COLON TARGETED DRUG DELIVERY SYSTEMS – A REVIEW

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ABSTRACT
Colonic drug delivery has gained increased importance not just for the delivery of the drugs for the treatment of local diseases associated with the colon like Crohn’s disease, ulcerative colitis, irritable bowel syndrome and constipation but also for the systemic delivery of proteins, therapeutic peptides, antiasthmatic drugs, antihypertensive drugs and antidiabetic agents. Bioavailability of drug may be low due to potentially binding of drug in a nonspecific way to dietary residues, intestinal secretions, mucus or faecal matter. The surface area of the colon is much less compared to small intestine and is compensated by absence of endogenous digestive enzymes and long residence time of colon (10-24 hours). Time dependent systems are not ideal to deliver drugs to the colon specifically for the treatment of colon related diseases. Appropriate integration of pH sensitive and time release functions into a single dosage form may improve the site specificity of drug delivery to the colon. Since the transit time of dosage forms in the small intestine is less variable i.e. about 3±1 hr.30 The time-release function (or timer function) should work more efficiently in the small intestine as compared the stomach. In the small intestine drug carrier will be delivered to the target side, and drug release will begin at a predetermined time point after gastric emptying. The ideal drug candidates for colonic drug delivery include agents that are useful for disorders such as IBD, ulcerative colitis, amoebiasis and colon cancer.

Keywords: Bioavailability, colon, Crohn’s disease, pH sensitive.

INTRODUCTION
The oral route of drug administration is the most convenient and important method of administering drugs for systemic effect. Nearly 50% of the drug delivery systems available in the market are oral D.D.S. and these systems have more advantages due to patient acceptance and ease of administration[1,2] During the last decade there has been interest in developing site-specific formulations for targeting drug to the colon. Colonic drug delivery has gained increased importance not just for the delivery of the drugs for the treatment of local diseases associated with the colon like Crohn’s disease, ulcerative colitis, irritable bowel syndrome and constipation but also for the systemic delivery of proteins, therapeutic peptides, antiasthmatic drugs, antihypertensive drugs and antidiabetic agents. [3,4] Coating of the drugs with pHsensitive polymers provides simple
approach for colon-specific drug delivery. In the past two decades, the pharmaceutical scientists are extensively investigated in the area of colonic region for targeted drug delivery system. Targeted drug delivery to the colon is mainly for the treatment of colonic diseases, for drugs like proteins and peptides, for the treatment of diseases sensitive to circadian rhythms such as Asthma, Angina and Rheumatoid arthritis and for delivery of steroids, which absorbable in colon. The advent of slow release technologies increase the chances for a drug to be released in the colon and thus this organ has an important role to play in drug absorption from oral sustained release formulations.

In 1942, Svartz discovered that sulfasalazine; the sulfanilamide prodrug of 5- amino salicylic acid (5-ASA) is effective in the treatment of rheumatoid arthritis and anti-inflammatory disease. The exact mode by which the drug target itself to the colon was elucidated much latter in 1970 i.e., colon specific azoreductase splits sulfasalazine causing the release of the active moiety 5- aminosalicylic acid.

Colon-specific drug delivery system offers the following therapeutic advantages \cite{16,17,18}

1. Reducing the adverse effects in the treatment of colonic diseases (ulcerative colitis, colorectal cancer, crohn’s disease etc.)
2. By producing the ‘friendlier’ environment for peptides and proteins when compared to upper gastrointestinal tract.
4. Preventing the gastric irritation produced by oral administration of NSAIDS.
5. Delayed release of drugs to treat angina, asthma and rheumatoid arthritis.

To achieve successful colon targeting it should overcome the following limitations \cite{19}

1. The location at the distal portion of the alimentary canal, the colon is difficult to access.
2. Successful delivery requires the drug to be in solution before it arrives in the colon, but the fluid content in the colon is lower and more viscous than in upper GIT, which is the limiting factor for poorly soluble drugs.
3. Lower surface area and relative tightness of the tight junctions in the colon can restrict drug transport across the mucosa in to the systemic circulation.
Advantages of colon targeting drug delivery system:[5,6,9]

- Colon is an ideal site for the delivery of agents to cure the local diseases of the colon.
- Local treatment has the advantage of requiring smaller drug quantities.
- Reduces dosage 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).
- Bye pass initial first pass metabolism.
- Extended daytime or nighttime activity.
- Improve patient compliance.
- Targeted drug delivery system.
- It has a longer retention time and appears highly responsive to agents that enhance the absorption of poorly absorbed drugs.[10]
- It has low hostile environment, less peptidase activity so peptides, oral vaccines, insulin, growth hormones, can be given through this route.[11]

Limitations of colon targeting drug delivery system:

- Multiple manufacturing steps
- The resident microflora could also affect colonic performance via metabolic degradation of the drug
- Incomplete release of drug
- Bioavailability of drug may be low due to potentially binding of drug in a nonspecific way to dietary residues, intestinal secretions, mucus or faecal matter.
- Drug should be in solution form before absorption and there for rate limiting step for poor soluble drugs.
- Non availability of an appropriate dissolution testing method to evaluate the dosage form in-vitro.[12]
• An important limitation of the pH sensitive coating technique is the uncertainty of the location and environment in which the coating may start to dissolve. Normal in patients with ulcerative colitis.\textsuperscript{[13,14]}

• Limitations of prodrug approach is that it is not very versatile approach as it’s formulation depends upon the functional group available on the drug moiety for chemical linkage.

ANATOMY AND PHYSIOLOGY OF COLON
Irrespective of therapy desired for local (colonic) or systemic delivery of drug, the development and aim of the drug delivery to colon remains same\textsuperscript{[16]} that is

• The drug must not absorb from other regions of the gastro intestinal tract (GIT).

• It should only suffer negligible degradation in the small intestine lumen.

• The release of the drug in the colon should be at quantitatively controlled rate and the released drug in the colon should be absorbed from the lumen of the large intestine without any appreciable degradation.

In order to meet these properties, a thorough knowledge of the anatomy and physiology of GIT is required. In GIT, large intestine starts from the ileocecal junction to the anus with a length of about 1.5 meters (adults) and is divided into three parts; they are colon, rectum and anal canal. The colon is the upper five feet of large intestine and mainly situated in the abdomen. The colon is a cylindrical tube lined by mucosa. The cecum, colon ascends, colon transversale, colon descendens and recto sigmoid colon made of the colon. Colon is made up of four-layers, serosa, muscularisexterna, sub mucosa, and mucosa. The colon does not have villi, but due to presence of plicaesemilunares (crescentic folds) the intestinal surface of the colon is increased to approximately 1300 cm\textsuperscript{2}. CDDS is primarily dependent on the following physiological factors; they are the pH level, the transit time and the microbial environment in the colon, which are governing the release rate of drug from different designs of CDDS\textsuperscript{[16]}

Approaches used for Site Specific Drug Delivery to Colon (CDDS)
Several approaches are used for site-specific drug delivery. Among the primary approaches for CDDS, These include:

1) Primary Approaches for CDDS
a. pH Sensitive Polymer Coated Drug Delivery to the Colon

In the stomach, pH ranges between 1 and 2 during fasting but increases after eating. The pH is about 6.5 in the proximal small intestine, and about 7.5 in the distal small intestine. From the ileum to the colon, pH declines significantly. It is about 6.4 in the cecum. However, pH values as low as 5.7 have been measured in the ascending colon in healthy volunteers. The pH in the transverse colon is 6.6 and 7.0 in the descending colon. Use of pH dependent polymers is based on these differences in pH levels. The polymers described as pH dependent in colon specific drug delivery are insoluble at low pH levels but become increasingly soluble as pH rises. Although a pH dependent polymer can protect a formulation in the stomach, and proximal small intestine, it may start to dissolve in the lower small intestine, and the site-specificity of formulations can be poor. The decline in pH from the end of the small intestine to the colon can also result in problems, lengthy lag times at the ileo-cecal junction or rapid transit through the ascending colon which can also result in poor site-specificity of enteric-coated single-unit formulations.

b. Delayed (Time Controlled Release System) Release Drug Delivery to Colon

Time controlled release system (TCRS) such as sustained or delayed release dosage forms are also very promising drug release systems. However, due to potentially large variations of gastric emptying time of dosage forms in humans, in these approaches, colon arrival time of dosage forms cannot be accurately predicted, resulting in poor colonical availability. The dosage forms may also be applicable as colon targeting dosage forms by prolonging the lag time of about 5 to 6 h. However, the disadvantages of this system are:

i. Gastric emptying time varies markedly between subjects or in a manner dependent on type and amount of food intake.

ii. Gastrointestinal movement, especially peristalsis or contraction in the stomach would result in change in gastrointestinal transit of the drug.

iii. Accelerated transit through different regions of the colon has been observed in patients with the IBD, the carcinoid syndrome and diarrhea, and the ulcerative colitis.
Therefore, time dependent systems are not ideal to deliver drugs to the colon specifically for the treatment of colon related diseases. Appropriate integration of pH sensitive and time release functions into a single dosage form may improve the site specificity of drug delivery to the colon. Since the transit time of dosage forms in the small intestine is less variable i.e. about 3±1 hr.\textsuperscript{30} The time-release function (or timer function) should work more efficiently in the small intestine as compared the stomach. In the small intestine drug carrier will be delivered to the target side, and drug release will begin at a predetermined time point after gastric emptying. On the other hand, in the stomach, the drug release should be suppressed by a pH sensing function (acid resistance) in the dosage form, which would reduce variation in gastric residence time.\textsuperscript{25} Enteric coated time-release press coated (ETP) tablets, are composed of three components, a drug containing core tablet (rapid release function), the press coated swellable hydrophobic polymer layer (Hydroxy propyl cellulose layer (HPC), time release function) and an enteric coating layer (acid resistance function).\textsuperscript{26,31} The tablet does not release the drug in the stomach due to the acid resistance of the outer enteric coating layer. After gastric emptying, the enteric coating layer rapidly dissolves and the intestinal fluid begins to slowly erode the press coated polymer (HPC) layer. When the erosion front reaches the core tablet, rapid drug release occurs since the erosion process takes a long time as there is no drug release period (lag phase) after gastric emptying.

c. Microbially Triggered Drug Delivery to Colon

The microflora of the colon is in the range of 10\textsuperscript{11} -10\textsuperscript{12} CFU/mL, consisting mainly of anaerobic bacteria, e.g. bacteroides, bifidobacteria, eubacteria, clostridia, enterococci, enterobacteria and ruminococcus etc.\textsuperscript{26} This vast microflora fulfills its energy needs by fermenting various types of substrates that have been left undigested in the small intestine, e.g. di- and tri-saccharides, polysaccharides etc.\textsuperscript{31,32} For this fermentation, the microflora produces a vast number of enzymes like glucoronidase, xylosidase, arabinosidase, galactosidase, nitroreductase, azareducatase, deaminase, and urea dehydroxylase.\textsuperscript{33} Because of the presence of the biodegradable enzymes only in the colon, the use of biodegradable polymers for colon-specific drug delivery seems to be a more site-specific approach as compared to other approaches.\textsuperscript{31} These polymers shield the drug from the environments of stomach and small intestine, and are able to deliver the
drug to the colon. On reaching the colon, they undergo assimilation by micro-organism, or degradation by enzyme or break down of the polymer back bone leading to a subsequent reduction in their molecular weight and thereby loss of mechanical strength.\textsuperscript{34,35,36,37,38} They are then unable to hold the drug entity any longer.\textsuperscript{39}

**Transit through GIT:**\textsuperscript{42}

The drug delivery systems first enter into stomach and small intestine via mouth and then reach colon. The nature and pH of gastric secretion and gastric mucus influence the drug release and absorption. In order to successfully reach colon in an intact form, the drug delivery systems should surpass the barriers in the stomach and small intestine. Gastrointestinal transit varies from 1 hr to 3 hrs depending upon the condition (fasting or non-fasting). Normally, the small intestinal transit is not influenced by the physical state, size of the dosage form and presence of food in the stomach. The mean transit time of the dosage form is about 3-4 hrs to reach the ileocecal junction and the time period is consistent. During this period the dosage form is exposed to enzymes present in small intestine. Compared to the other region of GIT, movement of material through the colon is slow.

**Colonic Microflora:**\textsuperscript{43}

The human alimentary canal is highly populated with bacteria and other microflora at both ends, the oral cavity and the colon/rectum. In between these two sites, the GIT is very sparsely populated with microorganisms. Microorganisms of the oral cavity do not normally affect oral drug delivery systems and as such will not be considered here further. However, gut microflora of the colon have a number of implications in health and the treatment of disease such as IBD. This section presents some background information on gut micro flora as it relates to colonic-based delivery system. Concentration of gut microflora rises considerably in the terminal ileum to reach extraordinarily high levels in the colon. The gut bacteria are capable of catalyzing a wide range of metabolic events. Many colon-specific drug delivery systems rely on enzymes unique to gut micro flora to release active agents in the colon. However, only two or three enzyme systems have been exploited in this area: azoreductases and glycosidas (including glucuronidase). A large number of polysaccharides are actively hydrolyzed by gut microflora leading to the possibility of using naturally occurring biopolymer as drug carriers. In addition, ethereal
sulphate prodrugs or carboxylated prodrugs may be metabolized in the colon to the parent drug leading to local delivery in the colon.

**Stomach and Intestinal pH:**

Generally, the release and absorption of orally administered drugs are influenced by the GI pH. The 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 conditions respectively.\(^ {45} \)

**Drug candidates for colon delivery:**\(^ {44} \)

Theoretically, any drug can be a candidate for colon targeted drug delivery. However only those drugs, which show poor bioavailability from the stomach or intestine and peptide drugs, are the most suitable for colonic targeting. The ideal drug candidates for colonic drug delivery include agents that are useful for disorders such as IBD, ulcerative colitis, amoebiasis and colon cancer.

**Gastrointestinal Disease State:**\(^ {45} \)

General intestinal diseases such as IBD (inflammatory bowel disease), crohn's disease, constipation, diarrhoea and gastroenteritis may affect the release and absorption properties of colon-specific drug delivery system.

**CONCLUSION**

From past two decades, considerable amount of research work has been carried out in the area of colon targeting. Colon is an ideal site for the delivery of agents to cure the local diseases of the colon. 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. Extended daytime or nighttime activity. Coating of the drugs with pH sensitive polymers provides simple approach for colon-specific drug delivery. In the past two decades, the pharmaceutical scientists are extensively investigated in the area of colonic region for targeted drug delivery system. Targeted drug delivery to the colon is mainly for the treatment of colonic diseases, for drugs like proteins and peptides, for the treatment of diseases sensitive to circadian rhythms such as Asthma, Angina and Rheumatoid arthritis and for delivery of steroids, which absorbable in colon
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