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Colon Targeted Drug Delivery Systems – A Review

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ABSTRACT
Day by day there are new developments in field of colon specific drug delivery system. Colonic drug delivery has gained increased importance not just for the delivery of the drugs for the treatment of local diseases associated with the colon like Crohn's disease, ulcerative colitis, etc but also for the systemic delivery of proteins, therapeutic peptides, anti-asthmatic drugs, antihypertensive drugs and anti-diabetic agents. 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.

Keywords: Colon drug delivery, Crohn's disease, Ulcerative colitis.

INTRODUCTION

The oral route of drug administration is the most convenient and important method of administering drugs for systemic effect. Nearly 50% of the drug delivery systems available in the market are oral D.D.S. and these systems have more advantages due to patient acceptance and ease of administration. [1-2] During the last decade there has been interest in developing site-specific formulations for targeting drug to the colon. Colonic drug delivery has gained increased importance not just for the delivery of the drugs for the treatment of local diseases associated with the colon like Crohn's disease, ulcerative colitis, irritable bowel syndrome and constipation but also for the systemic delivery of proteins, therapeutic peptides, anti-asthmatic drugs, antihypertensive drugs and anti-diabetic agents. [3-4] There are various methods or techniques through which colon drug targeting can be achieved, for example, formation of prodrug, coating with pH-sensitive polymers, coating with biodegradable polymers, designing formulations using polysaccharides, timed released systems, pressure-controlled drug delivery systems, osmotic pressure controlled systems. [5-6] Coating of the drugs with pH-sensitive polymers provides simple approach for colon-specific drug delivery.

Advantages of colon targeting drug delivery system: [7-9]

- Colon is an ideal site for the delivery of agents to cure the local diseases of the colon.
- Local treatment has the advantage of requiring smaller drug quantities.
- Reduces dosage frequency. Hence, lower cost of expensive drugs.
- Possibly leading to a reduced incidence of side effects and drug interactions.
- The colon is an attractive site where poorly absorbed drug molecules may have an improved bioavailability.
- Reduce gastric irritation caused by many drugs (e.g. NSAIDS).
- Bye pass initial first pass metabolism.
- Extended daytime or nighttime activity.
- Improve patient compliance.
- Targeted drug delivery system.
- It has a longer retention time and appears highly responsive to agents that enhance the absorption of poorly absorbed drugs. [10]
- It has low hostile environment, less peptidase activity so peptides, oral vaccines, insulin, growth hormones, can be given through this route. [11]

Limitations of colon targeting drug delivery system:

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

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- Limitations of prodrug approach is that it is not very versatile approach as it's formulation depends upon the functional group available on the drug moiety for chemical linkage. Furthermore prodrugs are new chemical entities and need a lot of evaluation before being used as carriers. [15]

ANATOMY AND PHYSIOLOGY OF COLON

1. Structure of Colon

Colon is the lower part of the gastrointestinal tract and runs from ileocecal junction to the anus. It includes proximal part (ascending colon), transverse colon, descending colon, sigmoid colon, rectum and anus (Fig. 1). In contrast with small intestine surface area of colon is low but effective absorption take place due to presence of villi, microvilli and long residence time. The colon is cylindrical tube which is lined by moist, soft pink lining called mucosa and it is 2 -3 inches in diameter. The colon and rectum have an anatomic blood supply. Lymph nodes are also present with blood vessels.

Activity in the colon can be divided into segmenting and propulsive movements. Segmenting movements, caused by circular muscle and causing the appearance of the sac-like haustra, predominate and result in mixing of the luminal contents. Significant propulsive activity, associated with defecation and affected by longitudinal muscle is less common and occurs at an average of three or four times daily. [16]

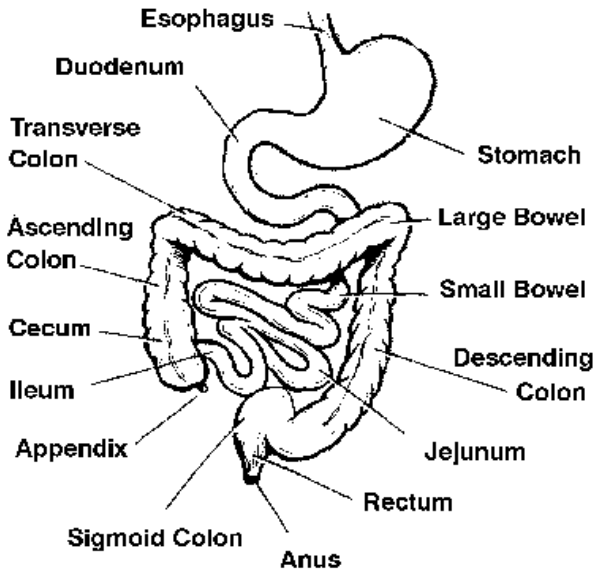


Fig. 1: Diagram of various regions in gastrointestinal tract

2. Colonic Microflora

The slow movement of material through the colon allows a large microbial population to grow there. Over 400 distinct bacterial species have been found. Most of these isolated bacteria are anaerobic in nature. A small number of fungi are also present. The rate of microbial growth is greatest in the proximal areas because of high concentration of energy source. The principal source of nutrition for the colonic microorganisms is carbohydrates arriving in intestinal chime. The carbohydrates are degraded by the action of polysaccharidase and glycosidase enzymes and the ultimate products of fermentation are short chain fatty acids, carbohydrate fermentation predominates and results in a relatively low pH. In the distal regions, there is little carbohydrate fermentation, resulting in a higher pH. The bacteria within the colon are predominantly anaerobic and there is a low redox potential.

Table 1: Following table gives summery of colonic microorganism acting on the some component

S. NO	COMPONENT	CONVERTED INTO
1.0	Carbohydrate	CO_2, Organic acid
1.1	Cellulose	Carbonic acid, Methane
2.0	Fats	Lower fatty acid and glycerol
2.1	Choline	Neurine
3.0	Proteins	Amino acid, Ammonia
3.1	Tryptophan	Indole, Skatole (Bad order of Faces)
3.2	Tyrosine and Phylalenin	Phenol and Cresol
3.3	Histidine	Histamine
3.4	Tyrosine	Tyramine
3.5	Arginine	Putrescine
3.6	Lysine	Codaverine

3. Functions of Colon

1. Suitable site and environment for the growth of colonic microorganism
   a. These bacteria are very rich in cytochrome. The normal flora of the large intestine prevents the growth of other pathogenic bacteria and serves a useful purpose.
   b. Some bacteria can breakdown cellulose. It has been concluded that people suffering from constipation can breakdown cellulose more than normal ones, thus reducing the bulk. [17]
2. Formation of stool and storage reservoir of facial contents.
3. Absorption of potassium and water from lumen resulting in formation of facial content. Saline, glucose, some anesthetics, amino acid are better absorbed here.
4. Secretion and excretion of potassium and bicarbonate, bismuth, mercury, arsenic, etc.
5. Synthesis function: microorganism in colon synthesizes vitamin k, folic acid. Large amount of vitamin B_{12} are also synthesis by these microorganism but are not absorbed.

4. Absorption of Drugs from the Colon

Drugs are absorbed passively by paracellular or transcellular routes. Transcellular absorption involves the passage of drugs through cells and this is the route most lipophilic drugs takes, whereas paracellular absorption involves the transport of drug through the tight junctions between cells and is the route most hydrophilic drug takes. The poor paracellular absorption of many drugs in the colon is seen due to the fact that epithelial cell junctions are very tight. The slow rate if transit in colon lets the drug stay in contact with the mucosa for a longer period than in small intestine which compensates the much lower surface area. The colonic content becomes more viscous with progressive absorption of water as one travels further through colon. This causes a reduced dissolution rate, slow diffusion of dissolved drug through the mucosa.

5. pH of Various Area of Gastrointestinal Region

In the stomach pH ranges between 1 and 2 during fasting but increase after eating. From the ileum to the colon pH declines significantly. It is about 6.4 in the caecum.

Table 2: Following table summarizes the ph of various regions in gastrointestinal tract

S. No	MAIN PART OF GIT	SUB PART	pH OF THAT AREA[18-21]
1.0	Stomach		1 to 2
2.0	Small Intestine		
2.1		Proximal Small Intestine	6.5
2.2		Distal Small Intestine	7.5
3.0	Large Intestine		
3.1		Ascending (proximal) colon	5.7
3.2		Transverse colon	6.6
3.3		Descending colon	7.0

6. **Transit Time under Normal Conditions**

Using a radiopaque marker technique, the transit times in a group of 73 healthy adults has been estimated. The mean mouth-to-anus transit time was 53.3 h. Result is tabulated in Table 3. The surface area of the colon for absorption is smaller than that of the small intestine, and this is compensated by the slow transit time. [22]

Table 3: Following table summarizes the transit time in gastrointestinal tract under normal conditions

S. No.	MAIN PART OF G.I.T.	SUB PART	TRANSIT TIME UNDER NORMAL CONDITIONS
1.0	Stomach		1-2 h
2.0	Small Intestine		3-4 h
3.0	Large Intestine		
3.1		Right (ascending + portion of transverse)	11.3 h
3.2		Left (descending + portion of transverse)	11.4 h
3.3		Rectosigmoid colon	12.4 h

Table 4: Table showing length of various parts of large intestine in centimeter

REGION OF GASTROINTESTINAL TRACT (Large intestine)	LENGTH (cm)
Cecum	6-7
Ascending colon	20
Transverse colon	45
Descending colon	30
Sigmoid colon	40
Rectum	12
Anal canal	3

7. **Factor Effecting Colonic Transit**

There are various factors which affects the colonic transit. These include diet, mobility, stress and disease state. Dietary fiber influences greatly the colonic motility. Dietary fiber increases faecal weight, partly by retention of water and partly by increasing bacterial mass and reduces colonic transit times. For example, addition of 20 g/day of bran to the diet of group of healthy subjects increased stool weight by 127% and reduced whole gut transit by 73 ± 24 h to 43 ± 7 h. [23]

COLONIC DISEASES [24]

1. **Angiodysplasia**

Tortuous dilution of sub-mucosal and mucosal blood vessels is seen most often in the cecum or right colon, usually after the age of 60. They are prone to rupture and bleed into lumen. Such lesion account for 20% of significant lower intestinal beading. Angiodysplasia is a small vascular malformation of the gut. It is a common cause of otherwise unexplained gastrointestinal bleeding and anemia. Lesions are often multiple, and frequently involve the cecum or ascending colon, although they can occur at other places. Treatment may be with endoscopic interventions, medication, or occasionally surgery. Diagnosis of angiodysplasia is often accomplished with endoscopy, either colonoscopy or esophagogastroduodenoscopy (EGD). [25]

2. **Inflammatory Bowel Disease**

Crohn disease may affect any portion of the gastrointestinal tract from esophagus to anus but most often involves the ileum. The cause of inflammatory bowel disease is multi-factorial and it is due to the inflammatory responses, abnormal local immune response against the normal flora of the gut, genetic factors such as multiple genetic factors, candidate genes, chromosome location, infectious agents like Escherichia coli, Measles virus, Cytomegalovirus, etc., dietary factors such as saturated fats, milk products, allergic foods etc. Crohn's disease and ulceration colitis are chronic relapsing inflammation disorder of unknown origin, collectively known as idiopathic inflammatory bowel disease (IBD). The main drugs used in the treatment of ulcerative colitis and Crohn's disease are the amino salicylates and corticosteroids. [26] These diseases and other inflammatory bowel disease have been linked with an increased risk of colorectal cancer. [27]

Ulcerative colitis: Ulcerative colitis occurs only in the large intestine. Ulcers form in the inner lining of the intestine, or mucosa, of the colon or rectum, often resulting in diarrhea, blood, and pus. The inflammation is usually very rigorous in the sigmoid and rectum and usually reduces in the colon.

Crohn's disease: Crohn's disease, also called regional enteritis, is a chronic inflammation of the intestines which is usually confined to the terminal portion of the small intestine, the ileum.

Table 5: Marketed drug products for the treatment of various diseases of colon [28]

S. No.	MARKETED NAME	COMPANY NAME	DISEASE	DRUG
1	Mesacol tablet	Sun pharma, India	Ulcerative colitis	Mesalamine
2	Mesacol enema	Sun pharma, India	Ulcerative colitis	Mesalamine
3	Asacol	Win-medicare, India	Ulcerative colitis, crohn's disease	Mesalamine
4	SAZO	Wallace, India	Ulcerative colitis, crohn's disease	Sulphasalazine
5	Intazide	Intas, India	Ulcerative colitis	Balsalazide
6	Lomotil	RPG Life, India	Mild ulcerative colitis	Diphenoxylate hcl, atropine sulphate
7	BUSCOPAN	German Remedies, India	Colonic motility disorder	Hyoscine butylbromide
8	COLOSPA	Solvay, India	Irritable colon syndrome	Mebeverine
9	CYCLOMINOL	Neol, India	Irritable colon syndrome	Diclomine
10	Eldicet	Solvay, India	Irritable colon syndrome, Spastic colon	Pinaverium bromide
11	Equirex	Jagsonpal Pharmaceutical, India	Irritable colon syndrome	Clordiazepoxide
12	Normaxin	Systopic labs, India	Irritable colon syndrome	Clidinium bromide
13	Pro-banthine	RPG Life, India	Irritable colon syndrome	Propenthline bromide
14	Entofoam	Cipla, India	Ulcerative colitis	Hydrocortisone acetate

3. **Colorectal cancer**

Large bowel cancer includes cancerous growths in the colon, rectum and appendix. 98% of all cancers in the large intestine are adenocarcinomas. Several studies suggested that use of aspirin and other NSAIDs have a protective effect against colon cancer. Colorectal cancers arise from adenomatous polyps in the colon. These mushroom-shaped growths are usually benign, but some develop into cancer over time. Localized colon cancer is usually diagnosed through colonoscopy. Invasive cancers that are confined within the wall of the colon (TNM stages I and II) are curable with surgery. If untreated, they spread to regional lymph nodes (stage III), where up to 73% are curable by surgery and chemotherapy. Cancer that metastasizes to distant sites (stage IV) is usually not curable, although chemotherapy can extend survival, and in rare cases, surgery and chemotherapy together have seen patients through to a cure. Radiation is used with rectal cancer. [29]

Drugs used in colon cancer [30]

1. 5-fluorouracil
2. 9-aminocamptothecin
3. Capecitabine
4. Cetuximab
5. Trinotecan
6. Levamisole hydrochloride
7. Oxaliplatin
8. Trimetrexate
9. UFT (ftorafur and uracil)
10. Bevacizumab
11. Cisplatin

4. **Constipation**

Constipation (also known as costiveness, dyschezia, and dyssynergic defaecation) refers to bowel movements that are infrequent and hard to pass. Constipation is a common cause of painful defecation. Severe constipation includes obstipation and fecal impaction. Treatments include changes in dietary habits, laxatives, enemas, biofeedback, and surgery. Because constipation is a symptom, not a disease, effective treatment of constipation may require first determining the cause. [31]

5. **Diarrhea**

Diarrhea is the condition of having three or more loose or liquid bowel movements per day. The loss of fluids through diarrhea can cause dehydration and electrolyte imbalances. Inflammatory diarrhea occurs when there is damage to the mucosal lining or brush border, which leads to a passive loss of protein-rich fluids, and a decreased ability to absorb these lost fluids. Features of all three of the other types of diarrhea can be found in this type of diarrhea. It can be caused by bacterial infections, viral infections, parasitic infections, or autoimmune problems such as inflammatory bowel diseases. It can also be caused by tuberculosis, colon cancer, and enteritis. [32]

6. **Diverticulitis and Diverticulosis**

A diverticulum is a blind pouch that communicates with the lumen of the gut. Congential diverticula have all three layers of the bowel wall and are distinctly uncommon. Acquired diverticula may occur anywhere in the alimentary tract, but by far the most common location in the colon. Diverticulitis results if diverticula become inflamed. An initial episode of acute diverticulitis is usually treated with bowel rest (i.e., nothing by mouth), IV fluid resuscitation, and broad-spectrum antibiotics which cover anaerobic bacteria and gram-negative rods. However, recurring acute attacks or complications, such as peritonitis, abscess, or fistula may require surgery, either immediately or on an elective basis. [33]

7. **Hirschsprung's disease (aganglionosis)**

Hirschsprung disease result when, during development, the migration of neutral crest- derived cells along the alimentary tract arrests at some print before reaching the anus. The critical lesion in hirschspring disease is the lack of ganglion cells, and of ganglia, in the muscle wall and sub-mucosa of the affected segment. [34] Hirschsprung's Disease is a rare congenital (present at birth) abnormality that results in obstruction because the intestines do not work normally. It is most often found in males. It is commonly found in Down syndrome children. It can be life-threatening or a chronic disorder. In a newborn, the chief signs and symptoms are failure to pass a meconium stool within 24-48 hours after birth, reluctance to eat, bile-stained (green) vomiting, and abdominal distension. During infancy the child has difficulty gaining weight, constipation, abdominal distension, episodes of diarrhea and vomiting. Explosive watery diarrhea, fever and exhaustion are signs of enterocolitis (inflammation of the colon) and are considered serious and life-threatening. If these symptoms occur, notify your child's doctor immediately. In older children, symptoms become chronic and include constipation, passage of ribbon-like, foul-smelling stools, abdominal distension and visible peristalsis (wave-like movement of the intestines). The older child is usually poorly nourished and anemic. [35]

8. **Ileus**

It is defined as intestinal obstruction. Ileus is a disruption of the normal propulsive gastrointestinal motor activity due to non-mechanical causes. In contrast, motility disorders that result from structural abnormalities are termed mechanical bowel obstruction. Ileus is of three types, i.e., Postoperative Ileus, Paralytic Ileus and Acute colonic pseudoobstruction. [36]

9. **Intussusception**

An intussusception is a medical condition in which a part of the intestine has invaginated into another section of intestine, similar to the way in which the parts of a collapsible telescope slide into one another. The telescoped segment is called the intussusceptum and lower receiving segment is called the intussuscipiens. This can often result in an obstruction. The part that prolapses into the other is called the intussusceptum, and the part that receives it is called the intussuscipiens. The condition is most common in infants and children. [37] The condition is not usually immediately life-threatening. The intussusception can be treated with either barium or water-soluble contrast enema or an air-contrast enema, which both confirms the diagnosis of intussusceptions and in most cases successfully reduces it. The success rate is over 80%. However, approximately 5-10% of these recur within 24 hours. [38]

10. **Irritable bowel syndrome**

Irritable bowel syndrome (IBS) or spastic colon is a diagnosis of exclusion. It is a functional bowel disorder characterized by chronic abdominal pain, discomfort, bloating, and alteration of bowel habits in the absence of any detectable organic cause. IBS may begin after an infection, or a stressful life event.

Although there is no cure for IBS, there are treatments that attempt to relieve symptoms, including dietary adjustments,

medication and psychological interventions. Patient education and a good doctor-patient relationship are also important. Several conditions may present as IBS including celiac disease, Fructose malabsorption, mild infections, parasitic infections like giardiasis, several inflammatory bowel diseases, functional chronic constipation, and chronic functional abdominal pain. In IBS, routine clinical tests yield no abnormalities, though the bowels may be more sensitive to certain stimuli, such as balloon insufflation testing. The exact cause of IBS is unknown. The most common theory is that IBS is a disorder of the interaction between the brain and the gastrointestinal tract, although there may also be abnormalities in the gut flora or the immune system. [39]

11. **Pseudomembranous colitis**

Pseudomembranous colitis, also known as antibiotic-associated diarrhea (AAD), is an infection of the colon. It is often, but not always, caused by the bacterium Clostridium difficile. The illness is characterized by offensive-smelling diarrhea, fever, and abdominal pain. In severe cases, life-threatening complications can develop, such as toxic mega-colon. [40]

12. **Haemorrhoids**

Haemorrhoids or piles are the varicosities of the haemorrhoidal veins. They are common lesions in elderly and pregnant women. They commonly result from increased venous pressure. The possible causes include portal hypertension, chronic constipation and straining at stool, cardiac failure, venous stasis of pregnancy, hereditary predisposition, tumors of the rectum.

METHODS USED FOR DRUG TARGETTING TO THE COLON

1. Formation of prodrugs: (Example: Azo-Prodrug, Glucuronide conjugate, etc.)

Prodrug is defined as an inert drug that becomes active only after it is transformed or metabolized by the body. [41] Covalent linkage is formed between drug and carrier, which upon oral administration reaches colon without being absorbed from upper part of GIT. In the colon drug release is triggered by high activity of certain enzymes in comparison to stomach and small intestine.

a) **Azo bond conjugate**: Sulfasalazine is mainly used for the treatment of inflammatory bowl diseases. It is 5- Amino Salicylic Acid (5-ASA) prodrug. 85% of oral dose of sulfasalazine reaches to the colon unabsorbed, where it is reduced by the anaerobic environment into 5-ASA and sulphapyridine as shown in Fig. 2. [42]

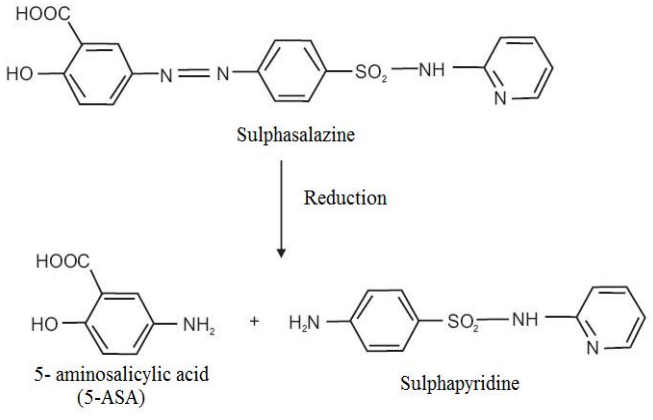


Fig. 2: Reduction reaction of sulphasazine in 5-ASA and sulphapyridine

Various studies are conducted on sulphapyridine which lead to the formation of other prodrug like Olsalazine, Balsalazine, 4-amino benzoyl-β-alanine. [43] Intestinal microflora produces glycosidase, one of prominent group of enzyme.

Colon specific formulation of flurbiprofen had been evaluated by using azo-aromatic and pH-sensitive polymer and it was concluded that azo-aromatic polymer (poly-methylmethacrylate- hydroxy rthylmethacrylate: 1:5) and pH sensitive polymer eudragit S can successfully be used for colonic drug delivery. [44] Pulsincap drug delivery of salbutamol sulphate had been investigated. An empty gelatin capsule was coated with ethyl cellulose keeping the cap portion as such. A hydrogel plug made of gelatin was suitably coated with cellulose acetate phthalate in such a way that it was fixed to the body under the cap. Eudragit microspheres containing the salbutamol sulphate were prepared by emulsion solvent evaporation method and were incorporated into this specialized capsule shell. In vitro dissolution results indicated that the onset of drug release was after 7 to 8 hr of the experiment started. [45] Mutual azo prodrug of 5-aminosalicyic acid with histidine, was synthesized by coupling L-histidine with salicylic acid, for targeted drug delivery to the inflamed gut tissue. [46]

b) **Glucuronide conjugate**: Glucuronide and sulphate conjugation is the major mechanisms for the inactivation and preparation for clearance of a variety of drugs. Bacteria of the lower gastrointestinal tract secrete glucuronidase that glucouronidate a variety of drugs in the intestine. Since the glucuronidation process results in the release of active drug and enables its reabsorption, glucuronide prodrugs would be expected to be superior for colon targeted drug delivery. [47]

c) **Cyclodextrin conjugates**: The hydrophilic and ionisable Cyclodextrins can serve as potent drug carriers in the immediate release and delayed release-formulations, while hydrophobic Cyclodextrins can retard the release rate of water. Moreover, the most desirable attribute for the drug carrier is its ability to deliver a drug to a targeted site. Conjugates of a drug with Cyclodextrins can be a versatile means of constructing a new class of colon targeting prodrugs soluble drugs. [48] Ibuprofen prodrugs of α- , β-and γ-Cyclodextrins were investigated. [49] Methotrexate prodrugs of α- and γ-Cyclodextrins were also synthesized and result established the primary aim of masking the ulcerogenic potential of free drug, by using 12-fold dose of the normal dose of methotrexate and equivalent doses of the esters. [50]

d) **Dextran conjugates**: Dextran ester prodrugs of metronidazole have been prepared and characterized. Dextran ester prodrugs of dexamethasone and methyl prednisolone was synthesized and proved the efficacy of the prodrugs for delivering drugs to the colon. Methyl prednisolone and dexamethasone were covalently attached to the dextran by the use of a succinate linker. [51]

e) **Amino-acid conjugates**: Due to the hydrophilic nature of polar groups like NH2 and COOH, that is present in the proteins and their basic units (i.e. the amino acids), they reduce the membrane permeability of amino acids and proteins. Various prodrugs have been prepared by the conjugation of drug molecules to these polar amino acids. Non-essential amino acids such as tyrosine, glycine, methionine and glutamic acid were conjugated to Salicylic acid. [52]

2. Hydrogels

Hydrogels can be used for site specific delivery of peptide and protein drugs through colon. The Hydrogels are composing of acidic commoners and enzymatically degradable azo aromatic cross-links. In the acidic pH, gels shows less swelling that protect the drug against degradation in stomach. As the pH of environment increases i.e. become basic, swelling increases. This result is easy access of enzymes like azoreductase, which ultimately release of drug. [53]

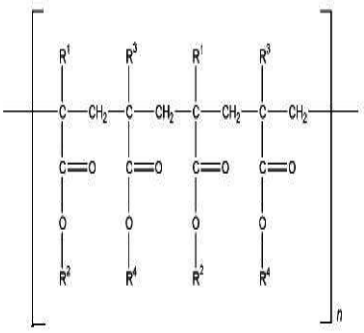
3. Coating with pH dependent polymers

The pH in the terminal ileum and colon in higher than in any other region of the gastrointestinal tract and thus dosage forms which disintegrate at high pH ranges can be target into the region. A level of pH is higher in the terminal ileum region then in the cecum. Dosage forms are often delayed at the ileocecal junction, careful selection of enteric coat composition and thickness is needed to ensure that disintegration does not occur until the dosage from moves through the ileocecal junction from the terminal ileum into the cecum. Synonyms for eudragit are Eastacryl, Kollicoat MAE, polymeric methacrylates. [54] Delayed release tablets containing mesalazine and coated with eudragit S-100 were studied. These tablets dissolved at a pH level of 7 or greater, releasing mesalazine in the terminal ileum and beyond for topical inflammatory action in the colon. The formulation was successful in achieving site specific delivery of mesalazine, failure of the coating to dissolve has been reported. [55] The most commonly used pH dependent polymers are derivatives of acrylic acid and cellulose. For colonic drug delivery, drug core is coated with pH sensitive polymers. The drug are includes tablets, capsules, pellets, granules, micro-particles and nanoparticles.

Disadvantages of this method are:

a) Lack of consistency in the dissolution of the polymer at the desired site.
b) Lack of site specificity of pH dependent systems.

The dissolution of the polymer can be in the distal portion of the colon or at the end if ileum, depending on the intensity of the GI motility. [56]



For *Eudragit L* and *Eudragit S*:
$R^1, R^3 = CH_3$
$R^2 = H$
$R^4 = CH_3$

For *Eudragit FS*:
$R^1 = H$
$R^2 = H, CH_3$
$R^3 = CH_3$
$R^4 = CH_3$

For *Eudragit RL* and *Eudragit RS*:
$R^1 = H, CH_3$
$R^2 = CH_3, C_2H_5$
$R^3 = CH_3$

Fig. 3: Structure of various grade of Eudragit polymers

pH- dependent microbeads of theophylline hydrochloride were developed and evaluated by using alginate and chitosan by ionotropic gelation method followed by enteric coating with eudragit S100. [57] Investigation concentred with the formulation of prednisolone containing 1% eudragit RS PM had been carried out which shows 100% drug release. [58] Tablet containing mesalazine were investigated which was coated with two polymers eudragit L100 and eudragit S100 in combination 1:0, 4:1, 3:2, 1:1, 1:5, and 0:1. [59] Chitosan microspheres contain Ondansetron were prepared by emulsion cross linking method. Work combines eudragit S100 and chitosan polymers. Analysis regression values suggest that the possible drug release was Peppas model. [60] Mebeverine Hydrochloride microspheres formulated using eudragit S100 and L100 which showed biphasic release pattern with non-fickian diffusion release in 12 hr. [61]

Table 6: Various pH dependent polymer

S. No.	Polymer	Threshold pH Range
1.	Cellulose acetate phthalate (CAP)	5.0
2.	Polyvinyl acetate phthalate (PVAP)	5.0
3.	Hydroxyl propyl methyl cellulose phthalate (HPMCP)	4.8 - 4.8
4.	Cellulose acetate trimelliate	4.8
5.	Eudragit L-30D	5.6
6.	Eudragit FS 30D	6.8
7.	Eudragit L 100 - 55	5.5
8.	Eudragit L 100	6.0
9.	Eudragit S 100	7.0
10.	Kollicoat 30 D	5.5

4. Timed released systems: (Example: Pulsatile release, Pulsincap, Delayed release, Sigmoidal release system)

It is based on the concept of preventing the release of drug 3-5 h after entering into small intestine. In this approach, drug release from the system after a predetermined lag time according to transit time from mouth to colon. The lag time depends upon the gastric motility and size of the dosage form. One of the earliest approaches is the Pulsincap device. This device consists of a non disintegrating half capsule body sealed at the open end with a hydrogel plug, which is covered by a water-soluble cap. The whole unit is coated with an enteric polymer to avoid the problem of variable gastric emptying. When the capsule enters the small intestine, the enteric coating dissolves and the hydrogel plug starts to swell. The amount of hydrogel is adjusted so that it pops out only after the stipulated period of time to release the contents. [62] In another approach, organic acids were filled into the body of a hard gelatin capsule as a pH-adjusting agent together with the drug substance. The joint of the capsule was sealed using an ethanolic solution of ethylcellulose. The capsule was first coated with an acid soluble cationic polymer, then with a hydrophilic polymer hydroxypropyl methylcellulose and finally enterically coated with hydroxy propyl methyl cellulose acetate succinate. After ingestion of the capsule, the outermost enteric layer of the coating prevents drug release in the stomach. The enteric layer and the hydrophilic layers dissolve quickly after gastric emptying and water starts entering the capsule. When the environmental pH inside the capsule decreases by the dissolution of organic acid, the acid soluble layer dissolves and the enclosed drug is quickly released. [63] Pressure-controlled drug delivery systems: This approach relies on the strong peristaltic waves in the colon that lead to a temporarily increased luminal pressure. In the upper GIT, the drug delivery system is not directly subjected to the luminal pressure, since sufficient fluid is present in the stomach and small intestine. Due to raised luminal pressure in the colon,

the system raptures and releases the drug. [64] Chronomodulated drug delivery system of salbutamol sulphate had been developed for the treatment of nocturnal asthma. The cores containing salbutamol sulphate were prepared by direct compression method use of microcrystalline cellulose and effervescent agent (sodium bicarbonate) and then coated sequentially with an inner swelling layer containing a hydrocolloid (hydroxypropylmethylcellulose E5) and an outer rupturable layer having eudragit RL/RS (1:1). [65] Drug delivery system was investigated which was built on the principles of the combination of pH and time sensitivity. Press- coated mesalamine tablets with a coat of HPMC E-15 were over-coated with eudragit S100. [66] A novel time and pH dependent system was investigated. The system consists of the core tablet of mesalamine which is compression coated with hydroxypropyl methylcellulose (HPMC K4M). This is then coated with eudragit L100. The result revealed that as the amount of HPMC increases, the lag time and t50 value also increases. [67]

Osmotic pressure controlled systems: The unit reaches intact to the colon where drug release takes place due to osmotic pressure generated by the entry of the solvent. It is also known as OROS.

There are two OROS systems for colon drug delivery:

1. **Osmet pump**: It consists of an enteric coated semi-permeable shell which encloses an osmotic layer along with a central impermeable and collapsible reservoir filled with drug. The interior of this compartment is connected with the external environment through a delivery orifice at one end. After dissolution of the gastric-resistant film, water is allowed to penetrate through the semi-permeable membrane, thus raising the pressure inside the device. Which cause inner reservoir to shrinks and drug formulation to pump out.

2. **OROS CT**: Immediately after ingestion, the hard gelatin capsule shell dissolves. The push and pull unit is prevented from absorbing water in the acidic medium of stomach by enteric coating. The osmotic pumping action results when the coating dissolves in the drug is delivered out of the orifice at a rate controlled by the rate of water transport across the membrane. [68]

5. Designing formulations using polysaccharides: (Example: bacterial Enzymes):

Dosage forms enjoy the shielding effect of polysaccharide in upper part of GIT and drug is released in the colon by swelling and biodegradable action of polysaccharidases. Polysaccharides naturally occurring in plant (e.g., pectin, guar gum, inulin), animal (e.g., chitosan, chondroitin sulfate), algal (e.g., alginates), or microbial (e.g., dextran) origins were studied for colon targeting. These are broken down by the colonic microflora to simple saccharides by saccharolytic species like bacteroides and bifidobacteria. Hydrolysis of the glycosidic linkages on arrival in the colon triggers the release of the entrapped bioactive. Although specifically degraded in the colon, many of these polymers are hydrophilic in nature, and swell under exposure to upper GI conditions, which leads to premature drug release. To overcome this problem, the natural polysaccharides are chemically modified and mixed with hydrophobic water insoluble polymers, whereas in the case of formulations they are usually coated with pH sensitive polymers. A pectin/chitosan-based colonic delivery system has been developed. [69] The use of calcium pectinate as a carrier was based on the assumption that, like pectin, it can be decomposed by specific pectinolytic enzymes in the colon but retains its integrity in the physiological environment of the small bowel. Other derivatives such as methoxylated and amidated pectins are also developed. The formulation of Guar gum based matrix tablets of metronidazole/tinidazole were developed and the influence of the concomitant administration of these drugs on the usefulness of guar gum as a carrier for colon-specific drug delivery using guar gum matrix tablets of albendazole was studied as a model formulation. [70] The fast disintegrating core tablets of budesonide were coated with khaya gum followed by further coating with eudragit S100 by dip coating technique. Khaya gum did not completely protect the drug release in the upper digestive tract and exhibited different release profile in presence and absence of rat cecal contents and it was concluded that khaya gum alone cannot be used for targeting the drug to the colon. [71] Tablet formulation using pectin as carrier and diltiazem HCl and indomethacin as model drug had been developed. The tablets were coated with inulin followed by shellac. It was revealed that polysaccharides as carriers and inulin and shellac as a coating as a coating material can be used effectively for colon targeting of both water soluble and insoluble drugs. [72]

6. Redox sensitive polymer coating

Analogues to azo bond cleavage by intestinal enzymes, novel polymers that hydrolyzes nonenzymatically by enzymatically generated flavins are being developed for colon targeting. [73] A common colonic bacterium, Bacteroidesfragilis was used as test organism and the reduction of azo dyes amaranth, Orange II, tartrazine and a model azo compound, 4, 4'-dihydroxyazobenzene were studied. It was found that the azo compounds were reduced at different rates and the rate of reduction could be correlated with the redox potential of the azo compounds.

7. Bioadhesive systems

Bioadhesion is a process by which a dosage form remains in contact with particular organ for an augmented period of time. This longer residence time of drug would have high local concentration or improved absorption characteristics in case of poorly absorbable drugs. This strategy can be applied for the formulation of colonic drug delivery systems. Various polymers including polycarbophils, polyurethanes and polyethylene oxide polypropyline oxide copolymers have been investigated as materials for bioadhesive systems. [74]

8. New Systems

The complex was prepared by dialdehyde konjac glucomannan and adipic dihydrazides to form steady Schiff base, and crosslinking with 5-aminosalicylic acid (5-ASA) through gularaldehyde as a cross-linking agent. In vitro release of 5-ASA from complex after 24hr in buffer solution at pH 1.2, 6.8 and 7.4 was found to be 4, 59 and 21% respectively. [75]

REFERENCES

1. Barbara L, Teresa C, Federica B, Isabella O, Vittorio Z: pH-sensitive polymeric physical-mixture for possible site-specific delivery of ibuprofen. Eur J Pharm Biopharm 2003; 55: 199-202.
2. Lachman L, Lieberman HA, Kanig JL: The theory and practice of industrial pharmacy. 3rd edition. Bombay, Varghese publishing house: Hind Rajasthan building; 1991. p. 293.
3. Antonin KH, Rak R, Beick PR, Schenker U, Hastewell J, Fox R: The absorption of human calcitonin from the transverse colon of man. Int J Pharm. 1996; 130: 33-39.
4. Tozaki H, Komoike J, Tada C, Maruyama T, Terabe A, Suzuki T, Yamamoto A, Muranishi S: Chitosan capsules for colon specific

drug delivery: Improvement of insulin absorption from the rat colon. J Pharm Sci 1997; 86(9): 1016-1021.
5. Van-den GM, Kinget R: Oral colon-specific drug delivery: a review. Drug Delivery 1995; 2: 81-93.
6. Rama Prasad Y, Krishnaiah Y, Satyanarayana S: In vitro evaluation of guar gumas a carrier for colon-specific drug delivery. J Controlled Release 1998; 51: 281-287.
7. Jain NK: Advances in Controlled and novel Drug Delivery. 1st edition. New Delhi, Cbs publisher and distributors; 2008. p. 86-90.
8. Halsas M, Penttinen T, Veski P, Jurjenson H, Marvola M: Time controlled release pseudoephedrine tablets: bioavailability and in vitro/in vivo correlations. Pharmazie 2001; 56: 718 - 723.
9. Kinget R, KalalaW, Vervoort L, van denMooter G: Colonic drug targeting. J Drug Targeting 1998; 6(2): 129-149.
10. Yang L, Chu JS, Fix JA: Colon-specific drug delivery: new approaches and in vitro/in vivo evaluation. Int J Pharm 2002; 235: 1-15.
11. Rathod S: Colon Targeted Pulsatile Drug Delivery: A Review. Pharm Rev. [serial on the Internet]. 2007; 5(2). Available from: http://www.pharmainfo.net
12. Ratna V. Prabhakaran L, Prushothaman M: Colon targeted drug delivery system - an overview. Pharm Rev. [serial on the Internet]. 2010; 8(2). Available from: http://www.pharmainfo.net
13. Nugent SG, Kumar D, Rampton DS, Evans DF: Intestinal luminal pH in inflammatory bowel disease: possible determinants and implications for therapy with aminosalicylates and other drugs. Gut 2001; 48: 571-7.
14. Jose S, Dhanya K, Cinu TA, Litty J, Chacko AJ: Colon targeted drug delivery: Different approaches. J Young Pharm 2009; 1(1): 13-19.
15. Gaurav T, Ruchi T, Pranay W, Ankita W, Awani KR: Primary and novel approaches for colon targeted drug delivery –A review. International Journal of Drug Delivery 2010; 2(1): 01 – 11.
16. Stirrup V, Ledingham SJ, Thomas M, Pye G, Evans DF: Gastrointestinal intraluminal pH in normal subjects and those with colorectal adenoma or carcinoma. Gut 1990; 31(12): 1355-1357.
17. Chatterjee CC: Human Physiology, Part 1, 11th edition. Calcutta, Medical allied agency; 2002. p. 496-497.
18. Bussemer T, Otto I, Bodmeier R: Pulsatile drug delivery system: Crit Rev Ther Drug Carrier Syst 2001; 18(5): 433-458.
19. Evans DF, Pye G, Bramley R, Clark AG, Dyson TJ, Hardcastel J.D: Measurement of gastrointestinal pH profiles in normal ambulant human subjects. Gut 1988; 29(8): 1035-1041.
20. Rubinstein A: Approaches and opportunities in colon-specific drug delivery. Crit Rev Ther Drug Carrier Syst 1995; 12: 101-149.
21. Peter JW, Lisbeth L: Colonic Drug Delivery. Drug Dev Ind Pharm 1997; 23(9): 893 - 913
22. Edwards CA: Anatomical and physiological basis. In physiological factors influencing drug absorption. Colonic drug absorption and metabolism. New York, bieck PR (ed), Marcel Dekker, Inc., 1993. p. 1-28
23. Sarasija S, Hota A: Colon-Specific Drug Delivery Systems. Indian J Pharm Sci 2000; 62(1): 1-8.
24. Wexner SD, Stollman N: Diseases of the colon. 1st edition. New York, Informa Healthcare USA, Inc. 2007. p. 23-24
25. Jarbandhan S, van der Veer WM, Mulder CJ: Double-balloon endoscopy in the diagnosis and treatment of hemorrhage from retrovalvular angiodysplasias. Journal of Gastrointestinal and Liver Diseases 2008; 17(3): 333-334.
26. Bennett PN, Brown MJ: Clinical Pharmacology, 9th edition. New York, Churchill Livingstone, 2003. p. 645
27. Vijaya R, Prabhakaran L, Prushothaman M: Colon targeted drug delivery system - an overview. Pharm Rev. 2010; 8(2). Available from: http://www.pharmainfo.net
28. Gulhati CM: Monthly index of medical specialties 2010; 30(2): 22-24.
29. Markowitz SD, Bertagnolli MM: Molecular Basis of Colorectal Cancer. New Engl J Med 2009; 361(25): 2449-2460.
30. Consumer's guide to cancer drugs. 2nd ed. New York, American cancer society; 2008.
31. Annells M, Koch T: Constipation and the preached trio: diet, fluid intake, exercises Original Research Article. International Journal of Nursing Studies 2003; 40(8): 843-852.
32. Ericsson CD: Travellers' diarrhoea. Int J Antimicrob Agents 2003; 21(2): 116-124.
33. Fang JF, Chen RJ, Lin BC, Hsu YB, Kao JL, Chen MF: Aggressive resection is indicated for cecal diverticulitis. The American Journal of Surgery 2003; 185(2): 135-140.
34. Vinay K, Abul KA, Nelson F, Richach NMR: Basic pathology, 8th edition. India, Elsevier 2009. p. 600- 629
35. Coran AG. Response: Letter to the editor—Hirschprung's disease. Journal of Pediatric Surgery 2005; 40(5): 890
36. Keshari MK, Gupta P, Siddiqui AA: Dictionary of pharmacy, 2nd edition. Delhi, Birla publication, 2001; pp 316
37. Harsh M: Textbook of Pathology, 6th edition. New Delhi, Jaypee Brothers Medical Publishers (P) Ltd, 2010. p. 563-59.
38. Bramson RT, Blickman JG: Perforation during hydrostatic reduction of intussusception: Proposed mechanism and review of the literature. Journal of Pediatric Surgery 1992; 27(5): 589 – 591.
39. Camilleri M, Mangel AW, Fehnel SE, Drossman DA, Mayer EA, Talley NJ: Primary Endpoints for Irritable Bowel Syndrome Trials: A Review of Performance of Endpoints. Clin Gastroenterol Hepatol 2007; 5(5): 534-540.
40. Larson HE: Pseudomembranous colitis is an infection. Journal of Infection 1979; 1(3): 221 - 226.
41. Taber's cyclopedic medical dictionary. 20th ed. F A davis company:Philadelphia. 2001. p.1779
42. Klotz U: Clinical pharmacokinetics of sulfasalazine, its metabolites and other prodrug of 5-aminosalicylic acid. Clinical pharmacokinetics. 1985; 10(4): 285-302.
43. Chan RP, Pope DJ, Gilbert AP, Sacra PJ, Baron JH, Lennard- Jones JC. Studies of two novel sulfasalazine analogue, ipsalazine and balsalazine. Digestive Diseases and Sciences 1983; 28(7): 609-615.
44. Jain SK, Chourasia MK Dengre R: Azo polymers for colon targeted drug delivery. Indian J. Pharm. Sci 2005, 67(1): 43-50.
45. Samanta MK, Suresh NV, Suresh B: Development of Pulsincap drug delivery of salbutamol sulphate for drug targeting. Indian J. Pharm. Sci 2000, 62(2): 102-107.
46. Nagpal D, Gairola RS, Bodhankar SL, Suneela SD: Mutual azo prodrug of 5-aminosalicylic acid for colon targeted drug delivery: synthesis, kinetic studies and pharmacological evaluation. Indian J. Pharm. Sci 2006, 68(2): 171-178.
47. Scheline RP: Drug metabolism by intestinal microorganism. J Pharm Sci 1968; 57: 2021-2037.
48. Tanaka H, Kominato K, Yamamoto R: Synthesis of doxorubicincy clodextrin connjugates. J Antibio 1994; 47: 1025-1029
49. Mhaske DV, Bariwal J, Dev S, Kadam SS, Dhaneshwar SR: Synthesis and pharmacological evaluation of cyclodextrin conjugates prodrugs of Ibuprofen. Indian J Pharm Sci 2005, 67(4): 432-437.
50. Gupta D, Mhaske DV, S.S. Kadam SS, DhaneshwarSR: Synthesis and evaluation of pharmacological activities of cyclodextrin conjugates of methotrexate. Indian J Pharm Sci 2004, 66(1): 26-30.
51. Johansen M, Larsen C: Stability kinetics and of hydrolysis of metronidazole monosuccinate in aqueous solution and in plasma. Int J Pharm 1984; 21: 201-209.
52. Nakamura J, Asai K, Nishida K, Sasaki H: A novel prodrug of salicylic acid, salicylic acid-glutamic acid conjugate utilising hydrolysis in rabbit intestinal microorganism. Chem Pharm Bull 1992; 40: 2164-2168.
53. Brondsted H, Kopecek J: Hydrogels for site specified oral drug delivery: synthesis and characterization. Biomaterials 1991; 12(6): 584 - 592.
54. Rayond C, Rowe RC, Paul JS: Hand book of pharmaceutical excipients, 6th ed., London, Pharmaceutical Press, 2009. p. 525-526.
55. Schroeder KW, Tremaine WJ, Ilstrup DM: Coated oral 5-ASA therapy for milding to moderately active ulcerative colitis: A randomized study. New Engl J Med 1987; 317(26): 1625 – 1629.
56. Ashford M, Fell JT, Attwood D, Sharma H, Woodhead PJ: An in vitro investigation into the solubility of pH dependent polymer for colonic targeting. Int J Pharm 1993; 95(1-3): 193 - 199.
57. Khan MS, Sridhar BK, Srinatha A: Development and evaluation of pH-dependent microbeads for colon targeting. Indian J Pharm Sci 2010, 72(1): 18-23.
58. Sahib MN, Abdulameer SA, Rasool AAA: Design and in vitro evaluation of prednisolone tablets as a potential colon delivery system. Asian journal of pharmaceutical and clinical research 2009, 2 (4): 84-93
59. Khan MZI, Stedul HP, Kurjakovic N: A pH-dependent colon – targeted oral drug delivery using methacrylic acid copolymers. Ⅱ. Manipulation of drug release using eudragit L100 and eudragit S100 combination. Drug Development and industrial pharmacy 2000; 26(5): 549-554.
60. Jose S, Dhanya K, Cinu TA, Aleykutty NA: Multiparticulate system for colon targeted delivery of Ondansetron. Indian J Pharm Sci 2010, 72(1): 58-64.

61. Danagi PM, Mastimolimath VS, Gadad AP, Kulkarni AR, KonnurBK: pH- sensitive mebeverine microspheres for colon delivery. Indian J. Pharm. Sci 2009, 71(4): 464-468.
62. MacNeil ME, Rashid A, Stevens HN: Dispensing device, World Patent; WO 9009168, 1990.
63. Ishibashi T, Hatano H, Kobayashi M, Mizobe M, Yoshino H: Design and evaluation of a new capsule-type dosage form for colon-targeted delivery of drugs. Int J Pharm 1998; 168(1): 31-40.
64. Brahmankar DM, Jaiswal SB: Biopharmaceutics and pharmacokinetics - a treatise, 2nd ed., Delhi, Vallabh Prakashan, 2009. p. 462-463.
65. Qureshi J, Amir M, Ahuja A, Baboota S, Ali J: Chronomodulated drug delivery system of salbutamol sulphate for the treatment of nocturnal asthma. Indian J Pharm Sci 2008, 70(3): 351-356.
66. Mukesh C. Gohel, Rajesh K. Parikh, Stavan A. Nagori, Mahesh R. Dabhi: Design of a potential colonic drug delivery system of mesalamine. Pharmaceutical development and technology 2008, 13: 447-456.
67. Patel MM, Shah TS, Amin AF: Design, development and optimization of a novel time and pH-dependent colon targeted drug delivery system. Pharmaceutical development and technology 2009; 14:62-69.
68. Theeuwes F, Guittard GV, Wrong PSL (1990) US patent no. 4,904,474
69. Fernandez-Hervas MJ, Fell JT: Pectin/Chitosan mixtures as coating for colon specific drug delivery: an in vitro evaluation. Int J Pharm 1990; 169(1): 115-9.
70. Krishnaiah YS, Seethadevi A, Nageswara RL, Bhaskar RP, Karthikeyan RS, Satyanarayana V: Guar gum as acarrier for colon specific delivery; influence of Metronidazole and Tinidazole in In Vitro release of Albendazole from Guar gum matrix tablets. Int J Pharm Pharm Sci 2001; 4(3): 235 - 243.
71. Prabhakara Prabhu, Nissara Ahmed, Harish N M, Mohd. Gulzar Ahmed, R. Narayana Charyulu, D. Satyanarayana, Marina Koland: Investigation of colon specificity of novel polymer khaya gum. Indian J Pharma Educ Res 2010; 44(1): 56-65.
72. V. Ravi, T.M. Promod Kumar, Siddaramaiah: Novel colon targeted drug delivery system using natural polymers. Indian J Pharm Sci 2008, 70(1): 111-113.
73. Gingell R, Walker R: Mechanism of azo reduction by non-specificity of Streptococcus faecalisazoreductase. Xenobiotica 1975; 5: 563-571.
74. Lenaerts, V. and Gurny, R: Bioadhesive drug delivery systems. CRC Press, Boca Raton, 1990.
75. Dong-Ying Xu, Guang-Ji Li, Zheng-Fu Liao: Preparation and in vitro controlled release behaviour of a novel pH-sensitive drug carrier for colon delivery. Polym Bull 2009; 62:183-193.