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Review

Progress in Drug Delivery Systems Targeted for the Colon: Technologies, Challenges, and Future Outlook

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Abstract

Colon-targeted drug delivery systems (CTDDS) have gained significant importance due to their ability to deliver drugs selectively to the colon, thereby improving therapeutic efficacy while minimizing systemic side effects. Conventional oral drug delivery often results in premature drug release and degradation in the upper gastrointestinal tract, making targeted colonic therapy challenging. This review provides a comprehensive overview of the progress, strategies, challenges, and future prospects of colon-specific drug delivery systems. Various physiological factors influencing colonic drug delivery, including pH variation, transit time, colonic microflora, and enzymatic activity, are discussed in detail. The article highlights primary approaches such as pH-dependent systems, time-controlled release systems, and microbially triggered drug delivery, along with advanced techniques like prodrug strategies, polysaccharide-based systems, pressure-controlled devices, osmotic systems, nanoparticle based delivery, microbiota-responsive systems, and 3D-printed drug delivery platforms. Evaluation methods, marketed formulations, advantages, limitations, and recent technological advancements are also reviewed. Despite remarkable progress, challenges such as formulation variability, site-specificity issues, scale-up difficulties, and physiological variability remain. Future perspectives emphasize the integration of advanced predictive tools, novel polymers, nanotechnology, and manufacturing techniques like hot-melt extrusion and 3D printing. Overall, CTDDS represents a promising and evolving approach for effective management of colonic diseases and systemic drug delivery.

Keywords: Colon-targeted drug delivery systems, pH-dependent drug delivery, Microbially triggered drug delivery, Prodrug approach, Nanoparticle-based drug delivery.

INTRODUCTION

For patients, oral medication administration is the most practical approach. But, Drugs usually absorb in the gastrointestinal tract (GIT) after dissolving in the stomach, making Drug delivery to the colon, where localized treatment is necessary, is difficult. This is an significant drawback when managing bowel conditions like cirrhosis and ulcerative colitis illness, amoebiasis, local colonic pathologies, colonic cancer, and systemic protein and delivery of peptide therapy. To get around this problem, a colon-targeted medication delivery system (CTDDS), which can shield the medication from the hostile environment, is very desirable of the upper gastrointestinal tract release and absorb only after it gets to the colon. This system ought to stop the stomach and small intestine from releasing and absorbing drugs while avoiding the bioactive agent's breakdown at either of the dissolution sites [1].The delivery of colon drugs The term "system" describes the targeted delivery of drugs to the lower gastrointestinal tract, mainly the colon or large intestine. The localized delivery of medications directly to the colon is beneficial for treating various colonic conditions such as inflammatory bowel diseases (including Crohn's disease and ulcerative colitis), colon cancer, and irritable bowel syndrome. Moreover, this method can facilitate chronotherapy, prevent colon cancer, and assist in the treatment of nicotine addiction. Besides addressing local conditions, this delivery approach holds promise for the systemic delivery of therapeutic proteins and peptides, which are typically administered via injections. By utilizing oral delivery systems, drugs can be released in the colon once the system reaches that area. These delayed-release mechanisms aim to enhance drug effectiveness by targeting treatment where it is most needed, while also minimizing side effects and problems related to drug instability from early release in the stomach and small intestine[2]. Targeting drug delivery to the colon offers multiple advantages, including localized treatment, reduced dosages, and fewer side effects. Additionally, the colon can act as an entry point for systemic absorption of drugs, particularly for molecules like peptides and proteins that may be not absorbed well or broken down in the upper part of the digestive system. However, the lower fluid content in the colon can hinder the dissolution of drugs with poor water solubility. In some scenarios, it might be necessary to provide drugs in a pre-solubilized format or focus on the proximal colon, where free water is more abundant. The stability of the drug in the colonic environment is crucial since it can interact with dietary residues, intestinal secretions, mucus, or fecal matter, decreasing the concentration of free drug. Additionally, the resident microbiota can influence drug efficacy by breaking down the drug[3].The colon is also rich in lymphoid tissue, and the uptake of antigens by mast cells in the colonic mucosa can trigger a rapid immune response[4]

Why is colon targeted drug delivery needed?

- For addressing different conditions affecting the colon such as ulcerative colitis, Crohn's disease, colon cancer, irritable bowel syndrome, and infections[5].
- For addressing nicotine dependency[6].
- Additionally, colon delivery is necessary for medications that Are discovered to be absorbable in the colon. Steroids, boosting effectiveness and Lowering the necessary effective dose by[7].
- The ideal location for peptide absorption and protein medications are thought to be colon reduced proteolytic and digestive intensities Enzymes[8].
- Systemic medication administration to the colon causes administration of lower dosages and lower adverse effects brought on by high dosages[9].
- Minimizing first pass metabolism is necessary of medications[10].

ANATOMY AND PHYSIOLOGY OF COLON

The gastrointestinal (GI) tract consists of the stomach, small intestine, and large intestine. The large intestine, which extends from the ileocecal junction to the anus, is divided into three main parts: the rectum, anal canal, and colon. The colon itself has five primary sections, each approximately 5 feet (150 cm) long. Mesentery refers to the peritoneal folds that support the ascending and descending colon. The right colon includes the cecum, ascending colon, hepatic flexure, and the right portion of

the transverse colon, while the left colon encompasses the left transverse colon and descending colon, along with the sigmoid and splenic flexure. The rectum is the final anatomical segment before the anus. As illustrated in Figure 1, the human colon plays essential roles such as creating a suitable environment for colonic microbes, serving as a storage site for feces, controlling the timing of waste release, and absorbing potassium and water from its

contents. The ileocecal valve permits approximately 2000 ml of fluid to enter the colon, where over 90% of this fluid is absorbed[11].

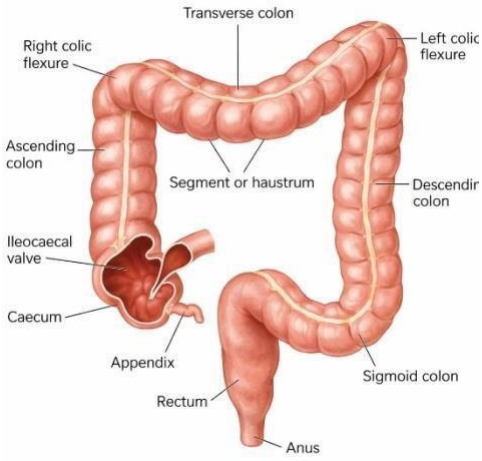

Figure 1: Anatomy of colon

Considerations for Colon-Specific Drug Delivery System Design

❑ Colon pH

The pH of the gastrointestinal tract (GIT) varies between individuals and even within the same person. Factors such as diet, health status, and food intake influence GIT pH. These pH changes are effectively used in colon-targeted drug delivery systems. Radio-telemetry studies show that the terminal ileum has the highest pH (7.5 ± 0.5). When the dosage form enters the colon, the pH drops to about 6.4 ± 0.6. The mid-colon pH is around 6.6 ± 0.8, while the left colon pH increases slightly to 7.0 ± 0.7. The decrease in pH in the colon is mainly due to the production of short-chain fatty acids formed by bacterial fermentation of polysaccharides. For example, colonic bacteria ferment lactose to produce lactic acid, which lowers the colonic pH [12].

❑ Gastro Intestine Transit

Transit of materials through the colon occurs at a slower pace compared to other parts of the gastrointestinal tract. The duration of this transit can vary significantly and is influenced by various factors such as diet, especially the amount of dietary fiber, activity level, stress, health conditions, and medication. Colonic transit times can range from 50 to 70 hours, while stool weights tend to increase notably when there is active disease, likely due to secretions from inflamed epithelium, heightened mucus production, and decreased reabsorption of fluids and electrolytes[13].

❑ Colonic Microflora and Enzymes

A wide array of anaerobic and aerobic bacteria inhabit the entire length of the human gastrointestinal tract (GIT). Intestinal enzymes play a crucial role in releasing drugs at different sites within the GIT. Typically, these enzymes are sourced from the abundant gut microflora found primarily in the colon. They function to disintegrate coatings or matrices and disrupt the bonds between an inactive carrier

and an active agent, facilitating drug release. The human colon harbors around 1000 CFU/mL of bacteria, with over 400 distinct bacterial species identified, including bacteroid representing 20-30% of these species. Noteworthy anaerobic bacteria in the colon include Bacteroides, bifidobacterium, eubacterium, peptococcus, Pepto streptococcus, ruminococcus, and clostridium[14].

❑ Drug Absorption in the Colon

Drugs are absorbed passively by either the paracellular or transcellular route. Transcellular absorption entails The movement of medications through cells, where paracellular absorption occurs for the majority of lipophilic medications. Entails the drug's passage through the tight junction between cells, which is the path taken by the majority of hydrophilic drugs. The medication can remain in contact with the mucosa for a longer amount of time in the colon due to its slower rate of transit than in small Intestine, which makes up for the significantly reduced surface area. The contents of the colon become more viscous with Water is gradually absorbed as one passes through the colon. This results in a lower rate of dissolution, Slow drug diffusion through the mucosa after dissolution [15].Giving glucocorticoids, such as dexamethasone And methyl prednisolone administered intravenously or orally causes adenosuppression and other systemic side effects. Bone resorption, cushinoid symptoms, and immunosuppression Consequently, medication delivery to the colon is selective. Could lessen both the necessary dosage and the systemic adverse effects brought on by high dosages[16].

APPROACHS USED FOR SITE SPECIFIC DRUG DELIVERY TO COLON (CDDS)

Several approaches are used for site-specific drug delivery. The following are some of the main strategies for CDDS:

1.PRIMARY APPROACHES FOR CDDS

A.pH-Sensitive Polymer Coated Method for Delivering Drugs to the Colon

In the stomach, the pH levels range from 1 to 2 when fasting but rise after a meal[17] Figure 2.

The proximal small intestine has a pH of about 6.5, while the distal small intestine's pH is around 7.5[18]. From the ileum to the colon, the pH decreases significantly, measured at about 6.4 in the cecum, with some healthy individuals showing pH levels as low as 5.7 in the ascending colon[19]. The pH in the transverse colon is 6.6, and in the descending colon, it is 7.0. These variations in pH form the basis for the use of pH-dependent polymers in colon-targeted drug delivery. Such polymers are insoluble at low pH levels but become more soluble as the pH increases[20]. While a pH-dependent polymer can safeguard a formulation in the stomach and proximal small intestine, it may begin to dissolve in the lower small intestine, which can lead to poor site-specificity in the formulations[21]. Additionally, the drop in pH from the end of the small intestine to the colon can introduce challenges, such as delays at the ileo-cecal junction or fast transit through the ascending colon, further compromising the site specificity of entericcoated single-unit formulations[22]

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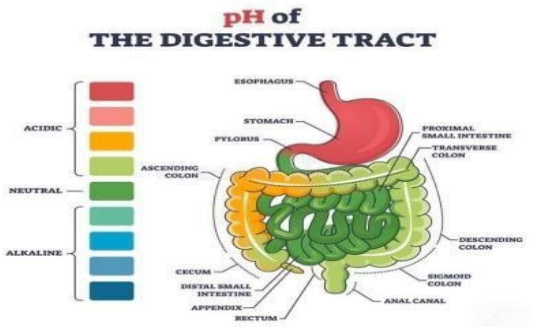

Figure 2 : The pH values of the GIT

B. Delayed Drug Delivery to the Colon (Time-Controlled Release System)

Sustained and delayed release dosage forms are examples of time-controlled release systems (TCRS). These systems are designed to release drugs after a specific time. However, they are not ideal for colontargeted drug delivery because the time taken for a dosage form to reach the

colon varies widely among individuals [23].

The main drawbacks of time-dependent systems are:

1. Variation in gastric emptying time, which depends on food type and quantity.
2. Gastrointestinal movements such as stomach contractions and peristalsis can alter drug transit.
3. Faster intestinal transit is seen in conditions like inflammatory bowel disease, diarrhea, carcinoid syndrome, and ulcerative colitis.

Because of these factors, colonic drug availability is low with purely time-dependent systems.

To improve site specificity, a combination of time-controlled and pH-dependent systems is preferred. Since the small intestine transit time is relatively constant (about 3 ± 1 hours), timerelease systems work more reliably there than in the stomach [24]. Drug release is prevented in the stomach using acidresistant (enteric) coatings.

Enteric-coated time-release press-coated (ETP) tablets consist of:

- A core tablet with the drug (immediate release),
- A hydrophobic polymer layer (HPC) that controls lag time,
- An enteric coating that protects the drug in the stomach.

After gastric emptying, the enteric coat dissolves in the intestine, the HPC layer slowly erodes, and once it reaches the core, the drug is released rapidly. The lag time depends on the thickness or composition of the HPC layer [25].

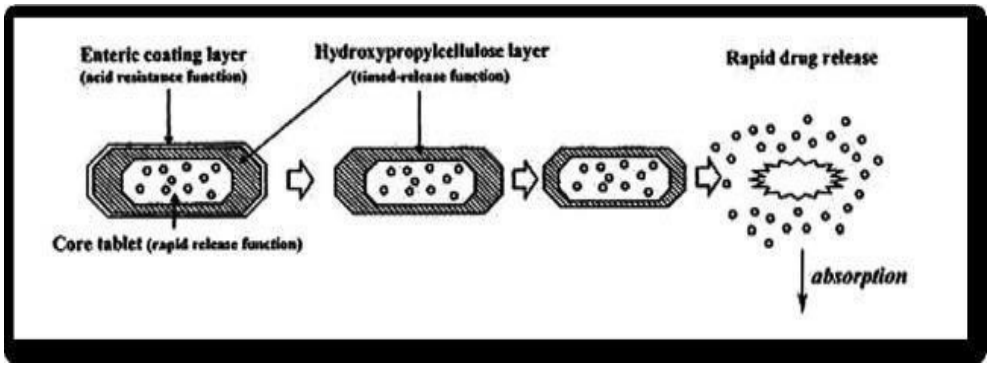

Figure 3: Design of enteric coated timed-release press coated tablet (ETP Tablet)

C. Microbially Triggered Drug Delivery to Colon

The colon's microflora ranges from 1011 to 1012 CFU/mL, primarily made up of anaerobic bacteria like Bacteroides, clostridium, enterococci, enterobacteria, bifidobacteria, eubacteria, and ruminococcin, etc. 25 This enormous microflora meets its energy requirements by fermenting a variety of substrates, such as polysaccharides and di- and tri-saccharides, that have been left undigested in the small intestine etc.[26].The microflora for this fermentation generates a massive several enzymes, including arabinosidase, xylosidase, and glucoronidase, urea, deaminase, azareducatase, galactosidase, and nitro reductase dehydroxylase[27]. Due to the biodegradable only in the colon, the application of biodegradable polymers for colon-specific medication administration appears to be a more site-specific strategy in contrast to alternative methods. These polymers protect the medication from the conditions of the small intestine and stomach, and are capable of to transport the medication to the colon. When they get to the colon, they go through

absorption by microorganisms, breakdown by enzymes, or down of the polymer backbone, which subsequently results in a decrease in loss of mechanical strength due to their molecular weight [28].After that, they can no longer contain the drug entity[29].

i)Prodrug Approach for Drug Delivery to Colon

A prodrug is a parent drug's pharmacologically inert derivative. Molecule that needs to undergo enzymatic or spontaneous transformation in Vivo to make the active medication available. The prodrug is made to experience little hydrolysis in the upper GIT tracts for colonic delivery. And are hydrolyzed by enzymes in the colon, releasing The drug carrier's active drug component. Intestinal bacteria's metabolism of azo compounds is one of the most widely investigated the metabolic processes of bacteria[30]. Several additional connections Vulnerable to bacterial hydrolysis, particularly in the colon, have been Prepared by attaching the medication to hydrophobic moieties Such as cellulose, glucose, galactose, amino acids, and glucuronic acids, among others. One of the prodrug approach's drawbacks is its lack of versatility. Approach since the functional group determines how it is formulated. Accessible for chemical bonding on the drug moiety. Additionally, Prodrugs are novel chemical entities that require extensive assessment Prior to being employed as carriers[31].

ii) Azo-Polymeric Prodrugs

More recent methods focus on using polymers as carriers for drug delivery specifically to the colon. Both synthetic and naturally derived polymers have been employed for this purpose. Subsynthetic polymers have been utilized to create polymeric prodrugs featuring azo linkages between the polymer and the drug component[32]. These have undergone evaluation for colonspecific drug delivery systems (CDDS). Various azo polymers have also been tested as coatings for drug cores, demonstrating similar susceptibility to cleavage by azoreductase in the large intestine. Additionally, peptide capsules coated with polymers cross-linked with azoaromatic groups have been shown to safeguard the drug from being digested in the stomach and small intestine. In the colon, the azo bonds are broken down, leading to the release of the drug [25].

iii) Polysaccharide Based Delivery Systems

The utilization of naturally occurring polysaccharides is gaining considerable attention in the field of drug delivery to the colon. These polysaccharides, composed of monosaccharide units, are abundant, readily available, cost-effective, and exhibit diverse structures with varying properties. They can be easily chemically or biochemically modified, offering high stability, safety, nontoxicity, hydrophilicity, gel-forming ability, and biodegradability. Examples of these polysaccharides include guar gum and inulin from plants, chitosan and chondroitin sulfate from animals, alginates from algae, and dextran from microbes. Colonic microflora can break down these polysaccharides into simple saccharides[22], making them classified as "generally regarded as safe" (GRAS).

2. NEWLY DEVELOPED APPROACHES FOR CDDS

a. Pressure Controlled Drug-Delivery Systems

Peristalsis causes higher pressures in the colon compared to the small intestine. Takaya et al. designed colon-delivery capsules using ethyl cellulose, a water-insoluble material[33]. Drug release in these capsules happens when the water-insoluble polymer disintegrates due to colon pressure. The thickness of the ethyl cellulose membrane is crucial for the capsule's breakdown[34]. The system's efficiency is also affected by capsule size and density. The colon's higher water reabsorption leads to thicker luminal content compared to the small intestine, potentially hindering drug dissolution[35]. In pressurecontrolled ethyl celluloses capsules, the drug is in liquid form, and human studies have shown lag times of three to five hours for drug absorption after administration.

b. Novel Colon Targeted Delivery System (CODESTM)

CODESTM represents a unique Controlled Release Drug Delivery System (CDDS) technology's created to overcome the challenges associated with pH or time-dependent systems[36]. Unlike conventional methods, CODESTM combines pH dependence and microbial triggers to achieve controlled drug release. The technology leverages lactulose as a catalyst for targeted drug delivery in the colon. Through a specialized process, a tablet core containing lactulose is coated with acidsoluble material, Eudragit E, followed by an enteric material coating, Eudragit L. This design ensures that the tablet is protected in the stomach by the enteric coating, dissolves after gastric emptying, and remains shielded by the acid-soluble material in the intestines[37]. ,Upon reaching the colon,

bacterial action breaks down lactulose into organic acid, altering the pH and facilitating drug release by dissolving the acid-soluble coating. This innovative method ensures precise and effective drug deliver.

c. Osmotic Controlled Drug Delivery (ORDS-CT)

The OROS-CT system from Alza Corporation is designed to deliver medication directly to the colon for treating diseases or to achieve systemic absorption that would not be possible otherwise[38]. This system can consist of a single osmotic unit or include up to 5-6 push-pull units, each measuring 4 mm in diameter, all housed within a hard gelatin capsule Figure 4[39]. Each bilayer push-pull unit features an osmotic push layer and a drug layer, both enclosed by a semipermeable membrane. An opening is drilled through the membrane next to the drug layer. Once the OROS-CT is swallowed, the gelatin capsule that contains the push-pull units dissolves. Thanks to its drug-impermeable enteric coating, each push-pull unit does not absorb water in the acidic environment of the stomach, meaning no drug is released at this stage. When the unit reaches the small intestine, the coating dissolves in this higher pH environment (pH >7). Water then enters the unit, making the osmotic push compartment swell and creating a flowable gel in the drug compartment. The swelling of this compartment pushes out the drug gel through the opening at a rate that is carefully controlled by how quickly water moves through the semipermeable membrane. To effectively treat ulcerative colitis, each push-pull unit includes a 34 hour delay after leaving the stomach to stop drug delivery in the small intestine. The release of the drug starts when the unit arrives in the colon. OROS-CT units can provide a steady release of medication for as long as 24 hours in the colon, or they can release it over a shorter time frame of just four hours. Recently, new systems that change phases have been introduced, offering a promising way to deliver drugs specifically to the colon[40]. Several methods for testing how well these Controlled Drug Delivery Systems (CDDS) work and how stable they are have been created and suggested.

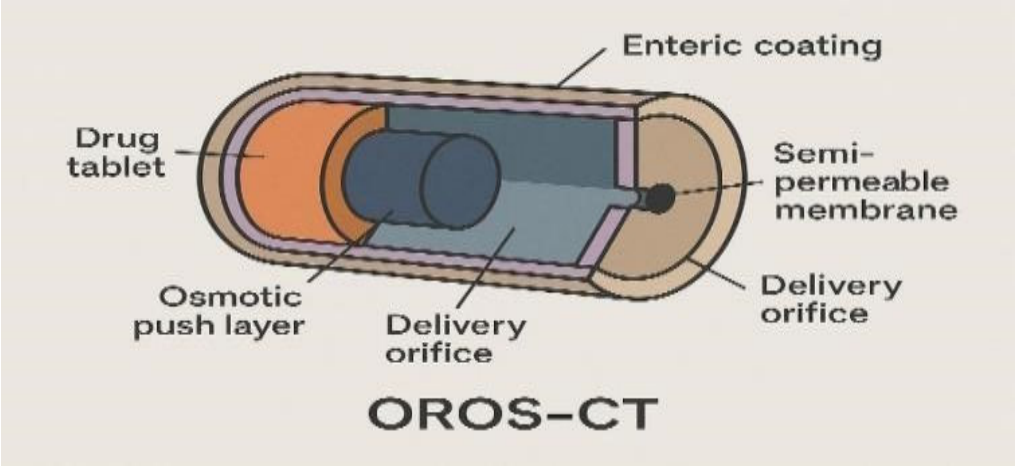

Figure 4: OROS-CT colon targeted drug delivery system cross-section

EVALUATION PARAMETERS

1. In vivo evaluation

a) X-ray imaging :

The researchers used dogs to test the dosage form using an x-ray method. They gave the dogs 50 ml of a radio diagnostic agent called omnipaque. After specific time intervals following the administration of omnipaque, they performed x-ray imaging. This was done to obtain reference xray images of the dogs' gastrointestinal tracts for comparison. Before taking the x-rays, the animals fasted overnight but had unlimited access to water. A radiograph was taken before giving them the substance being tested. Then, they administered the units along with 50 ml of water. The radiographs of the animals were captured at different times: 0 hours, 0.5 hours, 2.5 hours, 4 hours, 5 hours, 6 hours, 7 hours, and 8 hours after they ingested the substance being tested[41].

b) Gamma scintigraphy:

This technique helps determine how different colon-targeted systems behave inside the body. It uses a non-invasive imaging method. This involves adding small

amounts of gamma-emitting radionuclides to the dosage forms, which shows the patterns of how they travel through the gastrointestinal tract (GIT) and indicates when and where they break down[42].

- In vivo imaging on rabbits

For this study, researchers used 12 male albino rabbits that were one year old to observe how the dosage form moved within their bodies. The rabbits were split into two groups and fasted for 12 hours before the experiment began. The first group received polymer-coated radiolabeled pellets containing medication in a liquid form, while the second group got uncoated pellets along with enough drinking water. The animals were then monitored using a gamma camera. The 140 keV gamma rays emitted by 99mTc were captured and recorded by a computer system, which helped analyze how the dosage form spread throughout the gastrointestinal tract (GIT). During breaks in gamma scanning, the rabbits could move around, but they were not allowed to eat or drink until their stomachs were clear of the formulation[43]. It was observed that the coated pellets released their contents in a controlled manner. A comparison of scintigraphy studies between the coated and uncoated pellets showed that the coated versions stayed intact in the colon for up to 10 hours.
Once they reached the colon, the pellets broke down and released the drug[44].

c) High-frequency capsule:

Doctors mainly use colonoscopy and intubation to study how medicine works inside the body. Highfrequency capsules are smooth plastic capsules that you swallow. Inside these capsules, there is a small latex balloon, a drug, and a radiotracer substance. An impulse releases the drug and radiotracer, allowing doctors to analyze how they behave in different parts of the gastrointestinal tract (GIT). This method helps monitor how well drugs are absorbed in the colon[45].

2. In vitro evaluation

In vitro evaluation methods simulate the conditions of the gastrointestinal tract (GIT) in a lab setting, including factors like pH, volume, bacteria, enzymes, and food particles. Researchers typically use the conventional basket method to conduct dissolution studies on a dosage form. These studies take place in various buffer solutions to replicate the GIT environment and observe how the dosage form behaves under different pH levels. For enteric-coated systems, in vitro tests involve placing them in simulated stomach conditions (0.1 N HCl) for 2 hours, which represents the average time it takes for the stomach to empty, and then moving them to simulated intestinal conditions for another 3 hours, reflecting the average time they spend in the small intestine. This process helps predict where and how much of the dosage form breaks down and dissolves during in vitro studies[46].

ADVANCES IN COLON TARGETED DRUG TECNOLOGIES

A) 3D-PRINTED DELIVERY SYSTEMS

One problem with traditional solid oral medications is that they are made in large quantities, which means they cannot be customized for individual needs[47]. This can be a significant issue since patients can respond differently to treatments, suggesting that a “one size fits all” method might not work well for everyone. A possible answer to this challenge is 3D printing ,which has recently advanced personalized medicine by allowing for specific dosage strengths and designed release patterns, and it has begun to appear in clinical studies[48].

In the area of colonic delivery, researchers have used 3D printing to create formulations specifically targeting budesonide[49]. In a recent lab study, scientists developed a pH-responsive budesonide tablet through 3D printing that released the drug steadily in the colon. It also targeted particular areas like the ileum and proximal colon based on how thick the outer layer was printed. This ability to control the release makes it possible to treat inflammatory bowel disease (IBD) in different parts of the body with varying doses.

The flexibility of 3D printing is also evident In its use for encapsulating liquid medicines. This has always been tough for the pharmaceutical industry because there haven’t been many capsule designs that can keep liquids stable as they pass through the gastrointestinal tract while containing water-based products[50]. 3D-printed cap Vessels that could hold liquids were built for fecal transplants used to treat CDI, enabling quick screening of various designs and appropriate ties of the capsules, in addition to quick testing of a range of formulations compared to conventional manufacturing techniques [51].Additional crea The following proactive measures

have been implemented: printing of suppositories that have been effectively inflix, budesonide, and tofacitinibcitrateimab [52], demonstrating the effectiveness of 3D printing as a customizable platform for the treatment of IBD. However, their limited application in clinical settings must be before their viability can be thoroughly evaluated and contrasted with goods available on the market.

B) MICROBIOTA-RESPONSIVE APPROACHES

The density of microbiota and the enzymes they produce increase along the gastrointestinal tract.

This characteristic can be used to create colonic delivery systems that respond to microbiota[54]. Colon-targeted prodrugs have been successful in clinical settings, with traditional azo prodrugs like sulfasalazine, olsalazine, and balsalazide being activated when azoreductase enzymes from the colonic microbiota break down the azo bond. However, designing these prodrugs is specific to each drug due to limitations in their chemical structure, as well as requirements for solubility and bioavailability of the active drug. On the other hand, a formulation-based approach to drug design provides a more flexible option since one formulation can work for multiple drugs, offering a consistent release mechanism—like what happens with polysaccharides.

Certain polysaccharides such as pectin, chitosan, xanthan gum, and guar gum have been studied for use in colonic delivery systems because they are broken down by microbial enzymes in the colon to release their drug content[55]. Starch is another promising option; specifically, amorphous amylose— a type of retrograded starch— (a water-insoluble polymer) is necessary because using amylose causes too much swelling when it comes into contact with water[56].

C) NANOPARTICLE

The use of micro- and nanoparticles for colon-targeted drug delivery has gained importance due to their ability to improve drug solubility, stability, targeting, and controlled release. Nanoparticles (1– 100 nm) can easily enter cells, making them effective for intracellular drug delivery and targeting specific cells. Nanocarriers enhance the solubility of poorly water-soluble drugs, protect drugs from degradation, reduce rapid renal clearance, and allow controlled drug release. Passive targeting nanoparticles exploit the Enhanced Permeability and Retention (EPR) effect, especially for tumor targeting [57]. Studies have shown that chitosan-based nanoparticles loaded with oxaliplatin and resveratrol significantly improved solubility, stability, and anti-colorectal cancer activity compared to free drugs. The ideal nanoparticle size (10–100 nm) helps avoid liver and kidney clearance while improving tumor accumulation.PLGA nanoparticles are widely used due to their biocompatibility and sustained drug-release properties and show promise in cancer therapy, including gene, protein, and peptide delivery. Folate-conjugated nanoparticles enable pH-dependent drug release in acidic tumor environments, enhancing cellular uptake and apoptosis. Recent developments include hybrid natural polymer nanoparticles, such as curcumin-loaded systems for colon delivery, and nanosuspensions of mebendazole, which showed enhanced dissolution and strong anticancer effects [58].

MARKETED PRODUCTS

Many cutting-edge medications in the pharmaceutical industry There are colon-focused delivery methods available for the therapy for colon disorders and are sold under various different dosage[59].

BRAND\PRODUCT NAME	DRUG	TECHNOLOGY\MECHANISM	TARGET SIZE	INDICATION
Asacol® / Asacol HD®	Mesalamine	pH-dependent coating (Eudragit S, dissolves at pH ≥7)Terminal ileum & colon Ulcerative colitis	Terminal Ileum & colon	Ulcerative colitis
Lialda®	Mesalamine	MMX® (Multimatrix system) – hydrophilic/lipophilic matrix + pH coatin	Entire colon	Ulcerative colitis
Pentasa®	Mesalamine	Time-dependent ethylcellulosemicrogranule s	Duodenum → colon(extended release)	UC, Crohn's
Apriso®	Mesalamine	pH-dependent (Eudragit L) + extended-release granules	colon	UC maintenance
Colazal® (Balsalazide)	Balsalazide disodium	Azo-bond prodrug cleaved by colonic bacteria	Colon	UC

ADVANTAGES OF COLON DRUG DELIVERY SYSTEMS

Colon medication delivery systems provide a number of benefits for The management of digestive issues. A few of the Among the main benefits are:

Targeted Delivery

Colon drug delivery systems allow for the targeted administration of Medications to the colon rather than the stomach and the upper digestive system. This was meant to Method is particularly beneficial in situations that Mainly affect the colon, including ulcerative colitis and Crohn's disease. Disease in addition to colorectal cancer. By administering drugs directly Increased concentrations in the affected region may Achieved at the site of action, improving therapeutic efficacy.

Localized Treatment

For many gastrointestinal conditions, localized Therapy to the impacted areas. Drug delivery in the colon Systems make it possible to administer drugs directly to the Colon, enabling targeted therapy. This localized Approach can be particularly beneficial in circumstances like Bowel inflammation, in which inflammation is Restricted to particular colonic regions. By distributing medications It lowers the risk and minimizes systemic exposure locally Of adverse systemic effects.

Enhanced Drug Stability

Certain medications can break down in an acidic environment. The stomach's environment or the breakdown of enzymes in The upper digestive system. Drug delivery in the colon Systems can prevent medications from deteriorating and guarantee Their stability by avoiding these areas.

This conservation Of medication integrity can enhance the efficacy of the Medicine and extend its shelf life.

Prolonged and Controlled Drug Release

Certain digestive disorders require prolonged or Controlled drug release to maintain therapeutic levels over A long period of time. Colon drug delivery systems can be Designed to provide either sustained or delayed release Of substances. By controlling how quickly drugs are released,

these Systems ensure a consistent and prolonged medication Concentration in the colon, enhancing treatment efficacy[60].

Reduced Systemic Side Effects

By administering medications straight to the colon, colon drug Systems for delivery can reduce systemic exposure to Drugs. This method of localized medication delivery lowers The possibility of systemic adverse effects from Traditional oral drugs. It permits a greater drug concentration at the site of action while Lowering the body's exposure to other areas.

Improved Patient Compliance

Long-term care is frequently needed for digestive disorders. Medication schedules and patient adherence can be a difficulty. Colon drug delivery systems are inconvenient and patientfriendliness. They do away with the requirement for regular dosing and can lessen the burden of pills related to with several oral drugs. This enhanced Convenience and a patientfriendly strategy can improve medication compliance and treatment results in general.

LIMITATIONS OF COLON TARGETING DRUG DELIVERY SYSTEM

- Various manufacturing processes
- The drug should be in solution form prior to absorption; this is the stage that limits the rate of medications that are poorly soluble. The dosage cannot be evaluated using an appropriate invitro dissolving testing method form [61].
- The unpredictability of the location and surroundings where the coating might start to One major disadvantage of the pH-sensitive coating technology is that it solves. Typical in patients with ulcerative colitis [62].
- One of the prodrug technique's drawbacks is that its formulation is reliant on the drug moiety's functional groups available for chemical coupling. Prodrugs are new chemical compounds that need to be thoroughly tested before being used as carriers [63].

CHALLENGESAND FUTURE PERSPECTIVE INCOLONICDRUG DELIVERY

Despite notable progress in colon-targeted medication delivery systems, there are still a number of difficulties in developing efficient formulations. These difficulties include navigating the gastrointestinal tract's anatomical and physiological complexities intestinal tract, guaranteeing accurate delivery to the colon, the intended site of action, obtaining a very specific SShemodynamic effect, and adjusting medication release according to Patho-physiological circumstances [64].

This work deeply discussed The most recent approaches in colon drug delivery, such as Multiparticulate systems, 3D printing, microsystems, andnanosystems.ms. Although these methods offer promising Advancements over traditional forms like tablets and cap-slues, they currently face limitations such as low drug load-Ing capacity, limited stability, and constrained controlled Release capabilities [65].In terms of preparation, Basic experimental data is noticeably lacking and strong, dependable models for controlling and optimizing the final product's characteristics, especially with regard to crystallinity and particle size distribution [66].Since many of these methods were created in labs, we need to Recognize the difficulties that come with scaling them up for industrial use. Some Specific problems related to microsystems and nonsystems include a lack of Standard procedures for measuring the micro/nano systems produced and the Limitations of most current tools and methods used to analyze nanoparticles, Especially at the smaller end of the nanoscale. Even though various engineering Sciences have been successfully incorporated into modern drug delivery systems For colon treatments, it remains unclear what relevant pharmaceutical products Have been developed from these approaches due to a shortage of published studies. More attention is needed on assessing the quality of the final formulations[67]. There are great chances to predict success in real-life results by using advanced Predictive technologies. These include design of experiments (DOE), molecular Dynamics, mechanistic modeling, and machine learning during the development of Formulations and in vitro to in vivo correlations. SIMGI (SISSMulator Gastro-Intestinal) is a computer model that precisely mimics physiological processes,Microbiota, and food impacts within the gastrointestinal tract. Using Hot Melt Extrusion

(HME) in colon drug delivery systems could greatly improve how we develop and produce effective treatments for colonic diseases. HME enhances efficiency because it works continuously and reliably, which might simplify the production process into one continuous step that improves product stability. This method can address various challenges during preparation, resulting in formulations with higher drug concentrations. HME shows a strong potential to be adapted and included in current colonic delivery systems, making it possible to apply these methods on an industrial scale. This can happen by creating stronger partnerships focused on technology between industry and academia. Once it's clear that some additional lab-scale improvements are made, new opportunities for promising colon delivery systems will likely emerge in many pharmaceutical products[68].

CONCLUSION

Colon-targeted drug delivery systems (CTDDS) have emerged as an effective strategy for the treatment of colonic disorders and for the systemic delivery of drugs that are unstable or poorly absorbed in the upper gastrointestinal tract. By utilizing the unique physiological characteristics of the colon, such as pH variation, extended transit time, and the presence of metabolically active microflora, these systems enable site-specific drug release with enhanced therapeutic efficiency and reduced systemic side effects. Conventional approaches including pH-dependent coatings, time-controlled release systems, microbially triggered delivery, prodrug strategies, and polysaccharide-based carriers have demonstrated promising outcomes. Recent advancements in nanotechnology, microbiota-responsive systems, osmotic devices, and 3D-printed drug delivery platforms have further improved precision, personalization, and controlled release profiles. Despite these advancements, challenges such as interindividual variability, formulation complexity, and scale-up limitations remain. Continued research integrating advanced modeling tools, innovative polymers, and scalable manufacturing techniques is essential to translate these technologies into effective clinical applications**.**

DISCUSSION

Colon-targeted drug delivery systems provide an efficient approach for delivering drugs specifically to the colon by overcoming challenges associated with conventional oral therapy. Various strategies such as pH-dependent systems, microbially triggered delivery, prodrug approaches, and polysaccharide-based carriers utilize the unique physiological environment of the colon. Recent advances including nanoparticles, microbiota-responsive systems, and 3D-printed formulations have improved drug stability, targeting accuracy, and controlled release. However, variability in gastrointestinal conditions and formulation complexities still pose challenges for clinical translation.

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