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A Review on Ocular Drug Delivery Systems for Glaucoma

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Abstract: *The human eye is a highly sensitive and complex organ whose proper function is essential for maintaining quality of life. Visual impairment resulting from disorders such as cataract and glaucoma continues to pose major global health challenges. Cataracts remain the leading cause of blindness worldwide, while glaucoma, often symptomless in its early stages is the second most common cause of irreversible blindness. Conventional ophthalmic drug delivery systems, primarily eye drops and ointments, suffer from rapid precorneal elimination and poor bioavailability, necessitating frequent dosing. To overcome these limitations, advanced ocular drug delivery approaches such as in-situ gels, nanoparticles, liposomes, nanosuspensions, microemulsions, iontophoresis, and ocular inserts have been developed to provide sustained, controlled, and targeted drug release. These innovative systems not only enhance corneal contact time and therapeutic efficacy but also improve patient comfort and compliance. As the prevalence of glaucoma continues to rise, these newer delivery technologies hold significant promise in improving disease management and preventing progressive vision loss.*

Keywords: Glaucoma, Ocular Drug Delivery

I. INTRODUCTION

Eye is a very sensitive organ with a sophisticated physiology. It is composed of anterior and posterior segments. Generally, quality of life is significantly influenced by visual impairment resulted from various diseases. Cataract is the main cause of blindness worldwide. About 40–60% of blindness in the world is caused as a complication of cataract. Early cataract development results from mutations in α, β, and γ crystallin and its associated genes. Glaucoma is a well-known optic neuropathy disease that relates to elevation in intraocular pressure. [IOP].[1]There are many eye ailments which affected to eye and one can loss the eyesight also. Therefore, many ophthalmic drug delivery systems are available. These are classified as conventional and non-conventional (newer) drug delivery systems. Most commonly available ophthalmic preparations are eye drops and ointments about 70% of the eye dosage formulations in market. But these preparations when instilled into the culde-sac are rapidly drained away from the ocular cavity due to tear flow and lachrymal nasal drainage. Only a small amount is available for its therapeutic effect resulting in frequent dosing. So overcome to these problems newer pharmaceutical ophthalmic formulation such as in-situ gel, nanoparticle, liposome, nanosuspension, microemulsion, iontophoresis and ocular inserts have been developed in last three decades increase the bioavailability of the drug as a sustained and controlled manner.[2]Glaucoma is the second most common cause of irreversible blindness worldwide. By 2010, it had affected more than 60 million people around the world, leading to 8.4 million cases of sight loss. The number of glaucoma cases was predicted to exceed 111 million people by the year 2040.[3] Glaucoma is often called 'the silent thief of sight' as it is symptomless in the early stages and can cause irreversible damage before vision is affected. However, in advanced glaucoma, patients frequently have trouble in night vision, with gradual deterioration of their eyesight, leading to blindness from damage to the optic nerve. The primary risk factor for developing glaucoma is high intraocular pressure (IOP).[4]The primary approach for managing adult glaucoma is through medical care, which has shown significant and rapid breakthroughs in therapeutic interventions for

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this illness.[5] The reduction of intraocular pressure (IOP) by either increasing aqueous drainage through trabecular and/or uveoscleral outflow or by reducing aqueous production. Medical management is often limited by poor adherence, polypharmacy, as well as local and systemic side effects. Extended-release drug delivery devices could contribute to overcoming some of these limitations. Laser trabeculoplasty may be used as first-line therapy or for those in whom conservative medical treatments are inadequate but is limited by efficacy and repeatability. For patients who fail laser and medical treatment, surgical interventions are often required. In addition to trabeculectomy and glaucoma drainage devices, recent advancements in minimally invasive glaucoma surgical (MIGS) devices have expanded therapeutic options available to patients and providers.[6]

II. CAUSES

- Increased intraocular pressure (IOP) due to poor drainage of aqueous fluid inside the eye.
- Genetic predisposition, especially if close family members have glaucoma.
- Eye injuries or trauma, which can damage the drainage system and raise eye pressure.
- Medical conditions like diabetes, high blood pressure, or severe eye infections.
- Age-related changes, particularly in people over 40, affect fluid regulation and optic nerve health. [7]

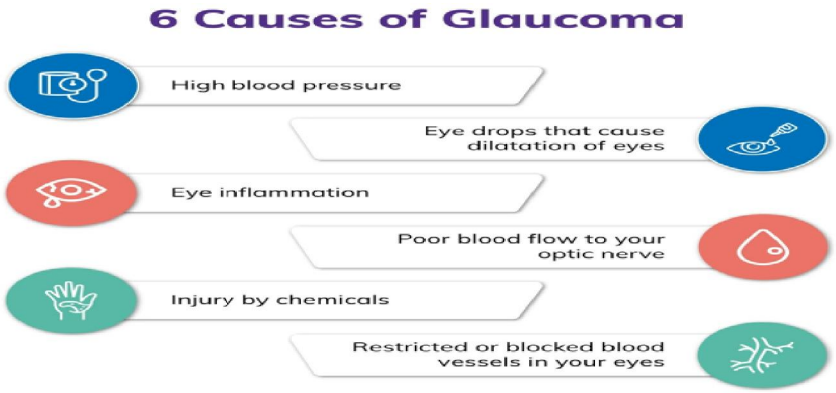

Figure: -1 causes of glaucoma [8]

III. TYPES OF GLAUCOMA

a) Primary Glaucoma: -

Occurs without any known eye disease or cause.

1. Primary Open-Angle Glaucoma (POAG)

• Most common type
• Drainage angle remains open, but fluid (aqueous humour) outflow is reduced
• Slow and painless increase in intraocular pressure (IOP)

2. Primary Angle-Closure Glaucoma (PACG)

• The angle between iris and cornea is narrow or closed, blocking fluid drainage
• Sudden increase in IOP
• Painful and emergency condition

b) Secondary Glaucoma:-

Occurs due to another eye disease, trauma, drug, or systemic condition.

Examples:

• Uveitic glaucoma – due to eye inflammation
• Neovascular glaucoma – due to abnormal new blood vessels (seen in diabetes)
• Steroid-induced glaucoma – due to long-term corticosteroid use
• Traumatic glaucoma – after eye injury

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• Pigmentary glaucoma – pigment from iris clogs the drainage system

c) Congenital (Developmental) Glaucoma: -

• Present at birth or early childhood

• Due to developmental defect in the drainage angle

• May be hereditary

d) Normal-Tension Glaucoma: -

• Optic nerve damage occurs even with normal intraocular pressure

• Cause may be poor blood flow to the optic nerve.[9]

IV. PATHOPHYSIOLOGY

• Fluid production: - eye produces a clear fluid called aqueous humor to nourish tissues.[10]

• Drainage problem: - the fluid normally drains out through a mesh-like channel. In glaucoma, drainage is blocked or reduced.

• Optic nerve damage: -high pressure damages the optic nerve, especially at a weak spot called lamina cibrosa.

• Increased pressure: - fluid builds up inside the eye, causing high intraocular pressure (IOP).[11]

• Vision loss: - damage starts with side (peripheral) vision and can lead to blindness if untreated.[12]

• Retinal ganglion cell death: - Pressure and reduced blood flow cause retinal ganglion cell death, impairing visual signalling.

V. SIGNS AND SYMPTOMS

a. Open-Angle Glaucoma (Most Common Type)

No symptoms in early stages, Gradual loss of peripheral (side) vision, Patchy blind spots in vision, Difficulty seeing in later stages

b. Angle-Closure Glaucoma (Medical Emergency)

Severe eye pain, Headache, Nausea or vomiting, Blurred vision, Redness in the eye, Sudden vision loss

c. Normal-Tension Glaucoma

No symptoms early on, Gradual blurred vision, Loss of peripheral vision in advanced stages

d. Glaucoma in Children

Cloudy or dull-looking eyes (infants), Excessive blinking or tearing without crying, Progressive near-sightedness, Headaches, Blurred vision

e. Pigmentary Glaucoma

Halos around lights, Blurred vision during physical activity, Gradual peripheral vision loss[13]

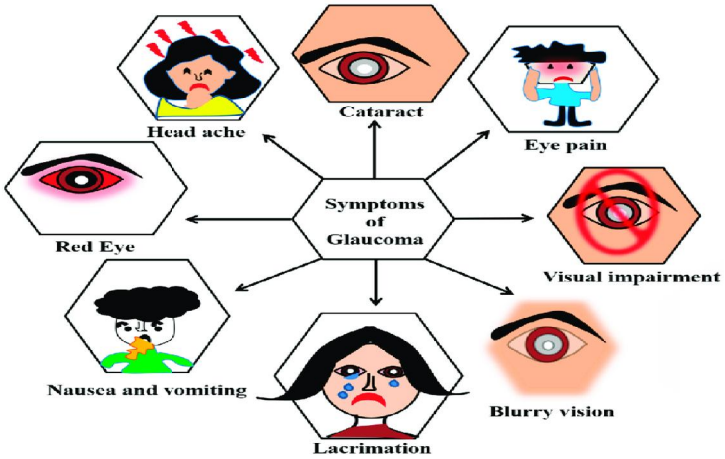

Figure: - 2 Symptoms of glaucoma [14]

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VI. DIAGNOSIS OF GLAUCOMA

1) Tonometry: - Purpose: - Measure intraocular pressure [IOP][15]

Common methods: -

• Goldmann applanation tonometry—gold standard.

• Non-contact (air puffy) tonometry screening.

• Tono-pen Perkins portable options.[16]

Normal IOP: 10-21 mmHG

Interpretation: - Elevated [IOP] (>21 mmHG) Suggests risk for glaucoma, but normal-tension glaucoma can occur. [17]

2) Gonioscopy: -

Purpose: - Evaluates the anterior chamber angle to differentiate open-angle vs. angle closure glaucoma.

Method: - a gonioscope lens is placed on the cornea with coupling fluid to visualize the trabecular meshwork and angle structures. [18]

3) Ophthalmoscopy (fundus examination)

Purpose: -Examines the optic disc for glaucomatous changes.

Findings:

• Increased cup-to-disc ratio (>0.6)

• Notching of neuroretina rim

• Disc haemorrhage

• Loss of rim tissue following the ISNT Rule (Inferior> superior> nasal > temporal >thickness)[19]

4) Visual field testing: (perimetry)

Purpose: - detects functional vision loss, especially peripheral fields defects.

Common test: Humphrey visual field (HVF) 24-2 or 30-2.

Typical findings: -

• Nasal step

• Arcuate scotoma

• Paracetamol scotoma [20]

5) Optical coherence tomography (OMT)

Purpose: - provides quantitative measurements of retinal nerve fibre layer (RNFL) and optic nerve head structures. [21]

Use: - detects early structural damage before visual fields loss.[22]

6) Pachymetry: -

Purpose: -measures central corneal thickness (CCT), which affects IOP accuracy.

• Thin corneas—underestimation of IOP

• Thick corneas—overestimation of IOP[23]

7) Optic nerve photography/ scanning laser polarimetry

Purpose: - documentation and quantitative analysis of optic nerve head and RNFL over time.[24]

VII. TREATMENT OF GLAUCOMA

A. Conventional Therapy Limitations: -

• Traditional eye drops deliver less than 5% of the drug to intraocular tissue due to tear drainage and blinking. [25]

• Frequent dosing is required, leading to poor patient compliance. [26]

B. Novel ocular drug delivery system for glaucoma: -

1. Nanoparticles

• Polymeric nanoparticles (PLGA, chitosan) improve drug stability and provide sustained release

• Example: - Timolol-loaded PLGA nanoparticles show prolonged IOP reduction compared to eye drops. [27]

2. liposomes

• Liposomes encapsulate both hydrophilic and lipophilic drugs, enhancing corneal penetration

• Example: - Pilocarpine liposomes improve ocular retention and reduce dosing frequency. [28]

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3. Niosome

• Non-ionic surfactant vesicles that are stable and enhance ocular bioavailability

• Example: - Timolol maleate niosomes provide sustained IOP control. [29]

4. Dendrimers

• Highly branched polymeric carriers with high drug loading and controlled release properties.

• Example: - Brimonidine dendrimer formulations enhance ocular residence time. [30]

5. In situ gelling system

• These are polymeric solutions that undergo sol-gel transition upon contact with tear fluid.

• Example: Timolol maleate in-situ-gel provides a prolonged IOP lowering effect.[31]

6. Ocular inserts and implants

• Provides sustained drug release over weeks or months [32]

• Example: - bigatures sustained release implant (Durysta) approved by FDA in 2020 for glaucoma treatment. [33]

7. Nano micelles and Nanogels

• Increase solubility of poorly soluble drugs and improve corneal permeation.

• Example: - Lanto Prost nano micelles enhance ocular bioavailability. [34]

VIII. RECENT ADVANCES IN OCULAR DRUG DELIVERY SYSTEMS FOR GLAUCOMA

1. Intracameral sustained-release implants (real-world approvals and trials)

Long-acting intracameral implants that release prostaglandin analogues or other IOP-lowering drugs have moved into clinical use, reducing reliance on daily drops and improving adherence. The traverso I dose TR implant is a prominent recent example with regulatory progress and clinical data demonstrating sustained IOP lowering.[35]

2. Microneedle (MN) platforms for targeted ocular delivery

Dissolving, hollow and polymeric microneedles (applied to sclera, conjunctiva, contact lenses, or as micro-patches) enable minimally invasive, localised delivery to anterior and posterior segments. MNs improve bioavailability and can be engineered for controlled release. A hot area of translational research and multiple 2023–2025 reviews/experiments detail design, materials, fabrication and early in vivo results.[36]

3. Nanocarriers and nanomedicine (liposomes, SLNs, dendrimers, nano micelles, exosomes)

Nanoparticles are widely investigated to enhance corneal penetration, extend residence time, and permit sustained release of IOP-lowering agents or neuroprotective. Reviews in 2023–2024 synthesise advances in formulation strategies and preclinical efficacy for glaucoma drugs.[37]

4. Drug-eluting contact lenses and in-situ gelling/hydrogel systems

Contact lenses loaded with drugs (or microneedle-integrated lenses) and stimuli-responsive in-situ gels/hydrogels provide prolonged anterior-segment delivery while being non-invasive and patient-friendly. These platforms are advancing in preclinical and early clinical testing as long-acting ophthalmic preparations (LAOPs).[38]

5. Combination & next-generation strategies: stimuli-responsive, gene/exosome delivery, and neuroprotection

Research is moving beyond purely IOP-lowering to platforms that deliver neuroprotective agents, gene therapy vectors, exosome-based cargos and stimuli-responsive releases (pH, enzymes, light). These are largely preclinical but are an important future direction.[39]

IX. CONCLUSION

Glaucoma is a complex and progressive optic neuropathy that remains a leading cause of irreversible blindnessworldwide. It encompassesvariouscategories, including primaryopen- angle, angle-closure, and secondary glaucoma, each with distinct pathophysiological mechanismsandclinicalpresentations.

Thediseaseisprimarilydrivenbyelevatedintraocular pressure, although other factors such as genetic predisposition, vascular dysregulation, and neurodegenerative processes also contribute. Early signs and symptoms are often subtle, makingatimelydiagnosisthroughcomprehensiveeyeexaminationssuchastonometry,visual field testing, and optic nerve imaging crucial for effective management. Treatment strategies focus on lowering intraocular pressure using topical medications, laser therapy, or surgical interventions. However, conventional ocular drug delivery faces challenges like

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poor bioavailabilityand patient non-compliance. Recent advances inocular drug deliverysystems, including nanoparticles, insitugels,andsustained-release implants,offerpromisingsolutions to enhance therapeutic efficacy and patient adherence. Overall, a deeper understanding of glaucoma's pathogenesis, coupled with innovative diagnostic and treatment approaches, is essential for preserving vision and improving qualityof life for affected individuals.

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