

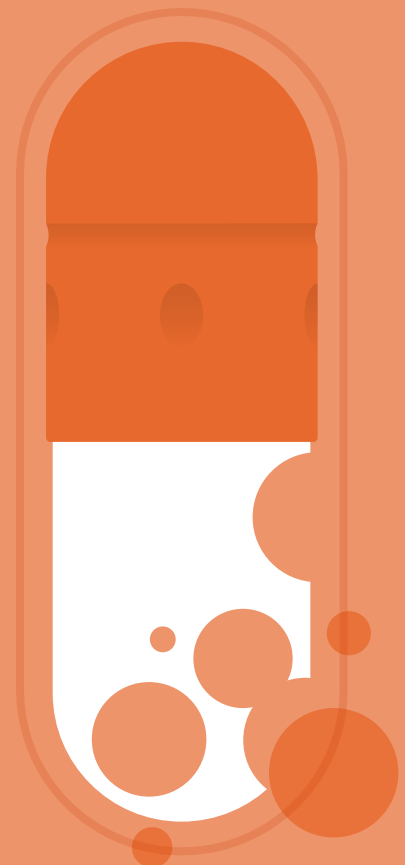
Advancing Oral Drug Delivery: The Innovation Behind Capsugel® Enprotect® Capsule

How Capsugel's polymer science and capsule manufacturing expertise led to a breakthrough in enteric protection

The challenge of enhancing oral dosage delivery

Oral administration remains one of the most widely used and preferred routes for drug delivery, offering convenience, high patient compliance, and cost-effectiveness. However, its effectiveness is often limited by several critical factors, including the degradation of acid-labile active pharmaceutical ingredients (APIs) in the harsh gastric environment, the difficulty of targeting release at the optimal intestinal absorption site, and the potential for gastrointestinal irritation caused by certain compounds.¹

Overcoming these barriers is essential to ensuring that oral drug formulations can provide predictable, effective, and well-tolerated treatment outcomes.



An evolution of enteric protection

To protect APIs from the acidic conditions of the stomach and control their site of release in the small intestine, a range of enteric protection strategies have been developed over the years. Early methods included sugar-based coatings (SC), but these were designed to fundamentally improve palatability, rather than provide enteric protection of the API.² Film coating (FC) followed, which provided manufacturing efficiencies over SC, and offered modified drug release dynamics, together with protection of the API from light, temperature, and humidity.² However, these rudimentary techniques provided inconsistent results and were eventually replaced by more advanced polymer-based coatings.

The introduction of polymer coatings, such as phthalate derivatives, cellacelate, cellulose acetate phthalate, methylcellulose, and HPMC-AS (hypromellose acetate succinate) enabled more reliable enteric protection and controlled-release properties. However, despite their improved performance, these coating-based approaches introduced additional complexities into the manufacturing process.²

The need for solvents—water, aqueous solvents, or non-aqueous organic solvents—to apply these coatings raised concerns about potential interactions with the API, leading to stability issues. Additionally, the application of heat during the drying process posed further risks of API degradation.² The extra processing steps of traditional coating methods also extended production timelines and increased manufacturing costs.

The advantages and limitations of HPMC

The development of hydroxypropyl methylcellulose (HPMC), or hypromellose, represented a significant advance in capsule materials.³ A cellulose derivative, HPMC offered several advantages over gelatin, including improved stability, greater tolerance of a wider range of temperatures and humidities without adversely affecting its mechanical properties, and reduced interactions with APIs.² Its lower moisture content also minimized the risk of degradation, making it well suited for sensitive drug formulations. The specific mechanical robustness HPMC brings to the capsules is linked to the ability to use them at very low water content and/or with hygroscopic excipients without the risk of capsules breaking in their lifecycle.

However, while HPMC offers many desirable properties, it does not provide acid resistance. As a result, traditional HPMC-based capsules still required secondary coating processes to achieve enteric protection.² This limitation spurred the need for a more advanced solution—one that retained the benefits of HPMC while integrating intrinsic enteric protection without the need for additional coatings.

A new approach: Developing an intrinsically enteric capsule

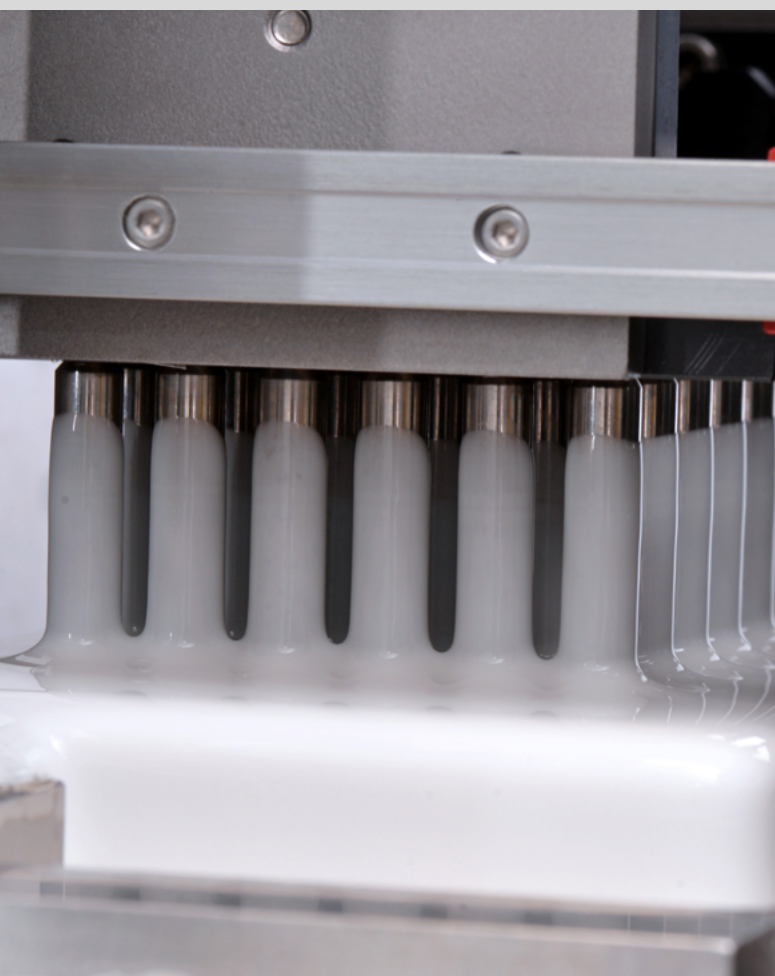
Recognizing the limitations of existing enteric protection technologies, a multidisciplinary task force within Capsugel was established. This task force, involving a vast array of skills and expertise, and including different R&D groups, embarked on an ambitious project to develop an intrinsically enteric capsule. The goal was to create a capsule that would offer robust gastric acid resistance, customizable enteric release profiles, and compatibility with large-scale manufacturing processes. However, achieving this objective required overcoming significant scientific and engineering challenges.

Addressing polymer suitability and regulatory considerations

The concept of an intrinsically enteric capsule had been explored before, but its realization was hindered by several practical constraints. One of the primary challenges was the selection of suitable polymers.² While numerous polymeric materials exhibit acid-resistant properties, regulatory considerations also need to be taken into account.

To minimize the need for extensive clinical testing and accelerate development, the Capsugel team focused on using polymers that comply with the regulatory requirements pertaining to pharmaceutical products, and the US Food and Drug Administration.⁴ This approach narrowed the field of potential candidates and imposed limitations on the extent to which these materials could be modified or re-engineered.

*HPMC-AS is not approved for food in Europe.



Overcoming manufacturing challenges

A key requirement in capsule manufacturing is achieving uniform and structurally robust capsule walls. This meant that there were several key challenges that needed to be overcome: gelation of polymers to deliver consistent film formation and drying; ensuring capsules were not too brittle to withstand high-speed filling and handling.

Furthermore, the capsule needs to withstand the full production process, including both our and the customer's manufacturing processes. Another challenge involved the application of a second coating over the water-soluble inner layer of the capsule.

Outer layer

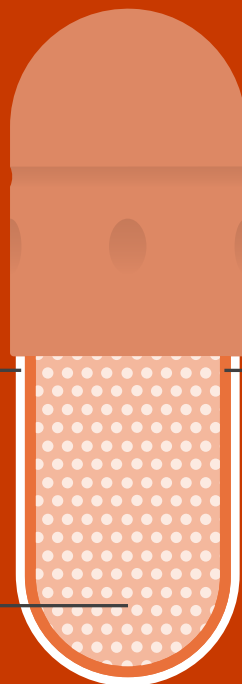
- HPMC-AS, only dissolves in pH > 6

Active drug (API)

- Protected from gastric acid by outer layer
- In contact with HPMC inner layer

Inner layer

- HPMC, dissolves easily at any pH



Engineering a dual-dipping manufacturing process

To resolve these issues, attention shifted toward optimizing the manufacturing process itself. Working with the available polymers, the team worked to refine the manufacturing process and the conditions under which the capsule layers were formed. Key process parameters—including temperature, drying conditions, properties of the polymeric solutions, viscosity, and pH were established for consistent layer formation and adhesion properties of the polymeric solutions.

Drying conditions played a critical role in enabling the manufacturing of the dual layer capsules and determining the mechanical properties of the final capsule. In a continuous production cycle, drying steps can also influence pin temperature, impacting layer adhesion and polymer deposition.

The breakthrough Capsugel® Enprotect® capsule

After extensive research, testing, and manufacturing process optimization, the Capsugel team had successfully delivered a new and unique type of capsule with the performance and properties sought. Capsugel® Enprotect® is a bi-layered capsule and the outcome of the first-of-its-kind enteric technology. This breakthrough innovation offers formulators a capsule with:

- Acid resistance up to around pH 6.0, with dissolution occurring at about pH 6.2, enabling precise delivery of drug to the desired site in the small intestine
- No need for secondary coatings, eliminating the risks associated with traditional enteric coating processes
- Compatibility with high-speed filling machines, ensuring seamless integration into existing production lines
- Mechanical properties that provide superior durability and handling performance
- Bespoke or customized release of APIs. Through Innovaform® Accelerator we support a wide range of pharmaceutical applications, from small-molecule drugs to complex biologics

“This project showcases our commitment to providing formulators with innovative solutions. Capsugel® Enprotect® capsule was our baby, and it truly takes a village to raise one.”

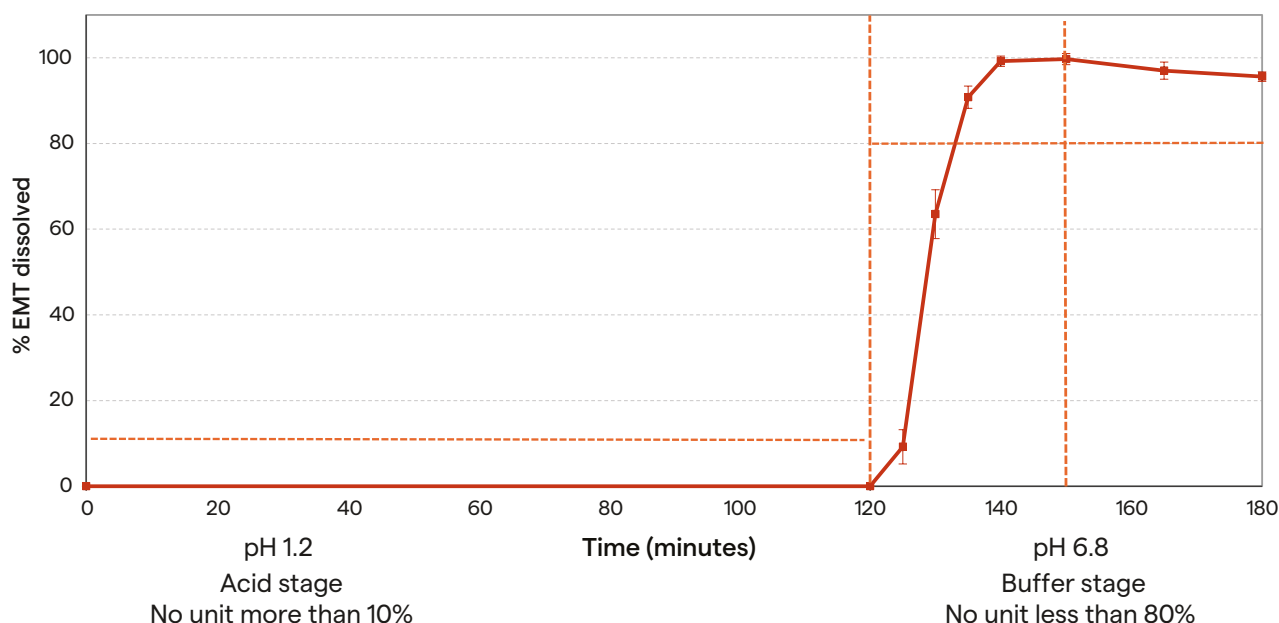
Ljiljana Palangetic,
Head of Hard Capsules R&D,
Capsugel

Dissolution performance

Dissolution confirmed in compendial tests

In lab tests, the Capsugel® Enprotect® capsule was compliant with USP requirements for dissolution of delayed release dosage forms.

Average dissolution profiles with standard deviation interval



Release of esomeprazole magnesium trihydrate (EMT) uncoated pellets from the capsules conforms to the USP esomeprazole magnesium delayed-release capsules monograph.

The future of oral drug delivery

The development of Capsugel® Enprotect® capsule marks a significant innovation in oral drug delivery, offering formulators new possibilities for designing more effective and patient-friendly therapies. By eliminating the need for secondary coatings, this innovation streamlines manufacturing, reduces the risk of API degradation, and expands the range of APIs that can be effectively delivered via oral administration. It also provides opportunities for oral delivery of certain APIs that before couldn't be formulated in oral dosage forms.

Looking ahead, the technological innovations behind Capsugel® Enprotect® capsules unlock potential future developments in capsule design and new opportunities for enteric drug delivery. The ability to create intrinsically enteric capsules also opens the door to new polymer combinations with even more advanced properties, enabling more precise drug targeting and aiding bioavailability. Furthermore, this technology offers the potential for oral capsules to deliver therapeutic payloads with greater specificity, even to the lower regions of the distal intestine.

Conclusion

Capsugel® Enprotect® capsules represent a pivotal progression in pharmaceutical capsule technology. By combining cutting-edge polymer science with innovation in manufacturing, Capsugel has advanced the opportunities for enteric drug delivery.

This innovation not only aids the bioavailability, stability, and targeted delivery of APIs, but it also supports the delivery of a broad range of therapies, from small-molecule drugs to complex biologics.

By providing pharmaceutical companies with a next-generation oral delivery system, Capsugel® Enprotect® capsules ensure that modern medicines can be delivered to patients with greater precision and keep pace with therapeutic demands.



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