NATURAL POLYMERS IN DRUG DELIVERY

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ABSTRACT
Polymers have been in use for many years with the aim of facilitating the effectiveness and efficiency of drugs and their delivery. Biodegradable polymers are widely being studied as a potential carrier material for site specific drug delivery because of their non-toxic, biocompatible nature. Natural polysaccharides have been investigated for application in drug delivery industry as well as in biomedical fields. Modified polymer has found its application as a support material for gene delivery, cell culture, and tissue engineering. Nowadays, polymers are being modified to obtain novel biomaterials for controlled drug delivery applications. The aim of this review is to provide an overview of the ongoing research in the field of drug delivery with emphasis on the role of natural polymers.

KEYWORDS: Natural polysaccharides, gene delivery, cell culture, and tissue engineering.

INTRODUCTION
Natural polymers have emerged as one of the most widely researched materials for enhancing the therapeutic effects of the existing drug molecules. Natural polymers are biodegradable, biocompatible and relatively safer when compared to synthetic resources.

The various sources of natural polymers include plants, animals and microbes like bacteria and fungi. Carbohydrates have been widely used in various forms. Carbohydrate polymers are being extensively studied for biomedical and pharmaceutical applications.
Polysaccharides like starch, pectin, guar gum etc are used for the preparation of different types of dosage forms of drugs. Controlled release preparations of isoniazid and diltiazem have been prepared with the help of guar gum.

The film forming ability of gums recognised recently, has helped in actualizing the concepts and products like breath films, cough strips and sore throat strips. Similarly, xyloglucan and borax –gaur gum have influenced the colon specific drug delivery formulations.

Xanthan gum, polysaccharide is extracted from microbe. It is a highly branched glucamannan and has shown consistency in its properties over a wide pH range which in turn has its application in food, pharmaceutical and cosmetic formulations. It is found in number of drug preparations including cefdinir oral suspension and nitazoxanide tablets. We present here a review of the most widely studied and researched polymers with respect to their roles in improving the availability and efficiency of drug delivery systems.

Natural polymers and their role in drug delivery

The following natural polymers are being extensively studied for their role as a facilitator in drug delivery systems.

<table>
<thead>
<tr>
<th>Plant Origin</th>
<th>Animal Origin</th>
<th>Marine Origin</th>
<th>Microbial Origin (fungi &amp; bacteria)</th>
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<tbody>
<tr>
<td>Starch</td>
<td>Chitin</td>
<td>Agar</td>
<td>Glycan</td>
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<td>Pectin</td>
<td>Alginates</td>
<td>Carrageenans</td>
<td>Pullulan</td>
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<td>Guar gum</td>
<td>Psyllium</td>
<td>Alginites</td>
<td>Dextran</td>
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<td>Karaya gum</td>
<td>Carageenans</td>
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<td>Inulin</td>
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<td>Gum Acacia</td>
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Pectin: (Polysaccharide of the Plant Cell Wall)

Pectins are non-starch, linear polysaccharides present in the walls that surround growing and dividing plant cells. It is soluble in water, insoluble in ethanol (95%) and other organic solvents. The main sources of commercial pectin are citrus peel (lemon, lime and grapefruit), apple pomace and sugar beet pulps. Pectin polysaccharides are predominantly linear polymers of primarily α-(1,4)-linked D-galacturonic acid residues interrupted by 1,2-linked L-rhamnose residues having an average molecular weight of about 50,000 to about 180,000. (Fig. 1)
Uses

- Pectins are widely used as gelling agents, thickeners, texturisers, emulsifiers and stabilizers in food, pharmaceutical and many other industries.
- Pectin gel beads are an effective medium for controlling the release of a drug within the gastrointestinal tract.

Floating hollow calcium pectinate beads were developed by Badve et al. These beads were hollow and porous and had density less than 1. They were intended to release diclofenac sodium in a pulsatile manner. These beads could retain the drug up to 5 hours in the stomach of rabbits.\(^1\) Mishra et al., utilised low methoxy polysaccharide, pectin, to formulate oil entrapped floating microbeads of loratidine. The gastro retentive as well as the controlled release properties were found to be highly efficacious when the formulations were designed for therapeutic purposes.\(^2\) Similarly pectin containing anti-reflux drugs were studied by Washington et al and their floating characteristics were evaluated with the help of Gamma Scintigraphy. The pectin containing drug formed a distinct layer over the gastric contents and hence its evacuation was delayed from the stomach.\(^3\) Intragastric delayed release of pectinated drugs was also studied by Sriamornsak et al. Lower degree of esterification, calcium carbonate use, acidified gelation medium along with high drug concentration were found to be significantly helpful in prolonging the release of drug in the gastric content.\(^4\)

Pectin has established itself as one of the most interesting polymers for the development of newer drug delivery systems and is being used by many scientists for developing floating therapeutic forms.

Guar Gum: Guar gum is obtained from the endosperm of the seed of the plant Cyamopsis tetragonoloba. It is a polysaccharide composed of repeating units of galactose and mannose. The backbone is a linear chain of 1, 4-linked mannose residues to which galactose residues are 1, 6-linked at every second mannose, forming short side-branches. Guar gum stable over a wide range of acidic pH (range 5-7) and temperature. Strong acids (pH 3 or less) and temperature more than 50°C cause hydrolysis and loss of viscosity of guar gum. (Fig. 2)

Uses

- Guar gum is used as a thickener in cosmetics, sauces, as an agent in ice cream that prevents ice crystals from forming and as a binder or as disintegrator in tablets.
Krishnaiah et al, studied the influence and usefulness of guar gum as a colon-specific drug carrier, based on the metabolic activity of colonic bacteria, using matrix tablets of albendazole (containing 20% of guar gum) as a model formulation.[5] Badmapriya et al, formulated 5-Aminosalicylic acid matrix tablets using guar gum for colon targeting. These tablets were coated with polymeric layers, to protect them from gastrointestinal environment. [6] Amit Kumar Panigrahi et al, studied the efficacy of matrix tablet for colon targeting.

Natural gums (guar gum and xanthan gum) were used for the preparation of colon targeted drug delivery system. Different concentrations of guar gum and xanthan gum and their combinations were used to prepare the matrix tablets.[7] Sourabh Jain et al fabricated sustained release tablets of furosemide using pectin, guar gum and xanthan gum. A better controlled drug release (80.74%) was obtained using matrix tablet made-up of the guar gum than with the pectin and xanthan gum. The dissolution of furosemide matrix tablets, prepared using different natural polymers, was retarded by approx 15 hrs.[8] Amit S. Yadav et al formulated the oral controlled release zidovudine matrix tablets by using Guar gum as rate controlling polymer and evaluated drug release parameters as per various release kinetic models. The tablets were prepared by wet granulation method. All the formulations showed compliance with Pharmacopoeial standards. The in vitro dissolution study was carried out for 12 hours using paddle (USP type II) method in phosphate buffer (pH 6.8) as dissolution media. Some formulation failed to sustain release beyond 10 hours whereas on the other hand, one of the formulation showed 95.97% of drug release at the end of 12 hours and had shown stability for 3 months with respect to release pattern. Fitting the in vitro drug release data to Korsmeyer equation indicated that diffusion along with erosion could be the mechanism of drug release.[9] Swati Singh et al, prepared sustained release matrix tablets of phenytoin sodium using wet granulation method and matrix materials like guar gum, sodium alginate, tragacanth and xanthan gum in varying percentages. The granules showed satisfactory pharmacotechnical properties for tested parameters. The most successful formulation (55% guar gum with 10% acacia) of the study, exhibited satisfactory drug release and could extend the release up to 12 hours. The mechanism of drug release from all the formulations was diffusion coupled with erosion.[10, 11]

Karaya Gum: It is the dried gummy exudate obtained from the tree Sterculia aurens Roxb. (Family—Sterculiaceae). It is also known as Sterculia, Karaya, Indian Tragacanth or Bassora Tragacanth gum. It is produced in India, Pakistan and to a small extent in Africa. It
also differs from tragacanth in that it contains no starch and stains pink with solution of ruthenium red. Karaya gum consist of an acetylated, branched heteropolysaccharide with a high component of D-galacturonic acid and D-glucuronic acid residues.

**Uses**

- The granular grades are used as a bulk laxative.
- The powdered gum is used in lozenges, pastes and dental fixative powders and it has proved particularly useful as an adhesive for stoma appliances.
- The cross linked Tragacanth (Epichlorhydrin) exhibits superior wicking and swelling action and hence can be used as a potential disintegrant.\(^\text{[12]}\)

**Raghavendraraon G. et al.,** developed a sustained release matrix tablet of water soluble Tramadol hydrochloride using different polymers viz. Hydroxy propyl methyl cellulose (HPMC) and natural gums like Karaya gum (KG) and Carrageenan (CG). Varying ratios of drug and polymer like 1:1 and 1:2 were selected for the study. After evaluation of physical properties of tablet, the in vitro release study was performed in 0.1N HCl pH 1.2 for 2 hrs and in phosphate buffer pH 6.8 up to 12 hrs. Korsmeyer-Peppas power law expression and modified power law expression were used to analyze the dissolution data. It was observed that matrix tablets containing polymer blend of HPMC/CG successfully sustained the release of drug up to 12 hrs. Formulation containing 20% HPMC K15M and 80% of CG released the drug, which followed Zero order kinetics, via swelling, diffusion and erosion and the release profile of the formulation was comparable with the marketed product. Stability studies (40±2°C/75±5%RH) for 3 months indicated that tramadol hydrochloride was stable in the matrix tablets. The DSC and FTIR studies revealed that there was no chemical interaction between drug and excipients.\(^\text{[13]}\)

**Tamarind Gum**

Tamarind xyloglucan is obtained from the endosperm of the seed of the tamarind tree, *Tamarindus indica*, a member of the evergreen family. Tamarind Gum, also known as Tamarind Kernel Powder (TKP) is extracted from the seeds. Tamarind gum is a polysaccharide composed of glucosyl: xylosyl: galactosyl in the ratio of 3:2:1. Xyloglucan is a major structural polysaccharide in the primary cell walls of higher plants. Tamarind xyloglucan has a (1 4)-D-glucan backbone that is partially substituted at the O-6 position of its glucopyranosyl residues with "-D-xylopyranose". It is insoluble in organic solvents and
disperses in hot water to form a highly viscous gel such as a mucilaginous solution with a broad pH tolerance and adhesively. The properties of tamarind gum include noncancerogenicity, mucoadhesivity, biocompatibility, high drug holding capacity and high thermal stability.

Uses
- Tamarind gum is widely used as stabilizer, thickener, binder and gelling agent in food and pharmaceutical industries.
- It is also used as an excipient in hydrophilic drug delivery system.

R.Deveswaran et al, isolated the tamarind seed polysaccharide (TSP) from tamarind kernel powder and this polysaccharide was utilized in the formulation of matrix tablets containing Diclofenac Sodium by the granulation technique and evaluated for its drug release characteristics. Hardness of the tablets was found to be in the range of 4.0-6.0 kg/cm². The swelling index increased with the increase in concentration of TSP. Increase in polymer content resulted in a decrease in drug release from the tablets. The tablets showed 96.5-99.1% of the labelled amount of drug, indicating uniformity in drug content. The drug release was extended over a period of 12h. The release of the formulations matched with the marketed sustained release tablets with a similarity factor of 83.52. The in-vitro release data of the formulations followed zero order kinetics.[14]

Chitin

Chitin \((C_{8}H_{13}O_{3}N)_{n}\) is a long-chain polymer of a N-acetylglucosamine, a derivative of glucose, and is found in many places throughout the natural world. It is the main component of the cell walls of fungi, the exoskeletons of arthropods such as crustaceans (e.g., crabs, lobsters and shrimps) and insects.

Chitin is a modified polysaccharide that contains nitrogen; it is synthesized from units of N-acetylglucosamine. Chitin may be described as cellulose with one hydroxyl group on each monomer replaced with an acetyl amine group. This allows increased hydrogen bonding between adjacent polymers, giving the chitin-polymer matrix increased strength.Chitosan comes from the deacetylation of chitin, a natural biopolymer originating from crustacean shells. Chitosan is a biocompatible, biodegradable, and nontoxic natural polymer with excellent film-forming ability. Being of cationic character, chitosan is able to react with polyanions giving rise to polyelectrolyte complexes. Hence chitosan has become a promising
natural polymer for the preparation of microspheres/nanospheres and microcapsules. The techniques employed to microencapsulate with chitosan include ionotropic gelation, spray drying, emulsion phase separation, simple and complex coacervation.

Uses

Chitosan microspheres have several applications in novel drug delivery systems.

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

Ubaidulla et al., described chitosan succinate and chitosan phthalatemicrospheres for oral delivery of insulin. The chitosan succinate is more hydrophilc than chitosan phthalate. The relative pharmacological efficacy for chitosan phthalate and chitosan succinate microspheres was almost three-fold higher than the efficacy of the oral insulin administration.\textsuperscript{[15]} Ercelen et al., described Methoxy poly(ethylene glycol)-grafted-chitosan (mPEG-g-CS) conjugates by formaldehyde linking method mono-disperse nanoparticles in aqueous media and showed a potential as a sustained release carrier of methotrexate (MTX). Low molecular weight (LMW) alkylated chitosans have potential interesting properties as nonviral vectors for gene therapy.\textsuperscript{[16]} Pan et al., prepared the insulin-loaded chitosan nanoparticles by ionotropic gelation of chitosan with TPP anions. The ability of chitosan nanoparticles to enhance the intestinal absorption of insulin and the relative pharmacological bioavailability of insulin was investigated by monitoring the plasma glucose level of alloxan-induced diabetic rats after the oral administration of various doses of insulin-loaded chitosan nanoparticles. Chitosan nanoparticles enhanced the intestinal absorption of insulin to a greater extent than the aqueous solution of chitosan in vivo. After administration of 21 iu/kg insulin in the chitosan nanoparticles, hypoglycaemia was prolonged over 15 h. The average pharmacological bioavailability relative to subcutaneous injection (SC) of insulin solution was up to 14.9%.\textsuperscript{[17]} Kushwaha et al., had described various target-specific carriers, based on chitosan and its derivatives, towards low molecular weight drug delivery. This paper emphasized on pace of development of delivery systems that could target drugs to specific body sites and control release of drug.\textsuperscript{[18]} Agiskydonieus et al., invention provides methods and compositions for delivering a therapeutic agent across a membrane that has limited permeability for the therapeutic agent. The method includes delivering the therapeutic agent
to the membrane in a composition which includes a sulphated chitinous polymer as a primary carrier.\textsuperscript{[19]} BaeKeun Park et al, current bioactivities of chitin derivatives, which are all correlated with their biomedical properties. They exert an excellent antioxidant effect as well as antimicrobial effect. In particular, COS and their derivatives are potential candidates capable of preventing or treating diverse chronic inflammation.\textsuperscript{[20]}

Gelatin

Gelatin (from Latin: gelatus meaning "stiff", "frozen") is a translucent, colourless, brittle (when dry), flavourless solid substance, obtained by partial hydrolysis of collagen derived from skin, white connective tissue and bones of various animals such as domesticated cattle, chicken, pigs, and fish. Photographic and pharma grades of gelatin are generally made from beef bones.

Uses

- It is used in preparation of suppositories, pastes, pastilles, coating of tablets and formation of hard and soft capsule shells.
- It is used for microencapsulation of drugs.
- Gelatin typically constitutes the shells of pharmaceutical capsules in order to make them easier to swallow. Hypromellose is a vegetarian-acceptable alternative to gelatin, but is more expensive to produce.

Saxena et al (2011) prepared agar-gelatin compositions and tablets made of agar, gelatin A gelatin B and their blends agar-gelatin A, agar-gelatin B, gelatin A-gelatin B in 1:1 ratio. Salbutamol is the model drug. \textsuperscript{[21]} Daocheng et al (2008) prepared Adriamycin gelatinnanogel, modified with fluoride anion by co-precipitation method with fluoride anion and Sodium sulfate targeted and controlled drug release delivery system for cancer and other diseases.\textsuperscript{[22]} Ofokansi K et al described Gelatin-based systems have the ability to control release of bioactive agents such as drugs, protein, and dual growth factors. It has been reported that it is possible to incorporate liposome-loaded bioactive compounds into PEG-gelatin gel which function as porous scaffold gelatin-based temporary depots with controlled drug release over prolonged periods of time.

Alginates: Alginate is a water soluble linear polysaccharide extracted from brown seaweed and is composed of alternating blocks of 1-4 linked α–l-guluronic and α-D-mannuronic acid residues. They are abundant in nature and are found as structural components of marine
brown algae and as capsular polysaccharides in some soil bacteria. Commercial alginates are extracted from three species of brown algae. These include Laminaria hyperborean, Ascophyllumnodosum, and Macrocystispyrifera in which alginate comprises up to 40% of the dry weight. Bacterial alginates have also been isolated from Azotobactervinelandii and several Pseudomonas species. Alginates are naturally derived polysaccharide block copolymers composed of regions of sequential β-D-mannuronic acid monomers (M-blocks), regions of α-L-guluronic acid (G blocks), and regions of interspersed M and G units. The length of the M- and G-blocks and sequential distribution along the polymer chain varies depending on the source of the alginate. Alginate-based materials are pH-sensitive. Biomolecules release from alginate-based materials in low pH solutions is significantly reduced which could be advantageous in the development of a delivery system.

Demiroˇz et al prepared alginate based mesalazine tablets for intestinal drug delivery. Moebus et al used hydrogel-forming polymers (e.g., alginates and poloxamers) as encapsulation materials for controlled drug delivery to mucosal tissue. Pinhas et al prepared mucoadhesive drug delivery systems based on hydrated thiolated alginate. Extensive studies have shown that dry, non-crosslinked, compressed tablets made from thiolated polymers adhere better to the mucus layer compared to the native polymers. Mennini et al developed chitosan-Ca-alginate microspheres for colon delivery of celecoxib-hydroxypropylbeta- cyclodextrin-PVP complex. Ciofani et al developed alginate-based drug delivery system for neurological applications, specifically, by considering the target application of neural regeneration and neuroprotection.

Carrageenans

They are marine polysaccharides obtained by the extraction from some members of the class Rhodophyceae. It is named after Irish moss (Chondruscrispus) also known as Carrageen moss. It was originally isolated from algae. Carrageenans are high-molecular weight polysaccharides made up of repeating galactose units and 3,6-anhydrogalactose (3,6-AG), both sulfated and nonsulfated. There are three basic types of carrageenans, (1) Kappa (κ) carrageenans mainly used as a gelling agent, Kappa forms strong, rigid gels in the presence of potassium ions, it reacts with dairy proteins and mainly used in bakery products. It is mainly obtained from Eucheumacottonii. Kappa carrageenans form a brittle gel. (2) Lambda (λ) carrageenans, non-gelling agent mainly used as binder and thickener in dairy products.
obtained from Gigartina from South America. (3) Iota (ι) carrageenans forms soft and brittle gels in presence of calcium ions obtained from Eucheumaspinosum. (Fig. 3)

Drug metabolism flow chart

Oral

Drug administration

intravenous

Absorption
Enteric transport
Enteric metabolism

Distribution
Intravascular space
Extravascular space
Protein binding

Metabolism
Hepatic influx transport

Phase 1 metabolism: - it can involve reduction or hydrolysis of the drug, but the most common biochemical process that occurs is oxidation. Oxidation is catalysed by cytochrome P450 enzymes and results in the loss of electrons from the drugs.

Phase 2 metabolism: - its involves conjugation- that is the attachment of an ionized group to the drug. These groups include glutathione, methyl or acetyl groups. These metabolic processes usually occur in the hepatocyte cytoplasm.

Billary excretion
Efflux transport

Intestinal excretion

Renal excretion
Efflux transport
PECTIN

Fig 1

Guar Gum

Fig 2

Beta-D-galactose
C1 type
equatorial conformation

Alfa-D-galactose
1C type
axial conformation

kappa carrageenan

Fig 3
Uses

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

**Bonferoni et al** prepared carrageenan–gelatinmucoadhesive systems for ionexchanged based ophthalmic delivery. As a model drug, an alkaline anti-glaucoma drug, timolol maleate, was chosen.\[^{28}\]**Piyakulawat et al** prepared chitosan/carrageenan beads for controlled release of sodium diclofenac. Sankalia et al improved stability of alphaamylase by entrapping in kappa-carrageenan beads.\[^{29,30}\]**Ghanam et al** observed the suitability of K-carrageenan pellets for formulation of multiparticulate tablets with modified release. Sufficient prolonged release properties were obtained with K-carrageenan pellets containing theophylline as a model drug and coated with Kollicoat r SR30 D.\[^{31}\]**Vlieghe et al** prepared covalently bound kappacarrageenan- AZT conjugates with improved anti-HIV activities.\[^{32}\]

**CONCLUSION**

Natural biodegradable polymers have received much more attention in the last decades due to their applications in the fields related to environmental protection and the maintenance of physical health. From the discussion, it can be concluded that natural polymers and their modified derivatives are very promising candidates for the mucosal, colonic and different targeted protein/peptide, gene/vaccine, and anticancer drug delivery. This review is based on several research reports and their outcomes have been cited here in a concise manner. This article will contribute to the new researchers for further investigations. I wish to cordially thank all of the contributing authors for their excellent reviews that convey the latest information on and new aspects of natural polymers used in promising materials for the controlled drug delivery, gene therapy, and tissue engineering scaffolds, pharmaceuticals and biopharmaceuticals and biomedical engineering.
REFERENCES


31- Ghanam D, Kleinebudde P. Suitability of carrageenan pellets for the formulation of multiparticulate tablets with modified release. 2011.