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Review Article

**DISEASES, APPROACHES AND EVALUATION PARAMETERS FOR COLON SPECIFIC DRUG DELIVERY: A REVIEW**

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**ABSTRACT**

In the area of targeted drug delivery, the colonic region of 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, but also for systemic delivery of drugs like proteins and peptides. These are otherwise degraded and/or poorly absorbed in upper GIT but may be better absorbed from the more benign environment of the colon. The treatment of disorders of the large intestine (colon), such as Colon cancer, irritable bowel syndrome (IBS), inflammatory bowel disease (IBD) i.e. Ulcerative colitis and Crohn’s disease, Diverticulitis and other colon diseases, where it is necessary to attain a high concentration of active agent, maybe efficiently achieved by colon specific delivery. This is also a potential site for the treatment of diseases sensitive to circadian rhythms such as asthma, angina, hypertension and arthritis. The primary approaches used to obtain colon specific delivery were based on prodrugs; pH dependent, time dependent systems or microflora activated systems has achieved limited success. However, recently continuous efforts have been taken on designing colon specific delivery systems with improved site specificity and versatile drug release kinetics to accomplish different therapeutic needs. Evaluation is performed by maintaining simulated condition using dissolution testing method closely mimic the in vivo colonic environment with regard to pH, the volume and distribution of fluids, bacteria, composition and activity of enzymes, and the mixing intensity, while being able to discriminate the impact of upper GI tract transit on the delivery system. The focus of this review is to provide detailed insight into the various colon diseases, approaches used to target the therapeutic agents specifically to the colon and evaluation parameters for colon specific drug delivery.

**Keywords**: Inflammatory bowel disease, pH dependent, Prodrug, Circadian rhythms, Colon specific drug delivery.

**INTRODUCTION**

Oral route is the most preferred route for drug administration, especially for chronic therapies where repeated administration is required, till to date. In addition, greater convenience, less pain, higher compliance, reduced risk of cross infection and needle stick injuries are the added advantages for oral delivery when compared to other routes of administration.1 Hence, oral drug delivery systems continue to dominate more than fifty percent market share of the drug delivery.2 Despite these advantages, the oral route is not amenable to the administration of drug for lower gastro intestinal (GI) diseases due to their release at upper GI tract, which leads to their limited availability at the lower GI tract. To overcome
this obstacle, new strategies of drug delivery have been developed. Among them, colon specific drug delivery systems have been extensively explored during last two decades. Different delivery vehicles from synthetic as well as natural polymers have been exploited for colon specific drug delivery. However, the design of oral drug delivery vehicles that effectively carry drugs to the colon site is challenging as it requires fulfilling the following criteria: i) they need to remain intact when traveling through the upper GI tract in order to prevent the release as well as chemical and enzymatic degradation of the incorporated drug, ii) they should be able to release the incorporated drugs immediately upon arriving in the colonic region. The efficiency of these formulations is estimated by the difference between the drug released at the colon site and the initial dosage of the drug. The smaller in this difference, the better will be the delivery system. 3

During the last decade there has been interest in developing site specific formulations for targeting drug delivery to the colon. The colon is a site where both local and systemic drug delivery can take place. A local means of drug delivery could allow topical treatment of inflammatory bowel disease, e.g. ulcerative colitis or Crohn’s disease (Figure 1). Such inflammatory conditions are usually treated with glucocorticoids and sulphasalazine. 4,5 Treatment might be more effective if the drug substances were targeted directly on the site of action in the colon. Lower doses might be adequate and, if so, systemic side effects might be reduced. A number of other serious diseases of the colon, e.g. colorectal cancer, might also be capable of being treated more effectively if drugs were targeted on the colon (Table 1).

Site specific means of drug delivery to colon could also allow oral administration of peptide and protein drugs, which normally become inactivated in the upper parts of the gastrointestinal tract. Vaccines, insulin and growth hormone are examples of candidates. However, the permeability of the epithelium of the colon to peptide and protein drugs is fairly poor, and bioavailabilities are usually very low. 6, 7

Colon specific systems could also be used in conditions in which a circadian rhythm is evident, e.g. asthma, rheumatic disease, ulcer disease and ischaemic heart disease. The incidence of asthmatic attacks is, for example, greatest during the early hours of the morning. Because dosage forms remain longer in the large intestine than in the small intestine, colon specific formulations could be used to prolong drug delivery. 7

Figure 1: Diagrammatical presentation of Colon associated diseases 8
Table 1: Drugs used in colon associated disease condition

<table>
<thead>
<tr>
<th>Target Sites</th>
<th>Disease Conditions</th>
<th>Symptoms</th>
<th>Drugs and active</th>
</tr>
</thead>
<tbody>
<tr>
<td>Topical /Local action</td>
<td>Inflammatory Bowel Disease (Crohn’s disease)</td>
<td>Diarrhea, Abdominal pain and cramping, blood in stool, ulcers, reduced appetite and weight loss</td>
<td>Hydrocortisone, Budenoside, Prednisolone, Sulfasalazine</td>
</tr>
<tr>
<td></td>
<td>Ulcerative colitis</td>
<td>Inflammation in the rectum, rectal bleeding, rectal pain</td>
<td>Mesalamine, Balsalazide, Sulfasalazine, and mercaptopurine</td>
</tr>
<tr>
<td></td>
<td>Irritable bowel syndrome</td>
<td>Abdominal pain or cramping, a bloated feeling, flatulence, diarrhea or constipation people with IBS may also experience alternating bouts of constipation &amp; diarrhea, mucus in stool</td>
<td>Dicyclomine, Hyoscine, Propantheline, Cimetropium, Alosetron, Tegaserod</td>
</tr>
<tr>
<td></td>
<td>Colorectal cancer</td>
<td>A change in bowel habits, narrow stools, rectal bleeding or blood in stool, persistent abdominal discomfort, such as cramps, gas or pain, abdominal pain with a bowel movement, unexplained weight loss</td>
<td>5 Fluourouracil, Leucovorin, and cetuximab</td>
</tr>
<tr>
<td></td>
<td>Diverticulitis</td>
<td>Formation of pouches (diverticula) on the outside of the colon due to bacterial infection</td>
<td>Bactrim, Flagyl, Sulfatrim, Metronidazole</td>
</tr>
<tr>
<td></td>
<td>Antibiotic associated colitis</td>
<td>Overgrowth of Clostridium difficile and its subsequent toxin production</td>
<td>Clindamycin, broadspectrum penicillins (e.g., ampicillin, amoxicillin), and cephalosporins</td>
</tr>
<tr>
<td></td>
<td>Hirschsprung's disease</td>
<td>Severe form of constipation in which bowel movement occurs only once or twice a week</td>
<td>Metronidazole, Vancomycin, Loperamide, Botulinum toxin</td>
</tr>
<tr>
<td></td>
<td>Systemic action</td>
<td>Ulcerative proctitis, pancolitis, fulminant colitis</td>
<td>Prednisolone metasulfobenzoate, tixocortol pivalate, fluticasone propionate, beclometasone</td>
</tr>
</tbody>
</table>

**Rationale for colon targeting**

The challenge of targeting drugs to the colon part of the GI tract has been embraced by scientists over the past two decades. The research on colon targeting has been driven primarily by the need to improve the treatment of the colonic pathologies. These disease states range in severity from constipation and diarrhoea, to irritable bowel syndrome and inflammatory bowel disease (Ulcerative colitis and Crohn’s disease), through to infection and colon carcinoma. While some of these disorders are fairly innocuous, the majorities...
are debilitating and life threatening (e.g., colorectal cancer is the third most common cause of cancer related death in human being).\textsuperscript{10} Generally, surgical intervention is required in some patients as the current pharmacotherapy for colonic disorders is generally inefficient. Hence, the introduction of new therapeutic agents would no doubt improve the current treatment. Furthermore, the new and improved delivery strategies for targeting the drugs specifically to the colon would provide significant clinical benefits. This would ensure direct treatment at the disease site. In addition, there will be a great possibility of reduction in the administered dose and associated systemic adverse effects. These are the benefits that can be obtained from the perspective of colonic drug delivery. Additional interest in colon targeted drug delivery system has generated from the potential of the colonic site for the entry of some drugs into the systemic circulation. The colonic region is believed to contain lower levels of luminal and mucosal digestive enzymes in comparison with stomach and small intestine.\textsuperscript{11} Colonic region therefore can be a preferred site for the systemic absorption of many drugs, especially peptides and proteins that are degraded and/or poorly absorbed in the upper gut.\textsuperscript{12} Furthermore, colon specific drug delivery could be beneficial when an intentional time delay in absorption is required for the treatment of diseases that are sensitive to circadian rhythms (chronotherapy), such as angina pectoris, arthritis, and asthma.\textsuperscript{13}

**COLON DISEASES**

**Inflammatory Bowel Disease (IBD)**

Inflammatory bowel disease is broadly classified into three types: ulcerative colitis, Crohn’s disease, and indeterminate colitis. IBD is characterized by chronic inflammation in the mucosal membrane of the small and/or large intestine.

**Ulcerative colitis**

Ulcerative colitis was first described by Wilks in 1859.\textsuperscript{14} In ulcerative colitis, inflammation is classically limited to the colon and is usually continuous, starting at the rectum. Approximately 80% of children with ulcerative colitis have pancolitis with inflammation extending proximal to the splenic flexure or involving the entire colon.\textsuperscript{15, 16} The endoscopic features of ulcerative colitis include ulcers, erythema, and loss of vascular pattern, friability, spontaneous bleeding, and pseudopolyps. Histologically, inflammation in ulcerative colitis is confined to the mucosa; other histologic features include crypt distortion, crypt abscesses, goblet cell depletion, and rarely mucin granulomas. Individuals with ulcerative colitis may also have other histological features such as inflammation of the ileum or stomach, periappendiceal inflammation, patchy distribution, and relative rectal sparing at the time of diagnosis; the presence of these features does not exclude a diagnosis of ulcerative colitis.\textsuperscript{17} Frequency and extension of inflammation in the colon is calculated depending on the site of colon shown in Figure 2. Edoscopic classification of disease and Histology is given in Figure 3 and Table 2.

Ulcerative colitis first manifestation signs are indicated by abdominal pain, diarrhea, bleeding, anal fistula and fissures (Table 3).

![Figure 2: Frequency and extension of inflammation in the colon](http://www.ijdrt.com)
Table 2: Endoscopic classification of disease

<table>
<thead>
<tr>
<th>Grade 0</th>
<th>Remission</th>
<th>Pale mucosa, torqued vessels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>(slight activity)</td>
<td>Erythema, slightly granulated surface, loss of vascular pattern</td>
</tr>
<tr>
<td>Grade 2</td>
<td>(moderate activity)</td>
<td>Single ulcers, velvety mucosa, contact and spontaneous bleeding</td>
</tr>
<tr>
<td>Grade 3</td>
<td>(high activity)</td>
<td>Pus, spontaneous bleeding, larger ulcerations</td>
</tr>
</tbody>
</table>

Figure 3: Histology Mucosal inflammation Proportioned, crypt abscesses, continuous

Table 3: Indicating signs of UC at first manifestations

<table>
<thead>
<tr>
<th>Intestinal</th>
<th>Extraintestinal</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Initial 1st year</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>47% 35%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>52% 85%</td>
</tr>
<tr>
<td>Bleeding</td>
<td>80% 100%</td>
</tr>
<tr>
<td>Anal fistulae</td>
<td>0% 0%</td>
</tr>
<tr>
<td>Anal fissures</td>
<td>4% 4%</td>
</tr>
</tbody>
</table>

Crohn’s disease

Crohn’s disease was initially described by Crohn, Ginzberg, and Oppenheimer in 1932, although case reports of the same clinical and pathologic condition were published as early as the nineteenth century. In contrast to ulcerative colitis, Crohn’s disease affects any region of the gastrointestinal tract and is characteristically segmental with areas of sparing throughout the gastrointestinal tract. Approximately 35 to 40% of individuals with Crohn’s disease will have disease limited to the ileum and cecum, 30 to 40% will have disease limited to the small intestine, and 15 to 25% will have only colonic disease. Compared to ulcerative colitis, inflammation in Crohn’s disease affects all layers of the bowel. Gross inspection of the bowel in well-established Crohn’s disease demonstrates marked wall thickening from chronic transmural inflammation accompanied by luminal narrowing. Because of transmural inflammation, bowel loops may become matted together, fistulae may develop from extension of inflammation through the serosa into adjacent structures, and strictures may form. The appearance of “creeping fat” with fat extension over the serosal surface of the bowel may also be present on gross inspection. The endoscopic features of Crohn’s disease include aphthous, stellate, or linear ulcers, cobblestoning, and skip areas of normal mucosa (Figure 4 A&B). The microscopic features of Crohn’s disease include transmural inflammation, granulomas, and skip areas of normal uninfamed mucosa (Figure 5). A diagnosis of indeterminate colitis is based on endoscopic, histologic, and radiologic findings when the criteria for either Crohn's
disease or ulcerative colitis cannot be definitively established. There are no definitive criteria for diagnosing indeterminate colitis (Table 4). However, a working group for the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition suggested that an individual may be given a putative diagnosis of indeterminate colitis if inflammation is limited to the colon and features inconsistent with the diagnosis of ulcerative colitis are present. These features include colitis with a normal rectum on endoscopy and histology (absolute rectal sparing), mild ileitis with features atypical for backwash ileitis (eg. ileal aphthous ulcers), microscopic ileitis with colitis limited to the left colon, severe focal gastritis, pancolitis with anal fissures or anal tags, and colitis with growth failure.17

![Figure 4: Endoscopy of colon (A) Normal (B) Crohn’s disease Map shaped ulcer with raised red border](image)

![Figure 5. Histology Transmural inflammation Asymmetric, discontinuous, granulomas](image)

**Table 4: Indicating signs of UC at first manifestations**21

<table>
<thead>
<tr>
<th>Intestinal</th>
<th>Extraintestinal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal pain</td>
<td>Weight loss</td>
</tr>
<tr>
<td>77%</td>
<td>54%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>Fever</td>
</tr>
<tr>
<td>73%</td>
<td>35%</td>
</tr>
<tr>
<td>Bleeding</td>
<td>Anemia</td>
</tr>
<tr>
<td>22%</td>
<td>27%</td>
</tr>
<tr>
<td>Anal fistulae</td>
<td>Arthralgia</td>
</tr>
<tr>
<td>16%</td>
<td>38%</td>
</tr>
<tr>
<td></td>
<td>Eye involvement</td>
</tr>
<tr>
<td></td>
<td>10%</td>
</tr>
<tr>
<td></td>
<td>Erythema nodosum</td>
</tr>
</tbody>
</table>

Although many treatments have been recommended for IBD, they do not treat the cause but are effective only in reducing the inflammation and accompanying symptoms in up...
to 80% of patients. Thus, current medical management of IBD consists of anti-inflammatory and immunosuppressive agents and biologic drugs, as well as surgery.\textsuperscript{22, 24} The mortality rate of patients with Crohn’s disease is 40% greater than those without evidence of disease including Ulcerative disease. In a retrospective, population based cohort study of mortality by medication use among IBD included 9032 patients during 1996-2002; with the exception of immunomodulators, the medications for IBD were not significantly associated with mortality among IBD patients. However, infections, respiratory diseases and digestive diseases other than IBD have been important specific cause of death in IBD patients. Despite medical intervention, many patients with IBD suffer from complications including abscesses, fistulae, intestinal obstruction, chronic blood loss, and intestinal neoplasia. Also, colorectal cancer is increased in IBD, particularly among male patients.\textsuperscript{23}

**Colon Cancer**

A polyp is an abnormal protruding growth that develops in certain parts of the body. Colon polyps grow in the large intestine. While most polyps are benign (not cancerous), some types of polyps can grow and turn cancerous over time. Often, people don’t know they have colon polyps until the doctor finds them during a regular checkup or while testing them for something else. When symptoms do occur, they commonly include bleeding from the anus or blood on stool. There are 2 types of polyps Hyperplastic polyps and Adenomatous polyps. In general, the larger the polyp, the more likely it is to become cancerous. In cases of larger or multiple polyps, more extensive surgery is required.

Colorectal cancer is cancer that develops in the colon or the rectum.\textsuperscript{25} Colorectal cancer usually develops slowly over a period of many years. Before a true cancer develops, it usually begins as a noncancerous polyp which may eventually change into cancer. A polyp is a growth of tissue that develops on the lining of the colon or rectum. More than 95% of colorectal cancers are adenocarcinomas, which evolve from glandular tissue. For approximately 85% of colon and rectum cancers, the tumor arises from an adenomatous polyp that is visible through a scope or on an x ray. The information on early detection in this document is about this type of cancer. Once cancer forms in the large intestine, it eventually can begin to grow through the lining and into the wall of the colon or rectum. Cancers that have invaded the wall can grow into blood vessels or lymph vessels, which are thin channels that carry away cellular waste and fluid. Cancer cells first drain into nearby lymph nodes, which are bean shaped structures that help fight against infections. The process through which cancer cells travel to distant parts of the body through blood or lymphatic vessels is called metastasis. The extent to which a colorectal cancer has spread is described as its stage. Cancers that have not yet begun to invade the wall of the colon or rectum are called carcinomas in situ, and are not counted in cancer statistics. More than one system is used for the clinical staging of cancer.\textsuperscript{26}

**Diverticulosis**

Diverticulitis is defined as the inflammation of one or more diverticula. The inflammatory process may be limited to the immediate vicinity of the diverticula or may extend to surrounding structures and organs. Diverticula can occur at any point in the gastrointestinal tract (esophagus, stomach, small bowel and colon). Diverticula of the colon are, in most cases, acquired outpouchings of the mucosal layer of the bowel through gaps in the bowel wall musculature. Figure 6 showing left side normal conditions, while, on the right, one sees a diverticulum, which is an outpouching through a vascular gap in the musculature. Endoscopic findings of extensive diverticulosis showing the pouches forming on the side walls of colon (Figure 7).
The most common complication of diverticulosis is the inflammation of the diverticula (diverticulitis), which occurs in about 20% of cases. Thought to trigger this inflammation is the entrapment of stool particles (fecoliths) in the diverticula, the constant pressure of which can lead to the formation of tiny ulcerations within the area of the diverticula. The importance of diverticular disease has been recognized since the 1930’s. With advancing age, there is a significant increase in the frequency of diverticula. While less than 10% of persons aged 30–40 years suffer from diverticula, this proportion rises to 20–35% in persons aged 50–60 years, increasing to over 40% in persons over 70 years of age. With advancing age, there is increase in both the number and size of diverticula. Men and women are about equally affected. Although the exact causes remain unknown, it is today considered very probable that diverticulosis results primarily from segmental motility disturbances in the colon that result in localized areas of high intra luminal pressure within the bowel. Further factors include acquired weakness of the bowel wall in the area of vascular and muscular gaps and changes in lifestyle and nutritional habits. Symptoms observed during this condition include tenesmus, meteorism and feeling of fullness, spontaneous pain, stool irregularities (constipation/diarrhea), fever, rectal bleeding and painful urination.

STRATEGIES OR APPROACHES FOR COLON TARGETING

Initially, delivery of drugs to the colon was tried through the rectal route using suppository and enema formulations. Nevertheless, such formulations rarely succeed in spreading beyond the descending colon, with little or no drug reaching the proximal colon. Moreover, the rectal route is inconvenient or unacceptable for most patients. The oral route is therefore the preferred mode of administration for this purpose.

To achieve colon specific delivery through oral route, the formulation must prevent drug release in the stomach and small intestine but allow release after their arrival in the colon. Although the concept looks quite simple, this is difficult to achieve in practice as the colon is the most distal segment of the GI tract. The formulation will be exposed to a range of conditions and environments during its passage through the GI tract, including pH, enzymes, electrolytes, transit time, and pressure. Furthermore, these parameters are subject to considerable inter and intra individual variation and are also affected by disease. Thus, these factors make the delivery of
drugs to the colon via the oral route a challenging proposition.\textsuperscript{30-33}

The basis of targeting any organ is the identification and exploitation of a characteristic that is unique in that target organ. In the context of colon targeting, the exploitable GI features are transit time, pH, pressure, and microflora. Although a range of approaches have been proposed and systems have been developed based on these features, most of them have never progressed beyond the bench, with very few reaching the stage of clinical evaluation. Some of them have been investigated in humans and have the greatest potential for future clinical use. Nevertheless, few colon specific drug delivery systems have been commercialised.

To achieve colon specific drug delivery, current approaches could be categorized into four categories:\textsuperscript{34, 35}

(i) Release the drug at a predetermined time after administration,
(ii) Utilize pH changes within the GI tract,
(iii) Make use of GI pressure differences, and
(iv) Exploit microbial enzymes predominantly present in the colonic region of the GI tract.

\textit{Drug release based on gastrointestinal transit time}

The time of transit through the small intestine is independent of formulation. It has been found that both large single unit formulations and small multiple unit formulations take three to four hours to pass through the small intestine.\textsuperscript{36-38}

Transit time through the small intestine is unaffected by particle size or density, or by the composition of meals. Because the time taken by formulations to leave the stomach varies greatly the time of arrival of a formulation in the colon cannot be accurately predicted. However, the effects of variation in gastric residence time can be minimized by using systems that are protected in the stomach, and drug release can be targeted on the colon by means of formulations that release the drug they contain a certain time after gastric emptying. Such formulations pass through the stomach and small intestine and drug is then released at the end of the small intestine or beginning of the colon.\textsuperscript{39}

Accordingly, formulations that depend for drug release on time of transit through the small intestine also usually depend for drug release on changes in pH in the gastrointestinal tract. Transit times through the colon that are faster than normal have been observed in patients with irritable bowel syndrome, diarrhoea and ulcerative colitis. Systems that depend on gastrointestinal transit time for drug release are therefore not ideal for drug delivery in the colon for treatment of colon related disease.\textsuperscript{40}

Combinations of hydrophilic (hydroxypropylmethylcellulose, HPMC) and hydrophobic polymers have been used as coatings for tablets that release drug from a core after a lag time.\textsuperscript{41}

When the in vivo behaviour of such tablets was studied scintigraphically it was found that disintegration occurred in the proximal colon after about 5.5 hours (range 5 to 6.5 hours). Lag time could be adjusted by changing the thickness of the polymer layer. HPMC and hydroxypropylcellulose (HPC) have been used as swellable polymers in delayed release formulations.\textsuperscript{42, 43} In such formulations enteric polymers can also be used as coatings to protect the formulation in the stomach. Using gammascintigraphy, investigated the in vivo behaviour of tablets with a drug containing core coated with hydrophilic HPMC and an enteric polymer (Eudragit™ L30D).\textsuperscript{44} The lag time in relation to absorption was found to be 7.3 ± 1.2 hours when the thickness of the polymer layer was greatest. The formulation disintegrated in the colon in all six volunteer subjects. Time controlled formulations have also been prepared using waterinsoluble ethylcellulose and swellable polymer (HPC).\textsuperscript{45, 46}

Each of the formulations consisted of a core, drug, swelling agent and a water insoluble membrane. The swelling agent HPC absorbed liquid and the ethylcellulose coat disintegrated as the core swelled. A lag time of 4.0 ± 0.5 hours in
relation to absorption was found for this formulation in a human bioavailability study, and it was not influenced by food. A drug delivery system (Pulsincap™), from which there is rapid drug release after a lag time, has been developed to allow release of drug in the large intestine.47

The system involves an insoluble capsule body with a hydrogel plug. The plug is ejected from the capsule when it has swelled after a particular lag time. A release profile is characterized by a period during which there is no release followed by rapid and complete drug release. Release using this system was found to be reproducible in vitro and in vivo. When gastrointestinal transit of the formulations was followed by means of gamma scintigraphy it was found in six of the eight subjects that the device reached the colon before drug was released.48

The formulation had been administered with the subjects in a fasting state. Effects of food and gastric retention time were not investigated. In later scintigraphic studies it was found that the site of release of drug in the gastrointestinal tract varied. In one subject the formulation even remained in the stomach for a long time, and drug was also released in the stomach.49

**Drug release based on variation of pH**

In the stomach pH ranges between 1 and 2 during fasting but increases after eating.50, 51 The pH is about 6.5 in the proximal small intestine and about 7.5 in the distal small intestine.52 From the ileum to the colon pH declines significantly. It is about 6.4 in the caecum. However, pH values as low as 5.7 have been measured in the ascending colon in healthy volunteers.53 The pH in the transverse colon is 6.6, in the descending colon 7.0. 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.54 There are various problems with this approach, however. The pH in the gastrointestinal tract varies between and within individuals. During acute stage of inflammatory bowel disease colonic pH has been has been found to be significantly lower than normal. In ulcerative colitis pH values between 2.3 and 4.7 have been measured in the proximal parts of the colon.55 Although a pH dependent polymer can protect a formulation in the stomach and proximal small intestine, it may start to dissolve even in lower small intestine, and site specificity of formulations can be poor.56

Contrariwise, failure of enteric coated dosage forms, especially single unit dosage forms, because of lack of disintegration has been reported. 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 caecal junction or rapid transit through the ascending colon can also result in poor site specificity of enteric coated single unit formulations Eudragit™ products are pH dependent methacrylic acid polymers containing carboxyl groups. The number of esterified carboxyl groups affects the pH level at which dissolution takes place. Eudragit™ S is soluble above pH 7 and Eudragit™ L above pH6. Eudragit™ S coatings protect well against drug liberation in the upper parts of the gastrointestinal tract and have been used in preparing colon specific formulations.57 When sites of disintegration of Eudragit S coated single unit tablets were investigated using a gamma camera they were found to lie between the ileum and splenic flexure. Sitespecificity of Eudragit S formulations, both single and multiple unit, is usually poor. Eudragit™ S coatings have been used to target the anti inflammatory drug 5-aminosalicylic acid (5-ASA) in single unit formulations on the large intestine Eudragit L coatings have been used in single unit tablets to target 5-ASA on the colon in patients with ulcerative colitis or Crohn’s disease.58 The polypeptide hormone vasopressin and insulin have been administered to rats orally in Eudragit S coated single unit capsules Eudragit S coated insulin capsules have also been administered orally to hyperglycaemic beagle dogs.59 In the latter study it was concluded that plasma glucose levels were lowered gradually and reproducibly

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but that delivery by means of the oral route was not bioequivalent to delivery by means of parenteral route. Eudragit S has been used in combination with another methacrylic acid copolymer, Eudragit L100, in colon targeted systems to regulate drug delivery.\(^6\)

**Pressure controlled drug delivery systems**

As a result of peristalsis, higher pressures are encountered in the colon than in the small intestine. Takaya have developed pressure-controlled colon delivery capsules prepared using an ethylcellulose, which is insoluble in water. In such systems drug release occurs following disintegration of a water insoluble polymer capsule as a result of pressure in the lumen of the colon. The thickness of the ethylcellulose membrane is the most important factor for disintegration of the formulation.\(^6\)

The system also appeared to depend on capsule size. When salivary secretion of caffeine after oral administration of pressure controlled capsules was studied in human volunteers, a correlation was found between ethylcellulose membrane thickness and the time of first appearance of caffeine in the saliva. Because of reabsorption of water from the colon, the viscosity of luminal content is higher in the colon than in the small intestine. It has therefore been concluded that drug dissolution in the colon could present a problem in relation to oral drug delivery systems. In pressure controlled ethylcellulose single unit capsules the drug is in a liquid. Lag times of three to five hours in relation to drug absorption were noted when pressure controlled capsules were administered to human subjects.\(^6\) It was concluded that the capsules disintegrated in the colon because of increases in pressure. It was also concluded that the formulation studied was advantageous in that the drug release mechanism is independent of pH. The site at which the formulations disintegrated was not demonstrated in the studies mentioned above. The mechanism of disintegration was also not clarified. As discussed above, ethylcellulose coatings have also been used in connection with timecontrolled drug delivery. Disintegration of the formulation can therefore also occur some time after administration, even in the small intestine.\(^6\)

**Drug release based on the presence of colonic microflora**

Both anaerobic and aerobic microorganisms inhabit the human gastrointestinal tract.\(^6\) In the small intestine the microflora is mainly aerobic, but in the large intestine it is anaerobic. Almost 400 distinct bacterial species have been found, out of which 20% to 30% are of the genus Bacteroides. The upper region of GIT consists of very small number of bacteria and predominantly gram-positive facultative bacteria. The concentration of bacteria in the human colon is around 1000 CFU/mL. The most important anaerobic bacteria are Bacteroides, Bifidobacterium, Eubacterium, Peptococcus, Peptostreptococcus, Ruminococcus, Propionibacterium and Clostridium (Figure 8). Most bacteria inhabit in the proximal areas of the large intestine, where energy sources are greatest. Carbohydrates arriving from the small intestine form the main source of nourishment for bacteria in the colon. The carbohydrates are split into short chain fatty acids, carbon dioxide and other products by the enzymes glycosidase and polysaccharidase. Protease activity in the colon can result in cleavage of proteins and peptides. In the proximal colon the pH is lower than at the end of the small bowel because of the presence of short chain fatty acids and other fermentation products. Diet can affect colonic pH. The presence of colonic microflora has formed a basis for development of colon specific drug delivery systems. Interest has focused primarily on azo reduction and hydrolysis of glycoside bonds. However, the colonic microflora varies substantially between and within individuals, reflecting diet, age and disease. Such variations need to be taken into account in developing colon specific formulations depending on the presence of colonic microflora. There is also significant proteolytic activity in the colon, although this is 20 to 60 times less than in the small bowel. Even when proteolytic activity is relatively low a drug may remain much longer in the colon than in the...
small intestine, with the result that it is exposed longer to proteolytic activity.  

Figure 8: Distribution of selected bacteria in the GI tract

Prodrugs have been used in targeting drugs on the large intestine. Sulphasalazine, used in the treatment of ulcerative colitis and Crohn’s disease, is a prodrug. In the colon sulphasalazine is split by bacterial azoreduction into 5-ASA and sulphapyridine (Figure 9). Sulphapyridine can cause side effects, and other carriers for delivery of 5-ASA to the colon have therefore also been investigated. Olsalazine consists of two molecules of 5-ASA linked by an azo bond.

Ipsalatsine and balsalatsine are other 5-ASA containing prodrugs. Polymers and polyamides containing azo groups have been used to convey 5-ASA to the large intestine.

Azo polymers have been used as film coatings. Colon targeting by means of azo polymers is associated with many problems. Microbial degradation of azo polymers is usually slow, and drug delivery can be incomplete and irregular. Not enough is yet known about the safety of azo polymers. In vivo absorption studies with azo polymers have mostly been carried out using rats. No results of studies in human beings are available. Although the gastrointestinal microflora of rats and humans differ, results of in vivo experiments with rats can give some indications regarding biodegradation of azo polymers. Hydrogels containing azo aromatic cross links have been investigated in connection with site specific drug delivery of peptide and protein drugs.

In the low pH range of the stomach the gels have a low equilibrium degree of swelling and the drug is protected against digestion by enzymes, but at
high pH levels they swell. So in the stomach a drug will be protected, but released in the colon, where cross links become degraded. The colonic microflora produces a wide range of glycosidases capable of hydrolysing glycosides and polysaccharides.

Glycosides of glucocorticosteroids have been synthesized, and tested in rodents. The problem in these studies was that some drug was hydrolysed even in the small intestine. However, in rodent bacterial glycosidase activity in the small intestine is some 100 times greater than in human beings. It is likely that drug delivery in man would be more predictable than in rodents. Glucuronides, which are less subject to hydrolysis in the small intestine than glycosides, have also been used as drug carriers. An extensive range of drug delivery systems based on polysaccharides has been investigated. The advantage of these materials is that most are easily available. Disadvantages are that most of polysaccharides are hydrophilic and gel forming. In preparing dosage forms from polysaccharides it is necessary to ensure that no drug is released until it reaches the colon. Amylose has been used in coatings of colon specific formulations.

Amylose, a major component of starch, swells too much on its own, but amyllose ethylcellulose coatings have been investigated in connection with targeting of drug release on the colon. From the results of in vitro studies it was concluded that amyllose ethylcellulose coatings could be suitable for colon specific formulations. Pectin is a polysaccharide, found in the cell walls of plants. It is totally degraded by colonic bacteria but is not digested in the upper gastrointestinal tract. One disadvantage of pectin is its solubility. This can however be adjusted by changing its degree of methoxylation, or by preparing calcium pectinate. The film coating properties of pectin have been improved through use of ethylcellulose. Pectin has also been used with chitosan and HMPC.

It has been shown in studies in which gamma camera was used that pectin coated tablets disintegrate in the colon during transit. Cross linked guar gum has been used as a drug carrier in matrix tablets.

**Judgement concerning colon specific drug delivery methods**

During the last decade many investigations have been carried out with the aim of study an ideal formulation for colon specific drug delivery. Many approaches have been demonstrated. All have some Merits as well as Demerits (Table 5). The microflora of the colon can split polymers. However, such enzymatic degradation is usually excessively slow. The bioavailabilities of drugs from such formulations can be low. In addition, little is known about the safety of the polymers and few have been accepted for use in relation to medicines. Most studies relating to biodegradable polymers have been carried out only in vitro or in laboratory animals. Time controlled formulations have also been investigated and developed in connection with targeting of drug delivery on the colon. Formulations of this kind need to be manufactured in such a way that they remain intact in the stomach, in the presence or absence of food. Manufacture of such formulations on an industrial scale is often complicated and expensive. Formulations involving enteric polymers that react to changes in gastrointestinal pH have been extensively used in connection with colon specific drug delivery. Enteric polymers have been shown to be safe, and have been accepted for use in drug products. The enteric polymers that have been used are soluble above pH 6 to 7. The pH at the end of the small intestine is about 7.5. It is therefore obvious that drug release from enteric coated formulations can begin from the end of the small intestine. pH levels also decline from the ileum to the colon. If an enteric coated formulation is still intact after passage through the small intestine there may be a significant delay in relation to drug release in the colon, where the pH value is lower. Rapid drug release in the ascending colon is however usually required when colon specific formulations are used in treatment of colon diseases. It is advantageous if drug release from a formulation can begin immediately after it enters the colon,
even though drug release may subsequently be retarded. It may be concluded that no ideal formulation for colon specific drug delivery yet exists. Drug release from an ideal formulation should begin in the ascending colon, at a predetermined rate. The manufacturing process for the formulation should also be simple and not too expensive.

<table>
<thead>
<tr>
<th>Method</th>
<th>Merits</th>
<th>Demerits</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time dependent systems</td>
<td>Small intestine transit time fairly consistent</td>
<td>Substantial variation in gastric retention time</td>
<td>36,40,54</td>
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<tr>
<td></td>
<td></td>
<td>Transit through the colon more rapid than normal in patients with colon disease</td>
<td></td>
</tr>
<tr>
<td>pH dependent systems</td>
<td>Formulation well protected in the stomach</td>
<td>pH levels in the small intestine and colon vary between and within individuals</td>
<td>39,40,54</td>
</tr>
<tr>
<td></td>
<td></td>
<td>pH levels in the end of small intestine and caecum are similar</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Poor site specificity</td>
<td></td>
</tr>
<tr>
<td>Microflora/ Bacteria activated systems</td>
<td>Good sitespecificity with prodrugs and polysaccharides</td>
<td>Diet and disease can affect Colonic microflora</td>
<td>40,64</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Enzymatic degradation may be excessively slow</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Few have been accepted for use in relation to medicines</td>
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**Table 5: Merits and demerits of various oral colon specific drug delivery methods**

**In vitro and in vivo evaluation of drug colon specific delivery system**

In vitro dissolution testing is important in the development of solid dosage forms. The method used should simulate the environment to which the dosage form being developed will be exposed in the gastrointestinal tract. In the United States Pharmacopoeia (USP) dissolution procedures are described for conventional oral formulations and for extended release and delayed release formulations (USP 23). In the case of enteric coated formulations the test for delayed release articles” should be used. However, controlled release formulations used for colon specific drug delivery are usually complex, and the dissolution methods described in the USP cannot wholly mimic in vivo conditions such as those relating to pH, bacterial environment and mixing forces. The conventional method involving dissolution in various buffers is useful for assessing the ability of an enteric colon specific coating to prevent drug release in the stomach and small intestine. Dissolution studies of this kind can be used in relation to both time release systems and formulations with enteric coatings. Dissolution tests relating to colon specific drug delivery systems may be carried out using the conventional basket method. Parallel dissolution studies in different buffers may be undertaken to characterize the behaviour of formulations at different pH levels carried out dissolution tests of a colon specific formulation in various media simulating pH conditions at various locations in the gastrointestinal tract. The media chosen were, for example, pH 1.2 to simulate gastric fluid, pH 6.8 to simulate the jejunal region of the small intestine, and pH 7.2 to simulate the ileal segment. Consecutive dissolution tests in different
buffers for different periods of time best simulate the transit of a formulation through the gastrointestinal tract. In gradient dissolution studies a particular formulation unit is exposed to buffers representing successive conditions in the gastrointestinal tract. Enteric coated capsules for colon specific drug delivery have been investigated in a gradient dissolution study in three buffers. The capsules were tested for two hours at pH 1.2, then one hour at pH 6.8, and finally at pH 7.4.

The relationship between percentage of drug released in vitro and percentage of drug absorbed in vivo was observed when pulsatile release tablets were tested in vitro for two hours at pH 1.2 followed by a dissolution study at pH 6.8.

A dissolution study was then carried out at pH 6.8. It was concluded that the dissolution profiles of formulations that had not been kept in buffer at pH 1.2 did not differ markedly from dissolution profiles of formulations that had been kept in buffer at pH 1.2. Exposure to acid in the stomach should therefore not affect the dissolution properties of such formulations in the lower gastrointestinal tract. On the basis of these findings it is obvious that sufficient information regarding dissolution properties of formulations can often be obtained using parallel dissolution tests. Gradient dissolution tests are usually unnecessary. To allow the performance of colon specific delivery systems containing biodegradable polymers to be assessed, the contents of animal caecum have been used in dissolution studies. Such studies provide no information about the physical and chemical functionality of a system.

In vivo bioavailability tests in human beings are important in developing controlled release drug delivery systems. From the results of bioavailability tests, sites of drug liberation in vivo can be determined, if the formulation has been administered to the subjects in the fasting state. However, it is impossible to predict times of arrival of formulations in the colon accurately, because gastric emptying times vary so greatly. In recent years gammascintigraphy has become the most popular means of investigating the gastrointestinal performance of pharmaceutical dosage forms, especially site colon specific dosage forms. By means of gammascintigraphic imaging, information can, for example, be obtained regarding time of arrival of a drug 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.

Gammascintigraphic studies can also provide information about regional permeability in the colon. Information about gastrointestinal transit and the release behaviour of dosage forms can be obtained by combining pharmacokinetic studies and gammascintigraphic studies (pharmacoscintigraphy). Good correlations between appearance of a drug in plasma and observed disintegration times have been recorded. When gammascintigraphy was used to investigate the suitability of a Eudragit™ S coated tablet for drug delivery to the colon results of the study were found to be in accordance with results of in vitro dissolution studies. Gammascintigraphy has also been used to determine gastrointestinal transit times and sites of disintegration of calcium pectinate tablets intended to allow colon specific drug delivery. Although the tablets disintegrated completely in the colon it was concluded that gammascintigraphy did not allow exact information about the mechanism of disintegration to be obtained. Many pharmacoscintigraphic studies have been reported.

**EVALUATION PARAMETERS FOR COLON SPECIFIC DRUG DELIVERY**

**In vitro release study**

In invitro release study can be used as a tool to assess drug release kinetics, impact of pH and hydrodynamic conditions on drug release characteristics, implications of formulation and manufacturing process changes, drug release controlling mechanism, batch to batch consistency, and possibly to act as an in vivo
substitute. Dissolution testing has been an integral component in pharmaceutical research and development of solid dosage forms. It is the most widely accepted technique to evaluate the drug release pattern from oral dosage forms including colon specific drug delivery systems. It provides information on formulation type, critical processing variables, in vitro–in vivo correlation and quality assurance during manufacturing. Development of dissolution method is an essential part of drug product applications to regulatory agencies as it is employed as quality control tool. Dissolution testing method should be scientifically justifiable, reproducible and most importantly bio relevant i.e. should be conducted in physiochemically and hydrodynamically defined conditions to simulate the environment that the dosage form encounters in the GI tract. Presently, dissolution study of modified release oral drug delivery systems is carried out using four types of dissolution apparatus: USP dissolution apparatus I (basket method), II (paddle method), III (reciprocating cylinder) and flow through cell. But, some modification of conventional dissolution methodology was deemed necessary for complex drug delivery systems like colon specific targeted dosage forms, as certain restraints associated with routine dissolution methods were discerned. The dissolution testing method should closely mimic the in vivo colonic environment with regard to pH, the volume and distribution of fluids, bacteria, the composition and activity of enzymes, and the mixing intensity, while being able to discriminate the impact of upper GI tract transit on the delivery system. However, limited quantity of fluids particularly in the distal colon, the diversity and anaerobic nature of colonic microflora, the heterogeneity of fermentation activity in different regions, as well as the transient occurrence of motility patterns make the development, standardization and validation of such dissolution method highly challenging, if possible at all. Nevertheless, several approaches were attempted in the literature for the testing of microbially triggered colon specific delivery systems.

**USP dissolution methods**

It is widely accepted that during dissolution method development, the compendial apparatus and methods be first used for dissolution or release study of any exceptional/special kind of dosage forms. Few scientists used USP dissolution apparatus II and III with slight modification to evaluate microbially triggered colon specific delivery system, whereas apparatus III (reciprocating cylinder) is more popular due to its unique setup (the dissolution tubes can be programmed to move along successive rows of vessels). In addition, the drug release can be evaluated using a gradient of media to simulate the passage through different sections of the GI tract, varying hydrodynamic conditions and residence time in different media to simulate motility patterns and passage time under fasting and fed states (programmed with changes in sampling time, agitation rates, and medium).

To mimic the GI tract physiological condition, three media are generally used for in vitro release of colon specific delivery systems: simulated gastric fluid (SGF), simulated intestinal fluid (SIF) and simulated colonic fluid (SCF). The SGF and SIF is mainly phosphate buffer of pH 1.2 and 6.8 and 7.5, respectively. The SCF is also a phosphate buffer of pH 5 – 6; but, it normally includes enzyme which degrades specifically polysaccharides used in the delivery system; for example, pectinase for pectin, galactomannanase for guar gum. For better representation of the transit time in the GI tract, the duration of testing in each medium is usually set i.e.1- 2 h in simulated gastric fluid (SGF), 3-4 h in simulated intestinal fluid (SIF) and 7 – 8 h in simulated colonic fluid (SCF, contain enzyme which specifically degrade the biopolymer used in the formulation), successively. Many researchers reported the use of USP dissolution apparatus for drug release study of colon specific formulations.
Although USP dissolution testing is simple and convenient however, it is not known whether one can predict the in vivo performance of these products from in vitro dissolution data as the volume and composition of dissolution media and the mixing intensity are not representative of the conditions present in the colon due to scarcity of fluid and reduced motility in the colon. It is mainly used to evaluate the integrity of a delivery system and provides essential information on the consistency of its manufacturing process. Therefore, the drug release determined from the current USP dissolution setting is primarily qualitative in nature and may not be correlated with the in vivo situation.

In an effort to minimize unnecessary human testing, investigations of in vitro / in vivo correlations (IVIVC) between in vitro dissolution and in vivo bioavailability are increasingly becoming an integral part of controlled release drug product development.

**Dissolution using rat caecal contents**

The use of rat caecal content to overcome the limitations of the conventional dissolution study is a widely accepted alternative dissolution medium due to the similar microflora present between human and rodent. Bacteroides and Bifidobacteria, are the two predominant polysaccharide degrading bacteria, present in human large intestine and rat caecum. The caecal contents were then diluted with phosphate buffered saline (PBS, pH 7) to obtain an appropriate concentration. This step was conducted under a CO₂ or nitrogen atmosphere to maintain the anaerobic condition. The drug release studies were usually carried out in sealed glass vials at 37 °C for a defined period of time. Samples were then withdrawn at different intervals to quantify the amount of drug released with an appropriate method. Several drug release studies have been carried out using rat caecal contents. However, standardisation of the experimental procedure, such as, pH and viscosity of the media, the agitation intensity, the concentration and source of rat caecal contents, and volume of testing medium is required to allow meaningful comparison of different delivery systems and to establish in vitro- in vivo relationship.

**Dissolution using human fecal slurries**

Use of human fecal slurries in the drug release study from polysaccharides based formulation is also an alternative approach. The slurries were prepared by homogenizing fresh feces obtained from healthy human volunteers in anaerobic 0.1 M sodium phosphate buffer (pH 7.0). These volunteers usually had no preceding history of gastrointestinal disorder and had not taken antibiotics for at least 3 months prior to the study. During a 48 h period, gas head space and liquid samples were collected at predetermined time intervals from the fermentor and analysed for drug release. This method was adopted for the dissolution testing of colonic drug delivery systems activated by colon microflora.

**Multi stage compound culture system**

The colon, particularly caecum and the ascending colon resembles a continuous culture system as the indigestible residues from small intestine are fermented and condensed during transit through the colon. Considering this situation, a three stage continuous culture system was designed to simulate the colonic microfloral characteristics at various colonic regions. This multi stage system comprises three glass fermentation vessels arranged in series as follows: 1st stage working volume of 200 ml at pH 5.5, (simulates proximal colon); 2nd stage working volume of 200 ml at pH 6.2, (simulates transverse colon); and lastly, 3rd stage working volume of 280 ml at pH 6.8 (simulates distal colon). Each fermentation vessel was inoculated with 100 ml of freshly prepared 20 % (w/v) fecal slurries from healthy non methanogenic donors with continuous stirring at 37°C under CO₂ atmosphere. The whole procedure is described elsewhere.

Based on the above concept, a five step multi chamber reactor (simulated human intestinal microbial ecosystem (SHIME)) to simulate both small and large intestinal microbial ecosystem was fabricated. Each reactor in the SHIME
represented each segment of human GI tract (duodenum and jejunum, ileum, caecum and ascending colon, transverse colon, and descending colon). Despite the possibility of standardizing drug dissolution studies using multi stage culture systems, the complexity in setup and operation (e.g., strength and sources of the fecal inoculate, buffering of the medium, continuous addition of nutrients for bacterial growth and the requirement of special containment facilities) prevent them from routine use. Though dissolution study in medium containing caecal contents or human fecal slurries or in a multi stage culture system indicates whether or not drug release will be initiated by degradation of polysaccharides when exposed to the colonic environment, this provide very little information about the delivery system, formulation and process development. Hence, it is advisable to employ USP dissolution testing together with the dissolution in bio relevant media containing rat caecal contents or human fecal slurries or the multi stage culture system to fully characterize a formulation activated by microflora.

In vivo study

Colon specific drug delivery systems based on their in vitro drug dissolution profiles compared with the in vivo study can be problematic. The viscosity, pH, bacterial composition, and enzyme activities in the dissolution medium together with agitation intensity are only qualitatively comparable to the colonic conditions. When the formulation design is formulated and trial model formulation with acceptable in vitro characteristics is achieved, in vivo studies are usually conducted to evaluate the site specificity of drug release and to obtain relevant pharmacokinetics information of the delivery system.

These factors suggest that the rate of polysaccharide fermentation and dissolution kinetics would be different in vitro than in vivo. As the dissolution testing conditions differ significantly from each other and from the actual in vivo condition, actual in vivo experiments are essential to prove the efficacy of the formulations. Although various animal models are used for evaluating colon specific drug delivery systems, but human subjects are increasingly approved for studying this type of delivery systems. Variety of techniques such as String technique, Endoscope technique, Roentgenography and Gamma scintigraphy are applicable for monitoring the in vivo behaviour of colon specific drug delivery systems in human are:

Gamma scintigraphy

The most useful technique, to date, to evaluate the in vivo behavior of dosage forms in animals and humans is external scintigraphy or gamma (γ) scintigraphy. γ Scintigraphy is an imaging modality, which enables the in vivo performance of drug delivery systems to be visualized under normal physiological conditions in a non invasive manner. Since first employed to investigate the functionality of formulations in vivo more than two decades ago. Work in this area began in the 1970s through the modification of standard nuclear medicine methods, to monitor the in vivo behavior of dosage forms. Gamma scintigraphy requires the presence of a γ emitting radioactive isotope in the dosage form that can be detected in vivo by an external gamma camera. The dosage form can be radio labeled using conventional labeling or neutron activation methods. γ scintigraphy has become an established technique and extensively used to monitor the performance of novel drug delivery systems within human GI tract.

γ Scintigraphy based imaging technology has immensely helped in generating good evidence of the actual in vivo behaviour of colon targeted dosage forms. Gamma scintigraphy is a nuclear medicine technique that is used to visualise the in vivo behaviour of pharmaceutical dosage forms in a non invasive manner. For example, the performance of Eudragit® S coated tablets in seven healthy volunteers was assessed using gamma scintigraphy. In one study, efficacy of their Ca-pectinate beads in rats was evaluated. One rat from each group was sacrificed at predetermined time interval after the administration of the formulation. The GI tract was removed and segmented into the stomach,
small intestine, caecum, and colon. The amount of drug recovered in different segments of GI tract at different time intervals were determined by HPLC analysis.

Pharmacokinetic study has also been used to check the formulation efficiency. Pharmacokinetics study of chloroquine loaded pectin beads in rats. Blood samples were collected at predetermined time interval following oral administration of the formulations and amounts of chloroquine were measured.\textsuperscript{111} Formulation efficacy was evaluated after oral administration of insulin loaded pectin beads in streptozotocin diabetic rats. Blood samples were collected for insulin and glucose measurements at different time intervals.\textsuperscript{112}

**In Vitro & In Vivo Correlation:**

The empirical in vitro & in vivo correlation of the colon absorption of the drug model is essentially based on two assumptions

- The kinetics of drug absorption along the GIT varies because of different resident time values in different regions & variations in the drug permeability across the epithelial walls along the alimentary canal.

- The correlation between dissolution data and in vivo cumulative absorption data can be derived by superimposing the linear transformations of the time axis if each other( homomorphic)

The linear & biphasic nature of the obtained plots are suggestive of a shift in the rate of absorption at a given time. The larger ratio in the slopes of linear segments of continuous correlation plots indicates more variation in absorption rate constants at different locations of GIT. In case of sustained release formulations, the total release time is more than the orocecal transit time.

**CONCLUSION**

Many investigations have been carried out with the aim of discovering an ideal formulation for colon specific drug delivery and have a number of important implications in the field of pharmacotherapy. These include the topical treatment of colonic disorders, such as irritable bowel syndrome (IBS), inflammatory bowel disease (IBD) such as Crohn’s disease, Ulcerative colitis, Colon cancer, Diverticulosis, Diarrhea, Amebiasis etc. Crohn’s disease is most commonly occurring inflammatory disease condition which has symptoms mostly similar as that of Ulcerative colitis. Many approaches have been demonstrated. All have some advantages and disadvantages. Of all the approaches discussed pH dependent delivery appear more promising compare with the rest. The microflora of the colon can split polymers and such enzymatic degradation is usually excessively slow. The bioavailabilities of drugs from such formulations can be low. Most research relating to biodegradable polymers has limitations that are carried out only in vitro or in laboratory animals. Time dependent formulations have also been investigated and formulations of this kind need to be developed in such manner that they remain intact in the stomach and small intestine, in the presence or absence of food. Formulations involving enteric polymers or pH dependent that react to changes in gastrointestinal pH have been extensively used recently. Enteric polymers have been shown to be safe and have been accepted for use in drug products. For in vitro evaluation of a colon specific drug delivery system, it seems that more than one testing method is necessary to characterize drug release and justify system design rationale. Considering the sophistication of colon specific drug delivery systems and the uncertainty of current dissolution methods in establishing possible in vitro/in vivo correlation, challenges remain for pharmaceutical scientists to develop and validate a dissolution method that incorporates the physiological features of the colon and yet can be used routinely in an industry setting for the evaluation of colon specific drug delivery systems. On the other hand, $\gamma$ scintigraphy imaging allows the visualization of in vivo functioning of a colon specific drug delivery system, thereby ascertaining the location of drug release and substantiating the design rationale.
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