Capsules filled with liquids or semi-solids offer a greater range of formulation options than other dosage forms do, particularly when the API is lipophilic, poorly bioavailable, or highly potent. This article highlights advances in the design and production of liquid-filled hard capsules and summarizes how they perform compared to liquid-filled soft gelatin capsules.

Combinatorial chemistry and high-throughput screening have led to the discovery of many drug candidates that are difficult to deliver using traditional tablets or capsules. Many are highly lipophilic and have high molecular weights [1]. Consequently, they likely have poor solubility in aqueous solutions and, hence, low and variable bioavailability [2, 3]. The physiochemical properties of peptide and protein-like macromolecules also pose problems for oral administration [4].

In response, formulators have turned to liquid-filled hard capsules (LFHCs) and liquid-filled soft gelatin capsules (softgels). These formats—often in combination with lipid-based formulations—are routinely used to improve bioavailability and reduce food effects; stabilize active pharmaceutical ingredients (APIs) with respect to oxygen, moisture, and light exposure; improve the dose uniformity of highly potent APIs; and reduce the risk of handling hazardous agents.
**Consumer use of liquid-filled capsules**

In addition to improving bioavailability, LFHCs and softgels preserve the oral route of administration that patients generally prefer. Given that preference, and coupled with the challenges of bioavailability and lifecycle management that today’s formulators face, it is not surprising that the number of applications involving liquid-filled capsules continues to increase, in both the pharmaceutical and nutritional markets.

In addition to the formulation challenges that are driving the growth of lipid, liquid, and semi-solid dosage forms, consumer preference for liquid-filled dosage forms is increasing. In 2002, an attitude and usage survey on dosage forms indicated that 40 percent of US consumers said they used liquid-filled dosage forms, and 10 percent said they used them most often [5]. In 2012, the ongoing study showed that 59 percent of consumers used liquid-filled dosage forms, and 21 percent used them most often.

**Choosing the capsule type**

Each encapsulation technology—LFHCs and softgels—has its advantages (Table 1) [6], but it is the formulation that often dictates which is used.

<table>
<thead>
<tr>
<th>Fill types</th>
<th>Hard capsules</th>
<th>Softgels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of encapsulated components</td>
<td>One to several</td>
<td>One</td>
</tr>
<tr>
<td>Formulation</td>
<td>Flexible excipient options</td>
<td>Limited excipient options</td>
</tr>
<tr>
<td>Fill temperature</td>
<td>≤70°C</td>
<td>≤35°C</td>
</tr>
<tr>
<td>Stability</td>
<td>More effective barrier to water, light, and oxygen</td>
<td>Less effective barrier to water, light, and oxygen</td>
</tr>
<tr>
<td>Shell</td>
<td>Not plasticized</td>
<td>Plasticized (glycerin, propylene glycol, sorbitol)</td>
</tr>
<tr>
<td>Manufacture</td>
<td>Shells made separately from filling and sealing</td>
<td>Formed and filled in one operation</td>
</tr>
<tr>
<td>Closure</td>
<td>Friction, interlock, banding, and liquid sealing</td>
<td>Inherently hermetically sealed</td>
</tr>
<tr>
<td>Sizes and shapes</td>
<td>Limited</td>
<td>Many</td>
</tr>
<tr>
<td>Machinery availability</td>
<td>Small-scale and benchtop units available to small organizations</td>
<td>Limited to a few facilities</td>
</tr>
<tr>
<td>Uses</td>
<td>Drug development and clinical trials</td>
<td>Large-scale manufacture</td>
</tr>
</tbody>
</table>

Softgels generally comprise API in either liquid or suspension. They are formed and filled in a single operation, sometimes at speeds that exceed the rate at which LFHCs can be produced. Specialty vendors usually handle both small-scale development and commercial production.

Hard capsules are manufactured before filling and sealing occur and are versatile because they can contain one or more APIs in powder, multiparticulate, liquid, or semi-solid formats. Furthermore, the machinery used to fill and seal liquid and semi-solid formulations into hard capsules is simple and readily available for in-house, small-scale development, such as for clinical trial materials. Commercial production is typically outsourced.

To obtain their elasticity, softgels require plasticizers, such as glycerol or sorbitol, which hard capsules do not need. These plasticizers may migrate into the formulation, affecting the solubility of the API. Conversely, the API may migrate into the capsule shell, causing physical instability. Such migration is typically resolved by formulating to ensure the mutual insolubility of the capsule shell components and the fill.

Hard gelatin capsule shells have low oxygen permeability, and capsule shells made of hydroxypropyl methylcellulose (HPMC) contain little moisture, which minimizes the risk of water-induced degradation during storage. The small pores of hard capsule shells can also prevent the release of unpleasant tastes or odors from the API. Hard shells tolerate formulations as warm as approximately 70°C, whereas softgels tolerate no more than about 35°C. Hard capsules can also accommodate large particles or fibrous materials in suspension or paste-type formulas that are troublesome to fill into softgels, because such materials can interfere with sealing. That is not true of the seals applied to hard capsules.

**Characteristics of liquid formulations**

As noted, the poor aqueous solubility of APIs is a major reason to use liquid-filled capsules. Liquid formulations range from oils (Type I) to oil-free combinations of surfactant and co-solvent solutions (Type IV). See Table 2. Self-(micro-) emulsifying drug delivery systems (SEDDS and SMEDDS) use oils, water-soluble or water-insoluble surfactants and, in some instances, hydrophobic co-solvents to form rapidly dispersing lipid formulations (Type II and Type III).

SEDDS/SMEDDS contain a small number of components that spontaneously form a fine oil-in-water emulsion under gentle agitation [7]. For instance, amphotericin B is a hydrophobic polycene antifungal antibiotic that is negligibly absorbed in the gastrointestinal tract when the neat API is orally administered to rats. Yet a SEDDS formulation of amphotericin B that comprises glyceryl monooleate, polysorbate 80, polyethylene glycol 400, and propylene glycol significantly improved mean area-under-curve values compared with the pure API [8]. Similar results have been demonstrated for exemestane [9], paclitaxel [10], tacrolimus [11], acyclovir [12], and celecoxib [13], among many others.

Another factor driving the increase in liquid-filled capsules is the surge in high-potency APIs, which must be administered at low doses. In a dry formulation, these APIs present formulators with the challenge of ensuring content uniformity [14], but in liquid formulations it is more easily addressed. Furthermore, liquid fills improve the safety of workers because they reduce their exposure to dust [15].

The API in liquid fills is homogeneously distributed, and the pumps used to fill the capsules can achieve weight variations of less than 1 percent [16]. Content
uniformity thus corresponds very closely to filled-capsule weight. That may not be true of tablets. After all, for tablets that weigh less than 130 milligrams, USP standards allow weight variation of as much as 10 percent [17], and content uniformity may vary much more, especially in smaller batches. This is particularly significant with potent APIs such as cytotoxic chemotherapeutic agents or hormones, in which a 10 percent variation could result in adverse side effects from under- or overdosing. In extemporaneously micro-dosed captopril capsules, for example, the amount of API delivered to patients with congestive heart failure varied by as much as 24.5 percent, even though the capsules met USP limitations for weight variation [18].

**Excipients and LFHCs**

In hard capsules, the fills can be liquids, thixotropic gels, or thermo-softened matrices that are liquid at elevated temperatures and solid or semi-solid at ambient temperatures. Formulating with a matrix that solidifies in the capsule helps maintain the dispersion during storage and eliminates capsules that leak, called leakers.

Both gelatin and HPMC capsules accept liquid fills, and HPMC capsules are gaining popularity among vegetarians and other consumers who avoid animal-sourced products. HPMC is also favored when the APIs and/or excipients interact with gelatin to the detriment of the formulation or the capsule [19]. HPMC capsules are more broadly applicable to new drug development than gelatin capsules because they are inert and compatible with a wide range of excipients, including those used for LFHC formulations. HPMC's interaction with formulations differs, in part, because it does not use water as a plasticizer, as gelatin does [20]. While the in vitro dissolution rates of gelatin and HPMC capsules differ [21], advances in HPMC capsule technology have reduced those disparities, reduced weight variation and powder leakage, and improved machinability [22-24].

**Filling and sealing hard capsules**

A variety of machines can fill hard gelatin capsules with liquids or semi-solids at rates suitable for both large- and small-scale production (Table 3). A benchtop machine that our company offers (photo right) fills and seals as many as 750 capsules per hour and can accept the full range of capsule sizes.

Capsules are sealed using one of three methods: friction lock, gelatin banding, or fusion technology, formerly known as liquid encapsulation microspray sealing, or LEMS. Using commercial-scale fusion equipment, 44,000 capsules per hour can be sealed, with a leaker rate of fewer than 20 per 100,000 before inspection; after passing through an inline high-speed inspection system, the leaker rate is zero.

Unlike banding, fusion technology does not involve applying gelatin strips to the cap-body joint. Rather, it takes advantage of the melting point of gelatin and applies moisture at the cap-body joint, allowing it to fuse at moderate temperatures [16, 25].

In both the benchtop and commercial-scale filling and sealing systems that use fusion technology, the capsules are rectified and separated by vacuum. Next, a drip-free dosing pump fills the capsule body volumetrically with 0.1 to 1.2 milliliters of fluid at temperatures as high as

---

**Table 2**

<table>
<thead>
<tr>
<th>Types of liquid capsule fills and excipients</th>
<th>Content of formulations (% w/w)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oils: Tri-, di-, and monoglycerides</td>
<td>Type I: 100, Type II: 40-80, Type IIIA: 40-80, Type IIIB: &lt;20, Type IV: -</td>
</tr>
<tr>
<td>Water-insoluble surfactants</td>
<td>Type I: -, Type II: 20-60, Type IIIA: -, Type IIIB: -, Type IV: 0-20</td>
</tr>
<tr>
<td>Water-soluble surfactants</td>
<td>Type I: -, Type II: 20-40, Type IIIA: 10-50, Type IIIB: 30-80</td>
</tr>
<tr>
<td>Hydrophilic co-solvents</td>
<td>Type I: -, Type II: 0-40, Type IIIA: 20-50, Type IIIB: 0-50</td>
</tr>
<tr>
<td>Type of dispersion</td>
<td>Limited or no dispersion, Rapidly dispersing, Rapidly dispersing, Transparent dispersion, Micellar solution</td>
</tr>
<tr>
<td>Digestion requirement</td>
<td>Required, Likely to be digested, Digestion may not be necessary, Limited digestion</td>
</tr>
</tbody>
</table>

**Table 3**

<table>
<thead>
<tr>
<th>Production and leakage rates: Hard capsules versus softgels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capsule type</td>
</tr>
<tr>
<td>Liquid-filled hard capsules</td>
</tr>
<tr>
<td>Liquid-filled softgels</td>
</tr>
</tbody>
</table>
70°C. To fuse the capsule halves, approximately 50 microliters of a water-ethanol solution is sprayed onto the cap-body joint through ports in a clamp that holds the capsule throughout filling and sealing with minimal contact with the capsule exterior (Figure 1). The fluid is rapidly drawn into the cap-body joint by capillary action, and a vacuum removes excess fluid. Next, a stream of air warms the capsule to 45° to 50°C, melting the gelatin inside the joint zone and fusing the capsule together. The seal cures as the filled capsule returns to room temperature.

To ensure a precise, complete seal, fusion technology requires capsules designed for that purpose, with double barriers at the top of the sealing zone that prevent leakers (Figure 2). Furthermore, the capsule shells have no dim-

### Conclusions

Lipid, liquid, and semi-solid fills are increasingly useful in addressing the pharmaceutical industry’s most pressing formulation challenges: enhancing solubility and bioavailability and delivering high-potency APIs. LFHCs are versatile in terms of content (dry, liquid, semi-solid, large particles), number of APIs, and excipient choice. Advances in liquid filling and sealing technology (capsule design, precise pumps, and automated inspection) have increased production speeds while minimizing or eliminating defective capsules.

**References**

6. Cole, E. T., Cade, D., and Benenauer, H. Challenges and opportunities in the encapsulation of liquid and semi-solid formula-