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Polysaccharides in colon specific drug delivery

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Abstract

Polysaccharides are bacterial enzymes have been used extensively in targeting of the drugs. Various polysaccharides have been investigated for colon specific drug delivery, including pectin, guar gum, amylase, inulin, and dextran, Chitosan, and chondroitin sulphate. These natural polymers exhibit potential for drug delivery as they are comprised of polymers with a wide range of molecular weights resembles in the indigestion in the stomach and the small intestine, a large number of derivatizable groups. Moreover, the polysaccharides are inexpensive, naturally occurring, abundantly available and varying chemical compositions. The most favorable property of these materials is their approval as pharmaceutical excipients. Here we provide an overview on polysaccharide-based colon specific drug delivery system. This discussion includes parameters relevant for drug delivery that involve a general overview of the gastrointestinal tract, the pH of different gastrointestinal regions, digestive enzymes that are secreted in mouth, stomach and intestines, and the microflora that are presented in colon region. Properties, mechanisms, applications, and patents of various polysaccharides that can be used to target the colon and their advantages and limitations are presented.

Introduction

The gastrointestinal tract begins in the mouth, then the esophagus and reaches to the stomach, small and large intestine, and finally to the anus. The tube that initiates from the mouth to the anus in which the movement of muscles took place and release of hormones exist and digestion of enzymes took place. The gastrointestinal tract initiates with the mouth and goes through the esophagus, stomach, duodenum, small intestine then moves to the large intestine (colon), rectum and, finally, the anus, Which is also known as alimentary canal, digestive tract and, perhaps commonly known as the GI tract. In an adult male human, the Gastrointestinal (GI) tract is 5 metres (20 ft) long, or up to 9 metres (30 ft) without the effect or action of muscle tone, and comprisesof the upper and lower GI tracts [1]. The gastrointestinal (GI) tract consists of the:

- Mouth (oral cavity)
- Pharynx
- Esophagus
- Stomach
- Small intestine
- large intestine
- Rectum and anus

The esophagus

The esophagus is about 10 inches long and connects the oral cavity with the stomach.It is basically a muscular tube which passes from the lungs, heart, and through the diaphragm.Thus, it is affected by the pressures of the chest cavity and within the abdomen respectively.

The stomach

The wall of the stomach is made up of with millions of gastric glands, which basically secrete 400–800 ml of gastric juice at each and every meal. Many Kinds of cells are majorly found in the gastric glands. Example: parietal cells like chief cells, mucus-secreting cells and hormone-secreting (endocrine) cells .

The small intestine

The Small intestine has three parts:

- Duodenum - Here the digestive juices from the pancreas (digestive enzymes) and gallbladder (bile) combine in a way together. The digestive enzymes led down the breakdown of proteins and bile emulsifies fats and results into micelles. Duodenum has a presence of Brunner's glands, which led to the production of bicarbonate and pancreatic juice, which contains bicarbonate to neutralize hydrochloric acid of stomach.

- Jejunum - It is the middle part of the intestine, lays as a connecting part between the duodenums to the ileum. Incorporates with pilli circulares, and villi which led to increase in surface area.

- Ileum - It has villi, where all soluble molecules are absorbed into the blood (capillaries and lacteals).

- Digestion within the small intestine results in a combination of disaccharides, peptides thereafter fatty acids, and monoglycerides. The final digestion and absorption of above substances took place in the villi, which is present in the inner surface of the small intestine [2].

The large intestine (colon)

Large intestine also has three parts:

- Cecum (the vermiform appendix is attached to the cecum).
- Colon (ascending colon, transverse colon, descending colon

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and lastly sigmoid flexure). The main function of colon specifically is water absorption, but it also has the presence of bacteria that produce beneficial vitamins like Vitamin K.

- Rectum

The large intestine receives the liquid residue after digestion and thus absorption is said to be complete. This residue consists mostly of water as well as any materials that have not led to digestion. While the contents of the small intestine are considered to be normally sterile, the colon contains an enormous (approx 10^{14}) population of microorganisms. (Our bodies consist of only approx 10^{13} cells!).

High intracolonic drug concentration is required for the treatment of diseases associated within colon; that is the Ulcerative colitis, Crohn's disease, colon cancer, and amebiasis, which can be achieved by targeting delivery of drugs to the colon. Moreover, specific systemic absorption in the colonic region offers interesting possibilities for the treatment of diseases susceptible to the diurnal rhythm for example: asthma, arthritis, or inflammation.

Obstacles of the colon specific drug delivery (The gastrointestinal tract factors)

With regard to the rectal route, the drugs do not always reach the specific sites of the colonic disease and the sites of colonic absorption. To reach the colon and to be able to specifically deliver and absorbed there, the dosage form must be formulated taking into account the likely obstacles of the gastrointestinal tract. That is, pH, microflora, enzymes, reducing medium and transit time [3]. These parameters can vary from one individual to next and also pathological condition and diet. Majorly affecting factors are:

pH

Before reaching to the colon, the dosage form must pass through the stomach, the duodenum, the intestine and the caecum. In the colon, the pH ranges from 6.4 (ascending colon) to 7.0 (descending colon). The colon resembles the reducing medium with a mean redox potential of -200 Micro Volts. Taking inter- and intra-individual variation into account, this redox potential can range from -100 Micro Volts down to -400 Micro Volts. The relatively high value of the pH before and in the colon has led to the development and synthesis of polymers that dissolve at pH >7. These consist of copolymers of methacrylic acid, methylmethacrylates and ethylacrylates [4-6]. pH of the different region of Gastrointestinal tract is given in Table 1.

Enzymes

Digestive enzyme secretion goes with the mouth, stomach and intestines. Digestive enzymes are secreted by many different exocrine glands, also salivary glands, secretory cells in the stomach, pancreas and in the small intestine respectively. Digestive enzymes are enzymes that led to the breakdown of polymeric macromolecules into their smaller building blocks, in order to enhance their absorption in the human body. Digestive enzymes are present in the digestive tract of animals (including humans) where they help in the digestion of food as well as inside the cells, especially in the lysosomes where they function as to maintain cellular survival. Digestive enzymes are classified based on their target substrates like proteases and peptidases led to the breakdown of proteins into their monomers and the amino acids. Lipase distinguishes fat into three fatty acids and a glycerol molecule. Carbohydrates split carbohydrates such as starch and sugars into simple sugars such as glucose, the most common sugar on earth. Nucleases break nucleic acids into nucleotides.

Table 1. pH of the different region of gastro intestinal tract.

Region of GIT	pH
Stomach	1-3.5
Duodenum	5-7
Jejunum	6-7
Ileum	7
Colon	5.5-7
Rectum	7

In the oral cavity, salivary glands secrete an array of enzymes and substances that aid in digestion and also disinfection. They include the following lingual lipase, amylase, mucin, lysozyme, haptocorrin. The enzymes that are secreted in the stomach are called gastric enzymes. The enzymes produced by the stomach are pepsinogen, Hydrochloric Acid (HCl), Intrinsic Factor (IF), gastrin. Two populations of cells in the pancreatic parenchyma make up its digestive enzymes; ductal cells stimulate acinar cells of the pancreas to produce their pancreatic enzyme. Acinar cells are mainly responsible for the production of inactivate pancreatic enzymes zymogens. Mancreatic juice, made up of the secretions of both ductal and acinar cells, composed of the following digestive enzymes trypsinogen, chymotrypsinogen, carboxypeptidase, elastases followed by pancreatic lipase as well ascholesterol esterase and also phospholipase, nucleases and lastly goes with pancreatic amylase. The enzymes/hormones are produced in the duodenum are secretin, cholecystokinin, gastric inhibitory peptide, motilin, somatostatin. Throughout the lining of the small intestine there are numerous "brush border" enzymes like sucrase, lactase and maltase [7].

Microflora

Gut (the adjective) is particularly get referenced with intestinal *flora* with microbiota and microflora.

Gut flora consists of microorganisms that live in the digestive tracts of animals and is the largest reservoir of human flora, are able to break down certain nutrients such as carbohydrates otherwise could not digest. A healthy adult has about 2 kg of these bacteria in the gut. Bacteria make up most of the flora in the colon and up to 60% of the dry mass of feces. Somewhere between 300 and 1000 different species live in the gut, with most estimates at about 500. However, it is probable that 99% of the bacteria come from about 30 or 40 species. Fungi and protozoa also exist in the gut flora, but little functions less. The majority of these common bacteria are anaerobe, which means they survive in an anaerobic environment. Normal flora bacteria can act as realistic pathogens at times of lowered immunity [8-12].

Most bacteria belong to the genera Bacteroides, Clostridium, Fusobacterium, and also Eubacterium, Ruminococcus, Peptococcus then after Peptostreptococcus, and specifically Bifidobacterium. Other genera and families like Escherichia and Lactobacillus possess the presence to a lesser extent. Species from the genus Bacteroides particularly constitute about 30% of all bacteria present in the gut, making that this genus is particularly important in the functioning of the host. The currently known genera of fungi in the gut flora include Candida, Saccharomyces, Aspergillus, and many more. Some bacteria with their range of incidence found in the large intestine of humans are *Bacteroides fragilis* (100), *Bacteroides melaninogenicus* (100), *Bacteroides oralis* (100), *Lactobacillus* (20-60), *Clostridium perfringens* (25-35), *Clostridium septicum* (5-25), *Clostridium tetani* (1-35), *Bifidobacterium bifidum* (30-70), *Staphylococcus aureus* (30-

50), *Enterococcus faecalis* (100), *Escherichia coli* (100), *Salmonella enteritidis* (3-7), *Klebsiella sp.* (40-80), *Enterobacter sp.* (40-80), *Proteus mirabilis* (5-55), *Pseudomonas aeruginosa* (3-11), *Peptostreptococcus sp.* (common), *Peptococcus sp.* (common) [13-16].

Transit time

In order to reach colon in an intact form, the drug delivery systems should pass the barriers in the stomach and then after the small intestine. Normally in certain conditions, the small intestinal transit is not being affected by any of the physical state, the size of the dosage form or the presence of food which is beared in the stomach. The mean transit time of the dosage form is estimated approximately at 3-4 hours to achieve the ileocecal junction. During this period the dosage form is fully in contact to enzymes are in small intestine. As by making comparison to the other region of GIT, passage of material through the colon is slow. The colonic transit time of a capsule basically deals with adult 20-35 hours. Improved residence time with reference to longer transit time and the contact of dosage form with micro flora in colon take over the release and absorption of the drug.

Any drug can set the proforma for colon targeted drug delivery. However, only those drugs, which show poor bioavailability from the stomach or intestine and peptide drugs, are the most common for colonic targeting. The ideal drug candidates for colonic drug delivery include agents that are useful for disorders such as intestinal bowel diseases, ulcerative colitis, and amoebiasis and colon cancer [17].

There are several ways in which drugs can be targeted on the colon when they are administered by mouth. In time-dependent formulations the drug concerned is released during the period of gastrointestinal transit time. Release from final drug formulations that contain pH-dependent polymers take place on the fact that pH is higher in the terminal ileum and colon than in the upper parts of the GIT tract. The colon is also placing to large numbers of bacteria of several kinds. Prodrugs and dosage combinely forms from which drug release is triggered by the action of colonic bacterial enzymes have therefore been devised (Table 2) [4,5].

Every system has advantages as well as disadvantages also. The poor site-specificity led to the starting of pH-dependent systems, because of large differences in the pH of the gastrointestinal tract, is very well documented. The site-specificity of timed-release dosage forms is considered poor because of large variations in gastric emptying time and passage across the ileo-caecal junction. However, microflora-activated systems based on non-starch polysaccharides are highly promising because the polysaccharide remain undigested in the stomach and the small intestine and can only be degraded by the vast anaerobic microflora of the specified colon. Moreover, this strategy exploiting the abrupt increase of the bacterial population and corresponding enzyme activities will also accomplish greater site specificity of initial drug release. The polysaccharides for colonic drug delivery are also inexpensive, naturally occurring and abundantly available [18,19].

Major polysaccharides involved in colon specific drug delivery system

Many natural polysaccharides such as chondroitin sulphate, pectin, dextran and more particularly guar gum, etc. has started with basis of investigation for their potential in innovating colon specific drug delivery. These are led to break down by the colonic microflora to simple saccharides. Most of the polysaccharide based drug delivery systems led to the protection of the bioactive from the hostile conditions of the upper gastrointestinal tract. Hydrolysis of the glycosidic linkages led to the arrival in the colon trigger the release proforma of the entrapped bioactive. The main saccharolytic species or we may say particular species which is responsible for this biodegradation are Bacteroides, Bifidobacterium and also Eubacterium, Peptococcus very specifically Peptostreptococcus and most importantly Ruminococcus, Propionibacterium, and Clostridium.

Pectin

Pectin is a polysaccharide that acts as a cementing material in the cell walls of all plants bearing tissues. Pectin is considered as methylated ester of polygalacturonic acid, which bears the chains of 300 to 1000 galacturonic acid units which is elegant joined with 1alpha→4 linkages. The degree of Esterification affects the gelling characteristics of pectin. The structure shown here has consisted of three methyl ester forms ($-COOCH_3$) for every two carboxyl groups (-COOH), hence it has a 60% degree of esterification property, normally resemble a Degree of esterification-60 pectin. Pectin is considered as a specified ingredient

Table 2. Different approaches used for colonic drug delivery.

Approach	Basic features
Chemical approaches	
Azo conjugates	conjugation *via* an azo bond
Cyclodextrin conjugates	conjugation *via* cyclodextrin
Glycosidic conjugates	conjugation *via* Glycoside
Glucuronide conjugates	conjugation *via* Glucuronide
Dextran conjugates	conjugation *via* dextran
Polypeptide conjugates	conjugation *via* polypeptide
Polymeric conjugates	conjugation *via* polymer
Pharmaceutical approaches	
pH dependent system	Formulation which is coated with enteric polymers release the specified drug when pH moves towards alkaline side
Time released system	Based on the conceptual mode of delaying the release of drug after a lag time of 3-5 hours that is equivalent to small intestine transit time
Pressure dependent system	Based on conceptual mode of the strong peristaltic waves that lead to a temporary increase in luminal pressure in the colon
Microbially triggered system Polysaccharides	Drug are released following degradation of the polymer due to the action of colonic bacteri
Osmotic controlled delivery	Based on the utilization of chitosan gelable properties at acid condition to produce osmotic pressure and its colon specific biodegradation to form in-situ delivery pores for drug release
Bioadhesive system	Drug coated with bioadhesive polymer they provide adhesive property at colonic mucosa
Micro particulate carrier system	Based on microparticles which absorb through macrophages present in colon and increase resident time of drug

Table 3. Colonic application of pectin.

Pectin	Bioactive	Dosage Form	Performance	References
Calcium pectinate	Indomethacin	Matrices	Enhanced drug release in rat caecal contents.	[22]
	Indomethacin	Compression coated/matrix tablet	*In-vitro* release increased in presence of pectinolytic enzymes and compression coat gave better results.	[23]
	Insulin	Compression coated/matrix tablet	Initial leak of insulin in both type of tablets *in-vivo* and additional protection required for colon delivery.	[24]
	Bovinserum albumin	Beads	Types of pectin and extent of cross-linking affect the targeting to the colon.	[24]
Zn-pectinate	Ketoprofen	Microparticle	Retards 5-37 times, the release in simulated intestinal fluid when compare to ca-pectinate.	[25]
Methoxylated pectin	Radioactive tracer	Compression coat	Drug protected in upper GIT and matrix degraded in colon. *In vitro*-results confirmed with *in-vivo* study.	[26]
	Paracetamol	Matrix tablet	Not suitable for colon delivery.	[27]
Amidated pectin	Indomemethacin, Sulphamethoxazole	Chitosan- coated beads	Release reduced in both simulated gastric and intestinal fluid. Released completed in 2 h in simulated colon condition.	[28]
	Theophylline	Enteric-coated microsphere	100% released was achieved with in less than 24 hr.	[29]

Table 4. Colonic application of chitosan.

Polymer	Drug	Dosage	Reference
Chitosan	5-acetyl salicylic acid	Matrices	[32]
Chitosan	Calcitonin	Microsphere	[33]
Chitosan/Kollicoat	5-acetyl salicylic acid	Film coated pellet	[34]
Chitosan	Sodium diclofenac	Microsphere	[35]
Chitosan coated pectin	Mangiferin	Beads	[36]
Chitosan/pectin	Erytrocin, Paracetamol	Film	[37]
Chitosan	5-fluorouracil	Matrices	[38]
Chitosan-Ca-alginate	5-acetyl salicylic acid	Microparticles	[39]
Chitosan-β-cyclodextrin Complex	Ketoprofen	Microsphere	[40]
Chitosan-Chondroitin sulphate	Metoclopramide	Microsphere	[41]

of fruit preserves, jellies, and jams [20]. Excessive solubility of pectin in water creates problem in the fabrication of colon targeted delivery systems. Pectin alone is unable to protect the vast load of drug as GI fluids quickly moves into and releases the drug by the means of the process called as diffusion. This problem can be ruled off through choice of suitable pectin type or in the presence of additives. Coating of pectin remains unaffected in presence of gastric and small intestinal enzymes, but is completely digested in the presence of colonic bacterial enzymes [21]. Different colonic applications of pectin are given in table 3.

Chitosan

Chitosan (CS) is natural aminopolysaccharides biopolymer having immense structural possibilities for chemical and mechanical modifications to generate novel properties as well as functions and also applications especially in the biomedical area. Commercially, it is produced by the exhaustive deacetylation of chitin (>60%), a structural element in the exoskeleton of crustaceans and insects, which is the second most abundant natural biopolymer after cellulose. The most easily exploited sources of chitin are basically the shell wastes of shrimp, lobster and also krill, and specifically the crab. In this era, several million tons of chitin are being harvested annually as per the sources.

This polymer is distinct from other commonly available polysaccharides due to the presence of nitrogen in specific properties like its molecular structure, it cationicity, and most importantly its capacity to form polyelectrolyte complexes. The cationic nature of the polymer allows it to become water-soluble after the formation of carboxylate salts, such as formate, particularly the acetate, lactate, malate and in a specified manner ascitrate, glyoxylate, pyruvate, glycolate, and ascorbate. Chitosan is an excellent excipient because it is non-toxic, stable, biodegradable, and can be sterilized. These properties also make chitosan a very versatile material with extensive application in the biomedical and biotechnological fields [30,31]. These attractive properties also make the polymer an ideal candidate for controlled release formulations.

Chitosan was selected as a drug carrier for colon-selective delivery of drugs based (Table 4) on its specific biodegradability by the specified enzyme, lysozyme, which is said to be highly concentrated in the mucosa, and with the help enzymes said to be secreted by the colonic bacteria, and also on its mucoadhesive character. In addition, Chiotosan has the advantage of being widely approved as a food ingredient, which suggests its acceptability as a new excipient for oral administration. Despite these promising characteristics, a limitation of Chitosan is its rapid dissolution in the gastric cavity. Chemical crosslinking with aldehydes has been, so far, a way of overcoming this problem [42].

Guar gum

It is a naturally occurring said to be as galactomannan polysaccharide; consists of chiefly high molecular weight hydrocolloidal polysaccharide, with galactan and mannan units combined through glycosidic linkages and shows degradation in the large intestine due to the presence of microbial enzymes.

It contains about 80% galactomannan, 12% water, 5% protein, 2% acid soluble ash, and 0.7% fat. Guar gum has a molecular weight of approximately particularly calculated as 1 million, with the providence of a high viscosity in solution. The high viscosity of guar gum results from both of its high molecular weight and long chain structure [43-46].

Guar gum is used to deliver of drugs to the colonic site because of its drug release retarding property and the susceptibility to microbial degradation in the large intestine. Being of the hydrophilic nature of guar gum, it swells in dissolution media causes the premature release of drug. So, in order to reduce the enomous swelling nature of guar gum various chemical modifications of guar gum has been developed in order to increase of hydrophobicity, in some cases it used in formulation by combining with the conventional hydrophobic polymers [47]. Various chemical modifications are as phosphate cross linked guar gum, hydrogels, borax cross linked guar gum, cross linked carboxy methylated guar gum, carbomylmethylated guar gum, hydroxyl propyl guar gum. Guar gum as Hydrogel was not suitable for colonic drug delivery (Table 5) because of fast delivery. Increases the crosslinking density leads to reduction in solvent uptake. Borax guar gum is a biodegradable nature, which is cross linked with borax. The time required to for degradation of this borax guar gum showed that release of the drug would be in proximal colon [48]. Phosphates cross linked guar gum showed the reduction of enomorous swelling nature of guar gum. Carboxymethylated guar gum is one of the chemically modified guar gum, which increases the solubility of guar gum, the anionic nature of this carboxy methylated guar gum is when cross linked with the oppositely charged ionic compounds helpful for reduction of swelling nature and promotes colonic delivery [49]. Carboxymethylated guar microspheres were also developed by dropping of CMG in divalent or trivalent metal ions. This cross linking nature helps in protecting the drug from environmental conditions of upper GIT. The cross linked structures are resistant to dissociation in acidic pH but slowly degrade in intestine. The crosslinking efficiency of trivalent ions was found to be more, due to of higher valency [50].

Chondroitin sulfate

Chondroitin sulphate (ChS) is polysaccharides that can potentially be used on the development of new therapeutic systems with a high specificity degree. Chondroitinsulfate, a soluble mucopolysaccharide consisting of beta-1-3, Dextro rotatary-glucuronic acid linked to N-acetyle-D-galactosamide utilized as a substrate by the bacteroid inhabitants of the colon. This mucopolysaccharide is found on animal connecting tissues, mainly on cartilages 4. Chondroitin sulphate serves as a substrate to colonic microflora, and in this portion of the GIT it is degraded by anaerobic bacteria, mainly *Bacteriodes thetaiotaomicron, B. ovatus* 4. However, since natural ChS is highly water-soluble, it becomes impossible to use it in an oral dosage form, because the polysaccharide would be promptly dissolved in the aqueous content of the digestive tube, completely releasing the drug. The cross linking reaction was done by Cavalcanti scientist between the carboxyl group in chondroitin and the amino group in diaminododecane, resulting in the formation of a dimer of chondroitin sulphate [65]. The crosslinked products have less water affinity, when we do a comparison to the natural polysaccharide. These results lead to the conclusion that modified ChS presents good perspectives for its use on modified release pharmaceutical formulations [62].

Table 5. Colonic application of guar gum.

Drug investigated	Methodology	Reference
Indomethacin	Tablet	[51]
5-fuorouracil	Tablet	[52]
Mebendazole	Immediate release tablet	[53]
Bovine serum albumin	Hydrogel	[54]
Theophylline	Matrix tablet	[55]
5- aminosalicylic acid	Tablet	[56]
Methotrexate	Microspheres	[57]
Sophoraalopecuroides (alkaloid)	Matrix tablet	[58]
Ibuprofen	Hydrogel	[59]
Celecoxib	Tablet	[60]
Ornidazole	Immediate release tablet	[61]

Table 6. Colonic application of chondroitin sulfate is as follows.

Polymer	Drug	Methodology	Reference
Chondroitin sulphate/Chitosan	Ovalbumin	Microspheres	[63]
Chondroitin 4-sulphate	Bovine serum albumin	Hydrogel	[64]
Chondroitin sulphate/Chitosan	5- fluorouracil	Microcapsule	[65]
Chondroitin/chitosan	Metoclopramide	Microsphere	[66]
Chondroitin/chitosan	Budesonide	Tablet	[67]

Table 7. Colonic application of dextran.

Polymer	Drug	Methodology	Reference
Dextran	Hydrocortisone	Hydrogel	[76]
Dextran/polyaspartamide	Beclomethasone- dipropionate	Hydrogel	[77]
Dextran	Hydrocortisone	Capsule	[78]
Dextran	Salmon calcitonin	Hydrogel	[79]
Dextran	Insulin	Hydrogel	[79]
Dextran	Propranolol- hydrochloride	Matrix tablet	[79]

Inulin

Inulin is a naturally occurring polysaccharide found in many plants, such as onion, garlic, chicory, artichoke. Chemically, it consists of 2-1 linked fructose molecules, which possess a glucosyl unit at the reducing end particularly. Inulin is not hydrolysed by the secretions of the human digestive tract. Bacteria present in the colon, especially bifidobacteria, which constitute up to 25% of the normal gut flora in man, are known to ferment inulin and to overcome the poor film forming property and to control the swelling of inulin's, and they have been evaluated for colon-targeting in combination with synthetic film forming polymers. The mixed films thus prepared resist degradation in the upper GIT and fermented in the colon by Bifidobacteria and Bacteroides. Vervoort and Kinget (1996) incorporated highly polymerised inulin in Eudragit RS films which were degraded in human fecal medium. Also, the permeability of these membranes increased significantly after incubation in the fecal medium. A series of studies were carried out on chicory inulin [68].

Vinyl groups were introduced in inulin chains to form hydrogels by reacting with glycidyl methacrylate. Methacrylate inulin was synthesized and aqueous solutions of Methacrylate inulin upon free radical polymerization were converted to cross-linked hydrogels. Rheological studies and characterization of their hydrogels showed that higher substituted inulin's had better network and higher mechanical strength. These hydrogels were then studied for their swelling properties and degradation in vitro. Degradation studies carried out in the presence of inulinase derived from *Aspergillus niger* showed that the increasing enzyme concentration and incubation time degraded inulin faster. However, increasing the substitution on inulin molecules resulted in stronger hydrogels with less enzyme diffusion thereby less degradation [69]. Maris, prepared and characterizedinulin-azo hydrogels designed for colon targeting [70].

Dextran

Dextrans are a class of polysaccharides consisting of alpha1, 3 and alpha-1, 6 glycosidic linkages and having unique properties, such as

Table 8. Recent patents granted for colon specific drug delivery.

Name of patented author	Patent specified	Year	Publication No.	References
Gulati Monica, Singh Sima, DuggalSanjiv, Satyakam Rahul, Sharma Mamta	Oral targeted drug delivery system	2014	US20140154312 A1	[80]
FH Richard	Compositions and methods of treatment for inflammatory	2014	US8629127 B2	[81]
Andremont A	Colonic release bills using Zn/ pectin with a coating of Eudragit;	2014	BRPI0719319 A2	[84]
John MA	Small peptides specifically bind to colorectal cancers.	2013	US8435490 B2	[82]
Helene CH	Site-specific intestinal delivery of adsorbents, alone or in combination with degrading molecules	2013	US8388984 B2	[83]
Tang L	A colon-targeted prodrug and its preparation method based on nano-cellulose carrier translated from Chinese	2013	CN103405778 A	[85]
Xi P	Indigestible polymer: starch acetate-based film coatings for colon targeting	2013	CN102883714 A	[86]
Basit AW	Colonic drug delivery formulation	2013	RS52434 B	[87]
Imamura N	Colon drug delivery system preparation	2011	JP2011105654 A	[88]
Moon YI	Development of mastic indicated for inflammatory bowel disease (IBD) applied with colon targeting drug delivery system (DDS)	2010	KR20100022200 A	[89]

biodegradability at specific body sites, e.g. the colon. Dextranases are the enzymes, which hydrolyse these glycosidic linkages. Dextranase activities on the colon are shown by anaerobic gram-negative intestinal bacteria especially the Bacteroides. The Bacteroides are the numerically predominant anaerobes in the colonic region of humans. They number about 1011 per gram of intestinal contents and constitute approximately 30% of total cultivable gut flora. The majority of strictly anaerobic bacteria in the colon are saccharolytic. The bacteria drive their energy from the fermentation of carbohydrates, which results in the production of short chain fatty acids [9]. Dextranase activity in human caecostomy effluent samples were reported to be 650 deltaunits/ml, equivalent to 30units/ml measured in conventional enzyme units and 15 deltaunits/gram equivalent to 0.69 Units/gram in human fecal samples [10]. Due to its degradability in the colon, dextran is an ideal candidate for oral drug delivery systems. However, dextran itself cannot be used as drug carrier due to its high water solubility and therefore the first need is to make it more hydrophobic [71,72].

Dextran is a polysaccharide which is suitable for colon drug delivery (Table 7), especially the high molecular weight types which are less soluble in the aqueous media. Previous studies on the chemical conjugation of budesonide with dextran using hemisuccinate spacer showed promising results as a prodrug for colon specific delivery of budesonide [73,74].

Various drug-dextran prodrugs in which the drug molecule is linked to the polar dextran macromolecule remain intact and unabsorbed from the stomach and the small intestine, but when the prodrug enters into the colonic microflora containing as much as 1011 Bacteroides per gram, it is acted upon by dextranases which cleave the dextran chain randomly and at the terminal linkages releasing the drug, free into the colon. Increasing interest is being focused on dextran prodrugs. The First attempt was carried out by Harbo (1989) who conjugated naproxen to dextran by an ester linkage. Dextran ester prodrugs of ketoprofen and naproxen using dextran with molecular weight 10 000-500 000 were shown to release the drug specifically in the colon region of pig. The release of naproxen was up to 17 times higher in the cecum and colon homogenates of pig than in control medium or homogenates of SI. A series of prodrugs, naproxen-dextran, ketoprofen-dextran and ibuprofen-dextran have been [75].

Cyclodextrins

Cyclodextrin (CD) is a family of cyclic oligosaccharides with a hydrophilic outer surface and also a lipophilic central cavity particularly. Cyclodextrin molecules are relatively large with a number of hydrogen donors and acceptors and, thus, in common way they do not involve in lipophilic membranes. Cyclodextrin are mostly called to be as "molecular cages". The cyclodextrins consist of vast and wide range of applications in different areas of drug delivery and pharmaceutical industry due to their complexation ability and other versatile characteristics. Cyclodextrin (CDs), with lipophilic inner cavities and hydrophilicsurfaces which is outer, are enough sufficient of interacting with a large variety of guest molecules to form noncovalent inclusion complexes. Cyclodextrin consists of (alpha-1,4)-linked alpha-glucopyranose unit with a lipophilic central cavity and the structures are as shown . Due to the chair formation of the glucopyranose units, cyclodextrin molecules are likely to be shaped as cones with secondary hydroxyl groups extending from the wider edge and the primary groups from the narrow edge. This provides the cyclodextrin molecules to be a hydrophilic outer surface, whereas the lipophilicity of their central cavity is comparable to an aqueous ethanolic solution. The naturally occurring cyclodextrins are mostly known to be as a, beta and gama types which contains 6, 7 and 8 glucopyranose units respectively [76].

Application of cyclodextrin in colon specific drug delivery

- Maestrelli developed microspheres for colonic drug delivery ketoprofen hydroxypropyl-beta-cyclodextrin complex [73].
- Yano developed colon specific drug delivery of prednisolone-appended alpha-cyclodextrin conjugate [74].
- Zou prepared and evaluated cyclodextrin based prodrug of 5-aminosalicylic acid [75].
- Kamel developed and evaluated cycldextrin based prodrug of anti-inflammatory drug Naproxan, Sulindac, Flurbiprofen [76].
- Fetzner developed beta-cyclodextrin incorporated film and studied degradation of film *via* enzymes and colonic bacteria [77].

Locust bean gum

It is also called carob gum, as it is derived from carob (Ceratonia siliqua) seeds. Locust bean gum has an shape of irregular molecule with branched beta1, 4-galactomannan units. This neutral polymer is only slightly soluble in cold water; it requires heat to achieve full hydration and maximum viscosity. Cross-linked galactomannan however, may initiate to water-insoluble film forming product showing degradation in colonic microflora particularly. The colon-specific drug delivery systems which are based on polysaccharides, locust bean gum and chitosan possess the ratio of 2:3, 3:2 and 4:1 were evaluated by the method of *in vitro* and *in vivo* methods. Core tablets which basically contain Mesalazine with average weight of 80 miligram were prepared by compressing the materials using 6-mm round and more specifically flat, and plain punches on a single station tablet machine in a systematic way. The formulated core tablets were resulted as a compression coated having different quantities of locust bean gum and chitosan. *In vitro* drug release studies and *in vivo* studies revealed that the locust bean gum and chitosan as a coating material applied over the core tablet was capable of protecting the drug from being released in the physiological environment of the stomach and small intestine and was susceptible to Colonic bacterial enzymatic actions with resultant drug release in the colon [78]. Dunstan *et al.* studied the rheology of locust bean gum and k-carrageenan and characterized by compression and shear measurements [79].

Mechanism to which polysaccharides work in reference with colon specific drug delivery

Coating with polymers

Whole drug molecule can be targeted at colon without absorbing in the upper part of the small intestine with a suitable coating of drug with a suitable polymer which has property to degrade only in the colon [78].

Coating with pH sensitive polymers

The pH sensitive system goes with the fact that as the pH value increases with the stomach to the small intestine, the phenomena of coating with Ph sensitive polymers on the drug delayed the action of release and protects it from gastric fluid or stomach. Example of some polymers is EUDRAGIT L 100, EUDRAGIT S100, Polyvinyl acetate phthalate etc.

Coating with biodegradable polymers

Examples are AZO polymers using styrene HEMA as cross linker etc.

Conclusion

Colon targeted drug delivery systems are exploited to selectively target the drug release to the colon. Several innovative steps have been made to achieve site specificity to the colon. The polysaccharides based colon specific drug delivery is relatively easy due to the presence of various derivatizable groups, wide range applicable to of molecular weights, vast chemical compositions, most particularly low toxicity and high stability. The selection of suitable polysaccharide is a critical parameter in the fabrication of colon specific drug delivery. The main limitation of this approach is their excessive water solubility. This high hydrophilicity cause to lose the strong network of polysaccharides and consequently drug is slowly released in the upper part of GIT. This can be overcome by using cross-linking agents. This particular approach has brought in a breakthrough in delivery system design and development.

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