add antioxidant(s) to prevent oxidation during processing and improve the formulations’ shelf life.

**DO follow the handling instructions of each lipid excipient.**

DON’T use water baths to heat lipid-based systems, and DON’T scoop semi-solid excipients from top.

Lipid vehicles should be stored under nitrogen. Self-emulsifying excipients can absorb moisture, so you should avoid high humidity and water baths. Semi-solid or block excipients (such as Gelucire 44/14) need to be melted and homogenized before sampling rather than scooped from the top.

**DO evaluate the temperature and viscosity profiles of semi-solid formulations to find the optimal filling temperature.**

Inayet Ellis, PhD, is scientific affairs manager at Gattefossé USA (201 265 4800, www.gattefosse.com), a global supplier of specialty excipients and formulation solutions for the healthcare industry. For additional information, please contact the author (iellis@gattefossecorp.com).