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## *Liquid capsule filling for poorly soluble drugs*

Hard capsules have traditionally been used to deliver powder or granule formulations, but in recent years, formulators have increasingly used them to deliver oily liquids and semi-solid formulations. These lipid-based formulations (LBFs) typically improve the solubility, dissolution, and absorption of poorly soluble APIs. For example, systems comprising mixtures of surfactant and oil, or self-emulsifying drug delivery systems (SEDDS), result in a dispersion of fine emulsion droplets in situ [1].

Softgel capsules have been widely used for LBFs, but liquid-filled hard capsules (LFHCs) provide an attractive alternative. LFHCs are typically composed of a shell of gelatin, a blend of gelatin and polyethylene glycol (PEG), or hydroxypropyl methylcellulose (HPMC). Unlike softgels, hard capsules don't contain plasticizers — except for PEG-gelatin or other special cases — reducing the potential for API migration from the fill to the capsule shell. Also, assuming proper engineering controls are in place to protect the operator, hard capsules offer the ability to fill at higher temperatures than softgels, up to 50°C for gelatin and 70°C for HPMC.

When formulating a LFHC, you must ensure that the fill material is compatible with the capsule shell to maintain the formulation's physical and chemical stability. A key factor is the extent of water exchange between the formulation and the capsule, which can lead to unacceptable changes in the capsule's mechanical behavior. Understanding how the presence of water or hydrophilic components in a formulation may affect the capsule shell can guide formulators and help to minimize the time and costs associated with compatibility tests [2].

Because gelatin capsules contain

13 to 16 percent moisture, hygroscopic excipients such as glycerin, propylene glycol, and liquid PEGs cannot be used on their own as they will cause the gelatin capsule shell to become brittle and fracture. HPMC capsules contain less moisture and can be a good option for hygroscopic excipients. However, PEG 400 and 600 can cause PEG diffusion in HPMC capsules, resulting in distortion and swelling of the capsule wall. PEG excipients with a molecular weight of 900 or greater do not cause this problem [3]. Several compatibility studies have evaluated the effect of many popular liquid and semi-solid excipients on hard gelatin, HPMC, and PEG-gelatin capsules containing up to 5 percent PEG [4].

Most LFHC filling systems are optimized for nominal fill-solution viscosities between 100 and 1,000 centipoise. Unlike traditional powder- or pellet-filled capsules, LFHCs require band sealing to ensure product integrity. Sealing systems either chemically bond the capsule's cap and body or apply an external band-sealing solution. The band-sealing solution should match the composition of the capsule, and solutions are available in various colors to provide additional product differentiation and branding options.

Because LFHCs can be accurately filled using manual or semi-manual filling methods, they are a viable alternative for early formulation evaluation and human or animal studies. External band seals may be applied by hand or using table-top, R&D-scale equipment, providing a quick and efficient way to evaluate new prototypes. This speeds up the initiation of human clinical studies and helps companies match manufacturing output to clinical demand.

Scale-up is very linear, allowing manufacturers to scale the process

train in proportion to demand without the need for dedicated drying equipment and prolonged curing time, as with many softgel formulations. Commercial capsule fillers often use extremely accurate volumetric pumps to ensure dose uniformity. Automated filling and band sealing equipment can readily achieve commercial production capacities while maintaining operational efficiencies typically associated with traditional capsule-filling. T&C

### References

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