The Frontier of Targeted Therapies: Breakthroughs in colon - Specific Drug Delivery for Precision Health

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Abstract: The purpose of this review is to investigates the progression and effectiveness of colon-targeted drug delivery systems, offering a comprehensive understanding of the colon's anatomy and physiological environment. All figures designed using by Bio-render website. The Colon is a site where both local and systemic delivery of drugs can take place. To attain the successful Colon targeting drug delivery system, a drug must be protected from degradation in the upper portion of the GIT and then to be ensured abrupt or Controlled release in the proximal colon. The article outlines several approaches. pH controlled drug release. Prodrug approach. Time controlled drug delivery. Osmotically controlled drug delivery. Microbially triggered controlled drug delivery. Enzyme controlled drug delivery. Novel drug delivery system. The precision medicine play an important role in the cancer therapy. Although precision medicine have resulted in some clinical successes, the use of many potential therapeutics has been hindered by pharmacological issues, including toxicities and drug resistance. By using various approaches and precision medicines may be the best way to cure colon diseases using an optimized colon drug delivery system.

Keywords: pH-controlled drug release. Prodrug approach. Time controlled drug delivery. Osmotically controlled drug delivery. Microbially triggered controlled drug delivery. Enzyme controlled drug delivery. Novel drug delivery system.
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Introduction

Colonic drug delivery is becoming popular because of its many benefits. To make effective colon-based drug delivery, we need to understand the colon's environment where disease happen (1). The GI tract changes a lot in movement, pH, and enzyme activity from the stomach to the intestines. Targeting drugs to the colon can treat local diseases better and reduce side effects (2). Targeting drugs to the colon is important to treat colon diseases directly, since regular methods might have side effects and be less effective. It was mostly used for diseases like IBD and colorectal cancer (3). This method optimises drug concentration at the target site and limits exposure to the rest of the of the body (4). The Colon is considered a good place in the body for absorbing peptide and protein drugs. This is because, the colon has fewer and less intense digestive enzymes than other parts of the digestive system. The proteolytic (protein-breaking) activity in the colon's lining is much lower compared to the small intestine. With these characteristics, colon-targeted drug delivery systems (CDDS) can protect peptide drugs from breaking down by enzymes in the duodenum and jejunum (parts of the small intestine). These systems then release the drug in the ileum or colon, allowing it to enter the body more effectively and reach a higher level in the bloodstream (5). The amount of drug that reaches the colon depends on a few key factors, Formulation factors - How the drug is designed and prepared, Extent of retrograde spreading –How much the drug moves backward in the digestive tract, Retention time – How long the drug stays in the colon (6). Coating drugs with pH-sensitive polymers is an effective and straightforward method for targeting drug delivery to the colon. These coatings are designed to resist the acidic environment of the stomach but dissolve at the higher pH levels in the colon, allowing the drug to be released precisely where it is needed (7).

1.Colon drug delivery system:

Colon drug delivery has achievied increased importance not just for the drugs for the treatment of local disease associated with the colon but also for its potential for the delivery of proteins and therapeutic peptides[8]. To achieve successful colonic

delivery a drug needs to be protected from absorption or the environment of the upper gastrointestinal tract (GIT) and then be abruptly released into the proximal colon which is considered the optimum site for colon targeted delivery of drug and also lead to improve the systemic bioavailability[9]. Colon targeting is naturally of value for the topical treatment of disease of colon such as Crohn's disease, ulcerative colitis, colorectal cancer and amebiasis[10].

2.Advantages of colon specific drug delivery;[11-12]

- Colon is an ideal site for the delivery of agents to cure the local disease of the colon.
- Local treatment frequency. Hence lower cost of expensive drugs.
- Possibly leading to a reduced incidence of side effects and drug interactions.
- The colon is an attractive site where poorly absorbed drug molecules may have an improved bioavailability.
- Reduce gastric irritation caused by many drugs (e.g., NSAIDS).
- By-pass initial first pass metabolism.
- Targeted drug delivery system.
- It has a longer retention time and appears highly responsive to agent that enhance the absorption of poorly absorbed drugs.
- It has less hostile environment, less peptidase activity so peptides, oral vaccine, insulin, growth hormones can be given through this route.

3.Limitation and challenges of colon specific delivery :[13-14]

- The colon is difficult to access due to its location at the distal portion of alimentary canal.
- The reliability and delivery efficiency are also doubtful due to presence of wide range of pH values and different enzymes present in the GI tract which are encountered by the drugs before reaching the target site.
- Colon contents are considerably viscous because of high water absorption capacity of the colon there by decreasing the availability of most drugs to absorptive membrane.
- Dissolution could be problematic for poorly water-soluble drugs because of less free fluid and more viscosity in the colon than in small intestine.
- Drug transport across the mucosa into the systemic circulation is restricted due to lower surface area and relative tightness of tight junction in colon.

4.Colon targeting drug necessity:[15-16]

- For the treatment of various colonic disease like ulcerative colitis, Crohn's disease, colon cancer, irritable bowel syndrome and infections.
- Delivery to colon is also required for drugs that are found to be absorbable in colon like steroids there by increasing efficiency and reducing the required effective dose.
- Diseases sensitive to circadian rhythms such as asthma, angina and arthritis are treated efficiently by colon targeting of drugs.
- Systemic drug delivery to colon results in administration of reduced dose and reduced undesired side effects due to high doses.
- This site is used for delivery of drugs that undergo degradation in gastric acidic environment or irritate gastric mucosa.

5.Anatomy and Physiology of colon :

- The colon is a part of gastrointestinal tract (Figure.1). The colon id a tube-like organ in the abdominal cavity.

Figure 1: Structure of human colon

Histologically the colon can be divided into four layers (figure 2:) mucosa, sub mucosa, muscularis externa and serosa. The serosa is the exterior coat of large intestine and consists of areolar tissue that is covered by a single layer of squamous myoepithelial cells. The muscularis externa composed the major muscular coat of inner circular layer of fibre that surrounds the bowel and an outer longitudinal layer[17]. The sub mucosa is a connective tissue that lies immediately beneath the mucosa. The mucosa is composed by the epithelium, lamina propria and muscularis mucosae. The mucosa has a layer of smooth muscles and detached the submucosa from the lamina propria which supports the epithelium. The blood capillaries and lymphatic vessels supply biofluids to lamina propria[18].

Figure 2: Structure of different colonic layers

The colon is a place in the body where medicines can be delivered both locally (to a specific area) and throughout the body. It is a good site for absorbing certain types of medicines. Like peptide drugs, when taken by mouth. This is because the colon is less harsh and has fewer enzymes that break down proteins. Various drugs can be used to treat diseases in the colon, and they work in different way.

Table. 1: Targeting diseases, drugs and sites for colon:

Sr. No	Target Sites	Disease conditions	Drug and their active ingredients

1.	Topical action	Inflammatory Bowel Disease, Irritable bowel Disease and Crohn's Disease. Chronic pancreatitis	Hydrocortisone, Budenoside, Prednisolone, Sulfaselazine, Olsalazine, Mesalazine
2.	Systemic action	To prevent gastric irritation To prevent first pass metabolism Of orally ingested drugs oral delivery of peptides oral delivery of vaccines	NSAID Steroids Insulin Typhoid
3.	Local action	Pancreatactomy and cystic Fibrosis,Colorectal Cancer	Digestive enzyme supplement 5-Flourouracil

pH in the GI tract:

The release and absorption of orally administered drugs are influenced by the gastrointestinal ph. The pH gradient in the GIT is not in an increasing order. In stomach the pH is 1.5-2 and 2-6 in fasted and fed condition respectively. The acidic pH is responsible for degradation of various pH sensitive drugs.[19] In the small intestine the pH is increases slightly from 6.6-7.5 and decreases to 6.4 in right colon. The pH of mid colon is 6.6 and 7 respectively. So, variation in the GIT pH leads to the successful development of various colon specific drug delivery system.[20]

The average pH peak in the GIT as shown in Table 2

Table.2: Average pH in the GIT.

Portion of GI Tract	pH Range
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	Jejunum:5.0-6.5 Illeum:6.0-7.5
Large intestine	Right colon:6.0-7.5

Colonic transit:[21]

The constant transit time in the small intestine approximately 3-5hrs should be necessary to achieve colon specificity. The bioavailability of drugs released from the dosage forms can be highly influenced by the colonic transit time and this will show considerable variability. The transit times of small dosage form in GI tract as follows:

Colonic microflora :

- The colon, which is part of our large intestine, is home to many tiny living things called microbes, mostly bacteria.
- These microbes help us digest food, protect us from getting sick, and keep us healthy.
- They work together with what we eat and our body to keep everything balanced and running smoothly.
- The **human** digestive system, called the alimentary canal, has lots of bacteria and tiny living things at both ends the mouth and the colon/rectum[22].
- There are many types of bacteria, both that need oxygen (aerobic) and that don't (anaerobic), throughout the digestive system.
- The number of bacteria gets really high in a part called the ileocecal sphincter.
- The number of bacteria gets really high in a part called the ileocecal Sphincter.
- In the colon, there are many bacteria, especially types like Bifidobacterium, Eubacterium, and Pepto coccus[23].
- The colon also has other bacteria, like Pepto streptococcus, Ruminococcin, Propionibacterium, Veillonella, and Clostridium.
- Some important ones are Escherichia coli and Lactobacillus.
- These bacteria release enzymes and other substance that can help deliver drugs directly to the colon.
- The metabolic reactions carried out by the enzymes and secretory products released from the microflora can be used to deliver drugs selectively to colon.
- The concentration of bacteria in the human colon is 10^{11}–10^{12}CFU/ml (colony forming unit/ml)[24].

COLONIC ABSORPTION:[25]

- Drugs are absorbed into the body either by passing between cells (paracellular) or through the cells themselves(transcellular).
- Transcellular absorption means drugs pass through the cells, which is common for fat-loving (lipophilic) drugs.
- Paracellular absorption means drugs move between the tight spaces between cells, usually for water-loving (hydrophilic) drugs.
- In the colon, tight cell junction makes it hard for drugs to pass this way.

- This means drugs stay in contact with the colon lining longer than in the small intestine.
- As water gets absorbed, the colon's contents get thicker, slowing down drug dissolution and diffusion.

Factors to be considered for colonic drug delivery:

- The physicochemical and biopharmaceutical properties of drugs like solubility, permeability, stability should be considered.
- The colon specific drug delivery system should be able to control drug release and absorption in the stomach and upper part of GIT and allowing drug release only in colon.[26]
- The drug should be released at controlled rate and the release drug should be absorbed from intestinal lumen without any significant degradation.
- The chemical nature, partition coefficient, stability of drug is some of the factors to be considered for the selection of carrier.[27]

Colon Targeted drug delivery approaches:[28]

- pH controlled drug release.
- Prodrug approach.
- Time controlled drug delivery.
- Osmotically controlled drug delivery.
- Microbially triggered controlled drug delivery.
- Enzyme controlled drug delivery.
- Novel drug delivery system.

pH controlled drug release:

Colonic drug release systems are like regular enteric – coated ones but use special polymer that can handle low to neutral pH levels and stay intact for at least 5 hours. To prevent early release of the drug in the upper intestine, a mix of polymers with different solubility and water absorption rates is used, or the coatings are made thicker. The thickness of the coating depends on how easily the drug dissolves and the desired release profile.[24] Coating is a simple method for delivering drugs to the colon. The coatings are made with materials that react to different pH levels, helping the drug dissolve properly in the right part of the digestive system.[29]

Mechanism of action of pH dependent system

Among the different approaches to achieve targeted drug release to the colon the use of biodegradable polymers was hold good. Prednisolone a corticosteroid is used in the treatment of IBD and ulcerative colitis. Similarly, an approach by using an experimental pH sensitive polymer eudragit S100 allowing further retention of the drug release as the polymer dissolves at pH 7.5. Sodium alginate which is a polysaccharide originally obtained from marine brown algae it contains two uronic acids arranged in homopolymer block.[30]

Prodrug Approach:[31]

A prodrug is a type of drug that is in active until it gets transformed in the body. Some drugs can't easily get into cells if they love water (hydrophilic). Prodrugs can carry these drugs to the colon by staying bulky and water-loving, so they aren't absorbed too early in the digestive system. Once in the colon, the prodrug changes into a fat-loving (lipophilic) drug that can be absorbed. Enzymes like azoreductase and others help transform these prodrugs in the colon. This method is useful for drugs like glucocorticoids, which can cause side effects if absorbed too soon.

Time Controlled Drug Release:[32]

Time controlled drug release also called pulsatile drug delivery, this system controls the timing of drug release, ignoring factors like pH or enzymes. These systems are designed to wait a set amount of time after the stomach empties before quickly releasing the drug. This makes sure the drug gets released in the colon, despite difference in how fast people's stomachs empty or the pH in their intestine or the presence of anaerobic bacteria in the colon. On average oral drugs usually spend around 2 hours in the stomach and 3 hours traveling through the small intestine to reach the colon. The time spent in the small intestine is fairly consistent compared to how long it takes for the stomach to empty, and time- release systems are dependent on it.

Osmotically controlled drug delivery: [33]

- This system, called the OROS system, was made by Alza.
- The system is composed of a core tablet surrounded by a semi permeable membrane coating having a 0.4 mm diameter holes produced by laser beam.
- The core tablet has two layers one containing the drug and other containing a polymeric osmotic agent.
- The system operates on the principle of osmotic pressure.
- When water enter, it creates pressure, pushing the drug out through a small hole.
- This osmotically controlled drug delivery system can be used to target the drug locally to the colon for the treatment of diseases or to achieve systemic absorption.

Microbially triggered controlled drug delivery:

- The microbially triggered colon targeted osmotic pump (MTCT-OP) was studied and found that this will deliver better release to the colonic region.

- Budesonide is the steroidal drug which was used to targeted drug it was formed by using pore former (chitosan) and pH regulating excipient (citric acid).
- The effects of variation in the level of citric acid and chitosan in the core formulation on drug release were studied[34].
- The different levels of enteric coating membrane could prevent cellulose acetate membrane (containing chitosan as pore former pore or rupture before contact with simulated colonic fluid but had no effect on the drug release.
- Budesonide release from the development formulation was inversely proportional to the osmotic pressure of the release medium confirming that osmotic pumping was the major mechanism of drug release.
- This result showed that MTCT-OP based on osmotic technology and microbially triggered mechanism had a high potential for colon specific drug delivery[35].

Enzyme Controlled drug delivery:

The human colon part contains a variety of bacteria with population of 10 to 102 CFU/ml with Bacteroides, Bifidobacterium, Eubacterium, Lactobacillus etc.[36] These bacteria produce a variety of enzymes, including azo reductase, glycosidase and amidases that help release drugs.Certain enzymes are not found in the stomach or small intestine but are present in the colon. These enzymes also involve in many processes in the colon such as carbohydrate and protein fermentation, bile acid, metabolism of xenobiotics and steroid transformation.[37]

Novel drug delivery system:

The novel drug delivery systems can include those based on physical mechanisms and those based on biochemical mechanisms. Physical mechanisms also referred to as controlled drug delivery systems include osmosis, diffusion, erosion, dissolution and electro transport. Biochemical mechanisms include monoclonal antibodies, gene therapy and vector system, polymer drug abducts and liposome. These systems also include the optimization of the duration of action of drug decreasing dosing frequency, controlling the site of release and maintaining constant drug levels.[38] The therapy consist mainly of orally or rectally administered small drug molecule such as corticosteroids or potent systemic immune suppressants. Due to minimal systemic absorption and maximal intestinal wall drug levels are desired so to achieve this goal novel approaches must require to deliver the drug to the target sites. Such as liposomes, multiparticulate system, super porous hydrogels as well as gas empowered drug delivery to protect the dug from the harsh environment of the Gi tract prolonging the drugs transit time at a specific site of the GI tract and prolonging the drugs transit time at a specific site of the GI tract for an optimum drug bioavailability.

- Liposomes.
- Multiparticulate based drug delivery.
    - Microsphere.
    - Microcapsule.
    - Nanoparticles.
- Hydrogels based drug delivery.
- Gas empowered drug delivery.[39]

Evaluation of Colon specific drug delivery system.[40]

- In vivo methods.
- In vitro methods.

In vivo methods:

- String technique.
- Endoscope technique.
- Radiotelemetry.
- Roentgenography.
- Gamma scintigraphy.

In vitro methods :[41]

These techniques simulate the conditions of the digestive system (like pH, volume, bacteria, enzymes, and food particles) in a lab. The usual method, called the basket method, is used to study how a drug dissolve. The drug is placed in different solutions to copy the environment of the digestive system and see how it behaves under different pH levels. For enteric-coated systems, tests are done by keeping them in a simulated stomach environment (acidic) for 2 hours and then in a simulated intestinal environment (less acidic) for 3 hours. This helps predict where and how much the drug will dissolve in the body.

Precision Medicine:

Precision medicine is a way of treating patients based on their unique characteristics, such as their genes, lifestyle, and environment. Instead of using the same treatment for everyone, doctors choose the best approach for each person. Precision medicine means creating treatment specifically for each patient's unique cancer, based on details like gene mutations and other characteristics. This approach has made genome-driven cancer treatment very exciting worldwide.[42] The article discusses how precision medicine is transforming cancer treatment, especially for colorectal cancers. Precision medicine uses advanced technologies like molecular imaging, gene sequencing, and bioinformatics to create targeted therapies based on individual patient and tumour characteristics. This approach has led to better outcomes and fewer side effects compared to traditional treatments.[43]

Several important advancements:[44-45]

- Genetic Risk Score (G-score): New risk prediction models like G-score help refine the risk of colorectal cancer (CRC) by increasing discriminatory accuracy.

- Non-invasive Blood Tests: Tests like the mSEPT9 assay can improve CRC screening rates by detecting cancer through a simple blood test.
- Liquid Biopsy: This technique has the potential to be used for CRC screening, diagnosis, post-treatment analysis, and treatment decisions.
- Next-Generation Sequencing: This technology helps in early-stage disease management, reducing recurrence risk and enabling tailored adjuvant therapy.
- Targeted Therapy: Drugs like EGFR inhibitors, VEGF inhibitors, and anti-HER-2 agents have improved outcomes in metastatic CRCs.
- Patient-Derived Organoids (PDOs): These lab-grown mini-tumours can mimic tumour-specific characteristics and are valuable in precision oncology.

Colorectal cancer:

Colorectal cancer which is also called bowel cancer, happens in the colon, rectum, or appendix. Studies shows that cancer cells in these areas are genetically the same (46). This type of cancer is the second most common in females and third in males (47), and the fourth in most common worldwide (48). Every year, more than a million people are diagnosed with colorectal cancer around the world (49). This cancer is more common in development countries, where about 60% of the cases were diagnosed (50), unfortunately, many of these cases result in death (51). There are many reasons why colorectal cancer can start. Today, doctors are better at finding and diagnosing this cancer. They use different methods to understand it better. Different treatments and ways to predict the outcome are now used to try and successfully cure this type of cancer (49). According to the Global cancer statistics 2020 colorectal cancer represents the third most frequent malignancy worldwide and is the second in term of mortality (52). CRC (colorectal cancer is one of the dangerous cancer and it may be caused by smoking, heavy alcohol intake, obesity, consumption of processed or red meat and low dietary fiber, vegetable intake. Various herbal medicines are also used i.e curcumin & polyphenol derived from turmeric can inhibit growth and metastasis of the cancer cells. Nanomedicines are also used. Various approaches are use i.e Laproscopic and other developed process are robotic assisted surgery are evolving for rectal cancer. The nano particle brings considerable promise for the early detection, staging and treatment of CRC (53).

Natural Product	-Source
EGCG	plant
Resveratrol	plant (54).

CAUSES AND PREDISPOSITION

Colorectal cancer can happen to many different people. Most of them have been or still are exposed to several risk factors. The rest either have a genetic tendency to develop it or have other bowel diseases.

Risk Factors

It's estimated that more than 80% of people with colorectal cancer have been exposed to certain factors. Some of these factors include being male and getting older (49), eating a lot of red meat or fat, smoking and being obese (55). The risk of getting colorectal cancer goes up if you drink more than one alcoholic drink per day (56). Also around 10% of these cases are related to not getting enough physical activity (57).

Conclusion: The colonic region of the GIT has become an increasingly important site for drug delivery and absorption. The advantages of targeting drugs specifically to the disease related to colon are reduced the incidence of systemic side effect, lower the dose of drug and maintenance of the drug in its intact from as close as possible to the target sites. All the approaches of colon drug delivery provide means for treatment of local diseases associated with the colon or for systemic absorption of poorly absorbable drugs. It is better to use new approaches and precision medicines for the colon disease i.e colorectal cancer using an optimized colon drug delivery system.

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