COLON DRUG DELIVERY SYSTEM AND THEIR BENEFITS AND THE CARRIERS FOR DELIVERY OF DRUGS TO COLON: A REVIEW

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ABSTRACT

The colon drug delivery system is undergoing a designed novel drug delivery system. In this system the drug directly absorbed in colon sites. Normally protein or those drugs which are less absorbed in the stomach or small intestine that type of drugs are targeted to colon site. In the colon site, the bioavailability of drugs is higher than the stomach. Through colon drug delivery system inflammatory bowel disease (IBD), Chron's disease, as well as asthma and in serious conditions such as colonic cancer. Into the colon through model novel drug formulation drugs are directly targeted to the colon. This review shows the study of benefit criteria for colon targeting of drugs and also the study of formulation type and factor for colon-specific drug delivery systems (CSDDS).

Keywords: Colon drug delivery system, Inflammatory bowel disease, pH of the colon.

INTRODUCTION

Novel drug delivery system (NDDS) is a method of carrying drugs to the chosen site in optimum dosage with more patient obedience and safety in assessment to other conventional delivery systems. NDDS can diminish the injurious things of drugs, rises bioavailability and accumulation at the embattled site due to its control over pharmacokinetics and pharmacodynamic profile of the drug ¹. A targeted drug delivery system aims to offer a chosen drug concentration in the body by distributing a therapeutic amount of drug to a target site. It is appropriate and mandatory for the drugs having

instability, low solubility, short half-life, a large volume of distribution, poor absorption, low specificity, and therapeutic index. Targeting may give supreme therapeutic activity (by avoiding dilapidation or inactivation of a drug)². This tactic has been used effectively in targeting drugs to the colon site. Colon-specific drug delivery system (CDDS) has become the most discriminatory methods for the local action of IBDs. IBD is the ailment of chronic inflammation of the gastrointestinal tract that leads to the generation of definite diseases like ulcerative colitis and Crohn's disease³. Site-specific delivery into the colon is not only desired for local action of a various type of colon diseases, such as ulcerative colitis, Chron's diseases, amoebiasis, colon cancer, but also the systemic distribution of proteins and peptides this is because of low diversity and intensity of digestive enzymes and low proteolytic action of colon mucosa than that detected in the small intestine. Besides the colon diseases, this system is also supportive to treat asthma, angina and rheumatoid arthritis for the enhancing benefit of chronotherapeutic drug delivery and delivery of steroids⁴.

Few features to be measured for efficacious colonic drug delivery, with the assets of the drug, the form of the delivery system and its interface with health or disease gut. The lengthier residence period, fewer peptidase action, absorptive characters and high reaction to absorption emulators creates the most favorable site for drug delivery. The absorption emulators are subcategorized into classes of complexing agents, NSAIDs, surfactants (mostly as mixed micelles), phenothiazines and an overall group of molecules which include fatty acids, acylcarnitive, acyl amino acids and dicarboxylic acid⁵⁻⁶.

1.1. Advantages

- a) Dosage frequency is less so, cost-effective.
- b) lesser side effects and drug interactions occur.
- c) Perfect spot for the delivery of active agents to cure colon diseases (ulcerative colitis, Chron's diseases, amoebiasis, *etc.*).
- d) Smaller drug quantities should be required for local treatment.
- e) Deficiency of a proper dissolution challenging system to estimate the dosage form *in-vitro*.
- f) The lengthier retention period of the colon, upgraded bioavailability of slowly absorbed drug molecules (approximately 5 days).
- g) Diminish gastric irascibility triggered by various drugs by avoiding their absorption in superior GIT (*g.*, NSAIDs).

1.2. Disadvantages

- a) Multiple manufacturing steps.
- b) The resident microflora could also affect colonic act through metabolic damage of the drug.
- c) Imperfect discharge of the drug.
- d) Bioavailability of drugs may be less due to the potential binding of the drug in a broad-spectrum way to dietary residues, intestinal secretions, mucus or fecal matter.

Need for colon targeted drug delivery systems

As per record, the conservative drug delivery systems for handling colon disorders like IBD, transferrable diseases, and colon malignancy are dying as because the drugs does not have the capability to influence the spot of action in correct concentration. Thus, operative and harmless remedy of these colonic illnesses using site-specific drug delivery systems. The helpful benefits of aiming the drug to the diseased organ include,

- Delivery of drug in its intact form as close as possible to the target site.
- The ability to cut down the conventional dose.
- Reduced incidence of adverse side effects.

In recent times the CSDDS are also acquiring valuable for the delivery of protein and peptide drugs. This is because,

- As the peptide and protein drugs are destroyed and inactivated in the acidic atmosphere of the stomach or by pancreatic enzymes (or) by the parenteral path which is inconvenient and expensive.
- Due to the tiny activity of brush border membrane peptidase activity and less activity of pancreatic enzymes the colon is considered as the most suitable site.

The colon delivery of analgesic peptides, contraceptive peptides, oral vaccines, insulin, Human growth hormone, erythropoietin, interferons, and interleukins was tried for systemic absorption further drug aiming to colon would show the effective where attentively postpone drug absorption is expected from the therapeutic point of view (e.g.: - in the cure of nocturnal asthma)⁷.

Factor to be considered in the design of colon targeted drug delivery system (CTDDS)⁸

- Anatomy and physiology of colon.
- pH of the colon.

- Gastrointestinal transit.
- Colonic microflora
- Drug absorption in the colon

Physiology & Anatomy of the colon

The colon averages 150cm in length, and can be divided into four parts (proximal to distal): ascending, transverse, descending and sigmoid.

1. Ascending Colon

The colon starts as the ascending colon, a retroperitoneal structure that starts authoritatively from the cecum. When it reunites the right lobe of the liver, it goes 90 degrees to passage parallel. This curve is known as the right colic flexure (or hepatic flexure) and results from the outset of the transverse colon ⁹.

2. Transverse Colon

The transverse colon covers from the right colic flexure to the spleen, wherever it goes another 90 degrees to point inferiorly. This curve is known as the left colic flexure (or splenic flexure). At this point, the colon is conferred to the diaphragm by the phrenic colic ligament. The transverse colon is the tiniest stable portion of the colon and is variable in point (it can dint into the pelvis in tall, thin individuals). Nothing like the ascending and descending colon, the transverse colon is intraperitoneal and is walled by the transverse mesocolon ¹⁰.

3. Descending Colon

On later the left colic flexure, the colon passages inferiorly just before the pelvis and is called the descending colon. It is retroperitoneal in the mainstream of individuals but is situated anteriorly to the left kidney, fleeting over its lateral boundary. When the colon activates to turn medially, it grows into the sigmoid colon.

4. Sigmoid Colon

The 40cm long sigmoid colon is sited in the left inferior quadrant of the abdomen, extending from the left iliac fossa to the side by side of the S3 vertebra. This voyage bounces the sigmoid colon its

specific “S” shape. The sigmoid colon is involved in the subsequent pelvic wall by a mesentery the sigmoid mesocolon. The extensive size of the mesentery licenses this segment of the colon.¹¹

Figure -1: Physiology and anatomy of the colon

5. Anatomical Structure

The large intestine has various characteristic features, which tolerated to be distinguished from the small intestine: Devoted to the seeming of the large intestine are omental appendices tiny pockets of the peritoneum, full up with fat. Running longitudinally laterally the seeming of the large bowel are three tiles of muscle, known as the teniae coli. They are called the mesocolic, free and omental coli. The teniae coli agreement to condense the wall of the bowel, making sacculations known as haustra. The large intestine has a far broader diameter linked to the small intestine. These features cease at the rectosigmoid junction, where the smooth muscle of the teniae coli broadens to form a whole film within the rectum¹².

6. pH of colon

The pH of GIT diverges stuck between different individuals. The food intakes, sickly state, etc. affect the pH of the GIT. This modification in the pH in different portions of GIT is the basis for the expansion of colon targeted drug delivery systems. Covering with different polymers is finalized to mark the drug to the site¹³.

Table 1: pH of the different parts of the intestine.

Part of GIT	pH
Stomach	Fasted state- 1.5 – 2 Fed state 2 – 6
Small Intestine	6.6 – 7.9
Distal small intestine	6.80 – 7.88
Proximal small intestine	6.15 – 7.35
Colon	
Ascending colon	6.4
Transverse colon	6.6
Descending colon	7.0

Based on the pH of the colon the preparation for the colon targeted delivery are several types such as pH-dependent, enteric-coated, delayed released, sustained released, prodrug approached, microbes triggered, etc. Also, for suitable delivery novel drug delivery systems can be used such as Microspheres, Transfersomes, Niosomes, Hydrogel, Nanoparticles, Liposomes, Pharmacosomes, Aquasomes, etc.

7. Colonic microflora and enzymes

The GIT comprises a variability of micro-organisms that release many enzymes required for metabolism. The development of this microflora is organized by GIT matters and peristaltic activities. The enzymes produced by many micro-organisms *E. coli*, *Clostridia*, *Lactobacilli*, *Eubacteria*, *Streptococci* are the main reason for the countless metabolic responses that passed out in the GIT¹⁴.

Table 2: Different microflora, enzymes released and action

Microorganism	Enzyme	Metabolism
<i>E. coli</i> , <i>Bacteroides</i>	Nitro reductase	Reduces aromatic & heterocyclic nitro compounds
<i>Clostridia</i> , <i>Lactobacilli</i>	Hydrogenase	Reduces carbonyl groups & aliphatic double bonds
<i>Clostridia</i> , <i>Eubacteria</i>	Glucosidase	Cleavage of glycosidase of alcohols & phenols
<i>Eubacteria</i> , <i>Clostridia</i> , <i>Streptococci</i>	Sulfatase	Cleavage of Osulphates & Sulfamates

8. Gastrointestinal transit time

As related to added portions of the GIT, the materials pass over the colon is very slow. The total duration for transit inclines to be vastly adaptable and many by many features like diet, in specific nutritional fiber matter, mobility, stress, any type of disease, and drugs. Colonic travel periods vary between 50 to 70 hours. Stool masses higher than before expressively with the incidence of lively sickness apparently due to exudates from inflamed epithelium, improved mucus secretion and drop in reabsorption of liquid and electrolyte¹⁵.

9. Absorption of a drug in the colon

Drugs are fascinated inertly by either paracellular or transcellular routes. Transcellular absorption includes the channel of drugs over the cells and this is the path most lipophilic drugs receipts, whereas paracellular absorption contains the transportation of drugs over the tight joint between cells and this is the path of the most hydrophilic drug takes place. The low rate of travel in colon leases the drug halt in interaction with the mucosa for more time than in the small intestine that recompenses the wider surface area. The colonic matters turn into more viscid with advanced water absorption as one moves over the colon. This causes a lowers dissolution rate, slow distribution of liquified drugs through the mucosa¹⁶.

METHODS USED FOR DRUG TARGETTING TO THE COLON

There is a different kind of preparation procedure to mark the drug to the colon. That is explained in the following criteria:

Formation of prodrugs:

The prodrug is defined as an inert drug that becomes active only after it is transformed or metabolized by the body. Covalent linkage is made among the drug and carrier, which upon oral administration influences colon without absorbed by the upper portion of the Gastrointestinal tract. The colon drug discharge is activated by extreme action of specific enzymes in comparison to the stomach and small intestine. So, these tactics successfully implanted by various kinds of conjugation¹⁷.

- Azobond conjugation
- Glucuronide conjugation
- Gluteraldehyde conjugation
- Cyclodextrin conjugation

Dextran conjugates

Amino-acid conjugation

Hydrogels:

Hydrogels can be depleted for site-specific delivery of peptide and protein drugs through the colon. The Hydrogels are uniting of acidic commoners and enzymatically degradable azo aromatic cross-links. In acidic pH, gels uttered a smaller amount blister which shields the drug against deactivation in the stomach. As the pH of the environment rises i.e. come to be basic, blistering is high. These results easy contact of enzymes like azo reductase, which eventually liberate the drug ¹⁸.

Coating with pH-dependent polymers:

The pH in the terminal ileum and colon is greater than in any further portions of the GI and thus dosage forms that break at extreme pH limits can be affected into the part. A degree of pH is greater in the terminal ileum part than in the cecum. Dosage forms are habitually delayed at the ileocecal junction, watchful collection of enteric layer composition and thickness is required to confirm that breakdown does not happen until the dosage form passes through the ileocecal junction from the terminal ileum into the cecum. Synonyms for eudragit are Eastacryl, Kollicoat MAE, polymeric methacrylates ¹⁹.

pH-dependent microbeads of theophylline hydrochloride were prepared and evaluated by using alginate and chitosan by ionotropic gelation manner tailed by enteric overlaying with eudragitS100. Examination concentrated with the formulation of prednisolone containing 1% eudragit RS PM had been carried out which shows 100% drug release ²⁰.

Table 3: pH of the polymer used in pH-dependent microbeads

Sl No.	Polymers	pH
1	Cellulose acetate phthalate (CAP)	
2	Polyvinyl acetate phthalate (PVAP)	5.0
3	Hydroxyl propyl methylcellulose phthalate (HPMCP)	4 . 8 – 4 . 8
4	Cellulose acetate trimellitate	4.8
5	Eudragit L-30D	5.6
6	Eudragit FS 30D	6.8
7	Eudragit L 100	5.5
8	Eudragit L 100	6.0
9	Eudragit L 100	7.0
10	Kollicoat 30D	5.5

Timed released system

On the source of avoiding the delivery of drugs 3–5 hours after inserting into the small intestine. In this tactic, drug release from the system after a programmed lag time according to the travel time from mouth to colon. The lag time depends upon the GIT motility and size of the dosage form. One of the earliest devices is the Pulsincap device. This system contains a non-decomposing half capsule body closed at the exposed end with a hydrogel plug, which is encircled by a water-soluble cap. The entire part is covered with an enteric polymer to evade the tricky of adaptable gastric voiding. When the capsule arrives the small intestine, the enteric covering softens and the hydrogel plug jerks to swell up. The quantity of hydrogel is accommodated so that it dissolved only after the restricted predetermined period to discharge the components²¹.

Designing formulations using polysaccharides

Dosage forms the defending effect of polysaccharide in the superior portion of the Gastrointestinal Tract and drug is discharged in the colon by enlarging and decomposable property of polysaccharides. Polysaccharides naturally present in the plant (e.g., pectin, guar gum, inulin), animal (e.g., chitosan, chondroitin sulfate), algal (e.g., alginates), or microbial (e.g., dextran) origins were studied for colon directing. These are disintegrating by the colonic microflora to simple saccharides by saccharolytic species such as *Bacteroides* and *bifidobacteria*. Hydrolysis of the glycosidic linkages on the entrance in the colon activates the discharge of the encapsulate bioactive. Although specifically deteriorated in the colon, certain polymers are hydrophilic and swell under contact to upper GIT conditions, which primes to premature drug release. To overcome this problem, the natural polysaccharides are chemically altered and mixed with hydrophobic water-insoluble polymers, whereas in the case of preparations they are commonly covered with pH-sensitive polymers. A pectin/chitosan-based colonic delivery system has been developed²².

Redox sensitive polymer coating

Analogous to azo bond breaks by intestinal enzymes, novel polymers that hydrolyzes non enzymatically by enzymatically produced flavins are being progressed for colon delivery²³. An ordinary colonic bacterium, *Bacteroides fragilis* was applied as a trial organism and the decline of azo tints amaranth, Orange II, tartrazine and a model azo compound, 4,4C-dihydroxy azobenzene was studied. It was established that the azo compounds were compacted at altered

amounts and the degrees of diminution could be interconnected with the redox aptitude of the azo compounds.

Bioadhesive systems

Bioadhesion is a kind of dosage form that stays in dealings with a specific organ for an augmented time. This lengthier holding capability of drugs would have abnormal local concentration or upgraded absorption qualities in case of slowly absorbable drugs. This policy can be useful for the invention of CDDS. There are countless polymers that take in polycarbophil, polyurethanes, and polyethylene oxide polypropylene oxide copolymers have been scrutinized as resources for bioadhesive systems²³.

New systems

The complicated was equipped by dialdehyde konjac glucomannan and adipic hydrazides to establish a fixed Schiff base and jointing with 5-amino salicylic acid (5-ASA) over glutaraldehyde as the cross-linking mediator. In vitro release of 5-ASA from the complex after 24hr in buffer solution at pH 1.2, 6.8 and 7.4 was originated to be 4, 59 and 21% respectively.

CONCLUSION:

From the above review article, one thing is concluded that the colon drug delivery is quite important for local aiming the drug too small intestine. Such this modern as well as control drug delivery system some modern and artistic carriers like nanoparticle, macroparticle, liposomes, Niosomes, etc. were investigated and proved that they can successfully carry the drug and delivered also as per aiming.

Moral authorization

This review article does not take account of any animal researches done by any of the writers.

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