



Review

Next generation capsules: emerging technologies in capsule fabrication and targeted oral drug delivery

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ABSTRACT

Capsule-based drug delivery has undergone significant advancements, offering enhanced protection for active pharmaceutical ingredients (APIs) and enabling precise, site-specific release in the gastrointestinal (GI) tract. Recent innovations such as enteric coatings, dual-layer encapsulation (double-dipping), and advanced polymer formulations have expanded the functional capabilities of capsules, offering opportunities to enhance bioavailability and stability of sensitive molecules like peptides, proteins, and RNA-based therapies. Additionally, cutting-edge manufacturing techniques—including injection molding and 3D printing—are facilitating the production of customized capsules with controlled release profiles, thereby minimizing systemic side effects and enhancing patient adherence.

This review examines the technological advancements from single-layer to double-layer capsules, a crucial development to achieve enteric properties and enhance drug protection against degradation in gastric fluids. We explore key capsule manufacturing technologies, including double-dipping, enteric coating, and emerging approaches such as 3D printing and injection molding, which offer new possibilities for precise drug delivery and formulation flexibility. By integrating these advancements, capsule technology continues to evolve as a promising platform for personalized and targeted oral drug delivery. Future research will focus on overcoming production constraints and further refining capsule design to optimize therapeutic efficacy across a broader range of gastrointestinal and systemic diseases.

1. Introduction

Oral solid dosage forms remain the cornerstone of modern therapeutics, with tablets historically the most common format due to their cost-effectiveness and robust manufacturing processes (Stegemann, 2002). However, capsules have progressively gained attention as a versatile oral dosage form, offering distinct advantages such as the ability to encapsulate powders, semi-solids, liquids, as well as devices (Cole et al., 2002; Hoffmann et al., 2024). Capsules also provide opportunities for rapid product development and flexible dosing, making them especially valuable in both clinical trials and personalized therapies. In addition to their role as inert containers, capsule shell material can actively modify drug release properties depending on the material used for formation (A.M. Dos Santos et al., 2021).

Capsule fabrication technologies have advanced steadily over recent decades. While gelatin-based capsules have a long-established history of use, the dominance of gelatin as the shell forming material of choice has

been increasingly challenged by alternative polymers such as hydroxypropyl methylcellulose (HPMC), pullulan, and alginate. These materials offer enhanced functionalities that go beyond structural support, addressing patient-specific needs, and facilitating the development of next-generation drug delivery systems (Sonia and Sharma, 2014; Awad et al., 2022). This technological evolution has enabled innovative approaches to site-specific drug delivery, particularly in the areas of enteric protection and targeted release within the gastrointestinal tract (Grimm et al., 2024).

In parallel, progress in closure mechanisms and manufacturing processes has improved the safety, stability, and reproducibility of capsule-based products. More recently, enabling technologies such as advanced coating methods, double-dipping processes, and even 3D printing have expanded the functional landscape of capsules, transforming them from passive carriers into active components of sophisticated drug delivery strategies (J. Dos Santos et al., 2021; Grimm et al., 2024).

This review provides an integrated perspective on capsule

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technologies, tracing their historical development through to current innovations. By examining conventional processes, material transitions, functional polymers, and emerging technologies, we highlight the growing role of capsules as a next-generation platform for oral targeted drug delivery, capable of meeting increasingly complex therapeutic demands.

2. Current state of the art in capsule technology

2.1. Historical evolution of capsules

The term "capsule" is derived from the Latin *capsula*, meaning "small box." Capsules are classified into two primary types: hard capsules and soft capsules. Hard capsules comprise two distinct, semi-closed cylindrical components namely, the cap and the body while soft capsules are single-unit structures that can adopt various shapes. Hard capsules are predominantly utilized for the encapsulation of powders and granules, whereas soft capsules are more suitable for liquid or semi-solid formulations.

Capsules have been used as an oral dosage form from the early 1830s, when gelatin capsules were first developed, primarily for liquid formulations (Podczec and Jones 2004). In the 1940s, technological advancements led to the encapsulation of powders, significantly expanding their use. At that time, capsule production was entirely manual. Manufacturers used silver-coated metal pins, which were dipped into a gelatin solution and then dried to form the capsules. It wasn't until 1931 that Arthur Colton industrialized the process. Modern capsule manufacturing still relies on the same fundamental dipping mechanism, though it has been highly automated—particularly in the dipping station and the transfer process from dipping to drying (Stegemann, 2002).

Capsule usage varies across regions, with different sizes and volumes available, typically ranging from size 000 (largest) to size 5 (smallest) (Table 1). Size 0 capsules are predominantly used for oral administration, while size 3 is preferred for respiratory applications.

2.2. Process description of hard capsule shell fabrication

Capsule fabrication is an established process known as dip-molding or dipping. The process generally consists of four main steps: (1) polymer solution or dispersion preparation, (2) dipping, (3) drying, and (4) assembly and joining of the capsule body and cap (Begum et al. 2018). This method requires precise control over multiple parameters to ensure capsules are defect-free and possess the desired mechanical and dimensional properties.

2.2.1. Polymer solution or dispersion for shell preparation

The selection of polymer represents the first critical step in capsule development, with gelatin remaining the most widely used material. Gelatin is derived from the hydrolytic extraction of collagen from animal tissues or bones. In recent years, however, plant-based alternatives such as hydroxypropyl methylcellulose (HPMC) have gained increasing

importance, driven by ethical considerations and changing consumer preferences.

Other polymers, including pullulan, blends of HPMC derivatives, and combinations of HPMC with gellan or carrageenan, are also employed at an industrial scale (Bandi et al., 2025). These polymers are particularly suitable for capsule fabrication, as the structural layer must provide sufficient mechanical strength, especially tensile resistance. In addition, the selected polymer must exhibit an appropriate gelation point to support the dip-molding process (Lafargue, 2020).

Beyond these established materials, the growing demand for advanced drug delivery systems has stimulated the exploration of alternative polysaccharides at the laboratory scale. For instance, chitosan and dextran have been investigated for the development of capsules designed for colon-specific drug delivery (Tozaki et al., 2002; Brøndsted et al., 1998).

The capsule shell solution/dispersion preparation is a critical step that requires precise control of formulation parameters to ensure optimal thickness, mechanical properties, and defect-free production. While some polymers readily dissolve at room temperature and can be processed without heating, others exhibit limited solubility under ambient conditions and require elevated temperatures for complete dissolution. For these materials, a hot formulation process is essential to ensure proper solubilization. Alternatively some polymers not soluble in water can be used as dispersion (Lafargue 2020). Maintaining precise temperature control is vital for ensuring stable viscosity and preventing gelation within the tank. For example, in the case of gelatin, the solution is typically maintained at around 55–60 °C in temperature-regulated tanks, then additional components such as colorants, preservatives, and surfactants can be introduced (Jones, Podczec, and Lukas 2017).

2.2.2. Capsule shell formation

Once prepared, the polymer solution/dispersion is maintained in an overflow dish at a controlled temperature and viscosity, with water regulation to prevent evaporation-induced viscosity changes. Continuous homogenization is needed to maintain a constant bath height and ensure solution uniformity (Lafargue 2020).

The dipping process is essential in capsule fabrication, where temperature-controlled molding pins interact with the polymer solution to initiate gelation and form a uniform film (Fig. 1). The temperature difference between the pins and the solution is key to this process, where cooled pins are employed for heated polymer solution/dispersion whereas heated pins are applied when working with cold polymer solutions. This temperature difference between the pins and the polymer triggers gelation upon contact, forming a uniform film around the pins that will, after drying, create the capsule shell. The viscosity of the solution directly influences the amount of material deposited, thereby determining the final capsule thickness and weight (Jones, Podczec, and Lukas 2017; Villiers 2004).

2.2.3. Drying of the capsule shell

The drying phase is a critical step in capsule shell fabrication, designed to remove excess water while maintaining the mechanical integrity and flexibility of the capsule shell. This drying process takes place in controlled drying tunnels, where temperature, relative humidity (RH) and air flow are precisely regulated to prevent defects such as cracking and wrinkling (Lafargue 2020).

The drying temperature is adjusted according to the properties of the capsule material. For capsules formed from a solution, the drying temperature should be sufficient to solidify the polymer and remove water, allowing the formation of a continuous and stable film. In the case of capsules made from a dispersion, the temperature must exceed the Minimum Film-Forming Temperature (MFFT) to facilitate uniform drying and maintain structural integrity (Steward, Hearn, and Wilkinson 2000). As illustrated in Fig. 2 drying begins with solvent evaporation, which concentrates the polymer particles on the surface. If the temperature is below the MFFT, particles retain their spherical shape,

Table 1

Capsule size with their main characteristics (Lonza 2023).

Size	Overall Capsule Length (cm)	Average capacity (mg)	Volume capacity (mL)
000	2.61	800–1600	1.37
00 ^E	2.53	612–1224	1.02
00	2.34	546–1092	0.91
0 ^E	2.31	468–936	0.78
0	2.16	408–816	0.68
1	1.94	300–600	0.50
2	1.76	222–444	0.37
3	1.57	180–360	0.30
4	1.43	126–252	0.21
5	1.11	78–156	0.13

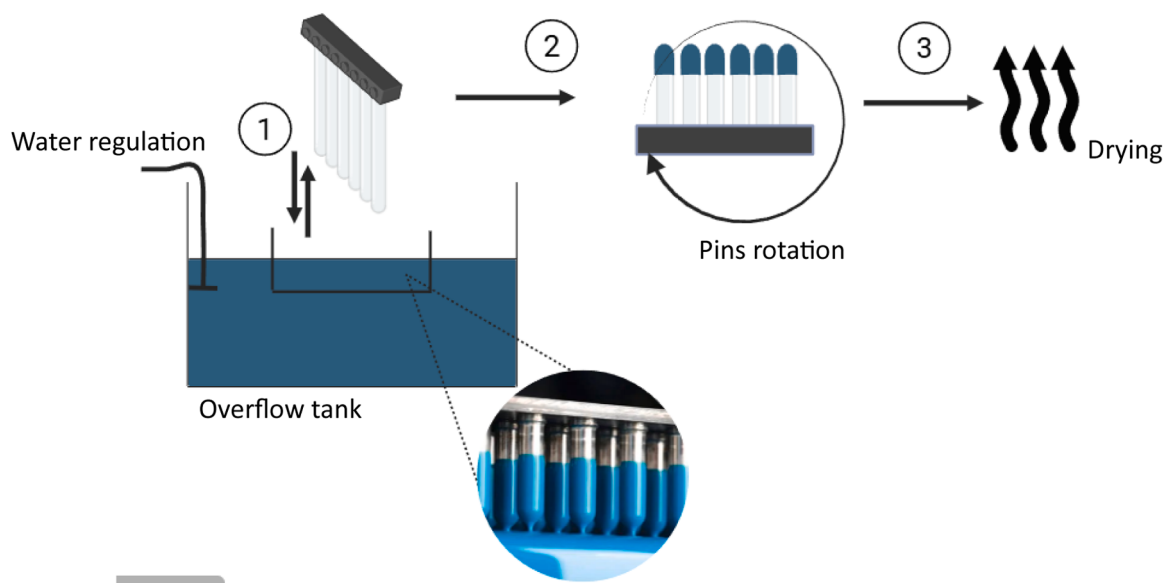


Fig. 1. Formation of capsules with the dipping process . 1) pins are dipped into the polymer solution/dispersion; 2) transfer into the rotation station to have a homogeneous polymer layer onto the pins; 3) water is removed to obtain the capsule shell.

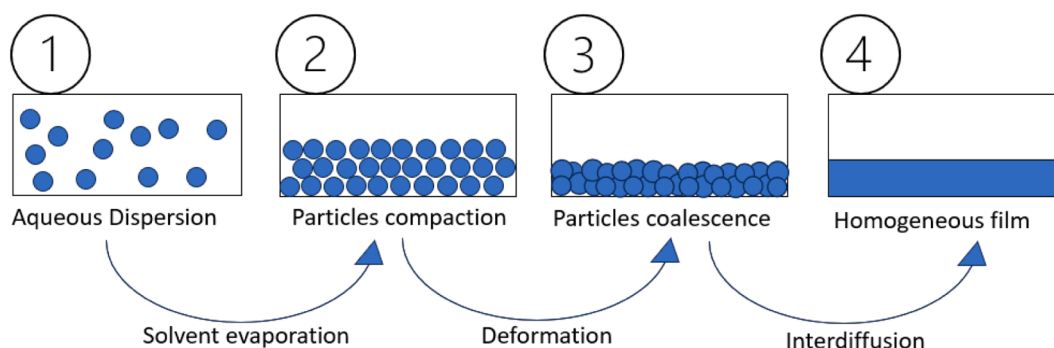


Fig. 2. Film formation mechanism from colloidal aqueous dispersion. Modified from [Keddie and Routh 2010](#).

preventing film formation. In contrast, temperatures above the MFFT cause particle deformation into dodecahedral structures, resulting in a dry, transparent, and handleable film. The final stage involves particle interdiffusion and coalescence, forming a homogeneous film—this step depends on both temperature and particle structure ([Keddie and Routh 2010](#)).

Humidity control is equally critical, particularly for hydrophilic polymers where loss of flexibility can occur when moisture levels drop below critical levels. Excessively dry conditions can lead to structural defects, including cracks, wrinkles, or surface irregularities. A controlled process of gradual moisture reduction combined with regulated temperature increases ensures that the capsules achieve optimal mechanical properties while avoiding deformation or brittleness ([Jones, Podczek, and Lukas 2017](#)).

2.2.4. Stripping and cutting

Once dried, the capsules undergo further processing, including stripping, trimming, joining, and final quality checks. During the stripping phase, metal jaws gently remove the capsule parts from the molding pins. To facilitate smooth removal and prevent contamination, the molding pins are lubricated and cleaned after each cycle, ensuring no material residues affect subsequent production batches ([Jones, Podczek, and Lukas 2017](#)).

Capsules are initially formed longer than their final dimension to compensate for potential thickness variations at the base of the cap and

body. A trimming (deburring) step eliminates these irregularities, ensuring uniform and precise capsule length. This is a critical step before assembly, where the capsule body is inserted in the cap in pre-lock position ([Lafargue 2020](#)).

2.2.5. Joining

The cap and body of a capsule are joined in pre-lock position using different methods depending on the capsule's design. The simplest approach relies on the natural fit between the cap and body, often supported by pre-formed locking rings that provide basic closure (as Coni-Snap in [Fig. 3](#)).

Post filling, additional sealing techniques can be applied to enhance integrity of the final dosage form. One widely used method is banding, in which a thin layer of polymer solution is applied around the junction of the cap and body to ensure tamper evidence and improved protection against leakage. Another approach is fusion sealing, where localized heat or solvents are used to weld the two parts together, resulting in a stronger and more durable joint. More recently, specialized closure systems have been developed that integrate advanced design features directly into the capsule geometry to facilitate sealing (as Licaps in [Fig. 3](#)).

3. Alternatives materials and new opportunities

As capsule technologies have diversified, new designs have been

Coni-snap®	Licaps®
Design for powder fills	Design adapted for liquid fills

Fig. 3. Description the different capsule items of the two designs of hard capsules.
Source: (Capsules and Health Ingredients | Lonza,” n.d.)

developed to overcome the limitations of conventional capsules, particularly their inability to protect sensitive contents from the harsh gastric environment. This has led to the creation of enteric capsules, specifically tailored for targeted intestinal delivery. Unlike structural layer polymers, which require gelation properties, these alternative materials function as functional polymers. They do not necessarily need a gelation point; instead, they can be highly fluid while still forming a continuous film during the drying process (Smith et al., 2010).

Enteric capsules are engineered to resist gastric acid, enabling controlled release of their contents in the intestine. These formulations are commonly described as gastric-resistant, enteric-soluble, or simply enteric capsules (Jones, Podczek, and Lukas, 2017).

The earliest documented attempts at enteric protection date back to Dr. Unna, who applied keratin-based coatings (Podczek and Jones, 2004). Following this, the Pohl firm developed keratinized capsules composed of keratin, shellac, borax, and colophony, though these early formulations exhibited limited effectiveness. In 1895, Dr. Weyland patented a method using formaldehyde treatment to improve capsule rigidity and acid resistance. Later, in 1907, Evans, Sons, Lescher, and Webb introduced double-layered capsules; however, in vivo performance remained inadequate, restricting their practical application.

A timeline summarizing the key milestones in the development of capsules and enteric capsules since the 19th century is presented in Fig. 4.

3.1. Functional polymers for enteric release

The aim of functional polymers is to protect sensitive API from the highly acidic conditions of the stomach, ensuring their release in more alkaline environments, typically in the small intestine or colon.

By carefully selecting the appropriate enteric polymer, formulators can achieve targeted drug release at specific sites in the GI tract. This is particularly beneficial for diseases with localized inflammation, such as those affecting the colon or terminal ileum. Enteric polymers enable the active ingredient to bypass the stomach and upper small intestine, ensuring its release directly at the site of inflammation. This targeted release approach enhances therapeutic efficacy while minimizing systemic side effects, as the drug acts locally rather than being absorbed throughout the body.

3.1.1. Polymethacrylates

Polymethacrylates contain ionizable carboxylic acid or ester groups whose solubility changes with pH. At low pH, the carboxyl groups remain largely protonated, keeping the polymer insoluble. As the pH rises above their pKa, the groups ionize, leading to electrostatic repulsion, swelling, and solubilization—making them ideal for enteric and site-specific drug delivery systems. Eudragit materials such as I-100 and S-100 are methacrylic acid-methyl methacrylate copolymers whose solubility is precisely engineered by adjusting the carboxyl-to-ester ratio. Eudragit I becomes soluble at pH 6, while S becomes soluble at

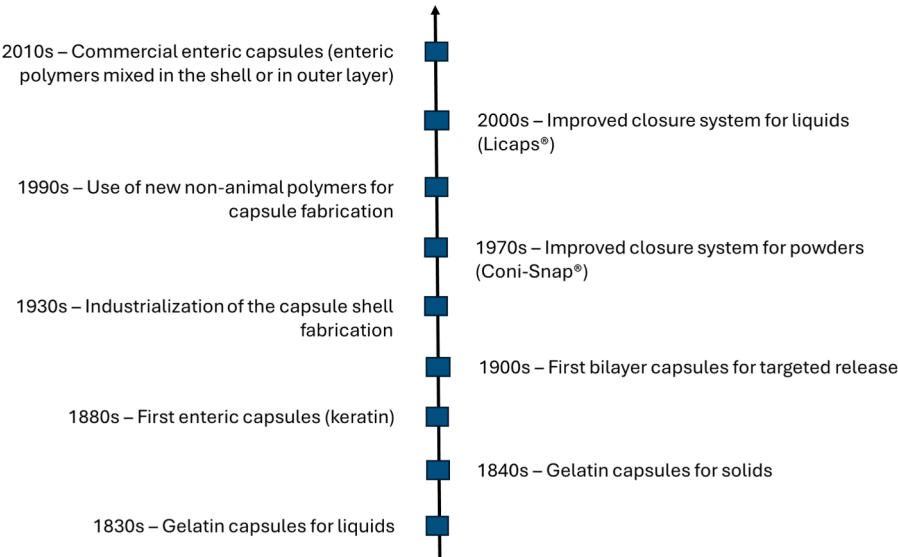


Fig. 4. Timeline of Capsule & Enteric Capsule Development.

pH 7; this tunability underpins their widespread use in pH-triggered oral formulations (A.M. Dos Santos et al., 2021).

3.1.2. Cellulose derivatives

Cellulose-based polymers represent another major class of materials used for enteric coating. Examples include 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). Their functional properties depend largely on the ratio of succinyl to acetyl groups in their structure. These polymers are consistently insoluble in highly acidic media but dissolve at defined pH thresholds: pH $\geq$ 5.5 for LG grade, pH $\geq$ 6.0 for MG grade, and pH $\geq$ 6.8 for HG grade. In addition, they are available in both fine (F) and granular (G) particle forms (Maderuelo et al., 2019).

Another example, modified release can be achieved by combining ethylcellulose (EC) an insoluble polymer in the GI tract- with pore-forming agents such as carboxymethylcellulose or sodium alginate. This approach enables the development of formulations with modified release patterns and is already available for the nutrition market as Colorcon® Nutratric® (Czarnocka and Alhnan 2015). By incorporating such strategies, drug developers can optimize therapeutic outcomes, reducing side effects on healthy tissues while ensuring steady and targeted drug delivery. This is particularly advantageous for the treatment of localized diseases, such as those affecting the colon, where site-specific and controlled drug release can significantly enhance efficacy and patient compliance (Karrouit et al. 2009).

3.2. Innovations in functional drug delivery system

While pH dependent polymers remain a mainstay in targeting release in the GIT, a range of alternative strategies have been developed to achieve region-specific drug delivery within the gastrointestinal tract:

- Microbiota-dependent approaches utilize polysaccharides such as pectin, alginate, or guar gum that are degraded by colonic bacteria, or prodrug conjugates that are cleaved by microbial enzymes, although interindividual differences in microbiota composition limit reproducibility (McCoubrey et al., 2023).
- Time-dependent coatings are designed to release drugs after a pre-determined lag phase of 3–6 h, circumventing pH variability but remaining sensitive to motility and gastric residence time; for improved robustness, these systems are frequently combined with pH-sensitive polymers (Awad et al., 2022).
- Osmotic-controlled systems achieve near zero-order release by generating osmotic pressure across semi-permeable membranes, but their complexity and manufacturing cost hinder widespread application (Waterman et al., 2011).
- Finally, “smart” capsules incorporate stimuli-responsive polymers or embedded electronics to achieve precise site-specific release or even combined diagnostic–therapeutic functions, offering promise for conditions such as Crohn’s disease, although regulatory and scalability challenges remain (Hoffmann et al., 2024).

4. Coating technologies for enteric protection of capsules

Enteric coating of hard capsules has recently emerged as an important alternative to traditional enteric-coated tablets, offering greater flexibility in formulation design and broader applicability across diverse therapeutic areas. This approach enables delayed release for APIs that cannot withstand compression, supports complex or sensitive formulations (Von Orelli and Leuenberger, 2004), and aligns with the growing demand for targeted delivery and precision medicine, especially for small patient cohorts in clinical trials. Furthermore, enteric-coated capsules are now applied in innovative therapies such as fecal microbiota transplantation (FMT), where maintaining microbial viability

during the manufacturing process as well as until colonic delivery is essential (Fülöpová et al., 2024). The broader shift toward precision medicine has also reinforced their role in improving efficacy and reducing side effects in pH-sensitive environments (Seo et al., 2020).

Recently Evonik has launched on the market Eudracap® enteric capsule as a capsule designed for enteric release produced by spray coating of Eudragit® polymer onto empty HPMC capsules. The Eudracap® platform utilizes pH-sensitive polymers such as Eudragit®, which ensures the controlled release of the API above a critical pH level in the intestine. This technology provides a flexible and customizable platform for pharmaceutical companies looking to develop targeted drug delivery systems for sensitive APIs. Eudracap® capsules have been shown to provide consistent dissolution profiles, overcoming some of the challenges associated with traditional enteric coatings, such as variability in coating thickness and adhesion issues (Guo et al. 2024). In a clinical case study, Eudracap® capsules containing albendazole nanosuspension-coated granules have been explored for colorectal cancer treatment, demonstrating rapid localized release and targeted drug action. This approach enhances therapeutic efficacy while potentially reducing systemic exposure (Guo et al., 2024).

Alternatively, enteric coating can be performed on filled capsules. One commercial example of enteric coating technology for targeted drug delivery is Nefecon, marketed as TARPEYO® budesonide delayed release capsules (Calliditas Therapeutics AB), which delivers budesonide to the distal ileum. This formulation bypasses the stomach and proximal small intestine, to reach the Peyer’s patches located in the small intestine usually in the ileum area. The aim is to target the overproduction of galactose deficient immunoglobulin A types 1. Both in vitro and in vivo studies have demonstrated its efficacy in reducing inflammation with minimal systemic side effects, making it a promising solution for localized GI therapies (Grimm et al., 2024). Additionally, Mycapssa® (Chiesi Farmaceutici S.p.A.), an oral octreotide formulation, exemplifies the adaptation of enteric-coated gelatin capsules for delivering peptide-based therapies that are traditionally administered via injection. Clinical trials have shown that Mycapssa® effectively maintains biochemical control in patients with acromegaly while offering a more patient-friendly oral alternative. By eliminating injection-site reactions, reducing GI side effects, and improving patient satisfaction, Mycapssa® highlights the potential of modern capsule technologies to enhance treatment adherence and outcomes (Brayden and Maher, 2021).

Collectively, these innovations underscore the versatility and effectiveness of advanced enterically coated capsule technologies in addressing site-specific drug delivery challenges across a range of therapeutic applications (Table 2).

However, the development of enteric-coated capsules faces some challenges like adhesion of the coating material on the capsule surface and environmental concerns due to the use of solvents and heat. A key issue is material coating adhesion, which is highly dependent on the material of the capsule shell. Indeed, both gelatin and HPMC, the two most commonly used materials, present unique challenges. Gelatin is more flexible but may cause adhesion problems, while HPMC has a smoother surface, which can make coating more difficult. When coating filled capsules, there is the risk of exposing the API to the coating solvent, potentially compromising its stability and efficacy (Fülöpová et al., 2022).

To increase the adhesion, a seal coating can be applied as a protective layer before additional coatings. It shields sensitive active ingredients from moisture and oxidation, improves the adhesion of subsequent functional coatings, and prevents ingredient migration. This layer also enhances product durability and appearance while contributing slightly to the control of initial drug release, ensuring that the final dosage form remains stable, effective, and of high-quality (Salawi, 2022). Uneven coating application can result in non-uniform thickness, leading to inconsistent drug release profiles, which can be detrimental to treatment efficacy (Cole et al., 2002).

Table 2

Recent pre-clinical and clinical applications of enteric capsule technologies.

TYPE OF STUDY	TECHNOLOGY	STUDY DESIGN	RESULTS	SOURCE OF THE STUDY
ENTERIC COATED CAPSULE CLINICAL EXAMPLES				
CLINICAL: EUDRAGIT® (COATING) HPMC (CAPSULE) TESTING THE EFFICACY OF A COATED FILLED CAPSULE TO LOOK AT THE SITE OF RELEASE WITH AN IN VIVO STUDY	Nefecon®: coated filled capsule with budesonide beads. The target of this capsule is the end of the ileum.	<u>Population:</u> Healthy volunteers with nine females and three males. The average age is 23.8 years old with a body mass index average equals to 21.4 kg/m ² <u>Conditions of test:</u> Test in the morning after fasting overnight (at least 10 h) and some products were forbidden before the test (like caffeine, chocolate, ...) Clinical trial phase 1b 21 patients were selected and divided in five cohorts. Each cohort had a dose and not the same treatment duration.	• Resistance in acidic media • Rapid release at higher pH levels • Improve bioavailability • Reduce side effects associated with acid sensitive drugs • For 10 out of 12 subjects the capsule opened in the distal ileum • Nefecon® product deliver the drug to the Peyer's patches concentrated in the distal ileum. • Resist in acidic media • Rapid release at higher pH levels • Improve activity • Robust to deliver sensitive molecules	(Grimm et al. 2024)
CLINICAL: TEST THE TOLERABILITY AND THE DOSE OF THE DRUG.	Eudracap® coated capsule filled with FMT.	Population: Enrolled 146 adult patients with acromegaly. After a six-month run-in phase, 92 patients (55 on Mycapssa®, 37 on injectable SSAs) were randomized for a nine-month controlled treatment phase. <u>Inclusion criteria:</u> Patients with controlled IGF-1 (<1.3 × ULN) and growth hormone levels (<2.5 ng/mL) who had undergone ≥6 months of prior SSA treatment. <u>Conditions of test:</u> Capsules were administered under fasting conditions to ensure consistent absorption	• Resist in acidic media • Rapid release at higher pH levels • Improve activity • Robust to deliver sensitive molecules • Mycapssa® was non-inferior to injectable SSAs in maintaining biochemical control of acromegaly. • 85.7 % of patients on Mycapssa® maintained IGF-1 < 1.3 × ULN. • Common GI issues included nausea, diarrhea, and abdominal pain. • Mycapssa® improved convenience and reduced injection-related adverse effects, making it more patient-friendly.	(Cusin et al. 2024)
CLINICAL: EVALUATION OF THE EFFICACY, SAFETY, AND PATIENT ACCEPTABILITY OF MYCAPSSA®, AN ORAL FORMULATION OF OCTREOTIDE, COMPARED TO INJECTABLE SOMATOSTATIN ANALOGS (SSAs), WHICH ARE THE STANDARD TREATMENT FOR ACROMEGALY.	Mycapssa® is a gelatin capsules with a delayed-release enteric coating using AcryIEZE®, which ensures protection against gastric degradation and controlled release in the intestines.			(Fleseriu et al. 2022) (Brayden and Maher 2021)
DOUBLE LAYER CAPSULE CLINICAL APPLICATIONS				
CLINICAL: EVALUATION OF PERFORMANCES OF ENPROTECT® CAPSULES IN FASTED CONDITION.	Enprotect® bilayer capsule made with HPMC and HPMC-AS a pH dependent polymer.	<u>Population:</u> healthy volunteers with three males and five females. The average age is 27.1 years old with a body mass index average equals to 22.5 kg/m ² <u>Conditions of test:</u> Test in the morning after fasting overnight (at least 10 h).	• Robust acid protection • 38 % of release in the jejunum, 50 % in the ileum and 12 % in the cecum • Release in the small intestine about 40 min after gastric emptying whatever the gastric residence time.	(Rump et al. 2022)
CLINICAL: EVALUATION OF PERFORMANCES OF ENPROTECT® CAPSULES IN POSTPRANDIAL CONDITION.	Enprotect® bilayer capsule made with HPMC and HPMC-AS a pH dependent polymer.	<u>Population:</u> healthy volunteers nine males and seven females. The average age is 27.4 years old with a body mass index average equals to 24.2 kg/m ² <u>Conditions of test:</u> Test in the morning after fasting overnight (at least 10 h) and some products were forbidden before the test (like caffeine). 30 min before dosing the capsule, subjects were administered a light meal (~500 kcal) to be eaten in <15 min.	• Robust acid protection • 62 % of release in the ileum; 38 % in the jejunum • Release in the small intestine about 40 min after gastric emptying whatever the gastric residence time. • Same performance as in fasted conditions.	(Grimm et al. 2023)
PRECLINICAL APPLICATION OF 3D PRINTING FOR ENTERIC DRUG DELIVERY PRECLINICAL: PILOT IN VIVO STUDY TO LOOK AT THE BEHAVIOR OF FOUR DIFFERENT 3D PRINTING FDM STRUCTURES.	3D printing capsules by FDM with four polymers were tested: PVA-PEG, HPC, EC and HPMC-AS. Capsules were filled with a radiotracer to track the device along the GIT.	<u>Animal type:</u> Study carried out on Sprague-Dawley rats (male) with an average weight equals to 300 g. Four rats per polymer were tested. <u>Living conditions:</u> In individual cage with a free access to food and water. The temperature and the humidity are controlled and they have day-night cycles <u>Capsule administration:</u> Induced by anesthesia and the capsule was directly placed in the stomach.	The results indicated that the FDM 3D printing has a good viability and the disintegration of the capsule was dependent to the type of polymer. PVA-PEG and HPC: 60 min (immediate release) EC: not disintegrated (insoluble polymer) HPMC-AS: 420 min (pH dependent polymer)	(Goyanes et al. 2018)

Furthermore, the reliance on solvent-based coatings presents health, safety, and environmental concerns, as well as potential interactions with the API, further complicating the development process (Seo et al., 2020). These limitations underscore the need for new and innovative approaches to enteric capsule design and manufacturing to enhance reliability and repeatability. For empty capsule shell coating, an additional issue arises as the potential for coating damage during the filling process. Indeed, as the coating material is deposited on top of the empty capsule standard dimension, it will induce coated capsule with higher diameters that may affect the capsule's machinability, potentially causing disruptions in mass production processes and loss of API.

5. Dipping technologies for multilayered capsules offering enteric protection

Among recent advancements in capsule technology, a key development is the emergence of a novel manufacturing approach that simplifies large-scale production of delayed-release capsules—exemplified by the Capsugel® Enprotect® capsule. Capsugel® Enprotect® is a ready-to-use enteric capsule launched in 2022 by Lonza Capsules and Health Ingredients using a novel double dipping approach. Unlike traditional enteric coating processes, which require complex coating steps, Capsugel® Enprotect® capsule provides an enteric release system without the need for post-manufacturing coating, thereby streamlining production.

This solution offers significant advantages in terms of manufacturing efficiency but also regarding the filling process. Capsugel® Enprotect® capsules are designed to resist the acidic conditions of the stomach and only dissolve in the more neutral/alkaline environment of the intestine, thus providing targeted delivery to the GI tract and protection of the payload from the harsh environment of the stomach: acid pH and enzyme as proven with pancrelipase as a model protein drug (Jannin Jannin et al., 2023). This capsule has been extensively tested in healthy volunteers and shown a robust delivery of the payload in the jejunum-ileum section of the GI tract whatever the dosing conditions (Rump et al., 2022; Grimm et al., 2023). Capsugel® Enprotect® capsule outer layer is composed of the pH dependent polymer HPMC-AS that dissolves from pH 6.5 (Fig. 5).

5.1. Manufacturing process and optimization

The dip-molding process used for single-layer capsule fabrication can be adapted to manufacture bilayer capsules through a double-dipping technique, in which two consecutive polymer layers are deposited on the same pin. The second dipping step is performed only after the first layer has dried, enabling the creation of capsule shells with distinct and complementary functionalities. In this configuration, the first (structural) layer provides the necessary mechanical integrity, while the second (functional) layer—subject to fewer processing constraints—offers opportunities for incorporating targeted release properties. Such bilayer designs are particularly advantageous for enteric applications, where the inner layer can be optimized for controlled intestinal release, while the outer layer protects against gastric acid (He et al., 2023). The use of different polymer solutions in successive dipping steps further expands formulation flexibility, allowing customized drug release profiles. However, to ensure consistent capsule quality, critical process parameters such as polymer viscosity, pin temperature, and drying conditions

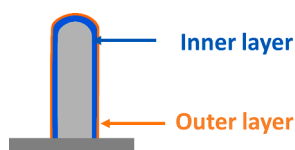


Fig. 5. Schematic representation of the bilayer films formed on a metal pin during the double dipping process.

must be carefully controlled (Lafargue, 2020).

5.2. Double layer capsule clinical applications

Research has demonstrated the promising piercing and dissolution characteristics of double-layer capsules in vitro models (Table 2). A notable study by He et al. (2023) highlighted the efficacy of double-layer capsules, particularly their dissolution behavior under simulated gastrointestinal conditions. Additionally, Jannin et al. (2023) investigated the use of these capsules for delivering pancrelipase, an acid-sensitive enzyme essential for patients with exocrine pancreatic insufficiency. Using an advanced ex vivo model that mimics the human digestive system, the study confirmed the protective function of the double-layer capsule. This design effectively prevented enzymatic degradation in the stomach while ensuring targeted release in the small intestine. The findings emphasized the potential of the Capsugel® Enprotect® capsule for the precise delivery of proteins and peptides to the small intestine.

Supporting these findings, Rump et al. (2022) and Grimm et al. (2023) conducted two studies in healthy volunteers to assess the performance of the Enprotect® capsule under both fasted and postprandial conditions. The study in fasted condition involved 8 healthy volunteers who received the capsule after overnight fasting. The study in postprandial condition involved 16 volunteers who received the capsule 30 min after consuming a light meal (~500 kcal). Magnetic resonance imaging (MRI) and caffeine detection in saliva were used to localize the capsule in the GI tract (MRI) and assess capsule disintegration (MRI and caffeine). Both methods revealed no signs of capsule disintegration in the stomach, confirming the double-layer capsule resistance to acidic gastric environments. Capsule disintegration occurred consistently in the jejunum and ileum, ensuring targeted release of the active ingredient. Importantly, the study found no significant difference in performance between fed and fasted conditions, as all capsules disintegrated in the same regions of the small intestine. Remarkably, the capsule's disintegration time post-gastric emptying remained constant, regardless of the stomach's residence time, which varied from 5 to 240 min.

Hansen et al. 2024 describes the application of Enprotect® capsules in fecal microbiota transplantation (FMT). FMT is a well-established treatment of *Clostridium difficile* infections, a condition caused by bacteria capable of producing various toxins with different levels of virulence (Gateau et al. 2018). Clinical manifestations range from mild diarrhea to severe, life-threatening fulminant colitis. Currently, FMT is considered an effective therapeutic option for recurrent *C. difficile* infections (Zyoud 2022). The use of Enprotect® capsules in FMT aims to facilitate delayed release, protecting the microbial content from gastric degradation and ensuring targeted delivery to the lower GI tract. The study by Hansen et al. (2024) demonstrated that this encapsulation technology preserves the integrity of the microbiota during processing and storage, thereby enhancing the stability and handling of FMT capsules. The incorporation of delayed-release technology represents a significant advancement in optimizing the efficacy and practicality of FMT.

5.3. Limitations and challenges

One of the significant challenges in bilayer capsule development is the potential incompatibility between the polymers used for the inner and outer layers. This incompatibility can result in adverse chemical interactions, leading to instability or degradation of the capsule, as noted by He et al. (2023). However, the versatility of the technology provides a significant advantage. Bilayer capsules can utilize a variety of materials, such as gelatin or hydroxypropyl methylcellulose (HPMC), allowing customization to address specific incompatibility issues with the filled material (Lafargue, 2020). For example, certain APIs that might interact with gelatin can instead be encapsulated in HPMC-based capsules, as highlighted in patents describing the dual compatibility of

these materials. This adaptability enhances the utility of bilayer technology across diverse formulations (He et al. 2023).

6. Emerging techniques to manufacture targeted release capsules

6.1. 3D and 4D printing of enteric capsules

Advancements in material science and fabrication technologies have opened new possibilities for enhancing capsule functionality, with emerging technologies, such as 3D and 4D printing and pushing the boundaries of capsule design. In this context, 3D printing refers to the additive manufacturing process where structures are built layer by layer, allowing for intricate design and precise control over drug release characteristics through spatial placement of materials. 3D printing enables precise customization of drug release profiles by employing a layer-by-layer deposition of enteric materials (Choudhury, Murty, and Banerjee, 2021). In contrast, 4D printing extends this concept by incorporating time as the fourth dimension - incorporating stimuli-responsive materials that can dynamically alter their properties over time or in response to environmental factors such as pH, temperature, or enzymatic activity (Aufa, Ismail, and Zaki Hassan, 2023). These innovative approaches are also reflected in the manufacturing process, where advanced design strategies—such as those enabled by 3D printing—allow for enhanced control over drug release and absorption

6.1.1. Manufacturing process and optimization

3D printed capsule may present some advanced designs incorporating an inner layer or a compartment that separates the API from excipients or other functional ingredients. This compartmentalization is key in creating multi-layered dosage forms or delaying the release of certain drugs, allowing for more precise targeting of drug delivery within the gastrointestinal tract. This modular design allows for precise control over how the drug is released and where it is absorbed in the GI tract (Choudhury, Murty, and Banerjee 2021).

Although capsule design is of major importance to the efficacy of the final drug product, process parameters, particularly using Fused Deposition Modeling (FDM), are also essential to ensure the successful creation of stable, functional dosage forms. Factors such as viscosity, temperature regulation, and print speed significantly influence the printing process. Controlling these parameters ensures that the polymer filaments flow smoothly during deposition, preventing structural defects. Temperature control is particularly critical to ensure that both the polymer and the API remain stable throughout the process (Racaniello et al. 2024).

The importance of precision in capsule wall thickness for applications like FMT is supported by research and development in the field. Capsules used for FMT, such as the FMT Capsule G3 developed by OpenBiome (<https://openbiome.org/feature/fecal-transplant-pills-large-scale-production-begins-following-successful-dosing-study/>), highlight the necessity of maintaining structural integrity to prevent premature release in the stomach or small intestine. This technology is designed to ensure the stability and viability of the encapsulated microbiota, which is essential for effective delivery to the colon. Any inconsistencies in capsule thickness or design could jeopardize this targeted delivery, potentially diminishing therapeutic efficacy (Franc, Vetchý, and Fülöpová 2022).

6.1.2. Preclinical application of 3D printing for enteric drug delivery

The application of 3D printing in pharmaceutical research has gained significant attention, particularly in the development of drug delivery systems using various polymer filaments. For instance, Green Buzhor et al. (2024) demonstrated that polycaprolactone (PCL)-based capsules, characterized by minimal water ingress and delayed-release properties, are effective in simulated intestinal fluid (SIF). The biodegradability and excellent barrier properties of PCL make it a promising candidate for

ensuring drug release at specific intestinal sites. Similarly, Choudhury et al. highlighted the use of Eudragit® polymers for enteric protection *in vitro*. The study utilized 3D printing to precisely apply polymer coatings that dissolve in the intestinal environment, facilitating targeted drug release in media simulating the small intestine or colon.

Several studies have explored the potential of 3D-printed capsules (Table 2) for drug delivery, spanning immediate-release systems and targeted-release mechanisms. Goyanes et al. (2018) highlighted the use of 3D printing for creating capsules designed for regional absorption studies in the GI tract. This work, while focusing primarily on immediate-release profiles, also demonstrated the potential of modifying capsule designs for region-specific drug delivery through imaging and material testing. The study investigated four polymers—poly(vinyl alcohol) (PVA) – polyethylene glycol (PEG), hydroxypropyl cellulose (HPC), EC, and HPMC-AS—by filling capsules with a radiotracer to track their transit through the GI tract in animal models. The results showed varying disintegration times based on the polymer used: PVA-PEG, an immediate-release polymer, and HPC, a water-soluble polymer, released their contents within 60 min. Ethylcellulose, being insoluble, exhibited no disintegration, while HPMC-AS, a pH-dependent polymer, demonstrated a delayed release at approximately 420 min.

For enteric protection specifically, Berg et al. (2021) advanced this concept with pressure-triggered release mechanisms, showcasing 3D printing's capability in ensuring payload release under specific intestinal conditions. Seoane-Viaño et al. (2021) further contextualized these advancements, discussing the versatility of 3D printing in designing enteric-coated capsules to bypass the stomach and target the intestine effectively. Collectively, these studies illustrate the evolving applications of 3D printing in capsule design, including both immediate release and targeted enteric protection.

Beyond time or pH control, 3D-printed capsules offer innovative solutions for complex treatments such as FMT. As reported by Green Buzhor et al. (2024), 3D printing enables the production of enteric capsules capable of protecting donor microbiota and delivering them intact to the colon. This technology is particularly valuable for conditions like recurrent *Clostridium difficile* infections.

The versatility of 3D printing in pharmaceutical applications lies in its ability to rapidly prototype customized capsules tailored to pharmacokinetic and therapeutic requirements. These advancements are particularly beneficial for early-phase clinical trials and the development of patient-specific treatments. By providing precise and controlled-release platforms, 3D printing addresses the challenges associated with diverse drug modalities and complex delivery systems (Choudhury, Murty, and Banerjee, 2021).

6.1.3. Limitations and challenges

While 3D printing, particularly FDM, holds significant promise for the development of enteric capsules, it also presents several challenges that limit its widespread use. One of the primary challenges in FDM is maintaining API stability during the heating and extrusion process, as many APIs, particularly biologics or thermally sensitive compounds like proteins and peptides, may degrade when exposed to the elevated temperatures required for printing (Seoane-Viaño et al., 2021). However, this limitation can be overcome by utilizing FDM to produce capsule shells or carrier systems rather than incorporating the API directly into the printing process. In such cases, the capsules can be fabricated first, and the API can be encapsulated post-production using filling techniques that avoid exposure to heat. This alternative approach expands the range of APIs that can benefit from FDM, enabling the development of complex, multi-layered, and targeted drug delivery systems while preserving API integrity.

Moreover, only a limited selection of pharmaceutical-grade polymeric carriers are compatible with FDM. Many polymers used in other industries may not meet the strict regulatory and quality requirements needed for pharmaceuticals. Additionally, the polymers must possess both appropriate melting points and drug release properties, making the

material selection process even more restrictive (Choudhury, Murty, and Banerjee 2021). Still, Hu et al. (2024) used PVA to produce filaments to print multi-layer capsules for controlled drug delivery used for personalized medicine. Some studies have shown that Eudragit®-based filaments can provide controlled, delayed drug release while being compatible with FDM 3D printing requirements (Choudhury, Murty, and Banerjee 2021).

Currently, FDM is most suitable for hospital settings or small-scale production where customized, on-demand medications are needed. Fused Deposition Modeling (FDM) 3D printing, while promising for personalized medicine, is not yet viable for mass production in the pharmaceutical industry. This limitation stems primarily from the stringent material-specific requirements needed to produce printable filaments—parameters such as thermal behavior, mechanical strength, viscosity, and filament diameter must be precisely tuned. These factors are difficult to standardize and often require complex, trial-and-error-based formulation strategies. Moreover, machine-specific constraints, such as printer precision, extrusion control, and batch size limitations, further restrict scalability. As a result, FDM remains largely confined to small-scale or prototyping applications, rather than large-scale drug manufacturing (Parulski et al. 2021).

This limits its application to personalized medicine rather than broad commercial use. However, the technology has potential in niche markets where rapid, individualized treatments are needed (Racaniello et al. 2024).

6.2. Injection molding

Injection molding (IM) is a highly efficient and versatile manufacturing process widely used in the plastics industry to produce components of various sizes, shapes, and complexities. This technique involves the high-pressure injection of molten thermoplastic or thermosetting materials into a precisely designed closed mold. Under controlled temperature and pressure conditions, the material fills the mold cavity, takes its intended shape, and undergoes cooling and solidification. Once fully formed, the finished product is ejected, completing the manufacturing cycle. Due to its speed, precision, and scalability, injection molding is extensively applied in industries such as automotive, medical devices, consumer goods, and pharmaceuticals, enabling the mass production of high quality, consistent parts. (Zema et al. 2012)

6.2.1. Manufacturing process and optimization

IM is carried out using specialized injection molding machines, which generally consist of two main units: the plasticating/injecting unit and the clamping unit. Depending on the configuration of these units, IM machines can be categorized as horizontal, vertical, or hybrid, with hybrid machines featuring a combination of horizontal and vertical components.

The plasticating/injecting unit is responsible for melting and injecting the polymer into the mold. It consists of a hopper, which feeds solid polymer granules into a heated barrel where they undergo heating, mixing, compression, and melting. The temperature along the barrel is controlled using heater bands, ensuring optimal melting of the material. Inside the barrel, a reciprocating screw plays a critical role in both mechanical heating and material transport. As the screw rotates, it pushes the polymer forward while generating shear forces that contribute to additional heating. The screw consists of three main zones:

- Feed zone: where solid granules are introduced and begin heating.
- Melt zone: where the polymer transitions from solid to molten state.
- Metering zone: where the molten polymer is compressed and homogenized before injection.

A non-return valve, located before the screw tip, prevents backflow of the melt and ensures uniform injection pressure. The molten polymer

is then forced through the heated nozzle into the mold cavity.

The clamping unit ensures that the mold remains securely closed during injection, counteracting the high injection pressures applied to the polymer. The mold itself consists of two halves that form a cavity, defining the final shape of the molded object. Some molds feature multiple cavities, allowing for the simultaneous production of several units in a single cycle. The mold temperature is precisely controlled using cooling systems, typically circulating water, to ensure proper solidification of the polymer. Once the part has sufficiently hardened, it is ejected using pins or ejector systems.

To optimize the efficiency, precision, and repeatability of injection molding, manufacturers fine-tune several key parameters, including injection speed, pressure, mold temperature, and cooling time. Advanced technologies, such as computer-aided engineering (CAE), real-time process monitoring, and automation, help reduce defects such as warpage, shrinkage, and short shots. Additionally, innovations like micro-injection molding, multi-material molding, and gas-assisted injection molding enable the production of complex, high-performance components across various industries, including automotive, medical, and pharmaceutical sectors. By integrating data-driven process control and sustainable material selection, injection molding continues to evolve as a highly efficient and adaptable manufacturing technique. (Zema et al. 2012)

6.2.2. Clinical application of injection molding for pulsatile release

Gazzaniga et al. (2011) have investigated the development and evaluation of an innovative capsular device designed for pulsatile drug release using injection molding technology.

The researchers used HPC as the primary polymer to fabricate capsule shells via injection molding. A specially designed mold and a bench-top injection molding press enabled the simultaneous production of capsule bodies and caps with varying wall thicknesses (300, 600, and 900 μm).

An in vivo evaluations was performed with different wall thicknesses of capsules and were administered to healthy fasting volunteers, and acetaminophen concentration in saliva was measured at specific time intervals. The study found a delayed drug appearance in saliva, followed by a rapid increase in concentration, indicating that drug release was not controlled by swollen capsules but by their structural disintegration.

This study demonstrates that injection-molded HPC capsules can effectively be used for pulsatile and/or colonic drug delivery. The ability to modulate the lag time based on wall thickness offers a flexible approach to designing targeted drug delivery systems for specific therapeutic needs.

6.2.3. Limitations and challenges

As for the 3D printing, injection molding requires a high thermal stability of drugs and also of excipients. The selected polymer is expected to be fully or partially suit the release performance expected and have a suitable flow index, as mentioned before a thermal stability and a stable behavior upon cooling. Another point concerned the limitations of quantitative and qualitative aspect of the formulation. Indeed in this category the dose, physico-chemical properties and stability profile of drug are very important. Reproducibility is also a challenge (Melocchi 2015).

7. Conclusion and future perspectives

Advances in capsule technologies are transforming the treatment of various chronic intestinal conditions, with a strong emphasis on site specific and localized intestinal drug delivery. Innovations such as enteric coatings, double-dipping techniques, and pH-sensitive polymers have significantly enhanced the precision and effectiveness of oral dosage forms. These advancements allow capsules to bypass the stomach, protecting sensitive APIs, including peptides, proteins, and RNA-based therapies from degradation and ensuring their release at the

intended site in the GI tract like the ileum, colon, and other targeted GI regions. These advancements are expanding the scope of oral capsule drug delivery technologies beyond inflammatory bowel disease (IBD) and ulcerative colitis, extending their application to a broader range of conditions. This is especially significant for disorders such as celiac disease, colorectal cancer, and gut microbiota imbalances, where targeted release within the gastrointestinal tract can enhance therapeutic efficacy while minimizing systemic side effects.

Emerging manufacturing techniques, such as 3D printing and injection molding, enable the development of customized capsules with controlled-release profiles, improving bioavailability and reducing systemic side effects. These technologies hold particular promise for delivering hormones, enzyme-replacement therapies, and microbiome-targeted treatments, where precise release timing and localization are critical. However, despite their potential, these approaches remain challenging for large-scale production due to high costs, slower production rates, and process variability.

Ongoing research, including nanoparticle-enabled delivery systems and next-generation capsule manufacturing, seeks to overcome current challenges related to drug stability, site-specific release, and scalability. By incorporating these advanced technologies, oral capsules are increasingly positioned as a precise, efficient, and patient-friendly platform for drug delivery, enhancing therapeutic outcomes across a broad spectrum of medical conditions.

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Elisa Millet: Writing – original draft, Conceptualization. **Joseph P O'Shea:** Writing – review & editing. **Brendan T Griffin:** Writing – review & editing. **Camille Dumont:** Writing – review & editing. **Vincent Jannin:** Writing – review & editing, Supervision, Funding acquisition.

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