RESEARCH PAPER

Innovations in Colon-Specific Drug Delivery: A Review

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ABSTRACT

Drug delivery systems engineered to target the colon represent a significant therapeutic advance. They overcome the limitations of conventional oral drugs by controlling a medication's release to the colonic region. This review explores the mechanisms, methods, and recent progress in this area. The colon's unique environment with its near-neutral pH, prolonged transit time of 20-70 hours, and abundant microbiota makes it an ideal site for administering treatments for both local and systemic conditions. These targeted delivery systems offer significant advantages for treating local colonic conditions such as inflammatory bowel disease (IBD) and colorectal cancer. By concentrating the medication directly at the site of disease, they maximize therapeutic impact while minimizing systemic exposure and its associated side effects. Furthermore, CTDDS protect vulnerable pharmaceutical compounds including proteins, peptides, and other biologics—that would otherwise degrade in the harsh environment of the stomach and small intestine, thereby improving their absorption.

This review provides a detailed examination of the colon's anatomy and physiology as it relates to drug delivery, covering its structure, luminal environment, and enzymatic activity. It also explores the key design strategies for achieving targeted release, from established methods like pH-dependent and time-dependent formulations to newer techniques involving microbially-triggered prodrugs and bioadhesive systems. A dedicated section focuses on cutting-edge developments, including "Trojan horse" nanoparticles, multi-drug devices fabricated via 3D printing, and intelligent hydrogels that react to specific biological triggers.

Despite this promise, the development of CTDDS faces considerable challenges, including the colon's relative inaccessibility, limited fluid volume, and inherent absorption barriers. The review also outlines the critical in vitro and in vivo evaluations needed to validate the efficacy of these sophisticated systems. Ultimately, this analysis underscores the potential for colon-targeted delivery to transform therapeutic strategies for a range of diseases.

Keywords: Colon, Inflammatory bowel disease, Polymers, Colorectal Cancer, Nanoparticles, Targeted Drug delivery.

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1. Introduction

The oral route is the most common method for administering drugs, largely because patients find it convenient and are more likely to adhere to their treatment. After a drug is swallowed, it must first dissolve in the gastrointestinal fluids before it can be absorbed into the systemic circulation. The success of both dissolution and absorption is primarily determined by the drug's unique physicochemical properties.

Delivering drugs directly to the colon provides major therapeutic benefits for localized pathologies. By concentrating the medication at the site of action—such as in ulcerative colitis, Crohn's disease, or colon cancer—this strategy enhances local efficacy and minimizes systemic circulation, thereby reducing

unwanted side effects. This method is also advantageous for systemic drug delivery, as it can be used for compounds best absorbed in the colon, like some steroids, or for managing systemic diseases including asthma, angina, and rheumatoid arthritis.[1]

Designing an effective colon-specific drug delivery system (CDDS) demands precise engineering to prevent the drug from being released and absorbed prematurely in the upper gastrointestinal tract. A key design requirement is to protect the active pharmaceutical ingredient from the harsh acidic and enzymatic conditions of the stomach and small intestine. The ultimate goal is to ensure the therapeutic agent remains completely protected until it reaches the colon, where it can then be released for local action or systemic uptake. The colon's distinctive environment, characterized by a long transit time and high hydration levels, is highly conducive to drug absorption. This unique physiology positions the colon as a favorable site for enhancing the bioavailability of drugs that are poorly absorbed elsewhere.

Colon-specific drug delivery systems (CDDS) are designed to capitalize on the colon's unique physiology, with several core goals in mind. These include providing sustained drug release to lessen dosing frequency, and intentionally delaying the release of the active ingredient until it reaches the distal gut to maximize local concentration for treating regional diseases. Furthermore, CDDS can be timed to synchronize with the acute phase of circadian illnesses like rheumatoid arthritis and asthma. A primary objective is also to shield sensitive therapeutic agents—such as peptides and proteins—from the metabolically aggressive environment of the upper GI tract, utilizing the colon as a more stable site for absorption. [2]

The primary function of colon-targeted drug delivery systems is to protect a pharmaceutical compound as it travels through the upper gastrointestinal tract. By preventing early degradation and release, these systems significantly increase the amount of intact medication that reaches the colon. This site-specific strategy enhances therapeutic efficacy by concentrating the drug at its intended target, which in turn minimizes systemic exposure and its associated adverse effects. The colon itself is well-suited for this purpose; its mucosal lining has a permeability that facilitates the absorption of various compounds, including delicate biologics like peptides and proteins that cannot survive the upper GI tract. An extended colonic residence time of up to five days further provides a long duration for absorption, making the colon an ideal site for achieving efficient and sustained drug delivery. [3].

Drug delivery to the colon is typically achieved via two primary routes: oral and rectal. The oral method is favored for its strong patient compliance and the adaptability it provides for creating diverse drug formulations. Conversely, rectal administration is less reliable for reaching the proximal colon, as it frequently results in insufficient drug distribution to these upper areas[4]. The efficacy of a colon-targeted formulation depends on a combination of key elements, such as the drug's physicochemical properties, the delivery system's design, gastrointestinal transit time, and potential interactions with gut contents. A core principle for success is to engineer the system to bypass the stomach and small intestine without releasing its payload. This intentional delay is designed to cease upon colonic arrival, facilitating a sustained and localized drug release[5]. Standard pharmaceutical forms like solutions, foams, and suppositories are often used for this purpose [6]. While suppositories and foams generally act locally in the rectum and sigmoid colon, enema solutions offer more extensive coverage due to their superior ability to spread throughout the colonic region [7].

2. Advantages of Colon-Targeted Drug Delivery Systems

Colon-targeted drug delivery (CTDD) offers several significant therapeutic benefits:

- For localized colonic diseases like ulcerative colitis, Crohn's disease, and colorectal cancer, CTDD enhances treatment efficacy by delivering medication precisely where it is needed. This site-specific approach elevates drug concentration at the affected area for a stronger therapeutic outcome, while simultaneously minimizing systemic circulation and the associated adverse effects.
- The colon's environment is significantly less hostile than the upper GI tract, featuring lower acidity and fewer digestive enzymes. This stability is particularly beneficial for delivering vulnerable macromolecules, such as peptides and proteins, that would be broken down before reaching their target.
- Colon-targeted drug delivery (CTDD) offers a way to bypass first-pass metabolism for drugs like corticosteroids that are heavily broken down by the liver. By enabling drug absorption through the colonic wall, CTDD increases the amount of active compound that enters the bloodstream, thereby improving its overall bioavailability.
- CTDD helps prevent gastric irritation by keeping potentially damaging drugs, such as NSAIDs, encapsulated until they have passed through the stomach. This prevents the drug's release in the gastric

region, thereby reducing the risk of harm to the stomach lining.

- CTDD can be harnessed for chronotherapy, leveraging the predictable journey to the colon. This enables the timing of drug release to match the circadian patterns of diseases like asthma, angina, and rheumatoid arthritis, ensuring peak therapeutic action occurs when symptoms are most acute.

3. Challenges and Limitations of Colon-Targeted Drug Delivery Systems

Despite its advantages, achieving effective colonic delivery faces several physiological and technical hurdles:

- Difficult Access: The colon's location at the end of the GI tract means a drug must pass through the stomach and small intestine intact, making reliable site-specific delivery a complex engineering problem.
- Limited Dissolution: The colon has a small volume of thick fluid, which can prevent dosage forms from breaking down properly and poses a major challenge for dissolving drugs with poor solubility.
- Poor Absorption: The colon is not designed for efficient absorption. It has a much smaller surface area than the small intestine, and its mucosal lining is less permeable due to tighter cellular connections, significantly limiting how much drug can enter the bloodstream.

4. Need for colon targeting drug delivery

Colon-targeted drug delivery (CTDD) systems represent an advanced therapeutic strategy that localizes drug release to the colonic region. This site-specific action is especially beneficial for treating local diseases, as it focuses the therapeutic impact directly on the affected tissue. Consequently, this targeted approach can allow for lower dosages while simultaneously minimizing systemic adverse effects [8].

A key utility of this technology is enabling the oral delivery of sensitive bioactive compounds, like peptides and proteins, which are normally degraded in the upper GI tract. By shielding these vulnerable molecules, CTDD facilitates their absorption. Additionally, the colon's inherently slow transit can be leveraged to develop sustained-release formulations that provide a prolonged therapeutic effect [9].

The foremost advantage of colon-specific drug delivery lies in its ability to treat colonic diseases locally, delivering a high concentration of medication directly to the affected tissue for superior efficacy [9]. This makes the colon a versatile target for therapy. Topical treatments for inflammatory bowel disease (IBD), including ulcerative colitis and Crohn's disease, are particularly well-suited to this method, as seen with agents like glucocorticoids and sulphasalazine. [10].

The potential of colonic drug targeting extends beyond IBD to other serious diseases. For example, in colorectal cancer, it can concentrate therapeutic agents directly at the tumor site, enhancing their local efficacy [11]. Furthermore, the colon's physiological conditions are ideal for administering drugs that are vulnerable to the upper GI tract or hepatic metabolism. This positions CTDD as a crucial platform for delivering sophisticated, orally administered therapeutics like peptide and protein drugs. [11]

Drug absorption mechanism in colon

Colon-targeted drug delivery systems (CTDDS) are specifically designed to protect a drug's formulation during its transit, ensuring it remains intact until it reaches the colon for controlled release at a therapeutic concentration [12].

Drug absorption itself proceeds through two main mechanisms. Lipophilic compounds typically cross the intestinal lining via the transcellular pathway by passing directly through epithelial cells, while hydrophilic drugs often move paracellularly, diffusing through the tight junctions connecting these cells. A key anatomical distinction is that the small intestine, with its villi and microvilli, possesses a vast surface area ideal for absorption. The colon, lacking these structures, has a much lower inherent absorptive capacity. This physiological limitation is the primary reason specialized CTDDS are necessary to facilitate adequate drug uptake in the colon. [13].

The colonic epithelium also presents a significant barrier to absorption, as its tighter cellular junctions and higher electrical resistance substantially reduce paracellular permeability compared to the small intestine [14]. A key pharmacokinetic benefit of the colon, however, is its prolonged transit time. This allows for an extended window for drug-mucosa contact, which can partially compensate for its lower permeability. This potential advantage is often offset by the colon's viscous contents, which can impede drug dissolution and diffusion. It is important to note that these conditions are not static and fluctuate with factors like segment length and fluid volume [15]. Although the entire gastrointestinal tract can absorb drugs, the duodenum and proximal jejunum remain the most efficient sites for conventional oral medications.

Engineered to bypass the upper gastrointestinal tract, delayed-release dosage forms are crucial for ensuring effective drug delivery to the colon. Their release kinetics can range from an immediate burst to a sustained or precisely localized pattern. These systems are typically divided into single-unit forms like

tablets and multi-particulate forms such as pellets. A key limitation of single-unit systems is their higher risk of failure, where they may disintegrate prematurely due to manufacturing inconsistencies or the inherent variability of the gastrointestinal environment [15]. This variability is further influenced by patient-specific factors including age, ethnicity, genetics, and health status, all of which can alter GI transit and lead to unpredictable drug absorption [16].

In contrast, multi-particulate systems are frequently favored because they offer several key benefits. These formulations provide more consistent gastric emptying, a decreased likelihood of causing localized irritation, and a reduced risk of the entire dose being released at once. Consequently, they typically yield more predictable and improved bioavailability than their single-unit counterparts[16].

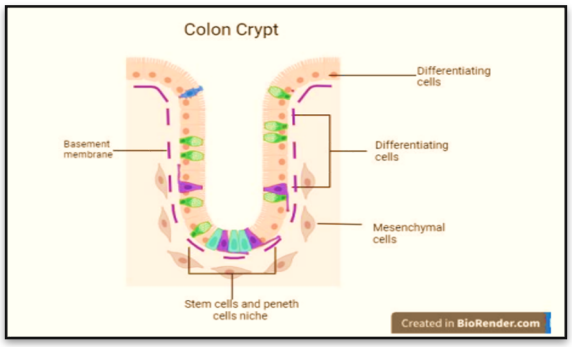

Fig. 1: Colonic crypt and the types of cells [17-19]

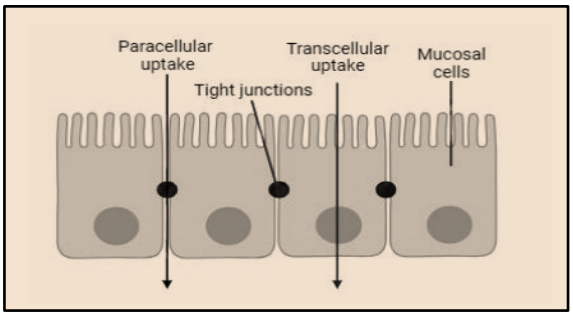

Fig. 2: Drug uptake pathways in the cell [20,21]

ANATOMY OF LARGE INTESTINE

Acting as the terminal portion of the digestive tract, the large intestine is crucial for water absorption, electrolyte regulation, microbial fermentation, and the storage and expulsion of waste. It extends approximately 1.5 meters from the ileocecal valve to the anus, with a typical diameter of 6–7 cm. Its anatomical structure consists of the cecum, a colon divided into ascending, transverse, descending, and sigmoid sections, followed by the rectum and anal canal [22].

The cecum, a pouch-like structure located in the right iliac fossa, receives chyme from the ileum through the ileocecal valve and is connected to the lymphoid-dense vermiform appendix. The ascending colon extends upward from this point along the right abdomen, curving beneath the liver at the hepatic flexure to form the transverse colon, which traverses the abdominal cavity. Near the spleen, at the splenic flexure, it becomes the descending colon, running down the left side before connecting to the S-shaped sigmoid colon. The sigmoid colon empties into the rectum, which subsequently opens into the anal canal for the expulsion of feces [23].

Three distinct anatomical features characterize the external surface of the large intestine and help distinguish it from the small intestine. These are the taeniae coli, which are three longitudinal muscular bands (mesocolic, free, and omental) whose contractions form the characteristic pouch-like haustra; and the epiploic appendages, small, fat-filled sacs attached to the serosal surface [23].

The large intestinal wall is composed of four primary tissue layers. Its inner mucosa is lined with a simple columnar epithelium rich in mucus-secreting goblet cells, which lubricate the passage of fecal matter. This surface lacks the villi found in the small intestine but is densely packed with intestinal crypts (crypts of Lieberkühn). Beneath this lies the submucosa, a connective tissue layer containing blood vessels, lymphatics, and Meissner's nerve plexus. The muscularis externa is composed of an inner circular muscle layer and an outer longitudinal layer that is consolidated into the taeniae coli. The outermost serosa, a protective peritoneal membrane, supports the epiploic appendages [24]. Notably, the lining of the anal canal transitions to a tougher, stratified squamous epithelium to withstand the stress of defecation.

The colon's blood supply is directly linked to its embryonic origins. The proximal colon, derived from the midgut, is perfused by the superior mesenteric artery (SMA) through its ileocolic, right colic, and middle colic branches. Conversely, the distal colon and rectum, which develop from the hindgut, are supplied by the inferior mesenteric artery (IMA) via the left colic, sigmoid, and superior rectal arteries. These two major arterial networks are linked by the marginal artery of Drummond. Venous drainage mirrors this pattern, with blood from the respective regions draining into the superior and inferior mesenteric veins, which ultimately converge at the hepatic portal vein [24].

The colon's nerve supply varies along its length. Parasympathetic input to the proximal colon, extending to the transverse colon, comes from the vagus nerve. In

contrast, the distal colon and rectum receive parasympathetic signals via the pelvic splanchnic nerves (S2–S4). Sympathetic control is facilitated by the superior and inferior mesenteric plexuses. Additionally, the intrinsic enteric nervous system—which includes Auerbach's and Meissner's plexuses—orchestrates local functions such as motility and secretion [25].

The large intestine performs the critical tasks of consolidating waste by absorbing water and electrolytes, resulting in the formation of solid stool. It also sustains a dense and complex microbial ecosystem, with bacterial concentrations reaching roughly 10^{11} per gram of content. These microbes anaerobically ferment undigested carbohydrates, generating short-chain fatty acids (SCFAs) that serve as an energy source for colonic cells and impact systemic metabolic processes. Furthermore, this gut flora is instrumental in synthesizing essential vitamins like vitamin K and B vitamins, and it significantly contributes to immune system regulation [26]. In essence, the sophisticated interplay between the structure and function of the large intestine underpins its vital role in both digestion and overall physiological balance.

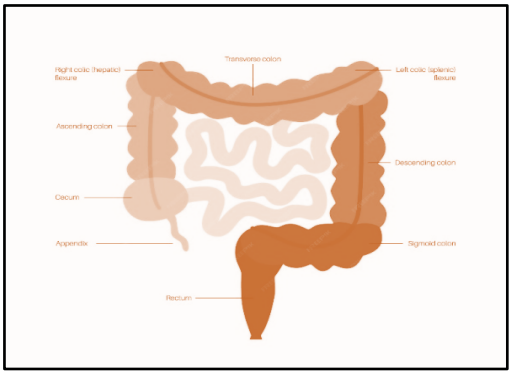

Fig. 3: Anatomy of large intestine [26]

DISEASES OF COLON

I. Inflammatory Bowel Diseases (IBD)

- **Crohn's Disease**: A chronic inflammatory disorder of unknown origin, Crohn's disease can manifest anywhere in the gastrointestinal tract, with a predilection for the terminal ileum and colon. Its hallmark pathological features include transmural inflammation and the formation of non-caseating granulomas [27].
- **Ulcerative Colitis**: This chronic inflammatory bowel disease is marked by continuous, superficial inflammation and ulceration limited to the colon's mucosal and submucosal layers. The disease almost invariably originates in the rectum and can spread continuously to affect other colonic segments. Patients typically experience flare-ups characterized by bloody diarrhea, pus, and abdominal cramps [28].

II. Infectious Colonic Diseases

- **Amoebiasis:** It is an infectious disease caused by the protozoan parasite Entamoeba histolytica. The lifecycle begins when a person ingests its cysts. These cysts release active amoebae (trophozoites) in the small intestine, which then travel to the large intestine. There, the trophozoites invade the colonic lining, penetrating the mucosal and submucosal layers to create distinctive "flask-shaped" ulcers [29].
- **Salmonellosis**: Frequently originating from non-typhoidal Salmonella species present in contaminated food or water, this infection triggers intestinal inflammation. This inflammatory response produces characteristic symptoms, including diarrhoea, abdominal cramps, and fever, and typically necessitates antibiotic treatment for resolution [33].
- **Traveler's Diarrhea:** This condition, often contracted while traveling to endemic areas, is commonly triggered by bacterial pathogens like enterotoxigenic E. coli (ETEC), Campylobacter, Salmonella, and Shigella. It is characterized by the sudden development of loose stools, nausea, vomiting, and abdominal pain [35].

III. Structural and Functional Disorders

- **Diverticulosis**: This condition is characterized by the development of small pouches, or diverticula, which form when the inner layers of the colon wall push through weakened areas in the muscle. While frequently asymptomatic, it can present with symptoms including abdominal pain, constipation, or sporadic bleeding [30].
- **Diverticulitis**: arises when one or more diverticula become inflamed and infected. This complication triggers more pronounced symptoms, such as intense abdominal pain, fever, and alterations in bowel habits [31].

- **Hirschsprung's Disease:** Hirschsprung's disease is a congenital condition caused by the lack of ganglion cells in the myenteric plexus, which creates a functional obstruction in the bowel. This results in severe, chronic constipation and megacolon, with symptoms typically appearing in infancy or early childhood [34].

IV. Motility and Secretory Disorders

- **Diarrhea**: Diarrhea is characterized by more frequent, loose, and watery bowel movements. It occurs when the intestines fail to absorb sufficient water, often due to accelerated motility that speeds transit through the colon. This can result in complications like dehydration and electrolyte loss. The causes are varied, ranging from infections and food intolerances to certain medications and inflammatory conditions [35].
- **Hemorrhoids (Piles):** Hemorrhoids are dilated veins within the hemorrhoidal venous plexuses. The internal type, arising from the superior plexus, are often painless but can cause bleeding. In contrast, external hemorrhoids, originating from the inferior plexus, are frequently associated with pain. A common presentation for both is the appearance of bright red blood on the stool or after wiping [32].

V. Neoplastic Conditions

- **Colorectal Polyps:** Colonic polyps are abnormal tissue growths that protrude from the mucosal lining into the intestinal lumen. They most commonly occur in the rectosigmoid region and are categorized as either neoplastic, such as adenomas which carry a risk of cancer, or non-neoplastic, like hyperplastic or inflammatory polyps [36].
- **Colon Cancer:** Colorectal cancer (CRC) ranks among the most common and deadly cancers globally, accounting for hundreds of thousands of deaths each year. A significant proportion of cases originate from pre-cancerous adenomatous polyps, progressing through a well-defined, multi-stage sequence to become malignant [36].

Table1: Drug used for colon targeting

Drug	Indication	Dosage Form	Absorption
Bisacodyl	Constipation	Suppository, Enema	Local
Glycerol	Constipation	Suppository	Local
Saline laxatives	Bowel preparation	Enema	Local
Mesalazine	Inflammatory bowel disease	Suppository, Enema, Rectal Foam	Local
Budesonide	Anti-inflammatory	Rectal foam	Local
Prednisolone	Anti-inflammatory	Rectal foam	Local
Hydrocortisone	Anti-inflammatory	Suppository, Enema	Local
Polystyrene sulfonate resins	Hyperkalaemia	Enema	Local
Glyceryl trinitrate	Anal fissure, haemorrhoids	Ointment	Local
Acetaminophen	Pain, fever	Suppository	Systemic
Oxycodone	Pain	Suppository	Systemic
Ondansetron	Nausea and vomiting	Suppository	Systemic
Caffeine +ergotamine	Migraine	Suppository	Systemic
Prochlorperazine	Nausea and vomiting	Suppository	Systemic
Promethazine	Antihistamine	Suppository	Systemic
Ibuprofen	Pain, fever	Suppository	Systemic
Diclofenac	Pain, fever	Suppository	Systemic
Indomethacin	Pain	Suppository	Systemic
Diazepam	Seizures, sedation	Enema, Gel	Systemic

Method of colorectal examination

- **Digital Rectal Examination (DRE)**

A digital rectal exam (DRE) is a physical assessment where a clinician uses a gloved and lubricated finger to manually feel for abnormalities within the rectum, such as masses, polyps, or changes in tissue structure.

- **Fecal Occult Blood Test (FOBT)**

The fecal occult blood test (FOBT) is a non-invasive screening method that identifies hidden blood in stool, a potential sign of bleeding caused by colorectal cancer, polyps, or other inflammatory diseases. It is commonly used as an initial screening tool for detecting colonic abnormalities.

- **Barium Enema**

A barium enema is a radiological procedure that involves introducing a barium sulphate suspension into the colon to coat its lining. This coating makes the colon more visible on X-rays, allowing for the detection of structural issues. In a double-contrast version, air is added after the barium to provide finer detail of the mucosal surface.

- **Sigmoidoscopy**

Sigmoidoscopy is a diagnostic procedure that utilizes a flexible, lighted instrument called a sigmoidoscope to examine the lining of the rectum and sigmoid colon.

This technique enables direct visualization to identify abnormalities such as polyps, inflammation, or tumors in the lower portion of the large intestine.

- **Colonoscopy**

A colonoscopy is a thorough endoscopic procedure that utilizes a long, flexible camera to inspect the entire colon. This highly accurate technique allows clinicians to directly examine the colon lining, identify abnormalities like polyps or cancer, and perform therapeutic procedures such as biopsies or polyp removal during the same examination.

- Fibreoptic Colonoscopy

This procedure utilizes a fibreoptic colonoscope to inspect the entire colon and rectum, mirroring a standard colonoscopy. To enhance visibility, the colon is gently inflated with air, while real-time video provides guidance. The technique is especially useful for detecting lesions in the distal colon and permits the immediate removal or biopsy of suspicious tissue [37].

- **Colonic pH Monitoring**

The acidity level throughout the gastrointestinal tract varies dramatically, ranging from the strong acidity of the stomach to the near-neutral environment of the small intestine and the slightly acidic colon. While factors like diet and disease can influence these local pH conditions, the consistent gradient is strategically utilized in pharmaceuticals. By employing polymeric coatings that dissolve at specific pH thresholds, oral medications can be shielded from early release in the upper GI tract, enabling precise drug delivery to the colon for localized or systemic treatment:

Table 2: Showing pH of gastrointestinal tract [38]

Region	pH (Fasting)	pH (Fed)
Stomach	1.5	2 - 5
Small Intestine		
- Duodenum	6.1	5.4
- Jejunum	5.4	
- Ileum	7.8	
Large Intestine	5.5 - 7	
Rectum	7 - 8	

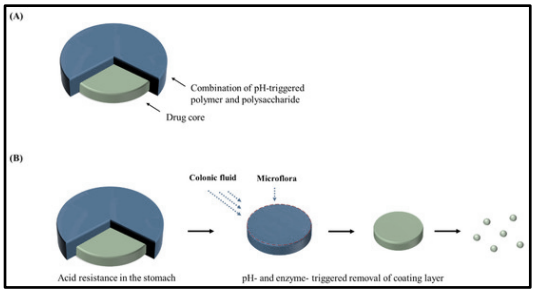

Fig 4: pH dependent systems

Transit through GIT

After being swallowed, a drug formulation travels through the stomach and small intestine before arriving in the colon. The drug's release and absorption are heavily dependent on the gastric environment, especially its acidity. Therefore, a delivery system must be specifically designed to resist degradation in the upper GI tract to ensure it arrives fully functional in the colon.

The time a dosage form takes to travel through the gastrointestinal tract is inconsistent. While gastric emptying can vary from about one hour when fasting to three hours after a meal, movement through the small intestine is more predictable, generally requiring 3 to 4 hours to reach the colon. This small intestinal transit time remains fairly constant regardless of the formulation's properties, during which the drug is subjected to the region's digestive enzymes.

In contrast to the upper GI tract, colonic transit is markedly slower and more unpredictable. Its pace is affected by numerous variables, including dietary fiber, exercise, stress, medical conditions, and medications. While normal transit through the colon typically takes 20 to 30 hours, this can prolong to 50–70 hours during active disease. This extended duration, combined with intimate exposure to the abundant microbial population, critically influences how a drug is released and absorbed from its formulation [39].

Colonic fluid volume

The colon efficiently absorbs around 90% of the fluid it receives, leaving the lumen with a much lower volume of liquid. This reduced fluid content can hinder the breakdown and dissolution of solid medications. Furthermore, undigested proteins, carbohydrates, and fats that enter the colon become food for the native microbial community, whose enzymatic processes can subsequently alter how drugs are metabolized and absorbed in this region.

Colonic luminal viscosity

Due to the efficient reabsorption of water, the contents of the colon are significantly more viscous than those in the upper GI tract. This thickened environment can slow the dissolution of drugs and limit their overall absorption. It also creates a barrier, impeding drug

molecules from diffusing through the luminal material to reach the intestinal wall for uptake or to interact with pathogenic microbes.

Colonic enzymes

The colon hosts a complex community of aerobic and anaerobic bacteria, including species like Clostridium and Escherichia coli. These organisms generate various hydrolytic and reductive enzymes that metabolize foreign compounds, inactivate drug metabolites, and ferment proteins. Consequently, pharmaceuticals traversing the colon are vulnerable to this enzymatic breakdown, which can produce metabolites that are either therapeutically active or inactive.

Formulation forms

Creating effective colon-targeted drug delivery systems requires a multifaceted approach to formulation. Key elements, including the drug's dosage and its inherent physicochemical characteristics, play a decisive role in determining both the therapeutic bioavailability and the commercial feasibility of the final product [40].

Factor affecting drug absorption

1. Physiochemical properties of drug

a. Drug solubility and dissolution rate

For hydrophobic drugs like griseofulvin and spironolactone, the slowest part of the absorption process is their dissolution into solution. Conversely, the primary barrier for hydrophilic drugs is their ability to cross the biological membrane.

b. Particle size and effective surface area

A fundamental principle in pharmaceutics is the inverse relationship between particle size and surface area; reducing particle size results in a greater total surface area. This total area is distinguished as the absolute surface area of the particle versus the effective surface area, which is the specific portion in contact with the dissolution fluid. According to the Noyes-Whitney equation, it is this effective surface area that directly governs the dissolution rate of a solid drug.

c. Polymorphism

Polymorphism describes the capacity of a solid material to crystallize into multiple distinct forms, each with its own unique set of physical characteristics such as solubility, melting point, and density. A fundamental principle is the inverse link between a polymorph's stability and its solubility. The most thermodynamically stable polymorph has the highest melting point and lowest energy, leading to the poorest aqueous solubility. Conversely, metastable polymorphs, which are in a higher energy state, feature lower melting points and consequently greater solubility, which can enhance a drug's bioavailability. In contrast to crystalline forms, an amorphous solid possesses no long-range molecular order. This disordered, high-energy state confers the highest aqueous solubility. Consequently, the general hierarchy of solubility among these solid forms is: amorphous form, followed by the metastable polymorph, and finally the stable polymorph.

d. Pseudopolymorph

A solvate is a crystalline complex where solvent molecules are integrated directly into the solid's lattice structure. These forms, which display distinct crystal habits, are known as pseudopolymorphs. If the incorporated solvent is water, the complex is specifically called a hydrate. In terms of solubility, the anhydrous (water-free) form of a compound is generally more soluble in water than its hydrate counterpart. This occurs because the hydrate's crystal structure is pre-stabilized by water molecules, diminishing the energy needed for the lattice to disassociate and dissolve.

e. Drug lipophilicity

Lipophilic drug better absorb than hydrophilic drug.

f. Drug stability

Several factors can contribute to poor oral bioavailability. A drug may be degraded into an inactive compound before it enters the bloodstream, interact adversely with its own formulation ingredients, or form complexes with gastrointestinal contents that hinder its absorption.

2. Patient related factors

a. Age

Drug absorption patterns differ significantly between infants and the elderly due to distinct gastrointestinal physiology. Infants have a less acidic stomach, a proportionally larger intestinal surface area, and a relatively underdeveloped blood supply to the gut. Conversely, elderly individuals often experience increased stomach acidity, a smaller intestinal surface area, and changes in gastrointestinal blood flow. These age-related physiological differences are key determinants of variations in how quickly and completely drugs are absorbed.

b. Gastric emptying time

Gastric emptying, the transit of stomach contents into the small intestine, is regulated by multiple variables. The volume, composition, and physical nature of a meal are key determinants; large, fatty, or solid foods significantly slow the process. Body posture and emotional states like stress or depression also exert influence. Furthermore, various medications can alter emptying rates—antacids and narcotics typically delay it, while prokinetic agents accelerate it. Beyond motility, the pH gradient from the acidic stomach to the more neutral colon is a critical factor affecting drug absorption.

Table 3: Effect of drug pka and GI pH on Drug Absorption [41]

Drug	pKa	Site of absorption
Weak acidic drug	pKa > 8.0	Unionized at all pH, absorbed through entire length of GI
pentobarbital	8.1	
hexobarbital	8.2	
Moderately Weak acidic	pKa 2.5 to 7.5	Unionized at gastric pH but ionized at intestinal pH, better absorbed from stomach
Cloxacillin	2.7	
Aspirin	3.5	
Stronger acid	pKa < 2.5	Ionized at all pH, poorly absorbed from GI
Disodium cromoglyate	2.0	
Very weak base	pKa < 5.0	Unionized at all pH, absorbed through entire length of GI
oxazepam	1.7	
diazepam	3.7	
Moderately Weak base	pKa 5 to 11.0	Ionized at gastric pH, relatively unionized at intestinal pH, better absorbed from intestine
Reserpine	6.6	
Heroin	7.8	

6. Disease state

The presence of certain disease states can significantly alter drug release and absorption within the gastrointestinal tract. Below is an overview of how specific conditions may influence these processes:

- **Diarrhea**: This condition, marked by accelerated intestinal motility and the frequent passage of watery stool, significantly shortens the time a drug has to be released and absorbed.
- **Colon Cancer and Inflammatory Bowel Diseases (e.g., Crohn's Disease, Ulcerative Colitis):** These disorders frequently present with symptoms like diarrhea, fever, anemia, and lymphatic issues, all of which can disrupt the normal processes of drug release and absorption. Furthermore, when inflammation penetrates the full intestinal wall, it can compromise the lymphatic system, resulting in the malabsorption of fats and fat-soluble drugs. A reduction in the effective absorptive surface area can also occur due to mucosal thickening, creating an additional barrier to drug diffusion.
- **Constipation:** Sluggish bowel motility slows the passage of intestinal material, which restricts a drug's ability to diffuse and reach the sites where it is absorbed. This effect is compounded in severe constipation, where infrequent evacuation can significantly delay the transit of oral dosage forms.
- **Gastrointestinal Infections**: Infections caused by bacteria or protozoa can speed up the movement of contents through the gut and trigger excess mucus production. These changes can prevent a drug from staying in the right location long enough for proper absorption. Additionally, some infectious agents produce toxins that directly disrupt the cellular processes needed for drug passage.
- **Cardiovascular Disorders:** Intestinal edema, or swelling in the gut wall, can impair circulation to the gastrointestinal tract, resulting in reduced drug uptake.

APPROACHES USED IN COLON TARGETED DRUG DELIEVERY SYSTEM

Primary Approaches:

Azo polymeric prodrugs

Prodrugs are inactive precursors of therapeutic agents, engineered to transform into their active form after administration. Common examples are aspirin, which becomes salicylic acid; codeine, which is metabolized to morphine; and L-Dopa, which is converted into dopamine. This activation frequently relies on enzymatic reactions, like the hydrolysis of enalapril to enalaprilat by liver esterases or the reduction of prodrugs like CB1954 into cytotoxic compounds by nitroreductases.

Azo polymeric prodrugs are a specialized approach for delivering drugs to the colon. Their mechanism depends on the cleavage of azo bonds (–N=N–) by azoreductase enzymes produced by colonic microbiota. A key example is salicylazosulfapyridine (SAS), which is broken down in the colon to liberate the active moiety, 5-aminosalicylic acid (5-ASA), along with sulfapyridine. For this targeting to be successful, the prodrug must remain stable throughout the upper GI tract and only become active upon reaching the colonic environment.

These delivery systems utilize both synthetic and natural polymers as drug carriers. A significant drawback of directly attaching a drug to a polymer via an azo bond is the requirement for particular functional groups on the drug, which limits its broad applicability. To improve colon-specific targeting, more sophisticated designs integrate pH-sensitive components and azo cross-linkers into hydrogel networks. These engineered hydrogels remain compact in the stomach's acidic conditions but expand considerably in the neutral-to-basic environment of the lower GI tract. This swelling action makes the azo bonds accessible to bacterial enzymes, leading to the breakdown of the gel and the subsequent release of the drug.

Another strategy for achieving controlled drug release is to integrate degradable linkages, such as mustard oil derivatives, within the hydrogel's structure [42]. Among the various options, azo-based conjugates continue to be a predominant choice for creating prodrugs that target the colon [43]. This is demonstrated by a metronidazole prodrug, which utilizes sulphate groups to block uptake in the upper GI tract and guarantee its activation occurs specifically in the colon [44].

Sulfasalazine, a prodrug for 5-ASA, demonstrates this principle effectively. Around 85% of an oral dose arrives intact in the colon, where anaerobic bacteria then reduce it to release the active compound. Research

confirms that azo-based polymer systems achieve this colon-specific delivery, showing negligible drug release in the stomach's acidic setting and precise activation in the colon.

A related method for shielding drugs involves chemically bonding them to larger carrier molecules like cyclodextrins or dextran using azo linkages. This conjugation improves stability during passage through the upper GI tract and promotes selective drug liberation upon reaching the colon [45].

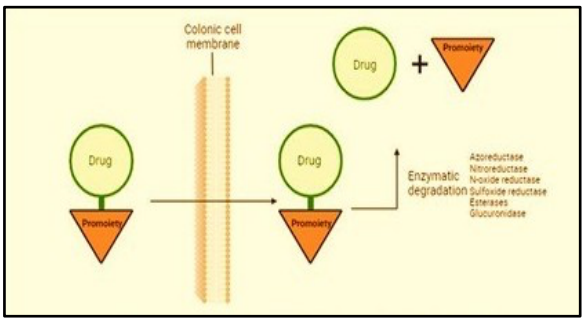

Fig 5: Enzyme degrading prodrugs to active metabolites

Time-controlled release system

Time-controlled, or pulsatile, release systems are engineered to liberate a drug following a pre-programmed delay [46]. While their goal is to provide sustained colonic release, their effectiveness is often compromised by the natural fluctuations in human digestive physiology.

A primary drawback is the inconsistency of gastric emptying, which is affected by food, medical conditions like IBS, and medications that alter gut motility. This unpredictability hinders accurate forecasting of a drug's arrival in the colon, risking unreliable treatment outcomes. The high degree of variation in gut transit times between and within individuals presents a further obstacle for strategies that rely solely on a timer.

To enhance targeting precision, system design incorporates the "lag time"—the interval for a drug to pass from ingestion to the colon. Although transit through the small intestine is fairly stable at 3–4 hours, the total lag time is generally set at approximately 5 hours. This method is especially beneficial for medications that must activate at a particular intestinal location or in sync with a biological rhythm.

Despite this, system performance can be undermined by intense peristalsis, sporadic accelerations in gut movement, and inconsistencies in stomach emptying. To overcome these issues, integrated systems have been engineered that merge a timed-release mechanism with polymers that respond to pH changes. This combined strategy enhances location accuracy and improves reliability, leading to more predictable colon-specific drug delivery [46].

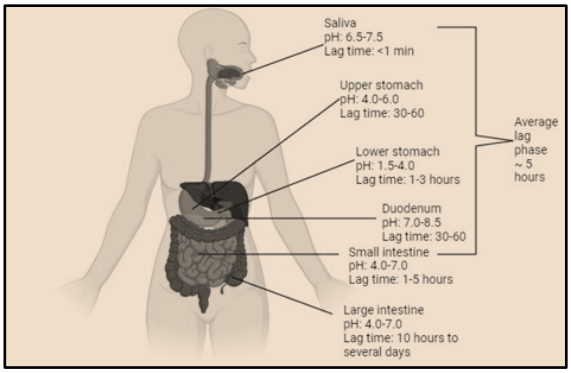

Fig 6: pH and Lag time throughout GIT

Bio-adhesive systems

To increase the contact time of drug formulations with the colonic mucosa, mucoadhesive polymers such as polycarbophil and polyethylene oxide are employed. This prolonged retention is particularly beneficial for enhancing the absorption of drugs with low solubility [47,48]. Research has confirmed that bioadhesive microspheres remain in the colon for longer durations, which results in significantly improved drug uptake.

In vitro analyses confirm the efficiency of these delivery systems. Research demonstrates that a formulation combining a drug with a mucoadhesive polymer released a minimal 10% of its payload in simulated gastric fluid and only 25% in intestinal conditions. In contrast, the same formulation exhibited a rapid and near-complete release of over 90% when exposed to a colonic pH environment [49].

A subsequent study engineered a rectal hydrogel for Tolmetin Sodium, featuring a drug core enveloped by mucoadhesive polymers like HPMC, sodium alginate, and CMC. This configuration promoted attachment to the rectal wall and provided a controlled release of the medication. By maintaining prolonged contact at the site, such mucoadhesive systems substantially improve therapy by increasing drug absorption.[50]

RECENT ADVANCES IN COLON TARGETED DRUG DELIVERY SYSTEM

1. Advanced Microbially Triggered Systems

Traditional approaches rely on natural polysaccharides like chitosan and pectin, which are broken down by the resident colonic bacteria. To enhance the precision and consistency of this process, newer strategies are being developed. These include the direct inclusion of enzymes such as pectinase into the formulation to guarantee degradation even when a patient's microbiome is altered. Other advances involve the use of custom-designed synthetic prebiotics for more uniform bacterial breakdown, and the exploration of biosynthesized carriers like bacterial cellulose, prized for their purity and high drug-loading potential [51].

2. pH-Responsive and Time-Dependent Combination Systems.

Dual-mechanism systems enhance reliability by combining multiple release triggers, moving beyond the constraints of single-stimulus methods. One type uses a sequential pH-time approach: an outer layer first delays release for approximately 3-4 hours to mimic small intestinal transit. After this lag, an inner coating made of a pH-sensitive polymer like Eudragit S100 dissolves in the neutral pH of the lower gut, enabling drug release. Another strategy employs a hybrid microbial/pH system, where an outer pH-sensitive shell dissolves in the colon to reveal a natural polymer core, such as guar gum. This core is then broken down by bacterial enzymes, providing a backup activation mechanism [52].

3. Novel Fabrication Techniques: 3D Printing

Additive manufacturing, or 3D printing, provides unparalleled design freedom for creating advanced colon-targeted drug delivery systems. This technology facilitates the production of "polypills" that combine several medications—such as an anti-inflammatory agent and a probiotic—within a single tablet, each with its own distinct, spatially controlled release timing. Furthermore, it allows for the fabrication of tablets with complex geometric structures, like honeycomb patterns, which can be engineered to fine-tune the rate of drug diffusion and tablet erosion. The use of multi-material printers also simplifies the creation of sophisticated devices, enabling the concurrent printing of an outer pH-sensitive coating and an inner core designed to be broken down by gut bacteria [53].

4. Nanoparticle-Based 'Trojan Horse' Systems

Nanocarriers mark a transition from traditional macroscopic forms to precise, nano-scale therapies. This approach leverages the Enhanced Permeability and Retention (EPR) effect, where biodegradable nanoparticles passively gather in diseased tissues through permeable blood vessels. To increase specificity, ligands such as antibodies can be attached to these particles, enabling them to actively bind to overexpressed receptors on target cells. Furthermore, engineering nanoparticles to be mucoadhesive allows them to cling to the colonic lining, prolonging their local presence and enhancing drug uptake [54].

5. Stimuli-Responsive Hydrogels

"Smart" hydrogels are engineered to react to particular conditions found in the colon. One type, known as redox-responsive systems, uses disulfide crosslinks that remain stable through the upper digestive tract but quickly break apart in the colon's unique chemical environment. Another version is designed with specific molecular links, such as azo bonds or sugar-based chains, that are selectively broken down by bacterial enzymes like azoreductases and glycosidases. [55].

6. Self-Microemulsifying Drug Delivery Systems (SMEDDS)

For water-insoluble drugs, Self-Micro emulsifying Drug Delivery Systems (SMEDDS) improve dissolution by forming lipid-based nanoemulsions. In one advanced approach, liquid SMEDDS are sealed within capsules designed to dissolve either after a timed delay or at the specific pH of the colon. Once this outer shell breaks down, the microemulsion is released, significantly enhancing the absorption of lipophilic compounds in the colonic region [56]. Collectively, these innovations signal a clear movement toward sophisticated, multi-targeted systems designed for greater precision and improved clinical results in colon-targeted therapy.

Current issues with press coating technology

The press-coating method, which involves compressing an outer layer around a pre-made core tablet, encounters major difficulties when scaled for mass production. Although straightforward in a laboratory, this process demands specialized equipment in an industrial setting. A key obstacle is ensuring the inner core remains perfectly centered during high-speed operation, as misalignment can disrupt the intended drug release timing and profile. This results in variable drug absorption and unreliable performance. Emerging solutions like ENCORETM technology, alongside non-destructive monitoring techniques such as X-ray CT scanning, are being devised to correct core misplacement and detect missing cores in a single, efficient step [57].

Evaluations of CTDDS

Advancing dependable colon-targeted drug delivery systems (CTDDS) depends on thorough assessment through both laboratory and animal studies. A major hurdle for in vitro models is their inability to faithfully mimic the complex and changing environment of the human gut. Critical factors like shifting pH levels, varying fluid volumes, microbial populations, and digestive enzymes—all of which are influenced by an individual's diet and stress levels—must be precisely reproduced to generate reliable data [58]. The key criteria for evaluating CTDDS are outlined below:

In Vitro Evaluations

The choice of in vitro test depends on the release mechanism of the formulation, such as pH-dependent dissolution or enzymatic degradation by colonic microflora.

1. Dissolution Testing:

Analyzing drug release from controlled-release formulations presents significant complexity. Conventional USP dissolution apparatuses frequently fail to adequately replicate the dynamic environment of the human gastrointestinal tract. To achieve a more accurate simulation, researchers employ sequential

media, transitioning from an acidic pH of 1.2 (stomach) to a neutral pH of 6.8 (jejunum), and finally to a slightly alkaline pH of 7.2-7.4 (ileum/colon). A standard evaluation for an enteric-coated system targeting the colon involves two hours in acidic medium, one to two hours at small intestinal pH, and a final transfer to colonic pH. A successful formulation will demonstrate minimal release in the upper GI phases, with the bulk of the drug being liberated only upon reaching the colonic environment [58, 59].

2. Enzymatic Tests:

To replicate the microbial conditions of the colon, drug delivery systems are placed in a culture containing specific bacterial strains like Streptococcus faecium or enzymes such as pectinase. The amount of drug released is then tracked at set time points. Another common method utilizes fresh fecal matter from laboratory animals, which remains a rich source of colonic enzymes like azo-reductase even after collection. In these tests, the speed at the polymer breaks down directly determines the rate of drug release over time [58, 59].

3. In Vivo Evaluations

- For reliable in vivo evaluation, animal models that share key anatomical, physiological, and microbial traits with humans are indispensable. Rats, guinea pigs, dogs, and pigs are among the most commonly selected species. Guinea pigs are often chosen for studies of inflammatory bowel disease (IBD), whereas rats and rabbits are favored for their high levels of azo-reductase and glucuronidase, enzymes that closely mirror the metabolic activity found in the human colon [60].
- **String Technique**: In this assessment technique, a tablet is tethered to a string and swallowed by the subject, with the string's end kept accessible. The tablet is then retrieved at designated times by pulling the string back, allowing for a direct visual examination of its physical breakdown. A less frequently used variation of this method involves recovering the formulation by inducing emesis [59].
- **Endoscopic Technique:** This technique requires sedating the subject and inserting a gastroscope to directly observe the position and physical condition of the dosage form within the gastrointestinal tract at predetermined intervals [59].
- **Roentgenography (X-ray Imaging):** In this approach, a radio-opaque substance such as barium sulfate is integrated into the solid formulation. Following oral intake, X-ray scans allow researchers to monitor the formulation's transit and structural breakdown non-invasively as it progresses through the digestive system [60].
- **Radiotelemetry:** A patient swallows a miniaturized, pH-sensitive electronic capsule. As it passes through the digestive tract, the device wirelessly transmits real-time pH measurements. This data enables researchers to link specific pH zones with the precise timing of a drug formulation's breakdown [59].
- Drug Delivery Index (DDI) and Clinical PK Evaluation: The Drug Delivery Index (DDI) is a pharmacokinetic measure that evaluates the performance of colon-targeted prodrugs. It is derived by comparing the relative concentration of the drug in colonic tissue to its relative concentration in the bloodstream. A greater DDI value signifies a more effective and localized delivery to the colon, accompanied by reduced systemic circulation [58].
- **γ-Scintigraphy:** Gamma scintigraphy is a highly effective, non-invasive imaging method. A radioactive tracer such as ^{99m}Tc-DTPA is integrated into a delivery system, like a guar gum-based tablet. Following oral intake, a gamma scanner records sequential images, enabling qualitative and quantitative, real-time monitoring of the formulation's movement, breakdown, and drug release profile. The primary constraints of this technique are its significant expense and the need for highly trained staff and sophisticated instrumentation [60].

Conclusion

In conclusion, colon-targeted drug delivery (CTDD) is a pivotal and refined strategy in modern therapeutics, offering a powerful solution to the drawbacks of conventional oral administration. By leveraging the colon's specific environment—such as its prolonged residence time, unique pH, and rich microbiota—CTDD enables accurate, localized treatment of conditions like IBD and colorectal cancer. This site-specific approach not only enhances therapeutic efficacy but also reduces systemic exposure, curtailing unwanted side effects. Additionally, its ability to protect vulnerable macromolecules from upper GI degradation opens new avenues for the oral delivery of biologic agents.

The field has progressed significantly from basic single-stimulus designs to complex, multi-mechanism platforms. Innovations such as dual pH-time polymers, enzyme-activated prodrugs, targeted nanoparticles, and 3D-printed devices reflect major strides in achieving precise and reliable delivery. Despite this progress, their path to clinical use depends on navigating key physiological challenges like inconsistent gut transit, scarce luminal fluid, and the colon's poor absorption. Advancing these technologies will require a deeper synergy between intelligent biomaterials, sophisticated fabrication methods, and a more nuanced grasp of the gut microbiome. With ongoing refinement, colon-targeted systems are set to significantly enhance patient adherence and therapeutic success, establishing

themselves as a cornerstone of treatment for both local and systemic diseases.

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