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Review Article

Colonic drug delivery systems: Exploring the potential of biodegradable polymers for systemic effects

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ABSTRACT

Targeted drug delivery to the colon is highly desirable for the local treatment of various bowel diseases, including ulcerative colitis, Crohn's disease, amebiasis, and colonic cancer, as well as for the systemic delivery of protein and peptide drugs. The colon-specific drug delivery system (CDDS) must protect the drug during transit through the stomach and small intestine, ensuring that release and absorption occur only in the colon. The colon is an ideal site for drug absorption due to its lower enzymatic activity compared to the small intestine, which helps protect peptide drugs from degradation, and its long residence time, which enhances systemic bioavailability.

While the oral route is the most convenient for CDDS, rectal administration is also used, though it can be uncomfortable and less effective for targeting the proximal colon. Intrarectal drug preparations, such as solutions, foams, and suppositories, are used for both systemic dosing and local treatment of the large intestine. The efficacy of these drugs often depends on their formulation, spreading capacity, and retention time.

The colon's high water absorption capacity and viscous contents can limit drug availability to the absorptive membrane. However, the presence of a diverse bacterial flora in the colon can be leveraged for drug metabolism and targeted delivery of peptide-based macromolecules, such as insulin. Understanding the anatomy and physiology of the gastrointestinal tract (GIT), including variations in pH, is crucial for designing effective CDDS. This knowledge helps optimize drug release and absorption, ultimately improving therapeutic outcomes for patients.

1. Introduction

Targeted drug delivery to the colon is highly desirable for treating various bowel diseases such as ulcerative colitis, Crohn's disease, amebiasis, colonic cancer, and other colonic pathologies. It is also beneficial for the systemic delivery of protein and peptide drugs.[1,2] A colon-specific drug delivery system (CDDS) must protect the drug during its journey to the colon, ensuring that release and absorption do not occur in the stomach or small intestine. The drug should only be released and absorbed once it reaches the colon.[3]

The colon is an ideal site for absorbing peptides and protein drugs for several reasons: it has fewer and less intense digestive enzymes, the proteolytic activity of the colon mucosa is much lower than in the small intestine, and the colon has a long residence time of up to five days, making it highly responsive to absorption enhancers.[4] This helps protect peptide drugs from hydrolysis and enzymatic degradation in the duodenum and jejunum, leading to greater systemic bioavailability.[5]

While the oral route is the most convenient and preferred for CDDS, other routes can also be used. Rectal administration offers a direct route to the colon but can be

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uncomfortable for patients and may not effectively target the proximal colon.[6] Intrarectal drug preparations, such as solutions, foams, and suppositories, are used for both systemic dosing and local treatment of the large intestine. The efficacy of these drugs depends on formulation factors, the extent of retrograde spreading, and retention time. Foams and suppositories are mainly retained in the rectum and sigmoid colon, while enema solutions have a greater spreading capacity.[7]

The colon's high water absorption capacity and viscous contents can limit drug availability to the absorptive membrane. However, the colon's diverse bacterial flora, with over 400 distinct species, can be leveraged for drug metabolism and targeted delivery of peptide-based macromolecules, such as insulin. These metabolic processes, including azoreduction and enzymatic cleavage,[8] can be applied to colon-targeted drug delivery, enhancing the effectiveness of treatments.

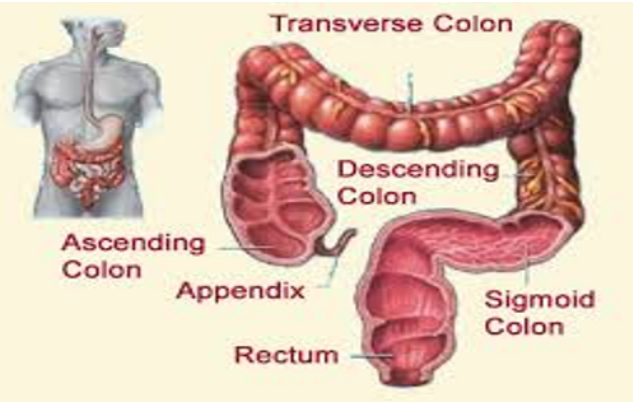

Figure 1: Human colon

2. Factors to Consider in the Design of Colon-Specific Drug Delivery Systems Anatomy and Physiology of the Gastrointestinal Tract (GIT)

The gastrointestinal tract (GIT), also known as the alimentary canal, is a muscular digestive tube that winds through the body. It serves as a selective barrier between the external environment and systemic circulation. The GIT's primary functions include digesting dietary food, absorbing nutrients, electrolytes, and fluids, and preventing the absorption of potentially harmful substances.[9]

The small intestine is the longest part of the GIT, where most enzymatic digestion and virtually all nutrient absorption occurs. The large intestine, the last major subdivision of the GIT, includes the cecum, colon, rectum, and anal canal. Understanding the anatomy and physiology of the GIT is crucial for designing effective colon-specific drug delivery systems.[10]

2.1. pH in the colon

Table 1: The pH of the GIT is subjected to both inter and intra subject variation.[11]

Location	pH
Oral cavity	6.2-7.4
Oesophagus	5.0-6.0
Stomach	Fasted condition: 1.5-2.0 Fed condition:3.0-5.0
Small intestine	Right colon:6.4 Mild colon and left colon :6.0-7.6

2.2. Gastrointestinal transit

The gastric emptying of dosage forms is highly variable and primarily depends on whether the subject has eaten, as well as the properties of the dosage form, such as its size and density. The arrival of an oral dosage form at the colon is determined by the rate of gastric emptying and the transit time through the small intestine.[12]

Table 2: Transit time of dosage forms in GIT

Organ	Transit time(h)
Stomach	<1(fasting) and, >2(fed)
Small intestine	3-4
Large intestine	20-30

2.3. Colon bacteria

Nearly 400 distinct bacterial species have been identified throughout the gastrointestinal tract (GIT), with 20% to 30% belonging to the genus Bacteroides. The upper region of the GIT contains a relatively small number of bacteria, predominantly gram-positive facultative bacteria. The most significant anaerobic bacteria include Bacteroides, Bifidobacterium, Eubacterium, Peptococcus, Ruminococcus, Propionibacterium, and Clostridium.

The bacterial count (colony-forming units per milliliter, CFU/mL) in different regions of the GIT is as follows:

1. Stomach: 10^2-10^3 CFU/ml
2. Small intestine: 10^3-10^4 CFU/ml
3. Colon: 10^{10}-10^{12} CFU/ml[13]

3. Advantages of CDDS over Conventional Drug Delivery

Chronic colitis conditions, such as ulcerative colitis and Crohn's disease, are typically treated with glucocorticoids and other anti-inflammatory agents.[13] However, administering glucocorticoids like dexamethasone and methylprednisolone orally or intravenously can lead

Table 3: Colon targeting diseases, drugs and sites [14]

Target sites	Disease conditions	Drug and active agents
Topical action	Inflammatory Bowel Diseases, Irritable bowel disease and Crohn's disease.	Hydrocortisone, Budenoside, Prednisolone, Sulfaselazine, Olsalazine, Mesalazine, Balsalazide.
Local action	Chronic pancreatitis. Pancreatactomy and cystic fibrosis, Colorectal cancer	
Systemic action	To prevent gastric irritation to prevent first pass metabolism of orally ingested drugs Oral delivery of peptides Oral delivery of vaccines	Digestive enzyme supplements 5-Flourouracil. NSAIDS Steroids Insulin Typhoid

to systemic side effects, including adenosuppression, immunosuppression, Cushingoid symptoms, and bone resorption. [12] Selective delivery of drugs to the colon can reduce the required dose and minimize these systemic side effects. [15]

3.1. Criteria for selection of drugs for CDDS

The best candidates for CDDS are drugs that show poor absorption from the stomach or intestine, including peptides. Drugs used to treat inflammatory bowel disease (IBD), ulcerative colitis, diarrhoea, and colon cancer are ideal for local colon delivery. [16] The criteria for selecting drugs for CDDS are summarized in Table 4. [17–20]

3.2. Drug carrier selection for CDDS

The choice of drug carrier significantly influences the effectiveness of CDDS. The selection depends on the physicochemical nature of the drug and the disease being treated. Factors such as the chemical nature, stability, partition coefficient of the drug, and the type of absorption enhancer used are crucial in carrier selection. Additionally, the functional groups of the drug molecule play a role. For instance, aniline or nitro groups on a drug can be linked to another benzene group through an azo bond. Carriers containing additives like polymers, which may be used as matrices, hydrogels, or coating agents, can influence the release properties and efficacy of the drug delivery system. [16]

4. Primary Approaches for Colon-Specific Drug Delivery Systems (CDDS) pH-Sensitive Polymer Coated Drug Delivery to the Colon

In the stomach, the pH ranges between 1 and 2 during fasting but increases after eating. [21] The pH is about 6.5 in the proximal small intestine and about 7.5 in the distal small intestine. [22] From the ileum to the colon, the pH declines significantly, being around 6.4 in the cecum. However, pH values as low as 5.7 have been measured in the ascending colon in healthy volunteers. The pH in the transverse colon is 6.6 and 7.0 in the descending colon. [23] The use of pH-dependent polymers in colon-specific drug delivery is based on these pH differences. These polymers are insoluble at low pH levels but become increasingly soluble as the pH rises. [23] Although pH-dependent polymers can protect a formulation in the stomach and proximal small intestine, they may start to dissolve in the lower small intestine, leading to poor site-specificity. [24] Additionally, the decline in pH from the end of the small intestine to the colon can cause issues, such as lengthy lag times at the ileo-cecal junction or rapid transit through the ascending colon, resulting in poor site-specificity of enteric-coated single-unit formulations. [23]

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

Time-controlled release systems (TCRS), such as sustained or delayed release dosage forms, are also promising for drug delivery. However, due to the potentially large variations in gastric emptying time of dosage forms in humans, the colon arrival time of these dosage forms cannot be accurately predicted, resulting in poor colonic availability. [25] These dosage forms may still be applicable as colon-targeting dosage forms by prolonging the lag time to about 5 to 6 hours.

6. Disadvantages of This System

1. **Variable Gastric Emptying Time**: Gastric emptying time can vary significantly between individuals and is influenced by the type and amount of food intake.
2. **Gastrointestinal Movement**: Gastrointestinal movements, especially peristalsis or stomach contractions, can alter the transit of the drug through the GIT. [26]
3. **Accelerated Transit in Certain Conditions**: Patients with inflammatory bowel disease (IBD), carcinoid syndrome, diarrhea, or ulcerative colitis may experience accelerated transit through different regions of the colon. [27–29]

Table 4: Criteria for selection of drugs for CDDS

Criteria	Pharmacological class	Non-peptide drugs	Peptide drugs
Drugs used for local effects in colon against GIT diseases	Anti-inflammatory drugs	Oxyprenolo, Metoprolol, Nifedipine	Amylin, Antisense oligonucleotide
Drugs poorly absorbed from upper GIT	Antihypertensive and antianginal drugs	Ibuprofen, Isosorbide, Theophylline	Cyclosporine, Desmopressin
Drugs for colon cancer	Antineoplastic drugs	Pseudoephedrine	Epoetin, Glucagon
Drugs that degrade in stomach and small intestine	Peptides and proteins	Bromophenaramine, 5-Flourouraci, Doxorubicin	Gonadoreline, Insulin, Interferons
Drugs that undergo extensive first pass metabolism	Nitroglycerin and corticosteroids	Bleomycin, Nicotine	Protirelin, sermorelin, Saloatonin
Drugs for targeting	Antiarthritic and antiasthamatic drugs	Prednisolone, hydrocortisone, 5-Amino-salicylic acid	Somatropin,Urotoilitin

7. Novel Colon Targeted Delivery System (CODESTM)

CODESTM is an innovative CDDS technology designed to overcome the limitations of pH or time-dependent systems.[30,31] It combines pH-dependent and microbially triggered mechanisms. The system uses lactulose as a trigger for site-specific drug release in the colon. It consists of a traditional tablet core containing lactulose, coated with an acid-soluble material (Eudragit E), and then with an enteric material (Eudragit L). The enteric coating protects the tablet in the stomach and dissolves after gastric emptying. The acid-soluble coating then protects the preparation as it passes through the alkaline pH of the small intestine. Once in the colon, bacteria enzymatically degrade the lactulose into organic acids, lowering the pH around the system and dissolving the acid-soluble coating to release the drug.[32]

8. Osmotic Controlled Drug Delivery (ORDS-CT)

The OROS-CT system, developed by Alza Corporation, targets drugs locally to the colon for disease treatment or systemic absorption.[33] The system can be a single osmotic unit or include 5-6 push-pull units, each 4 mm in diameter, encapsulated within a hard gelatin capsule (Figure 2).[34]Each bilayer push-pull unit contains an osmotic push layer and a drug layer, both surrounded by a semipermeable membrane with an orifice next to the drug layer. After swallowing, the gelatin capsule dissolves, and the enteric coating prevents water absorption in the stomach. In the small intestine, the coating dissolves in the higher pH environment, allowing water to enter the unit, causing the osmotic push compartment to swell and create a flowable gel in the drug compartment. The swelling forces the drug gel out of the orifice at a controlled rate. For treating ulcerative colitis, each push-pull unit is designed with a 3-4-hour post-gastric delay to prevent drug delivery in the small intestine. Drug release begins in the colon, maintaining a constant release rate for up to 24 hours or delivering the drug over a shorter period.

Recent advancements in phase-transited systems show promise for targeting drugs to the colon.[35–38] Various in vitro and in vivo evaluation techniques have been developed to test the performance and stability of CDDS.

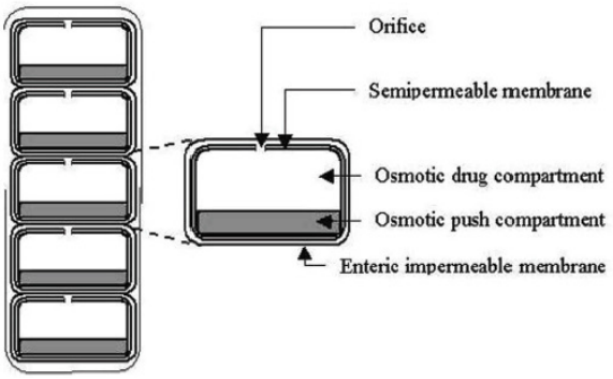

Figure 2: Cross-Section of the OROS-CT colon targeted drug delivery system

9. *In Vitro* Models Used for CDDS

9.1. In Vitro dissolution test

The dissolution of controlled-release formulations for colon-specific drug delivery is complex, and the methods described in the USP cannot fully replicate in vivo conditions, such as pH, bacterial environment, and mixing forces.[32] Dissolution tests for CDDS can be conducted using the conventional basket method. Parallel dissolution studies in different buffers can characterize the behavior of formulations at various pH levels. For example, dissolution tests of colon-specific formulations in media simulating the pH conditions and times likely encountered in the gastrointestinal tract have been studied.[39] The chosen media include pH 1.2 to simulate gastric fluid, pH 6.8 for the jejunal region of the small intestine, and pH 7.2 for the ileum segment. Enteric-coated capsules for CDDS have been investigated in gradient dissolution studies in three

buffers, tested for two hours at pH 1.2, one hour at pH 6.8, and finally at pH 7.4,[40]

9.2. In vitro enzymatic tests

Carrier drug systems are incubated in a fermenter containing a suitable medium for bacteria (e.g., Streptococcus faecium and Bacteroides ovatus). The amount of drug released at different time intervals is determined. Drug release studies are conducted in buffer media containing enzymes (e.g., pectinase, dextranase) or cecal contents from rats, guinea pigs, or rabbits. The amount of drug released over time is directly proportional to the rate of degradation of the polymer carrier.

9.3. In vivo evaluation

Various animals, such as dogs, guinea pigs, rats, and pigs, are used to evaluate drug delivery to the colon because their anatomical and physiological conditions, as well as their microflora, resemble those of the human GIT. When choosing a model for testing CDDS, it is important to consider models relevant to colonic diseases. Guinea pigs are commonly used for experimental IBD models. The distribution of azoreductase and glucuronidase activity in the GIT of rats and rabbits is comparable to that in humans.[41–43] For rapid evaluation of CDDS, a novel model has been proposed where the human fetal bowel is transplanted into a subcutaneous tunnel on the back of thymic nude mice. This bowel vascularizes within four weeks, matures, and develops a mucosal immune system from the host.

10. Conclusion

The colonic region of the GIT has become an increasingly important site for drug delivery and absorption. CDDS offers significant therapeutic benefits for both local and systemic treatments. Colon specificity is more likely to be achieved with systems that utilize natural materials degraded by colonic bacterial enzymes. Given the sophistication of colon-specific drug delivery systems and the challenges in establishing possible in vitro/in vivo correlations with current dissolution methods, pharmaceutical scientists face the task of developing and validating a dissolution method that incorporates the physiological features of the colon and can be routinely used in an industrial setting for evaluating CDDS.

11. Source of Funding

None.

12. Conflict of Interest

None.

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