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Novel Prospective in Colon Specific Drug Delivery System

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A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation; D – writing the article; E – critical revision of the article; F – final approval of the article

Abstract

This review deals with the targeting of drugs to the lower gastrointestinal tract i.e. colon. Colonic drug delivery becomes important for localized action as well as for improved systemic availability of peptide and proteins. Drugs which have absorption window in the colonic region have been targeted using different novel technologies. pH sensitive polymers and prodrug based formulation have been used for the delivery of drugs into the colon. Different natural polymers have been used successfully for the delivery of drugs into the colon. Natural polymers are less toxic, biodegradable and easily available with a wide range of molecular weight and varying chemical compositions. One of the supporting properties associated with these polymers is that natural polymers can be used as approved pharmaceutical excipient (Polim. Med. 2014, 44, 2, 109–118).

Key words: targeted drug delivery, colonic delivery, natural polymer, colonic bacteria.

Oral administration of conventional dosage forms normally dissolves in the gastrointestinal fluid and then the absorption of drugs primarily depends upon physicochemical characteristics of the drug. Conditions become critical when a drug needs to be delivered only to the colon or when a drug needs to be protected from the pH and enzymatic environment of upper gastrointestinal tract. Colon targeted drug delivery can be defined as drug delivery into the lower gastrointestinal part known as the colon [1, 2].

Formulations that deliver drugs into the colonic region rather than the upper GI tract offer a number of advantages. In certain conditions, oral delivery of drugs to the colon is valuable in the treatment of certain diseases, such as ulcerative colitis, Crohn’s disease, carcinomas, infections and colon cancer [3].

The colon is attracting interest as a site where poorly absorbed drug molecules may have improved bioavailability. The colon is a specific part of the body that contains numerous bacteria. Prodrugs and formulations that are degraded by the action of colonic bacterial enzyme are promising in their use for the delivery of drug into colon. Colonic drug delivery has a promising interest for drugs that are acting as a substrate for cytochrome P450 3A, as an activity of these class of enzymes are comparatively lower in the colonic part. Drug targeting to the colon for delayed absorption is also effective in the chronotherapy of diseases such as asthma, inflammation, hypertension, arthritis or cardiac arrhythmias [2, 4].

Advantages and Disadvantages of Colon Targeting

Colon targeting is recognized to possess several clinical advantages for drugs that are destroyed in the stomach by stomach acid and/or metabolized by pancreatic enzymes. Colon targeting provides better patient compliance due to the reduction in dose and dosage frequency. Localized treatment of colonic pathogens, such as colorectal cancer, ulcerative colitis, and Crohn’s disease, is more effective with the delivery of drugs to the infected area [1, 2, 4]. In some disease cases, pH of the GIT changes significantly and so a pH dependent system
releases drugs in a different manner e.g., in inflammatory bowel disease, the pH of the colon decreases than normal pH. Although pH dependent polymer system can be able to protect formulations in the upper gastrointestinal tract, it may start to dissolve to a certain extent in the lower intestinal tract, and the desired site targeting of formulations can be altered. The consideration of solubility of drug molecules is important for its colonic delivery. The colon contains relatively lower fluid content than small intestine [5], so it becomes critical in the case of drugs having lower water solubility, leading to the poor dissolution of drugs. So in the case of such drug candidates, drugs are used in presolubilized form and generally targeted in the proximal colon, which has relatively more fluid than in the distal colon [6].

Peptides and Proteins

Peptides and proteins can be absorbed from the GIT, but the bioavailability of peptides and proteins by this route is too low, their oral absorption is limited by various factors such as the degradation of protein and peptides in the acidic medium of stomach, enzymatic degradation of proteins and peptides in the intestine, low mucosal permeability of proteins and peptides, extensive first pass metabolism of therapeutic proteins and peptides. Drug targeting to the colon has proved to be an efficient site for the delivery of peptides and protein, as colon has a longer transit time (20–30 hrs), larger residence time, less enzyme (peptidase) activity, natural absorptive characteristics, and a high response to the absorption enhancers. Therapeutic molecules like insulin, calcitonin and vasopressin cytokine inhibitors and antibiotics (e.g., nisin) may be delivered systemically through colonic absorption. Besides this vaccine, antigens can also be delivered systemically through the colon, as it is rich in lymphoid tissue [7, 8].

Criteria for Drugs Selection

The best Candidates for colon targeting are those which show less absorption from the upper part of GIT.

Approaches to Colonic Drug Delivery through Oral Route

Colon targeted formulations are useful in the treatment of inflammatory bowel diseases and this type of targeting has been designed using the following approaches:

pH Dependent Delivery

In a healthy person, it has been observed that pH increases from the duodenum (pH = 6.6 + 0.5) to the terminal ileum (pH = 7.5 + 0.4), then decreases in the cecum (pH = 6.4 + 0.4), and again there is a slight increase in pH from the right to the left colon with a final value of 7.0 + 0.7. Drug release is triggered by a change in the local pH as the formulation passes the GIT and prevents drug dissolution until the formulation passes into the small intestine. Enteric polymers are generally used and they are insoluble in the contents of the stomach; it is very essential that pH dependent formulation should maintain their physical and chemical integrity during their passage through upper GIT and small intestine. Table 1 shows

<table>
<thead>
<tr>
<th>Polymers</th>
<th>Threshold pH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poly vinyl acetate phthalate</td>
<td>5.0</td>
</tr>
<tr>
<td>Cellulose acetate trimellitate</td>
<td>5.5</td>
</tr>
<tr>
<td>Hydroxypropyl methylcellulose phthalate HP-50,</td>
<td>≥ 5.0</td>
</tr>
<tr>
<td>HP-55 and HP-55S</td>
<td>≥ 5.5</td>
</tr>
<tr>
<td>Hydroxypropyl methylcellulose acetate succinate</td>
<td></td>
</tr>
<tr>
<td>MF grade</td>
<td>≥ 5.5</td>
</tr>
<tr>
<td>HF grade</td>
<td>≥ 6.0</td>
</tr>
<tr>
<td>Cellulose acetate phthalate</td>
<td>≥ 6.8</td>
</tr>
<tr>
<td>Acrylic acid copolymer</td>
<td></td>
</tr>
<tr>
<td>Eudragit L100-55</td>
<td>≥ 5.5</td>
</tr>
<tr>
<td>Eudragit L30D-55</td>
<td>≥ 5.5</td>
</tr>
<tr>
<td>Eudragit L-100</td>
<td>≥ 6.0</td>
</tr>
<tr>
<td>Eudragit L12,5</td>
<td>≥ 6.0</td>
</tr>
<tr>
<td>Eudragit S-100</td>
<td>≥ 7.0</td>
</tr>
<tr>
<td>Eudragit S12,5</td>
<td>≥ 7.0</td>
</tr>
<tr>
<td>Eudragit FS30D</td>
<td>≥ 7.0</td>
</tr>
<tr>
<td>Hydroxyl propylethyl cellulose phthalate</td>
<td>≥ 4.5</td>
</tr>
<tr>
<td>Shellac</td>
<td>7.0</td>
</tr>
</tbody>
</table>

Table 1. Enteric polymers and their threshold pH

Design and Consideration of Colon Targeted Drug Delivery

Dosage forms for colon targeted delivery are usually delayed release and depend upon various factors such as:

a) If the formulation is intended for localized treatment, then its pathological conditions and disease pattern should be considered.
b) Biopharmaceutical and physicochemical properties of the active ingredient.
c) Release characteristics of drug.
d) pH gradient throughout the gastrointestinal tract.
e) Transit of materials into and through the colon.
f) Effect of diet on colonic transit.
g) Colonic bacteria.
the threshold pH of various enteric polymers used for intestinal targeting and Table 2 shows the list of some marketed formulations used in the treatment of inflammatory bowel disease.

A simplest approach to design a pH dependent colon targeted delivery system is to prepare enteric coated granules. An enteric coating polymer has been used as a binder as well as a coating polymer for granules and these polymers also protect the release of the drug in the upper GI tract. By utilizing the knowledge of polymers and their solubility in different pH, the formulation can be designed for the targeted site. Acrylic acid polymers and cellulose derivatives are most commonly used pH dependent polymers for colonic delivery. There are various forms and grades of Eudragit as a colon targeting polymer is available. Eudragit (RS 100 and RL 100) are copolymers of methacrylic acid and acrylic acid esters in different ratios. Both these copolymers are insoluble in water, but they hydrate in GI fluids independent of pH. RS grade of Eudragit is relatively less hydrophilic because it contains less percentage of quaternary ammonium groups in comparison to RL grade. Eudragit-L is an anionic, copolymer of methacrylic acid and methyl methacrylate, which dissolves above pH 6. Mesalazine is an anionic, copolymer of methacrylic acid and methyl methacrylate, which dissolves above pH 6. Mesalazine tablets coated with EudragitL-100 are commercially available under the trade name in market as Claversal, Salofalk, Mesalax, and Rowasa. The use of Eudragit-S as a colon targeting polymer was first described in 1982. In one study, tablet containing 5-Amino-salicylic acid with barium sulphate was coated with Eudragit-S was analyzed. At the end of twelve hours, twenty tablets were in the stomach and four tablets were in the colon, while, at the end of twenty-four hours, all the tablets reached the colon [9]. A combination of Eudragit S100 and Eudragit L100 ensures the release of drug even if the pH of the GIT remains below 6.8 due to the alteration of pH in disease condition. In a study, 5-fluorouracil matrices were prepared to release the drug in the colonic region. In the formulation of matrices, glyceryl palmitostearate was used as the retardant. Prepared granules were incorporated in capsules to target drug release in ileum.

Soravoot et al. prepared a formulation with the potential for site specific delivery to the colon. In this system, we see prepared the pH-erosion-controlled and pulsatile release based on compression-coatings of tablet cores containing model drugs of varying solubility (acetaminophen, carbamazepine and chlorpheniramine maleate) with enteric polymer Eudragit L100-55 and the extended release polymer ethylcellulose at different compression forces and tablet core: compression coat ratios. All drugs were released after a lag time at a higher pH in a pulsatile manner. The addition of ethylcellulose protects the release of the drug in the lower pH-media and also enhances the lag time in higher pH-media because of a reduction in wettability, erosion of the compression-coatings. The lag time could also be increased by increasing the compression force and also by decreasing the core: compression coat ratio [10].

Karrout et al. described the effect of novel polymeric film coating for colon targeting. In this study, extrusion spheronization technique was used to formulate 5-Aminosalicylic acid loaded beads and afterward these beads were coated with Nutriose: ethylcellulose blends in a different ratio. In this article, in vitro drug release studies were performed under various conditions, including fresh fecal samples of patients suffering from inflammatory bowel disease. The investigated nitroso polymer (starch derivative) in this study was FB type which is a mixture of glucose polymers having a number average molecular weight in the range of 2000–4000 Dalton. It is partially hydrolyzed (10–15%) in the small intestine. Due to the incorporation of ethylcellulose in the formulation, dissolution of polymeric coating in the upper gastrointestinal tract was prevented. The release of drug from the formulation could effectively be protected in the simulated upper GIT fluid, without effect of agitation and enzymes. But when prepared formulation interact with fecal samples of diseased patients (inflammatory bowel disease), the release rate was significantly increased and the drug was released in a controlled manner. This type of novel formulation can be easily adopted for in vivo correlation in diseased condition [11].

Karrout et al. described the effect of novel polymeric films for the site-specific delivery of drugs to the colon of patients suffering from inflammatory bowel disease. In this study, starch derivatives responsive to various bacteria were blended with ethylcellulose. Prepared formulations were analyzed for water uptake and mass loss kinetics in simulating media (stomach, small intestine, colon, fresh fecal samples of diseased patients). In simulated media, polymers (ethylcellulose: Nutriose FB 06, ethylcellulose: Peas starch N-735 films) showed water uptake and mass loss kinetics, thereby showing an ability to protect the release of the drug from the prepared formulation in the upper GIT, and when the

Table 2. Marketed drug products for the treatment of inflammatory bowel disease

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Trade Name</th>
<th>Formulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Budesonide</td>
<td>9 mg</td>
<td>Entocort</td>
<td>Eudragit-L coated beads</td>
</tr>
<tr>
<td>Mesalazine</td>
<td>0.8–2.4 g/day</td>
<td>Asacol</td>
<td>Eudragit-S coated tablet (dissolves at pH 7)</td>
</tr>
<tr>
<td>Mesalazine</td>
<td>1–2 g/day</td>
<td>Claversal, mesazal calitoflak, rowasa</td>
<td>Eudragit-L coated tablet</td>
</tr>
<tr>
<td>Mesalazine</td>
<td>1–4 g/day</td>
<td>Salofac</td>
<td>Eudragit-L coated tablet (dissolves at pH 6)</td>
</tr>
</tbody>
</table>
prepared formulation comes in to contact with the fecal samples of inflammatory bowel disease patients, the release rate was significantly increased which is due to these starch derivatives being catalyzed by the enzymes produced by the colonic microflora, and the drug was released in a time-controlled manner. Furthermore, Nutriose may be beneficial for patient suffering from inflammatory bowel diseases due to its prebiotic potential [12].

**Enzyme Dependent Delivery**

- **Prodrugs**

These systems are generally based on the enzymatic activity of the microfloras present in the colon, such as bacteroides, lactobacillus, eubacterium, bifidobacterium, peptococcus, clostridium etc., which secrete a wide range of enzymes such as b-glucuronidase, urea hydroxylase, a-arabinosidase, nitroreductase, azoreductase, b-xylosidase, b-galactosidase, deaminase etc [13].

These enzymes are capable of metabolizing substrates such as carbohydrates (di, tri and polysaccharides), proteins etc., that are not degraded in the upper gastrointestinal tract. Site targeted delivery of protein and peptide have been carried out using azo linked polymers. Colon specific drug delivery using these polymers may cause some problems such as microbial degradation of azo crossed links polymers is generally slow, resulting in incomplete and irregular drug absorption. Crohn’s disease and ulcerative colitis has been treated with salfa drug (Sulphasalazine). Sulphasalazine is split by bacterial azoreductase into 5-Aminosalicylic acid and Sulphapyridine in the colon. There are other formulations based on enzyme dependent drug delivery, such as balsalatsine, olsalazine and ipsalatsine are prodrugs contained 5-aminosalicylic acid [6]. Dextran-naproxen prodrugs containing ester linkage has been prepared to deliver drug into colon. This is based on the fact that esterase present in colon, degrade the ester linkage, resulting in drug release [1, 2, 14].

Azo linked formulations are stable in the upper gastrointestinal tract, as azo linkage is unaffected by the chemical and enzymatic degradation in the stomach and small intestine, but due to its hydrophobic nature, its degradation by enterobacteria is slow [15]. Another limitation of azopolymer based formulation is that origination of some harmful substance on long-term use. These limitations can be overcome by the use of natural polymer materials with glycosidic linkage [5].

**Enzyme Dependent Delivery**

- **Coatings and Matrices**

A number of naturally occurring polysaccharides are stable in the upper intestine but yet susceptible to hydrolytic degradation in the lower intestine, to release the drug at a specific site. Colonic microorganisms, present in colon, are taken into consideration during the development of colon targeted delivery systems. Anaerobic and aerobic microorganisms are present into the gastrointestinal tract of a human. Research has found that that small intestine contains mainly aerobic microorganism, while the large intestine contains anaerobic. Most bacterial species are found in the proximal areas of the large intestine, where energy sources are greatest. Carbohydrates metabolized in to short chain fatty acids and carbon dioxide by glycosidases and polysaccharidases are the major source of nourishment for microorganism. These polymers are easily available but most of them have a hydrophilic nature

### Table 3. List of some prodrug evaluated for colon specific drug delivery with *in vitro*/*in vivo* performance

<table>
<thead>
<tr>
<th>Carrier</th>
<th>Drug</th>
<th>Linkage</th>
<th>Performance of the prodrug/conjugates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glycine</td>
<td>5-ASA</td>
<td>Amide linkage</td>
<td>Prodrug was unaffected in the stomach and was hydrolysed by the cecal content to release 5-ASA</td>
</tr>
<tr>
<td>Sulphapyridine</td>
<td>5-ASA</td>
<td>Azo linkage</td>
<td>Released in the colon, but associated with side effects due to sulphapyridine</td>
</tr>
<tr>
<td>5-ASA</td>
<td>5-ASA</td>
<td>Azo linkage</td>
<td>Released two molecules of 5-ASA</td>
</tr>
<tr>
<td>Glucuronic acid</td>
<td>Naloxone</td>
<td>Glucuronide linkage</td>
<td>It was given to the morphine dependent rat; it reverses the side effect caused by morphine without causing CNS withdrawal symptoms because of activation in large intestine followed by resultant diarrheas which excreted the prodrug</td>
</tr>
<tr>
<td>Glucose/galactose/ cellubioside</td>
<td>Prednisolone, hydrocortison, fludrocortison</td>
<td>Glycosidic linkage</td>
<td>Prodrug undergoes some degradation in the upper GIT, increases in distal colon and maximum in cecal content. Galactose conjugates hydrolyzed faster than glucosides which is faster than cellubioside</td>
</tr>
<tr>
<td>L-Alanine/D-Alanine</td>
<td>Salicylic acid</td>
<td>Amide linkage</td>
<td>L-Alanine conjugates hydrolyzed by colonic microbes to salicylic acids while D-Alanine conjugates show negligible hydrolyse thereby showing enantiospecific activity.</td>
</tr>
</tbody>
</table>
and gel forming ability. This reduces the penetration of enzymes into the polysaccharide matrix. Chitosan, pectin, guar gum, amylase, inulin, gellan gum etc have been applied as a carrier for colonic drug delivery. Pectin and amylose have film-forming properties and have been used as coating material for colon-targeted formulations [1, 2, 4, 14].

**Time Dependent Delivery**

(Pulsatile Drug Delivery)

Pulsatile drug delivery assumed to delay drug release until the formulation reaches the colon. Time dependent systems release the drug after a specific period of time and mimic gastrointestinal transit time. As transit time for small intestine is 3–4 h, so a lag time of 5 h is generally observed sufficient for the movement of formulation from the mouth to the colon [1, 2, 4]. A colonic disorder significantly alters colonic transit time and so it requires special attention in formulation of such type of system. Different combinations of hydrophilic and hydrophobic polymers have been used as coating material on solid formulations to formulate time dependent colonic delivery system. Swellable system has been produced to deliver the drug after specific period of time. This type of formulation uses hydrophilic polymer that swells when coming in the contact with water and releases the drug, based on gastric transit. Lag time can be adjusted by altering the thickness of the coating polymer. A combination of a water insoluble polymer (e.g. ethyl cellulose) and hydrophilic polymers (e.g. hydroxypropyl methyl cellulose, hydroxypropyl cellulose) has been used to produce time dependent system.

**Novel Approaches for Colon Targeting**

**Pressure Dependent Delivery**

It is based on the relatively higher pressure of the luminal contents of the colon as compared to the upper gastrointestinal tract, which is due to the peristaltic movement occurring in the colon. In the large intestine, the viscosity of the luminal contents increases due to the re-absorption of water resulting in increased intestinal pressure [27]. The intestinal pressure further increases due to peristalsis in the distal intestine, providing a potential means to trigger active ingredient release from a formulation susceptible to pressure changes [1, 2, 5].

**Colon Targeted Novel Delivery System (CODESTM)**

This system is a combination of pH dependent as well as microbiologically dependent drug delivery into the colonic part and thereby overcomes the limitation associated with the pH sensitive formulations and time dependent systems [28]. In this system, an acid soluble coating (Eudragit E) was applied over the tablet core loaded with an active part lactulose, which was again coated with an enteric polymer (Eudragit L). The enteric coating material protects the tablet from the upper part of GIT and dissolves in the small intestine and when the tablet comes into contact with the colonic fluid, polysaccharide (lactulose) was enzymatically degraded by

<table>
<thead>
<tr>
<th>Drug</th>
<th>Polymer(s)</th>
<th>Remark</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-Acetyl salicylic acid</td>
<td>Alginites, Amylose</td>
<td>Bacteria dependent/Polysaccharide based</td>
<td>16</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>Chondroitin sulphate, Pectin</td>
<td>Bacteria dependent/Polysaccharide based</td>
<td>17</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>Guar gum</td>
<td>Bacteria dependent/Polysaccharide based</td>
<td>18</td>
</tr>
<tr>
<td>Diclofenac sodium</td>
<td>Chitosan</td>
<td>Bacteria dependent/Polysaccharide based</td>
<td>19</td>
</tr>
<tr>
<td>Diltiazem HCl</td>
<td>Hydroxy propyl methyl cellulose acetate succinate (HPMCAS)</td>
<td>Time dependent</td>
<td>20</td>
</tr>
<tr>
<td>Theophylline</td>
<td>Hydroxy ethyl cellulose, ethyl cellulose, microcrystalline cellulose</td>
<td>Time dependent</td>
<td>21</td>
</tr>
<tr>
<td>Pseudo ephedrine HCl</td>
<td>Hydroxy propyl methyl cellulose</td>
<td>Time dependent</td>
<td>22</td>
</tr>
<tr>
<td>Paracetamol</td>
<td>Eudragit L 30 D-55 and Eudragit FS 30 D</td>
<td>pH dependent</td>
<td>23</td>
</tr>
<tr>
<td>Diclofenac sodium and 5-ASA</td>
<td>Eudragit L100 and S100</td>
<td>pH dependent</td>
<td>24</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>Eudragit S, Eudragit FS, Eudragit P-4135 F</td>
<td>pH dependent</td>
<td>25</td>
</tr>
<tr>
<td>Mesalazine</td>
<td>Eudragit L100 and S100</td>
<td>pH dependent</td>
<td>26</td>
</tr>
</tbody>
</table>
the colonic microfloras into organic acid [29]. Further organic acid decreases the pH around the formulation and subsequent drug release takes place due to the dissolution of acid soluble coating.

**Osmotic Controlled Drug Delivery**

These types of systems can also be used to target the drug locally to the colon for the treatment of disease or to achieve systemic absorption. In this device, a semi permeable membrane containing an osmotic agent with the drug is used to deliver the drug into colonic region. An orifice is drilled through the membrane next to the drug layer. This membrane is then coated with an enteric coated polymer to prevent the drug being released in the upper gastrointestinal tract. As this system enters into the small intestine, the enteric polymer dissolves due to the higher pH; water moves towards core, which increased the volume within the osmotic compartment, forcing the active agent out of the devices through the delivery [30].

**Role of Natural Polymers in Colon Targeting**

Natural polymers have been applied for the targeting of drugs into colon. Polysaccharide based formulation are quite common to fulfill the objective of site specific targeting. The most favorable properties of these materials are that they are already approved for use as a pharmaceutical excipient. These types of materials are considered safe because they are derived from dietary fibers. Their hydrophilicity and so water solubility is a major problem in the formulation of colonic delivery of active substance. These materials are either soluble or prone to being soluble in the aqueous environment of GIT [1, 2, 4, 14].

Pectin has been used as a single polymer as well as with a combination of other polymers for colon targeted delivery. It was found that when pectin is used alone, it needed relatively large quantities to control the release of the drug through the core, while a combination of polymers (pectin, chitosan and hydroxypropyl methyl cellulose) was proven to be very efficient in the colon targeting of tablets. Natural polymers such as pectin, inulin and xylan etc. are not digested in the GIT but they are fermented by colonic flora. The degradation product consists of natural gases such as methane, carbon dioxide, hydrogen and short chain fatty acids. These products are nontoxic and so natural polysaccharides are generally better carriers for the colonic delivery of drugs. Different natural polymers used for colon targeting were summarized in Table 5.

**Polysaccharides Obtained from Plants**

**Starch**

It is a polysaccharide obtained from the grains of maize, wheat, rice, potato etc. It contains chemically two different polysaccharides, namely amylose and amylopectin in the ratio of 1:2. Amylose is water soluble and amylopectin is water insoluble, but swells in water. The α-1, 4-linkage present in both amylose and amylopectin is attacked by amylases, while α-1, 6-linkage present in amylopectin is degraded by glycosidase. Amylose polymer can be used as an enteric coated polymer and are insensitive to pancreatic α-amylase, but susceptible to colonic microbial enzyme [31].

**Cellulose**

It is the most widely distributed plant polysaccharide. It forms the main constituent of the cell walls of plants. It consists of cellobiose units in a repeated manner. In colon region of human, anaerobic bacteria produces endo- and exo-enzymes, some enzymes form complexes and these complexes are important for nutrition of microorganism as they degrade cellulose to form carbohydrate nutrients. Combinations of amylose and ethyl cellulose as coatings have been used for colonic drug delivery [32].

<table>
<thead>
<tr>
<th>Polymers</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diasaccharides</td>
<td>Lactose&lt;br&gt;Maltose</td>
</tr>
<tr>
<td>Oligosaccharides</td>
<td>Cellobiose&lt;br&gt;Cyclodextrins&lt;br&gt;Lactulose&lt;br&gt;Raffinose&lt;br&gt;Stachyose</td>
</tr>
<tr>
<td>Polysaccharides</td>
<td>Alginites&lt;br&gt;Pectins&lt;br&gt;Chitosan&lt;br&gt;Chondroitin sulphate&lt;br&gt;Dextran&lt;br&gt;Inulin&lt;br&gt;Xantham gum&lt;br&gt;Guar gum&lt;br&gt;Starch&lt;br&gt;Tragacanth&lt;br&gt;Locust bean gum&lt;br&gt;Cellulose&lt;br&gt;Araibinogalactan&lt;br&gt;Amylase</td>
</tr>
</tbody>
</table>
**Pectin**

It is a complex polysaccharide found in the middle lamella of plant cells. They are obtained from the inner portions of the rind of citrus fruits or other vegetative matter, such as papaya, sun-flower etc. It is soluble in 20 parts of water, aqueous solution being viscous and mobile. It is almost degraded by the bacterial enzymes present in colon [33].

**Inulin**

Inulin is a naturally abundant polymer found in garlic, onion and artichoke. Inula is the chief source and it contains 40–50% of Inulin. Inulin is susceptible to Bifidobacteria found in colon. It has been used with Eudragit RS to deliver drug in to colon, inulin prevents drug release in upper gastrointestinal tract but ferment in presence of Bifidobacteria and Bacteroides to release drug in colon [34].

**Locust Bean Gum (Carob Gum)**

It is derived from the seeds of Ceratonia siliqua. It is translucent-white, opaque at the edge and is very difficult to break. It is insoluble in alcohol, but is incompletely dispersed in water at room temperature. It mainly contains D-galactomannan. It forms water-insoluble film which gets digested by the colonic microflora. It has been used successfully with different ratios of Chitosan for colonic delivery [35].

**Gaur Gum**

It is the most commonly used polymer for colon targeting, obtained from the endosperm of the seeds of Cyamopsis tetragonolobus [36]. It is colorless or yellowish-white coloured powder which rapidly swells in water. It is chemically composed of water-soluble and water insoluble parts. The water-soluble fraction constituting about 85% of the gum is known as guaran. It has a gelling property and shows degradation in the large intestine by the microbial enzymes. Gaur gum has been used as a carrier with drugs such as metronidazole, indomethacin, albendazole, mebendazole for colon targeting.

A colon targeted formulation using natural polysaccharide, guar gum was evaluated in healthy human male volunteers, with gamma scintigraphic study using technetium 99m-DTPA as tracing agent. It was observed that only traces of technetium were released in the stomach and small intestine while the remainder was released in the colon.

**Polysaccharides from Animal Origin**

**Chondroitin Sulfate**

Chondroitin sulphate is a water-soluble polysaccharide, can be used for colon targeting as it is digested by the enzymes secreted by the Bacteroides thetaiotaomicron and B. ovatus present in the large intestine [37].

**Hyaluronic Acid**

It is a biopolymer, concentrated in vitreous humor of eye and synovial fluid of articular joints. It constitute linear, unbranched, anionic disaccharide units consisting of glucuronic acid (GlcUA) an N-acetyl glucosamine (GlcNAc) cross linked by β-1, 3 and β-1,4 glycosidic linkage [38].

**Chitosan**

Chitosan is a functional copolymer consisting of 2-amino-2-deoxy-D-glucose units linked with β-(1 > 4) bonds. Chitosan has been used as polymer for colon specific delivery as it can ne degrade by colonic microflora [39]. M.L. Lorenzo-Lamosa et al prepared pH responsive particulate contain diclofenac sodium, entrapped in enteric coated microspheres. In vitro drug release study performed and no release was observed in gastric pH, while a continuous release was observed in the intestinal pH [19].

**Polysaccharides Obtained from Bacterial**

**Dextran**

This polysaccharide is produced by growing bacteria on the substrate sucrose, structurally it is a linear chain of α-D glucose molecules, 95% of the chains consist of α-D (1-6). Commercially, it is obtained from Leuconostoc mesenteroides, Leuconostoc dextranicum organisms of the family Lactobacillus. Dextrans are colloidal, water soluble and insoluble in alcohol. It is hydrolyzed by the dextranase and these enzymes are produced by the anaerobic bacteria present in the colon. Its esteric form is widely used for the colon targeting [40].

**Cyclodextrins**

These are oligosaccharides containing 6-8 glucose units linked through α-1, 4 glucosidic bonds. It remains intact during passage from upper gastrointestinal tract and get degraded in to monosaccharide in the presence
of colonic micro-organism [41]. These are poorly absorbed from the GIT due to their size and hydrophilicity and degraded in the large intestine, it is possible to use as carrier for delivery of drugs in the small intestine.

**Polysaccharides Obtained from Algae**

**Alginate**

It is a linear copolymer polysaccharide derived from seaweed, consisting of 1–4, linked d-mannuronic acid and l-glucuronic acid residues. Sodium salt of alginic acid is readily soluble in water forming a viscous colloidal solution and is insoluble in chloroform, alcohol, ether and strong acids. Sodium alginates can be easily crosslinked with the interaction of calcium ion. Cross linking of alginate beads can be achieved by adding a sodium alginate solution into a calcium chloride solution. Dried alginate beads are nontoxic and swell to form controlled release systems when coming in contact with the dissolution fluid. Enteric-coated polymers can be coated on calcium alginate beads to achieve targeted drug release [42].

**Polysaccharides from Fungal Scleroglucan (Sclg)**

It is a nonlinear polysaccharide consisting of a (1-3)-linked β-D glucopyranosyl units. Resistant to hydrolysis and constant viscosity even presence of more ions is advantageous for controlled release of drugs [43].

Drug Delivery Index of Colon-Specific Drug Delivery Systems: After the administration of single or multiple doses of prodrugs based colonic drug delivery, pharmacokinetic parameters are measured in terms of the drug delivery index. Drug delivery index is a relative measurement of RCE (relative colonic tissue exposure to the drug) to RSC (relative amount of drug in blood). Relatively high value of drug delivery index indicates better colonic delivery. Absorption of drugs through the colonic region is preferentially monitored by a colonoscopy and intubation. Gamma scintigraphy is a common technique used to evaluate colon specific drug delivery systems. For in vitro - in vivo correlation conditions such as diet, physical stress, pH, volume of dissolution media, microbial activity, quality and quantity of enzyme should be taken in consideration. In vitro models used for colon targeted delivery are:

a) **In vitro** dissolution test: Colon targeted delivery of drugs cannot be justified by USP relating to pH, bacterial activity etc [44]. Dissolution characteristucs of colonic drug delivery can be carried out using the USP apparatus type 1, i.e. basket method. Usually dissolution may be carried out at different pH to simulate various gastrointestinal regions.

b) **In vitro** enzymatic tests valuation: This type of evaluation is carried out by placing the prepared formulation in fermenter enriched with microflora such as Streptococcus faecium, B. ovatus etc. Further formulation incubates in fermenter containing Streptococcus faecium and B. ovatus. Drug release should be carried out in the presence of suitable animal cecal contents and enzymes. Drug released is depending on degradation of polymer in presence enzymes or cecal microflora.

c) **In vivo** evaluation: Animals like rats, dogs, guinea pigs has been used to evaluate colon targeted delivery of drugs as they mimic in vivo conditions of a human gastrointestinal tract. Guinea pigs have been used as an experimental model for inflammatory bowel disease.

**Future Prospects of Colonic Drug Delivery**

It has been observed that the concentration of colonic microflora altered in disease conditions. So the degradation profile of various natural polymers degraded by colonic bacteria should be studied in its disease state for future prospects. This will provide a new approach for the formulation of a colonic drug delivery system. There is also a need to standardize in vitro methods for an evaluation of CDDS.

**Conclusions**

It has been concluded from the study that the colon is an interesting site for the delivery of acid labile drugs as well as proteins and peptides. There are several approaches for colon targeting, such as pH dependent, pressure dependent, enzyme dependent etc, but each of these approaches has certain limitation in terms of site specificity, toxicity, uncertainty pattern of drug release due to change in gastro-luminal pH or due to change in enzyme population. These limitations can be overcome by the use of natural polymers or a combination of polysaccharide with synthetic polymers. These types of combinations have the greatest potential for colon specific delivery in terms of site specificity and safety. This article has described the application of various polysaccharides for colon targeting that are non-toxic and that are selectively degraded in the colon. So, challenges in the future will be to find the polysaccharide or its combinations to obtain an impermeable film coating that exhibits high microbial degradability in the colon.
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