Liquid-filled hard capsules are an important and versatile solid oral dosage form. This article provides a basic explanation of the form and explains how it can help to overcome common formulation challenges.

Hard capsules have traditionally been filled with powders, but they can also be filled with non-aqueous liquids, suspensions, semisolids, thixotropic gels, self-emulsifying drug delivery systems (SEDDS), thermo-softened matrixes, and hot melts that flow at temperatures below 70°C (the temperature at which a hard capsule begins to soften). These flowable fill materials are typically mixed with an active pharmaceutical ingredient (API) to form a homogeneous suspension and then filled into hard capsules made of either gelatin or hydroxypropyl methylcellulose (HPMC). The mixture's viscosity at the filling temperature should be between 80 and 80,000 centipoise to ensure that the liquid adequately fills the capsules. If the liquid fill is flowable at ambient temperature, the capsules must be sealed after filling to prevent leakage.

Liquid-filled hard capsules (LFHCs) allow companies to formulate drug products using many APIs that would be difficult or even impossible to formulate as other solid dosage forms. LFHCs can be a cost-effective alternative to some softgel products and can also improve product stability and enhance an API's bioavailability.
sulation technology can eliminate many problems associated with softgel capsules, including high manufacturing cost, gelatin waste, cross-contamination, migration of the API into the capsule shell, and bioavailability problems [1]. In this article, I will discuss how LFHCs can help to overcome common formulation problems and provide examples of successfully marketed LFHC products.

Combination products

LFHCs can contain tablets or microtablets, pellets, smaller capsules, or a combination of these in addition to the liquid fill, as shown in Photo 1. This allows formulators to develop products with multiple APIs without causing compatibility problems or to easily manage different release patterns for a single or multiple APIs. For example, the GlaxoSmithKline LFHC product approved in 2010 and marketed as Jalyn in the US and Combodart in Europe contains 0.4-milligram tamsulosin hydrochloride modified-release pellets and a 0.5-milligram dutasteride softgel capsule.

The ability to combine multiple fill materials can be beneficial in the nutritional supplement industry as well. For example, a product might consist of an outer hard capsule that contains both plant oils and a smaller enteric-coated HPMC capsule filled with probiotic bacteria. The coated inner capsule would create an effective moisture barrier for the probiotic bacteria in the stomach, allowing these otherwise incompatible ingredients to be administered together in a single dosage form.

Hygroscopic APIs

Processing hygroscopic APIs and keeping them dry and stable during the shelf life of a product can be difficult. Incorporating such APIs into a molten excipient such as PEG, poloxamer, or wax at temperatures up to 70°C and filling the hard capsules while the material is hot can help solve this problem. The excipient solidifies at ambient temperature, providing a stable matrix that protects the API from moisture. For example, vancomycin hydrochloride was initially formulated as lyophilized powder in ampoules for injection. Mixing the API into molten PEG 6000 and filling it into hard gelatin capsules protected the hygroscopic API from moisture and allowed it to be successfully marketed as a solid oral dosage form (SODF).

Liquid or low-melting-point APIs

Processing liquid or low-melting-point APIs and SEDDS into an SODF other than an LFHC is difficult. Processing such APIs for use in tablets or powder-filled capsules requires large excipient amounts and multiple processing steps but is often much simpler for LFHCs. For example, combining ibuprofen, which has a melting point of 75°C, with PEG 6000 at 70°C forms a flowable mass that can easily be filled into hard capsules.

Highly potent APIs

Highly potent APIs (HPAPIs) pose three major problems for formulators. First, it can be difficult to achieve content uniformity because the HPAPI is present in smaller quantities than with a typical API. Second, you must protect workers from exposure to the dust generated when processing HPAPI formulations such as anti-cancer treatments, immunosuppressants, steroids, hormonal treatments, and anti-diabetics. Third, potential residue left on the equipment after processing HPAPIs makes the cleaning process tedious. Using LFHCs can help avoid these problems. Because the API in a LFHC is uniformly distributed in liquid, variations caused by bulk density, particle size, or flow properties are eliminated. The mixture is filled by volume using accurate, servo-based dosing pumps. As a result, content uniformity is generally much better in LFHCs than in powder-filled capsules or tablets.

Poorly soluble APIs

Many new APIs have poor aqueous solubility (BCS Class II and IV) or permeability (BCS Class III). Adding a solubilizer or emulsifier or processing the API as a SEDDS can enhance bioavailability. Formulating a poorly soluble API as a lipid system may increase permeability because inducing lymphatic absorption can bypass hepatic degradation.

The FDA approved Absorica, a LFHC made by Ranbaxy/Sun Pharma, via a 505(b)(2) application because the API (isotretinoin) absorbed better in fasting patients than it did in the original Roaccutane/Accutane softgel capsules from Roche. Formulators can use lipid excipients to target lymphatic transport or circumvent the impact of transporters and metabolizing enzymes in the gastrointestinal (GI) tract. Also, milling an API in a liquid medium avoids agglomeration of nanoparticles, and the API can then be filled into LFHCs as a suspension. For example, itraconazole nanocrystals prepared according to a process patented by MW Encap in 2016 initiate dissolution much faster than unmilled itraconazole [2].

Sustained-release APIs

LFHCs also make it possible to formulate a sustained-release drug product while easily keeping part of the API as an immediate-release portion. Companies have prepared such products by using excipients that influence the hydrophilic-lipophilic balance of the semi-
solid matrix [3]. For example, propranolol capsules contain a rapid-release phase of propranolol in oleic acid and a sustained-release phase of the API contained in an erodible matrix.

**Enteric and targeted-release capsules**

As previously mentioned, LFHCs can also be coated, allowing for enteric and targeted API release. Band sealing the capsule shell, as shown in Photo 2, protects the contents from the coating material and also smooths the edge between the capsule cap and body. For example, Colpermin capsules, manufactured by Tillotts Pharma, contain a thixotropic gel with 0.2 milliliter (187 milligrams) of peppermint oil in an enteric-coated hard capsule for the treatment of irritable bowel syndrome. Making a tablet containing the same amount of peppermint oil would be very difficult. LFHCs are ideal for drug products requiring API release in the colon as well, where water content is low. The capsules can be coated with a starch that resists digestion in the upper GI tract but ferments in the colon, releasing the API.

**Abuse-deterrent formulations**

Liquid- and semisolid-filled capsules cannot be powdered or crushed to increase API release. Extracting the API from a LFHC is also difficult, which makes the dosage form useful as an abuse deterrent for drug products that treat pain (such as opioids), anxiety, depression, and hyperactivity. For example, technology by Durect uses a high-viscosity base matrix of sucrose acetate isobutyrate to contain the API. In November 2017, the FDA issued a guidance for industry on general principles for evaluating the abuse deterrence of generic solid oral opioid products [4]. Any generic solid oral opioid product should meet these requirements.

**Improved stability**

Softgel capsules contain about 30 percent glycerin as a plasticizer, which results in higher moisture absorption and can lead to migration of the API into the gelatin film. The plasticizer creates channels that increase the capsule shell’s permeability to air/oxygen. LFHCs don’t require a plasticizer, so they provide better stability. Manufacturers can further improve stability with LFHCs by flushing the capsules with nitrogen and applying an airtight seal.

**Simplified development and manufacture**

LFHC manufacture essentially involves mixing the ingredients and filling the capsules, so it generally requires fewer processes and ingredients than other SODFs. This can speed up product development and launch, simplify technology transfer and scale-up, and reduce manufacturing space requirements. It can also reduce the size and weight of the drug product. Piascledine (Pharmascience) contains a mixture of avocado oil and soya oil and was initially marketed in France as a tablet that required five manufacturing steps. The product has since been changed to a LFHC, which requires only mixing and filling and is also smaller than the original tablet.

**Product differentiation, brand image, and counterfeit prevention**

Hard capsules can have a range of colors for both the capsule body and cap, and each can be preprinted around its circumference (360-degree printing). For example, ACG’s Brandshield 4C hard capsules feature four-color circular-oriented printing (two colors on the capsule body and two colors on the cap) [5]. Because companies can print logos, brand names, and graphics right on the capsule, LFHCs provide excellent brand awareness and product differentiation. The printing also serves as an effective anti-counterfeiting measure.

**References**


Milind K. Biyani is research and development director at Aspire Advisors, Mumbai, India (http://aspire-advisors.net/). He has more than 40 years of experience in dosage form development with various global and Indian pharmaceutical companies. He can be contacted at drmilind@aspire-advisors.net.