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Review Article

BIODEGRADABLE NATURAL POLYMERS: CARRIERS FOR COLON TARGETTING DRUG DELIVERY SYSTEM

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Abstract

Now a day, polymer science is the emerging field for the development of new delivery system. In the coming years, polymers will play a vital role in delay, controlled or sustained drug delivery. This review article is emphasis on types of polymers and factors of polymer affecting drug release. Biodegradable natural polymers are highly desirable because they degrade in the body to biologically inert and compatible molecules. Targeting of drugs to the colon has been achieved by using biodegradable polysaccharides. Detailed description of various biodegradable polysachharides used for colon targeting such as guam gum, okara gum, locust bean gum, inulin, pectin, amylose, chondroitin sulfate, cyclodextrin, chitosan, dextran, alginate, xanthan gum etc., has been discussed in the review article.

Keywords: Biodegradable, Polysaccharides, Colon, Polymer

INTRODUCTION:

Polymers are natural or synthetic high molecular weight macromolecules made up of repeating monomer units. At first in the initial stages, the use of polymers was restricted for only packaging materials rather than drug delivery. The amalgamation of polymer science and pharmaceutical science led to the introduction of polymers in the design and development of drug delivery systems (DDS). By using the polymers, we will deliver the drugs in the targeting organ. Now a day, polymer science is the emerging field for the development and invention of new delivery system. The main intension of these polymeric drug delivery systems was to achieve delay, controlled or sustained drug delivery. Oral controlled release formulations for colon have received considerable attention in the past 20-25 years for variety of reasons including pharmaceutical superiority and clinical benefits derived from the drug release pattern that are not achieved with traditional immediate or sustained release formulation.[1]

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CLASSIFICATION OF POLYMERS

Polymers basically classified into two types:

1. Hydrophobic polymers
2. Hydrophilic polymers

1. Hydrophobic polymers

- **Digestible base (fatty compounds):** Glycerides such as; glyceryl tristearate, fatty alcohols, fatty acids, compritol ATO 888, and waxes like; carnauba wax.[2]
- **Nondigestible base (insoluble plastics):** Methylacrylate, methylmethacrylate, polyvinyl chloride, polyethylene, ethyl Cellulose etc.

2. Hydrophilic polymers: Methylcellulose, sodium carboxymethylcellulose, HPMC, sodium alginate, xanthan gum, guar gum, okara gum, Polyethylene oxide and carbopols.

Polymers mostly used in oral controlled release formulation are listed in table 1.[3]

Table 1: Examples of polymers used in oral controlled release formulation

Soluble polymers	Hydrogels	Biodegradable polymers
Hydroxypropylmethyl cellulose (HPMC)	Polyhydroxyethyle methylacrylate (PHEMA)	Polylactic acid (PLA)
Polyethylene glycol (PEG)	Cross-linked polyvinyl alcohol (PVA)	Polyglycolic acid (PGA)
Polyvinyl alcohol (PVA)	Cross-linked polyvinyl pyrrolidone (PVP)	Polycaprolactone (PCL)
Polyvinyl pyrrolidone (PVP)	Polyethylene oxide (PEO)	Polyanhydrides
	Polyacrylamide (PA)	Polyorthoesters
Nonbiodegradable polymers	**Mucoadhesive polymers**	**Natural gums**
Polyethylene vinyl acetate (PVA)	Polycarbophil	Xanthan gum
Polydimethyl siloxane (PDS)	Sodium carboxymethyl cellulose	Guar gum
Polyether urethane (PEU)	Polyacrylic acid	Karaya gum
Polyvinyl chloride (PVC)	Tragacanth	Okaram gum
Cellulose acetate (CA)	Methyl cellulose	Locust bean gum
Ethyl cellulose (EC)	Pectin	

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FACTORS RELATED TO POLYMERS AFFECTING THE DRUG RELEASE

The mechanistic analysis of controlled release of drug reveals that physicochemical properties of polymer play important role for rate determining in the controlled release of drugs from capsules, matrix, reservoir and sandwich type drug delivery systems.

Polymer hydration

It is important to study polymer hydration/swelling process for the maximum number of polymers and polymeric combinations. The more important step in polymer dissolution include absorption/adsorption of water in more accessible places, rupture of polymer-polymer linkings with the simultaneous forming of water-polymer linkings, separation of polymeric chains, swelling and finally dispersion of polymeric chain in dissolution medium.[4]

Polymer diffusivity

The diffusion of small molecules in polymer structure is energy activated process in which the diffusant molecules moves to a successive series of equilibrium position when a sufficient amount of energy of activation for diffusion E_d has been acquired by the diffusant is dependent on length of polymer chain segment, cross linking and crystallinity of polymer.[5] The release of drug may be attributed to the three factors:

i. Polymer particle size

ii. Polymer viscosity

iii. Polymer concentration.

i) Polymer particle size

When the content of hydroxypropyl methylcellulose is higher, the effect of particle size is less important on the release rate of propranolol hydrochloride, the effect of this variable more important when the content of polymer is low. He also justified these results by considering that in certain areas of matrix containing low levels of hydroxypropylmethylcellulose led to the burst release.

ii) Polymer viscosity

With cellulose ether polymers, viscosity is used as an indication of matrix weight. Increasing the molecular weight or viscosity of the polymer in the matrix formulation increases the gel layer viscosity and thus slows drug dissolution. Also, the greater viscosity of the gel, the more resistant the gel is to dilution and erosion, thus controlling the drug dissolution.

iii) Polymer concentration

An increase in polymer concentration causes an increase in the viscosity of gel as well as formulation of gel layer with a longer diffusional path. This could cause a decrease in the effective diffusion coefficient of the drug and therefore reduction in drug release. The mechanism of drug release from matrix also changes from erosion to diffusion as the polymer concentration increases.

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Thickness of polymer diffusional path

The controlled release of a drug from both capsule and matrix type polymeric drug delivery system is essentially governed by Fick's law of diffusion:[6]

$J_D = D * dC/dX$ …….. (1)

Where, J_D means flux of diffusion across a plane surface of unit area, D is diffusibility of drug molecule and dC/dX is concentration gradient of drug molecule across a diffusion path with thickness dX.

ROLE OF BIODEGRADABLE NATURAL POLYMERS (BIODEGRADABLE POLYSACCHARIDES) IN COLON TARGETING

In the nature, so many polymers are available. The natural polymers can be proteins and polysaccharides in chemical origin. With this natural polymers will not shows any interactions with the API. Biodegradable natural polymers are highly desirable in their conditions as they degrade in the body to biologically inert and compatible molecules and cleared by the body.[7] Biodegradable natural polymers are attractive class for controlled drug delivery since they are:

- Derived from natural sources
- Easily available
- Relatively cheap
- Qualified for a number of chemical modification
- Free of leachable impurities
- Produce degradation by-products that must be tolerated with little or no adverse reactions within the biological environment.
- Chemically inert

The oral route is considered to be most convenient for administration of drugs to patients. The gastrointestinal tract (GIT) is divided into various regions like stomach, small intestine and large intestine (colon). The conventional oral dosage forms normally dissolve in the stomach fluid or intestinal fluid and are absorbed from these regions of the gastrointestinal tract (GIT). Localized delivery of the drugs in the colon region is possible only when the drug is protected from the hostile environment of upper GIT.[8] Dosage forms that deliver drugs into the colon region rather than upper GIT offers number of advantages:

- Colonic delivery of drugs is valuable for the treatment of diseases of colon (ulcerative colitis, chron's disease, colon cancer and colonic infections)
- High local concentration in colonic tissue is achieved
- Minimizing side effects and unnecessary systemic absorption due to no release of drugs in the upper GIT[9]
- The colon is rich in lymphoid tissue. So, the uptake of antigens into the mast cells of the colonic mucosa produces rapid local production of antibodies and this helps in efficient vaccine delivery.[10]
- Specific systemic absorption of drugs from colonic region offers possibilities of the treatment of disease that follow diurnal rhythm such as hypertension, ulceration, asthma, arthritis or inflammation.[11]

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- The colon is more suitable for delivery of peptides and protein in comparison to small intestine.[12]
- Besides this low hostile environment, the colonic transit time (20-30 hours) and the colonic tissue is highly responsive to the action of absorption enhancers.[13,14]

Several approaches have been investigated to targeting drug to colon. Targeting of drugs to the colon following oral administration has been done by using biodegradable polysaccharides. A biodegradable polymer is a polymer in which the degradation results from the action of naturally occurring microorganisms such as bacteria, algae or fungi. The inability of GIT enzymes to digest certain plant polysaccharides (pectin, xylan) is taken as an advantage to develop colon specific drug delivery systems.[15] The drug is embedded in the matrix core of the biodegradable polymer by compressing the blend of active drug, a degradable polymer and additives. Various polysaccharides such as pectin, guar gum, inulin, amylase, cyclodextrins etc. have been investigated for their use in colon targeted drug delivery systems. The bacterial enzymes of colon degrade the carrier polysaccharides and release the contents for localized or systemic absorption through colon.[16] Natural polysaccharides and their derivatives represent a group of polymers widely used in pharmaceutical dosage forms. Various kinds of natural gums are used in the food industry and are regarded as safe for human consumption. These polysaccharides are obtained usually as plant exudates containing various sugars other than glucose and having significant quantities of oxidized groups in adjunct to their normal polyhydroxy format. Polysaccharides are usually soluble in water, they must be made water insoluble by cross-linking or hydrophobic derivatisation. Very important is an optimal proportion of the hydrophobic and hydrophilic parts and the number of free hydroxy groups in the polymeric molecule. Various biodegradable polysachharides used for colon targeting are guam gum, locust bean gum, inulin, pectin, amylose, chondroitin sulfate, cyclodextrin, chitosan, dextran, alginate, xanthan gum, okara gum etc. With the increase in demand for natural polysachharides, it has become necessary to explore the newer sources of polysachharides to meet the industrial demands.[17]

GUAR GUM

Its nonproprietary name as per british pharmacopeia is guar galactomannan. It is also known as galactosol, guar flour, jaguar gum, Meyprogat, Meyprodor, and Meyprofin. Chemical name of guar gum is Galactomannan polysaccharide, its empirical formula is $(C_6H_{12}O_6)_n$ and molecular weight is around 220 000. Guar gum as a gum obtained from the ground endosperms of Cyamopsis tetragonolobus (L.) Taub. (Family: Leguminosae). It consists chiefly of a high-molecular weight hydrocolloidal polysaccharide; composed of galactan and mannan units combined through glycoside linkages, which may be described chemically as a galactomannan. Guar gum consists of linear chains of (1, 4)-b-D-mannopyranosyl units with a-D-galactopyranosyl units attached by (1, 6) linkages as shown in figure 1. The ratio of D-galactose to D-mannose is between 1: 1.4 and 1: 2. Guar gum is being obtained from the seeds of Cyamopsis tetragonolobus (L.) Taub. by grinding the endosperms and subsequent partial hydrolysis.[18] Guar gum occurs as an odorless, white to yellowish-white powder with a bland taste. It is practically insoluble in organic solvents. In cold or hot water, guar gum disperses and swells almost immediately to form a highly viscous, thixotropic sol. The optimum rate of hydration occurs at pH 7.5–9.0. Finely milled powders swell more rapidly and are more difficult to disperse. Dynamic viscosity of 1% w/v guar gum dispersion is 4860 centipoise. Viscosity is

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dependent upon temperature, time, concentration, pH, rate of agitation, and particle size of the guar gum powder.

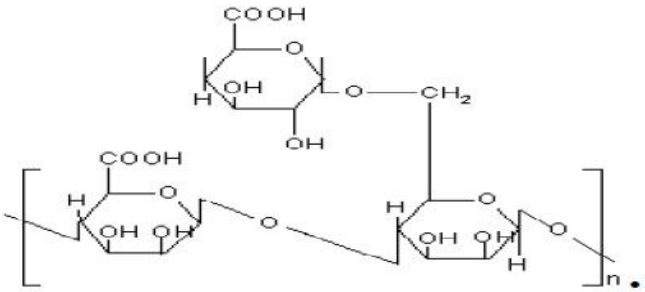

Figure 1: Chemical Structure of Guar gum

Guar gum is commonly used in cosmetics, food products, and pharmaceutical formulations. In pharmaceuticals, guar gum is used in solid-dosage forms as a tablet binder and disintegrant, in oral and topical products as a suspending, thickening, viscosity increasing and stabilizing agent, and also as a controlled-release carrier. It has also been investigated in the preparation of sustained-release matrix tablets in the place of cellulose derivatives such as methylcellulose. Guar gum has also been examined for use in colonic drug delivery of metronidazole and tinidazole.[19] Guar gum is GRAS listed and included in the FDA Inactive Ingredients Guide (oral suspensions, syrups, and tablets; topical preparations; vaginal tablets). Synthetic derivatives of guar gum such as guar acetate, guar phthalate, guar acetate phthalate, oxidized guar gum, and sodium carboxymethyl guar, have also been investigated for their pharmaceutical applications.[20] In particular, sodium carboxymethyl guar gives a transparent gel and has been used as a polymer matrix in transdermal patches.[21]

OKRA GUM

Okra gum is obtained from the fruits of Hibiscus esculentus (Lady Finger, family: Malvaceae), are a polysaccharide consisting of D galactose, L-rhamnose and L-galacturonic acid.[22] The gum is naturally available, inexpensive, consistent in quality and reliable in supply. These attributes of okra gum are sufficient to justify a detailed assessment of the material as hydrophilic matrix in controlled-release delivery system. Okra gum has been investigated as a binding agent in tablet dosage forms, and has been shown to produce tablets with good hardness, friability and drug release profiles.[23] Okra gum matrices were found to be useful in the formulation of sustained release paracetamol tablets for up to 6 hr, and the appropriate combination of okra gum and HPMC was used to provide a time-independent release for longer periods.[24] Okara gum in combination of Carbopol 941 used to prepare bioadhesives tablet of indomethacin and results indicate that tablets with equal ratio of C-941 and okra gum (1:1) gave the highest bioadhesive strength and percentage of drug release ranged from 53-90% in 0.1 N HCL after 8 hrs.[25] V D Kalu prepared and evaluated sustained release tablet from okra gum and compared with sodium carboxymethylcellulose (NaCMC) using aspirin as the model drug to provide near zero-order release of aspirin from the matrix tablets.[26]

LOCUST BEAN GUM

Locust bean gum is a high molecular weight (3,10,000) hydro colloidal polysaccharide derived from the endosperm of the seed of *Ceratonia siliqua Linn* (Family- Leguminosae). It consists of α -1,4- D - galactomanan units. The gum contains 88% D-galacto-D-mannoglycan, 4% pentan,

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6% of proteins, 1% cellulose and 1% ash. This is neutrally occurring slightly soluble polymer in cold water. Locust bean gum in combination of chitosan were evaluated for colon specific drug delivery systems and concluded that capable of protecting the drug from being release in the stomach and small intestine and was susceptible to colonic bacterial enzymatic actions with resultant drug release in the colon.[27] Josephine et al., *In vitro* drug release studies were carried out on Mesalazine core tablets compression coated with different quantities of locust bean gum in simulated gastro intestinal fluids in the presence and absence of rat caecal contents.[28]

INULIN

Inulin is a naturally occurring polysaccharide which is not hydrolyzed by the endogenous secretions of the human digestive tract and metabolized only in colon.[29] The chemical structure of inulin is shown in figure 2. Coating containing high degree polymerized inulin with eudragit RS was evaluated for colonic drug delivery. Stubbe et al., developed azo-inulin containing polysaccharide gels.[30]

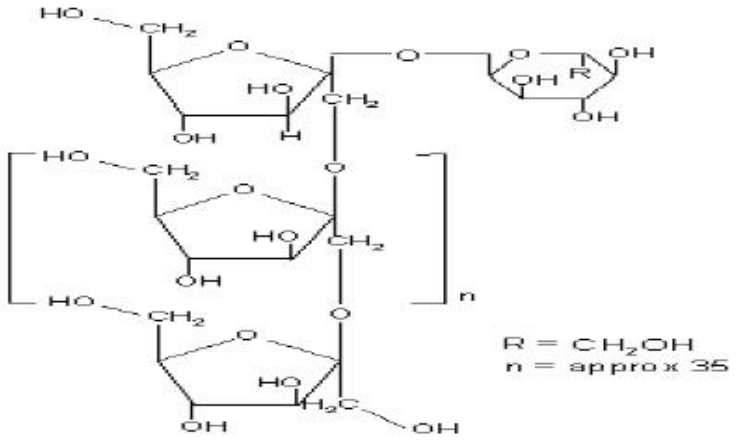

Figure 2: Chemical structure of inulin

PECTIN

Pectin an anionic polysaccharide extracted from plant primary cell wall (shown in figure 3). Higher water solubility of pectin creates problem in fabrication of colon targeted delivery systems. Pectin alone is unable to protect the load of drug as GI fluids penetrates into and releases the drug by diffusion. This problem can be manipulated through choice of suitable pectin type or the presence of additives.[31] Coating of pectin remains unaffected in presence of gastric and small intestinal enzymes but is completely digested in presence of colonic bacterial enzymes. Pectin in the form of compression coat was evaluated for drug targeting to colon.[32] Compression coated core tablets of 5- Amino Salicylic acid (5-ASA) were prepared using pectin and HPMC.[33] Pectin containing varying degree of high and low methoxy ester substituents evaluated for colonic drug delivery.[34] Amidated pectin is used for colonic drug delivery of indomethacin and sulfamethoxazole.[35] Combination of pectin with ethyl cellulose is used as film coating for drug delivery to the colon.[36]

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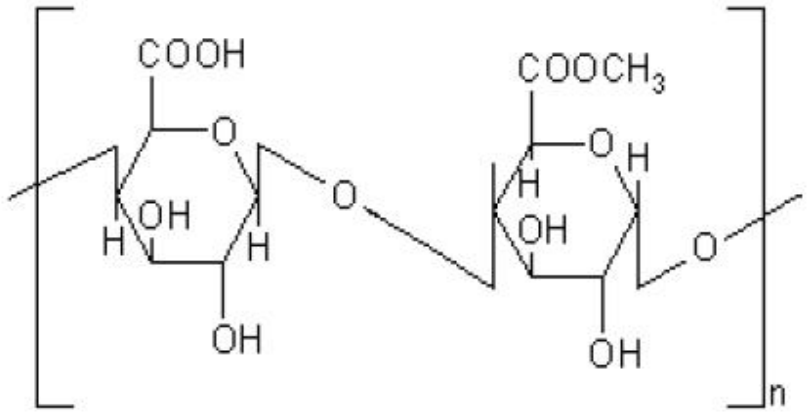

Figure 3: Chemical structure of pectin

AMYLOSE

Amylose is a safe, nontoxic, and easily available polysaccharide as shown in figure 4. Amylose, one of the major fractions of starch, possesses the ability to form films through gelation. The microstructure of the film is potentially resistant to the action of pancreatic amylase, but is digested by amylases of the colonic microflora.[37] Colon-specific drug delivery may be possible by the application of dried amylose films to pharmaceutical formulations.[38] However, under simulated gastrointestinal conditions, coatings made solely of amylose will become porous and allow drug release. Insoluble polymers such as ethyl cellulose (Ethocel) are incorporated into the amylose film, to control amylose swelling. Ephichlorhydrin treated cross-linked amylose was introduced as a matrix for controlled release of theophylline.[39]

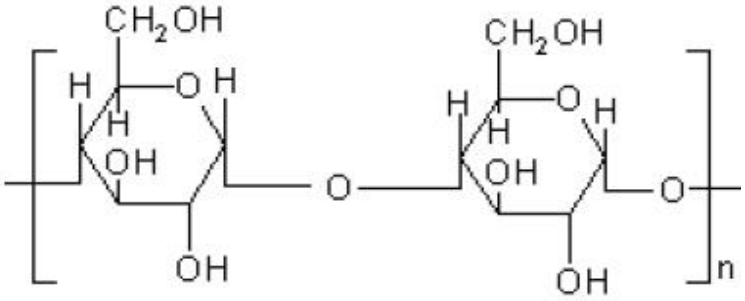

Figure 4: Chemical structure of Amylose

CHONDROITIN SULFATE

It is a water soluble mucopolysacharide and its chemical structure represent in figure 5. It is utilized as a substrate by the bacteriodes present in colon mainly by *Bacteriohdes thetaiotaomicron* and *B.obvatus*. However, cross-linked chondroitin sulfate is less hydrophilic. Chondroitin sulfate and cross-linked chondroitin sulfate were evaluated for Colon Specific drug delivery.[40] Colonic delivery of indomethacin was achieved using crosslinked chondroitin sulfate.[41]

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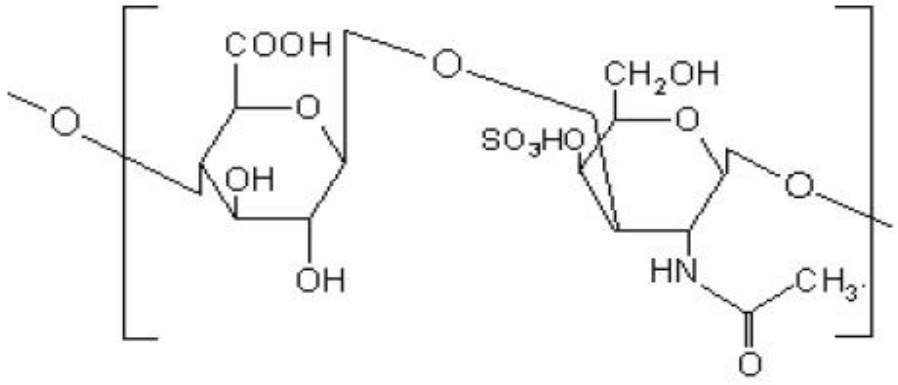

Figure 5: Chemical structure of Chondroitin Sulfate

CYCLODEXTRIN

They are cyclic oligosaccharides consisted of six to eight glucose units joined through a α-1,4 glucosidic bonds. They remain intact in stomach and small intestine, they are metabolized in the colon due to the presence of colonic microflora. Hiramaya et al., prepared two cyclodextrin conjugates i.e. ester and amide conjugates and it was shown that ester conjugate released the drug preferentially in colon.[42] The colon specific drug delivery of prednisolone was achieved using α-cyclodextrin.[43] The chemical structure of α-cyclodextrin is shown in figure 6**.**

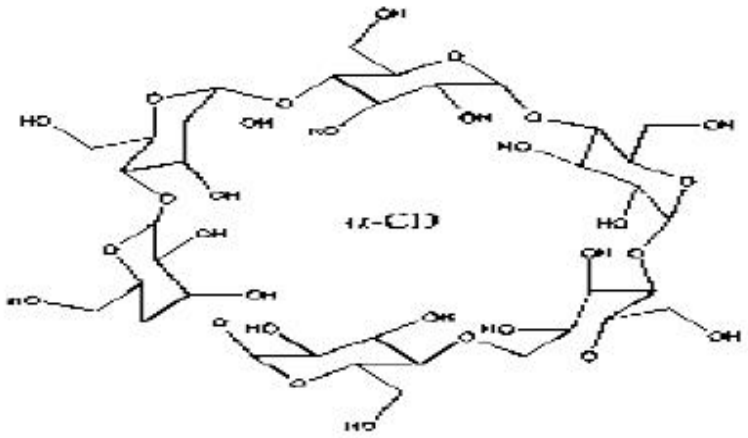

Figure 6: Chemical Structure of α-Cyclodextrin

CHITOSAN

It is chemically poly (N- gluocosamine), high molecular weight polycationic polysaccharide obtained by deacetylation of naturally occurring chitin and shows resistance to enzymes of upper GI tract 98. It is a linear polycationic polymer of D-glucosamine (N-acetyl-2-amino-2-deoxy-D-glucopyranose) units linked by β-D(1-4) bonds. It is nontoxic, biocompatible and biodegradable. Chitosan capsules R-68070 and hard capsules of chitosan with enteric polymers are developed to deliver insulin to colon.[44,45] A new colon specific drug delivery system developed using chitosan dispersed in hydrophobic polymer as drug release regulating layer.[46] A pH sensitive chitosan hydro gels developed by shu et al., and Jain et al.,developed albendazole microspheres

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for colon specific delivery using Chitosan HCl.[47,48] The chemSical structure of Chitosan is shown in figure 7**.**

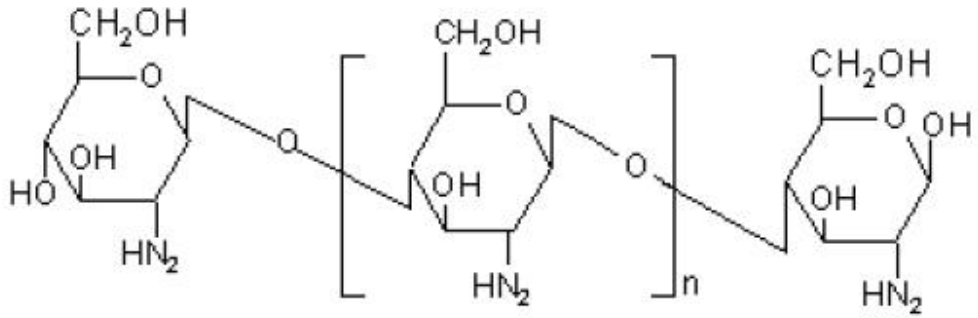

Figure 7: Chemical Structure of Chitosan

DEXTRAN

Dextrans are hydrophilic substances, obtained from microorganisms of the family of Lactobacillus. dextran T-70- naproxen ester prodrug, dextran ester prodrugs of Metronidazole, dextran-nalidixic acid ester prodrug, dextran ester prodrugs of 5-ASA have been prepared and evaluated for their efficacy to deliver drugs to colon.[49,50] The side effects of steroid therapy, which are used in the treatment of chronic colitis, decrease by selectively delivering the drug to the colon using dextran.[51] The chemical structure of dextran is shown in figure 8.

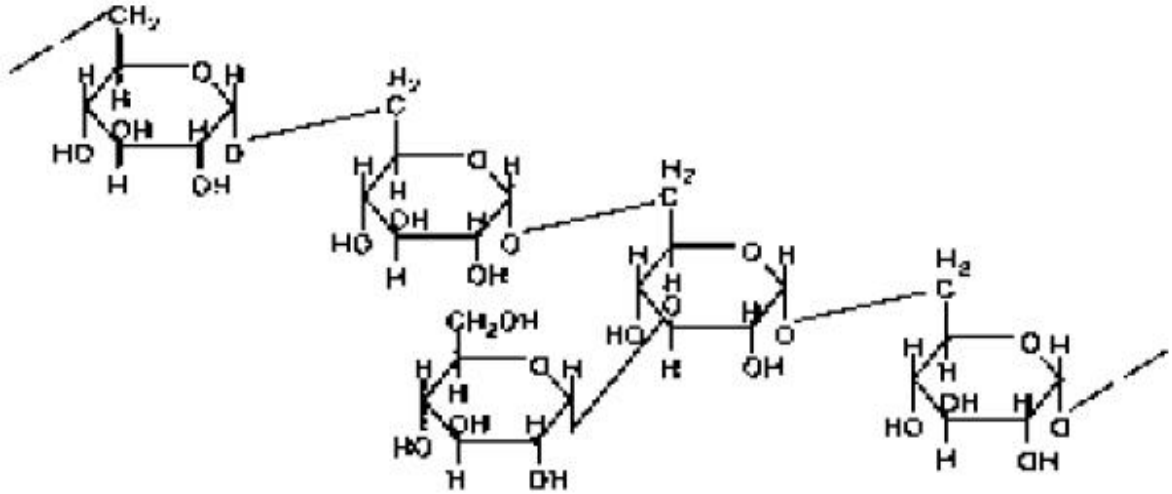

Figure 8: Chemical Structure of Dextran

ALGINATES

Alginates are naturally occurring hydrophilic polysaccharide obtained from seaweed and 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/cross-linking is due to the stacking of the glucoronic acid blocks of alginate chains. Shun et al., prepared calcium alginate beads containing 5-ASA, coated with Aqua coat® that is a pH independent polymer followed by 2% w/v coating of eudragit L-30D for colon targeting it.[52] Alginate microspheres have been effectively used for oral delivery of vaccines and antigens by protecting vaccines/antigens

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against degradation in gastro intestinal tract. Kiyoung et al., prepared alginate beads and coated with dextran acetate.[53] The chemical structure of alginate is shown in Figure 9.

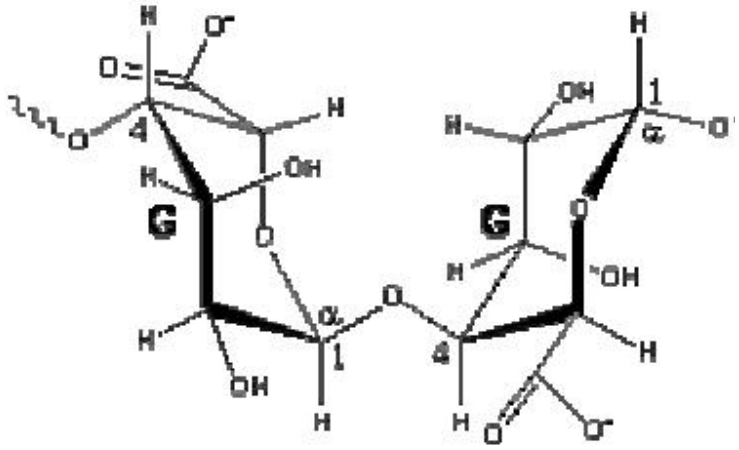

Figure 9: Chemical Structure of Alginate

KHAYA GUM

Khaya gum is a polysaccharide obtained from the incised trunk of tree *Khaya grandulifolia*, Family Meliaceae, a typical West African mahogany tree. Odeku *et al.*, reported that khaya gum is capable of protecting the drug from being released in the acidic environment prevailing in the stomach and small intestine. They are degraded by the colonic bacterial enzymes, thereby releasing the drug in the colon where there is local action and improved absorption.[54] Oluwatoyin investigated the khaya gum as a directly compressible controlled release agent in modified release matrices in comparison with hydroxypropylmethylcellulose (HPMC) using paracetamol (water soluble) and indomethacin (water insoluble) as model drugs. Khaya gum matrices provided a controlled release of paracetamol for up to 5 h.[55]

XANTHAN GUM

Xanthan gum is a commercial hydrophilic polymer, secreted from *Xanthomonas campestris*. Xanthan gum is used as matrix former and potential excipient for oral controlled release tablet dosage forms.[56] P. G. Yeole used xanthan gum for developing sustained release matrix tablets of diclofenac sodium and attempt has been made to increase therapeutic efficacy, reduce frequency of administration, and improve patient compliance.[57] M. P. Venkataraju et al., developed locust bean gum-xanthan gum matrix tablet of the propranol HCL.[58] Sujja-areevath et al. (1998) observed that Fickian diffusion type of the dissolution of diclofenac sodium mini matrices prepared using different ratios of xanthan gum. Xanthan and galactomannan (from *M. scabrella*) used to prepare the matrix tablets for oral controlled delivery of theophylline.[59]

CONCLUSION

A wide variety of natural biodegradable polymers have been investigated and used for drug targeting or prolonged or controlled drug release. Colon targeted drug delivery systems are used to selectively release the drug to the colon. The polysacharides 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.

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