The importance of lipid screening in the development of lipid-based formulations

Jul 02, 2016
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Pharmaceutical Technology
Volume 40, Issue 7, pg 20

Lipid-based drug delivery is increasingly being used to tackle oral bioavailability challenges resulting from poor solubility. This type of formulation exploits the body's lipid disgestion and absorption pathways.
"Many poorly soluble drugs are associated with a positive food effect in that their bioavailability increases with food intake," observes Kaspar van den Dries, senior director formulation sciences, solid dosage forms, and softgels at Patheon. "This endogenic effect of food makes lipid systems a suitable formulation option to enhance the bioavailability of poorly soluble drugs."

The development of lipid-based formulations, however, requires a multifaceted approach. "It is insufficient to just explore the API's solubility in different lipid excipients and use this information to formulate a lipid system," explains van den Dries. He recommends that aspects such as lipid digestions in simulated gastric and intestinal fluid, phase diagrams, and emulsification behavior should be covered as well as part of the formulation characterization. According to van den Dries, the number of excipients for lipid-based formulations has expanded over the years.

"Besides the traditional medium and long-chain triglycerides (e.g., castor oil), there is a wide range of other excipients available to generate lipid-based formulations, from chemically modified glycerides to polar and non-polar surfactants and cosolvents," he says. "Which excipients to select will depend on multiple factors, such as API solubility in these excipients, whether the excipients are sensitive to lipid digestion, and the emulsification behavior."

Van den Dries believes that lipid screening is an important aspect in the development of lipid-based formulations. "The solubility data in a sufficiently broad range of lipid excipients will provide an initial assessment of the excipients that can be used and the expected drug loading," he explains. "However, combining the right excipients in the correct ratio and subsequently establishing the emulsification behavior in physiologically relevant media is essential to evaluate whether the formulation also provides the required emulsification behavior and could work in an in-vivo environment."

The key for lipid solubility screening is to standardize the protocol for the screen, says van den Dries. These protocols should be designed to minimize drug usage and at the same time, perform a rapid screening. According to him, a general approach to developing lipid-based formulations should typically involve:

- Rapid solubility screening in up to 20 lipid excipients with minimal API consumption
- Formulation design using phase diagrams
- In-vial stability program to assess chemical and physical stability prior to batch manufacturing to reduce risk and API consumption
- Formulation characterization to assess rheology and emulsification behavior
- Lipid digestion screening to predict in-vivo behavior of lead candidate formulations
- Prototype development for animal studies or GMP batches for human clinical studies with International Council for Harmonization (ICH) stability testing on prototypes
- Optional testing such as permeability studies and gastric intestinal model, among others.

Along with the standard experimental work to screen lipid formulations, Patheon also uses in-silico modeling, van den Dries points out. "We employ modeling to provide estimates of the solubility of drug compounds in typical excipients used for lipid formulations. Modeling does not replace all experimental work, but these computational approaches significantly reduce the amount of up-front experiments that might otherwise be performed in the process of selecting and developing robust formulation approaches to overcome bioavailability challenges."

Article Details
Pharmaceutical Technology
Vol. 40, No. 7
Page: 20

Citation
When referring to this article, please cite it as A. Siew, "The importance of lipid screening in the development of lipid-based formulations," sidebar to "Taking On Mission Insoluble with Polymers," *Pharmaceutical Technology* 40 (7) 2016.