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Colon Specific Drug Delivery System: Review

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ABSTRACT

Colon is the site where both local and systemic delivery of drugs is applicable. Local delivery allows the topical treatment of inflammatory bowel diseases. Treatment can be made effective if the drugs can be targeted directly into the colon, thus reducing the systemic side effects. Targeted drug delivery into the colon is applicable for local treatment of many bowel diseases such as ulcerative colitis, Crohn's disease, amoebiasis, colonic cancer and systemic delivery of protein and peptide drugs. Colon-specific systems are the most important delivery of the drugs which are normally inactivated in the upper parts of the gastrointestinal tract (GIT). Primary approaches for CTDDS (Colon Targeted Drug Delivery System), includes the prodrugs, pH and time-dependent systems, bacterial enzyme dependent colonic DDS and pH and bacterial enzyme dependent colonic DDS.

Keywords: Colon, Targeted delivery, Time dependent system, Gastro intestinal tract

INTRODUCTION

Treatment of a variety of bowel diseases such as ulcerative colitis, Crohn's disease, amebiosis, colonic cancer can be achieved by targeted drug delivery system.[1] The colon specific drug delivery system (CDDS) is capable of protecting the drug to the colon i.e. drug release and absorption should not occur in the stomach as well as the small intestine, but only released and absorbed once the system reaches the colon.[2] Colon is believed to be a suitable absorption site for peptides and protein drugs for the following reasons; (i) less diversity, and intensity of the digestive enzymes, (ii) comparative proteolytic activity of the colon mucosa is much less than that observed in the small intestine, thus CDDS protects peptide drugs from hydrolysis, and enzymatic degradation in duodenum and jejunum, and releases the drug into ileum or colon which leads to greater systemic bioavailability.[3]

The colon has a long residence time which is up to 5 days and is highly responsive to absorption enhancers.[4] Oral route is the most convenient and preferred route but other routes for CDDS may be used.[5] The concentration of drug reaching the colon depends on formulation factors, the extent of retrograde spreading and the retention time.[6] The human colon has over 400 distinct species of bacteria, a possible population of up to 1010 bacteria per gram of colonic contents. The reactions carried out are azoreduction and enzymatic cleavage i.e. glycosides. These metabolic processes is responsible for the metabolism of many drugs and may also be applied to colon-targeted delivery of peptide based macromolecules.[7]

Criteria for Selection of Drug for CDDS

The drugs for CDDS are those which show poor absorption from the stomach or intestine including peptides. The drugs used in the treatment of IBD, ulcerative colitis, diarrhea, and colon cancer are ideal candidates for local colon delivery. The criteria for selection of drugs for CDDS is summarized in the table.

Criteria	Pharmacological class	Non-peptide drugs	Peptide drugs
Drugs used for local effects in colon against GIT diseases	Anti-inflammatory drugs	Oxyprenelol,Metoprolol,Nifedipine	Amylin,Antisense,Oligonucleotide
Drugs poorly absorbed from upper GIT	Antihypertensuve and antianginal drugs	Ibuprofen,Isosorbides, Theophylline	Cyclosporine, Desmopressin
Drugs for colon cancer	Antineoplastic drugs	Pseudoephidine	Epoetin,Glucagon
Drugs that degrade in stomach and small intestine	Peptides and proteins	Brompheneramine,5-Flourouracil,Doxorubicin	Gonadroreline, Insulin,Interferones
Drugs that undergo extensive first pass metabolism	Nitroglycerin and corticosteroids	Bleomycin,Nicotine	Protirellin,Sermorelin,Saloatonin
Drugs for targeting	Antiarthritic and antiasthmatic drugs	Prednisolne,hydrocortisone,5-Amino-salicylic acid	Somatropin,Urotoilitine

FACTORS INFLUENCING COLON-SPECIFIC DRUG DELIVERY AND COLONIC BIOAVAILABILITY

Several factors may influence the /development of a colon-specific drug delivery system (CDDS) and the colonic bioavailability of the drugs.[8] Some of these factors are briefly discussed below.

Anatomical/Physiological Factors

The rectum is a small distal portion of the 1.5 m long human large intestine, which forms the colon (ascending, transverse, and descending). The colon has a lumen coated with mucus and measures 2-3 inches in diameter. The colon's physiology is very different from that of other gastrointestinal tract (GIT) segments. Additionally, there are differences in the physiological and physical characteristics of the colonic contents in the ascending, transverse, descending, and sigmoidal colons. Furthermore, food and dose forms flow differently throughout the colon, which could be problematic for the development of colonic medication delivery systems.[9] The GIT's fluctuating pH is another physiological element that influences colonic medication administration and absorption. There is notable variation both within and between subjects when it comes to the pH of the gastrointestinal tract in humans of different ages, sexes, fasted or fed states, and illness states.[10] The performance of CDDS is further influenced by parameters such the amount and viscosity of colonic fluids, the presence of microbial enzymes, and the subsequent colonic metabolism.

Time of Intestinal-Colonic Transit

The intestinal-colonic transit period is crucial to the effectiveness of CDDS. States of colonic illness, such as UC and CD, affect transit times. Colic times in patients with UC are known to be less than those in healthy persons (~24 h versus ~52 h).[11] The orocecal transit time was slowed in IBD patients.[12]

The kind of dosage form, the timing of administration, and the presence or absence of food all affect how dose forms transit. The impact of dawn and dusk on the motility of dosage forms in the colon was investigated by Stubbs et al. The findings demonstrated that colonic transit was slowed down during sleep and that larger dosage forms—like capsules—transformed more quickly than smaller ones—like scattered particles.[13]

Volume of Colonic Fluid

Humans consume about 1.5 kg of food on average. The food's constituents may act as substrates for the microbial enzymes in the colon.[14] The colon may absorb about 90% of the water due to its great capacity for water absorption.[15] The volume of colonic fluid ranges from 1 to 44 milliliters, with an average of about 13 milliliters.[16]

Viscosity of Colonic Luminal Contents

The colonic luminal contents have a higher viscosity than the upper GIT contents because of their greater potential to absorb water, which makes it more difficult for CDDS to dissolve. As the contents go from the ascending colon to the descending colon, their viscosity gradually rises, which reduces the amount of medicine that dissolves and the amount of absorption by the mucosa.[17]

Viscosity affects how well a medication penetrates the colon's disease-causing germs. It has been demonstrated that the viscosity of the colon's contents affects the motility of bacteria within it.[18]

Colonic pH

The various GIT areas have considerably varying pH values. As an illustration pH of gastrointestinal contents can be as low as 1 to 2 in the stomach and rise to 7.5 in the distal small intestine. The pH then declines from the end of the small intestine to the colon and gradually increases once again in the colon.[19] Polysaccharide-based drugs may also alter colonic pH. Laxative drugs like lactulose are known to be fermented by colonic bacteria to produce lactic acid and reduce colonic pH..[20] The pH of the colon affects the pharmacokinetic and pharmacodynamic behavior of CDDS by the solubility of drugs in the colonic fluid.

Colonic Enzymes and Metabolism

The colon consists of over 400 different species of aerobic and anaerobic microorganisms like *Escherichia coli* and *Clostridium* species, respectively.[21] The colonic enzymes catalyze a range of reactions, including the metabolism of xenobiotics (*e.g.*, drugs) and other biomolecules (*e.g.*, bile acid), deactivation of harmful metabolites as well as carbohydrate and protein fermentation .[22] Polysaccharides such as chitosan, guar gum, pectin, *etc.*, are commonly employed as the release rate-controlling components in colon-targeted dosage forms. These polysaccharides are known to be resistant to gastric and intestinal enzymes, but are metabolized by anaerobic bacteria in the colon .[23].Drugs are also known to be susceptible to biotransformation by colonic enzymes. The metabolism of drugs by the colonic enzymes may result in the formation of metabolites that are pharmacologically active, inactive, or sometimes even harmful.[24] .Formation of a pharmacologically active metabolite by the colonic metabolism of drugs is commonly used "prodrug" approach for colon-specific drug delivery systems.

CONVENTIONAL APPROACHES FOR ACHIEVING COLONIC DELIVERY

Prodrugs

Prodrugs are inactive derivatives of a drug molecule that release the active ingredient after being hydrolyzed by enzymes, such as in the colon.[25] To optimize colon-specific drug delivery, the extent of this hydrolysis should be minimal in the upper gastrointestinal tract and much greater in the colon. Kim et al. prepared a prodrug of metronidazole, using a sulfate group, and showed that that this formulation remained intact in the upper intestine, but was cleaved in the presence of rat cecal contents and active metronidazole was released. Similar to the first prodrug, much less of the conjugated prodrug was degraded and absorbed in the small intestine compared to the active drug after oral administration. As a result, the minimum quantity is absorbed by the cycle of the system.[26]

Vaidya et al compared the release of drugs from this composition to the formation of a pectin mixty fair, which physically seized drugs by combining metronidazol and pectin to combine a pectin. The prodrug pectin-metronidazole (PT-ME) showed significantly reduced drug release in the upper gastrointestinal tract compared to metronidazole-loaded pectin microspheres. In vitro and in vivo studies showed that the drug-pectin binding resulted in no drug release from the prodrug PT-ME at acidic pH and nearly 100% of the metronidazole was physically entrapped, allowing successful targeting of delivery to the colon. pectin microspheres were released into the same environment. A significantly higher percentage of drug was released from the PT-ME prodrug in the colon.[27]

Colon-Specific Biodegradable Delivery Systems

The column contains many kinds of anaerobic bacteria that receive energy by fermenting substrates. Bacteroids, uvoquettelia, chrostridium, iliacococci, and osteiotism are some examples of these species specific to the colon, and to ferment these polimers, glucronidase, xylocidase, nitro ductase, azolesic acid, etc. Produces a large number of enzymes.[28] Since these enzymes are localized in the colon, this is a more promising approach to the special delivery of the large intestine. Polymers used in the development of CDDS can be chemically modified, and these modifications can influence the extent of enzymatic degradation.[29] For example, Roos et al. synthesized an acetyl derivative of guar gum (AcGGM) and used this polymer to prepare bovine serum albumin (BSA) hydrogels. Hida et al. conducted a study to coat metronidazole capsules with films of azo-aromatic polymer and pH-sensitive polymer. In vitro and in vivo results showed that colon-specific microbiota degrade these polymers and release metronidazole locally in the colon.[30]

Matrix-Based Systems

Approaches to colon-targeted drug delivery include embedding drugs in polymer matrices for uptake and release in the colon. These matrices can be pH-sensitive or biodegradable. Ahmad et al. developed matrix tablets of metronidazole using a natural polymer called Assam-Bora rice starch. The prepared tablets were evaluated by using the pH 7.4 phosphate stamps and the HCL 0.1 n, which

is the content of the fecal goat substance, to use the research on the release of in vitro in Vitro. The results indicate that tablets indicate stable release of drugs in alkaline environments. This is related to polymer erosion and dissolution during long -term exposure to this environment.[31] However, the release of drugs was observed throughout Git. This indicates that these matrix tablets are not colon-specific delivery systems but rather controlled release systems**.**

Timed-Release Systems

These are based on the fact that the drug is released into the colon after a certain time and depends on the time it takes to pass through the small intestine. Gastric emptying time varies from person to person and also depends on food intake.[32] Colon-related diseases such as irritable bowel syndrome and ulcerative colitis can affect colonic transit time. Gazzaniga et al. He created a specific colon of the colon using a combination of a polymer that is sensitive to pH and a temporary release approach.[33] The composition is composed of a nucleus, containing a drug trapped in a three -layer polymer (a closely hydrophilic layer between two PH -sensitive layers).

Bioadhesive system

With this system, the composition can keep contact with organs for a long time to absorb the absorbed drug.[34] Part of the polymer that is studied in the form of biological detacial components of these systems contains polycarbo files, polyurethane, and polyethylexide. Ahmad et al used Assam-Bora rice starch to develop a bioadhesive microsphere (BAM) for targeted delivery of metronidazole to the colon. These BAMs have been shown to have a long colonic residence time and promote drug absorption in the colon. In vitro drug release studies have shown that only 10-12.5% of metronidazole is released under simulated gastric conditions and less than 25% is released in the simulated small intestine. However, over 90% of the drug was rapidly released into the cecal contents. Additional in vivo studies showed that the drug was released only when the BAM reached the colon and was pharmacologically effective as the commercial formulation.[35]

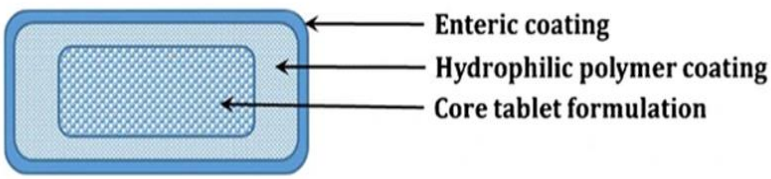
Multiparticulate systems

Studies have shown that multiparticulate systems have smaller particle size than single unit systems and pass through the digestive tract more easily, allowing them to reach the colon more quickly. Microspheres are one example of a multiparticulate system that can be loaded with a drug for colonic delivery. Micross fair, which is prepared using biodegradable components, is absorbed by macrophages.[36]

Colon targeting by coatings

By incorporating drugs into a polymer that is sensitive to pH, the release is delayed by protecting the active ingredient from the acid pH of the stomach. These polimers are broken down with the more basic pH of the terminal Erene and provide drugs targeting the colon.[37] PH fluctuations along the Git will lead to the dissolution of the formula at the start of the small intestine, and the delay time may be too long for the Eleo cerebral junction and the ascending colon.[38] Several examples of polymers that are commonly used in pHs that are commonly used in the design of the colon drug administration system include a metacricrylate polymer, also known as EUDRAGIT®.

Intestinal melting polymer is resistant to dissolving the stomach into the acid environment, but may dissolve with a higher pH value of the intestine. These polymers have been extensively studied for their use as coatings in formulations designed to deliver active pharmaceutical ingredients specifically to the colon. Polymethacrylate-based polymers such as Eudragit® L and Eudragit® S have often been used for this purpose, and each has its own unique pH value at which it dissolves. These two polymers were mixed in different proportions to form a coating with an optimized dissolution rate. In addition, coatings with these polymers are designed to be relatively thick in order to prolong their dissolution and ensure controlled or sustained release of the drug.[39]



Schematic representation of the cross-section of the enteric-coated colon-targeted drug delivery system.

Yasin et al. applied a granular chitosan coating to a colon-targeted formulation of 5-fluorouracil using compression coating, aiming to specifically target this drug to the colon to more effectively treat colon cancer with fewer toxic side effects. [40] In vitro evaluation of the formulation showed that increasing the coating thickness gradually decreased drug release at acidic pH. Furthermore, in vivo studies have shown that the formula is not degraded before reaching the colon.

CONCLUSIONS

The development of colon-targeted oral drug delivery systems has attracted increasing interest among formulation scientists in recent years. Colon-targeted drug delivery systems offer therapeutic benefits to patients in terms of safety, efficacy and patient compliance. Factors including the physicochemical characteristics of the drug, formulation and process variables, as well as the GI physiological factors influence, and may present a challenge to the successful formulation of a colon-specific drug delivery system. The formulation approaches utilized to overcome these challenges mainly focus on the mechanism of drug delivery, such as the pH environment of upper GIT by the dosage form, preventing the drug release and drug-absorption in the upper GIT, and releasing the drug in the colon for absorption. The metabolic capabilities of colonic enzymes are also being investigated for targeted delivery to the colon. This combination of traditional and novel approaches is essential for the development of colon-specific drug delivery systems.

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