Research & Reviews: Journal of Pharmacognosy and Phytochemistry e-ISSN: 2321-6182
p-ISSN: 2347-2332

Polysaccharide Polymers for Glaucoma Treatment-A Review

Tanvir Ahmed*, Md. Nazmul Islam, Rina Monalisa

Departmeznt of Ophthalmology, National Taiwan University, New Taipei, Taiwan

Review Article

Received: 07-Sep-2022, Manuscript No. JPRPC-22-73984; **Editor assigned:** 9-Sep-2022, PreQC No. JPRPC-22-73984 (PQ); **Reviewed:** 23-Sep-2022, QC No. JPRPC-22-73984; **Revised:** 05-Jan-2023, Manuscript No. JPRPC-22-73984 (R); **Published:** 12-Jan-2023, DOI: 10.4172/2321-6182.11.1.001

***For Correspondence :** Tanvir Ahmed, Department of Ophthalmology, National Taiwan University, New Taipei, Taiwan;
Email: tanvirsust2011@gmail.com

Citation: Ahmed T, et al. Polysaccharide Polymers for Glaucoma Treatment-A Review. J Pharmacogn Phytochem. 2023;11: 001.

Copyright: © 2023 Ahmed T, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution and reproduction in any medium, provided the original author and source are credited.

ABSTRACT

One of the major challenges in preventing glaucoma progression is patient compliance with medication regimens. Since conventional ophthalmic dosage forms have numerous limitations, researchers have been intensively working on developing polymers based delivery systems for glaucoma drugs. Specifically, research and development efforts have increased using polysaccharide polymers for sustained release to the eye to overcome treatment challenges, showing promise in improving drug release and delivery, patient experience, and treatment compliance. In the recent past, multiple research groups have successfully designed sustained drug delivery systems, promoting the efficacy as well as the feasibility of glaucoma drugs with single/combinations of polysaccharides to eliminate the drawbacks associated with the glaucoma treatment. Thus, this review aims to provide an overview of the pre-clinical and clinical studies of polysaccharide polymers applied for glaucoma treatment along with their therapeutic outcomes.

Keywords: Glaucoma; Polymers; Polysaccharides; Drug delivery systems; Formulations

ABBREVIATIONS

IOP: Intraocular Pressure; SA: Sodium Alginate; P: Pectin; CS: Chitosan; EC: Ethyl Cellulose; HPMC: Hydroxypropyl Methyl Cellulose; CMC Na: Sodium Carboxy Methyl Cellulose; STP: Simulated Tear Fluids; LBG: Locust Bean Gum; API: Active Pharmaceutical Ingredients; CD: Cyclodextrin; HA: Hyaluronic Acid; TSP: Tamarind Seeds; DHCL: Dorzolamide Hydrochloride; PH: Pilocarpine HCL; TM: Timolol Maleate; NF: Nifedipine; BLZ: Brinzolamide; HP-β-CD: Hydropropyl-β-Cyclodextrin; NLZ: Nanoliposomes; BRT: Brimonidine Tartrate; LNPs: Lipid Nanoparticles; CMC: Carboxymethyl Chitosan; HPC: Hydroxypropyl Chitosan; TMC: Trimethyl Chitosan; TET-LNPs: Tetrandrine Lipid Nanoparticles; HGC: Hexanol Glycol Chitosan; CS-P: Chitosan-Pectin; SA-P: Sodium Alginate-Pectin; SA-CS: Sodium Alginate-Chitosan; LVFX: Levofloxacin; HB: Hydrogel Ball; RAPA: Rapamycin; SA-HPMC: Sodium Alginate Hydroxypropyl Methyl Cellulose; ACZ-Acetazolamide

INTRODUCTION

Glaucoma is a chronic eye condition characterized by optical nerve dysfunction and related vision field loss due to progressive deterioration or the death of retinal ganglion cells. Globally, glaucoma is the second most common cause of blindness after age related macular degeneration. In a report published by the world health organization in 2020, "world report on vision" states that at least 76 million individuals suffer from glaucoma, and that number is expected to surge 1.3 times by 2030. Many patients with glaucoma do not experience symptoms during the early stages and are unaware of the disease until the advanced stages [1].

Moreover, glaucoma sufferers require lifetime therapy and follow-up, and the condition has a major detrimental influence on patient's quality of life in terms of psychological well-being, daily life, anxiety, driving and confidence in healthcare. Besides, several papers suggest the effect is more profound in developing countries than in developed world. It is further exacerbated by the fact that as the disease advances, it becomes more expensive to manage.

Currently, the most common medication management and treatment options for glaucoma are available in the form of eye drops, subconjunctival injections, laser surgery, glaucoma filtration surgery, and glaucoma drainage devices.

In terms of treating retinal and optic nerve disease, the effectiveness of treatments is limited as a result of encumbrances made at the blood retinal barrier and entering systemic circulation. For instance, the eye drops that are widely used to reduce Intra Ocular Pressure (IOP) in patients with glaucoma and to preserve corneal endothelial cells. Nevertheless, bioavailability and efficacy of topical gel drops, eye drops, and eye ointments are limited by physiological eye barriers, such as corneal epithelial barriers. In addition, long term usage of eye drops raises the sensitivity of the ocular tissues, making the eye more prone to inflammation and less receptive to treatment due to the chronic use of preservatives. Similarly, laser surgery results are short term and can vary based on the patient, and some patients still require medication after the surgery. Many patients experience an irregular IOP after the surgery due to the blockage of some of the newly formed channels. On the other hand, current glaucoma drainage devices have a major concern with flow management in the first few weeks before the fibrous capsule is formed, which can lead to hypotony (IOP<5 mmHg). Even though the materials are used for years as glaucoma drainage devices, they can still cause irritation, inflammation, and scarring due to foreign body reactions. In a study of Skuta and Parrish reported that glaucoma filtration surgery has a major problem with wound healing. The wound healing process results in inflammation, deposition of collagen, and scarring at the surgical site. Consequently, the newly formed channel may be closed, and the operation may fail [2].

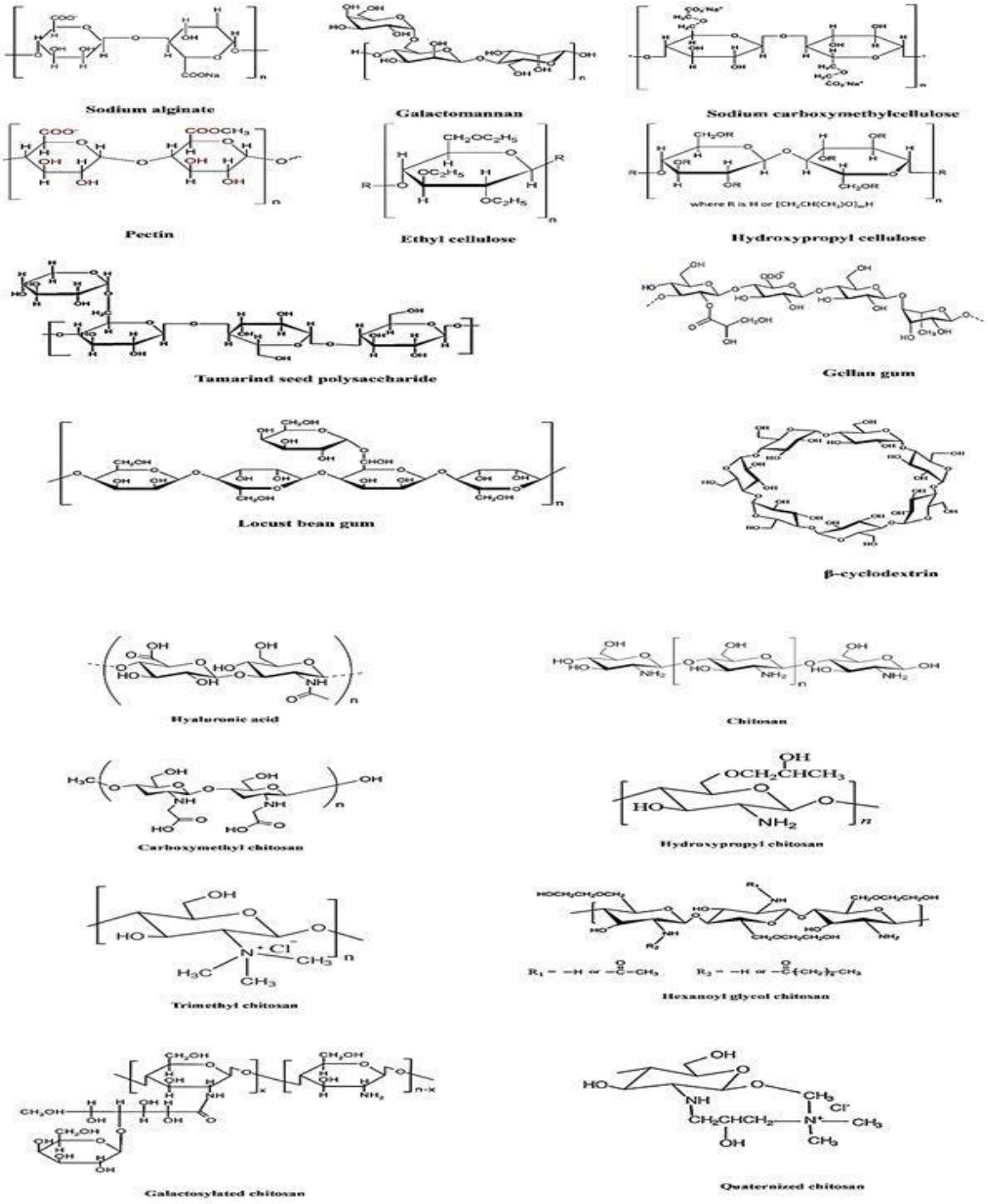
To overcome the abovementioned physical barriers, newly emerging ocular drug delivery technology has focused on the use of polymeric biomaterials. Polymers, notably carbohydrate polymers have been used widely in the recent years for several treatments because of their excellent features, including high water absorption capacity, resemblance to living tissues, excellent biocompatibility, and structural stability in aqueous conditions. In the last few decades, researchers have published a number of scientific articles related to the use of carbohydrate polymers to treat glaucoma in the form of various applications, including *in situ* gel systems (temperature-sensitive, pH sensitive, ion-activated), nano-systems, ocular inserts, contact lenses, ocular implants, microneedles, and ocular iontophoresis. In the recent years, polysaccharides are attractive options among various carbohydrate polymers for the formulation of glaucoma treatment because they are inexpensive, easily accessible, non-toxic, potentially biodegradable, generally biocompatible, and generally amenable to chemical modification. Numerous researches on polysaccharide based polymers is going on with new therapeutics being investigated to help reduce the frequency of application. However, there has not yet been published a review that focuses on the application of diverse polysaccharide polymers in various forms for the improvement of glaucoma treatment. Thus, in this review, we summaries the pre-clinical and clinical studies of polysaccharide polymers and their structurally/chemically modified forms employed for glaucoma treatment along with their therapeutic effects, related mode of action, and also future challenges. We anticipate that providing a comprehensive review of existing research on polysaccharide polymers for improving therapeutic efficacies in glaucoma therapy would assist researchers in defining future research directions based on scientific data that will benefit people's health and well [3].

LITERATURE REVIEW

Polysaccharides used in glaucoma drug delivery system

Sodium alginate, pectin, chitosan, cellulose, gellan gum, galactomannans, locust bean gum, cyclodextrin, hyaluronic acid, and tamarind seed are some of the major polysaccharides utilized in the treatment of glaucoma with various drugs. Chemical structure of different polysaccharides is showed in Figure 1. The structural features of polysaccharide differ from those found in synthetic hydrophilic polymers because of numerous hydrophilic functional groups such as OH, -COOH, and -NH_2 that participate in the water absorption and eventual degradation. A polysaccharide based system may be able to exhibit bio adhesion, sustain, and control release properties by utilizing these functional groups [4].

Figure 1. Structural units of different polysaccharides.



Sodium Alginate (SA) is a co polysaccharide that is linear in structure and originates from brown seaweeds as well as some microorganisms. It can be described chemically as a (1–4) linked block copolymer of a-D-mannuronate and its C-5 epimer R-l-guluronate. It has residues arranged in homo polymeric sequences of both sorts and in regions that are similar to the structure of disaccharide repeating units. Gels are formed when SA interacts with a divalent cation (Ca^{2+}) in lachrymal fluid (pH 7.4) to form calcium alginate. When exposed to divalent cations, SA transforms into a gel that cannot be easily eroded by tear fluid [5-9].

Pectins (P) belong to the family of polysaccharides, and the backbone of the P molecule is predominantly made up of residues of -(1,4)-d-galacturonic acid. In the presence of free calcium ions, which cross-link the galacturonic acid chains, low methoxy P with an esterification level of less than 50% can form a gel in aqueous solution. Due to the fact that P can be dissolved in water, it is possible to exclude the use of organic solvents in the formulations. In a United States patent, it is stated that the *in situ* gelling of P that is triggered by calcium ions does present in lacrimal fluid. Additionally, the pectin based *in-situ* gel has been used to prolong the release of various drugs [10].

A topically applied ophthalmic drug's residence time is its duration of contact with the surface of the eye. In the formulation of topical ocular drug carriers, mucoadhesive polymers are frequently utilized as a technique to extend the drug's residence time. When utilizing a mucoadhesive polymer, the release of the medicine is regulated by the mucus turnover rate, which is substantially slower than the tear turnover rate. Enhanced ocular drug bioavailability is implied by this prolonged retention, as the formulation has good permeability properties. Chitosan (CS) belongs to the class of polymers that has mucoadhesive property. Its mucoadhesive properties are based on the attraction between its positively charged amino groups and the negatively charged residues of sialic acid in the mucus, as well as other factors, such hydrogen bonds. In addition to this special property, CS is a unique option for ocular drug delivery due to its biodegradable, penetration enhancing, great ocular tolerance, and favorable rheological properties.

In ophthalmic formulations, cellulose is among the polymers that are utilized the most frequently. Various cellulose derivatives are employed extensively in ocular formulations because cellulose itself is insoluble in water. Ethyl Cellulose (EC), Hydroxyl Propyl Methyl Cellulose (HPMC), and sodium Carboxy Methyl Cellulose (CMC Na) derivatives are commonly used in ocular formulations. The viscosity raising qualities that cellulose derivatives possess are particularly beneficial and can be put to good use in polymer based ophthalmic formulations in order to improve bioavailability. These macromolecules also exhibit potential promise for use as carriers in the topical administration of drugs to the eye. Moreover, the swelling properties, chemical properties, and structural morphology of these derivatives have a significant impact on the release mechanism of the drugs placed into these systems.

Polysaccharides such as gellan gum have the ability to trigger the formation of ion sensitive hydrogels. This linear anionic heteropolysaccharide is formed from a tetra saccharide repeating unit of rhamnose, glucuronic acid, and glucose in the ratio 1:1:2. Gellan is made up of functional groups such as hydroxyl and carboxylic, and these groups have the potential to interact with other polymers through electrostatic attractions and/or hydrogen bonding. When monovalent or divalent cations are present, a low-acetyl gellan gum goes through the process of gelation. Upon instillation as a liquid solution into the cul-de-sac, the electrolytes in the tear fluid, particularly Na^{+}, Mg^{2+} and Ca^{2+} cations, are known to cause gel formation of the polymer. As a result of incorporating optimal amounts of calcium gluconate into gellan formulations, Simulated Tear Fluid gels (STF) with gellan calcium gluconate have a significantly greater strength than gellan alone mixed with STF. Gelation can be induced by either a temperature sensitive or a cation induced mechanism. Gelation may occur through a process that begins with the formation of double helical junction zones, which is then followed by the aggregation of double-helical segments into a three dimensional network through hydrogen bonding with water and complexation with cations [11].

Galactomannans and a few of its derivatives, in particular Locust Bean Gum (LBG), have been proposed as constituents for the manufacture of new topical ophthalmic compositions that are able to alleviate some of the issues that are associated with standard ophthalmic solutions, suspensions, or ointments. In an ophthalmic formulation containing galactomannans and cross linkers such as borates, specific polysaccharide blends enable gelation after contact with artificial tears, indicating a better pre-corneal residence and local sustained release of different drugs, such as Timolol Maleate (TM) and Dorzolamide Hydro Chloride (DHCL).

It is necessary for the Active Pharmaceutical Ingredient (API) to be dissolved in lachrymal fluid and to overcome the barrier posed by the tear film in order to achieve maximal penetration. In order to assure optimal permeation, a steady concentration of API should be maintained near the corneal epithelium. The fact that the APIs used in ophthalmology are almost all lipophilic compounds with low water solubility presents a major obstacle. Application of solubility enhancer additives, such as Cyclodextrins (CD), may be the initial step in optimizing ophthalmic formulations. CDs are

examples of cyclic oligosaccharides that contain -(1,4)-linked-D-glucopyranose units. The bacterial breakdown of starch in nature results in the formation of three different types of CD: α-CD with 6, β-CD with 7, and γ-CD with 8 glucopyranose units. Due to the orientation of hydroxyl groups, the exterior surface of these molecules is hydrophilic because they form hydrogen bonds with surrounding water molecules. Because the environment inside the cavity of CDs is hydrophobic, it is possible for an inclusion complex to be created with lipophilic substances through interactions such as hydrogen bonds, van der Waals forces, and charge transfer. The free CD and drug molecules, as well as the complex, come to a state of dynamic equilibrium when they are exposed to aqueous conditions. After being applied to the surface of the eye, only the free lipophilic molecule will be able to pass through the cornea; the hydrophilic CD will be left behind and will eventually be removed *via* the nasolacrimal pathway [12].

Furthermore, increased lacrimation and tear turnover after the administration of ocular formulations most frequently contribute to a short precorneal residence period, which in turn results in poor drug absorption. Intriguingly, the addition of Hyaluronic Acid (HA) into drug containing ophthalmic solutions can increase drug retention in tear fluid as well as drug contact time with the ocular surface, hence enhancing drug bioavailability. Viscosity, bio adhesion (also known as muco adhesion), and physical attachment are thought to play a significant role in the underlying mechanisms that are responsible for drug retention. HA may also be cross-linked and produced as films or contact lenses in order to extend drug release, drug action, and/or precorneal residency.

The efficacy of Tamarind Seed (TSP) for ocular preparations is currently the subject of extensive investigation. Due to its mucoadhesive qualities and pseudoplastic rheological behavior, TSP has been reported in few studies to be beneficial as an artificial tear for the treatment of dry eye syndrome. In addition to this, TSP has a high viscosity and a unique mucoadhesive strength, which makes it a potential choice for enhancing the pre-corneal residence time of several topical ocular formulations (Table 1).

Table 1. Single/modified polysaccharide polymers in glaucoma drug delivery applications.

Polysaccharides (PS) used	Type of formulation	Therapeutic agents	Action mechanism	Therapeutic effects
Galactomannans	Nanoparticles	DHCL	The polymer matrix contains hydrophilic drug molecules that are transported along long diffusion paths, causing sustained release of the drug.	Optimized nanoparticles showed higher corneal permeation (87.88% in 12 h), maximum IOP reduction (33.56%) after 4 h and the reduction in IOP was sustained till 12 h (16.12%).
LBG	Gel	PH	Increase viscosity of LBG in polymer solution results in effective bio adhesion, which retains the formulation in contact with the eye for a long period of time.	The formulation (3% w/w of LBG, 100 mg cholesterol, 40 mg PH) showed higher bio adhesive strength (2564 ± 0.39 dynes/cm^2), higher stability while slower drug release in 8 h.
CMC Na	Niosomal gels	TM	The entrapment of TM in CMC Na chains at higher polymer concentrations as well as higher viscosity and it is structured by its close proximity to those polymer molecules thus increasing the diffusional resistance.	Formulations showed a sustained release within 24 h (96% and 97.10%, respectively), higher stability (t90 values of 78.05 and 87.6 days), and increased the bioavailability of TM by 1.5–1.6 times than marketed TM.
EC	Micro particles	TM	The possible barrier involved in restricting the drug release could be the long tortuous pathway created by the matrix of EC.	Microparticles laden hydrogel delivered drug up to 48 hours (zero order kinetics) with low drug loading of 50 µg.
HPMC	*In situ* gels	NF	Hydrophobic nature of NF and HPMC form tight gel	The in situ gels showed sustained *in vitro* release of NF

			structures *via* hydrogen bonding in the aqueous solution, which delays the release rate of the drug.	where about 76% of the loaded drug was released over 12 h and a 45.83 ± 2.91% reduction in the IOP, with no sign of toxicity or irritation to the eye in rabbits.
TSP	Film	TM	Controlled drug release due to the TM molecule may be interlocked in between the gel network structures as the polymer mesh becomes more condensed due to the addition of TSP, and gel porosity decreases.	The TM release from the films was found to be controlled over a period of 8 h and reduce the intraocular pressure for 24 h in a more efficient manner than the eye drops.
Gellan gum	*In situ* gel	BLZ	Gelation reduced the rate of diffusion and erosion of polymers and associated drugs, thereby enhancing drug retention.	The release of BLZ from in situ gels in tear fluid solution occurred after more than 12 h, and IOP decreased slightly by 18.2% after 1 h before slowly increased to 18.6 mmHg below baseline values after 6 h.
βCD	Hydrogel contact lens	Puerarin	The delayed release was a result of enhanced interaction between drug molecule and hydrogel network, which coming from inclusion associations between β-CD and drug molecules and barrier of crosslinking.	Sustained and stabilized release was detected within 48 h. IOP of eye continuous decreased with time until the balanced IOP of 13 mmHg had been reached during the detection time of 5 days.
HPβCD	NLS	BLZ	The sustained release profile due to BRZ might release from the dissociated inclusion complex inside NLS followed by diffusion out of the nanoliposomes and dispersion through the dialysis bag.	A sustained release phase was observed in NLS within a period of 9 h (1–10 h). Furthermore, IOP was significantly lower in the NLS group at any time point from 2 to 12 h.
HA	Contact lens	TM	The diffusion of the tear fluid from the aqueous channels of the contact lens matrix into the highly resistant cross-linked structure of implant matrix, followed by the drug diffusion into the release media.	HA containing contact lens showed sustained release up to 96 h, and reduction in IOP till 144 h with low drug loading.
CS	Ocular inserts	BRT	The slow erosion of the gel due to neutrality of the medium pH, which did not induce the protonation of glucosamine amino groups of the chitosan.	Inserts provided the controlled release of BT (34 µg per day) for 30 days without a burst effect.
CMC/HPC/TMC	LNPs	TET	The viscosity and the electrostatic effect of TET-LNPs modified by cationic materials extended the contact time between TET and the cornea, thereby prolonging the action time of the drug.	Compared with CMC-TET-LNPs and HPC-TET-LNPs, TMC-TET-LNPs had longer corneal retention time (After 12 h, approximately 76.1% of TET had been released from TMC-TET-LNPs).

HGC	Thermo-sensitive gel	BRT	Improved the preocular retention of BRT due to a thermally induced increase in viscosity with the formation of a physical network.	The thermos-sensitivity of HGC could be successfully utilized to prolong its retention on the preocular surface and thus can enhance ocular bioavailability, leading to a 2-fold increase in the IOP-lowering duration compared with marketed BRT.
Galactosylated Chitosan	Nanoparticles	BRT	Prolonged retention period due to the ionic interaction between positively charged amino groups of chitosan and negatively charged sialic acid residues in the mucous layer of the cornea.	Nano-brimonidine is also more effective at ten-times lower concentration (0.2 mg/mL) than the free brimonidine (2 mg/mL), with only 33% release in 24 h.
Quaternized chitosan	Hydrogel	TM	The ionic interaction in the hydrogel effectively strengthened the cross-linked network and confines the drug molecules in the strong crosslinked network.	TM was sustained released from the porous architecture of hydrogel over 1 week.

Note: LBG: Locust Bean Gum; CMC Na: Sodium Carboxymethyl Cellulose; EC: Ethyl Cellulose; HPMC: Hydroxypropyl Methyl Cellulose; TSP: Tamarind Seed Polysaccharide; βCD: β-cyclodextrin; HPβCD: Hydroxypropyl β-cyclodextrin; HA: Hyaluronic Acid; CS: Chitosan; CMC: Carboxymethyl Chitosan; HPC: Hydroxypropyl Chitosan; TMC: Trimethyl Chitosan; HGC: Hexanoyl Glycol Chitosan; NLS: Nanoliposomes; LNPs: Lipid Nanoparticles; DHCL: Dorzolamide Hydrochloride; PH: Pilocarpine HCL; TM: Timolol Maleate; NF: Nifedipine; BLZ: Brinzolamide; BRT: Brimonidine Tartrate; TET: Tetrandrine.

Polysaccharide based formulations for glaucoma treatment

It is believed that excessive levels of IOP are the major cause of the glaucoma. The only potential treatment strategy that can slow or stop the course of glaucoma is to reduce the levels of IOP that are abnormally high (which leads to vision loss) in glaucoma patient. However, medical therapy presents a distinct set of obstacles for the long-term treatment of glaucoma. For instance, purchasing, applying, and using IOP lowering medications consistently and at the proper time are the essential steps to achieving the desired result. The results of an observational study conducted in the United Kingdom revealed that over half of the 278 patients investigated had poor adherence. Several strategies are being researched with the goal of improving glaucoma medical adherence, including the use of financial incentives and smartphone based applications. Despite the promise of these methods, patients should still be actively involved in instilling the agents. Moreover, new drugs require a lot of time and expensive to develop, so more effective and safer methods of administering drugs will benefit disease treatment. To be more specific, the utilization of natural polymers in drug delivery presents unique opportunities for the development of techniques for sustained ocular delivery. Using polymers as a carrier, one can bypass the shortcomings of topical delivery and the adverse effects associated with more invasive techniques. A controlled drug release can be achieved over a prolonged period of time by preparing polymer based drug formulations for glaucoma. For any drug delivery system therapy to be effective, the drug delivery system must fulfill three major goals: (1) drug release must be targeted; (2) drug release should be controlled; and (3) the drug should maintain therapeutic efficacy at adequate dose levels. Researchers have developed formulations for glaucoma treatment using natural polymers, including polysaccharide-based polymers. By prolonging and sustaining the pharmacological activity of drug molecules, these systems could be able to reduce the need for frequent medical interventions, thus minimizing side effects (Table 2).

Table 2. Polysaccharide polymer mixtures in glaucoma drug delivery applications.

Polysaccharide mixtures used	Type of formulation	Therapeutic agents	Action mechanism	Therapeutic effects
CS-P	Nanocapsules	BLZ	Sustained drug release can be described by the entrapment of BNZ molecule within the polymer matrix, as well as travel longer path of diffusion of drug molecule from polymer matrix of nanocapsules.	The formulation (9 mg of CS, 18 mg of P) showed sustained drug release of 76.89 ± 0.25 % at 8 h and maintained 7.51 ± 0.65% sustained IOP lowering effect over a period of 8 h.
SA-CS	Nanosheet	Latanoprost and TM	The adhesiveness of SA-CS, which may be controlled with the thickness of the nanosheet and leads the slow and sustained drug release.	Nanosheet (3 layered) released only 25% of latanoprost and timolol over a period of 48 h, and reduced IOP from 23.1 ± 1.4 mm of Hg (Baseline) to 12.2 ± 1.2 mm of Hg (9th day).
	Nanoparticles	TM	Ionic interactions between carboxylate groups of sodium alginate and ammonium groups of chitosan to create a stable polymeric complex are leads to control the drug release through the cornea.	A burst release of about 20% took place in the first hour and approximately 35% of TM was released after a span of 5 h. The cornea penetration of TM loaded in nanoparticles was twice than that of TM.
	Coating	BRT	Sustained drug release due to the fact that the addition of chitosan provided a coating on the alginate beads surface increasing cross-linking density and decreasing pore size due to the polycationic property of chitosan.	Less than 40% of the brimonidine was released after 2 h compared to simple formulation of brimonidine solution which showed more than 80% release after 2 h.

	Hydrogel ball	TM and LVFX	ZnO modified biochar was employed as a polymer filler to boost the crosslinking density of HB (composed of SA-CS) and as a photo thermal conversion material to adjust the sustained release dose of drugs by near infrared irradiation to obtain a more tailored IOP lowering effect.	The release of LVFX and TM can be sustained *in vitro* for 9d, 17d, respectively. After implanting the HB into rabbit eyes, IOP returned to the normal range in 1 week and was maintained more stably in the following week.
	Microspheres	RAPA	Electrostatic interaction between carboxyl groups of the alginate and the amino group of chitosan may produce a compact surface layer that sustain the Rapamycin release.	After 49 days, the cumulative release rate of the microspheres reached 94.07% and the sustained release effect was significant within 45 days. Also, effectively inhibited the proliferation of fibroblasts and neonatal collagen fiber as well as no obvious inflammation or infiltration.
SA-P	*In situ* gel	BRT	An increase in the viscosity and low spread-ability of formulations resulted in delayed release of BRT and considerably less reduction in IOP.	The SA-P formulation released 76.04% of BRT in 8 h but produced only a small reduction in IOP.
SA-HPMC	*In situ* gel	DHCL	Sustained drug release and prolonged precorneal residence of the SA-HPMC formulation due to convert into transparent gel	*In vitro* drug release was found to be 91.27 ± 0.61% over a period of 10 h, and a maximum mean difference of 27.4% in

			via diffusion and mucoadhesive properties.	lowering IOP was observed between control and treated eyes.
EC-HPMC	Ocular inserts	DHCL and TM	Due to hydrophobic property, EC can produce a tight and nonporous matrix, inhibiting water penetration and slowing drug release.	Prepared ocuserts showed slow release of both drugs (88.8 ± 8.1% and 98.9±1.3% of DHCL and TM was released, respectively) up to 24 h with no signs of eye sensitivity.
SA-EC	Ocular inserts	TM	Sustained release due to addition of hydrophilic polymer (SA), the surface of inserts was easily wetted by tear fluids hence easy facilitation of drug release was seen but hydrophobic polymer (EC) acts as a release retardant.	The optimized ocuserts formulation (0.2% SA, 0.4% EC) showed 83.29 % drug released till 12 h, and the reduction in IOP was maintained for a period of 24 h, while it was recorded only for 4 hours in case of marketed eye drops.
HP-β-CD-HA	Film	ACZ	Enhanced the precorneal drug residence time because of a greater initial driving force for ACZ diffusion due to the larger concentration gradient.	The remarkable decrease of IOP in normotensive rabbits over the time, which reached the lowest point 6 h after the biofilm administration.

Note: CS-P: Chitosan-Pectin; SA-CS: Sodium Alginate-Chitosan; SA-P: Sodium Alginate-Pectin; SA-HPMC: Sodium Alginate-Hydroxyl Propyl Methyl Cellulose; EC-HPMC: Ethyl Cellulose-Hydroxyl propyl Methyl Cellulose; SA-EC: Sodium Alginate–Ethyl Cellulose; HP-β-CD–HA : Hydroxypropyl β-cyclodextrin-Hyaluronic Acid; HB: Hydrogel Ball; BLZ: Brinzolamide; TM: Timolol Maleate; BRT: Brimonidine Tartrate; LVFX: Levofloxacin; RAPA: Rapamycin; DHCL: Dorzolamide Hydrochlorid; ACZ: Acetazolamide.

Single polysaccharide

In ocular delivery, the topical route is preferred due to its convenient and affordable nature. Unfortunately, the most

prevalent topical drug delivery systems currently available are largely ineffective because of rapid and extensive pre corneal drug loss, which is caused by blinking and tear drainage through the lachrymal drainage system. Thus, novel ophthalmic dosage forms are being developed in order to solve the difficulties associated with conventional ophthalmic therapy and improve corneal drug absorption. Researchers are now investigating nanotechnology based drug delivery systems as a method of increasing efficacy, enhancing patient compliance, and reducing systemic side effects. To address this, Mittal & Kaur developed bio-adhesive polymeric nanoparticles for ocular delivery of DHCL using derivatized Leucaena leucocephala galactomannan. The optimized nanoparticles showed higher corneal permeation (87.88% in 12 h), maximum IOP reduction (33.56%) after 4 h and the reduction in IOP was sustained till 12 h (16.12%). Furthermore, the polymer matrix contains hydrophilic drug molecules that are transported along long diffusion paths, causing sustained release of the drug [13].

It is also known as Pilocarpine HCl (PH), which has been used for treating chronic open-angle glaucoma for over 100 years. Nevertheless, when PH was applied to the eye in the form of an eye drop, it had a poor ocular bioavailability (1-3%), and its precorneal residence period was very short. To minimize these problems, Jain, et al. developed and evaluated LGB-based niosomal gel formulations containing PH to achieve prolonged precorneal residence time and improved bioavailability. The formulation (3% w/w of LGB, 100 mg cholesterol, 40 mg PH) showed higher bio adhesive strength (2564 ± 0.39 dynes/cm^2), higher stability while slower drug release in 8 h. Increase viscosity of LBG in polymer solution results in effective bio-adhesion, which retains the formulation in contact with the eye for a long period of time [14].

Since the eye has several defense systems that make it challenging to acquire a high concentration of drugs in the desired location, delivering drugs successfully to the eyes is exceedingly challenging. A variety of ocular dosage forms such as suspensions, solutions, ointments etc., are still acceptable. Due to inadequate bioavailability, production of tear, corneal epithelial impermeability, transient residence time, and non-productive absorption, these dosage forms are no longer sufficient to treat various eye illnesses such as glaucoma. Nowadays, niosomes are employed to enhance the bioavailability of drugs. Since niosomes make intimate contact with corneal and conjunctival surfaces, they have an advantage over most ophthalmic drug delivery systems for ocular drug absorption. Considering that, Ramadan, et al. developed niosomal gels loaded with Timolol Maleate (TM) for prolonged duration and improved bioavailability for glaucoma treatment. The selected formulations were incorporated into CMC Na. Formulations a containing 3% CMC Na showed a sustained release within 24 h (96% and 97.10%, respectively), higher stability (t 90 values of 78.05 and 87.6 days), and increased the bioavailability of TM by 1.5–1.6 times than marketed TM. The authors explained that the entrapment of TM in CMC Na chains at higher polymer concentrations as well as higher viscosity and it is structured by its close proximity to those polymer molecules thus increasing the diffusional resistance and causing sustained drug release [15].

Numerous researchers have been working to develop therapeutic contact lenses that are capable of sustained drug administration as a treatment for glaucoma. By developing an extended-release device, such as contact lenses, glaucoma therapy could potentially minimize the problem of non-compliance associated with eye drops. Furthermore, contact lenses were found to increase bioavailability as well as reduce side effects, which ultimately led to better clinical outcomes and better care of glaucoma patient. TM side effects would also be avoided with this novel drug delivery method. For this purpose, Maulavi, et al. develops the TM loaded EC micro particles laden hydrogel material that can be used as extended wear contact lens. Micro particles laden hydrogel delivered drug up to 48 h (zero order kinetics) with low drug loading of 50 µg. The possible barrier involved in restricting the drug release could be the long tortuous pathway created by the matrix of EC. In another study, using modified cast moulding technology, Desai and coworkers developed a novel approach to developing TM and HA loaded semicircular acrylate rings implanted contact lenses. The aimed was to treat glaucoma and to provide comfort to the patient's eye using single contact lens, which co-deliver TM (anti-glaucoma agent) and HA (comfort enhancing agent). HA containing contact lens showed sustained release up to 96 h, and reduction in IOP till 144 h with low drug loading. The mechanism of the extended drug delivery involves the diffusion of the tear fluid from the aqueous channels of the contact lens matrix into the highly resistant cross linked structure of implant matrix, followed by the drug diffusion into the release media.

Furthermore, a study by El-Feky, et al. aimed to prepare Nifedipine (NF) loaded *in situ* gel, which composed of HPMC to achieve local and sustained effects on the eye controlling IOP. Since the prepared *in situ* gel is able to extend the ocular residence time, the frequency of dosing can be decreased resulting in better patient acceptance and the outcomes of the therapy. The *in situ* gels showed sustained *in vitro* release of NF where about 76% of the loaded drug was released over 12 h and a 45.83 ± 2.91% reduction in the IOP, with no sign of toxicity or irritation to the eye in rabbits. Hydrophobic nature of NF and HPMC form tight gel structures hydrogen bonding in the aqueous solution, which delays the release rate of the drug [16].

Recently, TSP based hydrogel has been used in the development of an ocular drug delivery system to treat glaucoma, both as a film forming and release controlling agent. To overcome the problems associated with eye drops, Kulkarni, et al. developed controlled release ocular films of TM using natural hydrogel from *Tamarindus indica* seeds as a sustaining and film-forming agent. The TM release from the films was found to be controlled over a period of 8 h and reduce the intraocular pressure for 24 h in a more efficient manner than the eye drops. Controlled drug release due to the TM molecule may be interlocked in between the gel network structures as the polymer mesh becomes more

condensed due to the addition of tamarind seed polysaccharide, and gel porosity decreases.
Moreover, it is believed that *in situ* gelling materials based on gellan gum are the most promising delivery systems for increasing ocular bioavailability. The gels formed are transparent, flexible, and do not cause irritation to the eye, making it possible to continue supplying drug molecules without compromising the comfort of the patient for long periods. Recently, *in situ* gel made from gellan gum have been utilized to provide sustained ocular delivery of Brinzolamide (BLZ) for the treatment of glaucoma. The release of BLZ from *in situ* gels in tear fluid solution occurred after more than 12 h, and IOP decreased slightly by 18.2% after 1 h before slowly increased to 18.6 mmHg below baseline values after 6 h. Gelation reduced the rate of diffusion and erosion of polymers and associated drugs, thereby enhancing drug retention.
Furthermore, to improve BLZ local glaucomatous therapeutic effect, Wang et al. encapsulated BLZ-hydropropyl-β-cyclodextrin (HP-β-CD) inclusion complex (HP-β-CD/BRZ) into Nano Liposomes (NLS). A sustained release phase was observed in NLS within a period of 9 h (1–10 h). Furthermore, IOP was significantly lower in the NLS group at any time point from 2 to 12 h. The sustained release profile due to BLZ might release from the dissociated inclusion complex inside NLS followed by diffusion out of the nanoliposomes and dispersion through the dialysis bag. Another study used hydrogel contact lenses composed of β-CD to reduce IOP in comparison to commercial eye drops. The results showed that sustained and stabilized release was detected within 48 h. IOP of eye continuous decreased with time until the balanced IOP of 13 mmHg had been reached during the detection time of 5 days. The delayed release was a result of enhanced interaction between drug molecule and hydrogel network, which coming from inclusion associations between β-CD and drug molecules and barrier of crosslinking.
It is worth noting that the use of ocular inserts as a therapeutic alternative to conventional eye drops, could overcome the drawbacks of the conventional treatments for glaucoma. For instance, CS based mucoadhesive inserts with Brimonidine Tartrate (BRT) have been designed to reduce IOP in glaucoma patients. A part of BRT was physically diffused within the polymeric chains of the CS as an amorphous form, as revealed by the inserts. The remaining portion was crystalline in nature and distributed on the inserts surfaces. It appears that the drug and polymer did not interact chemically, which caused the water to be absorbed by the polymer chains. Inserts provided the controlled release of BRT (34 µg per day) for 30 days without a burst effect. The hydration led to the gel formation, which controlled the drug release. A neutral pH of the medium further prevented erosion of the polymer and controlled lixiviation of the drug over a long period. During early studies, CS and its derivatives coated nanocarriers such as lipid nanoparticles (LNPs) and liposomes were reported to provide higher corneal permeation. In a study of Li, et al. three different CS, namely Carboxy Methyl Chitosan (CMC), Hydroxypropyl Chitosan (HPC) and Tri Methyl Chitosan (TMC) were used as cationic materials to prepare Tetrandrine Lipid Nanoparticles (TET-LNPs) for the treatment of glaucoma. Their findings revealed that compared with CMC-TET-LNPs and HPC-TET-LNPs, TMC-TET-LNPs had longer corneal retention time (After 12 h, approximately 76.1% of TET had been released from TMC-TET-LNPs). The viscosity and the electrostatic effect of TET-LNPs modified by cationic materials extended the contact time between TET and the cornea, thereby prolonging the action time of the drug. In another study, Barwal, et al. has developed a new and simple method for the synthesis of monodisperse ultrasmall (28 ± 5 nm) nanobrimonidine using galactosylated chitosan. The results showed that nano-brimonidine is also more effective at ten-times lower concentration (0.2 mg/mL) than the free brimonidine (2 mg/mL), with only 33% release in 24 h. Prolonged retention period due to the ionic interaction between positively charged amino groups of CS and negatively charged sialic acid residues in the mucous layer of the cornea. Also, to overcome the issue of ocular bioavailability of conventional eye drop, Cho et al. developed a thermosensitive Hexanoyl Glycol Chitosan (HGC) as a carrier for topical drug delivery to the eye. HGC was synthesized by the N-hexanoylation of glycol chitosan. The thermos-sensitivity of HGC could be successfully utilized to prolong its retention on the preocular surface and thus can enhance ocular bioavailability, leading to a 2 fold increase in the IOP-lowering duration compared with marketed BRT. The improvement of the preocular retention of BRT due to a thermally induced increase in viscosity with the formation of a physical network. Although several researchers exploited chitosan-based thermosensitive hydrogel for ophthalmic applications in the recent years. However, the use of this thermogel has been limited by non-transparency, relatively low solubility and prolonged gelation time. Considering that, Pakzad, et al. develop quaternized chitosan-based transparent thermo sensitive hydrogel with TM. The TM was sustained released from the porous architecture of hydrogel over 1 week. The possible reason of sustained release of TM that the ionic interaction in the hydrogel effectively strengthened the cross linked network and confines the drug molecules in the strong crosslinked network [17].

Polysaccharide mixtures

Several literatures stated that the combination of polysaccharide is more effective as compared to single polysaccharide. In this section we have discussed some important polysaccharide polymers and their combinations employed for glaucoma treatment.
Although CS can be used as an ingredient in controlled drug release matrices, the mechanical strength of the membrane is very low, making the membrane fragile. Moreover, as CS has low hydrophilicity properties, it can be chemically and physically modified to increase its mechanical strength and hydrophilicity. Adding anionic polysaccharides, which have a higher hydrophilicity than CS, is one of them. It is possible for P to increase the

hydrofility and mechanical properties of CS membranes. The carboxyl group in pectin makes it soluble in water. CS-P is known to generate a polyelectrolyte complex that can encapsulate drugs and bioactive molecules. To address this, Dubey et al. prepared BLZ loaded CS-P mucoadhesive nanocapsules by polyelectrolyte complex coacervation method for ocular delivery and evaluated for its anti-glaucoma therapy. The formulation (9 mg of CS, 18 mg of P) showed sustained drug release of 76.89 ± 0.25% at 8 h and maintained 7.51 ± 0.65% sustained IOP lowering effect over a period of 8 h. Sustained drug release can be described by the entrapment of BLZ molecule within the polymer matrix, as well as travel longer path of diffusion of drug molecule from polymer matrix of nanocapsules. Similar to CS, low methoxylated pectin can form a rigid and stable gel upon crosslinking with calcium ions. Cross linking with calcium ions produces crosslinked pectin by the presence of free -COOH and -OH functional groups in pectin. The combination of Sodium Alginate-Pectin (SA-P) can facilitate sustained drug release from a drug encapsulating matrix due to the crosslinking property of pectin with calcium ions. Mittal and co-workers formulated *in situ* gelling eye drops by combining the SA-P with BRT drug. The SA-P formulation released 76.04% of BRT in 8 h but produced only a small reduction in IOP. An increase in the viscosity and low spread-ability of formulations resulted in delayed release of BRT and considerably less reduction in IOP.

In the recent years, nanosheets show interesting properties because of their nanometer thickness, including high transparency, high adhesiveness without any adhesive agents, and high flexibility. It is anticipated that unfavorable consequences would be minimized by applying a small quantity of biodegradable polymer to the ocular surface. Taking into consideration, a biodegradable nanosheet that is infused with an antiglaucoma ophthalmic medication could be a potential contender for a new drug delivery method for glaucoma. Wang, et al. have developed a novel layer by layer method that uses SA as the polyanion and CS as the polycation to create a latanoprost and TM loaded biodegradable nanosheet for the glaucoma drug delivery to the cornea. With the use of polyanions and polycations (SA-CS), multilayer nanosheets can load lipophilic and hydrophilic compounds without modifying them chemically. The results showed that nanosheet (3 layered) released only 25% of latanoprost and TM over a period of 48 h, and reduced IOP from 23.1 ± 1.4 mm of Hg (baseline) to 12.2 ± 1.2 mm of Hg (9th day). The adhesiveness of SA-CS, which may be controlled with the thickness of the nanosheet and leads the slow and sustained drug release. Furthermore, to control the release of TM through the cornea, Ilka, et al. synthesized TM loaded nanoparticles based on SA-CS. A burst release of about 20% took place in the first hour and approximately 35% of TM was released after a span of 5 h. The cornea penetration of TM loaded in nanoparticles was twice than that of TM. Ionic interactions between carboxylate groups of sodium alginate and ammonium groups of CS to create a stable polymeric complex are leads to control the drug release through the cornea. In another study, magnetic nanoparticles were coated with SA-CS and loaded by BRT to prepare a drug delivery system applicable in glaucoma treatment. Less than 40% of the BRT was released after 2 h compared to simple formulation of BRT solution which showed more than 80% release after 2 h. Sustained drug release due to the fact that the addition of CS provided a coating on the alginate beads surface increasing cross-linking density and decreasing pore size due to the polycationic property of CS. Inspired by lollipop, Wang et al. developed a multilayered TM and Levofloxacin (LVFX) loaded Hydrogel Ball (HB) based on SA-CS as well as decorated by zinc oxide-modified biochar as a new drug delivery system for glaucoma treatment. The release of LVFX and TM can be sustained *in vitro* for 9 d, 17 d, respectively. After implanting the HB into rabbit eyes, IOP returned to the normal range in 1 week and was maintained more stably in the following week. Also, sustained release microspheres of Rapamycin (RAPA) with SA-CS as polymer carriers were synthesized by ion crosslinking to lower the amount of RAPA in surgical areas, and to extend its action period. After 49 days, the cumulative release rate of the microspheres reached 94.07% and the sustained release effect was significant within 45 days. Also, effectively inhibited the proliferation of fibroblasts and neonatal collagen fiber as well as no obvious inflammation or infiltration. Electrostatic interaction between carboxyl groups of the SA and the amino group of CS may produce a compact surface layer that sustained the RAPA release [18].

Few researchers hypothesized that SA and HPMC are hydrophilic polymers with high water solubility. Consequently, a drug carrier formed by them alone will not be able to control drug release since it will be water soluble. As a result, modifications or cross linking of these highly water soluble polymers are critical to fabricating a sustained-release drug carrier system. Recently, an efficient *in situ* gel forming system of DHCL for the treatment of glaucoma has been formulated using the mixture of SA-HPMC by Kataria, et al. *In vitro* drug release was found to be 91.27 ± 0.61% over a period of 10 h, and a maximum mean difference of 27.4% in lowering IOP was observed between control and treated eyes. Sustained drug release and prolonged precorneal residence of the SA-HPMC formulation due to convert into transparent gel *via* diffusion and mucoadhesive properties.

DISCUSSION

It is well documented that the ocular inserts composed of synthetic polymers formed through polymerization crosslinking or physiochemical crosslinking possess physicochemical stability and excellent mechanical strength. In contrast, ocular inserts made from natural polymers or synthetic polymers with a single network and microporous structure have a limitation in their ability to maintain sustained and desirable levels of drug concentration for a long period of time. Considering that, Nair and co-workers combined the SA-EC to develop TM loaded ocuserts for glaucoma

treatment. The optimized ocuserts formulation (0.2% SA, 0.4% EC) showed 83.29 % drug released till 12 h, and the reduction in IOP was maintained for a period of 24 h, while it was recorded only for 4 h in case of marketed eye drops. Sustained release of TM was recorded due to addition of hydrophilic polymer (SA), the surface of inserts was easily wetted by tear fluids hence easy facilitation of drug release was seen but hydrophobic polymer (EC) acts as a release retardant. In another study, to enhance patient compliance through providing controlled release of TM and DHCL drugs from EC and HPMC based polymer matrix, a novel ocuserts has been formulated by Abdou and Kandil. Prepared ocuserts showed slow release of both drugs (88.8 ± 8.1% and 98.9 ± 1.3% of DHCL and TM was released, respectively) up to 24 h with no signs of eye sensitivity. Due to hydrophobic property, EC can produce a tight and nonporous matrix, inhibiting water penetration and slowing drug release. Furthermore, a novel drug delivery film loaded with Acetazolamide (ACZ) has recently been able to combine desirable properties such as, biocompatibility, bio adhesion, absence of preservatives, lipophilic drug reticulation, and effectiveness in a single topical ocular drug formulation by combining HPβCD with HA. The remarkable decrease of IOP in normotensive rabbits over the time, which reached the lowest point 6 h after the biofilm administration. The film enhanced the precorneal drug residence time because of a greater initial driving force for ACZ diffusion due to the larger concentration gradient.

CONCLUSION

In summary, polysaccharides seem to be promising agents for anti-glaucoma drug delivery. Throughout this article, we described the various polysaccharides already used in the early stages of anti-glaucoma drug delivery. A number of drug delivery formulations based on polysaccharides for glaucoma treatment have shown superior efficacy over conventional dosage forms. These benefits include the drug's sustained and prolonged release, biocompatibility, good stability, patient compliance, ease of installation, and minimum chances of irritation. Numerous uses of polysaccharides in drug delivery systems for the treatment of glaucoma are currently in the early stages of development, with tremendous untapped innovation that could lead to substantial enhancements in the capability, quality, and convenience of these treatments.

In spite of the fact that polysaccharide based formulations offer a number of advantages, they are nevertheless susceptible to microbiological contamination, reduced viscosity during storage, and have an unregulated hydration rate. To circumvent these constraints, the modification of natural polysaccharides by cross linking, grafting, and mixing with natural and synthetic polymers is required. In a similar vein, the limited information regarding the mechanism of drug release by polysaccharides, as well as penetration enhancement decelerates the ongoing improvements in polysaccharide based drug delivery systems. In addition, the degradation of polysaccharides may affect the removal of material from the eye. If the rate of polymer degradation is slower than the rate at which the drug is released, this may result in "ghosts" of polymer that are empty and unnecessary and that remain in the eye for an excessively long time. Moreover, several publications have reported biocompatibility and no toxicity of polysaccharide-based formulations, but these conclusions should be treated with caution. A typical toxicity test involves cell viability tests (proliferation, inflammation, or viability), but the situation in the living eye is more complex. During extended treatment, many subtle mechanisms of toxicity can cause problems. Thus, polysaccharides-based formulations must be subjected to detailed immunological, biochemical, morphological, and functional testing before they can be accepted into clinical use.

Acknowledgement
Not applicable

Conflict of interest statement
The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Author contributions
Tanvir Ahmed: Conceptualization, investigation, data duration, writing original draft, writing review and editing
Md. Nazmul Islam: Data duration, investigation
Rina Monalisa: Data duration, investigation

REFERENCES

1. Patel KD, et al. Recent advances in drug delivery systems for glaucoma treatment. Mater Today Nano. 2022; 100178.
2. Wu Y, et al. Measures of disease activity in glaucoma. Biosens Bioelectron. 2022;196:113700.
3. Muramatsu C, et al. Detection of retinal nerve fiber layer defects on retinal fundus images for early diagnosis of glaucoma. J Biomed Opt. 2010;15:16021.

4. Chandramohan H, et al. Quality of Life and Severity of Glaucoma: A Study Using Glaucol-36 Questionnaire at University Kebangsaan Malaysia Medical Centre (UKMMC). Int Med J. 2017;24.
5. Lazcano-Gomez G, et al. Cost of glaucoma treatment in a developing country over a 5 years period. Med (Baltimore). 2016;95.
6. Varma R, et al. An assessment of the health and economic burdens of glaucoma. Am J Ophthalmol. 2011;152:515–522.
7. Urtti A, et al. Challenges and obstacles of ocular pharmacokinetics and drug delivery. Adv Drug Deliv Rev. 2006;58:1131–1135.
8. Han SB, et al. Application of novel drugs for corneal cell regeneration. J Ophthalmol. 2018.
9. Noecker R, et al. Effects of common ophthalmic preservatives on ocular health. Adv Ther. 2001;18:205–215.
10. Wise JB, et al. Ten year results of laser trabeculoplasty: Does the laser avoid glaucoma surgery or merely defer it?. Eye. 1987;1:45–50.
11. Ayyala RS, et al. Comparison of different biomaterials for glaucoma drainage devices: Part 2. Arch Ophthalmol. 2000;118:1081–1084.
12. Skuta GL, et al. Wound healing in glaucoma filtering surgery. Surv Ophthalmol. 1987;32:149–170
13. Zhao X, et al. Application of star poly (ethylene glycol) derivatives in drug delivery and controlled release. J Control Release. 2020;323:565–577.
14. Ni Z, et al. Recent research progress on polyphosphazene based drug delivery systems. J Mater Chem B. 2020;8:1555–1575.
15. Besford QA, et al. Glycogen as a building block for advanced biological materials. Adv Mater. 2020;32:1904625.
16. Allyn MM, et al. Considerations for Polymers used in Ocular Drug Delivery. Front Med. 2963.
17. ElHoffy NM, et al. Glaucoma: Management and future perspectives for nanotechnology based treatment modalities. Eur J Pharm Sci. 2021;158:105648.
18. Kianersi S, et al. Alginate nanoparticles as ocular drug delivery carriers. J Drug Deliv Sci Technol. 2021;66:102889.