Colon targeted drug delivery system – A novel perspective

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ABSTRACT

New developments have been taking place in the field of colon-specific drug delivery scheme in the latest years. Colonic drug delivery has become increasingly important not only for delivering the drug for the therapy of colon-related indigenous illnesses such as Crohn's disease, inflammatory bowel disease, etc. But also to provide protein, therapeutic peptides, anti-asthmatic drugs, medicine and anti-diabetic agents in particular. New colon targeting systems and techniques are created to overcome the constraints of the previous method. Colon targeting has great potential and still wants a lot of creative jobs. This review describes the implementation of colon, wishes, and approaches to the delivery of colonic drugs, the problem of colonic transformation, colonic diseases and thus the new and growing techniques.

Keywords— Colonic drug delivery, New colon targeting systems and techniques, New and growing techniques.

1. INTRODUCTION

Any drug delivery system's main objective is to deliver a useful quantity of the drug to an objective site in a body so that the required concentration of drugs can be reached rapidly and then retained. The oral route is the most appropriate path for drug administration. Oral delivery systems have benefits due to patient recognition and easy administration. In order to preserve drug absorption within the therapeutic range using conservative delivery schemes, it is often mandatory to take the drug dose several times a day, which can lead to significant variations in the concentration of plasma drugs. This has resulted in the development of controlled release dosage forms, where the dosage form is intended to control the release of the drug so that its plasma profile is maintained for an extended period of time within the therapeutic range. A controlled release dosage form, however, provides limited benefits for drugs that have a colon absorption window and better colon stabilization. Targeted drug delivery enables the drug to be selectively and effectively located at therapeutic levels with restricted access to non-target locations. In drugs with uncertainty, low solubility and brief half-life, high volume of production, bad absorption, low specificity and low therapeutic index, a targeted drug delivery scheme are chosen. The delivery of colonic drugs provides more effective therapy for colon-related illnesses such as irritable bowel syndrome, IBD including Crohn's illness and ulcerative colitis, and also has the ability to deliver orally macromolecular drugs. Colon-related illnesses range from constipation and diarrhea to incapacitating inflammatory bowel diseases to colon cancer, the third most common form of cancer in both males and females. [1][2]

1.1 Advantages of colon targeted drug delivery systems
Drug targeting to the colon can be attractive for several reasons:
- The colon is an optimal place to release agents for the treatment of local colon illnesses.
- Local therapy benefits from needing smaller amounts of drugs, thus reducing the price of costly drugs and improving patient compliance
- A reduction in the incidence of side effects and interactions may result.
- Delivery of colon can decrease gastric irritation induced by many drugs like NSAIDS.
- Colon aimed at first-pass metabolism bypass delivery.

1.2 Limitations of colon targeted drug delivery system
- To develop such shipping systems, multiple manufacturing steps are needed.
- Resident microflora may also influence colonic performance through the drug's metabolic degradation.
- Due to the potential non-specific binding of the drug to nutritional residues, intestinal secretions, mucus or faecal matter, medication bioavailability may be small.
- Before absorption, the drug should be in solution form, and thus this could be the rate-limiting step for poorly soluble drugs. [3]

2. ANATOMY AND PHYSIOLOGY OF COLON

The colon is split into caecum, ascending colon, rectum, and anal canal. The caecum has a dilated part that is internally blinded and is superior to the ascending colon. Ascending colon moves up from the caecum to the stage of the liver where it blends acutely to the left at the right colic flexure to become a transverse colon. The downward colon enters the left side of the abdominal cavity, then bends to the midline. [4][5][6]
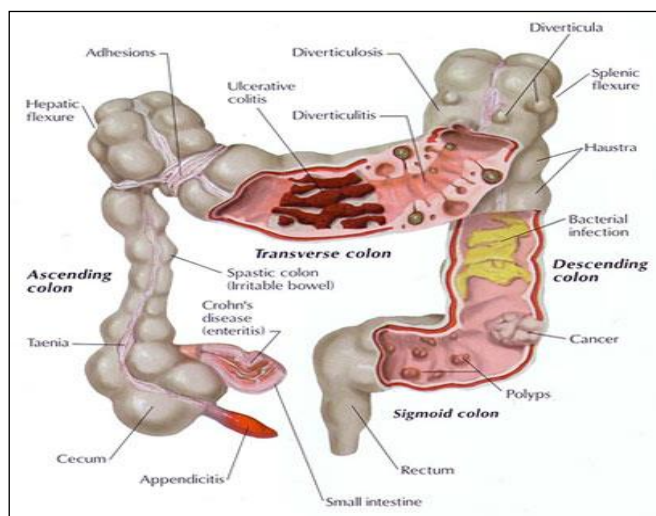

Fig. 1: Colon design

2.1 Criteria for Selection of Drug for CDDS

CTDDS are drugs that have bad stomach or intestine absorption, including peptides. Drugs used in the therapy of IBD, ulcerative colitis, diarrhea and colon cancer are prominent in the delivery of local colon drugs used for local colon impacts against GIT illnesses.

- Low-absorbed drugs from the upper GIT
- Colon cancer medicinal products that degrade
- In the belly and small intestine
- Drugs that undergo extensive first pass
- Metabolism Misabsorbed medicines from the upper GIT
- Drugs for targeting.[7]

2.2 Factors Affecting Drug Absorption from Colon

Two physiological variables mainly affect the colon-specific drug delivery, these are the pH level and the transportation time. The other variables that need to be taken into account are:

- The physical characteristic of the drug (PKA, degree of ionization),
- Colonic residence time as detected by gastrointestinal tract motility,
- Degradation by bacterial enzymes and byproducts,
- Selective and non-selective bindings to the mucus,
- Local physiological actions of drug,
- Disease state,
- Use of chemical absorption enhancers.

Variations in the gastrointestinal tract pH are recorded between and within the subject. Diet, illness, and consumption of food affect the pH of the gastrointestinal fluid. One of the significant determinants of colon compound absorption is formulation residence in some specific colon section. The transit time in the small intestine is reported to be quite consistent than the stomach and colon. It is noted that the transportation time in the small intestine is quite compatible with that of the stomach and colon.
The particle size affects the transportation of the colon CSDDS when dosage forms reach the colon. Small particles reach the colonic area slower than the bigger unit, while bigger unit density and size have no real impact.[8]

3. NEED OF COLON TARGETED DRUG DELIVERY

Targeted drug delivery to the colon would ensure direct treatment at the disease site, lower dosing, and fewer systemic side effects. Site-specific or targeted drug delivery scheme would enable peptide and protein drug oral administration, and colon-specific formulation could also be used to prolong drug delivery. In the therapy of colon illnesses, the colon-specific drug delivery scheme is regarded as useful. The colon is a place where the delivery of both local and systemic drugs, topical therapy of inflammatory bowel diseases, such as ulcerative colitis or Crohn's illness, could be accomplished. Such conditions of inflammation are generally handled with glucocorticoids and targeted sulphasalazine. Also, a number of other severe colon illnesses, e.g. colorectal cancer, could be more efficiently handled if drugs were aimed at the colon.

Colonic delivery formulations are also appropriate for the delivery of drugs that are polar and/or prone to chemical and enzymatic degradation in the upper GI tract, particularly therapeutically impacted by hepatic metabolism. [9][10]

Table 1: Criteria for selection of drug for colon drug delivery system (CDDS)

Criteria	Pharmacological Class	Non-peptide drugs	Peptide-drugs
Drugs used for local effects in colon against g.i.t.diseases	Anti-inflammatory Drugs	Oxyprenolol, Meoprolol, Nifedipine	Amylin, Antsense Oligonucleotide
Drugs poorly Absorbed from Upper g.i.t.	Antihypertensive and antianginal Drugs	Ibuprofen, Isosorbides, Theophylline	Epotein, Glucagon
Drugs that degrade in the stomach and small intestine	Peptides and Protein	Bromophenaramine, 5-Flourouracil, Doxorubicin	Gonadoreline, Insulin, Interferons
Drugs that undergo extensive first pass metabolism	Nitroglycerin and corticosteroid	Bleomycin, Nicotine	Protirelin, Sermorelin Saloatonin
Drugs for targeting	Antiarthritic and antiasthamatic drugs	Prednisolon, hydrocortisone, 5-Amino-salicylic acid	Somatropin, Urotoilitin
Drugs for colon cancer	Antineoplastic drugs	Pseudoephedrine	Epoetin, Glucagon

3.1 Drug Candidate

Drugs which show poor absorption from the stomach or intestine including peptide are most suitable for CDDS. The drugs used in the treatment of Intestinal Bowel Disease, ulcerative colitis, diarrhea, and colon cancer are ideal candidates for local colon delivery. Criteria for the selection of drugs for CDDS are summarized in the above table.

3.2 Drug Carrier

The carrier choice for a specific drug candidate relies on the physiochemical nature of the drug as well as the disease to be used for the scheme. Factors such as chemical nature, the drug's coefficient of stability and partition and the type of absorption enhancer selected impact the carrier selection. In addition, the selection of a drug carrier relies on functional drug organizations. Aniline or nitro groups on a drug, for instance, can be used to connect it through an azo bond to another benzene group. Carriers containing additives such as polymers (may be used as matrices and hydro gels or coating agents) may affect the system's release characteristics and effectiveness.

3.3 Formation of prodrugs

(Example: Azo- Prodrug, Glucuronide conjugate, etc.) A prodrug is described as an inert drug that only becomes active after the body transforms or metabolizes it. There is a covalent connection between drug and carrier that reaches the colon after oral administration without being absorbed from the upper portion of GIT. The release of certain enzymes in the colon is caused by elevated activity compared to the stomach and small intestine.[11]

4. DIFFERENT APPROACHES FOR THE COLON TARGETING

4.1 Azo bond conjugate

There are several trials on sulphapyridine that contribute to the creation of other drugs such as Olsalazine, Balsalazine, 4-amino benzoyl-β-alanine. Intesti: Sulfasalazine is used primarily to treat inflammatory diseases of the bowl. It is a prodrug of 5-Amino Salicylic Acid (5-ASA). Eighty-five percent of the oral dose of sulfasalazine enters the unabsorbed colon when the anaerobic environment reduces it. Flurbiprofen's colon-specific formulation was assessed using azo-aromatic and pH-sensitive polymer and it was found that azo-aromatic polymer and pH-sensitive polymer eudragite S can be used effectively for the delivery of colonic drugs. The delivery of salbutamol sulphate to pulsincap drugs was explored. An empty gelatin capsule was covered with ethyl cellulose that kept the cap as such. A hydrogel plug made of gelatin was appropriately covered with cellulose acetate phthalate to fix it under the cap to the body. Eudragit microspheres comprising salbutamol sulphate were prepared using the technique of evaporating emulsion solvents and integrated into this specific capsule shell. .The findings of the in vitro dissolution stated that the drug release began after 7 to 8 hours of the experiment. Mutual azoprodrug of 5-aminosalicyic acid was synthesized with histidine by combining L-histidine with salicylic acid to deliver targeted drugs to inflamed gut tissue.

4.2 Glucuronide conjugate

Glucuronide and sulphate conjugation are the main mechanisms for drug clearance inactivation and preparation. Lower gastrointestinal tract bacteria secrete glucuronidaseglucouronidating in the intestine a range of drugs. Since the method of glucuronidation outcomes in the release of active drug and allow its reabsorption,glucuronideprodrugs are anticipated to be superior for the delivery of the colon-targeted drug.

4.3 Cyclodextrin conjugates

In the instant release and delayed release-formulations, hydrophobic and ionizablecyclodextrins may serve as powerful drug carriers, while hydrophobic cyclodextrins may delay the release rate of water. In addition, the drug carrier's most desirable attribute is its capacity to deliver a drug to a specific site. Cyclodextrin conjugates of a drug can be a versatile means of building a fresh class of colon targeting drugs that are soluble. Ibuprofen prodrugs were explored for α—, β-and π-cyclodextrins. Methotrexate prodrugs of α-and πCyclodextrins were also synthesized and the primary goal was to mask the ulcerogenic potential of free drugs by using 12 times the normal dose.

4.4 Dextran conjugates

Metronidazole Dextran ester prodrof was prepared and distinguished. The dexamethasone and methyl prednisolone dextran ester prodrugs were synthesized and demonstrated the effectiveness of the prodrugs to deliver drugs to the colon. By using a succinate linker, methyl prednisolone and dexamethasone were covalently connected to the dextran**.**

4.5 Amino-acid conjugates
They decrease the membrane permeability of amino acids and proteins due to the hydrophilic nature of polar groups such as NH2 and COOH present in the proteins and their fundamental units (i.e. the amino acids). The conjugation of drug molecules to these polar amino acids has prepared various prodrugs. Non-essential amino acids such as tyrosine, glycine, methionine and glutamic acid were conjugated to Salicylic acid.

4.6 Hydrogels
For site-specific shipment of peptide and protein drugs through the colon, hydrogels can be used. The Hydrogels are made up of acidic commoners and aromatic crosslinks of enzymatically degradable azo. Gels show less swelling in the acid pH that protects the drug from stomach degradation. Increasing the pH of the setting, i.e. becoming fundamental, increases swelling. This result is easy access of enzymes like azoreductase, which ultimately release of the drug.

4.7 Coating with pH-dependent polymers
It is possible to target the pH in the terminal ileum and colon greater than in any other region of the gastrointestinal tract and thus dosage forms that disintegrate into the region at elevated pH ranges. In the terminal ileum area, a pH level is greater than in the cecum Dosage forms are often delayed at the ileocecal junction, careful selection of entry coat composition and thickness is necessary to ensure that disintegration does not occur until the dosage moves from the terminal ileum to the cecum through the ileocecal junction. Eastacryl, Kollicoat MAE, polymeric methacrylates are synonyms of eudragit. Delayed mesalazine-coated release tablets with eudragitS-100 have been researched. These tablets dissolved at a pH level of 7 or higher, releasing mesalazine for topical inflammatory action in the colon in the terminal ileum and beyond. The formulation was effective in obtaining site-specific mesalazine delivery, it was noted that the coating had failed to dissolve. Acrylic acid and cellulose derivatives are the most frequently used pH-dependent polymers. Drug core is covered with pH-sensitive polymers for colonic drug delivery. Tablets, capsules, pellets, granules, microparticles, and nanoparticles are included in the drug.

4.8 Timed released systems
(Example: Pulsatile release, Pulsincap, Delayed release, Sigmoidal release system) It is based on the idea of stopping drug release after entering the tiny intestine for 3–5 hours. In this strategy, after a predetermined lag moment, drug release from the scheme depends on the transit moment from mouth to colon. The lag time relies on the dosage form's gastric motility and size. The Pulsincap system is one of the oldest methods. This apparatus is a non-disintegrating half capsule body sealed with a hydrogel plug at the open end, which is covered by a water-soluble cap. To avoid the problem of variable gastric emptying, the entire unit is coated with an enteric polymer. The enteric coating dissolves when the capsule enters the small intestine and the hydrogel plug begins to swell. The quantity of hydrogel is adapted so that it appears to release the contents only after the specified period of moment. In another approach, together with the drug substance, organic acids were filled in the body of a hard gelatin capsule as a pH adjusting agent. The capsule joint was sealed using an ethanolicethylcellulose solution. First, the capsule was covered with an acid-soluble cationic polymer, then a hydrophilic polymer hydroxypropyl methylcellulose, and lastly enterically covered with hydroxy propyl methylcellulose acetate succinate.

4.9 Redox sensitive polymer coating
Analogs to azo bond cleavage by intestinal enzymes are being created for colon targeting, novel polymers which hydrolyze non-enzymatically by enzymatically produced flavins. Bacteroidesfragilis, a prevalent colonic bacterium, was used as a test organism and the decrease of azo amaranth, orange II, tartrazine and a model azo compound was researched. The azo compounds were discovered to be lowered at distinct levels and the decrease rate could be associated with the azo compounds ' redox potential.

4.10 Bioadhesivesystems
Bioadhesion is a method whereby for an increased period of time a dosage form stays in touch with a specific organ. In the event of poorly absorbable drugs, this longer drug residence would have elevated local concentration or enhanced absorption features. This approach can be used to formulate mechanisms for the shipment of colonic drugs. Different polymers were explored as components for bioadhesive structures, including polycarbophiles, polyurethanes, and polyethylene oxide polypropyline oxide copolymers.[12][13]

5. PLATFORM TECHNOLOGIES FOR COLON TARGETED DRUG DELIVERY SYSTEMS
The design of the dosage form is now becoming complex because there is a vast use of technology in the dosage forms to regulate various components. Few examples are discussed in the case of colon-targeted drug delivery.

5.1 Pulsincap
Pulsincap was the first formula based on the time-release principle. It was similar in appearance to a hard gelatin capsule. It consists of a water-insoluble entrance-coated cap that is soluble in the water of the body. With a wih hydrogel plug in the body, the contents are plugged. When given, after a predetermined time, the enteric coat dissolves and the hydrogel plug starts to swell.

5.2 CODES
CODES is a unique colon-targeted mechanism of drug delivery designed to avoid intrinsic pH or time-dependent problems. It consists of three layers of important polymer-coated tablets. The first coating is an acid-soluble polymer (Eudragit), and the exterior layer is enteric between them with an HPMC barrier layer to prevent any contact between the layer. The main tablet comprises one or more active components and polysaccharides. Enterobacteria degrade the organic acid produced by polysaccharides. During its journey through GIT, CODES remain intact in the stomach as a result of entry protection, but the entry barrier layer dissolves in the small intestine where pH is 6.

5.3 Port system
It comprises of a semi-permeable membrane gelatin sac (e.g. cellulose acetate) comprising an insoluble plug (e.g. lipid) and an active osmotic agent along with the drug formulation. When in contact with the aqueous medium, water diffuses through the semi-permeable membrane, resulting in increased internal pressure that ejects the plug after a time of lag.

5.4 Time clock system
It consists of a powerful dosage type with lipid barriers consisting of carnauba-wax and bee-wax together with surfactants such as polyoxyethylenesorbitanmonooleate, to prevent premature release of medication in the tiny intestine, the system was further coated with enteric polymers. The release of the drug is autonomous of the pH and digestive state of the intestines. The drug's release is independent of the pH and intestinal digestive state.
The release mainly depends on the thickness of the coat applied. After a predetermined moment of lagging, once the coat erodes or emulsifies in the aqueous setting, the core becomes subject to the colonic setting resulting in the drug being completely released.

5.5 Cronotropic system
It consists of a drug containing nucleus covered by a hydrophilic swell capable of HPMC, which is responsible for a lag phase in the initiation of discharge. In addition, by applying an external gastric-resistant enteric film, the variability in the gastric emptying time can be overcome and a colon-specific drug release can be obtained based on the relative reproducibility of the small intestinal time.

5.6 Targit technology
It is based on the application of a pH-sensitive coating to injection-shaped starch capsules. It is designed to supply site-specific medicines to the colonic area. This scheme was designed to treat local pathologies of decreased GI disease. The clinical data generated in the shipment of colon-targeted drugs showed its suitability.[14]

6. CONCLUSION
Because of its mainly colon-only action, developing an effective colon-specific acting drug remains a challenge. Some of the work done over the past two years has been particularly good at overcoming the side effects. Colon-targeted drug delivery will discover the key position in novel drug delivery in the future by mixing different other approaches.

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