1. Introduction

Ulcerative colitis (UC) is a chronic, immunologically-mediated disorder which affects the gastrointestinal tract. This disease is characterized by inflammation of the colonic or rectal mucosa, leading to rectal bleeding, diarrhea, and abdominal pain. UC, along with Crohn’s disease, is referred to as inflammatory bowel disease. The specific cause of this disease is unknown, but research has suggested that it is most likely initiated by a combination of host susceptibility and environmental triggers. These factors lead to an overly-aggressive T-cell response to bacteria in the gastrointestinal tract. An abnormal ratio between beneficial and detrimental microbes in the gut may also contribute to the development of this disease, as well as defects in the function of the intestinal mucosal barrier. No medical cure has been developed for UC; treatment focuses on inducing and maintaining remission (Sartor, 2006). Anti-inflammatory drugs, particularly those that contain 5-aminosalicylic acid (5-ASA), are often used to treat UC. The effectiveness of these aminosalicylate drugs is related to their mucosal concentration. Because free 5-ASA is rapidly absorbed in the small intestine, this drug must be encapsulated or conjugated to be effectively delivered to the colon. Methods for colonic delivery of 5-ASA include chemically attaching it to a carrier molecule or encapsulating it with pH or time-release polymers, but these methods exhibit various limitations (Caprilli et al., 2009).

The use of polysaccharides as conjugate or encapsulation materials has been explored as a means of targeting the delivery of 5-ASA to the colon. The purpose of this chapter is to discuss approaches to using polysaccharides as colon-targeted drug delivery systems, and to discuss how using polysaccharides in these drug formulations may provide therapeutic benefits beyond drug delivery.

1.1 Aminosalicylates in UC treatment

Aminosalicylates were the first drugs that were shown to be effective against UC. The first of this class of drugs was sulphasalazine. At the time of this drug’s development, it was thought that both rheumatoid arthritis and UC were caused by streptococcal infection and that UC symptoms began in the connective tissue of the submucosa. Sulphasalazine was developed by combining sulphapyridine, which was effective against bacteria, with 5-ASA,
which was active on connective tissue. Sulphasalazine was shown to improve both rheumatoid arthritis and UC. At the recommended dose of 500mg 4 to 6 times per day, however, approximately 15 to 20% of patients experienced side effects such as headaches, nausea, vomiting, fever, cyanosis, allergic reactions, jaundice, leucopenia and agranulocytosis (Caprilli et al., 2009). Later research demonstrated that 5-ASA was the part of sulphasalazine responsible for the drug’s therapeutic effects against UC. Enemas of sulphasalazine, 5-ASA and sulphapyridine were given to patients with UC. Improvement was seen in only 5% of patients receiving sulphapyridine, as opposed to 30% of those receiving either sulphasalazine or 5-ASA (Azad Khan et al., 1977). This discovery paved the way for other 5-ASA-containing drugs developed for the treatment of UC. Today, aminosalicylates are still the standard therapy for the induction and maintenance of remission in UC patients (Hanauer, 2004).

1.2 Mechanism of therapeutic action of aminosalicylate-containing drugs
Aminosalicylate drugs are able to decrease the symptoms of UC, although the exact mechanism by which they act is unknown. Aminosalicylates have a demonstrated inhibitory effect on pro-inflammatory mediators released by the colonic and rectal mucosa. 5-ASA can interact with the peroxisome proliferator activated receptor γ, which acts to inhibit the mucosal production of inflammatory cytokines (Caprilli et al., 2009). 5-ASA also exhibits antioxidant properties, and can act as a free radical scavenger (Osterman & Lichtenstein, 2009).

Aminosalicylates act at the site of inflammation topically; the effectiveness of 5-ASA-containing drugs is linked directly to their mucosal concentration. Therefore, it is necessary that aminosalicylates be delivered effectively to the colon. Delivery can be performed by administering the drug rectally or orally. When free 5-ASA is delivered orally, however, it is absorbed in the upper gastrointestinal tract, and does not reach the colon. Therefore, the drug must be protected in some way in order to ensure that it is delivered to the colon effectively (Caprilli et al., 2009).

2. Current 5-aminosalicylic acid formulations: Varieties and limitations
There are currently four main methods of orally delivering 5-ASA to the colon. These methods are through diazo compounds, pH-dependent formulations, time-controlled release, and a multi-matrix system (Table 1).

In the first method, 5-ASA is attached to a carrier molecule by a diazo bond, which is then split by bacteria in the gastrointestinal tract. Commercial drugs of this type are known as Olsalazine, Balsalazide, and Sulphasalazine (Table 1). Sulphasalazine has been associated with numerous side effects, as explained, while Olsalazine and Balsalazide have not been shown to cause side effects (Sandborn, 2006a).

The pH dependent release system involves an acid-resistant acrylic resin known as Eudragit-s. The acrylic protects the 5-ASA during its passage through the gastrointestinal tract, but is dissolved in the alkaline environment of the colon, releasing the 5-ASA (Dew et al., 1982). Asacol is a commercial drug of this variety. A limitation of this delivery system is that a high degree of variation exists in the pH levels of the gastrointestinal tracts of different individuals, especially for those who are in a diseased state. Also, pH differences between the distal ileum, cecum and proximal colon are small. Therefore, it is difficult to determine exactly where in the gastrointestinal tract the 5-ASA will be released (Hanauer, 2004).

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Example</th>
<th>Site of release</th>
<th>Unit (g)</th>
<th>Dose (g/d)</th>
<th>Active</th>
<th>Remission</th>
<th>Limitations</th>
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</thead>
<tbody>
<tr>
<td><strong>Conjugated</strong></td>
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<tr>
<td>5-ASA linked to sulfapyrazine by azo bond</td>
<td>Sulfasalazine</td>
<td>Colon</td>
<td>0.5</td>
<td>2-6</td>
<td>2-4</td>
<td>Diarrhea</td>
<td></td>
</tr>
<tr>
<td>5-ASA dimer linked by azo-bond</td>
<td>Olsalazine</td>
<td>Colon</td>
<td>0.5</td>
<td>Not effective</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-ASA linked to 4-amino-benzoyl-β-alanine by azo bond</td>
<td>Balsalazide</td>
<td>Colon</td>
<td>0.75</td>
<td>4.6-7.5</td>
<td>4</td>
<td></td>
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<tr>
<td><strong>Encapsulated</strong></td>
<td></td>
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<tr>
<td>Eudragit-S coated tablets</td>
<td>Asacol</td>
<td>Ileum, colon</td>
<td>0.4</td>
<td>1.6-4.8</td>
<td>0.8-1.6</td>
<td>No large change in pH from ileum to colon; pH differences among individuals</td>
<td></td>
</tr>
<tr>
<td>Ethylcellulose-coated microgranules (time-release)</td>
<td>Pentasa</td>
<td>Small intestine, colon</td>
<td>0.25-1.0</td>
<td>2-4</td>
<td>4</td>
<td>Variations in transit time</td>
<td></td>
</tr>
<tr>
<td>Eudragit-L-coated pellets with additional retarding polymer in the pellet core</td>
<td>Mesalamine pellets</td>
<td>Ileum, colon</td>
<td>0.5</td>
<td>1.5-4.5</td>
<td>Not studied</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eudragit-S-coated tablets with lipophilic and hydrophilic matrices in the tablet core</td>
<td>Lialda</td>
<td>Ileum, colon</td>
<td>1.2</td>
<td>2.4-4.8</td>
<td>Not studied</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 1. Aminosalicylate drugs: Examples, limitations, and doses (Sandborn, 2006b; Caprilli et al., 2009)
The time-controlled release system uses a microsphere of ethylcellulose to coat the 5-ASA. The microsphere swells and dissolves slowly as the drug moves through the gastrointestinal tract, releasing the 5-ASA mainly in the duodenum and proximal colon (Rasmussen et al., 1982). Pentasa is the commercial name for this delivery system. As for the pH dependent release system, the major limitation of this drug type lies in patient variation. The time it takes for the drug to travel through the gastrointestinal tract can vary from person to person, leading to a non-specific point of drug release. Moreover, in patients with UC, transit time through the colon can be accelerated, leading to incomplete drug release (Jain et al., 2007).

The newest delivery system developed for 5-ASA is the multimatrix, or MMX system. In this formulation, 5-ASA microparticles are trapped within a lipophilic matrix, which is then dispersed throughout a hydrophilic matrix. This tablet core is then coated with an acid-resistant polymer, which dissolves when the pH is above 7.0. When delivered via the MMX system, the 5-ASA is released beginning in the terminal ileum. This delivery system allows for slow release of 5-ASA along the length of the colon and rectum (Caprilli et al., 2009).

One limitation common to all of the drugs currently used to treat UC is the high dose needed to achieve therapeutic results (Table 1). Because the common dose of these aminosalicylate drugs is 225 to 500 mg per dose, patients may have to take over 10 pills per day in order to treat their conditions. This high pill burden often leads to low compliance rates among patients (Osterman & Lichtenstein, 2009).

All formulations of 5-ASA are metabolized to N-acetyl-5-ASA by the same pathway. A meta-analysis looking at the fecal and systemic (urinary) excretion of N-acetyl-5-ASA using various formulations was carried out. A wide range of excretion amounts was found for each 5-ASA formulation, due to differences in study designs. However, a clear trend was spotted in regard to fecal vs. urinary excretion, based upon whether the patients in the studies had active or quiescent colitis. It was found that patients with active colitis had higher levels of 5-ASA in their feces, while those in remission had higher urinary levels of the drug. This is because UC causes a decrease in transit time through the gastrointestinal tract, providing less time for 5-ASA to be absorbed (Hanauer, 2004). Therefore, higher doses of 5-ASA are required to treat active UC, in comparison to amounts required to maintain remission (Table 1).

3. Polysaccharides for colon-targeted drug delivery

The use of various polysaccharides has been explored as a means of colon-targeted drug delivery. Polysaccharides provide several benefits as carrier molecules or encapsulation materials. They generally have a predictable degradation pattern, allowing for consistent release of the drug from the encapsulation matrix. Polysaccharide matrices also hydrate and swell as they travel through the gastrointestinal tract, creating a barrier against diffusion of the drug. When they arrive at the colon, colonic bacteria and enzymes are able to degrade the polysaccharide matrices to release the encapsulated drug (Wong et al., 2011). Polysaccharides also exist with a wide variety of functional groups, molecular weights, and chemical compositions. Some have a high stability to temperature and heat, while also having high biodegradability and low toxicity. Many polysaccharides are approved as pharmaceutical excipients (Jain et al., 2007).
Polysaccharides have been shown to be useful carrier systems for the delivery of aminosalicylates, in both encapsulation matrices and as conjugate carrier molecules. The rate of drug release can be tailored by controlling the polysaccharide carrier used and the method of preparation of the final 5-ASA-polysaccharide product (Wong et al., 2011).

### 3.1 Encapsulation polysaccharides

Several polysaccharides have been used successfully as encapsulation materials for aminosalicylate drugs, and are discussed below.

#### 3.1.1 Starch

Enteric-coated starch capsules have been studied for the colon-targeted delivery of aminosalicylic acid. In one study, 5-ASA was placed into starch capsules produced by injection moulding, which were then covered with a Eudragit coating. The capsules were evaluated over time for capsule disintegration and drug release in gastric and intestinal media. The capsules were found to be stable in the gastric environment, but were disintegrated between one and two hours following immersion in the intestinal medium (Vilivalam et al., 2000). Another study by the same authors compared the release time of 5-ASA from 5-ASA beads manufactured by extrusion-spheronization. 5-ASA beads in an uncoated starch capsule and 5-ASA beads in an enteric-coated starch capsule yielded similar time release results, but the 5-ASA in the coated starch capsule had the largest lag time in 5-ASA release (Vilivalam et al., 2000).

The amylose portion of starch has also been studied for use as a coating for the delivery of 5-ASA to the colon, and similar results were seen as in the starch coating studies. A resin made of a combination of amylose and ethyl cellulose was used to coat 5-ASA pellets. The coated drug was stable in simulated gastric and small intestine solutions for 12 hours. The 5-ASA was released within 4 hours when placed in a simulated colonic environment (Milojevic et al., 1996).

#### 3.1.2 Pectin

Pectins are polysaccharides consisting of (1→4)-linked α-D-galacturonic acid with intermittent (1→2)-linked α-L-rhamnose units along the backbone with side chains of varying complexity containing galacturonic acid, galactose, rhamnose, arabinose, and other sugars. Most drug delivery studies use commercial pectin, which contains very few side chains (as these are removed during processing and purification). Backbone galacturonic acid units carry with them varying degrees of methylation. Low methyl esterified pectins can cross-link with divalent cations, which is important in encapsulation for drug delivery. Pectins are naturally resistant to gastric and small intestinal enzymes, but are degraded by colonic bacterial enzymes. They are soluble in water, which is a hurdle in the development of pectin-based drug delivery systems. This challenge can be overcome, however, through the choice of pectin type, the use of additives, or the use of accompanying hydrophobic polymers such as ethylcellulose (Jain et al., 2007).

Pectins have been used successfully as matrix materials in several studies (Jain et al., 2007). For example, a pectin matrix cross-linked by calcium ions has been used to successfully deliver chemotherapy drugs to the colon (Wong et al., 2011). Another study found that a compression coat of high methoxy pectin was able to protect a core tablet during mouth to colon transit. The in vitro portion of this study showed that the pectin coat was able to
In vivo scintigraphic (radioactive tracing) results confirmed this, and also showed that the pectin-coated tablets dissolved once they reached the colon (Ashford et al., 1993). A mixture of pectin and chitosan has been shown to give protective results similar to a pectin coating, but with a lower coat weight (Fernandez-Hervas, 1998).

### 3.1.3 Inulin

Inulin is a fructan consisting of 2 to 60 (2→1)-linked β-D-fructose units, with glucose often as the initial moiety of the chain. It is a storage polysaccharide which is found in many plants, including onion, garlic, artichoke and chicory. Inulin is resistant to degradation in the upper gastrointestinal tract, but is preferentially fermented by *Bifidobacteria* in the colon (Jain et al., 2007).

Inulin has been incorporated into Eudragit RS films, which are able to resist degradation in the upper gastrointestinal tract, but are metabolized by beneficial bacteria in the colon. Hydrogels of inulin have also been developed, in which vinyl groups are attached to inulin chains by free radical polymerization to induce intramolecular cross-linking (Van den Mooter et al., 2003). Methacrylated inulin has also been used as a hydrogel for targeted drug delivery. An *in vitro* stability study demonstrated that the higher the degree of substitution of the hydrogels, the more resistant they were to degradation by inulinase (Jain et al., 2007).

### 3.1.4 Galactomannan-containing gums

Galactomannan-containing gums have also been used as encapsulation materials for colon-targeted drug delivery. One such gum is guar gum, which is obtained from the endosperm of *Cyamopsis tetragonolobus*. It is comprised of a mannan backbone with galactose side chains. Guar gum can be used to coat colon-bound drugs by compression, retarding their release. The guar gum is then degraded in the large intestine by microbial enzymes, releasing the drug (Jain et al., 2007).

Alternatively guar gum can used to encapsulate drugs through derivatization of the hydroxyl groups. In one study, guar gum was substituted with carboxymethyl groups, which were then cross-linked with barium ion. This was used as a microencapsulation matrix for a model compound: bovine serum albumin. Very little of the drug was released when the capsules were exposed to a pH of 1.2, simulating the stomach, but the drug was released in a pH of 7.4., simulating the large intestine. The researchers concluded that this formulation would be useful for gastrointestinal drug delivery (Thimma & Tammishetti, 2001).

Locust bean gum has also been used as an encapsulation material. Locust bean gum is derived from carob seeds, and is also a mannan with galactose side chains, though less branched than guar gum. In one study, locust bean gum was combined with chitosan in the ratios of 2:3, 3:2, and 4:1. The locust bean gum/chitosan mixture was applied to 5-ASA cores, which were created by tablet pressing and the stability of the formulation was tested *in vitro* and *in vivo*. The results of both studies showed that this coating was able to protect the drug from being released in the stomach and small intestine, but was degraded by colonic bacterial enzymes (Raghavan et al., 2002).

The galactomannans in locust bean gum can be cross-linked, forming a water-insoluble film, which can then be degraded by bacteria in the colon (Hirsch et al., 1995). Locust bean gum
galactomannans were crosslinked by 1,4-butanedioldiglycidyl ether, yielding a low crosslinked product that can be used to form films. The crosslinked galactomannans were incubated anaerobically with the contents of a fresh pig cecum, representing the human colonic microflora, and degraded within 270 minutes. The material was then used to spray-coat theophylline tablets, which were used as a model drug. When placed under conditions representing passage through the small intestine, drug release was observed, but the researchers concluded that the lag time prior to drug release could be increased by applying a thicker coating of the crosslinked galactomannans (Hirsch et al., 1995).

### 3.1.5 Alginates

Alginates, which are derived from seaweed, have not been used as an encapsulation material, but have been utilized as a core for aminosalicylate drugs. Alginates consist of (1→4) linked β-D-mannuronic acid and α-L-glucuronic acid residues. Alginates are able to form gels in the presence of divalent cations (Jain et al., 2007). In one study, calcium alginate beads were formed through the drop-wise addition of sodium alginate into a solution of calcium chloride. 5-ASA was spray coated on the calcium alginate beads and coated by pH-dependent and time-released polymers. As the drug coated beads moved through the gastrointestinal tract, the calcium alginate beads swelled until they burst through the outer coatings due to an osmotic gradient, releasing the 5-ASA. This delivery system allows the 5-ASA to be delivered to the ileum (Lin & Ayres, 1992).

### 3.2 Conjugate polysaccharides

In addition to their use as encapsulation materials, polysaccharides have been used as conjugate carrier molecules for the delivery of 5-ASA to the colon. The polysaccharides can be attached either to the carboxyl group or the amino group of the 5-ASA. Conjugates prepared by these methods have been shown to survive conditions in the stomach and small intestine and are able to reach the colon intact. In the colon, the 5-ASA is cleaved from the carrier molecule through the action of bacterial azo-reductases, esterases, and glycoside hydrolases.

#### 3.2.1 Dextran

Dextrans are a class of polysaccharides consisting of linear chains of α-D glucose molecules. Ninety five percent of the chains have glucose linked (1→6), while the side chains are linked (1→3). Dextrans are obtained from lactobacilli organisms. *Bacteroides* in the gastrointestinal tract produce dextranase enzymes, which are capable of cleaving dextran chains (Jain et al., 2007).

Dextrans have been used as carrier molecules for 5-ASA in several studies. In one study, dextrans were oxidized using sodium periodate. The aldehyde groups of the dextrans were then attached to the α-amino group of 5-ASA. Dextrans were oxidized by incubating them with different amounts of NaIO₄. The amount of NaIO₄ consumed was determined by back titration. The more NaIO₄ consumed, the more oxidized the dextrans were considered to be. Degree of substitution was defined as the mg of 5-ASA per 100 mg of total product. Degrees of substitution between 15 and 50 were obtained, depending on the degree of oxidation of the dextran. It was found that dextran's with a high degree of oxidation gave the maximum degree of conjugation to 5-ASA, but were then resistant to hydrolysis by dextranase. Less
oxidized dextran bound a lower amount of 5-ASA, but were more able to be digested by dextranase, making them better candidates for carrier molecules (Ahmad et al., 2006). In another study, dextran prodrugs of 5-ASA were created by linking the dextran to the carboxyl group of the 5-ASA via an ester linkage. The conjugates were incubated with small intestinal and caecal contents of rats. It was found that no 5-ASA was released during the incubation with the intestinal contents, but incubation with the caecal contents induced drug release (Jung et al., 1998).

3.2.2 Cyclodextrins
Cyclodextrins are cyclic oligosaccharides which are made up of six to eight α-D-glucose units joined through (1→4) glycosidic bonds (Jain et al., 2007). There are three forms of cyclodextrins α-Cyclodextrin is a six-membered ring, β-cyclodextrin is a seven-membered ring, and γ-cyclodextrin is an eight-membered ring. Cyclodextrins are able to resist digestion in the stomach and small intestine, but are fermented in the colon. The interior of a cyclodextrin molecule is lipophilic, while the exterior is hydrophilic. This allows the cyclodextrins to form inclusion complexes with hydrophobic drugs (Zou et al., 2005). 5-ASA was linked to α, β, and γ cyclodextrins through an ester linkage to the carboxyl group of the 5-ASA. The degree of substitution, or the percent of hydroxyl groups containing 5-ASA, was measured. The impact of degree of substitution on the release of 5-ASA from cyclodextrin was also evaluated. It was found that cyclodextrins with degrees of substitution less than 30% provided the greatest release of 5-ASA in the caecal and colonic environment (Zou et al., 2005).

4. Therapeutic agents as carrier molecules
Using a therapeutic agent, rather than an inert compound, as the carrier molecule may improve the effectiveness of aminosalicylate drugs. Several polysaccharides have been shown to protect against UC inflammation, making them ideal candidates for carrier molecules (Ewaschuk, 2006). These polysaccharides can be incorporated into films, cross-linked, or conjugated through ester linkages.

There are several benefits of using polysaccharides as therapeutic carrier molecules. For one, drugs can be selectively released in the colon by bacterial esterases, rather than relying on gradual changes in pH or highly variable time release. Using polysaccharides can also allow for prolonged release of the drug in the distal colon, which is the site of most UC inflammation. The rate of release is dependent on the structure of the polysaccharide, as well as the activity of the bacterial esterases. Because polysaccharides have therapeutic benefits against UC, using them as carrier molecules might allow for a decrease in drug dosage requirements. On a lower dose of drugs, patients would likely experience fewer side effects, and patient compliance rates would increase. A polysaccharide carrier system would also increase the water solubility of the drugs. Increased solubility would allow for the administration of larger doses of the drug in beverage form, rather than in pills, which would also increase patient compliance.

5. Therapeutic benefits for polysaccharides against UC
Many of the polysaccharides described above are classified as dietary fibers. Dietary fiber encompasses a number of plant substances which are resistant to hydrolysis by digestive

enzymes in the small bowel. This includes non-starch polysaccharides, resistant starch, cellulose, hemicellulose, oligosaccharides, pectins, gums, lignin, and waxes (James et al., 2003).

When dietary fibers reach the large intestine, they are fermented by gut bacteria. In general, soluble dietary fiber is fermentable by colonic bacteria, producing short chain fatty acids, while insoluble fiber is poorly fermentable (Galvez et al., 2005). Different carbohydrate substrates produce different ratios of short chain fatty acids (SCFA). For example, resistant starch (RS) is butyrogenic, guar gum and psyllium are mainly propiogenic, while pectin is acetogenic (Rose & Hamaker, 2011).

SCFA have many effects in the gastrointestinal tract. For example, SCFAs lower the pH of the lumen of the large bowel. This prevents the growth of some pathogenic bacteria. Butyrate, especially, is important for the maintenance of colonic health. Butyrate has been shown to prevent colonic inflammation by inhibiting NF-κB activation (İnan et al., 2000). Butyrate may also help to prevent colon cancer, by playing a role in the repair of damaged DNA, and the induction of apoptosis in transformed epithelial cells (Lührs et al., 2002).

In addition to producing SCFA, many polysaccharides are prebiotics. Prebiotics are food substances that are not digested in the small intestine and promote the growth of certain beneficial species of bacteria in the colon (Gibson et al., 2004). Prebiotics such as lactulose, fructo-oligosaccharides (FOS), inulin, psyllium, and germinated barley foodstuffs have been shown to stimulate the growth and metabolism of protective bacteria endogenous to the human gut (Ewaschuk & Dieleman, 2006). These protective bacteria can secrete metabolites that can help to reduce the amount of pro-inflammatory factors produced by the colonic mucosa. Bacteria that are thought to be beneficial to gut health include *Lactobacilli, Bifidobacterium breve, Streptococcus thermophiles, B. bifidum, and Ruminococcus* (Ewaschuk & Dieleman, 2006). Many of the carbohydrate carrier molecules discussed above are prebiotics, which stimulate the growth of these protective bacteria.

### 5.1 *Plantago ovata* (psyllium) seeds

*Plantago ovata* seeds, commonly known as psyllium, have been tested as remission maintenance treatments in UC. Psyllium seeds include a complex glucuronoarabinoxylan that is composed of a β-(1→3 or 1→4)-D-Xylp backbone, with arabinoyxylan, xylose, glucuronic acid and galactose side chains (Rose & Hamaker, 2011). One of the earliest studies looked at the effects of ingesting psyllium husks on quiescent UC patients. The researchers found that the psyllium husks were effective in reducing UC symptoms in these patients. Patients on the psyllium husk treatment reported decreased symptoms such as bloating, diarrhoea, and abdominal pain. The researchers hypothesized that the therapeutic benefit was primarily a result of the fiber’s normalizing effect on transit time through the bowel. Also, because psyllium husks are mainly composed of soluble fermentable fiber, their fermentation in the ascending colon would cause an increase in SCFA production, possibly leading to further health benefits (Hallert et al., 1991).

In another study, UC patients in remission were given 5-ASA, psyllium seed (which contains dietary fiber) or a combination of the two. No difference in disease states were observed between any of the treatment groups. This indicates that psyllium seed might be as effective a treatment for maintaining the remission of UC as the 5-ASA drug mesalamine.
This study also showed an increase in SCFA production in patients receiving psyllium (Fernandez-Banares et al., 1999). \textit{Plantago ovata} seeds have also been shown to be therapeutic against an induced animal model of UC. Colitis was induced in rats via an enema containing 2,4,6-trinitrobenzene sulfonic acid (TNBS). There were 3 experimental groups; a non-colitic group, a colitic group which received a standard diet, and a colitic group which was fed a standard diet supplemented with psyllium seeds. Rats which received dietary fiber supplementation showed lower inflammation histologically, and had lower levels of myeloperoxidase, tumor necrosis factor $\alpha$, and nitric oxide synthase activity, some of the mediators involved in the inflammatory response (Rodriguez et al., 2002).

5.1.1 Germinated barley foodstuff
Germinated barley foodstuff (GBF) is made up of the aleurone layer and the scutellum fraction of brewer’s spent grain. GBF is comprised primarily of dietary fiber, in the form of low-lignified hemicellulose, and glutamine-rich protein. The dietary fiber portion of GBF is efficiently fermented by beneficial colonic bacteria such as \textit{Bifidobacterium} and \textit{Lactobacillus}, which increases the concentration of SCFA, especially butyrate, in the colonic lumen (Galvez et al., 2005).

Several studies have examined the effects of GBF on patients with UC. In one study, patients with mild to moderately active UC were administered a conventional anti-inflammatory treatment, either with or without the addition of GBF. After 4 weeks on these regimens, patients who had GBF added to their treatment showed a significant decrease in clinical activity scores as compared to those who were on the conventional treatment only. There were no side effects observed with the GBF treatment, and faecal concentrations of the beneficial gut bacteria \textit{Bifidobacterium} and \textit{Eubacterium limosum} were increased (Kanauchi et al., 2002). An earlier study which also used GBF as a supplementation to traditional anti-inflammatory treatment obtained similar results (Mitsuyama et al., 1998). Notably, this study found that inflammation significantly increased within 4 weeks of halting the GBF supplementation (Mitsuyama et al., 1998).

Additionally, GBF can be used as a maintenance therapy to help maintain UC remission. When given to quiescent patients daily, in conjunction with traditional treatments, GBF was correlated with a reduction in UC symptoms. The rate of UC relapse was also lower in the group receiving GBF in addition to standard maintenance therapy (Hanai et al., 2004).

GBF has been shown to be effective in an animal model of UC. Kanauchi et al. (2003) demonstrated that GBF was therapeutic in treating mice with dextran sodium sulphate (DSS)-induced colitis. Mice were divided in to two groups and fed either a control diet of cellulose, or a diet containing GBF. After one week on each diet, experimental colitis was induced by adding 2% DSS to their drinking water, and the mice were sacrificed 6 days later. The researchers found that mice that had been on the GBF diet showed significantly lower disease activity, weight loss, and inflammatory disease markers.

5.1.2 Resistant starch
RS is defined as starch and starch products which escape digestion in the human small intestine, acting as dietary fiber. In the large bowel RS is highly fermentable and contributes
greatly to colonic SCFA production. There are a number of types of RS: RS1 (physically inaccessibly starch), RS2a (uncooked starch), RS2b (high amylose starch), RS3 (retrograded starch), and RS4 (chemically modified starch). Some studies have demonstrated reduced postprandial glucose and insulin responses in patients who were fed RS. In animal models, RS has been shown to decrease serum lipid and cholesterol concentrations, although no such effect has been conclusively demonstrated in humans (Rose & Hamaker, 2010).

RS has been shown to be therapeutic in an experimental animal model of colitis. Colitis was induced in rats via a TNBS enema. The animals were fed standard diets either with or without the addition of granular pea starch (a source of RS2). They were sacrificed between 3 and 21 days after the induction of colitis, and the colons of the rats were examined. Rats which were fed diets including RS had an increased uptake of SCFA, and higher luminal concentrations of beneficial gut bacteria (Jacobasch et al., 1999).

5.2 Lactulose
Lactulose is a non-digestible disaccharide comprised of fructose and galactose produced by alkali isomerisation of lactose. It is not a common dietary carbohydrate, but is used in the pharmaceutical industry for the treatment of hepatic encephalopathy and constipation. It is a prebiotic carbohydrate, which is selectively digested by bacteria in the cecum and colon.

Lactulose was proposed as a possible treatment for UC based upon its demonstrated ability to clear infectious bacteria and bacterial endotoxins from the gastrointestinal tract (Liao et al., 1994). Lactulose was then tested for efficacy in treating a DSS-induced mouse model of colitis (Rumi et al., 2004). In this study, colitis was induced in the mice through the addition of DSS to their drinking water over a period of 7 days. The mice were then treated orally with lactulose twice daily for 6 days. Compared to control animals, mice treated with lactulose exhibited decreased UC symptoms such as colonic ulceration and myeloperoxidase activity. The prebiotic properties of lactulose are believed to be responsible for its therapeutic potential in treating UC (Rumi et al., 2004).

5.3 Fructooligosaccharides and inulin
FOS are composed of (1→2)-linked β-D-fructose units, with a terminal glucose unit (Rose & Hamaker 2011). FOS are resistant to digestion in the small intestine, and are fermented in the colon by gut bacteria (Le Blay et al., 1999). In one study, FOS were administered to rats with TNBS-induced colitis through intragastric infusions at a level of 1g/day for two weeks. The FOS were found to decrease the rats' gross inflammation score, myeloperoxidase activity and pH, and to increase the lactate, butyrate, and lactic acid-producing bacteria concentrations. The therapeutic effects of FOS are thought to be primarily due to their ability to increase lactic acid-producing bacteria counts in the intestine (Cherbut et al., 2003). In contrast, Moreau et al. (2007) showed that FOS were ineffective in improving DSS-induced colitis in rats, as compared with RS. The differences between the effects of these two carbohydrates could be due to differences in SCFA and pH profiles produced through bacterial fermentation in the colon.

Inulin is the same basic structure as FOS, except includes longer chain fractions (up to 60 units). Inulin is a prebiotic, and has been shown to be effective in treating UC. Inulin has been demonstrated to improve the symptoms of DSS-induced UC in a rat model. Rats with
DSS-induced colitis received inulin either orally or through an enema. Inulin given through an oral route was shown to decrease inflammation in the rats, while the inulin given via enema had no effect (Videla et al., 2001).

In a human clinical study, oligofructose-enriched inulin, which is a 50:50 mixture of FOS and long-chain inulin, was shown to alleviate inflammation associated with UC. The patients had been in remission with either 5-ASA maintenance or without any drug, and had experienced a relapse of their UC. The patients were treated with a combination of 5-ASA and oligofructose-enriched inulin or a placebo for a period of two weeks. Fecal calprotectin was measured as a marker of inflammation. Patients who received the oligofructose-enriched inulin showed lower fecal calprotectin levels than the control group, indicating that oligofructose-enriched inulin is able to reduce inflammation from UC (Casellas et al., 2007).

6. Conclusions

This chapter has discussed the use of polysaccharides for colon-targeted drug delivery. Polysaccharides offer several advantages over traditional colon-targeted drug delivery systems. For instance, polysaccharides are natural polymers with no toxicity. Furthermore, the variation in structure and mode of conjugation/encapsulation could lead to improved site-specific drug release, reducing the need for excessive amounts of the drug. Finally, polysaccharides may lead to reduction in disease severity beyond that provided by the drug due to fermentation of the polysaccharide by bacteria. In this way, the polysaccharides not only act as carrier molecules, but as therapeutic agents as well.

7. References


Polysaccharides for Colon–Targeted Drug Delivery:
Improved Drug–Release Specificity and Therapeutic Benefits


This book is intended to act as an up to date reference point and knowledge developer for all readers interested in the area of gastroenterology and in particular Ulcerative Colitis. All of the chapter authors are experts in their fields of publication and deserve individual credit and praise for their contributions to the world of Ulcerative Colitis. We hope that you will find this publication informative, stimulating and a reference point for the area of Ulcerative colitis as we move forward in our understanding of the field of medicine.

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