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Review Article

NATURAL POLYSACCHARIDES AS DRUG TARGETING TOOL TO COLON: RECENT APPLICATIONS AND FUTURE PROSPECTIVE

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ABSTRACT

Colonic diseases like ulcerative colitis, Crohn's disease, and colon cancer are on rise due to variations in the dietary and lifestyle habits. Increase in prevalence of such diseases has augmented the interest of researchers in colon targeted drug delivery systems. Natural polysaccharide based drug delivery has emerged as one of the most successful approaches in this direction. Natural polysaccharides are the most commonly available plant ingredients with a wide range of applications in pharmaceutical and cosmetic industries. They can also be modified in different ways to obtain tailor-made materials for drug delivery systems and thus can compete with the available synthetic excipients. Polysaccharidase producing microflora in the large intestine could facilitate the use of polysaccharides as the carriers for the drug delivery to the colon site to cure the local diseases of the colon because they can be degraded at constant rate of drug release. Polysaccharides have been applied to the area as controlled release systems with external coatings, matrices formation, gelling agent, as macromolecular and biodegradable carriers. The purpose of this review is to discuss the use of such natural polysaccharides for their potential as colon-specific drug carrier systems such as chitosan, pectin, chondroitin sulphate, cyclodextrin, dextrans, guar gum, inulin, amylose and locust bean gum.

Keywords: Natural polysaccharides, gastrointestinal tract, colon targeted delivery.

1. INTODUCTION

Natural Polysaccharides have emerged as one of the most widely researched materials for enhancing the therapeutic effects of the existing drug molecules[1]. The colon is a diverse anddynamic environment, which is not yet fully understood. Until recently, colon wasconsidered as a water absorption and residualcarbohydrate fermentation site in the gastro intestinaltract[2]. The colon is a site where both local and systemic delivery of drugs can take place. Local delivery allow topical treatment of inflammatory bowel disease, ulcerative colitis, Crohn's disease, cirrhosis disease, amoebiasis, and colonic cancer, local treatment of colonic pathogens and systemic delivery of protein and peptide drugs[3]. Besides this low hostile environment, the colonic transit time (20-30 hours) and the colonic tissue is highly responsive to the action of absorption enhancers. Colonic delivery can be accomplished by oral or rectal administration[4].Colon-specific drug delivery systems designed to prevent drug release in the stomach and small intestine, and provide an abrupt onset of drug release upon entry into the colon[5]**.** The colon, as a site for drug delivery, offers distinct advantages on account of a near neutral pH, a much longer transit time, relatively low proteolytic enzyme activity, and a much greater responsiveness to absorption enhancers [6].

2. COLONIC DRUG DELIVERY

Site-specific drug delivery to the colon has attracted considerable attention for the past few years inorder to develop drug delivery systems

that are able to release drugs specifically in the colon in apredictable and reproducible manner. A chronic inflammatory disease such as ulcerative colitis requires dailytreatmentwith aminosalicylates, and in some cases even daily treatments with corticosteroids such as Prednisolone[7]. The site specific drug delivery to colon is important for the treatment of diseasesassociated with the colon, reducing the side effects of the drug and reducing the administered dose. Thepharmaceutical formulations available for this treatment are slow release oral formulations orenemas and foams for rectal administration[5].

2.1 Factors to be Consideredin the Design of Colon Specific Drug Delivery System:

2.1.1 Anatomy and Physiology of the GIT

The entire colon is divided into five major segments across its 150 cm length. The right colon consists of the cecum, ascending colon, hepatic flexure and the right half of the transverse colon. The left colon consists of the left half of the transverse colon, splenic flexure, descending colon, and sigmoid (Fig.1). The main functions of the colon are elimination of waste material, storage of feces and reabsorption of water and electrolytes. All colonic area are capable of storing function but with different storage capacity[8,9].

2.1.2 Gastrointestinal pH profile

The pH in the GIT is subjected to both inter and intra subject variations.Diet, diseased state and food intake influence the pH of the gastrointestinal fluid. The change in pH along the gastrointestinal tract has been used as a means for targeted colon drug delivery(Table-1) [10,11].

2.1.3 Gastrointestinal Transit Time

This is affected by the state of fed or fast, size and caloric content of the ingested food[9]. The movement of materials through the colon is slow and tends to be highly variable and influenced by a number of factors such as diet, dietary fiber content, mobility, stress, disease and drugs(Table.2)[10].

2.1.4 Gastrointestinal Microflora

The human colon is a dynamic and ecologically diverse environment, containing over 400 distinct species of bacteria with a population of 1011 to 1012 CFU/ml, with Bacteroides, Bifidobacterium, Eubacterium, Lactobacillus, etc greatly outnumbering other species[10]. It also contains over 400 species and most of them are anaerobes and bacteroids.

- Stomach (<1000 CFU/ml)
- Small intestine (103-104CFU/ml)
- Colon (1011-1012CFU/ml).

2.2 Absorption of Drugs from the Colon

Drugs are absorbed passively by paracellular or transcellular routes. Transcellular absorption involves the passage of drugs through cells and this is the route most lipophilic drugs takes, whereas paracellular absorption involves the transport of drug through the tight junctions between cells and is the route most hydrophilic drug takes. The poor paracellular absorption of many drugs in the colon is seen due to the fact that epithelial cell junctions are very tight[11,12].

2.3Limitationsof Colonic Drug Delivery[13,14]

- Due to its location at the distal portion of the alimentary canal, the colon is particularly difficult to access. However, the targeting of drugs to the colon is very complicated.
- In addition, the wide range of pH values and different enzymes present throughout the GI tract, through which the dosage form has to travel before reaching the target site, further complicate the reliability and delivery efficiency.
- The drug could potentially bind in a nonspecific manner to dietary residues, intestinal secretions, mucus or fecal matter. The resident microflora could also affect colonic performance via metabolic degradation of the drug.
- Lower surface area and relative 'tightness' of the tight junctions in the colon can also restrict drug transport across the mucosa and into the systemic circulation.

3. DIFFERENT APPROACHES FOR COLON TARGETING

3.1 pH-Dependent Systems

In this system, drug can be formulated as solid dosage forms such as tablets, capsules, and pellets and coated with pH sensitive polymers as enteric coated. Use of pH-dependent polymers is based on the differences in pH levels in the GIT. A pH-dependent polymer protects the formulation in the stomach and proximal part of the small intestine, it may start to dissolve in the lower part of small intestine, and the site-specificity of formulations can be poor. The example of various pH sensitive polymers (Eudragit L-100,Eudragit S-100, Eudragit L-30D, Eudragit L-100-55, Eudragit FS 30D, Hydroxy Propyl Methyl Cellulose Phthalate 50, Cellulose Acetate Phthalate, CelluloseAcetate Trimellate, Shellac) which will produce delayed release and also give protection from gastricFluids[15]. Limitations of these systems include[12]**;**

- Lack of consistency in the dissolution of the polymer at the desired site.
- Lack of site specificity of pH dependent systems.

3.2 Time-Dependent Systems

In this approach, the basic principle is the release of the drug after a predetermined lag timefrom dosage form at the site of action at right time and in right amount[16]. Ideally,formulation was to be designed that are not affected by the individual difference in gastricemptying time, pH of the stomach, small intestine or presence of anaerobic bacteria in thecolon at the site of delivery[17].

3.3 Pressure Controlled Drug Delivery Systems

Peristaltic movements of intestines along with gastric contractile activity are responsible for thepropulsion of intestinal contents. These peristaltic movements constitute elevated luminalpressure conditions in the colon. The design of pressure controlled drug delivery system isbased upon above mechanism. Intensity and duration of this pressure varies with the musculararcontractions in the visceral organs[15].

3.4 Microbially Triggered Systems

Among the different approaches for targeting colon, microflora activated systems appear to be more promising, since the abrupt increase of the bacterial flora and associated enzymatic activity in the colon represents a non-continuous event among all approaches, independent of the GI transit time and pH.Microflora present in the colon survives by fermenting the various types of substrates such as non-starch polysaccharides, carbohydrates and fibers that have been left undigested in the small intestine. The microflora of the human gastrointestinal tract consists of a coexisting mixture of aerobic and anaerobic bacteria in a complex ecosystem especially in colonic region[5].

More commonly the anaerobic bacteria (Bifidobacteria, Bacteroides, Eubacteriumetc) present in the colon are able to react to the constantly changing the complex mixture of different polysaccharides entering into the colon by recognizing a variety of substances and producing the appropriate digestive enzymes. This approach triggers the drug release mechanism from the dosage form, which shows a promising mechanism to target the colon over pH and time dependant and prodrug approaches [3]. Few colonic bacterial species involved in the degradation of polysaccharides are showed in Table.3. In this review article we have made an attempt to focus on the natural polysaccharide based colon delivery systems.

4. NATURAL POLYSACCHARIDE BASED DRUG DELIVERY

Natural polysaccharides have been used as tool or carriers to deliver the drugs specifically to the colon. These polysaccharides remain intact in the physiological environment of stomach and small intestine but the once dosage form enters into the colon, it is acted upon by polysaccharidases, which degrade the polysaccharide and release the drug into the vicinity of bioenvironmental of colon[18]. 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 andswell 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. 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[20].

4.1 Need of Natural Polysaccharides[20]

1. Biodegradable- Naturally occurring polymers produced by all living organisms.They show no adverse effects on the environment or human being.
2. Biocompatible and non-toxic- Chemically,nearly all of these plant materials are carbohydrates in nature and composed of repeating monosaccharide units. Hence they are non-toxic.
3. Economic- They are cheaper and their production cost is less than synthetic material.
4. Safe and devoid of side effects- They are from a natural source and hence, safe and without side effects.
5. Easy availability- In many countries, they are produced due to their application in many industries.

4.2 Pharmaceutical Applications of Natural Polysaccharides[21]

4.2.1As Tablet Adjuvants

Natural Polysaccharides find applications in tablet formulation as binders because of their adhesive nature. They impart cohesiveness to the powder mass and convert them into granules, which are further compressed into tablets. They can also be used as disintegrantsin tablets. The disintegrant property of Natural Polysaccharides is due to their ability to absorb water and swell.
e.g.Guar gum, Gum acacia.

4.2.2 As Emulsifying and Suspending Agents
Natural Polysaccharides can act as emulsifying and suspending agents. They can effectively stabilize the emulsion via interfacial absorption and the subsequent formulation of condensed films of high tensile strength that resist coalescence of droplets.
e.g. Gum acacia, Xanthan gum.

4.2.3 As Sustaining Materials in Dosage Forms
Among various dosage forms, matrix tablets are widely accepted for oral sustained release as they are simple and easy to formulate. Matrix system is the specific type of release system, which prolongs and controls the release of drug that is dissolved or dispersed.
e.g.Locust bean gum, Xanthan gum, Karaya gum.

4.2.4 As Coating Agents
Many Natural Polysaccharides act as good coating agents, which can sustain the drug release, or can protect the drug from degradation in stomach.
e.g. Sodium alginate,pectin.

4.2.5 As Gelling Agents
Gums and mucilage's can form base for gels either alone or in combinations with others. Gelling is a results of numerous inter and intra molecular associations to produce a three-dimensional network, within which the water molecules areentrapped. Such associations are brought about by either physical (pH change, altering temperature) or chemical (addition of suitable reagents) treatments.
e.g. Carrageenan, Locust bean gum.

4.2.6 As Mucoadhesive Agents
Mucoadhesive drug delivery techniques are primarily controlled release drug delivery systems, which gets retained in the stomach for longer periodof time, thus helping in absorption of drug for the intended duration of time.
e.g. Sodium alginate, Karaya gum.

4.3 Intestinal Metabolism of Polysaccharides
The microbial ecology of the intestine exhibits an astonishing degree of spatial and temporalcomplexity that defining microflora as "normal" is a daunting task. At least 500 bacterial speciescolonize the adult intestine, with 30-40 species comprising up to 99% of the total population[21,22].
The colonic bacteria are predominately anaerobic in nature and secrete enzymes that are capable of metabolizing substrates such as carbohydrates and proteins that escape the digestion in the upper GI tract. The bacterial amount has been estimated about 10 per gram in the colon and having around 400 species (anaerobic in nature). The important bacteria present in the colon such as Bacteroides, Bifidobacterium, Eubacterium, Peptococcus, Lactobacillus, Clostridium secrete a wide range of reductive and hydrolytic enzymes such as β-glucuronidase, β-xylosidase, β-galactosidase, α-arabinosidase, nitroreductase, azoreductase, deaminase and urea hydroxylase. These enzymes are responsible for degradation of di-, tri- and polysaccharides (Table.3)[23].

4.4 Mechanism of Drug Release from Polymers[24]
4.4.1 Diffusion
Diffusion occurs when a drug or other active agent passes through the polymer that forms the controlled-release device. Diffusion occurs when the drug passes from the polymer matrix into the external environment. As the release continues its rate normally decreases with this type of system since the active agent has a progressively longer distance to travel and therefore requires a longer diffusion time to release.

4.4.2 Degradation
Biodegradable polymer degrades within the body as a result of natural biological processes, eliminating the need to remove a drug delivery system after release of the active agent has been completed. Most biodegradable polymers are designed to degrade as a result of hydrolysis of the polymer chains into biologically acceptable and progressively smaller compounds. For some degradable polymers, most notably the polyanhydrides and polyorthoesters, the degradation occurs only at the surface of the polymer, resulting in a release rate that is proportional to the surface area of the drug delivery system.

4.4.3 Swelling
They are initially dry and when placed in the body will absorb water or other body fluids and

swell. The swelling increases the aqueous solvent content within the formulation as well as the polymer mesh size, enabling the drug to diffuse through the swollen network into the external environment.

5. SOURCES OF POLYSACCHARIDES FOR TARGETINGCOLON [3]

The naturally occurring polysaccharides obtained from different sources such as plant, animal, algal, microbial and fungal sources.

- **Plant Source**
  Starch polysaccharides (Starch, Cellulose, Amylose),Pectin, Guar gum, Inulin, Loctus bean gum,Glucomannan,Khaya andAlbizia gum.
- **Animal Source**
  Chitosan, Chondroitin sulphate, Hyaluronic acid.
- **Microbial Source**
  Dextrans, Cyclodextrins, Curdlan, Gellan Gum, Xanthan Gum.
- **Algal/ Sea Weed Source**
  Alginates, Carrageenan.
- **Fungal Source**
  Scleroglucan, Pullulan.

5.1 Plant Source

5.1.1 Starch Polysaccharides

5.1.1.1 Starch

Starch is a polymer, which occurs widely in plants.In general, the linear polymer, amylose, makes upabout 20 % wt of the granule, and the branchedpolymer, amylopectin, the remainder. Amylose iscrystalline and can have a number averagemolecular weight as high as 500000, but it issoluble in boiling water. Amylopectin is insolublein boiling water, but in their use in foods, bothfractions are readily hydrolyzed at the acetal link byenzymes. The α-1, 4-link in both components ofstarch is attacked by amylases and α-1,6-link in amylopectin is attacked by glucosidases (Fig.2). Starch has been evaluated for colon-targeted delivery as enteric-coated capsules. The useof resistant starch was studied for the improvement of gut microflora and to improve clinical conditionsrelated to inflammatory bowel diseases, immuno-stimulating activities, and protection from colon cancer. The resistant starch was modified chemically, preferably by etherification, esterification, or acidification[5].

5.1.1.2 Cellulose

Cellulose was isolated for the first time some 150 years ago. Cellulose is the most widespread polysaccharide in Nature. It forms the primary structural component of plants and is made of repeated units of the glucose monomer. The molecular chain of cellulose is being very long and consisting of one repeating unit (cellobiose). Cellulose occurs in a crystalline state. From the cell walls, cellulose is isolated in microfibrils by chemical extraction. In all forms, cellulose is a very highly crystalline, high molecular weight polymer, which is insoluble in all but the most aggressive, hydrogen bond breaking solvents such as N-methylmorpholine-N-oxide. Cellulose is not much used as a potential carrier for the polysaccharide based colonic drug delivery system(Fig.3)[25].

5.1.1.3 Amylose

Amylose is a polysaccharide obtained from plant extracts and a component of starch presents in normal diet.Amylose is a poly (1-4-α-D-glucopyranose) that consists of D-glucopyranose residues linked by α- (1-4) bonds(Fig.4). Amylose is nontoxic to body, and easily available with resistant to pancreatic α-amylase, but is degraded by colonic bacterial enzyme. Mixed films of amylose and ethyl cellulose as coatingshave shown a great potential as colon delivery carriers. Delayed release compositions comprising glassy amylase and an active compound were designed to permit the release when the composition reaches the large intestine. Milojevic*et al.* formulated a system which is resistant to gastric acid and small intestine enzymes by Amylose- Ethocel coating system. This system easily degradable by colonic bacteria were prepared and evaluated in vitro for their potential as colon drug carrier. Varying concentrations of Amylose and Ethocel in the form of aqueous dispersions were used to coat 5-ASA pellets. A coating formulation comprising Amylose and Ethocel in the ratio of 1:4 w/w showed optimum drug releaseretarding properties in gastric and intestinal fluids[3,25].

5.1.2 Pectins

Pectins are non-starch linear polysaccharides that consist of α-1,4 D-galacturonic acid and 1,2 D-rhamnosewith D-galactose and D-arabinose side chains having average molecular weights between50,000 to 150,000 (Fig.5). Pectin tends to produce lower viscosities than other plant gums. Itis refractory to host gastric and small intestinal enzymes but is almost completely degraded by thecolonic bacterial enzymes to produce a series of soluble oligalactorunates[25]. Depending onthe plant source and preparation; they contain varying degrees of methyl ester substituent.Pectin is highly soluble in water, which put hurdles in the development of colon targeted drug deliverysystems. If used alone it

swells when it comes in contact with aqueous fluids of GIT and causes therelease of the entrapped drug through the diffusion.This problem can be manipulated through choice of pectin type or the presence of additives[26]. Another way to alleviate this problem is by the use of hydrophobic polymers, e.g., ethylcellulose. Itrestricts the entry of water and consequently swelling of polymer. Moreover, a better shieldingeffect can be obtained by reducing the solubility of pectin by forming its calcium salt, calciumpectinate. The degree of methylation (DM) has an essential influence on the properties of pectin,especially on its solubility and its requirements for gelation, which are directly derived from thesolubility. The DM of 50% divides commercial pectins into high methoxypectins and low methoxypectins. These two groups of pectin are gelled by different mechanisms. High methoxypectinsrequire a minimum amount of soluble solids and a pH within a moderate range around 3 to form gels. Low methoxypectins require the presence of a controlled amount of calcium ions for gelation andneed neither sugar nor acid. Low methoxy pectin gelation resembles the behavior of alginate(Table.4)[5].

Ashford *et al.* developed matrix tablets of calcium pectinate which had showed promising results *in- vitro*. Rubinstein *et al.* formulated Indomethacin matrices using pectin, the drug release was triggered by rat caecal content microflora and was found to be 60.8±15.7% as compared to 4.9±1.1% in control media (buffer media)[3].

Pectin is a non-toxic, biodegradable carrier which is selectively degraded into the colon. Many scientists worked on pectin polymer as a single entity and as in combination with other polysaccharides[27].

5.1.3 Guar Gum

A natural galactomannan polysaccharide obtained from the ground endosperms of Cyamposistetragonolobus, this gum chiefly contains high molecularweight hydrocolloidal polysaccharide, composed of galactan and mannan monomeric units combined throughglycosidic linkages and shows degradation in the large intestine due the presence of microbial enzymes[3]. The structure of guar gum is a linear chain of β-D-mannopyranosyl units linked (1→4) with single member α-D-galactopyranosyl units occurring as side branches (Fig.6) (Table.5). Guar gum has a molecular weight of approximately 1 million, giving it a high viscosity in solution. This galactomannan is soluble in cold water, hydrating quickly to produce viscous pseudoplastic solutions that although shear-thinning generally have greater low-shear viscosity than other hydrocolloids[5]. This gelling property retards release of the drug from the dosage form, and it is susceptible to degradation in the colonic environment[3].

Krishnaiah*et al*studied the influence and usefulness of guar gum as a colon-specific drug carrier, based on the metabolic activity of colonic bacteria, using matrix tablets of albendazole (containing 20% of guar gum) as a model formulation. Badmapriya*et al*formulated5-Aminosalicylic acid matrix tablets using guar gum for colon targeting. These tablets were coated with polymeric layers, to protect them from gastrointestinal environment.

Guar gum is used as a thickener in cosmetics, sauces, as an agent in ice cream that prevents ice crystals from forming and as a binder or as disintegrator in tablets.

5.1.4Inulin

Inulin is a naturally occurring storage polysaccharide found in many plants such as onion, garlic, artichoke, and chicory. Chemically, it belongs to the glucofructans and consists of a mixture of oligomers and polymers containing 2 to 60 (or more) β-2-1 linked D-fructose molecules (Fig.7) and (Table.6)[5]. Inulin is resistant to digestion in the upper gastrointestinal tract, but is degraded by colonic microflora.Inulin with a high degree of polymerization was used to prepare biodegradable colon-specific films incombination with Eudragit® RS that could withstand break down by the gastric and intestinal fluids. Itwas shown in another study where different Eudragits® were formulated into films with inulin that when a combination of Eudragit® RS and Eudragit® RL was mixed with inulin it exhibited better swelling and permeation properties in colonic medium rather than other gastrointestinal media[28].

Inulin derivatised with methacrylic anhydride and succinic anhydride produced a pH sensitive hydrogelby UV irradiation that exhibited a reduced swelling and low chemical degradation in acidic medium, butit had a good swelling and degradation in simulated intestinal fluid in the presence of its specific enzyme,inulinase[5].

5.1.5 Locust Bean Gum

Locust bean gum is also called carob gum, as it is derived from carob seeds of the plant called Ceratoniasiliqua belongs to the family Leguminosae. This gum has β-1, 4-Dgalactomannan units branched together (Fig.8). As this polysaccharide slightly soluble in

cold water; it requires heat to achieve full hydration and maximum viscosity. However this cross linked branches led to water-insoluble film forming product-showing degradation by colonic enzymes produced from colonic microflora to release the drug from the system. Ragavan C V *et al*. optimized ratios of locust bean gum with chitosan in the ratio of 2:3, 3:2 and 4:1. The *in-vitro* studies conducted in pH 6.8 phosphate buffer containing 2% w/v rat caecal contents showed that the cumulative percentage release of Mesalazine after 26 hr was 31.25 ± 0.56, 46.25 ± 0.96, and 97.5 ± 0.26, respectively. This indicates the increase in the ratio of locust bean gum on chitosan given good result among all[3,29].

5.1.6 Glucomannan

Glucomannan is a high-molecular weight watersoluble non-ionic Glucomannan extracted from tubers of the plant Amorphophalluskonjac belongs to the family Araceae. Konjacglucomannan is a linear random copolymer of (1→4) linked β-D mannose and β-D-glucose (Fig.9). It is similar to pectin, which is not hydrolyzed by digestive enzyme in human being and is considered as an indigestible dietary fiber that has received recognition for reducing the risk of developing diabetes, heart disease and insulin-resistance syndrome[30]. KGM could be hydrolyzed by β-mannanase to form manno-oligosaccharides which play important roles in biological systems[3].

5.1.7 Khaya and Albizia Gum

Khaya gum is a natural plant polysaccharide obtained from the incised trunk of the tree Khayagrandifoliola belongs to the family Meliaceae. Khaya gum contains D-galactose, L-rhamnose, D-galacturonic acid and 4-O-methyl-Dglucoronic acid. Most commonly it is used as a binding agent in tablet formulations**.** Khaya gum is a hydrophilic polymer and has been shown to possess emulsifying properties comparable with acacia gum. And also have a lot of advantages such as non-toxic, cost effective and easily available which make fostered the interest in developing the gum for pharmaceutical use. It can be used in directly compressible matrix system in the formulation of controlled release tablets[3].

In another hand, Albizia gum is obtained from the incised trunk of the tree Albiziazygia belongs to the familyLeguminosae. It consists of β-1– 3-linked D-galactose units with some β-1-6-linked D-galactose units. The genus *Albizia*containing twenty-six species is a member of the Mimosacez, a family which also includes the gum-bearing genera *Acacia* and *Prosopis.* Only two species of *Albizia, A. zygia*and *A. sassa*are however known to produce gum. Albizia gum has been investigated as a possible substitute for gum Arabic as a natural emulsifier for food and pharmaceuticals[31].

Important uses of these gums are;

- The granular grades are used as a bulk laxative.
- The powdered gum is used in lozenges, pastes and dental fixative powders and it has proved particularly useful as an adhesive for stoma appliances.
- The cross linked Tragacanth (Epichlorhydrin) exhibits superior wicking and swelling action and hence can be used as a potential disintegrant.

5.2 Animal Source

5.2.1 Chitosan

Chitosan is a polycationic polysaccharide derived from naturally occurring chitin by alkaline deacetylation. Chemically, it is a poly (*N*-glucosamine)(Fig.10)**.** Chitosan has favourable biological properties such as nontoxic in nature, biocompatibility**,** and biodegradability in humans[3]. Chitosan is soluble in dilute acid but precipitates at a pH above 7. Because of the solubility of chitosan at low pH ranges, its successful use in colon-specific delivery requires an enteric coating over the chitosan which would protect it against the acidic nature of the stomach. As the formulation reaches the intestine, the pH increases and the enteric coat dissolves releasing the chitosan coated core (where drug present). These cores are acted upon by microflora especially bacteroides of the colon, degrading the chitosan and releasing the drug. Microspheres of sodium diclofenac were prepared by spray drying technique using chitosan. These microspheres were enteric coated with Eudragit L-100 or Eudragit S-100. Eudragit coating gave a pH dependent release profile and the change in molecular weight of chitosan or use of different salt like chitosan glutamate could control the release rate of sodium diclofenac from the core [32].

Important uses of chitosan are;

- Chitosan microspheres have several applications in novel drug delivery systems.
- Chitosan is degraded by the microflora that is available in the colon and it was found to be promising for colon-specific drug delivery.
- It is a muco/bioadhesive polymer, so it is considered a good candidate for oral cavity drug delivery.

5.2.2 Chondroitin Sulphate

Chondroitin sulfate is a soluble mucopolysaccharidethat is used as a substrate by the bacteroid inhabitants. Chondroitin sulfate is a sulfated glycosaminoglycan (GAG) composed of a chain of alternating sugars (Nacetylgalactosamine and glucuronic acid)(Fig.11). The natural chondroitin sulphate is readily soluble in water, this is the major disadvantage of chondroitin sulphate to protect drug from upper GI tract. However, crosslinked chondroitin sulfate would be less hydrophilic and thus would provide a better shield to the drug core and promising the drug release in colon part. Crosslinking of chondroitin sulphate with 1, 12diaminododecanewas done using dicyclohexylcarbodiimide as a catalyst and formulated in a matrix with indomethacin as a drug core. The indomethacin release kinetics from the various formulations was analyzed in Phosphate buffer solution with and without rat caecal content at 37°C under carbon dioxide purging. It was concluded that the release of indomethacin depended upon the biodegradation action of the caecal content[3].

5.2.3 Hyaluronic Acid

Hyaluronic acid (HA) is a naturally occurring biopolymer which can be used in colon specific drug delivery systems. HA found in the tissue of animals, in particular as intercellular space filler and synovial fluid of articular joints. Its high level of biocompatibility has been the major advantage of this polymer to use in drug delivery systems. It is a linear, unbranched, polyanionic disaccharide consisting of glucuronic acid (GlcUA) and N-acetyl glucosamine (GlcNAc) joined alternately by β-1-3 and β-1-4 glycosidic bonds (Fig.12). It is a member of the glycosaminoglycan family and is a kind of biopolymer with wide uses, but still there are a lot of experiments to be investigated compared with other polysaccharides such as chondroitin sulphateetc., for understanding of this interesting biodegradable polysaccharide and more promising in colon drug delivery[5].

5.3 Microbial Source

5.3.1 Dextrans

This class of polysaccharide consists of linear chains of α-D glucose molecules, 95% of the chainsconsists of 1:6-α-linked linear glucose units while the side chains consist of 1:3-α-linked moieties. They are obtained from microorganisms of the family of Lactobacillus (Leuconostocmesenteroides)(Fig.13). Dextrans are colloidal, hydrophilic, and water-soluble substances, inert in biological system, and do not affect cell viability. Dextranases are the enzymes that hydrolyzeglycosidic linkages of the dextrans. Anaerobic Gram-negative intestinal bacteria show Dextranase activity of the colon especially by the Bacteroides[5]. Various dextran ester prodrugs have been prepared and evaluated for their efficacy to deliver the drug to the target organ, i.e., colon. Harboe et al.synthesized dextran ester prodrug. The side effects of steroid therapy, which are used in the treatment of chronic colitis, may be decreased by selectively delivering drug to the colon. One potential way of achieving this is to attach the drug to dextran, a polar macromolecule that prevents drug absorption in the small intestine [33].

5.3.2 Cyclodextrins

Cyclodextrins (CyDs) are cyclic oligosaccharides consisting of six to eight glucose units joined through α-1, 4 glucosidic bonds (Fig.14). CyDs remain stable during their passage through stomach and small intestine. As they reach to the colon, they undergo fermentation from the presence of dynamic colonic microflora into small saccharides and thus absorbed from these regions.CyDs form inclusion complexes with drug molecules because the interior of the molecule is relatively lipophilic while the exterior is hydrophilic. Ester conjugates of biphenylyl acetic acid with β- cyclodextrin released the drug preferentially whenincubated with rat's cecal contents and almost no release was observed on incubation with contents of stomach and small intestine[34].

5.3.3 Curdlan

Curdlan is a neutral, essentially linear (1→3)-β-glucan which may have a few intra- or inter-chain(1→6) linkages. Curdlan's unusual rheological properties among natural and syntheticpolymers underlie its use as a thickening and gelling agent in foods. Apart from being tasteless,colourless and odourless, the main advantages are that in contrast to cold-set gels and heat-set gels, theheating process alone produces different forms of curdlan gel with different textural qualities,physical stabilities and water-holding capacities. Gels of variable strength are formed depending onthe heating temperature, time of heat-treatment and curdlan concentration. The safety of curdlan hasbeen assessed in animal studies and *in-vitro* tests and it is approved in food use in Korea, Taiwan andJapan as an inert dietary fiber. It is registered in the USA as a food additive[35].

5.3.4 Gellan Gum

Gellan gum is an anionic microbial polysaccharide produced by fermentation of

pure culture of Sphingomonas elodea. The production organism is an aerobic, well characterized, nonpathogenic, and gramnegative bacterium. Gellan gum is available in two types, high and low based on the acyl content. Low acyl gellan products form firm, non-elastic, brittle gels, whereas acyl gellan gum forms soft, very elastic non-brittle gels.The general chemical structure of gellan gum consists of four linked monosaccharides including one molecule of rhamnose, one molecule of glucuronicacid, and two molecules of glucose. Gellan gum is water soluble, off white powder. It has a molecular weight greater than 70,000 daltons. It forms gels when cations are added[36]. HetangiRathod et al have done development, evaluation, and optimization of gellan gum based in situ gel using ambroxol-HCl as a model drug and it was concluded that gellan gum is excellent of sustain release formulation[37].

Important uses of gellan gum[36] are;

- It has applications in diverse fields in the food, pharmaceutical and many other industries.
- Gellan gum is one of the most interesting *in situ* gelling plymers that have been tested since it seems to perform very well in humans.

5.3.5 XanthumGum

Xanthan gum is a high molecular weight extra cellular polysaccharide produced by the fermentation of the gram-negative bacterium xanthomonascampestris. The primary structure of this naturally produced cellulose derivative contains a cellulosic backbone (β-d-glucose residues) and a trisaccharide side chain of β-d-mannose-β-d-glucuronicacid-α-d-mannose attached with alternate glucose residues of the main chain. The anionic character of this polymer is due to the presence of both glucuronicacid and pyruvic acid groups in the side chain[36]. The formulation and characterization of 5-flourouracil matrix tablets by using xanthum and pectin gum was studied for colon targeted drug delivery by yaswanthallamneni et al.

5.4 Algal/ Sea Weeds Source

5.4.1 Alginates

Alginates are one of the most commonly used algal source polysaccharide. These are natural hydrophilicpolysaccharides obtained from seaweed, consist of 1→4, linked D-mannuronic acid and L-glucuronic acid residues (Fig.15). Alginates are easily gelled in presence of a divalent cation as calcium ion. Calcium alginates beads can be prepared by drop-wise addition of the solution of sodium alginate into the solution of calcium chloride. The alginate beads have the advantage of being nontoxic, and dried alginate beads reswell in presence of dissolution media and can act as controlled release systems. Shun Y L *et al.*, formulated Calcium alginate beads as cores and 5-ASA was spray-coated on them[3].

5.4.2 Carrageenan

Carrageenans are present as structural components in various species of red seaweeds (*Rhodophyceae*). The three main types which are readily available commercially are kappa, Iota and lambda. Kappa is obtained from *Euchemacottonii*species and occurs together with lambda carrageenan in *Chondruscrispus*. Iota carrageenan is obtained from *Euchemaspinosum*. They differ essentially in their degree of sulphation.

The carrageenan backbone is based on a disaccharide repeat unit of β- D - galactopyranose residues linkedthrough the 1 and 3 positions and α- galactopyranose residues linked through the 1 and 4 positions. For bothkappa and Iota carrageenan the latter occurs in the 3, 6, anhydro form. Kappa carrageenan has a sulphate group at the 4 position of the β- D–galactopyranose[3]. Residues while iota carrageenan is sulphated additionally at the C2 position of the β- D-galactopyranose residues. Lambda carrageenan is further sulphated and consists of (1, 4) linked galactopyranose 2, 6 disulphate and (1, 3)-linked galactopyranose which are 70% substituted at the C2 position(Table.7)[3].

Important uses of Carrageenans are;

- Carrageenans are large, highly flexible molecules that curl forming helical structures, ability to form a variety of different gels at room temperature.
- They are widely used in the food and other industries as thickening and stabilizing agents.
- Carrageenan is a good substitute for gelatin in hard and soft gel capsules.
- It forms stable emulsions with insoluble drug preparations, enhances homogeneity in colloidal suspension, film forming agent in crystalclear soft capsules, acts as gelling agent in antacid gels.

5.5 Fungal Source

5.5.1 Scleroglucan

Among thesemacromolecules, scleroglucan (Sclg) also seems to be potentially useful for the formulation of modified release dosage forms and numerous studies have been devoted to this specific topic[5]. Scleroglucan (Sclg) is a branched homopolysaccharide consisting of a main chain

of (1-3)-linked β-D glucopyranosyl units bearing, every third unit, a single β-D-glucopyranosyl unit linked (1-6). This polysaccharide is resistant to hydrolysis and its solutions show an interesting rheological behavior: viscosity remains practically constant, even at high ionic strength, up to pH-12 and to 90°C [3].

The commercial product is termed Scleroglucan, but it is also known as with other brand names (e.g., Actigum, Clearogel, Polytetran, Polytran FS, Sclerogum)[38]. In pharmaceutical products, Sclg may be used as a laxativein tablet coatings and in general to stabilize suspensions. The use of Sclg as an antitumor agent and antiviral compound has also been investigated. Sclg has shown immune stimulatory effects. Compared with other biopolymers and its potential contribution to the treatment of many diseases should be taken into account in therapeutic regimens stillSclg as a successful agent for colonic disorders is to be investigated.

5.5.2 Pullulan

Pullulan is obtained from Fungi called aurebasidiumpullalans from the extracellular part. The main chain ofpullulan consists of Maltotriose in α-(1, 4) with side chains connected by α-1, 6 linkage. This carrier is not commonly used for the polysaccharide based drug delivery of colon. However, there is a need of research remains to be conducted and investigated to bring pullulan to use as a potential carrier for the colon specific drug delivery[39].

6. CONCLUSION

Over the past two decades, exciting innovations in colon targeted drug delivery have shown unprecedented potential for increasing the efficacy of drugs for colonic diseases. The polysaccharide based colon targeted delivery systems that have been reported are simple to use, effective and much safer for the patients as compared to the conventional dosage form.

In conclusion, polysaccharides appear to be promising agents for obtaining colon-specific drug delivery systems. This article has described the different polysaccharides that have already been used in the initial approaches for colon specific drug delivery. These natural polymers are strongly appealing to use in a truly colon-specific commercially available drug delivery system. The reasons for this are that they are nontoxic, easy to work with, and will be FDA approved. Also very important is that they are selectively degraded in the colon.

The Natural polysaccharides approachwhich shows a promising mechanism to target the colon over pH and time dependant and prodrug approaches. Among these guar gum, amylase, chitosan and pectin's are the most commonly used promising carriers for the colon specific drug delivery systems. A mixed ratio of these polysaccharides seems to be encouraging area for further research. The combination of colon-specific polysaccharide and insoluble polymer which is to prevent swelling and premature drug release has achieved consistent colonic targeting with a variety of drug molecules.

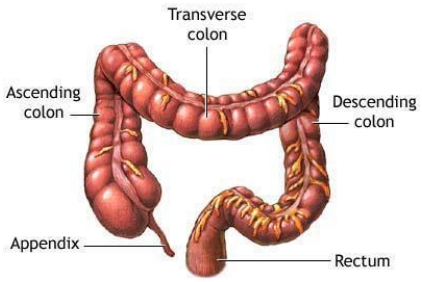

Fig. 1: Structure of Colon

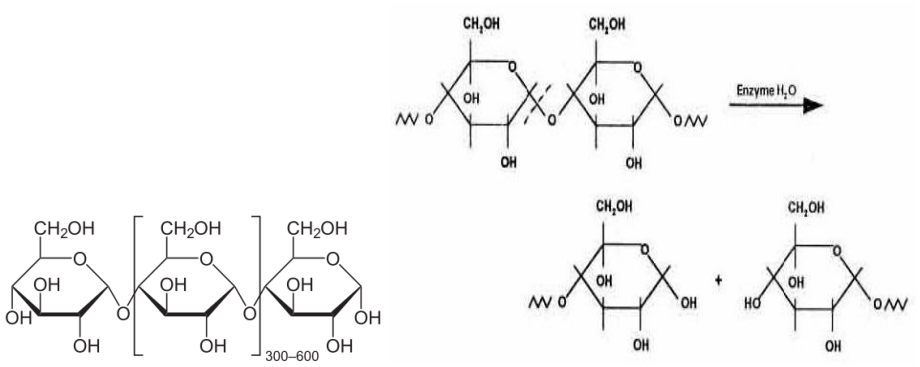

Fig. 2: Starch and its degraded products

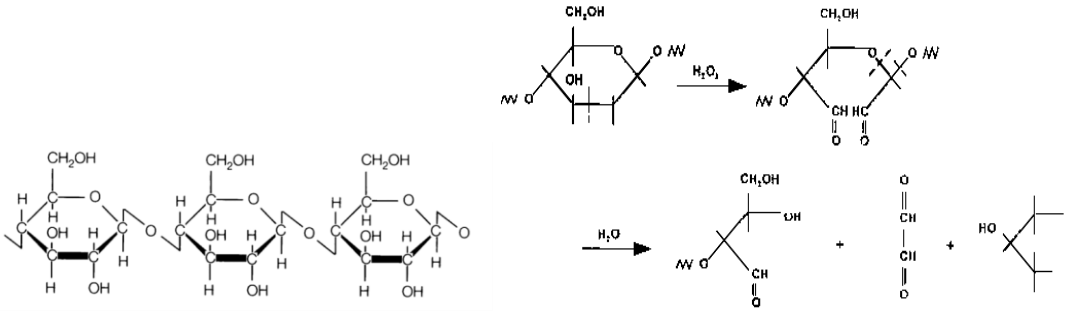

Fig. 3: Cellulose and degraded products

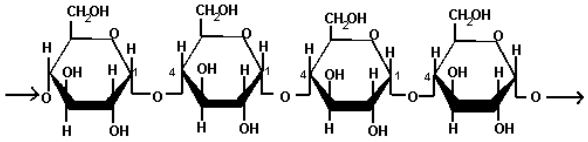

Fig. 4: Amylose

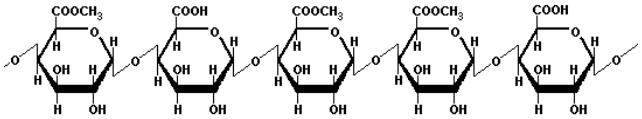

Fig. 5: Pectin

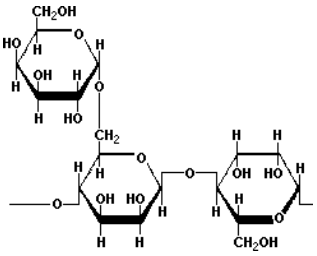

Fig. 6: Guar Gum

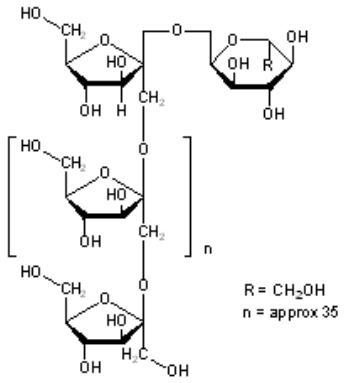

Fig. 7: Inulin

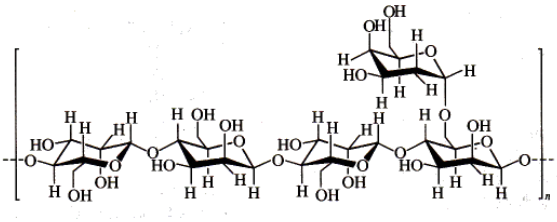

Fig. 8: Locust Bean Gum

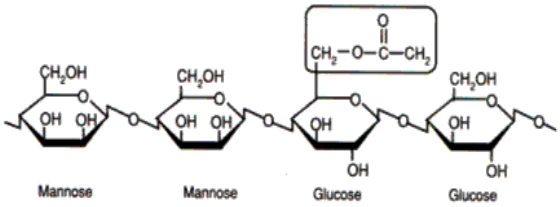

Fig. 9: Glucomannan

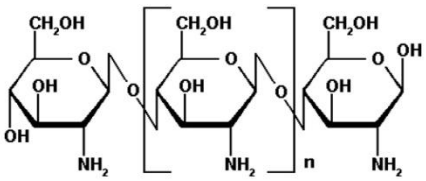

Fig. 10: Chitosan

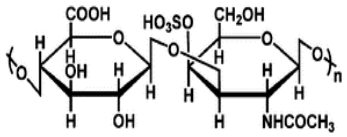

Fig. 11: Chondroitin Sulfate

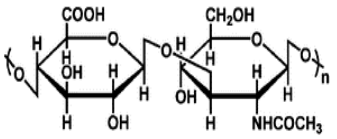

Fig. 12: Hylauronic acid

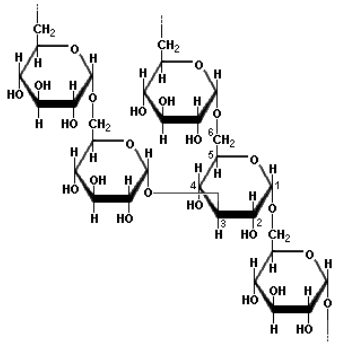

Fig. 13: Dextran

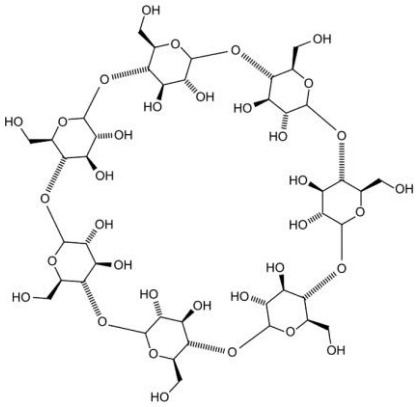

Fig. 14: Cyclodextrins

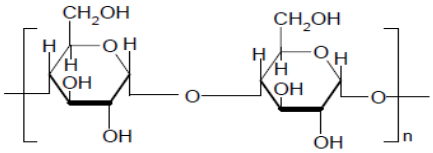

Fig: 15: Alginate

Table 1: Average pH in the GIT

Location	pH
Oral cavity	6.2-7.4
Oesophagus	5.0-6.0
Stomach	Fasted condition: 1.5-2.0 Fed condition: 3.0-5.0
Small intestine	Jejunum: 5.0-6.5 Ileum: 6.0-7.5
Large intestine	Right colon: 6.4 Mild and left colon: 6.0-7.6

Table 2: Gastrointestinal Transit time of contents

Organ	Transit Time (hr)
Stomach	<1(fasting),>3(fed)
Small intestine	3-4
Large intestine	20-30

Table 3: Colon Bacterial Species Involved in Degradation of Polysaccharides

Polysaccharide	Bacterial Species Involved in Degradation
Cellulose	Bacteroides
Chondroitin sulphate	Bacteroides
Cyclodextrin	Bacteroides
Dextrans	Bacteroides
Guar gum	Bacteroides, Ruminococci, Bifidobacteria
Gum arabic	Bifidobacteria
Pectin	Bacteroides, Bifidobacteria, Eubacterium
Starch	Bacteroides, Bifidobacteria
Xylan	Bacteroides, Bifidobacteria
Glucomannan	Bacteroides

Table 4: Pectin Specification

Parameter	Range
General description	White, yellowish
Taste	Tasteless
Solubility	Soluble in cold and hot water
pH	5 to 7
Moisture content	Max12
Total ash	Max 1%
Acid insoluble	Max 3%

Table 5: Guar Gum Specifications

Parameter	Range
General description	White to pale yellow free flowing powder
Taste	Tasteless and odourless
Solubility	Soluble in water forms viscous colloidal solution, insoluble in organic solvents
pH	6–7
Moisture content	4%–12%
Total ash	0.4%–1.2%
Acid soluble	2%–5%
Protein	2%–6%
Galactose	0.782
Mannose	0.218

Table 6: Inulin Specifications

Parameter	Range
General description	Yellowish powder
Acid insoluble	Max 1.5%
Solubility	Soluble in hot water
pH	7 to 10
Moisture content	Max18%
Total ash	Max 15%
Protein	Max 0.5%–0.7%

Table 7: Carrageenans Specifications

Parameter	Range
General description	White to yellowish powder
Taste	Slightly sweet, odourless
Solubility	Soluble in water
pH	6 to 7
Moisture content	Max 9.5%
Total ash	Max 1.5%
Total carbohydrates	Max 98%
Sucrose	Max 3%

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