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NATURAL POLYSACCHARIDES (A VITAL PHARMACEUTICAL EXCIPIENT FOR COLONIC DRUG DELIVERY)

Gharge Varsha* and Savitri Pol

Gourishankar Institute of Pharmaceutical Education & Research, Limb, Satara, India-41501.

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***Corresponding author: Gharge Varsha**

Gourishankar Institute of Pharmaceutical Education & Research, Limb, Satara, India-41501.

ABSTRACT

Colon specific drug delivery system offers several advantages in the treatment of colonic diseases such as ulcerative colitis, amoebiasis, Crohn's disease, irritable bowel syndrome, colorectal cancer. The polysaccharides based colon specific drug delivery is relatively easy due to the presence of various derivatizable groups, wide range of molecular weights, varying chemical compositions, low toxicity and high stability. Natural excipients present various advantages over the synthetic as they are inert, safe, non-toxic, biocompatible, biodegradable, low cost, ecofriendly and abundantly available in nature. In the present review different natural excipients were studied in terms of their use in various formulations for different purposes.

KEYWORDS: Natural polysaccharides, vital excipient, colon, biocompatible, biodegradable.

1. INTRODUCTION

For successful delivery of drugs to the target site, various drug delivery approaches have been explored and plays a challenging and crucial role. However, for sustained as well as controlled delivery system, the oral route of administration is considered to be the most convenient and preferred route for delivery of drug.[1]

Various drug delivery strategies have been employed to trigger the release of drug to the large intestine but however, they do not reach at the site of action in appropriate concentrations. Thus, to ensure an effective and safe therapy for the large bowel diseases, colon specific drug delivery system is considered to be the preferable approach.[2]

Targeted drug delivery into the colon is highly desirable for local treatment of bowel diseases such as ulcerative colitis, Crohn's disease, amebiosis, carcinomas and infection, local treatment of colonic pathologies with high local concentration can be achieved while minimizing side effect that occur because of the release of the drug in the upper part of GIT or unnecessary systemic absorption. The colon is rich in lymphoid tissue, produces rapid local production of antibodies with uptake of antigen into the mast cell of the colonic mucosa and this help in efficient vaccine delivery.[3] Colon specific drug delivery system offers several advantages in the treatment of colonic diseases such as ulcerative colitis, amoebiasis, Crohn's disease, irritable bowel syndrome, colorectal cancer.[4]

Delivery of drugs to the colon helps in reducing side effect thereby, achieving high local drug concentration at the afflicted site in the colon, hence results in optimal therapeutic effectiveness and good patient compliance.[5,6]

1.1. *Anatomy and Physiology of Colon.*[7, 8, 9]

The GI tract is divided into stomach, small intestine and large intestine. The colon is made up of the caecum, ascending colon, hepatic flexure, transverse colon and canal. The entire colon is about 5 feet (1.5 m) long and 6.5 cm in diameter extends from the ileum to the anus. It is attached to the posterior abdominal wall by its mesocolon, which is a double layer of peritoneum. The opening from the ileum into the small intestine is guarded by a fold of mucous membrane called the ileocecal junction, which allows material from the small intestine to pass into the large intestine. Hanging inferior to the ileocecal junction is the caecum, a small pouch about 6 cm long. Attached to the caecum is a twisted, coiled, measuring about 8 cm in length called the vermiform appendix.

The wall of the colon is composed of four layers: serosa, muscularis, submucosa and mucosa. The serosa consists of areolar tissue that is covered by a single layer of squamous mesothelial cells. The major muscular coat of the large intestine is the muscular is externa and is composed of an inner circular layer of fibres that surrounds the bowel and of an outer longitudinal layer. The submucosa is the layer of connective tissue that lies immediately beneath the mucosa and lining the lumen of the colon, the mucosa is divided into epithelium, lamina propria and muscularis mucosa. The muscularis mucosa consists of a layer of smooth muscle and separates the submucosa from the lamina propria. The lamina propria supports the epithelium and occupies space between the crypts and beneath the crypts. The epithelium consists of a single layer of cell which lines the crypts and covers the surface of the mucosa and three major cell types found in the epithelium are the columnar absorptive cells, goblet cells and enteroendocrine cells. The arterial blood supply to the proximal colon is from the superior mesenteric artery and inferior mesenteric artery supplies the distal colon. The arterioles and capillary branches pass to the epithelial surface between the crypts and form an extensive network of capillary plexus.

1.2. *Factors Governing the Colon Drug Delivery System*

Colon specific drug delivery system is effective therapy of colon related diseases such as irritable bowel syndrome, inflammatory bowel disease (IBD) including Crohn's disease and ulcerative colitis. Due to appropriate release pattern targeted delivery is effective therapy for colon diseases. Due to low proteolytic enzyme activity of protein and peptide drugs colon is preferred site for oral administration.[10]

But due to poor intrinsic permeability of proteins and peptides across colon luminal epithelium approach of applying absorption enhancers has been proposed. In order to obtain colon-specific delivery, various gradual changes in physiological parameters such as enzymatic activity, motility rate, fluid content and increase in pH must be suitable enough not to cause sudden and dramatic changes in the performance of a delivery system.[11]

In general following primary approaches have been proposed for targeted colon delivery

- Prodrug formation.
- pH-dependent systems.
- Time dependent systems.
- Microflora-activated systems.

Majority colon drug delivery is based on pH and time-dependent systems, but in pH dependent systems similarities between pH of small intestine and colon makes it less reliable. In time-dependent formulations, location of initial drug release depends on the transit time of system in GIT tract.[12] The performance of time-dependent formulations can be affected by inter subject variation in GI transits times, pathophysiological conditions associated with GI tract.[13, 14] In the design of colon-specific drug delivery systems colon microflora is recognized as a preferable triggering component. The colon contains over 400 distinct species of bacteria having a population of 1011-1012 CFU/ml. Polysaccharides present in dietary residues and host are primary source of carbon and energy for these bacteria. Enzymes responsible for the degradation of polysaccharides include α-L-arabinofuranosidase, β-D-fucosidase, β-D-galactosidase, and β-D-glucosidase.[15] The presence of colonic microflora could avoid the drawbacks inherent in time and pH dependent systems and therefore exhibit greater degree of site specificity. There are newly developed colon specific delivery systems that exhibited in targeting colon release as shown in Figure No.1.

Time-dependent drug release systems can be formulated by applying coats onto drug cores which are capable of delaying the release through different mechanisms.[17] However, drawback associated with these deliveries is the lack of site specificity due to large variation in gastric emptying time. Thus, time controlled and site specificity is difficult. A simple pH dependent approach is also not suitable to be used alone because of premature release of drug. Therefore, these problems can be overcome by using the combination of both time-dependent and pH-dependent polymers.[18]

Excipients are the largest components of any pharmaceutical formulation. They can be of natural or synthetic origin and synthetic excipients have become common place in today's pharmaceutical dosage forms. It is common knowledge that both synthetic and semi-synthetic products have enjoyed a long history of use, frequently offering unique properties and advantages over naturally derived compounds, including a low sensitivity to various ingredients or moisture, resulting in more efficient and effective pharmaceutical products. But despite the many potential benefits of synthetic excipients, manufacturers must still address a number of challenges before their current universe of implementation can be expanded.

Natural excipients and their application in the pharmaceutical industry are super imposed by the presence of synthetic excipients. Natural excipients are preferred over the synthetic as they are inert, safe, non-toxic, biocompatible, biodegradable, low cost, ecofriendly and abundantly available in nature.[19, 20] Also from the literature survey it was found that synthetic polymeric materials don't exhibit the biodegradability and bio-compatibility.

Traditionally, excipients were incorporated in dosage forms as inert vehicles but in modern pharmaceutical dosage forms they often fulfil multi task roles such as improvement of solubility of poorly soluble drugs enhance bioavailability, desired drug release, target

specific in the form of micro particles, and nanoparticles.[21]

Natural polysaccharides, as well as their derivatives, represent a group of polymers that are widely used in pharmaceutical formulations and in several cases their presence plays a fundamental role in determining the mechanism and rate of drug release from the dosage form. These naturally occurring polymers have been employed as excipients in the pharmaceutical industry in the formulation of solid, liquid and semisolid dosage forms in which they play different roles as disintegrates, binders, film formers, matrix formers or release modifiers, thickeners or viscosity enhancers, stabilizers, emulsifiers, suspending agents and mucoadhesives.[22,23] Specifically, they have been used in the formulation and manufacture of solid monolithic matrix systems, implants, films, beads, micro particles, nanoparticles, inhalable and injectable systems as well as viscous liquid formulations.[23-25]

Natural polysaccharides are often incorporated in the design of controlled drug delivery such as those target delivery of the drug to a specific site in the gastrointestinal tract (GIT), this can be achieved by various mechanisms including coating granules, pellets, tablets with polysaccharides having pH dependent solubility, or incorporating non-digestible polysaccharides that are degraded by bacterial enzymes present in the colon, this property makes these polysaccharides potentially useful in the formulation of colon-targeted drug delivery systems. Natural polysaccharides can be classified on the basis of their origin as shown in Table No. 1.

The review provides a comprehensive review of natural polysaccharides and synthetic polysaccharides that have recently gained importance and have a lot of scope in the design of controlled drug delivery systems.

2. Polysaccharides from Plant Source

2.1. *Guar Gum*

Guar gum, obtained from the ground endosperms of *Cyamposis tetragonolobus*, consists of chiefly high molecular weight hydrocolloidal polysaccharide, composed of galactan and mannan units combined through glycosidic linkages and shows degradation in the large intestine due the presence of microbial enzymes.[28-30]

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.[31] It contains about 80% galactomannan, 12% water, 5% protein, 2% acid soluble ash, and 0.7% fat.

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. This gelling property retards release of the drug from the dosage form, and it is susceptible to degradation in the colonic environment.

Vats A, Pathak K.et al.[32] prepared tabletted guar gum microspheres of piroxicam for targeted adjuvant therapy for colonic adenocarcinomas. In the study, crosslinked guar gum microspheres of piroxicam were directly compressed into matrix tablet and coated with Eudragit S100. The optimized tablet that displayed 0% release in simulated gastric fluid, 15% in simulated intestinal fluid and 97.1% in simulated colonic fluid underwent roentgenographic study in rabbits to check its safe transit to the colon. X-ray images revealed intactness of the tablet until it reached the colon where the tablet matrix eroded. They concluded that designed, conceptual formulation emerged as potential carrier for targeted adjuvant therapy of piroxicam.

In another study, Krishnaiah YS, Veer. et al.[33] developed colon targeted drug delivery systems for mebendazole using guar gum as a carrier. Matrix tablets containing various proportions of guar gum were prepared by wet granulation technique using starch paste as a binder. The tablets were evaluated for drug content uniformity, and were subjected to *in vitro* drug release studies. The results of the study show that matrix tablets containing either 20% or 30% of guar gum are most likely to provide targeting of mebendazole for local action in the colon.

Chaurasia M. et al.[34] prepared, guar gum microspheres containing methotrexate (MTX) and characterized it for local release of drug in the colon, which is a prerequisite for the effective treatment of colorectal cancer. Guar gum microspheres were prepared by the emulsification method using glutaraldehyde as a cross-linking agent. *In vivo* studies suggested that guar gum microspheres delivered most of their drug load (79.0%) to the colon, whereas plain drug suspensions could deliver only 23% of their total dose to the target site.

Therefore, they concluded that guar gum microspheres has a adequate potential in achieving local release of drug *in vitro* release studies, and this finding was further endorsed with *in vivo* studies.

Tuğcu-Demiröz F et al. developed colon-specific delivery systems for mesalazine (5-ASA) using guar gum as a carrier. A colon specific matrix tablet of mesalazine with guar gum was evaluated by *in vitro* and *in vivo* X-ray studies in humans. Two different types of guar gum were used in the experiments. The type and the amount of guar gum affected the *in vitro* release of drug from the matrix tablets. High viscosity guar gum, in the form of a matrix tablet was capable of protecting the drug from being released in the upper region of gastrointestinal (GI) system, i.e. stomach and small intestine. X- Ray studies showed that, the matrix tablets reached the colon; not being subjected to disintegration in the upper region of the GI system in all the subjects.[35]

Hashem FM. et al. evaluated guar gum in combination with hydroxyl propyl methylcellulose (HPMC) as compression coat for colonic delivery of prednisolone as well as improving the mechanical properties of the compressed coated tablets. The core tablets containing 5 mg prednisolone were compression coated with 125 mg of coating materials consisted of guar gum alone or mixtures of guar gum in combination with different ratios of HPMC. The compressed coated tablets were evaluated for their mechanical properties, *in vitro* drug release and *in vivo* performance in human volunteers. The compressed coated tablets with coats containing HPMC exhibited acceptable mechanical properties. *In vitro* drug release studies in pH 7.4 phosphate-buffered saline medium containing 2% (w/v) rat caecal content have shown that increase in concentration of HPMC in the prepared coats from 10% to 20% resulted in an increase in the release rate. However, further increase in HPMC concentration to constitute 30% caused a reduction in the release rate. Based on the drug release results, tablets coated with coat consisted of 80% guar gum and 20% HPMC were selected for *in vivo* evaluation.

They also studied *in vivo* gamma scintigraphic study on human volunteers using technetium-99m-diethylenetriamine pentaacetic acid as a tracer was performed. The results showed that tablets remained intact in stomach and small intestine, however partial and complete release of the tracer occurred in the colon. They concluded that guar gum in combination with HPMC can be successfully used as a carrier for drug delivery to the colon.[36]

2.2. *Inulin*

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. Most of these fructose chains have a glucose unit as the initial moiety.

It is not hydrolyzed by the endogenous secretions of the human digestive tract.[37] However, bacteria harboring in the colon and more specifically *Bifidobacteria* are able to ferment inulin[38-40] The inulin has been incorporated into Eudragit RS films for preparation of mixed films that resisted degradation in the upper GIT but digested in human\ cecal medium by the action of *Bifidobacteria* and *Bacteroids.*[41] Various inulin hydrogels have been developed that serve as potential carriers for the introduction of drugs into the colon.[42-45]

Maris et al.[46] synthesized and characterized new hydrogel systems composed of methacrylated inulin, copolymerized with the aromatic azo agent BMAAB and HEMA or MA. The hydrogels were assessed by studying the influence of various parameters on the dynamic and equilibrium degree of swelling. Inulin hydrogels have been developed and characterized for dynamic and equilibrium swelling properties and *in vitro* degradation study.[43-44]

Inulin derivatised with methacrylic anhydride and succinic anhydride produced a pH sensitive hydrogel that exhibited a reduced swelling and low chemical degradation in acidic medium, but had a good swelling and degradation in simulated intestinal fluid in the presence of its specific enzyme, inulinase.[47]

Stubbe et al.[48] developed azo containing polysaccharide gels more specifically azo- inulin and azo dextran gels.

2.3. *Pectin*

Pectin is another non-starch linear polysaccharides with mainly a-(1-4)-linked D-galacturonic acid residues interrupted by 1, 2-linked L-rhamnose residues. They are predominantly linear polymers of mainly (1–4)-linked D-galacturonic acid residues interrupted by 1,2- linked L-rhamnose residues with a few hundred to about one thousand building blocks per molecule (molecular structure is shown in figure 2), corresponding to an average molecular weight of about 50, 000 to about 180,000 daltons (Da).[49] It remains intact in the physiological condition of the stomach and intestine and is degraded by the bacterial inhabitants of intestinal human colon especially by *Bacteroides.*[50] To reduce the aqueous solubility of pectin, its calcium salt has been used. Matrix tablets of calcium pectinate showed promising results *in vitro.*[51]

For water insoluble drugs, compression coating of the core was found to be more suitable for colon drug delivery as compared to matrices.Different percentages of chitosan were incorporated in the pectin coat of multilayer tablets of mesalamine to give different coat: core ratio. The effect of this varying coat: core ratio was observed on drug release and found that high Pectin coat: core ratios of compression coated formulations were able to protect the tablet cores from premature drug release. Incorporation of chitosan (3% and 5%) in the Pectin coat offered better protection at a lower coat: core ratio.[52-53]

Malviya et al.[54] prepared matrix tablets of Diclofenac sodium using pectin polymer in different concentrations and studied its release profile. It was found from the whole study that 1:1.5 drug: polymer ratio proved to be the best formulated oral sustained release tablet.

Some researchers investigated the high-methoxy-pectin for its potential value in controlled-release matrix formulations. The effects of compression force, ratio of drug to pectin, and type of pectin on drug release from matrix tablets were also investigated. The results of the *in vitro* release studies showed that the drug release from compressed matrix tablets prepared from pectin can be modified by changing the amount and type of pectin in the matrix tablets.[55]

Walkerly et al.[56-59] used biodegradable coating containing pectin and ethyl cellulose for colon specific drug delivery. Ashford et al.[60] evaluated high and low methoxy pectin for colonic drug delivery. Rubinstein et al.[61] developed colonic specific drug delivery system using calcium pectinate by using calcium pectinate using indomethacin as model drug. Polymeric hydrogels are widely used as controlled-release matrix tablets. Some researchers[62] investigated the high-methoxy-pectin for its potential value in controlled-release matrix formulations. The effects of compression force, ratio of drug to pectin, and type of pectin on drug release from matrix tablets were also investigated. The results of the *in vitro* release studies showed that the drug release from compressed matrix tablets prepared from pectin can be modified by changing the amount and type of pectin in the matrix tablets. A very low solubility pectin-derivative (pectinic acid, degree of methoxylation 4%) was found to be well suited as an excipient for pelletisation by extrusion/spheronisation. The capacity as an extrusion aid was found to be high. Formulations containing only 20% pectinic acid resulted in nearly spherical pellets. All pectinic acid pellets were mechanically stable. They possessed an aspect ratio of approximately 1.15–1.20 and released 30–60% of a low solubility model drug within 15 min in simulated gastric fluid (0.1M HCl) and intestinal fluid (phosphate buffer pH 6.8).[63]

Micro particulate polymeric delivery systems have been reported as a possible approach to improve the low bioavailability characteristics observed in standard ophthalmic vehicles (collyria).[64] In this context pectin microspheres of piroxicam were prepared by the spray drying technique. *In vivo* tests in rabbits with dispersions of piroxicam-loaded microspheres also indicated a significant improvement of piroxicam bioavailability in the aqueous humour (2.5–fold) when compared with commercial piroxicam eye drops. Investigation on the suitability of amidated pectin as a matrix patch for transdermal chloroquine delivery has been reported.[65] This was in an effort to mask the bitter taste of chloroquine when orally administered. The results suggested that the pectin-chloroquine patch matrix preparation has potential applications for the transdermal delivery of chloroquine and perhaps in the management of malaria.

Calcium pectinate nanoparticles to deliver insulin were prepared as a potential colonic delivery system by ionotropic gelation.[66] In relation to cosmetics, using citronellal as a model compound, pectin gel formulations were evaluated for controlled fragrance release by kinetic and static methods. These formulations showed a prolonged duration of fragrance release and limitation of fragrance adsorption to the receptor skin layers. The increase in pectin concentrations suppressed the fragrance release by a diffusion mechanism, thereby proving that pectin/calcium micro particles are promising materials for controlled fragrance release.[67]

Drug delivery systems utilizing pectin is discussed by various researchers. Natural polysaccharides are now extensively used for the development of solid dosage forms for delivery of drug to the colon. The rationale for the development of a polysaccharide based delivery system for colon is the presence of large amounts of polysaccharidases in the human colon as the colon is inhabited by a large number and variety of bacteria which secrete many enzymes e.g. @b-d-glucosidase, @b-d-galactosidase, amylase, pectinase, xylanase, @b-d-xylosidase, dextranase, etc. Calcium pectinate (CaP), the insoluble salt of pectin--can potentially be used as a colon-specific drug delivery system. The use of CaP as a carrier was based on the assumption that, like pectin, it can be decomposed by specific pectinolytic enzymes in the colon but that it retains its integrity in the physiological environment of the small bowel. The biodegradation of the carrier was characterized by monitoring the percent cumulative release of the insoluble drug indomethacin, incorporated into pectin or CaP matrices. Certain plant polysaccharides such as amylose, inulin, pectin and guar gum remains unaffected in the presence of gastrointestinal enzymes and pave the way for the formulation of colon targeted drug delivery systems. The potential of pectin as a bacterially degradable polysaccharide for colon drug delivery has been demonstrated. Due to the high solubility and Swelling properties of pectin in aqueous media, it is frequently used in combination with water insoluble polymers for targeting drugs to the colon.[6-72]

2.4. Locust Bean Gum

It is also called carob gum, as it is derived from carob (Ceratonia siliqua) seeds. Locust bean gum has an irregularly shaped molecule with branched β-1, 4-D-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 led to water insoluble film forming product-showing degradation in colonic microflora.[73] The ratio of D-galactose to D-mannose differs based on the plant origin and also dependent on the growth conditions of plant during production. The physicochemical properties of galactomannan polysaccharides are strongly influenced by galactose content.[74] The longer the galactose side chain greater the viscosity. Mannose: galactose content is about 4:1 ratio.[75]

The colon specific drug delivery systems based on polysaccharides, locust bean gum and chitosan in the ratio of 2:3, 3:2 and 4:1, were evaluated using *in vitro* and *in vivo* methods. Core tablets containing mesalazine with average weight of 80 mg were prepared by compressing the materials using 6-mm round, flat, and plain punches on a single station tablet machine. The formulated core tablets were compression coated with different quantities of locust bean gum and chitosan. The *in vitro* studies 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. The *in vivo* studies conducted in nine healthy male human volunteers for the various formulations showed that the drug release was initiated only after 5 hr, which is the transit time of small intestine. *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 stomach and small intestine and was susceptible to colonic bacterial enzymatic actions with resultant drug release in the colon.[76]

2.*5. Glucomannan*

Konjac Glucomannan (KGM) is a high-molecular weight water-soluble non-ionic Glucomannan extracted from tubers of the Amorphophallus konjac plant. Konjac glucomannan (KGM) is a linear random copolymer of (1-4) linked β-D mannose and β-D glucose. It has mannose and glucose units in a molar ratio of 1.6:1 with a low degree of acetyl groups (approximately 1 acetyl group per 17 residues) at the C-6 position.[77-78] The degree of solubility is controlled by the presence of acetyl groups.

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 and heart disease. A diet rich in high-viscosity KGM is generally recommended for improved glucose and lipid profile control, suggesting a therapeutic potential in the treatment of the insulin-resistance syndrome.[79]

Combination of konjacglucomannan and xanthan gum in matrix tablets has been shown to effectively retard drug release by stabilisation of the gel phase of the tablets by a network of intermolecular hydrogen bonds between the two polymers.[80]

3. Polysaccharides from Animal Source

3.1. *Chitosan*

Chitosan is a functional linear polymer derived from chitin, the most abundant natural polysaccharide next to cellulose, and it is not digested in the upper part of the GIT by human digestive enzymes.[81] Chitosan is a copolymer consisting of 2-amino-2-deoxy- D glucose units linked with β-(1-4) bonds. It should be susceptible to glycosidic hydrolysis by microbial enzymes in the colon because it possesses glycosidic linkages similar to those of other enzymatically-depolymerized polysaccharides. Chitin is a structural polysaccharide which takes the place of cellulose in any species of lower plants and animals. It therefore occurs in fungi, yeast, green, brown and red algae and forms the main component of the exoskeleton of insects and shells of crustaceans.[82]

Shimono et al.[83] developed new colon specific drug delivery system containing chitosan dispersed drug delivery system composed of active ingredient, reservoir and drug release regulating layer dispersing chitosan powder in hydrophobic polymer. Orienti et al.[84] synthesized various salts of chitosan and evaluated for colon specific delivery system. Vandelli et al.[85] have developed a pH sensitive based chitosan hydro gels drug delivery system.

It was also found that the polyelectrolyte complex of chitosan with κ-carrageenan leads to the disappearance of the electrostatic linkage between the amino group of chitosan and the sulphonate group of κ-carrageenan in the prepared complex and thus contributes to the swelling of the complex gel. Complexation of chitosan with κ-carrageenan also retards drug release to some extent.[86]

Tozaki et al.[87, 88] developed colon specific insulin delivery system with chitosan capsules.

The objective behind this study was to estimate colon-specific insulin delivery with chitosan capsules. *In vitro* drug release experiments from chitosan capsules containing 5(6)-carboxyfluorescein (CF) were carried out by the Japan Pharmacopoeia (J. P.) rotating basket method with some slight modifications. The intestinal absorption of insulin was evaluated by measuring the plasma insulin levels and its hypoglycaemic effects after oral administration of the chitosan capsules containing insulin and additives. It was observed that little release of CF from the capsules was there in liquid 1, an artificial gastric juice (pH 1), or in liquid 2, an artificial intestinal juice (pH 7). However, the release of CF was markedly increased in the presence of rat cecal contents. A marked absorption of insulin and a corresponding decrease in plasma glucose levels was also observed following the oral administration of these capsules that contain 20 IU of insulin and sodium glycocholate (PA% = 3.49%), as compared with the capsules containing only lactose or only 20 IU of insulin (PA% = 1.62%).

The hypoglycaemic effect started from 8 h after the administration of chitosan capsules when the capsules entered the colon, as evaluated by the transit time experiments with chitosan capsules. These findings suggest that chitosan capsules may be useful carriers for the colon-specific delivery of peptides including insulin. Tozaki et al. used rats to study the colon specificity of chitosan capsules R-68070, a thromboxane synthetase inhibitor used for chemically induced ulcerative colitis.[89]

Vandelli et al, Shu et al. have developed a pH sensitive based chitosan hydro gels drug delivery system. In their observations, turbidimetric titration revealed that there were electrostatic attractive interactions between citrate and chitosan in the pH region of 4.3-7.6, depending on their degree of ionization. Citrate cross-linked chitosan

film was prepared simply by dipping chitosan film into sodium citrate solution. The swelling ratio of citrate/chitosan film was sensitive to pH, ionic strength etc. Under acidic conditions, citrate/chitosan film swelled and even dissociated in the pH less than 3.5, and the model drugs (brilliant blue and riboflavin) incorporated in the film were released quickly (usually within 2 h released completely in simulated gastric fluid at 37°C) while under neutral conditions the swelling ratio of citrate/chitosan film was less significant and the release rate of brilliant blue and riboflavin was low (less than 40% released in simulated intestinal fluid in 24 h). Sodium chloride weakened the electrostatic interaction between citrate and chitosan, and therefore facilitated the film swelling and accelerated drug release. Also, the parameters of film preparation such as citrate concentration, solution pH etc. influencing the film swelling and drug release profiles were examined. The lower concentration and the higher pH of citrate solution resulted in a larger swelling ratio and quicker riboflavin release. To improve the drug controlled release properties of citrate/chitosan film, heparin, pectin and alginate were further coated on the film surface. Among them only the coating of alginate prolonged riboflavin release noticeably (for 80% of drug released the time was extended from 1.5 to 3.5 h with 0.5% w/v alginate used). The results indicated that the citrate/chitosan film was useful in drug delivery such as for the site-specific drug controlled release in stomach.[90-91] Suzuki et al[92] prepared hard capsules of chitosan with enteric polymers for colon targeted drug delivery.

Jain et al. developed albendazole microspheres for colon specific delivery using Chitosan Hcl. Microspheres were prepared by an emulsion method using different ratios of drug and CH (1:1 to 1:5), agitation speeds (500 to 1500 rpm) and concentrations of glutaraldehyde in toluene as the cross-linking agent (0.25 to 1.0% w/v). The effect of polymer concentration, stirring rate and concentration of cross-linking agent on the particle size and drug loading was studied. It was found that with an increase in CH concentration, the average particle size was increased. Also, the increased agitation speed reduced the size of the microspheres but higher agitation speed resulted in irregularly shaped microspheres. Increasing the concentration of cross-linking agent produced more regularly shaped microspheres of smaller size.

The drug loading was highest at a drug: CH ratio of 1:3, stirring speed 1000 rpm and 0.75% w/v concentration of cross-linking agent. The effect of CH concentration on *in vitro* drug release from the microspheres was evaluated in simulated GIT fluids. A comparative *in vitro* drug release study of the optimized formulation was carried out in simulated colonic fluid, with and without 2% rat caecal content. The drug release in 24 h was 48.9% in colonic fluid without rat caecal content, and 76.5% in colonic fluid with rat caecal contents.[93]

3.2. *Chondroitin Sulphate*

Chondroitin sulphate is a mucopolysaccharide found in animal connective tissue. It consists of D-glucoronic acid linked to D-acetyl-D-galactosamide, which is sulphated at C-6. It is degraded by the anaerobic bacteria of the large intestine mainly by *Bacteriodes thetaiotaomicron* and *B. Ovatus*.

Though a number of polysaccharides are available for colon specific drug delivery, a usual problem encountered with them is their high water solubility. The high water solubility and poor film forming property is disadvantageous and would lead to premature drug release in the tracts of the upper GIT. One approach that may alter the solubility of the polysaccharide is chemical derivatization or cross linking. A balance between the derivatization/cross linking and solubility reduction is maintained so that have been investigated for colonic drug delivery. The derivatised or cross linked polysaccharide does not reduce the biodegradability.[94]

Some investigation has showed chondroitin is a promising excipient for colon targeted drug delivery containing indomethacin, drug release profiles indicated there was a constant degradation in the caecal content.[95]

Sintov et al 2004, prepared Indomethacin tablets with two cross-linked polymers and their water uptake and drug release characteristics were studied. Indomethacin tablets made of two types of cross-linked polymers, very low water soluble and relatively high water soluble were made and analysed for their water uptake and drug release characteristics. In this experiment, Chondroitin sulphate was cross-linked with 1, 12-diaminododecane to give a series of cross-linked products with reduced water solubility. Since the water solubility of the modified polymers is low, their chemical characterization is complicated. A new method based on the adsorption of the cationic dye, methylene blue, on the cross-linked polymers was developed to characterize the degree of cross-linking. It was found that the values of the adsorptive capacity of the adsorbate, Cp(s), decreased with the extent of cross-linking. However, the valves of the absorptive coefficient (K), and the free energy change of the absorption reaction, delta mu degrees, increased with cross-linking. The swelling of films made of the cross-linked polymers was measured in water and an exponential-like dependency between the degree of swelling and extent of cross-linking could be defined. Based on the physicochemical properties, an optimal product with a potential to serve as a colon-specific drug carrier was suggested.[96]

3.*3. Hyaluronic Acid*

Hyaluronic acid (HA) is a naturally occurring biopolymer, which serves important biological functions in bacteria and higher animals including humans. Naturally occurring HA may be found in the tissue of higher animals, in particular as intercellular space filler.

It is found in greatest concentrations in the vitreous humour of the eye and in the synovial fluid of articular joints. Since its discovery in human tissue, HA and its derivatives has been largely studied and applied in the biomedical arena. Its high level of biocompatibility has accentuated the appeal of this polymer. It has been used in viscosurgery to allow surgeons to safely create space between tissues.[97]

As a microcapsule it can be used for targeted drug delivery. The utility of this biopolymer is derived from a remarkably simple construct. HA is comprised of linear, unbranching, polyanionic disaccharide units consisting of glucuronic acid (GlcUA) an N-acetyl glucosamine (GlcNAc) joined alternately by b-1-3 and b-1-4 glycosidic bonds. It is a member of the glycosaminoglycan family which includes chondroitin sulphate, dermatin sulphate and heparan sulphate. Unlike other members of this family, it is not found covalently bound to proteins. When incorporated into a neutral aqueous solution hydrogen bond formation occurs between water molecules and adjacent carboxyl and N-acetyl groups. This imparts a conformational stiffness to the polymer, which limits its flexibility. The hydrogen bond formation results in the unique water-binding and retention capacity of the polymer.[98]

The viscoelastic property of HA solutions which is important in its use as a biomaterial is controlled by the concentration and molecular weight of the HA chains. The molecular weight of HA from different sources is polydisperse and highly variable ranging from 104 to 107 Daltons.[99]

4. Polysaccharides from Algal Source

4.1. *Alginates*

Alginates, natural hydrophilic polysaccharide derived from sea weed, consist of 1→4, linked D mannuronic acid and L-glucuronic acid residues. Alginates are easily gelled in presence of a divalent cation as calcium ion. The gelation or cross linking is due to the stacking of the glucuronic acid blocks of alginate chains. 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. Calcium alginate beads were prepared as cores and 5-ASA was spray-coated on them.[100] Different enteric as well as sustained release polymers were applied as coat on calcium alginate beads. A system was prepared by coating calcium alginate beads with Aquacoat® that is a pH-independent polymer followed by 2% w/w coating of Eudragit L-30D.

Kiyoung et al.[101-102] prepared alginate beads and coated them with dextran acetate. In the absence of dextranase, minimal drug release occurred whereas it was significantly improved in the presence of dextranase.

Alginates offer various applications in drug delivery, such as gel beads, liposomes, modulating gastrointestinal transit time, for local applications and to deliver the bio molecules in tissue engineering applications.[103]

Bio-adhesive sodium alginate microspheres of metoprolol tartarate for intranasal systemic delivery were prepared to avoid the first-pass effect, as an alternative therapy to injection, and to obtain improved therapeutic efficacy in the treatment of hypertension and angina pectoris.

The microspheres were prepared using emulsification-cross linking method. *In vivo* studies indicated significantly improved therapeutic efficacy of metoprolol from microspheres. There was sustained and controlled inhibition of isoprenaline-induced tachycardia as compared with oral and nasal administration of drug solution.[104]

The emulsion-solvent-evaporation technique was used for the preparation of nanoparticles in case of PLG and the cation-induced controlled gelling in case of alginate. In this comparative study, alginate formulation appeared to be better than the poly-lactide-co-glycoside (PLG) formulation in improving the bioavailability of two clinically important antifungal drugs clotrimazole and econazole.[105]

5. Polysaccharides from Microbial Source

5.1. *Dextrans*

This class of polysaccharide consists of linear chains of α-D glucose molecules, 95% of the chains consists of 1:6-α-linked linear glucose units while the side chains consist of 1:3-α linked. They are obtained from microorganisms of the family of *Lactobacillus* (Leuconostoc mesenteroides). Dextrans are colloidal, hydrophilic, and water-soluble substances, inert in biological system, and do not affect cell viability. Dextranases are the enzymes that hydrolyze glycosidic linkages of the dextrans. Dextrans of various molecular weights have been used as drug carriers. Harboe, et al. synthesized dextran ester prodrug. The bioavailability of naproxen after oral administration of aqueous solutions of various dextran–naproxen ester prodrugs in pigs was determined. The dextran prodrugs employed ranged in molecular weight from 10,000 to 500,000. As calculated relative to an equivalent oral dose of parent naproxen, the absorption fractions of all the derivatives were close to 100%. Only small interindividual variation of naproxen bioavailability was observed. The naproxen plasma profiles for all the administered prodrugs exhibited a characteristic lag time of naproxen appearance in the blood (2–3 hr). Compared to administration of the prodrugs alone, co administration of excess of the parent dextran further delayed the absorption of naproxen from the GI tract. The results of the present study demonstrate the potential of dextran prodrugs for colon site-specific delivery of drugs containing a carboxylic acid functional group. The

majority of drug candidates have molecular weights of about 200–500 Dalton. Bio reversible derivatives obtained by covalent attachment of a promoiety similar in size to drug candidates can be referred to as low molecular weight prodrugs. This approach has been used to improve drug performance by overcoming various barriers to drug delivery. The macromolecular prodrug approach, in which the small therapeutic agent is attached to a macromolecular promoiety, has been exploited to provide drug targeting. The basic rationale behind this approach is that the transport properties of the macromolecular prodrug should be dictated predominantly by those of the macromolecular transport vector. Thus, macromolecular conjugates derived from a wide array of macromolecules endowed with intrinsic target receptor affinities, especially of anticancer agents and other therapeutics have been evaluated.[106-107]

Dextran hydrogels have been shown to be the promising carrier for the delivery of drugs to colon. In the present study degradation of dextran hydrogels, potential drug carriers for colon-specific drug delivery, was studied in simulated small intestinal juices as well as in a human colonic fermentation model. Dextran hydrogels were shown to be stable when incubated at 37°C with the small intestinal enzymes amyloglucosidase, invertase and pancreatin. After 24 h incubation, less than 3.3% of free glucose was released. However, the hydrogels were still intact as measured by the dry weight remaining. The fermentation of dextran hydrogels and several mono- and polysaccharides to short-chain fatty acids (SCFA) was investigated after anaerobic incubation in a human colonic fermentation model at 37°C for 0-72 h. In addition, the dextranase activity of the incubations was determined. The amounts and ratios of SCFA formed varied considerably in relation to the type of substrate fermented (glucose, maize starch, potato starch, cellulose, soluble dextran and dextran hydrogels). Detailed SCFA analysis demonstrated that fermentable saccharides resulted in an increased SCFA production, in contrast to the metabolic inert polysaccharide, cellulose. The hydrogels were found to be completely degraded in the human colonic fermentation model. An increased cross linking density or a decreased degree of hydration resulted in a lower degradability. The pH of the incubations was found to be inversely proportional to the SCFA production as a result of the increased acid. Novel hydrogels based on dextran crosslinked with diisocyanate have been proposed for colon-specific drug delivery. The hydrogels have been characterized by equilibrium degree of swelling and mechanical strength. Degradation of the hydrogels has been studied *in vitro* using dextranase, *in vivo* in rats and in a human fermentation model. It was found that by changing the chemical composition of the hydrogels it is possible to control the equilibrium degree of swelling, mechanical strength and degradability. The dextran hydrogels were degraded *in vivo* in the caecum of rats but not in the stomach. Furthermore, the dextran hydrogels were degraded in a human colonic fermentation model, indicating that dextranases are indeed present in human colonic contents. Finally, release of hydrocortisone from the hydrogels was evaluated. It was found to depend on the presence of dextranases in the release medium. The results suggest that the dextran hydrogels are promising as drug carriers for colon-specific drug delivery.[108-110]

Dextran ester prodrugs of metronidazole have been prepared and characterized for colon specific drug release. The hydrolytic degradation rates of various aliphatic and aromatic esters of metronidazole in aqueous buffer solution and in human plasma were investigated at 37°C. Complete reversion to metronidazole was observed as determined by HPLC and in all cases the hydrolysis followed strict first-order kinetics. The susceptibility of the various ester derivatives to undergo enzyme-catalyzed hydrolysis was strongly influenced by the structure of the acyl moiety, but no unambiguous relationship between the degradation rate in aqueous buffer solution and in human plasma has been found. In aqueous solution the degradation of the aromatic esters was facilitated by low electron density at the reaction site as described by the Hammett equation. Concerning the decomposition of the aromatic esters in 2.5% human plasma a negative deviation from the Hammett plot was observed for the nitro benzoic acid ester derivatives. A change in rate-determining step together with the polar nature of the nitro group is suggested to contribute to this deviation. It has been found that the length of the linear carbon chain in the aliphatic esters influences the enzyme catalyzed degradation rate. The ratio between the degradation rates in 2.5% human plasma and in aqueous buffer solution, pH 7.4, was greatest for the valerate ester, the value being 3800.[111-113]

Lee et al.[114] developed a dextran-nalidixic acid ester with a varied degree of substitution for colon specific delivery.

Jung et al. synthesized dextran ester prodrugs of 5-ASA and drug release rate study revealed that drug release was accelerated in large intestine. Dextran-5-aminosalicylic acid ester (dextran-5-ASA) was synthesized as a colon-specific prodrug of 5-aminosalicylic acid (5-ASA) which is active against inflammatory bowel diseases. Chemical stability of dextran-5-ASA in the bath of pH 1.2 or 6.8 was investigated at 37°C for 6 hrs, and 5-ASA was not released on such conditions. Depolymerization (%) of dextran-5-ASA by dextranase with the degree of substitution (DS) of 18, 23, or 30 was 92, 62 or 45 in 8 hrs respectively, but was not affected by the MW of dextran (9,000, 40,600, 80,200 or 580,000). Distribution of 5-ASA in dextran, determined by gel filtration chromatography, appeared to be relatively uniform. Incubation of dextran-5-ASA (DS 18) in cecal contents of rats released 20% (28 g) and 35% (49 g) of 5-ASA in 8 hrs and 24 hrs, respectively, but no 5-ASA was liberated from small intestinal contents.[115]

Bauer & Kesselhut synthesized dextran fatty acid ester and showed that lauroyl dextran esters with molecular weight of approximately 250000 and degree of substitution ranging from 0.11 to 0.3 were suitable for colon targeted drug delivery as film coatings.[116]

In vitro studies with Lauroyl dextran esters bearing theophylline were carried out and it was shown that addition of dextranase accelerated the drug release.[117-118] The side effects of steroid therapy, which are used in the treatment of chronic colitis, may be decrease by selectively delivering the drug to the colon using dextran.[119-120] Various dextran ester prodrugs viz: sulasalazine, budenoside, mesalazine, olsalazine etc., were formulated for colon delivery of steroids for local and systemic action.[121-128]

5.2. *Cyclodextrins*

Cyclodextrins (CyDs) are cyclic oligosaccharides consisting of six to eight glucose units joined through α-1,4 glucosidic bonds. Cyclodextrins remain intact during their passage through stomach and small intestine. However, in the colon, they undergo fermentation from the presence of vast colonic microflora into small saccharides and thus absorbed from these regions.[129-131] CyDs form inclusion complexes with drug molecules because the interior of the molecule is relatively lipophilic while the exterior is hydrophilic.[132-133] It has been investigated through a study in healthy human volunteers that β CyDs are degraded to a very small extent in the small intestine but are completely digested in large intestine.

Tanaka et al.[134] have prepared several cyclodextrin complexes for colon specific drug delivery systems. Hiramaya et al.[135] prepared two cyclodextrin conjugates i.e. ester and amide conjugates and it was shown that ester conjugate released the drug preferentially in colon than in stomach /small intestine.

Yano et al.[136] have prepared the colon specific drug delivery system for prednisolone using a cyclodextrin. Various literatures available on formulation of prodrug of cyclodextrins with drug molecules, which provide a versatile means for construction of not only colon-targeted delivery systems but also delayed release system.[137-138]

5.3. *Curdlan*

Curdlan is a neutral, essentially linear (1"3)-b-glucan which may have a few intra- or inter-chain (1"6) linkages. Curdlan's unusual rheological properties among natural and synthetic polymers 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, the heating 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 on the heating temperature, time of heat-treatment and curdlan concentration. The safety of curdlan has been assessed in animal studies and *in vitro* tests and it is approved in food use in Korea, Taiwan and Japan as an inert dietary fibre. It is registered in the USA as a food additive. The name curdlan is due to the polymer curdles when heated. Curdlan is used as a thickening and gelling agent in food industry. Gels of various strengths are formed depending on the temperature. It is registered as a food additive in USA. Investigation has a dietary fibre reveals that curdlan is easily degraded by intestinal bacteria. Bacterial degradation studies of curdlan as a natural polysaccharide in controlled drug yet to be reported.[139]

The significant increase in the mass of the caecum was accompanied by a decrease in faecal mass. The transit time of the gastrointestinal tract was extended by curdlan supplementation. Significant decrease was observed in the total hepatic cholesterol and low values were measured in the proportion with secondary bile acids. All those parameters revealed that curdlan is easily degraded and fermented by intestinal bacteria in the caecum and lowers cholesterol concentration in the liver.[140]

6. Polysaccharides from Fungal Source

6.1. *Scleroglucan*

Natural polysaccharides, as well as their derivatives, represent a group of polymers that are widely used in pharmaceutical formulations and in several cases their presence plays a fundamental role in determining the mechanism and rate of drug release from the dosage form. Among these macromolecules, scleroglucan (Sclg) also seems to be potentially useful for the formulation of modified release dosage forms. Scleroglucan (Sclg) is a branched homopolysaccharide consisting of a main chain of (1-3)-linked b-D glucopyranosyl units bearing, every third unit, a single b-D-glucopyranosyl unit linked (1-6).This polysaccharide is resistant to hydrolysis and its solutions show an interesting rheological behaviour: viscosity remains practically constant, even at high ionic strength, up to pH-12 and to 90^{o}C.[141]

Sclg is a general term used to designate a class of glucans of similar structure produced by fungi, especially those of the genus Sclerotium. The commercial product is termed Scleroglucan, but it is also known with other names according to the company that produces the polysaccharide (e.g., Actigum, Clearogel, Polytetran, Polytran FS, Sclerogum). Because of its peculiar rheological properties and its resistance to hydrolysis, temperature and electrolytes, Sclg has various industrial applications, especially in the oil industry for thickening, drilling muds and for enhanced oil recovery and in food industry.[142-144] In pharmaceutical products, Sclg may be used as a laxative.[145] in tablet coatings[146] and in general to stabilize suspensions. The use of Sclg as an antitumor, antiviral and antimicrobial compound has also been investigated.[147-150] 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 still Sclg as a successful agent for colonic disorders is to be investigated.Recent investigations has showed that scleroglucan can be incorporated in sustain release monolithic swellable matrix. High viscosity of scleroglucan solution at a low concentration (1%–3%, w/w) together with its stability makes this polymer a subject of exploration for pharmaceutical preparation.

It is also used as a gelling polymer carrier matrix for sustained drug delivery systems. Another study shows that the drug release pattern from the matrix tablets containing scleroglucan is directly dependent on the rate of penetration of the solvent into the polymer matrix and not to the outward diffusion of the drug through the gel layer that is formed around the tablet.

Recently cross linked scleroglucan polysaccharides are investigated, dissolution profile is carried out at different environmental conditions. A carrageenan and cellulose derivative is very compatible and produces favourable drug release in various pharmaceutical products. Based on the investigation scleroglucan is a promising polysaccharide in controlled dosage forms.[151-152]

7. Other Natural Polysaccharides

7.1. *Amylose*

Amylose is a poly (1-4-α-D-glucopyranose) that consists of D-glucopyranose residues linked by α- (1-4) bonds. Those substances, present naturally in the diet, have the advantages of being safe, nontoxic, and easily available. These are resistant to pancreatic α-amylase, but are degraded by colonic bacterial enzyme.[153] Delayed release compositions comprising glassy amylose and an active compound were designed to permit the release when the composition reaches the large intestine.

The release of the active compound was reported to be delayed in an aqueous environment of pH 1-9 at 37 ^{0}C. The release was triggered when exposed to an enzyme capable of clearing the amylase.[154]

Milojevic et al.[155-156] prepared and evaluated *in vitro* potential of amylose-ethocel coating system for colon-targeted delivery. Aqueous dispersions were prepared using amylose and ethocel, which was used to coat 5-ASA pellets to make them resistant to gastric and small intestinal enzymes. Amylose and Ethocel in coating ratio of 1:4 was optimum with least drug release in stomach and intestinal fluids. *In vitro* release of 5- ASA from coated pellets with amylose and EC (1:4) was retarded in simulated gastric and small intestinal fluid over a period of 12 hr. It was fermented and drug was released in 4 hr in simulated colonic environment containing mixed faecal bacteria of human origin.

7.2. *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, non-pathogenic, and gram-negative bacterium.[157] 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 glucuronic acid, and two molecules of glucose. In the native form of the polysaccharide, there are approximately one and a half *O*-acyl groups per repeating unit.

Originally the *O*-acyl substituent was thought to be *O*-acetyl, resulting in the various forms of gellan gum being referred to as high-and low-acetyl, and so on. Kubo et al. suggest that gellan gum contains both *O*-acetyl and *O*-*L*-glyceryl substituents on the 3-linked glucose unit, the former tentatively assigned to the 6-position and the latter to the 2-position.[158]

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. Thus, the thickness and texture of gellan gum in various products can be controlled by manipulating the addition of potassium, magnesium, calcium, and/or sodium salts this will result in much stronger physical thermoreversible hydrogels. In the same way, its melting temperature can be modified to either below or above 100˚C.The biopolymer gellan is a more recent addition to the family of microbial polysaccharides that is gaining much importance due to its novel property of forming thermo-reversible gels when heated and cooled. It has applications in diverse fields.

A recent study reports the preparation of microspheres by emulsification technique using glutaraldehyde as a cross-linking agent, shows excellent morphology with a desired dissolution profiles with different dissolution medias.[159]

Gellan gum is one of the most interesting *in situ* gelling polymers that have been tested since it seems to perform very well in humans. Gellan gum can be used to produce easy-to-swallow solid dosage forms, such as gels and coated tablets, and to modify the rate of release of active ingredients from tablets and capsules. Gellan gum is also conveniently used for controlled or sustained release of various drugs[160] and also for microencapsulation preparation.

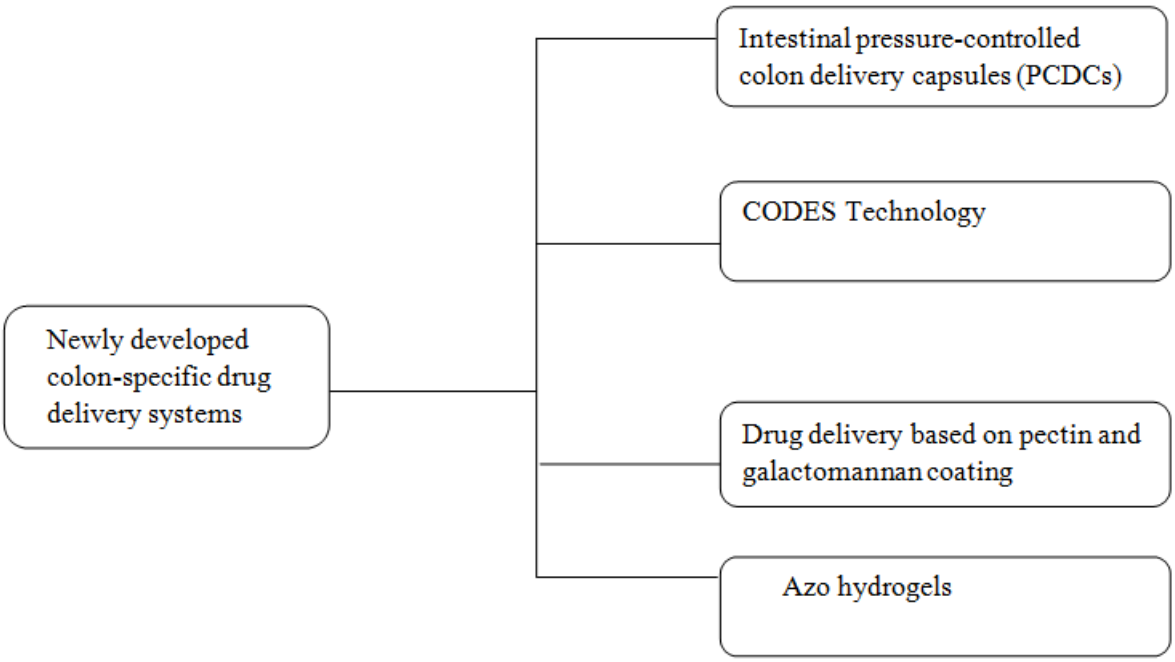
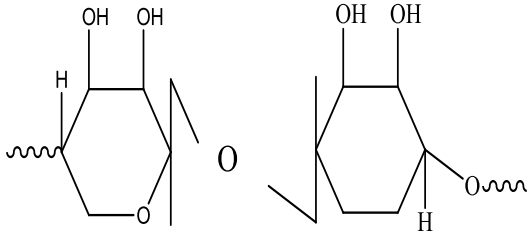
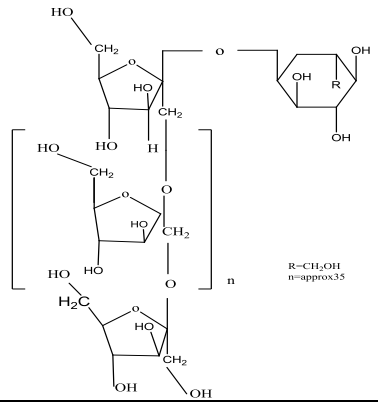


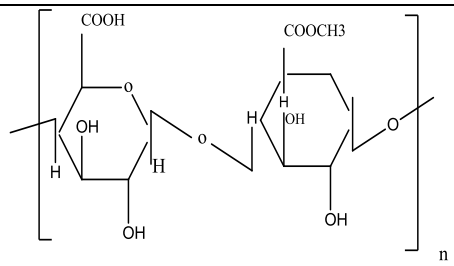
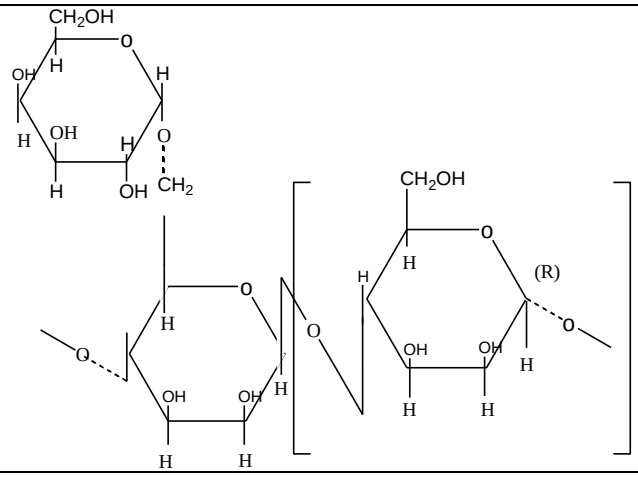
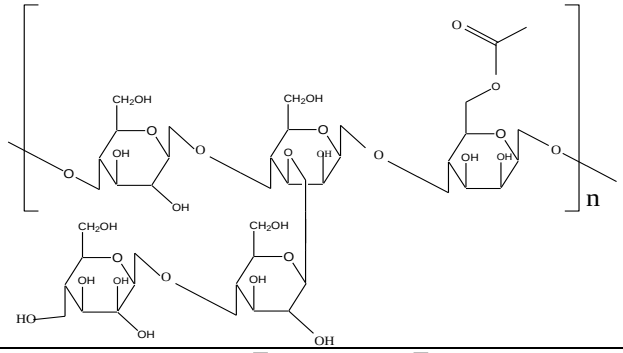
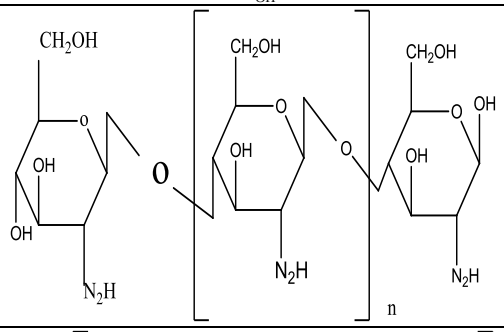
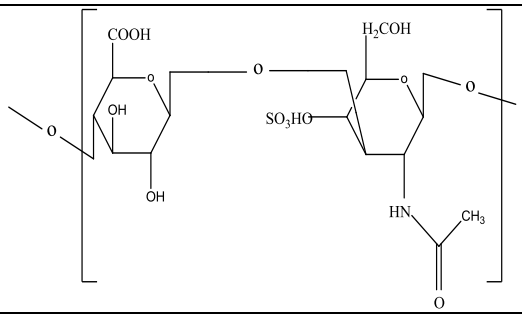
Figure 1: Schematic diagram of new approaches of colon-specific drug delivery systems.[16]

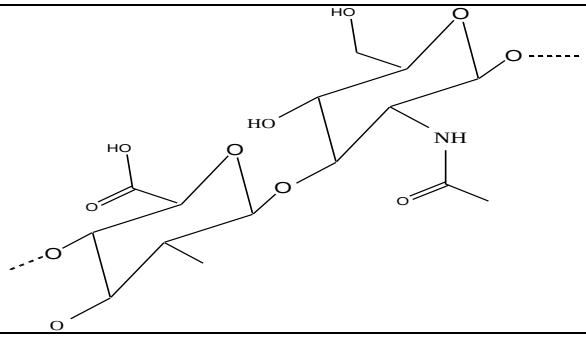
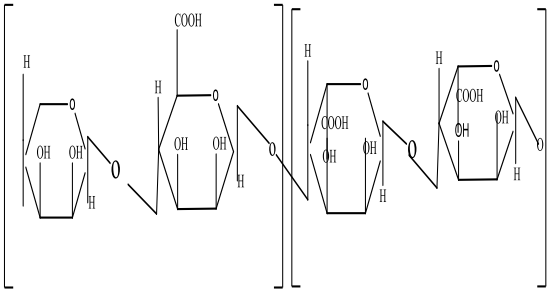
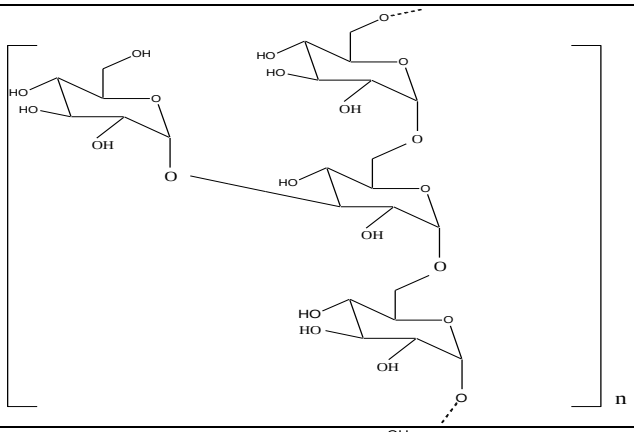
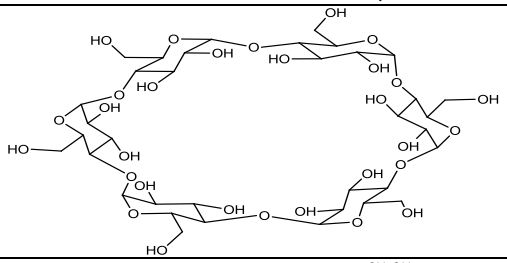
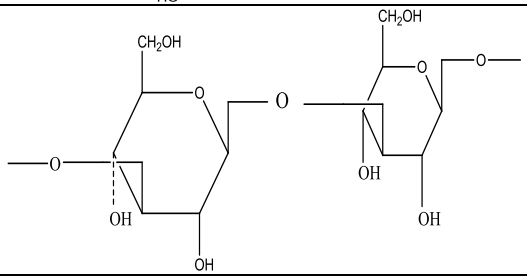
Table 1: Classification of natural polysaccharides based upon source of origin.[26, 27]

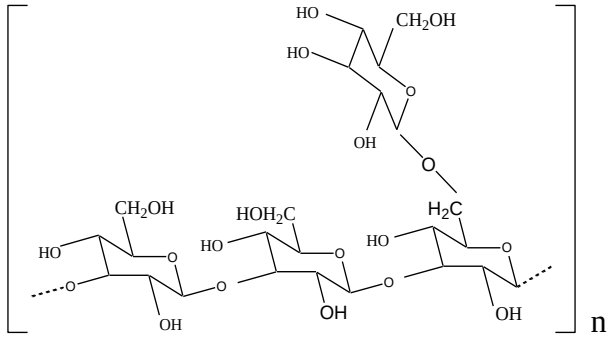
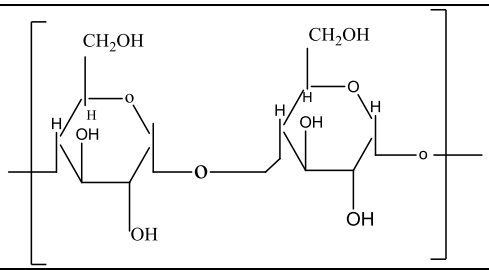
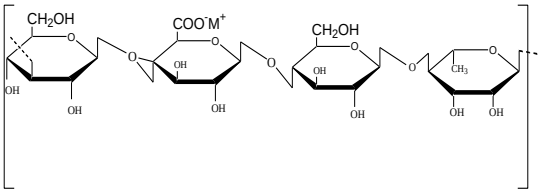
Source	Polysaccharides
Plant source	Guar gum, Inulin, Pectin, locust bean gum, Glucomannan
Animal source	Chitosan, Chondroitin sulphate, Hyaluronic acid
Algal source	Alginates
Microbial source	Dextran, Cyclodextrins, Curdlan
Fungal source	Scleroglucan

Table 2: Physicochemical properties of various natural polysaccharides for colon drug delivery systems.

Polymer	Structure	General Properties	References
Guar gum		Molecular weight- $12x10^6$ Daltons Charge- cationic Solubility-soluble in water	[157,158]
Inulin		Molecular weight- 3518 Daltons Charge- Cationic Solubility- Freely soluble in water Insoluble in ethyl ether, toluene.	[159,160]

Pectin		Molecular weight- 50,000 to180,000 Daltons Charge- Anionic Solubility- soluble in water	[161,162]
Locust bean gum		Molecular weight- 1.2×10^6 Daltons Charge-Neutral/negatively charged Solubility- incompletely soluble in cold water, insoluble in most organic solvents.	[163]
Glucomannan		Molecular weight- 200,000-2,000,000 Daltons Charge- Anionic Solubility- Water soluble.	[77,78]
Chitosan		Molecular weight- 3800-20,000 Daltons Charge- Polycationic Solubility- soluble in dilute acid	[164]
Chondroitin Sulphate		Molecular weight- $1\text{-}2 \times 10^6$ Daltons Charge-Anionic charge at physiological pH. Solubility-Soluble in water.	[165]

Hyaluronic acid		Molecular weight- 1.2-1.5 million Daltons Charge-Anionic charge Solubility-Soluble in water.	[166]
Alginates		Molecular weight- 10,000-600,000 Daltons Charge-Anionic Solubility-Salts of alginic acid with monovalent cations (Na-salt, K-salt, NH_4-salt) as well as Alginate Ester are all soluble to cold & hot water. Insoluble to fats & oils and organic solvents.	[167]
Dextran		Molecular weight- 10,000-500,000 Daltons Charge- Neutral or cationic Solubility- Soluble in water.	[168,169]
Cyclodextrin		Molecular weight- 972-1576 Daltons Charge-Anionic Solubility-Soluble in water	[170,171,172]
Curdlan		Molecular weight-$5.3x10^4$ to $2.0x10^6$ Daltons Charge-Neutral Solubility-Water insoluble	[173]

roglucan		Molecular weight-1.56x10^6 Daltons Charge-Anionic Solubility-Water soluble	[174,175]
Amylose		Molecular weight-20,000-225,000 Daltons Charge-Anionic Solubility-Water soluble	[176]
Gellan Gum		Molecular weight->70,000 Daltons Charge- Anionic Solubility- Water soluble	[177,178]

8. CONCLUSION

Colon specific drug delivery system offers several advantages in the treatment of colonic diseases such as ulcerative colitis, amoebiasis, Crohn's disease, irritable bowel syndrome, colorectal cancer. The polysaccharides based colon specific drug delivery is relatively easy due to the presence of various derivatizable groups, wide range of molecular weights, varying chemical compositions, low toxicity and high stability. The selection of suitable polysaccharide is a critical parameter in the fabrication of colon specific drug delivery.

Natural excipients are preferred over the synthetic as they are inert, safe, non-toxic, biocompatible, biodegradable, low cost, ecofriendly and abundantly available in nature. Also from the literature survey it was found that synthetic polymeric materials don't exhibit the biodegradability and bio-compatibility. Traditionally, excipients were incorporated in dosage forms as inert vehicles but in modern pharmaceutical dosage forms they often fulfil multi task roles such as improvement of solubility of poorly soluble drugs enhance bioavailability, desired drug release, target specific in the form of micro particles, and nanoparticles.

In the present review different natural excipients were studied in terms of their use in various formulations for different purposes. Although excipients traditionally were used as inert substances in pharmaceutical formulations, recently they are increasingly included in the various dosage forms to fulfil specific functions for advanced drug delivery. Most of the plant origin polysaccharides like gaur gum, locust bean gum, pectin have been investigated and reported as a potential excipient in the controlled drug delivery system. Natural polysaccharide like gellan gum from microbial origin, scleroglucan gum from marine origin and chondroitin sulphate from animal origin have been investigated for the film properties and found suitable for various controlled dosage forms. As most of the natural polysaccharides are degraded in the colon by intestinal micro flora there is a lot of scope for colon targeted drug delivery system. In addition natural polysaccharides are biocompatible, biodegradable, ecofriendly compared to synthetic polymers. Natural polysaccharide as a vital excipient for a controlled drug delivery system is an interesting challenge for future researches and has a wide potential in several pharmaceutical technologies.

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