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REVIEW PAPER ON NOVEL DRUG DELIVERY SYSTEM OF GLAUCOMA

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ABSTRACT

For a long time, the accepted treatment for glaucoma has been lowering intraocular pressure (IOP) through medication or surgery.

There are several great medications on the market that can lower IOP. Usually, eye drops are used to administer these medications. However, patients may not comply to their treatment plans, which lowers the medications' clinical efficacy. Current research is being done on a number of innovative delivery technologies intended to solve the problem of adherence and guarantee a steady decrease in IOP. Surgically implanted systems, injectables such biodegradable micro- and nanoparticles, and contact lens-releasing glaucoma medicines are some examples of these delivery methods. By providing a variety of administration modalities and having the ability to manage IOP over several months, these innovative technologies promise to increase clinical efficacy. Additionally, there is a wish to havein addition to IOP reduction, supplementary neuroprotective strategies for patients who still exhibit deterioration. For typical oral or drop formulations, many prospective neuroprotective drugs are unsuitable. The development of appropriate delivery mechanisms capable of delivering the medications to the retina and optic nerve in a localized, sustained manner is necessary to realize their promise. Drug delivery systems may enhance patient compliance, lessen adverse effects, boost effectiveness, and eventually help glaucoma sufferers maintain their vision. In this assessment, we go over the advantages and drawbacks of the existing distribution and application systems as well as those that are in the works.

Keywords: Nano Particle, PLGA, Drug Delivery, Clinical Trials, Glaucoma.

I. INTRODUCTION

Glaucoma

Glaucoma is a group of eye conditions that damage the optic nerve, often due to abnormally high pressure in the eye (intraocular pressure). This damage can lead to vision loss and, if untreated, can result in blindness.[1] Glaucoma typically develops slowly, and early stages may have no symptoms. As the condition progresses, it can cause gradual loss of peripheral vision and eventually central vision. Regular eye exams are crucial for early detection and management, as treatments like medications, laser therapy, or surgery can help control eye pressure and prevent further vision loss.

Fig 1: (Glaucoma)

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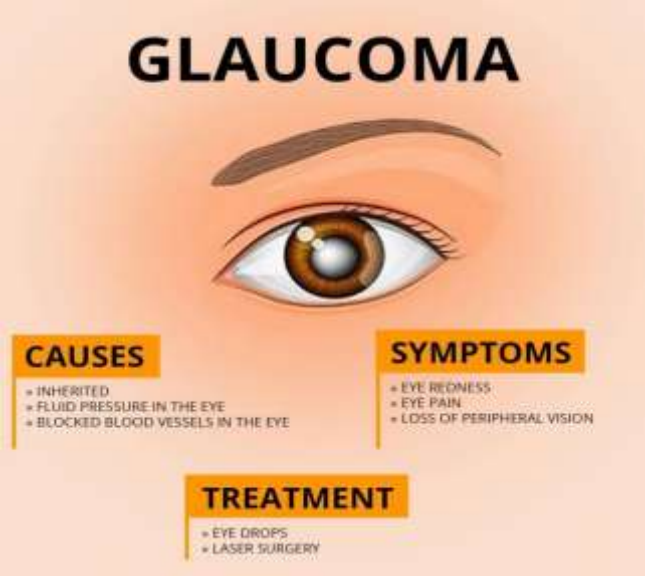

Fig 2: (Glaucoma)

Drugs and targets for glaucoma

Glaucoma is the second most common cause of permanent blindness, with an estimated 2.2 million Americans and 67 million people worldwide suffering from the condition.[3]

Degeneration of the axons of retinal ganglion cells (RGCs), which comprise the optic nerve, is a disorder known as glaucoma. If treatment is not received, the loss of RGCs results in blindness.[4] Glaucoma is more common as people age.4-6 It is predicted that within 15 years, 50% more Americans would suffer from this illness due to the aging of the US population. treatments that reduce intraocular pressure (IOP) constitute the mainstay of current glaucoma treatment, and when taken as directed, a number of glaucoma treatments can effectively reduce IOP. However, a basic issue that worsens with age is poor adherence, and about 20% of patients ultimately need surgery to lower their IOP.

A different approach to treatment could be the use of neuroprotective drugs, which are intended to increase RGC survival without regard to IOP.[5]Even in cases when there has been a sufficient IOP drop, some individuals nevertheless exhibit gradual loss of visual field, despite the fact that most people with glaucoma can be kept under control.[6]Alternatively or in addition to IOP lowering, these patients would benefit greatly from these techniques. Although no neuroprotective medications have now received FDA approval, neuroprotective medicines that can lessen the loss of RGCs and the degeneration of optic nerve fibers are desirable targets for therapy.[7]

Furthermore, systemic delivery of numerous promising neuroprotective medicines is associated with notable adverse effects. Thus, before neuroprotective medications are likely to be practical for the clinical treatment of glaucoma, the development of innovative, local drug delivery mechanisms is required.[8]

Lowering of IOP

IOP elevation is a major risk factor for primary open-angle glaucoma, even though some occurrences of glaucoma (also known as normal tension glaucoma) occur without IOP elevation.[9] Nonetheless, there is strong evidence that reducing the IOP, even in situations with normal tension glaucoma, slows the progression of glaucoma in about 90% of cases. Topical eye drops applied one or more times per day are the most popular method of lowering IOP.

Inappropriate administration of topical glaucoma medicines limits their effectiveness. It is necessary to apply topical drugs correctly by placing the eye drop on the globe's surface, administering the medication correctly several times a day, and timing the intervals between doses or treatments.[10]It calls for diligence and manual skill, which many patients—especially the elderly—find difficult. Less than half of patients are able to consistently maintain a decreased IOP with topical timolol, according to research, and there is a low level of medical adherence to topical medicine for glaucoma in practice.

Moreover, 1% of topical medication administration enters the aqueous humor. Depending on the kind of drug

used, eye drops can cause major systemic absorption (up to 80%), which may have unfavorable side effects. All of these characteristics together make topical treatment difficult, particularly in the elderly population, who show decreased adherence and increased susceptibility to side effects.Understanding the precise medicine to be administered, its chemical makeup, its mechanism, and any possible side effects are essential from the perspective of drug delivery systems. The IOP is lowered by a number of kinds of topical glaucoma medicines that are effective. Alphaadrenergics (like brimonidine), beta-blockers (like timolol), prostaglandin analogs (like latanoprost), carbonic anhydrase inhibitors (like dorzolamide), and cholinergics (like pilocarpine) are among them. These medication classes each have unique properties of their own that affect how they are delivered.[11]
Thus, it's critical to comprehend the distinctive qualities of the drugs in order to appreciate the advantages and possible drawbacks of their distribution.

One of the earliest medications used to treat glaucoma is pilocarpine hydrochloride (HCl), a parasympathomimetic that was first identified in 1877.[12] It lowers IOP by increasing the aqueous outflow. To maintain a lower IOP, four dosages must be taken daily. Along with a host of systemic side effects like nausea, vomiting, and diarrhea, it also causes brow aches, impaired vision, and a possible risk of retinal detachment.[13] After other drugs were tried, pilocarpine was used less frequently after they were introduced in the late 1970s and early 1980s. But in the 1970s, it was among the first medications incorporated into a sustained release implant, avoiding the requirement for daily administration and minimizing adverse effects.Timolol maleate was authorized for use in eye care in 1979. An average IOP reduction of 20–35% is achieved using timolol maleate, an antagonist of the b-adrenergic receptor. Timolol maleate has been the US Food and Drug Administration's (FDA) "gold standard" medication for lowering intraocular pressure (IOP) since it was approved.[14]To maintain a well-controlled IOP, timolol typically needs to be taken twice day due to its considerable cardiac adverse effects. The molecule is appealing for a variety of delivery techniques, such as innovative drop formulations, implants, and injectables, due to its exceptional stability and high water solubility.
Prescriptions for latanoprost, travoprost, and bimatoprost have surpassed those for timolol in the past several years due to the popularity of prostaglandin analogs. Prostaglandins stimulate the outflow of aqueous humor to lower intraocular pressure (IOP) even if timolol lowers its production.The very hydrophobic prodrugs known as prostaglandin analogs are broken into their active form by enzymes.[15] When used topically, the prostaglandin family of drugs usually has few systemic side effects since the enzymes that break these molecules are found in the eye but in low numbers systemically. Patients find them highly appealing because they just need to be taken once a day. The development of drug delivery methods for prostaglandin analogs is highly desired due to their significant performance, since it will further minimize the requirement for daily dose.[16] Because these medications are extremely hydrophobic, they can be delivered using a variety of popular hydrophobic polymers, like poly(ethylene-co-vinyl acetate) and poly(lactic acid), which are used to deliver medications in the eyes.

Neuroprotection

Although lowering eye pressure works for most people with glaucoma, there's growing interest in finding ways to protect the nerve cells in the eye as an additional or alternative treatment. Currently, there are no FDA-approved drugs specifically for this kind of nerve protection in glaucoma. For these potential treatments to be useful, how they are delivered needs to be carefully designed for each drug.

Several drugs have been tested to protect nerve cells in the central nervous system. These include small molecules like statins and progesterone, as well as larger proteins like glial cell-derived neurotrophic factor (GDNF) and ciliary neurotrophic factor (CNTF).[17] However, these drugs often have serious side effects when given throughout the body. For example, CNTF can cause weight loss and coughing, which limits the dose that can be safely used and affects how well the drug works.

To address this, one potential solution is to deliver these drugs directly to the eye in a way that provides a steady, localized treatment while minimizing side effects. Proteins are particularly difficult to deliver because they are large, need to maintain their structure to work properly, and can be broken down easily. They also don’t cross easily into the eye tissue and are expensive to produce.

To overcome these challenges, new methods are being developed to deliver these protective factors directly to the eye. These include using genetic techniques to get retinal cells to produce the needed factors or

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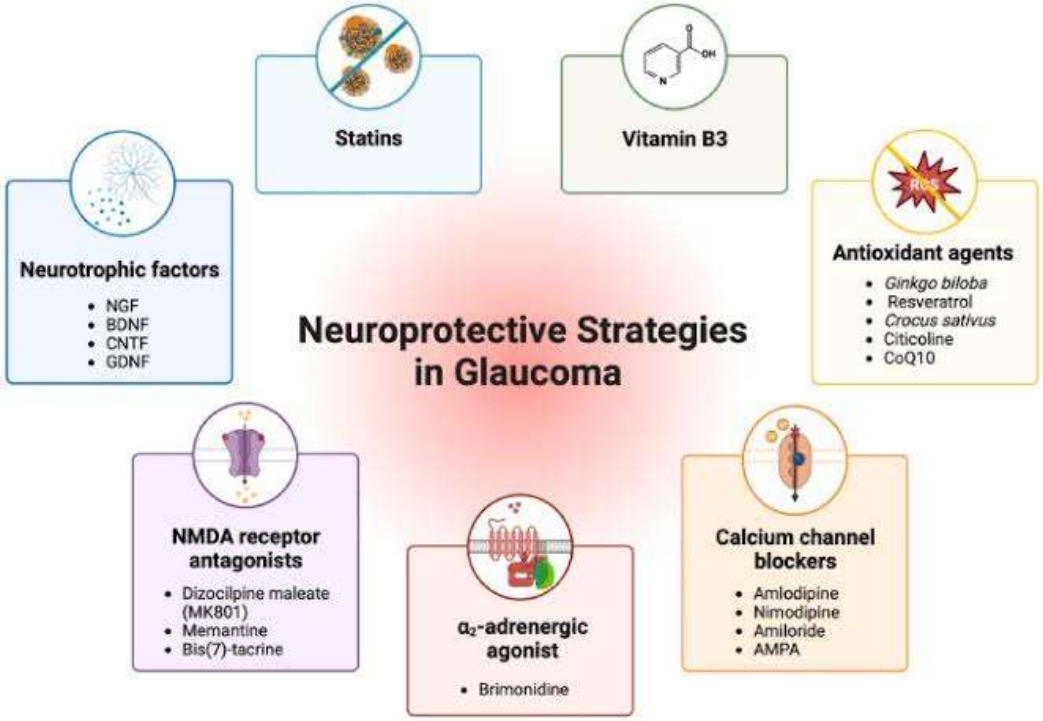
transplanting stem cells that are engineered to produce them. These innovative delivery methods might offer new options alongside the traditional treatments that lower eye pressure in glaucoma.

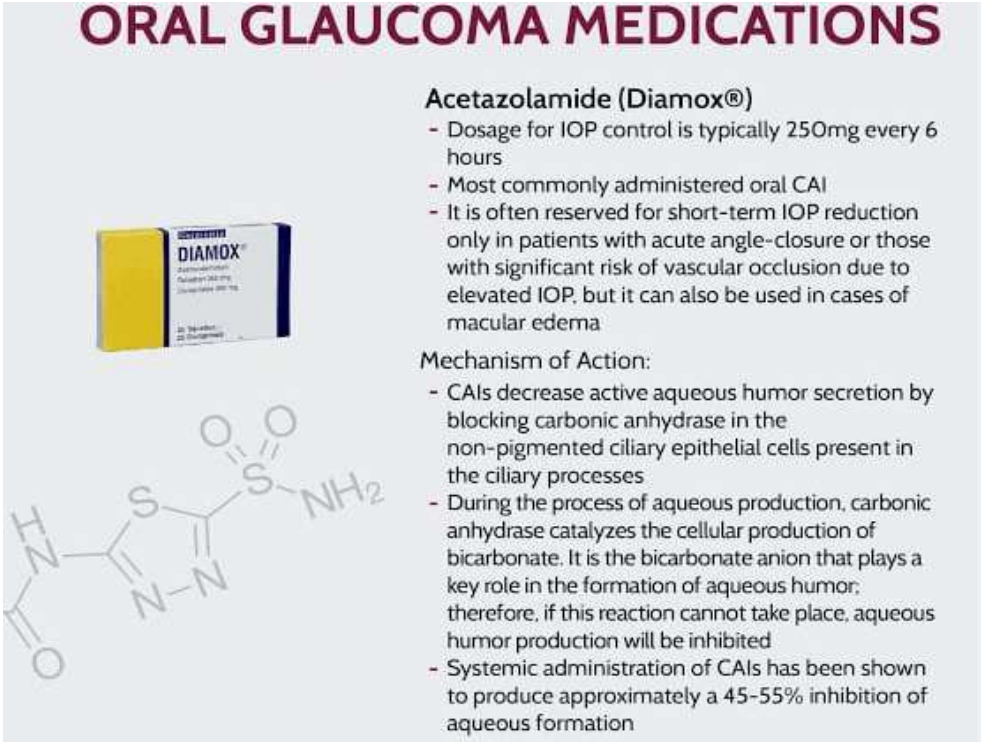


II. CLINICALLY AVAILABLE DELIVERY SYSTEMS

- **Oral medications**

Oral carbonic anhydrase inhibitors, like acetazolamide, have been used for a long time to lower eye pressure and are still quite effective. However, they can cause significant side effects throughout the body, such as tiredness, increased urination, and imbalances in electrolytes. These medications are usually given for a short period when eye pressure remains high despite using the strongest eye drops.[18]

Oral timolol can also be used to lower eye pressure, but it's not as effective as the eye drops.



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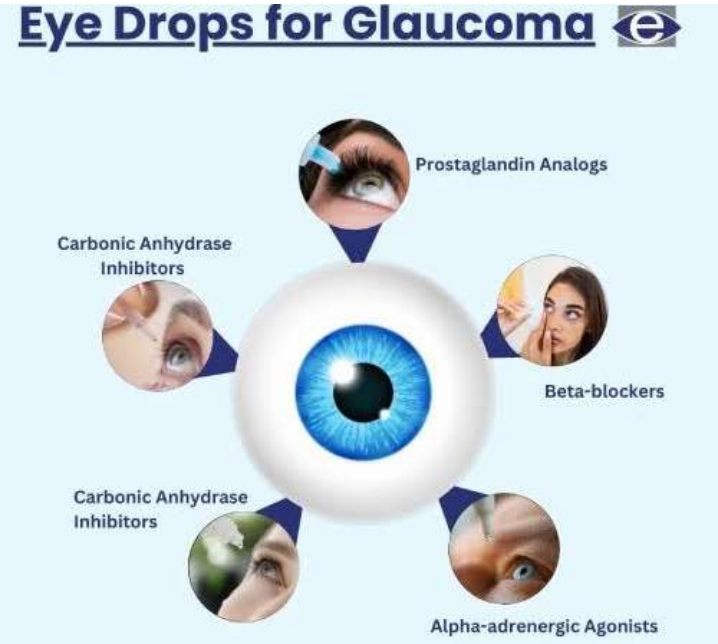
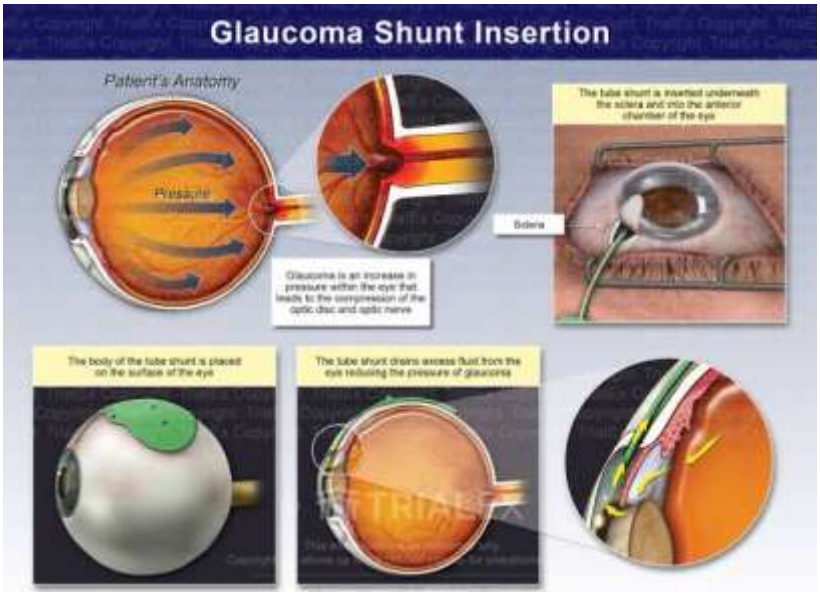
- **Topical eye drops and gels**



Because it's hard for oral medications to cross into the eye, they don't work well there. So, the usual way to treat glaucoma is by applying medication directly to the eye. However, only about 1% of the medication from eye drops actually reaches the inside of the eye, and multiple applications each day may be needed to be effective. Getting these medications to the deeper parts of the eye, like the vitreous and retina, is difficult, as many drugs don't penetrate well due to factors like increased tear drainage and low absorption through the cornea and other eye tissues.

To help with this, gel-based eye drop solutions have been developed. For example, timolol can be applied using gels that are designed to last all day, like Timoptic-XE and Nyogel. These gels are thicker than regular eye drops, which means they reduce the need for frequent dosing and might lessen side effects. However, they can sometimes cause blurred vision.

- **Inserts**



Ocular inserts have been created to deliver medication over several days. A well-known example is the Ocusert system, which contains pilocarpine inside a small ring made of a special material.[19] This insert is placed in the lower part of the eye and releases the medication for up to 7 days. Although it's effective, some people find that

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the insert can fall out or be uncomfortable. Improvements have been made to design better-fitting inserts that are less likely to fall out. Similar devices have also been developed for other glaucoma medications like timolol.[20] However, these devices still have limitations, such as needing proper patient training and good manual skills to use them correctly. Because of this, younger patients are more likely to successfully use and benefit from these devices compared to older patients.

- **Surgical implants**

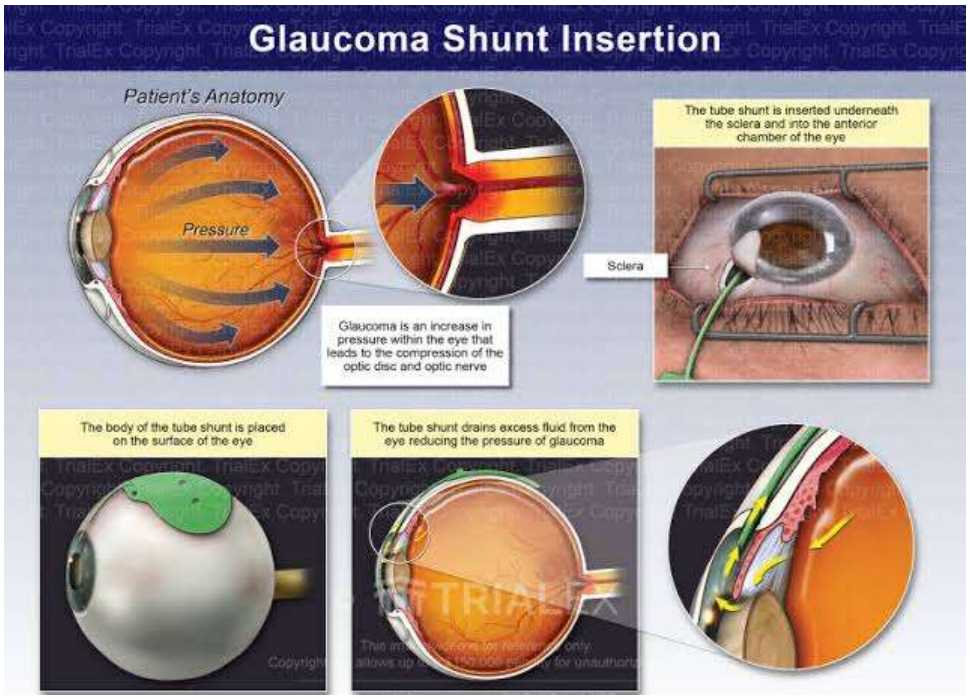
Surgical implants have the potential to deliver medication in the eye for extended periods. For example, implants like Ozurdex and Retisert are already available for long-term steroid delivery, with Ozurdex providing dexamethasone for 6 months and Retisert delivering fluocinolone acetonide for up to 30 months. Another implant, the I-vation by Surmodics, releases triamcinolone acetonide for up to 36 months and has been tested in early clinical trials.

Although these implants are effective for a long time, they have drawbacks such as high costs, the need for initial surgery, and the possibility of requiring additional surgery if complications arise. This can make them less appealing for many glaucoma patients who are concerned about these risks.[21]

For neuroprotective drugs, surgical implants might be a good option. They can deliver the drug to the retina for a long time. For instance, a small implant delivering CNTF has been tested and shown to be well-tolerated, with some patients experiencing improved vision.

An ideal drug delivery system for glaucoma would allow for sustained drug release for 3 to 4 months with just a single application in an office setting, rather than requiring surgery. This approach would fit well with regular glaucoma check-ups and could be a better option for older patients who might struggle with daily eye drops.[22]

Novel delivery systems



Liposomes and nanospheres:improving topical formulations

While pilocarpine is not commonly used anymore, it has been important in developing new eye drop formulations. Researchers have experimented with putting pilocarpine into liposomes and delivering it as eye drops. One study by Monem et al found that liposomes with a neutral charge reduced eye pressure just as well as traditional drops but lasted twice as long, meaning patients would need to use them only twice daily instead of four times. However, prostaglandin analogs are still preferred because they only need to be used once a day.

DeCampos et al looked into how the charge on nanocapsules (tiny particles) affects drug delivery when used as eye drops. They found that neutral nanocapsules delivered more of the drug (rhodamine, used as a model) than negatively charged ones.[23] The study also showed that the nanocapsules were absorbed into cells through the

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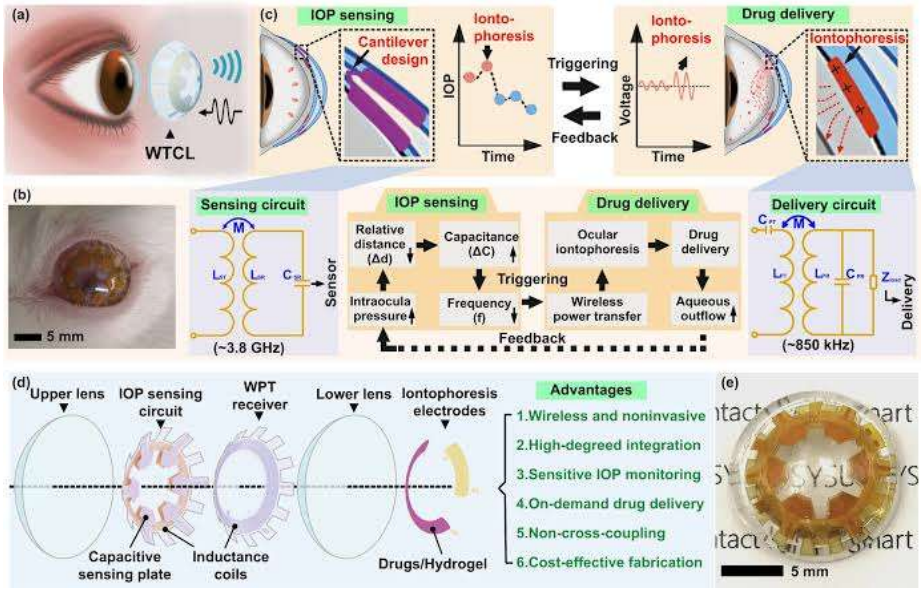
corneal epithelium. The nanocapsules, made from a combination of hydrophilic and hydrophobic materials, might be releasing their drug quickly or merging with cell membranes.[24]

Using carriers like these nanocapsules to keep drugs on the corneal surface longer can help reduce how often drops need to be applied. However, this technology still doesn't solve the basic issues of patient adherence and proper use of eye drops.

- **Contact lenses as delivery vehicles**



In the United States, at least 38 million people use contact lenses, and there is growing interest in using these lenses for drug delivery due to their familiarity and patient experience. Soft contact lenses are made from hydrogels, which are water-soluble polymers with many biomedical uses, including drug delivery. However, a major challenge is that water-soluble drugs, such as those used for glaucoma, often wash out too quickly from these highly hydrated polymers.[25]

Despite this, certain soft contact lenses made from polymers like N,N-diethylacrylamide and methacrylic acid have been able to deliver timolol for about 24 hours. A small study with three patients showed that contact lenses delivering timolol could effectively lower eye pressure. This indicates that contact lenses could be a promising alternative to traditional eye drops for treating glaucoma.[26]

However, there are some limitations. Patients need to wear the contact lenses continuously, and since the lenses are kept in a hydrated state, there is a risk that the drug might gradually leach out over time.

- **Sophisticated surgical implants**

Surgical implants can deliver medication to the eye for a long time, and new, more advanced implants are being developed. Ideally, a system would allow medication to be given in an ophthalmologist's office with minimal invasiveness and last for 3–4 months until the patient's next visit.

One innovative approach is a reservoir system implanted in the area just under the conjunctiva. This system, called a microelectromechanical system (MEMS), uses electrolysis to create bubbles that push the drug out of the reservoir. It can be refilled multiple times and has shown good results in early rabbit studies.[27] This system could potentially deliver both small and large molecules, such as growth factors.

A major benefit of the MEMS system is that it allows for controlled drug release by adjusting the electrolysis. This means the clinician can change how quickly the drug is delivered based on the patient's needs. It could also be used for delivering drugs directly into the eye or for administering multiple drugs with slight adjustments.

However, long-term studies are needed to ensure the device remains stable and works well over time. The main drawback is that the device requires surgical implantation, which involves both short-term and long-term risks.[28]

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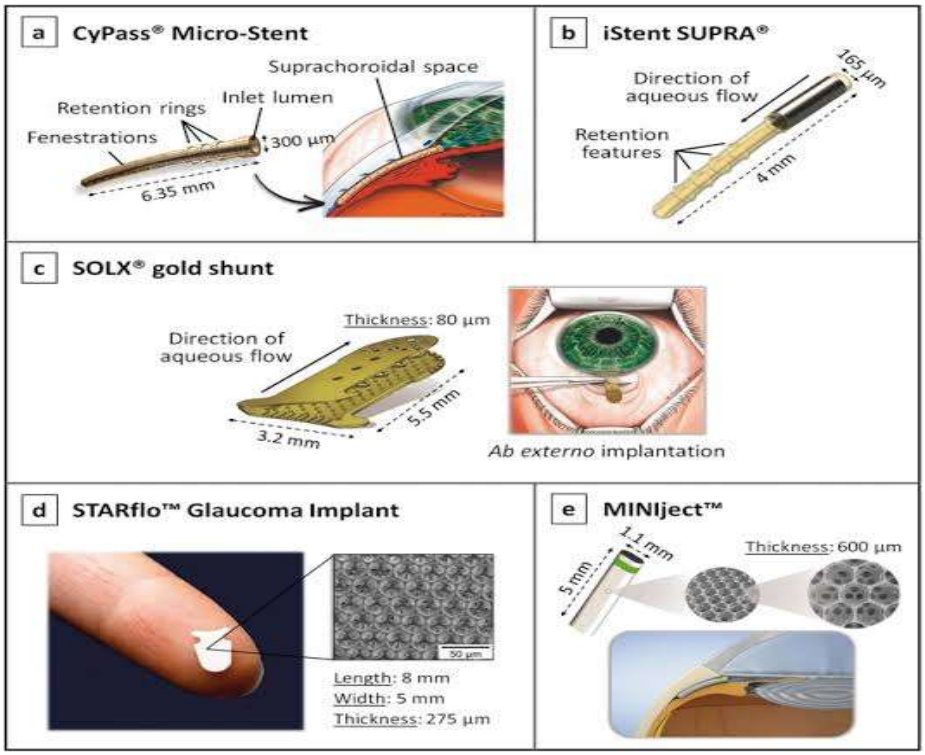
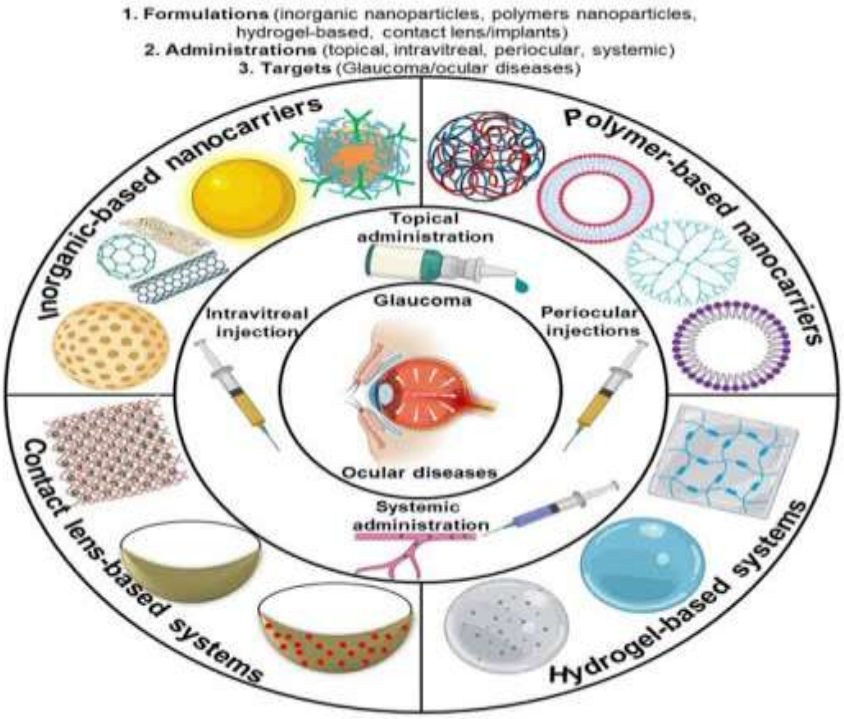


- **Injectable systems**



It's possible to create long-term release formulations of glaucoma medications that can be injected in an office setting, offering a more convenient option for patients. These formulations can avoid the problem of patient adherence, unlike MEMS devices, as they are passive systems that provide sustained medication delivery over time.

Injecting medications into the subconjunctival space can lead to longer delivery than just topical drops, lasting hours to days. For even longer delivery periods of weeks or months, using a polymer-based delivery vehicle is promising. Both degradable and non-degradable polymers have been studied for this purpose.[29]

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Non-degradable polymers like poly(ethylene-co-vinyl acetate) offer consistent drug delivery over time but can cause immune responses since they remain in the body. Degradable polymers, such as poly(lactic acid) or poly(lactic-co-glycolic acid), are attractive because they break down over time and can reduce the drug release burst effect with careful formulation. These polymers degrade through hydrolysis, and their degradation rate can be controlled by adjusting their composition.

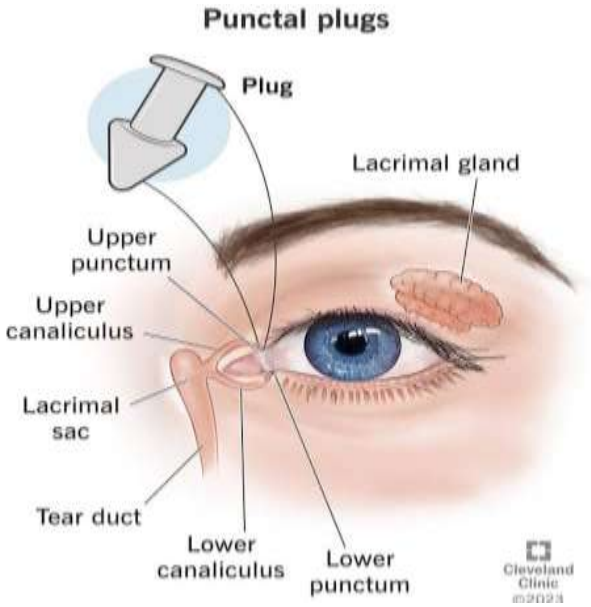
Degradable polymer systems are suitable for office-based injections and have been used for delivering drugs like antibiotics, carboplatin, and celecoxib. However, delivering traditional IOP-lowering glaucoma medications with these polymers is challenging due to poor drug-polymer interaction and rapid drug diffusion from the polymer particles.

One successful example is polyester microspheres that release timolol for over 90 days in vitro and can be injected through a small needle. For large molecules that may protect nerves, like growth factors, there are additional challenges such as maintaining the drug's activity and ensuring it reaches target tissues like the retina. Despite these challenges, intravitreal injection of drugs like brain-derived neurotrophic factor (BDNF) and glial cell-derived neurotrophic factor (GDNF) has shown promise in animal studies.

In summary, any slow-release injectable system must address three main issues: the effective dose of the drug, the drug's stability and interaction with the polymer, and whether the drug remains active after being released. Solutions that tackle these challenges have the potential to be effective alternatives to traditional eye drops.[30]

Punctal plugs

In obstructing the tear drainage process, punctal occluded with the plugs stops natural tears from running off the surface of the eye.[31] Many solid or semisolid modifications with another drug-eluting component to the punctal plugs have been developed in recent years for use in glaucoma to provide a sustained release of medication for three to four months.[32]It is a widely employed drug delivery technique since the plugs are simple to implant in an outpatient setting. For other individuals, however, the sensation of a foreign body after insertion could be a huge hurdle.[33]



Delivery method for Latanoprost punctual plugsTo lower IOP in OAG patients, Goldberg and Williams74 employed the Latanoprost Punctal Plug Delivery System (L-PPDS).[34] The authors' findings revealed a 5.7 mmHg drop in mean IOP. The study also revealed that 47% of the individuals had an IOP decrease of at least 6 mmHg, and 60% of the subjects had an IOP reduction of at least 5 mmHg or more. Subjects with L-PPDS showed a statistically significant mean decrease in IOP of 22.3% when compared to controls.[35]

Pentablock gels of copolymers

Drugs for glaucoma, such as bimatoprost, are delivered topically and intraocularly using pentablock copolymer gels. For use in the eye, the Food and Drug Administration (FDA) has currently authorized five distinct pentablock copolymers.[36] These include of PLA, PLGA, PCL, PEG, and polyglycolic acid (PGA).

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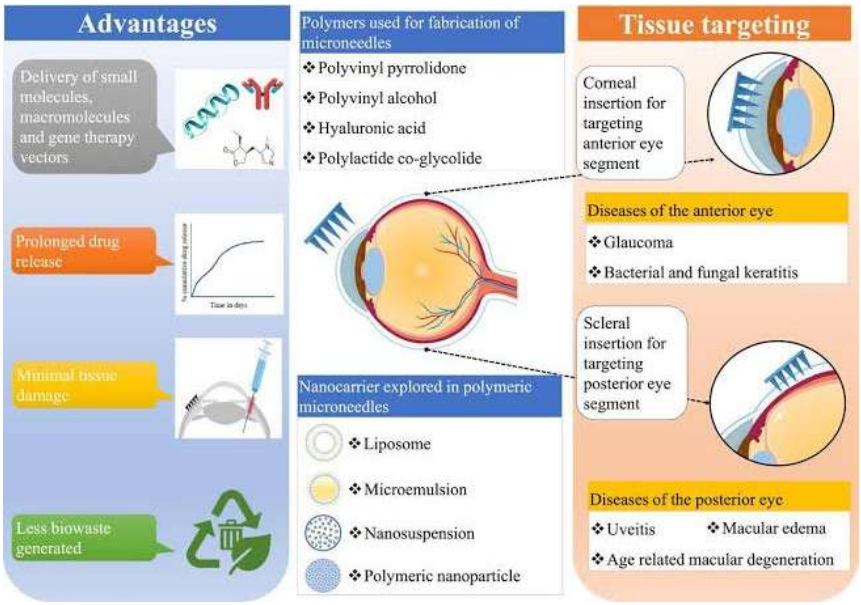
When the medicine is applied as an eye drop, its physical properties alter depending on the patient's body temperature.[37]

Microneedles



The drug delivery devices known as microneedles are made of metals or polymers and range in size from 10 to 200 µm. These devices' ultradimensions make drug delivery more precise and less intrusive at the locations of action.[38] Using coated stainless steel microneedles that ranged in length from 500 to 750 µm, Jiang and colleagues administered pilocarpine intrasclerally into the anterior chamber.[39] The authors found that the absorption of the medication was 45 times more than that of traditional eye drops.[40]

III. CONCLUSION

The review highlights the challenges and innovations in drug delivery systems for glaucoma treatment, emphasizing the need to improve patient adherence and clinical efficacy. Traditional eye drops, though effective, face issues like poor patient compliance and low drug absorption. Novel delivery methods, including surgically implanted systems, contact lenses, and injectables, offer promising alternatives by ensuring sustained, localized drug release and reducing the frequency of administration. Additionally, these systems could facilitate the delivery of neuroprotective drugs, which are crucial for patients who continue to experience vision loss despite IOP reduction. As these technologies evolve, they hold the potential to significantly enhance treatment outcomes and preserve vision in glaucoma patients.

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