WORLD JOURNAL OF PHARMACY AND PHARMACEUTICAL SCIENCES
SJIF Impact Factor 7.421
Volume 8, Issue 2, 336-359 Review Article ISSN 2278 – 4357

ALTERNATIVE APPROACH TO CURRENT MANAGEMENT STRATEGIES IN ULCERATIVE COLITIS

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Article Received on
30 Nov. 2018,

Revised on 21 Dec. 2018,
Accepted on 11 Jan. 2019

DOI: 10.20959/wjpps20192-13091

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ABSTRACT

The colon is a site where both the local and systemic delivery of drug takes place. Ulcerative colitis is a chronic idiopathic inflammatory disease of GIT which affects mucosal lining of the colon. Problem related to the colonic formulation can be overcome by optimizing various therapeutic strategies. This review compares primary approach for colon targeted drug delivery, some newer approaches including possible polymers used. It triggers the use of some innovative therapeutic strategies for the development of formulation for colon targeted diseases. The limitations of traditional colon targeted delivery system may be overcome by understanding these better approaches having the careful understanding of the clinical particularities of disease. The future management of ulcerative colitis appears promising as new promising therapies continue to evolve. The therapeutic avenues which are thought out of the box may provide better treatment and quality of life for patient with this disabling disease and it could foster the development of future avenues for translational research.

KEYWORDS: Ulcerative colitis, new therapeutic approaches, polymers.

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 drug delivery system and these systems have more advantages due to patient acceptance and ease of administration.[1-3] During the last decade there has been interest in developing site-specific formulations for targeting drug tothe colon. Colonic drug delivery has gained increased importance not just for the delivery of thedrugs for the treatment of local diseases associated with the colon like crohn's disease, ulcerative colitis,

irritable bowel syndrome but also for the systemic delivery of proteins, therapeutic peptides, antiasthmatic drugs, antihypertensive drugs and antidiabeticagents.[4,5] 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.[6,7] Coating of the drugs with pH-sensitive polymers providessimple approach for colon-specific drug delivery.

Advantages of colon targeting drug delivery system[8–10]

- Colon is an ideal site for the delivery of agentsto cure the local diseases of the colon.
- Local treatment has the advantage of requiringsmaller drug quantities.
- Reduces dosage frequency. Hence, lower costof expensive drugs.
- Possibly leading to a reduced incidence of sideeffects and drug interactions.
- The colon is an attractive site where poorly absorbeddrug molecules may have an improvedbioavailability.
- Reduce gastric irritation caused by manydrugs (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 appearshighly responsive to agents that enhance theabsorption of poorly absorbed drugs.[11]
- It has low hostile environment, less peptidaseactivity so peptides, oral vaccines, insulin, growth hormones, can be given through thisroute.[12]

Limitations of colon targeting drug delivery system

- Multiple manufacturing steps.
- The resident microflora could also affect colonicperformance via metabolic degradationof the drug.
- Incomplete release of drug.
- Bioavailability of drug may be low due to potentiallybinding 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[13]
- 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[14,15]

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 [16]

COLONIC DISEASES

Angiodysplasia

Tortuous dilution of sub-mucosal and mucosal blood vessels are 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, althoughthey 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) [17].

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, Cytomegalo virus, 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 inflammatorybowel disease (IBD). The main drugs used in the treatment of ulcerative colitis and Crohn's disease are the amino

salicylates and corticosteroids.[18] These diseases and other inflammatory bowel disease have been linked with an increased risk of colorectal cancer.

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 1).

Table no 1.[19]

SN	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	Asaco	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	Hyosinebutylbromide
8	COLOSPA	Solvay, India	Irritable colon syndrome	Mebeverine
9	CYCLOMINOL	Neol, India	Irritable colon syndrome	Diclomine
10	Eldicet	Solvay, India	Irritable colon syndrome, spastis 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

Table no 2.[20]

E1	Ulcerative proctitis	Involvement limited to the rectum (that is, proximal extent of inflammation is distal to the rectosigmoid junction
E2	Left sided UC (disal UC)	Left sided UC (disal UC) Involvement limited to a proportion of the colorectum distal to the splenic flexure
E3	Extensive UC (pancolitis)	Extensive UC (pancolitis) Involvement extends proximal tothe splenic flexure

Treatment[21,22]

The following are the categories of drugs prescribed to treat UC:

1. Antibiotics

Metronidazole, ciprofloxacin, and other antibiotics may be used when infections occur, or to treat complications of ulcerative colitis.

2. Aminosalicylates (5-ASAs)

Given either orally or rectally, these drugs work to decrease inflammation in the lining of the intestines and are usually used to treat mild to moderate UC symptoms.

3. Corticosteroids (Steroids)

Given orally, as an injection, rectally, or intravenously, these medications help reduce inflammation by suppressing the immune system and are usually given to help with moderate to severe UC symptoms. Steroids are not intended for long-term use; they are best suited for short-term control of IBD symptoms and disease activity. If not used appropriately, patients can become steroid dependent or resistant.

Eg:-prednisolone, hydrocortisone, methylprednisolon

4. Immune modifiers (Immunomodulators)

Given orally or injected, these medications suppress the body's immune response so that it cannot cause ongoing inflammation.

Eg:-Azathioprine, mercaptopurine, Methotrexate, cyclosporine, calcinurin inhibitor, Mycophenolatemoefetil

5. Biologicaltherapies (Biologics)

Given intravenously or injected, this class of drugs suppresses the immune system to reduce inflammation by targeting a specific pathway, and is usually given to people who have not responded to conventional therapy.

Eg:-Monoclonal antibodies—Infliximab,TNF-a.

Nonprescription medications

Depending on ulcerative colitis symptoms, over-the-counter (OTC) medications may be recommonded such as:

- Antidiarrheals:-Ioperamide,Orcodein
- Pain relievers
- Nutritional supplements

Approaches used for Site Specific Drug Delivery to Colon (CDDS)[23]

Several approaches are used for site-specific drug delivery. Among the primary approaches for CDDS, These include:

Primary Approaches for CDDS

pH Sensitive Polymer Coated Drug Delivery to the Colon:- Use of pH dependent polymers is based on these differences in pH levels.[24]

Delayed (Time Controlled Release System) Release Drug Delivery to Colon Time controlled release system (TCRS) such as sustained. delayed release dosage forms are also very promising drug release systems.[25]

Microbially Triggered Drug Delivery to Colon:-the presence of the biodegradable enzymes only in the colon, the use of biodegradable polymers for colon-specific drug delivery seems to be a more site-specific approach as compared to other approaches.[26] On reaching the colon, they undergo assimilation by micro-organism, or degradation by enzyme or break down of the polymer back bone and release the drug at the targeted site to give therapeutic effect.

1. Prodrug Approach for Drug Delivery to Colon- For colonic delivery, the prodrug is designed to undergo minimal hydrolysis in the upper tracts of GIT, and undergo enzymatic hydrolysis in the colon there by releasing the active drug moiety from the drug carrier.
2. Azo-Polymeric Prodrugs:- Newer approaches are aimed at the use of polymers as drug carriers for drug delivery to the colon.
3. Polysaccharide Based Delivery Systems.

Newly Developed Approaches for CDDS

a. Pressure Controlled Drug-Delivery Systems

b. Novel Colon Targeted Delivery System (CODESTM)

c. Osmotic Controlled Drug Delivery (ORDS-CT)

a. Pressure Controlled Drug-Delivery Systems

As a result of peristalsis, higher pressures are encountered in the colon than in the small intestine. Takaya et al. developed pressure controlled colon-delivery capsules prepared using

ethylcellulose, which is insoluble in water.[27] In such systems, drug release occurs following the disintegration of a water-insoluble polymer capsule because of pressure in the lumen of the colon. The thickness of the ethylcellulose membrane is the most important factor for the disintegration of the formulation.[28,29] The system also appeared to depend on capsule size and density. Because of reabsorption of water from the colon, the viscosity of luminal content is higher in the colon than in the small intestine. It has therefore been concluded that drug dissolution in the colon could present a problem in relation to colon-specific oral drug delivery systems. In pressure controlled ethylcellulose single unit capsules the drug is in a liquid.[30]Lag times of three to five hours in relation to drug absorption were noted when pressure-controlled capsules were administered to humans.

b. Novel Colon Targeted Delivery System (CODESTM) CODESTM is an unique CDDS technology that was designed to avoid the inherent problems associated with pH or time dependent systems.[31,32] CODESTM is a combined approach of pH dependent and microbially triggered CDDS. It has been developed by utilizing a unique mechanism involving lactulose, which acts as a trigger for site specific drug release in the colon, (Fig. 2). The system consists of a traditional tablet core containing lactulose, which is over coated with and acid soluble material, Eudragit E, and then subsequently overcoated with an enteric material, Eudragit L. The premise of the technology is that the enteric coating protects the tablet while it is located in the stomach and then dissolves quickly following gastric emptying. The acid soluble material coating then protects the preparation as it passes through the alkaline pH of the small intestine.[33] Once the tablet arrives in the colon, the bacteria enzymetically degrade the polysaccharide (lactulose) into organic acid. This lowers the pH surrounding the system sufficient to effect the dissolution of the acid soluble coating and subsequent drug release

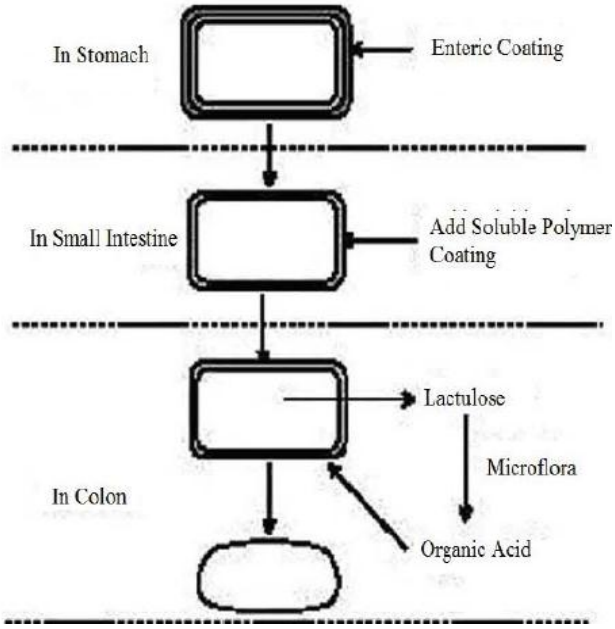

Fig 1: Schematics of the conceptual design of CODES.

c. Osmotic Controlled Drug Delivery (ORDS-CT) The OROS-CT (Alza corporation) can be used to target the drug locally to the colon for the treatment of disease or to achieve systemic absorption that is otherwise unattainable.[34] The OROSCT system can be a single osmotic unit or may incorporate as many as 5-6 push-pull units, each 4 mm in diameter, encapsulated within a hard gelatin capsule, (Fig. 3).[35] Each bilayer push pull unit contains an osmotic push layer and a drug layer, both surrounded by a semipermeable membrane. An orifice is drilled through the membrane next to the drug layer. Immediately after the OROSCT is swallowed, the gelatin capsule containing the push-pull units dissolves. Because of its drug-impermeable enteric coating, each push-pull unit is prevented from absorbing water in the acidic aqueous environment of the stomach, and hence no drug is delivered. As the unit enters the small intestine, the coating dissolves in this higher pH environment (pH >7), water enters the unit, causing the osmotic push compartment to swell, and concomitantly creates a flowable gel in the drug compartment. Swelling of the osmotic push compartment forces drug gel out of the orifice at a rate precisely controlled by the rate of water transport through the semipermeable membrane. For treating ulcerative colitis, each push pull unit is designed with a 3-4 h post gastric delay to prevent drug delivery in the small intestine. Drug release begins when the unit reaches the colon. OROS-CT units can maintain a constant release rate for up to 24 hours in the colon or can deliver drug over a period as short as four hours. Recently, new phase transited systems have come which promise to be a good tool for targeting drugs to the colon.[36-38]

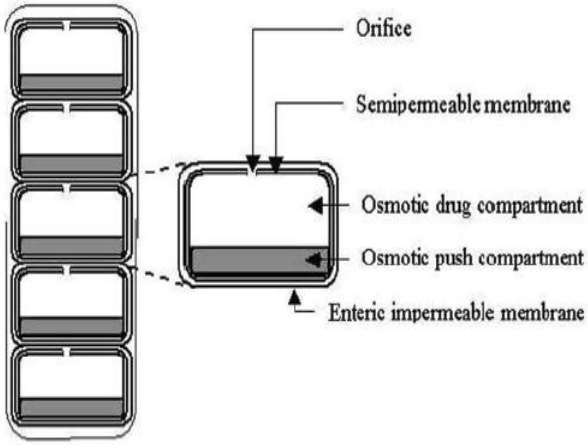

Fig 2: Cross sectionof the OROS-CT colon targeted drug delivery system.

Polymers for Colon Targeted Drug Delivery

To reach the colon and release the drug, a dosage form must be formulated taking into account various obstacles introduced by the gastrointestinal tract. Successful delivery of a drug to the colon requires protection of the drug from degradation or release in the stomach and then controlled release of drug in colon.[39,40] The desired properties of colon targeted drug delivery systems can be achieved by using some polymers either alone or in a combination because it is now recognized that polymers can potentially influence the rate of release and absorption of drugs and play an important role in formulating colon targeted drug delivery systems.

BIODEGRADABLE POLYMERS

Natural polysaccharides are extensively used for the development of solid oral dosage forms for colonic delivery of drugs.[41] Biodegradable polymers are generally hydrophilic in nature and have limited swelling characteristic in acidic pH. Various bacteria present in the colon secretes many enzymes which can cause hydrolytic cleavage of glycosidic bonds e.g. β-D-galactosidase, amylase, pectinase, β-D- glucosidase, dextranase, α-D-xylosidase These polymers are inexpensive and are available in a variety of structures.

Guar gum

Guar gum is derived from the seeds of the *cyomopsistetragonolobus* (Fam. Leguminosae). Chemically, guar gum is a polysaccharide composed of the sugars galactose and mannose. The backbone is a linear chain of β 1,4-linked mannose residues to which galactose residues are 1,6-linked at every second mannose, forming short side-branches (fig. 3).[42] Guar gum is used in colon targeted drug delivery systems due to its drug release retarding property and

susceptibility to microbial degradation in large intestine. guar gum, in the form of directly compressed matrix tablets, is a potential carrier for colon-specific drug delivery.

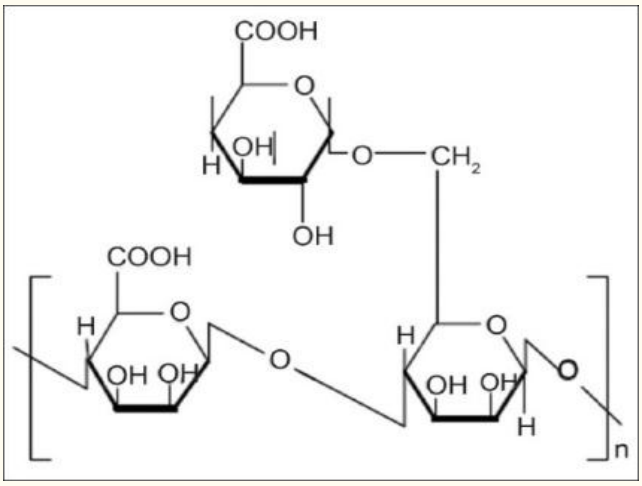

Fig. 3: Structure of Guar Gum.

Pectin

Pectin is a linear, heterogeneous polysaccharide which is mainly composed of galacturonic acid and its methyl ester. These are predominantly linear polymers of mainly (1→4) linked D-galacturonic acid residue interrupted by 1,2-linked L-rhamnose residue with a few hundred to about one thousand building blocks per molecule.[43] (fig. 4) It is one of the major sources of dietary fiber and is extracted from fruit and vegetable cell walls.

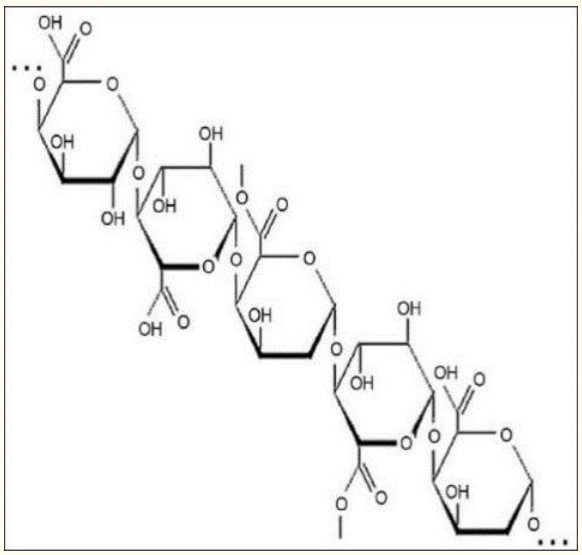

Fig. 4: Structure of Pectin.

A novel colon targeted tablet formulation using pectin as a carrier and diltiazem hydrochloride and indomethacin as model drugs has been developed.[44] *In vitro* study showed

that prepared dosage forms have limited drug release in stomach and small intestine and released maximum amount of drug in the colon. The study revealed that pectin can be used effectively for colon targeting of both water soluble and insoluble drugs.

Calcium/zinc pectinate is a less water soluble pectin salt used in fabrication of colonic delivery system.[40] pectin microspheres prepared by spray drying and crosslinking methods are potential carriers for colon-specific drug delivery.[45]

Chondroitin Sulfate

Chondroitin sulfate is a soluble mucopolysaccharide that is used as a substrate by *Bacteroides* species in the large intestine mainly by *B. thetaiotaomicron* and *B. ovatus*. Chondroitin sulfate consist of β-1,3-D-glucuronic acid linked to N-acetyl-D-galactosamide(fig. 3). Natural chondroitin sulfate is cross linked and readily water soluble but it may not be able to sustain the release of most drugs from the matrix.[40,46]Chondroitin sulfate is degraded by the anaerobic bacteria of the large intestine mainly by *Bacteroidsthetaiotaoimicron* and *B. ovatus*[47]

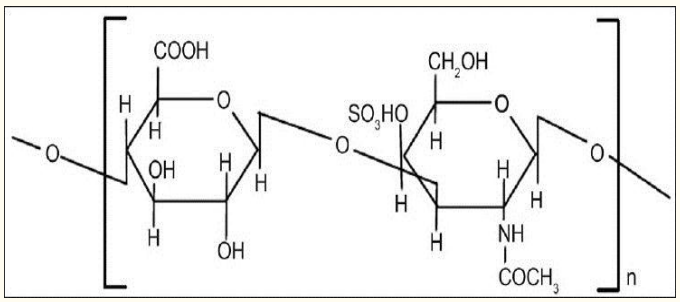

Fig. 5 Structure of chondroitin sulfate.

Chondroitin sulfate is highly water soluble and this property act as a barrier in the formulation of the colon targeted drug delivery. Rubinstein *et al*.[48] cross linked chondroitin sulfate with 1,12-diaminododecane. The cross linked chondroitin sulfate was used as a carrier for indomethacin specifically for the large bowel. Cross linking took place between the carboxyl group in chondroitin and the amino group in diaminododecane and formed a dimer of chondroitin sulfate. The degree of cross linking was determined by measuring the amount of methylene blue which was adsorbed as a result of cation exchange. The cross linked polymer was mixed with indomethacin and compressed into tablets. An enhanced release was observed on incubation with rat cecal contents.

Dextran

Dextran is a polysaccharide consisting of α-1,6 D-glucose and side chain of α-1,3 D-glucose units (fig. 6)[41,46] These highly water soluble polymers are available commercially as different molecular weights with a relatively narrow molecular weight distribution. Dextran contains a large number of hydroxyl groups, which can be easily conjugated to drugs and proteins. Dextran gets degraded by the microbial enzyme dextranases, which is found in the colon.[49]Pharmacodynamically, conjugation with dextran has resulted in prolongation of the effect, alteration of toxicity profile, and a reduction in the immunogenicity of drug.

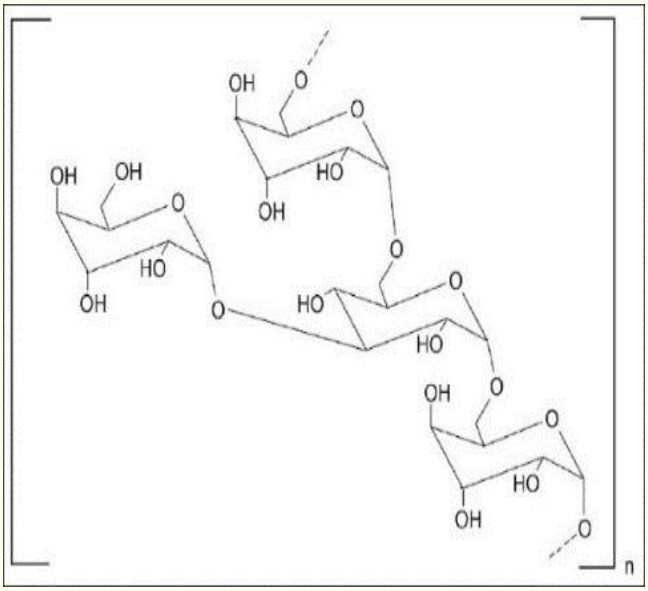

Fig. 6: Structure of dextran.

Dextran was oxidized using sodium periodate and coupled the aldehyde product with the α-amino group of 5-amino salicylic acid (5-ASA). [50] It was reported that less oxidized dextran yields the minimum 5-amino salicylic acid conjugation, which were susceptible to dextranase hydrolysis while highly oxidized dextran yields the maximum 5-ASA conjugation, which were resistant to dextranase hydrolysis. Therefore, it was concluded that dextran can potentially be used to treat bowel inflammatory diseases. McLeod *et al*. synthesized glucocorticoid-dextran conjugates in which dexamethasone and methylprednisolone were attached to dextran using dicarboxylic acid linkers (succinate and glutarate). [51] Dextran conjugates resisted hydrolysis in upper GI tract contents but were rapidly degraded in cecal and colonic contents where the bacterial count is high. The results of this study indicate that dextran conjugates may be useful in selectively delivering glucocorticoids to large intestine for the treatment of colitis.

Chitosan

Chitosan is functional linear polymer obtained from the alkaline deacetylation of chitin. Chitosan is consisting of the repeated units of (2-amino-2-deoxy-D-gluco-pyranose) which are linked by (1-4) β-bonds (fig. 7)[41,46] Chitosan is a nontoxic, biodegradable, biocompatible and bioactive polymer. Chitosan is used as excipient and drug carrier in drug delivery systems. Chitosan is used for the colon targeted drug delivery because it has a tendency to dissolve in acidic pH of stomach but get swollen in the intestinal pH.

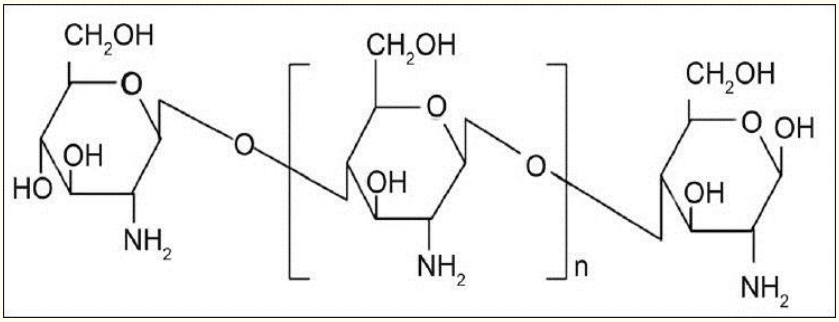

Fig. 7: Structure of chitosan.

Lorenzo-Lamosa *et al.*[53] designed a system consist of chitosan microcores entrapped within acrylic microspheres for the colonic delivery of sodium diclofenac. The drug was efficiently entrapped within chitosan microcores using spray-drying and then microencapsulated into Eudragit. The release rate was adjustable by changing the chitosan molecular weight or the type of chitosan salt. Furthermore, by coating the chitosan microcores with Eudragit, perfect pH-dependent release profiles were attained. A combined mechanism of release is proposed, which considers the dissolution of Eudragit coating, the swelling of chitosan microcores and the dissolution of sodium diclofenac and its further diffusion through the chitosan gel cores. This work presented new approaches for the modification of chitosan as well as a new system with a great potential for colonic drug delivery.

Chitosan capsules were used for colonic delivery of an antiulcerative colitis drug. 5-Aminosalicylic acid (5-ASA) was used as model drug. A marked increase in the release of drug from chitosan capsule was observed in the presence of the rat cecal content. From the results of this study it was concluded that chitosan capsules could be an effective carrier for the colon targeted delivery of antiinflammatory drugs.[54]

Cyclodextrin

Cyclodextrin is a cyclic oligosaccharide consisting of six to eight glucopyranose units joined by α-(1→4) glucosidic linkage (fig. 8). These are potential high performance carrier molecules that have the ability to alter physical, chemical and biological properties of the drug molecule through the formation of inclusion complexes. Cyclodextrins consist of six, seven or eight glucose monomers arranged in a ring shape and these are denoted as α-cyclodextrin, β-cyclodextrin and γ-cyclodextrin, respectively.

Cyclodextrins consist an internal lipophilic cavity, which can make complex with hydrocarbon materials. Cyclodextrins are slowly hydrolysable in upper gastrointestinal tract while it gets fermented to small saccharides by colonic microflora and get absorbed in large intestine. Cyclodextrins are used to improve the drug properties such as solubility, stability, bioavailability[41,46]

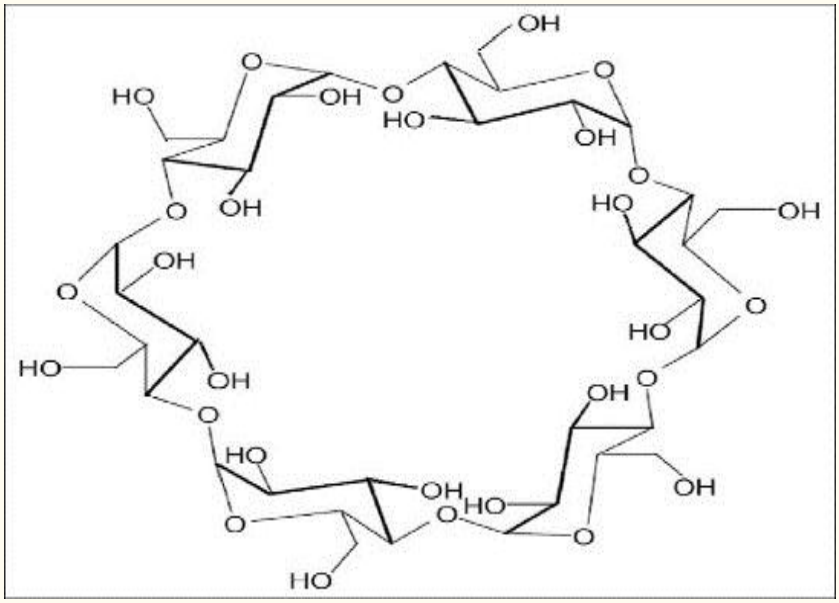

Fig:-8 Structure of α-cyclodextrin.

Inulin

Inulin is a naturally occurring glucofructan and consists of β 2-1 linked D-fructose molecule having a glycosul unit at the reducing end (fig. 9). It can resist the hydrolysis and digestion in the upper gastrointestinal tract. Inulin can be fermented by colonic microflora. Vervoort *et al*[]developed inulin hydrogels for colonic delivery of drugs and swelling property of these hydrogels was investigated.[55] The influence of various parameters such as the degree of substitution, feed concentration of methacrylated inulin, varying concentrations of the

initiators of the polymerisation reaction, the effect of pH, ionic strength on the swelling property of hydrogels were studied. In another study Vervoort and Rombaut[56] investigated the *in vitro* enzymatic digestibility of the inulin hydrogels using an inulinase preparation derived from *Aspergillus niger*. It was concluded that the inulinase enzyme can diffuse into the hydrogels resulting in the degradation of the hydrogels.

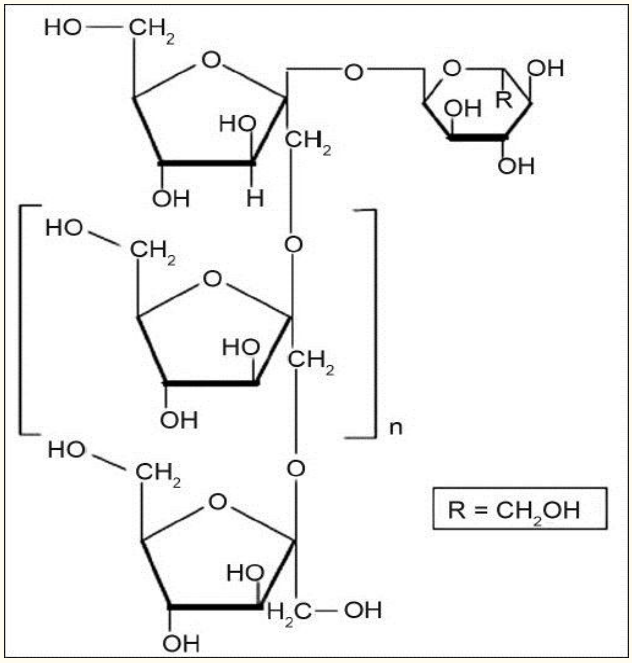

Fig. 9: Structure of inulin.

Amylose

Amylose is the polysaccharide which is obtained from the plant extracts and a component of starch. Amylose is unbranched linear polymer of glucopyranose units (α-1,4-D-glucose) linked through α–D-(1-4) linkage (fig. 10). Amylose is resistant to pancreatic amylases in its glassy amorphous form but it gets degraded by the bacteroids, bifidobacterium.

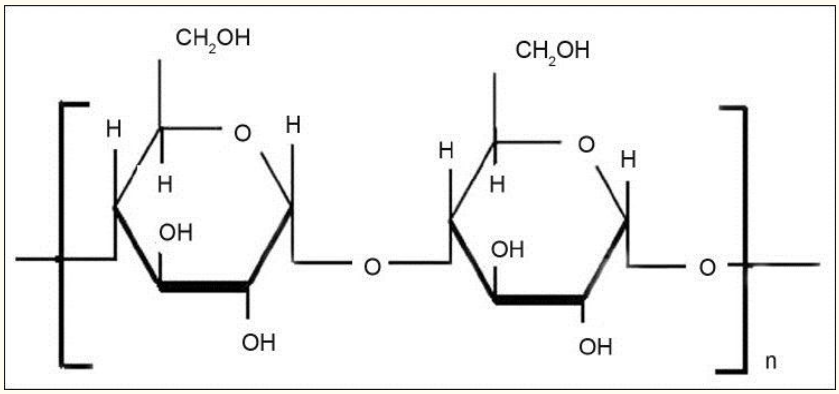

Fig.10 Structure of amylose.

Amylose can form film by gelation, which can be used for tablet coating purpose. But coating made up of amylose solely becomes porous and release the drug under simulated gastrointestinal conditions. To avoid this problem, water insoluble polymers are added to the amylose film as these water insoluble polymers control the amylose swelling. Addition of ethylcellulose to amylose gives a suitable polymer mixture for colon targeting. *In vitro* dissolution of various coated pellets was performed under simulated gastric and simulated intestinal conditions and it was concluded that amylose:ethylcellulose coat (1:4) resist these conditions over a period of 12 hr.[57] Pellets were prepared by extrusion and spheronisation using glucose as model drug.[58]

Locust bean gum

Locust bean gum contains natural polysaccharides which have a molecular weight of 310000. Locust bean gum is also known as 'Carob gum' as it is derived from the endosperm of the seed of the 'Carob' (*Ceratonia Siliqua Linne*, Fam: Leguminosae). It is irregular shaped molecule with branched β-1,4-D-galactomannan units. Locust bean contains about 88% D-galacto-D mannoglycan, 4% of pentane, 6% of protein, 1% of cellulose and 1% of ash.

Studies on the polysaccharides done by Raghavan *et al*. proved that the combination of locust bean gum and chitosan, as a coating material, is capable of protecting the core tablet containing mesalazine during the condition mimicking mouth to colon transit. The coating was susceptible to the colonic bacterial enzymes which causes the release of drug. It was concluded that the formulation containing locust bean gum and chitosan in the ratio of 4:1 held a better dissolution profile, higher bioavailability and hence a potential carrier for drug targeting to colon[59]

Interest in the biodegradable polymers is increasing day by day because these are safe, non-toxic, economic and are chemically compatible with the other excipients in the formulation. the various types of biodegradable polysaccharides that have already been used in the initial approaches for colon specific drug delivery. Polysaccharides exhibit favorable properties for fabrication of colonic delivery system. The colon is rich in harboring excellent microflora, which can be used for targeting of drug release to colon. Formulation containing the microbial degradable polymers passes intact from the upper GIT and release the drug in the colon. Thus polysaccharides appear to be promising agents for obtaining colon-specific drug delivery systems.[60\]

Innovative therapeutic targets in UC

Reinforcing the mucosal barrier

The normal mucosal barrier is composed of a mucus layer, epithelial cells (including goblet cells and Paneth cells) and non-epithelial cells and intercellular and tight junctions, all intrinsically interconnected and working together to synthesise antimicrobial peptides and prevent luminal antigens and pathogenic organisms from invading the underlying lymphoid tissue. Disturbance of this barrier integrity is undoubtedly a key step in the pathogenesis of UC. Barrier dysfunction enables the influx of luminal antigens, which will continuously trigger immune cells in the lamina propria resulting in chronic inflammation.Restoring altered barrier function is therefore a strong potential therapeutic target in UC.

Phosphatidylcholine (PC)

The mucus layer coating the gastrointestinal (GI) tract is predominantly composed of water, glycoproteins, lipids, other proteins and nucleic acids.[61] Phospholipids, although minor constituents of the GI mucus, are indispensable for the maintenance of an intact barrier function where they play a role in establishing the hydrophobic surface by virtue of their amphipathic nature.[62] Phosphatidylcholine (PC), the major mucus phospholipid, has been found to be substantially reduced in the mucus of patients with UC compared with patients with Crohn's disease (CD) and healthy controls, independent of the state of inflammation.[61,63] A lack of PC could result in a reduction in surface hydrophobicity, enabling the invasion of luminal noxious agents. Therefore, it has been hypothesised that PC reconstitution in the colonic mucus of patients with UC could help to restore the structure and density of the mucus, improving the barrier function and preventing inflammation in UC.[64]

Peroxisome proliferator-activated receptor gamma agonists

Peroxisome proliferator-activated receptor gamma (PPARγ) is a nuclear receptor originally identified for its role in controlling the expression of a large number of regulatory genes involved in lipid metabolism, adipocyte differentiation and insulin sensitisation. More recently, high PPARγ expression has been reported in the gut, particularly in colonic epithelial cells where microorganisms such as bacteria and yeast are able to increase its expression and/or activation.[65] PPARγexpression is impaired in colonic epithelial cells of patients with UC, both in diseased and healthy mucosa, and negatively correlated with the severity of endoscopic disease activity.[65,66]

Endoplasmic reticulum stress

Within the colonic mucosa, goblet cells play a central role in epithelium protection.[67] decrease in mucosecretion is a histological pattern of UC. ER stress is a highly regulated physiological mechanism that allows the cell to adapt and survive through the activation of the three proximal sensors (IRE1, ATF6 and PERK) that sense the accumulation of misfolded proteins in response toenvironmental changes (infection, ischaemia, nutrients).[68] Impairment of proper ER stress resolution induces proinflammatory responses and ER stress-dependent apoptosis. impairment of ER stress resolution leads to spontaneous enteritis and colitis.[69,70,71]

Improving hypoxia-related pathways

There is a close relation between hypoxia, microvascular dysfunction and inflammation in IBD.Hypoxia is believed to activate NF-κB in intestinal epithelial cells. This leads to increased production of TNFα and expression of Toll-like receptors, which stimulates leucocyte recruitment, phagocytosis and adaptive immunity. Additionally, hypoxia-inducible factorImproving hypoxia-related pathways.[72,73]

CONCLUSION

The disturbed mucosal barrier is an initiating factor, and subsequent attacks from colonic commensal bacteria by a continuous, hydrophobic and adherent mucus layer in Ulcerative colitis. Problem related to the colonic formulation can be overcome by optimizing various therapeutic strategies. This review triggers the use of some innovative therapeutic strategies for the development of formulation for colon targeted diseases. The limitations of traditional colon targeted delivery system may be overcome by understanding these better approaches having the careful understanding of the clinical particularities of disease. The future management of ulcerative colitis appears promising as new promising therapies continue to evolve. The therapeutic avenues which are thought out of the box may provide better treatment and quality of life for patient with this disabling disease and it could foster the development of future avenues for translational research. Phosphatidylcholine (PC) is largely responsible for protective hydrophobic surface and therefore plays the key role in mucosal defense. Reduction of the PC in the colonic mucus impairs the mucosal barrier, thus in the treatment incorporating it may give synergistic effect. This will surely help in restoration of the bacterial flora, ease of enzymatic degradation and release of drug in colon and a better absorption of drug through colon.

ACKNOWLEDGEMENTS

Authors are thankful to Gurunanak College of Pharmacy.

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