SELECTING OPTIMAL FORMULATION TECHNOLOGY FOR BETTER PATIENT TREATMENT

In this article, with a focus on lipid-based formulations, Stephen Tindal, Director, Scientific Affairs, Catalent Pharma Solutions, provides insights into Catalent's strategies for oral formulation selection which can lower attrition rates, and therefore development costs and time to market.

Drug development is an expensive business. With the average cost of bringing a molecule from idea to marketplace put at more than US$2.6 billion (£2 billion) by the Tufts Center for the Study of Drug Development (Boston, MA, US),[1] innovative strategies that can speed up this journey by reducing product development cycles are much needed.

There are many areas where innovative strategies can be advantageous, but one of the most important is in the drug formulation area. One such strategy is to identify compounds that are likely to present development challenges such as poor solubility or poor permeability, or both, and apply an appropriate bioavailability-enhancing formulation technology early in development. Given the number of these enabling technologies available, it is important that the formulator select a technology during preclinical development that is most likely to provide optimal delivery of the drug in a format that is most likely to result in patient compliance. Catalent's recommended strategy for achieving this is by employing parallel screening of the various enabling technology options while the molecule is still in the preclinical pipeline. By choosing the right option early – and rejecting those that are unlikely to make it through the later stages of development with the ultimate goal of obtaining regulatory approval – the notoriously high attrition rates that are common can often be reduced,[2] and low productivity rates might be increased.[3]

The Biopharmaceutics Classification System (BCS) has proven valuable in providing a system by which compounds can be grouped into one of four classifications based on the compound's dose, solubility, and permeability.[4] Many of the challenges arising in formulation result from the fact that about two-thirds of all small molecules in current development pipelines fall into Class II of the BCS – those that have poor solubility but reasonable permeability. These poorly soluble compounds tend to have poor bioavailability including reduced absorption, variable (nonlinear) pharmacokinetics and, often, significant food effects.

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Selection of a suboptimal formulation approach can result in patient drug exposure outside of the desired therapeutic range, i.e., levels of absorption too low for the therapeutic effect, or too high, with the occurrence of side-effects and associated toxicity implications. The food effect that often accompanies BCS II compounds is particularly pernicious, as drug absorption will vary considerably depending on whether or not the patient's stomach is empty and the nature of what they have eaten. This poses significant patient compliance issues and in many cases safety or toxicity concerns.

The BCS provides minimal insight into formulation strategies that should be considered based upon a drug's classification. It was instead designed as a regulatory aid identifying those compounds (BCS I) that would not require bioequivalence studies based on their dose, solubility and permeability. As such, it is of limited value for formulators,

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especially when it comes to determining the right formulation approach(es) for the problematic Class II compounds. As a result, Butler and Dressman devised an alternative, the "Developability Classification System" (DCS).[5] This provides an additional level of granularity to BCS Class II compounds that are poorly soluble by identifying drugs that are dissolution-rate limited (DCS Class IIa), and those drugs that are solubility-limited (Class IIb). This further differentiation of a drug's poor solubility behaviour (dissolution-rate limited *versus* solubility-limited) is useful in identifying the proper choice of formulation strategy at an early stage of development.

This is important because in recent years a number of solubility-enabling formulation technologies have been employed that permit poorly soluble compounds to be successfully formulated into drug products. These widely used technologies include particle-size reduction, solid amorphous dispersions, and lipid-based formulations. The placement of a compound in DCS IIa or IIb facilitates the proper selection of a formulation strategy based upon the compound's solubility characteristics.[5] While computer-based prediction tools can assist in the selection of a formulation strategy, there remains no substitute for preformulation studies in the lab followed by the development of prototype formulations incorporating proposed formulation approaches, and their subsequent PK testing in animals and humans. The parallel screening of multiple formulation approaches during the preclinical stages of development (or, at the latest, in the early stages of clinical development), increases the probability of achieving acceptable efficacy while addressing potential safety concerns. This results in faster development timelines, and reduced attrition rates for new chemical entities.

LIPID-BASED DELIVERY

Lipid-based drug delivery systems have been employed successfully for challenging compounds with poor solubility for many years. Enhanced bioavailability is a result of the development of lipid formulations that initially solubilise the compound prior to administration and maintain the drug in solution as it travels the gastrointestinal tract. During development, often the dispersion and digestion properties of lipid formulations are studied *in vitro* as a means of predicting the formulation's behaviour *in vivo*.[6,7]

Lipid-based formulations are classified according to the lipid formulation classification system (LFCS). This system was proposed in 2006 and initially classified lipid-based formulations into four different categories (Type I – IIIB),[8] with a fifth category (Type IV), being added a year later (see Table 1).[9]

Drug product	Characteristics	Excipients in formulation Content of formulation (%w/w)			
		Oils: triglycerides or mixed mono and diglycerides	Water-insoluble surfactants (HLB < 12)	Water-soluble surfactants (HLB > 12)	Hydrophilic cosolvents (e.g. PEG, proylene glycol, transcutol)
Type I	• Pure oils • Limited or no dispersion • Digestion required	100	-	-	-
Type II	• SEDDS • Moderate dispersion needed to form an emulsion • Likely to require digestion	40-80	20-60	-	-
Type IIIA	• SMEDDS • Rapid dispersion to form micro- or nano-emulsion • May need digestion	40-80	-	20-40	0-40
Type IIIB	• SMEDDS • Rapid dispersion to form micro- or nano-emulsion • Digestion likely not needed	<20	-	20-50	20-50
Type IV	• Oil free • Rapid dispersion results in micellar solution • No digestion needed	-	0-20	30-80	0-50

Table 1: Lipid formulation classification system.[8,9]

The formulations are assigned to a category based on the types and amounts of excipients, and predicted behaviour (characteristics) *in vivo*. Type I lipid formulations are pure oils and require digestion whereas Type IV lipid formulations do not contain oils and rapidly disperse into micelles.

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A comprehensive screening process should be used to determine the optimal excipient and ratio for each individual compound, and it is possible to speed up this process if parallel studies are carried out.

Parameters that should be considered during the screen include the solubility of the drug in the different excipients, media and lipid digestion products, the compatibility of the excipients, whether the API is prone to degradation, and how likely the API is to precipitate out on dispersion and digestion.

The soft capsule (Figure 1) has been, and continues to be, the dosage form of choice for the oral delivery of lipid-based formulations and in large part has been responsible for the majority of successful drug products utilising lipid technology on the market.[10] The reasons for this are: 1) most lipid formulations as well as the excipients making them up are liquid in nature, or semi-solids with low melting points; 2) the vast majority of lipid excipients, surfactants, and cosolvents comprising lipid-based fills are compatible with the soft capsule shell given the formulator's ability to tailor the shell composition to a specific fill formulation; 3) properly formulated soft capsule shells rupture and dissolve quickly once administered thereby allowing rapid release of the lipid-based fill and its uncompromised performance (dispersion and digestion) in the gastrointestinal tract; and 4) process parameters established on a small scale in the lab and pilot plant are readily scalable to a robust commercial scale manufacturing process, in contrast to many other dosage forms.

Other advantages offered by the soft capsules include:[10] 1) utilisation for highly potent drug compounds, often microgram doses, where uniformity of dose is best achieved by precisely dosing the fill solution of the drug into the soft capsule; 2) minimisation of safety concerns associated with dusty operations for conventional solid dose manufacture given the drug is wetted early in the soft capsule manufacturing process; and 3) coupled with closed manufacturing processes, the soft capsule provides excellent protection for those APIs that are oxygen sensitive as it is hermetically sealed with no headspace and the shell of the soft capsules generally exhibits very low oxygen transmission rates.

It has been well established that lipid-based formulations filled into soft capsules and engineered to release the fill immediately upon administration and spontaneously disperse to form fine, thermodynamically stable emulsions, often enhance the bioavailability of poorly soluble (DCS II) compounds. This can result in improved absorption, or a reduction in the variability of that absorption. More recently, in addition to immediate-release applications, the filling of lipid semi-solid formulations into soft capsules has been used for extending the release of DCS II drugs.[11] Targeted release of lipid-based fills containing API can also be accomplished through the application of functional film coatings (for example, enteric coatings) to the soft capsule.

The conventional softgel utilises a gelatin-based shell but, more recently, alternative shells containing plant polysaccharides as a replacement for gelatin have been developed. Not only have these non-gelatin soft capsules found wide application and appeal to the vegetarian segment of consumers, but the shells have found a number of new pharma applications owing to the expanded range of lipid fill formulations that can now be encapsulated into soft capsules. These include higher melting point fills that can be heated to temperatures not possible with a gelatin-based shell, thereby allowing encapsulation of very viscous liquids and semi-solid fills as well as improved shell compatibility with a number of medium chain fatty acids, surfactants and cosolvents.

In addition to the technical applications described above, soft capsules are believed to have gained wide acceptance by patients

Figure 1: The soft capsule continues to be the dosage form of choice for the oral delivery of lipid-based formulations.

> "It has never been more important to determine the optimal delivery form at an early stage. Many of these challenging molecules could have significant benefits for patients, yet if they cannot be successfully delivered then that potential will never be realised."

Drug	DCS	Formulation	F (%)	PK Variability (coefficient of variation, CV%)[13,14]	Food Effect	Drug-Drug Interactions		
						Substrate	Inhibitor	Inducer
Abiraterone acetate	Class IIb	Tablet	50%	Relative bioavailability for the modified fasting state Inter-subject 61.1% Intra-subject 71.3%	• Formulation in olive oil increased exposure 4.5-fold • 2-4.4 fold increase in exposure when administered with high-fat meal to cancer patients • Recommended to take under fasting conditions	CYP3A4 (minor) SULT2A1 (major)	CYP2D6 (strong) CYP2C8 (moderate) CYP1A2 (weak) CYP2C8 (weak)	

Table 2: Profile of abiraterone acetate.

and consumers. This is clearly evidenced in the consumer healthcare products area where many dietary supplements, such as omega-3 oils, are available in the soft capsule format. These products are easier to swallow than tablets and provide odour-masking of the fill contents making for a more positive consumer experience. The impact of soft capsules in another consumer product category, painkillers, has also been significant, where solutions of API have resulted in a faster onset of action, which is advantageous for consumers seeking fast relief.[12]

The drug abiraterone acetate represents a good example of a drug product that is marketed in a conventional dosage form (tablet) that may have benefited from the use of a lipid-based drug delivery system. Abiraterone acetate is a steroidal antiandrogen drug that is prescribed for the treatment of metastatic castration-resistant prostate cancer, dosed along with the steroid drug prednisone, and acts by inhibiting the body's synthesis of ligands that bind to the androgen receptors. It is given as a once-daily oral dose.

This compound falls into DCS Class IIb, given that its lack of solubility is due to its poor intrinsic solubility. Labelling for the marketed dose form indicates a significant positive food effect and it is recommended to be taken on an empty stomach. This raises serious safety concerns if patients do not follow labelled instructions, which in all likelihood will result in increased and variable absorption

Based on its DCS classification (IIb), this compound may have been better developed using a solubilisation-enabling technology. The increased exposure observed when formulated with olive oil or co-administration with a high-fat meal would suggest that a lipid-based formulation approach may have resulted in improved and less variable absorption.

CONCLUSION

Lipid-based drug delivery systems are well established in the market, and a proven technology for enhancing the bioavailability of poorly soluble compounds. Yet there are many instances where this technology is not considered during development and drugs that would have benefited from its use have instead been developed in suboptimal dosage forms. With the increasing number of drugs in the development pipeline that are poorly soluble, poorly permeable, or both, it has never been more important to determine the optimal delivery form at an early stage.

Many of these challenging molecules could have significant benefits for patients, yet if they cannot be successfully delivered then that potential will never be realised. To accomplish this most successfully, it is therefore important to carry out parallel screening of bioavailability-enhancing technologies at an early stage by in-house formulation experts, or to seek assistance from a reputable, quality CRO that has the expertise to perform this work.

Regardless of whether a lipid-based formulation, or another technology is selected as the right formulation approach based on the API's physicochemical properties, doing so at the early stages of development will reduce overall development cycle times and, most importantly, improve patient outcomes.

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