Liquid-filled hard capsules (LFHCs) require a seal to prevent their fills from leaking. And all over-the-counter (OTC) drug products sold in hard capsules require a tamper-evident seal. This article summarizes the features and operation of equipment that seals hard capsules using banding, liquid spraying, and ultrasonic welding. It is adapted from the chapter “Hard Shell Capsule Filling Machines,” which will appear in the book “Pharmaceutical Dosage Forms: Capsules,” edited by L. Augsburger and S. Hoag. Published by CRC Press/Taylor & Francis, the book will be available later this year.

Sealing two-piece hard capsules serves two basic purposes: It creates a leak-proof closure to contain oils, pastes, and other liquids and non-solids. It also enables manufacturers to comply with regulatory requirements for OTC capsule products sold in the USA.

LFHCs get the most attention today because demand for them has re-emerged. Their comeback is traceable to several developments:

- Ability to handle active pharmaceutical ingredients (APIs) that have a low melting point;
- Effectiveness with compounds that are unstable when exposed to moisture or oxygen [1];
- Better content uniformity when encapsulating low-dose drug products;
- Fewer safety concerns when highly potent APIs, such as cytotoxins, are handled;
- Fewer excipients needed;
- Less expensive manufacturing and plant infrastructure [2];
- Better effectiveness at overcoming poor aqueous solubility, thereby improving oral bioavailability [3]. (About 60 percent of compounds in development exhibit poor solubility [4].)

The regulatory requirement, which applies to OTC capsules with liquid or solid fills, is outlined in the FDA’s Compliance Policy Guide 400.500 [5]. It states:

“1. For two-piece, hard gelatin capsule products subject to this requirement, a minimum of two tamper-resis-
tant packaging features is required, unless the capsules are sealed by a tamper-resistant technology.

2. For all other products subject to this requirement, including two-piece, hard gelatin capsules that are sealed by a tamper-resistant technology, a minimum of one tamper-resistant feature is required.”

And:

“Technologies for sealing two-piece hard gelatin capsules are available that provide evidence if the capsules have been tampered with after filling. Such sealing technologies currently in use include sonic welding, banding, and sealing techniques employing solvents and/or low temperature heating. These examples are not intended to rule out the development and use of other capsule sealing technologies. Manufacturers may consult with FDA if they are considering alternative capsule sealing processes. Sealed capsules are not tamper-resistant packages. They are required to be contained within a package system that utilizes a minimum of one [tamper-resistant package].”

The main methods of sealing capsules are banding, liquid spray, and sonic welding. Table 1 lists the suppliers of capsule sealing equipment, and each of the machines is described below. [Editor's note: All images and illustrations used in this article were provided by the manufacturers and are used with their permission.]

### Banding

Capsule banding machines orient filled capsules and place them in a carrier slat that exposes the area where the cap and body meet. A roller then applies a solution to the cap-body seam. Some machines employ a second application roller. After the solution is applied, capillary action causes some of it to migrate into the interstitial space between the cap and body, thereby sealing—to a degree—those surfaces. Next, the capsules are transferred to a carrier that moves them through the machine’s drying section, causing the moist, exposed bands to set up before the sealed capsules discharge into a receiver.

Each manufacturer has its own approach to banding. Qualicaps. The HiCapSeal 40 operates automatically. It applies seals to filled capsules that pass from the hopper through a feed roller, rectifier roller, and the transfer roller. The capsules rest in pockets in a conveyor belt slot as they move through the process. See the photo on page 10.

The slat's cavities are cut at a slight angle (θ degrees according to capsule size) from the axis of the slat. As the belt moves, the capsules rotate counterclockwise, which keeps the cap dome in contact with a cap guide and ensures that the capsules are accurately positioned over the sealing discs. Their position is controlled by the length of the caps, which compensates for any variation in the closed (joined) length of the capsule (Figure 1). The first sealing disc applies a band of sealing solution to the circumference of the capsule’s cap-body seam, and the second sealing disc applies another band to ensure a good seal (Figure 2). The sealing solution is maintained at a constant temperature and circulates continuously between the supply and sealing pans to maintain its uniformity (photo page 12). Next, the machine transfers the sealed capsules from the conveyor's slats to carriers that move them into a drying unit. There, filtered, ambient air dries the capsule seals.

<table>
<thead>
<tr>
<th>Manufacturer or supplier</th>
<th>Model</th>
<th>Sealing method</th>
<th>Maximum output (capsules/hr)</th>
<th>Capsule sizes</th>
<th>Other features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Qualicaps</td>
<td>S-1</td>
<td>Band</td>
<td>100 to 1,000</td>
<td>00 to 4</td>
<td>Bench-top unit (manual)</td>
</tr>
<tr>
<td></td>
<td>HiCapSeal 40/100</td>
<td>Band</td>
<td>50,000 (100,000 with HiCapSeal drying unit)</td>
<td>00 to 4</td>
<td>Commercial-scale unit</td>
</tr>
<tr>
<td>FS3 LabScale</td>
<td>Band</td>
<td>3,000</td>
<td>00 to 4</td>
<td></td>
<td>R&amp;D filler-sealer</td>
</tr>
<tr>
<td>Schaefer Technologies</td>
<td>LabTop</td>
<td>Band</td>
<td>100 to 1,000</td>
<td>00 to 4</td>
<td>Bench-top unit (manual)</td>
</tr>
<tr>
<td></td>
<td>Dott. Bonapace BD-3000</td>
<td>Band</td>
<td>3,000</td>
<td>00 to 4</td>
<td>R&amp;D sealer for use with In-Cap capsule filler with liquid filling station</td>
</tr>
<tr>
<td></td>
<td>STI CB-15</td>
<td>Band</td>
<td>15,000</td>
<td>000 to 4</td>
<td>Commercial-scale unit</td>
</tr>
<tr>
<td>IMA Active</td>
<td>Hermetica</td>
<td>Band</td>
<td>50,000 (upgradable to 100,000)</td>
<td>00el and 00 to 4 (option for 000 and 000el)</td>
<td>Commercial-scale unit</td>
</tr>
<tr>
<td>Capsugel</td>
<td>FS 1200</td>
<td>Liquid</td>
<td>1,200</td>
<td>00el to 4</td>
<td>R&amp;D filler-sealer</td>
</tr>
<tr>
<td></td>
<td>CFS 1500 C</td>
<td>Liquid</td>
<td>1,500</td>
<td>000 to 4</td>
<td>R&amp;D filler-sealer with containment</td>
</tr>
<tr>
<td></td>
<td>LEMS 70</td>
<td>Liquid</td>
<td>70,000</td>
<td>000 to 4</td>
<td>Commercial-scale unit</td>
</tr>
</tbody>
</table>
Qualicaps also offers a lab-scale unit, the FS3 LabScale (Figure 4) that automatically fills and seals as many as 3,000 capsules per hour. The machine's single disc (for the capsule caps) and its segments (for the capsule bodies) handle capsule sizes of 00 to 4 without using change parts. In operation, the body segments lift the capsules to the filling nozzles, which prevents low-viscosity liquids from splashing and high-viscosity fills from creating strings. The sealing section uses the same technology as the company's high-speed equipment. Upon discharge, filled and joined capsules are immediately fed into cavities in a sealing disc, which band-seals them. The capsules are then transferred into the drying disc-stacking unit (Figure 5). The capsules rotate 10 times within the drying disc before dropping to a drying disc. It cradles the capsule while room-temperature, filtered air is blown
across the sealed areas of the capsules to ensure they dry before the capsules exit the unit [7].

**Schaefer Technologies.** The S-1 is a lab-sized capsule band sealer (also available from Qualicaps). See Figure 6. In operation, filled capsules are manually loaded into carrier slats, and those are placed on feed tracks that guide them through a band sealing process identical to what the company's commercial-scale machines use. Slats containing the band-sealed capsules are then transferred to the drying rack, where they dry under ambient conditions [8]. The unit seals 100 to 1,000 capsules per hour, depending on the capsule size and change parts [9].

The CB-15 capsule banding machine automatically band-seals as many as 15,000 capsules per hour (photo). The hopper introduces the capsules into the rectification system, which orients the capsules in conveyor belt slats (similar to the Qualicaps configuration). Banding takes place as the capsules pass over two rollers that are partially immersed in temperature-controlled pans of gelatin solution; the solution contacts only the cap-body joint. Once banded, the capsules pass over drying fans as they move toward the pull-off station, and they’re discharged by vacuum.

The BD-3000 is an automatic banding machine built in Italy by Dott. Bonapace and sold in North America by Schaefer Technologies (photo). Its top output is 3,000 sealed capsules per hour. In operation, the liquid-filled capsules are rectified and positioned into the cavities of a rotating disc; the disc, in turn, transports them to the sealing station, where they’re held and rotated three times to ensure constant and uniform application of the sealing solution to the circumference of the body-cap junction. Once sealed, the capsules are transferred in the vertical position, cap down, to a second disc, where they dry for 4 minutes. Fans that circulate ambient-temperature air facilitate drying. The capsules are ejected through a chute. A programmable-logic controller handles all operations [10].
IMA. The Hermetica capsule banding machine applies a double gelatin band using two rollers, each with independent speed control (photo). By applying the second band, the unit eliminates any air bubbles or unevenness in the first band. The rollers are housed in separate gelatin bowls and you can adjust the gelatin temperature and viscosity of each bowl independently. A pre-drying unit (photo) guarantees that the gelatin band affixes to the capsule quickly, before the capsule moves to the drying box (photo) for final drying. Both the sealing and drying transport plates contain a double row of capsules (Figure 7), which reduces the number of pieces to be changed and cleaned. A camera-based system can be fitted to the unit, allowing you to check 100 percent of the capsules and to control and select individual banded capsules [11].

Liquid spray

Only one company offers machinery that seals capsules using a non-gelatin liquid. Capsugel. The company's technique is called Licaps Fusion Technology. It uses a micro-spray to convert two-piece capsules into one-piece fused capsules (Figure 8). In the first stage of the process, a very small amount of sealing fluid (a water-alcohol solution) is sprayed into the filled capsule's cap-body joint. Capillary action draws the fluid into the interstitial space between the cap and the body, and a suction device removes excess solution from the capsule surface. In the second stage, air heated to between 40° and 60°C gently blows across the capsule, completely melting and fusing the two gelatin layers and providing an impervious seal. In the third and final stage, the capsule is allowed to reach room temperature, which sets the gelatin [12].

Fusion ensures a tamper-evident seal, and its seal integrity has been verified by x-ray tomography [13].
Should someone attempt to open a fusion-sealed Licaps capsule, tampering becomes readily apparent and the capsule loses its integrity.

Capsugel also offers Licaps capsules that provide secure and robust containment of liquids and semi-solids (Figure 9). They differ from standard capsules in their use of several proprietary features, such as a larger contiguous sealing area that extends along the length of the capsule above its midpoint. Other capsules have a narrower body-cap junction for applying a capsule band.

Incorporated into the Licaps capsule are full-circumference rings that not only define the large sealing zone, but isolate and contain the liquid within the capsule. The capsule also includes both a liquid-entry channel that ensures consistent sealing conditions and vents that allow air to escape rapidly, which is critical for high-speed encapsulation [14].

Three machines employ the company's spray sealing technique: the CFS 1200, CFS 1500 C, and LEMS 70.

The CFS 1200 (photo) is a bench-top machine suitable for R&D labs and GMP manufacture of clinical supplies. It combines liquid filling and sealing to produce as many as 1,200 capsules per hour. It can handle both liquids and semisolids using a robust temperature-controlled filling pump with dosing accuracy of 0.1 to 1.2 milliliters. The CFS 1200 is scalable to commercial size LEMS manufacturing equipment [15, 16].

The CFS 1500 C (photo) functions similarly to the CFS 1200 but includes containment features that allow safe liquid filling and capsule sealing when handling potent compounds in early-phase clinical trials. The CFS 1500 C has a top output of 1,500 capsules per hour [17]. It weighs every capsule to determine whether to reject or accept it and records the result. An intuitive software interface saves the machine's settings and stores method development work for later recall. Most important, the machine cleans easily because of removable parts and a verification system that prevents cleaning fluid from entering the working elements of the machine [18].

The LEMS 70 (photo) is a production-scale sealing system with a top output of 70,000 capsules per hour. Key components include high-capacity micro-spray bars and a contiguous tumble dryer fitted with a rotating air lock. It is built with FDA-approved materials, and its software complies with 21 CFR Part 11 requirements. The sealing range covers viscosities of 30 to 30,000 centipoise.

In commercial installations, the sealing machine connects to standard capsule fillers that use a liquid filling head. Inspection stations would also typically be added [19].

Ultrasonic welding

Rainbow Medical Engineering. The term ultrasonic applies to sound waves whose frequencies exceed 20 kilohertz, and an ultrasonic welding system comprises four basic components:
1. A generator or power supply;
2. A transducer that converts electrical energy into vertical, low-amplitude mechanical motion (vibration);
3. A booster that modulates the transducer’s vibrations; and
4. A sonotrode or horn that applies the vibrations to the material being welded.

Ultrasonic welding involves the application of a vibrating sonotrode to a thermoplastic-thermoplastic interface, thereby inducing a high degree of localized frictional heat that causes the thermoplastics to melt and form a molecular bond at the interface. Welding usually takes only 0.1 to 1 second, a key element to its success in high-speed capsule filling operations.

Thermoplastic polymers have two properties that make them particularly suited to ultrasonic welding: low thermal conductivity and melting points between 100° and 200°C. Most pharmaceutical polymers—celluloses, starches, and biopolymers such as gelatin—have these thermoplastic properties. In fact, these thermoplastics are often molded or extruded into capsule-shaped components for use in a number of drug delivery applications.

As illustrated in Figure 10, the capsule components are positioned in a fixture such that the sonotrode encircles the circumference of the cap-body interface. Upon contact with the active sonotrode, the capsule parts are mechanically vibrated at 20,000 to 40,000 cycles per second. That causes localized friction between the two capsule sections that leads to molecular melting and the capsule halves fuse [20].

Once sealed using Rainbow Medical Engineering’s ultrasonic method, hard gelatin capsules will show clear evidence of tampering if the capsule body is separated from the cap: The capsule body will break along perforations and show tell-tale crescent-shaped edges [21].

Acknowledgements

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