eye on excipients

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This edition of the column discusses using functional lipids and self-emulsifying drug delivery systems (SEDDS) to overcome the poor solubility and permeability of today's APIs.

The majority of new chemical entities (NCEs) being evaluated for therapeutic use exhibit low solubility, low permeability, or both, indicating that they are BCS Class II, Class III, or Class IV compounds. There are numerous and varying strategies for improving the solubility of BCS Class II active pharmaceutical ingredients (APIs), including

- Micronizing and nano-sizing them to increase the surface area;
- Using solid dispersions and spray drying to hold the API in a higher energy state;
- Adding surfactant to aid in dissolution;
- Adjusting micro-environmental pH;
- Using organic salt conjugation to create more soluble ion pairs; and
- Using flash precipitation.

When it comes to improving the intrinsic permeability of APIs, there are even fewer options. Lipid-based formulations, however, offer a very safe and effective method of potentially improving both the solubility and permeability of APIs. The benefits of lipid-based formulations include:

- A large increase in the solubility of BCS Class II APIs by incorporating them into an oil-water emulsion;
- The potential to greatly improve the permeability of polar APIs by means of stimulating bile salt secretion from lipolysis to improve the emulsification of API in the lumen and possibly effect para-cellular transport;
- The potential to reduce the P-glycoprotein mediate efflux of certain APIs, improving bioavailability;
- The reduction of fasted and fed pharmacokinetic differences of APIs;
- APIs that can be readily digested and metabolized;
- Formulations that can be easily filled into soft and hard capsules (gelatin or non-gelatin) for oral administrations; and
- Higher-molecular-weight lipids that are solid at room temperature and have the potential to be readily incorporated into direct-compression tablets while still providing the advantages cited above.

There are two basic approaches to formulating with functional lipids: dissolution of the API in a neat lipid or dissolution of the API in a SEDDS pre-concentrate. In the former, the API is simply dissolved in a lipid excipient and then filled into a soft or hard capsule. Once the capsule is ingested, the API-containing lipid is released and undergoes digestion through the actions of lipases. This results in the body creating an emulsified system containing the API, lipid, bile salts, and phospholipids. The API remains in the solubilized state in the emulsion and is thus absorbed from the gastrointestinal (GI) tract. In the latter, a SEDDS pre-concentrate is developed by employing a combination of functional lipids, including any permutation of the following: a primary solubilizer, a secondary surfactant/co-emulsifier, and a primary surfactant. The optimized pre-concentrate is filled into a soft or hard capsule for oral administration. Upon contact with GI fluid, the pre-concentrate forms an emulsion or micro-emulsion, which carries the API until it is absorbed.

Components of a stable SEDDS pre-concentrate

Solubilizers. These are typically fully esterified lipids manufactured by the esterification of glycerol or propylene glycol with free fatty acids of varying chain lengths. These products are highly lipophilic and have no hydrophilic-lipophilic balance (HLB).

Secondary surfactants or co-emulsifiers. These are typically partially esterified lipids manufactured by the partial esterification of glycerol or propylene glycol with free fatty acids or oils (via a catalyst). These emulsifiers provide a range of HLB values according to their degree of esterification, fatty acid chain length, and saturation, and that allows you to select a suitable emulsification system for specific APIs. For certain APIs with similar solubility parameters, an emulsifier can be employed as a solubilizer and used alone.

Primary surfactants. The production of optimal SEDDS formulations often requires high concentrations (greater than 30 percent) of surfactant agents. There are many types of surfactants that can be employed in the pre-concentrate to emulsify oil and water and even facilitate the formation of nano-emulsions. The most common types employed for SEDDS

formulations are pegylated esters, polyethoxylated sorbitan esters, and polyethoxylated glycerides. Pegylated esters are manufactured through the esterification of polyethylene glycol with its respective fatty acids, the rearrangement of oils and alcohols, or the direct in situ ethoxylation of partial glycerides. Polyethoxylated castor oil is prepared by reacting ethylene oxide with castor oil, and polyethoxylated sorbitan esters are made through the esterification of polyethoxylated sorbitan with its respective fatty acids after cyclization of sorbitol.

Pre-concentrate formulation

There are four general steps in formulating a pre-concentrate for a SEDDS: 1) select the pre-concentrate component candidates, 2) determine the maximum API solubility in the pre-concentrate components, 3) determine the emulsion's characteristics upon pre-concentrate dilution, and 4) conduct in vitro evaluation of the pre-concentrate, including dissolution testing and other physiochemical characterization.

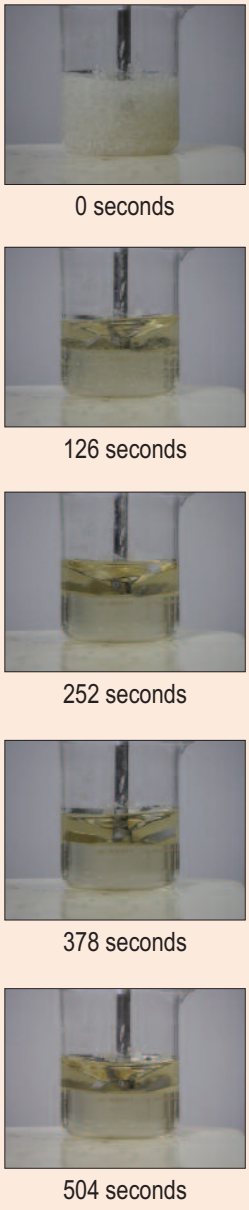
Select component candidates. First, determine the aqueous solubility, log P, melting point, and solubility parameter of the API. Typically, a log P greater than four indicates that a fully esterified solubilizer should be included in the pre-concentrate [1]. By matching the required HLB of the solubilized API to the HLB values of the proposed SEDDS components, you can select SEDDS pre-concentrate candidates for a solubility study.

Determine maximum API solubility. Once you identify candidate SEDDS pre-concentrate components, determine the maximum API solubility in all candidates. This can be done by adding an excess of API to each of the SEDDS pre-concentrate candidate components individually or in combination, if desired. These combinations are then vortexed in order to adequately disperse the API in the SEDDS pre-concentrate candidates. Next, the vortexed combinations are shaken by wrist action for 24 hours at 37°C, and the solutions are then allowed to stand for 24 hours at 25°C. The last step is to filter and analyze the combinations for API content in order to determine the maximum API solubility in each pre-concentrate candidate or in selected candidate mixtures.

Determine the emulsion's characteristics. After you determine the maximum solubility, the SEDDS pre-concentrate components that can dissolve the greatest amount of the API are plotted in various concentrations on a phase diagram. Typically, individual known combinations of the SEDDS pre-concentrate components are plotted on two vertices and water occupies the third vertex. Next, binary mixtures—containing different concentrations of the pre-concentrate base components and of the pre-concentrate surfactant components—are diluted systematically with water, and the phase characteristics of these combinations are observed (usually by eye). You can then evaluate the droplet size where desired in the phase diagram. The most common phase observations are emulsion formation, micro-emulsion formation, or gel formation. Figure 2 shows an example of a phase diagram [2].

FIGURE 1

Time-elapsed photos of simvastatin dissolving in SEDDS pre-concentrate



The emulsion's characteristics can be very important to bioavailability considerations. This has been shown in the case of cyclosporine A, where the micro-emulsion was much more bioavailable than the emulsion [3]. The optimization of SEDDS pre-concentrate components focuses on both maximizing the solubility of the API in the SEDDS pre-concentrate and on the emulsion performance of the pre-concentrate upon dilution with water. The emulsion's droplet size and its stability are of specific interest because they will ultimately affect the absorption of the API and, subsequently, the API's bioavailability. Table 1 provides a classification system for lipid formulations according to their makeup and droplet size [1].

Conduct in vitro evaluation, including dissolution testing. In vitro dissolution testing is important to demonstrate the API's superior aqueous solubility in the optimized SEDDS system compared to the same API in a non-SEDDS formulation. Additionally, in vitro testing can allow you to analyze the pre-concentrate behavior under sink conditions. The dissolution parameters you choose can be adjusted based upon each individual formulation project. Researchers at St. John's University have suggested an in vitro dispersion test [4], a method that employs a dissolution tester outfitted with USP Apparatus 2 (0.01 M HCl, 37°C, 50 rpm). Both API concentration and emulsion droplet size are analyzed over time as a means of determining API release and how the SEDDS per-

Figure 2

Example of a pseudo-ternary phase diagram [2]

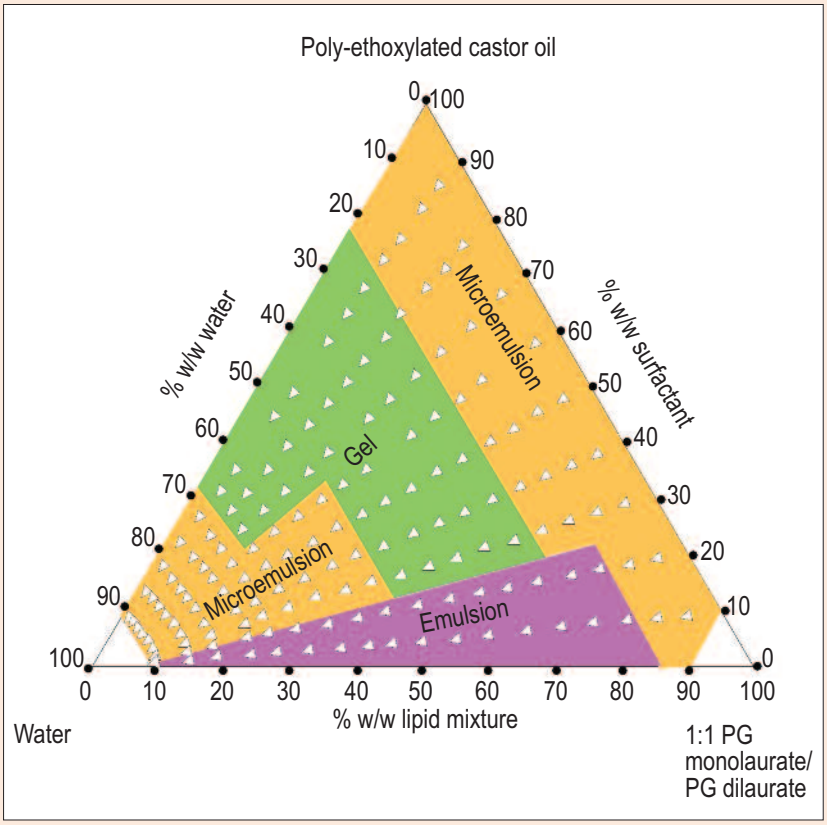


Table 1

Lipid formulation classification system [1]

Typical composition (%)	Emulsion type Type I	Type II	Type IIIA	Type IIIB
Triglycerides or mixed glycerides	100	40 to 80	40 to 80	< 20
Surfactants	-	20 to 60	20 to 40	20 to 50
Hydrophilic cosolvents	-	-	0 to 40	20 to 50
Particle size of dispersion (nm)	Coarse	100 to 250	100 to 250	50 to 100
Significance of aqueous dilution	Limited importance	Solvent capacity unaffected	Some loss of solvent capacity	Significant phase changes and potential loss of solvent capacity
Significance of digestibility	Crucial requirement	Not crucial but likely to occur	Not crucial but may be inhibited	Not required and not likely to occur

forms under simulated gastric conditions. It is important to understand the nature of a proposed SEDDS system before designing in vitro testing. For example, if an API were dissolved in a neat lipid, you would need to consider including simulated gastric and intestinal fluid, which includes lipases and bile salts, because the neat lipid system only generates an emulsion under biological conditions.

Solid lipid formulations

Higher-molecular-weight lipids, which are solid at room temperature, may also be employed in lipid formulations. Typically, these lipids are melted and the API is dissolved in the liquefied lipid while heating. It's also possible to formulate a solid dispersion by melting the lipid and the API together. The most common methods of generating a solid dispersion with lipids are spray congealing, hot-melt granulation, and hot-melt extrusion. In these formulations, it is desirable that the melting point of the lipid materials be as close as possible to the melting point of the API. In certain cases, however, the API's melting point can be higher and the API will still dissolve in the molten lipid(s). Additionally, you must not exceed the degradation temperatures of the lipid excipients during the melt formation.

Once the API is melted with the lipids, the materials should be rapidly cooled to solidify them to ensure the API is dispersed amorphously throughout the lipid matrix. One form of solid lipid formulations is solid lipid nano-particles (SLNs). These nano-sized lipid carrier particles are generated by melting that is followed by high-pressure homogenization and subsequent cooling. SLNs have been reported to provide a means for controlling drug delivery, enhancing bioavailability through both dissolution modification and enhanced tissue distribution, and targeting drug delivery through various application routes [5]. SLNs have been proposed as potential carriers for cyclosporin A, insulin, calcitonin, and somatostatin. Formulation of proteins in SLNs can improve the stability of the protein, reduce proteolytic degradation, and provide sustained release of the protein [6].

Conclusion

The majority of NCEs exhibit solubility and/or permeability challenges. Functional lipid formulations, including SEDDS, can overcome these challenges. Specific APIs can be dissolved in neat lipids or formulated in a SEDDS pre-concentrate containing an

optimized mixture of functional lipids, which form an emulsion upon dilution with GI fluids. The development of a SEDDS pre-concentrate focuses on optimizing API solubility in the SEDDS while still generating a stable micro-emulsion that increases API aqueous solubility. Both neat lipid formulations and SEDDS formulations can be loaded in either soft or hard capsules for oral administration. Additionally, SEDDS pre-concentrates are candidates for loading in or on various multi-particulate systems for incorporation into hard capsules or tablets.

Furthermore, lipid-based excipients are being used in a variety of new areas of drug delivery, ranging from spray congealing for solid oral dosages to the application of nano-structured lipid carriers for the non-invasive delivery of macromolecules. The versatility and functionality of the lipid excipients available today provides drug formulators with numerous options and capabilities to address and overcome many historic delivery and performance challenges. While there is an ongoing requirement to further understand the physical and chemical stability of various API classes within lipid-based systems, it is clear that lipids will play an expanding and pivotal role in enhancing bioavailability of poorly soluble NCEs. *T&C*

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