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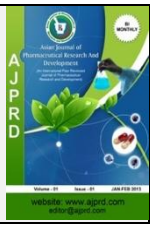

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Review Article

Colon-Targeted Oral Drug Delivery Systems: A Review

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A B S T R A C T

The colon is a site where both local and systemic delivery of drugs can take place. Local delivery allows topical treatment of inflammatory bowel disease. However, treatment can be made effective if the drugs can be targeted directly into the colon, thereby reducing the systemic side effects. This review, mainly compares the primary approaches for CDDS (Colon Specific Drug Delivery) namely prodrugs, pH and time dependent systems, and microbially triggered systems, which achieved limited success and had limitations as compared with newer CDDS namely pressure controlled colonic delivery capsules, CODESTM, and osmotic controlled drug delivery which are unique in terms of achieving in vivo site specificity, and feasibility of manufacturing process. New systems and technologies have been developed for colon targeting and to overcome pervious method's limitations. Colon targeting holds a great potential and still need more innovative work. This review article discusses, in brief, introduction of colon, factor effecting colonic transition, colonic diseases and the novel and emerging technologies for colon targeting.

Key Words: Colon Drug Delivery, Crohn's Disease, Inflammatory Bowel Disease, Eudragit S 100.

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INTRODUCTION

Targeted drug delivery, sometimes called smart drug delivery is a method of delivering medication to a patient in a manner that increases the concentration of the medication in some parts of the body relative to others. The goal of a targeted drug delivery system is to prolong, localize, target. It has a protected drug interaction with the diseased tissue. The conventional drug delivery system is the absorption of the drug across a biological membrane, whereas the targeted release system is when the drug is released in a dosage form.

The advantages of the targeted release system is:

- The reduction in the frequency of the dosages taken by the patient,
- Having a more uniform effect of the drug,
- Reduction of drug side effects, and
- Reduced fluctuation in circulating drug levels.

The disadvantage of the system is:

- High cost which makes productivity more difficult and
- The reduced ability to adjust the dosages.
- Targeted drug delivery systems have been developed to optimize regenerative techniques. The system is based on a method that delivers a certain amount of a therapeutic agent for a prolonged period of time. This system is in a targeted diseased area within the body. This helps to maintain the required plasma and tissue drug levels in the body, avoiding any damage to the healthy tissue via the drug

Colon-targeted drug delivery System:

Colon-targeted drug delivery has been the focus of numerous studies in recent years due to its potential to improve treatment of local diseases affecting the colon, while minimizing systemic side effects. Some examples of disease states which impact the colon include Crohn's disease (CD), ulcerative colitis (UC), and irritable bowel syndrome (IBS) [1]. Some of the frequently used drugs for the treatment of these ailments include sulfasalazine, dexamethasone, hydrocortisone, metronidazole, prednisolone, and others[2]. The delivery of these drugs specifically to the colon without being absorbed first in the upper gastrointestinal (GI) tract allows for a higher

concentration of the drug to reach the colon with minimal systemic absorption[3]. The colonic contents have a longer retention time (up to 5 days), and the colonic mucosa is known to facilitate the absorption of several drugs, making this organ an ideal site for drug delivery [3, 4]. A drug can be delivered to the colon via the oral, or the rectal route. Oral dosage forms are the most preferred delivery route for colon-specific delivery due to their convenience[4]. Oral dosage forms also allow for a greater degree of flexibility in their manufacturing, design, improved patient adherence, relatively safe administration, and they do not require sterile preparation[2]. Direct rectal delivery of drugs is challenging with respect to targeting a drug to specific sites within the colon. Additionally, the extent of drug distribution varies for different rectal dosage forms depending on their spreading capacity and retention time.

Colon drug delivery system

Drug delivery to the colon is beneficial for the oral delivery of proteins and peptide drugs degraded by digestive enzymes of the stomach and small intestine and for the delivery of low molecular weight compounds. Delivery of drug substances to the colon may improve systemic bioavailability to a level which is not feasible by un-modified oral drug delivery. This may improve efficacy of drug treatment or open up the possibility to switch to oral instead of parenteral administration. Targeted drug delivery into the colon is highly desirable for local treatment of a variety of bowel diseases such as ulcerative colitis, cirrhosis disease, amebiasis, colonic cancer and local treatment of colonic pathologies and systemic delivery of protein and peptide drugs. This route may also be useful in the treatment of diseases susceptible to diurnal rhythm such as asthma, arthritis, etc. In addition, the colon has a long retention time.

As a site for drug delivery, colon offers a near neutral pH, reduced digestive enzymatic activity with a long transit time and an increased responsiveness to absorption enhancers. The colon specific drug delivery system (CDDS) should be capable of protecting the drug in route to the colon means drug release and absorption should not occur in the stomach or small intestine. The bioactive agents should not be degraded either of the dissolution sites, but only released absorbed once the system reaches the colon. Colon is rich in lymphoid tissue, e.g., Uptake of antigen into mast cells of the colonic mucosa produces rapid local production of antibodies and this helps in efficient vaccine delivery. Region of the colon is recognized as having a somewhat less hostile environment with less diversity and intensity of activity than stomach and Small intestine. The most critical challenge in such drug delivery approach is to preserve the formulation during its passage through the stomach and about first six meters of the small intestine. This has led to the development of various systems for targeting drugs to the colon. These include pH-controlled release systems, enzyme-controlled delivery system (including prodrugs and polysaccharide based delivery systems), time- controlled release systems and pressure/ osmotically controlled release systems. However, the coated dosage forms, especially the enteric coated dosage forms are most popular. CDDS is primarily dependent on the microbial environment; transit time and pH level in the colon control the release of drug from different designs of CDDS. These conditions may vary depending on various factors, which limit the success of CDDS. The disadvantage of single unit colon targeted drug delivery system may have unintentional disintegration of the formulation due to manufacturing deficiency or unusual gastric physiology. It may lead to drastically compromised systemic drug bioavailability or loss of local therapeutic action in the colon.

Formulations for colonic delivery are also suitable for delivery of drugs, which are polar and / or susceptible to chemical and enzymatic degradation in upper GIT. Therapeutic proteins and peptides are suitable for colonic deliveries. Proteins and peptides such as insulin, calcitonin and vasopressin may be delivered systematically via colonic absorption. Other examples include novel peptides such as cytokine inhibitors useful in treatment of Intestinal Bowel Syndrome (IBS) and antibiotics which are useful in GI infections. A colonic targeted approach has found to be effected in minimizing uncertain side effects. The colon, as a site for drug delivery has distinct advantages,

- On the account of near neutral pH,
- A much longer transit time,
- Relatively low proteolytic enzymatic activity and
- Offers a much greater responsiveness to absorb enhances

Colon specific delivery systems should prevent the release of drug in the upper part of the GIT. It requires a triggering mechanism to release the drug on reaching the colon. The colon is having high water absorption capacity. The colonic contents are viscous and their mixing is not efficient, thus availability of most drugs is low to the absorptive membrane. The human colon has over 400 distinct species of bacteria as resident flora, a possible population of up to 1010 bacteria per gram of colonic contents. Among the reactions carried out by these gut flora are azo reduction and enzymatic cleavage i.e. glycosides. These metabolic processes may be responsible for the metabolism of many drugs. It may also be applied to the colon-targeted delivery of peptide based macromolecules such as insulin by oral administration. Large intestine is difficult to reach by per oral delivering. It is still deemed to be the ideal site for the delivery of agents to cure the local diseases of the colon by using rectal dosage forms such as suppositories and enemas. The high variability in the distribution of these forms is observed because of these systems are always not effective, irrespective of therapy desired for local (colonic) or systemic delivery of drug. The aim and development of the drug delivery to colon remains same which is

- The drug must not absorb from other regions of the 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.

Oral colon-specific drug delivery is proposed as a diagnostic tool to investigate fermentation processes in the colon. The colon harbours large amounts of bacteria (1012 CFU/ml) of more than 200 species. It is accepted that the human colon is a complex ecosystem which is mutually beneficial for men and bacteria. Specific targeting of drugs to the colon has several therapeutic advantages. Drugs, which destroyed by the stomach acid and / or metabolized by pancreatic enzymes, are slightly affected in the colon. Sustained colonic release of drugs can be useful in the treatment of nocturnal asthma, angina and arthritis. Colonic diagnostic agents require smaller doses. Treatment of colonic diseases such as ulcerative colitis, colorectal cancer and Crohn's disease is more effective with direct delivery of vermicides.

Recent studies have revealed that diseases have predictable cyclic rhythms and that the timing of medication regimens can improve outcome in selected chronic conditions .There are many conditions that demand pulsatile release like:

- Many body functions follow a circadian rhythm. e.g.: Secretion of hormones, acid secretion in the stomach, gastric emptying, and gastrointestinal blood transfusion.
- Chronopharmacotherapy of diseases shows circadian rhythms in their pathophysiological conditions like bronchial asthma, myocardial infarction, angina pectoris, rheumatic disease, ulcer, and hypertension
- Drugs that produce biological tolerance demand for a system. It will prevent their continuous presence at the bio-phase as this tends to reduce their therapeutic effect.
- The lag time is essential for the drugs that undergo degradation in gastric acidic medium (e.g. peptide drugs) and irritate the gastric mucosa or induce nausea and vomiting.
- Targeting a drug to distal organs of the gastrointestinal tract (GIT) like the colon requires that the drug release is prevented in the upper two-third portion of the GIT.
- The drugs that undergo first-pass metabolism resulting in reduced bioavailability, altered steady state levels of drug and metabolite, and potential food drug interactions require delayed release of the drug to the extent possible.
- All of these conditions demand for a time controlled therapeutic scheme releasing the right amount of drug at the right time. This requirement is fulfilled by Pulsatile Drug Delivery Systems which is of two types:
- Single pulse (Rupturable dosage form)
- Multiple pulse (Drug containing in a core, covered by swelling layer and an outer insoluble, but semi permeable polymer coating membrane.

Need of Colon Drug Delivery System

- Targeted drug delivery to the colon would ensure direct treatment of the disease site, lower dosing and fewer systemic side effects.
- Site-specific or targeted drug delivery system would allow oral administration of peptide and protein drugs, colon-specific formulation could also be used to prolong the drug delivery.
- Colon-specific drug delivery system is considered to be beneficial in the treatment of colon diseases.
- The colon is a site where both local or systemic drug delivery could be achieved, topical treatment of inflammatory bowel disease, e.g. Ulcerative colitis or Crohn's disease. Such inflammatory conditions are usually treated with glucocorticoids and sulphasalazine (targeted).
- A number of others serious diseases of the colon, e.g. colorectal cancer, might also be capable of being treated more effectively if drugs were targeted to the colon.
- Formulations for colonic delivery are also suitable for delivery of drugs which are polar and/or susceptible to chemical and enzymatic degradation in the upper GI tract, highly affected by hepatic metabolism, in particular, therapeutic proteins and peptides.

Factors to be considered in the design of colon-specific drug delivery system

Anatomy and Physiology of Colon

The GI tract is divided into the stomach, small intestine and large intestine. The large intestine extending from the ileocaecal junction to the anus is divided into three main parts.

- The Colon
- The rectum
- The anal canal.

The colon is made up of the cecum, the ascending colon, the hepatic flexure, the transverse colon, the splenic flexure, the descending colon and the sigmoid colon. It is about 1.5 m long, the transverse colon being the longest and most mobile part and has an average diameter of about 6.5 cm, although it varies in diameter from approximately 9 cm in the cecum to 2 cm in the sigmoid colon.

The wall of the colon is composed of four layers: the serosa, the muscularis externa, the submucosa and the mucosa. The serosa is the exterior coat of the large intestine and consists of areolar tissue that is covered by a single layer of squamous mesothelial ells. The major muscular coat of the large intestine is the muscularis externa. This is composed of an inner circular layer of fibres that surrounds the bowel and of an outer longitudinal layer. The submucosa is the layer of connective tissue that lies immediately beneath the mucosa. Lining the lumen of the colon, the mucosa is divided into epithelium, lamina propria and the muscularis mucosae. Closely spaced crypts extend down into the surface of mucosa. The muscularis mucosae consist of a layer of smooth muscles and separate the submucosa from the lamina propria. The lamina propria supports the epithelium, and occupies the space between the crypts and beneath the crypts. Within the lamina propria are located blood capillaries and lymphatic lacteals.

The arterial blood supply to the proximal colon is from the superior mesenteric artery and the inferior mesenteric artery supplies the distal colon. The venous drainage is via the superior (proximal colon) and inferior (distal colon) veins. The arterioles and capillary branches pass to the epithelial surface between the crypts and form an extensive network of capillary plexi.

The colon serves four major functions;

- Creation of suitable environment for the growth of colonic micro-organisms;
- Storage reservoir of faecal contents;
- Expulsion of the contents of the colon at an appropriate time and
- Absorption of potassium and water from the lumen, concentrating the faecal content, and secretion and excretion of potassium and bicarbonate.

The physiology of the proximal and distal colon differs in several respects that have an effect on drug absorption at each site. The physical properties of the luminal content of the colon also change, from the liquid in the cecum to semisolid in the distal colon.

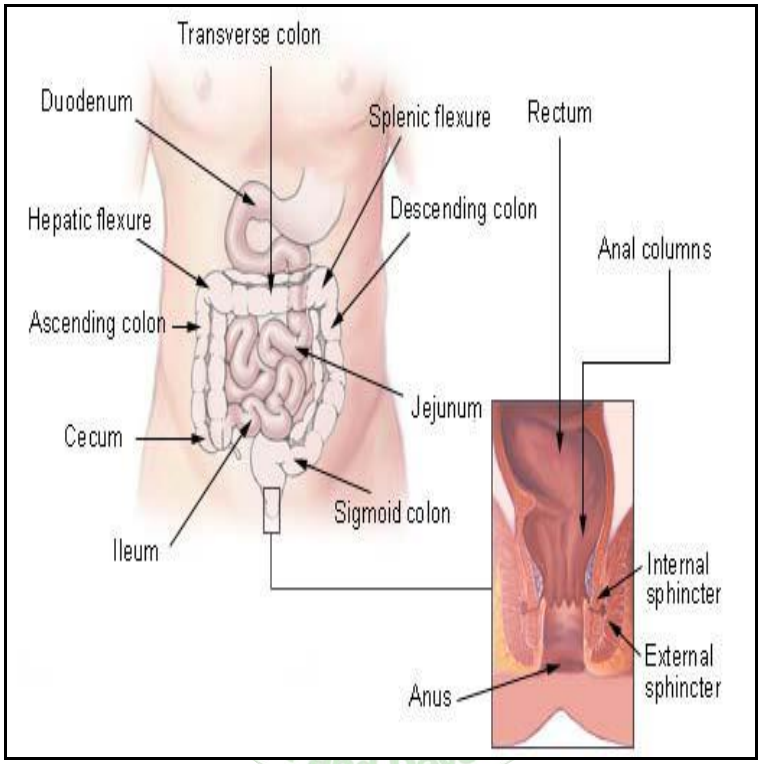

Figure: 1 Small and Large Intestine

Table: 1 Summary of anatomical and physiological features of small intestine and colon

Region of Gastrointestinal Tract		Length (cm)	pH	Internal diameter (cm)
Stomach			1.5-3 (fasted) 2-5 (fed)	
Small intestine	Duodenum	20-30	6.1(fasted) 5.4(fed)	3-4
	Jejunum	150-200	5.4	
	Ileum	200-350	7-8	
Large intestine	Cecum	6-7	5.5-7	6
	Ascending colon	20		
	Transverse colon	30		
	Descending colon			
	Sigmoid colon	40		
	Rectum	12		
	Anal rectum	3	7-8	

Factors affecting colon absorption

- Physical properties of drug such as pKa and degree of ionization.
- Colonic residence time as commanded by GIT motility.
- Degradation by bacterial enzymes and metabolic products.
- Local physiological action of drug.
- Selective and non-selective binding to mucus.
- Disease state.

pH of colon

The pH of the gastrointestinal tract is subjected to both inter and intra subject variations. Diet, diseased state and food intake influence the pH of the gastrointestinal fluid. The change in pH along the gastrointestinal tract has been used as a means for targeted colon drug delivery. There is a pH gradient in the gastrointestinal tract with value ranging from 1.2 in the stomach through 6.6 in the proximal small intestine to a peak of about 7.5 in the distal small intestine (Table 2). The pH difference between the stomach and small intestine has historically been exploited to deliver the drug to the small intestine by way of pH sensitive enteric coatings. There is a fall in pH on the entry into The Colon Due To the Presence of Short Chain Fatty Acids Arising from Bacterial Fermentation of Polysaccharides.

Table: 2 Ranges of pH of Gastrointestinal Tract

Region	pH
Stomach (before meal)	1-2
Stomach (during digestion)	4
Small intestine	6-7
Duodenum	6.6 ±0.5
Ileum	7.5 ±0.4
Cecum	6.4 ±0.4

GI transit time

Gastric emptying of dosage forms is highly variable and depends primarily on whether the subject is fed or fasted and on the dosage form such as size and density. The arrival of an oral dosage form at the colon is determined by the rate of gastric emptying and the small intestinal transit time. The transit times of small dosage forms in the GI tract are as follows.

Table: 3 Average transit time

Organ	Transit time (hr.)
Stomach	<1 (fasting) >3 (fed)
Small intestine	3-4
Large intestine	20-30

Colonic Microflora

The human alimentary canal is highly populated with bacteria and other microflora at both ends,

The oral cavity

The colon/ rectum

In between these two sites, the GIT is very sparsely populated with microorganisms. Microorganisms of the oral cavity do not affect oral drug delivery system. Gut microflora of the colon have a number of implications in health and the treatment of disease like Intestinal Bowel Syndrome (IBS). Many colon-specific drug delivery systems rely on enzymes unique to gut micro flora to release active agents in the colon. A large number of polysaccharides are actively hydrolyzed by gut microflora leading to the possibility of using naturally occurring biopolymer as drug delivery. There is certainly route for innovative approaches to carry and release the drug in the colon which is based on the metabolic capabilities of colon microflora. Azo reductase produced by colon plays central role in a number of delivery systems. The second class of enzymes is glycosidase which is used to trigger the release of drugs in the colon. As with azo-reductase activity, the level of bacterial glycosidase activity in the GIT is associated with the concentration of bacteria in a given region.

Approaches to Colon-specific Drug Delivery

Colon-specific drug delivery has been attempted in several ways. Coating with pH dependent polymers, design of timed-release dosage forms, Prodrugs, and the use of carriers that are exclusively by colonic bacteria are an array of such attempt.

The targeting of orally administered drugs to the colon is accomplished by:

- Coating with pH dependent polymer
- Timed release dosage forms
- Delivery systems based on the metabolic activity of colonic bacteria.

Coating with pH dependent polymer

The pH approach has been shown to lack site-specificity because of inter / intrasubject variation and the similarity of the pH between the small intestine and the colon. In these systems, drugs are formulated into solid dosage forms such as tablets, capsules and pellets and coated with pH sensitive polymers as in enteric coating. The most widely used polymers are Methacrylic resins (Eudragit), which are available in water-soluble and water-insoluble forms. Eudragit L and S are copolymers of Methacrylic acid and methyl methacrylate. Eudragit L is water soluble at pH 6 or above and is used as an enteric coating polymer. Eudragit S is water soluble at pH 7 or above and is used to deliver drugs to the end of the small bowel and large intestine.

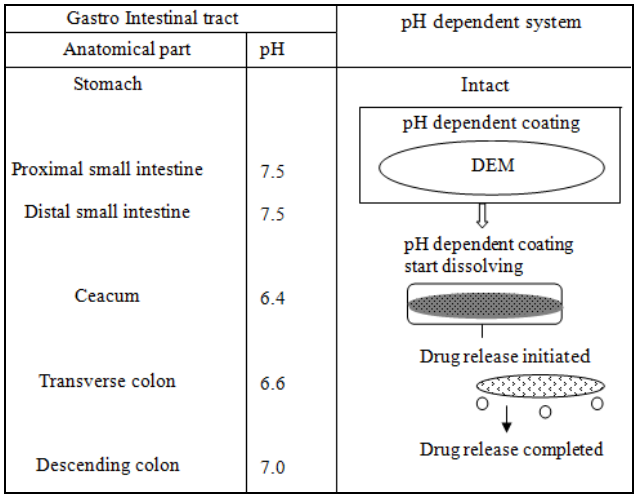

Figure: 1 Presentation of pH Dependent Release

Time release dosage forms

Timed-release systems depend on the relative consistency of the small intestinal transit times, but the high variability in gastric retention times makes prediction of the accurate location of drug release.

Time Controlled Release System (TCRS) such as sustained or delayed release dosage forms are also very promising drug release systems. 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.

The disadvantages of this system are:

- Gastric emptying time varies markedly between subjects or in a manner dependent on the type and amount of food intake.
- Gastrointestinal movement, especially peristalsis or contraction in the stomach would result in a change in gastrointestinal transit of the drug.
- Accelerated transit through different regions of the colon has been observed in patients with the intestinal bowel syndrome (IBS), the carcinoid syndrome and diarrhoea, 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 h. The time-release 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 resistant) in the dosage form, which would reduce variation in gastric residence time. E.g. 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). 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. The duration of lag phase is controlled either by the weight or composition of the polymer (HPC) layer.

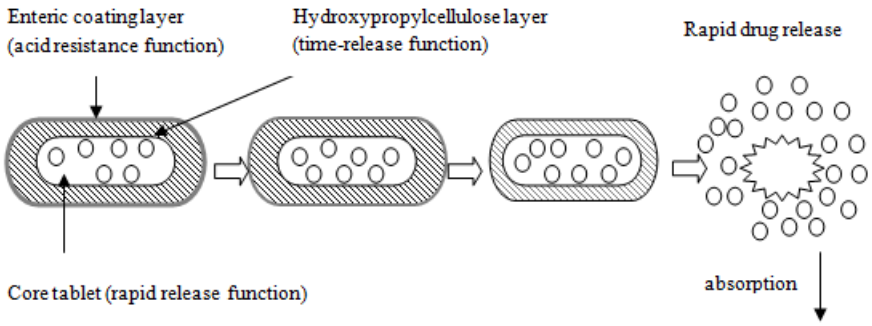

Figure: 2 Design of Enteric Coated Timed-Release Press Coated Tablet

Delivery system based on the metabolic activity of colonic bacteria

The colonic bacteria carry out a variety of metabolic reactions. The most important of them are hydrolysis and reduction reaction. Based on these actions different strategies were used to target drugs to the colon. Site-specificity is the main feature of these systems. Different strategies are described below:

Coating with biodegradable azo polymers

The principle of biodegradable azo polymers is unusual in the sense that the majority of biodegradable polymers are designed to be disintegrated by hydrolysis rather than azo reduction. While there is extensive information available on biodegradation of polymers by hydrolysis, relatively little is known about biodegradation of azopolymers. Although the ability of many bacteria and mammalian cells to cleave the azo bonds in low-molecular-weight azo compounds and water-soluble high-molecular-weight polymeric derivatives of certain azo dyes have been demonstrated, there is no reliable evidence to suggest that the insoluble azo polymers are degradable through azo reduces by biological systems.

Prodrugs

The specific delivery of drug to the colon by prodrugs, polymeric prodrug and polymeric systems has great interest in recent times. Essentially there are three approaches to achieve site specificity:

- Utilizing pH changes in the gastrointestinal tract,
- Timed release capsules and
- Polymeric carriers degraded by the microflora located in the colon.

The enzyme trigger mechanism in such delivery systems makes them highly site-specific. The mechanism of these colon-specific drug delivery systems is presumed to take place due to enzymatic cleavage by the normal colonic microflora. The rich microflora of the human colon is

responsible for the conversion of laxatives such as sennosides to active therapeutics. Another well known demonstration of the use of this mechanism is the localization of 5- amino salicylic acid in the human colon by bacterial azo reduction of sulphasalazine and olsalazine. There are only a few studies performed on polymeric systems that could carry a variety of drugs to the colon. A more universal approach to utilize bacterial degradation of the azo bond to achieve specific release has been the synthesis of a polymer suitable for coating and the use of hydrogels with azo aromatic cross-links.

Prodrugs and polysaccharide-based delivery systems depend on the enzymatic degradation carried out by the inherent bacterial flora present in the colon, thereby resulting in drug release. Prodrugs are considered as new chemical entities from a regulatory perspective which requires a detailed toxicological study to be performed, before being used as drug carriers.

The colon is known to be a reductive medium in which azo groups can be cleaved with the formation of the corresponding amines. The metabolic reduction of azo compounds is considered as an important detoxification route .

Hydrogels

Polysaccharides, the polymer of monosaccharide retains their integrity because they are resistant to the digestive action of gastrointestinal enzymes. The matrices of polysaccharides are assumed to remain intact in the physiological environment of stomach and small intestine but once they reach in the colon, they are acted upon by the bacterial polysaccharides and results in the degradation of the matrices. A large number of polysaccharides have been investigated for their use in colon targeted drug delivery systems.

The most important fact in the development of polysaccharide derivatives for colon targeted drug delivery is the selection of suitable biodegradable polysaccharides. Very important is an optimal proportional of the hydrophobic and hydrophilic parts respectively and the number of free hydroxy group in the polymeric molecule. The rationale for the development of a polysaccharide based delivery system for colon is due to the presence of large amounts of polysaccharidases in the human colon, as the colon is inhabited by a large number and variety of bacteria which secrete many enzymes e.g. β-D -glucosidase, β-D -galactosidase, amylase, pectinase, xylanase, β-D -xylosidase, dextranase, etc. A large number of polysaccharides have been studied for their potential as colon-specific drug carrier systems, such as chitosan, pectin, chondroitin sulphate, cyclodextrin, dextrans, guar gum, inulin, amylose and locust bean gum.

Evaluation of colon-specific drug delivery system

A successful colon-specific drug delivery system is that intact in the physiological environment of the stomach and small intestine; release the drug in the colon. Different methods are used to evaluate the colonic drug delivery system:

- *In vitro* method
- *in vivo* method
- Clinical evaluation

***In vitro* method**

The ability of the various delivery systems, under study, to protect the drug in the physiological environment of the stomach and small intestine and allow its release into the colon was assessed by carrying out drug release studies in 0.1 N Hydrochloric acid for 2 h, pH 7.4 buffer for 3 h and phosphate buffer solution (PBS) pH 6.8 in the absence (control). Currently, four dissolution apparatus is recommended in the USP to accommodate different actives and dosage forms: basket method, paddle method, Bio-Dis C method and flow-through cell method. However, certain constraints associated with USP dissolution methods were recognized, especially in the dissolution evaluation of complex controlled release drug delivery systems for oral application, and modification of USP dissolution methods to evaluate such delivery systems were deemed necessary. The amount of drug released at different time intervals during the incubation is estimated to find out the degradation of the carrier under study.

Alternative method for evaluation of colon-specific delivery system *in vitro*

To overcome the limitation of conventional dissolution testing for evaluating the performance of colon-specific delivery systems triggered by colon-specific bacteria, animal caecal contents including rats, rabbits, pigs have been utilized as an alternative dissolution medium. Because of the similarity of human and rodent colonic microflora, predominantly comprising *Bifidobacterium*, *Bacteroides* and *Lactobacillus*, rat caecal contents were more commonly used in the dissolution studies .

***In vivo* method**

Animal models: different animal models are used for evaluating *in vivo* performance of colon-specific drug delivery systems like guinea pig, rat and the pig. Different techniques are used for monitoring the *in vivo* behavior of colon-specific delivery systems in human: a variety of techniques like,

String technique: In these studies, a tablet was attached to a piece of string and the subject swallowed the tablet, leaving the free end of the string hanging from his mouth. At various time points, the tablet was withdrawn from the stomach by pulling out the string and physically examining the tablet for the signs of disintegration. In some studies, the tablets were recovered by inducing a vomiting reflex. The presence of foreign object, such as the string in the GI tract may alter its motility and physicochemical environment. The psychological stress and anxiety associated with this method also affect the motility of the GI tract.

Endoscope technique: it is an optical technique in which a fibre scope (gastroscope) is used to directly monitor the behavior of the dosage form after ingestion. This method requires administration of a mild sedative to facilitate the swallowing of the endoscopic tube. The sedative itself may

alter gastric emptying and GI motility. The psychological factors also contribute to the change in the motility of the GI tract.

Roentgenography: the inclusion of a radio-opaque material into a solid dosage form enables it to be visualized by the use of X-rays. By incorporating Barium Sulphate into a pharmaceutical dosage form, it is possible to follow the movement, location and the integrity of the dosage form after oral administration by placing the subject under a fluoroscope and taking a series of X-rays at various time points. The radio-opaque material, such as Barium Sulphate, has high density and may not be a good model for most pharmaceuticals.

Clinical evaluation

Absorption of drugs from the colon is monitored by colonoscopy and intubation. Currently gamma scintigraphy and high frequency capsules are the most preferred techniques employed to evaluate colon drug delivery systems.

High frequency capsule: Smooth plastic capsule containing small latex balloon, drug and radiotracer taken orally. Triggering system is high frequency generator. Release of drug and radiotracer triggered by an impulse, the release is monitored in different parts of GIT by radiological localization. It checks the absorption properties of drug in colon.

Gamma Scintigraphy: By means of gamma scintigraphic imaging, information can be obtained regarding time of arrival of a colon-specific drug delivery system in the colon, times of transit through the stomach and small intestine, and disintegration. Information about the spreading or dispersion of a formulation and the site at which release from it takes place can also be obtained. Gamma scintigraphic studies can also provide information about regional permeability in the colon. Information about gastrointestinal transit and the release behavior of dosage forms can be obtained by combining pharmacokinetic studies .

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