EXPERT OPINION

Ocular drug delivery system: a reference to natural polymers

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Introduction: Ocular drug delivery is a very challenging endeavor due to the unique anatomical and physiological barriers. The low ocular bioavailability (<10%) obtained from conventional formulations has forced the scientists to develop new formulations to deliver drugs to ocular tissues at a controlled rate to reduce frequent instillations. The natural polymers have represented the potential to deliver drugs topically through the limited precorneal area and release over a prolonged time period.
Areas covered: The important points to be considered during the fabrication of ophthalmic formulations for example, properties of drug molecule and polymer which affect the release rate are discussed. Novel polymers, like arabinogalactan, xyloglucan, gum cordia, locust bean gum, carrageenan and *Bletilla striata* polysaccharide, besides the conventional polymers like chitosan, starch, sodium alginate, sodium hyaluronate, xanthan gum, gelatin, gellan gum, guar gum, collagen and albumin, have demonstrated the potential to safely deliver drugs at a controlled rate in different ophthalmic formulations.
Expert opinion: The limitations of topical delivery of genes and chemotherapeutic drugs can be overcome by using natural polymers with characteristic properties. Despite the wide applicability, tremendous efforts are required to establish natural polymers in novel formulations on a commercial scale.

Keywords: formulation approaches, natural polymers, ocular bioavailability, ocular drug delivery

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1. Introduction

The eye is a unique organ, both anatomically and physiologically, containing several widely varied structures with independent physiological functions that render the organ highly impervious to foreign substances. The cornea and crystalline lens are the only tissues in the body besides cartilage that have no blood supply. The inner and outer blood–retina barriers have no cellular components that separate the retina and the vitreous body from the systemic circulation thereby reducing the diffusion of molecules. This complexity of the eye imposes challenges in front of the pharmaceutical scientist to circumvent the protective barriers of the eye without causing any permanent tissue damage [1]. An assumption is made that a correlation exists between the concentration of a drug at its interrelated site of action and the resulting pharmacological effect. Therefore, the specific aim of designing a therapeutic system is to achieve an optimal concentration of drug at the active site for the appropriate duration that is, the drug molecule must reach aqueous humor for its therapeutic effect.

The eye is the most accessible organ for the delivery of drugs directly at the site without introducing it into the systemic circulation. The different layers of the cornea, conjunctiva, sclera, and the other tissues of the anterior segment such as the iris and ciliary body (anterior uvea) are targeted by the topically administered drugs [2]. Direct, localized delivery to the target tissue, avoidance of hepatic first-pass

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Article highlights.

- The article briefly discusses the limitations posed by conventional ophthalmic formulations and barriers to low ocular bioavailability.
- The properties of drug molecule influence the selection of the polymer and formulation type so as to obtain maximum permeation through cornea.
- Natural polymers due to their high biocompatible nature are ideal carriers to safely deliver drugs to the eyeball.
- The polymers possessing different properties like mucoadhesive (chitosan, tamarind seed polysaccharide (TSP), arabinogalactan and *Bletilla striata* polysaccharide (BSP)) form *in situ* gels (gellan gum, gelatin, xanthan gum, carrageenan (iota and kappa)), swelling property (sodium alginate, drum dried waxy maize starch) can be used in different ophthalmic formulations to improve bioavailability.
- Synergistic effect can be obtained by using polymers with inherent corneal healing properties (arabinogalactan) or mucomimetic properties (guar gum, TSP, BSP) to reduce the drug toxicity and increased bioavailability.

This box summarizes the key points contained in the article.

metabolism and convenient, painless and better accessibility into the intraocular environment than achieved by systemic delivery are the advantages of delivery of drugs topically to the ocular tissues. Additionally, the self-protective mechanisms like blinking, reflex lacrimation and immediate drainage largely reduce the bioavailability of the drug [3]. Tear evaporation, non-productive absorption/adsorption, limited corneal area and poor corneal permeability and binding with the lachrymal proteins are the other factors that limit the absorption of the drug [4]. The incorporation of polymers in the conventional dosage forms like solution, ointment, suspension, emulsion and gelling system have been found to be an efficient method to increase the retention time of the dosage form on corneal tissue to enhance the ocular bioavailability. Recently, various novel carriers like colloidal systems (nanoparticles and nanosuspension), matrix system (ocular inserts, minitablets and collagen shields) and highly viscous solution like gel types (pH triggered or thermosensitive) have been used to achieve a controlled release of drug to the ocular tissues. Since natural polymers are biocompatible, they are widely used in several dosage forms in ocular drug delivery. In this review an attempt has been made to emphasize on the reported studies of polymers obtained from natural sources in ophthalmic formulations.

1.1 Barriers to ocular drug delivery

The most anterior portion of the outer part of eye, the cornea, forms the strongest refractive medium of the eye [5] and offers resistance to the passage of most drugs due to the presence of layers: hydrophobic epithelium, the hydrophilic stroma and a hydrophobic endothelium (less than epithelium). The epithelium and the stroma prevent the entry of the hydrophilic and hydrophobic molecules respectively, making cornea the rate-limiting membrane for the absorption and also act as a reservoir of drugs. Because of a large surface area, the conjunctiva acts as a more favorable site for the penetration of the topically administered drugs. The goblet cells, lacrimal glands and the meibomian glands secrete a trilaminar layer tears composed of mucin, aqueous and lipid layers which keep the cornea hydrated, prevent the adhesion of bacteria and other foreign materials and also influence the distribution and toxicity of the foreign materials. The tears flow through the superior and inferior punctum lachrimal followed by their passage into the superior punctum canaliculus and lachrimal sac [6]. The normal volume of tears has been estimated to be 7 µl and without blinking, the eyeball can accommodate 30 µl without spillage. Instillation of eye drops from the dropper (50 µl) causes the reflex blinking of the eyelids. More than 90% of the dose is drained through the nasolacrimal duct to the nasal cavities. Through the highly vascular mucosa of the nasal epithelium, it is absorbed into the systemic circulation. Tears dilute the remaining drug in *cul-de-sac*, which reduces the transcorneal flux of the drug [7]. The mechanism and routes of drug transportation are depicted in **Figure 1**.

2. General considerations for the design of ocular drug delivery formulations

For the treatment of eye diseases the drugs are administered directly to the eyeball for quick onset of action and to minimize dose and side effects exerted by drugs, especially antibiotics, when given through oral route. General considerations for design of ocular drug delivery formulations are depicted in **Table 1**.

Physicochemical and biopharmaceutical properties of the drug such as solubility, stability and permeability should be taken into consideration for the dissolution of drug at pH 7.4 and its diffusion through the corneal and non-corneal sites. The formulations should have a pH 6.6 – 9.0 to avoid irritation. Ideally, an ophthalmic formulation should have a viscosity between 15 cps and 50 cps which can significantly improve contact time [8]. A low drop volume and less tear drainage are required for the drug molecules with a low partition coefficient, that is, low permeability, whereas for drug molecules with higher partition coefficient tear secretion and drop volume are relatively unimportant [9].

2.1 Solutions and suspensions

Although eye drops in the solution and suspension forms have been the most common formulation approach for the treatment of anterior segment diseases, they have several drawbacks. In a study it was found that a large number of patients found it difficult to instill the drop [10]. The secretion and drainage of tears at the rate of 1 µl/min leads to a tear turnover at the rate of 16% which dilutes the drug solution and eventually increases its drainage [11,12]. The rate of drainage increases with an increase in the volume of the solution instilled in the eye,

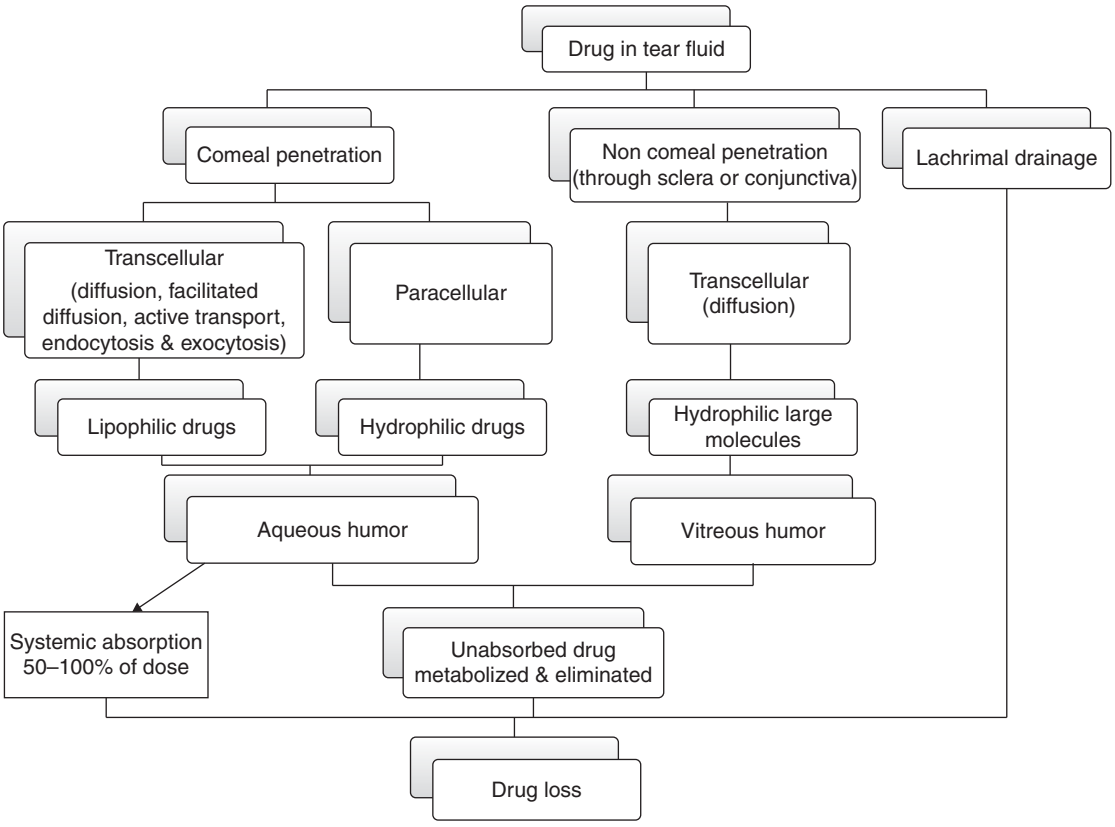

Figure 1. Mechanism and routes of drug transportation [8,256,248].

Table 1. General considerations for design of ocular drug delivery formulations [248-251].

Component	Properties
Drug molecule	Optimum partition coefficient and should remain in the unionized form to cross the corneal epithelium and stroma Lipophilic as well as hydrophilic and should be small in size (less than 10 A°) to cross corneal epithelium. The stroma may act as a greater barrier than endothelium for macromolecules Optimum partition coefficient in the range of 10 – 100. pH should be 7.4 to avoid irritation and consequent lacrimation
Carrier	Small size, <10 mm in diameter (drug particle size < 10 μm) Release the drug for a prolonged period of time without itself deteriorating No dose dumping should occur Undergo hydration quickly in tears to facilitate the release of drug
Buffers	Used in low concentrations to avoid irritation

therefore, less bioavailability [13]. The amount of drug absorbed cannot be estimated due to the limited volume-holding capacity of the *cul-de-sac*. The most widely used preservative benzalkonium chloride causes peeling of the corneal epithelium cells at their borders, inhibits the growth of the cells and enlarges the intercellular spaces in the superficial cells of the cornea [14-16]. Corneal calcification can occur due to the phosphate buffer present in the eye drops [17,18]. Ointments are the conventional dosage forms used to increase the precorneal residence time but their use is limited as they interfere with vision and are not suitable for use during the daytime [19-21].

2.2 *In situ* gels

In situ gels are the low-viscosity solutions that undergo phase transition in the conjunctival *cul-de-sac* to form viscoelastic gels due to conformational changes of polymers in response to the physiological environment change (pH, ion activated or temperature). The viscous gels reduce the drainage and improve the contact time better than the conventional eye drops. Gellan gum, Gelrite® (Merck & Co, San Diego, CA, US), xanthan gum, chitosan, sodium alginate, carbopol, pluronic, poloxamers and pluronic copolymers are reported to exhibit the sol-gel transition [22-26].

2.3 Ocular inserts

Ocular inserts are the solid ophthalmic devices, usually of 8 mm diameter, with drug dispersed in the polymer reservoir or matrix system intended to increase the precorneal contact time, increase bioavailability and maintain a therapeutic drug concentration in the target tissues. The release rate and the mechanism can be controlled by the use of different natural and synthetic polymers like sodium alginate, collagen, gelatin, Eudragit® RS-100 and RL-100, p-HEMA, polyethylene oxide, cellulose acetate phthalate and hydroxypropylmethyl cellulose (HPMC) [27-32].

2.4 Contact lenses

Sedlacek, in the year 1965, described [33] the use of contact lenses to increase the residence time (typically days) of the drug in the eye, patient comfort and to limit the drug loss by drainage, lacrimation or conjunctival absorption [34]. Medicated soft contact lenses can be used to treat ocular diseases in addition to the correction of refractive deficiencies. Contact lenses loaded by soaking technique [35] are not therapeutically effective due to a very low uptake of drug by the lens and a rapid release might lead to low residence time. The other limitations like the limited drug incorporation in lens matrix, incompetence to offer slow and extended drug release, wastage of large fraction of drug during loading procedure have limited its use in Ocular Drug Delivery System (ODDS). The uptake and release of the drug depends on the material of the lens (as a function of ionicity, water and silicone content), loading solution, time during which the lens is placed in the loading solution and molecular weight of the drug incorporated [36]. Novel techniques such as molecular imprinting and supercritical solvent impregnations have surmounted all these issues. Molecular imprinting produces synthetic macromolecular networks template-mediated polymerization mechanisms with specific affinity, capacity and selectivity for the diffusion of drug molecules. A therapeutically relevant amount of drug can be loaded and released over an extended period of time and this technique is applicable to daily-wear and extended-wear contact lenses. In the supercritical fluid impregnation technique, drug is impregnated and dispersed in a polymer matrix by dissolving in compressed high volatile fluids (like carbon dioxide) at temperatures and pressures near or above their critical temperatures and pressures and bringing the resultant mixture in contact with the polymer matrix [37-39].

2.5 Collagen shield

Collagen is the most abundant primary fibrous protein present in the animal tissues. The fibrils of the connective tissue in skin, bones, eyes, tendons and ligaments mainly comprise of collagen. Stroma, which forms 90% of the cornea, and the Bowman's layer are lamellas of collagen, which imparts mechanical strength to the eyeball [40,41]. Collagen derived from porcine sclera and molded into clear thin pliable sheets was fabricated as a potential vehicle to promote the healing of the de-epithelialized corneal conditions, to eliminate the painful use of contact lenses and to achieve a sustained delivery of drugs [42,43]. Bio-Cor® marketed by Bausch and Lomb was the first commercially available porcine collagen shield. Glucan/collagen therapeutic eye shields were the patented products of Biosource Genetics Corp. used to deliver glucan through the collagen shields [44].

2.6 Colloidal systems

Colloidal systems in the submicron range can be incorporated in the eye drops as an alternative to the conventional dosage forms [45,46]. In a study, higher drug loading was obtained in the nanospheres than in the microspheres due to a larger surface area. Microparticles were slowly eliminated from the precorneal compartment but nanoparticles were better tolerated by the patients due to their small size and can be used for targeting due to their adherence to the inflamed corneal tissues [47,48]. Modification with the use of mucoadhesive and viscous polymers can be used to improve the corneal retention and bioavailability of the formulation [49].

2.7 Liposomes

Smolin *et al.*, Schaeffer and Krohn *et al.* introduced the use of the phospholipid vesicles to increase the precorneal time and as carriers for water soluble and lipid soluble drugs [50,51]. Positively charged liposomes showed a higher binding affinity to the anionic corneal and conjunctival mucoglycoproteins and better entrapment efficiency than the neutral and negatively charged vesicles [52]. Mixed brain gangliosides were incorporated into the membranes of phosphatidyl choline liposomes to provide receptor sites for wheat germ agglutinin, a lectin that binds strongly to corneal epithelium, led to enhanced topical drug flux [53]. Collasomes, liposomes coupled to collagen matrices and polyamido amine (PAMAM) dendrimer-coated puerarin liposomes were prepared to increase the adhesion capacity and penetration of liposomes [54,55]. Niosomes were found to be better vesicle system to deliver hydrophilic and lipophilic drugs to eyes due to their better stability than the liposomes [56,57]. Large disc shaped vesicles, discomes, were derived from niosomes by the addition of a non-ionic surfactant Solulan™ C24 [58]. The large size of discomes fit in *cul-de-sac* thereby preventing its drainage into the systemic pool as well as disc shape [59].

2.8 Ocular minitablets

These are the bioerodible tablets weighing about 6 mg and 8 mm (4*2 mm) in diameter. Minitablets with matrix system were prepared by direct compression of the powdered blend of drug, polymer and other excipients. The drug release occurs due to the swelling of the polymer followed by dissolution in the tear fluid. High drug concentration can be maintained in tear fluid using minitablets for a prolonged period. On insertion, the tablet absorbs the tear fluid and sustains the drug release on to get hydrated [60,61].

2.9 Ophthacoil

Pills R.T. *et al.* developed a novel medical device consisting of a drug-loaded hydrogel coated onto a thin metallic wire and later modified it with p-HEMA (p-hydroxyethyl methacrylate)/NVP (*N*-vinyl pyrrolidone) microspheres loaded in the lumen of the core wire to increase the loading capacity on the wire. It was found to release drug from two types of mechanisms when inserted in the eye: immediate drug release followed by the controlled release from the drug-loaded microspheres. Atropine and chloramphenicol in human volunteers and pradofloxacin in dogs were successfully delivered through ophthacoil without causing discomfort [62-65].

2.10 Ocular iontophoresis

It is an advanced non-invasive technique to avoid the complications associated with administration of frequent, high dose subconjunctival injections or eye drops, which require hospitalization of the patient [66-68]. Direct current of low intensity 0.2 mA – 4 mA for 10 – 20 min is applied that drives charged molecules across the cornea, sclera and the adjacent tissues [69-73]. It is limited to drug molecules which can ionize and have low molecular weight. Singh RP *et al.* proposed a new efficient technique Macroesis™ (patent filed by Buckeye Pharmaceuticals, Beachwood, OH, USA) which uses alternating current instead of direct current. Therapeutic concentrations were achieved in the ocular tissues in less time and it is possible to deliver the drug to the posterior segment of the eyeball [74].

3. Natural polymers

The inert, biodegradable, biocompatible and lack of immunogenicity properties have conferred in natural polymers as potential carriers in drug delivery systems. The eyes are the most sensitive body organ responsible for vision. So, it is important to carefully deliver the drugs through this route. Natural polymers are promising carriers of drugs due to their favorable properties and can be used to prolong the contact time. The major problem with the ocular disease treatment is to provide and maintain an adequate concentration at the site of action for a longer time interval. The solutions have been found to exhibit a very short residence time in the *cul-de-sac* due to rapid clearance, nasolachrymal drainage or ocular irritancy. Different formulations have been prepared with polymers to overcome the problems associated with the ocular delivery. Classification of natural polymers is shown in **Table 2**.

3.1 Properties of natural polymers

The natural polymers have the following properties:

i. Biocompatible
ii. Biodegradable
iii. Fewer side effects
iv. Easily available from the natural sources
v. Relatively inexpensive
vi. Nontoxic
vii. Can be modified to obtain the desired effect

4. Natural polymers used in ophthalmic drug delivery

The summarized information about following natural polymers with respect to their physiochemical properties is presented in **Table 3**.

4.1 Chitosan

Chitosan is a cationic polysaccharide of co-polymers glucosamine and *N*-acetylglucosamine. The *N*-acetyl-2-amino-2-deoxy-D-gluco-pyranose units are linked by β-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. Deacetylation of chitin renders chitosan free of cellulose-like properties due to the presence of four elements in its formula, positive charge and consequent capacity to form polyelectrolyte complexes and nitrogen derivatives, according to the chemistry of the primary amino group. It possesses the ability to form films which is absent in cellulose [75]. A deacetylation of 85% or higher is preferred due to its stronger mucoadhesive properties and biocompatibility [76]. Increasing the molecular weight and decreasing the deacetylation degree lead to increased irritation scores in rabbits [77]. Strong mucoadhesion occurs due to strong electrostatic interactions which occur between the positively charged amino groups present in chitosan and negatively charged sialic acid residues present in mucus [78]. It is a nontoxic and biodegradable polymer. 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 [79].

The poly cationic chitosan HCl significantly increased the residence time of formulation and the drug penetration as compared to the polyanionic *N*-carboxymethyl chitosan and poly(vinyl alcohol) [80]. Chitosan–hydrochloride ofloxacin microparticles dispersed polyethylene oxide (PEO-900) inserts showed increased insert erosion and transcorneal penetration of ofloxacin. Significantly higher peak concentrations (greater than the MIC 90%) in the aqueous humor were obtained than PEO inserts [81]. Chitosan can disrupt the corneal tight junctions and enhance the transcorneal permeation of hydrophilic drugs like acyclovir by diffusion [82]. Trimethyl chitosan significantly increased the transcorneal transport of dexamethasone through the transcellular route, but did not affect tobramycin transport through the paracellular route [83]. Similarly the fluorescent chitosan–hyaluronic acid nanoparticles were found to have transported through the transcellular route [84].

Table 2. Classification of natural polymers.

Type	Sub type	Examples
Chemical Nature	Polysaccharides	Gellan gum (Gelrite), guar gum, locust bean gum, tamarind gum, xanthan gum, gum cordia, chitosan, sodium alginate, starch, sodium hyaluronate, arabinogalactan, bletilla striata polysaccharide, carrageenan
	Proteins	Albumin, collagen, gelatin
Source	Plant	Bletilla striata polysaccharide, tamarind gum, locust bean gum, gum cordia, guar gum, starch, arabinogalactan
	Animal	Chitosan, hyaluronic acid, albumin, collagen, gelatin
	Microbial	Xanthan gum, alginic acid, gellan gum, carrageenan
Charge	Cationic	Chitosan
	Anionic	Gellan gum, hyaluronic acid, alginic acid, xanthan gum, albumin, carrageenan, arabinogalactan, sodium hyaluronate
	Non ionic	Tamarind seed gum, locust bean gum, bletilla striata polysaccharide
	Amphoteric	Gelatin, collagen

N-carboxymethyl chitosan was found to have a higher diffusion kinetic constant than other derivatives of chitosan like *N*-carboxybutyl chitosan and *N*-succinyl chitosan and so interacted with flurbiprofen [85]. 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. Stronger intraocular pressure lowering activity was observed when using the poly (*N*-isopropylacrylamide) combination than the conventional eye drop solution [86]. A 1:16 ratio of chitosan and poloxamer was used to prepare *in situ* gels for stronger mucoadhesive properties and to get improved mechanical strength. The solution formed gel at 32°C and was able to withstand low shearing forces at 35°C and the retention obtained was four times higher than in the conventional formulation [87]. 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 [23]. Another study comprised of *in situ* pH triggered gelling system of timolol maleate using chitosan and carbopol for better gelling strength and prolonged drug release [88]. The formulation of *in situ* nanoparticle dispersions of hydrophilic drugs using cationic chitosan and anionic tripolyphosphate has been reported. The combination of chitosan and tripolyphosphate reduced the critical gelling temperature and critical micellization of poloxamer 407 and both hydrophilic and hydrophobic drugs could be incorporated in the formulation without using organic co-solvents [89].

Chitosan-loaded gatifloxacin ocular inserts with a combination of gellan gum provided 24 hours sustained drug release [90]. Similarly, a mucoadhesive ciprofloxacin hydrochloride chitosan-coated liposomal formulation gave a higher precorneal retention and bioavailability as compared to the uncoated liposomal formulations and Ciprocin® (a three times higher residence time than the marketed formulation). The negatively charged liposomes exhibited higher coating efficiency than the positively charged or uncharged vesicles due to electrostatic forces of attraction [91].

Liposomes encapsulating coenzyme Q10 were prepared using trimethyl chitosan (TMC) of different molecular weight. TMC prolonged the precorneal contact time due to its intense positive charge and internal hydrophobic interactions with the phospholipid bilayer due to the presence of acetyl groups. The precorneal retention was about 3 – 5 times and the bioavailability increased with increase in TMC molecular weight [92]. High cyclosporine A association efficiency and loading were obtained in chitosan-coated nanoparticles. A fast release during the first hour followed by a more gradual drug release during a 24-hour period was obtained in the *in vitro* study. The zeta potential of the nanoparticles was unaffected by the chitosan concentration [93], whereas a sustained release of cyclosporine A for 48 hours was obtained with cholesterol-modified chitosan self-aggregated nanoparticles. On administration, the ^{99m}Tc radiolabeled nanoparticle suspension showed good spreading over the precorneal surface; a part of the suspension was drained in the first 15 min through lachrymal apparatus leaving behind the nanoparticles on the corneal surface whose activity was observed at different time intervals [94].

Cholesterol-modified chitosan was used as a stabilizer to prepare rapamycin nanoparticles with polylactic acid. The fluorescence-labeled nanoparticles remain attached to cornea and conjunctiva for more than 24 hours. The immunosuppression in corneal transplantation of the nanoparticles was obtained for about 27 days and 50% grafts were still active at the end of the observation as compared to the group treated with 0.5% rapamycin suspension which was active for 23.7 ± 3.20 days. The survival time of drug-free nanoparticles group and untreated groups were 10.9 ± 1.45 and 10.6 ± 1.26 days, respectively [95]. Bovine serum albumin chitosan nanoparticles were found to be internalized by the conjunctival epithelial cell lines and uniformly distributed in the human conjunctival epithelial cells (IOBA-NHC) cells [96].

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 complex and nanogel. Addition of high amounts of tripolyphosphate with constant mass of chitosan could saturate the cationic sites in chitosan and increase the size of the nanoparticles and may also cause the pH to rise, eventually increasing the overall negative surface charge that can affect particle size as well as 5-fluorouracil encapsulation. Increase in chitosan concentration also affected the surface charge of

Table 3. Summary of physical and physicochemical characteristics of natural polymers used in ocular drug delivery.

S. No.	Polymer	Charge	Solubility	Molecular weight	Property	Formulation
1.	Chitosan	Positive [133]	Sparingly soluble in water Practically insoluble in ethanol (95%), other organic solvents [133]	10,000 – 10,00, 000 [133]	Mucoadhesive	Solutions [80,82,83], *in situ* gel [78,86-89], inserts [81,90], supercritical solvent impregnation [85], Chitosan-coated liposomes [91,92], nanoparticles [84,93-97], solid lipid nanoparticles [98], ocular minitablets [99], nanosuspension [100,101], niosomes [102,103], lipid emulsion [104], nanostructured lipid carrier [105]
2.	Sodium hyaluronate	Negative [133]	Soluble in water Slightly soluble in mixtures of organic acids and water [133]	Hyaluronic acid 300 – 2000 kDa [133]	Increase break up time (of tear film), increase the retention time	Lubricant and viscous solutions [114,116-124], *in situ* gels [115], bioadhesive nanoparticles [126,127,130-132]
3.	Sodium alginate	Negative [133]	Soluble in alkali hydroxides, very slightly soluble in ethanol (95%) and other organic solvents [133]	20,000 – 2,40,000 [133]	Swelling property	Solutions [134-136], inserts [30,137-140], microspheres [141], ocular minitablets [148,149], *in situ* gels [144-147]
4.	Gellan gum Gelrite	Negative [165]	-	$5*10^5$ Da	Forms gels in the presence of cations, with hyaluronic acid and Ca^{2+}, forms rigid gel structure at body temperature	*In situ* gel [154,156-163], scleral implants [164]
5.	Collagen	Amphoteric [177]	Soluble in acidic pH [177]	100 and 200 kDa for α and β chains [252]	Highly compatible with ocular tissues	Soaked Collagen discs and shields [168-176], inserts [177-179]
6.	Gelatin	Amphoteric [133]	Soluble in hot water, glycerin, weak acids and weak alkalis Practically insoluble in acetone, chloroform, ethanol (95%), ether and methanol[133]	15,000 – 2,50,000 [133]	Film-forming capacity, form gels at pH levels	Gelfoam and Gelfilm as soaked inserts [181-188], ocular inserts [189-192], tertiary system eye drops [193]
7.	Albumin	Negative [133]	Freely soluble in water and salt solutions [133]	66,500 [133]	Tear supplement, interacts with drug molecules and increases the precorneal retention time	Artificial tear solutions [194], microspheres [195], nanoparticles [47,48,196-198]
8.	Xanthan gum	Negative [133]	Soluble in cold or warm water, practically insoluble in ethanol and ether [133]	$2*10^6$ [133]	Viscosity-enhancing agent, mucoadhesive	Viscosity-enhancing solutions [202,203], *in situ* gels [199,201,204-206]
9.	Carrageenan	Negative [133]	Lambda freely soluble in water Iota and kappa-Sodium salt of carrageenan soluble in water at 20°C Soluble in hot water [133]	Iota-100 – 3000 kDa Kappa-25 – 900 kDa [253]	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	Iota and kappa- *in situ* gels [207] Lambda- Microspheres, films [208]

Table 3. Summary of physical and physicochemical characteristics of natural polymers used in ocular drug delivery (continued).

S. No.	Polymer	Charge	Solubility	Molecular weight	Property	Formulation
10.	Drum dried waxy maize starch	-	Dispersion in water, solubility increases with an increase in temperature [210]	400 million units [210]	Bioadhesive, swelling property	Ocular minitablets [61,211-213]
11.	Guar gum	Non-ionic [219]	Disperses in hot and cold water, practically insoluble in organic solvents [133]	1000–5000 kDa [133]	Highly thixotropic gels, mucomimetic	Lubricant eye drops, artificial tear solutions [216-219]
12.	Tamarind seed polysaccharide (xyloglucan)	Non-ionic	Disperses quickly in cold water and forms a viscous solution on heating	620,000 [229]	Forms viscosity-enhancing solutions, mucoadhesive mucomimetic, bioadhesive activities and promotes cell viability	*In situ* gels [221,222], tear substitutes [223-225], solutions [227-229], viscous solutions [230-232]
13.	Arabinogalactan	Negative [254]	Soluble in water [233]	10,000 – 1,20,000 Da [233]	Corneal wound healing capacity, mucoadhesive	Solutions [235,236]
14.	Gum cordia	Negative [240]	Soluble in water on addition of sodium hydroxide [240]	-	Forms matrix system and helps to sustain release	Nanoparticles [240]
15.	Bletilla Striata	Non-ionic [243]	Freely soluble in water but insoluble ins organic solvents [243]	99,658 Da [243]	Mucomimetic, mucoadhesive	Solutions [243]
16.	Locust bean gum	Non-ionic [255]	Soluble in hot water and partially soluble in water at ambient temperature. Insoluble in most organic solvents including ethanol [244]	50,000 – 3,000,000 [244]	Viscosity-enhancing agent	Viscous solutions [245]

nanoparticles because of more unneutralized NH^{3+} on the surface of nanoparticles formed [97].

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 in the *in vitro* and through excised pig cornea in the *ex vivo* studies as compared with the cyclosporine A suspension [98]. Lyophilized sponge like Acyclovir ocular minitablets were prepared using chitosan 1%; these minitablets of acyclovir showed the slowest swelling rate and higher sustained release than sodium carboxymethylcellulose, HPMC, xanthan gum and Carbopol 943P. The acyclovir minitablets with chitosan gave the highest C_{max} and AUC (713.74 µg/g.h) when compared with the marketed ointment (563.88 µg/g.h) [99].

The pupil size of rabbit treated with pilocarpine nanosuspension prepared using a combination of chitosan and polyacrylic acid remained decreased for more than 5 hours as compared with pilocarpine in simulated tear fluid and commercial eye drops which were effective for only 4.5 hours and 2.5 hours respectively [100]. 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 [101].

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 and the commercial eye drops for only 1.5 hours. Intraocular pressure lowering in the contralateral eye was observed with commercial timolol maleate eye drop solution which was very low in case of chitosan-coated niosomal preparation [102]. In another study the chitosan-coated timolol maleate niosomes exhibited 2.34 times higher bioavailability than the marketed formulation [103].

Chitosan and HPMC-coated indomethacin ophthalmic lipid emulsions were reported. Chitosan coated the nanoparticles as the size and the zeta potential increased, while HPMC was only dispersed in the lipid emulsion as the size and zeta potential did not change. 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 [104]. The flurbiprofen nano-sized lipid vesicles showed higher solubility with a combination of chitosan-modified oligosaccharide coating which due to a positive charge effect showed superior mucoadhesive properties and penetration of flurbiprofen [105].

4.2 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. Chemically, it is a high-molecular-weight polyanionic linear mucopolysaccharide composed of alternating units of *N*-acetylglucosamine and D-glucuronic acid [106,107]. 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 [108]. 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 [109,110]. 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 [111,112]. In another study, early cases of retinal detachment were treated successfully with external retinal-detachment surgery using intravitreal Healon [113].

Pilocarpine solutions prepared from high-molecular-weight sodium hyaluronate exhibited a greater miotic response than those prepared from low molecular weight [114]. 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 24 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 [115]. 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 [116]. Pilocarpine (0.5%) combined with sodium hyaluronate increased 1.75 times the bioavailability than the 1% pilocarpine marketed solution [117]. Sodium hyaluronate at a concentration of 0.25% provides better bioavailability of gentamicin sulfate than phosphate buffer solution of gentamicin [118].

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 [119]. Sodium hyaluronate solutions with pseudoplastic behaviors have low viscosity at a high shear rate and so the solution is evenly distributed on the precorneal surface after blinking. While the Newtonian behavior exhibiting HPMC solution forms high viscosity solutions which do not distribute uniformly over the precorneal surface and also interfered in vision [116]. Sodium hyaluronate was found to have higher viscosity and better

tolerability than hydroxylethyl cellulose on the elimination of a fluorescent tracer [120].

In a study on isolated chick corneal epithelium, sodium hyaluronate (0.1%) showed better protective activity against dryness than sodium hyaluronate (1%) and hydroxyethyl cellulose (0.1%). The combination with 0.01% benzalkonium chloride also reduced the toxic effect on corneal epithelium [121]. The optimum concentration of sodium hyaluronate (0.1%) was essential to increase the precorneal tear film breakup time (BUT) for the treatment of dry eyes [122]. Commercial lubricant eye drops containing carbomer 934 (0.3%) and sodium hyaluronate (0.18%) were equally effective in treating moderate dry eyes. The carbomer 934 formed more viscous isosmotic solutions which caused visual problems in patients while the sodium hyaluronate drops were relatively less viscous and hypotonic [123]. Sodium hyaluronate is also reported to improve conjunctival epithelial healing marked by the presence of goblet cells. Sodium hyaluronate promotes cell migration and stabilizes epithelium to promote wound healing in dry eyes. It was hypothesized that hyaluronate binding to CD44 receptors (expressed on the conjunctival and corneal cells) induced cell proliferation [124]. Some marketed ophthalmic solutions like Vismed and Rejena are available for dry eye syndrome treatment [125].

A hydrogel of oxidized hyaluronic acid crosslinked with adipic acid dihydrazide can be used as vitreous humor substitute due to its equivalent human vitreous humor refractive index which can be maintained for 35 days [126]. A synergistic mucoadhesion was obtained from hyaluronic acid-modified chitosan nanoparticles of dorzolamide hydrochloride and timolol maleate due to the oppositely charged polymers. A higher therapeutic effect about two times decreased intraocular pressure and a lesser systemic absorption was obtained with chitosan–hyaluronic acid drug-loaded nanoparticles than the marketed formulation [127].

Tropicamide solutions, gels and matrices prepared with hyaluronic acid showed good to excellent mucoadhesive properties than polyacrylic acid [128]. With a decrease in molecular weight, the mucoadhesive strength of hyaluronic acid increased on buccal, vaginal porcine mucosa and rat jejunum [129].

Chitosan and hyaluronic acid were combined to prepare nanoparticles to deliver plasmid-DNA. Hyaluronic acid can enter the cell nucleus and interact with CD44 receptors expressed on the ocular surface and it can also act as a transcription activator. The hyaluronic acid–chitosan oligomer nanoparticles showed high levels of gene expression, and positive transfection results were maintained for up to 7 days [130]. The hyaluronic acid–chitosan oligomer nanoparticles were internalized by corneal and conjunctival cell lines by an active transport mechanism mediated by CD44 hyaluronic acid receptor through a caveolin-dependent endocytic pathway. This uptake did not compromise cell viability. Therefore, the bioadhesive nanoparticles can be used in immune mediated diseases or corneal transplants [131]. Hyaluronic acid-coated gatifloxacin and prednisolone nanoparticles significantly prolonged drug release without any burst release and provided higher bioavailability of gatifloxacin [132].

4.3 Sodium alginate

It is a hydrophilic colloidal polysaccharide of white to buff color, odorless and tasteless sodium salt of alginic acid. 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 [133].

Sodium alginate possesses mucoadhesive properties forms low-viscosity solutions even at high concentrations without causing any blurring effect. Cartelol alginic acid ophthalmic solutions gave a sustained release for upto 8 hours and its once a day administration could replace standard cartelol solution given twice. Sodium alginate exhibited better bioadhesive properties than hydroxyethyl cellulose [134,135]. A sustained release of over 12 hours was obtained from gatifloxacin ophthalmic solutions prepared using different concentrations of sodium alginate with or without sodium carboxymethyl cellulose. With increase in sodium alginate concentration from 0.4% w/v to 1% w/v and 2% w/v, the release was sustained significantly while sodium carboxymethyl cellulose controlled the burst release of drug [136].

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 [137]. 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 24 hours [138]. 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 [30]. 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 [139]. The azithromycin inserts prepared using sodium alginate showed sustained drug delivery over an 8 hours period and followed first-order release kinetics [140].

Bovine serum albumin-loaded alginate microspheres incorporated in a collagen hydrogel can be used as medicated contact lenses to constantly release drug or as a corneal substitute for transplantation. A sustained release of bovine serum albumin was obtained for 11 days through the microsphere hydrogel matrices without any burst release due to two barriers: microsphere barrier and the hydrogel barrier [141].

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 [142]. 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 [143].

Ion-activated *in situ* gel of gatifloxacin prepared using sodium alginate as a gelling agent and hydroxypropylmethyl cellulose as a viscosity-enhancing agent sustained the drug release for 8 hours [144]. Similarly a sustained release of 8 hours was obtained from ofloxacin *in situ* gel prepared using sodium alginate (1.5% w/v) and hydroxypropylcellulose [145]. While prolonged drug release for upto 8 hours was obtained from both sodium alginate and carboxymethyl cellulose atenolol *in situ* gel formulations [146]. The sustained drug release obtained from the *in situ* gel formulation is directly proportional to the sodium alginate concentration. Diclofenac sodium gel prepared using sodium alginate at 5%, 4% and 3% w/v concentrations gave a prolonged release of 9, 8 and 6 hours respectively [147].

Gatifloxacin nanoparticles and minitablets prepared using chitosan and sodium alginate gave a sustained release for 24 hours preceded by an immediate release during the first hour [148]. Gatifloxacin non-crosslinked ocular minitablets containing sodium alginate and chitosan prolonged the drug release for about 24 hours in contrast to the crosslinked minitablets which sustained the release for only 12 hours [149].

4.4 Gellan gum

Gellan gum (formerly known as PS-60 and S-60) is an extracellular polysaccharide secreted by aerobic, well-characterized, non-pathogenic, gram-negative strains of *Pseudomonas, Sphingomonas paucimobilis* and *Auromonas elodea* [150,151]. 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 initially discovered by Kelco Div., Merck & Co [152].

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 [153-155].

Ion-activated technetium-99 m radiolabeled diethylene triamine penta-acetic acid *in situ* gels of Gelrite 0.6% w/v were retained for significantly longer time periods on the precorneal surface than hydroxyethyl cellulose 0.5%w/v solution and saline solution in human volunteers, whereas in rabbit hydroxyethyl cellulose was better retained on the precorneal surface than Gelrite [156]. However, timolol maleate *in situ* gels of Gelrite and hydroxyethyl cellulose gave similar release rate profiles [157].

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 24 hours as opposed to the 4 hours effect from the standard indomethacin dispersion [158].

Environmentally responsive ophthalmic gel formulations of carteolol hydrochloride using different concentrations of Gelrite were prepared. As the concentration of polymer was increased, viscosity increased and a decrease in release was observed. It was due to the formation of a compact gel which posed a barrier for the drug to release. The diffusion coefficient also decreased with increase in polymer concentration but the diffusion coefficient decreased as the drug concentration increased at all polymer concentrations. Carteolol HCl (1% w/v) with Gelrite (0.4% w/v) showed more than twofold higher concentration than the Arteoptic® (Carteolol HCl (1% w/v)) marketed ophthalmic solution [159].

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 [160]. 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 [161]. 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 [24]. 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) [162].

In another study flurbiprofen axetil nanoemulsion was mixed with gellan gum to formulate an *in situ* gel system. The nanoemulsion *in situ* gel in pharmacokinetic studies showed a 2.7 and 2.9 times greater mean residence time and ocular bioavailability than the marketed eye drops. Ion-activated gellan gum with nanoemulsion enhanced the solubility of the poorly soluble drugs. In addition, gel formation occurs when Gelrite interacts with the tear fluid [163]. Indomethacin crosslinked scleral implants, prepared using Gelrite 0.25%, significantly retarded drug release for 8 hours [164].

In a combination study, gellan gum and hyaluronic acid (9:1 or 8:2) with or without calcium chloride showed 5600 or 5950 cP, respectively, at 0.512/s shear rate in vitreous

humor. However, formulation, that is, 8:2 ratio was most suitable vitreous humor substitute due to its gel forming property at ocular temperature [165].

4.5 Collagen

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. 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 [166]. The difference in the collagen types occurs due to the segments that interrupt the triple helix and that fold into other kinds of three-dimensional structures. Collagen is absorbed within 84 days due to its high biodegradability and biocompatibility [167].

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. Collagen shields with different dissolution times 12, 24 and 72 hours depending on the crosslinking induced by ultraviolet light are available. The non-crosslinked shield dissolves in 12 hours while the crosslinked corneal shields dissolve in 24 hours or 72 hours. The 72 hour collagen shield has disadvantages of variable dissolution rate and corneal irritation [168]. 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 [169].

The porcine collagen shield without crosslinking, soaked with gentamicin, vancomycin and their combination, was used to study drug release through the inserts. A sustained release of vancomycin for 6 hours was obtained but gentamicin was released within 30 min in the *in vitro* studies [170]. In another study the efficacy of collagen shields to deliver gentamicin was compared with that of soft contact lens, subconjunctival injections and frequently instilled eye drops. The collagen corneal shield significantly increased gentamicin concentration more than all the other methods [171].

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 [172].

Cephradine collagen shields have been reported to have about 1.3 times higher permeation through corneal epithelium than conventional eye drops and soft contact lenses of cephradine [173]. The ocular pharmacokinetics of netilmicin from presoaked collagen shields showed higher netilmicin concentrations in aqueous humor as compared with concentrated drug solution [174]. Subconjunctivally implanted 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 [175]. Collagen shield-incorporated cyclosporine A provided maximum concentration after 4 hours and sustained for 8 hours while with corn oil drops, peak concentrations were obtained after 1 hour and decreased thereafter with undetectable drug concentrations [176].

The native collagen is only soluble at acidic pH < 5 and completely insoluble at the body pH. Some patentable files provide information about dissolution rate of collagen derivatives. Ocular inserts prepared with succinylated and methylated 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. The charged polymer retains oppositely charged drug molecules for a longer duration. Inserts of pilocarpine with succinylated collagen and dexamethasone with methylated collagen were also prepared, which formed gel at the physiological pH and effectively sustained the drug release [177]. Similarly, gentamicin-impregnated succinylated collagen and insoluble collagen films were prepared. Succinylated collagen films released significantly higher levels of antibiotic than the insoluble films, and maintained mean inhibitory concentrations (MIC_{90}) for *Moraxella bovis* for 24 hours [178]. Pilocarpine nitrate-loaded hydrazide-derived ocular inserts of collagen were reported to sustain drug release for 15 days as compared to plain collagen and ocular inserts crosslinked with glutaraldehyde (1% v/v), which gave sustained release for only 5 and 7 days, respectively [179].

4.6 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. These sequences are responsible for the triple helical structure of gelatin and its ability to form gels, where helical regions form in the gelatin protein chains immobilizing water. 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. The alkaline pretreatment of the collagen extracts obtained from approved abattoirs and meat works yields type-B gelatin with an isoelectric point of approximately 5.0 and acid pre-treatment of pork skin material produces gelatin with an isoelectric point between 7.0 and 9.0 [133]. It is a mucoadhesive polymer but has low mechanical strength; therefore, mostly a modified form of gelatin is used [180].

Gelfoam® and Gelfilm® are the patented products of Pfizer containing gelatin as the absorbable sponge and film. In ophthalmic drug delivery system, Gelfoam (absorbable gelatin sponge) has been reported as a carrier and it can be comfortably

placed in the fornix of eyelids. It becomes soft and pliable on contact with tears [181,182]. The bioavailability of melanotan II through eye drops and device was 25% and 67%, respectively [183]. The Gelfoam-loaded insulin ocular device showed sustained release at 8 hours in the *in vivo* studies [184]. In another study, an increase in blood glucose levels was observed immediately on removal of the device [185]. Matrix system Gelfoam inserts were prepared by embedding pilocarpine in cetyl ester wax and impregnating it with polyethylene glycol 400 monostearate, which sustained the drug release for 5 hours in the *in vitro* studies [186]. Higher drug release was obtained from the Gelfoam-impregnated pilocarpine inserts than from conventional eye drops and gel in the *in vivo* studies [187]. Gelfoam pre-soaked with tropicamide and phenyl epinephrine was administered comfortably and produced a 1.75 times higher dilation of the pupil and increased the pupil viewing area by three times than the eye drops [188].

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 [189]. Matrix-type inserts of ciprofloxacin showed controlled drug release for up to 10 hours with 18%w/v of gelatin [190]. 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 24 hours as compared with the half an hour release from conventional eye drops [191]. Aceclofenac-incorporated gelatin ocular inserts, crosslinked using glutaraldehyde, sustained the release for 24 hours. Therefore, it is an ideal formulation for once a day administration for the treatment of Prostaglandin E_2-induced ocular inflammation [192].

Tetrahydrozoline hydrochloride polyelectrolyte gelatin-based eye drops were reported to have better physical stability, maximum mucoadhesion on cornea and low viscosity as compared with eye drops prepared using chitosan, hyaluronic acid and polyacrylic acid [193].

4.7 Albumin

Albumin is a protein naturally found in blood. It is produced in liver and is also found in many food products, predominantly in milk and egg white. Human serum albumin is a single polypeptide chain of 585 amino acids and contains seven disulfide bridges. Albumin appears as brownish amorphous lumps, scales or a powder. It is biodegradable, highly compatible and non-antigenic and has no toxic effects [133].

Albumin is used as a tear supplement in the treatment of severe dry syndrome. 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% [194].

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 [195]. Pilocarpine-loaded albumin nanoparticles had a higher loading capacity and a higher bioavailability than microspheres without albumin [47]. Pilocarpine-loaded 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 [48]. Aspirin-incorporated albumin nanoparticles were prepared as intraocular release agents in the posterior chamber for treatment of diabetic retinopathy. Aspirin was found to form strong bond with ε-lysine amino group of albumin which contributed to aspirin sustained release of 72 hours [196]. Hydrocortisone delivery to the healthy and inflamed eyes was studied by preparing albumin nanoparticles and ophthalmic solution containing micellar polysorbate [80]. 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 [197]. 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 [198].

4.8 Xanthan gum

It is a high–molecular-weight polysaccharide of sodium, calcium or potassium 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 exists as a white or cream colored, tasteless powder with a slightly organic odor [133].

TobraDex (tobramycin 0.3% with dexamethasone 0.1%) and TobraDex ST (tobramycin 0.3% with dexamethasone 0.05% in a xanthan gum vehicle), registered trade names of Alcon Laboratories, Inc., Fort Worth, TX, USA, 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). The xanthan gum-containing formulation showed reduced signs of inflammation even though it contained half the amount of dexamethasone. It was because xanthan gum increased the corneal permeability of dexamethasone [199].

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. It was hypothesized that heating caused conformational changes in xanthan gum structure and sonication decreased

the molecular weight of the macromolecule of xanthan gum which enhanced the formation of secondary bonds between xanthan gum and mucin [200]. 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 [201].

Gamma scintigraphic studies conducted on xanthan gum-based pilocarpine eye drops resulted in delayed clearance of solutions from ocular cavity due to increased viscosity. The study showed that 77% of formulation was retained on the precorneal area after 1 min of instillation, whereas only 23% of reference formulation (without viscosity-enhancing agent) was retained [202]. Xanthan gum forms psuedoplastic solutions due to the formation of highly ordered entangled network. Ophthalmic delivery of dorzolamide hydrochloride (2% w/w) in hypotonic 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 [203]. Linezolid ion-triggered *in situ* gel prepared using xanthan gum, sodium alginate and carbopol 934 were reported to sustain 57% release compared with the formulation containing hydroxypropyl guar, hydroxyethyl cellulose and sodium alginate over a period of 6 hours [204]. *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 [205]. Timolol maleate 0.5% w/v solution with xanthan gum (Falcon) and Timoptic-XE (timolol maleate 0.5%w/v in gellan gum by Merck) significantly reduced the intraocular pressure [206].

4.9 Carrageenan

A yellow-brown to white colored, coarse to fine, odorless and tasteless anionic hydrocolloid polysaccharide 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 is classified into three families on the basis of sulfate group position and presence or absence of 3,6-anhydro galactose [133].

Binary systems with different ratios of carrageenan [iota (ι-CG) and kappa (κ-CG)] to methylcellulose (MC) were used to prepare ion-sensitive and thermoresponsive *in situ* gels for trans-scleral delivery of macromolecules. MC and κ-CG at a ratio of 20:80 formed gels below 20°C and above 30°C, whereas ι-CG formed gels at high temperatures only [207].

λ-carrageenan has the property to interact with alkaline drugs like timolol maleate microspheres and films. Timolol maleate-incorporated λ-carrageenan microspheres showed fourfold increased aqueous humor concentration than with marketed formulation [208]. λ–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 [209].

4.10 Starch (drum-dried waxy maize starch, pregelatinized starch)

Genetically modified variants of corn have led to the cultivation of waxy maize which contains highly branched amylopectin unit of starch. 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. Amioca® is also a food grade starch consisting of only amylopectin which imparts it viscosity-enhancing properties without causing gel formation [210]. Pregelatinized starch is a physically modified starch which can form dispersions and gels with cold water. It is moderately coarse to fine, white to off-white colored powder, odorless with a slight characteristic taste [133].

A study comprising ciprofloxacin-incorporated drum-dried waxy maize (DDWM) 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 24 hours [211].

Sodium fluorescein tablets prepared with co-spray-dried mixture Amioca and Carbopol 974P sustained the drug release for about 11 hours, while the physical mixture of DDWM and Carbopol 974P sustained the release for only 6 hours. Carbopol 974P when used in high concentrations caused mucosal irritation while a high concentration of Amioca did not cause any mucosal irritation. The reflex lacrimation on the placement of minitablets in the lower fornix caused the tablets to hydrate and form gel which slowly released the drug [61]. Ciprofloxacin minitablets were reported to sustain the release for 8 hours when the combination of DDWM, Carbopol 974P and sodium stearyl fumarate was used [212].

Bioadhesive minitablets of gentamicin and vancomycin were prepared as a physical mixture or co-spray-dried mixture of pregelatinized starch and Carbopol 974. The co-spray-dried mixture tablets 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 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 [213].

4.11 Guar gum

It is a high-molecular-weight hydrocolloid polysaccharide gum obtained from the ground endosperms of *Cyamopsis*

tetragonolobus (L.) Taub. (family *Leguminosae*). It consists of linear chains of (1,4)-β-D-mannopyranosyl units with α-D-galactopyranosyl units attached by (1,6) linkages. It is a white to yellowish-white, odorless powder with a bland taste [133]. It is used to prepare matrix tablets to achieve prolonged release and has found wide applicability to target colon [214,215]. Modified form of guar gum, hydroxypropyl guar (HPG) is used to form gelling eye drops with demulcents, polyethylene glycol 400 and propylene glycol (marketed as Systane™ eye drops, Alcon Laboratories Inc, Fort Worth, TX) without any preservative for treating dry eyes [216]. A sustained release of demulcents on the cornea is obtained due to adherence of high-molecular-weight and pH-sensitive HPG molecules with the mucin layer. HPG is a pH-sensitive molecule and forms a stiff chain as the degree of substitution increases [217]. On instillation, the viscosity of eye drops increases significantly due to formation of cross-linked 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 [218]. Systane™ had a protective effect on the damaged corneal epithelium which was absent in the corneas treated with commercial artificial tear containing carboxymethylcellulose and Purite® in the *in vivo* desiccation model [219].

4.12 Tamarind seed polysaccharide (xyloglucan)

Tamarind kernel powder is a high-molecular-weight polysaccharide obtained from the kernels of the seeds of tree *Tamarindus indica* (family *Cesalpiniaceae*). The powder consists of a high content of carbohydrate and is composed of cellulose-like backbone of xylose and galactoxylose. The 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 [220]. Xyloglucan at a concentration of 1.5% w/w was equally effective as Pluronic F127 at 25% w/w concentration in the preparation of pilocarpine thermosensitive gels [221]. Therefore, it can be used to prepare pH sensitive and temperature sensitive *in situ* gels.

The bacterial components lipoprotein and lipoteichoic acid increase the production of mucin, and TSP has high binding affinity toward mucin due to its structural similarity with it. TSP possesses cell surface intensifying effect and increases the contact time between the drug molecules and biological membrane [222]. 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 [223]. 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. The viability of the conjunctiva cells significantly increased with TSP with timolol and merthiolate and completely prevented fluoroquinolones induced cellular changes thereby showing a protective effect on the conjunctival cells [224]. An evidence of TSP protective properties is available in an open label clinical study. TSP 1% 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% and 1% were equivalent to hyaluronic acid 0.2% 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 [225].

The mucoadhesive properties of TSP were confirmed by NMR spectroscopy using ketotifen fumarate as low-molecular-weight interaction probe. TSP showed high affinity toward mucin almost two to three times more than arabinogalactan [226]. In another study higher transcorneal disposition and aqueous humor concentrations were obtained with TSP-based rufloxacin eye drops than with ofloxacin and rufloxacin eye drops in infected eyes than in non-infected rabbit eyes [227]. 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 [228]. 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 only 8 hours [229].

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. Higher drug aqueous humor concentrations (3 and 4.5 times) were obtained for ofloxacin-TSP and gentamicin-TSP than without seed polysaccharide in drug solutions [230]. In another study, TSP viscosified rufloxacin suspension and rufloxacin HCl solution significantly increased the bioavailability, whereas the availability of drug decreased from the hydroxypropyl-β-cyclodextrin solubilized rufloxacin solution [231]. Similarly, more prolonged residence of ketotifen and diclofenac in precorneal area was obtained with TSP than with arabinogalactan, hyaluronan and hydroxyethyl cellulose [232].

4.13 Arabinogalactan

Arabinogalactan is a long, densely branched 3,6-β-D-galactan polysaccharide abundant in most plants and microflora but is usually obtained from the bark of the Larch trees (*Larix occidentalis, L. decidua*) of Larix species. It is a fine, dry, off-white slightly sweet powder with mild pine-like odor. It

is formed of arabinose and galactose in a ratio of 1:6 and with a small quantity of glucuronic acid. The macromolecule with a molecular weight ranging from 10 kDa to 120 kDa has been approved by FDA for human consumption as a dietary fiber even in large quantities [233]. Decreasing the molecular weight from 37kDa to 9 kDa did not affect the potency of arabinogalactan as a carrier to target liver. The decreased molecular weight increased its diffusion across the membranes when administered through the subcutaneous and intramuscular routes [234].

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 [235]. 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 24 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 [236].

4.14 Gum cordia

The mucilaginous substance extracted from the raw fruits of *Cordia obliqua* Willd. (vernacular name lassora) (family *Boraginaceae*) [237]. It is a novel polymer which can be used as a tablet binder, emulsifier and to sustain drug release from the formulations at very low concentrations as compared with the commonly used gums [238]. Gum cordia (1.5% w/w) was more effective than gum acacia (10% w/w) as an emulsifying agent [239].

The fluconazole nanoparticles prepared using gum cordia had a high surface area and with di-octyl sodium sulfosuccinate reverse micelles were formed which acted as nanoreservoirs for drug encapsulation. The nanoparticle suspension showed similar permeation in the *in vitro* studies as compared to the marketed formulation Zocon® [240]. The polymer requires further investigation for its use in ocular formulations.

4.15 *Bletilla striata* polysaccharide

It is obtained from the tubers of *B. striata* (family *Orchidaceae*), a traditional medicinal Chinese herb. It has antibacterial, antifungal properties and is used to treat alimentary canal mucosal damage, ulcers, bruises, bleeding and burns [241]. 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 delivery [242].

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. It has good mucomimetic properties and an almost twofold higher concentration of levofloxacin was found in the aqueous humor due to its mucoadhesive nature. In the experimentally induced keratitis in the rabbits greater antibacterial activity was exerted against *Staphylococcus aureus* compared to the conventional drop solution [243]. The polymer is an ideal carrier for ocular formulations especially for dry eye treatment due to its structural similarity with the lachrimal fluid.

4.16 Locust bean gum (carob bean gum)

The white to yellowish white polysaccharide obtained from the endosperm of the seeds present in the kernels of *Ceratonia siliqua* (carob tree), (family *Leguminosae*). It is composed of galactomannans consisting of a linear chain of (1–4)-linked β-D-mannopyranosyl units with (1–6)-linked α-D-galactopyranosyl residues as side chains. The mannose and galactose units are present in the ratio 4:1 [244].

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 [245].

5. Conclusion

Natural polymers are promising carriers to deliver drugs topically to the ocular tissues. The polymers with different properties can be used to overcome the bioavailability issues associated with ocular drug delivery system and can also be used to control the release of different drugs. The properties of polymers can be combined to prepare different formulations with different release mechanisms. With the ongoing research new polymers have been found which have widened the choice of polymers to be used in different formulations.

6. Expert opinion

During the past two decades, research in ophthalmic drug delivery has undergone major advancements from the use of conventional solutions, suspensions and ointments to viscosity-enhancing *in situ* gel systems, different inserts, colloidal systems, etc. Even though significantly higher bioavailability and controlled release systems have been obtained with the use of different novel formulation approaches in ophthalmic drug delivery, research is highly confined to *in vitro* and *in vivo* studies with very limited reports on Phase I clinical trials. It is a major limitation in the commercialization of newer dosage forms. Extensive research is required to solve the physical stability issues associated with vesicular systems which is another limiting factor in the marketing of novel dosage forms.

Gene therapy is one of the recent technologies for the treatment of certain chronic diseases caused by defective

genes, for example, glaucoma. The introduction of correctly functioning genes into cells is a major hurdle posed to the scientists. Studies on delivery of plasmid DNA through hyaluronic acid–chitosan oligomer nanoparticles due to hyaluronic acid binding to CD44 receptors and uptake of bovine serum albumin–chitosan nanoparticles by human conjunctival epithelial cells have been reported. Therefore, nanoparticles of natural polymers are ideal carriers as vectors for gene delivery, proteins and macromolecules to penetrate through the anterior segment of the eyeball. Similarly, other polymers can be tailored to obtain properties with desired effect. Prolonged use of soft contact lenses is known to cause dry eyes. Polymers with wound-healing property like hyaluronic acid, albumin, collagen and guar gum in small quantities can be incorporated in the contact lenses to prevent dry eyes while simultaneously correcting vision.

Topical administration of chemotherapeutic drugs for the treatment of ocular melanoma (uveal, corneal and conjunctival melanoma) is limited due to the lack of penetration of drugs into deeper tissues [246]. The bioavailability of chemotherapeutic drugs can be enhanced by using chitosan as a penetration enhancer due to its property to disrupt the deeper corneal layers instead of synthetic penetration enhancers like EDTA, azone compounds, sodium deoxycholate, polycarbophils etc. Chemotherapeutic drugs-loaded nanoparticles marked with specific moieties can be formulated for targeting melanoma cells and also to obtain a sustained release.

Natural polymers are preferred over synthetic polymers due to their properties like high biocompatibility, biodegradability, inertness, easy availability and reduced cost. A transient reduction of visual quality is observed in a recent comparative random study of five different OTC eye solutions containing synthetic polymers: polyethylene glycol-400, carboxymethyl cellulose, polyvinyl alcohol/PEG-400 and glycerin/polysorbate-80 [247]. On the contrary, hyaluronic acid, albumin, TSP and guar gum have demonstrated high compatibility and patient compliance. Novel polymers such as arabinogalactan, TSP and BSP are structurally similar to human lachrimal fluid and can be used to treat dry eye syndrome. A synergistic effect can be obtained by using these natural polymers due to their protective properties and as carriers to safely deliver drugs while reducing their toxicity and hastening the recovery process of infected tissues. Novel polymers like gum cordia, sterculia foetida and locust bean gum have shown the potential to deliver drugs to ocular tissues but are yet to be exploited.

Despite the superiority of natural polymers in topical drug delivery in conventional as well as novel ophthalmic formulations, the utility of these dosage forms is limited due to the lack of efficient scale up technologies and sterility problems of ophthalmic dosage forms. Tremendous efforts are required for the extraction, purification and authentication of natural polymers at industrial level to overcome the complications during the regulatory approval.

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Declaration of interest

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