Bioavailability Enhancement with Lipid-Based Drug-Delivery Systems

Moderated by Adeline Siew, PhD

Experts from Capsugel and Catalent discuss the rationale of using lipid-based formulations to improve the oral bioavailability of poorly soluble drugs.

Poor solubility remains an ongoing challenge in formulation development. “The abundance of poorly soluble drugs is often attributed to the manner by which companies build large compound libraries (usually via combinatorial chemistry techniques) and/or the use of high-throughput screening assays to identify potential candidates,” explain Eduardo Jule, PhD, senior manager, and Hywel Williams, PhD, senior scientist, both with Capsugel’s Dosage Form Solutions business unit. “In the latter, the identification of potential hits will often be measured by how readily a particular compound binds to a receptor. Because receptor binding will involve a level of hydrophobic interactions between the drug and receptor, these assays may, therefore, preferentially select those drugs that are intrinsically hydrophobic.”

Julien Meissonnier, R&D platform director, Pharmaceutical Softgel Europe, Catalent, notes that while poorly soluble drugs are here to stay, this issue is, however, not currently addressed appropriately due to the multiple existing and emerging technologies arising in the area, as well as the lack of clarity around the benefits and options that these technologies can provide to formulation scientists. “Also, a large portion of the current solubility-enhancing technologies bring incremental development complexity (such as increased incompatibilities, complex scale-up, and clinical acceptability) resulting in loss of time and additional risks,” says Meissonnier. “As a result, achieving a clear picture of the solubility-enhancement space has become increasingly complex.”

There is a growing interest in lipid-based drug-delivery systems as a means to improve the bioavailability of poorly soluble drugs. Jule, Williams, and Meissonnier discuss the advantages of this approach and the challenges in developing lipid-based formulations.

PharmTech: First of all, what is the rationale of using lipid-based drug-delivery systems?

Jule and Williams (Capsugel): Lipid-based drug-delivery systems have the proven capacity to improve the oral bioavailability of a drug via several mechanisms, with the unique potential to address both physicochemical and biological obstacles to systemic exposure. It is, therefore, appropriate to describe these mechanisms in relation to the fate of a lipid-based formulation in the gastrointestinal (GI) tract:

Stomach. Lipid-based formulations containing the drug, either dissolved or suspended, are typically administered via hard or soft capsules. Following rupture and disintegration of the capsule shell in the stomach, the formulation mixes with gastric fluid to an extent that is governed by formulation composition and stomach contents. In the fasted state (which is usually more challenging for poorly soluble drugs than fed-state conditions), those formulations containing a mixture of oil and surfactant(s) will self-emulsify before entering the small intestine—the primary site of drug absorption.

Small intestinal lumen. Here, a high dissolved drug concentration at the intestinal wall will promote passive drug diffusion across the enterocyte membrane. For a poorly soluble drug, enabling technologies are required to increase solubility and dissolution so that a high dissolved concentration that drives intestinal absorption can be attained. This may be achieved via lipid-based formulations, wherein the potential to administer the drug predissolved in the formulation matrix is such that dissolution can be bypassed altogether, while the lipidic components of the formulation (dispersed and/or digested) mix with endogenous bile salts and phospholipids to form a range of colloidal species that increase drug solubility and present the drug in a well-dispersed and readily absorbable form. Small colloidal species formed by lipidic excipients and endogenous solubilizers will also enhance drug transport through the unstirred water layer, which can be slow and potentially limiting to absorption when the drug is lipophilic.

Enterocyte. Lipid-based formulations may also impact post-absorption events to improve bioavailability of drugs that are subject to:
Lipid systems may include triglycerides, mono- and diglycerides, lipophilic surfactants, hydrophilic surfactants and cosolvents—excipients with a wide variety of physicochemical properties.

In 2000, Colin Pouton first established an effective classification system for lipid-based formulations, which was completed in 2006 (1). Based upon their qualitative and quantitative composition, the lipid formulations might exhibit different behaviors upon dispersion and digestion. The classification system consists of four broad categories (1).

Briefly, Type I formulations are oils that require digestion; Type II formulations (hence, majority of high-first-pass metabolism—surfactants have been shown to inhibit cytochrome P450 enzymes known to extensively metabolize drugs in the intestinal wall, while lipidic excipients can, for highly lipophilic drugs, increase the fraction of absorbed drug that enters into the lymphatic system where hepatic metabolic pathways are avoided.

Lipid-based technologies offer the possibility to address both physicochemical and biological barriers to bioavailability—Jule and Williams, Capsugel.

Meissonnier (Catalent): Lipid-based formulations of poorly soluble drugs generally exist during development where drug substance solutions remain in a solution form in the GI fluids prior to facing the GI walls. This means the formulation must first resist its dispersion in the GI fluids by maintaining the drug in solution. Upon dispersion, the formulation could be present in different states, ranging from coarse emulsions to thermodynamically stable microemulsions, which present different features. After the lipid components of the formulation are subjected to the action of the lipase (pancreatic lipase being the primary contributor), which acts specifically at the oil/water interface, the lipids undergo de-esterification into fatty acids and partial glycerides. Again upon digestion, it is important to ensure that the poorly soluble drugs remains in solution form before facing the enterocytes.

Lipid systems have the advantage that they can present the drug as a stable liquid solution, but the term ‘lipid formulation’ has come to mean one of a large group of formulations that share some common features.

PharmTech: What are the benefits of using lipid-based drug-delivery systems for solubility/bioavailability enhancement compared with other available methods?

Meissonnier (Catalent): Lipid systems allow manufacturing operations to progress rapidly, and may accelerate access to early clinical phases and future scale-up steps. Using a rational approach in preformulation operations with liquid systems not only enables accelerated predictability of drug/ingredient interactions but also, with the use of in-vitro and in-silico development tools, assists in tailoring the optimum lipid formulation system and increasing predictability of in-vivo performance. Working with liquid and semi-solid systems, Catalent has developed a standard procedure, whereby low batch sizes (hundred grams of formulation) are produced under cGMP conditions using
commercial encapsulation equipment, enabling quality-by-design integration from the first preclinical batches through to manufacture.

**Jule and Williams (Capsugel):** As mentioned previously, lipid-based technologies offer the possibility to address both physicochemical and biological barriers to bioavailability, which is particularly advantageous when events post-absorption are such that bioavailability remains low, in spite of increased solubility and dissolution rate. Owing to fast capsule rupture and the absence of dissolution, lipid-based formulations also may be designed to provide fast rate of absorption, which is often desirable when a rapid onset of action is needed.

**Lipid systems allow manufacturing operations to progress rapidly, and may accelerate access to early clinical phases and future scale-up steps—**Meissonnier, Catalent.

Aside from performance advantages, lipid-based formulations offer a straightforward way of formulating drugs that are low melting (i.e., < 100 °C) while avoiding process-related issues when attempting to mill, granulate, and produce tablet formulations. The potential to formulate a drug dissolved in a non-aqueous vehicle also circumvents the risk of solid-state polymorphism (during manufacture and/or on storage).

Additionally, liquid-filled hard or soft capsules offer an optimal approach for formulating highly potent/low-dose drugs, ensuring dose uniformity and reducing exposure risks associated with handling solids. Lastly, liquid-filled capsules offer an established scale-up route, particularly when working with homogenous solutions.

**PharmTech:** Can you describe a stepwise approach for formulation development of lipid-based drug-delivery systems?

**Jule and Williams (Capsugel):** Once a lipid-based approach is determined to be the optimal technology for improving bioavailability, the first step to the development of a robust lipid-based formulation is to further qualify the drug candidate in terms of physicochemical and biopharmaceutical properties. This ensures that a range of lipidic excipients (oils, cosurfactants, surfactants, and cosolvents) is selected based on the drug characteristics. From here, solubility testing is performed to identify excipients toward which the compound exhibits a high affinity. Selected excipients are then progressed into the formulation design phase; this stage of development can often be slow and rate-limiting given that a wide number of potential excipients and excipient combinations can be theoretically explored. To accelerate the formulation design process, Capsugel uses a lipid expert system—an *in-silico* database based on hundreds of phase diagrams coupled to a decision tree—to identify concept formulations based on drug solubility in lipid excipients, target dose, and the dispersibility of several hundred different placebo formulations across a range of different dilutions.

Concept formulations are then progressed into a performance testing program. Here, formulations are subjected to dispersion and simulated digestion tests to ascertain the likely fate of the incorporated drug as the lipid formulation is processed via the highly efficient lipid digestion and absorption pathway. The most robust formulations are those that solubilize high compound concentrations in both the dispersed and digested state (i.e., minimizing drug precipitation), with limited change in performance on changing certain experimental factors, such as bile salt concentration and extent of dilution. Our experience tells us that such formulations are less likely to show variable and/or poor performance *in vivo.*

Alongside a physical and chemical stability program, lead formulation(s) undergo capsule compatibility studies and physical characterization before a technical batch is manufactured. During these latter stages of development, our understanding and capabilities in this area are also leveraged to ensure rapid process development and supply of clinical batches.

**Meissonnier (Catalent):** The development of lipid systems encompasses the standard steps found in pharmaceutical development. The state of excellence is reached through the internal development of formulation-specific analytical techniques, enabling access to a more complete and accurate dataset earlier and faster to ensure proper risk mitigation earlier in the development cycle.

Complementing further drug characterization studies, preformulation studies are based upon the kinetic evaluation of drug solubility in various classes of ingredients, in parallel with chemical compatibility screens. These tests are enabled by specific automated platforms and predictive tools.

When progressing to the formulation development stage, to select a formulation that is resistant to precipitation under dispersion and digestion, Catalent operates proprietary *in-vitro* and *in-silico* models, including a computerized database of digestion profiles, and also pseudo-ternary diagrams generated at its five primary global development sites dedicated to lipid-based systems development. These systems improve the efficiency of formulation determination, as well as predictability to progress in further clinical studies. The excipient selection process is also based upon careful selection of the ingredients in light of their global approvability and existing safety status. A wide majority of lipid ingredients are generally recognized as safe (GRAS) and several studies are under way on novel functional lipids to broaden their existing safety data.

**Reference**

1. C.W. Pouton et al., *Eur J Pharm Sci* 29 (3-4) 278-287 (2006). *PT*