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Review

Overview of biopolymers as carriers of antiphlogistic agents for treatment of diverse ocular inflammations

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Highlights

- Numerous eye inflammations pose troubles in vision functions.
- Low bioavailability by conventional drug delivery systems due to eye constraints
- Drug carriers ensuring improved bioavailability to the eye are need of the hour.
- Chitosan - most explored amongst all biomaterials for ocular delivery.
- Emergence of novel synthetic carriers in ophthalmology

Abstract

Inflammation of the eye is a usual clinical condition that can implicate any part of the eye. The nomenclature of variety of such inflammations is based on the ocular part involved. These diseases may jeopardize normal functioning of the eye on progression. In general, corticosteroids, antihistamines, mast

cell stabilizers and non-steroidal anti-inflammatory drugs (NSAIDs) are used to treat inflammatory diseases/disorders of the eye. There have been several attempts via different approaches of drug delivery to overcome the low ocular bioavailability resulting from shorter ocular residence time. The features like safety, ease of elimination and ability to sustain drug release have led to application of biopolymers in ocular therapeutics. Numerous polymers of natural origin such as gelatin, collagen, chitosan, albumin, hyaluronic acid, alginates etc. have been successfully employed for preparation of different ocular dosage forms. Chitosan is the most explored biopolymer amongst natural biopolymers because of its inherent characteristics. The emergence of synthetic biopolymers (like PVP, PACA, PCL, POE, polyanhydrides, PLA, PGA and PLGA) has also added new dimensions to the drug delivery strategies meant for treatment of ophthalmic inflammations. The current review is an endeavor to describe the utility of a variety of biomaterials/polymers based drug delivery systems as carrier for anti-inflammatory drugs in ophthalmic therapeutics.

Previous Next

Keywords

Ocular inflammations; Nanoparticles; Biodegradation; Aqueous humor

1. Introduction

The occurrences of inflammation have been well recognized and documented since the ancient times. Celsius explained the four striking symptoms of inflammation (rubor, calor, dolor, and tumor, or redness, heat, pain, and swelling) in 30 CE [1]. *Functio laesa* (dysfunction of the organs participating) added as 5th feature of inflammation in the work of Rudolf Virchow in the 1850s [2]. Inflammation encompasses host of pathophysiological events and varies individually such as acute or chronic, reversible or irreversible, organ specific or generalized however, one fact is correct above all that this is taking place via the agency of several mediators ranging from amines (histamine,5-HT), peptides (bradykinin,interleukin-1 IL-1) lipids (prostaglandins PGs, leukotrienes LTs)enzymes, complements and many more. The results from competitive antagonists acting on same receptors and inhibitor of synthesis studies confirm their role in inflammation [1], [2], [3]. In the late 19th century, Elie Metchnikoff brought the notion of phagocytosis, a basic component of innate immunity, subsequent to observing protozoa ingest particulate matter and testing blood leukocytes engulf foreign bodies. Inflammation play an important role in host defenses against infectious agents and injury, however it also leads to the pathophysiology of several chronic diseases like diabetes, cardiovascular disease, some cancers and bowel diseases, arthritis and osteoporosis [2].

Inflammation of the eye is a common clinical problem that may involve any part of the eye. Prostaglandins

(PGs) are regarded as mediators of the inflammatory process in many organs, including the eye. High levels of PGs have been demonstrated in aqueous humor of human and laboratory animals in some forms of ocular inflammation [4]. Role of cytokines [IL-l, IL-6, IL-S, tumor necrosis factor (TNF), granulocyte macrophage-colony stimulating factor (GM-CSF)] in ocular inflammation has been demonstrated in experimental animals [5]. Further, neurokinins (SP, NKA and NKB) are also involved in the modulation of the local ocular inflammation initiated by the surgical perforating trauma of the anterior pole. By increasing the vascular permeability SP, NKA and NKB make an important linkage by which the nervous system mediators contribute to the modulation of eye inflammatory responses whose intimate mechanisms are not entirely known yet [6].

2. Ocular inflammations

There are various ocular inflammatory eye diseases such as blepharitis, conjunctivitis, keratitis, scleritis and uveitis embracing iritis, iridocyclitis, choroiditis, chorioretinitis, retinitis etc., which upon worsening may impair normal functioning of the eye [7], [8], [9], [10], [11], [12], [13], [14], [15], [16], [17].

3. Treatment of ocular inflammations and drug delivery

There are four major categories of anti-inflammatory drugs used to provide therapeutic as well as prophylactic effects in eye inflammatory diseases viz. - corticosteroids, antihistamines, mast cell stabilizers and non-steroidal anti-inflammatory drugs (NSAIDs). There should be selection of an appropriate drug class based on pathophysiology of the eye condition. The physician must be very careful while primary care of ocular inflammatory conditions. Mast cell stabilizer should be prescribed only for prophylaxis. Antihistaminic drops may be prescribed for acute symptomatic relief. Topical steroids should be prescribed after consultation with ophthalmologist [18].

At present, topical delivery via eye drops makes approximately 90% of all ophthalmic products. Nevertheless, this delivery route is very inappropriate and in few cases contributes to grave side effects. Topical delivery of ophthalmic drops leads to altering extent of drug delivery to the ocular tissues and therefore, restrains their therapeutic effectiveness [19], [20], [21], [22]. An eye-drop, notwithstanding of the introduced bulk, is frequently cleared swiftly in 5–6 min following application, and merely a minor volume (1–3%) of an eye-drop essentially extents the intraocular tissue. There have been attempted a number of dosage forms like viscous solutions, suspensions, emulsions, ointments, aqueous gels, and polymeric inserts etc., in order to enhance ophthalmic bioavailability and to prolong the retention over the surface of the eye. Biodegradable polymers (natural as well as synthetic) provide several merits as compared to non-biodegradable polymers for controlled drug delivery. They do not require surgical removal after application, considered as the most obvious advantage in ocular drug delivery since it can contravene surgical intricacies linked with non-biodegradable implanted devices. These biodegradable polymers have many beneficial features like biocompatibility with tissues of the eye, biodegradability and mechanical strength. They offer least toxicity and besides their decomposition, substances are innocuous with respect to local and systemic

reaction. Due to the adequate mechanical characteristics, they may be designed to offer wide range of properties.

4. Biodegradation mechanisms and biomaterials in ocular drug delivery

Biodegradation may be defined as an enzymatic or non-enzymatic hydrolysis of the polymeric structure into water soluble or insoluble substances. Biodegradation contain two parallel methods, degradation and erosion. In the degradation step, schism of the polymeric foundation into low molecular weight fragments takes place, while the erosion mechanism deals with the physical event such as dissolution and diffusion of low molecular weight portions from the polymer matrix. The degradation outputs are eventually cleared from the body through routine metabolic passage [23]. Heller has explained 3 core mechanisms of polymer degradation and categorized the polymers on the basis of the degradation mechanisms [24]. Schematic portrayals of polymer degradation mechanisms are shown in Fig. 1.

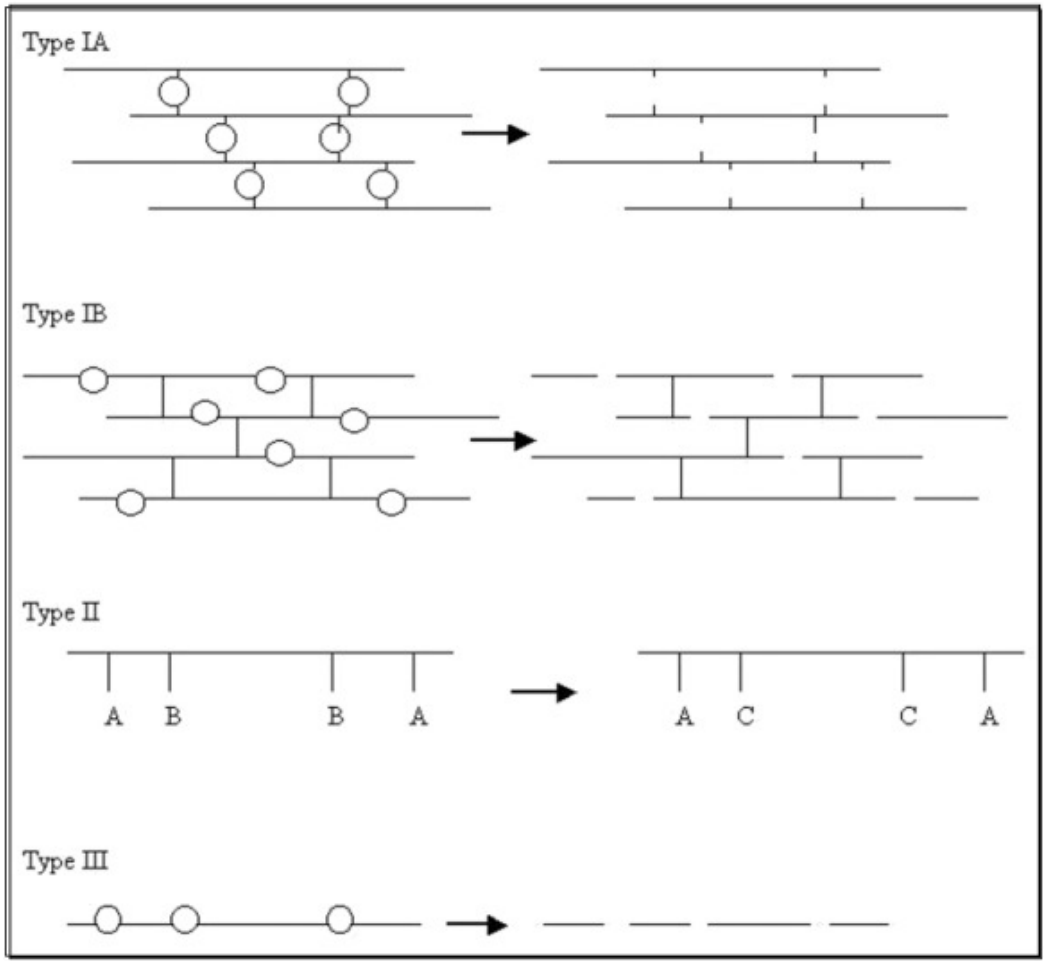

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Fig. 1. Schematic portrayal of degradation mechanisms A - hydrophobic substituent, B to C - indicate

hydrolysis, ionization or protonation. Type I explains the degradation of water-soluble macromolecules. Type II discusses the dissolution of water insoluble macromolecules. Type III entails the degradation of insoluble polymers with labile bonds.

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Mechanism I elaborate the degradation of water-soluble macromolecules that are entangled to make 3-D structure. The network is sturdy and is insoluble unless crosslinks remain intact. Degradation in such systems may either happen at crosslinks (type IA) or at the principal chain (type IB). Usually, degradation of type IA polymers yields high molecular weight, water-soluble fractions, whereas degradation of type IB polymers results in low molecular weight, water-soluble oligomers and monomers.

Mechanism II explains the dissolution of water-insoluble macromolecules having side groups that are transformed to water-soluble polymers because of ionization, protonation or hydrolysis of the groups. By this mechanism, the polymer does not decompose and its molecular weight keeps in fact unaltered. Materials showing type II erosion are cellulose acetate derivatives and fractionally esterified copolymers of maleic anhydride. These polymers turn soluble by ionization of carboxylic group as exhibited by type II erosion.

Mechanism III discusses the degradation of insoluble polymers with labile bonds. Hydrolysis of labile bonds leads to cleavage of the polymer structure, thus producing low molecular weight, water-soluble molecules. Polymers experiencing type III erosion are poly(lactic acid), poly(glycolic acid) and their copolymers, poly(orthoesters), polyamides, poly(alkyl-2-cyanoacrylates) and polyanhydrides. The 3 mechanisms explained are not relatively exclusive; combinations of them may take place.

The intricate anatomy of the eye poses obstacles for the access of drugs as well as their carriers. In general, the ocular bioavailability of active pharmaceutical substances upon topical application is below 5%. This may be attributed to spillage due to blinking, shorter stay period in cul-de-sac and nasolacrimal elimination. Moreover, lipophilic characteristic of epithelium of cornea and hydrophilic nature of adjacent stroma also present hurdles in transit of hydrophilic and lipophilic drug molecules, respectively. Besides, the occurrences of various efflux pumps like P-glycoprotein, multi-drug resistance related proteins and breast cancer resistant protein on variety of ocular tissues limit the access of the drug molecules inside the eye [25]. Numerous attempts have been made in order to achieve a successful ocular drug delivery. Biodegradable polymers of natural origin such as gelatin, albumin, chitosan, hyaluronic acid and synthetic biodegradable polymers like PVP, PACA, PCL, PEO, polyanhydrides and thermoplastic aliphatic polyesters such as PLA, PGA and PLGA have been entirely exploited for ophthalmic delivery systems [26]. FDA has also permitted these polymers for human uses. The polymers (natural and synthetic) are discussed in detail encompassing formulations aspects, evaluation and significant findings from different ocular dosage forms in forthcoming sections, which are employed as carriers for anti-inflammatory agents. A summary of such biopolymers is provided in Table 1 and Table 2.

Table 1. Summary of natural biomaterials used as carriers for anti-inflammatory drugs.

Polymer	Drug	Formulation	Key findings	Ref
Gelatin	Pilocarpine + hydrocortisone	Nanoparticles	Prolonged ocular retention	[28]
	Dexamethasone, aceclofenac	Ocular insert	Improved ocular bioavailability, inflammation control	[29], [30]
	Ketorolac tromethamine	Ocular film	Better tolerance to the eyes	[31]
Collagen	Dexamethasone, flurbiprofen, gentamicin + dexamethasone	Corneal shields	Improved ocular bioavailability, patient compliance, sustained drug release	[34], [35], [36]
	Ketorolac tromethamine	Gel	sustained drug release upon topical application	[37]
Chitosan	Indomethacin	Nanoparticles, nanoemulsion	Alterations of paracellular and transcellular passage by chitosan without distururbing cellular fabric, prolonged ocular retention	[42]
	Ketorolac tromethamine	Nanoparticles	Sustained drug release	[47]
	Celecoxib	Nanoparticles	Safe for ocular application	[48]
	Indomethacin	Nanocapsules	Prolonged ocular retention	[49]
	Prednisolone	Nanoparticles	Improved corneal permeation	[51]
	Diclofenac sodium, bromfenac	Liposomes	Longer ocular residence due to bioadhseion	[53], [54]
	Flurbiprofen	NLC	Enhanced corneal penetration	[55]
Albumin	Hydrocortisone, meloxicam	Nanoparticles	Higher drug permeation in inflamed cornea, better tolerance	[60], [61]
	Piroxicam	Microspheres	Improved ocular bioavailability	[62]
Alginates	Indomethacin	Implants	Significant improvement in clinical features	[66]
	Indomethacin, flurbiprofen, Diclofenac sodium, diclofenac potassium	in situ gel	Prolonged ocular retention, improved ocular bioavailability	[67], [68], [69], [70]
	Naproxen	Microspheres	Mucoadhesion facilitated longer ocular residence	[71]
	Celecoxib	Nanoparticles	Safe of ocular applications	[48]

	Betamethasone sodium phosphate	Nanoparticles	Sustained drug release	[73]
	Azelastine hydrochloride	Microspheres	Effective conjunctivitis control	[74]
Hyaluronic acid	Methylprednisolone, hydrocortisone Naproxen Diclofenac sodium	Microspheres Films Hydrogel Porous particles	Improved ocular bioavailability, sustained drug release Suitable for drug delivery Linear drug release	[79], [80], [81], [82] [87], [88]
	Methylprednisolone	Corneal shields	Prolonged ocular retention	[82], [89]
	Vasoactive intestinal peptide	Liposomal gel	Appreciable reduction of inflammation	[90]
	Gatifloxacin/prednisolone	Nanoparticles	Sustained drug release	[92]
Miscellaneous **1. Pectin** **2. Gellan** **3. Gelrite** **4.Gelrite-alginate**	Piroxicam	Microspheres	Improved ocular bioavailability, sustained drug release	[93]
	Methylprednisolone	Films,eye drops	Sustained drug release	[94]
	Indomethacin	In situ gel	Effective inflammation control	[95]
	Matrine	In situ gel	Better tolerance	[96]

5. Natural biodegradable polymers

5.1. Gelatin

Gelatin is a polymer from natural origin, procured from the crude protein collagen through chemical processing. Owing to its biocompatibility and biodegradability gelatin is commonly employed in pharmaceutical and medical uses. In market gelatin is supplied in two types like type A and type B. Type A gelatin is the acid treated collagen, while type B gelatin comes from alkaline processed collagen. These chemically treated gelatins possess changing isoelectric points, 7–9 for type A and 4–5 for type B. Ocular delivery systems of gelatin may be honed by changing the electrical and physical features of gelatin [27]. Vandervoort and Ludwig formulated gelatin nanoparticles entrapping pilocarpine HCl and hydrocortisone for topical ocular uses. They summarized that gelatin could be a potential polymeric carrier because of sustained stay period at surface of the eye [28]. Attia et al. prepared a cross-linked gelatin insert to enhance bioavailability of dexamethasone in the rabbit eye. The dexamethasone concentrations in the aqueous

humor were recorded as 4 fold higher compared to a dexamethasone suspension [29]. Mathurm and Gilhotra formulated soluble ocular inserts of aceclofenac by solvent casting method in order to improve its bioavailability in the eye. They observed that cross-linked formulation (AF 8) sustained the drug release up to 24 h. The formulation was found to be nonirritant and well tolerated upon ocular irritation check by hen's egg chorioallantoic membrane test (HET-CAM). Further, in vivo studies demonstrated a higher inhibitory effect of aceclofenac inserts over the eye drops formulation against PGE2-induced ocular inflammation as the values of lid closure score (0 v/s 0.200 ± 0.447 after 8 h) and PMN count (Fig. 2) was less in case of formulation versus eye drops [30].

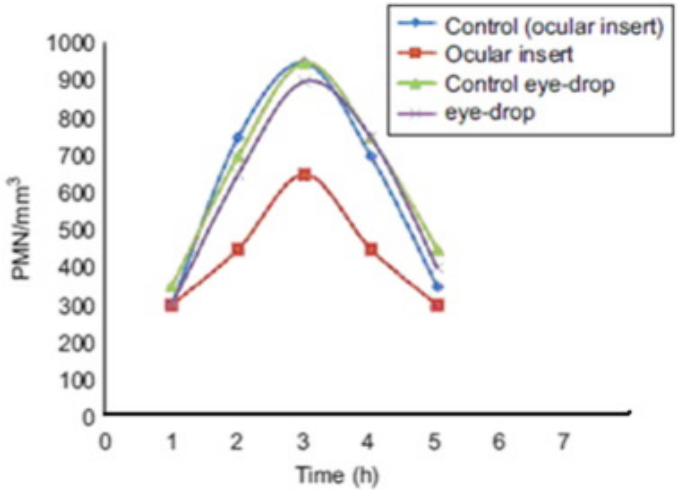

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Fig. 2. Comparison of effect of Aceclofenac Ocular film with aqueous solution of drug on PGE2 induced PMN migration in tears of rabbit.

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Potu et al. prepared and characterized ocular films of Ketorolac tromethamine. The thickness of films were in the range of 0.19 ± 0.01 μm to 0.29 ± 0.01 μm with drug content of 93.49 ± 0.05%–99.00 ± 0.05%. The films did not cause any irritation upon application in cul de sac of rabbit eye [31]. Tseng et al. formulated cationic gelatin nanoparticles, which were evaluated for in vitro biocompatibility using human corneal epithelium (HCE) cells, and in vivo safety by administering them as eye drops to New Zealand rabbits. The nanoparticles were found to be non-toxic to HCE cells. Further, the nanoparticles having positive charge were retained for prolonged periods in the corneal tissue. This was attributed to the fact that the cornea and conjunctiva possess negative surface charges [32].

5.2. Collagen

Collagen is a significant biodegradable and biocompatible natural polymer broadly spread in tissues of the

eye like the sclera, stroma and cornea. Various types of collagens are traced in human body, which are usually 300 nm in length of molecular weight about 300,000. Collagen type I is the usual and completely used protein of mammals [33]. Collagen generated from the animal sources like porcine and bovine could be exploited for human uses, due to secondary and tertiary structural resemblance with the human collagen. One of the most commonly investigated drug carrier uses of collagen are inserts and shields for drug delivery to the surface of the cornea or to the cornea alone and intraocular drug delivery. Hwang et al. developed collagen corneal shields containing dexamethasone for improvement in its penetration into corneal tissue. The collagen shields presoaked with dexamethasone yielded higher drug concentration against conventional eye drops. Thus, it was concluded that shields offered improved penetration and improved patient compliance too by reducing the application frequency of concerned drug [34]. Milani et al. investigated the application of collagen shields soaked with an antibiotic-corticosteroid (gentamicin-5 mg + dexamethasone-3 mg) mix to deliver both drugs to rabbit eyes [35]. The release of dexamethasone was observed in sustained fashion. The findings from in vitro drug release was corroborated by in vivo studies as the concentration of dexamethasone in aqueous humor was less ($P = 0.004$) after 1 h of application but significantly higher($P = 0.028$) after 6 h time point in comparison with subconjunctival injection (Fig. 3). Similar results were observed using flurbiprofen and other drugs in combination with collagen shields by Aquavella et al. [36]. A European patent has described a collagen containing gel as a carrier for ketorolac tromethamine for ocular application. The formulation is flowable liquid at ambience temperature and forms a gelled sustained release matrix after administration to the mammalian eye [37]. The favorable characteristics of collagen such as excellent biocompatibility, absorption capacity and low immunogenicity have facilitated its corneal applications [38], [39].

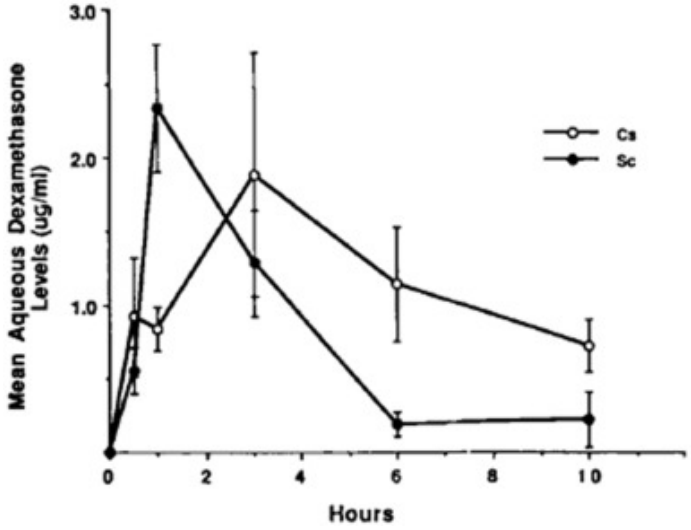

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Fig. 3. (Milani and associates). Comparison of mean aqueous humor dexamethasone concentrations attained with collagen shield (Cs) vs. subconjunctival injection (Sc) therapy at 5 time points over 10 h. Vertical bars

represent standard error of the mean (SEM). Sample size for every group is ten eyes for individual time point.

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5.3. Chitosan

Chitosan (CS) is a polymer from nature procured from chitin that on deacetylation yields chitosan. Chitin makes exoskeleton of arthropod and mainly made up of D-glucosamine linked via 1–4 linkage [40]. Chitosan has different physical features like mucoadhesiveness and penetration improving habit, which endorse its potential for ocular drug delivery. Its mucoadhesive characteristic is due to the positive charge of amino groups, which interacts with the negatively charged ocular tissues like the cornea and sclera. Its mucoadhesive trait is favorable for enhancing the ocular bioavailability [41]. CS enhances the permeability of drug moiety by altering the tight junctions of the corneal epithelial cells in a reversible fashion. Findings propose that CS modifies the paracellular and transcellular passages sans disturbing the cellular make up [42], [43]. The history of its use in ophthalmology started with its employment as a viscosity and permeation agent, evolving to its use as the main constituent of different nanometric delivery systems. De Campos et al. made an effort to decipher the mechanism of fluorescent-labeled chitosan nanoparticles interaction with corneal cells upon instillation into rabbit eyes. The findings of the study revealed close interaction of chitosan nanoparticles with corneal and conjunctival epithelia yielding a higher retention as compared to chitosan solution. Further, these nanoparticles were found to have penetrated across corneal epithelium [41]. De Salamanca et al. achieved similar results while studying in vitro and in vivo behavior of chitosan nanoparticles with epithelial cells on the surface of the eye. In addition, the chitosan nanoparticles were better tolerated as evident through absence of any signs of ocular inflammation on rabbit eyes. The nanoparticles were internalized into Human conjunctival epithelial cells (IOBA-NHC) showing presence of fluorescein isothiocyanate-bovine serum albumin (FITC-BSA) fluorescent signal (Fig. 4). This was concluded from the study that chitosan nanoparticles might serve as promising carriers for drug molecules for ocular delivery [44]. Badawi et al. developed nanoparticles as well as nanoemulsions based on chitosan in order to improve bioavailability of indomethacin and prolong its precorneal residence time. The both nanocarriers were formulated by methods described previously by Calvo et al. The mean size of nanoparticles was 280 ± 6.4 nm. The entrapment efficiency of indomethacin was also good (84.8 ± 0.81%). The globule size of nanoemulsion was in the range of 220–690 nm varied with type of surfactant used. The results from in vivo studies indicate clear healing of chemical induced ulcers in rabbit eyes. The AUC for nanoemulsion was 17-fold higher than drug solution in aqueous humor. It was concluded that it was not due to additive chitosan mechanisms of mucoadhesion and the influence on the tight junctions but the non-ionic surfactant poloxamer F 68 as a component also could be responsible for the enhanced penetration and the noted modified healing rate [42], [45], [46]. Asik et al. prepared and characterized ketorolac tromethamine (ketorolac) loaded chitosan nanoparticles for treatment of different ocular diseases such as pseudophakic cystoid macular edema, allergic conjunctivitis and diabetic macular edema. Chitosan nanoparticles were prepared by using co-precipitation technique. The average size of the spherical nanoparticles was in the

range of 180–200 nm. The drug loading was up to 41% (maximum for drug concentration 3.2 mg). The drug release profile exhibited primarily burst release succeeded by sustained drug release until 72 h. Based on these in vitro studies they suggested that chitosan nanoparticles are promising drug carriers in treatment of ocular diseases [47]. Ibrahim et al. developed bioadhesive cationic chitosan nanoparticles containing celecoxib. The preparations were evaluated for size, surface morphology and drug content. Moreover, these nanoparticles were incorporated to topical ocular dosage forms such as eye drops, temperature-stimulated in situ gelling system and preformed gel. Findings of the ultimate formulations celecoxib-loaded chitosan nanoparticles are: particle size of 113.33 ± 4.08 nm; zeta potential of + 36.92 ± 3.38 mV and incorporation efficiencies of 89.88 ± 4.17%. Transmission electron microscopic studies showed that all nanoparticles have unique spherical shapes having a solid dense core coated with uniformly distributed covering. In vitro release data of ocular preparations exhibited a prolonged release sans any burst effect and the formulations obeyed a Higuchi non-Fickian diffusion mechanism. The outcome of in vitro cell toxicity showed that all the preparations are non-toxic, since the % cell viability ranged from 89.9 to 97.7%. This could therefore, work as a promising drug delivery system for anterior as well as posterior eye diseases [48]. Calvo et al. formulated chitosan-coated and poly-L-lysine-coated poly-ε-caprolactone nanocapsules containing indomethacin. The average size of chitosan-coated nanocapsules was 384 ± 60 nm with zeta potential of + 37.1 ± l.8 and incorporation efficiency was 91.8 ± 8.9%. The drug release was independent of polymers coatings as about 85% of drug released in 2 h. Findings report that, at 30 and 60 min after application, the amount of indomethacin in the cornea was about 4–6 fold greater for the nanocapsules versus indomethacin eye drops. Same outcome were achieved upon determination of the aqueous humor. It was seen that that the CS-coated nanocapsules enhanced the indomethacin content in the cornea as well as aqueous humor to more extent than other colloidal systems. The improved uptake of the CS-coated nanocapsules can be assigned to distinct character of CS not the positive charge. Moreover chitosan did not contribute significant disturbance in the epithelial cells therefore could safely be employed for ophthalmic delivery [49]. Similarly De Campos et al. compared the efficiency of polyethylene glycol and chitosan with reference to interaction with rabbit cornea by coating poly-ε-caprolactone nanocapsules. Results suggested that chitosan could be a better alternate to other available coating materials [50]. Qu et al. formulated Quaternary ammonium palmitoyl glycol chitosan aggregates containing prednisolone. The loading of prednisolone to polymer formulation A7 (Mol. wt. – 19.9 kDa) resulted in drug polymer clusters of particles size in the range of 10–100 nm. These carbohydrate nanoparticles ease drug absorption from the cornea to the aqueous humor albeit not successful to carry drug to the back of the eye. Nevertheless, this is normal with respect to the topical route of delivery and properties of the drug [51]. Diebold et al. formulated liposome-chitosan nanoparticle complexes and evaluated their promise to carry drugs to the ocular surface. The complex has exhibited retention in mucus cells and penetration into conjunctival cells to varying extent. Further, the system has shown minimum toxicity and nice tolerance upon in vitro- in vivo studies. These findings (similar to De Salamanca et al.) indicate the complex to be utilized as drug carrier in the future [44], [52]. Li et al. formulated liposomes containing diclofenac sodium coated with low molecular weight chitosan. First, chitosan after treatment was converted to varying molecular weight chitosan fractions. To this, the liposomes prepared by injection method were added slowly under magnetic agitation. The entrapment

efficiency up to maximum values of 100% were observed. The coating with chitosan has changed the surface characteristics of the liposomes as zeta potential value of + 10.1 mV was observed against − 26.1 mV for uncoated liposomes. Apparently, coatings had no impact on entrapment efficiency and drug release from the vesicles. The pre-corneal retention was significantly higher in case of coated liposomes versus uncoated ones owing to positive charge and inherent bioadhesive features of chitosan. Similarly, corneal penetration was found to be better in coated liposomes with keeping corneal cells intact. Hence, they proposed the coated liposomes as novel drug delivery system to the eye [53]. Tsukamoto et al. prepared and optimized bromfenac-loaded liposomes having surface coatings of chitosan by acetate salt pH gradient method. The particle size of almost all vesicles was under 100 nm. The liposomes were found to achieve 100% drug entrapment. The concentration of chitosan (0.15%) used for surface alterations was selected based on its property to offer mucoadhesion without triggering aggregation. The drug release was observed for prolonged periods in case of coated liposomes versus drug solution. The inferences indicated that such system might be able to deliver drug to the posterior segment of the eye [54]. Luo et al. formulated NLC (nanostructured lipid carrier) containing flurbiprofen by melt-ultrasonic method and afterwards coated with COS (Chitosan Oligosaccharides) having molecular weight of 3000–6000 kDa. The prepared formulations were spherical in shape and bilayered in case of COS coatings. The coating with COS caused a slight increase in size of vesicles 77.9 nm (0.5% COS coating) against average size of 55.4 nm in case of uncoated liposomes. The corneal permeation was found to be higher in COS coated NLCs as compared to uncoated NLCs and flurbiprofen eye drops (0.03%). The lipids confers the compatibility with corneal surface whereas COS offers bioadhesion as well as improvement in penetration. Results from gamma scintigraphy also confirm prolonged retention of COS coated NLCs. Further, the histopathology of corneal tissue, which have undergone treatment with combination of COS-NLCs revealed no damage thus heralding tolerance and safety of applied formulations [55].

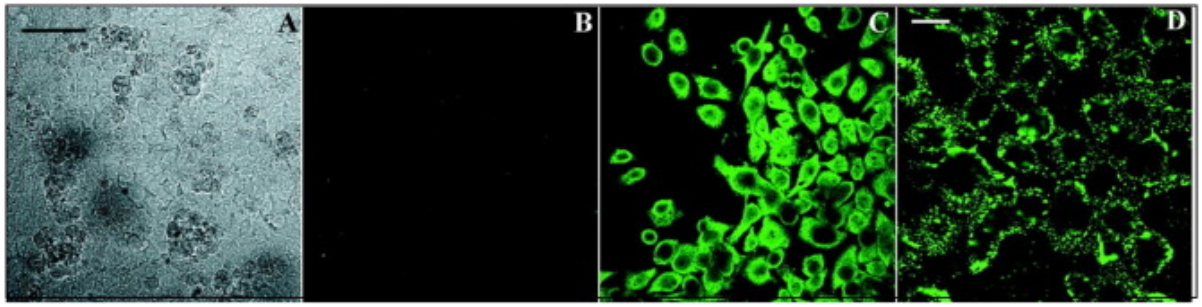

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Fig. 4. Confocal images of control IOBA-NHC cells. In the control cells, green fluorescence represents CSNPs and not to the endogenous fluorescence or FITC-BSA liberated from the CSNPs. (A) Transmitted light micrograph of control cells exposed to culture medium. (B) No green fluorescence was observed in control cells exposed to the culture medium only. (C) Cells exposed to FITC-BSA solution had an equal spread of fluorescence in the cytoplasm. (D) Cells exposed to CSNPs had nanometer-sized fluorescent dots within

them (n = 3). Magnification: (A–C) × 40; (D) × 63. Scale bar: (A–C) 50 μm; (D) 25 μm.

Source: Investigative ophthalmology & visual science, reproduced with permission from Association for Research in Vision and Ophthalmology.

5.4. Albumin

Albumin is a protein that can be obtained from a variety of sources, including egg white (ovalbumin), bovine serum albumin (BSA), and human serum albumin (HSA). Albumin is a major soluble protein of the circulating system and involved in the maintenance of osmotic pressure and binding and transport of nutrients to the cells. Many drugs and endogenous molecules are known to bind to albumin. Albumin serves as a depot and transporter protein [56]. The high solubility of albumin (up to 40% w/v) at pH 7.4 makes it an attractive macromolecular carrier capable of accommodating a wide variety of drugs. It possesses stability in the pH range of 4 to 9 and may withstand 60 °C up to 10 h sans any ill consequence [57]. Albumin is widely used in the preparation of nanospheres and nanocapsules [58]. These albumin nanocarriers are biodegradable, easy to prepare, and have well-defined sizes and reactive functional groups (thiol, amino, and carboxyl) on their surface that can be used for ligand binding and other surface modifications. The biodegradation of albumin in vivo is a factor of the enzymatic activity. In vivo human serum albumin nanoparticles and microparticles of an average size of 1.5 μm and a maximum size of approximately 5 μm decompose from their centre subsequent to phagocytes by human macrophages [59]. Zimmer et al. formulated albumin nanoparticles containing hydrocortisone by modified desolvation process using glutaraldehyde as cross-linker. The nanoparticles so formed were 100 to 300 nm in size. The strength of hydrocortisone solution was kept 0.03% corresponding to its aqueous solubility (i.e. – 0.00298 mg/ml). The incorporation efficiency of hydrocortisone was found to be in the range of 42–52%. The trans-corneal flux values were significantly reduced when compared to hydrocortisone reference solution (reference solution - 4.65 $\mu g\ cm^{-2}\ h^{-1}$ versus formulation-2.52 $\mu g\ cm^{-2}\ h^{-1}$). After inflammation, drug delivery to the eye compartments was relatively greater with the nanoparticles preparation than with the solution. This suggested that the inflammatory processes seem to lead largely of nanoparticles mediated hydrocortisone tissue adhesion or even tissue uptake than after administration of a reference solution. As a result, in the inflamed eye, nanoparticles facilitated hydrocortisone targeting to the precorneal area beyond the internal segments of the eye [60]. Zhang et al. strived to address postcataract endophthalmitis by preparation of bovine serum albumin-meloxicam nanoaggregates employing acid-base neutralization reactions. The nanoaggregates were further processed with HEMA in order to give gel preparation. The mean particle size of such nanoaggregates was recorded to be 99.48 ± 0.53 nm. There was observed a decrease in corneal permeation of meloxicam nanoaggregates gel as compared to meloxicam solution in gel (solution-Jss = 0.056 $\mu g\ cm^{-2}\ s^{-1}$ versus nanoaggregates-Jss = 0.038 $\mu g\ cm^{-2}\ s^{-1}$). The gel formulations were well tolerated by the rabbit eyes as evaluated by Draize test whereas the meloxicam solution was found to cause mild redness in iris upon frequent instillations. The BSA coating was found to non-irritant to rabbit eyes on histopatological investigations. Therefore, the researchers suggested introducing this technique for the cure of postcataract endophthalmitis treatment with other medical devices and as carrier for low molecular

weight drugs. The BSA coatings conferred the formulation capability to retard the drug release (about 80% drug release after 12 h) [61]. Giunchedi et al. formulated albumin microspheres loaded with piroxicam by spray drying process. The yield of microspheres was up to maximum of 55%. The microspheres were of irregular shape and their sizes were below 10 μm. The dissolution of drug was slower as about 70% of piroxicam was released in 8 h. The in vivo bioavailability was found to be 1.8 times higher than commercial eye drops of piroxicam [62].

5.5. Alginates

Alginates are derived from marine brown algae cell walls. It is anionic polysaccharide comprised of a chain of (1–4)-linked β-D-mannuronic acid and α-L-guluronic acid in several arrangements of residues. Alginate is a natural, biodegradable, and mucoadhesive polymer that does not produce toxicity in administration [63], [64]. Alginates form hydrogels in the appearance of divalent cations such as Ca^{2+}. The alginate monomer make up is documented to possess a great effect on the drug release characteristics of the various preparations [65]. Balasubramaniam et al. developed as well as characterized scleral implants of indomethacin using sodium alginate. The implants were further subjected to pharmacodynamic studies in uveitis triggered rabbit eye-model. The pharmacodynamic investigations revealed an appreciable refinement in different clinical criteria such as congestion, keratitis, flare, clot, aqueous cells and synechias, in the implanted eye while comparing with the control eye in the rabbits [66]. Pandit et al. prepared in situ gelling systems of indomethacin in sodium alginate. The drug content was uniform (i.e. 100 ± 5% of indomethacin). It was observed that autoclaving caused a decrease in viscosities of the gels (up to 31–50%). The reduction was much prominent at pH 7.4 suggesting nature of sodium alginate to coacervate at physiological pH. Upon addition of gelation media alginate formed a polyelectrolyte complex, which were least affected by dilution or ion- exchange reactions and keep their network in physiological conditions. Besides the ionotropic gelling of alginate, its mucoadhesivity is also probably leads to prolongation of retention period. It was anticipated that the dissolution of the gels in cul-de-sac would occur much slowly than that observed in the in vitro experiments because of less resident volume of the lachrymal fluid in the human eye, i.e. 7.5–10 μl [67]. Verma et al. prepared in situ gels of flurbiprofen by simple dispersion method using sodium alginate and carbopol along with HPMC. The drug content was in the range of 98.3–103.1% meant uniformity in all formulations. The alginate exhibited gelling features upon addition of bivalent cations (sol to gel at physiological pH). The gel formulations were isotonic, as they did not cause any change in blood cells (RBCs). Ocular irritation of the prepared formulation was assessed by hen's egg chorioallantoic membrane method. The mean score indicated that developed formulations were non-irritant and well tolerated. The results of anti-inflammatory activity against PGE2-induced ocular inflammation were also good as parameters such as lid closure score; polymorphonuclear leukocytes migration was lower as compared to their respective control. Thus, it was concluded that the prepared formulation is a robust substitute to custom eye drops owing to its capability to improve bioavailability via its sustained precorneal retention and capability to prolong the drug release and the readiness of its application offered and reduced dosing frequency yielding good patient compliance [68]. Preetha et al. formulated and evaluated diclofenac

sodium gel using sodium alginate exploiting the notion of pH stimulated in situ gelation. Based on in vitro characterization data it was suggested that developed formulation would likely to offer the increased residence time and sustained drug release [69]. Subimol et al. formulated in situ gel formulation of diclofenac potassium using sodium alginate and hydroxy propyl methylcellulose (HPMC). It was summarized that the in situ gels had desirable characteristics for the localized delivery of the drug within the eye [70]. Kumar et al. prepared microspheres containing naproxen sodium by ionic gelation method employing sodium alginate, carbopol 974, and hydroxyl propyl methylcellulose K15 M (HPMC) as mucoadhesive polymers. The microspheres were spherical in shape and homogenous in size (particle size range of 129.7–395.9 μm). The maximum drug entrapment of 76.27% was observed at alginate (1% w/v) plus carbopol (1.5% w/v).The drug release followed non-fickian pattern governed by swelling and relaxation of polymer chain. Thus, they suggested that mucoadhesive microspheres could be designed for sustained delivery of naproxen sodium and for improved patient acceptance [71]. Zhu et al. formulated thiolated chitosan (TCS)-sodium alginate (SA) nanoparticles containing fluorescein isothiocyanate (FITC) by a modified ionic gelation method. The average size of TCS-SA nanoparticles was 265.7 ± 7.4 nm. The prepared nanoparticles were positively charged which were effective mucoadhesive on the negatively charged cornea. TCS-SA nanoparticles had better delivery capability, suggesting they have good potential for ophthalmic drug delivery applications. The in vitro cell uptake study and in vivo experiments provided further evidence to support these conclusions [72]. Ibrahim et al. developed celecoxib loaded sodium alginate nanoparticles by spontaneous emulsification solvent diffusion technique. The particle size, zeta potential and incorporation efficiency of nanoparticles were 154.67 ± 5.06 nm, − 36.5 ± 4.7 mV and 75.38 ± 2.98%, respectively. The ophthalmic formulations containing sodium alginate nanoparticles exhibited pseudoplastic behavior. The celecoxib liberated from all the preparations obeyed the Higuchi model, suggesting diffusion as the release mechanism. The results from cytotoxicity studies indicated the safety of nanoparticles formulation towards the eye [48]. Attia Shafie et al. formulated mucoadhesive chitosan-sodium alginate nanoparticles of betamethasone sodium phosphate by ionotropic gelation method. The developed nanoparticles were spherical with average particle size ranging 16.8 nm–692 nm. The pH was close to that of tear fluid (5–7) which is compatible to ocular administration. Therefore, it was suggested that chitosan alginate nanoparticles would be a promising system for the sustained release delivery of betamethasone sodium phosphate to the posterior segment of the eye [73]. Recently Shinde et al. fabricated chitosan-sodium alginate (CS-ALG) microspheres of azelastine hydrochloride using modified ionotropic gelation technique. There was observed a change in particle size from 2.42 μm to 6.66 μm as the concentration of CS: ALG ratio was changed from 3:1 to 1:2. All the microspheres were spherical and positively charged due to the presence of chitosan. The drug release was initially higher (20–25% burst release within 1 h) followed by sustained release over 8 h. The CS: ALG (3:1) ratio yielded highest mucin binding efficiency of 65.79%. The eye scratching behavior of formulations were at par with marketed product. Thus, from all the above mentioned results it was concluded that AZT-loaded CS-ALG microspheres showed better efficacy in lowering conjunctivitis than marketed eye drops hence proved better in action [74].

5.6. Hyaluronic acid

Hyaluronic acid also termed Hyaluronan and Hyaluronate (HA) and Sodium Hyaluronate (SA) are sodium salt form of hyaluronic acid) is a biodegradable, biocompatible and viscoelastic linear polysaccharide of broad molecular weight ranges (1000 to 10,000,000 Da). It is made up of alternatively positioned disaccharide units of *d*-glucuronic acid and *N*-acetyl-*d*-glucosamine having (1 → 4) inter glycosidic linkage and is scattered across the extracellular matrix, connective tissues, and organs of all higher animals. Metabolism of HA takes place via the enzymatic hydrolysis by hyaluronidase (HAase) which prevails in different mammalian tissues. The HA molecule is freely soluble in water, yielding a gel that serves as a lubricant. It imbibes water too, rendering it hygroscopic and homeostatic features [75], [76], [77], [78]. Several researchers have investigated the release of hydrocortisone, which has been linked with backbone of hyaluronate esters. Hyaluronate esters having approximately 50% methylprednisolone and 50% sodium fluorescein were prepared as microspheres of size ranging 1–10 μm in diameter using spray drying technique. The microspheres so formed showed sustained drug release, as time taken for all drug was 600-fold higher than physical matrices of drug and polymers. Pharmacokinetic parameter like AUC was about 2.5 times higher in case of microspheres as compared to respective controls. These findings apparently suggested that by employing macromolecular prodrug approach, therapeutic agents could be transported for prolonged time with acquiring fewer peak drug concentrations and as a result yielding lowered systemic side effects and greater bioavailability [79], [80], [81]. Kyyronen et al. prepared films and microspheres from different esters of hyaluronic acid containing methylprednisolone. Drug-loaded films were formulated through casting on glass plates. Circular matrices of 4 mm diameter were cut afterwards from dry films using a cork borer. Every matrix had 420 ± 38 μg of methylprednisolone. After 8 h, all of the entrapped methylprednisolone was liberated from ethyl ester films, whereas only approximately 40% was leached from benzyl ester films. It was observed that the loss of drug in tear flow was minimum for films. Interestingly the hyaluronate ester films offered near fixed tear fluid amounts till 8 h whereas microspheres retained up to 4.5 h. Drug delivery systems composed of hyaluronic acid derivatives can sustain the absorption time and improve the ocular delivery of other steroids [82]. Sahiner and Jia developed and characterized submicron hydrogel HA particles. The researchers demonstrated least cytotoxicity while use of these particles indicating innocuousness of such particulates in variety of drug delivery applications [83]. Sahiner et al. fabricated and evaluated cross linked HA hydrogel particles possessing promise for application in different drug delivery applications [84]. Ilgin et al. synthesized and evaluated HA particles. It was suggested that such particles have promise for drug targeting relevant to pharmaceutical and biomedical areas [85]. Ekici et al. synthesized and evaluated HA hydrogel particles containing Trimethoprim and naproxen. The investigators suggested utility of HA particles in drug delivery application in particular to pH/thermo-responsive systems [86], [87]. Sahiner et al. synthesized and characterized porous as well as modified HA particles containing trimethoprim and sodium diclofenac. Based on the in vitro drug release findings the authors concluded that these particles offer drug release in linear manner. Therefore, the HA particles could be fabricated by altering porosity for a number of drug delivery applications [88]. Bucolo et al. compared release of methylprednisolone from hyaluronic acid derivative corneal shields (Hyalobend)

against suspension of the drug. Ocular anti-inflammatory effect in the rabbit eye was also evaluated. A constant amount of drug was maintained in tear fluid upon application of Hyalobend. The suspension yielded higher concentration initially that faded away beyond 3.5 h. There was significant reduction in conjunctival inflammation induced by sodium arachidonate by Hyalobend shields when compared with control. Thus, Hyalobend corneal shields increased the retention of methylprednisolone in rabbit tear fluid, enhanced the outreach into the aqueous humor, and decreased the initial signs of ophthalmic inflammation [89]. Lajavardi et al. evaluated the use of vasoactive intestinal peptide (VIP) liposomes dispersed in hyaluronic acid gel for treatment of uveitis. This investigation exhibited appreciable lowering of inflammation and proposed that the incorporation of hyaluronic acid even enhanced the efficacy and effect span of liposomal VIP. The profile of an ophthalmic anti-inflammatory drug, which was not only influential moreover devoid of custom side effects of steroids appeared promising [90]. Barbault-Foucher et al. formulated poly-ε-caprolactone (PCL) nanospheres (NS) enveloped with hyaluronic acid (HA). The study dealt with variety of approaches to link HA on NS surface. The HA attachment with NS was very strong in the presence of surfactant like stearylamine or benzalkonium chloride in contrast to its poor binding with PCL NS when used alone. Therefore, by employing an easy formulation procedure, it was feasible to procure sturdy HA and uniform HA-covered NS [91]. Ibrahim et al. prepared nanoparticles containing gatifloxacin/prednisolone employing Eudragit RS 100 and RL 100 and covered with hyaluronic acid. The spherical nanoparticles had mean particle size ranging 315.2 to 973.65 nm and negatively charged. Eudragit nanoparticles were readily enveloped using HA yielding enhanced ophthalmic bioavailability versus the marketed eye drops. Thus, the prepared nanoparticles suspension could improve patient acceptance because of its effortless application to the eye and its sustained action [92].

5.7. Miscellaneous

Several other materials of natural origin have been used for ocular delivery such as polysaccharides, amino acids etc. Giunchedi et al. prepared pectin microspheres containing piroxicam by spray-drying technique. The microspheres were spherical having average particle size below 10 μm. The incorporation efficiency was in the range of 97–100%, although percentage yields was reported low (41–46%) which was attributed to loss due to manufacturing by spray drying. The aqueous humor AUC values were also higher with microspheres as compared to eye drops (22.06 ± 3.67 h μg/ml versus 6.45 ± 0.75 h μg/ml). Thus, the microspheres provided sustained release of piroxicam in conjunctival sac and showed promise as potential drug carrier in ocular delivery [93]. Sanzgiri et al. prepared and evaluated films and eye drops of gellan-methylprednisolone (MP). The films were prepared by casting into mould. The drug content was 87.5 ± 4 μg in each film so casted. The drug release from gellan films were based on permeation of water into the matrices, swelling of the matrix, hydrolysis of covalent ester bonds and diffusion of drug across the matrix ($n = 0.93$). The eye drops also sustained the release at par with the films. To conclude, the MP ester of gellan appears to offer an appropriate mode of prolonged MP delivery to the eye and a model for ocular delivery of other polymeric prodrugs [94]. Balasubramaniam et al. prepared ion-activated in situ gel of Gelrite (deacetylated gellan gum) containing indomethacin. The developed preparations were therapeutically

effective (in a uveitis stimulated rabbit eye model) and offered prolonged liberation of the drug over 8 h span in vitro [95]. Liu et al. formulated ion-activated in situ gel of Gelrite-alginate containing matrine, which has apparent anti-inflammatory activity. The viscosities observed were highest for Gelrite-alginate (0.2: 0.8% w/w) i.e. – 671 ± 8.1 cP along with immediate gelation lasting longer. The in vivo human corneal contact time was also found to be prolonged with combined solutions. There were not any ocular ill effects or weird clinical symptoms to the cornea, iris, or conjunctivae upon application of gel. Therefore, the Gelrite/alginate system may be employed as the in situ gelling vehicle for ocular drug applications [96].

6. Synthetic biodegradable polymers

Biopolymers having varying specific features are warranted for in vivo uses owing to the multiplicity and intricacies of in vivo ambiences. In present age, synthetic biopolymers appears interesting substitutes for biomedical uses because of the ensuing reasons: (1) though majority of biologically originated biodegradable polymers have nice biocompatibility, few can stimulate an immune response within the human body, probably one that could be surpassed by employing an adequate synthetic biopolymer; (2) chemical alterations to biodegradable polymers are not easy; and (3) chemical changes are supposed to bring about modification of the bulk characteristics of biologically derived biodegradable polymers. A number of features may be procured and future alterations are feasible with aptly fabricated synthetic biopolymers sans changing the bulk traits [97]. Some of the synthetic biomaterials that have been used as carriers for anti-inflammatory agents are listed in Table 2.

Table 2. Synthetic biomaterials used as carriers of anti-inflammatory agents.

Polymer	Drug	Formulation	Key finding	Ref.
PLA	Dexamethasone	Nanoparticles	Improved inflammation control	[102]
	Betamethasone	Nanoparticles	Improved inflammation control	[103]
	Triamcinolone acetonide	Micro/nanoparticles	Sustained drug release	[104]
	Budesonide	Micro/nanoparticles	Sustained drug release	[105]
	Celecoxib	Nanoparticles	Low cytotoxicity	[106]
	Triamcinolone acetonide	Implant	Control of uveitis upto 4 weeks	[107]
PLGA	Flurbiprofen	Nanoparticles	Improved inflammation control, Better ocular tolerance	[110], [111]
	Dexamethasone	Nanoparticles	Improved ocular bioavailability	[112], [113], [114],

				[115]
	Dexamethasone	Nanoparticles	Sustained drug release	[116]
	Dexamethasone acetate	Implant	Better ocular tolerance	[117]
	Diclofenac sodium	Nanoparticles	Better ocular tolerance	[118]
	Naproxen	Nanoparticles	Promising for ocular delivery	[119]
	S-ibuprofen	Nanoparticles	Non-toxic to ocular surfaces	[120]
	Pranoprofen	Nanoparticles	Better ocular tolerance Improved inflammation control	[121]
	Dexamethasone	Microspheres	Improved inflammation control	[122]
	Triamcinolone acetonide	Films	Biocompatibility, sustained drug delivery, Improved inflammation control	[123], [124]
	Difluprednate	Implant	Sustained drug delivery, Improved inflammation control	[125]
	Prednisolone	Nanoparticles	Sustained drug delivery	[126]
PCL	Indomethacin	Nanocapsules, nanoparticles, nanoemulsion	Better ocular tolerance, Improved inflammation control	[128], [129]
	Flurbiprofen	Nanospheres	Sustained drug delivery	[130], [131]
	Celecoxib	Nanoparticles	Improved inflammation control Sustained drug delivery	[106], [132]
	Diclofenac	Polymeric micelles	Improved inflammation control, Better ocular tolerance Improved ocular bioavailability	[133], [134], [135], [136], [137]
	Triamcinolone acetonide	Implants, microfilms	Improved inflammation control, Better ocular tolerance	[139], [140], [141]
	Dexamethasone	Implants	Improved inflammation control Sustained drug delivery	[142], [143]
PACA	Tramcinolone acetonide	Nanocapsules	Sustained drug delivery	[148]

POEs	Dexamethasone	Liquid	Sustained drug delivery	[150]

6.1. Polylactide (PLA)

The PLA is a polymer of polyester class which has short aliphatic ester linked backbone. The presence of extra methyl group confers the PLA more hydrophobicity than polyglycolide (PGA). The PLA has three isomers such as D (+), L (−) and racemic (D, L) lactide [98]. The polymers of polyester category are degraded by bulk erosion; the degradation products (lactic acid and glycolic acid) are non-toxic and cleared as carbon dioxide and water through Krebs cycle [99].

Moritera et al. formulated microspheres of PLA by encapsulating a fluorescent dye, 1, 4-bis [2-(5-phenyloxazolyl)]-benzene (POPOP). The drug delivery potential of these microspheres was assessed in retinal pigment epithelial (RPE) cells. By this study it can be said that surface modified microspheres could be used for drug delivery to retina [100]. Further, Bourges et al. have studied the mechanism of localization of PLA nanoparticles in the eyes of rats by employing two dyes viz. Rh-6G and Nile red. The researchers also investigated the ability of releasing the confined drug in nanoparticles. The particles sizes of nanoparticles were 140 ± 20 nm and 310 ± 40 nm for Rh-6G and Nile red, respectively. The release of Nile red from PLA nanoparticles was observed about 0.4% after 30 days which indicated its affinity towards PLA. On the contrary the Rh-6G was released rapidly from the nanoparticles. They have concluded that the nanoparticles reached retina fast following injection and were observed to stay in retinal pigment epithelium (RPE) cells even after 4 months. Thus the PLA nanoparticles could be used as drug carriers for targeting to retina or RPE [101]. Beck et al. formulated and evaluated PLA nanoparticles containing dexamethasone. The drug encapsulated in nanoparticles was found more effective in controlling carrageenan induced rat paw oedema versus the marketed Decadron® [102]. Sakai et al. evaluated the effects of intravenously administered PLA nanoparticles containing betamethasone phosphate on experimental autoimmune uveoretinitis in Lewis rats. The clinical scores on day 15–31 of PLA nanoparticles were significantly lower than drug or saline alone. Thus, the systemic application of these nanoparticles may be promising in intraocular inflammations [103]. Kadam et al. have investigated the drug release retarding ability of micro/nanoparticles of PLA containing triamcinolone acetonide for choroidal and retinal delivery. Interestingly, the microparticles were found to sustain the drug release longer than nanoparticles of PLA [104]. Similarly the capability of PLA micro/nanoparticles containing budesonide to sustain the drug release was demonstrated by Kompella et al. [105]. Ibrahim et al. prepared and evaluated PLA nanoparticles containing celecoxib. The inferences from cytotoxicity studies suggested non toxicity of nanoparticles with percentage cell viability ranged from 90.7 to 99.5 [106]. Shin et al. developed an implant containing triamcinolone acetonide and evaluated it for efficacy to treat experimental uveitis in rabbits. The implant successfully alleviated the symptoms of inflammation upto 4 weeks [107].

6.2. Poly(lactide-co-glycolide) (PLGA)

This is a copolymer of lactide and glycolide. The PLGA along with PLA have been exploited for ocular drug delivery in the form of implants, microparticles and nanoparticles. Moreover, PLGA has been approved by FDA for human applications by virtue of its marvelous biocompatibility and degradation patterns [108]. Jain et al. prepared fluorescent dye-chitosan-PLGA nanoplexes. The movement of stained nanoparticles and mechanism of internalization was then studied. The findings indicated towards applicability of these nanoplexes in ocular delivery [109]. The PLGA nanoparticles containing flurbiprofen were formulated and evaluated. The nanoparticles appeared to be non-irritating to corneal surfaces as apparent from Hen's Egg Test Chorioallantoic Membrane (HET-CAM) results. The drug entrapped in nanoparticles successfully reduced the arachidonic acid induced ocular inflammation in rabbits [110], [111]. The steroid dexamethasone and its acetate was successfully encapsulated in nanoparticles of PLGA and thermosensitive polymer (PLGA)–polyethylene glycol) matrices. The particulate formulations have yielded higher area under the concentration–time curves (AUC) against conventional eye drops [112], [113], [114], [115]. The PLGA nanoparticles were formulated by combining with d-α-tocopheryl polyethylene glycol 1000 succinate (TPGS) and employed for ocular delivery of dexamethasone [116]. The dexamethasone acetate implant made up of PLGA was found to be well tolerated by rabbit eyes [117]. The diclofenac sodium confined in PLGA nanoparticles have been well tolerated by rabbit eyes as apparent from findings of Draize test [118]. Similarly naproxen PLGA nanoparticles were formulated and characterized. The results of this investigation suggested the probable application in ocular drug delivery [119]. The PLGA nanoparticles containing S-ibuprofen (aka Dexibuprofen) were formulated by solvent displacement method. The results of this investigation indicated non-toxicity upon ocular application [120]. Recently, Abrego et al. formulated PLGA nanoparticles having pranoprofen and evaluated them for ocular tolerance, anti-inflammatory activity against sodium arachidonate induced inflammation in the rabbit eyes. The inferences from the study demonstrated excellent tolerance and control of eye swelling [121]. The microspheres encapsulating dexamethasone were effective to reduce the ocular inflammation caused by injection of intravitreal lipopolysaccharide [122]. Another steroid triamcinolone acetonide was incorporated to PLGA which was then casted into films. The films were biocompatible and lowered postoperative eye inflammation [123]. Sabzvari et al. formulated and characterized PLGA nanoparticles containing triamcinolone acetonide. The findings sustained ocular drug delivery of selected steroid in endotoxin-induced uveitis [124]. Verma et al. developed an implant of PLGA in combination with polyepsilon caprolactone (PCL) containing difluprednate engineered using PRINT® technology. The implant has shown extended drug release with effective control of ophthalmic inflammation [125]. Recently, contact lenses loaded with PLGA nanoparticles containing prednisolone were formulated and characterized. The nanoparticles have exhibited promise to sustain drug delivery to the eye [126].

6.3. Poly-ε-caprolactone (PCL)

PCL is an aliphatic polyester crystalline polymer. Its applications as release rate retardant material are because of its permeability to numerous drug molecules and slow degradation [127]. The NSAID Indomethacin was confined in nanocarriers such as capsules, particulates and emulsions. The ocular

tolerance study findings suggested that these were well tolerated by rabbit eyes [128], [129]. The PCL nanospheres containing flurbiprofen were prepared and characterized. The results of in vitro studies indicated that PCL may sustain delivery of flurbiprofen to the eyes [130], [131]. The celecoxib was also entrapped in biodegradable nanoparticles and their efficacy was assessed versus arachidonic acid induced inflammation in rabbit eyes. The particulates successfully controlled the parameters of ocular inflammation, thereby appearing promising for delivery of celecoxib to the eye [106], [132]. The PCL was copolymerized with methoxy poly(ethylene glycol) and diclofenac was added to make polymeric micelles. These micelles were devoid of toxicity to corneal surfaces. The micelles yielded improved movement of drug across cornea. The AUC values of diclofenac in aqueous humor were higher than suspension alone. Thus, it could serve as a potential drug delivery system in ocular therapeutics [133]. Shi et al. synthesized chitosan grafted methoxy poly(ethylene glycol) and PCL polymeric micelles for ocular delivery of diclofenac. The hydrogel was observed to be having low cytotoxicity. The movement of dye (Nile Red) across the transcorneal epithelium suggested improved penetration of polymeric nanocarriers. The aqueous humor concentration for diclofenac nanosupension was higher than corresponding aqueous suspension [134]. Recently a thermosensitive triblock PEG-PCL-PEG (PECE) hydrogel containing diclofenac sodium was formulated and evaluated. The in situ gel was found to be non-irritant to various parts of eyes and with enhanced ocular bioavailability of diclofenac as compared to conventional eye drops [135], [136]. Zhang et al. formulated methoxy poly(ethylene glycol) and PCL polymeric micelles for ocular delivery of diclofenac. The hydrogel was less cytotoxic towards L-929 and HCEC cells. The aqueous humor concentration for hydrogel entrapped diclofenac was higher than corresponding aqueous suspension. Moreover, the thixotropic behavior of gel suited its ocular application [137]. Another triblock polymer system was prepared using poly(ethylene glycol)-poly(ε-caprolactone)-g-polyethyleneimine. A dye namely fluorescein diacetate (FDA) was incorporated into micelles. The deeper penetration of FDA loaded micelles following 30 min of application suggested the capability of such polymeric micelles to deliver hydrophobic molecules to the eye [138]. The steroidal drug triamcinolone acetonide was incorporated into PCL implants. The implant released the drug and there was no sign of inflammation till 4 weeks of insertion. Therefore, it may be used as safe alternative to existing eye drops [139]. The same drug was encapsulated in nanoparticles of pentablock copolymers comprising polylactide–polycaprolactone–polyethylene glycol–polycaprolactone–polylactide. Based on in vitro results the researcher suggested these nanoparticles application for ophthalmic delivery of drugs [140]. Recently, Triamcinolone acetonide was embedded to PCL microfilms. The findings of this study recommend use of such engineered microfilm for the treatment of retinal ailments [141]. The dexamethasone was added to implants and evaluated tor retention and safety to ocular membranes. The implants showed prolonged retention due to slower degradation of PCL [142], [143].

6.4. Polyalkyl cyanoacrylates (PACA)

The PACA is a polymer comprised of alkyl cyanoacrylate units. This polymer has bioadhesive characteristics thereby expression of strong binding to polar surfaces including living tissues. Wood et al. studied the distribution of (^{14}C) labeled poly(hexyl) cyanoacrylate nanoparticles in ocular tissues. The elimination

kinetics of these nanoparticles was observed linear with an approximate half-life of 20 min. Similarly, poly(butyl)-2-cyanoacrylate nanoparticles were radiolabeled using ^{111}Indium-oxine by Fitzgerald et al. and their residence in the eye was investigated. The half-life in this study was reported as 10 min which was attributed to release of radiotag. The authors recommended the use of such nanoparticles for ophthalmic delivery of lipophilic drugs [144], [145]. A more exhaustive study conducted by Diepold et al. compared the distribution of radiolabeled particles in healthy and eyes with inflammation of rabbits. The conjunctiva was the tissue with highest retention. It would be appropriate to mention that the concentration of nanoparticles in inflamed eyes was approximately 3–5 folds higher than healthy eyes at initial time points. Hence, these may be used as drug carriers for steroids [146]. Das et al. formulated poly(isobutylcyanoacrylate) nanoparticles and characterized for variety of parameters. Based on in vitro results the researchers suggested utility of PIBCA nanoparticles for mucoadhesion to ocular surfaces [147]. The steroidal drug tramcinolone acetonide was encapsulated into poly(isobutylcyanoacrylate) nanoparticles. The findings of study indicated sustained ocular delivery of triamcinolone acetonide [148]. However, the PACA's ability to cause disruption of integrity of biomembranes limits its application.

6.5. Polyanhydrides and polyorthoesters (POEs)

Polyanhydrides are a category of polymers that has 2 carbonyl groups linked by an ether bond. Leong et al. investigated the biocompatibility of bioerodible implants of polyanhydrides with rabbit corneas. The implants were devoid of any sort of inflammatory response till 6 weeks of application [149]. The polyorthoesters are hydrophobic polymers with hydrolytically labile orthoester bonds. The POEs containing dexamethasone and 5-fluorouracil were found biocompatible upon subconjunctival injection to rabbit eyes. The addition of dexamethasone also slowed down POE degradation along with sustained drug release [150]. Similar study by Einmahl et al. have demonstrated innocuousness of synthesized POEs and retention in rabbit eyes till 6 months without appreciable deterioration [151].

7. Inflammation sensitive biopolymers

The immune response is mainly represented by inflammation through the agency of several components of which polymorphonuclear leukocytes (PMN) being the principal [152]. The key feature of inflammation is presence of free radicals. Thus, the polymer which lyse upon reaction to free radicals will facilitate drug release at the place of inflammation [153]. Nobuhiko et al. have developed hydrogels (cross-linked with glycidylether) and polymeric matrices of hyaluronic acid which released the entrapped drug upon stimulation by inflammation mediators (like hydroxyl ions) [154], [155]. Recently, Lu Toit et al. developed a chitosan–poly(ε-caprolactone) nanosystem and evaluated its suitability for delivery to the ophthalmic posterior portion. The findings of present investigation indicated improved control of inflammation, increased movement across the corneal laminas and smaller particle sized well tolerated by the eyes. Thus, such smart polymers may facilitate the drug delivery as well as may help to diminish dose requirements of anti-inflammatory agents in ocular therapeutics by virtue of their responsiveness towards inflammation mediators [156].

8. Conclusion

Polymeric substances play a vital part in the sustained drug delivery. Specially, biodegradable polymers have been elaborately attempted for ophthalmic therapeutics in the latest decades. In present review, we have compiled mostly preparation, characterization and uses of biodegradable polymers of natural origin as well as synthetic ones. The utility of biodegradable polymers as carriers for anti-inflammatory drugs to the eye has been discussed. Two main merits of polymeric drug delivery systems like improving drug bioavailability and avoiding side effects are important in ophthalmic drug delivery. The growth of novel biodegradable polymers has achieved outstanding pace in the past few years. These polymers will be beneficial in delivering novel therapeutic substances like genes, therapeutic antibodies and bioactive proteins. Thus, fabrication of new biodegradable polymeric systems is presently in research for site-specific delivery of drug molecules.

Recommended articles

References

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> …Albumin, as a main soluble protein of the circulating system, is oriented from different resources, i.e., egg white (vis. ovalbumin), bovine serum albumin (BSA), or human serum albumin (HSA) (Sharma et al., 2016). A vast variety of bioactives/drugs have revealed the ability of binding with albumin owing to its potential of serving as a depot/transporter molecule (Larsen et al., 2016)….

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