Review Article

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Current Update on Clinical Therapeutic Strategies for Colon-Targeted Delivery Systems

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ABSTRACT

Oral colon-targeted drug delivery systems represent a significant advancement offering both systemic and local therapeutic effects for a range of intestinal diseases, including irritable bowel syndrome, inflammatory bowel disease, colonic bacterial infections, and colorectal cancer. These systems facilitate the delivery of both small molecules and macromolecular compounds such as peptides, proteins, antibodies, oligonucleotides, RNA, and probiotics. This review provides an up-to-date exploration of the critical factors crucial for the effective design and development of drug delivery systems targeting the colon. The chosen strategy takes into account various aspects of colon physiology that influences the profile of drug release, absorption, dissolution, and stability in the colon, including pH, retention time, presence of enzymes, pressure, presence of reactive oxygen species due to inflammation, and specific receptors. Site-targeted drug release allows for high concentrations in the colon while minimizing systemic adverse effects by reducing or preventing drug absorption in the small intestine.

Keywords: *colon-targeted; intestinal diseases; drug delivery; site-targeted*

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INTRODUCTION

Oral delivery systems are the most convenient option due to their simplicity of administration, thus potentially enhancing patient compliance (Dugad et al., 2018). These systems include colon-targeted drug delivery systems, yet they encountered various challenges. To meet therapeutic target, modifications must address the intricate physicochemical properties and mechanisms controlling drug release from the formulation. The development of colon-targeted drug delivery systems (CTDDS) serves four primary purposes: ensuring continuous drug delivery, achieving high local concentrations by delaying drug release in the colon, providing delayed drug release for acute disease treatment, and preventing drug degradation from the metabolic system (Rathbone et al., 2003).

In recent years, colon-targeted drug delivery systems have experienced a resurgence, offering numerous benefits and opportunities in the pharmaceutical field (Awad et al., 2022). Targeting the colon for treatment, particularly locally, enhances treatment effectiveness and offers benefits such as improved accessibility, minimal systemic drug exposure, reduced risk of unexpected side effects, and enhanced drug bioavailability (McCoubrey et al., 2023). Diseases that can be cured by colon-targeted drug delivery systems can be categorized based on their action site (Figure 1) (Dugad et al., 2018). Traditionally, these delivery systems have primarily addressed topical and localized diseases like intestinal inflammation and colorectal cancer (Foppoli et al., 2019). However, with an increased understanding of the colon and rectal environment, these systems now offers systemic therapeutic effects by leveraging factors such as microbiota, the enteric immune system, and the lymphatic system (McCoubrey et al., 2023).

An ideal CTDDS releases the drug at the beginning of the large intestine, the intended site of action, rather than in the upper and middle digestive tract. Formulation strategies must consider factors like pH variations and residence time differences along the digestive tract (Amidon et al., 2015). Notably, differences in surface area and permeability between colon and the upper or middle digestive systems significantly impact drug release and flux to the colonic mucosa. Additionally, the presence of various bacteria in the colon may lead to potential drug degradation, necessitating adjustments in the delivery system (Rathbone et al., 2003). This review aims to provide a comprehensive overview of colon-targeting drug delivery systems, encompassing the physiological conditions of the colon, physicochemical properties of drugs, and insights into both traditional and advanced colonic drug delivery technologies, with a specific focus on clinical and commercial aspects.

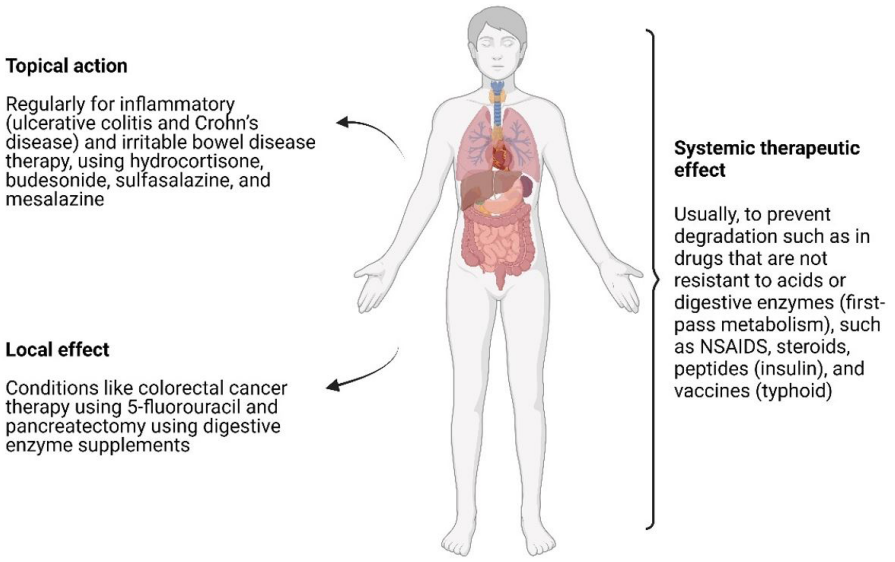

Figure 1. Target sites of colon-targeted drug delivery systems

Table 1. Groups of compounds potential for of CTDDS

Criteria	Drugs	Reference
Compounds intended for local treatment of digestive tract disease, including those affecting the colon	Oxyprenolol, metoprolol, nifedipine	(Dugad et al., 2018)
Compounds with systemic effects	Penicillin, ampicilin, amoxicilin	(Babu et al., 2022)
Compounds for colorectal cancer treatment	5-Fluorouracil, doxorubicin, bleomycin	(Kumar et al., 2019)
Compounds susceptible to degradation in the stomach and small intestine	Peptide and proteins	(Teruel et al., 2020)
Compounds susceptible to first-pass metabolism	Prednisolone, hydrocortisone	(Dugad et al., 2018)
Compounds for targeting action	Somatropin, urotoilitin	(Dugad et al., 2018)

Selection Criteria for Potential Compounds Suitable for CTDDS

Key criteria for developing a colon-targeted delivery system involves compounds that that specifically target the colon to provide localized therapeutic effects for intestinal diseases. Additionally, compounds with minimal absorption in the upper digestive tract are preferred, especially those intended for rectal or colon cancer therapy. Consideration is also given to compounds that susceptible to degradation by stomach acid or enzymes and those subject first-pass metabolism (Amidon et al., 2015). Moreover, this system also holds potential for vaccine delivery, leveraging the abundance of lymphoid tissue in the colon, including immune cells such as microfold (M) cells, crucial for maintaining human immune tolerance to gut microbiota (Awad et al., 2022; Dugad et al., 2018)). For further details, see Table 1.

Colon Physiology and Associated Diseases

Oral drug delivery systems encounter the challenge of achieving the optimal bioavailability at the target site of action, despite the complex environment of the gastrointestinal tract (Lou et al., 2023). The gastrointestinal tract comprises a complicated system consisting of various specialized organs responsible for food digestion and the absorption of water, electrolytes, and nutrients (Kurakula et al., 2021). The colon is extending from the distal end of the ileum to the anus (Iyengar et al., 2020), which spans approximately 1.5 meters long and located in the distal part of the digestive tract. It is segmented into three parts: ascending, transverse, and descending, each characterized by distinct physiological features (Figure 2) (Kurakula et al., 2021). For a detailed overview of the colon's physiological conditions, refer to Table 2.

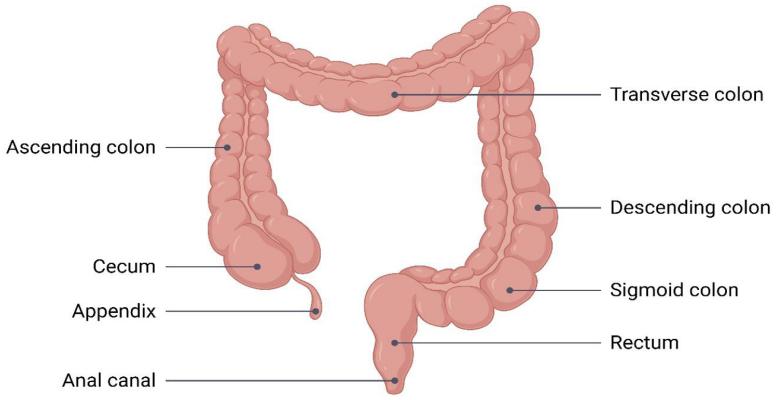

Figure 2. Anatomical structure of colon

Table 2. Consideration of colonic conditions in the development of colon-targeted drug delivery systems

Parameter	Specific Information	Reference
pH value	Ascending ~6.7 – 7.3 Transverse ~6,4 Descendent ~6.0 – 7	(Dugad et al., 2018)
Time to reach the colon	Average 4 hours on the subject fast	(Kurakula et al., 2021)
Transit time in the colon	20 – 30 hours	(Dugad et al., 2018)
Liquid volume	Average 13 mL	(Amidon et al., 2015)
Viscosity of luminal content	Thicker compared channel digestion on it	(Amidon et al., 2015)
Number of microorganisms	10^{11} up to 10^{12} CFU/mL	(Kurakula et al., 2021)
Enzyme: - Nitro reductase - Azo reductase - Esterase and Amidase - Glycosidase - Glucuronidase	Microorganisms' producer: - *Escherichia coli, Bacteroides* - *Clostridia, Lactobacilli, Escherichia coli* - *Escherichia coli, Proteus vulgaris, Bacillus subtilis, Bacillus mycoides* - *Clostridia, Eubacterium* - *Escherichia coli, Aerobacter aerogenes*	(Dugad et al., 2018)

Irritable Bowel Syndrome

Irritable bowel syndrome (IBS) is a multifaceted functional disorder of the digestive tract characterized by abdominal pain, altered bowel habits, and/or variations in stool consistency (Wang et al., 2023). In general, stool patterns in each IBS patients can be classified into 4 subtypes, namely: Bristol stool form scale (BSFS), constipation-predominant IBS (IBS-C), diarrhea-predominant IBS (IBS-D), and mixed or non-subtype/unclassified (Longstreth et al., 2006). Despite its prevalence, reliable measurement indicators are lacking, and traditional radiological or endoscopic methods do not provide insights into its pathophysiology (Pimentel et al., 2014).

The pathophysiological mechanisms of IBS include infection, autoimmunity, serotonin imbalance, central nervous system disturbances, dysregulation of brain-gut interactions, genetic predisposition, and bacterial overgrowth (Goll et al., 2020). Modification in colonic bacteria can trigger immune response and inflammation in the gut mucosa that lead to enhanced permeability of mucosa, disrupting epithelial barrier function, and upregulating specific proteins (Langhorst et al., 2009). Additionally, hormonal fluctuations, such as increased prostaglandin production during menstruation, may accelerate drug transit time through the digestive tract in women (Bharadwaj et al., 2015). Current therapeutic approaches for IBS involve the use of antispasmodics (e.g., otilonium bromide), peppermint oil (menthol), antidepressants (desipramine), agents acting on opioid receptors (eluxadoline), 5-HT3 receptor antagonists (alosetron), and antibiotics (rifaximin) (Wang et al., 2023).

Inflammatory Bowel Disease

Inflammatory bowel disease (IBD) is an autoimmune condition characterized by a decreased in the number of secretory cells, leading to reduced antimicrobial secretion and epithelial tissue damage (Teruel et al., 2020). Additionally, inflammation in affected areas contributes to a reduction in goblet cells number, leading to decreased mucus production (Yasmin et al., 2022). Numerous microorganisms found in the intestine are derived from the intestinal flora, typically maintain digestive health and prevent the colonization of unwanted species. However, an abnormal response to gut flora can trigger intestinal inflammation, characterized by excessive immune reaction against cells in the digestive tract, resulting in chronic inflammation and tissue damage. Common symptoms that including cramps, abdominal pain, weight loss, and bloody diarrhea. Inflammatory bowel conditions manifest various physiological effects on individuals. For example, in colitis patients, small intestinal transit time is often delayed by 30%, while colonic transit time significantly increases due to the possibility of diarrhea, which is a characteristic of the disease. pH alterations, ranging from 2.3 to 5.5, and changes in the composition of the intestinal microbiota occur due to inflammatory processes, enzymatic bacterial metabolism, and intestinal physiology shifts (Teruel et al., 2020).

Ulcerative colitis and Crohn's disease, depicted in Figure 3, are the primary types of inflammatory bowel disease targeted in the development of colon-targeted preparations. Both of these are chronic inflammatory diseases which currently lack a cure (Teruel et al., 2020). While ulcerative colitis was first documented by a doctor from England named Sir Samuel Wilks in 1859, Crohn's disease was initially identified by German surgeon Wilhelm Fabry in 1623 and later described by American doctor named Burrill B. Crohn (Baumgart, 2008).

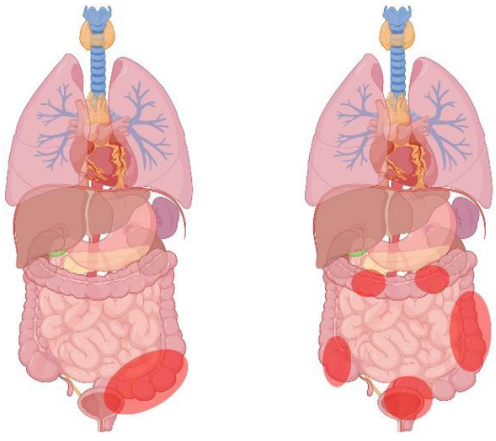

Figure 3. Pathological features of inflammatory bowel disease

Ulcerative colitis typically affects the colon area, originating in the rectum and extending further into the colon, with the extent of the affected area indicating the distribution of the disease (Ordás et al., 2012). It arises from a complex interplay of infectious, immunological, environmental, and microbial factors, with healing difficulties ranging from several months to decades depending on the duration and severity of inflammation. Approximately 18% of patients with long-standing ulcerative colitis face an increased risk of developing colorectal cancer (Abraham & Cho, 2009). Common treatment including adrenal corticosteroids (e.g. prednisone) and aminosalicylic acid (mesalazine), primarily provide symptom relief with potential side effects. Additionally, the immunosuppressive agent azathioprine, while effective for some ulcerative colitis patients, exhibits variable effects among individuals (Porter et al., 2020).

Crohn's disease may involve widespread inflammation affecting all layers of the intestine (transmural) and can occur anywhere along the digestive tract, mostly affecting the ileum and colon. It can lead to additional complications such as mouth sores, anal fissures, or strictures, which are not typically seen in ulcerative colitis. Endoscopically, ulcerative colitis presents a mucosa with a 'sandpaper' appearance, while Crohn's disease displays a 'stone-like' mucosal pattern (Yu & Rodriguez, 2017). Mesalazine (5-aminosalicylic acid) is a therapeutic option being developed to cure this disease on a moderate to severe Chron's disease cases where medication proves ineffective. In cases of severe condition, surgery may be necessary, although the possibility of recurrence exists, and the surgical process may impact the patient's overall well-being (Teruel et al., 2020).

Colorectal cancer

Colorectal cancer ranks as the third most prevalent type of cancer globally, characterized by its high morbidity and mortality rates. Early diagnosis is often feasible through colonoscopy (Kumar et al., 2022). The cancer initiation process begins with the presence of polyps in the inner walls of colonic epithelial cells, which then develops into the lymph nodes and surrounding muscles (Wang et al., 2023). Histologically, the stages of cancer are classified into four categories: stage 0, marked by when the initial presence of polyps in the colonic mucosa; stage 1, when the polyp turns into a tumor affecting the mucosal layer of the colon; stage 2, characterized by tumor infiltration into the outermost layer of the colon and nearby lymph nodes; stage 3, indicating continued cancer growth with lymph nodes and surrounding intestinal walls involvement; and stage 4, the last stage where cancer metastasizes to other organs or tissues in the body (Labianca et al., 2010).

Colorectal cancer can arise from a combination of genetic and environmental factors. Contributing factors include obesity, modern lifestyle habits including smoking, alcohol consumption, and high-fat diets, insulin resistance, acromegaly, kidney transplants, and MMR gene mutations (Yuhara et al., 2011). Inflammatory bowel disease alters the composition of intestinal microflora, leading to an increase in microbiological toxins and reactive oxygen species, which are believed to play a role in the epigenetic and genetic mutations associated with colorectal cancer (Bhaskaran & Kumar, 2021). The development of targeted therapy is crucial as current treatments involving surgery and chemotherapy often cause side effects that cause discomfort to patients (Kumar et al., 2022). Commonly administered therapies include chemotherapy drugs such as 5-fluorouracil, capecitabine, oxaliplatin, and irinotecan, as well as molecularly targeted drugs (such as monoclonal EGFR antibodies and VEGF receptor inhibitors) (Wang et al., 2023).

Diarrhea due to digestive tract infections

This condition is prevalent worldwide and ranks as the second leading cause of death among children under the age of five (Fletcher et al., 2013). Pathogens responsible for the disease include parasites, viruses, and bacteria such as enterohemorrhagic Cyclospora, calicivirus, enteric viruses, *Escherichia coli, Shigella, Salmonella, Campylobacter jejuni, Clostridium difficile, Cryptosporidium,* and *Giardia*. The pathology of diarrhea can impact the effectiveness of localized-acting drug formulations. In cases of diarrhea, bacterial overgrowth may occur, leading to enhanced colon motility, as observed in inflammatory bowel disease (Grover *e*t al., 2008). For the treatment of diarrhea, dosage forms can be modified to be controlled release or based on triggers for compounds with limited absorption, such as macrocyclic antibiotics (rifamycin) for the treatment of *C. diff* infections in the colon (Bak et al., 2018).

Strategies of CTDDS

i) Prodrug approach

Prodrugs are the earliest approach utilized in the development of colon-targeted preparations, which are formed by covalent bonds of the drug with other chemical substances (Jornada et al., 2016). They are primarily designed to prevent drug absorption and hydrolysis in the upper digestive tract, thereby facilitating drug release in the colon due to enzyme activity or favorable pH conditions (Sardo et al., 2019). Research conducted by Sousa et al., (2014) revealed that 5-aminosalicylic acid (5-ASA), an anti-inflammatory drug frequently used to treat colitis and inflammatory bowel disease, could be converted into prodrugs like sulfasalazine and olsalazine through conjugation with sulphapyridine via an azo bond. This conversion increases drug release at the colon's site of action due to the activity of azoreductase, an enzyme produced by colonic bacteria that cleaves the azo bond in the prodrug. Similarly, a study by Kim et al., (2020) exhibited that 4-phenylbutyric acid (4-PBA), an endoplasmic reticulum stress attenuator used in colitis treatment, when conjugated with glutamic acid, forms a prodrug that capable of accumulating in the colon and effectively relieves colitis in mice.

The prodrugs approach is not without limitations, as it relies on chemically reactive functional groups. These novel chemical entities require thorough evaluation before being used as carriers (Dugad et al., 2018). Prodrugs may lead to the production of undesirable metabolites, resulting in side effects and toxicity, such as the sulfapyridine component produced upon the breakdown of sulfasalazine. Additionally, this approach may result in significant product losses in cases of diarrhea, where insufficient activation time limits drug effectiveness (Sardo et al., 2019).

ii) Primarily-used approach

This approach stands as one of the foremost methods employed in the development of colon-targeted preparations. It relies on a pharmaceutical technology point of view, combining the physicochemical properties of drugs with those carriers/polymers, while considering the physiological conditions of the gastrointestinal tract (GIT). Through this integration, effective drug delivery in the colon area is established. Nonetheless, commercial products using this strategy remain limited due to challenges related to production costs and/or location specificity (Sardo et al., 2019).

pH-dependent drug delivery systems

Utilization of pH-sensitive polymers is the first primary strategy to achieve a colon-targeted drug delivery system, leveraging the pH variations along the gastrointestinal tract (Teruel et al., 2018). This approach is among the simplest formulation strategies for colon-targeted drug delivery systems and offers advantages such as lower cost and easier manufacturing. Coated formulations can be either single or multi-layered, enhancing their versatility (Dugad et al., 2018).

Commonly used synthetic copolymers for colonic drug delivery are methacrylic acid copolymer and methyl methacrylate (Eudragit®), renowned for their mucoadhesive characteristics and tolerance to low pH levels in the stomach and proximal small intestine. However, they dissolve in the terminal ileum and colon due to increased pH levels, typically releasing drugs at pH 6.0–7.0 (Maroni et al., 2013). These polymers contain free carboxylic acid groups which remain ionized in acidic environments such as the stomach but remain

deprotonated in higher or neutral pH environments, making the macromolecules more hydrophilic thus facilitates the drug release (Awad et al., 2022). Other polymers employed in colon-targeted drug delivery systems are cellulose acetate phthalate (CAP) and hydroxypropyl methyl-cellulose phthalate (HPMCP) 50 and 55 (Nidhi et al., 2016).

Development of a dexamethasone preparation was performed by Oshi et al., (2018) with a multi-layer consisting of chitosan oligosaccharide, alginate, and Eudragit S100, exhibited low drug release at low pH in the upper digestive tract but increased drug release at pH 7.4. This system was effective for treating mice with colitis models because it can increase targeting to inflamed colonic tissue and reduce the side effects of conventional dosage forms. Research by Bazan et al. (2016) was able to prove that utilization of Eudragit® S100 and Eudragit® L100-55 in microparticle formulations provided a controlled release of celecoxib, potential to reduce injury and inflammation in the colon. The resulting microparticles showed a delayed release mechanism as they maintained minimum drug release in an acidic medium (pH 1.2) for 2 hours and released celecoxib from the coated system at pH 7.4 within 15 minutes (Eudragit® S100) and 30 minutes (Eudragit® L100-55).

Furthermore, Iswandana, et al., (2017) demonstrated optimal protection using 10% (w/v) Eudragit® L100 to prevent premature release of tetrandine, with *in vivo* tests confirming effective delivery of calcium pectinate beads to the colon, compared to other pH-sensitive polymers such as Eudragit® L100-55, hydroxypropyl methylcellulose phthalate (HPMCP) HP-55 or cellulose acetate phthalate (CAP). The targeting characteristic to the colon of these beads was also confirmed by the *in vivo* tests. Apart from that, Iswandana et al., (2018) also conducted other research which revealed that a pellet preparation using 10% (w/v) Cellulose Acetate Phthalate (CAP) coating containing tetrandrine was the best formulation that can deliver the drugs (67.67%) to colon as the target action with a pH-sensitive mechanism, compared to the systems utilizing Eudagrit® L100-55, Eudagrit® L100, and HPMCP H-55 coatings. Another study by Iswandana et al., (2018), explored the opportunity to utilize a combination of chitosan (one of the colon-targeted polymers) and HMPC (a pH-sensitive polymer with a pH range of around 3-11) as an alternative delivery systems for colon-targeted preparations. The findings revealed that all combinations are insufficient in sustaining tetrandrine release in the upper gastrointestinal tract (Iswandana et al., 2018).

Despite their advantages, pH-dependent systems are subject to high variability during *in vivo* study both within and between subjects due to GI transit time, pH, motility, and fluid volume, making them less effective in site-specific drug release (Maroni et al., 2017). Additionally, other factors including water intake, microbial metabolism, diet, and illness conditions may affect significantly on the pH range along the GIT (Bak et al., 2018). Therefore, pH-dependent drug release systems may become less effective due to various internal and external dynamic pH changes, which frequently result in less site-specific drug release (Ibekwe et al., 2006).

Integrating pH-dependent system with time- or enzyme-approaches can become an alternative to overcome those limitations. One method utilized the mixture of Eudragit® S with high-amylose corn starch to enable system-dependent integration on pH and degradation based on microbes in the colon system. Liu et al., (2010) employed a double coating approach using Eudragit® S alkaline solution as a buffer material for the inner layer and Eudragit® S organic solution for the surface layer, resulting in enhanced drug release at pH greater than 7. In addition, Varum et al. (2013) found that this double-layer system disintegrated more consistently, particularly in the lower intestinal tract.

Moreover, multi-unit technology like Eudracol® utilized Eudragit® RL/RS and Eudragit® FS 30D to coat pellets, providing targeted drug release to the colon through time- and pH-dependent mechanisms (Patel, 2011). In general, integrating multiple drug-release triggering mechanisms is more beneficial in promoting pathophysiological diversity in the colon, however, additional research is still required. Additionally, nano- and microparticles can selectively target colonic tissue inflammation, further enhancing drug absorption (Lee et al., 2020).

Enzyme-sensitive drug delivery systems

This system relies on the activity of specific enzymes produced by colonic bacteria and polymers susceptible to degradation by these microorganisms. Enzymes such as amylase, pectinase, and D-galactosidase can hydrolyze specific bonds within polysaccharides like guar gum, pectin, chitosan, and inulin (Wahlgren et al., 2019). While these polysaccharides can maintain their integrity in the upper gastrointestinal tract, they may be metabolized by colonic bacteria, thereby releasing encapsulated drugs (Lin et al., 2015). This microbiota-triggered system, reliant on polysaccharides, offers promise as a drug delivery strategy due to its ability to enhance drug release profiles, stability, and specificity for the desired target of action. Moreover, these systems possess mucoadhesive properties that facilitate drug absorption by maintaining continuous contact between the drug delivery carrier system and the mucosal surface. Polysaccharides are advantageous as they are readily available on a large scale, cost-effective, exhibit high

biocompatibility and biodegradability, and possess low toxicity and immunogenicity (Lee et al., 2020). However, polysaccharide-based delivery systems also present several potential disadvantages, such as a wide range of molecular weights and chemical variables (Barclay et al., 2019), excessive hydrophilicity and water solubility leading to undesired early drug release, and low solubility in most organic solvents, restricting chemical modification of polysaccharides (Sinha & Kumria, 2001).

To mitigate these challenges, polysaccharides-based system are often combined with polymers to delay drug release in the upper gastrointestinal tract. For colon-targeted drug delivery systems, water-insoluble polymers like Eudragit® RS and ethyl cellulose are frequently combined with other polysaccharides (Lee et al., 2020). Additionally, cross-linking agents are commonly employed to overcome polysaccharide limitations. Research by Iswandana et al., (2017), where chitosan was modified using tripolyphosphate (TPP) as the cross-linking agent, demonstrates that this approach can effectively deliver pellet forms containing the active compound Tetrandrine with anti-fibrosis activity to the colon target site compared to control pellets lacking this layer (Iswandana et al., 2017).

Time-dependent drug delivery systems

Time-dependent strategies for targeted drug delivery to the colon rely on the average transit time in the gastrointestinal tract (Awad et al., 2022). This approach utilizes a polymer film that will either erode, dissolve slowly, or exists within a matrix unaffected by enzymes, pH variations, or other compounds present in the lumen such as bile salts (Wahlgren et al., 2019). Intestinal motility and transit time are influenced by several factors, such as gender, age, and body mass index (BMI). Gender plays a role due to the interaction and influence of endogenous hormones, although further research is needed to validate this association. Age-related changes in intestinal conditions lead to longer total transit time in the colon, although the rectosigmoid time tends to decrease. Additionally, increases in BMI may prolong colonic transit time while reducing stomach emptying and overall gut transit times. Faster stomach emptying associated with increased BMI may elevate the risk of overeating by diminishing negative feedback on satiety signals (Awad et al., 2022).

Formulations typically involve a drug-containing core surrounded by three polymer layers, consisting of a hydrophilic layer sandwiched between two pH-sensitive layers. In vitro evaluations of such formulations demonstrated sustained drug release attributed to hydrogel formation and pH protection (Amidon et al., 2015). Various methods capable of achieving a predefined delay interval theoretically offer this effect. To ensure reproducible effects and a predictable lag phase, drug-laden areas are frequently isolated, or the interior of drug sacs is covered with layers or plug sealants made of erodible and swellable polymers. Reservoir, capsular, and osmotic devices are systems that allow for time-controlled colonic targeting (Awad et al., 2022).

iii) Currently-developed approach

Pressure-dependent drug delivery systems

This system relies on the high viscosity conditions within the colonic lumen and the contractile activity of smooth muscle, which generates mechanical pressure capable of rupturing either the film layer or the drug-carrying capsule (Wahlgren et al., 2019). Exploiting the substantial mechanical pressure in the colon, significantly greater than the small intestine, the capsule can integrate and initiate drug release. This effect is facilitated by the phasic and tonic contractions of the colon, coupled with the dense colonic contents. Ethyl cellulose emerges as a suitable polymer for this system. However, limitations may arise due to the restricted amount of water in the drug release area, making it preferable to formulate drugs in a solution form within capsules (Lemmens et al., 2021). It is noteworthy that this development has not widely observed in various individuals and is typically applied postprandially (Dinning et al., 2014).

Osmotic controlled drug delivery systems

The Osmotic-Controlled Release Oral Delivery System (OROS-CT) system includes either a single osmotic unit or up to six push-pull units, each measuring 4 mm in diameter and enclosed in a hard gelatine capsule. Within each bilayer push-pull unit, both the drug layer and the osmotic push layer are both enclosed by a semi-permeable membrane, featuring a puncture in the membrane alongside the drug layer. Upon consumption, the push-pull unit dissolves in the gelatine capsule that contains the OROS-CT.

Due to its drug-impermeable enteric coating, each push-pull unit remains impermeable to water absorption in the acidic environment of the stomach. The unit goes through the small intestine, where the pH exceeds 7, leading to the dissolution of the coating. To target ulcerative colitis, every push-pull unit is designed with a 2–4-hour post-gastric delay, preventing drug distribution in the small intestine. Upon reaching the colon, the drug is released, facilitated by water entry, causing the osmotic push compartment to enlarge while simultaneously forming a flowable gel in the drug compartment.

The precisely controlled swelling of the osmotic push compartment, regulated by the semi-permeable membrane's water passage rate, forcing the drug gel through the aperture.

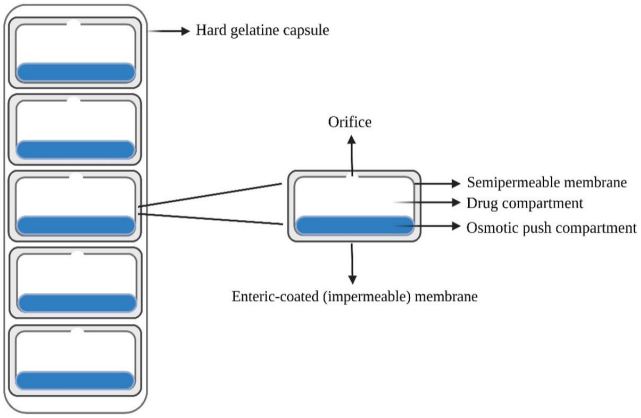

Figure 4. Schematic representation of the OROS-CT colon- targeted drug delivery system (Iyengar et al., 2020 with modification)

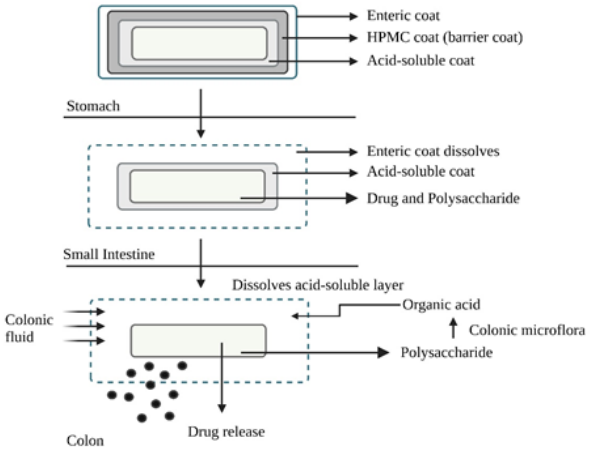

Figure 5. Schematic of the conceptual design of CODESTM (Trivedi, 2017 with modification)

A schematic depiction of the OROS-CT colon-targeted drug delivery system is illustrated in Figure 4. OROS-CT devices in the colon can provide medication over as short as four hours or maintain a steady release rate for up to twenty-four hours (Dugad et al., 2018).

Novel colon targeted delivery system (CODES^{TM})

The CODES^{TM} method combines pH-dependent and microbially triggered strategies. In its development, a novel mechanism utilizing lactulose as a trigger for drug release within the colon was introduced. The technology comprises a lactulose layer enveloping a standard tablet core, with two additional layers applied: Eudragit® E, an acid-soluble polymer, and Eudragit® L, an enteric polymer. The concept behind this approach is that the tablet quickly dissolves once the stomach empties, as the enteric coating protects it during gastric transit. Subsequently, the preparation traverses the alkaline pH of small intestines, protected by the covering of an acid-soluble polymer (Katsuma et al., 2004).

Within the colon, bacterial enzymes break down the polysaccharide (lactulose) in the tablet, producing organic acid. Consequently, the dissolution of the acid-soluble coating lowers the pH of the surrounding environment to affect the drug release. A schematic illustrating the conceptual design of CODES^{TM} is depicted in Figure 5.

iv) Advance Developmental Approach

Minitablet systems

Minitablet formulations involve a variety of strategies, such as the utilization of core mini-tablets containing Pulsincap^{TM}, which comprises polymers with time-dependent drug release properties. Another technique involves the use of microsomal enzyme-dependent and pH-dependent polymers to create capsules filled with either coated mini-tablets or matrix mini-tablets (Belali et al., 2019). According to Hadi et al., (2018), colon-targeted minitablets within the hydroxy propyl methyl cellulose (HPMC) capsule shells containing lornoxicam and naproxen for rheumatoid arthritis

treatment demonstrated excellent patient compliance and consistent drug release.

Microspheres and microparticulate systems

Protein-based microspheres exhibit free-flowing characteristics and have a particle size of approximately 5200 nm. These microspheres offer several advantages over traditional drug delivery vehicles, including enhanced stability for sensitive medications and the ability to facilitate targeted and prolonged drug delivery. They are available in various matrix types, such as pectin metronidazole microspheres, polysaccharide-based microspheres, and prodrug microspheres combined with a multi-particulate system approach (Belali *et al*., 2019). For instance, microspheres composed of pH-sensitive polyacrylamide-graft-gum karaya (PAAm-g-GK) copolymer, cross-linked with glutaraldehyde, and loaded with capecitabine serve as effective drug carriers to target the colon. In vitro studies demonstrated that the action of colonic bacteria on PAAm-g-GK copolymer in fecal contents accelerates drug delivery, resulting in significant drug release after 5 hours (Alange et al., 2017).

Nanoparticle and nano vehicle system

Nanoparticles

Nanoparticle-based drug delivery systems hold considerable promise for enhancing patient treatment outcomes. Advances in this field often utilize materials such as poly (lactic-co-glycolic acid) (PLGA), lipids, chitosan, or silica, with a focus on targeting mucosal areas affected by inflammation (Wahlgren et al., 2019.) Inflammation in these areas is frequently triggered by an imbalance in reactive oxygen species (ROS) levels, overwhelming protective capacity of antioxidants present in human body (Lou et al., 2023). Excessive ROS can disrupt cellular function and signalling pathways, exacerbating inflammatory conditions (Zhang et al., 2016). Recent research by Huang et al., (2021) demonstrated that PLGA-based nanoparticles loaded with catalase and curcumin can effectively increase the release rate of curcumin, leading to significant suppression of pro-inflammatory cytokines secretion in environment rich in H_2O_2.

In another innovative approach, Iswandana et al., (2021) developed solid lipid nanoparticles incorporating bovine serum albumin (BSA) as a model drug, coated with Eudragit® S100 polymer to prevent premature drug release in the stomach. In vitro testing revealed the magnitude of drug release in the large intestine, as indicated by the cumulative percentage of drug release. This formulation holds promise for the targeted delivery of drugs to the colon, offering potential therapeutic benefits for various conditions.

Liposomes

Liposomes are nanosized phospholipid bilayer vesicles that offer a targeted approach to colon medication delivery (Belali et al., 2019). Gabizon (2001) highlighted the advantages of PEGylated doxorubicin liposomes, which exhibit prolonged half-life, enhanced biocompatibility, and decreased macrophage recognition. In another study, liposomes loaded with 5-fluorouracil and targeted to colon cells were synthesized utilizing folic acid as a ligand. The findings revealed that the system showed promising efficacy *in vivo*, demonstrating superior cancer cell killing ability compared to conventional formulations (Handali et al., 2018).

Table 3. List of marketed products available for orally colon-targeted drug delivery systems

Drug	Brand name	Dosage form	Intended therapy	Reference
Prednisone	Deltasone	Enteric-coated tablets	Adrenocortical steroid that is used to treat many health problems	(Kesisoglou & Zimmermann, 2005)
Mesalamine	Asacol, Salofac, Claversal	Enteric-coated tablets	Ulcerative colitis	(Friend, 2005)
Cyclosporine A	Sandimmune Neoral	Capsules	Calcineurin inhibitor	(Y. Zhang et al., 2010)
Balsalazide	Colazal	Capsules	Crohn's disease	(Edsbacker & Andersson, 2004)
Budesonide	Entocort	Enteric-coated tablets	Crohn's disease	(Edsbacker & Andersson, 2004)
Beclomethasone	Clipper	Coated tablets	Ulcerative colitis	(Rizzello et al., 2002)
Sulfasalazine	Azulfidine	Enteric-coated tablets	Ulcerative colitis	(Ibrahim, 2023)

Table 4. Strategies for orally-administered colon-targeted drug delivery systems

Approach System	Dosage form	Drug	*In vitro* model	*In vivo* Model	Reference
pH-dependent	NPs: Eudragit FS30D/PLGA nanoparticles	Cyclosporine A	Dissolution tests in buffered solutions with varying pH levels	Colitis mice were induced with Dextran Sulphate Sodium (DSS)	(Naeem et al., 2018)
pH-dependent	Microcrystals: Chitosan/alginate/ Eudragit S multilayers	Dexamethasone	Dissolution tests in buffered solutions with varying pH levels	Colitis mice were induced with DSS	(Oshi et al., 2018)
pH-dependent	Eudragit microparticles	Celecoxib	Both *in vivo* and *in vitro* assays	Rat model	(Bazan et al., 2016)
pH-dependent	Colo pulse-coated tablets	Budesonide	Both *in vivo* and *in vitro* assays	Human	(Gareb et al., 2019)
Enzyme-sensitive	MPs: Microparticles of mesoporous silica capped with a large azo derivative	Safranin O (Dye for preliminary studies)	Dissolution tests in buffered solutions with varying pH levels (Using or not using enzyme stimulation).	Healthy mice	(Ferri et al., 2018)
Enzyme-sensitive	NPs: Amphiphilic curcumin polymer (PCur)	Curcumin	Dissolution tests in buffered solutions with varying pH levels reductive environment. Cytotoxicity and permeability: Caco-2 cells.	Colitis Sprague–Dawley (SD) rats and C57BL/6 mice were induced with DSS	(Qiao et al., 2017)
Inflammation-targeted	NPs: PLGA nanocarriers	Cyclosporine A	Dissolution tests with simulated gastric fluid (pH = 3.0).	Acute colitis Balb/C mice were induced with DSS	(Melero et al., 2017)
Inflammation-targeted	NPs: Cationic lipid-assisted nanoparticles (CLAN)	Tacrolimus (FK50	Dissolution tests in buffered solutions with varying pH levels	Acute colitis C57BL/6 mice were induced with DSS	(Wang et al., 2018)
Inflammation-targeted (Redox-responsive)	NPs based on 4-amino thiophenol-carboxymethyl inulin conjugate	Budesonide	Dissolution tests with simulated GIT fluids. Cytotoxicity: Caco-2 cell line.	Acute colitis mice were induced with DSS	(Sun et al., 2018)
Dual pH-/time-triggered	NPs: Eudragit FS30D, Eudragit RS100	Budesonide	Dissolution tests in buffered solutions with varying pH levels	Colitis mice were induced with DSS	(Yoo et al., 2015)

Table 4. Continued

Approach System	Dosage form	Drug	*In vitro* model	*In vivo* Model	Reference
Swelling properties and enzyme-sensitive	Microspheres vehicle: Cationic konjac glucomannan (cKGM) phytagel	Antisense oligonucleotide anti-TNFα	Dissolution tests in buffered solutions with varying pH levels Cytotoxicity: Raw 264.7 and CT-26 cell lines.	Colitis mice were induced with DSS	(Z. Huang et al., 2015)
Dual pH-/enzyme-triggered	Hydrogel nanocomposite based on graphene oxide, which is biocompatible and pH sensitive. It contains poly (polyvinyl alcohol) (PVA) (GO–N = N–GO/PVA) and azo aromatic crosslinks.	Curcumin	Dissolution tests in buffered solutions with varying pH levels	Healthy Sprague-Dawley rats gastrointestinal distribution, pharmacokinetic studies, and imaging analysis	(Hou et al., 2016)
Magnetically driven and pH-responsive microparticles	Azo-derivative molecular gate in magnetic mesoporous microparticles	Hydrocortisone	Both *in vivo* and *in vitro* assays	Colitis Sprague Dawley (SD) rats were induced with TNBS	(Teruel et al., 2020)

DSS = Dextran Sulphate Sodium

Dendrimers

Dendrimers, versatile drug delivery agents known for outstanding encapsulation and conjugation capacities, have emerged as promising tools for targeted cancer therapy. Recent study has seen the development of various dendrimer types tailored for delivering drugs to cancer patients. These dendrimers, incorporating entities such as folic acid, DNA, chemotherapeutic agents, antibodies, and contrast agents for magnetic resonance imaging treatments, offer precise drug delivery at the cellular level through covalent linkage with biological molecules. Particularly noteworthy are dendrimers conjugated with antibodies, which enhance sensitivity and applicability in detecting circulating tumor cells for cancer detection (Banerjee et al., 2017). Additionally, water-soluble conjugates of polyamidoamine dendrimers containing 5-ASA, linked via azo-bond to two different spacers–p-amino hippuric acid (PAH) and p-amidobenzoic acid (PABA)–exhibited resistance to premature drug release before reaching the colon. The result suggested the potential ulitity of these dendrimers as carriers for colon-specific drug delivery (Wiwattanapatapee et al., 2003).

Mucoadhesive systems

Mucoadhesive systems offer a promising strategy for prolonging drug residence time in the colon to increase drug absorption and achieve high concentrations, particularly beneficial for drugs with limited absorption capacity (Iyengar et al., 2020). This strategy is designed to withstand high-viscosity environments such as the colon, employing mucoadhesive polymers in the formulation. These polymers enable sustained drug release into the colon and promote adhesion to the mucosal layer. An example of this approach is seen in naproxen sodium, a mucoadhesive formulation composed of sodium alginate and Eudragit®100, used effectively in the medication of ulcerative colitis (Belali et al., 2019).

Ligand/receptor-mediated systems

Investigations into ligand/receptor-mediated systems are underway to enhance target specificity through ligand-receptor interactions, thereby targeting carrier surfaces and the specific receptors expressed at the disease site. The overarching goal is to achieve more effective therapy while mitigating toxic side effects. Various ligands, such as

peptides, folic acid, hyaluronic acid, and antibodies, are incorporated into the design of these systems, selected based on receptor/protein expression profiles on target cells/organs. When appropriately employed, this approach can be used in conjunction with pH-dependent systems to optimize site specificity and stability throughout the gastrointestinal tract (Lee et al., 2020).

Magnetic-based systems

These novel formulations for targeted and controlled drug delivery systems, known as magnetic microcarriers, encompass magnetic emulsions, magnetic nanoparticles, magnetic discs, and magnetic liposomes. To enhance colorectal cancer targeted treatment by mAb198.3 (a FAT1-specific monoclonal antibody), Grifantini et al. (2018) created two novel drug delivery systems with distinct magnetic properties to enhance the treatment of colorectal cancer. In one approach, mAb198.3 was embedded into a magnetic carrier based on human erythrocytes, while in another approach, it was directly bound to super-paramagnetic nanoparticles. Both techniques effectively identified and arrested the proliferation of colon cancer cells, underscoring the potential of magnetic-based drug delivery systems to improve bioavailability and specificity against the anti-FAT mAb198.3 target. Furthermore, other studies have demonstrated increased effectiveness with externally applied magnetic field in the treatment of intestinal inflammation. For instance, in hydrocortisone therapy administered using a magnetic belt in mice, a nanodevice consisting of magnetic microparticles loaded with hydrocortisone showed prolonged retention time at the intended target of action, highlighting the potential of magnetic-based systems in colon targeted drug delivery (Teruel et al., 2018).

CURRENT UPDATES

Colon-targeted drug delivery systems represent a promising technology, yet face regulatory limitations during the marketing process, often concerning the degree of site specificity, toxicity, manufacturing scalability, and production costs (Dugad et al., 2018). Currently, only pH-dependent-based oral colon-targeted drug delivery systems have been released onto the market, primarily identified as delayed-release formulations targeting the colonic region (Ibrahim, 2023). For a comprehensive list of available products refer to Table 3.

Meanwhile, numerous approaches have been explored over decades to develop drug delivery systems targeting the colon. For instance, Naeem et al. (2018) investigated a pH-sensitive approach utilizing cyclosporine A in Eudragit FS30D/PLGA, which exhibited enhanced drug release at colonic pH during the dissolution testing. *In vivo* studies in a mouse model showed an improved disease outcomes after administration of E/PNP nanoparticles compared to other formulations (Naeem et al., 2018). Additional examples utilizing various approaches are detailed in Table 4.

CONCLUSION AND FUTURE PERSPECTIVE

Achieving an ideal colon-targeted drug delivery system necessitates effectively distinguish the target location of action from other parts of the digestive tract. This review has outlined how recent advancements in the design and development of colon-targeted medications offer significant promise for delivering safer and more efficacious treatments to clinical practice. Such advancements mitigate the risk of premature drug release or degradation in the upper gastrointestinal tract, such as the stomach and small intestine, owing the extreme pH conditions and enzymatic activity.

The complexity inherent in its developing are related to the physiological variations observed in the colon, especially when treating patients with infections, colorectal cancer, irritable bowel syndrome, and inflammatory bowel disease. These variations are distinct from those present in healthy individuals. Future research could focus on formulating indication-specific preparations with triggers based on pathophysiology mechanisms or tailored to specific patient populations.

Limited research on macromolecular compounds as alternative treatments for colon diseases poses a notable challenge, prompting ongoing development efforts aimed at meeting market demands for such formulations. Additionally, the development of dosage forms utilizing nanoparticle systems presents an opportunity to enhance drug delivery to the target epithelial tissue.

It is imperative for all colon-targeted delivery strategies to address factors such as reproducibility, scalability in production, and manufacturing processes suitable for larger-scale applications. Furthermore, comprehensive preclinical and clinical testing are indispensable prerequisites for establishing these strategies as viable therapeutic options for patients, particularly those with intestinal disorders.

CONFLICT OF INTEREST

There is no conflict of interest declared by the authors.

AUTHOR CONTRIBUTIONS

All authors contributed to the writing of the manuscript, and they have all read and approved the final version.

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