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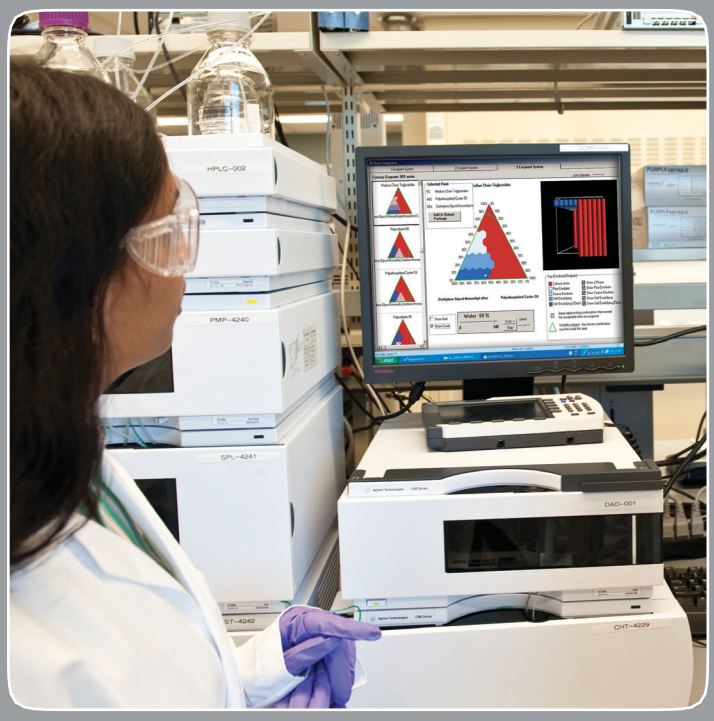
Accelerating Lipid-Based Drug Formulation Through Application of an Expert System



abstract

Formulation scientists are increasingly pivotal to pharmaceutical product development. They are often faced with the daunting challenge of identifying the most suitable drug delivery platform among myriad of options and developing and validating robust systems that address the challenges posed by ingreasingly complex drug candidates. Further, these challenges must be overcome in ever-shortening time frames. Among platforms, lipid-based formulations, in either soft gelatin or liquid hard shell capsule formats, have become a well-established approach that has been shown to improve the bioavailability and reduce the food effects and uptake variability of poorly soluble compounds. Capsugel has developed an enhanced lipid-based formulaiton approach that moves beyond predictive modeling and excipient high-throughput screening. This system utilizes a database of experimentally generated phase diagrams, providing unique formulaiton development support and resulting in increased speed to market.

Introduction

Today, up to 90% of new chemical entities in development are said to fall under either Biopharmaceutics Classification System (BCS) Class II (70%) or Class IV (20%)[1]. In other words, the bioavailability of the vast majority of drug candidates is expected to be low and/or variable because of their poor solubility in physiological (aqueous) media. And while most Class IV candidates are sent back to chemistry groups, where efforts concentrate on further optimization, Class II compounds can have their solubility increased through a number of different technology platforms including, but certainly not limited to, pH adjustment, salt formation, particle size reduction, and lipid-based formulation[2]. Lipid-based formulations, however, can be complex multi-component systems that form a variety of phases upon dispersion in the gastric environment. An expert system can reduce time-consuming trial and error formulation efforts.

An Overview of Lipid-Based Drug Delivery

a well-established platform with many benefits

Lipid-based formulation has been extensively investigated because of the wide variety of possibilities it can offer, from straightforward solutions or dispersions, to self-microemulsifying drug delivery systems (SMEDDS) and self-emulsifying drug delivery systems (SEDDS), all while increasing solubility across several orders of magnitude, from ng/mL to mg/mL.

From a clinical perspective, aside from providing great relief to transplant recipients, the development of Sandimmune® then Neoral® elucidated three major benefits of SMEDDS over SEDDS:

- Increase in solubility and bioavailability
- Reduction of food effects
- Reduction of inter- and intra-individual absorption variability[3,4]

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[5]. An increasing wealth of data suggest that lipids can serve as dynamic substances that inhibit certain biological phenomena, such as drug efflux by P-glycoprotein or Breast Cancer Receptor Protein[6] and metabolism by cytochrome P450 sub-enzyme family. 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 so far 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, such as nanocrystals and solid dispersions, have emerged from an investigational standpoint but are yet to result in major commercial successes.

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. Lipid excipients are inherently composite materials, 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, and their chemistry requires a good level of understanding. Combining two or more lipid systems can then be interpreted as combining mixtures of mixtures and can, at first, deter less experienced formulation scientists from pursuing this proven approach.

formulation complexity

Dispersion in the gastric environment raises another variable to a potentially 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 microemulsions, liquid crystals, or bi-continuous emulsions[8].

In 2006, Pouton proposed the Lipid Formulation Classification System (LFCS[9]) in an attempt to establish an orderly way of identifying lipid-based formulations and evaluating their performance through key criteria, including dispersion and digestion. In 2010, the LFCS went on to form a consortium (www.lfcsconsortium.org), a non-profit organization aimed at deploying universally accepted protocols to evaluate formulation performance *in vitro*[10], generating *in vitro/in vivo* correlations, and opening communication lines with regulatory bodies.

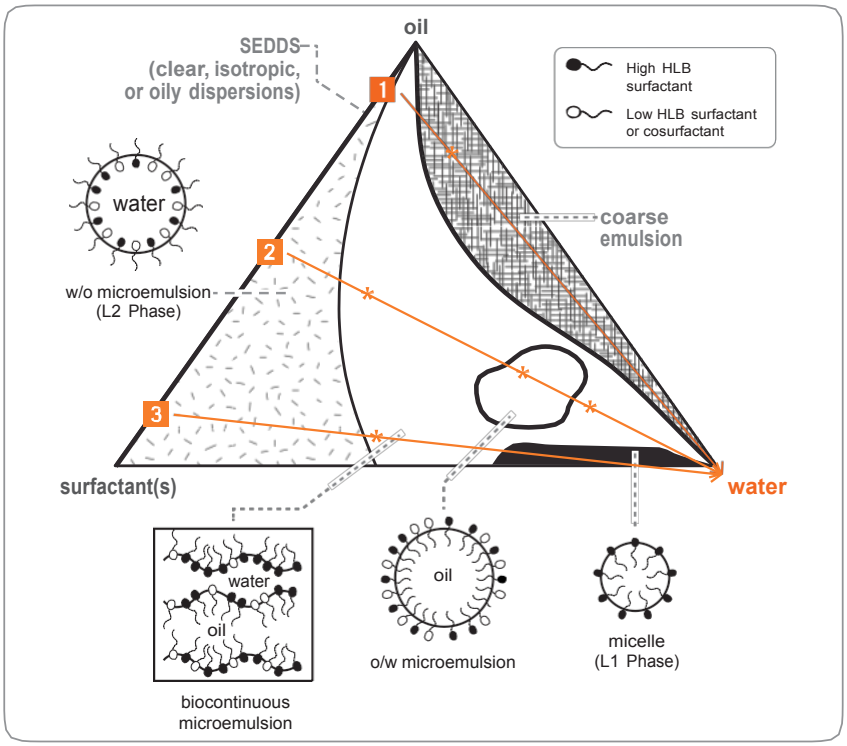


Figure 1: Theoretical Phase diagram, along with dilution pathways (1: 90% Oil/10% Surfactant; 2: 50% Oil/50% Surfactant; 3: 10% Oil/90% Surfactant).

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 a 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 program, which might become excessive in searching for the optimal types and amounts of excipients"[11].

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 viable – if still challenging – level.

Capsugel's Lipid Expert System – a Game Changer

the concept

Capsugel's lipid expert system is aimed at supporting and accelerating lipid-based formulation development by leveraging a database of phase diagrams, now numbering several hundred, and continues to be expanded.

Experimentally generated by a team of experienced formulation scientists, these phase diagrams utilize 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, centralized, 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

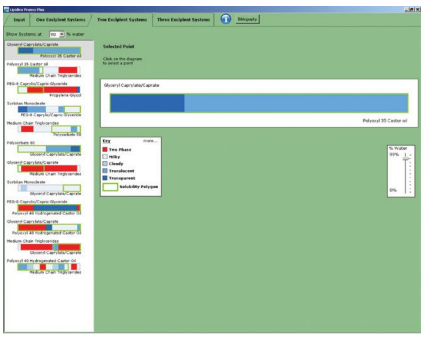
The lipid expert system is accessed by determining drug candidate solubility in a selection of individual excipients, a process that can be completed in a matter of days, and is generally supported by at least one month of stability data. Solubility values are then entered, along with the targeted dose and desired dosage form size. At this stage, a unique 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
- Solubilize the drug at the desired dose – based, again, on the solubility achieved in single components

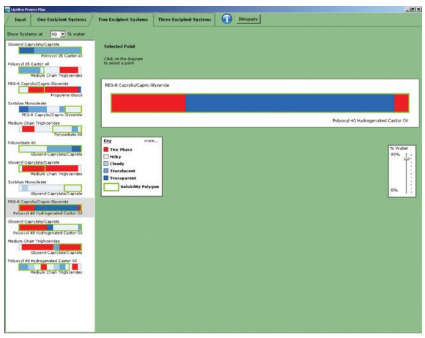
The formulation scientist then has the option to select formulation types, such as simple solutions, coarse, SEDDS or SMEDDS, and confirm that the selected ratios solubilize the drug at the target dose. Critically, the formulation scientist also has the possibility to evaluate the dilution pathway or whether the selected formulation holds the ability to disperse into one system regardless of the amount of available dispersing medium, from 1% to 100%, 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 described in Figures 2 and 3, 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 10 mg defined. In addition to seven obvious single-excipient formulation candidates, the database immediately provided three binary and three ternary self-emulsifying and self-microemulsifying systems that met the target dose and provided consistent results along the dilution pathway.

Several distinct advantages result from the utilization of the lipid expert system. Identifying formulations that meet pre-defined endpoints upfront amounts to including Quality by Design early on in the development program. Starting off with a refined list of 13 formulation candidates is a unique way to optimize and manage precious formulation resources and speed the development process. Of critical relevance, having a formulation specifically designed for the drug candidate provides a unique advantage towards defining the overall formulation space and thereby strengthening intellectual property rights.



a) Glyceryl caprylate/caprate (Capmul® MCM) and Polyoxyl 35 castor oil (Kolliphor® EL).



b) PEG-8 caprylic/capric glycerides (Labrasol®) and Polyoxyl 40 hydrogenated castor oil (Kolliphor® RH40).

Red:
Immiscible mixture

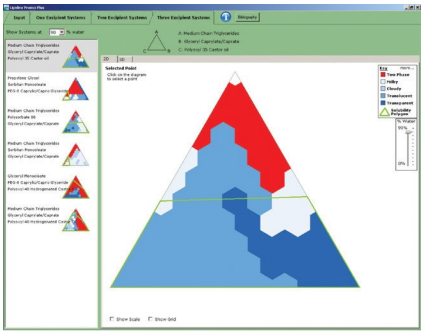
White:
Coarse emulsifying

Light Blue:
Self-emulsifying

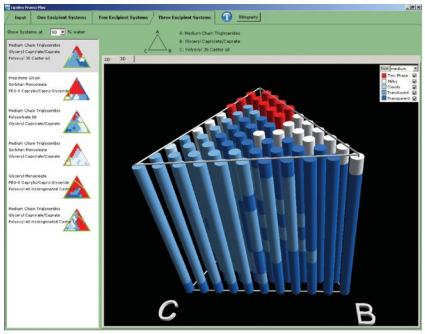
Dark Blue:
Self-microemulsifying

Green:
Danazol solubility range

Figure 2: Lipid expert system sample output package: binary phase diagrams.



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 3rd 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 2-, 3-D ternary phase diagrams, where the 3rd dimension represents the dilution pathway.

In another example, a poorly soluble new chemical entity undergoing clinical development at a Cambridge, MA 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 in hard capsules to fasted dogs, along with an aqueous suspension. Figure 4 summarizes the pharmacokinetic profiles of the different enabling formulations.

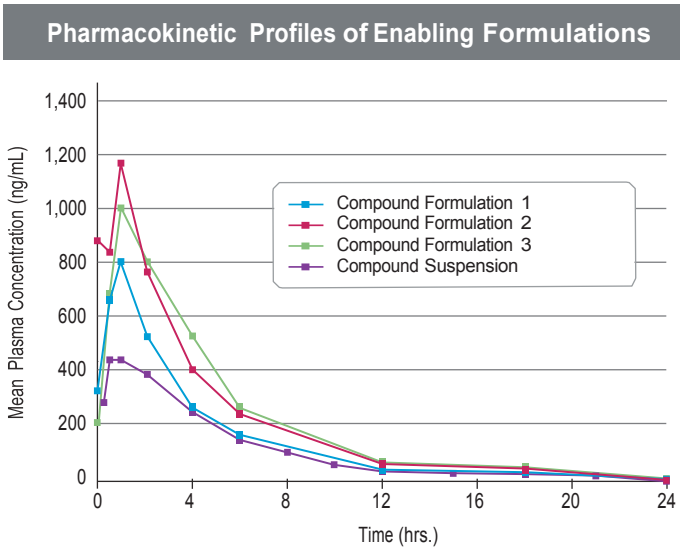


Figure 4: Dog pharmacokinetic profile of Compound suspension and Formulations 1, 2, and 3.

When comparing pharmacokinetic values, all formulations dosed at 30 mg provided a significant improvement over the unformulated compound dosed at 300 mg (Figure 5). C_{max} was found to range from 60% (suspension) to 187% (lipid formulation 2); area-under-the-curve (AUC) from 60% (suspension) to 117% (lipid formulation 3) that of the powder in capsule but at 1/10th the dose. Further, whereas the suspension provided an already significant exposure increase vs. the powder in capsule, its performance was exceeded by lipid formulations 2 and 3, with exposures of 62% and 63% respectively, clearly demonstrating the benefits of lipid formulation over more conventional forms.

This development program, from feasibility to capsule supply for dog studies, was completed in ten weeks.

Formulation	T_{max}(h)	C_{max}(ng/mL)	$t_{1/2}$(h)	AUC_{last} (h·ng/mL)	F (%)
Compound in Capsule (300 mg)	1.00	792	3.34	4030	NA
Compound Suspension (30 mg)	0.88	481	4.2	2430	33
Compound Formulation 1 (30 mg)	0.83	805	9.4	3213	46
Compound Formulation 2 (30 mg)	0.75	1480	4.0	4560	62
Compound Formulation 3 (30 mg)	1.75	1124	4.3	4725	63

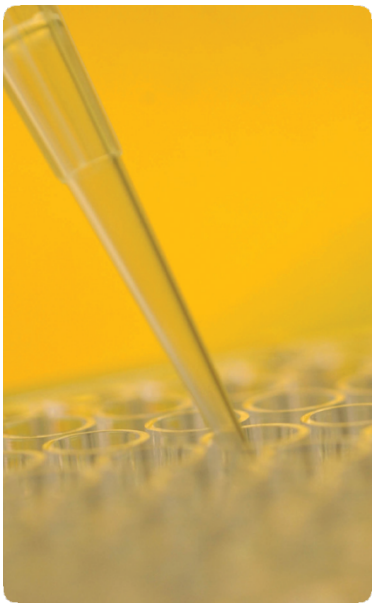
Figure 5: Dog pharmacokinetic values for unformulated Compound, Compound aqueous suspension, and Compound lipid-based Formulations 1, 2, and 3.

Time and Cost Savings – the Value Proposition

The benefits of the lipid expert system in terms of time and cost savings are compelling, with development time significantly compressed from drug candidate selection, to dosing validated lead formulation in animals for proof of concept. Although formulation candidates in the output package may require optimization, a full-blown program, from feasibility (5 weeks to evaluate solubility and 1 month stability) to evaluation (solubility, stability, *in vitro* dilution, and digestion) and supply of pilot quantities can be completed in 10-12 weeks.

In addition, lipid-based formulations, whether liquid or semi-solid, can be filled in soft gelatin or liquid hard shell capsules of different sizes to achieve different doses[12] and further accelerate scale-up into clinical and commercial manufacturing. In particular, Licaps® two-piece hard capsules further facilitate streamlined dosage form development, as they can readily be filled and fused into one-piece capsules using Capsugel's advanced *Fusion* capsule sealing technology.

To date, several products have reached the clinic having leveraged the lipid expert system and Capsugel's lipid formulation expertise and may become the commercial successes of tomorrow.



Conclusions

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 increasingly being considered as commercially viable. Initiatives such as the LFCS Consortium continue to establish the means to select formulation types based on compound properties, evaluate their *in vitro* performance through universally accepted protocols, and predict their *in vivo* behavior to a reasonable extent. Investments in understanding the role of lipids in formulating novel drug entities continue to enhance the formulator scientist's toolbox.

Having access to expert systems, such as Capsugel's lipid expert system, to support and accelerate lipid-based formulation development enhances the technology's commercial viability. This system provides an unparalleled means of effectively managing resources and critically shortening times to animal and clinical dosing and, thus, the market and patients in need. Furthermore, incorporating Quality by Design early on in the process can support regulatory filings, while also strengthening intellectual property through a tailored formulation based on the lipid expert system approach.

References

1. Kawabata et al., *Int J Pharm* 2011, 11, 420, 1
2. Brouwers et al., *J Pharm Sci* 2009, 98, 2549-2572
3. Mueller et al., *Pharm Res* 1994, 11, 151-154, 301-304
4. Mueller et al., *Transp Proc* 1998, 30, 1694-1696
5. Porter et al., *Nature Reviews* 2007, 6, 231-248
6. Yamagata et al., *Drug Met Disp* 07, 35, 1142-1148
7. Bravo et al., *Biopharm Drug Disp* 04, 25, 37-49
8. Benameur, *Gattefossé Bulletin Technique* 2006, 99, 63-75
9. Pouton et al., *Eur J Pharm Sci* 2006, 29, 278-287
10. Williams et al., *J Pharm Sci* 2012, 101, 3360-3380
11. Bulletin Technique Gattefossé 88, 1995, 22-26
12. Cole et al., ADDR 2008, 60, 747-756

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