This article discusses the increasing use of lipid-based formulations for delivering challenging active pharmaceutical ingredients and describes the factors formulators must consider when selecting whether to use hard-shell capsules or softgels to deliver such formulations.

Lipid-based drug delivery systems have found widespread acceptance for the development of drug products containing active pharmaceutical ingredients (APIs) that pose development challenges for formulators. This is evidenced by the significant numbers of FDA-approved drug products that have been formulated using lipid-based formulations (LBFs) when a bio-enhancing technology is required [1].

Poor bioavailability often results from an API’s limited aqueous solubility and/or membrane permeability and can lead to target exposure levels not being achieved and/or a greater risk of intra- and inter-subject absorption variability (food effects). Formulators can overcome many API challenges by using LBFs, especially as the formulation can include a wide range of excipients to improve solubility and absorption, and importantly, to make bioavailability more consistent. Excipients can also be used to improve membrane permeability—another cause of poor bioavailability. LBFs can also be beneficial for products with low API doses where ensuring content uniformity proves difficult. The use of LBFs is widely recognized by regulatory authorities, and there is an established selection of orally safe excipients that are inactive ingredients (IIGs) or generally recognized as safe (GRAS).
Lipid formulation classification system

The lipid formulation classification system, shown in Table 1, provides an approach for classifying LBFs based on their composition and predicted \textit{in vivo} digestion and dispersion behavior [2]. LBFs containing lipophilic components, such as triglycerides, fatty acids, and mono/diglycerides, are digestible and further dispersible \textit{in vivo} to micelles and mixed micelles upon digestion. Surfactants with a low hydrophilic-lipophilic balance (HLB) (<12) and a high HLB (>12) can be used to aid in the formulation’s dispersion and solubilization. Although not truly lipids, hydrophilic components such PEG 400, PEG 600, propylene glycol, glycerin, water, and ethanol can be added to LBFs when the API solubility favors more polar solvents.

Development considerations for lipid-based formulation

The first step in LBF development is to achieve a thorough understanding of the API’s properties and the clinical deliverables. For APIs with bioavailability issues, LBFs in solution are generally preferred; however, dose loading issues may require the LBF to be formulated as a suspension. Solution formulations require solubility studies to identify solvent systems that can dissolve enough API to support the target dose; whereas suspensions require particle size characterization and identification of a suitable rheology profile to prevent sedimentation and allow adequate flow during processing.

Once candidate excipients have been identified, compatibility studies are performed to ensure that the excipients and API are compatible. Prototype formulations can be prepared based on solubility and compatibility studies and then evaluated using several tools, including dispersion testing, to compare relative dispersibility in simulated gastric and intestinal fluids. Digestibility can be studied using lipolysis testing to determine the rate and extent of formulation digestion. The API’s kinetic solubility can be studied in both standard media and in media containing products of digestion using fiber optic dissolution. This provides useful information when predicting the \textit{in vivo} dispersion and digestion performance of the formulation system, allowing the formulator to rank order prototype formulations for subsequent animal or clinical studies.

The physical and chemical properties of both the API and the LBF containing the API should be considered in selecting the LBF’s delivery method. Since LBFs often rely on the body’s digestive process as part of their performance profiles, the API’s solubility in the formulation as well as the formulation’s degree of digestibility and dispersion can influence the absorption process and should be understood and characterized. In other instances, LBFs are not required to enhance bioavailability but rather just serve as a convenient delivery platform, such as for use with pediatric populations, to provide oxidative protection for sensitive APIs, or to improve the content uniformity of low-dose products.

Regardless of the end delivery platform, adequate formulation characterization is required to identify and control the formulation’s critical attributes as well as enough stability to support its use. In addition, the LBF and delivery platform need to be compatible with each other.

After developing the LBF, formulators must consider several factors when selecting a suitable delivery platform, especially for clinical studies. Paramount among these factors are timing and resource needs to match clinical schedules. Ideally, the platform should allow for flexible dosing and be easy to handle and administer at the clinic. Adequate formulation stability is necessary to ensure formulation performance (potency, dispersion, and/or digestibility) over the expected duration of study. Finally, if possible, the delivery method should be reflective of the dosage form that will be deployed for later development stages.

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<th>Table 1</th>
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<tr>
<td>Lipid formulation classification system</td>
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<tr>
<td><strong>Composition %</strong></td>
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<td>Triglycerides or mixed glycerides</td>
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<td>Surfactants (HLB&lt;12)</td>
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<td>Hydrophilic co-solvents</td>
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<td><strong>In vivo behavior</strong></td>
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Liquid-filled capsules

The most common delivery vehicles for LBFs during early-stage development studies are liquid-in-bottle formulations and liquid-filled capsules (LFCs). LFCs, which can be either hard-shell capsules or softgels, are typically preferred for clinical studies because they are convenient for patients and widely accepted in both pharmaceutical and consumer health products. Formulation and scale up methodologies are widely understood, and LFCs are compatible with most excipients used in LBFs.

LFCs are an effective means of unit-dose delivery of liquid, semi-solid, and thermosetting formulations and allow for precise volumetric filling of liquid formulations, providing increased dose uniformity compared to other delivery vehicles. Also, LFCs enhance product stability because the capsule shell protects the API from exposure to oxygen or water. The encapsulation technology also has negligible adverse impacts on the fill formulation's performance properties (such as dispersion and digestibility) or the API release from the dosage form over time (dissolution rate). From a practical, manufacturing point of view, small-scale batches of a few dozen LFCs are easy to produce, which saves API, time, and money and makes development fast and efficient.

Both hard-shell and softgel capsules can be either animal-based (gelatin) or non-animal-based. Non-animal-based shells use a variety of polysaccharides, such as hydroxypropyl methylcellulose (HPMC), starch, and carrageenan. The choice of shell material is based on the final dosage form's target product profile (TPP), as well as the formulation's physicochemical properties.

Hard-shell capsules offer some advantages over softgels, such as the ability to fill at higher temperatures. Also, HPMC hard capsules can encapsulate compounds and fills that are very moisture sensitive, acidic, or alkaline. However, hard-shell capsules also have some drawbacks, such as sensitivity to crosslinking and a maximum fill volume of only approximately 0.9 milliliter. Also, HPMC films have a relatively high rate of oxygen permeability compared to gelatin films, which can limit the applicability of HPMC capsules in the development of oxygen-sensitive compounds.

Softgel manufacturing

Softgel manufacturing technology has a long history in the pharmaceutical industry and produces a plasticized, hermetically sealed shell. While softgels are typically composed of gelatin, non-gelatin shells, usually made from polysaccharide (starch and/or carrageenan), are becoming more common because of their appeal to populations whose cultural or religious beliefs preclude the use of gelatin.

Softgel formulations include plasticizers—typically glycerin, sorbitol, maltitol, or mannitol—however, these materials can sometimes be reactive with the fill formulation and may result in the formation of glycerol esters when used with weakly acidic APIs. Such reactions can impact the APIs chemical stability within the drug product.

As a result, it is important to evaluate the choice of plasticizer as a part of the shell compatibility process. If this evaluation determines that the plasticizer is preventing suitable stability, a hard-shell capsule may be a more appropriate delivery method.

A big advantage of softgels is that they offer a wide range of options in terms of shapes and colors for market and product differentiation, with rounds, oblongs, and ovals being the most common shapes for oral delivery. The practical fill volume limit for softgels is approximately 1.2 milliliters before the capsule becomes too large to swallow.

Softgels provide a fast route of development, as manufacturers typically have a library of gel-mass formulas that they can either apply directly or modify slightly to accommodate the fill composition. This library approach leverages knowledge of shell performance across a broad base of products. Changes to the library, such as a change in the gelatin source, undergo rigorous evaluation to ensure that the change doesn’t alter product performance. An organization that has built and diligently maintains a shell library spanning many LBFs is in a very strong position to offer innovators a stable and robust shell system, and this knowledge base and expertise is indicative of a successful softgel operation.

Gelatin capsules have a longer developmental and manufacturing history than non-gelatin capsules, so most products on the market are gelatin-based. Gelatin shells are compatible with fill formulations in a 4 to 7 pH range [3], however, the maximum processing temperature is approximately 40°C because of the relatively low melting point of the gel-mass used to form the capsule.

Gelatin softgels are susceptible to crosslinking, which can impact in vitro dissolution testing. Formulators can minimize crosslinking by using fill excipients with low levels of impurities known to catalyze the crosslinking reaction (such as peroxides and aldehydes) and reducing exposure to excessive heat and oxygen during processing. In instances where significant crosslinking cannot be avoided, either due to the API itself or to impurities in the formulation, gelatin-free capsules are a suitable alternative.

Polysaccharide-based softgels that use starch and/or carrageenan as capsule-forming polymers have a higher melting point than gelatin. This allows for fill temperatures up to 75°C, which expands the number of excipients that can be used compared with gelatin shells. It also opens up the possibility for modified-release applications, as formulators can control the rate of dissolution or dispersion of the fill material by including different excipients with varying melting points.
points. Calcifediol is an example of an approved product that incorporates a semi-solid lipid formulation into a polysaccharide-based softgel with extended-release properties [4].

Polyaccharide softgels are also compatible with alkaline fills up to pH 12.0 [5], and because they eliminate the potential for cross-linking associated with gelatin capsules, further expand the number of materials that can be filled into a softgel format.

**LFC selection**

Selecting which type of LFC to use for the final dosage form begins with the TPP, which defines the product’s desired properties. However, if the TPP does not explicitly define the choice between LFCs, developers should consider compatibility and stability data when selecting the LFC type and material. Both business and development considerations may influence the choice with respect to the amount of work that can be performed in-house versus work that must be outsourced to a contract development and manufacturing organization (CDMO) that specializes in a platform. Manufacturers should perform a preliminary risk analysis with respect to commercial viability within the project’s development scope and the optimization of the project’s time and resource needs.

For the most part, hard-shell capsules and softgels are equivalent, but there are subtle practical differences between them. Generally, softgels are manufactured by experienced CDMOs that can apply their expertise early in the process to avoid problems later in development. This knowledge, coupled with the ability to adjust and fine-tune the shell formulation, provides greater flexibility in solving problems—particularly those associated with challenging APIs—when working with softgels compared with hard-shell capsules. The most common issues associated with softgels involve compatibility problems with the plasticizer system, or an API in the fill that cannot tolerate exposure to water. If developers identify and address these issues early, transitioning the product to a hard-shell capsule is a viable and economical option.

**Summary**

LBFs are well established as an enabling technology for challenging APIs. They offer flexible approaches for early stage formulation development, generally require only minimal API for formulation development, and are easily scaled up to commercial volumes. Although a liquid-in-bottle approach may be a good option for early development work, such as animal and first-in-human testing, commercially it is limited to specific markets, such as pediatrics.

Softgel capsules are widely compatible with excipients commonly used for LBFs and can accurately dose products in the microgram dose range with excellent content uniformity. Softgels are also well suited to small-scale batch manufacture with minimal effort and API consumption yet are easily scaled to commercial levels with minimal risk. Potent APIs can be contained easily within the liquid fill material, and the manufacturing process and shell systems are well suited to protect APIs and excipients from oxidation. Since the shell is essentially a container for the fill material, there is minimal impact on in vitro/in vivo fill formulation performance such as dissolution and dispersion. In cases where softgel manufacture is incompatible with the API, the predictable interchangeability between softgels and hard-shell capsules is straightforward.

Selecting one versus the other can be based on TPP, technical limitations, or development phase. Empty hard-shell capsules are readily available from several vendors, making in-house formulation studies practical for companies that do not have access to softgel manufacturing, and this can be extended to in-house manufacturing for early animal or clinical studies.

On the other hand, softgels are typically manufactured by an experienced CDMO, allowing rapid development and a choice of dosage form designs. The ability to modify the softgel’s composition offers greater flexibility in tailoring the shell to the fill to improve compatibility, and softgel manufacturing has a well-established and extensive knowledge base and history of regulatory acceptance. Hard-shell capsule technology is less mature and has experienced several issues, such as spontaneous cracking with hygroscopic fills. Selection depends on the API, the properties of the fill formulation, and ultimately, which technology best meets the defined TPP.

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**References**


