ISSN Print: 2664-6536
ISSN Online: 2664-6544
Impact Factor: RJIF **5.4**
IJBB 2025; SP-7(2): 05-09
www.biosciencejournal.net
Received: 10-05-2025
Accepted: 11-06-2025

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Two-Days National Conference on Multidisciplinary Approaches for Innovation and Sustainability: Global solution for contemporary Challenges-NCMIS (DPG Degree College: 17 th-18th 2025)

Nanoparticles as intra ocular pressure reducer in glaucoma patients

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DOI: https://www.doi.org/10.33545/26646536.2025.v7.i2a.122

Abstract
Glaucoma is a group of eye diseases which is characterized by progressive optic neuropathy. It has multifactorial risk factors. It finally leads to blindness if not treated on time. Primary open angle glaucoma or POAG is a type of glaucoma. Here, elevated intraocular pressure is the most prevalent risk factor. Glaucoma is associated with sensitivity to IOP (Intraocular Pressure) and lowering IOP through tropical application of hypotensive drugs is one of the therapeutic approaches for its treatment. In humans, around 60-80% of aqueous humor drains out through Trabecular pathway (Trabecular Meshwork + Schlemm's Canal) and 20-40% by uveoscleral pathway by diffusion through interstitial spaces of the ciliary muscle into suprachoroidal space. There becomes increase in resistance to the drainage of fluid at interface between Trabecular Meshwork and inner wall of Schlemm's Canal. As elevated IOP is the main modifiable risk factor and daily eye drops are the primary treatment of choice. The drawbacks associated with the treatments are vision affected for weeks or months, eyesight may not be as good as before, not a complete cure, most people will have lower pressure last only a few years (3-4). There are several drugs involved in treatment (to decrease IOP) of Glaucoma as β-blockers, α2-antagonists, Prostaglandin Analogues, Cholinergic, Cholinesterase inhibitors etc. Maximum reduction in IOP (25-35%) is by Prostaglandin Analogue 8 hours. To increase its efficacy, we need drugs Nano formulation. Nanodrugs can be superior with respect to controlled release, targeted delivery and therapeutic impact. In traditional formulations, only a small amount of administered drug penetrates the cornea to reach the desired intraocular tissue due to corneal barriers. There is a requirement of biodegradable nanocarriers that can release drugs on specific sites for longer duration without interrupting the normal functions of eye.

Keywords: Trabecular meshwork, prostaglandin, nano formulation, biodegradable nanocarriers

Introduction
Glaucoma is a group of eye diseases which is characterized by progressive optic neuropathy. It has multifactorial risk factors. It finally leads to blindness if not treated on time. There are several types of glaucoma. Primary open angle glaucoma (POAG) is a type of glaucoma which is most common in comparison to others. Here, elevated intraocular pressure is the most prevalent risk factor. Glaucoma is associated with sensitivity to IOP and lowering IOP through either tropical application of hypotensive drugs or survey is the only form of treatment. Normally, IOP is maintained through a balance between the amount of aqueous humor produced in ciliary body epithelium and that drained from anterior chamber. In humans, around 60-80% of aqueous humor drains out through Trabecular pathway (Trabecular Meshwork + Schlemm's Canal) and 20-40% by uveoscleral pathway by diffusion through interstitial spaces of the ciliary muscle into suprachoroidal space. There becomes an increase in resistance to the drainage of fluid at interfacebetween Trabecular Meshwork and inner wall of Schlemm's Canal. Uveoscleral pathways have no relation with this resistance. As elevated IOP is the main modifiable risk factor and daily eye drops are the primary treatment of choice. Treatments include various strategies but there are drawbacks attached also like, vision affected for weeks or months, eyesight may not be as good as before, not a complete cure, most people will have lower pressure last only a few years [3-4].

Drugs therapy is used to control IOP by administration at a particular difference of time. There are several drugs involved in treatment (to decrease IOP) of Glaucoma as β-blockers, α2-antagonists, Prostaglandin Analogues, Cholinergic, Cholinesterase inhibitors etc. Maximum reduction in IOP (25-35%) is by Prostaglandin Analogs. Prostaglandins are latest class of drugs that are added to the list of Glaucoma medications. They are involved in constriction and relaxation of smooth muscles, regulation of immune response. They are local hormones that produce ocular inflammation and hypertension in high levels but in smaller amounts reduces IOP. Prostaglandins are fatty acids which structurally carry a negatively charged-COOH group. By chemical modifications to improve molecule solubility, carboxyl group modified into other groups as ethyl amide (Bimatoprost), isopropyl ester (Latanoprost, Travoprost). These analogues are also called Hypotensive Lipids. Besides the good reason to use Prostaglandin drugs to reduce IOP, it has side effects also as upper lid sulcus, periorbital fat atrophy, tight eyelids, deepening of upper lid sulcus, lengthening of eye lashes and increased pigmentation of iris and periorbital skin.

Current approaches for the treatment of glaucoma

Presently, prostaglandins have maximum effect in maintaining normal IOP is up to 8 hours. To increase its efficacy, we need drugs nano formulation. Nanodrugs can be superior with respect to controlled release, targeted delivery and therapeutic impact. Nanomedicines are influenced by particle size, surface charge, surface modifications and hydrophobicity. Nanotechnology promises to overcome poor drug stability and the difficulties in delivering drugs across biological barriers (improvement of bioavailability). In traditional formulations, only a small amount of administered drug penetrates the cornea to reach the desired intraocular tissue due to corneal barriers. Size governs the movement of nanoparticles inside tissues. In ophthalmic areas, the 10 to 1000 nm range of particle size allows for improved topical passage of large, water insoluble molecules through the barriers of the ocular system. I want to work on different nanocarriers formulations that have no immunogenicity and other severe effects on the eye. We need biodegradable nanocarriers that can release drugs on specific sites for longer duration without interrupting the normal functions of eye.

The prevalence of glaucoma in people between 40-80 years of age is 3.54% globally. Among these, Africans are at highest position with 4.20% prevalence rate in case of Open Angle Glaucoma. While in case of primary ACG, 1.09% of people are affected. It has been reported that approx. 76 million people were affected in 2020 from glaucoma worldwide [1, 2]. It has been reported in a study that the rate of OAG increased from 5.2% at 60 years to 12.2% at 80 years. When compared in between male and female, it was found that the rate was 1.30% more than in case of female. [3]. OAG is considered one of the most common reasons for blindness in UK. [4].

Nano delivery systems has developed high potentials in the lowering of intraocular pressure in case of ophthalmology [5]. Nanoparticles are being used in other forms also like, nano micelles and nanospheres [6]. The drugs get encapsulated in these carriers to lower the intraocular pressure. There are several advantages of using nanocarriers as they improve the stability and solubility of drugs and makes it more permeable. Drugs elimination rate also decreases i.e., slow elimination of drug from tissues may prolong the presence of drugs. The factors affect the drug efficacy and therapeutic effects includes size, surface and the mechanism of its release. The controlled release of drugs enhances the prolonged effect on tissue. The specific locations can be targeted using nanoparticles as in ciliary body, anterior chamber angle. The treatment includes different categories like Pharmacological and non-pharmacological treatments. Pharmacological treatments include uses of topical drugs like PGA, BB, AA, CAI, cholinergic agonists. [7]. The non-pharmacological treatments include Transscleral diode laser cyclophotocoagulation (TCP), Endoscopic diode laser cyclophotocoagulation (ECP), Selective laser trabeculoplasty, Trabeculectomy (TRAB), Deep sclerectomy, Viscocanalostomy (VC) and canaloplasty, iStent, CyPass microstent, Trabectome and Excimer laser trabeculotomy [8]. The antiglaucoma treatments focuses on lowering of intraocular pressure to maintain up to 12.3 mmHg.

New forms of nanoparticles as in carbon nanotubes, metals, graphene have been used in drug delivery system to improve drug penetration and absorption with their unique properties [9, 10].

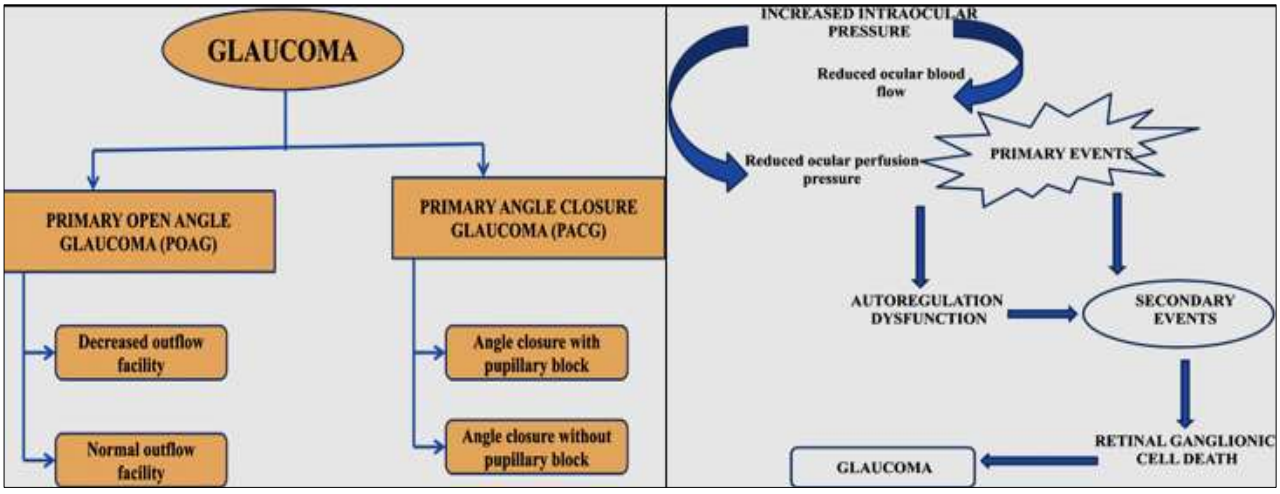

Fig 1: Types of Glaucoma and pathophysiology involved in Glaucoma

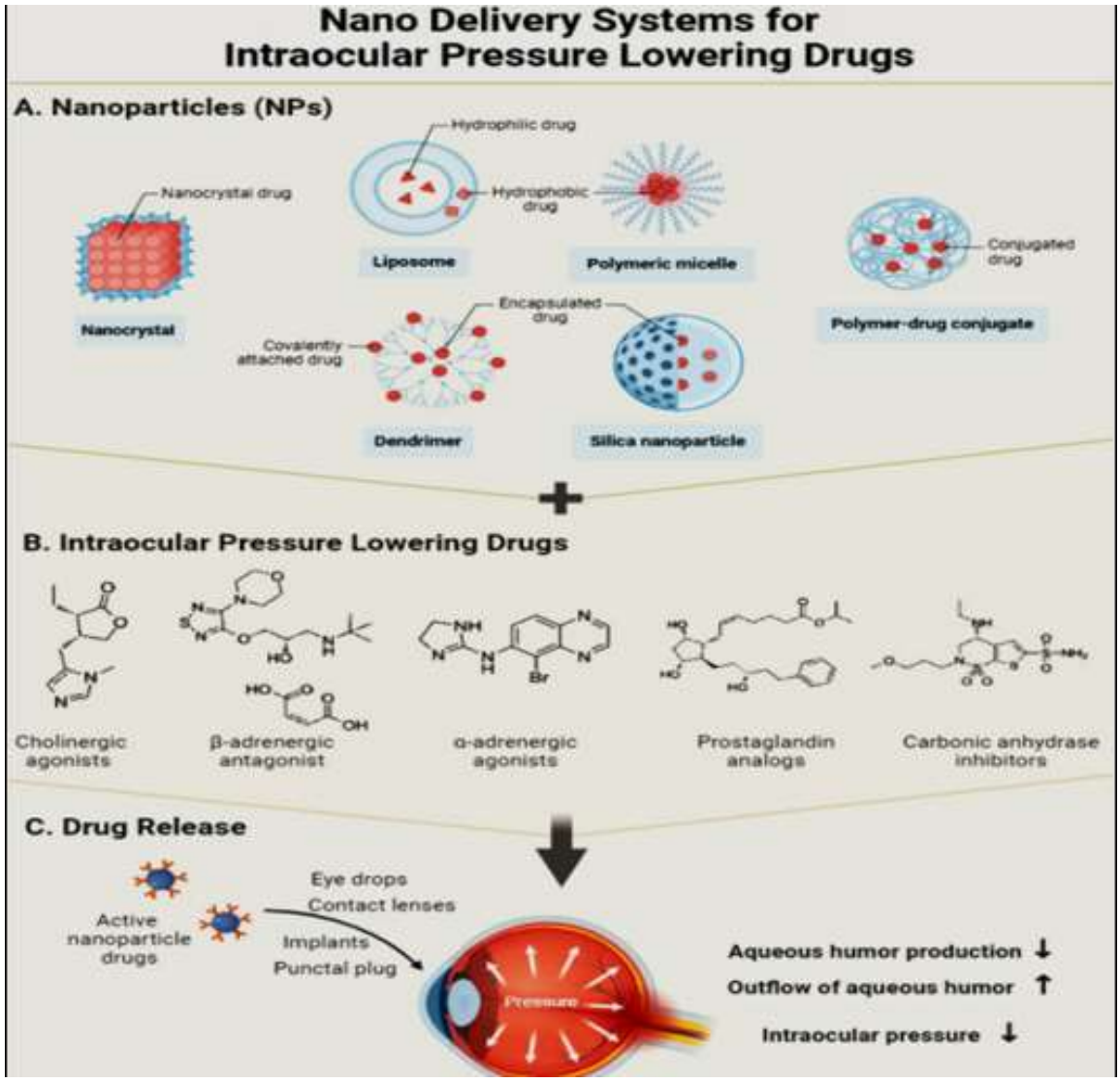

Fig 2: Nano drug delivery system with examples of various IOP lowering drugs.

Several studies are focusing on combination therapy using combination of drugs in the form of multi-drug delivery system to simplify medications [11]. In Surgical treatments, scarring is a major factor in obstructing drainage. Many studies and research has been done to prevent scarring as in case of amniotic membrane with nanoparticle PLGA [5-fluorouracil (5-Fu) poly (lactic-*co*-glycolic acid)] [12], a cationic dendrimer PAMAM [poly (amidoamine)] nanoparticles and 5-Fu graphite oxide and silver nanoparticles has been used for the regulation of anti-scarring [13, 14]. A novel adjustable PHBV basement film for inhibition of scarring [15]. The drugs used in lowering intraocular pressure includes cholinergic agonists, β and α adrenergic antagonists, prostaglandin analogs, carbonic anhydrase inhibitors, Rho-associated coiled-coil forming protein kinase inhibitors etc. Ophthalmology is working on improved nano delivery systems for anti-glaucoma drugs as well as the success rate of surgical treatments.

Prostaglandin analogs increases uveoscleral outflow rate and one of them increases conventional aqueous humor outflow as well. Usually with very strong effect, the drugs are prescribed for once a day. These are also considered as first choice in the treatment for clinical practice. Although many studies have claimed the relation between prolonged use of prostaglandin analogs and conjunctival hyperemia, corneal damage, decreased central corneal thickness etc.[16].

But the analysis has been disproportional and not including many of the factors like age, gender and the preservatives. Prostaglandin analogs include Latanoprost which is a liposomal formulation using phospholipids. Latanoprost was first tested on monkey having subconjunctival injection in eyes. [17]. The clinical study on six patients proved 3 months reduction in intraocular pressure [18].

Table 1: Treatment options for glaucoma using prostaglandin analogues [19]

Class of drug	Examples	Mechanism of action	Local side effects
Prostaglandin analogues	Latanoprost, Travoprost, Bimatoprost, Tafluprost	First-line therapy. Results in increased uveoscleral outflow	Eye colour and eyelashes changes, Redness in eye

Nanocarrier's nanomedicine

Nanocarriers are unique particle delivery devices that have nanometer-sized particles (ranging from 10 to 1000 nm) and have specific surface charge that increases the colloidal stability of these particles, as well as their ability to conjugate. Thus, they remain intact at specific sites.

Repulsive force due to same surface charges repels them from each other and it prevents the aggregation and of particles. During ocular delivery, conjunctiva and cornea plays the role of repulsion as they exhibit negative surface charges. Thus, they show higher affinity for cationic nanocarriers [20]. This electrostatic interaction results in enhanced retention of drug on ocular surface such as cornea thus facilitate the topical delivery to the anterior region of eye. Although as expected, anionic nanocarriers pass to retina upon administering intravitreal. Nanocarriers with small particles size are good at having capacity to deliver the therapeutic molecules to desired site by combating the ocular barriers [21, 22].

Examples of nanocarriers are liposomes nanoparticles, lipid nanoparticles, noisome, nanosuspensions, polymeric nano micelles, nanodiamonds, nano capsules, nanospheres, protein/peptide nanoparticles nanocrystals and polymeric nanofibers have been investigated for the development of nanomedicine in glaucoma treatment.

Conclusion

Use of nano delivery systems for the drugs used for the purpose of lowering intraocular pressure can lead to more effective drug delivery system which will be proved more effective and convenient as well. As already been proved the increase in efficacy of drugs has been noticed in the treatment of other disease as well. Although many potential applications of nano drug delivery system have been predicted and applied in many fields but still it is under developmental phase and require further validations. The nanoparticles need to be compatible and safe to use in human body which is also in developmental phase. Despite highly promising potential and the prospects of nanomedicine, there persists the issues that need to be resolved with full efficiency. Not only reliable, but also affordable production needs to be worked up on. Advanced formulation needs to be compatible with various stages of the lifecycle of target as well as in different intraocular environments.

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