This article describes a study in which an enteric coating was applied to empty capsule shells to protect an insulin compound from the acidic environment of the stomach. The method enabled the compound to enter clinical trials quickly, saving time and money.

Any active pharmaceutical ingredients (APIs) require enteric protection to prevent the acidic environment of the stomach from degrading them or to achieve a desired therapeutic effect by targeting absorption in the lower gastrointestinal tract. Enteric coatings provide a polymer barrier to high acidity but break down rapidly at a less acidic (higher) pH, such as that of the small intestine.

Solid ingredients, such as pellets and tablets, readily accept enteric coatings, and they can later be filled into capsules for oral delivery. But other ingredients—such as the liquid fills within hard capsules—cannot accept them. In those cases, there are two options: 1) Fill the capsules and then apply the enteric coating, or 2) coat the empty capsule shells first and then fill them. One drawback to applying the coating to capsules after filling is the possibility that the enteric properties will not be retained at the capsule junction. Coating the capsules before they're filled eliminates that possibility. In this case, enteric-coated capsules were a better option than developing pellets or tablets because only a limited supply of the insulin compound was available during the early stages of development. Furthermore, for liquid APIs that are unstable in acid, enteric-coated capsules are often the only way to administer them. The aim of the trials was to evaluate the reproducibility of the manufacturing process and to assess the dissolution performance of an insulin product prior to clinical trials.

Methodology. All the preliminary coating trials were performed using clear, size 00 hypromellose capsule shells (Vcaps from Capsugel, Greenwood, SC, and Quali-V from Qualicaps, Whitsett, NC). The shells were separated into caps and bodies using a Qualicaps F40 filler equipped with two custom-fabricated Plexiglas vacuum shoes, one installed at the filling position and the other after the ejection position. As the capsules passed beneath the vacuum shoes, the bodies and caps were sucked out of the body or cap disk and pneumatically conveyed (Line-Vac from Exair, Cincinnati, OH) into 5-gallon high-density polyethylene pails lined with polyethylene bags and covered with perforated lids to vent...
the conveying air. When the pails were full, the process was stopped, the pails emptied, and the process restarted.

Next, the caps and bodies were loaded separately into a Wurster-type fluid-bed coater (Model GPCG-5 from Glatt, Ramsey, NJ). In the Wurster process, a stream of air moves through the product bed while the coating is sprayed, as it is applied, the stream of air dries the film coating (Eudragit L 30 D-55 from Evonik Industries, Parsippany, NJ). The target weight gains were 16 percent, 20 percent, and 24 percent. Table 1 shows the composition of the enteric coating formulation.

To achieve the desired weight gains, an iterative coating process was used in which the actual weight gain was measured at various intervals during processing. The difference between the target gain and actual weight gain was determined. Next, based on the solids content of the coating suspension and on estimates of coating efficiency, the amount of additional coating required to reach the target weight was calculated. This iterative process was repeated until the actual weight gains were within 1 percent of the target weight gains.

Next, a 99-to-1 blend of acetaminophen and FD&C blue #1 aluminum lake was prepared in a polyethylene bag and passed through a 40-mesh hand screen. The powder was then filled into the coated capsules bearing the three different coating weights. The target weight was 505 grams. The bodies were then closed using the enteric-coated caps. Other capsule bodies bearing the three different coating weights were filled with a 99-to-1 placebo blend of microcrystalline cellulose and FD&C blue #1 aluminum lake. They too were closed using the enteric-coated capsule caps. All were visually inspected for leakage. As a positive control, uncoated capsule shells were filled with the same quantity of the acetaminophen blend as the enteric-coated capsules. Three batches of the 20-percent-weight-gain filled capsules were analyzed to evaluate batch-to-batch reproducibility.

Six capsules from each batch of the coated capsules were tested for acid resistance using USP <711> : Apparatus 2 with sinkers at 30 rpm for 2 hours. The USP monograph for acetaminophen (UV detection) was used to analyze them. The uncoated filled capsules were analyzed for acid resistance using the same dissolution method.

### Table 1

<table>
<thead>
<tr>
<th>Component</th>
<th>Suspension percentage (w/w)</th>
<th>Solids percentage (w/w)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methacrylic acid copolymer dispersion</td>
<td>40.8</td>
<td>76.1</td>
</tr>
<tr>
<td>Triethyl citrate</td>
<td>2.5</td>
<td>15.3</td>
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<tr>
<td>Glyceryl monostearate</td>
<td>1.0</td>
<td>6.2</td>
</tr>
<tr>
<td>Polysorbate 80</td>
<td>0.4</td>
<td>2.5</td>
</tr>
<tr>
<td>Purified water</td>
<td>55.4</td>
<td>(*)</td>
</tr>
</tbody>
</table>

* Removed during processing

### Figure 1

Uncoated and coated capsule bodies and caps (20 percent weight gain)

As the images in Figure 1 show, the clear capsule caps and bodies were successfully coated with an enteric composition (Table 1). After optimizing the equipment configuration and coating conditions, the coating became smooth and uniform in appearance; it was also flexible and robust enough to withstand closing after filling without cracking or flaking off.

Figure 2 shows the average dissolution results (n = 6) of acid-resistance testing for the coated and uncoated filled capsules. For all coating weight gains, there was an average release of 0 percent acetaminophen after 2 hours of exposure to an acidic medium in a dissolution bath. The results for the three batches coated to a weight gain of 20 percent demonstrated the reproducibility of the manufacturing process and dissolution performance. Even the appearance of the three batches was the same.

Figure 2 also shows the results for the uncoated filled capsules after 2 hours of exposure to an acidic medium in the dissolution bath for 2 hours. The average acetaminophen release from them was 93 percent, confirming that the acid resistance of the coated shells was not imparted by the shells but by the enteric coating. The
photos in Figure 3 show how the capsules and their fill appeared after dissolution testing.

Conclusions

Filled manually, the enteric-coated empty capsule shells described here performed well. However, they may not perform as well on high-speed encapsulation equipment and thus commercial application of the technique may be limited. Nonetheless, it is useful in providing acid resistance during non-traditional, early phase-1 formulations for evaluation and screening studies. Indeed, the coated capsules offered a faster path to an enteric-coated product for acid-labile compound drugs than was possible using other dosage forms, such as tablets or pellets, that require more elaborate formulation and coating processes.

The coating method is easy to use and can be applied at advanced clinical stages. Furthermore, the empty capsules enable development scientists to adjust the size of the dose easily. There are many types of enteric coatings that can be used. In this case, it was an aqueous film coating, which eliminated concerns about a non-aqueous solvent entering the finished product. Finally, the Wurster process is efficient and ideal for empty capsules compared to the conventional pan coating because it is more gentle and easier to observe.

Yogesh Chachare is scientist III; Theresa Estep is granulation group leader; and Mark Geis is senior technician at Patheon Pharmaceuticals, 4721 Emperor Blvd., Suite 200, Durham, NC 27703. Tel. 919 226 3200. Website: www.patheon.com. Michael Gosselin, formerly of Patheon, is manager, formulation at Aptalis. John Dela Cruz is formerly of Patheon.