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Next-Generation Capsules: Emerging Technologies in Capsule Fabrication and Targeted Oral Drug Delivery

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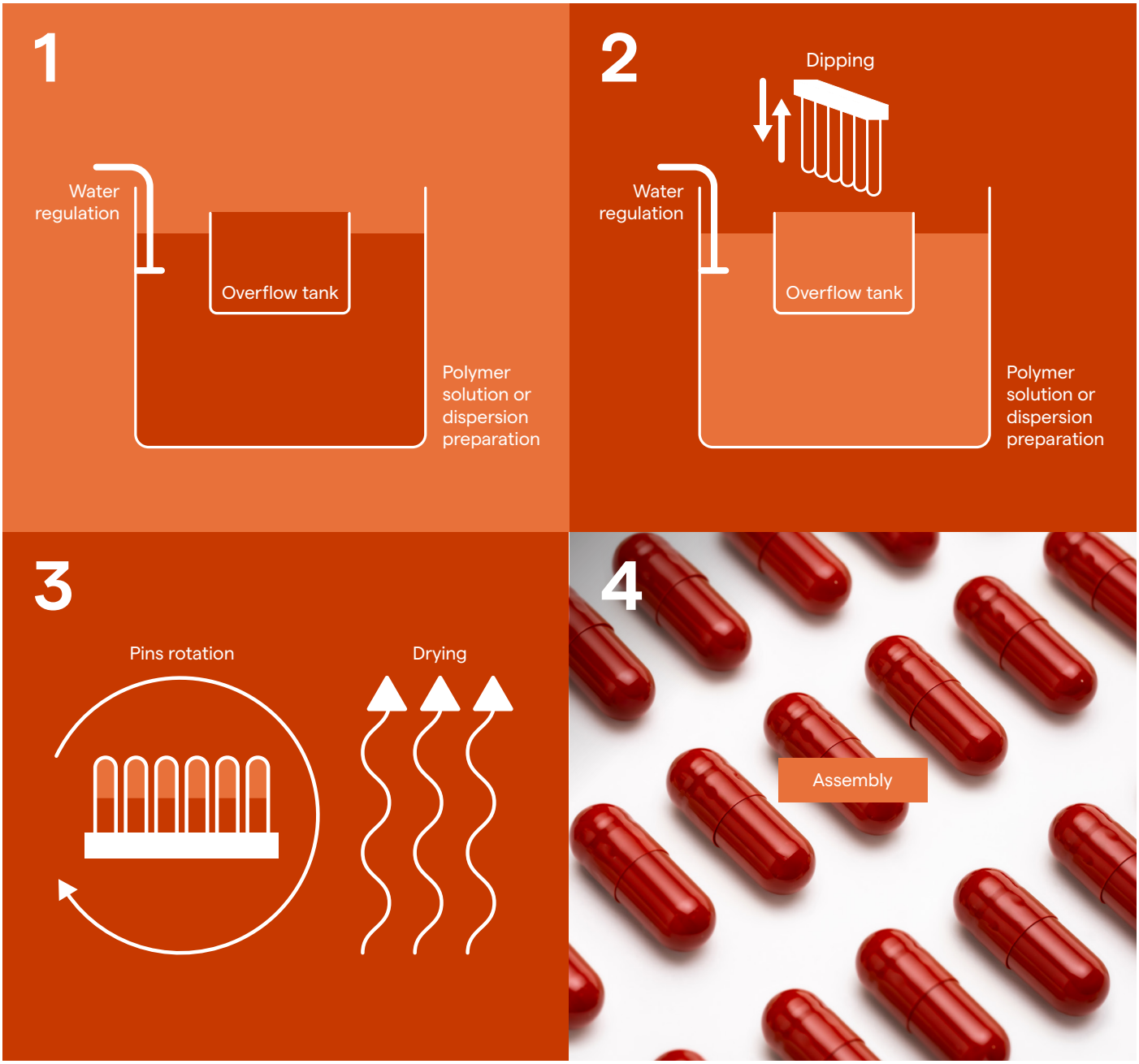
Introduction

Capsule technologies have been advancing steadily for decades. Progress in closure mechanisms and manufacturing processes has improved the safety, stability, and reproducibility of capsule-based products.

Technologies such as enteric coating now offer the opportunity to enhance bioavailability and stability of sensitive molecules such as peptides, proteins, and RNA-based therapies. Building on the foundation of enteric coating, new innovations such as ready-to-use Capsugel® Enprotect® capsules and 3D printing technologies are expanding the functional possibilities of capsule design.

Modern capsule options have evolved beyond passive carriers into active components of sophisticated drug delivery strategies. By examining the changing landscape, this review highlights the growing role of capsules as a next-generation platform for oral targeted drug delivery, capable of meeting increasingly complex therapeutic demands.

Current state of the art in capsule technology



Capsules have been used as an oral dosage form since the early 1830s, when production was entirely manual, using pins dipped by hand. It wasn't until 1931 that Arthur Colton industrialized this process, creating the system that modern capsule manufacturing is built on. Today, capsule fabrication is an established process with four main steps:

1. **Polymer solution or dispersion preparation**
2. **Dipping**
3. **Drying**
4. **Assembly**

This method requires precise control over multiple parameters to achieve capsules are defect free, with the desired mechanical and dimensional properties.

Alternative materials and new opportunities

As capsule technologies have diversified, new polymers have enabled the creation of enteric coatings, specifically tailored for targeted intestinal delivery. The aim of functional polymers is to protect sensitive APIs from the highly acidic conditions of the stomach, ensuring their release in the small intestine's or colon's more neutral environments.

This is particularly beneficial for diseases with localized inflammation of the gut, as the local delivery can maximize therapeutic efficacy while minimizing systemic side effects. Several different strategies can be used to achieve targeted delivery:

- Polymers that utilize pH-dependent solubility, including polymethacrylates (e.g. Eudragit® L-100 and Eudragit® S-100) and cellulose-based polymers (e.g. cellulose acetate phthalate [CAP], cellulose acetate succinate [CAS], and cellulose ether esters, such as hydroxypropyl methylcellulose phthalate [HPMCP] and hydroxypropyl methylcellulose acetate succinate [HPMC-AS])
- Microbiota-dependent approaches that utilize polysaccharides degraded by colonic bacteria, or prodrug conjugates that are cleaved by microbial enzymes
- Time-dependent coatings designed to release drugs after a predetermined lag phase of 3–6h
- Osmotic-controlled systems that achieve near zero-order release by generating osmotic pressure across semi-permeable membranes
- "Smart" capsules that incorporate stimuli-responsive polymers or embedded electronics to achieve precise site-specific release or even combined diagnostic–therapeutic functions

Coating technologies for enteric protection of capsules

Enteric coating of hard capsules has recently emerged as an important alternative to traditional enteric-coated tablets. This approach enables delayed release of APIs that cannot withstand compression, supports complex or sensitive formulations, and aligns with the growing demand for targeted delivery and precision medicine, especially for small patient cohorts in clinical trials.

Capsules have been used as a versatile tool to address a wide variety of drug delivery challenges across diverse therapeutic areas: Eudracap® enteric capsules, created by spraying Eudragit® polymer onto empty hydroxypropyl methylcellulose (HPMC) capsules, have been used to deliver albendazole nanosuspension-coated granules locally for colorectal cancer treatment; TARPEYO® capsules are a delayed-release therapy delivering budesonide to the distal ileum for the treatment of immunoglobulin A (IgA) nephropathy; and Mycapssa® capsules are an example of using enteric capsules to orally deliver therapies traditionally administered by injection, in this instance octreotide.

However, the development of enteric-coated capsules faces some challenges:

- **Adhesion of the coating material on the capsule surface:** As both gelatin and HPMC present adhesion challenges, an intermediary seal coating can be applied; however, uneven coating application can result in inconsistent drug release profiles
- **Use of solvents and heat in post-filling coating:** Reliance on solvent-based coatings presents health, safety, and environmental concerns, as well as potential interactions with the API, which could compromise its stability and efficacy
- **The need for consistent machinability in pre-filling coating:** When coating empty shells, the coating material is deposited on top of standard capsules, resulting in capsules with higher diameters; this may affect the capsules' machinability, potentially causing disruptions in mass production processes and loss of API

Industry takeaway

Enteric coatings have supported the development of targeted strategies in oral drug delivery. These coatings can protect acid-labile APIs from the harsh conditions in the stomach, providing localized drug delivery for inflammatory gut conditions or enabling increased uptake in the intestine. Coated capsules provide an important alternative to coated tablets when complex formulas or small batches are needed, or if APIs are sensitive to the mechanical stress of compression.

However, coating tablets and filled capsules requires additional manufacturing steps, which can expose APIs to solvents and heat, potentially compromising stability and efficacy, and can result in machinability issues for capsules.

These limitations underscore the need for new and innovative approaches to enteric capsule design and manufacturing to enhance reliability and repeatability.

Dipping technologies for bi-layered capsules offering enteric protection

Capsugel® Enprotect® capsules are a notable breakthrough in the enteric delivery field. These capsules are created using a novel double-dipping approach, with two polymers deposited on the same pin.

The first layer provides mechanical integrity, while the second layer provides targeted-release properties (to learn more about the double dipping process for manufacturing bi-layered capsules, **click here to read the full article**). By using Capsugel® Enprotect® capsules, formulators can avoid exposure to the solvents or heat associated with the post-filling step of traditional enteric coating. Additionally, as the capsule is a ready-to-use system, production is streamlined, offering significant advantages in terms of manufacturing efficiency and filling process. Finally, the versatility of the technology allows for different polymer solutions to be utilized in the dipping steps to further expand formulation flexibility, allowing bespoke drug release profiles or customization to make the inner shell compatible with specific APIs.

Capsugel® Enprotect® capsules are designed to resist the acidic conditions of the stomach and dissolve in the more neutral/alkaline environment of the intestine. Advanced ex vivo models mimicking the digestive system have confirmed the protective function of the bi-layered capsule and have demonstrated the potential to deliver pancrelipase, an acid-sensitive enzyme for patients with exocrine pancreatic insufficiency. The findings emphasized the potential of the Capsugel® Enprotect® capsule for the precise delivery of proteins and peptides to the small intestine.

Another application that has been studied is the enteric delivery of fecal microbiota transplantation (FMT), an established treatment for Clostridium difficile infections. Encapsulation with Capsugel® Enprotect® capsules has been shown to preserve the integrity of the microbiota during processing and storage, enhancing the stability and handling of FMT capsules, making it a more practical therapeutic option.

The capsule has also been extensively tested on healthy volunteers in two studies, using fasted (N=8) and postprandial conditions (N=16). In both studies, magnetic resonance imaging was used to localize the capsule while caffeine detection in saliva was used to assess disintegration. Both methods consistently showed that disintegration occurred in the jejunum and ileum, and importantly, no significant difference was observed between fed and fasted conditions.

Industry takeaway

Capsugel® Enprotect® capsules represent a major innovation in targeted drug delivery as a ready-to-use enteric delivery system. As no post-filling coating is required, manufacturing is streamlined and APIs avoid the exposure to solvents and heat associated with this step. The bi-layered technology provides versatility, allowing customization of the inner and outer layers for bespoke capsule creation.

Emerging techniques to manufacture targeted-release capsules

Emerging technologies, such as 3D/4D printing and injection molding (IM), are also continuing to push the boundaries of capsule design. 3D printing can be used to create capsules with intricate designs, such as compartments that separate the API from excipients or other functional ingredients, allowing multi-layered dosage forms or delaying the release of certain drugs.

4D printing can extend this concept by incorporating the dimension of time, through stimuli-responsive materials that alter their properties over time or in response to environmental factors. IM, widely used in the plastics industry, has been used to create time-lag capsules, with the modulation of wall thickness determining the lag time.

While these technologies hold significant promise, they also face several challenges, which limit their widespread use. The primary challenge is maintaining API stability during the heat of the manufacturing process, as many APIs may degrade when exposed to the elevated temperatures required for printing or IM. An additional challenge is the limited selection of pharmaceutical-grade polymers compatible with printing or IM.

Moreover, machine-specific constraints for printing (such as printer precision, extrusion control, and batch-size limitations) and reproducibility issues with IM further restrict scalability. As a result, capsule printing remains largely confined to small-scale or prototyping applications, rather than large-scale drug manufacturing.

Industry takeaway

Technologies widely used in the plastics field, such as 3D printing and IM, are now being used to create customized capsules. While these technologies have promise, currently they are more compatible with small-scale productions, as there are significant issues with speed, cost, and variability to overcome for large-scale manufacturing.

Conclusion and future perspectives

Step-by-step innovations have been advancing the capabilities of oral drug delivery and transforming the treatment of chronic intestinal conditions. We have progressed from early capsules that passively carried APIs, through targeted delivery strategies with enteric coatings, to modern active delivery systems created using innovative and refined manufacturing processes. For example, Capsugel® Enprotect® capsules utilize a novel double-dipping technique to produce a ready-to-use enteric capsule, avoiding the need for post-filling coating. In the future, technologies such as 3D printing and nanoparticle-enabled delivery systems have the potential to further expand the capabilities of customized capsules with controlled-release profiles and improved bioavailability.

Advances in enteric delivery have a wide variety of therapeutic applications. Enteric capsules are a versatile tool that can protect acid-labile APIs from degradation in the stomach and the stomach from APIs that can cause gastric irritation; they can be used to extend release profiles and to deliver therapies locally to the intestine, to reduce systemic exposure, or to deliver oral versions of therapies traditionally injected. Modern oral capsules can be utilized as a precise, efficient, and patient-friendly platform for drug delivery, enhancing therapeutic outcomes across a broad spectrum of medical conditions.