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REVIEW

Recent Advances in Smart Polymers-Based Therapeutics in Ophthalmology

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Abstract: Ophthalmic diseases represent a significant burden on global health, contributing to widespread visual impairment and blindness. The distinct anatomical and physiological barriers of the eye significantly restrict the use of conventional ocular delivery techniques. This has prompted research into cutting-edge drug delivery methods that optimize therapeutic benefits and reduce adverse effects. The use of polymer-based drug delivery systems is a promising technique that provides regulated drug release over long periods of time, enhances drug stability, and guarantees localized distribution to specific ocular tissues. This field has been revolutionized by recent advancements in smart polymer-based systems, which enable the development of drug delivery platforms that react dynamically to certain stimuli like pH, temperature, light, and enzymes. By releasing the active pharmaceutical ingredients only when specific conditions are met, these stimuli-responsive devices are intended for delivering medications in a controlled manner, improving treatment precision and minimizing undesirable systemic effects. This review summarizes recent developments in smart polymer-based therapies for ophthalmology, highlighting advances in stimuli-responsive, biodegradable, and multifunctional polymers that have the potential to transform ocular drug delivery, enhance therapeutic efficacy, and improve patient adherence in managing various eye conditions.

Keywords: ocular diseases, nanotechnology, drug delivery, synthetic polymers, biocompatibility

Introduction

Globally, millions suffer from ocular diseases that, if left untreated, can result in partial or complete vision loss, significantly diminishing quality of life.[1] Conditions such as dry eye disease (DED), glaucoma, age-related macular degeneration (AMD), diabetic retinopathy (DR), and choroidal neovascularization (CNV) contribute substantially to the global burden of visual impairment.[2] Despite advances in ophthalmic science, effective treatment remains a major challenge due to the eye's unique anatomical and physiological barriers, including the blood-retinal barrier, corneal epithelium, and rapid tear clearance, all of which restrict drug penetration and retention.[3] Conventional treatment approaches including topical formulations and intraocular injections often suffer from poor bioavailability, short residence time, and patient non-compliance.[4] Topical eye drops, for instance, typically result in drug bioavailability of less than 5% due to rapid drainage and blinking reflexes.[5] Invasive delivery methods, while effective in some cases, are associated with considerable risks, such as retinal damage and increased chances of infection.[6] These limitations have accelerated interest in advanced drug delivery platforms that can overcome ocular barriers and sustain therapeutic concentrations at the target site.

Polymer-based drug delivery systems have emerged as promising tools for improving ocular therapy. Their biocompatibility, structural versatility, and tunable properties enable sustained drug release, improved solubility, and enhanced targeting.[7] Among these, hydrogels, nanoparticles, and polymer-drug conjugates have been explored extensively for their ability to enhance drug permeation and retention in ocular tissues.[8] However, static polymer systems may fall short in providing precise spatiotemporal control over drug release in the dynamic ocular environment. To address this, the focus has shifted towards smart polymers a class of stimuli-responsive materials that alter their physical or chemical behavior

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in response to specific external or internal stimuli such as pH, temperature, ionic strength, enzymes, or magnetic fields.[9,10] These intelligent systems allow for on-demand, site-specific drug release, aligning closely with the physiological and pathological conditions of the eye.[11] For instance, thermoresponsive polymers can adjust their solubility or swelling behavior at ocular surface temperatures, enabling temperature-triggered drug release,[12] while pH-sensitive hydrogels can deliver therapeutics preferentially in inflamed or infected tissues where the local pH deviates from normal values.[13] Enzyme-responsive carriers, likewise, can selectively degrade and release drugs in the presence of disease-associated enzymes. Such adaptability offers significant potential in treating complex ocular disorders, minimizing systemic exposure, and reducing adverse effects.[14,15]

This review critically explores recent advancements in smart polymer-based drug delivery systems within the field of ophthalmology. It provides an in-depth analysis of various responsive polymer types, their mechanisms of action, and their application in managing a range of ocular diseases. Furthermore, the review addresses current challenges, regulatory considerations, and future perspectives, aiming to shed light on how smart polymer technologies may shape the next generation of targeted ocular therapeutics.

Barrier in the Ocular Delivery System

In contrast to other body regions, the presence of many ocular barriers presents distinct obstacles for medication delivery, particularly with its application to the posterior section of the eyes.[16] Ocular barriers consist of static and dynamic barriers that impede the transport of medicines through the anterior into the posterior segment of the eye.[17] The structure of the eye can be categorized into different segments including the anterior one (comprising the cornea, ciliary body, conjunctiva, and aqueous humor) and the posterior portion (composed of the sclera, vitreous body, choroid, and retina as shown in Figure 1.[18,19] Every region is vulnerable to various ailments that may necessitate distinct methods of administration and treatment approaches.[20] These anatomical features collectively establish ocular barriers that delineate the ocular milieu and preserve the integrity of eye ocular tissue and cells, safeguarding the eye and sustaining its homeostasis. Nonetheless, these obstacles can significantly restrict drug penetration, leading to diminished bioavailability of pharmaceuticals in the ocular region.[21] The first barrier is the tear film, which comprises mucous, aqueous, and lipid layers that work collectively to protect, hydrate, and maintain the integrity of the anterior eye surface.[22] These

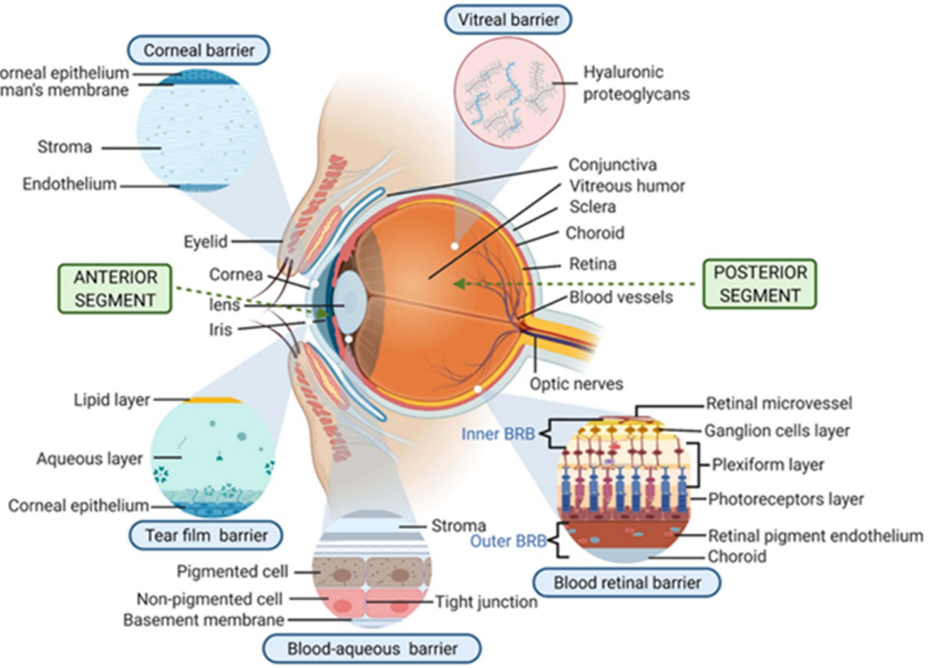

Figure 1 Structure of the eye and different barriers. Adapted Adrianto, M.F. et al, in vitro dissolution testing models of ocular implants for posterior segment drug delivery. Drug Delivery and Translational Research, 2022. 12(6): p. 1355–1375. © The Author(s) 2021. Creative Commons Attribution 4.0 International License.[31]

physiological barriers significantly influence the pharmacokinetics of ocular drug delivery systems. Following eye drop instillation (~35 μL), the precorneal drug half-life is 1–3 minutes, with up to 80% lost via systemic drainage through the nasolacrimal pathway.[23] Drug retention is influenced by blinking rate, drop volume, and physicochemical properties, including ionization and lipophilicity.[19] The cornea of the eye may be an additional obstacle to the administration of drugs.[18] Epithelial cells are interconnected by desmosomes, tight junctions, adherent junctions, and junctions with gaps, constituting the primary barriers to drug permeability.[24] The vitreous humour serves as a substantial obstacle to the infiltration of nanoparticulate ocular medication systems for administration. Hyaluronic acid, a negatively charged material present in the vitreous, can interact with positively charged molecules, resulting in the aggregation and immobilization of DNA/cationic polymers.[25] The eye is isolated from the human body by the conjunctival, scleral, and blood-ocular barriers, which include the blood-retinal barrier and the blood-aqueous barrier.[26] It comprises two primary components: the blood–aqueous barrier (BAB) and the blood–retinal barrier (BRB). The Blood-Aqueous Barrier consists of iris epithelial cells, the non-pigmented epithelium of the ciliary body, capillary endothelial cells, and all of which include tight junctions.[27] The blood-retinal barrier limits the entry of chemicals into the retina via tight junctions and active transport processes, preserving the integrity of the retinal environment.[28] The BAB regulates molecular exchange among blood arteries and the anterior chamber of the eye via tight junctions and controlled channels. Both of these lines of defense are crucial for preserving equilibrium within the optic nerve.[29] Consequently, increased molecular weight of this medicine leads to a reduced concentration of solutes that permeate the blood-aqueous barrier into the aqueous humor.[30]

Polymers-Based Drug Delivery Systems in Ophthalmology

Polymeric particles may comprise substances that decompose or non-biodegradable polymers sourced from synthetic or natural origins, resulting in a diverse array of conceivable structures and shapes.[32] The dimensions and arrangement of polymers particles can be controlled by choosing different polymer materials, adjusting the composition ratio, or employing various preparation methods such as solvent precipitation and emulsification. The alteration of physicomechanical characteristics in polymeric particles can be achieved by precisely modifying the structure, crosslinking, molecular mass, and connections with different polymer components to improve the efficacy of the injectable in the ocular environment, reduce the risk of bio-contamination, and enhance particle stability.[33] Figure 2 depicts various polymer-based drug delivery platforms, like eye drops, hydrogels, and contact lenses, designed to improve therapeutic outcomes in glaucoma management.

Biopolymers have gained greater prevalence in polymeric applications due to advancements in production technology and enhanced comprehension of material features. They are derived from naturally occurring monomers or component parts (animal, plant, fungi, bacteria) and generally demonstrate high biocompatibility, swift deterioration in aqueous conditions and a diverse range of viscoelastic properties, facilitating the creation of biological materials for ocular applications for delivering drugs. Common biological polymers employed in ocular biological materials and therapeutic delivery systems include cellulose, hyaluronic acid (HA), chitosan, collagen, pullulan, gelatin and guar gum. Natural polymers-systems to deliver different drugs for treating ocular diseases are listed in Table 1:

Hydrogels for Ocular Surface and Corneal Drug Delivery

Hydrogels are exceptionally efficient for ocular medication administration owing to their capacity to hold substantial volumes of water, rendering them suitable for the management of dry eye disease and superficial corneal disorders. Hydrogels comprise interconnected networks of synthetic and/or biological hydrophilic polymers that absorb aqueous solutions. A diverse array of hydrogels is accessible for intraocular and extraocular applications, such as contact lenses and vitreous substitutes[47] and prosthetics.[48] The broad spectrum of ocular applications is due to the hydrophilicity of hydrogels that are and the versatility of the constituent materials. The decreased viscosity in the sol state further safeguards cells against shear-induced death during syringe injection in tissue engineering procedures.[49] Thermogel can be sterilized through filtration in its sol state for practical application.[50]

Recent advancements in smart hydrogels have allowed them to react to environmental stimuli, including pH, ionic strength, and mechanical forces. Smart materials are a class of materials with distinct features and capabilities that allow

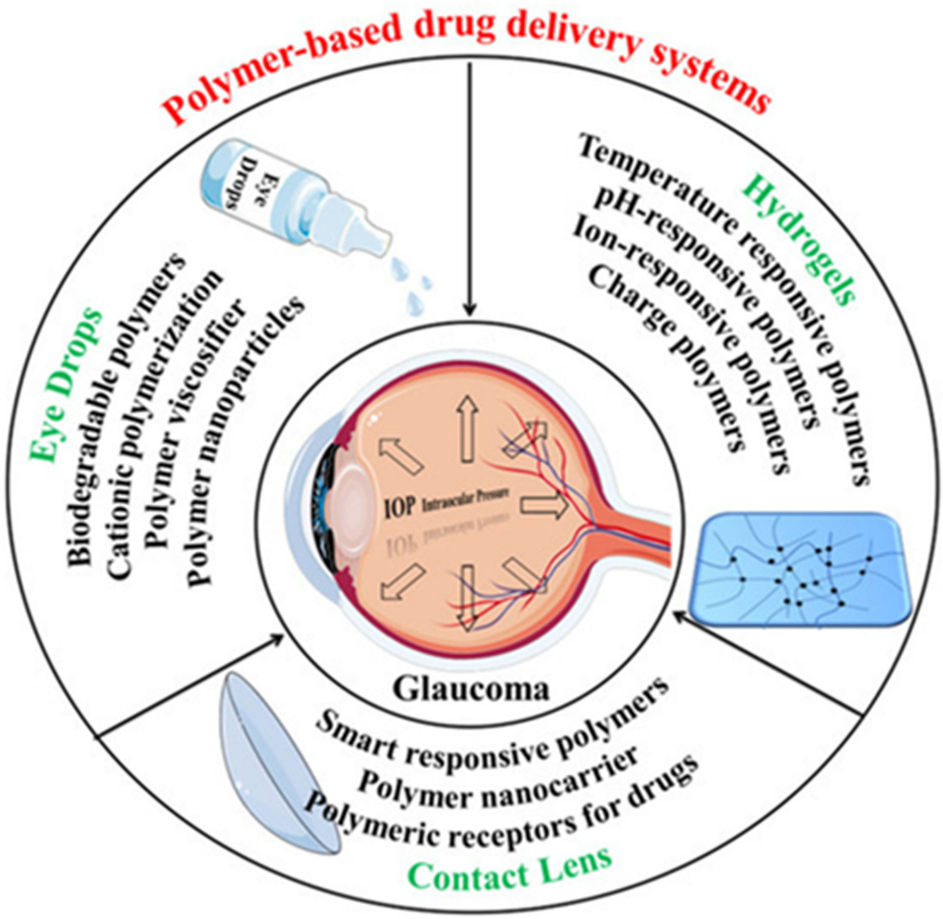

Figure 2 Polymer-based delivery systems for glaucoma treatment, including eye drops, hydrogels, and contact lenses, are designed to enhance bioavailability and enable controlled, sustained drug release. Smart polymers within these platforms respond to ocular stimuli (pH, temperature) for targeted intraocular delivery. Adapted from Sun H, Wang G, Feng Q, Liu S. Polymer-based self-assembled drug delivery systems for glaucoma treatment: design strategies and recent advances. Polymers, 2023. 15(22): p. 4466. © 2023 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (https://creativecommons.org/licenses/by/4.0/).[34]

them to react to inputs in the ocular environment.[51] These sophisticated systems integrate the adaptability of polymers with the precision of "smart" response mechanisms, facilitating regulated, targeted, and prolonged release of medicinal substances. Recent research and clinical advancements have markedly progressed this subject, providing more efficacious treatments and mitigating the constraints linked to conventional drug delivery techniques.

Table 1 Natural Polymers Based Nano Therapeutics for Ocular Delivery

Delivery System	Drug	Main Finding	References
PLGA microparticles containing Chitosan/ HA	Ranibizumab	Possibility for enhanced intravitreal administration of therapeutic proteins	[35]
Chitosan-based hybrid nanoparticles	Epoetin-β	Increase mucoadhesion and residence time	[36]
Chitosan-coated flexible liposomes	Metoprolol	Permeation across the cornea Promote corneal permeability by Relaxing intracellular	[37]

(*Continued*)

Table 1 (Continued).

Delivery System	Drug	Main Finding	References
Peptide-encapsulated gelatin nanoparticles	GNP-gp91	Positive charge slow-release behavior Evaluation of neovascularization-related factors	[38]
HA-GB eye drop	Ginkgo biloba	Effective in reducing dry eye disease receiving cataract surgery	[39]
HA based injectable hydrogels	Sunitinib	Eliminate oxidative stress Regulating the secretion of inflammatory factors.	[40]
pHEMA/PVP-HA-based layers	Timolol	Increase drug permeation for porcine cornea	[41]
PEGylated liposomes	Indocyanine green (ICG)	The accumulation of nanoparticles on the ocular surface increased with more surface alteration.	[42]
Maleimide-decorated liposomes	Maleimide	-increase conjunctival retention	[43]
Hyaluronic acid conjugate with pentratin nanogels	Chromophore contain trans retinol		[44]
Pullulan–dexamethasone conjugates self-assemble	Dexamethasone	Reduce frequency Targeted delivery into the retinal cells	[45]
Sodium alginate polymannuronate (SA) nanocarriers	Ciprofloxacin	Mitigate the scleral inflammation in rabbit uveitis models	[46]

Smart Polymer-Based Nanotherapeuctics for Ocular Drug Delivery

Smart polymer-based nanotherapeuctics for ocular drug delivery involves utilizing diminutive nanoparticles composed of polymers that react to specific stimuli within the eye, facilitating specific drug administration to the intended site in ocular tissue, thereby enhancing treatment efficacy and minimizing side effects through improved drug retention time and decreased frequency of management.[52] These polymers can alter their structure or characteristics in response to environmental stimuli such as pH, temperature, or light, facilitating targeted medication release at the specified area within the eye (Figure 3).[53] Polymers utilized in ocular nanotherapeuctics must exhibit excellent biocompatibility with ocular tissues, hence reducing irritation and inflammation.[54] The dimensions and surface characteristics of the

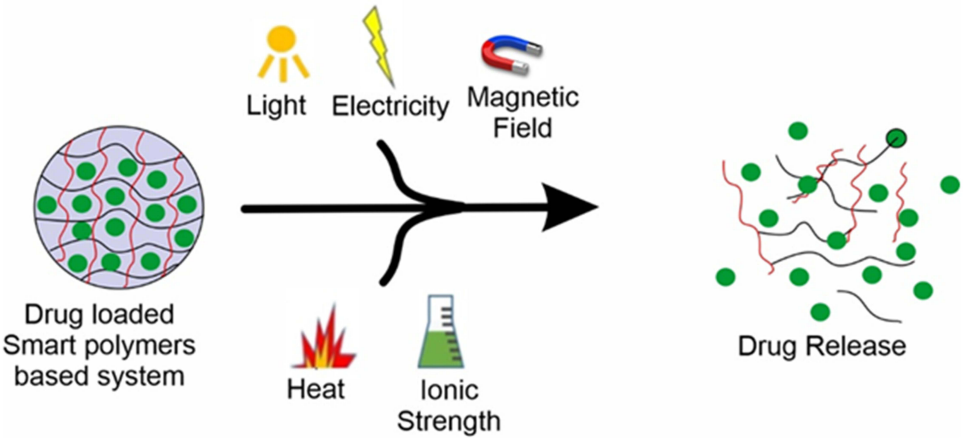

Figure 3 Schematic representation of the drug release from smart polymer based systems. These systems are composed of responsive polymers that can alter their structure or characteristics in response to environmental stimuli such as pH, temperature, magnetic field, ionic strength or light, facilitating targeted medication release at the specified area within the eye.

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nanoparticles are essential for maximizing their interaction with ocular tissues, hence improving medication penetration and retention.[55] Examples of intelligent polymers utilized in ocular medication administration include chitosan, a naturally sourced, positively charged polymer that effectively binds to the negatively charged mucosal lining of the eye, hence enhancing drug retention.[56] Poly(lactic-co-glycolic acid) (PLGA) is a biodegradable synthetic polymer characterized by adjustable degradation rates, facilitating the regulated release of the medication. Sodium alginate is a mucoadhesive polymer capable of forming gels in situ, hence prolonging medication retention on the ocular surface.[57] Derivatives of cellulose can be engineered to react to pH fluctuations in the eye, facilitating targeted medication administration.[58] Polyethylene glycol (PEG) is frequently employed to alter the surface of nanoparticles, enhancing their biological compatibility and inhibiting rapid clearance from the ocular environment.[59] Smart polymer-based nanotherapeutics may be utilized for ocular administration to administer anti-glaucoma medications directly to the targeted region in the eye, hence decreasing intraocular pressure.

Thermoresponsive Polymers for Sustained Ocular Drug Delivery

Thermo-sensitive system are system undergo transitions in phase change and modifications to structure in accordance with temperature, due to heightened hydrophilic properties, the formation of hydrogen bonds between molecules, and physical intertwining of chains of polymers. These gel-like substances are the most thoroughly researched stimuli-responsive agents and are utilised in the management of several visual disorders, including glaucoma, ocular infections, macular degeneration and dry eye syndrome.[13] The difficulties of ocular drug administration arise from the low solubility of hydrophobic therapies and the limited permeability and swift elimination of drugs, due to the complex anatomy and physiological of the eyes.[13] The biodegradable temperature-sensitive polymer PLGA-PEG-PLGA presents a promising ocular drug delivery strategy, creating an intravenous solution that in situ transforms into a gel for prolonged drug release. The research exhibited the remarkable biocompatibility of the blank PLGA-PEG-PLGA thermogel, revealing no significant disparities from saline in rat eye enucleation, in vivo inflammation assessments, and subconjunctival injections. The method improves patient adherence by decreasing injection frequency and mitigating related dangers, rendering it a secure and efficient choice for ocular drug delivery.[60]

This research established an injectable hydrogel for extended ocular delivery of dexamethasone, utilizing a healing themselves thermosensitive ABA triblock copolymer. The previously drug was covalently attached to the polymer via RAFT polymerisation, with methacrylated dexamethasone reacting with N-isopropylacrylamide (NIPAM) and N-acryloxysuccinimide (NAS). The hydrogel was synthesised by combining the thermosensitive polymer with cystamine at 37 °C, resulting in covalent cross-linking and self-healing properties due to disulphide bonds. Dexamethasone release from the hydrogel exhibited first-order kinetics over 430 days, sustaining therapeutic levels for up to 500 days. The system demonstrated favourable cytocompatibility with ARPE-19 retinal cells and exhibited no toxicity. This injectable hydrogel system presents a promising strategy for prolonged dexamethasone delivery in the management of ocular inflammatory disorders.[61]

Hirun et al, created a hybrid thermosensitive the poloxamer 407-based in situ hydrogel that incorporates moxifloxacin-loaded silk fibroin nanoparticle (MFX-FNPs) to enhance the retention duration of the antibacterial drug in the ocular region. Poloxamer 407, poloxamer 188, and polycarbophil (PCB) were used to enhance the mucoadhesive qualities and rheological attributes for in situ gel formation. The Box-Behnken design was employed to optimise the PCB composition, yielding a formulation of 20% P407, 7.35% P188, and 0.6% PCB. The amalgamation of these polymers improved the mucoadhesive characteristics, and the release of metronidazole from the composite adhered to an unconventional mechanism. The thermosensitive micellisation of the mix was validated via differential scanning calorimetry. This optimised thermosensitive hydrogel may function as an efficient platform for mucoadhesive ocular medication delivery, enhancing the duration of therapeutic efficacy.[62]

Hsiue et al, formulated controlled-release ocular preparations for glaucoma treatment utilizing temperature-sensitive poly-N-isopropylacrylamide (PNIPAAm). The linear and cross-linked PNIPAAm nanoparticles, infused with epinephrine, were synthesized, and their medication release kinetics and cytotoxicity were assessed in vitro. The formulations, comprising linear PNIPAAm or a combination of linear and crosslinked nanoparticles, were evaluated in rabbits to determine their impact on intraocular pressure (IOP) reduction. The linear PNIPAAm formulation decreased intraocular

pressure for six times longer than conventional eye drops, whilst the combination of linear and crosslinked nanoparticles persisted for eight times longer. The findings indicate that thermosensitive PNIPAAm hydrogels can efficiently modulate the release of antiglaucoma medicines, providing extended therapeutic effects.[63]

Ionic Strength-Sensitive Polymers for Ocular Drug Delivery

Due to the presence of various cations like Na+, K+, Mg2+, and Ca2+ in tears, anionic polysaccharides can interact with these cations, resulting in ionic interactions that induce conformational changes and the establishment of a three-dimensional network structure. Sai et al, formulated an in situ gel-forming solution utilising PEG-DSPE, gellan gum for the ocular administration of curcumin (CUR), having low bioactive molecule. The amalgamation enhanced curcumin's stability, solubility, and permeability. Cellular uptake experiments demonstrated that the mixed micelles were effectively internalised by human corneal epithelial cells. Chemical stability assessments indicated that the formulations exhibited negligible degradation (1.4% and 1.2%, respectively) during a 24-hour period in contrast to free CUR. Irritation tests conducted on rabbits indicated no visual effects, and histological investigation revealed no alterations in the cornea, iris, or conjunctiva.[64] Zhu et al, established a ion-activated ketotifen intraocular delivery system utilising deacetylated gellan gum, a natural polysaccharide. The inquiry evaluated its rheological properties, stability, in vitro gelation, release characteristics, and in vivo pharmacodynamic efficacy. The formulation exhibited ideal viscosity for liquid droplet creation, succeeded by a fast sol-gel transition resulting from ionic interactions. The viscosity stayed consistent for over 180 days of storage. In vitro release profiles demonstrated persistent ketotifen release, while scintigraphic tests validated increased residence time. In situ gels offered extended and sustained pharmacological effects at equivalent dosages compared to traditional drops.[65] In situ thermo-sensitive ocular drug delivery systems may serve as an effective method for the systemic administration of various lipophilic drugs.

pH-Sensitive Polymers for Targeted Ocular Delivery

pH-sensitive polymers represent a category of advanced materials capable of drug release in reaction to the acidic conditions commonly found in inflamed or diseased ocular tissues. The alteration in pH value can trigger drug release at targeted sites within various polymeric delivery systems, primarily through two distinct mechanisms.[66] These polymers exhibit ionization at a designated pH, resulting in an increase in the surface charge of the polymeric chains. The internal repulsions increase and expand through the absorption of water. The polymer chains remain compact and folded when the solvent inhibits ionization of the polymeric system.[67] With a minor alteration in ambient pH, the polymer's functional groups undergo ionization, leading to a phase transition characterized by dissolution or swelling.[68] The gradient of pH variation can be produced using enzymes like urease, which catalyses the hydrolysis of urea into CO2 and ammonium, thus modifying the pH. Numerous pH-responsive polymer substances have been created as delivery systems for ophthalmic applications, including cellulose acetate phthalate, hyaluronic acid, chitosan and polycarbophil.[53,69] In situ gel is defined as a polymer solution that is delivered in liquid form and, upon exposure to specific physiological conditions such as pH, ionic strength, temperature changes, or UV light, undergoes a phase transition to form a semisolid gel. Ketofen fumarate is classified as a histamine H1 receptor antagonist and is utilised in the management of allergic conditions such as conjunctivitis and rhinitis. This study investigates the effects of natural polymers, specifically xanthan gum and gellan gum, on the properties of a pH-triggered in situ ocular gel. The drug release rate of the optimized formulation is then compared to that of the commercially available ketotifen eye drop. Eight formulations (F1-F8) were developed utilizing varying concentrations of xanthan gum and gellan gum in conjunction with carbopol-based gel. The optimal formulation F5 was developed using 0.75% Carbopol 940 as a gelling agent, 0.3% xanthan gum as a viscosity enhancer, and 0.02% methyl hydroxyl benzoate as a preservative. The drug content was measured at 99.74%±1.31, with a pH value of 5.2±0.31 and a gel strength of 46.6±0.1 seconds, demonstrating sustained drug release over time.[70] Corneal neovascularisation (CoNV) leads to blindness, presenting a persistent challenge with few management alternatives. Small interfering RNA (siRNA) represents a promising approach for the prevention of CoNV. This study presents a novel approach utilising siVEGFA to inhibit vascular endothelial growth factor A (VEGFA) for the treatment of CoNV. A pH-sensitive polycationic mPEG2k-PAMA30-P(DEA29-D5A29) (TPPA) was developed to enhance the efficacy of siVEGFA delivery. TPPA/siVEGFA polyplexes utilise clathrin-mediated endocytosis for cellular entry, achieving

enhanced cellular uptake efficiency and comparable silencing efficacy to Lipofectamine 2000 in vitro. Haemolytic assays confirmed that TPPA is safe in normal physiological environments (pH 7.4) but can readily disrupt membranes in acidic mature endosomes (pH 4.0). Research indicates that the in vivo distribution of TPPA can extend the retention time of siVEGFA and enhance its penetration in the cornea. In a mouse model of alkali burn, TPPA effectively delivered siVEGFA to the lesion site, resulting in significant VEGFA silencing efficiency. The inhibitory effect of TPPA/siVEGFA on CoNV was comparable to that of the anti-VEGF drug ranibizumab. The use of pH-sensitive polycations for delivering siRNA to the ocular environment represents an innovative approach to effectively inhibit CoNV.[71]

Enzyme-Responsive Drug Delivery

Enzymes present in the ocular microenvironment according to both pathological and physiological conditions include matrix metalloproteinases in tissues, hyaluronidase in the vitreous, and lysozyme and esterase in tears.[72] A particular component of the enzyme-responsive polymer is the substrate or substrate mimic of the enzyme, and its physical and chemical properties can alter in response to a specific enzyme.[73] The other component of the polymer is the change of the internal interaction within nanomaterials, which may cause the instability of the nanocarriers and cause the release of drugs.[73] The system can alter its physical or chemical properties and release medicines under enzymatic catalysis. Monotherapy, particularly the use of antibodies directed against vascular endothelial growth factor (VEGF), has demonstrated constraints in the management of choroidal neovascularisation (CNV) due to the exacerbating role of reactive oxygen species (ROS) in CNV development. We created a combined therapy utilizing a DNA origami platform aimed at multiple elements of ocular neovascularisation. Our research indicated that ocular neovascularisation was significantly inhibited by intravitreal administration of a rectangular DNA origami sheet modified with VEGF aptamers (Ap) coupled to an anti-VEGF antibody (aV) through matrix metalloproteinase (MMP)-cleavable peptide linkers in a murine model of choroidal neovascularisation (CNV). The DNA origami-based therapeutic platform generally concentrates in neovascularisation lesions due to the dual-targeting capability of aV and Ap, subsequently leading to the breakage of the peptide linker by MMPs, which releases the antibody. The released antibody and Ap together suppressed VEGF activity. Furthermore, the remaining naked DNA origami may efficiently scavenge reactive oxygen species, diminishing oxidative stress at CNV sites and so optimising the synergistic effects of neovascularisation inhibition.[74] The findings indicated that the degradation of GelMA+ can be adjusted by altering the crosslinking density or varying the concentrations of MMP-9 exposure. The liberation of BLF from 30% w/v GelMA+ is facilitated by a synergy of diffusion and material degradation mediated by MMP-9 enzymes. Consequently, the therapeutic enzyme-responsive GelMA+ as a BCL may serve as a prospective treatment for RCE. Future endeavours will concentrate on enhancing the materials to administer additional therapeutic drugs at physiologically pertinent quantities of MMP enzymes present in tear fluid. This thesis aimed to create an enzyme-activated therapeutic release system utilising a distinctive gelatin methacrylate formulation (GelMA+) and bovine lactoferrin (BLF), which serves as a prospective treatment for corneal wound healing. Recurrent corneal erosion (RCE), resulting from the loss of superficial corneal epithelial cells, induces significant ocular pain that impacts productivity and quality of life. RCE was conventionally managed with ocular lubricants and occlusion (to prevent blinking).[75] Concurrently, tear fluid exhibits similarities to serum in some respects and comprises functional constituents including mucosal proteins, soluble antibodies, enzymes, and ions. Consequently, many ocular drug delivery systems have been developed for the tear fluid milieu, including pH-sensitive, thermo-sensitive, and ionic-triggered devices.

Gene Therapy and Smart Polymers for Ocular Gene Delivery

Gene therapy signifies a promising advancement in ophthalmology, particularly for hereditary disorders like Leber congenital amaurosis and retinitis pigmentosa. Recent advancements in smart polymer systems have concentrated on enhancing gene delivery vectors capable of safely and efficiently transporting genetic material (eg, CRISPR-based therapeutics) to retinal cells. The cationic polymer is combined with DNA to create nanoscale polyplexes (Figure 4). Polymer based example vectors include polyethylene imine and chitosan. Polymeric nanoparticles are increasingly significant in gene delivery owing to their structural plasticity, biodegradability, and inexpensive manufacturing. Notable synthetic polymers comprise.[76] Exceptional research by Naash et al shown that rod-shaped CK30-PEG (polyethylene glycol)-compacted nanoparticles

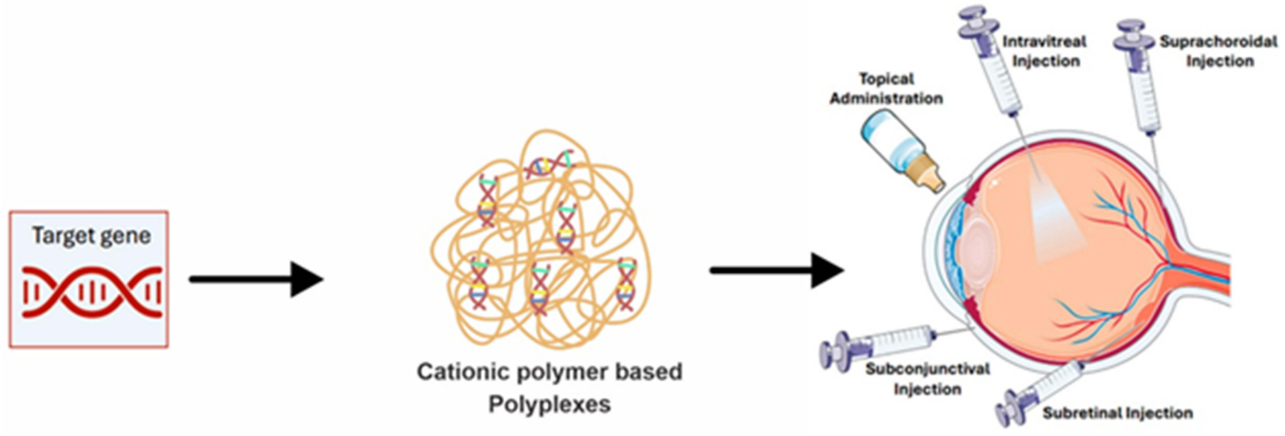

Figure 4 Representation of the polymers based non-viral vectors for Gene delivery to the eye. Cationic polymers are combined with genetic materials to create nanoscale polyplexes and injected to various parts of the eye. Adapted from Kharisova CB, Kitaeva KV, Solovyeva VV et al, Looking to the Future of Viral Vectors in Ocular Gene Therapy: Clinical Review. Biomedicines, 2025. 13(2): p. 365. © 2025 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (https://creativecommons.org/licenses/by/4.0/)[78].

effectively transfected both retinal pigment epithelium and photoreceptors, resulting in successful gene therapy for Rpe65−/− (retinal pigment epithelium 65; a model of Leber congenital amaurosis) and Abca4−/− animals.[77] Table 2 below enlist various stimuli responsive smart polymers based delivery systems for ophthalmic diseases.

Poss: Polyhedral oligomeric silsesquioxane

Table 2 Smart Polymer Based Nano Therapeutics for Ocular Delivery System

Delivery System	Composition	Induction Model	Findings	References
Thermo-responsive FK506 hydrogel	MPOSS-PEG-PPG, MPEP	Murine dry eye model	Good temperature-sensitive sol-gel transition Mucoadhesive long-acting ocular delivery system	[79]
In situ gel thermogels	PLGA-PEG-PLGA	Subconjunctival injection	Can deliver both hydrophilic and hydrophobic drug	[60]
PLGA-PEI loaded with Revesterol	PLGA-PEI and poloxamers 407 hydrogel	In Vitro Dry Eye Model	Exhibit sustained release Powerful antioxidants with anti-inflammatory effects on corneal epithelial cells	[80]
pH-Responsive polymer	PEG hydrophilic block A pH-responsive block	A murine model of hypoxia-induced angiogenesis	Significantly inhibits retinal angiogenesis	[81]
pH-responsive based on cellulose acetate	pH-Responsive Cyclosporine	Experimental dry eye model	Nanocarrier designed for dry eye disease	[82]
pH-trigger in situ ocular gel	Xanthan gum, gellan gum	Experiment model of conjunctivitis and rhinitis	Provide sustained drug release over period 8h	[70]
Nanozyme-thixotropic anionic hydrogel coating	Reaction occur that is Schiff based	Animal model of fungal keratitis	The retention time and permeability of voriconazole	[83]

(*Continued*)

Table 2 (Continued).

Delivery System	Composition	Induction Model	Findings	References
C-dots@Gel	In situ gel	Experiment model of dry eye disease	Adherence on corneal surface extend the ocular surface retention time	[84]
Enzyme responsive system	Phosphorylated peptide-drug conjugate to liberate active pharmaceuticals at the target location.	In-vitro studies performed on macrophages	Displays longer precorneal retention	[85]
Tannin composed nanozyme based hybrid hydrogels	Treatment option for P. aeruginosa	In animal model of fungal keratitis	Eye infectious disease	[86]
Microbubbles for ultrasound triggered drug delivery	Can deliver drug with high molecular weight	Experiment performed on retina of eye.	Useful for retinal disease	[87]

Application of Smart Polymer Based Drug Delivery System in Ocular Diseases

Vitrectomy

Vitrectomy is frequently performed to address various eye disorders.[88] An optimal intraocular tamponade is essential for vitreo-retinal surgery. Gade et al developed a biodegradable thermogelling copolymer and subsequently investigated its cytotoxicity on ARPE-19 cell culture as well as its intraocular biocompatibility in vitrectomised rabbit eyes. Aqueous solutions of Polymer hydrogels can be positioned above the plastic film featuring a punched hole of up to Φ 3 mm. The average cell viability associated with varying concentrations of hydrogel solutions was 92.1±16.6%, indicating no concentration-related effect. The Poly(PEG/PPG) solution (5%, 0.5 mL to 1 mL) can be readily injected into a vitrectomized eye using a 23G needle at room temperature, with gelation occurring within 3–5 minutes in vivo. Post-operatively, the intraocular pressure in the operated eyes ranged from 8.4 to 19.8 mmHg. Conjunctiva and anterior segment Thermosensitive hydrogels exhibited compatibility with cells in vitro. These materials were injectable and demonstrated an efficient sol-gel transition with enhanced surface tension during vitrectomy surgery. Long-term follow-up of in vivo biocompatibility studies is currently ongoing. The studies suggest a possible application of thermosensitive hydrogels as an intraocular tamponade.[89] PVA hydrogel was chosen as a vitreous substitute due to its excellent optical qualities, particularly its refractive index, which closely approximates that of human vitreous, rendering it indistinguishable from natural vitreous during the initial injection. Andreia et al utilised glutaraldehyde as a crosslinking agent to create a reticulated PVA/glutaraldehyde hydrogel, which exhibits a greater viscosity compared to PVA.[90]

Age-Related Macular Degeneration

Age-related macular degeneration is a vision-impairing condition that affects the posterior portion of the eye and is difficult to treat due to its intricate anatomy and physiology. Thermoresponsive hydrogels present a viable option, as they undergo a change from sol to gel at physiological temperatures, facilitating easier injection and extended drug release. This method streamlines management while guaranteeing prolonged therapeutic outcomes. Thermoresponsive hydrogels thus offer a promising alternative for enhancing treatment outcomes in AMD. A technique for grafting PNIPAAm onto chitosan was examined to improve the encapsulation of sunitinib (SUN), a hydrophilic tyrosine kinase inhibitor. Gade et al, examined various chitosan concentrations (10%, 30%, and 50%) and evaluated their impact on drug entrapment in conjunction with PNIPAAm. In vitro dissociation studies demonstrated that the dissolution of sunitinib might be modulated by the degree of chitosan grafting. Nonetheless, the gel strength of 30% Cs-g-PNIPAAm (3%-5% w/v) did not markedly affect drug release. The results indicate that the Cs-g-NIPAAm hydrogel can serve as a customizable

injectable system for intrascleral drug delivery, offering an attractive platform for tailored therapeutic uses.[91] Peng et al, developed a unique temperature-sensitive in situ hydrogel was created for the treatment of to address AMD. Furthermore, mPEG-CS-FL-TSG exhibited reduced cytotoxicity. The approach successfully addressed the constraints of brief retention and swift release of liposomes, as well as the inadequate drug permeation of hydrogels. This novel delivery device provides a non-invasive, efficient method for treating posterior ocular disorders, showing promise for improved medication delivery and therapeutic results.[92]

Traumatic Optic Neuropathy

Presently, there is a shortage of standardized treatment for traumatic optic neuropathy (TONNE). Diverse techniques have been formulated to safeguard and restore retinal ganglion cells (RGCs) following traumatic optic neuropathy (TONNE). Wang et al, prepared a thermosensitive hydrogel drug delivery system for injection was created to administer triamcinolone acetonide for the treatment of optic nerve degeneration. The hydrogel displayed a mechanical modulus of roughly 300 Pa, like the vitreous, and exhibited thermosensitivity with prolonged drug release. In vitro co-culture with primary retinal ganglion cells (RGCs) demonstrated a 38.5% enhancement in neurite length, underscoring its axon regeneration capability. A solitary intravitreal injection conferred extended neuroprotective and regenerative benefits lasting from 14 to 28 days. This hydrogel system, which integrates PLGA-PEG-PLGA with CNTF or TA, demonstrates potential as a novel therapeutic approach for optic nerve degeneration by enhancing RGC survival and facilitating axonal regeneration.[93]

Glaucoma

Glaucoma is defined as a progressive neuropathy of the optic nerve leading to an optic disc cupping and the death of retinal ganglion cells.[94] The disease, the foremost cause of irreversible blindness globally, presently impacts 3.5% of individuals aged 40 to 80 years. The objective of glaucoma management is to reduce intraocular pressure through pharmacological agents, laser interventions, and/or surgical procedures. First-line treatment typically involves pharmacotherapy, supplemented by laser and surgical interventions to achieve additional intraocular pressure reduction in cases with insufficient initial responses.[95] Recent research efforts have concentrated on the creation of biodegradable polymer-based drug delivery systems to address the deficiencies of existing glaucoma medicines. These provide focused, controlled drug delivery of therapeutic agents to surmount the challenges posed by the eye's distinct architecture and physiology, enabling efficient medication delivery to the anterior portion. These systems also seek to enhance patient adherence by decreasing dose frequency and mitigating systemic negative effects. Khallaf et al reported a thermosensitive in situ gel was developed utilizing poloxamers 407 and adhesive hydroxypropyl methylcellulose (HPMC), integrating a fasudil-phospholipid combination. These surfactant molecules self-assembled into micelles upon poloxamers 407 attaining their Critical Micelle Concentration, facilitating efficient drug encapsulation and release. The formulation exhibited improved absorption of fasudil and markedly decreased intraocular pressure in a rabbit ophthalmology model. The integration of thermosensitivity and sticky characteristics extended ocular retention and enhanced therapeutic effectiveness. This novel delivery system presents a promising method for optimizing glaucoma care by augmenting drug efficacy and minimizing the frequency of administration.[68] Fedorchak et al developed a hydrogel drug delivery system utilizing thermoresponsive n-isopropylacrylamide and polyacid microspheres, resulting in sustained release of brimonidine tartrate over 28 days.[96] Vijaya et al formulated a pH responsive gel through the incorporation of the polymer that is Carbopol® 934P. The formulation maintained liquid state condition at pH 4 and swiftly transitioned to a gel upon an elevation to pH 7.4 (tear pH). This pH-responsive in situ gelation technique provided sustained drug release over a 24-hour duration.[97] Ion-responsive hydrogels employ ions present in the ocular environment as a crucial element for in-situ gel production. Xu et al synthesized ion-sensitive in situ gel utilizing 0.45% gellan gum as the gel matrix was formulated for the management of glaucoma utilizing brimonidine tartrate. The gel converts from a sol to a gel upon interaction with tear fluid, improving its adherence to the ocular surface. Research on rabbit eyes revealed markedly enhanced bioavailability, ascribed to the extended residence period afforded by the ion-sensitive gel. This formulation facilitates prolonged medication administration, enhancing therapeutic results and decreasing dose frequency. The new method presents a viable approach to augmenting the efficacy of brimonidine tartrate in glaucoma treatment while maintaining patient comfort and adherence.[98] Rawat et al developed a dual-responsive in situ gel was formulated for

nebivolol, integrating poloxamers for thermoresponsiveness and kappa-carrageenan for ionic sensitivity. This formulation facilitated a sustained drug release of 86% over 24 hours, ensuring extended therapeutic effects. Furthermore, the gel demonstrated good tolerance in the ocular environment and efficiently controlled glaucoma. This novel delivery technology enhance patient adherence and decrease the dose frequency of glaucoma therapies.[99] Sun et al develop a nanocarrier based on PLGA-PEG-PLGA thermogel, incorporated with nanoparticles, was created for the sustained delivery of the treatment of glaucoma medication brimonidine (Bri). Nanoparticles efficiently encapsulated brimonidine, markedly decreasing its release rate due to robust interactions among the thermogel matrix and the drug, which impeded diffusion into eye tear film. Topical ocular administration, the solution produced a thermogel, facilitating extended drug retention. The thermogel significantly improved bioavailability for a minimum of 7 days and sustained intraocular pressure (IOP) reduction for 2–4 days, in contrast to merely 1 day of medication efficacy and a few hours of IOP relief provided by commercial eye drops.[100]

Uveitis

Uveitis denotes a classification of inflammatory disorders impacting the eye. Anterior uveitis refers to inflammation of the iris, anterior vitreous humour and ciliary body. Anterior uveitis is the most prevalent kind, comprising 50 to 60% of uveitis occurrences in the United States. In 50% of instances, uveitis is linked to a systemic disease process.[101] Certain forms of uveitis, particularly those with infectious etiologies, involve localized inflammation and biochemical changes, stimuli-responsive drug delivery systems (DDSs) offer a promising therapeutic strategy. Figure 5 depicts schematic representation of stimuli-responsive drug delivery systems (DDSs) for infectious ocular diseases. The therapy of uveitis aims to eradicate intraocular inflammation, alleviate discomfort, and prevent potentially vision-threatening therapeutic

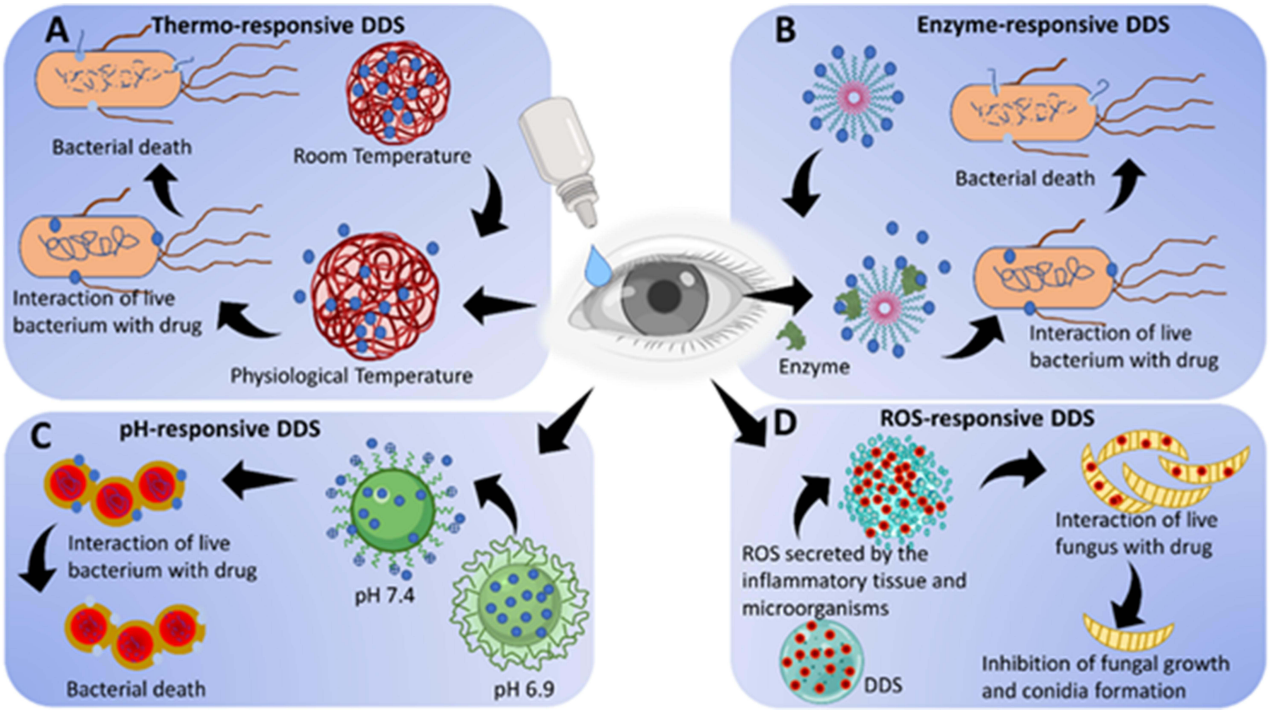

Figure 5 Schematic representation of stimulus-responsive drug delivery systems (DDSs) for infectious ocular diseases. (**A**) Thermo-responsive DDSs: Designed for controlled drug release in response to temperature changes, these systems undergo volumetric changes (swelling or shrinking) when exposed to elevated temperatures, triggering drug release at inflamed ocular sites. (**B**) Enzyme-responsive DDSs: Target specific ocular enzymes such as matrix metalloproteinases (MMPs), hyaluronidase, lysozyme, and esterase to initiate drug release, particularly in infected or inflamed tissues. (**C**) pH-responsive DDSs: Utilize polymers that respond to pathological pH shifts in ocular tissues. Drug-loaded nanoparticles can be engineered to release payloads efficiently at pH values deviating from the physiological tear pH (~7.4). (**D**) ROS-responsive DDSs: Leverage elevated reactive oxygen species (ROS) levels—associated with infection and inflammation to trigger site-specific drug release across ocular barriers. Adapted from Mahaling B, Baruah N, Dinabandhu A. Drug Delivery Systems for Infectious Eye Diseases: Advancements and Prospects. Journal of Nanotheranostics, 2024. 5(4): p. 133–166. © 2024 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (https://creativecommons.org/licenses/by/4.0/).[105]

side effects, including cataracts and increased intraocular pressure.[102] Chen et al examined the application of low-molecular weight chitosan and β-glycerophosphate as a nanocarrier for Adalimumab.[103] Zou et al developed an innovative intravenous, thermo-sensitive hydrogel, PNMHTI, was created for the prolonged delivery of indomethacin to treat inflammatory disorders such as uveitis. The hydrogel consists of poly(NIPAAm-co-MAA-co-HTI), incorporating NIPAAm for thermosensitivity, MAA for hydrophilicity, and HTI for drug conjugation. The sol–gel transition transpires at physiological temperatures (33–37 °C), facilitating in situ gelation post-injection. The release of indomethacin is prolonged for more than two weeks as a result of the hydrolytic destruction of PTMC chains inside the polymer. Rheological and histological evaluations validated its biocompatibility and anti-inflammatory effectiveness in vivo. This method provides a minimally invasive, extended drug delivery solution, decreasing the necessity for frequent treatments. PNMHTI hydrogels exhibit potential as a biomaterial-derived treatment option for ocular inflammatory disorders.[104]

Dry Eye Disease

Dry eye disease (DED) is a prevalent disease marked by atypical film composition and inflammation of the surface of eye. Patients with dry eye disease frequently exhibit a sense of foreign body presence and visual impairment. Female above 50 years, contact lens usage, drugs including antihistamines, hematopoietic stem cell and diuretics and transplantation are correlated with increased prevalence of DED. The estimated prevalence of dry eye disease (DED) of the United States is approximately 5%.1 DED is a formidable challenge for individuals and may pose diagnostic and management difficulties for professionals.[106] The backbone for DED treatment is artificial tears.[107] De Luca et al introduced an innovative application of thermosensitive Poloxamers 407 as a vehicle for resveratrol (RSV). Given that RSV possesses significant antioxidant and anti-inflammatory capabilities, the inclusion of this component in eye medicine may mitigate oxidative stress. Given that DED is frequently linked to an overproduction of reactive oxygen species in tears, this novel formulation presents a prospective remedy for counteracting ROS-induced ocular harm and minimizing the necessity for frequent topical applications during the day.[80] Luo et al chronicled the evolution of a carrier loaded with epigallocatechin gallate, comprising gelatin, thermoresponsive PNIPPAm, and lectin Helix pomatia agglutinin. Despite the extensive use of PNIPPAm hydrogels, their pronounced sensitivity to temperature stimuli significantly restricts the release of medicinal molecules. Moreover, the inadequate biodegradability of PINIPPAm hydrogels presents an additional obstacle to practical translation. To address these issues, the researchers integrate lectin, a bioadhesive molecule, to enhance the interaction between the drug-loaded nanocarrier and the carbohydrates on mucosal epithelial barrier, thus extending the drug-cornea contact duration. Furthermore, the incorporation of gelatin, a biodegradable matrix, alleviates the concern regarding biodegradability.[108]

Neurotrophic Keratopathy

Neurotrophic keratopathy (NK) is an autoimmune disease of the cornea, resulting from compromised corneal innervation.[109] A decrease in corneal sensitivity or total corneal anaesthesia is characteristic of this condition and leads to epithelial keratopathy, ulceration, and perforation. Zhu et al created a pH-responsive photothermal therapy (EtNBSS) is formed through the self-assembly by the use of phenothiazinium photo sensor dye, which has an amine group. Moreover, the acid-induced transition from cationic to anionic charge in EtNBSS enhanced their penetration within bacterial biofilms and facilitated mild photothermal biofilm elimination.[110] He et al similarly proposed novel Co-integrated small systems consisting of gallium ions and lyticase, activated by pH at the site of fungal keratitis, exhibited effectiveness in eradicating biofilms in a murine model of fungal disease, presenting a potential therapeutic strategy for the clinical Management of keratitis caused by fungi.[111]Table 3 below lists the application of smart polymer based ocular delivery in ophthalmic diseases.

Regulatory Status of Ocular Drug Delivery System

Despite considerable investment in the development of polymer-based ocular drug delivery systems, a primary obstacle remains their translation to clinical application. Several products have successfully entered the market in recent decades, with each of the four previously stated administration routes featuring at least one FDA-approved drug delivery system that incorporates polymers to augment their efficacy. Eyedrops, the most developed drug administration platform among

Table 3 Application of Smart Polymer Based Ocular Delivery in Ophthalmology

Ocular Disease	Polymer Based Nano Therapeutics	Important Feature	References
Vitrectomy	Injectable smart hydrogels	Comparable physiological features to those of natural aqueous vitreous	[112]
Age-related macular degeneration	Microsphere-hydrogel drug delivery systems	PLGA spheres the encapsulation of agents, for example ranibizumab.	[113]
	Bio-responsive hydrogel	Characteristics of Rosihydrogel facilitated controlled dissolution of drug in reaction for localized enzyme.	[114]
Diabetic retinopathy	Dual ligand hydrogel system (ICNPH)		[115]
Glaucoma	Sol to gel chitosan-g-poly (N-isopropylacrylamide)		[116]
Cataracts	PNIPAAm/PEG thermogel	A solitary drug-loaded GMS drop in rabbits resulted in intraocular pressure decreases akin to those achieved with brimonidine administered bi-daily as eye drops.	[96]
Fungal Keratitis		Initiated by pH at the site of fungal keratitis and capable of successfully eliminating both fungus and mature biofilms in an animal model of fungal keratitis	
Uveitis	Nanoparticles of polyester	The research indicating the treatment's efficacy in treating ocular inflammation.	[117]
Dry eye disease	Mucoadhesive thermogel	The extended duration of the gel's presence for almost 14 days resulted in an ongoing dissolution of the encapsulating drug.	[108]

the four, possess a considerable array of polymer products, with multiple formulations sanctioned for the treatment of conditions such as conjunctivitis and glaucoma, caused by bacteria, and uveitis.[21] Advancement in the intravitreal space has proven very slow, with merely seven intravitreal polymer systems currently receiving approval from the FDA for a limited range of disorders. The seven implants, Iluvien®, Retisert®, Ozurdex®, Vitrasert®, Dextenza, Yutiq® and DEXYCU®, are constructed from various polymers. Iluvien® and Yutiq® utilise polyimide implants for the administration of fluocinolone acetonide.[118] Ozurdex® employs a PLGA matrix that degrades to liberate dexamethasone. Retisert® comprises a fluocinolone acetonide tablet encapsulated in a silicone/PVA elastomer.[119] Vitrasert® delivers ganciclovir from a PVA/ethylene vinyl acetate matrix (200). Dextenza encapsulates dexamethasone within a PEG-fluorescein hydrogel.[8] Four of the seven implants are non-degradable; Ozurdex®, Dextenza, and DEXYCU® can be resorbed by the ocular tissue.[120] This regulates the medication release rate by establishing a consistent polymer membrane that facilitates drug diffusion into the intravitreal region. Nonetheless, it poses the difficulty of implant extraction and substitution after its therapeutic payload is depleted, necessitating surgical intervention and perhaps introducing further health concerns for the patient. A multitude of polymer implants are undergoing diverse stages of clinical and laboratory investigation utilising materials like PLGA and PEG, signifying substantial advancements remain to be achieved in the therapeutic application of polymer systems within the vitreal area,[121] Aerie is conducting a Phase 2 trial to evaluate biodegradable polymer implants for DME. Ongoing advancements in intravitreal microparticles, nanoparticles that and injectable hydrogels will likely result in a much broader array of intravitreal medication methods of administration for patients and doctors in the forthcoming years.[122] Subconjunctival medication distribution is a method that has only lately been investigated. Notwithstanding this, advancements have been made in the formulation of subconjunctival polymer drug delivery systems, exemplified by the Ologen® and Xen Gel systems that utilise collagen for implant construction, alongside research into alternative polymers like PLGA, which has demonstrated encouraging outcomes for implant efficacy.[123] Ultimately, although the suprachoroidal pathway remains the least investigated for ocular medication administration, devices like the XIPERE™ system's injectable triamcinolone acetonide solution are approaching market

authorization.[124] Alongside these encouraging advancements in suprachoroidal injections, other choroidal devices have achieved success in clinical applications.[125] The capacity to further these developments and integrate polymers utilised in delivery systems for ocular use will offer a significant and feasible avenue for advancing polymeric carrier available suprachoroidal injection. The restricted use of synthetic polymers in ocular drug administration is partially attributable to safety concerns. Even with approved medicines, drug-device combos are required to undergo more extensive evaluation than conventional medical tool via the approval procedure from FDA. Additional challenges encompass the likelihood that the polymer delivery system alters the necessary therapeutic dosage, typically resulting in diminished therapeutic requirements due to less therapeutic waste.[126]

Conclusion

Smart polymer-based systems represent a significant advancement in addressing the limitations of conventional ocular drug delivery. Innovative platforms leveraging the unique properties of smart polymers enable sustained, targeted, and stimuli-responsive drug release. Technologies such as in situ gelling formulations, nanoparticle carriers, dendrimers, and biodegradable polymeric implants have demonstrated considerable potential in enhancing the therapeutic efficacy of ocular medications. The integration of nanotechnology with smart polymers facilitates the design of site-specific delivery systems that overcome the complex pharmacokinetics of ocular tissues. For instance, smart polymer-coated nanoparticles can respond to environmental triggers like pH or temperature changes to achieve precise and controlled drug release. Biodegradable implants allow for sustained intravitreal drug administration, thereby reducing the frequency of invasive procedures and improving patient compliance. The future of smart polymer-based therapeutics in ophthalmology is promising, driven by ongoing innovations in polymer chemistry, nanotechnology, and biomaterials science. These advances are expected to yield therapies with enhanced efficacy, safety, and patient adherence. Personalized medicine approaches, including drug delivery systems tailored to individual patient needs, represent a key area of development. Furthermore, the incorporation of biosensors and artificial intelligence into smart delivery platforms has the potential to revolutionize ocular therapy by enabling real-time monitoring and adaptive treatment regimens. In conclusion, smart polymers have emerged as transformative agents in ocular therapeutics, addressing longstanding challenges and enabling novel treatment modalities. Their clinical translation promises not only to improve therapeutic outcomes but also to reduce healthcare burdens and enhance accessibility globally, thereby significantly advancing the management of eye diseases and improving patient quality of life.

Abbreviations

BAB, blood–aqueous barrier; BRB, blood–retinal barrier; AMD, age-related macular degeneration; CTA, chain transfer; CNV, choroidal neovascularization; DR, diabetic retinopathy; DES, Dry eye syndrome; PCL, polcarpolactone; PLGA, poly lactic-glycolic acid; ARPE, adult retinal pigment; Cur-MMs, curcumin mixed micelles; pNIPAAM, poly N(isopropylacrylamide).

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing or other interests that might be perceived to influence the results and/or discussion reported in this paper.

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