De-mystifying Lipid-based Formulations

The capacity of lipid-based formulation in addressing both physicochemical and biological obstacles to achieve enhanced drug exposure is explained by **Eduardo Jule** in this article.

A recurrent challenge for advancing new chemical entities in drug development is low and/or variable bioavailability (BA), mostly due to poor solubility in physiological (aqueous) media. Commonly used technologies to enable improved drug absorption and bioavailability have been extensively reviewed (Williams et al., *Pharmacological Reviews* 2013, 65, 315-499) and include salt selection, cocrystals, amorphous solid dispersions, particle size reduction, cyclodextrins, amorphorphous/ lipid micro- and nanoparticles, adsorbents, and lipid-based technologies.

Due to the wide applicability of enabling technologies, from new chemical entities to off-patent drugs, the BA enhancement landscape is innovative, dynamic, and diverse. Indeed, the formulation of poorly water-soluble drugs is a key focus for many dosage form solution providers supporting drug development work with one or more BA-enhancing technology approaches to advance or re-position compounds. Capsugel Dosage Form Solutions offers development and manufacturing capabilities (non- and GMP) with the technologies having commercial precedence: spray-dried dispersions (SDD) and lipid-based formulations (LBF).

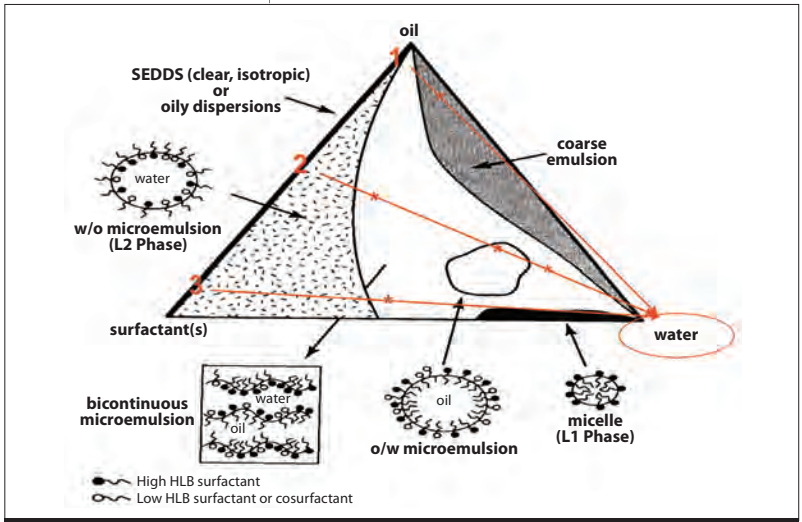


Figure 1: Multi-component phase diagram

The selection of the optimal technology for a given compound and target product profile is based on an in-depth understanding of key physicochemical and biological obstacles to drug exposure following oral administration. Physicochemical obstacles to oral BA include low aqueous solubility (a thermodynamic and form-dependent property) and a slow rate of dissolution (a kinetic property).

In many cases, it is necessary to overcome not only physicochemical obstacles to absorption, but also biological barriers, which include PgP- or BCRP-mediated efflux or pre-systemic drug metabolism in the small intestine (Benameur, *Gattefossé Bulletin Technique* 2006, 99, 63-75.) Additional considerations in choosing a BA-enhancing technology include target dose, excipient acceptance in target markets, preferred final dosage form and size, frequency of administration, storage and packaging requirements, and intellectual property.

Drug Production

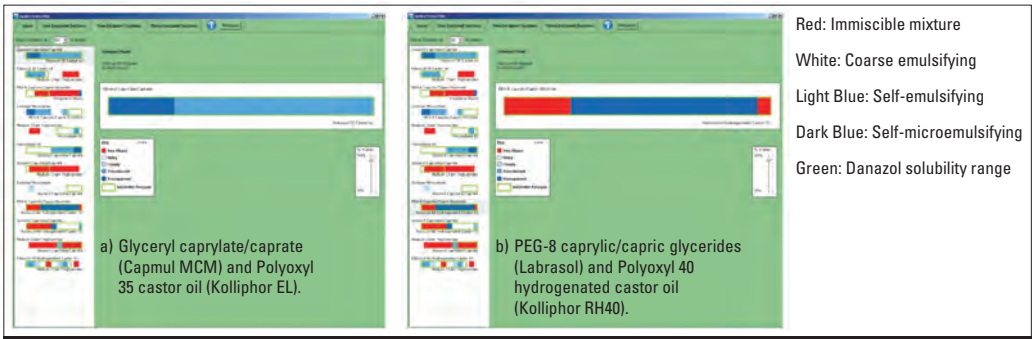


Figure 2: Lipid Expert System sample output package: binary phase diagrams

A mechanistic science-based process for identifying the optimal enabling technology for a specific compound to avoid the time, cost and risk of parallel assessment of multiple technologies has been previously presented (Williams et al., *Science-based Technology Selection and Formulation Development for Oral Bioavailability Enhancement*, Capsugel.) This article focuses on LBF technology, which has the capacity of addressing both physicochemical and biological obstacles to achieve enhanced drug exposure. A Lipid Expert System for simplifying and accelerating the development of multi-component systems is also discussed.

Benefits of lipid-based formulation

Lipid-based formulation has been extensively investigated because of the wide variety of possibilities it can offer – from straightforward solutions or dispersions to self-emulsifying and micro-emulsifying systems, all while providing solubility increase across several orders of magnitude, from mg/mL to ng/mL.

From a clinical perspective, aside from providing great relief to transplant recipients, the development of Sandimmune (then Neoral) elucidated three major benefits of self-micro emulsifying over self-emulsifying systems:

- Increase in solubility and bioavailability
- Reduction of food effects
- Reduction of inter- and intra-individual variability (Mueller et al., *Pharm Res* 1994, 11, 151-154, 301-304, Mueller et al., *Transp Proc* 1998, 30, 1694-1696)

There are additional benefits of lipid-based formulations to consider. To some extent, lipid-based formulation is a unique platform that can address both physical (solubility) and biological (efflux, metabolism) factors potentially affecting the absorption of a drug (Porter et al., *Nature Reviews* 2007, 6, 231-248.) An increasing wealth of data suggests that lipids can serve as dynamic substances that inhibit certain biological phenomena, such as glycoprotein or breast cancer receptor protein mediated efflux (Yamagata et al., *Drug Met Disp* 07, 35, 1142-1148) and CYP sub-enzyme family mediated metabolism (Bravo et al., *Biopharm Drug Disp* 04, 25, 37-49). There is also emerging evidence that lipids may be used to divert absorption from the portal vein to the lymphatic route, thus potentially avoiding first-pass metabolism of a drug.

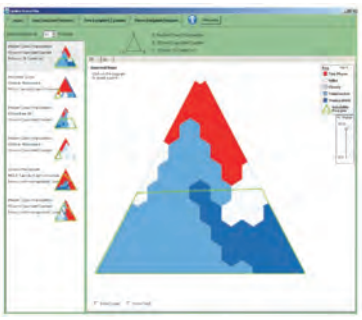
Yet, in spite of many commercially available lipidic products for enhanced bioavailability, only a limited number of lipid-based formulations have reached the market compared to more traditional dosage forms like tablets or powder- or pellet-filled capsules. However, these conventional forms do not always provide suitable answers to the challenges posed by poorly soluble compounds. Lipids, consistent with other drug delivery platforms (e.g., nanocrystals and solid dispersions), have emerged from an investigational standpoint, but are yet to result in major commercial success.

More products on the market?

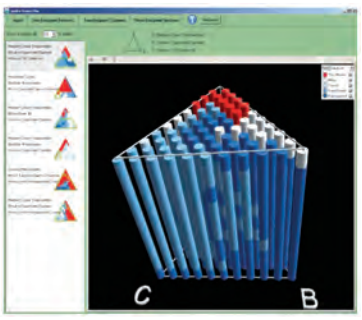
One of the most obvious reasons why lipid-based formulations have not truly fulfilled their potential may be their perceived complexity, as development often results in multi-component systems. Resulting from reactions between naturally occurring fats and functional groups (such as glycerol or propylene glycol) or polymeric materials (such as polyethylene glycol or polypropylene glycol), lipid excipients are inherently composite materials, and their chemistry requires a good degree of understanding. Combining two or more of such building blocks can then be interpreted as combining mixtures of mixtures and can, at first, deter formulation scientists.

Formulation complexity

Dispersion in the gastric environment raises another variable to an already complex equation, as formulations from a simple binary system see a third dimension added and may form dispersed systems, including simple oil-in-water or water-in-oil micellar systems, emulsions or micro emulsions, liquid



a) Sample 2-dimensional ternary diagram between medium chain triglycerides (Miglyol 812), Glyceryl caprylate/caprate (Capmul MCM) and PEG-35 castor oil (Kolliphor EL).



b) Sample 3-dimensional ternary diagram. The third dimension is the water dilution pathway.

Red: Immiscible mixture
White: Coarse emulsifying
Light Blue: Self-emulsifying
Dark Blue: Self-microemulsifying
Green: Danazol solubility range

Figure 3: Lipid Expert System output package: sample 2D, 3D ternary phase diagrams, where the 3rd dimension represents the dilution pathway

crystals, or bi-continuous emulsions (*Benameur, Gattefossé Bulletin Technique* 2006, 99, 63-75).

In 2006, Pouton proposed the Lipid Formulation Classification System (LFCS) (Pouton et al., *Eur J Pharm Sci* 2006, 29, 278-287) in an attempt to establish an orderly way of identifying lipid-based formulations and evaluating their performance through key criteria dispersion and digestion. In 2010, the LFCS went on to form a consortium (www.lfcsconsortium.org), a non-profit organisation aimed at deploying universally accepted protocols to evaluate performance *in vitro* (Williams et al., *J Pharm Sci* 2012, 101, 3360-3380) generating *in vitro/in vivo* correlations and opening communication lines with regulatory bodies.

In the meantime, however, formulation development often relies on existing default formulation prototypes or trial-and-error. While the former can yield lucky early winners, the latter is more likely and can be time-consuming. Full-blown formulation development requires the generation of phase diagrams for every new drug candidate, a far from trivial task. An example of a multi-component phase diagram is given as **Figure 1**.

As Meinzer described the problem: "A microemulsion formulation always has to be tailor-made according to the characteristics of the drug compound. Even slight changes in the chemical structure of an active molecule might affect the characteristics of the mixture up to a complete disappearance of the microemulsion structure. Each new compound requires a complete formulation development programme which might become excessive in searching the optimal types and amounts of excipients" (Bulletin Technique Gattefossé 88, 1995, 22-26).

While it is perhaps ambitious to generate multi-component phase diagrams for every new chemical entity, generating data that could be used to provide formulation development guidelines brings the task down to a more reasonable – yet still challenging – level.

The concept

Capsugel's Lipid Expert System is aimed at supporting and accelerating lipid-based formulation development, by leveraging a database of phase diagrams which continue to be expanded.

Experimentally generated by a team of experienced formulation scientists, these phase diagrams utilise some of the most widely used, commercially available excipients (ranging from oils to hydrophilic solvents) and across surfactants of increasing hydrophilic/lipophilic balance and assorted chemical families, among other inclusion criteria. Binary, ternary and even quaternary systems have been dispersed in aqueous media and relevant phases recorded. The resultant data has been collated, centralised and made available through a decision tree. Originated over a decade ago, the proprietary database contains a vast number of phase diagrams today.

How it works

The Lipid Expert System is accessed by determining drug candidate solubility in a selection of individual excipients – a process that can be completed in a matter of days – and is generally supported by at least one month of stability data. Solubility values are then entered into an input package, along with the targeted dose and desired dosage form size.

At this stage, a decision tree readily determines whether the target dose can be achieved with 1-, 2- or 3-excipient systems, and identifies all phase diagrams that match two simple criteria as to their ability to:

- Form solutions or dispersed systems upon *in vitro* dispersion
- Solubilise the drug at the desired dose – based, again, on the solubility achieved in single components

The formulation scientist then has the option to select

Drug Production

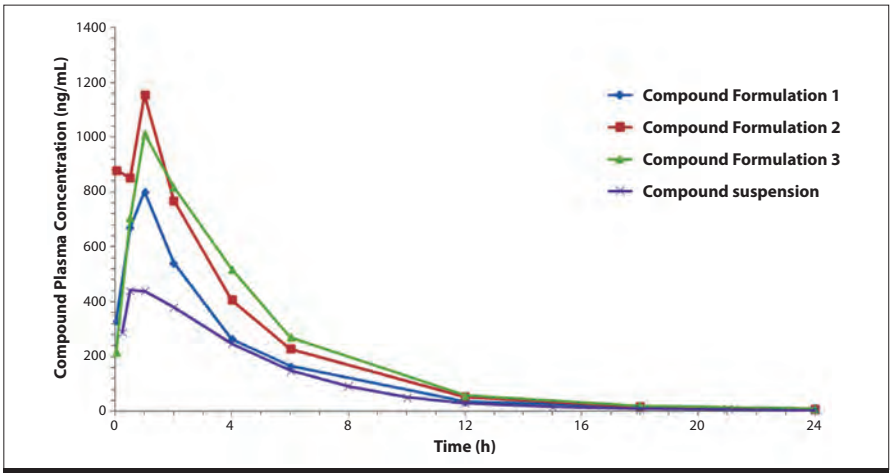


Figure 4: Dog pharmacokinetic profile of compound suspension and different enabling formulations

formulation types (such as simple solutions, coarse, self-emulsifying, or self-microemulsifying drug delivery systems) and confirm that the selected ratios solubilise the drug at the target dose. Critically, the formulation scientist also has the possibility to evaluate the dilution pathway, or whether the selected formulation holds the ability to disperse into one system regardless of the amount of available dispersing medium, from 1 to 100 per cent, or infinite dilution (see **Figures 2 and 3**).

Any phase transition entails a structural rearrangement of excipients in the formulation, and may have a significant impact on the levels of poorly soluble drug maintained in solution post-dispersion. This is of particular importance, as the amount of fluid available in the gastrointestinal tract is known to vary from one individual to another, between the fasted or fed states, and to decrease from the upper to lower gut. In this regard, ensuring that phase transitions are avoided amounts to a simplification, and significantly enhances the robustness of the formulation.

In the example, solubility data in single excipients for Danazol, a poorly soluble drug used to treat endometriosis, was entered into the Lipid Expert System and a target dose of 10mg defined. In addition to seven obvious single-excipient formulation candidates, the database immediately provided three binary and three ternary self-emulsifying and microemulsifying systems that met the target dose, and provided consistent results along the dilution pathway.

Several distinct advantages result from the utilisation of the lipid expert system. Upfront identification of formulations that meet pre-defined endpoints amounts to including quality by design early on in the development programme. Starting off with a refined 13 formulation candidates is a way to optimise and manage precious formulation resources and speed the development process. Ensuring a formulation specifically designed for the drug candidate provides an advantage towards defining the overall formulation space, thereby strengthening intellectual property rights.

In another example, a poorly soluble new chemical entity undergoing clinical development at a Cambridge, MA-based company was formulated using the Lipid Expert System approach. Several dozen formulations were readily identified and screened for drug solubility and stability. They were next evaluated through *in vitro* dispersion and digestion, leading to the selection of three lead compound formulations that were administered to fasted dogs in hard capsules, along with an aqueous suspension. **Figure 4** summarises the pharmacokinetic profiles of the different enabling formulations.

When comparing pharmacokinetic values, all formulations dosed at 30mg provided a significant improvement over the unformulated compound dosed at 300mg. c_{max} was found to range from 60 per cent (suspension) to 187 per cent (lipid formulation 2); area-under-the-curve (AUC) ranged from 60 per cent (suspension) to 117 per cent (lipid formulation 3) as compared to powder in capsule at 1/10th the dose. Further, whereas the suspension provided an already significant exposure increase versus the powder in capsule, its performance was exceeded by lipid formulations 2 and 3, with exposures of 62 per cent and 63 per cent respectively, clearly demonstrating the benefits of lipid formulation over more conventional forms. This development programme, from feasibility to capsule supply for dog studies, was completed in 10 weeks.

Conclusion

Access to the range of key technologies used for BA enhancement, fundamental scientific understanding of each technology's application and limitations, and extensive experience across the technology options are considered key in ensuring that an optimised, fit-for-purpose dosage form is rapidly identified and developed.

A mechanistic science-based approach, driven by technology

mapping and absorption models for selecting the optimal technology, is integral for the Capsugel Dosage Form Solutions product development process. Compound properties used for technology mapping are often already known (or otherwise measurable *in silico* or *in vitro*), but require knowledge of the technology boundaries in relation to product needs, as well as the experience acquired from advancing hundreds of compounds.

Lipid-based formulations have been demonstrated to address physical factors such as poor aqueous solubility, as well as biological factors such as efflux or even pre-systemic metabolism, and are extensively explored in product development. Initiatives such as the LFCS Consortium continue to establish the means to select formulation types based on their *in vitro* performance through standardised protocols that better predict *in vivo* behavior. Capsugel Dosage Form Solutions continues to support the LFCS Consortium and internal programmes to further advance the science behind LBF technology and its applications.

Having access to expert systems complements the technology selection process and further reduces the overall product development timeline. Based on a database of hundreds of experimentally generated phase diagrams, the Lipid Expert System determines the optimal excipient qualitative and quantitative combination for an LBF, thereby providing an optical decision tree process. Although formulation candidates in the Lipid Expert System output package may require optimisation, a full development programme from feasibility to formulation development, including evaluation and supply of pilot quantities, can be completed in as little as 10 weeks. **PA**

Eduardo Jule, PhD, is senior manager, Formulation and Pharmaceutical Development, at Capsugel. He joined the company in 2004 in Bornem, Belgium where he supported the expansion of the Strasbourg and Colmar (France)-based product development operations. In 2010, he relocated to the US and returned to R&D, supervising lipid-based formulation development, from feasibility to scale-up and manufacturing. Prior to joining Capsugel, he worked for a drug delivery firm NanoCarrier (Tokyo, Japan), where he was involved in licensing operations, technology acquisition and pharmaceutical development programmes with the industry, the academia and the National Cancer Center.