**A Review Study on Colon Targeting: Targeting Approaches and Polymers**

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**Abstract**

 The objective of this research was to explore the potential of a drug delivery system targeted specifically for the colon. Colon-targeted delivery has become increasingly significant, whether for delivering drugs intended for local action within the colon or for transporting proteins and peptides to this site. The gastrointestinal (GI) tract presents numerous barriers that necessitate protecting the drug from the conditions of the upper GI tract. This protection can be achieved through the utilization of various biodegradable and non-biodegradable polymers. This study primarily concentrates on strategies for colon targeting and the application of polymers for the development of drug formulations..

***Key words:*** Colon delivery, routes of administration, GI tract, drug delivery, modified release technologies, bowel disease, etc.

1. **INTRODUCTION**

In recent times, various drug delivery routes have been explored to enhance drug effectiveness. Oral administration stands out as the preferred route, especially for chronic therapies requiring repeated dosing. Oral drug delivery systems offer numerous advantages to patients, including reduced discomfort, greater convenience, improved compliance, and a lowered risk of cross-infection and needle stick injuries. Oral drug delivery formulations have gained significant traction in the market due to these benefits. Despite these merits, many protein and polypeptide drugs currently available face challenges when administered orally. They are highly susceptible to degradation by digestive enzymes in the gastrointestinal (GI) tract, exhibit poor absorption, and have limited capacity to traverse the intestinal epithelial barrier (Homayun et al., 2019). To overcome these limitations, novel drug delivery strategies have been developed, and among them, colon-specific drug delivery has garnered considerable attention over the past two decades (Liu et al., 2003), (Lautenschläger et al., 2014).

The colonic region of the GI tract is an area ripe for the development and utilization of modified release technologies. Despite its simple functions, including electrolyte and water absorption and the formation, storage, and expulsion of feces, the colon is susceptible to various disorders such as Crohn's disease, ulcerative colitis, inflammatory bowel disease, and carcinoma (Amidon et al., 2015). Targeting drug delivery to the colon, achieved through a combination of controlled release mechanisms that release the drug in the upper GI tract followed by rapid release in the colon upon oral administration, offers significant benefits. Specifically, delivering drugs to the colon can lead to reduced toxicity and enhanced safety when treating chronic local or systemic diseases (Qureshi et al., 2013) (Patel et al., 2015).

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1. **ANATOMY AND PHYSIOLOGY**

The gastrointestinal tract (GIT), also known as the alimentary canal, serves as a crucial selective barrier between the external environment and the systemic circulation. Its primary functions include the digestion of dietary food, as well as the absorption of electrolytes, fluids, and nutrients, while preventing the uptake of harmful substances. The largest segment of the GIT is the small intestine, where the majority of enzymatic digestion and nutrient absorption takes place. Most digestive enzymes in the intestine are secreted by the pancreas, and the small intestine undergoes peristaltic movements, completing digestion and absorption in approximately 3-6 hours.

The large intestine represents the final major segment of the GIT. Digested materials reaching the large intestine contain few remaining nutrients, and these residues typically remain in the large intestine for a duration of 12-24 hours (Liu et al., 2003) (Boutros et al., 2017). The primary regions of the large intestine include the cecum, colon, rectum, and canal. The colon constitutes the lowermost part of the GIT and extends from the ileocecal junction to the anus. The entire length of the colon is approximately 5 feet and is further divided into distinct segments (Boutros et al., 2017), (Sarasija et al., 2000).

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1. **APPROACHES FOR TARGETING DRUGS TO THE COLON**
2. **Prodrug Approach**

Prodrugs are pharmacologically inactive derivatives of parent molecules that are active at the site; to release the active molecule from the inactive state, an enzyme transformation must occur in the biological environment. Using this method, the drug and its carrier are covalently linked so that when taken orally, the drug's moiety stays intact in the upper section of the GIT and is regenerated by enzymatic cleavage once it reaches the colonic environment. Prodrug delivery qualities are superior to those of the parent drug. (Jose and others, 2009); (Belali and others, 2019)

1. **pH-dependent Approach**

It is reported that thepH in the terminal ileum and colon is found to be higher than any other region of the gastro intestinal tract. The dosage form disintegrates preferentially at high pH level good for targeted delivery system into the regions.

1. **Time dependent Approach**

Time dependent approach particularly useful in the circadian rhythms-based disease therapy (Vemula et al. 2015). Time-controlled formulation for colon drug delivery is also delayed-release formulation in which the delay in delivery are also delayed-release formulation in which the delay delivery of the drug is time-based (Brahma et al., 2007).

 A time-controlled system was employed to develop a colon drug delivery system for diclofenac sodium. In this approach, tablets containing diclofenac sodium were coated with ethylcellulose using an ethanol solution, with diethyl phthalate serving as a plasticizer and PEG-400 as a channeling agent. The delay in the release of diclofenac sodium was regulated by adjusting the thickness of the ethylcellulose coating. Specifically, increasing the coating thickness led to a longer lag time for drug release (Parekh et al., 2012).

 Hydroxy propyl methyl cellulose (HPMC) compression coated tablets of 5-fluorouracil were studied for colon delivery that based on time dependent approach. (Vemula et al., 2009).

1. **Pressure Dependent Approach**

The pressure within the gastrointestinal (GI) tract varies in terms of magnitude and duration, with the colon experiencing higher pressures primarily due to the peristaltic movements involved in stool formation. To address this issue, systems have been designed to withstand the elevated pressures in the colon and prevent rupture, particularly when transitioning from the upper GI tract to the colon (Sharma et al., 2014).

1. **Microflora Activated Drug Delivery System**

 The utilization of gastrointestinal (GI) tract microflora as a mechanism for drug release in the colon has garnered significant attention in recent times. While bacteria are distributed throughout the GI tract, the majority of them are concentrated in the distal part, and colonic bacteria predominantly exhibit anaerobic characteristics. Azo bond reduction and glycosidic-bond hydrolysis are the most commonly observed mechanisms of activation in the colon (Kotla et al., 2019).

Sulfasalazine, which is a prodrug containing the active component 5-aminosalicylic acid, was among the first drugs designed to be sensitive to bacteria for targeted delivery to the colon. The development of various novel azo polymers is based on the concept of prodrug biotransformation through azo reduction. When drugs are coated with these azo polymers, they remain unchanged in the upper GI tract, where microbial degradation activity is minimal and insufficient for polymer coating cleavage. Subsequently, the reduction and cleavage of azo bonds occur due to the presence of azo reductase enzymes released by azo bacteria in the colonic microflora. In vitro and in vivo studies have provided evidence supporting the feasibility of using these polymers to deliver drugs to the large intestine (Jose et al., 2009).

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1. **POLYMER PROFILE**

Recently the use of natural polymers in the design and development of drug delivery systems has gained much attention owing to their excellent biocompatibility and biodegradability.

1. **Chitosan**

Apart from cellulose, chitin is the most abundant natural polysaccharide. Chitosan is a functional linear polymer that is not broken down by digestive enzymes in the upper gastrointestinal system of humans. Chitosan is a copolymer made up of β-(1-4) links connecting 2-amino-2-deoxy-D-glucose units. It ought to be amenable to microbial enzymes released by colonic bacteria in the colon for glycosidic hydrolysis (Jain et al., 2007). (Kavianinia et al., 2016)

 It is simple to generate chitosan gel particulate by dispersing chitosan solution into alkaline media. It has been demonstrated that the particulate that is left over following chemical crosslinking operations has a strong affinity for heavy metal ions (Gotoh et al., 2003).

**Chemical properties of Chitosan** (Sinha et al., 2004)

* Cationic polyamine
* Adheres to negatively charged surfaces
* High molecular weight (3800-2000000)
* Strong H-bond form
* Chain flexibility

**Biological properties of Chitosan** (Sinha et al., 2004),(Lizardi-Mendoza et al., 2016)

* Biocompatibility
* Natural polymer
* Forms gels with polyanions
* Biodegradable to normal body constituents
* Safe and non-toxic
* Anticancerogen
* Anticholesteremic
* Antacid and
* Antiulcer activities
* Wound and burn Healing properties

**Pharmaceutical application of Chitosan** (Shariatinia, 2019)

* Chitosan formulations for the oral

Microparticulate

Liposomes

Buccal disk

Solution

Film coating

Tablets

Capsules

* Drug delivery for parental diseases

Microspheres

Solution

* Nasal delivery systems
* Chitosan formulations for Ocular
* Chitosan for gene delivery
* Chitosan for colon-specific drug delivery
1. **Alginate**

Alginate is a natural polysaccharide derived from seaweeds, and hydrophilic in nature, consists of 1-4, linked D-mannuronic and L-glucuronic acid residues. Alginate is easily gelled in presence of a counter ions. The gelation or crosslinking is due to the glucuronic acid blocks of alginate chains. Calcium alginates beads have the advantage of being nontoxic and compatible, and drieds beads reswell in the presence of dissolution medium and act as a controlled release. Different enteric and sustained release polymer were used for the coat on calcium alginate beads. (Jain et al., 2007), (Agüero et al., 2017)

 Beads of ranitidine hydrochloride capsule was providing over 12 hr sustain release studied, and this formulated by using expandable, gelling, swellable, hydrochloride polymer with light paraffin. Additionally, alginate also reduces interfacial tension between water and oil and it efficient for preparation of emulsion (Jaiswal et al., 2009).

1. **Guar gum**

A naturally occurring polysaccharide, guar gum is extracted from the seeds of the Leguminosae family plant Cyamopsis tetragonblobis. Using in vitro techniques, a novel tablet formulation for oral administration has been studied for colon-specific medication delivery. The formulation uses guar gum as the carrier and indomethacin as a model drug. Technetium-99m-DTPA (mTc-DTPA) was used as a tracer in in vivo gamma scintigraphy investigations conducted on the guar gum matrix tablets in order to assess the individuals' in vivo performance (Avachat et al., 2011).

1. **Pectin**

 Pectin is a plant-derived substance. One of the polysaccharides that has been studied the most for colon-specific medication delivery is pectin. It is a polysaccharide without starch. It is primarily a liner polysaccharide made up primarily of residues of D-galacturonic acids connected by α-1,4. It has been applied in various dose forms to deliver drugs specifically to the colon. Faster medication release in a pectin formulation made of pectin that is broken down by colon bacteria's pectinase. It also releases through a pH- and time-controlled mechanism. Unfortunately, because of its swelling capacity and water solubility, it is unable to properly hide the medication during its journey through the upper GI tract. In 2005, Atybi et al., and in 2013 Jung et al.

1. **CONCLUSION**

Colonic illnesses are currently effectively treated by delivering drug to the distal portion of the GIT, which has enormous value in this regard. Few delivery methods built in the past that relied on pH or time-dependent release mechanisms were successful because the physiological milieu of the GIT lacks discontinuity. Because natural polysaccharides are broken down by the enzymes produced by the colonic microbiota, they can be designed for specific delivery to the colon. Premature drug release in the upper part of the GIT can be restricted with a small chemical modification that might provide partial protection without affecting the polysaccharide's capacity to degrade. These polysaccharides can be employed as film-forming agents, pro-drug transporters, biodegradable coatings, or colon delivery matrices.

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