Journal of Materials Science: Materials in Medicine (2025)36:24
https://doi.org/10.1007/s10856-025-06868-5

DELIVERY SYSTEMS

Review Article

Oral dosage forms for drug delivery to the colon: an existing gap between research and commercial applications

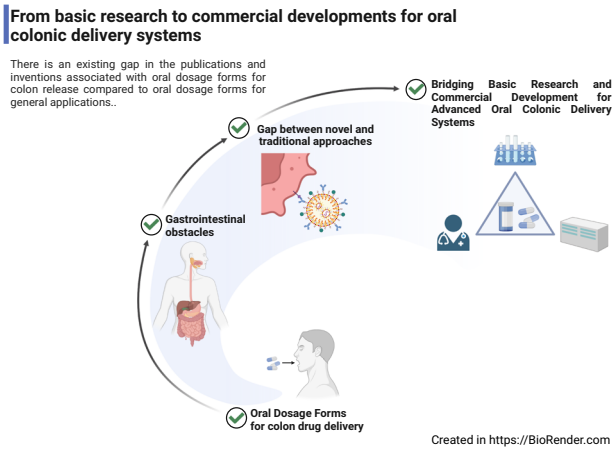
Estefanía Martínez[1] · Jennifer Gamboa[1] · Carla V. Finkielstein[2,3] · Ana Isabel Cañas[4] · Marlon Andrés Osorio[1,5] · Yesid Vélez[1] · Néstor Llinas[6] · Cristina Isabel Castro[1]

Received: 14 June 2024 / Accepted: 11 February 2025

Abstract

Oral drug administration is the preferred route for pharmaceuticals, accounting for ~90% of the global pharmaceutical market due to its convenience and cost-effectiveness. This study provides a comprehensive scientific and technological analysis of the latest advances in oral dosage forms for colon-targeted drug delivery. Utilizing scientific and patent databases, along with a bibliometric analysis and bibliographical review, we compared the oral dosage forms (technology) with the specific application of the technology (colon delivery) using four search equations. Our findings reveal a gap in the publications and inventions associated with oral dosage forms for colon release compared to oral dosage forms for general applications. While tablets and capsules were found the most used dosage forms, other platforms such as nanoparticles, microparticles, and emulsions have been also explored. Enteric coatings are the most frequently applied excipient to prevent the early drug release in the stomach with pH-triggered systems being the predominant release mechanism. In summary, this review provides a comprehensive analysis of the last advancements and high-impact resources in the development of oral dosage forms for colon-targeted drug delivery, providing insights into the technological maturity of these approaches.

Graphical Abstract



✉ Cristina Isabel Castro
cristina.castro@upb.edu.co

[1] Grupo de Investigación sobre Nuevos Materiales, Escuela de ingeniería, Universidad Pontificia Bolivariana, Medellín, Colombia

[2] Integrated Cellular Responses Laboratory, Fralin Biomedical Research Institute, Virginia Tech, Blacksburg, VA, USA

[3] Department of Biological Sciences, Virginia Tech, Blacksburg, VA, USA

[4] Micología médica y experimental, Corporación para Investigaciones Biológicas, Medellín, Colombia

[5] Grupo de Investigación Biología de Sistemas, Universidad Pontificia Bolivariana, Medellín, Colombia

[6] Departamento de Oncología Clínica, Clínica Vida, Fundación Colombiana de Cancerología, Medellín, Colombia

Published online: 05 March 2025

1 Introduction

Oral drug administration is the most advantageous route for gastrointestinal tract (GIT) treatments. Accounting for ~90% of the global pharmaceutical market, this route is favored by patients and healthcare professionals due to ease of use, non-invasiveness, self-administration, and cost-effectiveness [1, 2].

This drug delivery route serves two primary purposes: systemic treatments and localized interventions. For systemic treatments, drugs must be absorbed through the highly vascularized gastrointestinal mucosa, entering systemic circulation [3]. This absorption is a complex process involving drug dissolution in gastrointestinal fluids and permeation through the intestinal wall, which can significantly limit drug bioavailability [4].

In local interventions, oral formulations offer the advantage of reducing systemic side effects by minimizing hepatic metabolism and systemic drug distribution of active pharmaceutical ingredients (API) [5]. Therefore, this approach has been crucial for the treating diverse gastrointestinal conditions, including stomach and colorectal cancers, infections, inflammations, bowel diseases, gastro-duodenal ulcers, and gastroesophageal reflux disorders [2].

However, successful API-targeted delivery requires pharmaceutical formulations capable of navigating the unique and challenging environments of different GIT sections (Fig. 1). Each region presents distinct physiological conditions, including variations in pH, enzymatic activity, bacterial presence, and mechanical forces that can compromise drug integrity and efficacy [6]. For instance, the stomach presents an acidic environment (pH 1–3.5), enzymatic degradation (pepsin), variability in gastric emptying, prolonged retention, and mechanical stress from peristalsis, all of which can destabilize drugs. In the small intestine, enzymatic activity (e.g., trypsin, lipase), pH variability (6–7.5), and rapid transit times limit the absorption window,

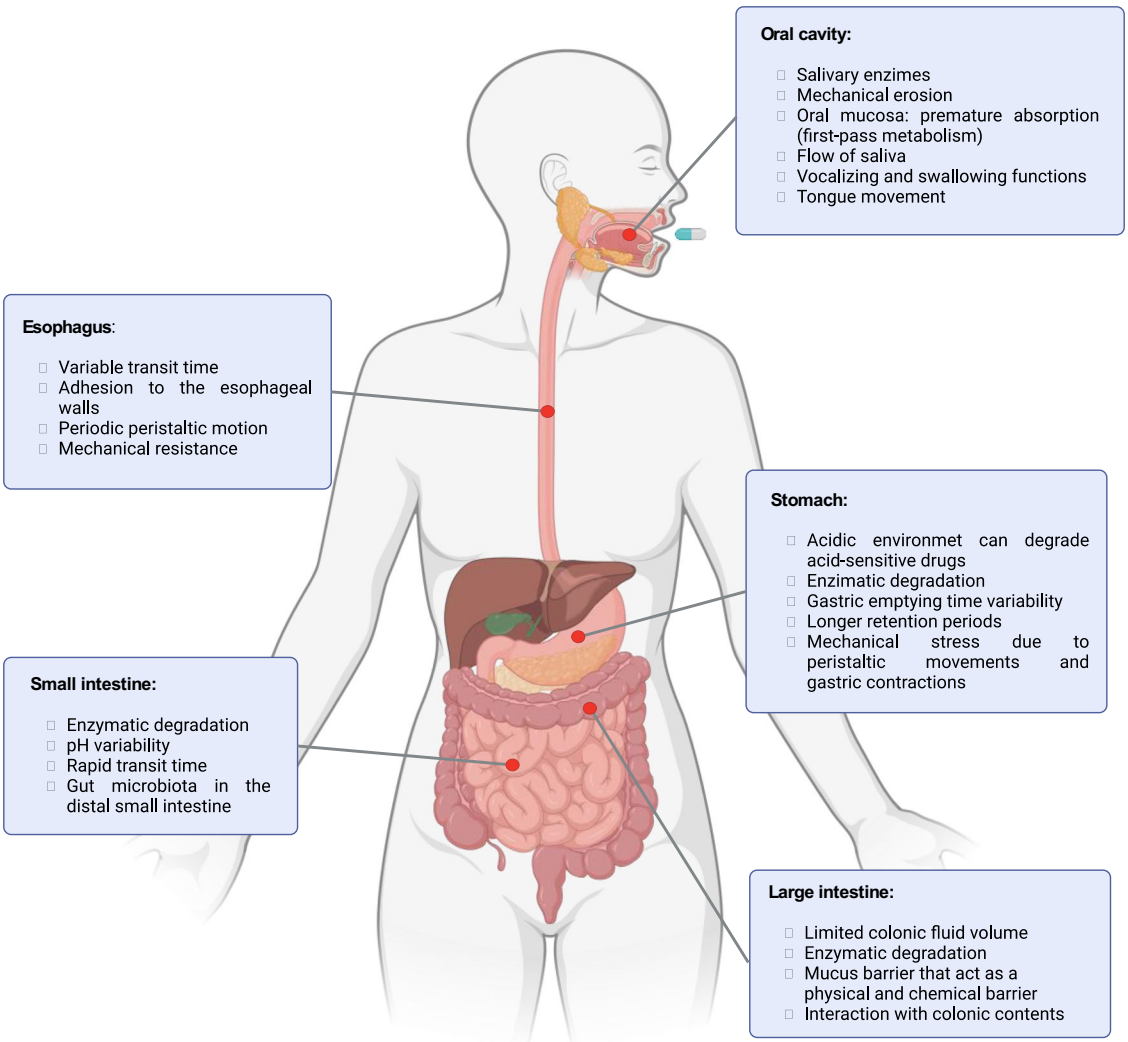


Fig. 1 Obstacles in the GIT for oral dosage forms targeting the colon. Adapted from [77]. Created in https://BioRender.com

while gut microbiota in the distal small intestine may alter drug efficacy [7, 8].

Unlike these organs, the colon is an ideal structure for drug delivery due to its long retention time and the presence of a complex mucosa that facilitates absorption [6]. Nevertheless, formulations targeting the colon must withstand and navigate the diverse physiological and chemical conditions of the upper GIT. Strategies for achieving this delivery often involve the use of inactive prodrugs that are cleaved and activated through hydrolysis in the colon, or the development of colon-specific biodegradable systems using materials like alginate, chitosan, pectin, guar gum, and starch that act as a pH-sensitive coating that protect the API until they reach the colon [6, 9]. For poorly absorbable drugs, mucoadhesive materials have proven effective in prolonging contact with the colonic mucosa [10].

Advanced approaches include the use of multiparticulate systems composed of small units or materials at the nanoscale capable of passing through the GIT to reach the colon quickly, and specialized coatings that protect APIs from the extreme conditions of the upper GIT while delaying their release until the colon [6]. Nano-drug delivery is a rapidly advancing field, leveraging lipid-based systems, metallic nanoparticles, polymeric materials, and hydrogels for the delivery of phytochemicals and chemotherapeutics [11].

Nanomaterials in delivery systems offer advantages over traditional methods including improved efficacy, reduced toxicity, and enhanced bio-distribution [11–13]. Notable commercially available formulations include Rapamune®, a formulation that includes nanoparticles to improve the solubility and bioavailability of sirolimus, a drug used primarily for preventing organ transplant rejection [14]; Aprepiant® and EMEND®, stable nanostructures used for preventing nausea and vomiting caused by chemotherapy [15, 16]; TriCor®, used to treat high levels of cholesterol and triglycerides in the blood contains fenofibrate nanoparticles with an average particle size of ~412 nm, which significantly improves the drug's solubility compared to conventional micronized formulations [17]; and Triglide®, other solid oral formulation that contains fenofibrate nanoparticles and is used to treat high cholesterol and high triglyceride levels in adults [18].

Despite these advancements, there remains a lack of commercial nanomaterial-based systems specifically designed to target the colon. Therefore, this work aims to provide a comprehensive scientific and technological analysis of current strategies for the development of oral dosage forms for drug delivery of therapeutics into the colon, using scientific and patent databases along with a bibliometric analysis and bibliographical review of the latest advances related to oral dosage forms to identify new technologies and their technological maturity level.

2 Methodology

2.1 Scientific and technological analysis

Patents and research articles were retrieved from the PatentInspiration and Scopus databases, respectively. VantagePoint software was used for data analysis. The SankyeMATIC tool was used for plotting Sankey diagrams. The scientific-technological analysis was carried out by comparing peer-reviewed research articles and patents to identify differences in the development of oral dosage forms according to the maturity of the technology.

The search equations used to retrieve relevant articles and patents are shown in Table 1. Equations 1 and 2 were used for the analysis of the technology (oral dosage forms) in the research articles and patents, respectively. In Eqs. 3 and 4 the operator AND was included to analyze the specific application of the technology (colon delivery and controlled release) in peer-reviewed research articles and patents, respectively.

The bibliometric analysis was performed using VantagePoint software. For this, two matrices were constructed with 35 selected patents and 65 research articles. The selection criteria for research articles were the authors that the development was for an oral dosage form in the abstract or discussion. Patents were chosen if the invention was specific for colon delivery. Information was organized using the following components:

- Research articles: title, year, abstract, keywords, API, excipients by functionality, excipients by material, oral dosage form, release mechanism, manufacturing processes, and characterization techniques.
- Patents: Name of the patent, assignation, classification, abstract, API, excipients by functionality, excipients by material, oral dosage form, release mechanism, manufacturing process, and characterization technique.

Word Clouds were developed for oral dosage forms, release mechanisms, excipients by functionality, API, and characterization techniques for visual representation of the most frequent terms using the matrices. Sankey diagrams, using the information obtained from Eqs. 3 and 4, were used to analyze the top 5 terms used by authors in relation to excipients by functionality and material, release mechanisms and oral dosage form, and manufacturing process and oral dosage forms.

We used the Cooperative Patent Classification (CPC) system for patent classification, which is, based on a set of international concepts, definitions, principles, and rules [19]. The coding system is hierarchical and consists of sections (first digit), groups (first three digits), classes (first four digits), and subclasses (all five digits together) [19].

Table 1 Search equations used to retrieve relevant articles and patents, according to the technology and the specific application

	Search equations	
Eq. 1	SUBJAREA (phar), TITLE-ABS-KEY ("oral dosage form" OR "oral formulation" OR "oral dosage composition" OR "oral dosage formulation" OR "oral pharmaceutical formulation" OR "oral pharmaceutical composition" OR "oral pharmaceutical forms" OR "oral form" OR "solid oral administration" OR "oral dosage form" OR "ingestible form") AND (LIMIT-TO (DOCTYPE, "ar"))	Technology
Eq. 2	Patents with ("oral dosage form" OR "oral formulation" OR "oral dosage composition" OR "oral dosage formulation" OR "oral pharmaceutical formulation" OR "oral pharmaceutical composition" OR "oral pharmaceutical forms" OR "oral form" OR "solid oral administration" OR "oral dosage form" OR "ingestible form") in title or abstract	
Eq. 3	SUBJAREA (phar), TITLE-ABS-KEY (("oral dosage form" OR "oral formulation" OR "oral dosage composition" OR "oral dosage formulation" OR "oral pharmaceutical formulation" OR "oral pharmaceutical composition" OR "oral pharmaceutical forms" OR "oral form" OR "solid oral administration" OR "oral dosage form" OR "ingestible form") AND (colon OR "colon mucosa" OR "colon epithelium" OR "colon tumor" OR colonic OR colorectal OR duodenum OR jejunum OR "colonic fluid" OR "proximal ileum") AND (release OR target OR delivery OR "target drug delivery" OR "drug delivery" OR "specific delivery" OR targeted OR liberation OR liberated OR "controlled release" OR "controlled delivery")) AND (LIMIT-TO (DOCTYPE, "ar"))	Specific application
Eq. 4	Patents with (("oral dosage form" OR "oral formulation" OR "oral dosage composition" OR "oral dosage formulation" OR "oral pharmaceutical formulation" OR "oral pharmaceutical composition" OR "oral pharmaceutical forms" OR "oral form" OR "solid oral administration" OR "oral dosage form" OR "ingestible form") AND (colon OR "colon mucosa" OR "colon epithelium" OR "colon tumor" OR colonic OR colorectal OR duodenum OR jejunum OR "colonic fluid" OR "proximal ileum") AND (release OR target OR delivery OR "target drug delivery" OR "drug delivery" OR "specific delivery" OR targeted OR liberation OR liberated OR "controlled release" OR "controlled delivery")) in title or abstract	

Section A corresponds to "Human necessities", B to "Performing operations; Transporting", C to "Chemistry; Metallurgy", D to "Textiles; Paper", E to "Fixed constructions", F to "Mechanical engineering; Lighting; Heating; Weapons; Blasting", G to "Physics", H to "Electricity", and Y to "General tagging of new technological developments; General tagging of cross-sectional technologies spanning over several sections of the IPC; Technical subjects covered by former USPC cross-reference art collections and digests" [20]. For this analysis, data from the 163 patents found with Eq. 4 was subtracted from PatentInspiration software and a sunburst plot was used to identify in what technological fields the inventions were related to oral dosage forms for colon-controlled release.

2.2 Bibliographic review

The bibliographic review was constructed to identify the most recent advances of the main terms identified in the Scientific and Technological Analysis, associated with the oral dosage forms, excipients by functionality, release mechanisms, and fabrication techniques.

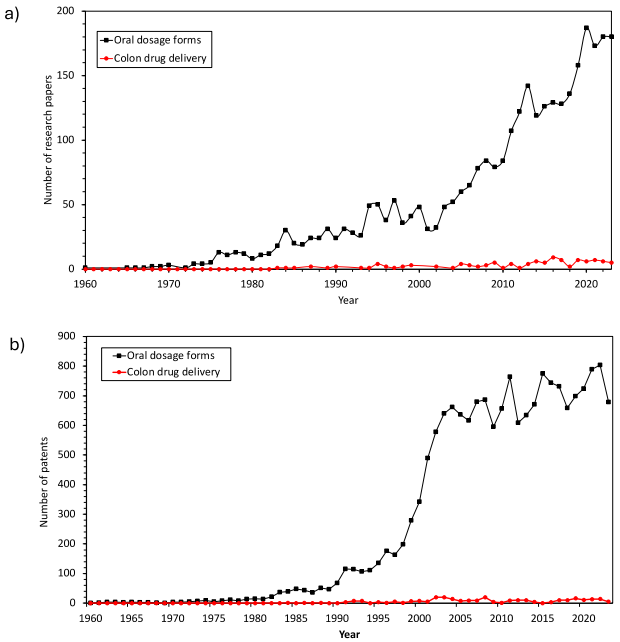


Fig. 2 Bibliometric analysis of the number of **a** research articles (1960–2023), and **b** patents (1985–2023) reported, according to the technology (oral dosage forms) and its specific application (colon delivery and controlled release). Data represent all countries

3 Results

3.1 Scientific and technological analysis

We found 3195 research articles from 1960 to 2023, and 17,768 patents from 1986 to 2023, using Eqs. (1) and (2) for the search equation, respectively. When considering the specific application (Eqs. 3 and 4) in the same period, the number of hits decreased to 112 research articles and 267 patents, respectively. According to the number of patents and papers published at the time this article was being written (Fig. 2), advances in oral dosage forms (technology)

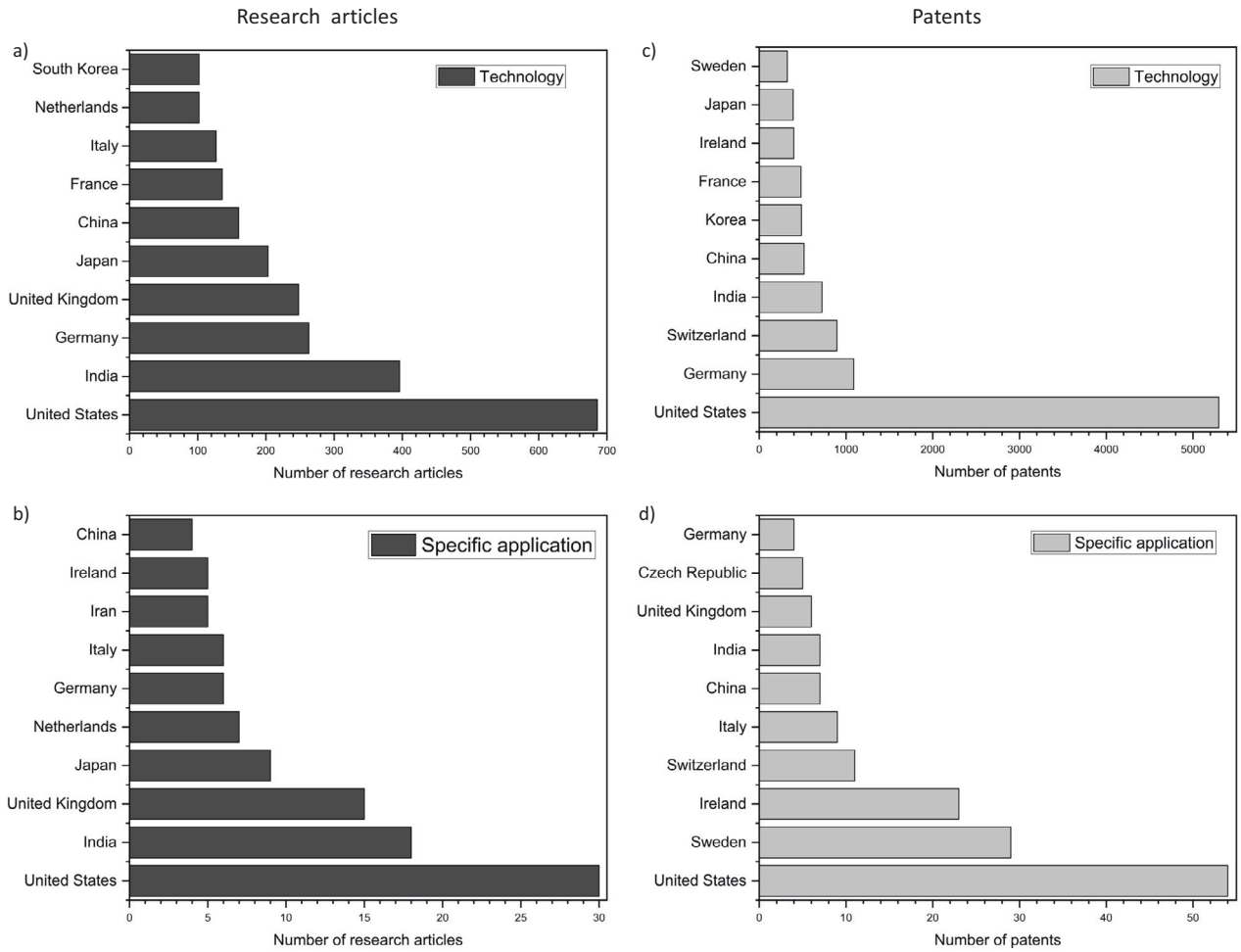


Fig. 3 The top 10 countries publishing the most scientific articles and patents related to **a**, **b** the technology (oral dosage forms), and **c**, **d** the specific application (oral dosage forms for colon-controlled release), respectively

have shown a rapid growth since the early 2000s in research articles and since 1998 in patents, while publications related to colonic delivery and controlled release (specific application) remained constant.

The gap in the publications and inventions associated with oral dosage forms for colon-controlled release (specific application) compared to oral dosage forms for any application (technology) may be due to inventors protecting their developments for potential applications in the GIT. In research articles, the reason why they do not mention that their research can be used for the fabrication of an oral dosage form may be due to the technological maturity level, where authors are not looking for a final product.

The United States, followed by European countries, such as Germany, Sweden, Switzerland, and Ireland, are among those that publish and patent the most on oral dosage forms for colon-controlled release (Fig. 3), reflecting that the research interest in colon-targeted drug delivery is indeed influenced by regional priorities and funding trends, as the increasing incidence of inflammatory bowel diseases and colorectal cancer has become a major concern in these industrialized and urbanized societies. These conditions are often linked to a "Westernized" lifestyle, which includes factors such as diet, stress, and environmental influences [21–23]. Thus, the focus on colon drug delivery is driven by both the growing need for better treatments for colonic diseases and the broader aim of enhancing pharmaceutical technology in response to regional health challenges.

Moreover, India is a close second in the number of publications of research articles, indicating that, besides playing an important role in the formulation of generic drugs (drugs that are not under patent), they are also interested in the development of advanced drugs for specialized applications like colon-controlled release, which are patentable technologies [24].

The Word Cloud plots of our bibliometric analysis highlight traditional oral dosage forms, such as tablets and capsules, but also show nanostructured systems, such as nanoparticles, nanoemulsions, and microparticles as the most reported forms of oral dosage in the literature.

Fig. 4 Word Cloud graphics of **a** drug dosage forms, **b** excipients by functionality, **c** release mechanisms, **d** APIs, and **e** characterization techniques in research articles (left) and patents (right). The size of the letters is directly related to the frequency in which the research articles and patents mention the terms (the larger the font, the higher the frequency)

Interestingly, the most patented oral dosage forms are tablets, capsules, multi-particulate systems, granules, powders, and pills (Fig. 4). Remarkably, the use of excipients in oral technologies is less commonly described in the scientific literature than in patents, where the dosage forms are at a higher technological maturity level. Regardless, the best excipients appear to be coatings.

Among release mechanisms, pH-responsive release is the most cited mode among research articles, whereas patents most often report pharmacopeia terms like dissolution and disintegration [25]. Nevertheless, the units that are most reported in patents related to oral dosage forms for colon-controlled release are pH and time (Fig. 5), indicating that dissolution and disintegration are

mainly dependent on these two stimuli, as explained in the next section.

Among APIs, most research articles were focused on the delivery of anti-inflammatory compounds, followed by chemotherapeutics drugs. Contrary, patents are not focused on specific drugs but are used for any API that can be administered orally, such as antineoplastics, anti-inflammatories, probiotics, antibiotics, cannabinoids, and bile acid sequestrants, as these drugs are related to colonic diseases like colorectal cancer, ulcerative colitis, and inflammatory bowel disease [26–28].

Lastly, characterization of materials using microscopy, thermal analysis, infrared spectroscopy, and particle size analysis related to pharmaceutical technology, such as encapsulation capacity, in vitro cellular studies, in vitro release analysis, and in vivo studies in animal models, were most represented in the scientific literature. On the other hand, patents mainly included pharmacopeial assays, e.g., the USP (United States Pharmacopeia) dissolution test, in vivo studies related to the effectiveness of the technology, and pharmacokinetic studies. Of note, due to the maturity of the technology and the applications (mainly pharmaceuticals), clinical trial studies were also reported.

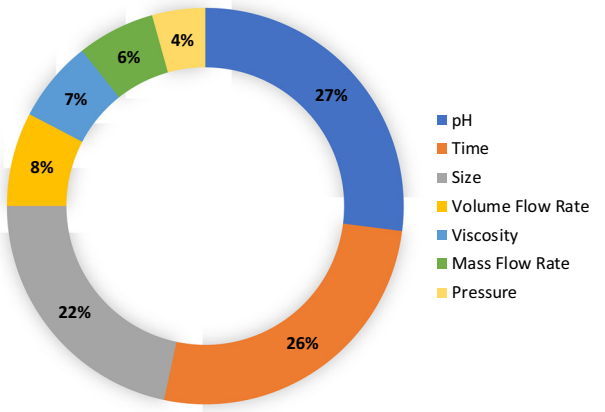


Fig. 5 Parameters reported in patents using Eq. 4, related to oral dosage forms for colon-controlled release. It shows that the parameters that most influence the development and properties of the oral dosage forms are pH, time, and the particle size. Data obtained from PatentInspiration

The two materials described the most in articles and patents and more widely as coatings, in both research articles and patents were methacrylic acid derivatives and cellulose derivatives (Fig. 6). In addition, surfactants were among the top 5 excipients named in research articles due to the fabrication of nanoparticles and nanoemulsions. However, traditional excipients, such as methacrylic acid and cellulose derivates, polyvinyl pyrrolidone, starch derivates, gelatin, magnesium stearate, talc, and lactose derivates were preferred among patented technologies. Of these, cellulose derivates were the material of choice in the fabrication of oral dosage forms.

The release mechanisms most reported by authors in research articles (Fig. 7a) were pH-responsive release, which was mainly related to tablets. To a lesser degree, dosage forms such as nanoparticles, capsules, pellets, and microparticles were also reported. In contrast, patents mainly reported disintegration and dissolution (Fig. 7b), which are pharmacopeia tests to determine drug release and the quality control of the final product [29]. This is another important difference in dosage oral form development that is in accordance with its technological maturity level.

Research papers report a variety of manufacturing techniques such as compression and granulation, which are the traditional techniques within the industry, but also other more sophisticated methods, such as emulsification,

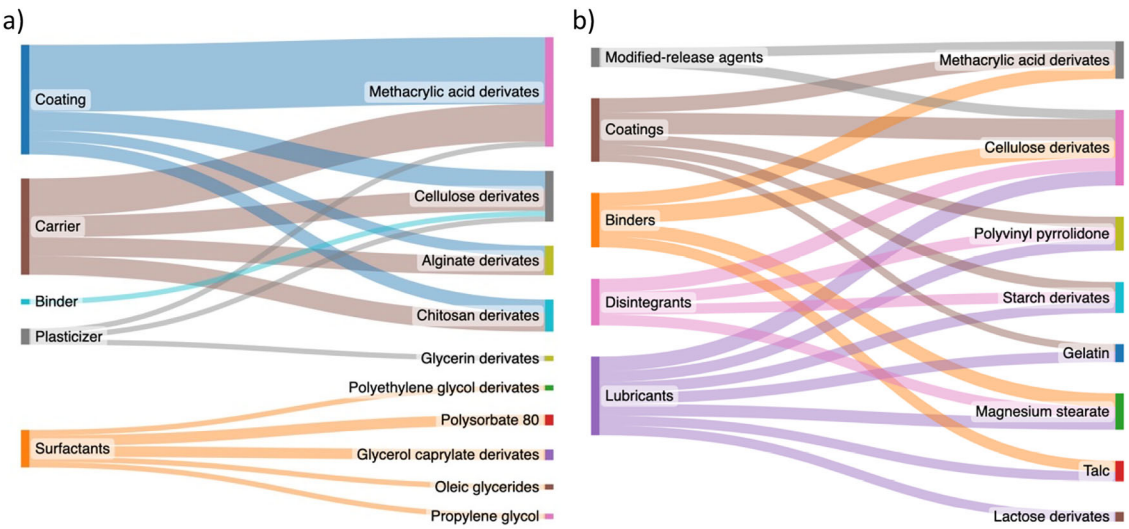


Fig. 6 Sankey diagram of the relationship between excipients and materials, in **a** research articles and **b** patents. The greater the width of the line, the greater the relationship between the terms and the number of times that the excipients were used. The overlapping terms mean that there are shared applications between the categories, resulting in lines converging

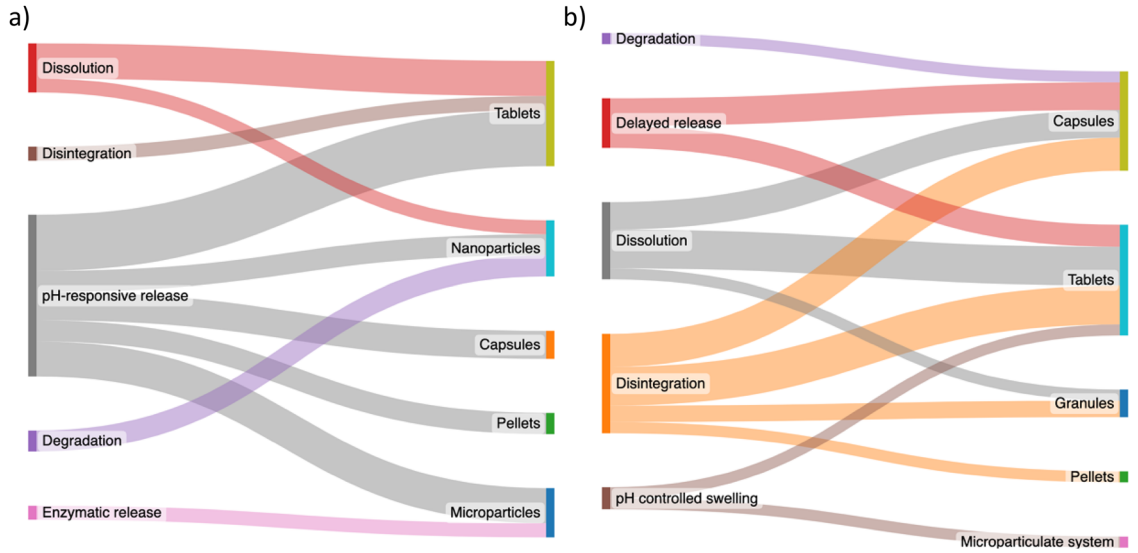


Fig. 7 Sankey diagram of the relationship between release mechanism vs oral dosage forms, in **a** research articles and **b** patents. The greater the width of the line, the greater the relationship between the terms and the number of times that the release mechanism and the oral dosage form were mentioned by authors and inventors. The overlapping terms mean that there are shared applications between the categories, resulting in lines converging

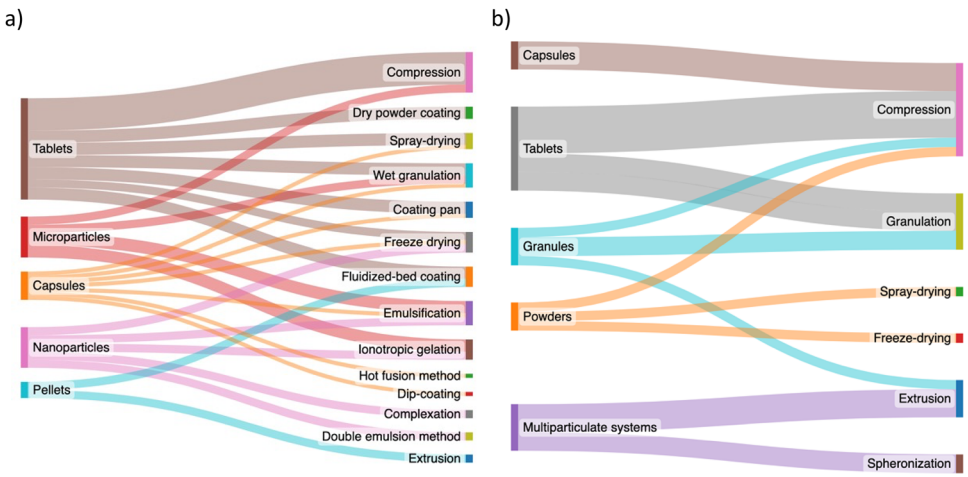


Fig. 8 Sankey diagram of the relationship between oral dosage form vs manufacturing process, in **a** research articles and **b** patents. The greater the width of the line, the greater the relationship between the terms and the number of times that the manufacturing technique and the oral dosage form were mentioned by the authors and inventors. The overlapping terms mean that there are shared applications between the categories, resulting in lines converging

ionotropic gelation, and complexation, for the development of nanoparticles and microparticles (Fig. 8a) [30–32]. Compression during capsules and tablets fabrication was widely reported in patents, albeit granulation, spray-drying, freeze-drying, extrusion, and spheronization remain important alternatives (Fig. 8b).

Lastly, the CPC of the 163 patents found using search Eq. 4 showed that most of them are classified as A61K9 and A61K31, which correspond to "Human necessities" (section A), specifically "Medical or veterinary science" (group A61), related to "Preparations for medical, dental, or toilet purposes" (class A61K), especially "Medicinal preparations characterized by special physical form" (sub-class A61K9) and "Medicinal preparations containing organic active ingredients" (sub-class A61K31) (Fig. 9). Fourteen percent

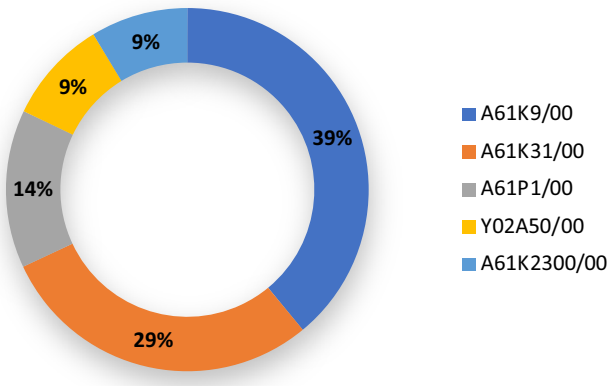


Fig. 9 CPC classifications of the 163 patents found using the search equation

Table 2 Advantages and disadvantages of the most reported oral dosage forms

Oral dosage form	Advantages	Disadvantages	Ref
Tablets	Design versatility	Higher costs of production than tablets for gastric absorption	[33, 95, 114]
	Tailored release properties	Large amounts of coating polymer needed	
	Resistance in gastric conditions	Can cause irritation in the gastrointestinal tract	
	Possibility of combining different APIs	Less palatable	
	Higher dosages	Breakdown inconsistently ()	
	Release of macromolecules and low molecular weight drugs		
Capsules	Easy to swallow	Breakdown more quickly (difficult to control the drug release over time)	[48, 115]
	Useful to increase the solubility and bioavailability of hydrophobic drugs	Greater losses in the gastrointestinal tract	
		Less dosage capacity	
		Higher drug absorption	
Micro-Nanoparticulate systems	Can be processed in different oral dosage forms	Higher costs of production than tablets and capsules	[18, 116]
	Increase the solubility of hydrophobic drugs	Difficult processability	
	Resistance to acidic conditions	There is not enough industrial machinery for its processing	
	Sustained release capacity		
	Tailored release properties		

of the patents were also classified as class A61P, which corresponds to "Specific therapeutic activity of chemical compounds or medicinal preparations" and sub-class A61P1, which corresponds to "Drugs for disorders of the alimentary tract or the digestive system." Nine percent of the patents were in sub-class A61K2300, which is for "Mixtures or combinations of active ingredients, wherein at least one active ingredient is fully defined in groups."

A small proportion of patents were also classified as Y02A50, which is related to "General tagging of new technological developments; general tagging of cross-sectional technologies spanning several sections of the IPC; technical subjects covered by former USPC cross-reference art collections [XRACs] and digests" (section Y); group Y02 related to "technologies or applications for mitigation or adaptation against climate change"; class Y02A corresponding to "technologies for adaptation to climate change"; and sub-class Y02A50 related to "human health protection."

3.2 Bibliographic review

3.2.1 Oral dosage forms

Table 2 summarizes the advantages and disadvantages of the oral dosage forms most reported for colon-targeted drug delivery. Tablets offer several advantages and disadvantages. One notable advantage is their design versatility, allowing for tailored release properties that are especially beneficial for treating local diseases in the colon. The resistance of tablets in gastric conditions ensures they reach the colon intact, minimizing exposure to the stomach and small intestine, thereby reducing systemic side effects. The possibility of combining different APIs in a single tablet provides a versatile platform for drug formulation with synergic activity. However, these advantages come with drawbacks. The higher production costs compared to gastric release, attributed to the need for large amounts of coating polymer, can be a limiting factor. Additionally, the tablets may cause irritation in the GIT and have lower palatability. Inter-individual variability in gastrointestinal transit times can affect the consistency in breakdown patterns and the challenge of achieving a sustained release adds further complexities. Despite these disadvantages, the targeted drug delivery approach remains a promising avenue for enhancing drug efficacy in colon-related conditions.

Capsules, on the other hand, offer ease of swallowing, which improves patient compliance, especially among those who have difficulty taking tablets. Additionally, capsules are particularly useful for increasing the solubility and bioavailability of hydrophobic drugs, which are otherwise challenging to deliver effectively through the GIT. This can lead to higher drug adsorption rates, ensuring that the medication exerts its intended systemic effect more efficiently.

However, there are notable drawbacks to using capsules for colon-target drug delivery. One significant disadvantage

is their tendency to break down more quickly in the digestive system, which can lead to a lack of control over the release of the drug over time. This rapid breakdown can result in greater losses of the drug in the GIT before it reaches the colon, diminishing the overall effectiveness of the treatment. Furthermore, capsules generally have less dosage capacity compared to other forms, such as tablets, limiting the amount of drug that can be delivered in a single dose.

Micro-nanoparticulate systems designed for colon-targeted drug delivery also exhibit both advantages and disadvantages in their application. One significant advantage is their versatility in processing, allowing for incorporation into various oral dosage forms, and providing flexibility for formulation based on specific therapeutic needs. Moreover, these systems demonstrate an enhanced ability to increase the solubility of hydrophobic drugs, contributing to improved bioavailability and overall drug efficacy.

However, the implementation of micro-nanoparticulate systems faces certain drawbacks. The higher costs of production can be a limiting factor in their widespread use. Additionally, the difficulty in processing these systems poses a challenge, potentially hindering their development and large-scale manufacturing. While micro-nanoparticulate systems show resistance to acidic conditions, ensuring their integrity until they reach the colon, the lack of developed industrial machinery for their processing remains an obstacle that is still under development. On a positive note, these systems offer sustained release capacity and tailored release properties, enabling a controlled and prolonged drug delivery to the colon. In conclusion, their advantages must be weighed against the challenges, emphasizing the need for ongoing research and technological advancements to fully harness their potential.

3.2.1.1 Tablets Tablets are the oral dosage form reported the most by authors and inventors. One strategy to deliver APIs in the colon is the use of single or multiple layers of polymer coatings to protect the active ingredient from degradation and early release in the stomach and small intestine. This technology is used for delivering macromolecules and low molecular-weight synthetic drugs [33]. For example, Nguyen et al. [34] developed a single-layer coating tablet for the delivery of prednisolone in the colon, using a combination of the polymer zein and the commercial polymer Kollicoat® MAE 100P to avoid formation of a weak film that leads to leaking of the drug in gastric and small intestine fluids. The authors reported that the ideal average coating to avoid early delivery of the active agent in the upper GIT was 8% by weight. However, the system exhibited a burst of drug release 45 min after being in contact with colonic fluid due to the thickness of the film coating [34].

As a result, others suggest the use of a dual controlled release mechanism for colon target-release, like Liu et al. [35] who applied a time-delay material, such as ethyl cellulose, and a pH-dependent polymer (enteric coating), such as polyacrylic resin II and III. Under these conditions, the optimum average enteric coating and time-delay polymer were 10% and 5% by weight, respectively, with the peak of drug release being at 5 h in the colonic fluid [35].

Other strategy is the one proposed by Kim et al. [36], who developed a double-layer-coated tablet using chitosan as the dispersed polymeric sub-coating and a mixture of Eudragit® E100 and ethyl cellulose as the enteric coating. The enteric coating was used by the authors to protect the API from stomach release and the sub coating was used to control the release of the drug in the latter part of the colon due to the formation of microporous channels by enzymatic chitosan digestion influenced by microflora [36]. Figure 10 shows these tablet coatings mechanisms for colon release.

Multiple-unit tablets, formed by units of coated or uncoated pellets, microparticles, or nanoparticles, were used for colon-target delivery [37, 38]. Park et al. [39] developed a multiple-unit tablet of doubly enteric-coated bisacodyl. First, bisacodyl was adsorbed over a porous carrier and then coated with a combination of pH-sensitive and time-dependent release polymers. The bisacodyl-loaded granules were then compressed into tablets and coated again with a combination of pH-sensitive polymers of the Eudragit family [39]. This technology is considered to be an advanced solid dosage form since it allows the combination of drugs with synergistic therapeutic activity and different delivery mechanisms and rates [40].

Multi-layer tablets are considered an advanced pharmaceutical platform and an alternative strategy for colonic-controlled delivery. They are formed by two or three layers of powder substances compressed together [41, 42] and are used for combination therapies, APIs for drugs with different release profiles, and chronotherapeutic delivery [41, 43]. Bilayer tablets are used for sequential and simultaneous release of two APIs, without dynamic or pharmacological interactions. Triple-layered tablets are composed of a first layer for immediate release, a second for sustained release, and a third layer in the middle applied as a barrier [44].

In an interesting study in humans performed by Patel et al. [45], researchers evaluated the effect of orally administrated resveratrol using an uncoated, immediate release caplets, on the concentration of the API in colorectal tissue. They found that the consumption of resveratrol reduced tumor cell proliferation by 5%, suggesting that daily oral doses of 0.5 or 1.0 g produce levels in the human colon tissue sufficient to elicit anticarcinogenic effects, the reason why the system merits further clinical evaluation as a potential colorectal cancer chemopreventive drug [45].

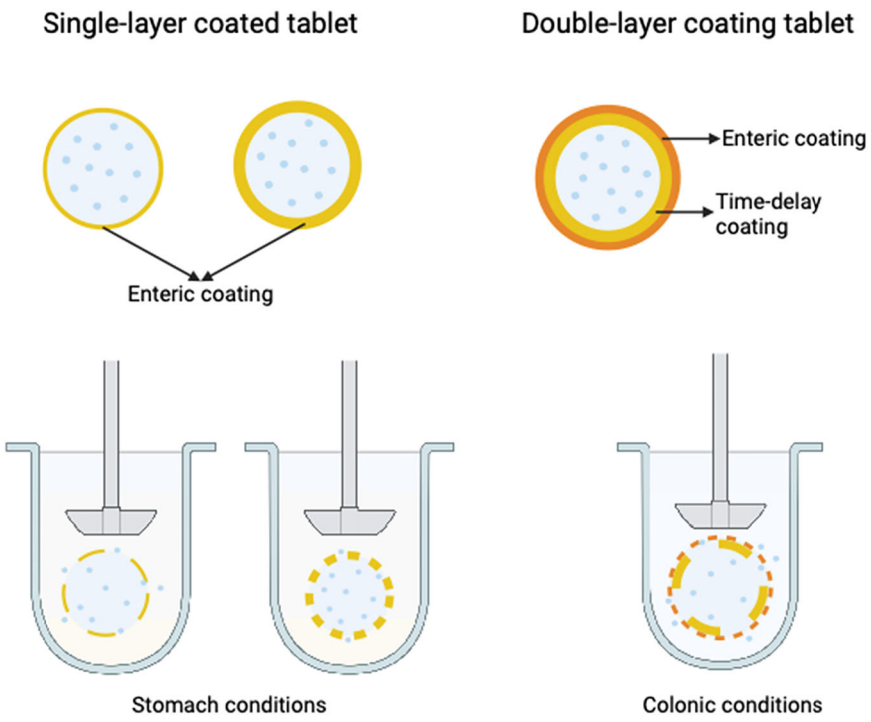


Fig. 10 Strategies for colon-targeted drug delivery tablets: single-layer coatings and double-layer coatings. Single-layer coatings use an enteric material to protect the API from gastric conditions, the thickness depends on the average percentage content used in the formulation phase. Double-layer coatings combine an enteric layer with a time-delay polymer, offering enhanced control over drug release by delaying delivery until the tablet reaches the colon. These approaches emphasize the importance of optimizing coating thickness during formulation to ensure effective and precise drug release. Created in https://BioRender.com

3.2.1.2 Capsules Capsules are solid preparations that contain drug substances enclosed in a soft or hard soluble shell normally made of gelatin [46]. For colon site-specific delivery, capsules can be hard shells containing enteric-coated pellets or minitablets or soft shells made of an acid-resistant polymer produced by coating standard capsules or modifying the shell material [47]. One approach for improving capsule shells is the exploration of materials with high gastro-resistance activity. Alternatives to gelatin are needed due to drawbacks such as cost, material supply, and isolation from animal sources. For example, Swiss Caps Rechte und Lizenzen AG has patented the use of high acyl gellan gum for the fabrication of soft shell capsules with a gastro-resistance activity of, at least, 120 min [48].

Barbosa et al. [49] reported a strategy to achieve a gastro-resistance activity of hard capsule shells without additional coatings using polymeric materials such as cellulosic (Hypromellose acetate succinate and Hypromellose phthalate) and methacrylic acid (methacrylic acid copolymer) derivates. Here, different proportions of polymers and plasticizers (glycerol and triethyl citrate) were evaluated to obtain desirable physicochemical and gastro-resistance characteristics and to target various regions of the colon [49].

Pulsatile drug delivery systems are another technology used for colon-specific delivery, especially for chronotherapy treatments, since they allow for rapid and transient release over a short period of time after a predetermined off-release period and can be processed as capsule dosage forms [50]. For example, Krögel et al. [51] developed a system that consists of an impermeable capsule body filled with a water-soluble drug closed by an erodible plug tablet. This system has an initial lag period followed by a stage of rapid drug release due to the included effervescent agent [51]. Moreover, these capsules can also be used to contain solid self-microemulsifying drug delivery systems (SMEEDS) that are processed into powders, granules, pellets, tablets, or solid dispersions, to increase the solubility and bioavailability of hydrophobic drugs, such as curcumin [52].

Haidari et al. [53] conducted a clinical trial aimed at investigating the effects of vitamin D and omega-3 fatty acids capsules co-supplementation on inflammatory factors and the tumor marker Carcinoembryonic Antigen (CAE) in colorectal cancer patients undergoing chemotherapy. A total of 81 patients with stage II or III colorectal cancer were randomly assigned to four groups: (1) Control, receiving a vitamin D placebo weekly, plus two omega-3 fatty acid placebo capsules daily; (2) omega-3 fatty acid, receiving two omega-3 fatty acid capsules (containing 330 mg), daily, plus a vitamin D placebo, weekly; (3) vitamin D, receiving a 50,000 IU vitamin D soft gel, weekly, plus two omega-3 fatty acid placebo capsules, daily; (4) co-supplementation, receiving a 50,000 IU vitamin D soft gel, weekly, plus two omega-3 fatty acids capsules. After 8 weeks, the co-supplementation group significantly decreased levels of TNF-a and IL-1b compared to the other groups. Additionally, serum levels of several inflammatory markers and CEA were significantly decreased in the omega-3, vitamin D, and co-supplementation groups compared to the control.

The study concluded that the oral co-supplementation of vitamin D and omega-3 fatty acids had beneficial impacts on colorectal cancer patients undergoing chemotherapy [53]. Moreover, the study shows the capacity of capsules to deliver hydrophobic drugs in the colonic tissue.

On the other hand, Fiorino et al. [54] carried out a phase IIa, multicenter, randomized, double-blind, parallel-group, placebo-controlled trial of a delayed-release formulation of 5-aminosalicylic acid (5-ASA) and sodium hyaluronate (IBD98-M) with potential therapeutic role in ulcerative colitis (UC), with the hypothesis that combining these two APIs in a unique oral formulation might increase the probability to induce clinical remission compared to placebo, add a steroid-free alternative to patients, and reduce the dose of 5-ASA needed. The study data exhibited a significant reduction in biomarkers of inflammation and a significant improvement in quality of life, demonstrating the synergic activity of the two APIs in the capsule formulation. However, the research did not show a statistically significant superiority of IBD98-M towards placebo in terms of primary endpoints of efficacy, reason why further clinical trials with longer time of exposure are needed for the formulation [54].

3.2.1.3 Micro-nanoparticulate systems Nanoparticulate systems are not oral dosage forms by themselves; they act as platforms or carriers (nanocarriers) that can be processed with other excipients to develop a dosage form, mostly tablets, capsules, or micro pellets, to improve their performance in the GIT. These systems are used to address the challenges of low oral bioavailability due to the poor water-solubility of APIs [18].

Nanocarriers are systems with at least one linear dimension between 1 and 100 nm, that are able to incorporate drugs into organic or inorganic matrices [55]. The most reported include lipid, metal, polymeric, and ceramic-based nanoparticles, small interfering RNA systems (siRNA), hydrogels, peptides, and extracellular vesicles [11, 56]. Liposomes are the lipid-based nanocarriers most used in colon drug delivery, consisting of spherical bilayer structures of lipid with amphipathic features able to uptake both water-soluble and lipid-soluble drugs into cells [57].

For example, Italiya et al. developed self-assembling polymeric micelles of lisofylline (LSF) that, when lyophilized and compressed into tablets, showed a higher oral absorption and a greater serum concentration than the free drug [58]. Shanmugam et al. [59] encapsulated the hydrophobic drug paclitaxel into self-assembled nanocochleates to overcome its poor oral bioavailability and to avoid drug resistance when it is administrated intravenously. The nanostructured system resisted acidic conditions of simulated stomach fluids and showed sustained drug release for over 48 h when in contact with the intestinal pH. The authors reported that in vivo oral administration of paclitaxel reduced tumor growth compared to the intravenous formulation and had a decrease in proliferation index and microvessel density [59].

A study in humans evaluated the safety and tolerability of ginsenoside-modified nanostructured lipid carrier containing hydrophobic curcumin (G-NLC), which showed improved bioavailability and cytotoxicity effect in human colon cancer cell lines. The study was performed by Jeon et al. [60], who aimed to evaluate the safety and tolerability with long-term survival rates in patients with colorectal cancer with unresectable metastases after treatment with first-line bevacizumab/FOLFIRI (folinic acid, bolus/continuous fluorouracil, and irinotecan) in combination with a dietary supplement of G-NLC. The study enrolled 44 patients between 2015 and 2019, and the median overall survival was 30.7 months, while the median progression-free survival was 12.8 months. None of the patients achieved complete response, but nine patients showed partial response, and three patients underwent conversion surgery. The most common grade 3 or higher adverse events were neutropenia, nausea, and vomiting. The study concluded that bevacizumab/FOLFIRI with G-NLC as first-line chemotherapy in patients with colorectal cancer with unresectable metastases presented comparable long-term survival outcomes with acceptable toxicity outcomes. However, additional randomized controlled studies are needed to establish definitive conclusions regarding this new regimen for metastatic colorectal cancer [60].

3.2.2 Excipients

Pharmaceutical excipients are constituents of a dosage form other than APIs [61]. Although excipients are inactive compounds, they have multiple functions permitting the efficient manufacturing of dosage forms and affecting the physical and chemical characteristics of active drug ingredients and their bioavailability. Principal examples of excipients include carriers, coating agents, binders, plasticizers, modified release agents, disintegrants, lubricants, and surfactants, as shown in Fig. 6. For the review of recent advances in the excipients by functionality, only coatings, carriers, modifying release agents, and surfactants were deepened, as they are the most reported in the research articles. More information about the functions of excipients and which are the most used, both in research articles and patents, is shown in (Table 3).

3.2.2.1 Coatings In both articles and patents, it was shown that the most used coatings were based on cellulose and methacrylic acid derivates. Other polymers like chitosan derivatives and alginate derivatives were also used in

Table 3 Main attributes and applications of principal excipients used for the development of oral dosage forms

Excipient	Materials	Applications	Attributes/Functionality	Ref
Coatings	Methacrylic acid derivates (Eudragit® L100 and S) Cellulosic derivates (Cellulose acetate phthalate, HPMCP) Chitosan Alginates Polyvinyl pyrrolidone Starch derivates Gelatin	To render the dosage form more palatable To protect the dosage form from deterioration To improve the appearance of the dosage form To improve mechanical properties To modify the release profile of the API	Stability in an acidic environment Dissolution capacity at intestinal pH Biocompatibility	[79, 117]
Carriers	Methacrylic acid derivates (Eudragit®) Cellulosic derivates (Cellulose ethers) Chitosan Alginate	To maintain drug concentration at the target site To control drug release To increase bioavailability	Chemical and physical stability Biocompatibility Biodegradability Physicochemical versatility Thermal stability	[61, 118, 119]
Release modifying agents	Methacrylic acid derivates (Eudragit® RS and RL) Cellulosic derivates (HPMC)	To delay or extend drug release	Insolubility in aqueous media Hydrophilicity/ hydrophobicity behavior Diffusion and erosion capacity Swelling upon hydration	[79, 119]
Plasticizers	Methacrylate acid derivates Cellulosic derivates (HPMC) Glycerin derivates	Film-forming agents To increase the flexibility of the resulting film To improve the processability of polymers by a reduction in elastic modulus, tensile strength, polymer melt viscosity, and the glass transition temperature To modify the drug release profile	Biocompatibility Compatibility with a given polymer Plasticization efficiency Low volatility	[119–121]
Binders	Cellulosic derivates (MCC) Methacrylate acid derivates Magnesium stearate Talc	To increase cohesion and aggregation To prolong drug liberation time To decrease hardness To increase disintegration time	High dilution potential Binding efficiency Particle size for optimum packing density and coverage	[118, 122]
Lubricants	Magnesium stearates Stearic acid Cellulosic derivates Polyvinyl pyrrolidone Starch derivates	To avoid friction and adhesion between materials during processing To improve the powder processing properties of formulations To prevent sticking during manufacturing To improve the flowability of blends	Low shear strength Capacity to form a durable layer covering the surface Biocompatibility Chemical compatibility with the API Low batch-to-batch variability	[123, 124]
Disintegrants	Cellulosic derivates (MCC, low-substituted HPC) Polyvinyl pyrrolidone Starch derivates Magnesium stearate	To enhance the dissolution of the API	Water absorption capacity Inertness Chemical stability Biocompatibility Swellable in aqueous media Colorless and odorless Good compressibility Poor water solubility	[125, 126]
Surfactants	Polyethylene glycol Polysorbate 80 Glycerol caprylate derivates Oleic glycerides Propylene glycol	To achieve the desired characteristics and size of nanoemulsion formulations To solubilize poorly aqueous soluble drugs	Amphipathic structure Biocompatibility	[82, 118]

research, and in the case of patents, other materials, such as polyvinyl pyrrolidone, starch derivates, and gelatin, were used thanks to their crosslinking phenomena, which causes considerable changes in the dissolution profiles of the drugs.

Methacrylic acid derivates exhibit diverse degrees of pH-dependent/independent solubility profiles, which allow them to be used as enteric coatings [62]. These polymers, commercially known as Eudragit® have an enteric effect attributed specifically to the presence of carboxylic groups that remain un-ionized in the low pH conditions that are found in the stomach by forming a water-insoluble film that is resistant to gastric juice and become ionized with increasing pH toward the alkaline zone of the GIT. The most employed Eudragit polymers include Eudragit® L 100 and S 100 [62]. Eudragit® S, which dissolves at pH > 7, was used for the first time in 1982 by Dew et al. [63] in a colonic delivery system for the management of patients with colitis and generate suitable for drugs such as 5-amino salicylic acid (5-ASA) or steroids [63]. Since then, these polymers have been used for colon targeting for a number of drugs such as 5-Fluorouracil (5-FU) [64], insulin [65], probiotic bacteria [66], and Paclitaxel (PTX) [67], among others.

Likewise, ether cellulose derivates, including cellulose acetate phthalate (CAP), cellulose acetate trimellitate (CAT), or cellulose acetate succinate, and cellulose ether ester derivates containing HPMCP or hydroxypropyl methylcellulose acetate succinate have potential applications for enteric coating of pharmaceutical formulations [68]. Since cellulose ethers are generally hydrophilic, they convert to a hydrogel after exposure to water and gradually dissolve in water until they fully degrade, while insoluble cellulose coatings remain as a viscose gel around tablets, and drug release is performed by diffusion of drug molecules within this layer [69].

Among these cellulose derivates, CAP was one of the earliest and most effective solutions to pH-controlled release and is still used today. For instance, Ganguly et al. [70] prepared polyethylene glycol cross-linked chitosan microspheres loaded with 5-FU with an enteric coating of CAP to facilitate direct targeting of the API to the colon. This study demonstrated that the coated microspheres were more suitable for colon targeting than the uncoated formulations as the former prolonged 5-FU release from 6 to 12 h by protecting 5-FU in the acidic environment of the stomach [70].

Chitosan, which is deacetylated chitin, and its derivates are biodegradable, biocompatible, and non-toxic cationic polysaccharides susceptible to degradation by microbial enzymes in the colon [71]. The presence of positive charges in chitosan has been shown to increase adhesion to the mucosa and as a result, increase retention time. However, chitosan solubility is of critical importance and is pH-dependent. Chitosan is water soluble below pH 6.5 due to the protonation of the primary amine group. Therefore, when soluble chitosan is required at neutral pH, two possibilities are available: either the use of chitosan oligomers, which are known to be highly soluble in water in a wide range of pH values, or the use of a chemically modified chitosan derivative [72].

In the same way, alginate is a linear anionic polysaccharide extracted from brown seaweeds that consists of alternating blocks of 1–4 linked α-L-guluronic and β-D-mannuronic acid residues [73]. Alginates have carboxyl groups that are charged at pH values higher than 3–4; thus, in acidic environments, alginate carboxyl groups are protonated, which limits drug release. However, in neutral or alkaline conditions, alginate is soluble, and the drug release is controlled by the formation of a hydrated viscous layer around the solid form. Water-soluble APIs are released primarily by diffusion of dissolved drug molecules across the gel layer, while poorly water-soluble drugs are released predominantly by erosion mechanisms [74]. Thus, the solubility and pH sensitivity of alginate make it a good biomaterial for drug-delivery systems. Narayari et al. [75] reported that alginate-coated gelatin capsules, used for the delivery of therapeutically active proteins and peptides (for example, insulin) or other drugs, were intact as long as they were retained in the stomach, but, after they passed into the small intestine, they degraded in the ileocecal region, due to the solubility of alginate at alkaline pH [75].

The last two polysaccharides, chitosan, and alginate are also used in literature studies such as blends. Rabiskoba et al. [76] prepared sodium alginate/chitosan-coated pellets intended for delivery of rutin in the colon to treat colitis. Results showed low-rate dissolution (12–14%) in upper GIT conditions and fast release (87–89%) under colon conditions in the presence of β-glucosidases that mimic the enzymatic activity of human colonic bacteria. Administration of rutin pellets coated with sodium alginate/chitosan to rats with pharmacologically induced transmural colitis significantly reduced the inflammatory response and induced mitigation of disease symptoms [76].

3.2.2.2 Carriers As shown in Fig. 6a, the most attractive carriers due to their chemical stability, compatibility properties, and a large variety of grades with different physicochemical characteristics, are the methacrylic acid derivates [62, 77].

Methacrylic acid derivates are anionic, cationic, and neutral synthetic polymers and copolymers obtained by polymerization of acrylic acid and methacrylic acids or their esters in varying proportions [62]. Eudragit polymers are known to form a swellable matrix, wherein drug release is controlled by continuously changing dimensions of the diffusive barrier [62]. For instance, Moustafine et al. [77]. developed particles of two oppositely-charged methacrylate

copolymers, Eudragit® E/PO (EPO) and Eudragit® S100 (S100) loaded with indomethacin (IND), which produced a chemically homogenous material and made the IND release process slower (7 h under GIT mimicking conditions) making this system suitable for colon-specific delivery [77].

Second, natural polymers have been also used as carriers due to their properties such as biocompatibility, biodegradability, flexibility to obtain a desirable drug release profile, cost-effectiveness, and wide regulatory acceptance. Especially, cellulose ethers are probably the most frequently used materials in pharmaceutical literature, and the most popular polymers in the formulation of commercially available oral controlled-release matrices or carriers [69].

As example, Sher et al. [78] designed a colon-targeted delivery of dicyclomine hydrochloride (DCH) microsponges based on different ratios of Hydroxypropylmethylcellulose (HPMC) and showed that the thermal stability of all microsponges was greater than the pure drug. Besides, pharmacokinetic results indicated an enhancement in the half-life, time of peak plasma concentration, maximum concentration, and area under the curve values of DCH in the microsponge compared to standard DCH, showing enhanced bioavailability of the drug after microsponge formation [78].

3.2.2.3 Modifying release agents Additionally, to accomplish therapeutic or convenience objectives not offered by conventional dosage forms, modified-release dosage forms have been designed. This strategy includes both delayed- and extended-release drug products [79].

A lot of patent inventions use methacrylic acid derivates and cellulose derivatives such as modified-release agents. In practice, hydrophobic polymers, like commercial Eudragit® RS and RL, are used as insoluble matrices that neither dissolve nor swell. Consequently, diffusion through the pores and erosion of the matrix in the GIT fluids is determined by the ratio of the high and low permeability materials, which governs the delayed release of the drug. On the other hand, blends of the hydrophilic polymer HPMC are popular modified release agents due to hydrophilic polymers that swell and dissolve upon hydration; hence, the drug is released slowly across the hydrogel that surrounds the dosage form [79].

For example, Shaikn et al. developed a successful microflora-triggered colon-targeted delivery of succinate and mesalamine, a gum ghatti together with hydroxypropyl methylcellulose sustained-released matrix coated with Eudragit® L100 and Eudragit® S100 was developed, and the in vitro dissolution profile of coated matrix tablets showed that 86.03 ± 0.43% of metoprolol succinate and 80.26 ± 0.67% of mesalamine were released at the end of 12 h, confirming a controlled drug release from the matrix [80].

3.2.2.4 Surfactants Apart from the traditional oral forms, recently advanced dosage forms based on nanoemulsions have attracted great attention in research due to advantages such as improved bioavailability and the loading of highly lipophilic drugs, since the decrease in droplet size to the nanoscale and the consequent increment of the surface area, leads to improved penetration, absorption, and delivery of compounds into the target site and a prolonged activity along time, drug transport, delivery, and absorption [79].

Nanoemulsions are oil-in-water (o/w) or water-in-oil emulsions with mean droplet diameters ranging from 50 to 1000 nm. As non-equilibrium systems of structured immiscible liquids, their preparation involves the input of a large amount of either energy or surfactants and in some cases a combination of both [81]. Surfactants or surface-active agents are amphipathic molecules that consist of a non-polar hydrophobic portion that is attached to a polar or ionic portion (hydrophilic). The hydrocarbon chain interacts weakly with the water or solvent molecules, whilst the polar or ionic head group interacts strongly with water molecules, squeezing the hydrophobic portion out, leading to their association in solution and the formation of micelles [81].

Moreover, the achievement of nanoemulsions with desired characteristics and size is the result of the selection of parameters that could affect their formation and stability, such as fabrication methods and the choice and quantity of surfactants. Due to their favorable properties, such as high solubilization capacity for poorly soluble drugs, low toxicity, and the ability to enhance the intestinal absorption of drugs [82], excipients such as polyethylene glycol derivatives, polysorbate 80, glycerol caprylate derivatives, oleic glycerides, and propylene glycol have been commonly used in research.

Dharwal et al. [83] developed a self-double emulsifying drug delivery system of pyridostigmine bromide with the aim of increasing its intestinal permeability and, hence, its oral bioavailability. For this, a water-in-oil emulsion was mixed with the optimized concentration of Tween 80, and the resulting emulsion was converted into spheroids and was then characterized as showing almost no toxicity, a high drug content of around 97.83%, and significantly improved drug release compared to the market formulation [83]. Liu et al. [84] proposed lipid-based nanocarriers, including microemulsions, niosomes, and solid lipid nanoparticles loaded with Thymopentin (TP5) using sorbitan esters, polysorbates, glycerol caprylate derivates, and oleic glycerides as surfactants and cosurfactants and found that these nanoformulations displayed superior protection under ex vivo intestinal luminal contents and mucosal homogenates for 6 h compared with the pure drug solution. These findings suggest that the use of nanocarriers can decrease peptide degradation and may improve the oral bioavailability of TP5 following oral administration [84].

Ćetković et al. [85] formulated a simvastatin (SV)-loaded self-microemulsifying drug delivery systems (SMEDDS) using various proportions of oils (PEG 300 oleic glycerides, propylene glycol monocaprylate, propylene glycol monolaurate), surfactants (PEG 400 caprylic/capricglycerides), and cosurfactants (polysorbate 80). According to the results, the drug displayed relatively high solubility in the investigated excipients, and the whole formulation was found to be helpful in protecting the drug against early degradation in proximal parts of the GI tract [85].

3.2.3 Release mechanisms

In the present review, we proposed a unification of the terms used in the description of the release mechanisms during oral administration. First, the release mechanisms that are most reported for oral dosage forms are disintegration, degradation, erosion, diffusion, and osmosis, all of which are triggered by internal colonic environmental stimuli such as pH, enzymatic concentration, microorganisms, ionic strength, or pressure, or by external stimuli such as light, and magnetic fields, among others. These release mechanisms then finish in a dissolution process of the API, which can be controlled or abrupted, determining the bioavailability of the API in the target region. Table 4 shows some release mechanisms and triggering stimuli for different solid dosage forms. Figure 11 summarizes the release mechanisms present in oral dosage forms.

3.2.3.1 Disintegration Refers to a mechanical break up of a tablet into small granules after ingestion, characterized by the breakdown of the interparticulate bonds formed during the compaction of the tablet. This reduction is influenced by the elastic and plastic deformation of the materials used as the disintegrant. The mechanisms involved in the disintegration process include swelling (enlargement of particles), strain recovery, and hydration [86]. This mechanism does not involve solid mass transformation, as shown in Fig. 11a.

Two approaches, derived from recent studies, can be used as mathematical models for tablet disintegration to incorporate both the liquid penetration and swelling dynamics, as these are critical in the breakdown process. One of the approaches is based on the capillary transport and liquid penetration, modeled by Eq. (1) describing the Washburn's Law, which assumes that liquid penetration into a porous tablet can be modeled as capillary flow, where the liquid moves through the pores, initiating disintegration. The penetration depth L over time f follows [87]:

$$L = \sqrt{\frac{2\gamma \cos\theta}{\eta} * t} \tag{1}$$

Table 4 Release mechanisms and triggering stimuli reported for some oral dosage forms

Oral dosage form	Release mechanism	Triggering stimuli	Description	Ref
Coated nanoparticles	Degradation	Colonic pH	Inulin was used for nanoparticles coating Inulin prevents the degradation of the API in harsh stomach conditions The dosage form exhibited site-specific targeting in the large intestine	[1, 127]
Coated capsule	Disintegration	Colonic pH	The spray-dried powder was packed into gelatin enteric-coated capsules The API remained encapsulated at a pH of 1, and released over 180 min at pH of 6.8 (proximal colon)	[128]
Granules	Erosion	Colonic pH	The system showed that the formulation remains intact in the stomach after 2 h, but has a burst release in the intestine	[129]
Beads	Swelling and erosion	Colonic pH	Formulations remained stable in the acidic pH of 1.2 after 6 h The swelling process was the result of water absorption and API release Swelling was attributed to the replacement of hydrogen ions by sodium ions in alkaline environment	[130]
Coated microparticles	Swelling and diffusion	Colonic pH	Complexes of enteric coating were shown to allow sustained and complete delivery of the drug within 7 h under GIT-mimicking conditions. The presence of Eudragit S100 within the formulation made the release process slower, making this system suitable for colon-specific delivery	[77]
Tablet	Disintegration	Colonic microbiota	Tablet was composed of microsponges compressed in enteric-coated tablets with Eudragit RS 100 Pectinase was the enzyme responsible for drug release in the proximal colon	[131]
Tablet	Erosion	Colonic enzymes	The formulation contains two control mechanisms: An enteric coating and a matrix of xyloglucan The polysaccharide xyloglucan exhibits erosion mechanism in the presence of colonic enzymes due to hydrolysis of the polymer	[99]
Nanoparticles	Degradation	Reactive oxygen species concentration	The system was formulated with poly-(1,4-phenyleneacetone dimethylene thioketal), which degrades in response to reactive oxygen species in specific sites of intestinal inflammation	[132]

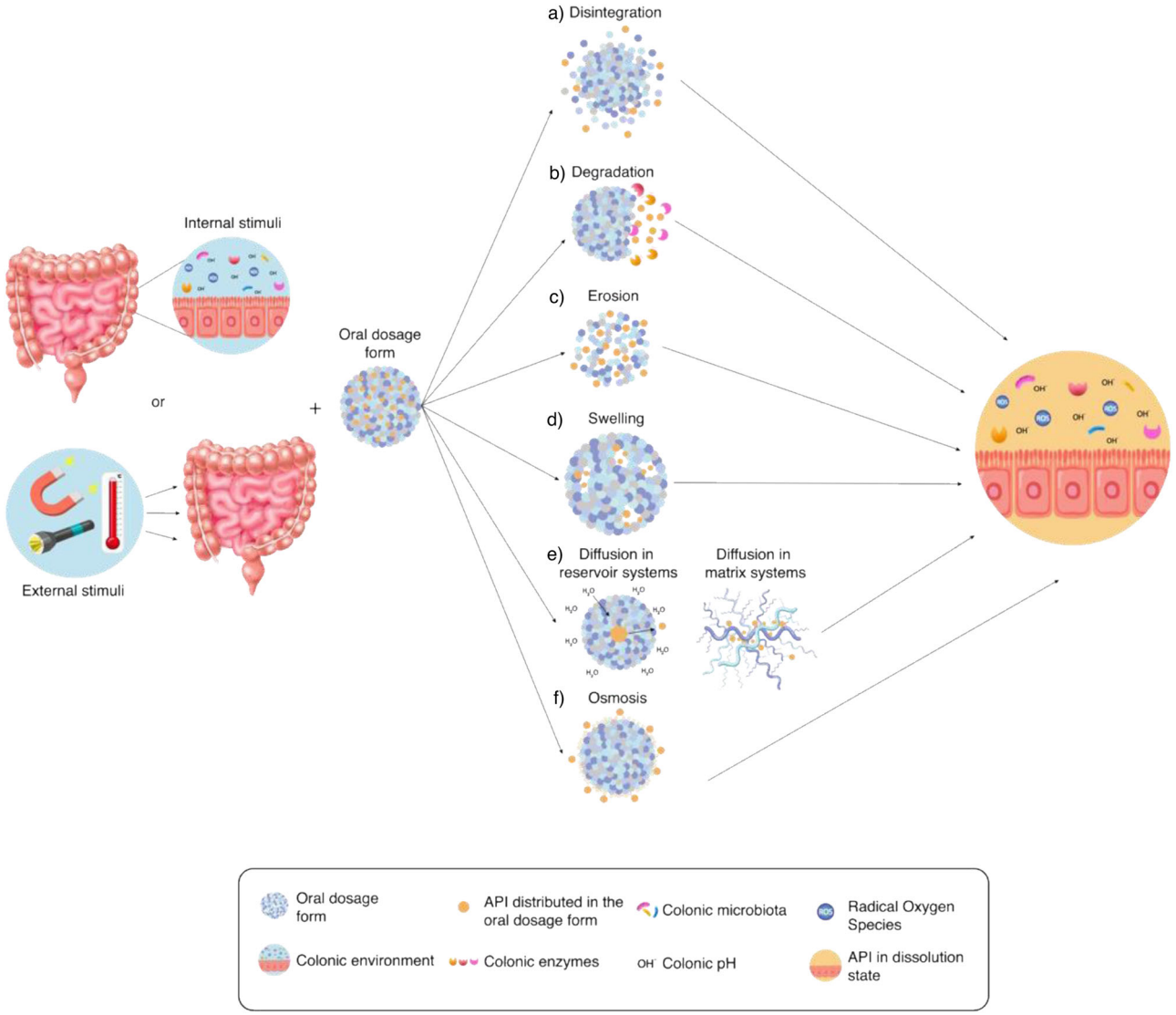


Fig. 11 Release mechanisms of oral dosage forms. Internal (colonic enzymes, microbiota, ROS, pH) or external (light, magnetic fields, temperature) stimuli come into contact with the oral dosage form and produce different responses such as disintegration, degradation, erosion, swelling, diffusion, or osmosis, which allows for dissolution of the API into the colonic environment

where γ is the surface tension of the liquid, θ is the contact angle, and η is the viscosity of the liquid. This model assumes the pores can be represented as cylindrical capillaries. The capillary effect is particularly important for initiating liquid absorption into the tablet surface [87].

The other model is based on a swelling and internal stress build-up approach, assuming that swelling occurs when excipients absorb water, generating internal stress that breaks the tablet apart. A simplified approach can describe swelling with a dynamic porosity model by Eq. (2) [88]:

$$\epsilon(t) = \epsilon_0 + k_s * t \tag{2}$$

Where $\epsilon(t)$ is the porosity at time t, ϵ_0 is the initial porosity, and k_s is the swelling rate constant. The swelling-induced porosity changes alter the liquid penetration dynamics, creating a feedback loop that accelerates the disintegration process [88].

3.2.3.2 Degradation Degradation involves interaction with the surrounding environment that degrades the solid form and currently delivers the API [89], see Fig. 11b. Mostly, it refers to the enzymatic degradation of polymeric excipients when they are in contact with colonic microorganisms, where the polymer backbone is broken down and the molecular weight is reduced [90]. Casati et al. developed a capsule shell with a blend of high-amylose starch and hydroxypropyl methylcellulose, in which the starch ensures enzyme-triggered drug release [91].

One of the mathematical models applied for the degradation process is based on degradation by enzymatic activity, modeled using Michaelis–Menten kinetics, which describes how

enzymes catalyze the breakdown of polymeric chains. The model is explained by Eq. (3) [92].

$$\frac{dM}{dt} = -k_e \frac{M}{K_m + M} \tag{3}$$

Where M is the polymer mass at time t, k_e is the maximum enzymatic degradation rate, K_m is the Michaelis constant, representing the concentration of polymer at half-time maximal enzyme activity. This model applies to polymers like starch and cellulose undergoing enzymatic degradation in the presence of colonic microorganisms [92].

3.2.3.3 Erosion Erosion is a process triggered by different factors (physical, chemical, or biological) which involves the mass loss of the material (Fig. 11c) [89]. There are two types of erosion mechanisms, bulk, and surface erosion. The first is related to the simultaneous loss of mass from the interior and exterior of the solid form. Surface erosion is the loss of mass from the surface. Therefore the initial geometry of the solid form is preserved while the size decreases with time [93]. For example, BDD Pharma patented a system named CologiK™ that consists of a tablet-in-tablet technology with an enteric-coated erodible barrier layer compressed around a drug-containing core tablet. When the tablet leaves the stomach, the barrier layer starts to erode at a constant rate through the small intestine until the core tablet is fully exposed to the colonic environment [94].

Another commercial solid form is Egalet®, a capsular device consisting of two erodible plugs of polyethylene glycol or polyethylene oxide and hydroxypropyl methylcellulose phthalate, which, after oral administration, interact with biological fluids undergoing surface erosion in the small intestine. When the plugs are completely dissolved, the inner formulation is exposed to the colonic fluids [95].

The mathematical models to explain the two erosion processes follow principles of mass loss kinetics. This approach is commonly used in pharmaceutical and material sciences to describe the degradation of materials due to environmental exposure. The bulk and surface erosion processes are frequently modeled this way in erosion studies, using Eq. (4) for surface erosion, and (5) for bulk erosion [96].

$$M_t = M_0 - k_e * t \tag{4}$$

Where M_t is the remaining material mass at time t, M_0 is the initial mass, and k_e is the erosion rate constant.

$$\frac{dM}{dt} \propto -\rho * \frac{dV}{dt} \tag{5}$$

Where ρ is the density of the material, and V is the volume change over time [96].

3.2.3.4 Swelling Polymers are the main materials able to swell when they are in contact with an aqueous fluid. Swelling occurs when the polymeric network is surrounded by water molecules leading to expansion of the network volume, illustrated in Fig. 11d, by the formation of chemical or physical bonds, with the consequent emergence of greater spaces between the polymeric chains. This mechanism is frequently accompanied by the diffusion of drug molecules through the polymeric matrix or reservoir and is mostly affected by the pH of the environment [97].

The swelling kinetics can be described by the Peppas equation, which has been validated in studies on hydrophilic polymer matrices. This model is especially useful in distinguishing between Fickian and anomalous (swelling-controlled) release behaviors. The swelling diffusion model is expressed by Eq. (6) [98].

$$Q_t = k_s * t^n \tag{6}$$

Where Q_t is the fraction of drug released at the time t, k_s is the kinetic constant, and n is the diffusion exponent, which indicates the release mechanism: Fickian diffusion for $n = 0.5$, and swelling-controlled release for n>0.5 [98].

3.2.3.5 Diffusion Diffusion is a process in which the difference in drug concentration in different regions drives API transport and differs in reservoir-type and matrix systems, as shown in Fig. 11e. For reservoir systems, the first step of diffusion is water diffusion, followed by dissolution of the solid form, and, finally, drug diffusion, the last and slowest step. In matrix-type systems, diffusion is a rate-limiting step since there is no barrier to control the release rate. Frequently, it is found to have an initial burst of drug release followed by a time-controlled release due to the drug being deposited in the innermost part of the matrix [89]. Doggwiler et al. developed a tablet formulation with dual release mechanisms based on the drug solubility of 5-aminosalicylate acid (5-ASA) and caffeine in which the latter diffused faster through the polysaccharide matrix than through 5-ASA [99].

The diffusion process can be modeled by Fick's law of diffusion and Higuchi's model. in which drug release due to diffusion through a polymeric matrix or reservoir system can be described by Eq. (7), or should follow Higuchi's model applying the equation for porous matrices (8) [100].

$$\frac{\partial C}{\partial t} = D \frac{\partial^2 C}{\partial x^2} \tag{7}$$

Where C is the concentration of the drug, D is the diffusion coefficient, and x is the distance from the source.

$$Q = \sqrt{D * A * (C_s - C)} \tag{8}$$

Where Q is the cumulative drug release, C_s is the solubility of the drug, and A is the exposed surface area [100].

3.2.3.6 Osmosis Osmosis is a process in which water molecules move across a selectively semi-permeable membrane due to differences in the concentration gradient of the solution (Fig. 11f.) [97]. Osmotic pressure appears when the higher-solute concentration side resists solvent flow [101]. Oral dosage forms are composed of a compressed tablet core with a semi-permeable coating membrane containing orifices for drug delivery. Factors affecting this release mechanism include drug solubility, delivery orifices, osmotic pressure, type of semi-permeable membrane, nature of the polymer used for the coating, membrane thickness, and the type and amount of plasticizer [101].

The osmotic pump equation stems from osmotic pressure and permeability theories. Such equations are the basis of osmotic drug delivery system designs, often used in controlled-release formulations like osmotic pumps. The drug release through a semipermeable membrane is governed by Eq. (9) [87].

$$\frac{dM}{dt} = \frac{A}{h} * k_0 * \Delta\pi \tag{9}$$

Where M is the drug released over time, A is the surface area of the membrane, h is the membrane thickness, k_0 is the osmotic permeability constant, $\Delta\pi$ is the osmotic pressure difference across the membrane [87].

3.3 Fabrication techniques

The advantages and disadvantages of the fabrication techniques are summarized in Table 5. For tablet manufacturing, the traditional methods used in research articles and patents include compression, where the material to be tableted is screened if necessary, mixed, and then compressed. Along with compression, granulation is also widely used. In general, the aim of this technique is to produce a granule that is bound in all the input materials, so they do not aggregate but are still sufficiently porous to allow compression and disintegration [25].

Nevertheless, pharmaceutical manufacturing used in academy has evolved significantly in terms of compositions and processes, allowing greater functionality, flexibility, and efficiency. For instance, in contrast to the liquid coating process, which utilizes a liquid coating suspension, dry powder coating is a dry finishing process that employs powdered coating material. Although it consists of the same sequence of steps that are employed with conventional solvent-based coatings, this method decreases the long processing times and overhead costs for conventional film coating operations [102].

Other techniques such as coating pan, spray and freeze drying, fluidized bed coating, emulsification, hot fusion, and dip coating are also widely used not only to produce tablets and capsules but also for pellets, granules, and powders production.

In academia these techniques are also used for the development of new trends in dosage forms such as microparticles whose sizes range from 1 to 1000 µm and are well-known matrix or reservoir structures (micropellets, microgranules, microspheres, microcapsules, microsponges, liposomal preparations), offering numerous advantages based on their structural and functional abilities, such as modified and targeted drug release and delivery, and more expected pharmacokinetics with reduced intra- or inter-subject variability [103].

Colon-targeted microparticles were designed to improve the antitumor effect of combined Capecitabine (CAP) and Osimertinib (OSI). This core-shell microparticle was composed of an Eudragit® S100 outer layer and a CAP/OSI-loaded PLGA (Poly(lactic-co-glycolic acid) core and successfully promoted the sustained release of CAP and OSI in the colon. Specifically, the release curve showed that CAP and OSI were released in a certain ratio. They were barely released prior to 2 h (pH 1.0), less than 50% was released between 3 and 5 h (pH 6.8), and sustained release of up to 80% occurred between 6 and 48 h (pH 7.4) providing a preoperative chemotherapy scheme for the treatment of colon cancer [104]. Moreover, different microparticles for the delivery of Metronidazole benzoate [105], Atorvastatin Calcium [106], probiotics [107], 5-FU and oxaliplatin (OX) [108], and insulin [109], among others have also demonstrated that they are effective for targeted drug delivery systems having longer duration and improved API bioavailability.

On a smaller scale, nanoparticles are structures with diameters ranging from 10 to 100 nm. Their optimized physicochemical and biological properties are more easily taken up by cells than larger molecules and, have been successfully developed using the same techniques and delivery tools for currently available bioactive compounds.

On the other hand, in the case of patents, many recent drug products in the marketplace use multiparticulate drug delivery technology, which is based on dosage forms consisting of many small discrete drug delivery units that are also known under terms such as multiple units, pellets, beads, granules, micro-granules, spheroids, or mini- or micro-tablets. In general, these multiparticulate formulations may contain single or multiple drug combinations ranging from orally dissolving particles and immediate release to various modified-release formulations [110]. Extrusion and spheronization are commonly used to produce these systems because of their advantages, including high drug loadings, narrow size distribution compared to

Table 5 Advantages and disadvantages of the major fabrication techniques for oral dosage forms

Manufacture technique	Advantages	Disadvantages	Ref
Tablet compression	Reduced cost of production Lower energy requirement Suitable for heat and moisture sensitive ingredients Less operational steps Short processing time Lower excipient requirement Less changes in dissolution profile during storage Less cross-contamination risk	Segregation of excipients Not suitable for excipients with low bulk density Affected by the powder characteristics of excipients (poor flow properties) High risk of particles agglomeration	[133, 134]
Wet granulation	Enhances the uniformity of the API Increases the density of the blend Improves the appearance of the dosage form Facilitates volumetric dispensing Reduces dust Narrow particle size distribution	Involves multiple unit processes Highly time consuming Expensive Requires large space and multiple pieces of equipment	[135–137]
Dry powder coating	Reduces cost of production High manufacture efficiencies Enhances brand identification Can be used for moisture-sensitive products Decreases the curing time	Requires specialized equipment Requires a higher coating level Is affected by the relative humidity The final product needs special storage conditions	[138]
Pan coating	Enhances the appearance of the dosage form Is a must have machine in the pharmaceutical industry	Requires air supply Implies the use of organic solvents Drying occurs only on the surface of the tablets Uniformity of the coating is affected by various factors such as temperature of the air, rate of spray, speed of the pan, residual moisture, and atomization pressure	[139–141]
Spray drying	Is a scalable process New technology advances to produce nanoscale and submicron drug carriers Allows for the control of particle properties during processing Is a rapid, continuous, and cost-effective process Can be used for the encapsulation of APIs	The yield of production depends on the work scale Ineffective separation capacity Affects the size distribution or particles	[142–144]
Freeze drying	Is a convenient separation method for delicate and decomposable products Products with high quality can be obtained	Requires extreme caution during processing to keep the properties of the product Requires long drying times than other methods Is a expensive technique due to the energy consumption	[145, 146]
Fluidized bed coating	Guarantee fast and homogeneous drying Is suitable for heat sensitive products Is a highly efficient process Is easy and less labor intensive Is suitable for continuous and batch product processing	Product loss possibility Difficult to drying sticky materials	[141, 147, 148]
Emulsification	Is suitable for non-soluble APIs in water Provides more stability to the product Guarantee a narrow particles size distribution	Requires high energy consumption Is difficult to scale up Many solvents used for the emulsification process are toxic	[149, 150]
Hot fusion	Is a simple method Is useful for screening of formulations	Is not suitable for large scale production The texture of the final product is hard Excipients should have a low melting point than the drug	[151–153]
Dip coating	Allows one to change the properties of the coating during the process Is easy to implement	Requires a high number of steps to obtain the desired coating properties	[154, 155]

other wet granulation or palletization techniques, nearly spherical shapes, robust and reproducible processes, among others [111].

4 Discussion

The developing oral dosage forms for drug release in the colon holds significant importance owing to their potential therapeutic advantages. Colon drug delivery is particularly important for treating localized gastrointestinal diseases like Crohn's disease or ulcerative colitis [2]. These formulations can minimize systemic side effects and degradation of drugs in the upper GIT, enhancing drug bioavailability at the site of action. Additionally, this targeted approach enables the delivery of sensitive drugs or biological agents, ensuring their protection from gastric acids and enzymes.

The present study explored publications on oral dosage forms for colon-targeted drug release, encompassing scientific articles and patents, to analyze technological differences. An important finding is that initial reports of oral dosage forms date back to 1960, while patents began in 1985. Notably, since then, authors seem more inclined towards patenting inventions rather than publishing them, resulting in a significantly lower yearly publication number compared to patents (Fig. 2).

Furthermore, a notable gap exists between scientific articles and patents concerning the development and design of oral dosage forms for releasing APIs in the colon (Fig. 2). In scientific articles, authors do not explore integrating their inventions into oral dosage forms, leading to limited records using search Eq. 3. This reflects in the smaller quantity of articles found using search Eq. 1 compared to patents (Eq. 2). Likewise, patents tend to omit colon release application to protect their unity of invention and most of reports of oral dosage forms in scientific articles (mention innovate micro and nanostructured formulations) are not FDA-approved [112], while patents predominantly report tablets, capsules, granules, powders, and multiparticulate systems (Fig. 4a). Furthermore, in most scientific articles do not report excipient development, and their main goal does not involve the developing final oral dosage forms but the analysis of delivery method, characterization, and the manufacturing process, in contrast to patents that include numerous excipients to protect their developments (Fig. 4b).

Despite of scientific articles have a lower technological maturity level than patents, they explore new materials, like chitosan derivates or alginates, surfactants, and nanoparticles systems as carriers that are not commercially available (which limits their Technology readiness level). Moreover, scientific articles report less-explored manufacturing processes like emulsification, ionotropic gelation, and methods for coatings such as dry powder coating compared to patents.

Finally, this paper aimed to consolidate terms found in both scientific articles and patents (Fig. 4c) following a bibliometric analysis of release mechanisms. It proposed that oral dosage forms release the API through mechanisms like disintegration, degradation, erosion, diffusion, and osmosis, mainly reported in patents. These mechanisms are triggered by internal or external stimuli (predominantly mentioned in scientific articles), like pH, enzymatic concentration, or light, culminating in the dissolution process of the API crucial for determining drug bioavailability. However, interchangeably reporting these mechanisms as the release mechanism, primarily in patents, makes understanding oral dosage forms' functionality challenging.

5 Future directions

This review highlights the critical need for scientific research in drug delivery systems to bridge the gap between laboratory advancements and their translation into commercially viable pharmaceutical dosage forms. According to the results here, the authors considered that future directions of oral dosage forms will be addressed the following points.

First, the literature reports significant progress in novel platforms such as nanoparticles, microparticles, and emulsions, the majority of patents remain focused on conventional dosage forms like tablets and capsules, as well as traditional excipients and manufacturing processes. To address this gap, future research should prioritize the technological maturation of innovative drug delivery systems, particularly for oral dosage forms targeting specific anatomical sites, such as the colon. Emphasis should be placed on advancing beyond proof-of-concept studies to include aspects of scalability, regulatory compliance, and integration into pharmaceutical manufacturing pipelines.

Secondly, the pharmaceutical industry should foster interdisciplinary collaborations with academia to accelerate the transition of promising technologies (see Fig. 12) - such as micro-nano robots, living microorganisms, 3D printing, and biomimetic DDS - into practical applications. Additionally, Researchers should also explore novel strategies to enhance the efficiency and precision of targeted release, aligning with the growing demand for personalized medicine.

These novel systems for colon drug delivery can be designed to address several critical aspects: enhancing drug stability while minimizing degradation in the gastric environment; improving drug distribution to achieve higher target-site concentrations and reduce systemic adverse effects; and lowering therapeutic dosages, thereby decreasing the toxicity associated with many APIs [113].

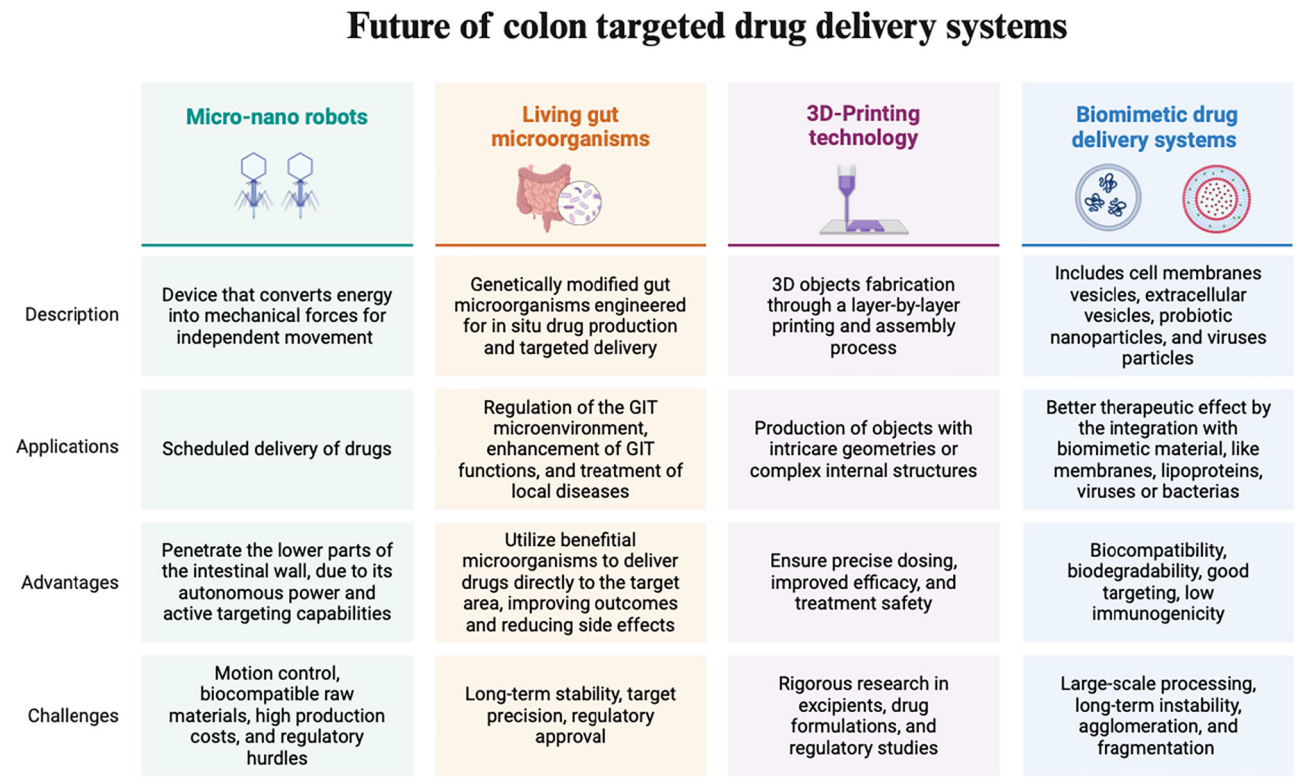


Fig. 12 Future perspectives on colon-targeted drug delivery systems. Detailed information is provided in [7, 8, 113] Created in https://BioRender.com

In summary, fostering technological readiness and aligning innovation with industry needs will enable the development of next-generation oral dosage forms that leverage the full potential of emerging materials and mechanisms, ultimately benefiting therapeutic outcomes for patients.

6 Conclusions

In the present work, a large volume of information related to oral dosage forms was found. Therefore, it was decided to analyze data from both patents and scientific articles. In the bibliometric study, an increase in publications associated with oral dosage forms, but not the same behavior in the specific application (colon release), was observed since patents do not specify the application of their invention. In the bibliometric analysis, it was found that the most important dosage forms for colon release are tablets and capsules, but research articles have explored other platforms such as nanoparticles, microparticles, and emulsions. The most applied excipient is an enteric coating to prevent API early release in the stomach, using mostly acrylate and cellulosic derivatives. Accordingly, the release mechanism most reported in both research articles and patents is pH-triggered systems, even though the word "dissolution" appears more frequently in patents.

In summary, the current review provides information about the highest trending resources on the development of oral forms for specific colon delivery according to the maturity of the technology, which is important due to the variety of information found in the literature.

Funding This study was funded by the Ministerio de Ciencia, Tecnología e Innovación (Minciencias), Proyecto Nanovehículos 92355 o Proyecto Preclínico 92391 del Programa 92332 "Avance en el desarrollo de alternativas preventivas y terapéuticas basadas en nanobioconjugados para el tratamiento del cáncer colorrectal en Colombia. NanoBioCancer 2.0 GAT 2.0. Código: 121092092332, Contrato: 621-2022".

Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

References

1. Hua S. Advances in oral drug delivery for regional targeting in the gastrointestinal tract—influence of physiological, pathophysiological and pharmaceutical factors. Front Pharm. 2020;11:524.
2. Alqahtani MS, Kazi M, Alsenaidy MA, Ahmad MZ. Advances in Oral Drug Delivery. Front Pharmacol. 2021;12:618411.
3. Zhang H, Zhang J, Streisand JB. Oral mucosal drug delivery. Clin Pharmacokinet. 2002;41:661–80.
4. Lin L, Wong H. Predicting oral drug absorption: mini review on physiologically-based pharmacokinetic models. Pharmaceutics 2017;9:41.
5. Belali N, Wathoni N, Muchtaridi M. Advances in orally targeted drug delivery to colon. J Adv Pharm Technol Res. 2019;10:100.
6. Amidon S, Brown JE, Dave VS. Colon-targeted oral drug delivery systems: design trends and approaches. AAPS PharmSciTech. 2015;16:731–41.
7. Zheng B, Wang L, Yi Y, Yin J, Liang A. Design strategies, advances and future perspectives of colon-targeted delivery systems for the treatment of inflammatory bowel disease. Asian J Pharm Sci. 2024;19:100943.
8. Zhang X, Chen G, Zhang H, Shang L, Zhao Y. Bioinspired oral delivery devices. Nat Rev Bioeng 2023;1:208–25.
9. Sarangi MK, Rao MEB, Parcha V. Smart polymers for colon targeted drug delivery systems: a review. Int J Polym Mater Polym Biomater. 2021;70:1130–66.
10. Tran PHL, Tran TTD. Mucoadhesive formulation designs for oral controlled drug release at the colon. Curr Pharm Des. 2021;27:540–7.
11. Kumari Singh S, Solanki R, Patel S. Nano pharmaceutical delivery in combating colorectal cancer. Med Drug Discov. 2024;21:100173.
12. Bahl D, Crowley KJ, Yu D. Solid oral dosage form containing nanoparticles and process for its formulation using fish jelly. Spain; 2010.
13. Zhang M, Merlin D. Nanoparticle-based oral drug delivery systems targeting the colon for treatment of ulcerative colitis. Inflamm Bowel Dis. 2018;24:1401–15.
14. Wyeth Pharmaceuticals Inc. Medication Guide: RAPAMUNE® (RAAP-a-mune) Tablets. Philadelphia; 2010. https://labeling.pfizer.com/showlabeling.aspx?id=508.
15. Filipcsei G, Ötvös Z, Heltovics G, Darvas F. Nanostructured aprepitant compositions, process for the preparation thereof and pharmaceutical compositions containing them. European Patent Office; 2011.
16. Agencia Española de Medicamentos y Productos Sanitarios. EMEND 125 mg cápsulas duras. The Netherlands, 2008. https://cima.aemps.es/cima/dochtml/p/03262006/P_03262006.html.
17. Ryde T, Gustow E, Ruddy S, Jain R, Patel R, Wilkins M. Nanoparticulate fibrate formulations. United States, 2007.
18. Lemasson O, Bourgeois S, Bourgeaux V. Nanoencapsulation: a new era for oral solid dosage forms. ONdrug Delivery; 2022. p. 16–20.
19. United Nations. Department of Economic and Social Affairs. Central Product Classification (CPC). 2015. p. 600.
20. Cooperative Patent Classification. CPC Scheme and Definitions, 2024.
21. Marcellinaro R, Spoletini D, Grieco M, Avella P, Cappuccio M, Troiano R, et al. Colorectal cancer: current updates and future perspectives. J Clin Med. 2023;13:40.
22. Alatab S, Sepanlou SG, Ikuta K, Vahedi H, Bisignano C, Safiri S, et al. The global, regional, and national burden of inflammatory bowel disease in 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet. Gastroenterol Hepatol. 2020;5:17–30.
23. M'koma AE. Inflammatory bowel disease: an expanding global health problem. Clin Med Insights Gastroenterol. 2013;6:33–47.
24. Horner R. The world needs pharmaceuticals from China and India to beat coronavirus. The Conversation. 2020.
25. Jones TM. Preformulation studies. In: Pharmaceutical formulation: the science and technology of dosage forms. Cambridge: Royal Society of Chemistry; 2018.
26. Yao D, Yu L, He W, Hu Y, Xu H, Yuan Y, et al. Antineoplastic prescription among patients with colorectal cancer in eight major cities of China, 2015-2019: an observational retrospective database analysis. BMJ Open. 2021;11:2015–9.
27. Long MD, Kappelman MD, Martin CF, Chen W, Anton K, Sandler RS. Role of non-steroidal anti-inflammatory drug in exacerbations of inflammatory bowel disease. J Clin Gastroenterol. 2017;50:243–58.
28. Kafil TS, Nguyen TM, MacDonald JK, Chande N. Cannabis for the treatment of ulcerative colitis. Cochrane Database Syst Rev. 2018;11:CD012954.
29. Ranjan A, Jha PK. Studying drug release through polymeric controlled release formulations in United States pharmacopoeia 2 apparatus using multiphysics simulation and experiments. Mol Pharm. 2021;18:2600–11.
30. Algharib SA, Dawood A, Zhou K, Chen D, Li C, Meng K, et al. Preparation of chitosan nanoparticles by ionotropic gelation technique: effects of formulation parameters and in vitro characterization. J Mol Struct. 2022;1252:132129.
31. Chen J, Pan S, Zhou J, Lin Z, Qu Y, Glab A, et al. Assembly of Bioactive Nanoparticles via Metal-Phenolic Complexation. Adv Mater. 2022;34:e2108624.
32. Hernández-Giottonini KY, Rodríguez-Córdova RJ, Gutiérrez-Valenzuela CA, Peñuñuri-Miranda O, Zavala-Rivera P, Guerrero-Germán P, et al. PLGA nanoparticle preparations by emulsification and nanoprecipitation techniques: effects of formulation parameters. RSC Adv. 2020;10:4218–31.
33. Lee SH, Bajracharya R, Min JY, Han JW, Park BJ, Han HK. Strategic approaches for colon targeted drug delivery: an overview of recent advancements. Pharmaceutics 2020;12:68.
34. Nguyen MNU, Tran PHL, Tran TTD. A single-layer film coating for colon-targeted oral delivery. Int J Pharm. 2019;559:402–9.
35. Liu DW, Yan H, Kong Y, You Y, Li Y, Wang L, et al. Preparation of colon-targeted acetylharpagide tablets and its release properties in vivo and in vitro. Front Pharm. 2018;9:1–9.
36. Kim MS, Yeom DW, Kim SR, Yoon HY, Kim CH, Son HY, et al. Development of a chitosan based double layer-coated tablet as a platform for colon-specific drug delivery. Drug Des Devel Ther. 2017;11:45–57.
37. Chen T, Li J, Chen T, Sun CC, Zheng Y. Tablets of multi-unit pellet system for controlled drug delivery. J Control Release. 2017;262:222–31.
38. Al-Hashimi N, Begg N, Alany RG, Hassanin H, Elshaer A. Oral modified release multiple-unit particulate systems: compressed pellets, microparticles and nanoparticles. Pharmaceutics 2018;10:176.
39. Park HJ, Jung HJ, Ho MJ, Lee DR, Cho HR, Choi YS, et al. Colon-targeted delivery of solubilized bisacodyl by doubly

enteric-coated multiple-unit tablet. Eur J Pharm Sci. 2017;102:172–9.
40. Warnke G, Carpanzano T. Layer by layer: the fundamentals of multi-layer tableting. JRS Pharma; 2021.
41. Blicharski T, Swiader K, Serefko A, Kulczycka-Mamona S, Kolodziejczyk M, Szopa A. Challenges in technology of bilayer and multi-layer tablets: a mini-review. Curr Issues Pharm Med Sci. 2019;32:229–35.
42. Akter R, Habibur Rahman M, Khairul Islam M, Islam R, Maharin Shapla M. An innovative approach of special layered tablet technology. World J Pharm Pharm Sci SJIF Impact Factor. 2018;7:238.
43. Khan Z, Choonara YE, Kumar P, Du Toit LC, Ndesendo VMK, Pillay V. A novel multilayered multidisk oral tablet for chronotherapeutic drug delivery. Biomed Res Int. 2013;2013:569470.
44. More S, Ghodekar S, Rane B, Bavaskar K, Patil M, Jain A. Multilayered tablet: a novel approach for oral drug delivery. Int J Pharm Sci Res. 2018;9:872–82.
45. Patel KR, Brown VA, Jones DJL, Britton RG, Hemingway D, Miller AS, et al. Clinical pharmacology of resveratrol and its metabolites in colorectal cancer patients. Cancer Res. 2010;70:7392–9.
46. Dash AK. Solid dosage forms. In: Dash AK, Singh S, Tolman J, editors. Pharmaceutics-basic principles and application to pharmacy practice. San Diego: Academic Press; 2014. pp. 165–168.
47. Maciejewski B, Arumughan V, Larsson A, Sznitowska M. Prototype gastro-resistant soft gelatin films and capsules-imaging and performance in vitro. Materials 2020;13:1771.
48. Sydow G, Sennhauser M, Schluetermann B, Prasch A, Nehring R. Gastro-resistant soft shell capsule and process for its manufacture. European Patent Office; 2014.
49. Barbosa JAC, Al-Kauraishi MM, Smith AM, Conway BR, Merchant HA. Achieving gastroresistance without coating: formulation of capsule shells from enteric polymers. Eur J Pharm Biopharm. 2019;144:174–9.
50. Singh DK, Poddar AS, Nigade SU, Poddar SS. Pulsatile drug delivery system: an overview. Int J Curr Pharm Rev Res. 2011;2:54–80.
51. Krögel I, Bodmeier R. Pulsatile drug release from an insoluble capsule body controlled by an erodible plug. Pharm Res. 1998;15:474–81.
52. Zhang Y, Bai Y, Chen H, Huang Y, Yuan P, Zhang L. Preparation of a colon-specific sustained-release capsule with curcumin-loaded SMEDDS alginate beads. RSC Adv. 2017;7:22280–5.
53. Haidari F, Abiri B, Iravani M, Ahmadi-Angali K, Vafa M. Effects of vitamin D and omega-3 fatty acids co-supplementation on inflammatory factors and tumor marker CEA in colorectal cancer patients undergoing chemotherapy: a randomized, double-blind, placebo-controlled clinical trial. Nutr Cancer. 2019;72:948–58.
54. Fiorino G, Sturniolo GC, Bossa F, Cassinotti A, Di Sabatino A, Giu P, et al. A phase 2a, multicenter, randomized, double-blind, parallel-group, placebo-controlled trial of IBD98-M delayed-release capsules to induce remission in patients with active and mild to moderate ulcerative colitis. Cells 2019;8:523.
55. Bhaw-Luximon A, Goonoo N, Jhurry D. Nanotherapeutics promises for colorectal cancer and pancreatic ductal adenocarcinoma. In: Grumezescu AM, editor. Nanobiomaterials in cancer therapy. Elsevier; 2016. pp. 147–201.
56. Garbati P, Picco C, Magrassi R, Signorello P, Cacopardo L, Dalla Serra M, et al. Targeting the gut: a systematic review of specific drug nanocarriers. Pharmaceutics 2024;16:431.
57. Shazleen Ibrahim I, Starlin Chellathurai M, Mahmood S, Hakim Azmi A, Harun N, Ulul Ilmie Ahmad Nazri M, et al. Engineered liposomes mediated approach for targeted colorectal cancer drug delivery: a review. Int J Pharm. 2024;651:123735.
58. Italiya KS, Singh AK, Chitkara D, Mittal A. Nanoparticulate tablet dosage form of lisofylline-linoleic acid conjugate for type 1 diabetes: in situ single-pass intestinal perfusion (SPIP) studies and pharmacokinetics in rat. Am Assoc Pharm Sci. 2021;22:144.
59. Shanmugam T, Joshi N, Ahamad N, Deshmukh A, Banerjee R. Enhanced absorption, and efficacy of oral self-assembled paclitaxel nanocochleates in multi-drug resistant colon cancer. Int J Pharm. 2020;586:119482.
60. Jeon Y, Sym SJ, Yoo BK, Baek JH. Long-term survival, tolerability, and safety of first-line bevacizumab and FOLFIRI in combination with ginsenoside-modified nanostructured lipid carrier containing curcumin in patients with unresectable metastatic colorectal cancer. Integr Cancer Ther. 2022;21:4–10.
61. Kalasz H, Antal I. Drug excipients. Curr Med Chem. 2006;13:2535–63.
62. Thakral S, Thakral NK, Majumdar DK. Eudragit®: a technology evaluation. Expert Opin Drug Deliv. 2013;10:131–49.
63. Dew MJ, Hughes PJ, Lee MG, Evans BK, Rhodes J. An oral preparation to release drugs in the human colon. Br J Clin Pharmacol. 1982;14:405–8.
64. Subudhi MB, Jain A, Jain A, Hurkat P, Shilpi S, Gulbake A, et al. Eudragit S100 coated citrus pectin nanoparticles for colon targeting of 5-fluorouracil. Materials 2015;8:832–49.
65. Chen S, Guo F, Deng T, Zhu S, Liu W, Zhong H, et al. Eudragit S100-coated chitosan nanoparticles co-loading tat for enhanced oral colon absorption of insulin. AAPS PharmSciTech. 2017;18:1277–87.
66. Ansari F, Pourjafar H, Jodat V, Sahebi J, Ataei A. Effect of Eudragit S100 nanoparticles and alginate chitosan encapsulation on the viability of Lactobacillus acidophilus and Lactobacillus rhamnosus. AMB Express. 2017;7:144.
67. Sood A, Dev A, Mohanbhai SJ, Shrimali N, Kapasiya M, Kushwaha AC, et al. Disulfide-bridged chitosan-Eudragit S-100 nanoparticles for colorectal cancer. ACS Appl Nano Mater. 2019;2:6409–17.
68. Maderuelo C, Lanao JM, Zarzuelo A. Enteric coating of oral solid dosage forms as a tool to improve drug bioavailability. Eur J Pharm Sci. 2019;138:105019.
69. Dias F, Duarte C. Cellulose and its derivatives use in the pharmaceutical compounding practice. In: Cellulose–medical, pharmaceutical and electronic applications. Rijeka: InTech; 2013. pp. 141–162.
70. Ganguly K, Aminabhavi TM, Kulkarni AR. Colon targeting of 5-fluorouracil using polyethylene glycol cross-linked chitosan microspheres enteric coated with cellulose acetate phthalate. Ind Eng Chem Res. 2011;50:11797–807.
71. Kato Y, Onishi H, Machida Y. Application of chitin and chitosan derivatives in the pharmaceutical field. Curr Pharm Biotechnol. 2005;4:303–9.
72. Jennings JA, Wells CM, McGraw GS, Velasquez Pulgarin DA, Whitaker MD, Pruitt RL, et al. Chitosan coatings to control release and target tissues for therapeutic delivery. Ther Deliv. 2015;6:855–71.
73. Dalmoro A, Barba AA, Lamberti G, Grassi M, d'Amore M. Pharmaceutical applications of biocompatible polymer blends containing sodium alginate†. Adv Polym Technol. 2012;31:219–30.
74. Tønnesen HH, Karlsen J. Alginate in drug delivery systems. Drug Dev Ind Pharm. 2002;28:621–30.
75. Narayani R, Rao KP. Polymer-coated gelatin capsules as oral delivery devices and their gastrointestinal tract behaviour in humans. J Biomater Sci Polym Ed. 1995;7:39–48.
76. Rabišková M, Bautzová T, Gajdziok J, Dvořáčková K, Lamprecht A, Pellequer Y, et al. Coated chitosan pellets containing rutin intended for the treatment of inflammatory bowel disease: in vitro characteristics and in vivo evaluation. Int J Pharm. 2012;422:151–9.
77. Moustafine RI, Sitenkov AY, Bukhovets AV, Nasibullin SF, Appeltans B, Kabanova TV, et al. Indomethacin-containing

interpolyelectrolyte complexes based on Eudragit® E PO/S 100 copolymers as a novel drug delivery system. Int J Pharm. 2017;524:121–33.
78. Sher M, Sarfaraz RM, Iqbal S, Hussain MA, Naeem-ul Hassan M, Hassan F, et al. Formulation and evaluation of hydroxypropylmethylcellulose-dicyclomine microsponges for colon targeted drug delivery: in vitro and in vivo evaluation. Curr Drug Deliv. 2022;19:686–96. https://pubmed.ncbi.nlm.nih.gov/34353263/.
79. Debotton N, Dahan A. Applications of Polymers as Pharmaceutical Excipients in Solid Oral Dosage Forms. Med Res Rev. 2017;37:52–97.
80. Shaikn M, Desai N, Momin M, Kumar Bhatt L. Formulation development and in-vitro/ex-vivo evaluation for a polysaccharide-based colon targeted matrix tablet. Curr Drug Deliv. 2021;18:1563–73.
81. Lovelyn C, Attama AA. Current state of nanoemulsions in drug delivery. J Biomater Nanobiotechnol. 2011;2:626–39.
82. Sekhon BS. Surfactants: pharmaceutical and medicinal aspects. J Pharm Technol Res Manag. 2013;1:43–68.
83. Dharwal S, Bajwa N, Madan J, Mandar UK, Singh KK, Baldi A. Self-double emulsified drug delivery system of pyridostigmine bromide augmented permeation across caco-2 cells. Lett Drug Des Discov. 2022;19:520–9.
84. Liu M, Svirskis D, Proft T, Loh J, Chen S, Kang D, et al. Exploring ex vivo peptideolysis of thymopentin and lipid-based nanocarriers towards oral formulations. Int J Pharm. 2022;625:122123.
85. Ćetković Z, Cvijić S, Vasiljević D. In vitro/in silico approach in the development of simvastatin-loaded self-microemulsifying drug delivery systems. Drug Dev Ind Pharm. 2018;44:849–60.
86. Markl D, Zeitler JA. A review of disintegration mechanisms and measurement techniques. Pharm Res. 2017;34:890–917.
87. Jange CG, Wassgren CR, Ambrose K. The significance of tablet internal structure on disintegration and dissolution of immediate-release formulas: a review. Powders. 2023;2:99–123.
88. Soundaranathan M, Al-Sharabi M, Sweijen T, Bawuah P, Zeitler JA, Hassanizadeh SM, et al. Modelling the evolution of pore structure during the disintegration of pharmaceutical tablets. Pharmaceutics 2023;15:489.
89. Wang S, Liu R, Fu Y, Kao WJ. Release mechanisms and applications of drug delivery systems for extended-release. Expert Opin Drug Deliv. 2020;17:1289–304.
90. Philip AK, Philip B. Colon targeted drug delivery systems: a review on primary and novel approaches. Oman Med J 2010;25:70–8.
91. Casati F, Melocchi A, Moutaharrik S, Uboldi M, Foppoli A, Maroni A, et al. Injection molded capsules for colon delivery combining time-controlled and enzyme-triggered approaches. Int J Mol Sci. 2020;21:1917.
92. Trucillo P. Drug carriers: a review on the most used mathematical models for drug release. Processes. 2022;10:1094.
93. Geraili A, Mequanint K. Systematic studies on surface erosion of photocrosslinked polyanhydride tablets and data correlation with release kinetic models. Polymers. 2020;12:1105.
94. BDD World Class Drug Delivery Company. https://www.bddpharma.com/technologies/cologik/. CologiKTM. 2025.
95. Gazzaniga A, Moutaharrik S, Filippin I, Foppoli A, Palugan L, Maroni A, et al. Time-based formulation strategies for colon drug delivery. Pharmaceutics 2022;14:2762.
96. Bisotti F, Pizzetti F, Storti G, Rossi F. Mathematical modelling of cross-linked polyacrylic-based hydrogels: physical properties and drug delivery. Drug Deliv Transl Res. 2022;12:1928–42.
97. Bruschi M. Main mechanisms to control the drug release. In: Strategies to modify the drug release from pharmaceutical systems. Woodhead Publishing; 2015. pp. 37–62.
98. Setapa A, Ahmad N, Mohd Mahali S, Mohd Amin MCI. Mathematical model for estimating parameters of swelling drug delivery devices in a two-phase release. Polymers. 2020;12:2921.
99. Doggwiler V, Lanz M, Paredes V, Lipps G, Imanidis G. Tablet formulation with dual control concept for efficient colonic drug delivery. Int J Pharm. 2023;631:122499.
100. Gouda R, Baishya H, Qing Z. Application of Mathematical Models in Drug Release Kinetics of Carbidopa and Levodopa ER Tablets. J Develop Drugs 2017;6:171.
101. Almoshari Y. Osmotic pump drug delivery systems—a comprehensive review. Pharmaceuticals 2022;15:1430.
102. Sauer D, Cerea M, Dinunzio J, McGinity J. Dry powder coating of pharmaceuticals: a review. Int J Pharm. 2013;457:488–502.
103. Lengyel M, Kállai-Szabó N, Antal V, Laki AJ, Antal I. Microparticles, Microspheres, and Microcapsules for Advanced Drug Delivery. Sci Pharm. 2019;87:20.
104. Chen R, Zhai R, Wang C, Liang S, Wang J, Liu Z, et al. Compound capecitabine colon-targeted microparticle prepared by coaxial electrospray for treatment of colon tumors. Molecules 2022;27:5690.
105. Preisig D, Varum F, Bravo R, Hartig C, Spleiss J, Abbes S, et al. Colonic delivery of metronidazole-loaded capsules for local treatment of bacterial infections: a clinical pharmacoscintigraphy study. Eur J Pharm Biopharm. 2021;165:22–30.
106. Dewangan HK, Sharma A, Mishra A, Singour P. Mucoadhesive microspheres of atorvastatin calcium: rational design, evaluation and enhancement of bioavailability. Indian J Pharm Educ Res. 2021;55:S733–41.
107. Cheng Q, Liu L, Xie M, Li H, Ma D, Xue W. A colon-targeted oral probiotics delivery system using an enzyme-triggered fuse-like microcapsule. Adv Health Mater 2021;10:1–10.
108. Jaswanth Gowda BH, Shankar SJ, Munisamy M, Akshatha RS, Sagar VS. Development of ph-dependent chronomodulated delivery systems of 5-fluorouracil and oxaliplatin to treat colon cancer. Int J Appl Pharm. 2020;12:118–30.
109. Meneguin AB, Beyssac E, Garrait G, Hsein H, Cury BSF. Retrograded starch/pectin coated gellan gum-microparticles for oral administration of insulin: a technological platform for protection against enzymatic degradation and improvement of intestinal permeability. Eur J Pharm Biopharm. 2018;123:84–94.
110. Rajabi-Siahboomi A. Overview of multiparticulate systems for oral drug delivery. In: Rajabi-Siahboomi A, editor. Multiparticulate drug delivery. New York: Springer; 2017. p. 1–4.
111. Thommes M, Kleinebudde P. The science and practice of extrusion-spheronization. In: Multiparticulate drug delivery. New York: Springer; 2017. p. 37–63.
112. Chaurasia M, Singh R, Sur S, Flora SJS. A review of FDA approved drugs and their formulations for the treatment of breast cancer. Front Pharmacol. 2023;14:1184472.
113. Chen Q, Yang Z, Liu H, Man J, Oladejo AO, Ibrahim S, et al. Novel drug delivery systems: an important direction for drug innovation research and development. Pharmaceutics 2024;16:674.
114. McCoubrey LE, Favaron A, Awad A, Orlu M, Gaisford S, Basit AW. Colonic drug delivery: formulating the next generation of colon-targeted therapeutics. J Control Release. 2023;353:1107–26. Elsevier B.V.
115. Ugwu CE, Kenechukwu FC, Diovu EO, Udodeme HO, Momoh MA, Onuigbo EB, et al. Exploitation of capsule system for colon targeted drug delivery of biopolymer-based microparticles: in vivo and in vitro applications. Heliyon 2022;8:e11390.
116. Dos Santos AM, Carvalho SG, Meneguin AB, Sábio RM, Gremião MPD, Chorilli M. Oral delivery of micro/nanoparticulate systems based on natural polysaccharides for intestinal diseases therapy: Challenges, advances and future perspectives. J Control Release. 2021;334:353–66.

117. Kar M, Chourasiya Y, Maheshwari R, Tekade RK. Current developments in excipient science. In: Basic fundamentals of drug delivery. London: Elsevier; 2019. pp. 29–83.
118. Dudhat MsKR. The overview of oral solid dosage forms and different excipients used for solid dosage formulation. Glob Acad J Pharm Drug Res. 2022;4:66–72.
119. van der Merwe J, Steenekamp J, Steyn D, Hamman J. The role of functional excipients in solid oral dosage forms to overcome poor drug dissolution and bioavailability. Pharmaceutics 2020;12:393.
120. Somwanshi SB, Dolas RT, Wagh VD, Kotade KB. Pharmaceutically used plasticizers: a review of biomedical and pharmaceutical sciences. Eur J Biomed Pharm Sci. 2016;3:277–85.
121. Tambe S, Jain D, Meruva SK, Rongala G, Juluri A, Nihalani G, et al. Recent advances in amorphous solid dispersions: preformulation, formulation strategies, technological advancements and characterization. Pharmaceutics 2022;14:2203.
122. Yohana Chaerunisaa A, Sriwidodo S, Abdassah M. Microcrystalline cellulose as pharmaceutical excipient. In: Pharmaceutical formulation design—recent practices. Rijeka: InTech; 2020.
123. Li J, Wu Y. Lubricants in pharmaceutical solid dosage forms. Lubricants. 2014;2:21–43.
124. Kanher PR. Lubricants in pharmaceutical solid dosage forms with special emphasis on magnesium stearate. World J Pharm Res. 2017;(9):131–46. https://doi.org/10.20959/wjpr20179-9170.
125. Kar M, Chourasiya Y, Maheshwari R, Tekade RK. Current developments in excipient science: implication of quantitative selection of each excipient in product development. In: Basic fundamentals of drug delivery. Academic Press; 2019. pp. 29–83.
126. Yohana Chaerunisaa A, Sriwidodo S, Abdassah M. Microcrystalline cellulose as pharmaceutical excipient. In: Pharmaceutical formulation design - recent practices. IntechOpen: London; 2020.
127. Kourani K, Jain P, Kumar A, Jangid AK, Swaminathan G, Durgempudi VR, et al. Inulin coated Mn_3O_4 nanocuboids coupled with RNA interference reverse intestinal tumorigenesis in Apc knockout murine colon cancer models. Nanomedicine 2022;40:102504.
128. Reeves MA, Royal JM, Morris DA, Jurkiewicz JM, Matoba N, Hamorsky KT. Spray-dried formulation of epicertin, a recombinant cholera toxin b subunit variant that induces mucosal healing. Pharmaceutics 2021;13:1–13.
129. Agrawal V, Sandal N, Singh AK, Pathak DP. pH-dependent release matrix oral formulation of Prussian blue to improve its efficacy as an internal decorporation agent. Curr Drug Deliv. 2021;18:1162–73.
130. Osmalek T, Milanowski B, Froelich A, Szybowicz M, Białowąs W, Kapela M, et al. Design and characteristics of gellan gum beads for modified release of meloxicam. Drug Dev Ind Pharm. 2017;43:1314–29.
131. Othman MH, Zayed GM, Ali UF, Abdellatif AAH. Colon-specific tablets containing 5-fluorouracil microsponges for colon cancer targeting. Drug Dev Ind Pharm. 2020;46:2081–8.
132. Wilson SD, Dalmasso G, Wang L, Sitaraman SV, Merlin D, Murthy N. Orally delivered thioketal-nanoparticles loaded with TNFα-siRNA target inflammation and inhibit gene expression in the intestines. Nat Mater. 2010;9:923–8.
133. Chauhan A, Rohilla S, Jain S. Direct compression method. World J Pharm Pharm Sci. 2019;8:692–701.
134. Patil K, Dali P, Mangal N, Kathpalia H. An update on advancements in tablet tooling technology. J Drug Deliv Sci Technol. 2023;80:104191.
135. Shanmugam S. Granulation techniques and technologies: recent progresses. BioImpacts 2015;5:55–63.
136. Wang L, Zhao L, Hong Y, Shen L, Lin X. Technological advances and challenges for exploring attribute transmission in tablet development by high shear wet granulation. Powder Technol. 2023;421:118402.
137. Vadaga AK, Gudla SS, Nareboina GSK, Gubbala H, Golla B. Comprehensive review on modern techniques of granulation in pharmaceutical solid dosage forms. Intell Pharm. 2024;2:609–29.
138. Vanamu J, Sahoo A. An overview on dry powder coating in advancement to electrostatic dry powder coating used in pharmaceutical industry. Powder Technol. 2022;399:117214.
139. Salawi A. Pharmaceutical coating and its different approaches, a review. Polymers. 2022;14:3318.
140. Chen J, Yang Q, Liu J, Jin M, He S, Zhou X, et al. Understanding the correlations between tablet flow dynamics and coating uniformity in a pan coater: experiments and simulations. Chem Eng J. 2023;471:144392.
141. Ganguly D, Ghosh S, Chakraborty P, Mitra S, Chatterjee S, Panja S, et al. A brief review on recent advancement of tablet coating technology. J Appl Pharm Res. 2022;10:7–14.
142. Sosnik A, Seremeta KP. Advantages and challenges of the spray-drying technology for the production of pure drug particles and drug-loaded polymeric carriers. Adv Colloid Interface Sci. 2015;223:40–54.
143. Baumann JM, Adam MS, Wood JD. Engineering advances in spray drying for pharmaceuticals. Annu Rev Chem Biomol Eng. 2021;12:217–40.
144. Sohail Arshad M, Zafar S, Yousef B, Alyassin Y, Ali R, AlAsiri A, et al. A review of emerging technologies enabling improved solid oral dosage form manufacturing and processing. Adv Drug Deliv Rev. 2021;178:113840.
145. Sadikoglu H, Ozdemir M, Seker M. Freeze-drying of pharmaceutical products: research and development needs. Dry Technol. 2006;24:849–61.
146. Pardeshi SR, Deshmukh NS, Telange DR, Nangare SN, Sonar YY, Lakade SH, et al. Process development and quality attributes for the freeze-drying process in pharmaceuticals, biopharmaceuticals and nanomedicine delivery: a state-of-the-art review. Futur J Pharm Sci. 2023;9:99.
147. Law Lim C, Mujumdar AS. Fluidized bed dryers. In: Mujumdar AS, editor. Handbook of industrial drying. Boca Raton: CRC Press; 2006.
148. de Freitas LAP. Pharmaceutical applications of spouted beds: a review on solid dosage forms. Particuology 2019;42:126–36.
149. Lubrizol Corporation. Emulsions and Emulsifications [Internet]. Cleveland; 2019 [cited 2025]. Available from: https://lubrizolcdmo.com/wp-content/uploads/2019/10/TB-9-Emulsions-and-Emulsification_lowres.pdf.
150. Maji I, Mahajan S, Sriram A, Medtiya P, Vasave R, Khatri DK, et al. Solid self emulsifying drug delivery system: Superior mode for oral delivery of hydrophobic cargos. J Control Release. 2021;337:646–60.
151. Srinarong P, De Waard H, Frijlink HW, Hinrichs WLJ. Improved dissolution behavior of lipophilic drugs by solid dispersions: the production process as starting point for formulation considerations. Expert Opin Drug Deliv. 2011;8:1121–40.
152. Tambe S, Jain D, Agarwal Y, Amin P. Hot-melt extrusion: highlighting recent advances in pharmaceutical applications. J Drug Deliv Sci Technol. 2021;63:102452.
153. Tan DK, Davis DA, Miller DA, Williams RO, Nokhodchi A. Innovations in thermal processing: hot-melt extrusion and KinetiSol® dispersing. AAPS PharmSciTech. 2020;21:312.
154. Kapoor D, Maheshwari R, Verma K, Sharma S, Ghode P, Tekade K. Coating technologies in pharmaceutical product development. In: Drug delivery systems. Academic Press; 2020. pp. 665–719.
155. Champeau M, Thomassin JM, Tassaing T, Jérôme C. Current manufacturing processes of drug-eluting sutures. Expert Opin Drug Deliv. 2017;14:1293–303.