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Polysaccharides Based Colon Specific Drug delivery: A Review

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ABSTRACT: Although oral delivery has become a widely accepted route of administration of therapeutic drugs, the gastrointestinal tract presents several formidable barriers to drug delivery. The delivery of drugs to the colon has a number of therapeutic implications in the field of drug delivery. In the recent times, the colon specific delivery systems are also gaining importance not only for local drug delivery of drugs but also for the systemic delivery of protein and peptide drugs. The various approaches that can be exploited to target the release of drug to colon include prodrug formation, coating with pH sensitive polymers, coating with biodegradable polymers, embedding in biodegradable matrices, hydrogel, timed release systems, osmotic and bioadhesive systems. In this review article we have made an attempt to give an overview on polysaccharide-based colon specific drug delivery system.
Key Word: Polysaccharide, Gastrointestinal tract, Hydrogel.

INTRODUCTION:

The oral route is considered to be most convenient for administration of drugs to patients. 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), which depend upon the physicochemical properties of the drug. Localized delivery of the drugs in the colon region is possible only when the drug is protected from the hostile environment of upper GIT. Dosage forms that deliver drugs into the colon region rather than upper GIT proffers number of advantages. Oral delivery of drugs to the colon is valuable in the treatment of diseases of colon (ulcerative colitis, Chron's disease, carcinomas and infections) whereby high local concentration can be achieved while minimizing side effects that occur because of release of drugs in the upper GIT or unnecessary systemic absorption. The colon is rich in lymphoid tissue.Uptake of antigens into the mast cells of the colonic mucosa produces rapid local production of antibodies and this helps in efficient vaccine delivery[1]. Specific systemic absorption of drugs and protein/peptides in the colonic region offers interesting possibilities for the treatment of disease susceptible to diurnal rhythm such as asthma, arthritis or inflammation[2-3]. The colon is considered to be more suitable for delivery of peptides and protein in comparison to small intestine [4,5]. 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 [6,7]. Colonic delivery can be accomplished by oral or rectal administration. Rectal dosage forms such as suppositories and enemas are not always effective since a high variability in the distribution of these forms is observed [8-10].The GIT is divided into various regions like stomach, small intestine and large intestine. The colon serves four major functions: viz; creation of suitable environment for the growth of colonic microorganisms, storage reservoir of faecal contents, expulsion of the contents of the colon at an appropriate time, absorption of potassium and water from lumen and excretion of potassium and bicarbonate. An overview of the pH details of the GIT[11] is shown in Table 1. Gastric emptying of dosage forms is highly variable and depends primarily on whether the subject is fed or fasted and on the properties of the dosage form such as size and density. The transit times of small dosage forms in GI tract is shown in Table 2.

TABLE1: AVERAGE pH IN THE GIT

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

Organ	**Transit time(h)**
Stomach	<1 (Fasting) >3 (Fed)
Small intestine	3-4
Large intestine	20-30

TABLE3: CRITERIA FOR SELECTION OF DRUGS FOR COLON SPECIFIC DRUG DELIVERY SYSTEMS:

Criteria	**Nonpeptide drugs**	**Peptide drugs**
Drugs used for local effects in colon against GIT diseases	Diclofenac, Metaprolol	Amylin, Calcitonin
Drugs poorly absorbed from upper GIT	Ibuprofen, Theophylline, Isosorbides	Cyclosporine, Desmopressin
Drugs for colon cancer	Pseudoephedrine	Glucagon, Epoetin
Drugs that degrade in stomach and small intestine	Bromophenaramine 5-Flourouracil	Gonadorelin, Insulin
Drugs that under go extensive first pass metabolism	Nimustine, Bleomycin	Sermorelin, Saloatonin
Drugs for targeting	5-Aminosalicylic- acid, Prednisolone	Vasopressin, urotoilitin

Drug candidate for colonic drug delivery:

Drugs which show poor absorption from the stomach or intestine including peptide drugs, are most suitable for colon specific drug delivery systems. The criteria for selection of drugs for colon specific drug delivery systems [12,13] is shown in Table 3. Selection of carrier for particular drug candidate depends on the physicochemical nature of the drug as well as the disease for which the system is to be used. The factors such as chemical nature, stability and partition coefficient of the drug and the type of the absorption enhancer chosen influence the carrier selection. Choice of drug carrier depends on the functional groups of the drug molecule[14.] There are several ways in which colon specific drug delivery has been attempted[15.] This includes prodrug formation, coating with pH sensitive polymers, coating with biodegradable polymers, embedding in biodegradable matrices and hydrogel, timed-release systems, osmotic systems, and bioadhesive systems. In this review article we have made an attempt to focus on the polysaccharide based colon delivery systems.

POLYSACCHARIDES BASED APPROACHES:

TABLE 4: CHARACTERISTICS OF VARIOUS BIODEGRADABLE POLYSACCHARIDES FOR COLON TARGETED DRUG DELIVERY.

Polymer	Chemical name	General properties	Bacterial species that degrade polysaccharide
Amylose	-1, 4 D- glucose	Unbranched constituent of starch, used as tablet excipients	Bactericides Bifidobacterium
Arabinogalactose	-1,4 and -1,3 galactose, -1,6 and -1,3 D- arabinose and D- galactose	Natural pectin, hemi cellulose Used as a thickening agent	Bifidobacterium
Chitosan	Deacetylated - 1, 4- N- acetyl –D-glucosamine	Deacetylated chitin, used as a absorption enhancing agent	Bactericides
Cyclodextrins	-1, 4 D- glucose	Cyclic structures of 6,7or 8 units used as a solubilising and absorption enhancing agent	Bactericides
Chondroitin sulphate	-1,3 D- glucoronic acid and N- acetyl –D-glucosamine	Mucopolysacharides, contains various amounts esters of sulphate at 4 or 6 position	Bactericides
Pectin	-1,4 D- galacturonic acid and 1,2 D- rhamnose with D- galactose and D-arabinose side chain	Partial methyl ester, commonly used as thickening agent	Bifidobacterium, Eubacterium,
Dextran	-1, 6 D- glucose -1,3 D- glucose	Plasma expanders	Bactericides
Guar gum	-1, 6 D-galactose -1,4 D- mannose	Galactomanan, used as a thickening agent	Bacteroides, Ruminococus
Xylan	-1,4 D- xylose with -1,3 L- arabinose side chains	Abundant hemi cellulose of plant cell wall	Bacteroides, Bifidobacterium

Biodegradable matrix and hydrogel systems:

The inability of GIT enzymes to digest certain plant polysaccharides (pectin, xylan) is taken as an advantage to develop colon specific drug delivery systems[16]. 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 polymer and release the contents for localized or systemic absorption through colon[17-21]. The most important fact in the development of polysaccharide derivatives for colon targeted drug delivery is the selection of a suitable biodegradable polysaccharide. As these 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. The general properties of polysaccharides used in colon targeted drug delivery are shown in Table 4.

Pectin: Pectin an anionic polysaccharide extracted from plant primary cell wall was used by Ashford etal,[22.] Depending on the plant source and preparation they contain varying degree of methyl ester substituents[23]. Excessive solubility of pectin in water 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[24,25]. 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[26]. Compression coated core tablets of 5- Amino Salicylic acid (5-ASA) were prepared using pectin and HPMC[27]. Munjeri et.al.[28,] investigated amidated pectin for colonic drug delivery using indomethacin and sulfamethoxazole as model drugs. Walkerly etal,[29-31] used biodegradable coating containing pectin and ethyl cellulose for colon specific drug delivery. Ashford etal,[32] evaluated high and low methoxy pectin for colonic drug delivery. Rubinstein et.al.[33] developed colonic specific drug delivery system using calcium pectinate by using calcium pectinate using indomethacin as model drug. Atyabi etal,[34] developed and evaluated Bovine serum albumin-loaded pectinate beads for colonic peptide delivery system. Ahmed etal,[35] studied the effect of simulated gastrointestinal conditions on drug release from pectin/ethyl cellulose as film coating for drug delivery to the colon. Bourgeois etal,[36] evaluated the pectin beads for colonic delivery of lactamases. Hiorth etal,[37] studied the immersion coating of pellets with calcium pectinate and Chitosan. Kosaraju etal,[38] Sande etal,[39] developed pectin-based oral drug delivery to the colon. Zhang etal,[40] developed calcium pectinate capsules for colonic drug delivery. Prabhashankar etal,[41] studied formulation and roentgenographic studies of naproxen-pectin-based matrix tablets for colon drug delivery. Zhambito etal,[42] studied matrices for site-specific controlled-delivery of 5-fluorouracil to descending colon. Fishman etal,[43] developed pectin-based systems for colon-specific drug delivery via oral route. Sinha etal,[44] formulated and evaluated colonic drug delivery of 5-fluorouracil .Ahrabi etal,[45] developed pectin matrix tablets for colonic delivery of model drug ropivacaine. Sriamornsak etal,[46] developed composite film-coated tablets intended for colon-specific delivery of 5-aminosalicylic acid by using deesterified pectin. El-Gibaly etal,[47] developed oral delayed-release system based on Zn-pectinate gel (ZPG) microparticles as an alternative carrier to calcium pectinate beads for colonic drug delivery. Turkoglu etal,[48] developed the *in vitro* evaluation of pectin-HPMC compression coated 5-aminosalicylic acid tablets for colonic delivery. Mura P[49] developed enteric-coated pectin-based matrix tablets for colonic delivery of theophylline. The chemical structure of pectin is shown in Figure 1.

Inulin:

Inulin is a naturally occurring polysaccharide found in many plants. It is not hydrolyzed by the endogenous secretions of the human digestive tract[50.] It is metabolized in colon [51-52]. Inulin HP (high degree polymerization) was incorporated in eudragit RS film was evaluated as a possible biodegradable coating for colonic drug delivery. Vervoort etal,[53] Maris etal,[54] have done preliminary studies on synthesis and characterization of various inulin hydro gels as carriers for colonic drug delivery system. Stubbe etal,[55] developed azo containing polysaccharide gels more specifically azo- inulin and azo dextran gels. The chemical structure of inulin is shown in Figure 2.

Guar gum:

Guar gum is a natural polysaccharide derived from the seeds of *Cyamopsis tetragonolobus*, having molecular weight of approximately 1,000000, giving it a high viscosity in solution[56]. Due to its high molecular weight it is metabolized in large intestine due to the presence of microbial enzymes[57-58.] Guar gum is hydrophilic in nature and swells in cold water forming viscous colloidal dispersions or sols [59]. This gelling property retards release of the drug from the dosage form as well as it is susceptible to degradation in the colonic environment. To reduce the swelling properties of the guar gum it was reacted with glutaraldehyde under acidic conditions to obtain different products with increasing cross-linking densities. The products were characterized by measuring their swelling properties in simulated and intestinal fluids and their cross linking densities.[60].Reduction in the enormous swelling by cross linking resulted in biodegradable hydrogel formation, which was able to retain poorly water-soluble drug. Krishnaiah etal,[61] studied the influence of metronidazole and tinidazole on the usefulness of guar gum, a colon-specific drug carrier. Compression coated tablets[62] of 5-ASA and matrix tablets of mebendazole have been prepared using guar gum as a carrier. Matrix tablets of guar gum with dexamethasone, indomethacin and budenoside have been investigated for colon targeted drug delivey[63,64.] Matrix tablets containing various proportions of guar gum were prepared by wet granulation technique using starch paste as a binder[65,66]. Das etal,[67] have studied cross-linked guar gum hydrogel discs for colon-specific delivery of ibuprofen: formulation and *in vitro* evaluation. Al-saidan etal,[68] studied *in vitro* and in vivo evaluation of guar gum-based matrix tablets of rofecoxib for colonic drug delivery. Krishnaiah etal,[69.-74] studied pharmacokinetics evaluation of various antiprotozoal drugs in healthy volunteers. Momin etal,[75] studied *in vitro* studies on guar gum based formulation for the colon-targeted delivery of Sennosides. Chourasia etal,[76] developed guar gum microspheres for target specific drug release to colon. Krishnaiah etal,[77] have tried guar gum as a carrier for colon specific delivery and they also studied the influence of metronidazole and tinidazole on *in vitro* release of albendazole from guar gum matrix tablets. Krishnaiah etal,[78] Studied of guar gum compression-coated 5-aminosalicylic acid tablets for colon-specific drug delivery. The chemical structure of guar gum is showninFigure(3).

Amylose: Amylose is a polysaccharide obtained from plant extracts and is a component of starch. These are safe, nontoxic, and easily available. Colon-specific drug

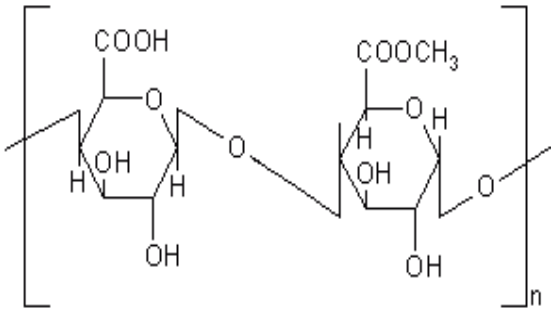

Figure1: Chemical structure of pectin.

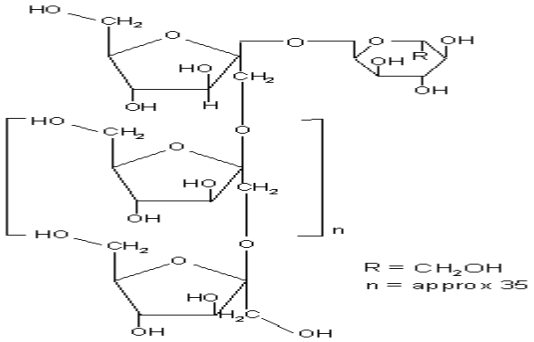

Figure 2: Chemical structure of inulin.

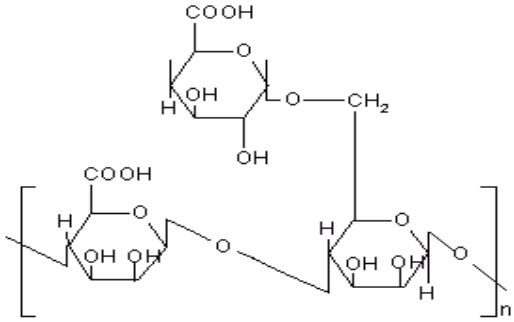

Figure 3: Chemical structure of guar gum

delivery may be possible by the application of dried amylose films to pharmaceutical formulations. Amylose, one of the major fractions of starch, possesses the ability to form films through gelation, when prepared under appropriate conditions. The microstructure of the film is potentially resistant to the action of pancreatic -amylase but is digested by amylases of the colonic microflora. However, under simulated gastrointestinal conditions, coatings made solely of amylose will become porous and allow drug release. Incorporation of insoluble polymers into the amylose film, to control amylose swelling, provides a solution to this problem. A range of cellulose and acrylate based copolymers were assessed, of which a commercially available ethyl cellulose (Ethocel) was found to control the swelling most effectively. Various works has been reported on formulation and evaluation of *invitro* potential of amylose- ethocel coating system for colon-targeted delivery[79-83]. A mixture of amylose and ethocel (1:4) has been developed for colonic drug delivery using [C^{13}] glucose as model drug[84]. Ephichlorhydrin treated cross-linked amylose was introduced as a matrix for controlled release of theophylline[85.] The chemical structure of guar gum is shown in Figure 4.

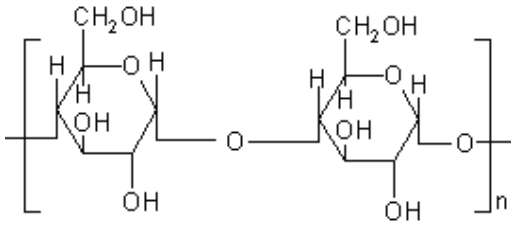

Figure 4: Chemical structure of Amylose

Chondroitin Sulfate:

Is a soluble mucopolysacharide utilized as a substrate by the bacteriodes mainly by *Bacteriodes thetaiotaomicron* and *B.obvatus*[86,87.] Natural chondroitin sulfate is water-soluble. However, cross-linked chondroitin sulfate is less hydrophilic and thus would provide a better shield. Colon Specific drug delivery systems based on chondroitin sulfate and cross-linked chondroitin sulfate were reported by Rubinstein eal,[88,89] have developed colonic drug delivery systems based on chondroitin sulfate and cross-linked chondroitin sulfate. Sintov et.al[90] have developed indomethacin colon specific drug delivery using crosslinked chondroitin sulfate and studied for water uptake and release characteristics. The chemical Structure of chondroitin sulfate is shown in Figure 5**.**

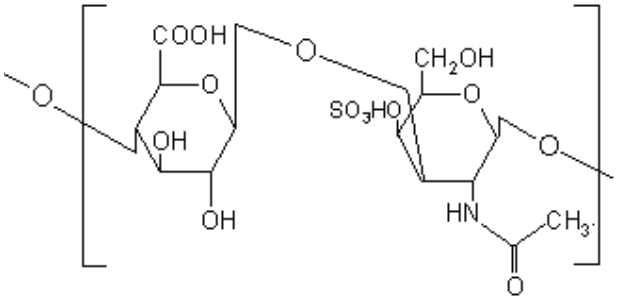

Figure 5: Chemical structure of Chondroitin Sulfate

Cyclodextrin:

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, in the colon they under go fermentation due to the presence of colonic microflora and absorbed from these regions[91,92]. Tanaka etal,[93] have prepared several cyclodextrin complexes for colon specific drug delivery systems. Hiramaya etal,[94] 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 etal,[95] have prepared the colon specific drug delivery system for prednisolone using α 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 systems[96-97]. The chemical structure of α-cyclodextrin is shown in Figure 6**.**

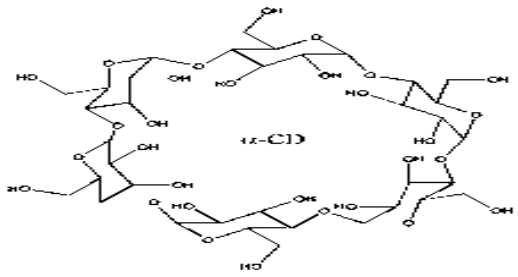

Fig 6: Chemical Structure of α-Cyclodextrin

Chitosan:

Chitosan is a high molecular weight polycationic polysaccharide derived from naturally occurring chitin by deacetylation. Chemically it is poly (N- gluocosamine) and shows resistance to enzymes of upper GI tract[98]. It is nontoxic, biocompatible and biodegradable. It is widely used as food ingredient[99.] Tozazki etal,[100,101] developed colon specific insulin delivery system with chitosan capsules. Tozaki etal,[102] used rats to study the colon specificity of chitosan capsules R-68070, a thromboxane synthetase inhibitor used for chemically induced ulcerative colitis. Shimono etal,[103] 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 etal,[104] synthesized various salts of chitosan and evaluated for colon specific delivery system. Vandelli etal,[105], shu etal, [106] have developed a pH sensitive based chitosan hydro gels drug delivery system. Suzuki etal, [107] prepared hard capsules of chitosan with enteric polymers for colon targeted drug delivery. Jain etal,[108] developed albendazole microspheres for colon specific delivery using Chitosan HCl . The chemical structure of Chitosan is shown in Figure 7**.**

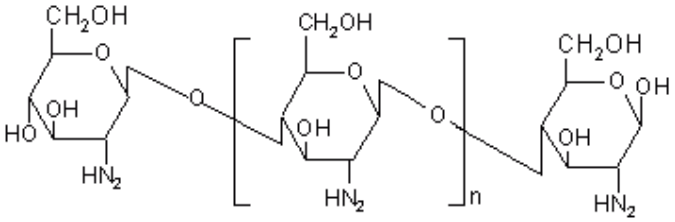

Fig 7:Chemical Structure of Chitosan

Dextran:

Dextrans are colloidal, hydrophilic and water soluble substances, obtained from microorganisms of the family of Lactobacillus. Dextrans of various molecular weights have been used as drug carriers. Various dextran ester prodrugs have been prepared and evaluated for their efficacy to deliver the drug to their target organ i.e. colon. Harboe, et.al[109,110] synthesized dextran ester prodrug. They formulated dextran T-70- naproxen ester and compared the bioavailability of prodrug form naproxen alone. They found that 100% bioavailability from prodrug form than the drug alone, they also found that the release of prodrug form of drug was released more in caecum homogenate than from the homogenate of small intestine of pig.[111-112]. Dextran ester prodrugs of metronidazole have been prepared and characterized for colon specific drug release[113-115]. Lee etal,[116] developed a dextran-nalidixic acid ester with a varied degree of substitution for colon specific delivery. Jung etal,[117] were synthesized dextran ester prodrugs of 5-ASA and drug release rate study revealed that drug release was accelerated in large intestine . Bauer & Kesselhut[118] 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. *In vitro* studies with lauroyl dextran esters bearing theophylline were carried out and it was shown that addition of dextranase accelerated the drug release[119-120.] 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[121-122]. Various dextran ester prodrugs viz:sulasalazine,budenoside,mesalazine,olsalazine etc., were formulated for colon delivery of steroids for local and systemic action[123-130]. The chemical structure of dextran is shown in Figure 8.

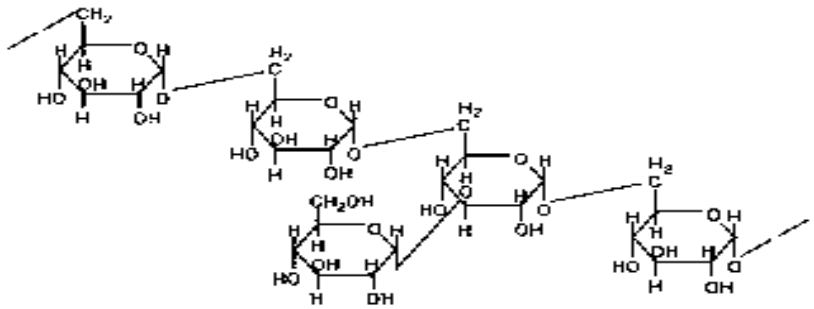

Fig 8: Chemical Structure of Dextran

Alginates:

Alginates are natural hydrophilic polysaccharide derived 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 etal.[131,132] developed calcium alginate beads as cores with a spray coat of 5-ASA on them. This system was prepared by coating calcium alginate beads with Aqua coat® that is a pH independent polymer followed by 2% w/v coating of eudragit L-30D. Being enteric polymer the release of drug in acidic medium was resisted and release was triggered in alkaline pH. Kiyoung etal,[133] prepared alginate beads and coated with dextran acetate. In the absence of dextranase the release was minimal. The chemical structure of alginate is shown in Figure 9.

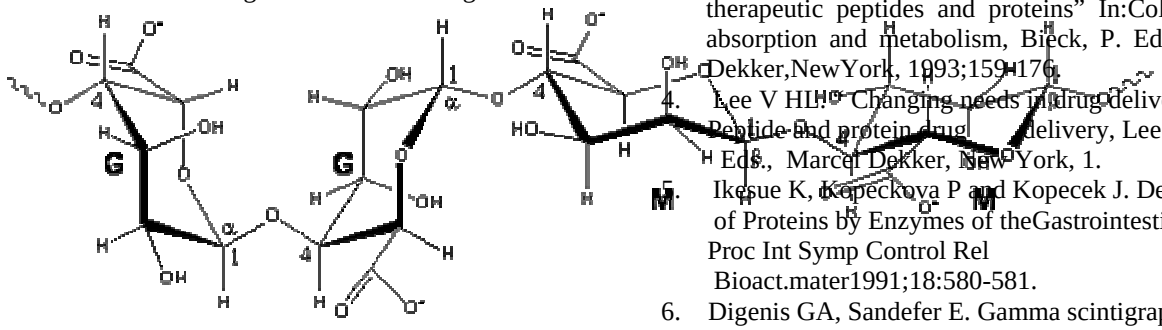

Fig 9:Chemical Structure of Alginate

Locust Bean Gum:

It is derived from carob (Ceratonia siliqua) seeds. It has as irregularly shaped molecule with -1,4- D-galactomanan units. This is neutral polymer slightly soluble in cold water. Raghav etal,[134] formulated and evaluated colon specific drug delivery systems based on poly sacharides; they used locust bean gum and chitosan in the ration of 2:3, 3:2 and 4:1 were evaluated using *invitro* and *in vivo* methods. From *invitro* and *in vivo* studies revealed that locust bean and chitosan was 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.

CONCLUSION

Colon targeted drug delivery systems are exploited to selectively target the drug release to the colon. Several approaches have been investigated to achieve site specificity to 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. The selection of suitable polysaccharide is a critical parameter in the fabrication of colon specific drug delivery. The main limitation of this approach is their excessive water solubility. This high hydrophilicity cause to loose the strong network of polysacharides and consequently drug is slowly released in the upper part of GIT. This can be over come by using cross-linking agents like glutaraldehyde, epichlorhydrin. This particular approach has brought in a break through in delivery system design and development.

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