Original Article

Ocular Drug Delivery With Special Reference To Natural Polymer

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Abstract

Because of the distinctive anatomical and physiological barriers, ocular medication administration is a particularly difficult task. The scientists were required to create novel formulation to medications to ocular tissues at a controlled rate to decrease the frequency of instillations due to the low ocular bioavalibility (10%) obtained from standard formulation. Natural polymers have demonstrated the ability to topically deliver medications throughout the small precorneal region and discharge them over an extended period of time. The discussion covers the key elements that must be taken into account when creating ophthalmic formulations, such as the features of the drug molecule and the polymer that influence the release rate. Chitosan, Polyvinyl alcohol, Sodium alginate, and Nanocrystalline cellulose are examples of novel polymers.

Key words: Biodegradable, natural polymers, biocompatible, ocular drug delivery

INTRODUCTION

Due to different anatomical and physiological barriers, ophthalmologists and drug delivery scientists have traditionally had difficulty delivering drugs into the eye. Distinctive ocular barriers stop xenobiotics from entering the eye as well as the active absorption of medicines. [1,2]Improved drug bioavailability and regulated drug release at the site of action, which can get through different ocular obstacles, should be included in the design of the perfect delivery system.[3] Traditional ocular treatments for anterior and posterior segment diseases, respectively, include topical eye drops and intravitreal injections of anti-vascular endothelial growth factor agents.[4,5] Modern innovations for prolonged and regulated medication release include iontophoresis, implants, contact lenses all of which are used to treat disorders of the anterior ocular section. The approval of a number of intravitreal implants is the result of ongoing research into ocular drug delivery technology for diseases of the back of the eye.[6,7,8] Researchers are progressively adopting cutting-edge medication delivery technologies, like liposome, nanomicelles, nanoparticle, dendrimers, microneedle, nanowafers, to study both anterior and posterior disorders.[9] Innovative methods for the noninvasive delivery of strong treatment drugs are becoming more popular in order to increase patient compliance for back of the eye illnesses.[10,11] In this review paper, we explore ocular drug delivery technology' previous accomplishments, current innovations, and upcoming difficulties. This expert opinion also examines the difficulties that ocular medication delivery systems may face in the future and the therapeutic application of nanotechnology from the lab to the bedside.[13,14]

Recent studies on ocular medication delivery have concentrated on developing fresh, secure, and patient-pleasant formulations that could get around these difficulties and keep higher drug levels in tissues.[15] Therefore, in count to the traditional ophthalmic dosage forms like gels, ointments, aquous suspension and solutions, many researchers have worked hard to develop novel ocular drug delivery systems such as ions or thermosensitive in situ gelling polymers, Liposomes, dendrimers nanoparticles, and ocular films.[16,17] This is done in order to achieve higher bioavailability, controlled ocular delivery. These systems are believed to increase corneal penetration and bioavailability of the drug by extending precorneal retention, which enhances dose frequency and patient compliance.[18] The polymers employed for the delivery techniques should be safe, biocompatible, stable, mucoadhesive and nonreactive because they are intended for ocular uses.[19,20] Natural polysaccharides like Chitosan, nano cellulose and alginate have been researched for developing innovative drug delivery strategies in light of this.[21] Biodegradable polymers are a beneficial choice in the ongoing quest for appropriate polymers to replace environmentally resistant synthetic polymers because they shouldn't have any negative effects on environment .[22] The definition of biocomposite polymers is those that experience microbially driven chain scission that results in mineralization.[23] Contrarily, since polyethylene is not easily metabolised by living things, it must be treated as being essentially nonbiodegradable for all intents and purposes.[24] This might entail the emergence of more resilient residuals as well as the incorporation of polymer-derived carbon into the microbial biomass.[25,26] However, in the environmental evaluations, all residues should be deemed harmless and all carbon should be accounted for (carbon balance).[27] Furthermore, the microbial biomass and residue should ultimately be integrated into the natural geochemical cycle. The process of biodegradation is influenced by a wide range of variables, including the environment, tempreture, moisture, pH, oxygen trace minerals and salts, nutrition, and the type of the polymer. The thin, flexible polymer frameworks that may or may not include plasticizers are referred to as polymeric films.[28,29,30] In contrast to conventional drug dosage forms, film matrices have been regarded as an effective drug release platform due to their convenience of handling, affordable preparation, simple transportation, and high patient compliance.[31] A three-dimensional network of hydrophilic polymers that can absorb and hold a significant amount of water without dissolving is known as a hydrogel.The hydrogels' biocompatibility, biodegradability, in situ gelling ability, adaptability, swellability, hydrophilicity, viscoelasticity, stimuli sensitivity, bioresorbability, bioadhesiveness, and mucoadhesive .[32,33]

polymers	Advantages	Disadvantages
Natural polymers	➢ Water solubility enhancer. ➢ Better transparency and swelling properties. ➢ Biocompatible and biodegradable. ➢ competent of incorporating with drugs ➢ Less immunogenicity. ➢ Inertness. ➢ Less side effect	➢ Microbial and heavy metal contamination. ➢ Hydration abandoned rate ➢ Batch to batch dissimilarity. ➢ Slow rate of production. ➢ Difficult extraction process.

Table. 1: Classification of natural polymers

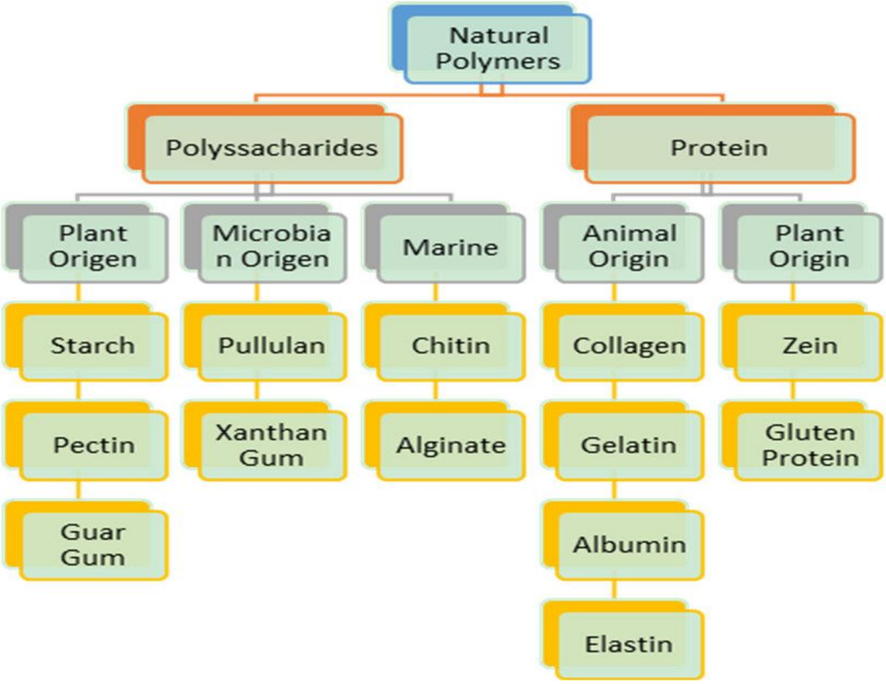
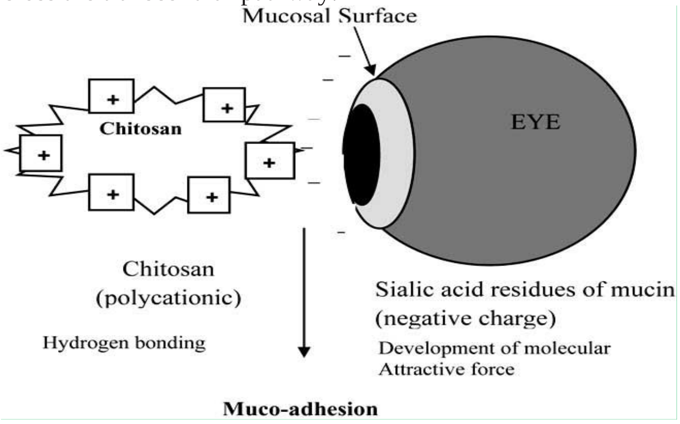


Fig. 1: Classification of natural polymers.[34]

CHITOSAN

Chitosan is a co-polymer of glucosamine and N-acetylglucosamine that is cationic in nature. It naturally exists in the cell walls of fungi.[35] It is made by alkaline deacetylating the chitin found in the lobster, crab, and crimps' crustacean shells. Chitin is deacetylated to produce chitosan, which lacks cellulose-like properties due to its 4 constituents, +ve charge, capacity to create polyelectrolyte complexes, ability to make nitrogen derivatives, and fundamental amino group chemistry.[36] It has the capacity to create films, which cellulose lacks. A deacetylation of 85 percent or more is favoured because to its improved biocompatibility and mucoadhesive properties. Strong mucoadhesion is a result of significant electrostatic interactions among the +ve charged amino groups within chitosan and the negatively charged sialic acid residues in mucus.[37,38] It is a biodegradable and non-toxic polymer. Chitosan is soluble at low pH (pH 5) but precipitates when the pH is raised to the physiological range (pH 7.4). In acidic and basic fluids, chitosan molecules pick up charges that cause them to swell, but not in neutral environments.[39] In comparison to polyanionic N-carboxymethyl chitosan and polycationic chitosan HCl, the latter extensively improved the formulation's residence time and drug penetration (vinyl alcohol) Improved insert erosion and transcorneal ofloxacin penetration were observed in polyethylene oxide (PEO-900) inserts distributed with chitosan-hydrochloride ofloxacin.[40] Compared to PEO inserts, the peak concentrations in the aqueous humour were much higher (more than the MIC 90%). Chitosan has the ability to break down corneal tight connections and increase the transcorneal diffusion of hydrophilic medications like acyclovir.[41] Trimethyl chitosan had no effect on tobramycin transport via the paracellular pathway, but it dramatically boosted the transcorneal transfer of dexamethasone via the transcellular route. Similarly, it was discovered that the luminous chitosan-hyaluronic acid nanoparticles had travelled across the transcellular pathway.[42,4 3]



24 hours of sustained drug release were provided by gatifloxacin ocular inserts that were chitosan-loaded and combined with gellan gum. Similar to Ciprocin, a mucoadhesive liposomal formulation of ciprofloxacin hydrochloride coated with chitosan increased precorneal retension and bioavailability which has 3 times more residence time than than marketed product.[44] As TMC molecular weight grew, precorneal retention was around three to five times better, and the bioavailability increased as well. High cyclosporine levels in nanoparticles with chitosan coatings, an association efficiency and loading were found. Nanoparticles was also impacted by an increase in chitosan content because more unneutralized NH3+ was produced on their surface.[45]

Chitosan 1% was used to create lyophilized sponge-like acyclovir ocular minitablets; these acyclovir minitablets outperformed HPMC, Carbopol 943P, Sodium carboxy methyl cellulose, Xanthan gum in terms of swelling rate and sustained release. When compared to the commercially available ointment (563.88 g/g.h).[46]

In comparison to pilocarpine in simulated tear and commercial eye drops, which were efficient for just 4.5 hour and 2.5 hour 4 correspondingly, the pupil size of rabbits treated with pilocarpine nanosuspension remained reduced for more than 5 hours.[47] Because of the forces of attraction, the positively charged chitosan-loaded nanosuspension was able to stay in touch with the negatively charged ocular surface for a longer period of time than the latter. Chitosan-coated timolol maleate niosomes effectively reduced intraocular pressure for 8 hours, but Carbopol_ coated and untreated niosomes were efficient for 6 and 2 hours, respectively, and commercial eye drops for just 1.5 hours. Commercial timolol maleate eye drop solution was used to reduce intraocular pressure in the contralateral eye, which was very low in the case of the chitosan-coated niosomal formulation.[48]

SODIUM ALGINATE:

It is a Sodium salt of alginic acid that is hydrophilic, colloidal, and has a hue ranging from white to buff. The cell walls of the Brown seaweeds Laminaria, Ascophylum contain alginic acid and Macrocystis.[49] D-mannuronic acid and L-glucoronic acid combine chemically to generate polyuronic acid. Because of its mucoadhesive properties, sodium alginate can produce low viscosity solutions even at high concentrations without causing any blurring.[50] Once daily dosing of the cartelol alginic acid ophthalmic solutions could replace the twice-day standard cartelol solution because they provided a continuous release for up to 8 hours. Sodium alginate show improved bioadhesive properties than hydroxyethyl cellulose. Gatifloxacin ophthalmic solutions provided a sustained release of the drug for more than 12 hours when formulated with varied concentrations of sodium alginate with or without sodium carboxymethyl cellulose. [51]

- The calcium chloride-crosslinked sodium alginate and hydroxypropylmethyl cellulose-made matrix type ciprofloxacin inserts were able to extend release from 1.5 to 2 days.
- The sodium alginate and chitosan–prepared surface crosslinked gatifloxacin sesquihydrate films demonstrated a long-lasting drug release for about 24 hours.
- Ciprofloxacin hydrochloride was released slowly over a period of more than five days using reservoir-type ocular inserts made with sodium alginate and sandwiched between polyvinyl acetate or eudragit films. The release of epidermal growth factor (EGF) from a few hours to several days was delayed by alginate—hydroxyethyl cellulose ocular implants that were crosslinked with calcium chloride.[52,53]
- The sodium alginate-prepared azithromycin inserts demonstrated sustained drug delivery over an 8-hour period and adhered to first-order release kinetics.
- Alginate microspheres filled with bovine serum albumin and embedded in a collagen hydrogel can be utilised as a corneal replacement for transplantation or as continuously releasing contact lenses. Due to 2 barriers—the hydrogel barrier and the microsphere barrier—a sustained release of bovine serum albumin was achieved through the

microsphere hydrogel matrices for 11 days. When divalent and trivalent cations, particularly calcium, are present, sodium alginate can form an ion activated in situ gel. Low quantities of calcium make a substance viscous.[54]

POLYVINYL ALCOHOL

A synthetic polymer called polyvinyl alcohol (PVA) is created by hydrolyzing polyvinyl acetate. It is a semi-crystalline polymer that is economically made and has demonstrated exceptional potential in a number of industries, including but not limited to food packaging, textiles, tissue engineering, wound healing, and drug delivery.[55] PVA's distinctive properties, counting its simple chemical structure, water solubility ,nontoxicity, bioadhesive properties, biocompatibility, elasticity, bioinertness, high swelling degree, water-solubility, non-toxicity, are beneficial in these various fields.[56] PVA is also biodegradable, and how much so depends on how many hydroxyl groups are present in the polymer chains' backbones. Over the years, researchers have investigated the polymer's adaptability to create glues, fibres, and hydrogels. However, when exposed to a biological environment, matrices are typically fragile. It's interesting to note that by chemically crosslinking the film matrixes using multifunctional reactive chemicals, such as glutaraldehyde (GTA), the mechanical performance can be improved.[57] PVA has outstanding compatibility with both natural and synthetic polymers thanks to its film-forming ability and other aforementioned characteristics.[58] In order to create PVA-based composite films with dramatically improved mechanical stability for drug delivery applications, various research groups have investigated this property. In order to overcome the limiting physicomechanical properties of PVA-based composite films, the research paradigm has more recently evolved toward the addition of diverse organic (like cellulose nanowhiskers) or inorganic (like clay, SiO2, or graphene oxide) filler materials.[59] It has been used in a variety of ophthalmic formulations, including eye drops, ocular solutions, and suspensions, as well as soft contact lenses, episcleral implants, vitreous substitutes, viscosity-enhancing polymers, ointment bases, and artificial tear substitutes for corneal wetting and the treatment of dry eye syndrome.[60]

- A 20-nor-20-deoxyguanosine-loaded PVA insert was created by Davies et al. to cure experimental herpes keratitis. Within seconds, the insert began to dissolve, and within an hour, it had fully dissolved.
- The antibacterial effectiveness of low and high molecular weight PVA inserts was tested by Balasubramaniam et al. From Eudragitcoated implants comprising PVA combined with Xanthan gum, jota carragenan, HPMC, glyceryl behenate and HCL hyaluronic acid, Saettone et al.[61]

NANOCELLULOSE:

Nanocellulose is a natural substance that may be obtained from a large variety of creatures, including plants, animals, and bacteria. It is renewable, biodegradable, and nanoscaled, and it has desirable features for use in the field of drug delivery systems (Babu et al. 2013). Because of its large surface area to volume ratio and high polymerization, nanocellulose is beneficial in drug delivery systems because it has a high loading and binding capability for therapeutic agents to control the drug release mechanism.[62] Advanced drug delivery systems can benefit from its exceptional qualities, including high mechanical strength, biocompatibility, stiffness and renewability,

Nanocellulose can be characterized into 3 types:

(1) Cellulose nanocrystal.
(2) Cellulose nanofibers.
(3) Bacterial cellulose.

Crystaline nanocellulose fibres are reported to be more efficient in reinforcing polymers than their microsized equivalents. Given adequate dispersion of the nanofibers in the matrix, interactions between nanosized particles result in the formation of a percolated network. (Angl`es and Dufresne, 2001).

- Khan et al (2010) investigated the effect of nanocellulose (0.1-1%) into methylcellulose-based film. They discovered that 0.25% CNC produces the best results, with pierce strength being unchanged (117%) and water vapour permeability (WVP) drastically declining (26%).
- In order to increase the barrier, mechanical and thermal properties of chitosan edible film. Azeredo (2010) optimised the effect of different quantities of nanocellulose (0-20g/100 g) and glycerol (0-30 g/100 g) (Azeredo et al., 2010).

polymers	Biological properties	Applications
Chitosan	➢ Biodegradable, Biocompatible, ➢ Hoemostatic action, ➢ mucoadhesive, ➢ antiinflamatory, ➢ analgesic action, ➢ antimicrobial	➢ Vaccine vector ➢ Wound dressing ➢ Combination therapy ➢ Reduce side effects ➢ Food preservation ➢ Warter purification
Sodium alginate	➢ Low toxicity ➢ Biocompatibility ➢ Biodegradability ➢ Gelling properties ➢ Thickening properties ➢ Good avaibility	➢ Preparation of pastes, creams, emulsions ➢ Textiles industries ➢ Dermatological preparation ➢ Used as general emulsifier
PVA	➢ High swelling degree	➢ Quick dissolver

	➢ Solubility ➢ Non-toxicity ➢ Bioadhesive ➢ Bio interness	➢ Drug delivery ➢ Tissue engineering
Nanocellulose	Nontoxic, high tensil strength, biodegradability,	Foodstuffs, biomedicines, textiles, food packaging, waste water treatment

CONCLUSION:

Due to their qualities and potential uses in domains relating to environmental preservation and the maintenance of physical health, natural polymers are chosen over synthetic polymers. Only a few of the aforementioned biopolymer groups are currently significant on the market. There aren't many brand-new ophthalmic drug delivery systems on the market right now, but current polymeric system research shows a lot of potential. Present time needs a multidisciplinary integration of novel delivery technologies to improve drug bioavailability at ocular tissue. Recent advancements in biomedical engineering, nanotechnology, and non-invasive drug delivery would make it possible to deliver required amounts of drugs to the ocular posterior segments for effective treatment of eye diseases.

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