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REVIEW ARTICLE

Colon Targeted Drug Delivery System

Biresh K Sarkar*[1], Devananda Jain [1], Angshu Banerjee [2], Mamta Parwal [2]

[1]Dept. of Pharmaceutics & Pharmaceutical Technology, Bhagwant University, Ajmer
[2]Dept. of Pharmaceutics, Sri Balaji College Of Pharmacy, Jaipur, Rajasthan
[3]Dept. of Biotechnology, Biyani Girls College, Jaipur.

ABSTRACT

The colon is a site where both local and systemic delivery of drugs can take place. Local delivery could, for example, allow topical treatment of inflammatory bowel disease. Treatment could be made more effective if it were possible for drugs to be targeted directly on the colon. Systemic side effects could also be reduced. Colon specific systems might also allow oral administration of peptide and protein drugs, which are normally inactivated in the upper parts of the gastrointestinal tract. Primary approaches for CDDS (Colon Specific Drug Delivery), which includes prodrugs, pH and time dependent systems and microbially triggered drug delivery system achieved limited success and having limitations. Newly developed CDDS, which includes pressure controlled colonic delivery capsules (PCDCS), CODESTM and osmotic controlled drug delivery are unique in terms of achieving in vivo site specificity and feasibility of manufacturing process. This review also focuses on evaluations of CDDS in general.

Keywords: Colon drug delivery systems, Primary approaches, newly developed approaches, evaluation of colon targeted drug delivery systems

Corresponding author
E-mail: bireshsarkar@gmail.com

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INTRODUCTION

Controlled rate, slow delivery and targeted delivery are some of the focus systems that are being pursued very vigorously in light of patients' needs and also to succeed in today's competitive business world. In the area of targeted delivery, the colonic region of the GI tract is the one that has been embraced by scientists and is being extensively investigated over the past two decades. Targeted delivery to the colon is being explored not only for local colonic pathologies, thus avoiding systemic effects of drugs or inconvenient and painful trans-colonic administration of drugs, but also for systemic delivery of drugs like proteins and peptides, which are otherwise degraded and/or poorly absorbed in the stomach and small intestine but may be better absorbed from the more benign environment of the colon [1]. This is also a potential site for the treatment of diseases sensitive to circadian rhythms such as asthma, angina and arthritis. Furthermore, there is urgent need for delivery to the colon of drugs that are reported to be absorbable in the colon, such as steroids, which would increase efficiency and enable reduction of the required effective dose [2]. The treatment of disorders of the large intestine, such as irritable bowel syndrome (IBS), colitis, Cohn's disease and colon disease, where it is necessary to attain a high concentration of the active agent, may be efficiently achieved by colon-specific delivery [3,4].

LIMITATION

As a site for drug delivery, the colon offers a near neutral pH, reduced digestive enzymatic activity, a long transit time and increased responsiveness to absorption enhancers; however, the targeting of drugs to the colon is very complicated. Due to its location at the distal portion of the alimentary canal, the colon is particularly difficult to access [5]. The wide range of pH values and different enzymes present throughout the GI tract, through which the dosage form has to travel before reaching the target site also requires the drug to be in solution form before it arrives in the colon or, alternatively, it should dissolve in the luminal fluids of the colon, but this can be a limiting factor for poorly soluble drugs as the fluid content in the colon is much lower and it is more viscous than in the upper part of the GI tract [6,7]. In addition, the stability of the drug is also a concern and must be taken into consideration while designing the delivery system. The tight junctions in the colon can also restrict drug transport across the mucosa and into the systemic circulation. The literature also suggests that the cytochrome P450 3A class of drug-metabolizing enzymes has lower activity in the colonic mucosa [8,9]. A longer residence time of three to five days results in elevated plasma levels of the drugs and therefore higher bioavailability in general, but especially for drugs that are substrates for this class of enzyme.

STRUCTURE AND FUNCTION OF COLON

In order to design an effective and successful colon specific drug delivery system a thorough understanding of the anatomy and physiology of GIT is required. The GI tract is divided into stomach, small intestine and large intestine [10]. The large intestine extending from the ileocaecal junction to the anus is divided into three main parts. These are colon, the

rectum and the anal canal. The colon itself is made up of the caecum, the ascending colon, hepatic flexure, the transverse colon, the splenic flexure, the descending colon and the sigmoid colon.

The colon is mainly situated in the abdomen; the rectum is primarily a pelvic organ [11,12]. The colon is a cylindrical tube which is lined by four layers: serosa, the mascularis externa, the submucosa and the mucosa. The serosa is the external coat of the large intestine and consists of aerolar tissue that is covered by single layer of squamous mesothelial cells. The major muscularis cost of the large intestine is the muscularis externa. This is composed of an inner circular layer of fibres that surrounds the bowel. The submucosa is the layer of connective tissue that lies immediately beneath the mucosa [13].

Colon is about 1.5m long, the transverse colon being the longest and most mobile part and has an average diameter of 6.5cm, although it varies in diameter from approximately 9cm in the caecum to 2cm in the sigmoid colon [14].

The first portion of the colon is spherical and is called caecum. The next portion of the colon, in order in which contents flow; is the ascending (proximal) colon: just under the liver, the angle or bend is known as hepatic flexure. The colon then turns along horizontal segment, the transverse colon, beneath the left rib cage, teh colon turns downwards at the splenic flexure, the become the descending (distal) colon. In the left lower part of the abdomen, the colon makes an S-shaped curve from the hip over the midline known as sigmoid colon. The colon and rectum have an anatomic blood supply. Along these blood vessels are lymph nodes, which are found in circulating lymphatic system of the body.

The major functions of the colon are as follows:

Creation of suitable environment for the growth of colonic microorganisms, storage reservoir of faecal contents [15,16]

Colonic activities can be divided into segmenting and propulsive movements. Segmenting movements caused by circular muscles, are responsible for mixing of luminal contents whereas propulsive movements caused by longitudinal muscles, are associated with defecation.

PRODRUG APPROACH:

A prodrug is a pharmacologically inactive derivative of a parent molecule that requires some form of transformation *in vivo* to release the active drug at the target site. This approach involves covalent linkage between the drug and its carrier in such a manner that upon oral administration the moiety remains intact in the stomach and small intestine [17,18]. The type of linkage that is formed between the drug and carrier would decide the triggering mechanism for the release of the drug in the colon. This biotransformation is carried out by a variety of enzymes, mainly of bacterial origin, present in the colon. The enzymes that are mainly targeted

for colon drug delivery include azoreductase, β-galactosidase, β-xylosidase, nitroreductase, glycosidase deaminase, etc. Generally, a prodrug is successful as a colon drug carrier if it is hydrophilic and bulky, to minimise absorption from the upper GI tract and, once in the colon, it is converted into a more lipophilic drug molecule that is then available for absorption. Certain drugs can be conjugated to different sugar moieties to form glycosides. Because they are bulky and hydrophilic, these do not penetrate the biological membranes upon ingestion. They break down upon action of glycosidase, releasing the drug part form the sugar. Glycosidase activity of the GI tract is derived from anaerobic microflora in the large bowel or exfoliated cells of the small intestine. Friend and Chang prepared dexamethasone-2-β-glucoside and prednisolone-2-β-glucoside for delivery of these steroids to the colon. When free steroids were administered orally, they were almost absorbed in the small intestine and less than 1% of the oral dose reached the colon. Various non-essential amino acids such as glycine, tyrosine, methionine, and glutamic acid were conjugated to salicylic acid. The conjugate showed minimal absorption and degradation in the upper GI tract and showed more enzymatic specificity for hydrolysis by colonic enzymes. Glucuronide and sulphate conjugation is the major mechanism for the inactivation and preparation for clearance of many drugs. Bacteria of the lower GI tract, however, secrete β-glucuronidase and can deglucuronidate a variety of drugs in the intestine. The azo linkage exhibits a wide range of thermal, chemical, photochemical and pharmaceutical properties. The azo compounds are extensively metabolised by the intestinal bacteria, both by intracellular enzymatic components and extracellular reduction. The use of these azo compounds for colon targeting has been in the form of hydrogels as a coating material for coating the drug cores, and as prodrugs. Sulphasalazine, which was used for the treatment of rheumatoid arthritis, was later known to have potential in the treatment of inflammatory bowel disease (IBD). This compound has an azo bond between 5-ASA and sulphapyridine. Numerous drugs have been described that form complexes with β-cyclodextrins, enhancing the drug stability and/or absorption performance [21, 22]. The β-cyclodextrins are practically resistant to gastric acid and salivary and pancreatic amylases. A clinical study has shown clear evidence that β- cyclodextrins are poorly digested in the small intestine but are almost completely degraded by the colonic microflora [23,24] The challenge of this approach is the need to identify the appropriate chemical usage for the covalent linkage, which can result in safe and effective release of the drug with minimum fluctuation in terms of site specificity.

pH-DEPENDENT APPROACH:

This approach is based on the pH-dependent release of the drug from the system. In this case the pH differential between the upper and terminal parts of GI tract is exploited to effectively deliver drugs to the colon. One should not forget that the pH in the intestine and colon depends on many factors such as diet, food intake, and intestinal motility and disease states.

This makes it more challenging for the specialists working in this field to design a delivery system that would be robust enough to withstand the variability in the gastric pH as it moves from the stomach to the small intestine. By combining knowledge of polymers and their solubility at different pH environments, delivery systems have been designed to deliver the

drug at the target site [25,26]. commonly used co-polymers of methacrylic acid and methyl methacrylate have been extensively investigated for colonic drug delivery systems. *In vitro* evaluation of Eudragit® S and Eudragit® FS was performed and it was found that the latter would be more appropriate for drug delivery to the ileocolonic region [27]. Several factors, such as combinations of different polymers, pH of the media, coating level of the tablets and presence of plasticisers, influence the dissolution rate of Eudragit®[28]. Inter- and intra-subject variability, electrolyte concentration and transit time are some of the key variables impacting success through this route. In spite of these limitations, pH-based systems are commercially available for mesalazine (5 ASA) and budesonide for the treatment of ulcerative colitis and Crohn's disease, respectively.

TIME-DEPENDENT APPROACH:

Usually, time-dependent drug delivery systems are designed to deliver drugs after a lag of five to six hours. This approach is based upon the theory that the lag time equates to the time taken for the dosage form to reach the colon. The lag time is dependent on size of dosage form and gastric motility associated with the pathological condition of the individual. The residence times can vary from a few seconds to a number of hours [29]. On the other hand the small intestine transit time is reported to be more consistent at three to four hours.[30] An example of such a dosage form would be an impermeable capsule body containing the drug, fitted with a hydrogel plug that is used to deliver the drug after a predetermined time. This dosage form, for example Pulsincap® [31,32], releases the drug once the hydrogel plug hydrates and swells in aqueous media and is ejected from the device, thereby allowing the release of the drug from the capsule [33]. Another example describes use of a hydrophobic material and surfactant in the tablet coating. The release of drug from the Time Clock® depends mainly on the thickness of the hydrophobic layer and is not dependent on the pH of the GI environment [34]. The rationale behind all time-release delivery systems is valid provided that small intestine transit times remain constant.

Changes in GI tract motility can significantly affect time-release drug delivery systems targeting the release of drugs to the colon [35].

BACTERIA-DEPENDENT APPROACH:

The use of GI microflora as a mechanism of drug release in the colonic region has been of great interest to researchers in recent times. The majority of bacteria are present in the distal gut although they are distributed throughout the GI tract. Endogenous and exogenous substrates, such as carbohydrates and proteins, escape digestion in the upper GI tract but are metabolised by the enzymes secreted by colonic bacteria [36]. Sulphasalazine, a prodrug consisting of the active ingredient mesalazine, was the first bacteria-sensitive delivery system designed to deliver the drug to the colon [37]. Use of polysaccharides offers an alternative substrate for the bacterial enzymes present in the colon. Most of the polymers are used in pharmaceutical compositions and are considered generally regarded as safe (GRAS) excipients. Pectin alone and in combination with other polymers has been studied for colon-specific drug

delivery. Pectin, when used alone, was needed in large quantities to control the release of the drug through the core. A coating composition of a mixture of pectin, chitosan and hydroxypropyl methylcellulose was proven to be very efficient as the tablets coated with this composition passed intact through the stomach and small intestine and broke in the colon.

The rate of microbial growth is greatest in proximal areas because of high concentration of energy source. The principal source of nutrition for the colonic microorganisms is carbohydrates. The A large number of anaerobic and aerobic bacteria are present throughout the entire length of human GI tract. Over 400 species of bacteria are found in the colon, which are predominantly anaerobic such as bacteroids, bifidobacterium , eubacterium and clostridium and a small number of fungi. The bacterial count (CFU/mL) in diggerent regions of gastrointestinal tract is:

Stomach	0-103	CFU/mL
Jejunum	0-105	CFU/mL
Ileum	103-107	CFU/mL
Colon	1011-1012	CFU/mL

Carbohydrates are degraded by the action of polysaccharidase and glycosidase enzymes and the ultimate products of fermentation are short chain fatty acids, carbon dioxide, hydrogen, and methane and hydrogen sulphide. The becteria within the colon are predominantly anaerobic and there is a low reducing environment (low reducing potential).

PRESSURE/OSMOTICALLY-DEPENDENT APPROACH:

GI pressure is another mechanism that is utilised to initiate the release of the drug in the distal part of the gut. The muscular contractions of the gut wall generate this pressure, which is responsible for grinding and propulsion of the intestinal contents. The pressure generated varies in intensity and duration throughout the GI tract, with the colon considered to have a higher luminal pressure due to the processes that occur during stool formation. Systems have therefore been developed to resist the pressures of the upper GI tract but rupture in response to the raised pressure of the colon. Capsule shells fabricated from a water-insoluble polymer such as ethyl cellulose have been used for this purpose.[38] the performance of these systems may be affected by the administered food as it may disintegrate the capsule in stomach.

***INVITRO/ INVIVO* PERFORMANCE:**

INDICATORS

One of the challenges in the development of such systems is to establish an appropriate *in vitro* dissolution method that can provide reasonable assurance of *in vivo* performance. This is because the rationale behind a colon-targeted drug delivery system is quite diverse. Additional factors that complicate the development of such dissolution testing include

inadequate understanding of the colon's hydrodynamics and motility and how they are affected by pathological states. Conventional US Pharmacopeia (USP) Apparatus I dissolution testing in different buffers is one of the relatively simple and convenient methods routinely used. This method provides essential information primarily on the functionality of the system performance rather than validity of the design selected. In addition to the complexity of the methods, other factors such as set-up and operating parameters can significantly affect the output of the results. USP Apparatus 3 (BioDis®) is another recommended method to predict the *in vivo* performance. This offers multiple advantages, such as using a gradient of media to simulate the passage through different sections in the GI tract, varying hydrodynamic conditions and residence times in different media to simulate motility patterns and passage times under fasting and fed states. Scintigraphy and magnetic moment imaging studies are other recent techniques to visualise the *in vivo* targeting properties of such systems. These techniques can provide realtime imaging of the dosage form transit in the GI tract [39]. Such studies are much more expensive and time-consuming but they are complementary to the USP Apparatus 3 system as described above and both these methods together can provide a valuable insight into system performance All the above-mentioned procedures are just the tip of the iceberg and, considering the inter- and intra-subject variability of physiological GI tract parameters, further research focus in this area is crucial in both the design and characterisation of the systems.

SUMMARY

Various approaches are being researched in attempts to understand and achieve the desired goal of targeting the delivery to a specific organ, the colon. All the available approaches have their own limitations and advantages and extensive research is being focused on these to improve further. Time-dependant systems are not a very practical solution due to variable GI tract transit times but may have a potential role in diseases that are subject to circadian rhythm. On the other hand, pressure-controlled systems hold some promise but currently little is known about the luminal pressures of different regions of GI tract, and at present the commercial manufacturing methods have some unresolved issues to be addressed. The only system available as of today is based on pH but these systems can possibly deliver the drug at the duodenum or may not deliver the drug at all. Further research is ongoing in different labs and it is quite likely that a day is not far off when new, improved polymers will replace the existing available polymers with improved performance. The bacterially activated systems seem to be have the greatest potential as of today as the levels of bacterial enzyme activity is most unique and exploitable in this region.

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