Innovative new drug molecules and technologies have paved the way for promising new therapies to some of the most pressing, life-threatening diseases. The FDA has affirmed that potential by granting fast-track designation to these new drug candidates and products. In 2018, there was a surge in pharmaceutical approvals, with a record 61 combined approvals from the FDA’s Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER) divisions [1]. Notably, within those approvals, relatively large percentages of products were classified as first-in-class (43 percent) and orphan drug (56 percent), and a significant

As formulators increasingly prioritize speed to market, innovations have led to next-generation HPMC capsules that provide consistent dissolution performance, prevent crosslinking, and improve compatibility with moisture-sensitive APIs. This article describes how these differentiators provide drug developers seeking immediate-release dosage forms with an alternative to gelatin capsules.
These next-generation HPMC capsules demonstrate improved performance compared to traditional HPMC capsules due to innovations around the gelling system. Traditional HPMC capsules use a gelling system that includes ionic gel promoters and secondary gelling agents to create the capsule’s shell exterior. However, these secondary gelling agents can negatively impact the dissolution profile of the HPMC capsule, causing variability in dissolution rates depending on the pH and ionic strength of the dissolution media.

The new class of HPMC capsules was engineered to mitigate these issues around dissolution. Scientists developed a thermo-gelation process that uses only water and HPMC to create the capsule’s hard shell, eliminating the need for secondary gelling agents and producing HPMC capsules with a dissolution profile comparable to that of gelatin capsules. Dissolution studies have shown greater performance variability in capsules that include a gelling system in the HPMC matrix, as shown in Figure 1a, and more consistent performance in capsules comprised of only HPMC and water, as shown in Figure 1b [2]. Consistent and predictable dissolution performance of the capsule excipient allows formulators to avoid costly and repetitive stability tests, saving time in the drug development process.

Thermo-gelation advances HPMC hard capsules

HPMC was well vetted as a pharmaceutical excipient long before its use as a capsule polymer. To that end, it has attained regulatory approval in all major pharmacopoeias as well as GRAS status by the FDA and food-additive status by the European Commission. Unfortunately, first-generation hard capsules made from HPMC do not dissolve quickly or consistently, potentially rendering the encapsulated compound ineffective and delayed in release. Delays and unreliable release are especially problematic in the formulation of immediate-release drug products.

Due to recent advancements, however, a new generation of HPMC capsules is available as an alternative to gelatin capsules for immediate-release formulations.

Table 1
Trends in key metrics for new drug approvals

<table>
<thead>
<tr>
<th>Classification</th>
<th>Percentage of approvals</th>
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<tbody>
<tr>
<td></td>
<td>2018</td>
</tr>
<tr>
<td>Big Pharma*</td>
<td>26%</td>
</tr>
<tr>
<td>Biologics</td>
<td>36%</td>
</tr>
<tr>
<td>First in class</td>
<td>43%</td>
</tr>
<tr>
<td>Orphan drug</td>
<td>56%</td>
</tr>
<tr>
<td>Fast track</td>
<td>39%</td>
</tr>
<tr>
<td>Breakthrough therapy</td>
<td>23%</td>
</tr>
<tr>
<td>Priority review</td>
<td>70%</td>
</tr>
<tr>
<td>Accelerated approval</td>
<td>8%</td>
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</tbody>
</table>

* “Big Pharma” includes: Abbvie, Amgen, AstraZeneca, Bayer, Bristol-Myers Squibb, GlaxoSmithKline, Johnson & Johnson, Eli Lilly, Merck, Novartis, Pfizer, Roche, and Sanofi.
Dissolution and crosslinking performance

Human bioequivalence studies have shown that next-generation HPMC capsules have comparable dissolution profiles to gelatin capsules. For example, one human bioequivalence study showed equivalent performance between next-generation HPMC capsules and hard gelatin capsules with three Biopharmaceutical Drug Disposition and Classification System (BDDCS) Class 1 biomarkers—acetaminophen, acetylsalicylic acid, and caffeine [3].

In this study, fixed-dose combination Excedrin Extra Strength caplets containing three different rapidly-absorbed drugs over-encapsulated with gelatin capsules, and the same caplets over-encapsulated with HPMC capsules using a thermo-gelation process (Capsugel Vcaps Plus) were tested to compare the dissolution rates of the HPMC and gelatin excipients. Each excipient released 95 percent of its drug contents within 30 minutes and demonstrated similar delays in release compared to un-encapsulated dosage forms.

There was no significant difference in in vivo pharmacokinetics in 24 human subjects, showing the comparable performance of HPMC capsules without gelling systems and gelatin capsules. Similar studies done on HPMC capsules containing gelling systems showed greater intra-patient variability as well as a notable difference in onset time of drug absorption (tlag) [4].

**Human bioequivalence studies have shown that next-generation HPMC capsules have comparable dissolution profiles to gelatin capsules.**

HPMC capsules can also help formulators address potential chemical incompatibilities associated with gelatin capsules. For instance, formulators have long known that gelatin capsules have the potential for crosslinking, a challenging phenomenon in which the contents of the gelatin capsule are released at a much slower rate than expected. Determining the cause of crosslinking can be complex but it occurs due to a chemical reaction with amino acids in the gelatin capsule. Crosslinking often causes costly delays in the development timeline when using gelatin capsules, but drug developers can avoid the issue entirely by using HPMC capsules, because the cellulose polymer does not contain amino acids. Similarly, formulations that can react with gelatin (such as reducing sugars, which produce a Maillard reaction) are more suitable for HPMC capsules.

**Encapsulating moisture-sensitive APIs**

Water content is a critical factor in the successful use of capsule polymers. Gelatin capsules have a higher water content than HPMC capsules, which can cause challenges with certain compounds. Gelatin capsules are manufactured with a consistent water content between 13 and 16 percent to ensure the shell’s flexibility and ideal mechanical properties. To maintain this water content, gelatin capsules must be stored and used in environments between 35 and 65 percent relative humidity and between 15 and 25°C. However, some formulations suffer from stability challenges within these conditions. Moisture-sensitive compounds, for instance, are not compatible with capsules that contain significant water content, as degradation can occur.

Capsules made from HPMC are more suitable for moisture-sensitive compounds, as they have an average water content within the 5 to 8 percent range and present fewer formulation concerns. The benefits of using HPMC capsules with moisture-sensitive compounds can be modeled well with acetylsalicylic acid formulations, as the moisture differential between hard gelatin and HPMC capsules has been shown to affect the extent of hydrolysis that occurs.

When an acetylsalicylic acid formulation is loaded into both gelatin and HPMC shells and placed on stability at 25°C and 65 percent relative humidity in inductively sealed bottles, the amount of degradation over time is considerably different between the two polymers, as shown in Figure 2. Over 18 months, approximately 8 percent degradation of the acetylsalicylic acid formulation in the hard gelatin capsules occurred versus approximately 2 percent in the HPMC capsules. As the bottles were inductively sealed, environmental moisture can be discounted, leaving the moisture differential contained within the capsule shells as the primary source of water for the hydrolysis. This impact can be extrapolated to increased shelf-life stability for moisture-sensitive compounds in HPMC capsules.

**Figure 2**

Degradation of acetylsalicylic acid over time in gelatin capsules (~14% moisture) versus HPMC capsules (~6% moisture)
Similarly, the amount of moisture content in the capsule shell can impact hygroscopic formulations. Hygroscopic compounds can often pull water from the environment and have been shown to pull moisture from the capsule shell as well. For gelatin, loss of moisture typically impacts the capsule’s mechanical resistance if the resultant water content drops below the recommended 13 to 16 percent described previously. Desiccants in packaging materials often produce the same result. Unlike gelatin capsules, HPMC capsules do not rely on water for plasticity, so they can tolerate a lower average water content and can sustain mechanical stability at a lower relative humidity range than gelatin capsules can, as shown in Figure 3.

An important differentiator of HPMC capsules from gelatin capsules is their ability to increase bioavailability for some high-energy formulation types (such as amorphous dispersions and salts) and molecules with low solubility. These formulation types are likely to become supersaturated and precipitate in the stomach’s acidic environment. Several publications list the ability of HPMC to affect crystallization, and some report an increase in API bioavailability via this method by reducing the potential for crystallization, which leads to a supersaturated state of the drug molecule(s) in vivo [5]. This benefit helps formulators select the appropriate dosage form for drug molecules with low aqueous solubility.

Conclusion
With the resurgence of pharmaceutical approvals, notably those of first-in-class molecules and those with shortened approval pathways, strategies to handle a broad array of drug molecules are critical. Next-generation HPMC capsules without gelling systems continue to gain traction for their ability to simplify the drug development timeline via a “right-first-time” development approach that can reduce or even eliminate the potential for repetitive formulation and stability studies. 

References

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