Recent Advancement in Colon Targeted Drug Delivery System

ChetanaYGautam, TejashwiniR Bagde, Bhagyashree H Raut, Roshani D Agrawal, Dr.P.Nimbekar, Dr.D.K.Sanghi
Shri Laxmanrao Mankar Institute of Pharmacy Amgaon-441902, Maharashtra, India

Abstract: **Colon-specific drug delivery has become increasingly important, not only for treating diseases that affect the colon, but also for delivering sensitive medicines like proteins and peptides. To achieve this, various strategies have been developed, including pro-drug formulation, pH sensitivity, time-dependent release, microbial degradation, and osmotic pressure. These approaches enable the creation of different dosage forms, such as tablets, capsules, and microspheres, that target the colon specifically. This article delves into the anatomy of the colon, exploring its structure and function. It also examines the factors that influence the effectiveness of colon-targeting drug delivery systems. Furthermore, the article discusses the benefits of colon-specific drug delivery, including its potential to improve treatment outcomes for colon-related diseases. Finally, it highlights the challenges and limitations associated with this approach, providing a comprehensive understanding of colon-targeting drug delivery systems.**

1.INTRODUCTION

The Novel Drug Delivery System (NDDS) is a cutting-edge approach that focuses on developing innovative formulations, technologies, and systems to transport pharmaceutical compounds within the body. This approach prioritizes achieving the desired therapeutic effects while ensuring safety. Unlike conventional dosage forms, NDDS offers superior benefits, including optimal dosing, efficient use of expensive medications, and enhanced patient comfort.

A Novel Drug Delivery System should fulfill two primary requirements. Firstly, it should deliver a precise amount of the drug at a rate dictated by the body's needs over the treatment period. Secondly, it should deliver the active drug moiety directly to the targeted site of action.

1.1 Advantages of novel drug delivery system

By achieving these requirements, NDDS offers several advantages, including optimal dosing, efficient use of expensive medications, cost-effectiveness, better therapy, and improved patient comfort. Additionally, NDDS minimizes adverse and toxic effects.

There are three basic modes of Novel Drug Delivery Systems:

1 .Targeted Drug Delivery
2. Controlled Drug Deliver
3. Modulated Drug Delivery.[1]

Targeted Drug Delivery is a "smart" system that delivers drugs directly to the desired site, increasing therapeutic efficacy while reducing toxicity.[2]

1.2 This approach can be classified into two categories:

1. Passive Targeting
2. Active Targeting.

1.Passive Targeting refers to the accumulation of drugs or drug-carrier systems at a specific site due to physicochemical or pharmacological factors.

2. Active Targeting involves a specific ligand-receptor interaction for intracellular localization, occurring after blood circulation and extravasation.[3]

1.3 Types of Drug Targeting:

1. First-order targeting: Delivering medicine to a specific organ or tissue.
2. Second-order targeting: Targeting specific cells within an organ or tissue.
3. Third-order targeting: Delivering medicine to specific parts within cells, like lysosomes.[4]

1.4 Characteristics of Targeted Drug Delivery:

1. Inert: The delivery system shouldn't interfere with the body's chemistry.
2. Non-toxic: The system shouldn't trigger an immune response.
3. Stable: The system should remain stable in the body and in lab tests.
4. Effective: The system should release the right amount of medicine.

5. Minimal leakage: The system should prevent medicine from leaking during delivery.
6. Biodegradable: The delivery system should break down naturally in the body.[5]

1.5 Advantages of Targeted Drug Delivery:
1. Simplified administration: Easier to give patients their medicine.
2. Better response: Smaller doses can achieve the desired effect.
3. Avoids first-pass effect: Medicine isn't broken down by the liver before reaching its target.
4. Improved absorption: Medicine is absorbed more effectively at the target site.

1.6 Disadvantages of Targeted Drug Delivery:
1. Frequent dosing: Medicine may be eliminated quickly, requiring frequent doses.
2. Immune response: The delivery system can trigger an immune response.
3. Limited targeting: The delivery system may not stay at the target site long enough.
4. Drug diffusion: Released medicine may spread to non-target areas[6]

1.7 Targeted Drug Delivery Strategies:
1. Passive Targeting: This approach uses the body's natural circulation system to deliver medicine to the target area.
2. Inverse Targeting: This strategy tries to avoid the body's natural defense system (RES) from removing the medicine carrier, allowing it to reach the target area.
3. Active Targeting: In this approach, the medicine carrier is modified to specifically target the desired area, increasing its effectiveness.
4. Dual Targeting: This strategy uses a carrier molecule that not only delivers the medicine but also has its own therapeutic effect, increasing the overall effectiveness.
5. Double Targeting: This approach combines two targeting strategies, temporal (time-based) and spatial (location-based), to deliver the medicine to the exact target area at the right time .[7]

1.8 Colon targeted drug delivery system
Colon-targeted drug delivery systems are designed to deliver medications to the lower gastrointestinal (GI) tract, primarily the large intestine. This site-specific delivery is beneficial for managing colonic diseases, such as inflammatory bowel disease, colon cancer, and irritable bowel syndrome. [8]The colon provides a favorable environment for drug delivery, with lower digestive enzymatic activities and a near-neutral pH. Additionally, the colon's longer transit time allows for increased drug absorption.[9]
Colon-targeting drug delivery systems offer several advantages, including reduced drug loss, higher concentrations of medication at the target site, and minimized systemic side effects.[10].To achieve successful colon-targeted drug delivery, the system must protect the medication during its journey to the colon, preventing premature release or degradation. [11] By optimizing drug concentration at the target site while limiting systemic exposure, colonic drug delivery can improve the treatment of local diseases. Recent studies have led to a greater understanding of the colonic and rectal environment, revealing new local targets, such as the microbiome, enteric immune system, and lymphatic system.[12] However, the colon's high water absorption capacity and viscous contents can hinder drug availability. Despite these challenges, colon-targeted drug delivery systems offer a promising approach for managing colonic diseases and optimizing medication efficacy.[13]
The colon plays a crucial role in maintaining the body's overall health, with functions including the creation of a suitable environment for colonic microorganisms, storage of fecal contents, expulsion of contents, and absorption of potassium and water..[14]

1.9 Advantages of Colon-Targeted Drug Delivery
1. The colon offers an optimal environment for delivering medications to treat local diseases, such as inflammatory bowel disease and colon cancer.
2. Localized treatment enables the use of smaller drug quantities, reducing the overall cost of therapy.
3. By delivering drugs directly to the colon, the frequency of dosing can be minimized, leading to improved patient compliance and reduced healthcare costs.
4. Targeted drug delivery to the colon may also decrease the incidence of adverse effects and drug interactions, enhancing overall patient safety.
5. The colon provides a unique opportunity for enhancing the bioavailability of poorly absorbed drugs, potentially leading to improved therapeutic outcomes.
6. Compared to other regions of the gastrointestinal tract, the colon exhibits lower levels of digestive enzymes, reducing the likelihood of drug degradation.

7. Colon-targeted drug delivery can also mitigate gastric irritation associated with certain medications, such as nonsteroidal anti-inflammatory drugs (NSAIDs).
8. By bypassing first-pass metabolism, colon-targeted drug delivery can increase the bioavailability of certain drugs, leading to improved efficacy.[15]

1.10 Disadvantages of Colon-Targeted Drug Delivery Systems

1. The prolonged residence time of drugs in the colon can lead to elevated plasma levels, potentially resulting in increased bioavailability but also higher risks of adverse effects.
2. Single-unit colon-targeted drug delivery systems are susceptible to unintentional disintegration due to manufacturing defects or unusual gastric physiology.
3. Developing colon-specific drugs poses significant challenges due to the presence of multiple biological barriers.
4. The colonic mucosa exhibits lower affinity for cytochrome P450 enzymes, which can impact the metabolism and efficacy of certain drugs.[16]

2. ANATOMY AND PHYSIOLOGY OF THE COLON

The gastrointestinal (GI) tract is divided into three main sections: the stomach, small intestine, and large intestine. The large intestine, extending from the ileocecal junction to the anus, is further subdivided into three primary parts: the colon, rectum, and anal canal. The colon itself is approximately 5 feet (150 cm) long and is divided into five major segments.

The colon is supported by a peritoneal fold called the mesentery, which attaches to the ascending and descending colon. The right colon comprises the cecum, ascending colon, hepatic flexure, and the right half of the transverse colon. In contrast, the left colon includes the left half of the transverse colon, descending colon, splenic flexure, and sigmoid colon. The rectum is the final anatomic segment before the anus.[17]

2.1 Colonic Microflora

The colon's slow movement of material allows for the growth of a large microbial population. Over 400 distinct bacterial species have been identified, with most being anaerobic in nature. A small number of fungi are also present. The rate of microbial growth is highest in the proximal areas due to the high concentration of energy sources.

The primary source of nutrition for colonic microflora is carbohydrates arriving in intestinal chyme. These carbohydrates are degraded by polysaccharides and glycosidase enzymes, producing short-chain fatty acids as the ultimate products of fermentation. Carbohydrate fermentation predominates in the proximal colon, resulting in a relatively low pH. In contrast, the distal colon exhibits minimal carbohydrate fermentation, leading to a higher pH.[18]

3. BENEFITS OF COLON-TARGETED DRUG DELIVERY SYSTEMS

1. Reduced adverse effects in the treatment of colonic diseases.
2. Creation of a more favorable environment for peptides and proteins compared to the upper GI tract.
3. Minimized extensive first-pass metabolism of steroids.
4. Prevention of gastric irritation caused by oral administration of nonsteroidal anti-inflammatory drugs (NSAIDs).
5. Delayed release of drugs to treat conditions such as angina, asthma, and rheumatoid arthritis.[19]

4. NEED FOR COLON-TARGETING DRUG DELIVERY SYSTEMS

Targeted delivery to the colon ensures site-specificity, enabling the targeting of protein and peptide drugs for both local and systemic action. Since catalytic degradation and hydrolysis are less pronounced in the colon, drugs that are polar in nature or prone to enzymatic degradation can be effectively delivered to the colon.[20]

5. LIMITATIONS OF COLON-TARGETING DRUG DELIVERY SYSTEMS

1. Multiple manufacturing steps.
2. Potential impact of resident microflora on colonic performance via metabolic degradation of the drug.
3. Incomplete release of the drug.
4. Potential low bioavailability due to non-specific binding of drugs to dietary residues, intestinal secretions, mucus, or fecal matter.

5. Requirement for the drug to be in solution form before absorption, which can be a rate-limiting step for poorly soluble drugs.
6. Lack of an appropriate dissolution testing method to evaluate the dosage form in vitro[21]

6. FACTORS AFFECTING COLON ABSORPTION

1. The physical properties of drugs, such as pKa and degree of ionization, play a crucial role in determining their absorption in the colon.
2. The length of time a drug spends in the colon, influenced by gastrointestinal tract (GIT) motility, affects its absorption.
3. The colon's bacterial enzymes can break down drugs, impacting their absorption and efficacy.
4. The physiological actions of drugs in the colon, such as their effects on gut motility and blood flow, can influence their absorption.
5. Drugs can bind to mucus in the colon, affecting their absorption and distribution.
6. Various disease states, such as inflammatory bowel disease, can alter the colon's physiology and impact drug absorption.[22]

7. APPROACHES TO COLON-TARGETED DRUG DELIVERY SYSTEMS

1)Primary Approaches
a). pH-Sensitive Polymer Coated Drug Delivery System
b) Delayed (Time-Controlled Release) Drug Delivery System
c) Microbial Triggered System
d) .Pro-Drug Approach
e) Polysaccharide-Based Delivery System
2)Newly Developed Approaches
a). Pressure-Controlled Drug Delivery System
b) Pulsatile Colon-Targeted Drug Delivery
i) Pulsin cap system
ii) Port system
c) CODES Technology
d) Osmotic Controlled Drug Delivery (OROS-CT)
e) Multiparticulate System-Based Drug Delivery[23]

7.1)Primary Approaches for CDDS

This approach is a prominent method utilized in the development of colon-targeted formulations. It adopts a pharmaceutical technology perspective, integrating the physicochemical properties of drugs with those of carriers or polymers, while taking into account the physiological conditions of the gastrointestinal tract (GIT). This integrated approach enables effective drug delivery to the colon. However, the commercial application of this strategy is limited due to challenges associated with production costs and location specificity.

7.1 a)pH-Dependent Drug Delivery Systems

The utilization of pH-sensitive polymers is a primary strategy for achieving colon-targeted drug delivery systems, leveraging the pH variations along the gastrointestinal tract. This approach is one of the simplest formulation strategies for colon-targeted drug delivery systems, offering advantages such as lower costs and easier manufacturing. Coated formulations can be either single-layered or multi-layered, enhancing their versatility.[24]
The pH in the stomach ranges from 1 to 2 during fasting, but increases after eating. The pH in the proximal small intestine is approximately 6.5, and approximately 7.5 in the distal small intestine. From the ileum to the colon, the pH declines significantly, reaching approximately 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.[25]
The use of pH-dependent polymers is based on these differences in pH levels. Polymers described as pH-dependent in colon-specific drug delivery are insoluble at low pH levels but become increasingly soluble as the pH rises. Although pH-dependent polymers can protect formulations in the stomach and proximal small intestine, they may start to dissolve in the lower small intestine, resulting in poor site specificity.[26]

7.1 b) Delayed (Time-Controlled Release System) Drug Delivery System

In these systems, the release of the drug is determined by the transit time of the formulation in the gastrointestinal tract (GIT), making it challenging to develop a formulation that achieves precise drug release in the colon. Time-release systems are designed to accommodate individual variations in gastric emptying time, stomach pH, and the presence of anaerobic bacteria in the colon, ensuring that the site of delivery remains unaffected .On average, an orally administered dosage form spends approximately 2 hours in the stomach and 3

hours traveling through the small intestine to the beginning of the colon ,[27]

7.1 c) Microbial Triggered System

Among the various approaches used for colon targeting, microbially controlled delivery systems are particularly appealing. This approach relies on the unique enzymatic capabilities of colonic microflora, enabling more specific targeting that is independent of pH variations along the gastrointestinal tract .These systems exploit the specific enzymatic activity of the microflora present in the colon. The colonic bacteria are predominantly anaerobic and secrete enzymes that can metabolize substrates such as carbohydrates and proteins that escape digestion in the upper gastrointestinal tract[28]

7.1 d)Prodrug Approaches

A prodrug is an inactive compound that is converted into an active drug through enzymatic transformation in the body. This approach involves designing prodrugs that resist absorption and breakdown in the upper digestive tract, instead undergoing enzymatic activation in the colon, where the active drug is released.

To achieve targeted release in the colon, researchers have developed various prodrug conjugates. These include:

- Biodegradable polymers linked by azo bonds
- Polymeric prodrugs connected through azo links
- Acrylic prodrugs

These conjugates have been successfully used to deliver 5-aminosalicylic acid (5-ASA) to the colon, where it is released to exert its therapeutic effect.[29]

7.1 e)Polysaccharide-Based Drug Delivery Systems

These polymers serve as a protective barrier, shielding the drug from the harsh environments of the stomach and small intestine. They are designed to deliver the drug to the colon, where they undergo degradation. This breakdown occurs through one of three mechanisms:

1. Microbial assimilation: Microorganisms in the colon break down the polymer.
2. Enzymatic degradation: Enzymes in the colon degrade the polymer.
3. Polymer backbone breakdown: The polymer's molecular structure is disrupted, leading to a reduction in molecular weight and loss of mechanical strength.

As a result, the polymer can no longer retain the drug, allowing it to be released in the colon.[30]

7.2) Newly Developed Approaches for Colon-Targeted Drug Delivery Systems (CTDDS):

7.2 a. Pressure-Controlled Drug Delivery System:

Researchers have explored the use of gastrointestinal (GI) pressure to trigger drug release in the distal gut. The pressure, which is generated by the muscular contractions of the gut wall, varies in intensity and duration throughout the digestive tract. The colon experiences higher pressure due to the processes involved in stool formation.

The large intestine moves contents from one segment to another through powerful muscle contractions known as mass peristalsis. For example, contents are propelled from the ascending colon to the transverse colon through this process.[31]

7.2 b)Pulsatile Colon-Targeted Drug Delivery

i. Pulsincap System:

The Pulsincap system is a capsule-based formulation where drug release is controlled by a plug within the capsule. The drug content is enclosed within swellable hydrogels. When these hydrogels come into contact with a dissolution fluid, they swell, and after a predetermined lag time, the plug is pushed out of the capsule, triggering the release of the drug.[32]

ii)PORT System:

In this system, the formulation is encapsulated in a capsule, where a plug controls the release of the drug. The drug content is sealed within swellable hydrogels. Upon contact with the dissolution fluid, the hydrogels swell, and after a predetermined lag time, the plug is expelled, releasing the medication.

Composition of Hydrogel Plugs:

The hydrogel plugs comprise polymers, specifically hydroxypropyl methylcellulose.[33]

7.2 c) CODESTM Technology

This system combines pH-dependent and microbially dependent drug delivery to target the colonic region, overcoming the limitations associated with pH-sensitive formulations and time-dependent system .The system consists of a tablet core loaded with the active ingredient lactulose, which is coated with an acid-soluble layer. This layer is then coated with an enteric polymer, providing a dual-layered coating.[34]

7.2 d) Osmotic Controlled Delivery

Although the concept of osmotic-controlled drug delivery has been established for several years, its application in designing colon-specific oral dosage forms has gained significant attention only over the past 10-15 years

A notable example of an osmotic pressure-regulated system is the OROS-CT. This system consists of a hard gelatin capsule that dissolves in the small intestine's pH environment, allowing water to enter the unit. As the unit swells, the drug is forced out. Each capsule can contain up to 5-6 units, each surrounded by a drug-impermeable enteric coating that prevents water entry in the stomach's acidic environment.[35]

7.2 e)Multiparticulate Approach

This approach has been developed to mitigate the risks associated with variations in drug release profiles and formulation behavior. These variations can arise from unit-to-unit differences, changes in gastrointestinal pH, and enzyme populations. The multiparticulate approach offers improved pharmacological effects in the colon, prompting significant interest in the development of multiparticulate dosage forms over single-unit system

Multiparticulate drug delivery systems are oral dosage forms comprising multiple small, discrete units. Each unit possesses the desired characteristics, with the drug substance divided into numerous subunits. Typically, these subunits consist of thousands of spherical particles with diameters ranging from 0.05 to 2.00 mm. Essentially, multiparticulate dosage forms are pharmaceutical formulations where the active substance is distributed across multiple small, independent subunits.[36]

8. Application of colon target drug delivery systems

1.Colon targeted drug delivery systems useful for local colonic diseases because drugs directly bind to the colon (site specific) such as ulcerative colitis, Crohn's diseases, and amoebiasis.

2.Colon targeting drug delivery systems useful for poorly absorbed molecules such as protein, peptides and amino acids.

3.This system is very useful for those drugs which degrade in the presence of the enzyme in GIT.

4. Reduce Dosage of the drug.

5.CTDDS mainly Used for the treatment of the local disease.

6. In this system the frequency of the dosage is less.

7. Due to longer resistance time of the drug in the colon, this system is very useful for poorly absorbed drug because in this system increases bioavailability.

8..Drugs which are used by CTDDS prevent the degradation of the drugs in acidic pH of the stomach.

9. It is useful for nicotine addiction.

10. This system helpful for those drugs that caused gastric irritation decrease the irritation of those drugs (NSAIDS). [37]

CONCLUSION AND FUTURE PROSPECTIVE

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

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

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