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REVIEW ARTICLE

An Insight of Natural Polymers in Ocular Drug Delivery Systems

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Abstract
To develop a carrier system for ocular drug delivery is a very promising job due to the unique anatomical and physiological nature of eye. The poor ocular bioavailability obtained from conventional formulations has insisted the researchers to develop novel carrier systems which can be easily deliver the drugs to ocular tissues at a controlled rate with prolonged corneal retention and hence reduce frequent instillations. Now days, natural polymers are playing promising role to deliver the drugs topically through the limited corneal surface and release over a prolonged time period.

The assertive points to be considered during the fabrication of ophthalmic formulations such as, attributes of drug molecule and polymer which affects the mucoadhesion, release rate, biodegradability are discussed. In the present review various novel polymers, like arabinogalactan, xyloglucan, gum cordia, locust bean gum, carrageenan and Bletilla striata polysaccharide along with the conventional polymers like chitosan, starch, sodium alginate, sodium hyaluronate, xanthan gum, gelatin, gellan gum, guar gum, collagen and albumin are discussed for their potential prospective in ocular drug delivery system.

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INTRODUCTION

Ocular drug delivery is one of the most challenging domain for the pharmaceutical researcher. Ocular drug delivery is significantly improved over past few 10-20 years. As an isolated organ the eye is very difficult to study from a drug point of view. It is very difficult to obtain eye tissue containing drugs from humans so one is compelled to use animal tissue. Due to these human ocular disposition characteristics of virtually important drugs is unknown or incomplete. Despite these severe limitations, significant improvements in ocular drug delivery have been made. The main objective of the improvement is to maintain the drug in the biophase for an extended period of time. The anatomy, physiology and biochemistry of the eye deliver this organ unreceptive to foreign substances.[1]

Ocular Disorders

According to location of diseases, ocular disorders are grouped as periocular and intraocular.

Periocular Disorders

Blepharitis: An infection of lid tructures (usuallyby staphylococcus aureus) with concomitant seborrhoea, rosacea, a dry eye and abnormalities in lipid secretions

Conjunctivitis: This condition in which redness of eye and presence of a foreign body sensation are evident. There are many causes of conjunctivitis but the great majority are the result of acute infection or allergy.

Keratitis: In keratitis, patient have decreased vision, ocular pain, red eye, and often a cloud / opaque cornea .It is mainly caused by bacteria, viruses, fungi etc.

Trachoma: Caused by the organism chalmydia trachoma, it is the most common cause of blindness in North Africa and Middle East.

Intraocular Disorders

Intraocular disorders are difficult to manage and include intraocular infection and glaucoma. Intraocular infections are the infections in the inner eye, including the aqueous humour, iris, vitreous humour and retina. Glaucoma is the disorder associated with increase in intraocular pressure. More than 2% of the population (< 40 year>) have this disorder in which an increased intraocular pressure greater than 22 mg Hg ultimately compromises blood flow to retina and thus causes death of peripheral optic nerves.

Routes of Drug Delivery

There are three main routes commonly used for administration of drugs to the eye topical, intraocular and systemic. The topical route is the most common method to administer medication to the eye .Introducing the drug directly to the conjunctival sac localizes drug effects, facilitates drug entry that is otherwise hard to achieve with systemic delivery and avoids first pass metabolism. The intraocular route is more difficult to achieve practically. Now research is concentrating on the development of intravitreal injections and use of intraocular implants to improve delivery to eye.[2]

Pathways of Drug Absorption

The main route for intraocular absorption of drug is across the cornea. Two features, which render the cornea an effective barrier to drug absorption, are its small surface area and its relative impermeability. Most effective penetration is obtained with drugs having both lipophilic and hydrophobic properties.

NATURAL POLYMERS IN OCULAR DRUG DELIVERY

The polymers obtained from nature (plants and animals) are called natural polymers. Starch, cellulose, natural rubber, proteins, etc. are some examples of natural polymers. Physicochemical properties and their role in ocular delivery system is summarized in Table 1.

A detailed account of the natural polymers used in ocular drug delivery systems is given in the following paragraphs.

Table 1. Summary of different natural polymers used in ocular drug delivery

Polymer	Charge	Solubility	Mol. Wt	Remark	Ocular delivery	References
Sodium hyaluronate	Negative	Soluble in water Slightly soluble in mixtures of organic acids and water1	300-2000kDa	Increase disintegration time	*in-situ gels,* lubricants and viscous solutions	37,38
Sodium alginate	Negative	Soluble in organic solvents	20,000-2,40,000	Swelling property	ocular minitablets, microspheres	39, 40, 41
Collagen	Amphoteric	Soluble in acidic pH	100 and 200 kDa	Highly compatible with ocular tissues	Soaked Collagen discs Ocular inserts	42, 43-51
Carrageenan	Negative	Soluble in hot water	100-3000kDa	exhibits gelling property in the presence of Ca++	*in situ* gels microspheres	52, 53, 54
Chitosan	Positive	Sparingly soluble in water Insoluble in organic solvents	10,000-10,00,000	Mucoadhesive	Chitosan coated liposomes, Nanoparticles, Supercritical Solvent impregnation	55, 56, 57
Xanthan gum	Negative	Soluble in cold water and warm water Insoluble in organic solvents	$2*10^6$	Viscosity enhancing agent	Viscosity enhancing solutions	58, 59
Gelatin	Amphoteric	Soluble in water Insoluble in organic solvents	15,000-2,50,000	Film forming capacity	Gelfoam, gel films	1, 60-67
Drum dried waxy maize starch		Dispersion in water, solubility increases with an increase in temperature	400 million units	Bioadhesive, swelling	Ocular mini tablets	68, 69, 70, 71, 24
Tamarind seed powder	Non-ionic	Disperses quickly in hot and cold water, practically insoluble in organic solvents	620,000	High thixotropic gels, mucomemitic	Lubricant eye drops, artificial tear solution	27, 72
gum cordial	Negative	Soluble in water on addition of sodium hydroxide		Forms matrix system and helps to sustain release	Nanoparticles	73
Bletilla Striata	Non-ionic	Freely soluble in water but insoluble in organic solvents	99,658 Da	Mucomimetic	Solutions	74
Locust bean	Non-ionic	Soluble in hot water, partially soluble in ambient temperature	50,000-3,000,000	Viscosity enhancing agent	Viscous solutions	75, 76

Chitosan

Chitosan is a cationic polysaccharide of co-polymers glucosamine and N-acetylglucosamine. The N-acetyl-2-amino2-deoxy-D-gluco-pyranose units are linked by *B*-D (1,4) glycosidic linkages. It is naturally found in the fungal cell walls. Commercially, it is obtained by the alkaline deacetylation of chitin present in the crustacean shells of crimps, lobster and crab. Chitosan is a nontoxic and biodegradable polymer. Chitosan have the positive charge ion.[3] Sparingly soluble in water Practically insoluble in ethanol and (95%) other organic solvents. Molecular weight of chitosan is 10,000--10,00,000. Chitosan is soluble at acidic pH (pH

<5) but precipitates as the physiological pH (pH 7.4) is restored. Charges are induced in chitosan molecules in acidic and basic media which lead to their swelling but they do not swell in the neutral media. Chitosan hydrochloride ofloxacin microparticles dispersed polyethylene oxide (PEO-900) inserts showed increased insert erosion and transcorneal penetration of ofloxacin. Chitosan can disrupt the corneal tight junctions and enhance the transcorneal permeation of hydrophilic drugs by diffusion.[4] Chitosan decreased the low critical solution temperature (LCST) of poly (N-isopropylacrylamide) to 32 C which was same as the surface temperature of the eye than poly (N-isopropylacrylamide) LCST value of 35°C. A combination of gellan gum and chitosan was used to prepare in situ gel which formed gel on instillation due to the presence of ions in tear fluid and change in pH.[5] Gatifloxacin loaded chitosan ocular inserts with a combination of gellan gum provided 6 hours sustained drug release. The zeta potential of the nanoparticles was unaffected by the chitosan concentration, whereas a sustained release of cyclosporine A for 48 hours was obtained with cholesterol-modified chitosan self-aggregated nanoparticles. Cholesterol-modified chitosan was used as a stabilizer to prepare rapamycin nanoparticles with polylactic acid. Chitosan is also suitable for the fabrication of nanogel/ nanoparticles of 5-fluorouracil due to its positive charge, solubility in acids and ability to interact with polyanions to form nanogel. Chitosan in solid lipid nanoparticle formulation of cyclosporine A improved the lipid carrier properties and increased the permeation of drug across the rabbit corneal epithelium and through excised pig cornea in the ex vivo studies. The chitosan-loaded mycophenolate mofetil nanosuspension was 391% and 159% more bioavailable than the negatively charged suspension and nanosuspension without chitosan.

The positively charged chitosan-loaded nanosuspension had a longer contact time with the negatively charged corneal surface while the negatively charged nanosuspension was quickly expelled from corneal surface due to the forces of repulsion. A significantly decreased intraocular pressure was obtained for 8 hours with chitosan-coated timolol maleate niosomes, while the Carbopol coated and uncoated niosomes were effective for 6 and 2 hours respectively and the commercial eye drops for only 1.5 hours. Chitosan and HPMC-coated indomethacin ophthalmic lipid emulsions were reported. Greater bioavailability was achieved with chitosan-coated emulsion after 1 hour of instillation. The force of detachment of the chitosan-coated emulsion from mucin was significantly higher than in the HPMC-coated emulsion indicating the higher mucoadhesive strength of chitosan.[6]

Sodium Hyaluronate

Hyaluronic acid is ubiquitously found in the connective tissue, umbilical cord, vitreous humor, synovial fluid of the human body and rooster comb and microorganisms from Streptococcus species can form sodium hyaluronate by the process of fermentation. The charge on sodium hyaluronate is negative charge ion is Soluble in water, slightly soluble in mixtures of organic acids and water. The molecular weight of Hyaluronic acid was 300--2000kDa. Increase breakup time increase the retention time. Chemically, it is a high-molecular-weight polyanionic linear mucopolysaccharide composed of alternating units of N-acetylglucosamine and D-glucuronic acid.[7-8] The polymer is used for stabilizing and hydrating cells and tissues of the body. Sodium hyaluronate (1%) solution is used as a viscoelastic substance in the intraocular surgery of the anterior and posterior segment to maintain the shape of eyeball and to protect cornea during surgery due to its gel forming and similar optical properties as the vitreous. Various marketed formulations like Viscoat (sodium hyaluronate and chondroitin sulfate), Healon, Healonid, Vitrax, Provisc and Amvisc are available which provide cushioning effect and protect the corneal endothelium during the cataract surgery. Intravitreal Healon-H injections were tried as vitreous replacement in complicated retinal detachment, but only two out of seven retinal attachments were observed and only 16 -- 18% success in retinal attachment was obtained with hyaluronic acid as vitreous substitute. In another study, early cases of retinal detachment were treated successfully with external retinal-detachment surgery using intravitreal Healon.

Pilocarpine solutions prepared from high-molecular-weight sodium hyaluronate exhibited a greater miotic response than those prepared from low molecular weight. The healing process and tissue regeneration increased proportionally with increase in sodium hyaluronate concentration. Sparfloxacin in situ gel prepared with sodium hyaluronate, Pluronic F127 and Pluronic F68 sustained the drug release for 6 hours than without sodium hyaluronate which only sustained the release for only 12 hours and less. Sodium hyaluronate at a concentration of 0.5% w/v healed the artificially induced bacterial conjunctivitis in rats

within 3 days while those containing 0.1% and 0.3% took 5 and 7 days, respectively. The viscous solution of Pilocarpine (1%) with sodium hyaluronate (0.75%) was more effective than hydroxypropyl methyl cellulose in increasing the precorneal time and also exhibited a greater miotic response.

Pilocarpine (0.5%) combined with sodium hyaluronate increased 1.75 times the bioavailability than the 1% pilocarpine marketed solution. Sodium hyaluronate at a concentration of 0.25% provides better bioavailability of gentamicin sulfate than phosphate buffer solution of gentamicin. The unpreserved sodium hyaluronate eye drops (0.1%) can be utilized for the treatment of dry eyes due to their non newtonian flow and viscoelastic properties. Immediate relief from grittiness and burning was observed in patients suffering from dry eye syndrome for about 1 hour.[9]

Sodium Alginate

Alginic acid is present in the cell wall of the brown seaweeds Laminaria, Macrocystis, Ascophyllum (Class Phaeophyceae). Chemically, it is polyuronic acid formed of D-mannuronic acid and L-guluronic acid.[10] Increase break up time (oftearfilm),increase the retention time. It is a hydrophilic colloidal polysaccharide of white to buff color, odorless and tasteless sodium salt of alginic acid. Soluble in water and Slightly soluble in mixtures of organic acids and water Molecular weight of Hyaluronic acid is 300-2000 kDa. Sodium alginate has negative charge ion. Gatifloxacin nanoparticles and minitablets prepared using chitosan and sodium alginate gave a sustained release for 6 hours preceded by an immediate release during the first hour. Gatifloxacin non-crosslinked ocular minitablets containing sodium alginate and chitosan prolonged the drug release for about 6 hours in contrast to the crosslinked minitablets which sustained the release for only 12 hours. The matrix type ciprofloxacin inserts prepared using sodium alginate and hydroxypropylmethyl cellulose crosslinked with calcium chloride were able to prolong release from 1.5 to 2 days. The surface crosslinked gatifloxacin sesquihydrate films prepared with sodium alginate (2% w/v) and chitosan (1% w/v) showed a prolonged drug release for about 6 hours.

Reservoir-type ocular inserts of ciprofloxacin hydrochloride prepared using sodium alginate and sandwiched between Eudragit or polyvinyl acetate films prolonged release for over 5 days. Alginate--hydroxyethyl cellulose ocular inserts of epidermal growth factor (EGF) crosslinked with calcium chloride prolonged the release from a few hours to several days. Alginates of different grades which constituted the different concentrations of guluronic acid and mannuronic acid and with different viscosities were used. Inserts with a high content of guluronic acid and a high viscosity exhibited the most sustained release of EGF.[11] Sodium alginate has the ability to form ion activated in situ gel in the presence of divalent and trivalent cations, especially calcium. Calcium in low concentrations increases the viscosity but at high concentrations interacts with guluronic acid moieties of sodium alginate and forms gels. Pilocarpine incorporated in situ gels, prepared using sodium alginate with more than 65% guluronic acid, gelled immediately on exposure to lachrimal fluid, and a constant decrease in intraocular pressure was obtained for 10 hours in contrast to the 3 hours effect obtained from pilocarpine nitrate in solution.[12]

Gellan Gum

Gellan gum was discovered by Kelco Div., Merck & Co. Gellan gum (formerly known as PS-60 and S-60) is an extracellular polysaccharide secreted by aerobic.[13-14] well-characterized, non-pathogenic, gram-negative strains of Pseudomonas, *Sphingomonas paucimobilis* and *Auromonas elodea*. It have the Negative charge ion. It forms gels in the presence of cations, with hyaluronic acid andCa2+, forms rigid gel structure at body temperature. It is a linear anionic heterosaccharide composed of rhamnose, glucuronic acid and glucose in a molar ratio of 1:1:2. Gelrite is the commercially available, highly purified deacetylated form of gellan gum. Gellan gum and Gelrite undergo sol to gel transformation in the presence of the monovalent and divalent cations present in the lachrymal fluid make it an ideal vehicle for in situ gelling systems. Ion-activated in situ gel-forming ophthalmic solutions using Gelrite of different osmolalities were prepared to study its influence on the rate of the sol-gel transition. With hypotonic solutions of Gelrite, the gels were retained for 20 hours which was greater than carbomer gels and poloxamer gels. Gelrite has the property of forming elastic solutions and at concentrations 0.6% and above, a longer retention time was obtained. Gelrite-loaded indomethacin in situ gels as an alternative to steroids for the treatment of uveitis has been studied. A concentration of 0.5% w/v of Gelrite was most suitable for the formulation, above that caused gelation at

40 C. The formed gels sustained the release for 8 hours in the in vitro studies. The in situ gel forming formulation immediately formed a translucent gel on instillation and a therapeutic concentration was maintained for 6 hours as opposed to the 4 hours effect from the standard indomethacin dispersion. The pefloxacin mesylate in situ gel with Gelrite (0.6% w/v) sustained the release for 12 hours. Increase in drug release was observed on increasing Gelrite concentration from 0.4% w/v to 0.6% w/v but further increase to 0.8% w/v decreased the drug release. A synergistic gelation effect was obtained with gellan gum (0.1% w/v) and L-carnosine (0.06% w/v) loaded timolol maleate in situ gel and comparable intraocular pressure lowering activity was obtained with Timoptic-XE. The buffer capacity of L-carnosine was superior when compared with that of tromethamine, commercially used buffer with Gelrite. Gellan gum in situ gels of ciprofloxacin hydrochloride alone produced effective formulations which sustained the drug release for 8 hours in the in vitro studies. Gelrite (0.2% w/v) has been reported as to have good gelling strength property and higher bioavailability in simulated tear fluid with a combination of alginate (0.6% w/v).[15]

Collagen

Collagen disc and shields were developed from porcine scleral tissue or bovine corium (dermis) as corneal bandage lens to heal wounds and have now found wide applications in ocular drug delivery. It having Amphoteric in nature. Collagen is Soluble in acidic pH. Collagen is an insoluble fibrous protein in natural polymer. Collagen is thin (about 1.5 nm in diameter), 300 nm long and has a triple-stranded helical structure consisting of three coiled subunits. Amino acids like glycine, proline and hydroxyproline are the basic repeating units in the collagen structure. collagen is only soluble at acidic pH < 5 and completely insoluble at the body pH. Collagens were degradable at the physiological pH. Acylation of the amino groups or esterification of carboxyl groups of collagen forms positively or negatively charged collagen.[16]

The triple-stranded helical structure is stabilized by hydrogen bonds which links a peptide bond between NH of a glycine residue and CO group in an adjacent polypeptide. Collagen is absorbed within 84 days due to its high biodegradability and biocompatibility. Collagen shields were used to deliver heparin to prevent postoperative fibrin formation in eyes after glaucoma filtration surgery, proliferative diabetic retinopathy or proliferative vitreoretinopathy. Higher concentration and a sustained release for 6 hours was achieved with heparin-hydrated collagen shields than subconjuctival injections with which heparin concentrations did not increase above base line level. Collagen shield-based gentamicin provides higher dissolution and better penetration than collagen disc and topical eye drops through cornea in New Zealand white rabbit model. Collagen shields showed higher netilmicin concentrations in aqueous humor as compared with concentrated drug solution collagen shields were evaluated to deliver 5-fluorouracil in rabbit and guinea pig eyes for 7 and 14 days. Less inflammatory response was found in guinea pig eyes and the collagen shields degraded in about 14 days.[17]

Gelatin

Gelatin is the partially hydrolyzed product of collagen and is composed of a unique sequence of amino acids high content of glycine, proline and hydroxyproline. The gelatin molecules contain repeating sequences of glycine-X-Y triplets, where X and Y are frequently proline and hydroxyproline amino acids. It is a light-amber to faintly yellow-colored, vitreous, brittle solid available as translucent sheets and granules, or as a powder. It is practically odorless and tasteless. It is highly compatible with ocular tissues and is amphoteric in nature. It is Soluble in acidic pH. Molecular weight of gelatin is 100 and 200kDa for **a** and **b** chains. Gelatin sustained the drug release of fluoroquinolones like ciprofloxacin from flexible and smooth reservoir-type ocular inserts with a combination of hydrophobic ethyl cellulose for 12 hours. Gelatin has been reported to exhibit a better mucoadhesive property with the synergistic effect of polyvinyl alcohol. Ciprofloxacin inserts of high mechanical strength and improved adhesion properties gave a sustained release for 6 hours as compared with the half an hour release from conventional eye drops.[18]

Albumin

Albumin is produced in liver and is also found in many food products, predominantly in milk and egg white. Albumin is a protein naturally found in blood. Human serum albumin is a single polypeptide chain of 585 amino acids and contains seven disulfide bridges.[19] It is negative charge ion. Freely soluble in water and salt solutions, molecular weight of albumin is 66,500. It interacts with drug molecules and increases the

precorneal retention time. Albumin's addition to serum deprived conjunctival cells inhibited caspase activity and increased cell viability, showing that albumin can compensate for some of the physiological properties of serum. Corneal erosions in albino rabbits healed significantly faster in eyes treated with albumin 10% compared with saline and sodium hyaluronate 0.3%. Pilocarpine nitrate microspheres prepared with egg albumin sustained the drug release for about 2 hours, whereas the release of Pilocar eye drops declined after 1 hour. Albumin nanoparticles coated with bioadhesive (hyaluronic acid, mucin, sodium carboxymethyl cellulose and polyacrylic acid) and viscosity-enhancing polymers (methylcellulose, polyvinyl alcohol and hydroxypropylmethyl cellulose) exhibited improved adhesion to the precorneal/conjunctival mucin layer and significantly higher prolonged retention. This study concluded that the strong binding between albumin and hydrocortisone retained the nanoparticles over the precorneal area and prevented the drug absorption in the conjunctival tissues. Albumin nanoparticles were developed as suitable carriers for the intravitreal delivery of an anti-viral drug ganciclovir. A strong covalent bond between drug and albumin was formed in the nanoparticles and a resulting sustained release for 5 days was obtained.[20]

Xanthum Gum

It is obtained from the aerobic fermentation of a carbohydrate with *Xanthomonas campestris*. Chemically, it consists of two D-mannose units and two D-glucose units as the main hexose units with one D-glucuronic acid. It having the negative charge ion. Soluble in cold or warm water, practically insoluble in ethanol and ether. Molecular weight of 2*106. It is a high molecular-weight polysaccharide of sodium, calcium or potassium. It exists as a white or cream colored, tasteless powder with a slightly organic odor.[21] Tobramycin 0.3% with dexamethasone 0.1% (TobraDex) and tobramycin 0.3% with dexamethasone 0.05% (TobraDex ST) in a xanthan gum vehicle, were evaluated for their efficacy in the treatment of Pseudomonas keratitis in rabbits. Eyes treated with TobraDex ST had significantly fewer log CFU (5.78 ± 0.30) than eyes treated with TobraDex (6.32 ± 0.29). Xanthan gum at a high concentration of 1%w/v was found to interact with mucin 16%w/v, while pre-heating or sonication of xanthan gum solutions reduced the mucin concentration to 8%w/v required for mucoadhesive interaction. Xanthan gum which enhanced the formation of secondary bonds between xanthan gum and mucin. Moxifloxacin HCl thermoreversible in situ gels were prepared using xanthan gum or sodium alginate and poloxamer (407 or 188) to obtain a synergistic increase in bioadhesion and gel strength. Maximum drug release was obtained from xanthan gum-based thermoreversible in situ gels. xanthan gum based pilocarpine eye drops resulted in delayed clearance of solutions from ocular cavity due to increased viscosity. Xanthan gum solution was used to obtain increased drug concentration in aqueous humor and reduce the frequency of dosing than with the marketed formulation. Xanthan gum has the tendency to resist the changes in transition temperature in pH triggered in situ gelling systems; hence, xanthan gum is used in combination with other polymers to increase the viscosity of the solutions. Linezolid ion-triggered in situ gel prepared using xanthan gum, sodium alginate and carbopol were reported to sustain 57% release compared with the formulation containing hydroxypropyl guar, hydroxyethyl cellulose and sodium alginate over a period of 6 hours. In situ gelling system with optimum concentration of xanthan gum had increased gelling capacity and produced a higher release of ofloxacin and ketorolac tromethamine up to 9 hours.[22]

Carrageenan

It is obtained by the aqueous or alkali extraction from species *Eucheuma, Chondrus*, and *Gigartina* (red seaweeds), class Rhodophyceae. It consists of potassium, sodium, calcium, magnesium and ammonium sulfate esters of galactose and 3, 6-anhydrogalactose copolymers. It having the negative charge ion. Freely soluble in water. Carrageenan has yellow-brown to white colored, coarse to fine, odorless and tasteless. It consists of potassium, sodium, calcium, magnesium and ammonium sulfate esters of galactose and 3, 6-anhydrogalactose copolymers. Carrageenan having property to interact with alkaline drugs like timolol maleate microspheres and films. It having Iota- Exhibits gelling property in the presence of Ca++. Kappa-Forms strong gels in the presence of K+. Lambda-Interacts with alkaline drugs, non-gelling polymer. Binary systems with different ratios of carrageenan [iota (i-CG) and kappa (k-CG)] to methylcellulose (MC) were used to prepare ion-sensitive and thermoresponsive in situ gels for trans-scleral delivery of macromolecules. MC and k-CG at a ratio of 20:80 formed gels below 20C and above 30C, whereas i-CG formed gels at high temperatures. Carrageenan type-IV inhibited feline herpes virus (FHV)-1 in an in vitro

model but did not significantly alter the clinical signs of disease in experimentally induced conjunctivitis in vaccinated cats.[23]

Starch (Drum-dried Waxy Maize Starch, Pregelatinized Starch)

Modified variants of corn have led to the cultivation of waxy maize which contains highly branched amylopectin unit of starch. It has no charge ion. It is moderately coarse to fine, white to off-white colored powder, odorless with a slight characteristic taste. It has a less stringy and less cohesive texture than the potato starch and exhibits a very high degree of polymerization and low rate of retrogradation which confer it better transparency and swelling. It has bioadhesive and swelling properties. Pregelatinized starch is a physically modified starch which can form dispersions and gels with cold water. When starch is dispersed in water, solubility increases with an increase in temperature. Molecular weight of Starch is 400 million. Starch minitablets showed that the tablets were affected by sterilization. The amylopectin branched chains were converted into linear chains that contributed to decreased release of ciprofloxacin from minitablets. The study showed that the non-sterilized tablets sustained the release for up to 6 hours. Gentamicin and Vancomycin minitablets were prepared as a physical mixture or co-spray-dried mixture of pregelatinized starch and Carbopol 974.

The spray dried mixture tablets show sustained release for up to 6 hours due to their higher viscoelastic properties which slowed the diffusion rate of the drug from the matrix tablets. A decreased and slow water uptake by minitablets prepared with DDWM(drum dried waxy maize) starch and Carbopol 974P after sterilization by gamma sterilization has been reported but no changed water uptake behavior was reported for vancomycin and gentamicin gamma sterilized tablets.[24]

Guar Gum

It is obtained from the ground endosperms of Cyamopsis tetragonolobus (L.) Taub. (family Leguminosae). It consists of linear chains of (1,4)-b-D-mannopyranosyl units with a-D-galactopyranosyl units attached by (1,6) linkages. Charge of Guar gum is non ionic. It is a high-molecular-weight. It is a white to yellowish-white, odorless powder with a bland taste. Highly thixotropic gels, mucomimetic Solubility of Guar gum Disperses in hot and cold water, practically in soluble inorganic solvents. Molecular weight 1000--5000KDa. Guar gum is used to prepare matrix tablets to achieve prolonged release and has found wide applicability to target colon. Modified form of guar gum, hydroxypropyl guar (HPG) is used to form gelling eye drops with demulcents, polyethylene glycol 400 and propylene glycol. On instillation, the viscosity of eye drops increases significantly due to formation of crosslinked mucin guar-demulcent network at pH 7.4 on the surface of the eye, which provides additional lubricity to the eye and serves as a temporary bandage to allow the surface epithelial cell natural repair processes to occur.[25]

Tamarind Seed Polysaccharide (Xyloglucan)

Xyloglucan is obtained from the kernels of the seeds of tree *Tamarindus indica* (family Cesalpiniaceae). It disperses in hot and cold water, practically insoluble in inorganic solvents. Molecular weight 1000-5000kDa. Tamarind kernel powder is a high-molecular-weight. High thixotropic gels, mucomimetic. The powder form consists of a high content of carbohydrate and is composed of cellulose like backbone of xylose and galactoxylose. Viscosity of tamarind seed polysaccharide (TSP) solutions is stable over a pH range of 5.5-8.0. The viscosity decreases as the pH is lowered to more acidic values.[26] It can be used to prepare pH sensitive and temperature sensitive in situ gels. TSP has high binding affinity toward mucin due to its structural similarity with it. TSP and hyaluronic acid synergistically healed the conjunctival mucosa affected by dry eye syndrome by inducing a remarkable improvement in the number and morphology of conjunctival microvilli. Interaction between internal glucose and galactose units of TSP and acetyl groups of hyaluronic acid occurred in the solution which indicated the potential of the polymers to be used as a tear substitute. TSP was found to be well tolerated and reduced the toxicity exerted on human conjunctival cells by different drugs timolol, ofloxacin and rufloxacin and a preservative agent merthiolate. TSP was used as a viscosity-enhancing agent for administration of gentamicin and ofloxacin. It increased the intraocular penetration of hydrophilic and hydrophobic antibiotics without modifying their intrinsic solubility.

An evidence of TSP protective properties is available in an open label clinical study. TSP 1% w/v, offered promising results due to high patient compliance as it reduced troubled blinking, ocular burning and sensation of foreign body. Both TSP concentrations 0.5% w/v, and 1% w/v, were equivalent to hyaluronic acid 0.2% w/v, in relieving dry eye symptoms. The structural similarity of TSP with mucin and natural tears due to its ability to crystallize in a fern-like shape makes it a better and cheaper alternative than hyaluronic acid in the treatment of dry eyes. TSP-based rufloxacin eye drops than with ofloxacin and rufloxacin eye drops in infected eyes than in non-infected rabbit eyes. The mixture containing TSP: hyaluronic acid in a ratio of 3:2 showed high mucoadhesive behavior than the individual polymers at low viscosity. The mixture prolonged the residence of ketotifen fumarate and diclofenac sodium in tear fluid but was unable to increase the permeability of the drugs across cornea. While in another study, the mucoadhesive strength of TSP was found equivalent to in situ gelling capacity of gellan gum. An equivalent drop in IOP was observed with timolol maleate 0.5% w/v solutions formulated with TSP 2% w/v and Timoptic XE (gellan gum based eye drops). But the effect was sustained for a longer period of 19 hours with TSP-based eye drops than with gellan gum-based eye drops, which lasted in only 8 hours.[27]

Arabinogalactan

It is **o**btained from the bark of the Larch trees (*Larix occidentalis*, L. decidua) of Larix species. It has negative charge ion and soluble in water. Molecular weight is 10,000-1,20,000 Da.[28] The decreased molecular weight increased its diffusion across the membranes when administered through the subcutaneous and intramuscular routes.[29] Arabinogalactan is a long, densely branched 3,6-b-D-galactan polysaccharide abundant in most plants and microflora. It is a fine, dry, off-white slightly sweet powder with mild pine-like odor. It shows corneal wound healing capacity and mucoadhesiveness. Arabinogalactan (5% w/w) formed very low viscosity eye drops and showed a very high adhesion index than TSP (0.5% w/w) and about five times higher than hyaluronic acid (0.2% w/w). It is reported as a novel mucoadhesive polysaccharide which can be used for the treatment of dry eyes and corneal wounds and to heal the dry spots on cornea. Arabinogalactan (5% w/w) drops did not show any cytotoxicity on the rabbit corneal epithelium, whereas 0.01%w/w benzalkonium chloride was highly toxic. After 6 hours the Arabinogalactan-treated cornea was well differentiated as an organized structure and after 48 hours it was normal, marked with the presence of microvilli and glycocalyx while an unorganized structure with cells of different sizes, lack of microvilli and glycocalyx were found in the control formulation even after several days of the administration.[30]

Gum Cordial

Gum cordial obtained from **e**xtraction of raw fruits of *Cordia obliqua* Willd (family Boraginaceae).[31] It is negatively charged ion and soluble in water. It comprises molecular weight of 10,000-1,20,000 Da. It has the corneal wound healing property and mucoadhesive ability. Being a novel polymer it can be used as a tablet binder, emulsifier and to sustain drug release from the formulations at very low concentrations as compared with the polymers which are used as common gums. Gum cordia (1.5% w/w) was more effective than gum acacia (10% w/w). Gum cordia had a high surface area and with di-octyl sodium sulfosuccinate reverse micelles were formed which acted as nano-reservoirs for drug encapsulation. The nanoparticle suspension have shown similar permeation in the in vitro studies as compared to the marketed formulation Zocon.[32] The polymer requires further investigation for its use in ocular formulations.

Bletilla striata Polysaccharide

This is obtained from the tubers of *Bletilla striata* (family Orchidaceae), a traditional medicinal Chinese herb.[33] It has nonionic charge as well freely soluble in water but insoluble in organic solvents. The molecular weight is 99,658Da. It has antibacterial, antifungal properties and is used to treat alimentary canal mucosal damage, ulcers, bruises, bleeding and burns. It consists of small white fibers. Due to the presence of glucose and mannose (1:4), the formulation containing BSP is reported to exhibit minimum cell cytotoxicity in ocular drug deliver. Bletilla striata polysaccharide is Mucomimetic, mucoadhesive. The levofloxacin (0.5%) drops prepared with BSP polymer (0.06 -- 1%) showed a concentration-dependent increase in proliferation of the human corneal endothelial cell line to a large extent as compared with the marketed eye drops Cravit and reducing the toxicity of the antimicrobial agents. In the experimentally induced keratitis in the rabbits greater antibacterial activity was exerted against Staphylococcus aureus compared to the conventional drop

solution. [34] The polymer is an ideal carrier for ocular formulations especially for dry eye treatment due to its structural similarity with the lachrimal fluid.

Locust Bean Gum (Carob Bean Gum)

It is derived from the endosperm of the seeds present in the kernels of *Ceratonia siliqua* (carob tree), (family Leguminosae).[35] It has nonionic charge. It is soluble in hot water and partially soluble in water at ambient temperature. Insoluble in most organic solvents including ethanol. The molecular weight is 50,000--3,000,000. Locust bean gum is white to yellowish white polysaccharide. It is Viscosity-enhancing agent. It is composed of galactomannans consisting of a linear chain of (1-4)-linked b-D-mannopyranosyl units with (1--6)-linked a-D-galactopyranosyl residues as side chains. The mannose and galactose units are present in the ratio 4:1. Locust bean gum gel (1-2.5%) was reported as a viscosity modifier and increased the bioavailability. Ophthalmic solutions of echothiophate iodide with locust bean gum reduced the systemic absorption of drug and increased its topical bioavailability.[36]

CONCLUSION

Natural polymers are now becoming as area of interest for topical ocular drug delivery. Due to the various properties of these polymers, they may be employed to enhanced the ocular bioavailability by reducing different ocular constrains associated with ophthalmic drug administration. These natural polymers can also play an important role in controlling the release of drugs. The assets of polymers can be used to develop different formulations with different release behaviours. Different new polymers have been investigated which have broaden the selection of polymers for developing different formulations.

DECLARATION OF INTEREST

It is hereby declared that this paper does not have any conflict of interest.

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