Leading the Way with Lipids

The Formulation Complex

Unravelling the challenges and trends in formulation best practice – and why lipids and softgels are leading the way.

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Formulation Best Practice

Sitting Down With

Foreword

Complexity and Collaboration

Formulation continues to challenge the industry, but collaboration and new technologies can tackle the issues head on

Today's patients and payers are demanding – they want the most effective medicines, in a convenient format, at a cost effective price, and there is huge pressure on pharma companies and formulators to get it right. On one hand, there is much criticism of the drug industry, but on the other there is also much confidence that the industry and its scientists have the ability to deliver. And why shouldn't they? There are more drug development technologies than ever before to help with the task, including sophisticated modelling techniques to help with the selection process, and an ever-expanding number of contract development and manufacturing organizations (CDMOs) and other experts dedicated to formulation and drug delivery.

Solubility, bioavailability and permeability, however, continue to pose significant obstacles in development. Many formulators reading this will no doubt have come across a molecule at some point in their career that was impossible to get absorbed into the human body in the right amounts. The simple truth is that development is difficult – every molecule is unique and there is no one-size-fits-all formulation panacea that will produce an optimal drug every time.

Ironically, formulators are victims of their own achievements – with more approaches to tackle previously unviable drugs, and many success stories, companies are more confident that solubility and other issues can be overcome with clever thinking, meaning that more and more challenging molecules are filling development pipelines. Formulation is also challenging from a time and cost perspective. In all sectors of the industry, people are being asked to do more with less, and the temptation for a scientist to quickly look to a previously successful formulation technology he or she has used in the past, rather than evaluating all available options in the toolbox, is high. One approach that can be overlooked are lipid-based drug delivery systems (LBDDS), which can be tricky to get right but are highly effective at solubilizing hydrophobic compounds. LBDDS are already influencing commercial success stories and are expected to be a prominent tool in the future, particularly given their potential to assist with the oral delivery of biopharmaceuticals.

The complex task of formulation does not need to be tackled by just one person or one team; collaborating with research organizations, other companies, CDMOs and suppliers makes sense. This supplement embodies the spirit of collaboration – jointly sponsored by BASF and Catalent, who collaborate to develop high-quality formulation options. In the following pages, experts discuss the challenges facing formulators today, the importance of excipients, and best practice tips for formulation with LBDDS.

Stephanie Sutton
Editor

Stephanie Sutton

Leading the Way with Lipids

Developing new drugs to treat and cure patients is what pharma does. But this task has become significantly more difficult with discovery pipelines pumping out increasing proportions of drugs with bioavailability or solubility issues. How is this changing the field of oral drug delivery? And what are the solutions?

Featuring Derek Bush (Catalent Pharma Solutions) and Frank Romanski (BASF).

Any technology field is subject to continual change – and oral drug delivery is no different. A 2012 analysis showed that in the year 2000, less than one drug was approved per billion US dollars of R&D spending (1). In addition to rising drug development costs, the so-called "patent cliff" of ~2000 led to increased generic competition and lower prices that forced the pharma industry to adopt cost-containment measures and smarter approaches to drug development and manufacture. To this day, cost pressures remain with drug prices constantly in the spotlight. In addition, patients are ever-demanding more effective and patient-centric medicines.

One response to industry challenges has been the "virtual model" where different aspects of drug development are outsourced to specialty companies, instead of a single company handling the complete drug development process. Increasing numbers of academic spin-offs and small specialty biotechs and pharma companies are entering the field – and although they may have innovative ideas and approaches, they often don't have the requisite formulation expertise. And the right formulation approach for a given drug is essential to help make it a commercial success. "Rather than getting very well-characterized APIs from large pharma, we are seeing more and more discovery-type compounds," explains Derek Bush, Manager, Product Development, at Catalent Pharma Solutions.

Bush has seen a marked increase in the number of projects requiring early stage in-vitro screening, with, for example, the aim of establishing in-vitro in-vivo correlation values to guide Phase I clinical studies. These small "discovery" companies are often significantly resource-limited and may have a lot riding on one drug candidate. As such, formulators are under great pressure to ensure that preclinical studies (in-silico and in-vitro screens, and pharmacokinetics work in animals) produce data that will reflect API performance in humans. "These companies can't afford to repeat their first-in-human trials due to poor formulation," says Bush. "Their next funding round – and their survival as a company – may depend on getting it right first time."

Access to top-flight formulation expertise for early stage drugs is essential, but the problems faced in early development are becoming more challenging. "Drug discovery programs are generating increasing proportions of complex APIs that fall into Class II-IV (poorly water-soluble and/or poorly permeable) of the Biopharmaceutics Classification System (BCS). Some of the drugs we have found ourselves working with are less water soluble than sand!" says Frank Romanski, Global Technical Marketing – Pharma Solutions at BASF.

Only a small proportion of molecules in the development pipeline are thought to have both adequate solubility and permeability, and many require sophisticated formulation technology if they are to reach their therapeutic targets in-vivo. The problem of bioavailability is further complicated by practical, patient-related considerations – not least, the linked issues of patient acceptability and regimen compliance. "It is not sufficient to make a compound more soluble if the excipients necessary to do so result in a large 5 g dosage form that then has to be split into many smaller tablets or capsules," says Romanski. "Increasingly, formulators are being required to turn highly lipophilic or highly crystalline early-phase APIs into drug products that are both bioavailable and reasonably convenient to administer."

Technology takes the strain

Problems with solubility, permeability and bioavailability have plagued the industry for decades, but the industry is not standing still. Romanski explains that he has seen formulation technology evolve from its simplest form – in which an API is mixed with standard powdered excipients and pressed into a tablet – into the more advanced methods favored by industry today, such as lipid-based drug delivery systems, hot melt extrusion and spray drying. "There is now a range of options available to formulators, depending on where the drug falls on the spectrum of physicochemical properties," says Romanski. "Liquid oral dosage forms, in particular, have become increasingly exciting, with technology moving on from simply solubilizing a dug in soybean oil and encapsulating it

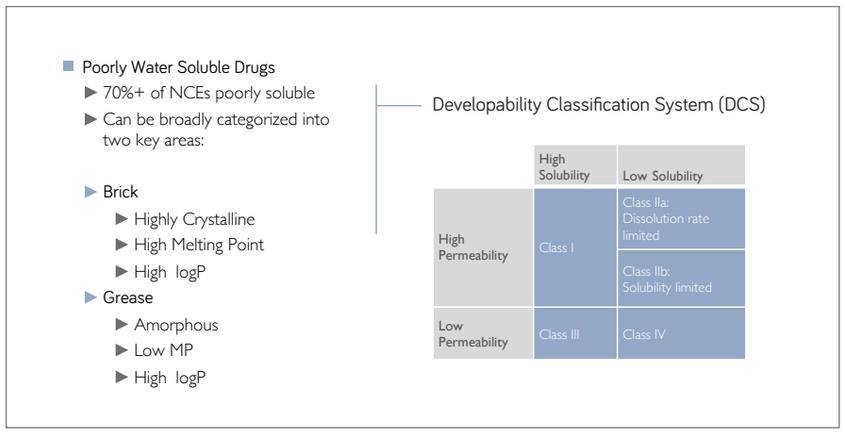

Figure 1: The solubility and bioavailability challenges. Future NCEs continue to exhibit poor water solubility. © BASF

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Article
From Brick Dust to Blockbuster?

Sustainable Formulations?

- In many sectors, consumer choice is putting increasing pressure on manufacturers to find sustainable solutions for products and processes.
- In the pharma sector, consumer choice historically has been strictly limited with the patient getting what the physician prescribes, but patients are also becoming more interested in their medicines and their ingredients.
- According to Frank Romanski from BASF, a number of pharmaceutical companies now wish to take sustainable sourcing into account for both over-the-counter and prescription medicines.
- Sustainability is particularly relevant to lipid formulations, since their principal ingredients are derived from natural sources in South East Asia: coconut oil and palm kernel oil.
- The future could see manufacturers under increasing pressure to buy raw lipid ingredients from certified, sustainable sources.

in soft gelatin. Now, we have access to complex, self-emulsifying, as well as digestible, systems that incorporate several interacting excipients." These types of sophisticated chemistry serve to not only physically stabilize the drug (when formulated as a self-emulsifying drug delivery system) while it is on the shelf, but also when it is released into the aqueous milieu of the gastrointestinal tract after rupture and dissolution of the capsule. Indeed, ensuring that the drug remains solubilized in the GI tract in a form optimized for efficient uptake, such as a population of nano-droplets, is a critical aspect of formulation.

Bush has also observed critical advances in formulation technology and highlights recent developments in modelling and screening technology. "In-silico models that can predict the BCS class of an API (i.e., if it will be solubility-limited or perhaps permeability limited) are incredibly useful," he says. "The virtual screening route has obvious advantages where time or physical materials are limiting, as is the case for many venture-funded discovery companies. We are also seeing tremendous advances with in-vitro technology. Real-time data analysis, real-time particle size analysis, real-time dissolution testing through fiber optic analysis, lipolysis testing to assess how lipid-based formulations are digested… all of these techniques not only speed up early phase development, but provide information critical for early phase clinical study design."

And technology is not the only driver helping to advance the formulation field; Romanski says that excipients also have an important role to play. "Excipients are no longer passive carriers or so-called 'inactive ingredients'. Many in the industry now recognize that excipients have an absolutely fundamental role. In terms of the final product, the excipient may be as important as the API, especially for BCS Class 2 or class 4. For poorly soluble and poorly permeable products, you must rely on excipients to make a functional product. Not only do these ingredients directly interact with the API to ensure bioavailability, but one must also consider how they interact with each other so as to maintain a highly complex dosage form over time."

Bush agrees, adding, "Our experience is that, without correct attention to excipients, drugs coming out of solution are often more 'difficult' than when they were first formulated – perhaps less soluble, for example. It is imperative to ensure that your excipients stabilize the API as the more soluble crystal or amorphous form, not the most stable crystal." These type of polymorphism challenges can usually only be addressed by applying advanced excipient expertise to ensure that the API is stabilized in the amorphous form or in the precise crystalline form of interest.

More advanced excipients can also confer a range of properties on the drug above and beyond solubilization, including product controlled release properties such as sustained, enteric, or delayed release. This could be particularly useful for acid-labile APIs, where drug release must be targeted to a specific region of the GI tract so that the API can avoid destabilizing pH levels. Finally, where the effects of first-pass metabolism are a consideration, well-designed formulations can potentially direct the drug to the lymphatic uptake, thus avoiding liver enzymes.

Lipid formulations

A number of different technologies exist to help with formulation challenges, but according to Romanski and Bush, lipid based drug delivery systems (LBDDS) are one of the most commercially successful drug development technologies in the industry – and have helped bring more than 50 poorly soluble new chemical entities

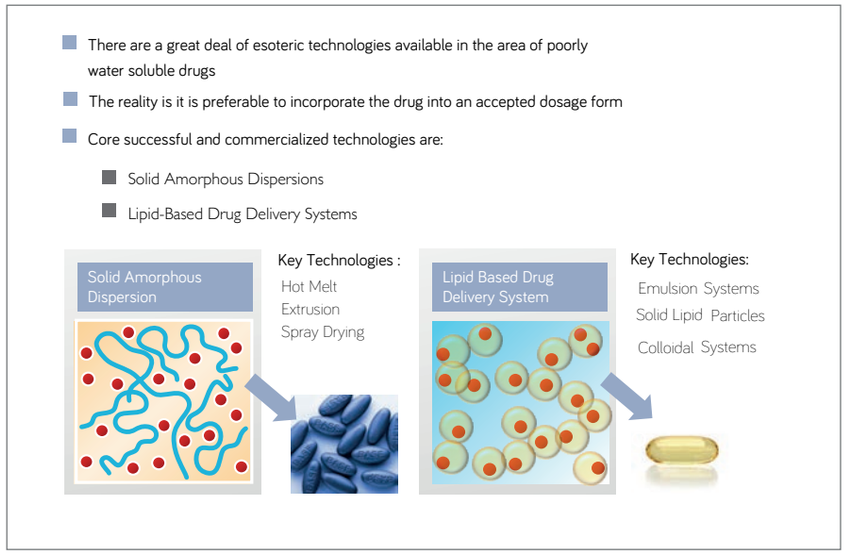

Figure 2: Successful techniques for poorly water soluble drugs. Despite the multitude of technologies available, traditions remain. © BASF

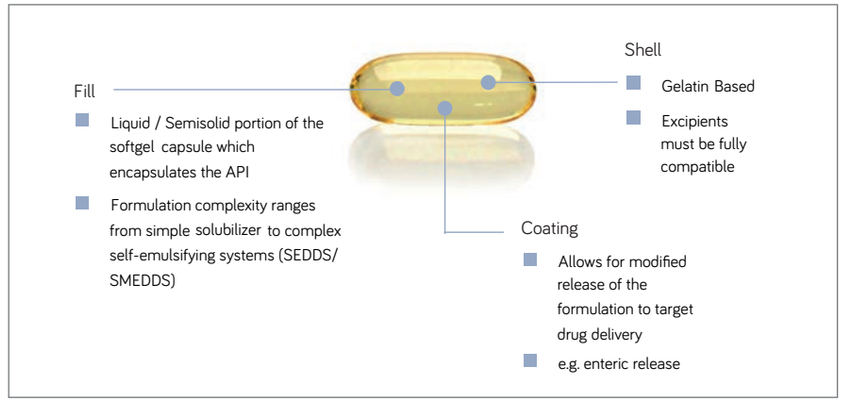

Figure 3: Softgel capsules are well matched as an oral drug delivery vehicle for lipid systems. © BASF

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to the market. Lipid-based formulations have an outstanding ability to solubilize hydrophobic compounds and also offer the possibility of protection for unstable compounds. "Lipids also avoid first-pass metabolism in certain cases and are one of the only ways to target lymphatic uptake," says Bush.

Although they offer many advantages, LBDDS also pose many challenges – for the simple reason that they are tricky to get right. "Lipid-based formulations require a lot of expertise and upfront work – and you need knowledge of both formulation and functional excipients," admits Romanski. "One of the main issues is the variability of lipid excipients. The lipids used in drug formulations are generally derived from natural ingredients, such as palm kernel oil or coconut oil (see sidebar, Sustainable Formulations?), and this is partly why lipid excipients are so well-tolerated – they are, in effect, part of the body's natural diet. As a consequence, however, the excipients used as raw materials in lipid formulations are inherently variable."

While traditional polymer excipients are usually made to 99 or 99.9 percent purity, the monographs for lipids are notably less specific. The end result is that a given lipid, while remaining within specification, can vary widely according to the manufacturing source, which is why getting lipid formulations to behave predictably in the body requires specific know-how and expertise.

There are a variety of ways in which lipids can be used. At one end of the spectrum, an API may be simply dissolved in a lipid medium such as a long-chain triglyceride oil. The next level of complexity involves the addition of more polar lipids and/or lipophilic surfactants to promote solubilization of the drug inside the capsule and/or its emulsification once released from the capsule into the GI tract. More complex formulations still may be constructed by adding hydrophilic surfactants to this mixture. "Such mixtures promote API solubility in the aqueous environment of the GI tract, thus preventing recrystallization once the capsule is ruptured or disintegrated," says Romanski. "In addition, they can self-emulsify in the body to form tiny droplets for maximum absorption." However, it is important to ensure that the drug doesn't crash out when exposed to the GI tract.

Bush adds that the mixture of lipids in the LBDDS are digested in the body to liberate free fatty acids, or other components of the excipients such as PEG – and these breakdown products themselves can further support product functionality.

According to Bush, the overwhelming majority of LBDDS are presented as softgel or hard gel capsules, which meet industry requirements in terms of commercial scale-up and shelf-life. "In particular, LBDDS pairs very well with softgel technologies," he explains. "A softgel capsule lends itself to advanced functionalization; for example, more complex LBDDS or different film coatings can be applied to give the capsule targeted release capabilities, such that it only dissolves and releases the API in a given region of the GI tract."

"Using a capsule also avoids the need to add taste-masking ingredients, which would unnecessarily complicate the formulation process," adds Romanski. "The softgel capsule is a perfect medium for the oral delivery of a liquid formulation because it protects the API, does not compromise the performance of the fill, permits controlled and targeted delivery, is convenient to manufacture, and is widely acceptable to patients. Combine these advantages with those inherent in LBDDS – solubilization, stabilization, avoidance of first-pass effects – and you have a platform applicable to many 'difficult' APIs."

Back to the future?

What does the next decade hold for oral drug delivery in general and lipid-based formulation in particular? Bush reiterates the evolutionary forces acting on the sector. "The lipid backbones have been in use for many years in the industry, but their functionality and our understanding of how they can be used has changed – and continues to evolve. As the technology becomes more sophisticated, the aims of formulators become correspondingly more ambitious. It is no longer enough just to solubilize a difficult drug in the formulation and keep the drug in solution in-vivo; now the object is to support patient compliance by ensuring the requisite dose is delivered in a convenient number of units. After all, who wants to take six or more tablets, three times a day?"

Bush also adds that the oral delivery of macromolecules using LBDDS is a growing area. Oral formulation of peptides and proteins is well known to be difficult, but it is not impossible. "Increasingly, the industry is moving to embrace the challenges and I think we will see increasing number of oral biologics in the next five to ten years," he says.

Romanski also agrees that the oral delivery of peptides and proteins will be a hot topic in the coming years. "It would be wonderful to put the new biologics into a solid oral dosage form, and scientific expertise and knowledge is building in this area," he says. "But I also think that we shouldn't forget about old drugs. Advances in excipient technology open up the possibility of re-formulating old drugs, previously discarded due to bioavailability issues – perhaps it is a case of back to the future. Clearly, we are nowhere near exhausting the potential applications of LBDDS formulation and exciting times lie ahead for the field!"

Softgel Advantages

- Softgel manufacturing can be scaled up to commercial supplies.
- Scale up is relatively straightforward compared with other dosage form manufacturing.
- The softgel has minimal to no interaction with the encapsulated fill.
- The dissolution and biopharmaceutical performance of the fill is not compromised when encapsulated within a softgel.

Reference

1. JW Scannell et al., Nat. Rev. Drug Discovery, 11, 191-200 (2012).

LINKS

Article
Lipid-Based Drug Delivery System to Bring Poorly Soluble Drugs to Market

Website
Functional solutions for all softgel parts – fill, shell and coating.

Formulation Best Practice

Are you in need of know-how about formulation best practices? In this technical roundtable, industry gurus Frank Romanski, Derek Bush and Kishor Wasan share their views and tips for success.

How should we approach the formulation of a poorly bioavailable API?

Wasan Kishor: It is important to remember that there is no magic bullet – no one excipient that can fix all bioavailability problems. You need to take a case-by-case approach and follow an iterative process. First, define the precise problem you are dealing with – is it a solubility issue, or a gut metabolism issue, or a release kinetics issue? Then assess the physical chemical properties of the API in question – are they compatible with an LBDDS? If so, you can proceed to the next step: identifying lipids that could both overcome the identified barrier to drug efficacy and be compatible with your API.

Derek Bush: First, establish whether the bioavailability issue is related primarily to solubility or permeability – or both. If you don't have those data, you need to conduct in-silico and in-vitro screening tests to establish if the API is Developability Classification System (DCS) Class II or Class IV. For Class II compounds, the next step is to identify the key factor that limits solubility – i.e., Class IIa (dissolution rate limited absorption), or Class IIb (solubility limited absorption). Addressing a Class IIa issue is relatively straightforward; micronization, milling or nano-milling technologies may help, as may lipid-based formulation approaches. Options for Class IIb compounds are more complex, and while it may be possible to improve solubility through covalent modification of the API, creating salts, or isolating polymorphs, the classic route for these high logP compounds remains lipid-based formulation. DCS Class IV, however, is the most challenging category; in addition to all the Class IIb hurdles, you have a permeability problem – the basis of which is often much more significant than simply first order absorption kinetics. Causes of low permeability include gut metabolism, P-glycoprotein (P-gp) efflux, and protein-API interactions in the gut. Significant experimentation may be required to clearly define the basis of low bioavailability, but a clear understanding of the problem you face is essential to guide formulation decisions. Excipient choice may vary according to whether you need to stabilize the API, or stimulate lymphatic transport, or inhibit PGP, prevent drug metabolism in the gut, or control the drug release profile so as to protect the API from gastric acid. You won't know which route to take until you understand the permeability constraints. That said, remember that the required dose will have a significant impact on your strategy, and that this may change during the development process – a Class IIb molecule can easily be shifted into Class IIa, or even Class I, by reducing the target dose. For example, as you improve API permeability you may find that the required dose is reduced. Consequently, the formulation may become more of a Class I than a Class IIb issue.

Frank Romanski: Most pharmaceutical companies want their drugs formulated as an oral dosage form, either a tablet or capsule, and they want the formulation available to achieve good oral bioavailability (>90 percent). For low bioavailability compounds, the most successful commercial approaches include preparation of a solid amorphous dispersion through hot melt extrusion or spray drying (techniques in which API is dissolved in a polymer matrix prior to forming a solid tablet), and lipid-based formulations primarily encapsulated in softgels. These newer amorphous dispersion techniques can be highly effective for the right APIs. For example, many years ago, as a student, I was working on the industry standard model poorly water-soluble drugs, fenofibrate and griseofulvin. We developed complicated nanosuspension formulations comprising countless different ingredients with multi-stage production schemes. When I moved to BASF, it took only a fortnight to adequately solubilize those same drugs – and at ten-fold higher concentrations than we had previously been able to achieve! Formerly novel techniques, such as solid amorphous dispersions and complex lipid systems (e.g. self-emulsifying drug delivery systems – SEDDS and SMEDDS) are becoming more and more mainstream solutions, and work well with existing oral dose technologies. Yet, the challenge remains that these complex systems rely heavily on functional excipients, and these difficult to understand API-excipient and excipient-excipient interactions are what drive these new techniques to higher levels of success than previously attainable.

How do you choose from the range of excipients that might be suitable for a given API?

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Website
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KW: Once you have defined the barrier for your drug in terms of its efficacy/toxicity ratio, you can start thinking about the most appropriate excipients. If the API is crystallizing out in the GI tract then a lipid formulation may provide an answer. Similarly, incorporating API into a lipid may help protect acid-labile drugs until they reach the more benign environment of the small intestine. So, first understand the problem you are facing, then assess the physicochemical properties of your drug – and only then start making decisions about excipients.

DB: Unless you are pursuing a suspension formulation approach (largely limited to compounds that are at least moderately soluble in biological media), the first goal is almost always to dissolve your drug and keep it dissolved. Therefore, you should undertake a solubility screen with broad classes of excipients to identify those that give maximum API solubility. If the outcome of that study is that you can only achieve very poor solubility levels relative to the required dose, you may have to consider API modification, or assess the potential of suspension formulation. The latter, however, is not suitable for compounds of low aqueous solubility and low permeability, especially where the dose requirement is high. Once you have an API of sufficient solubility, you may need a second tier solubility screen to assess excipient compatibility. In this step, you take the subset of excipients that gave the best solubility in the first screen, and test API stability with these excipient candidates under accelerated conditions. These two solubility screening studies are key in determining your formulation pathway.

FR: From an excipient supplier perspective, quality is very important, including assurance that the material was produced in accordance with appropriate pharmaceutical monographs, such as the USP, Ph. Eur. and JP/JPE, and produced under IPEC GMP quality standards. Apart from anything else, this allows for proper change control process, including identification and communication of raw material changes, which could impact product quality. This is especially important for lipids because of their broad specifications – changes in the lipid raw material supply chain and/or subsequent synthesis, purification and stability can impact the final characteristics of the product, yet still be within comparatively broad product specifications. It is important to ensure that an excipient supplier is committed to the quality standards of the pharmaceutical industry, as drug manufacturers need critical information – and as early as possible.

What is it about lipids that makes them a compelling formulation option?

KW: Lipid excipients are special in that the body does not see them as foreign products. Other excipients may trigger non-specific effects, but triglycerides and their breakdown products are part of the normal physiological environment and, hence, not associated with allergic reactions or other effects – one less thing that you have to worry about! Another differentiator is the amount of options they give you – the lipid category is very broad, so you have many variants to choose from, and many different possibilities in terms of molecular weight, melting point, and so on.

DB: The great advantage of LBDDS is that, being a natural dietary component, they are trafficked by natural systems. Thus, in a LBDDS, drugs are piggybacked across the GI tract in a natural metabolic process. In this way, they not only enhance absorption and permeation, but also provide an excellent safety profile.

FR: Lipids have distinct advantages in their applicability to hydrophobic, high logP molecules. They also demand uniquely sophisticated expertise. For example, lipid formulations tend to be non-equilibrium systems; accordingly, changes in ambient moisture or temperature may affect formulation thermodynamics and ultimately lead to stability problems. This specific challenge with lipid formulations makes it very difficult to predict their behavior over time, so you need significant experience to manage this issue.

Are the advantages of lipids well-understood, or do misconceptions remain in the industry?

KW: The industry has a better appreciation of LBDDS than they once did, but they still have a way to go. The lipid-based focus group at AAPS, which started about 20 years ago, has helped to educate the pharmaceutical community on the use of lipids. Furthermore, many papers are now available for the naive formulator who is considering lipids as a potential option. We ourselves recently published a paper showing examples of lipid-formulated FDA-approved products (1).

DB: People are aware of the advantages of LBDDS in terms of increasing the bioavailability of compounds with poor aqueous solubility. Less broadly appreciated are the complexities of lipid

Experts

Frank Romanski is Global Technical Marketing – Pharma Solutions, at BASF, Germany.

Kishor Wasan is Dean of the College of Pharmacy and Nutrition, University of Saskatchewan, Canada.

Derek Bush is Manager, Product Development, at Catalent Pharma Solutions, USA.

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Article
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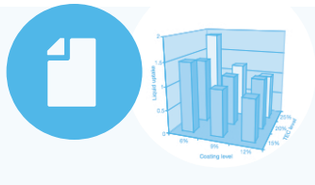

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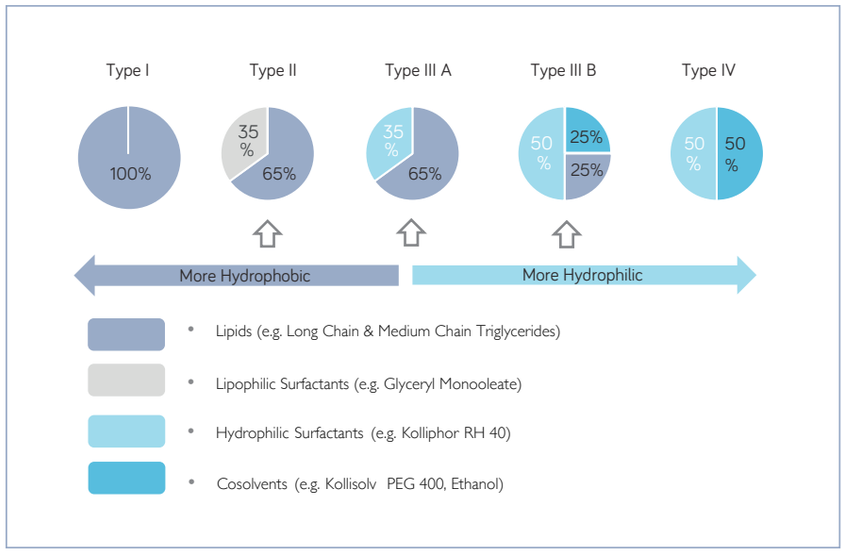


Figure 1: The lipid formulation calssification system. Complex multi-phase formulations are typically in Type II and III A/B. © BASF. *Pouton et al., LFCS Consortium*

formulation – it's not as straightforward as dissolving API in triglyceride and surrounding it with a softgel capsule. In particular, lipid raw materials are mixtures of multiple components and can be very variable in the ratios of the components depending on the source. We've actually seen cases of the exact same medium chain triglyceride, sourced from two different suppliers, giving different in-vivo clinical results depending on its manufacturer. It turned out that the fatty acid composition and breakdown products of these two products were different, even though they were supposed to be the same medium chain triglyceride – and met the corresponding USP requirements for being defined as such. More generally, in a given medium train chain triglyceride, the ratios of different fatty acids (for example, C6, C8, C10 and C12) can differ substantially; for instance, C6 and C12 vary by 20 to 30 percent from one supplier to another. Because of this, formulators need to emphasize the quality by design (QbD) approach – what are your critical material attributes, and how do they influence your critical quality attributes? Understanding the variability of your formulation materials, therefore, is a key part of lipid-based drug development. It not only affects aspects such as stability at certain processing temperatures, but also can influence product behavior in the human body, e.g., in terms of susceptibility to digestion. Another point that may be insufficiently recognized is that lipid excipients are dynamic – they change as they progress through your body, and without careful handling they will also change during the manufacturing process. Oxygen exposure, light exposure, and heat exposure can all affect lipid excipients in some way.

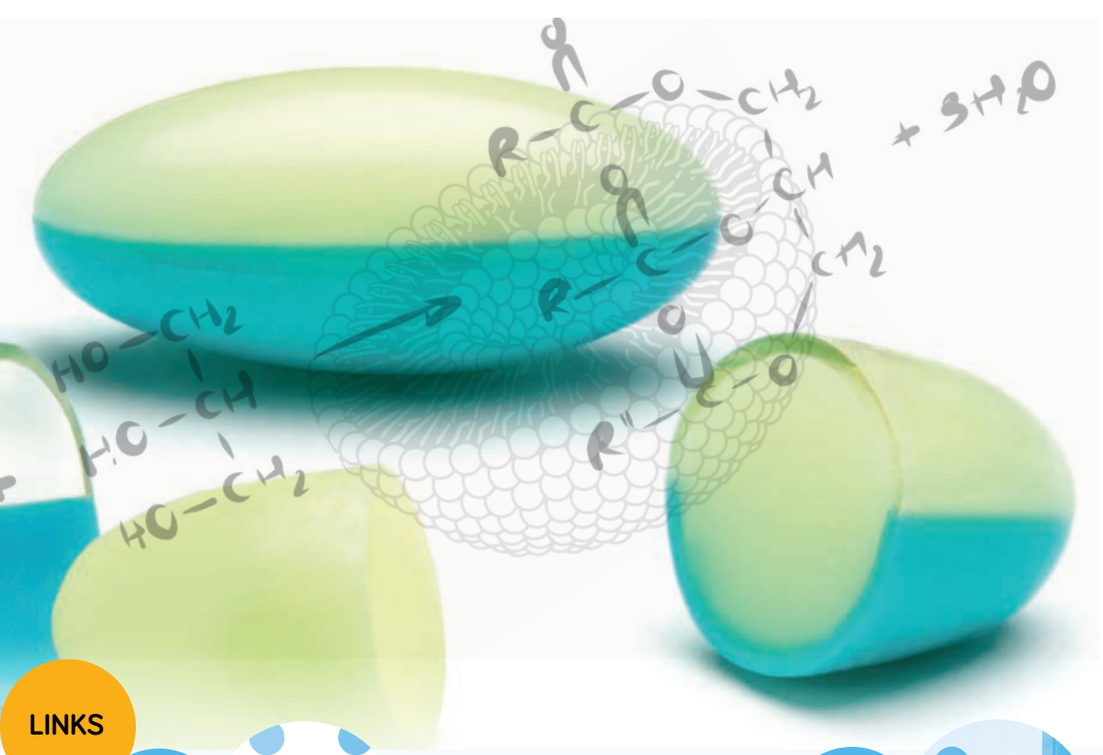
FR: People do not always appreciate the sophistication of lipid formulations. As lipidic formulations have evolved to multi-component, complex systems, formulators rely on the same "magic bullet" excipients, such as a single surfactant as the only excipient. Unfortunately, this is a fundamentally ineffective approach. For example, in more complex formulations such as self-emulsifying systems (e.g. SEDDS, SMEDDS), a formulator may now need multiple ingredients with specific functionality, including, but not limited to: primary emulsifier, secondary emulsifier, crystallization inhibitor, co-solvent, and so forth.

One particular area which needs significant improvement is the basic concept of HLB, also known as the hydrophilic-lipophilic balance. The idea, which has been around since 1949, is that the HLB number assigned to a given lipid system suggests that a single surfactant with this magic HLB value should ideally stabilize the system. However, in practice, while surfactants may have similar HLB values, they may also have vastly different chemistries, conformations, geometries, and capacities to interact with other molecules; and so, the idealized magic number is of little value. Strict reliance on the HLB number is perhaps one of the common misconceptions I see frequently with formulators of lipid formulations, regardless of application. Consequently, my advice is this: understand that the HLB value is a starting point only, and that ultimately other characteristics, such as excipient structures, chemistries and interactions, must be considered.

What advice would you give to those embarking on a lipid formulation project?

KW: A common mistake is failing to do the necessary homework. I would strongly advise formulators to assess the physicochemical properties of the API to confirm the applicability of the lipid-based formulation route. Failing to appreciate that not all compounds are appropriate for lipid excipients – and expecting the addition of a lipid to be like waving a magic wand – is a common error. It is also unnecessary because the key criteria for particular formulation objectives are reasonably well-known. For example, if first-pass metabolism is a problem, you may want to improve drug bioavailability by routing drug uptake via lymphatic transport, such that the drug is absorbed via the mesenteric lymph duct rather than the liver portal vein. If so, you should check your compound against known criteria for lymphatic uptake: does your API have a molecular weight of less than 500? Does it have a logP greater then 5? Does it have a triglyceride solubility value of 50 mg/ml or more? And does it partition into very low density lipoproteins? If so, you have a good chance of improving bioavailability via lymphatic transport, but not every drug candidate fits this profile. So make sure you understand the constraints of your system before making formulation decisions.

DB: Invest in upfront investigation to fully understand your excipients. If necessary, carry out tests to assess the effects of oxygen, light and temperature on the excipient itself, not just on the API; in many cases, product instability is a consequence of degradation of lipid excipients rather than due to true API instability. Fortunately, instability of lipid excipients can usually be addressed by the addition of an antioxidant. In fact, API stabilization is a secondary consequence of antioxidant addition, as the primary function of antioxidants is to



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stabilize excipients under the specific processing conditions required to solubilize and deliver the API. So those working with lipid-based excipients should focus on fully understanding them, with particular regard to their stability requirements – it's a key formulation point.

FR: Decide as early as possible what kind of solubility or bioavailability problem you are facing and what your formulation options are for dealing with it, and then choose the right partner to work with so as to devise the simplest possible formulation system. Above all, remember that there's no "one size fits all" approach.

What challenges and mistakes are commonly seen when making lipid-based formulations?

DB: People sometimes forget about the need to understand how lipid-based excipients behave after dispersion in intestinal fluid. What happens to your formulation in an aqueous environment in the presence of pancreatic enzymes – how is it digested? You need to know what kind of changes in API solubility you would expect in that environment. The solubility may not change, but equally it could go up or down (and in some cases, it can go down quite dramatically). Studies on solubilization kinetics during and after lipid digestion are very important, but are easily missed in the development process. It's not a difficult step, but sometimes it is overlooked.

FR: : A big challenge that is often under-appreciated relates to the dynamic nature of LBDDS. As noted earlier, these systems, particularly when encapsulated, are subject also to environmental fluxuations. In a softgel form, for example, water may pass between the gelatin capsule shell and the formulation it encloses (such movement is driven also by temperature changes). Oxygen and other components (e.g. plasticizer) may also move similarly. These fluxes may shift the thermodynamics of the system and thus must carefully be taken into account in order to ensure long term stability of a lipid formulation. Predicting how these formulations will behave over the long term is therefore very challenging. And again, the most common error of all is to assume that the HLB number will magically identify a surfactant that solves all your formulation problems. The HLB value cannot apply equally to all surfactants – it's no more than a rule of thumb.

When should companies start planning the final dosage form?

DB: The earlier they start to think about permeability and solubility, the better! I've noticed a consistent bias among API manufacturers – they always seek to maximize the aqueous solubility of the drug. As a consequence, they usually synthesize a very specific salt form that is soluble in an aqueous environment, but not in lipids. So, should you later find that you need a lipid-based formulation to enhance solubility or bioavailability, you have a problem, because it's very difficult to formulate a lipophilic form of that hydrophilic salt. If you instead formulate the API as a free base (assuming it has an amine group) at the start of your development process then it is far easier to make a lipid-based formulation. This is why I usually advise our customers to make the free base form of the compound, rather than the salt form.

FR: You should always make strategically important decisions as soon as you can. Whether you go for a lipid formulation, a spray-dried formulation, or a hot melt extrusion formulation, you need fast decisions if you want to be fast to market. And it is possible to make these decisions quickly – the characteristics of the API are known very early in the process, and will indicate the most appropriate dosage form – hence, guiding decisions on excipients that will favorably interact with the API to allow maximum stability, solubility and bioavailability.

Any final advice?

KW: Take the time to do the background work to fully understand your drug and the nature of the problem you need to overcome. You won't regret it.

DB: Begin with the end in mind. Clearly defined goals and objectives will help you to produce a development plan, which is very important. A key part of the exercise is to understand from a regulatory standpoint where you are going to end up, even if that is 10 years away. It can be disastrous to get 80 percent of the way through a development program and then realize you have to repeat some work or do an additional trial; it's always better to spend more time up front. From the very beginning, you should be matching critical attributes with the critical goals that you need to achieve. This may require you to seek expert advice at an early stage so that you understand the regulatory environment and the type of filing strategy you should undertake for your particular compound. In brief: know where you want to end up and work backwards from there!

FR: Don't ignore excipient suppliers. We have significant know-how regarding lipid formulation, manufacture and stability, and can guide companies through the many issues arising from the broad specifications associated with lipid and other solution enabling ingredients.

Reference

1. *R Savla et al., "Review and analysis of FDA-approved drugs using lipid-based formulations", Drug Dev Ind Pharm, 6, 1-16 (2017). PMID: 28673096*

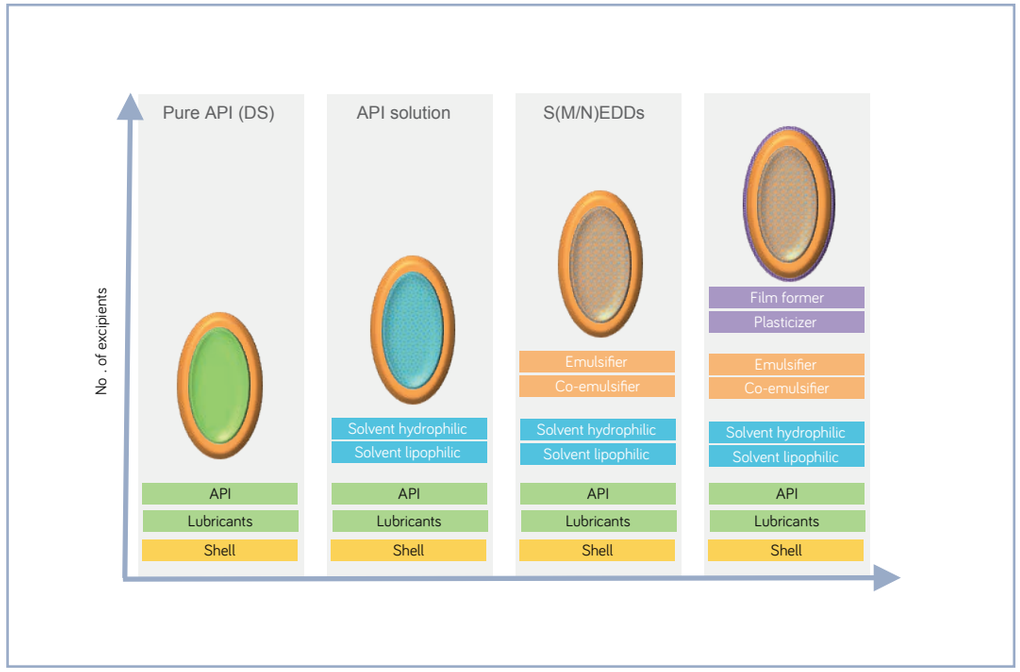

Figure 2: Softgel excipients. As complexity of LBDDS increases, so too does the excipient need. © BASF

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Article
Lipid-Based Drug Delivery System to Bring Poorly Soluble Drugs to Market

Case Studies and Collaboration

Derek Bush: Development of in-vitro screening methodology to guide clinical studies

A recent project required us at Catalent to generate in-vitro in-vivo correlation values for a Phase I clinical-stage molecule with high logP and low aqueous solubility. We started with a classical dissolution approach, in which we put the dosage form into an aqueous medium and analyzed samples at 15 minute time points. The data showed a linear increase over time, and on this basis we made decisions about the formulation for the in-vivo work.The subsequent animal pharmacokinetics data, however, showed hardly any correlation at all with our in-vitro results clearly, we had a problem. We began testing alternative methodologies, in particular fibre optic dissolution testing. This technique allows very frequent measurements of API concentration (every 2 or 3 seconds, if necessary) and it revealed a huge supersaturation parachute effect occurring in the first 15 minutes. During this time, the concentration rapidly spiked to a level much higher than the theoretical equilibrium solubility. It stayed high over most of this period, but came down by the time we would take our first sample in the classical dissolution testing approach – which is why we'd been missing the big spike. For a DCS Class 2 compound, which is purely solubility-limited, not permeability-limited, this was a very important finding. In fact, it fundamentally changed the way we designed the formulation and excipients for that API. This study was a key learning point for us, and made us rethink our in-vitro screening methodologies to ensure that we always made the best decisions possible for the molecule and for the product.

Kishor Wasan: Collaborative venture involving manufacturer, biotech and academic group

We have been working with iCo Therapeutics and Gattefosse on an oral formulation of amphotericin B (an anti-fungal agent): Gattefosse provides the lipids, we provide lipid expertise, and ICO Therapeutics undertakes formulation and Phase I clinical development. This is a fantastic example of a collaboration between an academic group, an excipient supplier and a biotech company, all contributing different resources and skills, and all working together towards a common goal. So far, pre-clinical studies confirm the ability to deliver amphotericin B orally and in high enough tissue concentrations to elicit biological activity without significant toxicity. iCo is due to start dosing human subjects in a Phase I study in Q4 2017.

Frank Romanski: Phase diagram for microemulsion design

We have done a lot of case study work in the field of microemulsions. These are specific, uniquely rich systems where surfactant and co-surfactant are in equilibrium with both water and oil – not a true emulsion of oil droplets in a continuous water phase, but a bicontinuous phase of oil and water tied together by tremendous amounts of surfactants. Microemulsions are unusual in a number of ways; their droplets are actually smaller than those in nano-emulsions, and unlike normal emulsions, which are cloudy or milky, they are as clear as water. But their critical advantage is that – unlike normal emulsions, which will eventually separate into oil and water phases (formulation only delays this outcome) – microemulsions remain emulsified permanently. The advantages for drug formulation are obvious. Furthermore, not only are microemulsions very stable inside the capsule, but they can be designed to form other structures, such as nano-emulsions, after capsule disintegration. This gives formulators the option of ensuring the API is presented to the gut in a form designed for maximal bioavailability.

The only disadvantage of microemulsions is that they are very challenging to make – you need exactly the right mix of surfactants if you are to produce a perfectly stable system, and it is very difficult to know which oils to pick. For that reason, we undertook a tremendous amount of high-throughput chemistry, assessing different pairings of surfactants and oil phases, from which we mapped out an entire phase diagram. This allows us to quickly and efficiently identify components that will generate thermodynamically stable microemulsions. From that starting point, we can tweak the system to achieve the required characteristics; for example in terms of drug release profiles.

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Webinar
Innovative Drug Delivery Technologies For Better Patient Treatments

Special report by the Medicine Maker

Formulating the Future

A Spotlight Interview with... Kishor Wasan, Dean of the College of Pharmacy and Nutrition, University of Saskatchewan, Canada.

What made you choose a career in science?

I come from a family of academics – my mother was a physician, my father was a professor at Queen's University in Ontario, and my uncle was a professor at the Illinois Institute of Technology – so perhaps it was inevitable! When I was a kid I used to hang out in their labs asking questions about why and how things happened. My dad told me I should be a scientist because I was so inquisitive, and I was certainly passionate about science fairs when I was in high school. I used to work in labs as a summer student, both at high school and when I was an undergraduate. So going into science was more the result of a gradual evolution rather than a single seminal moment.

And how did you become interested in drug delivery?

When I worked as a decentralized hospital pharmacist in the mid-eighties, supporting physicians and nurses in the wards, I noticed that many medications, particularly oncology drugs, were inefficient and prone to side effects. That started me thinking about drug delivery, and was a key factor in my decision to go to graduate school in the late eighties. I did my PhD at MD Anderson Cancer Centre, in Houston, with Dr Gabriel Lopez Berenstein, who was a world leader in parenteral lipid-based drug delivery. Specifically, I helped develop a liposomal form of the antifungal drug Amphotericin B. This work resulted in AmbiSome, a product which is still marketed today. After my PhD, I took a post-doctoral position at the Cleveland Clinic in Ohio in 1993; there, I was studying lipids and lipoproteins from a cardiovascular perspective. That's where my own work, focusing on the interactions of drugs with lipoproteins, started to take off. In 1995, I was recruited to the University of British Columbia in Canada, where I spent the better part of 20 years, before moving here to Saskatchewan.

How has lipid technology sustained your interest throughout this time?

The lipid field continually changes – there is still a lot to learn about using lipid functionality to improve drug performance. And it's very broad – there are different types of lipids, different pathways by which they are metabolized, and different functionalities. Even the term "lipid" covers many nuances and subsets. Also, as you get deeper into a specific field, you find that there are more questions than answers, so the longer I worked in lipid technology, the easier it was to stay. As I delved deeper into the subject, I shifted my focus, moving from lipid-based formulations for parenteral drug delivery to lipid-based formulations for oral drug delivery. But that in itself was a 30-year journey!

What key lipid research have you been involved with?

When I started at the University of British Columbia (UBC), I noticed that a lot of drugs, due to their intrinsic physicochemical properties, interacted with plasma lipoproteins, such as HDL and LDL, and these interactions actually influenced drug pharmacokinetics and pharmacology. So for my first 10 to 12 years at UBC, I focused on how lipoproteins affect drug disposition and behavior. This was important because many patients have lipid disturbances secondary to their disease, and these alterations in lipid profile modify drug behavior, resulting in less predictable clinical results compared with animal studies or healthy volunteer trials. I was one of very few people in the world working in this area, but my research resulted in the FDA recognizing the importance of lipoprotein drug interactions, and culminated in a paper (1), which summarized 25 years of lipid and lipoprotein work.

A second notable component of my research again involved Amphotericin B (I guess I'll never get away from that drug!), but this time I developed an oral lipid-based formulation. This project came about through pure serendipity. Inthe late 1990s, an infectious disease doctor asked if I could develop an oral amphotericin formulation because it would be cheaper, more accessible and easier to administer than the parenteral formulation. This was a very ambitious objective, but I thought that it might be worth applying our evolving knowledge of lipid nutrition and digestion to this aim. Long story short, we successfully developed an oral formulation that was efficacious in systemic fungal infections, which in turn caught the eye of individuals at the Gates Foundation. They then approached me about developing an oral Amphotericin B form for the sandfly-vectored parasitic infection leishmaniasis. Amphotericin B was already the drug of choice for leishmaniasis, but wasn't a realistic option for most people in the developing world, due to cost, poor access to hospitals and inadequate stability under the high temperatures and humidities associated with leishmaniasis-endemic regions. We partnered with the Gates Foundation to make a low cost, oral, "tropically-stable" formulation of Amphotericin B. We have now licensed the product to a Vancouver biotech, iCo Therapeutics, which is about to take the product into Phase 1. This project led to the establishment of the Neglected Global Diseases Initiative at UBC, which I started with Bob Hancock back in 2009.

What are you working on at the moment?

In 2014, I became Dean of the College of Pharmacy and Nutrition at the University of Saskatchewan. This is a great opportunity to continue my work on novel lipid formulations, including topical formulations and gel capsule work with partners such as Catalent. That is where I am at present, and getting here has been very rewarding and a lot of fun!

Reference

1. *KM Wasan et al., "Impact of lipoproteins on the biological activity and disposition of hydrophobic drugs: implications for drug discovery", Nat Rev Drug Discov, 7, 84-99 (2008). PMID: 18079757*

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Article

Review And Analysis Of FDA Approved Drugs Using Lipid-Based Formulations