



REVIEW ARTICLE

NANOTECHNOLOGY-BASED OCULAR DRUG DELIVERY SYSTEMS FOR GLAUCOMA MANAGEMENT: A COMPREHENSIVE REVIEW

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ABSTRACT: Damage to the optic nerve, permanent loss of visual field, and death of retinal ganglion cells are the results of glaucoma, a chronic and progressive optic neuropathy. Despite the fact that lowering IOP is the primary goal of treatment, traditional methods of administering eye medications through the skin have several drawbacks, such as low bioavailability, significant drug loss into the precorneal space, rapid post-dose IOP decline, frequent dosing, and poor patient compliance. Possible answers to these problems may lie in the novel methods for administering medications to the eye made possible by nanotechnology. Improved treatment effectiveness and drug distribution for glaucoma patients may be achieved by the use of nanotechnology, which is discussed in this paper. The potential of different types of nanocarriers, such as polymeric nanoparticles, liposomes, niosomes, nano-emulsions, nanomicelles, dendrimers, solid lipid nanoparticles, nanostructured lipid carriers, nanogels, and hybrid systems, is examined and discussed in relation to drug solubility, stability, retention, penetration, and controlled release in the eye. It is addressed how prostaglandin analogues, β -blockers, carbonic anhydrase inhibitors, α_2 -adrenergic agonists, and ROCK inhibitors may be delivered using nanocarriers. Furthermore, nanotechnology might enable the targeted delivery of brain-protective medications to the brain, hence reducing the degeneration of retinal ganglion cells. Unfortunately, there are a few drawbacks to consider. These include issues with regulations, biocompatibility, stability of formulation, ocular toxicity, weak clinical data, and manufacturing. A patient-friendly and long-lasting drug delivery medium for glaucoma therapy can be achieved by nanotechnology, it may be concluded. More studies and clinical trials are needed to confirm the long-term efficacy, safety, and therapeutic importance of these innovative delivery systems.

Keywords: Glaucoma, Nanotechnology, Ocular drug delivery, Nanocarriers, Intraocular pressure, Sustained drug release

I. INTRODUCTION

Retinal ganglion cell (RGC) loss, optic nerve injury, and irreversible loss of visual field (VF) are the hallmarks of glaucoma, a progressive chronic optic neuropathy. It is one of the main causes of blindness worldwide. Elevated intraocular pressure (IOP) is the most significant modifiable risk factor; individuals with normal IOP may nevertheless develop glaucoma. Nowadays, the primary goal of glaucoma treatment is to lower intraocular pressure (IOP) via medications, lasers, or surgery [1]. Topical eye drops are the most widely used pharmacological therapy for glaucoma. Among the main pharmacological classes are prostaglandin analogues, β -blockers, α_2 -adrenergic agonists, carbonic anhydrase inhibitors, and ROCK inhibitors. However, because of tear dilution, blanching, tear outflow from the eye, and corneal obstacles, traditional oral drug administration techniques are linked to limited bioavailability [2].

As a consequence, repeated dosages are required since very little of the injected medication reaches the intraocular tissues.

Local and/or systemic side effects, as well as patient noncompliance, may potentially have an impact on long-term therapy. Nanotechnology is a novel strategy that has been gaining popularity to get around these restrictions [3].

Drug solubility, stability, ocular retention, penetration, and controlled release may all be improved by nanocarriers. For ocular drug delivery, a variety of systems have been investigated, including polymeric nanoparticles, liposomes, niosomes, nanoemulsions, nanomicelles, dendrimers, solid lipid nanoparticles, nanostructured lipid carriers, and nanogels. Depending on the medication and the intended therapeutic outcome, their physicochemical characteristics may be optimized [4]. Numerous medications used to treat glaucoma, including prostaglandin analogues, β -blockers, carbonic anhydrase inhibitors, α_2 -adrenergic agonists, and ROCK inhibitors, have been studied for delivery by nanotechnology. Better therapeutic outcomes and reduced dosage needs may arise from nanoformulations' increased residence duration and prolonged drug release [5].

Although the majority of current approaches are still in the preclinical stage, nanocarriers may potentially be future therapeutic vectors for the administration of neuroprotective medications targeting RGC protection. The clinical translation of ocular nanomedicines, however, faces a number of obstacles, such as possible toxicity, biocompatibility, formulation stability, sterility, commercial scale manufacturing, repeatability, and regulatory approval [6]. Therefore, a comprehensive evaluation of effectiveness and long-term safety evidence is crucial. After outlining the pathophysiology and available treatments for glaucoma, the limitations of traditional ocular drug delivery systems, the main nanotechnology-based delivery systems, their application in glaucoma management, and their benefits, drawbacks, safety, and future prospects are reviewed [7].

2. Glaucoma: Pathophysiology and Current Therapeutic Approaches

Glaucoma is a chronic neurodegenerative disease that progressively damages the optic nerves and retinal ganglion cells (RGCs), leading to permanent loss of visual field. Although the most important modifiable risk factor is intraocular pressure (IOP), glaucoma may develop or worsen in individuals with normal IOPs. Glaucomatous neurodegeneration may be caused by oxidative stress, mechanical stress, vascular dysfunction, aberrant mitochondria, inflammation, and reduced axonal transport (Fig. 1, Table 1) [8].

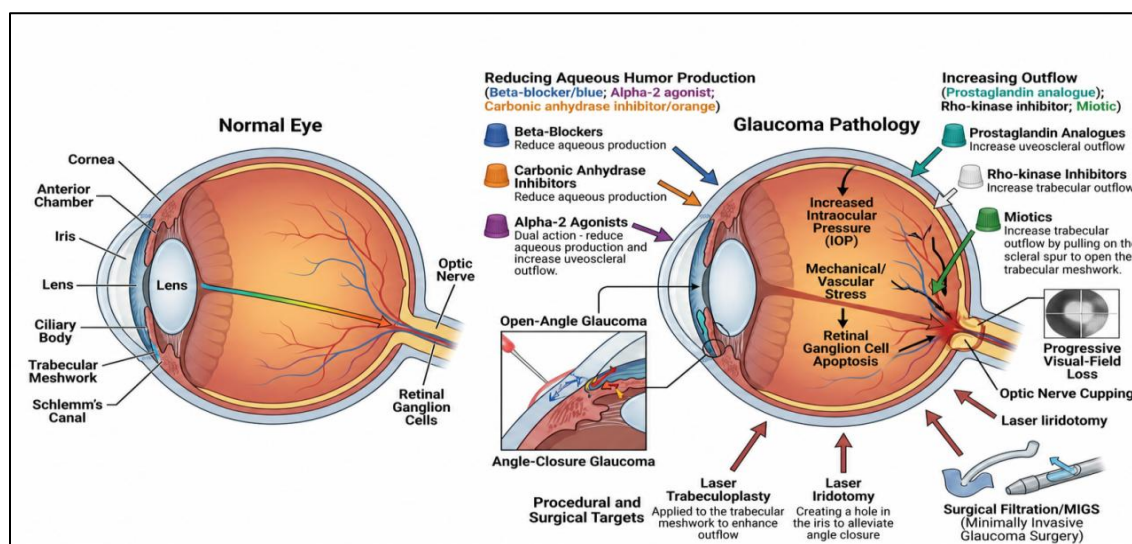


Figure 1: Pathophysiology of Glaucoma and Major Therapeutic Targets

Table 1: Major Antiglaucoma Drugs, Mechanisms of Action, and Therapeutic Characteristics

S. No.	Drug/Class	Representative Drug	Mechanism of Action	Main Therapeutic Role
1	Prostaglandin analogue	Latanoprost	Increases uveoscleral outflow	IOP reduction [9]
2	Prostaglandin analogue	Travoprost	Increases uveoscleral outflow	IOP reduction [10]
3	Prostaglandin analogue	Bimatoprost	Increases uveoscleral and trabecular outflow	IOP reduction [11]
4	Prostaglandin analogue	Tafluprost	Increases uveoscleral outflow	[IOP reduction 12]
5	β -Adrenergic blocker	Timolol	Decreases aqueous humor production	IOP reduction [13]
6	β -Adrenergic blocker	Betaxolol	Decreases aqueous humor production	IOP reduction [14]
7	Carbonic anhydrase inhibitor	Dorzolamide	Inhibits carbonic anhydrase and decreases aqueous humor production	IOP reduction [15]
8	Carbonic anhydrase inhibitor	Brinzolamide	Inhibits carbonic anhydrase and decreases aqueous humor production	IOP reduction [16]
9	α_2 -Adrenergic agonist	Brimonidine	Decreases aqueous humor production and increases uveoscleral outflow	IOP reduction [17]
10	α_2 -Adrenergic agonist	Apraclonidine	Reduces aqueous humor production	Short-term IOP reduction [18]
11	ROCK inhibitor	Netarsudil	Enhances trabecular outflow and reduces episcleral venous pressure	IOP reduction [19]
12	ROCK inhibitor	Ripasudil	Increases trabecular aqueous humor outflow	IOP reduction [20]
13	Cholinergic agonist	Pilocarpine	Contracts ciliary muscle and increases trabecular outflow	IOP reduction [21]
14	Cholinergic agonist	Carbachol	Increases trabecular outflow	IOP reduction [22]
15	Hyperosmotic agent	Mannitol	Increases plasma osmolarity and draws fluid from the eye	Rapid IOP reduction [23]
16	Hyperosmotic agent	Glycerol	Increases plasma osmolarity and reduces ocular volume	Rapid IOP reduction [24]
17	Prostaglandin + β -blocker	Latanoprost + Timolol	Increases outflow and decreases aqueous production	Combined IOP reduction [25]
18	Carbonic anhydrase inhibitor + β -blocker	Dorzolamide + Timolol	Decreases aqueous humor production through two mechanisms	Combined IOP reduction [26]
19	α_2 -agonist + β -blocker	Brimonidine + Timolol	Decreases aqueous production and increases outflow	Combined IOP reduction [27]
20	Prostaglandin + ROCK inhibitor	Latanoprost + Netarsudil	Enhances aqueous outflow through complementary pathways	Enhanced IOP reduction [28]

2.1 Pathophysiology of Glaucoma

The ciliary body continuously secretes the aqueous humour, which mostly leaves the eye via the uveoscleral and trabecular meshwork–Schlemm's canal pathways. An increase in IOP may result from both increased aqueous humour generation and reduced drainage. RGCs may gradually die as a consequence of the mechanical strain on the lamina cribrosa and optic nerve head. However, elevated IOP is not always the cause of glaucoma [29]. The degeneration of the RGCs may be caused by reduced ocular perfusion, oxidative stress, excitotoxicity and mitochondrial malfunction, neuro-inflammation, and aberrant axonal transport. In addition to lowering IOP, these pathways have sparked an increase in interest in treatment approaches for neuroprotection [30]. Primary open-angle glaucoma (POAG), angle-closure glaucoma, and secondary glaucoma are the three basic kinds of glaucoma. While POAG has an open anterior chamber angle and increasing optic nerve injury due to poor aqueous humour drainage, angle-closure glaucoma has an obstructed or constricted anterior chamber angle. Inflammation, trauma, drugs, other eye conditions, or an underlying illness may all result in secondary glaucoma [31].

2.2 Current Therapeutic Approaches

Lowering the intraocular pressure is the main therapy for glaucoma in order to stop more damage to the visual nerve. Treatment for glaucoma depends on a number of parameters, including the type of glaucoma, disease severity, baseline intraocular pressure, glaucoma progression, and patient considerations. Usually, pharmacological treatment is the first line of treatment; if sufficient IOP control is not obtained, laser and surgical procedures are recommended [32].

2.2.1 Prostaglandin Analogues

Prostaglandin analogues such latanoprost, travoprost, and bimatoprost are the first-line medications [33]. They may significantly lower intraocular pressure (IOP) by increasing aqueous humour outflow via the uveoscleral pathway. Conjunctival hyperaemia, eyelash development, and changes in periocular and iris pigment are examples of eye side effects.

2.2.2 β -Adrenergic Blockers

By opposing the β -adrenergic stimulation of aqueous humour production sites, timolol and other β -blockers reduce the formation of aqueous humour. Effective yet systemic absorption may have negative effects on breathing or the cardiovascular system, particularly in those who are vulnerable [34].

2.2.3 Carbonic Anhydrase Inhibitors

Topical carbonic anhydrase inhibitors, such as brinzolamide and dorzolamide, may be used alone or in combination with other antiglaucoma drugs to reduce the generation of aqueous humour. This brief duration in the eye may need many daily doses [35].

2.2.4 α_2 -Adrenergic Agonists

Brimonidine may marginally enhance uveoscleral outflow while decreasing the generation of aqueous humour. When further IOP reduction is required, it is often used as an adjuvant to the therapy. Effects on the eyes, allergic responses, and general system effects may restrict long-term usage in some individuals [36].

2.2.5 ROCK Inhibitors

Rho-associated protein kinase (ROCK) inhibitors, which include ripasudil and netarsudil, are a more recent family of antiglaucoma medications. They provide an alternate aqueous humour drainage channel for decreasing IOP and predominantly promote aqueous humour drainage via the trabecular outflow pathway [37].

2.2.6 Laser and Surgical Treatment

If medication therapies fail to reduce IOP, laser or surgical procedures may be explored. These include glaucoma drainage devices, laser trabeculoplasty, laser iridotomy, cyclophotocoagulation, trabeculectomy, and minimally invasive glaucoma surgery (MIGS). The kind of glaucoma, the severity of the ailment, the patient's underlying eye problems, and other variables will all affect the type of surgery [38].

Although current therapies may lower IOP, they are unable to stop the illness from becoming worse. Low bioavailability to the eye, frequent dosage, problems with patient compliance, and local or systemic toxicity are further drawbacks of long-term topical treatment. The development of more advanced delivery methods for the eye, such as those that use nanotechnology to improve ocular retention duration and permit more continuous drug release, is well justified by these limitations [39].

3. Challenges of Conventional Ocular Drug Delivery

Many anterior and posterior ocular illnesses are most often treated by topical drop administration, a traditional technique of ocular medicine delivery. Topical distribution is simple and non-invasive, but the eye has a number of physiological and anatomical obstacles that quickly remove medications from the ocular surface, making it ineffective. The aforementioned restrictions are particularly pertinent to glaucoma, since long-term medication usage is necessary for effective IOP management [40].

3.1 Precorneal Drug Loss

An eye drop will soon dilute after being administered by mixing with the tear film. Drugs are removed from the surface of the eyes by the constant production of tears and blinking. There is less time for the medication to be absorbed since the extra formulation passes via the nasolacrimal duct. This indicates that just a small portion of the injected dosage reaches the eye (Fig. 21) [41].

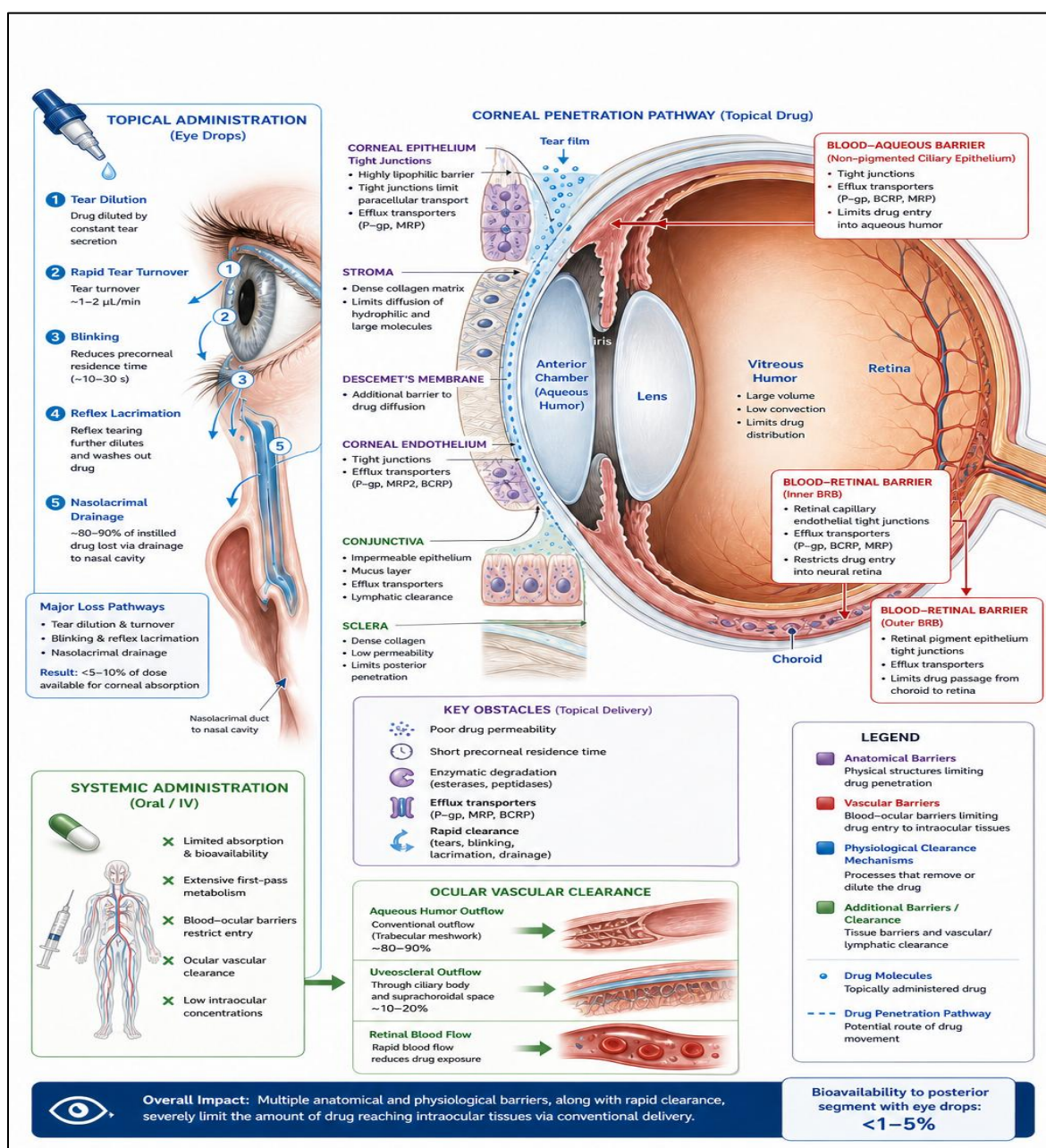


Figure 2: Anatomical and Physiological Barriers to Conventional Ocular Drug Delivery

3.2 Corneal Barrier

The primary obstacle to many topical medications' penetration is the cornea. The hydrophilic stroma, endothelium, and lipophilic epithelium make up its three layers. A medicine must have the right physicochemical characteristics in order to effectively traverse these different layers. Highly lipophilic molecules may be limited by the hydrophilic stromal barrier, while compounds with large molecular weight and hydrophilic characteristics often have low permeability to the cornea [42].

3.3 Conjunctival and Scleral Barriers

Drugs may also be administered to the intraocular tissues via the conjunctival and scleral routes. However, obstacles to

diffusion, vascular uptake, and conjunctival clearance may prevent medications from being absorbed by these pathways. A significant quantity of medication may enter the bloodstream and fail to reach the intended intraocular location [43].

3.4 Low Ocular Bioavailability

Ocular bioavailability is comparatively poor after topical treatment because to the combined effects of tear dilution, blinking, drainage, enzyme breakdown, and tissue barriers. To achieve therapeutic levels, this may need greater dosages or repeated doses. Higher dosages, however, may have greater adverse effects and are not necessarily better than lesser doses for getting the medication to the eye [44].

3.5 Short Drug Residence Time

The majority of traditional ophthalmic solutions only stay on the surface of the eye for a brief period of time. This implies a quick removal and that maintaining therapeutic levels for extended periods of time may be challenging. This is particularly important for glaucoma since the IOP is usually the primary aim of medication treatment and has to be continually regulated [45].

3.6 Frequent Dosing and Poor Patient Adherence

Repeated delivery is one of the main disadvantages of the standard glaucoma therapy. For many years, eye drops may be used once or more times daily. Forgetfulness, complicated treatment plans, difficulties handling the eye-drop bottles, incorrect instillation techniques, and treatment related pain may all contribute to poor adherence. Inadequate IOP management and an increased risk of disease development might result from noncompliance [46].

3.7 Systemic Exposure and Adverse Effects

The nasal mucosa may absorb medications that are washed out of the nasolacrimal duct and subsequently enter the systemic circulation. Particularly with pharmacologically potent antiglaucoma drugs like β -blockers and α_2 -adrenergic agonists, this might result in increased systemic exposure and negative consequences. Long-term topical use may potentially cause preservative reactions, toxicity to the eye's surface, and local irritation [47].

3.8 Limitations of Conventional Formulations

Other possible problems with typical solutions and suspensions include packaging, poor water solubility, chemical instability, and subpar medication retention and degradation. Due to all of these limitations, complex formulations that can improve solubility, provide superior protection for the active pharmaceutical ingredients, and lengthen the duration of residency in the eye have been developed [48].

The preservation of appropriate therapeutic levels in the target tissue for appropriate durations of time with little loss and undesirable side effects has often been the largest concern with traditional medication delivery to the eye. The limitations set out provide the scientific foundation for research into the creation of novel glaucoma delivery systems, such as liposomes, nanoparticles, nanoemulsions, nanomicelles, nanogels, and other nanotechnology-based delivery systems [49].

4. Nanotechnology-Based Ocular Drug Delivery Systems

Nanotechnology has the potential to overcome the drawbacks of traditional ocular medication delivery. The medications' solubility, stability, ocular retention, penetration, and controlled release may all be improved by nanocarriers. These characteristics in glaucoma may result in longer-lasting therapeutic medication levels in the eye and less frequent eye drops (Fig. 3, Table 2) [50].

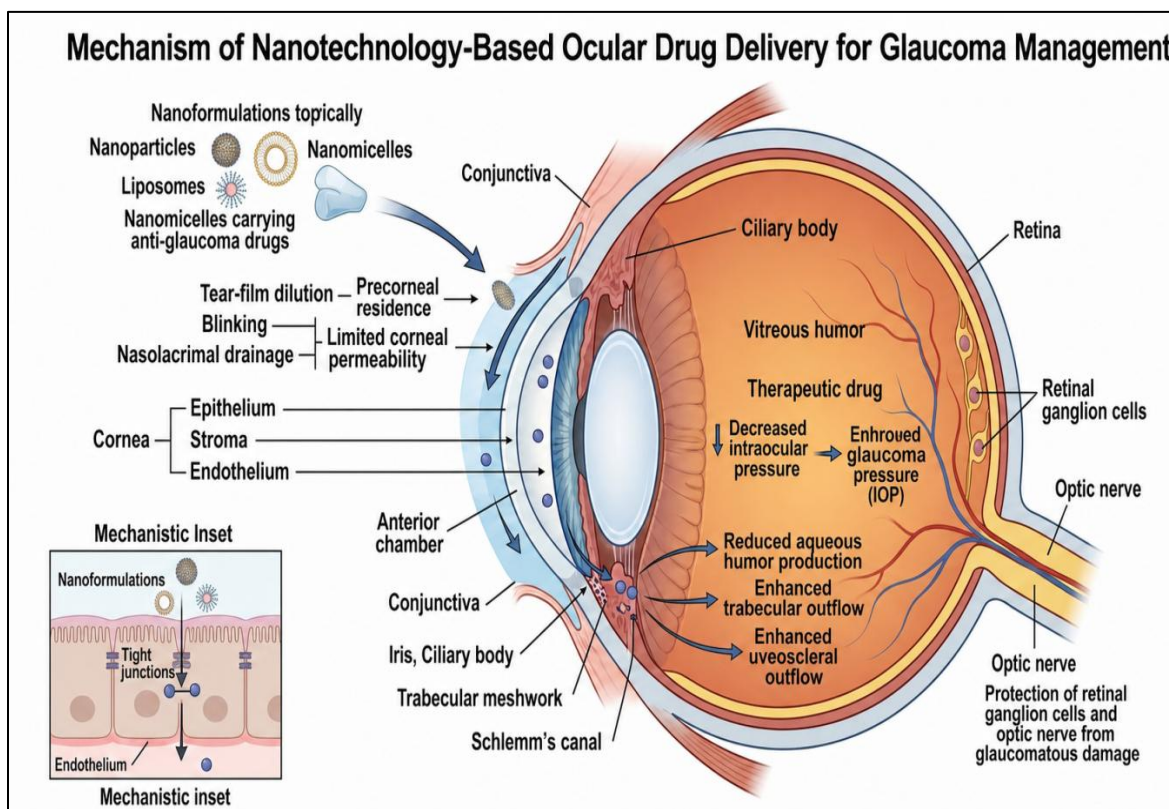


Figure 3: Mechanism of Nanotechnology-Based Ocular Drug Delivery for Glaucoma Management

Table 2: Major Nanocarriers Used in Ocular Drug Delivery: Characteristics, Advantages and Limitations

S. No.	Nanocarrier	Typical Composition	Major Advantages	Key Limitations
1	Polymeric nanoparticles	PLGA, PLA, chitosan	Controlled release, good drug protection	Complex formulation and scale-up [51]
2	Liposomes	Phospholipids + cholesterol	Carry hydrophilic and lipophilic drugs	Leakage and physical instability [52]
3	Niosomes	Non-ionic surfactants + cholesterol	Good stability and controlled release	Possible surfactant-related irritation [53]
4	Nanoemulsions	Oil + water + surfactant	Improve solubility of lipophilic drugs	Physical instability [54]
5	Nanomicelles	Amphiphilic surfactants/polymers	Enhance drug solubility	Drug leakage after dilution [55]
6	Dendrimers	Branched synthetic polymers	High drug-loading potential and surface modification	Potential cytotoxicity [56]
7	Solid lipid nanoparticles (SLNs)	Solid lipids + surfactants	Good stability and sustained release	Limited drug-loading capacity [57]
8	Nanostructured lipid carriers (NLCs)	Solid + liquid lipids	Higher loading and improved release	Formulation complexity [58]
9	Nanogels	Cross-linked hydrophilic polymers	High water content and controlled release	Stability and manufacturing challenges [59]
10	Nanosuspensions	Drug nanoparticles + stabilizers	Useful for poorly soluble drugs	Aggregation and physical instability [60]
11	Polymeric micelles	Block copolymers	Improve solubility and ocular distribution	Relatively low drug-loading capacity [61]
12	Hybrid nanoparticles	Polymer + lipid combinations	Combined advantages of multiple systems	Complex preparation [62]
13	Lipid-polymer nanoparticles	Lipid shell + polymeric core	Good stability and controlled release	Manufacturing complexity [63]
14	Mucoadhesive nanoparticles	Nanoparticles + mucoadhesive polymers	Prolonged ocular residence	Possible irritation with some polymers [64]
15	Stimuli-responsive nanocarriers	Responsive polymers/lipids	On-demand or environment-responsive release	Limited clinical validation [65]

4.1 Polymeric Nanoparticles

Polymeric nanoparticles are made from biodegradable polymers such as PLGA, polycaprolactone, and chitosan. has the ability to encapsulate medications and provide controlled or prolonged release. Additionally, its surface may be altered to improve ocular retention and mucoadhesion [66].

4.2 Liposomes

Phospholipids, which make up liposomes, are capable of delivering both lipophilic and hydrophilic medications. They may improve the solubility, stability, and ocular penetration of drugs. However, formulation stability, lipid oxidation, and drug leakage may be drawbacks [67].

4.3 Niosomes

Niosomes are vesicular systems that mostly contain cholesterol and non-ionic surfactants. They may provide prolonged medication release and improve a medicine's stability. Their composition has to be made to lessen the possibility of irritating the eyes [68].

4.4 Nanoemulsions and Nanomicelles

Oil and water droplets at the nanoscale (nanometre scale) make up nanoemulsions, which are particularly useful for improving the water solubility of medications that are poorly soluble in water. Lipophilic medications may be solubilised by assemblages of amphiphilic molecules with a hydrophobic center called nanomicelles. Both mechanisms may improve medication bioavailability and absorption in the eye [69].

4.5 Dendrimers

Dendrimers are highly branched nanostructures with a large number of functional groups on their surface. They may be regulated, released, or altered on the surface, and they can aggregate or encapsulate pharmaceuticals. However, there are

problems with manufacturing complexity and possible toxicity [70].

4.6 Solid Lipid Nanoparticles and Nanostructured Lipid Carriers

Nanostructured lipid carriers (NLCs) are composed of both liquid and solid lipids, whereas solid lipid nanoparticles (SLNs) are composed of solid lipid matrix. Drug stability, ocular retention, and prolonged release may all be improved by these approaches. NLCs may be able to carry more medication than SLNs because of the lipid matrix's increased disorder [71].

4.7 Nanogels and Hybrid Nanocarriers

Nanogels are cross-linked polymeric networks at the nanoscale with controlled drug release and high eye compatibility. To improve medication loading, stability, and release profile, a hybrid nanocarrier may include several delivery mechanisms. However, their intricacy may create production and regulatory challenges [72].

Generally speaking, nano-carriers provide a viable platform to improve antiglaucoma drug delivery to the eye. Drug characteristics, intended drug release time, drug target in the eye, drug stability, and safety concerns all have a role in the kind they choose to utilise. These systems serve as the foundation for the use of nanotechnology in glaucoma treatment (Table 3) [73].

5. Applications of Nanocarriers in Glaucoma Management

Because nanocarrier-based medication delivery increases drug retention in the eye and improves bioavailability and sustained release, it has a potential future in the treatment of glaucoma. Several nanocarrier methods have been investigated for the delivery of conventional IOP lowering medications and, more recently, potential neuroprotective medications [74].

Table 3: Nanotechnology-Based Drug Delivery Systems Investigated for Glaucoma Management

S. No.	Antiglaucoma Drug	Nanocarrier/System	Route	Main Purpose/Expected Benefit
1	Latanoprost	Polymeric nanoparticles	Topical	Sustained drug release and prolonged IOP reduction [75]
2	Latanoprost	Liposomes	Topical	Improved ocular retention and bioavailability [76]
3	Bimatoprost	Nanostructured lipid carriers	Topical	Prolonged release and reduced dosing frequency [77]
4	Travoprost	Nanoemulsion	Topical	Improved solubility and ocular absorption [78]
5	Timolol	Polymeric nanoparticles	Topical	Controlled release and enhanced ocular residence [79]
6	Timolol	Liposomes	Topical	Improved ocular delivery and reduced drug loss [80]
7	Dorzolamide	Polymeric nanoparticles	Topical	Sustained release and improved corneal penetration [81]
8	Dorzolamide	Solid lipid nanoparticles	Topical	Increased ocular retention and prolonged action [82]
9	Dorzolamide	Niosomes	Topical	Controlled release and improved ocular bioavailability [83]
10	Dorzolamide	Nanoemulsion	Topical	Enhanced solubility and corneal delivery [84]
11	Brinzolamide	Nanomicelles	Topical	Improved solubilization and ocular penetration [85]
12	Brimonidine	Nanoparticles	Topical	Prolonged ocular residence and sustained IOP reduction [86]
13	Netarsudil	Lipid-based nanocarrier	Topical	Sustained delivery and improved trabecular targeting [87]
14	Pilocarpine	Polymeric nanoparticles	Topical	Controlled release and prolonged IOP-lowering effect [88]
15	Neuroprotective agents	Nanocarriers/nanogels	Topical or intraocular	Potential RGC protection and targeted delivery [89]

5.1 Delivery of Prostaglandin Analogues

Prostaglandin analogues, including as latanoprost, bimatoprost, and travoprost, are often used to reduce intraocular pressure. These medications may be administered as nanocarriers to achieve extended release and increase the duration of drug residence in the eyes. Liposomes, nanoparticles, nanoemulsions, and lipid-based systems have been investigated to maintain therapeutic drug levels and may enable lower dose frequencies [90].

5.2 Delivery of β -Blockers

β -blockers, like as timolol, effectively decrease the intraocular pressure and reduce the generation of aqueous humour. By controlling the release and improving the drug's retention in the eye, nanoparticulate formulations may reduce the quick evacuation from the eye that is typical of conventional eye drops. They may also help lower systemic exposure because to nasolacrimal discharge [91].

5.3 Delivery of Carbonic Anhydrase Inhibitors

Brinzolamide and dorzolamide are crucial medications for controlling intraocular pressure, particularly carbonic anhydrase inhibitors. To improve penetration into the eye and prolong their retention period, they have been included into the formulation of liposomes, niosomes, nanoemulsions, nanoparticles, and lipid-based carriers. Thus, it may be able to improve therapeutic consistency and reduce the frequency of administration thanks to nanotechnology [92].

5.4 Delivery of α_2 -Adrenergic Agonists

Brimonidine has been widely utilised to reduce intraocular pressure by enhancing uveoscleral outflow and reducing aqueous production. Nanocarriers may boost the drug's bioavailability at the target tissues and prolong its residence duration at the eye site. Maintaining a more consistent medication level may also benefit from controlled release [93].

5.5 Delivery of ROCK Inhibitors

By blocking ROCK, ROCK inhibitors like ripasudil and netarsudil increase trabecular aqueous humour outflow. Using

nanotechnology, formulations comprising these more recent antiglaucoma medications may be created to provide long-lasting benefits. However, additional investigation is required to confirm their long-term safety and effectiveness in nanocarrier compositions [94].

5.6 Sustained and Controlled Drug Release

One of the main benefits of nanocarriers is the potential for controlled or prolonged medication release. Instead of releasing the active ingredient right away after delivery, nanocarriers may release it gradually over an extended period of time. This may reduce the number of doses required, minimise drug level variations, and maintain the medication's level in the body within the therapeutic range [95].

5.7 Improved Ocular Bioavailability

Increasing medication solubility, improving contact with the ocular surface, preventing drug degradation, and improving drug penetration across ocular barriers are the primary benefits of employing nanocarriers in the eyes. A higher proportion of the injected dosage may reach the targeted ocular tissues as a result of these effects [96].

5.8 Potential Neuroprotective Applications

The primary treatment for glaucoma is still IOP lowering, although even with well-controlled IOP, RGC degeneration may still happen. Neuroprotective medicines such as antioxidants and anti-inflammatory medications may be delivered to the optic neurones and retina by use of nanocarriers. Despite their potential, the majority of these techniques are currently in the experimental or preclinical stages [97].

5.9 Potential Reduction in Dosing Frequency

Nanocarriers have the added benefit of controlling the medication's release and increasing the drug's duration at the site, both of which have the potential to reduce the frequency of topical dosing. This might improve patient compliance and convenience, which is crucial for a chronic condition like glaucoma. Generally speaking, using nanocarriers for delivery systems may enhance the effectiveness of already available

antiglaucoma medications and get around some of the major problems with topical medication administration. To confirm their clinical use, however, long-term safety, effectiveness, stability, and patient outcomes need be further assessed [98].

6. Advantages, Limitations, Safety and Future Perspectives

When compared to the nanotechnology-based drug delivery system for the eyes, the eye drop formulation is one of the traditional drug delivery methods with a number of drawbacks. However, the clinical translation of their success is hampered by manufacturing, regulatory, and formulation and safety issues [99].

6.1 Advantages

The following are the primary advantages of using nanocarriers to treat glaucoma:

- Nanocarriers may enhance a drug's solubility, penetration, and retention at the ocular surface in addition to improving its bioavailability.
- Controlled drug release: Achieving therapeutic levels over an extended period of time might be facilitated by a slow or progressive drug release.
- Drugs may need fewer drops since they remain in the eye longer.
- Boosts the medicine's stability: Encapsulation may stop the substance from degrading and having negative impacts on the environment.
- Reduced systemic exposure: Increased eye retention may lead to less nasolacrimal discharge.
- Potential tailored delivery: Surface modification may make it possible to engage with certain eye tissue or cells.
- Potential neuroprotection: Compounds that might shield retinal ganglion cells could be delivered via nanocarriers [100].

6.2 Limitations

There are certain disadvantages, however. Particle size, surface charge, drug loading, and release properties must all be precisely controlled throughout the often complicated manufacturing process of nanocarrier formulations. Certain systems may have chemical and/or physical instability while being stored. The composition and surface features of nanoparticles may greatly affect their properties and how they interact with the tissues of the eye [101]. The paucity of clinical data is another drawback. There are very few ocular formulations based on nanotechnology that have progressed to clinical testing, despite the fact that several research have shown positive results in laboratory and animal trials. In conclusion, further investigation is required to validate their long-term therapeutic benefits [102].

6.3 Safety and Toxicity

The safety of the eyes is a major concern in the development of nanomedicines. Potential side effects include corneal

irritation, inflammation, cell toxicity, oxidative stress, and nanoparticle deposition. Important factors influencing nanocarrier toxicity include particle size, chemical make-up, concentration, surface charge, degradation characteristics, and exposure time [103].

Therefore, it is best to choose materials that are biocompatible and biodegradable while working with the eye. Complete assessment prior to clinical use requires in vitro cytotoxicity studies, animal models, and long-term safety testing [104].

6.4 Manufacturing and Regulatory Challenges

Nanocarriers cannot be mass-produced without stringent quality control and consistent production processes. Particle size distribution, morphology, drug content, sterility, stability, and release profile are among the many manufacturing batch requirements that must be met with absolute precision. Nanocarrier systems' physical properties and stability might be affected by sterilization [105]. Nanomedicines' intricate physicochemical characteristics mean that their biological activity may influence how they are regulated throughout development. Therefore, uniform characterisation methods and well defined safety and efficacy standards are essential for successful clinical translation [106].

6.5 Future Perspectives

More efficient, biocompatible, and readily deployed nanocarriers for the eye are likely to be the focus of future research. Subtle lipid-based systems, hybrid nanocarriers, surface-engineered nanoparticles, nanogels, or stimuli-responsive systems might all be used to fine-tune the drug's release and visual delivery [107]. Combining nanotechnology with hydrogels, microneedles, sustained-release implants, or other cutting-edge delivery methods may result in even better therapeutic outcomes. Developing a multifunctional nanocarrier that can deliver a neuroprotective drug and reduce intraocular pressure is another possible future glaucoma therapy [108]. In conclusion, nanotechnology has great potential for improving glaucoma therapy; nevertheless, it must be clinically shown to be long-term safe, repeatable, economical, and superior to existing formulations [109].

7. CONCLUSION

Long-term intraocular pressure management is the goal of treatment for glaucoma, a chronic, progressive visual neuropathy. Conventional antiglaucoma eye drops are effective, but they have drawbacks such as fast precorneal loss, limited ocular bioavailability, short residence duration, frequent administration, problems with patient compliance, and potential systemic and local adverse effects. Nanotechnology-based ocular medication delivery systems provide a potential remedy for the aforementioned drawbacks. Drug solubility, stability, ocular retention, penetration, and controlled release may be improved by using polymeric nanoparticles, liposomes, niosomes, nanoemulsions, nanomicelles, dendrimers, solid lipid nanoparticles, nanostructured

lipid carriers, and nanogels. These characteristics may assist reduce the frequency of dosages and enhance the administration of medications that lower intraocular pressure. The use of nanocarriers may potentially provide future prospects for the delivery of neuroprotectants to prevent degeneration of retinal ganglion cells. However, most sophisticated nanotherapeutic approaches are still in the experimental and preclinical stages. However, issues with ocular toxicity, biocompatibility, formulation stability, manufacturing, sterilisation, regulatory approval, and long-term clinical safety exist prior to their widespread clinical usage. All things considered, nanotechnology is a potential platform for glaucoma treatment in the future. The development of safer, more durable, and efficient ocular drug delivery systems that eventually improve treatment adherence and visual outcomes for glaucoma patients may be made possible by ongoing research into optimising nanocarrier design, carrying out comprehensive safety evaluations, and putting well-controlled clinical trials into practice.

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