REVIEW ARTICLE

Smart Reactive Oxygen Species-Sensitive Nanoplatforms for Enhanced Ocular Drug Deliver in Glaucoma

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Abstract

Glaucoma is a major cause of irreversible blindness and is associated with elevated intraocular pressure (IOP), retinal ganglion cell (RGC) degeneration, and oxidative stress–mediated trabecular meshwork damage. Increased reactive oxygen species (ROS) in glaucomatous tissues have promoted the development of ROS-responsive nanoplatforms for targeted ocular drug delivery. This review summarizes recent advances in ROS-sensitive nanocarriers, including thioketal-linked nanoparticles, boronic ester systems, selenium-based polymers, nano micelles, and hydrogel ocular inserts. Preclinical and *in vitro* studies evaluating drug release, ocular permeation, IOP reduction, and neuroprotection were critically analysed. ROS-responsive systems demonstrated selective drug release under oxidative conditions, achieving 70–90% release in high-ROS environments compared with <20% under physiological conditions. Peroxide-sensitive nanoparticles loaded with timolol or latanoprost reduced IOP by 32–45% for up to 7 days. Thioketal nano micelles provided 35–50% RGC protection, while ROS-sensitive ocular inserts sustained therapeutic levels for more than 1 week and reduced dosing frequency. Hybrid nano systems also improved corneal penetration and ocular retention. ROS-responsive nanotechnology represents a promising strategy for glaucoma therapy by enabling targeted delivery, prolonged drug residence, reduced dosing frequency, and enhanced neuroprotection. Further *in vivo* and clinical studies are required to confirm long-term safety and translational potential.

Key words: Glaucoma therapy, ocular drug delivery, oxidative stress, reactive oxygen species, responsive nanocarriers, stimuli-responsive systems

INTRODUCTION

Glaucoma is a progressive optic neuropathy characterized by retinal ganglion cell (RGC) degeneration and irreversible visual field loss. Although elevated intraocular pressure (IOP) is the primary modifiable risk factor, glaucoma is now recognized as a multifactorial disease involving oxidative stress, mitochondrial dysfunction, vascular dysregulation, and neuroinflammation.[1,2] Oxidative stress plays a central role in disease progression, as excessive reactive oxygen species (ROS) in the trabecular meshwork (TM) and retinal tissues induce mitochondrial damage, extracellular matrix remodeling, inflammation, and RGC apoptosis, while diminished antioxidant defences further exacerbate injury Conventional therapies, including prostaglandin analogues, β-blockers, carbonic anhydrase inhibitors, and α-agonists, are limited by poor ocular bioavailability due to tear turnover, blinking, and corneal barriers, resulting in frequent dosing and reduced patient compliance.[3] Nanotechnology-based ocular delivery systems improve drug retention and penetration; however, many lack disease-specific release mechanisms.

ROS-responsive nanocarriers have emerged as promising platforms because they exploit elevated oxidative stress in glaucomatous tissues. Incorporating ROS-sensitive linkers

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such as thioketal, boronic ester, and diselenide bonds enables site-specific drug release from nanoparticles, micelles, hydrogels, and contact lenses.[4] Preclinical studies demonstrate sustained IOP reduction, enhanced ocular retention, targeted delivery, and improved neuroprotection through antioxidant and antiglaucoma drug delivery.[5] Furthermore, surface-functionalized ROS-responsive systems may support personalized therapy by adapting drug release to disease severity. Despite challenges related to biocompatibility, scalability, and regulatory approval, these smart nanoplatforms show significant potential for future glaucoma management.[6,7]

OXIDATIVE STRESS IN GLAUCOMA: PATHOPHYSIOLOGICAL BASIS FOR ROS-TARGETED DELIVERY

Oxidative stress is a key contributor to glaucomatous neurodegeneration and provides the biological rationale for ROS-responsive ocular drug delivery systems. Elevated levels of ROS, including hydrogen peroxide, superoxide anions, and hydroxyl radicals, have been identified in the TM, aqueous humor, optic nerve head, and RGC layer of glaucomatous eyes. Concurrent depletion of antioxidant defenses such as superoxide dismutase, catalase, and glutathione disrupts redox homeostasis and promotes progressive ocular damage.[8] The TM is highly vulnerable to oxidative injury because it regulates aqueous humor outflow. Excessive ROS induces mitochondrial dysfunction, reduces ATP production, trigger TM cell apoptosis, and promotes extracellular matrix accumulation, leading to increased outflow resistance and elevated IOP.[9] Oxidative stress also contributes directly to RGC degeneration by impairing axonal transport and accelerating neuronal loss.

These pathological features create a favorable microenvironment for ROS-responsive nanocarriers. Elevated ROS levels selectively activate ROS-sensitive materials, enabling controlled drug release at diseased sites while maintaining stability under normal physiological conditions.[10] Preclinical studies have demonstrated enhanced ocular retention, sustained IOP reduction, targeted TM delivery, and improved neuroprotection using ROS-responsive formulations carrying antiglaucoma or antioxidant agents.[11] Consequently, ROS-responsive nanomedicine offers a promising strategy to improve therapeutic precision and address both pressure-dependent and neurodegenerative aspects of glaucoma [Figure 1].

DESIGN, PRINCIPLES OF ROS-RESPONSIVE POLYMERS AND LINKERS FOR OCULAR APPLICATIONS

ROS-responsive polymers for glaucoma drug delivery must balance oxidative sensitivity, ocular biocompatibility,

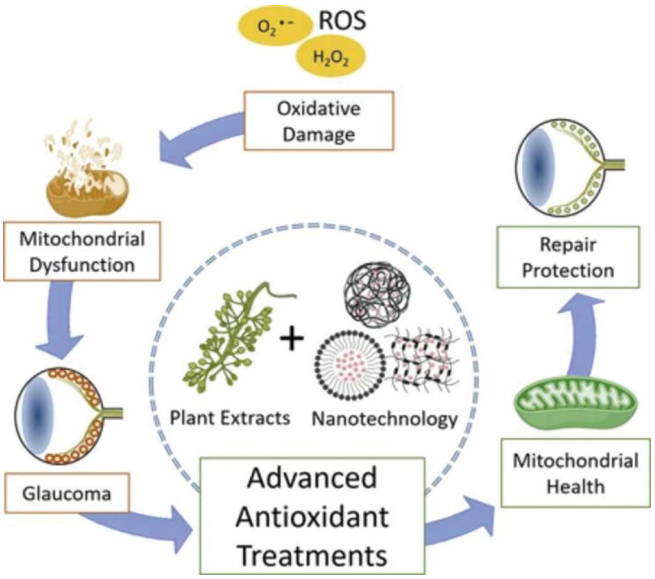

Figure 1: Restoring oxidative balance in glaucoma[6]

storage stability, and controlled degradation. Elevated ROS, including increased hydrogen peroxide and hydroxyl radicals in glaucomatous tissues, provides the basis for selective drug release in diseased ocular environments. An ideal carrier remains stable under physiological ROS levels (1–5 μM hydrogen peroxide) but rapidly degrades under pathological conditions (>20–40 μM). Biocompatibility is essential because ocular tissues are highly sensitive. ROS-responsive polymers should produce non-toxic degradation products while maintaining corneal integrity. Furthermore, polymer density, linker composition, and crosslinking can be optimized to achieve sustained and controlled drug release for prolonged glaucoma therapy.[12]

MECHANISMS OF ROS-TRIGGERED DRUG RELEASE IN GLAUCOMATOUS MICROENVIRONMENTS

Elevated hydrogen peroxide, superoxide, and hydroxyl radicals in glaucomatous tissues contribute to oxidative stress, impaired aqueous humor outflow, extracellular matrix accumulation, and RGC apoptosis. ROS-responsive nanocarriers exploit this oxidative microenvironment to achieve targeted and controlled drug release.[13] Thioketal-based nanoparticles selectively degrade under oxidative conditions, enhancing neuroprotection and reducing RGC loss.[14] Boronic ester nanocarriers respond to hydrogen peroxide, enabling sustained release of antiglaucoma drugs such as timolol and prolonged IOP reduction.[15] Peroxalate ester and diselenide-linked systems further improve ocular retention, targeted delivery, antioxidant activity, and neuroprotection, making them promising platforms for glaucoma therapy [Table 1].[16,17]

ADVANCES IN PEROXIDE-, THIOKETAL-, AND BORONIC ESTERBASED NANOCARRIERS

ROS-responsive delivery systems, including peroxide-sensitive, thioketal-based, and boronic ester-linked nanocarriers, have gained significant attention for targeted therapy in cancer, inflammatory disorders, neurodegenerative diseases, retinal degeneration, and glaucoma [Table 2]. These platforms exploit elevated ROS levels to achieve site-specific drug release while minimizing premature leakage and systemic toxicity.[18]

Peroxide-responsive nanocarriers contain peroxide-sensitive linkers such as peroxalate esters and percarbonate polymers that undergo oxidative cleavage in the presence of hydrogen peroxide, resulting in controlled drug release.[19,20] Thioketal-based systems remain stable under physiological conditions but selectively degrade in oxidative environments, enabling efficient delivery of therapeutic agents and enhanced neuroprotection in ocular and inflammatory disorders.[21] Boronic ester nanocarriers respond specifically to hydrogen peroxide through oxidative deboronation, promoting carrier disassembly and controlled drug release with minimal off-target effects.[22] These systems have demonstrated improved therapeutic efficacy in various disease models, including cancer, diabetic wound healing, neuroinflammation, and glaucoma.[23] Overall, ROS-responsive nanocarriers offer precise, disease-triggered drug delivery and represent promising platforms for future ocular nanomedicine.

Table 1: Comparative analysis of ROS-responsive nanocarrier systems for glaucoma therapy: Mechanisms, advantages, limitations, and translational status

ROS-responsive system	ROS trigger	Representative drug	Advantages	Limitations	Development stage
Thioketal linkers	Hydroxyl radicals, superoxide	N-acetylcysteine, BDNF	High physiological stability, controlled release, good ocular retention	Moderate degradation rate	Preclinical
Boronic ester systems	Hydrogen peroxide	Timolol, Brimonidine	Rapid ROS responsiveness, efficient drug release	Potential storage instability	Preclinical
Peroxalate ester systems	Hydrogen peroxide	Edaravone, Latanoprost	High sensitivity, possible ROS-scavenging effects	Limited long-term safety data	Preclinical
Diselenide systems	Hydrogen peroxide, superoxide	Brimonidine, antioxidants	ROS responsiveness plus intrinsic antioxidant activity	Potential selenium toxicity concerns	Preclinical
ROS-responsive hydrogels	Multiple ROS species	Neuroprotective agents	Sustained release, prolonged ocular retention	Sterilization and manufacturing challenges	Preclinical

ROS: Reactive oxygen species, BDNF: Brain-derived neurotrophic factor

Table 2: Representative advances in ROS-responsive nanocarriers[24-30]

Nanocarrier type	Key ROS trigger	Representative research outcome
Peroxalate polymer nanoparticle	H_2O_2	75% drug release in 4 h; 60% tumor reduction in mice
Poly (percarbonate) micelle	Peroxide radicals	Rapid disassembly in 30 min; improved inflammatory survival
Peroxide-cleavable polyurethane vesicle	H_2O_2	3-fold cellular uptake enhancement versus free drug
Poly (thioketal) siRNA nanoparticle	Hydroxyl radicals	>60% TNF-α gene silencing in macrophages
Thioketal-crosslinked hydrogel	Superoxide/H_2O_2	Complete gel degradation in 2 h; retinal protection in glaucoma
Thioketal lipid nanoparticle	Mixed ROS	10-fold release increase in inflamed intestine
Boronic ester–prodrug nanoparticle	H_2O_2	90% drug liberation in 1 h; major tumor regression
Boronic ester vesicle for wound therapy	Hyperglycemic ROS	70% faster wound closure in diabetic model
Boronic ester polymeric micelle	Oxidative burst	Efficient activation during macrophage ROS production
Hybrid boronic ester–thioketal nanogel	Mixed ROS	Sequential cleavage enabling multi-phase drug release

ROS: Reactive oxygen species

ROS-SENSITIVE HYDROGELS, INSERTS, AND CONTACT LENS PLATFORMS FOR SUSTAINED DELIVERY

ROS-responsive ocular delivery systems have been developed as accurate drug-release platforms to the treatment of diseases with oxidative stress, such as glaucoma, post-operative inflammation, diabetic keratopathy, uveitis, and retinal ischemic damage. Hydrogels, biodegradable inserts, and soft contact lens systems containing ROS-cleavable linkers based on primarily thioketals, boronic esters, peroxalate moieties, and ROS-labile poly(thioketal) backbones provide a sustained release that is triggered by pathological oxidative levels instead of passive diffusion. This specificity allows for reduced dosing, minimal burst release, and sustained therapeutic levels in the eye with minimal systemic exposure.[31]

Sustained ocular delivery via ROS-sensitive hydrogels

ROS-responsive hydrogels contain oxidatively cleavable linkers that degrade under elevated ROS levels [Figure 2]. Thioketal and boronic ester crosslinks remain stable under physiological conditions but rapidly dissociate during oxidative stress, enabling selective drug release in glaucomatous tissues where ROS concentrations are significantly increased. A thioketal-crosslinked poly (ethylene glycol) hydrogel loaded with brimonidine showed minimal leakage under normal conditions but rapidly degraded at high ROS levels, sustaining IOP reduction. Boronic ester hydrogels containing dexamethasone reduced post-operative inflammation, while peroxalate-modified gels releasing edaravone preserved retinal thickness and improved RGC survival in ocular injury models.[32]

ROS-responsive ocular inserts

ROS-responsive ocular inserts are solid drug depots placed in the conjunctival sac that remain stable under physiological conditions but rapidly degrade in oxidative environments. Unlike conventional inserts with passive drug diffusion, these systems provide selective and controlled drug release in glaucomatous tissues. Common materials include poly(thioketal) films, boronic ester-functionalized cellulose matrices, and silicone inserts containing ROS-labile linkers. By modifying linker density, degradation rates can be adjusted from hours to days.[10]

NEUROPROTECTIVE AND IOP-LOWERING AGENTS DELIVERED VIA ROS-RESPONSIVE SYSTEMS

A poly(thioketal) insert loaded with timolol maleate showed minimal drug release under low ROS conditions but released over 80% of the drug within 8 h in high oxidative environments, maintaining IOP reduction for 72 h in hypertensive rats. Similarly, boronic ester films containing cyclosporine demonstrated significantly enhanced release during oxidative inflammation without causing ocular irritation. Peroxalate-activated inserts also showed selective degradation under oxidative stress and improved retinal protection in injury models.[34]

Agents lowering IOP delivered by ROS-responsive nanocarriers

ROS-responsive nanocarriers are additionally used for delivering IOP-lowering and neuroprotective agents. Latanoprost, timolol, dorzolamide, and brinzolamide formulations exhibited enhanced corneal penetration, prolonged ocular retention, reduced dosing frequency, and sustained IOP reduction for up to 7 days. These systems also minimized systemic exposure and improved therapeutic precision in glaucomatous tissues.[35]

Neuroprotective agents delivered via ROS-responsive systems

RGC degeneration is closely linked to oxidative stress, making neuroprotection a key therapeutic goal in glaucoma.

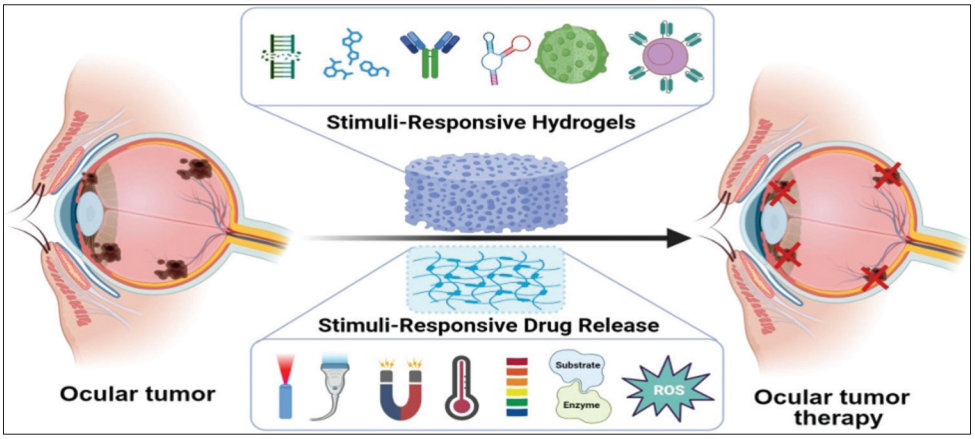

Figure 2: Stimuli-responsive hydrogels for ocular tumor therapy[33]

Conventional ocular formulations often provide limited neuroprotective benefits due to poor retinal penetration, rapid clearance, and inadequate tissue targeting. ROS-responsive delivery systems address these challenges by selectively releasing antioxidants, anti-inflammatory agents, and neurotrophic factors within oxidative microenvironments of the retina, optic nerve head, and TM.[36] Peroxalate ester-crosslinked hydrogels loaded with edaravone have demonstrated ROS-triggered drug release, resulting in improved RGC survival, preservation of retinal structure, and reduced lipid peroxidation in retinal injury models.[37] Similarly, thioketal-based nanoparticles delivering N-acetylcysteine reduced RGC apoptosis, while boronate nanocarriers loaded with the mitochondrial antioxidant MnTBAP preserved mitochondrial integrity, reduced microglial activation, and enhanced optic nerve axonal survival.[38]

ROS-responsive platforms have also improved the delivery of neurotrophic factors. Thioketal-based *in situ* gels carrying brain-derived neurotrophic factor provided sustained intravitreal release and enhanced RGC survival, whereas boronic ester nanoparticles delivering ciliary neurotrophic factor improved axonal transport and retinal functional recovery.[39] In addition, ROS-sensitive carriers have enhanced the ocular bioavailability of neuroprotective agents such as curcumin and tacrolimus, leading to reduced oxidative damage, suppression of inflammatory cytokines, preservation of retinal architecture, and decreased axonal degeneration. Overall, ROS-responsive neuroprotective systems offer targeted, sustained, and disease-triggered therapy for preventing RGC degeneration and improving glaucoma outcomes [Table 3].

NANOCARRIER-MEDIATED ENHANCEMENT OF CORNEAL PENETRATION AND TM TARGETING

Effective glaucoma therapy remains challenging due to the complex anatomical and physiological barriers of the eye, including tight corneal epithelial junctions, rapid tear turnover, mucin clearance, and efflux transporters. Typically, only a small fraction of topically administered drugs reaches intraocular tissues, while even lower concentrations penetrate the TM, a major pathological site in glaucoma characterized by oxidative stress, extracellular matrix accumulation, and impaired aqueous humor outflow.[34] ROS-responsive nanocarriers provide promising strategies to overcome these limitations through site-specific activation and enhanced ocular penetration.

Table 3: ROS-responsive delivery of neuroprotective and IOP-lowering agents[40-43]

Drug/Agent	ROS-responsive system	Key research outcome	Case details/Model data
Latanoprost	Boronic-ester nanoparticles	9-fold increase in corneal permeability under oxidative stress	Weekly subconjunctival dosing maintained IOP reduction comparable to twice-daily drops in glaucomatous rabbits
Timolol maleate	Thioketal nanospheres	80% release at ≥200 μM H_2O_2; minimal leakage physiologically	Inserts sustained IOP reduction for 72 h in hypertensive rats with reduced systemic absorption
Dorzolamide	Boronic-ester polymer nanosponges	60% release within 6 h in pathological ROS	30–35% IOP reduction sustained for 72 h in rabbits; reduced epithelial irritation
Brinzolamide	Thioketal hydrogel	8-fold higher intraocular retention time	Enhanced delivery to ciliary body and prolonged pressure control without burst release
Edaravone	Peroxalate- responsive hydrogel	70% release in 4 h under oxidative stress	45–55% increased RGC survival in retinal ischemia–reperfusion models
NAC	Thioketal nanoparticles	Significant ROS-triggered intracellular release	Reduced RGC apoptosis by >40% during oxidative injury in glaucoma models
MnTBAP	Boronic-ester nanocarriers	Improved mitochondrial integrity and reduced microglial activation	20–30% increase in optic nerve axon count in oxidative glaucoma models
BDNF (neurotrophic factor)	Thioketal *in situ* hydrogel	>60% release in ROS-rich tissue	Prolonged intravitreal retention (>24 h) and 36% higher RGC survival in optic nerve crush models
CNTF	Boronic-ester nanoparticles	Enhanced axonal repair signaling	Improved pattern electroretinography amplitudes and axonal transport function
Curcumin	ROS-responsive polymeric micelles	Enhanced axonal repair signaling	Preserved retinal thickness and significantly reduced caspase-3 activation *in vivo*

RGC: Retinal ganglion cell, ROS: Reactive oxygen species, NAC: N-acetylcysteine, MnTBAP: Mitochondrial antioxidant, BDNF: Brain-derived neurotrophic factor, IOP: Intraocular pressure

Physicochemical optimization for corneal penetration

Particle size and transport efficiency

Nanocarriers with particle sizes ranging from 20 to 200 nm exhibit improved corneal penetration because they can bypass paracellular barriers and reduce mucin entrapment. Smaller nanoparticles generally demonstrate superior ocular uptake compared with microscale systems. ROS-responsive polymeric micelles within the nanoscale range have shown significantly enhanced transcorneal flux under oxidative conditions associated with glaucomatous tissues.[44]

Surface charge modulation

Mildly cationic nanocarriers improve adhesion to the negatively charged corneal epithelium and increase ocular residence time. However, excessive positive charge may cause epithelial irritation. Thioketal-modified chitosan nanoparticles with optimized surface charge significantly enhanced corneal permeation of timolol while maintaining high epithelial cell viability.[45]

Hydrophilic–hydrophobic balance

PEGylation is widely used to improve nanocarrier stability, reduce protein adsorption, and prolong precorneal residence time. PEGylated boronic ester nanoparticles demonstrated prolonged ocular retention compared with non-PEGylated systems. ROS-sensitive PEGylated nanogels maintained detectable drug concentrations in aqueous humor for extended periods compared with conventional eye drops.[46]

Mucoadhesive and penetration-enhancing strategies

Mucoadhesive polymers

Bioadhesive materials such as chitosan, hyaluronic acid, and thiolated polymers enhance interaction with ocular mucins and improve corneal retention. Thiolated hyaluronic acid nanocarriers significantly enhanced corneal penetration and reduced washout during simulated tear flow conditions.[47]

Tight junction modulation

Transient and reversible modulation of epithelial tight junctions improves paracellular drug transport. Cell-penetrating peptide-functionalized ROS-responsive nanoparticles demonstrated markedly enhanced corneal delivery of hydrophilic drugs while preserving epithelial integrity.[48]

Strategies to avoid precorneal clearance

In situ gel systems

Combining ROS-responsive nanocarriers with thermosensitive or ion-sensitive hydrogels prolongs ocular retention and reduces tear-mediated clearance. Thioketal hydrogel–nanoparticle systems sustained corneal residence for prolonged periods and maintained IOP reduction for several days.[49]

Contact lens-mediated delivery

ROS-responsive nanoparticles incorporated into contact lenses provide sustained ocular drug release while minimizing tear dilution. Boronic ester nanoparticle-loaded lenses demonstrated significantly higher intraocular drug concentrations than conventional eye drops and enabled ROS-triggered release according to oxidative stress levels.

TM targeting

The TM is a small and anatomically challenging tissue to access. Nanocarriers improve TM delivery through particle size optimization, ligand-mediated targeting, and ROS-triggered activation.

Size-selective accumulation

Nanoparticles smaller than 100 nm exhibit enhanced penetration through Schlemm's canal and TM tissues. Thioketal nanoparticles demonstrated substantially greater accumulation within TM cells compared with larger particles in perfusion models.

Ligand-based targeting

Surface ligands targeting integrins, CD44 receptors, or TM-associated proteins improve selective uptake by trabecular cells. Integrin-targeted ROS-sensitive nanoparticles and hyaluronic acid-modified boronic ester micelles significantly enhanced TM drug accumulation.

Restoration of aqueous humor outflow

ROS-responsive delivery of latanoprost, timolol, ROCK inhibitors, and antifibrotic agents improves aqueous humor drainage by reducing extracellular matrix accumulation, modulating cytoskeletal organization, and reversing ROS-induced trabecular stiffening. Peroxalate ester nanoparticles and ROS-activated brimonidine micelles demonstrated prolonged IOP reduction and enhanced outflow facility in experimental glaucoma models.

Advantages of ROS-responsive TM targeting

Hydrogen peroxide levels within glaucomatous TM tissues are substantially higher than those in healthy eyes, providing an ideal trigger for ROS-responsive systems. Thioketal linkers selectively degrade in the presence of hydroxyl radicals, whereas boronic esters respond specifically to elevated peroxide concentrations.[50] Peroxalate esters additionally provide ROS-scavenging activity along with controlled drug release, offering combined cytoprotective and pharmacological benefits. Peroxide-sensitive timolol

nanocarriers demonstrated highly selective release within glaucomatous trabecular tissues while remaining relatively stable under normal conditions. These systems prolonged IOP reduction for several days and significantly reduced oxidative injury markers in TM cells.[51]

CHALLENGES IN CLINICAL TRANSLATION

Despite encouraging preclinical results, the clinical translation of ROS-responsive nanocarriers for glaucoma therapy faces several challenges. Ocular safety and biocompatibility remain primary concerns because the eye is highly sensitive and immune-privileged. Although thioketal, boronic ester, peroxalate ester, and diselenide-based systems generally demonstrate low toxicity and good short-term tolerability, their long-term safety after repeated administration remains unclear.[52] Potential risks include chronic inflammation, hypersensitivity reactions, nanoparticle accumulation within the TM, and impaired aqueous humor outflow. Regulatory approval also requires comprehensive assessment of retinal safety, corneal integrity, phototoxicity, lens transparency, and biodegradation profiles.[53]

Another major challenge is the variability of oxidative stress among patients and disease stages, which may lead to inconsistent drug release and therapeutic outcomes.[54] To address this issue, multi-stimuli-responsive systems combining ROS sensitivity with pH, enzymatic, or temperature triggers are being explored. Additionally, manufacturing scalability remains difficult because large-scale production requires strict control of polymer composition, linker density, particle size, and drug-loading efficiency. ROS-sensitive materials may also be vulnerable to degradation during sterilization, increasing production complexity and cost.[55] Therefore, successful clinical translation will require standardized manufacturing processes, robust quality control, long-term stability studies, and regulatory compliance to ensure safety, reproducibility, and therapeutic efficacy.[56]

FUTURE PERSPECTIVES

Advances in biosensors, smart materials, and precision medicine are accelerating the development of next-generation glaucoma therapies. Biosensor-integrated ocular platforms can continuously monitor IOP, ROS, pH, and tear biomarkers, enabling real-time disease assessment and personalized treatment. Integration of these sensors with ROS-responsive polymers has led to smart drug delivery systems, including thioketal nanogels, boronic ester micelles, and peroxide-sensitive hydrogels, which release therapeutic agents selectively under pathological oxidative conditions while minimizing premature drug leakage. Future glaucoma management is expected to become increasingly personalized through the use of ROS profiles, genetic biomarkers, metabolomic data, and retinal imaging. Artificial intelligence-assisted analysis of biosensor data may further optimize drug release kinetics and improve long-term retinal protection. In addition, hybrid wearable–implantable systems, such as smart contact lenses linked to intraocular drug reservoirs, offer continuous monitoring, feedback-controlled drug delivery, and adaptive therapy. Together, these technologies represent a promising step toward fully automated and precision-based glaucoma management.

CONCLUSION

Glaucoma is a leading cause of irreversible blindness characterized by progressive RGC degeneration, elevated IOP, oxidative stress, and TM dysfunction. Recent therapeutic strategies have shifted beyond IOP reduction toward targeting oxidative damage and neurodegeneration. ROS-responsive nanocarriers, hydrogels, and smart ocular delivery systems have emerged as promising approaches to overcome the limitations of conventional eye drops, including poor bioavailability, rapid clearance, and frequent dosing. Systems based on thioketal linkers, boronic esters, and peroxide-sensitive polymers enable site-specific and controlled drug release in ROS-rich glaucomatous tissues. Preclinical studies have demonstrated enhanced ocular retention, improved TM targeting, sustained IOP reduction, and protection against retinal degeneration. Additionally, advances in biosensor-integrated implants, smart contact lenses, and MEMS technologies support real-time monitoring of IOP and oxidative stress, enabling feedback-controlled and personalized therapy. Although challenges related to ROS variability, long-term safety, manufacturing scalability, and regulatory approval remain, continued progress in smart biomaterials and biosensor technologies highlights the strong potential of ROS-responsive systems. Their integration with patient-specific biomarkers may enable personalized, minimally invasive, and adaptive glaucoma management in the future.

CONSENT TO PUBLISH DECLARATION

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Ethics approval and consent to participate: Not applicable.

DECLARATION OF GENERATIVE AI AND AI-ASSISTED TECHNOLOGIES IN THE WRITING

Process During the preparation of this work, the author(s) used Quill Bot and Paper Pal for enhancing language, flow, and readability. For figure drawing and quality improvement, BioRender software was used. After utilizing these tools, the author(s) reviewed and edited the content as necessary and take(s) full responsibility for the final content of the publication.

AUTHOR CONTRIBUTION

Saravanan Ravindran is helpful for Writing - Original Draft, Supervision, and Methodology, AP. Chaithanya, helpful for writing methodology, Drafting, validation, and Data curation, V. Sebastin, helpful for analysis of data.

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