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Natural polysaccharides as potential excipients for colon drug targeting – a review

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ABSTRACT

Recent decades, the colon targeting drug delivery via oral route is one of the most convenient and popular systems, which deliver the drugs to the specific site for both local as well as systemic action. Oral conventional dosage forms basically disintegrate in the stomach and gastrointestinal tract (GIT) and it mainly depends on the physicochemical properties of the drug. But targeting the drug to the colon should be protected till it reaches to cecum by means of controlled polymers. Colonic drug delivery has become popular to treat diseases such as ulcerative colitis, Crohn's disease, carcinomas and other infections, where by local concentration can be achieved in specific site , and minimizing the side effects. Colon site has being investigated as a potential site for delivery of proteins and peptides. Biodegradable polymers from natural synthetic sources are very cheap, widely available and resistant to digestive action to stomach and GIT enzymes. Presently the numbers of studies have been carried and reported with natural polymers for targeting the drugs to colon. Generally, they have more potential advantages than the synthetic one. The present review is elaborately revealed the potential advantages of natural polysaccharides and its cross-linking derivatives.

Introduction

Colon targeting via oral route is considered to be the most convenient for the administration of drugs to the patients. Colon is a specific site for both local and systemic delivery of drugs[1]. But oral conventional dosage forms basically dissolved in the stomach and GIT and also absorption takes place from these regions depends upon the physicochemical properties of the drug. It is one of the major drawbacks for targeting of drugs to the colon, but the drug should be needed to protect from both hostile environment of stomach and GIT. The treatment of colonic diseases such as ulcerative colitis, Crohn's disease, carcinomas and other infections, where by local concentration can be achieved, while minimizing the side effects of the drugs. Colon site has being investigated as a potential site for delivery of proteins and peptides[2, 3], and other drugs such as nifedipine, theophylline and isosorbide etc[4-7]. Colon has comparatively longer transit time[7] than stomach and GIT; it highly appears, to enhance the absorption of poorly absorbed drugs and improved bioavailability[8, 9]. The effective delivery of vaccines are highly absorbed by colon due to the presence of high lymphoid tissue, uptake of antigen into mast cells of colonic mucosa, which produce rapid local production of antibodies[10]. The natural biodegradable polysaccharides and proteins are used for targeting the drugs to colon, is more advantages than synthetic biodegradable polymers[11]. Biopolymers are more attractive, obtained from both animal and plant kingdom, widely available, comparatively cheap and ease of chemical modifications. These polymers are also used as an approved pharmaceutical excipients[12]. A number of literatures are available for biopolymers in drug delivery systems, have concerned on polysaccharides and proteins[13]. Polysaccharides and proteins remain their integrity because they are resistant to digestive action to stomach and GIT, but once it reaches in the colon, they are acted upon by the bacterial enzymes, which result in the degradation of polysaccharides and liberation of entrapped drugs. The simplest method for targeting of drugs to the colon is to achieve slower release profiles or longer transit time of the different pharmaceutical controlled release dosage forms[14].

Biodegradable polysaccharides

The biodegradable polysaccharides are generally obtained from natural origin. Basically they have hydrophilic and swelling characters. Polysaccharides have been used widely in pharmaceutical, chemical and biochemical drug delivery. It has been approved to the area of controlled release coating, matrices, macromolecular carriers and biodegradable carriers[15]. These polymers are retaining their integrity, because till they reach the colon, they are resistant to the stomach and gastrointestinal fluids and are degraded by the colonic micro flora. The colonic micro flora secrets number of enzymes that are capable of degradation of polymers by means of fermentation. These enzymes include β-D-*glucosidase*, β-D-*galactosidase*, *amylase*, *pectinase*, *xylanase*, α-D-*galactosidase*, *dextranase* etc. The biodegradable polymers may have limited swelling properties in acidic pH but it swells in more neutral pH of the colon. Although the rate of drug release is depends upon the physicochemical properties of the drug substances. Most of the polysaccharides are used as binders in the formulation of pharmaceutical dosage forms[16].

Guar gum

Guar gum is a natural, abundantly available, non-ionic galactomannan polysaccharide derived from the seeds of *Cyamopsis tetragonalobus* (Family: *Leguminaceae*) [17]. It has basically β- 1, 4 D-mannose and L-1, 6 D-galactose unit linkages. Guar gum contains about 80% galactomannan, 12% water, 5% protein, 2% acid insoluble ash, 0.7% ash and 0.7% fat. It has low water solubility but hydrates and swells in cold

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water forming viscous colloidal dispersion or sols[18-20]. The Guar gum solution incubated with a homogenate of feces has reduced its viscosity by 75% over 40 min[21]. Guar gum is being used to deliver the drugs, due to its drug release sustaining property and susceptibility to microbial degradation in the colonic micro flora and also susceptible to *galactomannase* enzyme in the colon[22-24].It is used as binding agent, disintegrating agent (up to 10%) for oral solid dosage forms and also used as suspending agent, thickening agent and stabilizing agent (up to 2.5%) in liquid dosage forms. Guar gum based matrices of dexamethasone and budnesonide were evaluated their dissolution using USP dissolution apparatus III. The presence of different grades of hydroxyl propyl methyl cellulose(HPMC) in dexamethasone, the rate of degradation mainly depends upon HPMC grade[25].Other guar gum matrices containing albendazole as a drug, the matrices containing 20% guar gum was potential for targeting albendazole to the colon in the treatment of helmenthiasis and also influences the addition of metronidazole and tinidazole[26]. Guar gum was cross linked with increasing amount of trisodium trimetaphosphate to reduce its swelling properties and as a result of cross linking, guar gum lost its non-ionic nature and become negatively charged, which lost hydrogel network[27].Chemically modified guar gum retard enzyme degradation properties in the caecum and an enhanced release was observed by the addition of α-*galactosidase*, β-*mannase*[28-30]. A novel colon specific drug delivery system based on guar gum matrix tablets was observed by gamma- scintigraphic studies using Technitium-99m-DTPA as a tracer, in healthy human volunteers. Scintigraphs showed that some amount of tracer was present in stomach and intestine, but bulk of the tracer present in the tablet mass was delivered to the colon[31]. Different formulations of guar gum-sennoside matrix coated with HPMC-P and *in vitro* study was carried out. The 10% HPMC-P coating was suitable for sennoside which released at lower GIT[32].

Chitosan

It is a high molecular weight polycationic polysaccharide derived from naturally occurring chitin by alkaline deacetylation from shrimp or crab shells[33]. Chitosan is more susceptible to hydrolysis by *lysozyme*, *chitinase* than N- acetylchitosan[34]. Chemically it is a poly (2-amino-2-deoxy D-glucopyranose), and the number of units are linked by (1-4) β – bonds (Fig .1).

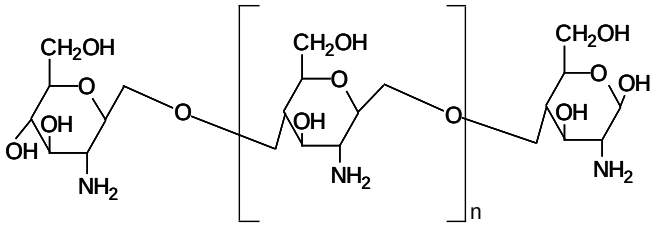

Fig 1. Chemical structure of chitosan

It is non-toxic, biodegradable and biocompatible. It dissolves in acidic pH of the stomach but swells at pH 6.8. It undergoes degradation by the action of colonic micro flora and hence posses its suitable candidature for colon targeting drug delivery systems. The pharmaceutical dosage forms are designed in presence of chitosan polysaccharide as a potential drug carrier for drug delivery systems[35]. Chitosan was cross-linked by reacting with succinic and phthalic anhydrate to prepare matrices and dissolution study was carried out in both acidic and basic conditions. Improved drug release was reported under basic conditions, indicating that these matrices are orally suitable for colon-specific drug delivery systems[36]. Colon targeting has been studied with chitosan on acetaminophen (paracetamol) [37], mesalazine (5-ASA) [38], sodium diclofenac[39], and insulin[40, 41]. Chitosan capsules have been used for colonic delivery of insulin to the colon[40]. These capsules coated with HPMC-P enteric polymer and contained apart from insulin, and addition of various absorption enhancers and enzyme inhibitors. It was found that the capsules specifically disintegrated in the colonic region and release the drug, due to the degradation of chitosan by colonic micro flora[42]. The cross-linked chitosan sponge has been reported the drug delivery over the period of 36 hrs. The delayed release was found due to the decreased chitosan solubility either by N- acetylation or by cross-linking[43].

Pectin

Pectin is a hetero-polysaccharide consists of α- 1, 4-D galactuonic acid and 1, 2 D- rhamnose linked with D- galactose and D- arabinose side chains (Fig. 2).

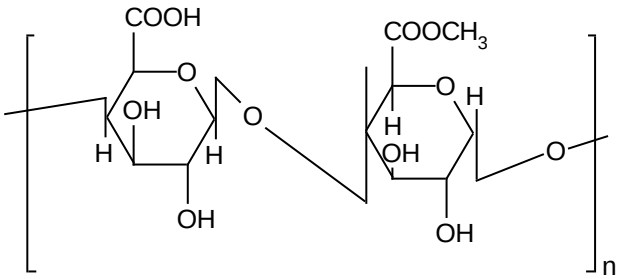

Fig 2. Chemical structure of pectin

It remains intact in stomach and small intestine, but it is degraded by colonic bacterial enzymes. Methylated pectin can be employed for colonic drug delivery. Pectin has basically low degree of methylation. Pectin carefully cross-linked with a divalent cation salt of calcium pectinate was used for colon targeted delivery of indomethacin[44]. The calcium pectinate as a carrier like pectin, it degraded by colonic pectinolytic enzymes, but it resist in the physiological environment. The compressed tablets contain indomethacin with calcium pectinate was shown to degrade by the presence of colonic bacteria *Bacteroids ovatus* and *Aspergillus* [45,46]. The pellets of theophylline were coated with calcium pectinate and reported a pH dependent *in vitro* release in 4 h [47]. Indomethacin and sulphamethoxazole inside contain amidated pectin, gelled in the presence of calcium. The formulation containing chitosan polyelecrolyte complex coating was used to modify the desired release pattern in simulated gastric fluid[48].

Two types of matrix tablets were developed, one matrix containing calcium pectinate and pectin and was designed to rapid disintegration in the ascending colon. The second formulation containing calcium pectinate and guar gum and was designed to disintegrate comparatively more slowly than calcium pectinate and pectin formulation, which releasing its contents up to the transverse colon. Both the formulations were enteric coated with aqueous dispersion of Eudragit- L and scintigraphic study was carried out in healthy human volunteers. The tablet formulation containing calcium pectinate and guar gum was appeared to be slower release than tablet formulation containing calcium pectinate and pectin[49, 50]. The tablets of paracetamol coated with a combination of pectin and ethyl cellulose and drug release was assessed by *in vitro* dissolution testing with or without colonic enzyme. The drug release depends upon the medium as well as the coating system used[51, 52]. High thickness coating of Pectin alone not able to protect the cores, but pectin and chitosan mixtures comparatively achieved better protection at a very thin coat comparatively. The pectin and chitosan mixtures were readily degraded by pectinolytic enzyme in the colon[53]. Biphasic release of pectin, chitosan and HPMC mixture was capable of delivering drugs to the colon and

allowing the release due to pectinolytic enzyme, which breakdown the coat of the formulations by scintigraphic evaluation[54-56].

Amylose

Amylose is a linear polymer of glycopyranose units (alpha-1, 4 D-glucose) linked through alpha- D (1, 4)-linkages. It consists of number of units ranging from 1000-5000 glucose units (Fig. 3). Amylose is one of the major components of starch, occurring 15-25% of the total weight. The glassy amorphous form of amylase has good film forming properties and is resistant to pancreatic enzymes in the small intestine but it undergo degradation due to fermentation by a broad range of bacterial *amylase* enzymes present in the colon. Amylose is freely water swell able, easily fragile and capable of high degradation, so the mixture of amylose and ethyl cellulose spray coated 5-ASA loaded pellets. The combined amylose and ethyl cellulose have been found to improve the physical and mechanical properties of the coating film, and it reaches to colon without any damage. Different amylase enzymes were added in to the fecal based fermentation model reported based on the product performance and dug release from coated pellets was accelerated, in the presence of different enzymes[57- 61]. It has been exploited as a carrier and film coating material[62] and shows an effective drug release in the colon[58, 63, 64].

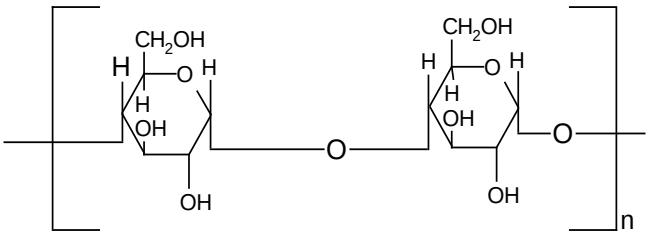

Fig 3. Chemical structure of Amylose

Inulin

Inulin is a natural polysaccharide obtained from many plants. It consists of β-2, 1 linked D-fructose molecules having glucosyl unit at the reducing end (Fig. 4).

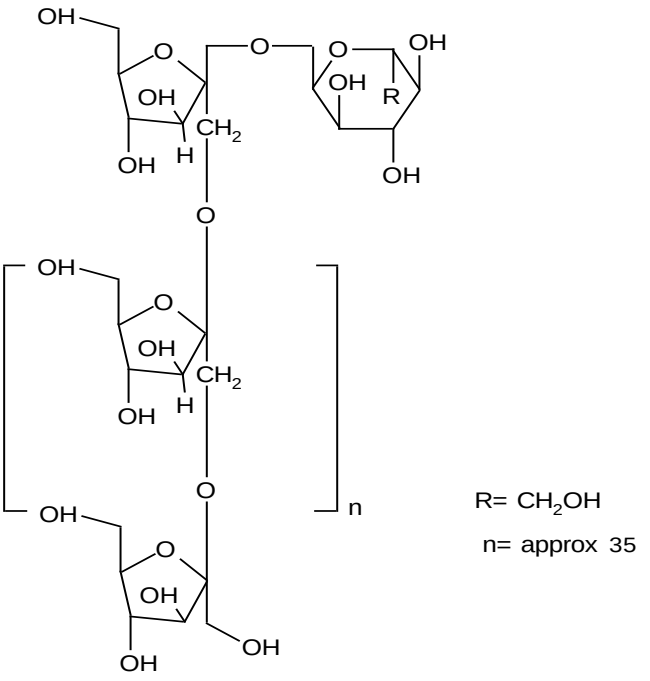

Fig 4. Chemical structure of inulin

It generally resists hydrolysis and digestion in the upper GIT. It is fermented in the colon by means of colonic micro flora. Highly polymerized inulin was formulated by suspending with Eudragit RS films. This film withstands gastric and intestinal fluid but was degraded by fecal media[65]. Hydrogels were formed by the introduction of vinyl groups and reaction with glycidyl methacrylate[66]. Enzyme digestion was assessed by performing *in vitro* study using an *inulinase* from *Aspergillus niger*. Mechanical strength and swelling ratio of hydrogels were studied, depends upon the swelling characters it was concluded that the enzyme *inulinase* diffuse in to the inulin hydrogel networks causing bulk degradation[67]. The hydrogel nature of inulin was studied by reaction with gelatin and compared with methacrylated inulin. The physical chain entanglements were determined by solution viscosity measurements. The gelatin kinetics and the elastic modulus were proportional to the degree of substitution and feed concentration of methylated inulin[68].

Dextran

Dextran is a polysaccharide, consists of α-1, 6 D-glucose and α-1, 3 D-glucose units. It is naturally obtained from plant kingdom. Dextran hydrogels were more stable when incubated at 37ºC with the small intestinal enzymes such as *invertase*, *amyloglycosidase* and *pancreatin*[69]. Dextran cross-linked with 4-amino butyric acid and 1, 10 diaminodeccane, which enhanced the release of bovine serum albumin from the hydrogels by the addition of *dextranase* in buffer solution[70] and cross-linked with diisocyanate which was degraded human colonic fermentation[71]. Various dextran hydrogels were developed and used as potential carriers for targeting of drugs into the colon. These hydrogels were characterized by mechanical strength and equilibrium degree of swelling property studies[70].

Chondroitin sulfate

Chondroitin sulphate is a soluble mucopolysaccharide, which consists of β-1, 3 D-glucuronic acid linked to N-acetyl-D-galactosamide (Fig. 5).

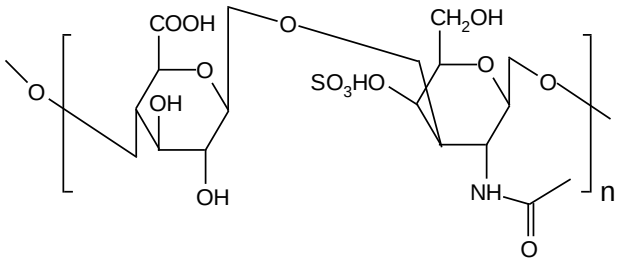

Fig 5. Chemical structure of chondroitin sulphate

It mainly degraded by b*acteroids* species in the human large intestine. Natural chondroitin sulphate is freely soluble, it may release the drugs immediately from the embedded matrix, and hence its cross-linking has been reported to release the drug slowly. Chondroitin sulphate was cross-linked with 1, 12-diaminodecane using dicyclo carbodiimide as a catalyst, to yield a number of cross-linked derivatives with low water solubility[72]. In this cross-linked chondroitin sulphate with indomethacin embedded matrix tablet was formulated and release kinetics from various formulations was found out in phosphate buffer solution with or without caecal content[73, 74].

Cyclodextrin

Cyclodextrins are cyclic oligosaccharides, composed of glycopyranose units. It basically consists of 6 to 8 glucose monomer arranged in a doughtnut-shaped ring, which are classified as α, β, or γ- Cyclodextrin, respectively. It has an excellent solubility, stability; attain better bioavailability and reacts to form both lipophilic and hydrophilic complexes with drug molecules, such as aromatics, alcohols, halides and hydrogen halides, carboxylic acids, and their esters[75]. β-Cyclodextrin monograph is available in *European Pharmacopoeia, Japanese Pharmacopoeia and United States*

Pharmacopoeia / National Formulary. β- Cyclodextrin has α-1, 4 glycosidic bonds are fairly stable in alkaline aqueous solutions, but are slowly hydrolyzed by strong aqueous acids to give a series of linear monosaccharide[76, 77]. It appears to have the most use in the pharmaceutical industry of all the natural cyclodextrins, because of its cavity size, efficiency of complexation, availability in pure form and relatively low cost. It has limited aqueous solubility and its interaction with lipophilic drugs or other compounds of limited solubility[78]. It is mainly used to convert liquid drugs into microcrystalline powders, prevent drug-drug or drug-excipients interactions, and reduce the drug irritation after oral or topical administration[79-82]. For this α, β, or γ- Cyclodextrins are selectively conjugated on an ester or amide linkage with 4-biphenyl acetic acid (BPAA) [83]. The BPAA was released after ring opening followed by ester hydrolysis and activated in the caecum and colon.

Starch

Starch is a polysaccharide, composed of amylose and amylopectin. Amylose, the unabranched type of starch, consists of glucose residues in α-1, 4 linkage. Amylopectin, the branched form, has about one α-1, 6 linkage per thirty α-1, 4 linkages of the chain. Both amylose and amylopectin are rapidly hydrolyzed by *amylase*, which is secreted by the salivary glands, pancreas and also in the colon[84]. It has around 10,000 units of glucose. Starch is hydrolyzed by *amylase* enzyme in the gut. The degradation products of starch are oligosaccharides, dextrin and maltose. Colon targeting by using starch capsules contain the drug followed by enteric coating. The coating may be a pH sensitive, redox-sensitive or broken down by enzyme or bacteria present in the colon[85, 86].

Locust bean gum

Locust bean gum is a neutralpolysaccharides, slowly soluble, ungelling at lower temperature and having a molecular weight of 3100 00 derived from the endosperm of the seed of the *Ceratonia siliqua* linne (Fam: *Leguminosae*). It contains about 88% D-galacto-D-mannogyl-can, 4% of pentan, 6% of protein, 1% of cellulose and 1% of ash. It is generally used as pharmaceutical excipients in tablet formulations and thickening agent for toothpaste. The different ratios of locust bean gum and chitosan mixture were used an a compression coating material of tablets containing mesalazine, and *in vitro* and *in vivo* human volunteers study has been carried out, which it triggered the release in the colonic environment by means of bacterial degradation[87].

Xanthan gum

Xanthan gum is heteropolysaccharides, having a molecular weight of approximately 300,000- 1,000,000. It is readily soluble and provides high viscosity without gel formation. Xanthan and guar gum mixture have greater drug release mimicking property and synergistically greater gelling property[88]. .Matrices of xanthan gum was known to retard drug release considerably under the category of polysaccharides[89-91].

Summary

For targeting of drugs to the colon via oral route, polysaccharides and cross-linked polysaccharides play an important role and optimization of pharmaceutical dosage regimen. Several potential systems have been emphasized or investigated for targeting the drugs to colon, in the form of polysaccharides and cross-linked polysaccharides matrices and coated with pH sensitive polymers. These coated matrices which remain intact the drug release up to the arrival of caecum, the polysaccharides and cross-linked polysaccharides matrices are degraded in the presence of colonic micro flora. The diet and pathological conditions of the individual may vary or alter the drug response for targeting the drugs in the colon. The polysaccharides and their cross-linking approach which can result in safe, effective and less expensive with slight variation in terms of targeting the drugs to the colon.

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