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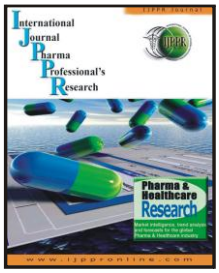
Review Article



COLON: APPROACHES,DISEASES AND POLYMERS-REVIEW ARTICLE

Shekhar singh[1*],Prashant kaushik[2] , Abdul Hafeez[1] ,Kapil kumar[1]
1.Teerthanker Mahaveer College of pharmacy, Teerthanker Mahaveer University, Moradabad
2.Chandigarh college of pharmacy,Mohali,Punjab

Abstract

In the present review, we have studied the different approaches which are made to deliver drug into the colon, without any degradation in the upper git. We also studied the different diseases which occur into the colon and have harmful effects [Ibd, ulcerativecolitis, crohn's, diverticulus,colon cancer].These diseases causes ,symptoms and other factors are known to us. For better delivery of the drug to the colon the knowledge of the right polymer is the must so we studied different types of polymers strategies to deliver drug into the colon. From the above studies it is concluded that with the help of different approaches and the different polymers we can deliver drug to the colon easily and with better action.

Keywords: - IBD, Colon diseases, polymers ,

Introduction

The oral route is considered to be most convenient for administration of drugs to patients. Oral administration of conventional dosage forms normally dissolves in the stomach fluid or intestinal fluid and absorb from these regions of the gastrointestinal tract (GIT) depends upon the physicochemical properties of the drug. It is a serious drawback in conditions where localized delivery of the drugs in the colon is required or in conditions where a drug needs to be protected from the hostile environment of GIT.[1] Oral delivery of drugs to the colon is valuable in the treatment of diseases of colon (ulcerative colitis, Crohn's disease ,carcinomas and infections) whereby high local concentration can be achieved while minimizing side effects that occur because of release of drugs in the upper GIT or unnecessary systemic absorption. The colon is rich in lymphoid tissue, uptake of antigens into the mast cells of the colonic mucosa produces rapid local production of antibodies and this helps in efficient vaccine delivery.[2] The colon is attracting interest as a site where poorly absorbed drug molecule may have an improved bioavailability. The colon has a longer retention time and appears highly responsive to agents that enhance the absorption of poorly absorbed drugs. The simplest method for targeting of drugs to the colon is to obtain slower release rates or longer release periods by the application of thicker layers of conventional enteric coatings or extremely slow releasing matrices.[3]

Correspondence Address:
Shekhar Singh*
Teerthanker Mahaveer University
Moradabad, India
PH: 09368902763
E-mail shekharsingh47@gmail.com

Approaches to deliver the intact molecule to the colon :-

1. Coating with polymers:-
   The intact molecule can be delivered to the colon without absorbing at the upper part of the intestine by coating of the drug molecule with the suitable polymers, which degrade only in the colon.
2. Coating with pH sensitive polymers:-
   The polymers used for colon targeting, however, should be able to withstand the lower pH values of the stomach and of the proximal part of the small intestine and also be able to disintegrate at the neutral of slightly alkaline pH of the terminal ileum and preferably at the ileocecal junction. These processes distribute the drug throughout the large intestine and improve the potential of colon targeted delivery systems.[4]
3. Coating with biodegradable polymers:-
   Drugs that are coated with the polymers, which are showing degradability due to the influence of colonic microorganisms, can be exploited in designing drugs for colon targeting. These bacterial degradable polymers especially azo polymers have been explored in order to release an orally administered drug in the colon.

Actually, upon passage of the dosage form through the gastrointestinal tract, it remains intact in the stomach and small intestine where very little microbial degradable activity is present that is quiet insufficient for cleavage of polymer coating. Release of the drugs from azo polymer coated formulation is supposed to take place after reduction and thus degradation of the azo bonds by the azoreductase enzymes released by the azobacters present in colonic microflora.[5],[6]

4. Embedding in matrices:-
   The drug molecules are embedded in the polymer matrix. The polymers used for this technique should exhibit degradability inthe colon for liberation of entrapped drug.
5. Embedding in biodegradable matrices and hydrogels:-
   The matrices of polysaccharides are assumed to remain intact in the physiological environment of stomach and small intestine but once they reach in the colon, they are acted upon by the bacterial polysaccharidases and results in the degradation of the matrices. A large number of polysaccharides such as amylase , guargum, pectin, chitosan , inulin , cyclodextrins, chondroitin sulphate, dextrans and locust bean gum have been investigated for their use in colon targeted drug delivery systems.
   Hydrogels are usually formed by the covalent cross linking of linear hydrophilic polymers to form a network of material capable of absorbing water, yet still remaining insoluble. Heterogenous polymer mixtures may also be used to form hydrogels without the need for covalent cross linking. Various hydrogels based on the azo polymeric networks have been developed for site-specific delivery of drugs to the colon.[7],[8]
6. Embedding in PH sensitive matrices:-
   Extrusion-spheronization and pelletization have been used for the preparation of pH-sensitive matrix pellets for colon targeted drug delivery.[9],[10] used ibuprofen as model drug and Eudragit® S and Aqoat AS-HF as enteric polymers for developing site-specific systems for release of a drug in the lower part of the small intestine or in the colon.
7. Time released systems:-
   This approach is based on the principle of delaying the release of the drug until it enters into the colon. Although gastric emptying tends to be highly variable, small intestinal transit time is relatively constant or little bit variation can be observed. The strategy in designing timed-released systems is to resist the acidic environment of the stomach and to undergo a lag time of predetermined span of time, after which release of drug take place. The lag time in this case is the time requires to transit from the mouth to colon.[11]
8. Redox sensitive polymers:-
   Analogues to azo bond cleavage by intestinal enzymes, novel polymers that hydrolyzes nonenzymatically by enzymatically generated flavins are being developed for colon targeting.[12],[13] 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.4,4'-Dihydroxyazobenzene (E1/2 -470 mV) was reduced at thefastest rate of 0.75 mol l -1 h -1, amaranth (E1/2 -568 mV) at 0.30 mol l-1h -1, Orange II (E1/2 -648 mV) at 0.2 mol l -1 h -1 and tartrazine (E1/2 -700mV) at 0.08 mol l-1 h-1.
9. 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.[14],[15]
10. Coating with micro particles:-
    Many of the protozoans especially Entamoeba-histolytica remains confined in the large intestine, which necessitates high intra colonic drug concentration.[16] Prepared and evaluated a formulation that was rather diverted from the mainstream of conventional therapy. It consisted of small silica particles covalently linked to a potent antiamoebicdrug,2-(4-aminophenoxymethyl)-5-nitro-1-methylimidazole. Silica-drug particles were injected into mice, hamsters and guinea pigs. It was found that trophozoites phagocytosed the particles in vivo and in vitro,followed by rapid cell death due to the released drug.
11. Osmotic controlled drug delivery:-
    The OROS-CT (Alza Corporation) can be single osmotic

unit or may incorporate as many as 5-6 push-pull units, each 4mm in diameter, encapsulated with in a hard gelatin capsule. As the unit enter the small intestine, the coating dissolve in this higher pH environment (pH >7), water enters the unit, causing the osmotic push compartment to swell and concomitantly forces drug gel out of the orifice at a rate precisely controlled by the rate of water transport through the semi permeable membrane.[17]

Covalent linkage of the drug with a carrier:-

It involves the formation of a covalent linkage between drug and carrier in such a manner that upon oral administration the moiety remains intact in the stomach and small intestine. This approach chiefly involves the formation of prodrug, which is a pharmacologically inactive derivative of a parent drug molecule that requires spontaneous or enzymatic transformation in the biological environment to release the active drug.

Azo bond conjugates

Sulphasalazine is introduced for the treatment of rheumatoid arthritis and anti-inflammatory disease. Chemically it is salicylazosulphapyridine (SASP), where sulfapyridine is linked to a salicylate radical by an azo bond. When taken orally, only a small proportion of the ingested dose is absorbed from the small intestine and the bulk of the sulphasalazine reaches the colon intact. There it is split at the azo bond by the colonic bacteria with the liberation of sulphapyridine(SP)and5-Aminosalicylicacid.[18]

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 GIT, however, secrete glucuronidase and can de glucouronidate a variety of drugs in the intestine. Since the de 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.[19]

Cyclodextrin conjugates

In an oral drug delivery system, the hydrophilic and ionizable Cyclodextrins (CyDs) can serve as potent drug carriers in the immediate release and delayed release-formulations, while hydrophobic CyDs 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 CyDs can be a versatile means of constructing a new class of colon targeting prodrugs soluble drugs.[20],[21]

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. In this study, methyl prednisolone and dexamethasone were covalently attached to the dextran by the use of a succinate linker. In addition dexamethasone was attached by glutaric acid to investigate the effect of linker molecule on hydrolysis kinetics.[22],[23]

Amino-acid conjugates

Due to the hydrophilic nature of polar groups like NH_2 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.[24],[25]

Diseases:-

Imflammatory Diseases

Inflammatory bowel disease (IBD) is the name of a group of disorders in which the intestines (small and large intestines or bowels) become inflamed (red and swollen). This inflammation causes symptoms such as:

- Severe or chronic (almost all of the time) pain in the abdomen (belly)
- Diarrhoea — may be bloody
- Unexplained weight loss
- Loss of appetite
- Bleeding from the rectum
- Joint pain
- Skin problems
- Fever

Symptoms can range from mild to severe. Also, symptoms can come and go, sometimes going away for months or even years at a time. When people with IBD start to have symptoms again, they are said to be having a relapse or flare-up. When they are not having symptoms, the disease is said to have gone into remission.

The most common forms of IBD are ulcerative colitis and Crohn's disease. The diseases are very similar. In fact, doctors sometimes have a hard time figuring out which type Of IBD a person has. The main difference between the two diseases is the parts of the digestive tract they affect. Inflammatory bowel disease (IBD) refers to two related but

different diseases: ulcerative colitis and Crohn's disease.

These diseases cause chronic inflammation of the intestinal tract, which leads to a variety of symptoms. The inflammation can also lead to involvement of organs other than the intestines. IBD is a lifelong disease with periods of active disease alternating with periods of disease control (remission). IBD is sometimes confused with but is different than irritable bowel syndrome.

Cause

The exact cause of IBD is not known but is related to protective immune cells that are present in the lining of the intestines. This immune system normally turns on and off to fight harmful substances like bacteria and viruses that pass through intestines. In IBD it appears that there is an initial trigger such as an infection or something taken in from the diet or the surrounding environmental that activates the immune system. However, the difference in those who develop IBD is that the immune system does not turn off once this initial trigger is eliminated. This leads to uncontrolled inflammation and attack on normal intestinal cells. The exact contributions of such factors are poorly understood and are difficult to define.

Symptoms

The most common symptoms seen in both ulcerative colitis and Crohn's disease are diarrhea, rectal bleeding, urgency to have bowel movements, abdominal cramps and pain, fever, and weight loss. In Crohn's disease, symptoms can result from complications of the disease. Fistulas can lead to openings in the skin and around the anal region that drain stool and infected material. An abscess can lead to symptoms of severe pain and fever. A stricture can lead to intestinal blockage with symptoms of filling up quickly after meals, nausea and vomiting.

Diagnosis

The most direct way to make a firm diagnosis of IBD involves the use of endoscopy (putting a tube with a light at the end into the intestines), biopsies, or special X-rays. With endoscopy, the lining of the intestinal tract can be directly seen by the doctor performing the procedure and biopsies can be obtained. Typical changes of IBD can be detected by endoscopy and by examining biopsies under a microscope. **Figure 1** shows the appearance of a normal colon at endoscopy while **Figure 2** shows an inflamed colon that is typical for the appearance of ulcerative colitis at endoscopy. **Figure 3** shows ulcers in the intestine that are typical for Crohn's disease. Barium X-rays known as small bowel series are also commonly used to diagnose IBD. Patients drink barium (a white fluid), which allows doctors to take X-ray pictures of the small intestine and to look for changes typical of IBD.[26]

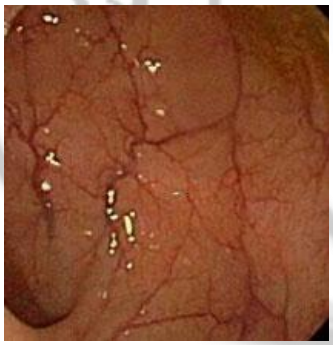


Figure 1.

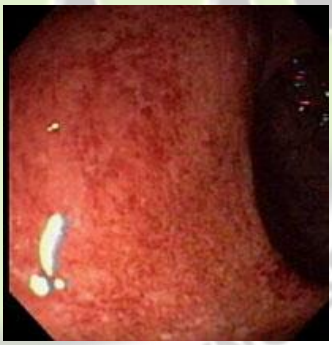


Figure 2.

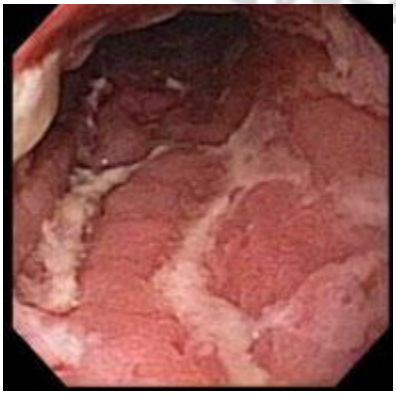


Figure 3.

Ulcerative Colitis

Ulcerative colitis is an inflammatory chronic disease primarily affecting the colonic mucosa; the extent and severity of colon involvement are variable. In its most limited form it may be restricted to the distal rectum, while in its most extended form the entire colon is involved. However, 80% of the patients present with disease extending from the rectum to the splenic flexure, and only 20% have pancolitis.

Epidemiology

Ulcerative colitis is usually associated with recurrent attacks with complete remission of symptoms in the interim. The disease is more common in Caucasians than in Blacks or Orientals with an increased incidence (three to six fold) in Jewish. Both sexes are equally affected. In Western Europe and in the USA, UC has an incidence of approximately 6 to 8 cases per 100,000 populations and an estimated prevalence of approximately 70 to 150 per 100,000 populations. While peak occurrence of both diseases (UC and CD) is between ages 15 and 35, it has been reported in every decade of life.

Etiology

The cause of UC is unknown. Although less evident than in CD, it is clear from twin studies that a genetic background is also present in UC. Indeed, a stronger association exists between genes of the human leucocyte antigen region - involved in regulating the immune response - and UC. Despite unclear effects due to ethnic origin and disease heterogeneity, this association is strongest in patients with extensive UC; a positive association with DR2 (in particular, DRB1*1502 subtype) and the rare alleles DRB1*0103 and DRB1*12, and a negative association with DR4 and Drw6 have been reported. However, genes associated with susceptibility to UC are probably not within the human leucocyte antigen region, and genome-wide scanning studies have shown a linkage between UC and regions of chromosomes 3, 7, and 12. Moreover, there are genes that appear to affect the severity and extent of the disease, steroid response, steroid requirements, and extra - intestinal manifestations.

Pathophysiology

While the cause of UC remains unknown, a number of findings in recent years point to an over stimulation or inadequate regulation of the mucosal immune system as a major patho physiological pathway, and particular emphasis has been given to either the study of mucosal inflammation or immunologic reactions.When the disease is active, the lamina propria of the mucosa becomes heavily infiltrated with a mixture of acute and chronic inflammatory cells. There is a predominant increase in mucosal IgG production, evidence of complement activation, and activation of macrophages and T cells. This immunological activity is associated with the release of a vast array of cytokines, kinins, leukotriens, platelet activating factor (PAF) and reactive oxygen metabolites. These mediators not only serve to amplify the immune and inflammatory response, but they also have direct effects on epithelial function, on endothelial function (which may increase permeability and lead to ischaemia), and on repair mechanisms, thus increasing collagen synthesis. In addition, many of the cytokines (interleukins 1 and 6, tumor necrosis factor) will activate an acute phase response, resulting in fever and a rise in serum acute phase proteins.

Symptoms, signs, and laboratory findings

The leading initial symptom of UC is diarrhea with blood and mucus, sometimes with pain (Table 1). Fever and weight loss are less frequent. Extra intestinal symptoms can be an initial manifestation or can occur later in the course of the disease.[27]

Table1: Initial symptoms of UC

Diarrhea		96.4%
Blood in stool		89.3%
Pain		81;3%
Generally unwell		40.2%
Weight loss		38.4%
Arthralgia		27.7%
Fever		20.5%
Skin changes		20.5%
Loss of appetite		15.2%
Ophtalmopathies		7.1%
Nausea		6.3%
Vomiting		4.5%
Abscesses		3.6%
Fistulae		3.6%
Lymphe node swelli		1.8%

Crohn'n Disease

Definition

The diagnosis relies on the accumulation of various criteria including clinical, endoscopical, histological and biological findings. The clinical manifestations depend on the

distribution and severity of the disease, together with the presence of complications. The most common symptoms are: diarrhea, abdominal pain, rectal bleeding, anorexia, weight loss.
They depend on the site of the disease (see table 2).

Table2

Frequency of affected site in Crohn disease Site	**Frequency**
Extensive small bowel disease	5%
Ileum only	25%
Ileocecal	40%
Colon only	25%
Miscellaneous (i.e confined to anorectum, oral, gastric)	2%

The main features in patients with small bowel disease are pain and weight loss. If it mainly occurs after meals, it may indicate partial intestinal obstruction. The prominent features in patients with colonic disease are diarrhea and bleeding.
CD may be revealed by surgical complications: complete or partial intestinal occlusion; intra-abdominal, pelvic, or perineal abscess, free peritoneal perforation.
Extra digestive manifestations may occur in parallel with the digestive symptoms during attacks such as fever, arthralgia, arthritis, buccalaphtosis, erythema nodosa, pyodermagangrenosum, iritis, episcleritis.

Physical examination

The main features to look for are: oral apoptosis, abdominal tenderness and masses, anal tags, fissure and fistulae, nutritional deficiency. An important feature in children is growth retardation.

Endoscopy

Rigid or flexible procto-sigmoidoscopy will establish the diagnosis of Crohn'sproctitis. Mild inflammation may consist of erythema, apoptous ulcers, granularity with increased contact bleeding but with intervals of preserved normal mucosa.
Colonoscopy helps to determine the pattern and severity of colonic and terminal ileum inflammation, and allows biopsies to be obtained. Endoscopic features are aphtous ulcers, deeper ulceration (sometimes spread like "geographical maps"), postinflammatory polyps (which indicate previous severe inflammation), but always accompanied by intervening normal mucosa, which is an important differential feature between CD and ulcerative colitis .

Biopsies

Rectal and colonic biopsies should be examined to find the nature of the inflammation (ulcerative colitis versus CD), collagenous colitis or microscopic inflammation if macroscopic appearance is normal, and infection. CD histology is characterized by preserved mucosal architecture, a deep inflammatory infiltrate toward the lamina propria, fissura, and pseudo-tuberculoid granuloma (found in only 20-30 % of patients with CD).

Radiology

In acute severe colitis, a plain abdominal radiograph is sufficient to diagnose the extent and severity of the attack. The colon may dilate (« toxic megacolon ») to a diameter superior to 8 cm. The presence of musocal islands indicates severe inflammation due to detached mucosa.
In long-standing CD, the colon may become tubular and shortened due to the loss of haustrations.
Small bowel enema is now the technique of choice for the barium examination of the small intestine; by his method, the extent of small bowel CD could be determined. The main features are: thickening and distortion of the valvulae conniventes, edema of the wall, ulcers and fissuring, luminal narrowing and strictures, prestenotic dilatation indicating severe stricture, fistulae to other abdominal organs or to the skin.

Blood tests

Anemia may be present due to blood loss (iron deficiency), chronic inflammation, or B_{12} malabsorption (macrocytic) in CD. Hypoalbuminemia suggests severe disease with denutrition.
The best markers of inflammation severity in CD are elevation of the C-reactive protein and platelet count.
Anti-saccharomyces cerevisiae antibodies (ASCA) are positive in 50-60% of CD patients while anti-neutrophil polynuclear antibodies (ANCA) are positive in 50-60% of UC patients. The combination ASCA+/ANCA- has a positive predictive value for the diagnosis of CD superior to 90%.

Etiology

Environmental factors

Smoking

Smoking increases the risk of developing CD and doubles the risk of postoperative recurrence, particularly in women.

Oral contraceptives

There may be a slight association between oral contraceptive use and the development of CD. This is insufficient to deny the oral contraceptive to a patient, unless she/he has had previous venothrombotic disease.

Infective agents

Despite much effort, incontrovertible evidence of an infective cause for CD has not emerged. The most studied agents have been measles virus, Mycobacterium paratuberculosis and E Coli.

Genetic factors

The genetic contribution to the etiology of CD is polygenic in pattern rather than simply Mendelian, it is stronger in CD than ulcerative colitis. Susceptibility loci on chromosomes 16, has been confirmed in different surveys of familial cases of CD leading to the discovery of three main mutations on gene NOD 2 in a subset of patients with CD.

Differential diagnosis

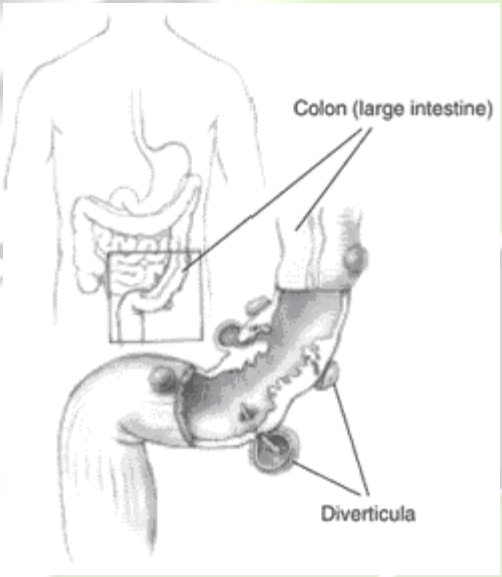
Other conditions to consider if there is terminal ileal or colonic inflammation include:Tuberculosis, Bacterial infection Yersinia (if only the terminal ileum is inflamed) , Parasitic infection including amoebiasis or schistosomiasis if the patient has been to or comes from an endemic area,Behçet'sdisase if there are deep punched-out ulcers. Infection can also occur in patients with established IBD (Inflammatory bowel disease), and should be excluded by routine stool culture during new acute episodes of diarrheal illness.[28]

Diverticulosis

Diverticulosis refers to the presence of small out-pouchings (called diverticula) or sacs that can develop in the lining of the gastrointestinal tract. While diverticula can be present anywhere in the entire digestive tract, they are most common on the left side of the large intestine, the area known as the descending and sigmoid colon (Figure).

cause

No one knows for certain why diverticulosis develops; however, a few theories have been suggested. Some experts believe that abnormal contraction and spasm (resulting in intermittent high pressure in the colon) may cause diverticula to form in a weak spot of the intestinal wall. Low fiber diets may play a role in the development of diverticulosis.



In rural Africa where the diet is high in roughage, diverticulosis is rare. There also appears to be a genetic predisposition to diverticulosis, that is, if your parent or grandparent had diverticulosis you may develop it as well.

Symptoms

Most patients with diverticulosis have no symptoms. Many will never know they have the condition until it is discovered during an endoscopic or radiographic (Xray) examination. While most people have no symptoms, some individuals may experience pain or discomfort in the left lower abdomen, bloating, and/or a change in bowel habits.

Diagonosed

Diverticulosis is generally discovered through one of the following examinations:

Barium enema: This x-ray test involves injection of liquid material into the colon through a tube inserted in the rectum. The x-ray image shows the anatomy of the colon, and can identify if diverticula, large polyps or growths are present.

Colonoscopy: This test uses a thin, flexible tube with a light and camera to view the inside of the colon. Diverticula as well as polyps and other growths can be seen with this instrument.

CT scan: This x-ray test takes multiple cross section pictures of the body. It is not generally performed to make a diagnosis of diverticulosis, but this type of exam may identify diverticula.[29]

Colon Cancer

Colon polyps

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.

Types of polyps

Hyperplastic polyps occur more often in the left (descending) colon and rectum and are usually less than 1/4 inch in diameter. ("Hyperplastic" refers to an increase in cells.)

Adenomatous polyps(sometimes referred to as adenomas) are divided into three subtypes based on their microscopic features: villous (hairy), tubular, and tubulovillous. Villous adenomas tend to be larger than the other types and are more likely to become cancerous. In general, the larger the polyp, the more likely it is to become cancerous

A person may have just a few polyps or, in the case of **familialadenomatous polyposis** (FAP), a hereditary polyp disorder, the number of polyps can run into the hundreds or even thousands. Usually, the surgeon can remove a polyp with a wire loop during a simple colonoscopy. But in cases of larger or multiple polyps, more extensive surgery is required.

Colorectal cancer is cancer that develops in the colon or the rectum. The colon and rectum are parts of the diges-tive system, which is also called the gastrointestinal, or GI, system. The digestive system processes food for energy and rids the body of solid waste (fecal matter or stool).

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. Certain kinds of polyps, called **adenomatous polyps** or **adeno-mas**, are most likely to become cancers.

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 infec-tions. 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. In this document, we will describe colorectal cancer stages as:

Local: Cancers that have grown into the wall of the colon and rectum, but have not extended through the wall to invade nearby tissues.

Regional: Cancers that have spread through the wall of the colon or rectum and have invaded nearby tissue, or that have spread to nearby lymph nodes.

Distant: Cancers that have spread to other parts of the body, such as the liver and lung.[30]

Polymers:-

Enteric coated

Drugs can be delivered locally and selectively to the colon by taking advantage of the difference in the pH of the different regions of the gastrointestinal tract.The pH in the gastrointestinal tract is low in the stomach but increases in the small intestine and the large intestine. For the purpose of targeting drugs to the colon, an outer enteric coating (for example, of cellulose acetate phthalate) can be used to tablets were coated using different combinations of Eudragit L and Eudragit S. The Eudragit L–Eudragit S combinations

protect the drug in the low pH of the stomach.

In the small intestine(pH, 7.5), the enteric coating dissolves, exposing a polymeric coating, typically of ethylcellulose with microcrystalline cellulose and plasticizers. The polymeric coating is designed to stay intact in the small intestine until the dosage form reaches the colon. In the colon, bacteria are expected to digest the microcrystalline cellulose to allow for the disintegration of the polymeric coating around the drug. Such a scenario has been confirmed in a study by Hirayama, Minami, and Uekama.[31] in which all the compressed tablets with dual coating remained intact in the small intestine and 85% of which disintegrated in the colon. The problem with this approach is that the intestinal pH may not be stable because it is affected by diet, disease and presence of fatty acids, carbon dioxide, and other fermentation products. Moreover, there is considerable difference in inter- and intraindividual gastrointestinal tract pH, and this causes a major problem in reproducible drug delivery to the large intestine.[32].Spherical pellets containing 5% triamcinolone acetonide were prepared by Villar-Lopez and coworkers[33] byextrusion/spheronization after formulation with microcrystalline cellulose and/or a hydrophilic excipient such as lactose, sodium carboxymethylcellulose, or *b*-cyclodextrin. Their suitability for coating, with a view toward colonic drug delivery, was assessed in terms of their size, sphericity, and dissolution testresponse. The best results were afforded by a 5 : 90 : 5 composition of microcrystalline cellulose, *b*-cyclodextrin, and triamcinolone acetonide, prepared by complexation of triamcinolone acetonide with *b*-cyclodextrin before the addition of microcrystalline cellulose.Formulations of 5-aminosalicylic acid that are commercially available use enteric coatings of pH-sensitive methacrylic resins called Eudragit_ (Fig. 4). Both water-soluble and water-insoluble forms of Eudragit have been tested for colon targeting. Eudragit-L dissolves at a pH level above 5.6 and is used for enteric coating, whereas Eudragit-S, which dissolves at a pH level above 7.0 (attributable to the presence of higher amounts of esterified groups in relation to carboxylicgroups) is used for colon targeting. Studies have revealed that Eudragit-S exhibits poor site specificity.[34]In a study performed by Khan et al.[35], lactose placebo (w/w) studied were 1 : 0, 4 : 1, 3 : 2, 1 : 1, 2 : 3, 1 : 4, 1 : 5, and 0 : 1. The disintegration data obtained from the placebo tablets demonstrate that disintegration rate of the tablets is dependent on 1) the polymer combination used to coat the tablets; 2) the pH of the disintegration media; and 3) the coating level of the tablets. It has been shown that polymers with non-esterified phthalic acid groups dissolve much faster and at a lower pH than those with acrylic or methacrylic groups. The presence of plasticizer and the nature of the salts in the dissolution medium influence the dissolution rate.[36] In a recent study by Peeters[37] the free carboxylic groups of Eudragit-S were partially methylated. The product was found to dissolve in water at a slightly higher pH compared with the original polymer. The effectiveness of this product as a colon-specific coating material had been established with human volunteersusing in vivo scintigraphic studies.[38] In a study by Gazzaniga and coworkers,[39] an oraldosage form was developed, consisting of a core with two polymeric layers. The outer layer, which was an enteric coating, dissolved at a pH level above 5. The inner layer, made up of hydroxypropylmethylcellulose, acted as a retarding agent to delay drug release for apredetermined period. The thickness of the inner layer determined the lag time. This system was found to release drug in the colon of the rat between the 5th and 10th h.

A pulsed system, called the Time-Clock System, has been developed. The system comprises a solid dosage form coated with a hydrophobic surfactant layer to which a water-soluble polymer is attached to improve adhesion to the core.[40] The thickness of the outer layer determines the time required to disperse in an aqueous environment. After the dispersion of the outer layer, the core becomes available for dispersion. An advantage is that common pharmaceutical excipients can be used to manufacture the system. Studies performed in human volunteers showed that the lag time was not affected by gastric residence time. Also, the dispersion of the hydrophobic film was not influenced either by the presence of intestinal digestive enzymes or by the mechanical action of the stomach.

Another system based on the same principle as the Time-Clock System, called the Time-Controlled- Explosion Drug-Delivery System, has also been developed.[41] It contains a four-layered spherical structure, with a core containing the drug, a swelling agent, and a water-insoluble polymer membrane made of ethylcellulose. This system is characterized by rapid drug release with a programmed lag time.

On contact with water through the polymeric membrane, the swelling agent expands and finally explodes, leading to release of the contained drug. Drug release is not affected by pH, but the lag time is a function of the thickness of the outer polymeric membrane. A similar approach based on ethylene–vinyl acetate polymerswas tested for release of the drug isosorbide-5-nitrate.[42] Ishibashi and coworkers have recently developed a Colon-Targeted Delivery Capsule based on pH sensitivity and time-release principles (Fig. 4).[43] The system contains an organic acid that is filled in a hard gelatin capsule as a pH-adjusting agent together with the drug substance. This capsule is then coated witha three-layered film consisting of an acid-soluble layer, a hydrophilic layer, and an enteric layer. After ingestion of the capsule, these layers prevent drug release until the environmental pH inside the capsule decreases by dissolution of the organic acid, upon which the enclosed drug is quickly released. Therefore, the onset time of drug release is controlled by the thickness of the acid-soluble layer. In fact, capsule disintegration (and, thus, drug release) does not start until 5 h after gastric emptying regardless of whether the formulation is administered to fasted or fed subjects

Recently, Yoshikawa et al.[44] reported a new in vitro dissolution test called the rotating beads method for drugs formulated in pressure-controlled colon delivery capsules. This dissolution method was applied to acetominophen sustained-release tablets and two other drugs having low solubility in the colon, tegafur and 5-ASA. There was good correlation between the in vitro dissolution rates and the in vivo absorption rates. In the development of the afore mentioned time dependent systems, care has to be taken to ensure a homogenous coating. If the coat is inhomogenous, there will be a modification of the coating rigidity, possibly leading to undesirable infiltration of the aqueous medium and, in turn, undesired alteration of the lag time before which the drug is supposed to be released.

Polymers sensitive to degradation by bacterial enzymes:-

Drugs can be administered locally and selectively to the colon if they are enclosed in a dosage form such as a capsule coated with an azo-aromatic cross-linked polymer subject to cleavage by azo-reductases of the colonic microflora. This approach of coating a drug with biodegradable material for colon targeting can be used to administer a large amount of the drug. Moreover, the rate of drug release is dependent on the activity of the bacterial enzymes in the colon ratherthan on that of the host.

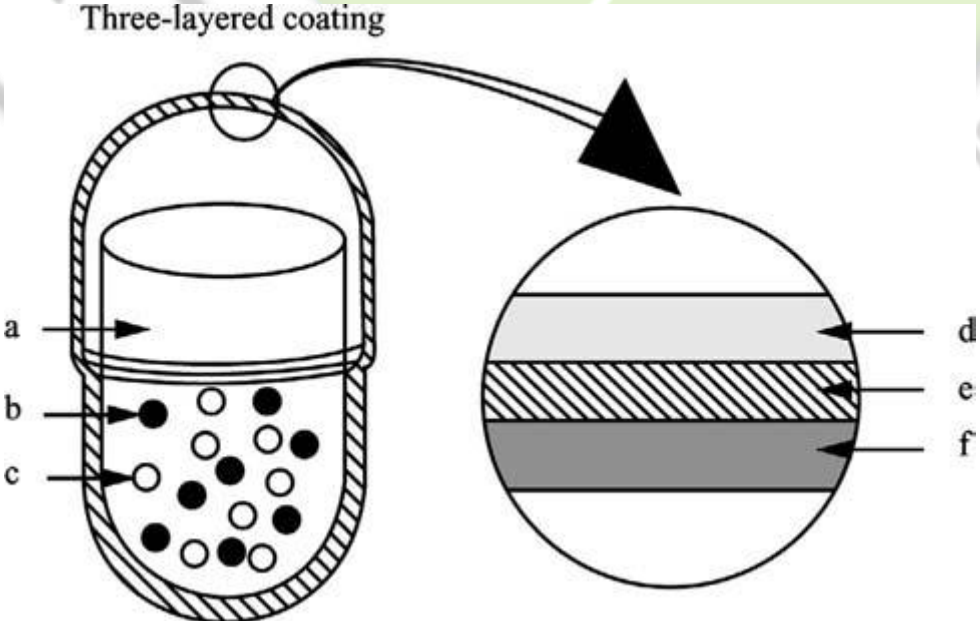
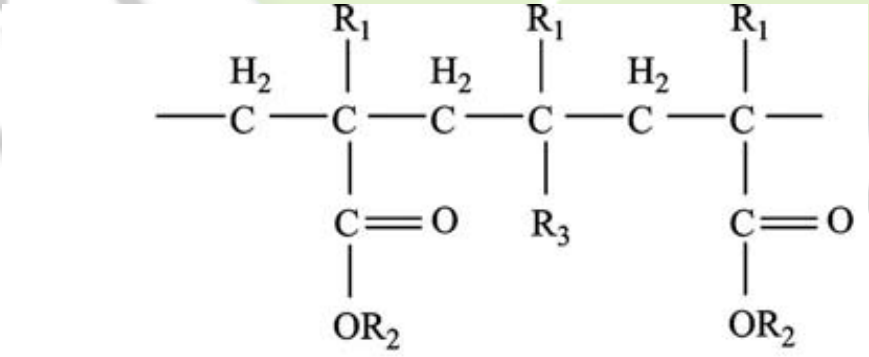


Fig. 4 Design of the colon-targeted delivery capsule: a) gelatin capsule; b) active ingredient; c) organic acid; d) enteric layer; e) hydrophilic layer; and f) acid-soluble layer.

A system was developed by Saffran and coworkers [42] in which insulin or vasopressin was encapsulated in a gelatin capsule coated with an impermeable polymer.

The coat, prepared by using azo functional cross-linking agents based on divinylazobenzene, wasresistant to degradation in the stomach and the small intestine. However, problems were encountered attributable to variability in absorption, which may be because of to intra- and intersubject differences in microbial degradation of the coating that may not be hydrophilic enough. Indeed, Kimura et al.[45] noted that only polymers with a sufficient degree of hydrophilicity could be degraded within an acceptable period of time. However, there is a possibility of premature drug release if the polymeric coating is too hydrophilic. The impact of the spacer length of the incorporated azo agent appears to be of limited importance.A popular theory with azo materials is that their degradation products are always aromatic amines suchas azo dyes. Ueda and coworkers observed that the azo bonds in segmented polyurethanes were reduced to hydrazo intermediates after incubation with human feces because no decrease in the molecular weight was observed.[46] It was then theorized that drug release from pellets coated with these azo polymers was attributable to both a conformational change and a breakdown of the film structure.

Other studies also concluded that the polymers were reduced to hydrazo intermediates or were completely degraded to aromatic amines depending on their hydrophilic/ hydrophobic nature. Their has been no definitive conclusion regarding the toxicity of azo polymers, although it is known that azo dyes contain several potential carcinogens.To avoid Possible azo-related toxicity issues, other biodegradable natural substances capable of forming coatings that degrade in the colon have been studied. Common problems encountered with these natural biodegradable materials are poor film-forming capability and excessive water solubility. Therefore, efforts are currently being made to mix these natural materials with other synthetic polymers to form a film-forming mixture or to derivatize them to decrease their water solubility. Natural polysaccharides such as pectin, xylan and guar gum are not digested in the human stomach or small intestine, but are degraded in the colon by the resident bacteria. Recent studies conducted with 5-ASA[47] and indomethacin [48] confirmed that selective delivery of these drugs to the colon can be achieved using guar gum as carrier because guar gum protects the drugs from being released in the physiological environment of the stomach and the small intestine.The polysaccharides under active investigation for colon specific drug delivery include pectin and its salts, chrondroitin sulfate, amylase and inulin.Veervort and Kinget [49] demonstrated that the incorporation of inulin in eudragit films resulted in increased permeability with increase in incubation time in the degradation medium (Figure 5.) After 8,16 and 24 hrs of incubation the permeability coefficients



$R_1 = CH_3$; H

$R_2 = CH_3$; CH_3 CH_2^-

$R_3 = -COOH$ (Eudragit® L and S)

$-COOCH_2CH_2N^+(CH_3)_3Cl^-$ (Eudragit® RL and R

Fig. 5 Chemical structures ofEudragit. (Adapted from Ref.[43].)

increased with a factor 6, 20, and 70, respectively. However, because of manufacturing problems resulting from the high methoxy pectin content, film coatings were developed consisting of ethylcellulose and pectin. Wakerly and coworkers manufactured[50] film coatings with ethylcellulose and pectin. In vitro degradation studies indicated that release was controlled by the ratio of ethylcellulose and pectin.Lorenzo-Lamosa and coworkers manufactured a system in which chitosan microcores were entrapped within acrylic microspheres of Eudragit L-100 and Eudragit S-100, forming a multireservoir system.[51] This system was designed to combine the specific biodegradability enforced by colonic bacteria with pH-dependent release of the drug sodium diclofenac and tested in in vitro systems. A continuous release for 8–12 h was obtained at the pH in which the Eudragit coats were soluble. The researchers have proposed a combined mechanism of release, comprising dissolution of the Eudragit coating, swelling of the chitosan microspheres, dissolution of the drug, and its further diffusion through the chitosan gel cores (Fig. 6).[51] Recent studies conducted by Tozaki et al.[52] with 5-ASA-containing chitosan capsules revealed that thedrug concentration in the colon was higher than that afforded by a suspension of the drug. Ramdas et al.[53] used the bioadhesiveness of polyacrylic acid, alginate, and chitosan in formulations with drugs such as 5-fluorouracil and insulin to bypass the acidity of the stomach and to release loaded drug for long periods into the intestine.[53] Chitosan succinate and chitosan phthalate have been used successfully as potential matrices for the colon specific oral delivery of sodium diclofenac as demonstrated by Aiedeh and Taha.[54] Another natural polysaccharide, amylose, when prepared under appropriate conditions, is not only able toproduce films, but is also found to be resistant to the action of pancreatic *a*-amylase while remaining vulnerable to the colonic flora.[55] However, incorporation of ethylcellulose was necessary to prevent premature drug release through simple diffusion.[56] In vitro release of5-aminosalicylic acid from pellets coated with a mixture of amylose–ethylcellulose in a ratio of 1 : 4 was complete after 4 h in a colonic fermenter. By contrast, it took more than 24 h to release only 20% of the drug under conditions that mimic that of the stomach and the small intestine . A suspension of natural polygalactomannans in polymethacrylate solution applied to a degradablecoating around the drug core delayed the drug release in the small intestine but was degraded by bacterial enzymes in the colon.[56] This formed the basis for studying the usefulness of guar gum containing polygalactomannans as a carrier for colonic drug delivery. Matrix tablets of dexamethasone wereevaluated for colon-specific drug; delivery with preparations containingguar gum.[57] In a *g*-scintigraphic study, guar gum in the form of matrix tablets was evaluated for its performance in healthy human volunteers using technetium-99m-DTPA as tracer.[58] It was observed that the matrix tablets entered the colon intact and released the bulk of the tracer in the colon by virtue of the enzymatic action of the colonic bacteria. Studies conducted by Bauer and Kusselhut have demonstrated that lauryl dextran esters can be filmforming and have been found to release tablets containing theophylline selectively in the colon.[59] Theophylline tablets were coated with a dispersion of 4% lauroyl dextran in a study performed by Hirsch and coworkers.[60] Theophylline dissolution was monitored for 4 h in a buffer of pH5.5, after which the passage to the cecumwas simulated by the addition of dextranase. Almost linear dissolution was observed during the first 4 h. The rate of release was inversely proportional to the amount of ester applied on the coating. After the addition of dextranase, the coatings were degraded, leading to the complete release of the drug in less than 2 h, after the addition of the enzyme. The results of these studies in which natural biodegradable polymers have beenderivatized using acceptable reactants are promising as far as colon-specific drug delivery is concerned.

Matrix and hydrogels susceptible to degradation by bacterial enzymes:-

In this design, the active ingredient, the degradable polymer, and other additives are compressed to form a monolithic or multiparticulate solid dosage form.The drug is embedded in the matrix core of the degradable polymer. Biodegradable matrix systems of crosslinked chondroitin sulfate with different levels of cross-linking have been tried for the delivery of indomethacin. A direct relationship was found between the degree of cross-linking of the polymer and the amount of drug released in the rat cecal content.[61] Rubinstein and Rudai[62] observed that highly compressed matrices based on pectin in the form of plain tablets or compression-coated tablets were able to retain indomethacin in simulated gastric and intestinal juice before becoming degraded in a medium that contained enzymes for degrading pectin. In vitro experiments showed that methoxyl pectin, when added as a compression coat, was capable of protecting a core tablet under conditions mimicking mouth-to-colon

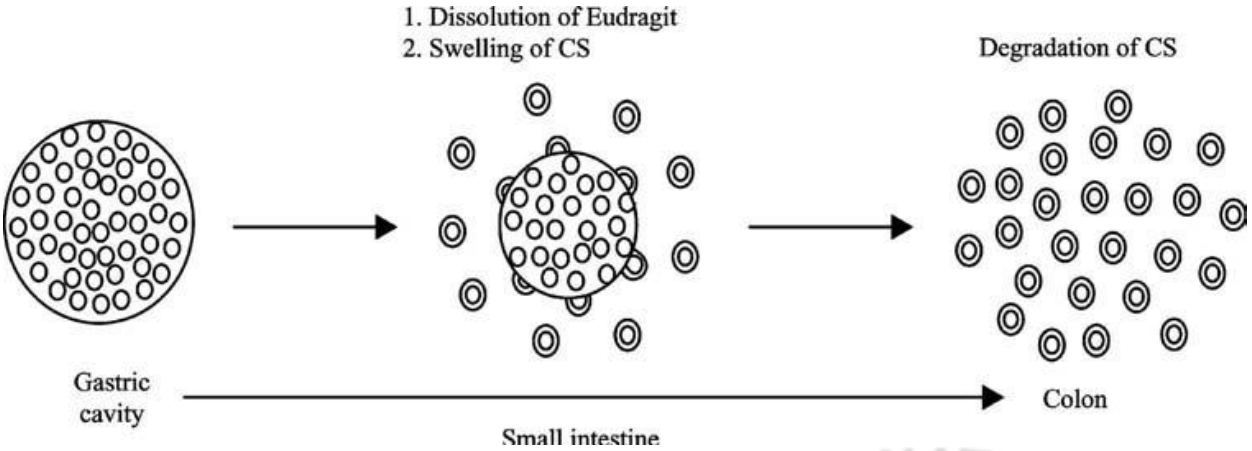


Fig. 6 Scheme of possible drug release from the Eudragit microencapsulated chitosan microspheres. (Adapted from Ref.[56]

transit and was susceptible to enzymatic attack in the colon. A greater degree of methoxylation of pectin resulted in lower susceptibility degradation to by colonic bacterial enzymes, whereas the presence of calcium increased the vulnerability to enzymatic attack.[63] The problem with the aforementioned monolithic unit system is that it tends to be detained at the ileocecal junction, leading to drug loss before entry in the colon. To circumvent this problem, multiparticulate dosage forms were devised that passed freely through the ileocecal junction. In a recent study, a multiparticulate system, which was based onamidated pectin, was tested.[64] Coating of the amidated pectin beads with chitosan significantly reduced the release of sulfamethoxazole and indomethacin in simulated gastricand intestinal juice compared with non-coated beads. Macleod et al.[65] have studied the potential of pectin: chitosan: hydroxypropylmethylcellulose films for colonic drug delivery.[65] The results showed that in all cases, the tablets were able to pass through the stomach and small intestine intact. The tablets started to break up once they were in the colon, as a result ofdegradation of the coating by colonic bacteria. Kopecek and coworkers (Fig. 7) [66] have developed novel types of hydrogel capsules, based on acrylic acid, N,N-dimethylacrylamide and N-tert-butylacrylamide cross-linked with 4,40-di(methacryloylamino)azobenzene.[67] These hydrogels did not swell significantly in the stomach. However, in transit through the small intestine, swelling increased because of increased pH. In the colon, the degree of swelling reached a threshold when the cross-links became accessible to bacterial azoreductases, which in turn, caused the breakdown of the hydrogel and release of the drug. The rate of degradation was found to be directly related to the equilibrium degree of swelling of the hydrogels and inversely proportional to the cross-linking density. Hydrogels prepared by cross-linking polymerization but having the same polymer composition and cross-link structure predominantly followed a bulk degradation like process. In contrast, hydrogels prepared by crosslinking polymeric precursors or by a polymer–polymer reaction predominantly followed a surface erosion process at a low degree of cross-linking and a bulk degradation-like process when the degree of crosslinking increased.[68] In a comparative study to determine the degradation rate of the azo functionality present in a soluble azo polymer and a hydrogel, it was observed that the degradation rate was 125 times lower than that of the soluble azo dye. Hydrogels of dextran that used diisocyanate as the cross-linking agent ware found to be capable of releasing a drug only in the distal part of the colon, where the conditions for absorption are not as conducive as the proximal part.[69] pH-sensitive dextran hydrogels were prepared by activation of dextran (T-70) with 4-nitrophenyl chloroformate, followed by conjugation of the activated dextran with 4-aminobutyric acid and cross-linking with 1,10-diaminodecane.[70] The release rate of bovine serum albumin from this system was further enhanced by the addition of dextranase in buffer solutions. However, in a study in which Hirsh et al.[71] investigated lauroyldextran and crosslinked galactomannam as microbiologically degradable film-coating materials for site-specific drug delivery to the colon, the ideal zero-order dissolution before and quick degradation after enzyme addition was not realized. On the other hand, hydrogels made by copolymerization of 2-hydroxyethyl methacrylate with 4-methacryloyl-oxyazobenzene led to the release of aniline when the hydrogel was degraded by the colonic bacterial enzymes.[72] Another study reportedthe biodegradable properties of guar gum, which was cross-linked with borax.

[73] This system was found to be capable of releasing drugs in the proximal part of the colon. Hydrogels that are based on natural products are more acceptable from the standpoint of toxicityrelated issues and are therefore preferable to azo-based polymers. However, chemical derivatization, if performedwithout proper understanding, can lead to modifications of the hydrogels to products that willnot degrade readily in the colon because it is possible that the new structures will not be recognized by the colonic bacterial enzymes for degradation. Also, bulk degradation is preferred to surface erosion because it leads to a more rapid rate of drug release. The one major drawback with the use of hydrogels and matrix systems is that only a limited amount of drug can beincorporated. Thus, when a large amount of drug is required at the target site in the colon, this may not be the most suitable carrier.

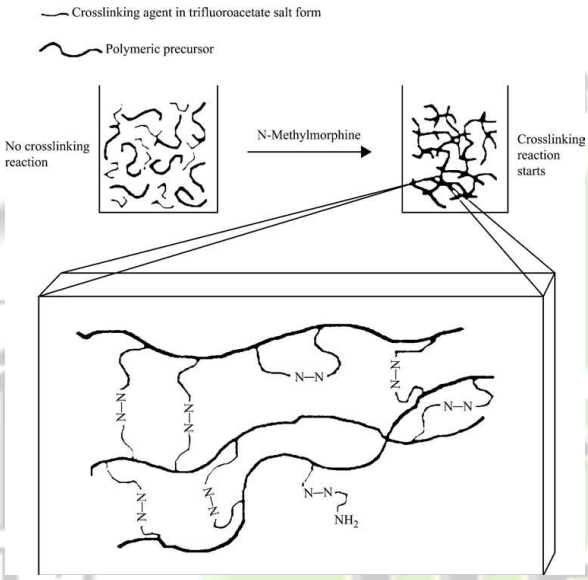


Fig. 7 Schematic representation of the synthesis of hydrogels by cross-linking of polymeric precursors. (Adapted from Ref.[66].)

Conclusion:-In this review we studied about the different colon approaches ,diseases and different polymers which is used to deliver the drug molecule into the colon.Frm this it Is concluded tht colon is the promising site for drug delivery with the help of different approaches and different polymers.It is also beneficial for the local action of the drug for the diseases of colon.

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