1 INTRODUCTION

1.1 Colon

The gastrointestinal tract (GIT) consists of stomach, small intestine and large intestine. The large intestine (covering from the ileocecal junction to the anus) is divided into three main parts i.e. colon, the rectum and anal canal\(^1\). The length of colon is about 59inch long, and has five major segments (Figure 1.1)\(^1,2\).

![Diagram of the Colon](image)

**Figure 1.1: Parts of Colon**

The ascending colon to proximal transverse colon develops embryologically from the midgut and the distal transverse colon to sigmoid colon develops from the hind gut. While observing the plain abdominal radiographs, the colon is seen to be filled with fecal material along with air.
1.1.1 Parts of Colon

1.1.1.1 Ascending Colon
It lies vertically in the utmost lateral right part of the abdominal cavity. The proximal blind end (pouch) of the ascending colon is known as caecum. The ascending colon takes a right-angled turn just below the liver (right colic or hepatic flexure) and converts to transverse colon, which has a horizontal course from right to left\(^2\).

1.1.1.2 Transverse Colon
Just below the spleen transverse colon turns to right angle and becomes the descending (left) colon, which lies vertically in the most lateral left part of the abdominal cavity. The descending colon lead to the sigmoid colon (inverted V-shaped), which then becomes the rectum\(^2\).

1.1.1.3 Paracolic gutters
Paracolic gutters lies to lateral to ascending and descending colon are the right and left of the peritoneal cavity, through which fluid/pus in the upper abdomen can trickle down into the pelvic cavity. The ascending and descending colon are related to the kidney, ureter, and gonadal vessels of the corresponding side that lie behind them in the retroperitoneum; the ascending colon is also related to the duodenum\(^2\).

1.1.1.4 Sigmoid Colon
The transverse colon and the sigmoid colon have a mesentery (ie, transverse mesocolon and sigmoid mesocolon, respectively), but the ascending colon and descending colon are retroperitoneal, while the cecum is intraperitoneal but uses the mesentery of the ileum. The transverse mesocolon base lies horizontally across the duodenum and pancreas. The greater omentum has several parts, including the 4 layered omental apron hanging down off of the transverse colon and the 2-layered gastrocolic ligament connecting the greater curvature of the stomach and the transverse colon.

Three longitudinal teniae coli are present in the cecum, ascending colon, transverse colon, descending colon, and sigmoid colon; they are not present in the rectum. In the ascending and descending colon, they are present anteriorly and on the posterolateral and posteromedial aspects. Appendages of fat, containing small blood vessels, called omental appendages (appendices epiploicae) are attached to colon\(^2\).
1.1.2 Blood Supply
One of themajor function of the colon is to provideenvironmentally friendly condition for the growth of colonic micro flora, absorption of potassium and water from the lumen as storing reservoir of faecal matter and discharge of its contents. The capacity of absorption of colon is very high. Approximate 2000 ml of fluid pass in the colon via the ileocecal valve among which more than 90% of the fluid gets absorbed. As per an estimate the colon holds only near about 220 g of wet material comparable to 35 g of dry matter. The major component of this dry matter consists of bacteria. The colon tissue contains the villi, lymph, muscle, nerves, and vessels\(^2\).

1.1.3 Common disorders of Colon
The severity of colorectal diseases may vary from mildly irritating to life threatening and comprise a broad range of conditions and ailments. Due to lack of awareness many patients did not take right medication in early stage. It is proven that screening and treatment of colorectal disease in early stage lead to increase in rate of survival\(^1,2\).

1.1.3.1 Colorectal Cancer
Cancer of colon and rectum is called colorectal cancer. More than 90 percent of patients suffering from colorectal cancer are elderly (over 40 years). As an estimate one lakh fourty thousand people strikes with colorectal cancer which may lead to death of sixty thousand patients every year. Colorectal cancer can be detected by chemical test of stool and digital rectal examination\(^2\).

If symptoms like bowel habits and rectal bleeding appear, the patient is advised to visit a colon and rectal surgeon for consultation. It may determine if the patient suffering from bowel disease or is a case of colon cancer. For complete cure, surgery is required in almost all cases of colorectal cancer\(^2\).

1.1.3.2 Ulcerative Colitis
Inflammation of colon is called ulcerative colitis. Chronic colitis may lead to colon cancer and affects about five lakh people worldwide, mainly under age of 30.
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1.1.3.3 Crohn's Disease
Chronic inflammatory condition of intestinal tract is called Crohn’s disease. It affects young adult between 16-40 years of age. Crohn’s disease is predominantly reported in developed countries (industrially advanced) mainly prevailed in United States and northern Europe. It is diagnosed by physical examination, barium X-ray of upper and lower intestinal tract and sigmoidoscopy or colonoscopy².

1.1.3.4 Irritable Bowel Syndrome (IBS)
It is a common intestinal muscle functioning disorder which affects more than 30 percent of the American population at some point of time, the data of Indian population is not verified but is expected that same percentage of Indians are also affected by the syndrome. It involves a cumulative symptoms of constipation, diarrhea or combination of both accompanied by pain. Sometimes the situation is life threatening².

1.1.3.5 Diverticular Disease
This is yet another type of colon related disorder and affects mostly the elderly patients. In the conditions there is a formation of some sort of pockets called diverticula on the wall of colon. The patients with age between 60-80 years of age, are at risk of diverticular disease.

With routine colon and rectal examinations, diverticula can be detected and diverticular disease may be prevented.

1.1.3.6 Hemorrhoids
Millions of patients currently suffering from hemorrhoids, which is one of the most common colorectal ailment. It effects more than 50 % the world population and the development of hemorrhoids, usually takes place after the age of 30.

If there is a formation of hard sensitive lumps then it may be a case of external hemorrhoids. These become painful when the blood clot develops in them.

The internal hemorrhoids grow inside the anus, underneath the linings and are well-known by painless bleeding and protrusion during the movements of bowel. It may be due to overuse of enema or laxatives. It also may result with the habit of spending long
**Chapter 1: Introduction**

period of time on toilet seat. It also may occur during pregnancy, chronic constipation and diarrhea.

1.1.3.7 Anal Fissure

These are small tears inside layer of the anus caused by hard, dry bowel movements, inflammation or diarrhea of the anorectal area. The diagnosis can be done by checkup following pain, hemorrhage and/or itching of the outer area of anus.

The disease can be cured by use of stool softeners, taking care of constipation and/or soaking in sitz bath (warm water).

1.1.3.8 Bowel Incontinence

Bowel incontinence is a condition in which the capability to control stool or gas release gets reduced due to weakened anal muscle caused by nerve or muscle injury. This type of problem are generally prominent in old age. Some women also suffers from bowel incontinence due to child birth.

It can be overcome by use of medicament meant for constipation, dietary changes and easier home exercises to toughen muscles. In some of the cases, biofeedback may be used to support patient sense when stool is ready to be evacuated. Weak anal muscles can be repaired with surgery.

1.1.4 Ulcerative colitis

Inflammation of GIT is known as inflammatory bowel disease (IBD). It is a broad term used for a group of chronic inflammatory disorders involving the gastrointestinal tract. The etiology of IBD is still unclear. There are two major types of the condition, Crohn's disease (CD) and ulcerative colitis (UC). These can be clinically characterized by repeated inflammatory participation of intestinal sections with numerous manifestations often resulting in an unpredictable course. Ulcerative colitis is the inflammatory condition of colonic mucosa of unknown etiology. In its most restricted form, ulcerative colitis may be limited to the distal rectum, however in its most comprehensive form the entire colon is involved. More than 80% of the patients present with disease spreading from the rectum to the splenic flexure, and about 20% have pancolitis. The epidemiology, natural history, diagnosis and treatment contributed significantly in current few years.


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1.1.4.1 Symptoms
Initial symptoms of ulcerative colitis include diarrhoea, blood in stool, pain, weight loss, arthralgia, fever, loss of appetite, ophtalmopathies, nausea, vomiting, abscesses, fistulae and lymph node swelli\(^5\). Symptoms of mild, moderate and chronic UC is reported in table 1.1.

**Table 1.1: Symptoms of mild, moderate and chronic UC**

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Chronic</th>
<th>Moderate</th>
<th>Mild</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stool frequency per day (mostly bloody)</td>
<td>&gt; 6</td>
<td>4–6</td>
<td>&lt; 4</td>
</tr>
<tr>
<td>Temperature (° F)</td>
<td>&gt; 100</td>
<td>99–100</td>
<td>Normal</td>
</tr>
<tr>
<td>Pulse (beats/min)</td>
<td>&gt; 100</td>
<td>90–100</td>
<td>&lt; 90</td>
</tr>
<tr>
<td>Weight loss (%)</td>
<td>&gt; 10</td>
<td>1–10</td>
<td>None</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>&lt; 3</td>
<td>3–3.5</td>
<td>Normal</td>
</tr>
<tr>
<td>Haematocrit (%)</td>
<td>&lt; 30</td>
<td>30–40</td>
<td>Normal</td>
</tr>
<tr>
<td>Erythrocyte sedimentation rate (ESR) (mm/h)</td>
<td>&gt; 30</td>
<td>20–30</td>
<td>&lt; 20</td>
</tr>
</tbody>
</table>

1.1.4.2 Epidemiology
Ulcerative colitis islinked with repeated attacks with complete remission of symptoms in the interim. The disorder is more common in certain type of population as compared to others. Caucasi\(\)

1.1.4.3 Pathophysiology
The cause of UC still remains unclear. The major pathophysiology involved in UC is inadequate regulation or over stimulation of mucosal immune system. So, the emphasis
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should be given to study of immunological reactions or mucosal inflammation. In active form of disease, the mucosa of lamina propria get highly infiltrated with acute and chronic inflammatory cells. There is a predominant escalation in mucosal Immunoglobulin G (IgG) production, indication of complement activation, and stimulation of macrophages and T cells. The above mentioned immunological activity is connected through the discharge of a vast array of leukotriene, platelet activating factor (PAF), cytokines, kinins and reactive metabolites of oxygen. Discharge of these mediators not only limited to intensify the immune and inflammatory response, but they also play a major role and have direct effects on epithelial function, on endothelial function (which may increase permeability and lead to ischemia), and on repair mechanisms, thus increasing collagen synthesis. On the other hand, many of the cytokines (interleukins 1 and 6, tumour necrosis factor) will trigger an acute phase response which may lead to fever and a rise in serum acute phase proteins.

1.1.4.4 Diagnosis
The diagnosis of UC is made on clinical suspicion. It can be confirmed by stool examinations, biopsy, barium radiographic examination, sigmoidoscopy or colonoscopy.

1.1.4.5 Complication
Foremost obstacles of UC comprise toxic mega colon, intestinal perforation, and massive bleeding. Toxic mega colon is characterized by a sepsis-like syndrome and extensive distension of the colon (>6 cm). Chronic blood loss lead to microcytic anaemia. Complication of chronic ulcerative colitis may lead to colon cancer. The risk for cancer are generally seen after ten years of colitis.

1.1.4.6 Medication
There is no an effective medicine to cure the UC but the mainstream treatment depends on reduction of the abnormal inflammation in the colon lining and thereby relieves the symptoms of diarrhoea, rectal bleeding, and abdominal pain. The treatment depends on the severity of the disease; therefore treatment is adjusted for each individual. Most people with mild or moderate ulcerative colitis are treated with corticosteroids (dexamethasone) to reduce inflammation and relieve symptoms. Near about 25% of patients with UC using steroids become steroid-dependent after one year, and virtually
all develop steroid-related adverse events. Other drugs as immune modulators (azathioprine and 6-mercapto-purine) that reduce inflammation by affecting the immune system and amino salicylates are available. However, the side effects associated with amino salicylates is typically accompanied with adverse side effects such as dizziness, nausea, changes in blood chemistry (including anaemia and leukopenia) and skin rashes.

1.1.5 Traditional and alternative medicine in treatment of ulcerative colitis

Proanthocyanidins isolated from grape seed were investigated for their activity in the healing of recurrent ulcerative colitis (UC) in rats. Another study confirmed this fact as, Proanthocyanidins is useful in anti-inflammatory activity in case of the acute phase of 2,4,6-trinitrobenzenesulfonic acid (TNBS) induced colitis in rats.

The administration of alcohol extract of *Garcinia cambogia* (Clusiaceae) in TNBS-induced colitis rats improved significantly the macroscopic damage and caused considerable reductions in myeloperoxidase (MPO) activity and Cyclooxygenase-2 (COX-2) expression. In adding, *Garcinia cambogia* extract was able to decrease prostaglandin E2 (PGE2) and IL-1.

*Zingiber Officinale* (Zingiberaceae) extract was evaluated for anti-ulcerative colitis activity. Activity against UC showed a prominent effect of ginger extract against acetic acid-induced ulcerative colitis. The effect may be possible due to antioxidant and anti-inflammatory properties of extract of *Zingiber Officinale*.

The protective effects of *Angelica sinensis* (Apiaceae) polysaccharides could be explained partially by oxidative stress and glutathione (GSH) depletion.

The effect of polysaccharide obtained from *Rheum tanguticum* (Polygonaceae) on hydrogen peroxide-induced human intestinal epithelial cell injury and it was found that, pre-treatment of the cells with RTP could significantly elevate cell survival. *Rheum tanguticum* polysaccharide may have cytoprotective and anti-oxidant effects of *Rheum tanguticum* polysaccharide for the treatment of ulcerative colitis in rats.
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_Camellia sinensis_ (Theaceae) extract was found to be effective in the treatment of ulcerative colitis. Both diarrhoea and loss of body weight can be significantly attenuated by the treatment with _Camellia sinensis_ extract\textsuperscript{21}.

Aqueous extract of root of _Withania somnifera_ (Solanaceae) showed anti-oxidant activity by reducing (Hydrogen peroxide) H\textsubscript{2}O\textsubscript{2} and (Nitric oxide) NO.\textsuperscript{22}

Glycoprotein isolated from _Gardenia jasminoides_ has reported effective in (Dextran sodium sulphate) DSS induced UC in mice\textsuperscript{23}.

The ethanol extracts of _Ficus bengalensis_ (Moraceae) may lead to decrease disease activity index and colon mucosal damage index in rats with inflammatory bowel disease\textsuperscript{24}.

_Patrina scabiosaefolia_ (Valerianaceae) are commonly used in anti-inflammatory diseases, mainly for colonic inflammations, hepatitis and other virus infections\textsuperscript{25}.

_Avicennia marina_ (Acanthaceae) decreased the glutathione peroxidase, lipid peroxides of colon, and serum nitric oxide\textsuperscript{26}.

Dried seeds aqueous extract of _Benincasa hispida_ (Cucurbitaceae) possess prominent antioxidant activity in a dose-dependent manner\textsuperscript{27}. The aqueous extracts of dried seed produced noteworthy reduction in ulcer index in Wistar albino rats\textsuperscript{28}.

Methanol extract of leaves of _Rhodomyrtus tomentosa_ has been investigated by researcher on the production of inflammatory mediator’s Nitrous oxide and prostaglandin E2. The methanol extract of leaves of _Rhodomyrtus tomentosa_ mediated inhibition, as well as target enzymes, were studied with RAW264.7peritoneal macrophage, and HEK293 cells to determine molecular mechanism. In addition, the in vivo anti-inflammatory activity of this extract was also carried out with mouse gastritis and colitis models. Methanol extract of leaves of _Rhodomyrtus tomentosa_ clearly inhibited the generation of NO and PGE2 in lipopolysaccharide activated RAW264.7 cells and peritoneal macrophages in a dose-dependent manner\textsuperscript{29}.

_Berberis vulgaris_ fruit extract (BFE) with three different doses (375, 750, and 1500 mg/Kg) was administered orally or rectally prior to ulcer induction. Berberine chloride
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(BEC) (10 mg/Kg), prednisolone (5 mg/Kg), hydrocortisone acetate enema (20 mg/Kg) and normal saline (5 mL/Kg) were considered as respective controls. The tissue was assessed macroscopically for damage scores, area, index and weight/length ratio. They were also examined histopathologically for inflammation extent and severity, crypt damage, invasion involvement and total colitis index. Results indicated that greater doses of oral BFE (750, 1500 mg/Kg) as well as BEC (10 mg/Kg) were effective to protect against colonic damage. By rectal pre-treatment, the extract was only effective to diminish the ulcer index and the efficacy was not significant for mucosal inflammation parameters. In conclusion BFE, which is nearly devoid of berberine, was effective to protect against colitis and this might be attributed to its anthocyanin constituents30.

UC has a lesser prevalence in smokers than non-smokers. Studies using a transdermal nicotine patch have shown clinical and histological improvement31.

Curcumin possesses marked activity against ulcerative colitis and Crohn’s disease32.

During clinical studies, it has been proved that Aloe vera is effective and safe for the treatment of ulcerative colitis33.

Bromelain is a proteolytic enzyme and is found effective in UC. It shows improvement of histologic and clinical severity of colonic inflammation for a murine colitis model of IL-10-deficient mice34.

During double-blind clinical trials, it has been reported that the Psyllium seeds possess marked activity against ulcerative colitis35.

Guggulsterone is found effective against DSS-induced murine colitis as evaluated by colon length, histology and clinical disease activity score36.

Diammonium glycyrrhizinate obtained from Glycrrhiza glabra and found effective against inflammation of intestinal mucosal in rats and, prominently, decreases expression of TNF-α significantly in inflamed colonic mucosa37.
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In a clinical study 30 patients were administered with 900mg of *Boswellia* gum preparation thrice a day and 10 patients were administered with sulphasalazine, 3gm, thrice a day. The *Boswellia* gum was found to be effective against ulcerative colitis\(^3\).

Tannins and flavonoids are found to be effective in treatment of ulcerative colitis. Green tea polyphenols was reported to possess marked activity against ulcerative colitis\(^3\).

Silymarin is a flavonoid component obtained from *Silybum marianum*. It is found to be active against ulcerative colitis\(^4\).

*Terminalia chebula* extract (600 mg/kg) also possess healing activity against acetic acid-induced colonic damage score and weight when administered orally daily for 14 days\(^4\).

1.1.5.1 Bacterial recolonization

Alteration in GIT flora may lead to UC. Probiotics as supplement is beneficial in such cases. The available clinical data shows the role of intestinal micro biota in the pathogenesis of IBD and there by provides an evidence that alteration in the intestinal micro biota with the help of probiotics can be helpful in the treatment of disease. E.g. *Bifidobacteria infantis* has been found to reduce the inflammatory response of the gut lining by inhibiting the bacteroides. *Lactobacillus plantarum* has also been reported to be used in IBD. A probiotic formulation containing no of microbes (VSL\#3) used in case of ulcerative colitis although its clinical efficacy is not certain. *E. coli* has also been used in case of ulcerative colitis but its clinical efficacy depends upon its dose\(^4\).

1.1.5.2 Iron supplementation

The gradual loss of blood from GIT often lead to anaemia. Adequate disease control usually improves anaemia of chronic disease, but iron deficiency anaemia should be treated with iron supplements. In Ayurveda lauha bhasma and mandur bhasma is recommended in iron deficiency anaemia\(^4\).
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Figure 1.2: Proposed hypothesis for mechanism of herbal and alternative medicine for treatment of ulcerative colitis.

1.1.5.3 Conclusion

Herbal and alternative medicine play important role in prophylaxis and cure of UC. As the pathophysiology of UC is still not clear but the possible mechanism of herbal and traditional medicine for treatment of UC is described in Figure 1.2. Alkaloids and terpenoids may be used in Ulcerative colitis because of antioxidant and antiulcerogenic activity. Anti ulcerogenic activity may be due to increase secretion of mucous. Phenolics (flavonoids, tannins) and saponins may act by antioxidant, cytoprotective and antiulcerogenic activity. Saponin and Ayurvedic bhasma may act by immunomodulation and anti-inflammatory activity. Prebiotic and probiotic helps in recolonisation of GIT flora. The proposed hypothesis may trigger the researcher to investigate new medicine which can be used in treatment of ulcerative colitis.

Traditional and alternative medicine in treatment of ulcerative colitis

The cancer of colon (large intestine) is called as colon cancer. It is a mucosal disease that initiates from caecum and continues throughout up to rectum. Colon cancer is the third most common type of cancer in US. Most of the medicine used for the treatment of cancer have severe side effects. Very few research have been carried out to investigate the role of herbal and traditional medicine especially in colon cancer. Taxol, Etoposide, Vinca alkaloid, Curcumin, Berberine are very few molecule which got attention of scientist but these
all molecules have major problem of stability and severe toxicity. In last decades it was reported by scientist that bhasma could be good candidate for treatment of cancer.

1.2 Approaches for Targeted Drug Delivery to Colon

The conventional drug delivery system for colonic disease may lead to absorption of drug across biological membrane of gastrointestinal tract (GIT). The absorption of drug throughout GIT may lead to increase in dose and associated side effects. Colon targeted drug delivery (CTDD) is a method of delivering medicament to increases concentration of the medicament in colon relative to other part of GIT. The aim of CTDD is to localize, prolong, target and have protected drug interaction to diseased tissue. The aim of targeted drug delivery (TDD) is effective and selective localization of medicament into the target site at therapeutic dose with restricted or no access to non-target sites. A targeted drug delivery system play important role in drugs having low solubility, instability, short duration of half-life, poor absorption, large volume of distribution, low specificity and narrow therapeutic index. Therapeutic efficacy of targeted drug delivery is maximum because it prevents degradation of medicament during transportation to the target site. It can also minimize adverse effects because of inappropriate disposition and minimize toxicity of potent drugs by reducing dose. The colon is a site where both systemic and local delivery of medicament is possible. Local delivery allows topical treatment variety of bowel diseases such as ulcerative colitis, Crohn’s disease, amebiosis, colon cancer and local treatment of colonic pathologies. The colon targeted drug delivery system can be used for systemic delivery of medicament (protein and peptide drugs).

1.2.1 Primary Approaches for Colon targeted drug delivery

Primary approaches that are used for colon targeted drug delivery (CTDD) are as follow (Figure 1.3)
1.2.1.1 pH Sensitive Polymer Coated Drug Delivery

The colon specific drug delivery using pH Sensitive polymer can be achieved as the pH in gastrointestinal tract (GIT) varies. The pH of some colon specific polymer is mention in Table 1.2. This can be accomplished by coating using suitable polymer that are resistant at lower pH of the stomach but that will dissolved/ degrade at neutral pH of the colon. The polymer used for coating should be resistant to the acidic condition of the stomach but gets ionize and get dissolved beyond a definite alkaline pH found in small intestine. Thus by using the same concept it is possible to deliver drugs to the terminal of ileum or colon by use of enteric polymers with a comparatively high threshold pH for dissolution and following drug release. Frequently used enteric polymer for targeting to colon is methacrylic acid and methylmethacrylate that dissolve at pH 6 (Eudragit L) and pH 7 (Eudragit S) have been examined. But the pH of the distal is 6. This colonic delivery system, thus have aninclination to release the drug prior reaching to colon. The problem of premature release can be overcome by using a copolymer of methacrylic acid, methyl methacrylate and ethyl acrylate (Eudragit FS) which gets dissolve at sluggish rate and at higher threshold pH 7 to 7.5 was stated. One must question the impact of gastrointestinal disease on targeting of medicament to colonsince patient suffering from ulcerative colitis are known to have distinctly
lower colon pH\textsuperscript{53-55}. Polymer used in pH Sensitive Polymer Coated Drug Delivery is shown in Table 1.2.

**Table 1.2: Polymer and their threshold pH for CTDD**

<table>
<thead>
<tr>
<th>Polymer</th>
<th>Threshold pH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eudragit® L 100-55</td>
<td>5.5</td>
</tr>
<tr>
<td>Eudragit® L-30D</td>
<td>5.6</td>
</tr>
<tr>
<td>Eudragit® L 100</td>
<td>6.0</td>
</tr>
<tr>
<td>Eudragit® FS 30D</td>
<td>6.8</td>
</tr>
<tr>
<td>Eudragit® S 100</td>
<td>7.0</td>
</tr>
<tr>
<td>Hydroxypropyl Methylcellulose Phthalate</td>
<td>4.5</td>
</tr>
<tr>
<td>Polyvinyl Acetate Phthalate</td>
<td>5.0</td>
</tr>
<tr>
<td>Hydroxypropyl Methylcellulose Phthalate 50</td>
<td>5.2</td>
</tr>
<tr>
<td>Cellulose Acetate Trimellate</td>
<td>5.0</td>
</tr>
<tr>
<td>Hydroxypropyl Methylcellulose Phthalate 55</td>
<td>5.4</td>
</tr>
</tbody>
</table>

1.2.1.2 Time dependent drug delivery

In this approach, drug release takes place after a predetermined lag time. The normal transit time of medicament in the stomach is about 2 hr. which may differ with situations, though in the small intestine it is comparatively constant and may take around 3 hr. For targeting of drug to colon, time taken to reach the drug to colon should be similar to lag time (5 h). The lag time of a medicament rely upon GITmotility and the dosage form size. Among all, one of the most primitive methods based on time dependent drug delivery is the Pulsincap device. This Pulsincap device comprises of a non-disintegrating half capsule body which is sealed at the open end with a hydrogel plug, which is enclosed by a water-soluble cap. The complete unit is coated using an enteric polymer to elude the problem of variable gastric emptying. When the capsule passes through the small intestine, the enteric coating gets dissolved and the hydrogel plug begins to swell. The quantity of hydrogel is adjusted so that it pops out only after the stated period of time to release the medicament to colon.\textsuperscript{56-59}
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1.2.1.3 Microbially Triggered Drug Delivery

The microflora found in the intestine varies from the range of $10^{11}-10^{12}$ CFU/mL, which may contain mostly the anaerobic bacteria, e.g. eubacteria, ruminococcus, clostridia, bifidobacteria, bacteroides, enterococci and enterobacteria. Fermentation of these substrates (disaccharides, trisaccharides and polysaccharides) is the energy source of this huge microflora with numerous types of substrates which have been remains undigested in the small intestine. For the purpose of fermentation of undigested food, the microflora produces a huge number of enzymes like aabinosidase, deaminase, azareducatase, xylosidase, galactosidase, nitroreductase glucuronidase and urea dehydroxylase. As the biodegradable enzymes present in the colon, use of biodegradable polymers for colon targeted drug delivery is recognised as a more site precisemethod as compared to other methods. Prodrug approach is another choice of microbially triggered drug delivery as bacteria present in colon produces numerous enzymes which help in biotransformation of prodrugs. These diversity of enzymes, chiefly of which are from bacterial origin present in the colon, are essential\textsuperscript{60,61}.

Microbially triggered drug delivery involve prodrug approaches of drug delivery and polysaccharide based drug delivery.

1.2.1.4 Prodrug Approach for Drug Delivery

Prodrug is defined as pharmacologically inert derivative of a parent medicament that needs spontaneous or enzymatic transformation in vivo to release the active drug. Various prodrug have been investigated which are susceptible to bacterial hydrolysis especially in the colon. In prodrug approach drug is attached to hydrophobic moieties like azo linkage, amino acids, glucoronic acids, glucose, lactose, cellulose etc\textsuperscript{62}.

Metabolism of azo compounds (Prodrug) by intestinal bacteria is one of the mostcomprehensively studied bacterial metabolic process\textsuperscript{63-66}.

Drawbacks of the prodrug approach is that it is not applicable to all types of drug. It depends upon the functional group present on drug moiety for chemical linkage.
1.2.1.5 Polysaccharide based drug delivery

The polymers used in polysaccharide based drug delivery protect the medicament from the surroundings of stomach and small intestine, and are capable to target the drug to the colon. The micro-organism present in colon causes assimilation of polysaccharide based polymer. Microflora of colon produces enzyme that break down of the polymer back bone leading to a consequent decrease in their molecular weight of polymer and thereby loss of mechanical strength. Once the mechanical strength of polymer reduces medicament liberated in colon\(^\text{67}\).

1.2.2 Recent approaches for CTDD

Primary as well as recent approaches of CTDD is shown in Figure 1.3. The recent approaches of CTDD is as follows

1.2.2.1 CODESTM technology

CODESTM is a recent and distinctive colon targeted drug delivery approach which was made to elude or overcome the intrinsic difficulties associated with pH dependent or time dependent drug delivery. CODESTM is a collectivetactic of microbially triggered and pH dependent drug delivery system. In this system lactulose play an important role and acts as a trigger for site specific drug release that is in colon. One of the example of configuration of CODESTM comprises of a core tablet which is coated with three layers of polymer using suitable coating technique. The outer layer of unit is composed of a Eudragit® L. Once the unit (CODESTM) passes through the pyloric and into the duodenum, Eudragit® L coating dissolves and exposes to second layer of coating. Second layer of coating is made up of Eudragit® E. Eudragit® E coating is resistant in the environment of the small as well as large intestine. The undercoating allows lactulose to gets release into the environment adjacent to the tablet. Metabolism of lactulose produces short chain fatty acids which may lead to decrease in pH. Once the pH lowerto certain level Eudragit E gets dissolves and drug release in colon. In this way CODESTM techniques deliver the drug to colon safely without releasing to nan target site\(^\text{68,69}\).

1.2.2.2 Osmotic controlled drug delivery (ORDS-CT)

If targeting of drug to colon is not achieved by other techniques then osmotic controlled drug delivery is the choice. ORDS-CT can be as simple as single osmotic unit or may
be a combination of as many as 5-6 push-pull units, each one of which may have
diameter of 4 mm and encapsulated with in a hard gelatine capsule. OROS-CT units can
release medicament with uniform rate up to 24 h in the colon\cite{70,71}.

1.2.2.3 Pressure Controlled Drug-Delivery Systems

The robust peristaltic waves in the colon that lead to a momentarily increased luminal
pressure is the basis of pressure controlled drug delivery in colon. Due to pressure in
the lumen of colon release of medicament takes place following disintegration of water
soluble polymer\cite{71}.

1.2.2.4 Bio adhesive system

This method has been developed upon principle of adhesion between drug and the
biological membrane by the virtue of which the medicament remains in contact with
particular organ for longer duration. It lead to extended residence time of the drug
molecule it tends to high local concentration. This approach can be applied to colon
target delivery system. Various polymers employed for bio adhesive system are
polycarbophil, polyurethanes, polyethylene oxide and polypropylene oxide\cite{72}.

1.3 References

   Wiley International 12: 922-23


   bacteria, genetic mutations, and immunoregulatory defects in the pathogenesis

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