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REVIEW

Novel drug delivery systems for glaucoma

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Abstract

Reduction of intraocular pressure (IOP) by pharmaceutical or surgical means has long been the standard treatment for glaucoma. A number of excellent drugs are available that are effective in reducing IOP. These drugs are typically applied as eye drops. However, patient adherence can be poor, thus reducing the clinical efficacy of the drugs. Several novel delivery systems designed to address the issue of adherence and to ensure consistent reduction of IOP are currently under development. These delivery systems include contact lenses-releasing glaucoma medications, injectables such as biodegradable micro- and nanoparticles, and surgically implanted systems. These new technologies are aimed at increasing clinical efficacy by offering multiple delivery options and are capable of managing IOP for several months. There is also a desire to have complementary neuroprotective approaches for those who continue to show progression, despite IOP reduction. Many potential neuroprotective agents are not suitable for traditional oral or drop formulations. Their potential is dependent on developing suitable delivery systems that can provide the drugs in a sustained, local manner to the retina and optic nerve. Drug delivery systems have the potential to improve patient adherence, reduce side effects, increase efficacy, and ultimately, preserve sight for glaucoma patients. In this review, we discuss benefits and limitations of the current systems of delivery and application, as well as those on the horizon.
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Glaucoma: drugs and targets

It is estimated that 2.2 million people in the United States and 67 million people worldwide have glaucoma,[1] and glaucoma is the second leading cause of irreversible blindness.[2,3] Glaucoma is a disease in which the axons of retinal ganglion cells (RGCs), which make up the optic nerve, degenerate. The loss of RGCs leads to loss of vision, and if untreated, to blindness.

The incidence of glaucoma increases with age.[4–6] With the aging of the US population, it is estimated that within 15 years, this disease will afflict 50% more people.[7] Current glaucoma therapy relies on drugs that lower intraocular pressure (IOP), and several glaucoma medications are effective at lowering IOP when administered properly. However, poor adherence is a fundamental problem that increases with the age of the patient,[8] and approximately 20% of patients eventually require surgery to lower IOP.[9]

An alternative treatment approach may lie in the use of neuroprotective agents, designed to promote RGC survival independent of IOP.[10,11] Although IOP reduction can maintain and control glaucoma in most patients, there are those who show progressive loss of visual field even with adequate reduction in IOP.[12] For these patients, alternative or complementary approaches to IOP reduction are highly desirable. Neuroprotective agents that can reduce the loss of RGCs and degeneration of optic nerve fibers are attractive targets for therapy, although, no neuroprotective drugs have been approved by the FDA at this time. In addition, many potential neuroprotective agents, when delivered systemically, have significant side effects.[13] Therefore, the development of novel, local drug delivery systems is necessary before neuroprotective drugs are likely to be viable for clinical treatment of glaucoma.

Novel delivery systems have great potential to mitigate the challenges of patient adherence and provide local, sustained delivery of the drug while reducing side effects. Because proper topical administration of drugs can be

challenging for many elderly patients, more effective delivery systems that bypass the patient adherence factor and reduce side effects have the potential to fundamentally improve patient care and clinical outcomes in glaucoma.

It is fortuitous that many effective drugs already exist for glaucoma, and the major challenge is their delivery. With clinically appropriate delivery platforms, there is real potential to fundamentally improve patient care and clinical outcomes.

IOP reduction

Elevated IOP is a significant risk factor for primary open-angle glaucoma, even though some cases of glaucoma develop in the absence of elevated IOP (sometimes referred to as normal tension glaucoma). However, there is good evidence that lowering the IOP reduces the progression of glaucoma in approximately 90% of cases,[12] including in cases of normal tension glaucoma.[14–17] The most common way to reduce IOP is topical administration of eye drops one or more times daily. Topical glaucoma medications are effective but only when administered appropriately. Proper administration of topical medications requires the correct placement of the eye drop onto the surface of the globe, the correct number of administrations per day, and the correct time interval between multiple dosings or multiple medications. It requires diligence and manual dexterity, which many patients, particularly older patients, find challenging. In practice, glaucoma medical adherence with topical medication is poor,[18,19] and studies suggest that fewer than half of the patients are able to maintain consistently lowered IOP with topical timolol.[20] Furthermore, $<1\%$ of topical administered drug reaches the aqueous humor.[21] Eye drops lead to significant systemic absorption (up to 80%),[22] which can result in adverse side effects, based on the types of medication used.[23] Together, these factors make topical application challenging, especially in the aging population, which exhibits lower adherence and greater vulnerability to side effects.[20,22]

From the standpoint of drug delivery systems, it is crucial to understand the chemical structure and mechanism of the specific drug to be delivered as well as the potential side effects associated with it. There are several classes of effective topical glaucoma medications that lower the IOP. They include prostaglandin analogs (eg, latanoprost), beta-blockers (eg, timolol), alpha-adrenergics (eg, brimonidine), carbonic anhydrase inhibitors (eg, dorzolamide), and cholinergics (eg, pilocarpine). Each of these classes of drugs has its own specific characteristics that impact their delivery. Therefore, it is important to understand the defining features of the medications to understand the delivery benefits and potential challenges.

Pilocarpine HCl is a parasympathomimetic first isolated in 1877 and one of the oldest drugs used to treat glaucoma.[24] It reduces IOP by increasing the outflow of the aqueous. As a drop, it requires four doses a day to maintain a reduced IOP. It has a number of side effects including brow ache, blurred vision, a risk for retinal detachment, as well as systemic effects including nausea, vomiting, and diarrhea. With the advent of other medications in the late 1970's and 1980's, pilocarpine use has declined steadily and is currently utilized after others have been tried.[24] However, it was one of the first drugs used in a sustained release implant in the 1970's to circumvent the need for repeated daily dosing and reduce the side effects as the Ocusert implant, described further below.

In 1979, Timolol maleate was approved for ophthalmic use. Timolol maleate, a β-adrenergic receptor antagonist, provides an average IOP reduction of 20–35%.[25,26] Since its approval, timolol maleate has become the US Food and Drug Administration's (FDA) 'gold standard' drug for IOP reduction.[22] Timolol, however, has significant cardiac side effects and usually requires dosing twice per day to maintain a well-controlled IOP. The molecule is extremely stable and highly water soluble, which makes it attractive for several methods of delivery, including novel drop formulations, implants, and injectables.

In recent years, the prostaglandin analogs have found favor and prescriptions of latanoprost, travoprost, and bimatoprost have outpaced timolol. Although timolol decreases the production of aqueous humor, the prostaglandins increase the outflow of the aqueous humor to lower IOP. The prostaglandin analogs are very hydrophobic prodrugs that are enzymatically cleaved to their active form. Because the enzymes that cleave these molecules are present in the eye but are present in low concentrations systemically, the prostaglandin family tends to have minimal systemic side effects when administered topically.[27] In addition, they require only once a day dosing, making them very attractive to patients.[27] Because of the great success with the prostaglandin analogs, there is strong interest to develop drug delivery systems for these molecules to further reduce the need for daily dosing. These drugs are very hydrophobic and thus, lend themselves to delivery via many of the common hydrophobic polymers used for drug delivery in the eye, such as poly(ethylene-co-vinyl acetate) and poly(lactic acid). It is important to realize that they are prodrugs and therefore, alterations of the drug conformation as a result of the delivery process could inhibit cleavage. The prostaglandins are also associated with local ocular side effects, including discoloration of the iris and surrounding skin, as well as

conjunctival hyperemia. There is a concern that sustained local delivery could exacerbate these side effects. However, ocular side effects can be reduced by using sustained delivery implants compared with bolus administration of the drug.[28]

Neuroprotection

Although reduction of IOP is effective in the majority of cases, there is great interest to develop neuroprotective strategies, either as a supplemental or as an alternative treatment regimen. Currently, there is no FDA-approved neuroprotective drug for glaucoma. Nevertheless, for neuroprotective drugs to be clinically viable, drug delivery paradigms need to be carefully considered, and each tailored to the particular compound under consideration.

A number of drugs have been studied in clinical trials for neuroprotection of the central nervous system. These include small molecules such as statins,[29] progesterone,[29] memantine,[30] and cyclosporine A,[29] as well as neurotrophic proteins including glial cell-derived neurotrophic factor (GDNF),[31] ciliary neurotrophic factor (CNTF),[32] and erythropoietin.[33] Results of neuroprotective drugs in clinical trials have revealed the challenges of using these drugs. Many of these neuroprotective agents exhibit significant side effects when administered systemically. For example, systemic delivery of CNTF in an amyotrophic lateral sclerosis clinical trial was associated with significant side effects including weight loss and cough. These side effects were severe enough to limit the dose, and ultimately, the efficacy of the drug.[13] Successful treatment strategies may involve local, sustained delivery of these drugs in a way that maximizes the efficacy while limiting side effect to an acceptable level.

The delivery of proteins is particularly challenging because of their large size, conformation necessary for bioactivity, susceptibility to enzymatic degradation, and relatively low affinity to typical materials used for drug delivery systems.[34] The significant production cost of many of the growth factors is also an important and potentially limiting factor in their application.

Subcutaneous, intravenous, oral, and topical administration usually result in very low doses in the target tissue of the eye (ie, vitreous, retina, or optic nerve), due to failure to cross the barriers including the cornea and blood–retina barrier,[35] as well as rapid degradation of the protein or peptide. As these methods are ineffective at delivering large molecules, several alternative approaches have been developed to deliver neurotrophic factors to the ocular target tissue for sustained periods. Among them are transfection of retinal cells with viral[36] or non-viral particles[37,38] carrying the gene of interest, and transplantation of stem cells to the retina, which are engineered to produce the neurotrophic factor of interest.[39]

Novel delivery systems for neuroprotective molecules are discussed below. These technologies may hold promise as complementary or alternatives to the conventional IOP-lowering treatment of glaucoma.

Clinically available delivery systems

Oral medications

Oral carbonic anhydrase inhibitors (eg, acetazolamide) have been available for decades and are still very effective in lowering the IOP. However, their use is associated with significant systemic side effects (eg, fatigue, diuresis, electrolyte imbalance). They are typically used as a short-term therapy when the IOP is still very high on maximal topical medications.[40,41] Although patients can take oral timolol to lower IOP, it is less effective than eye drops.[20]

Topical eye drops and gels

As a result of the challenges associated with crossing the blood–retinal barrier, oral medications have very low bioavailability in the eye. Topical delivery of IOP-lowering medications is the current standard for glaucoma treatment. As noted above, $<1\%$ of the drug reaches the aqueous after topical administration,[21] and multiple daily dosing may be needed to be clinically effective.[20] Delivery of topically applied drugs to the vitreous and retina is possible,[42,43] but transport of most medications to the vitreous and retina is very low with limited bioavailability. The barriers to transport with drops include the increase in tear drainage with administration of an eye drop, low corneal transport, and low conjunctival and scleral transport.[44] Transport through the ocular tissues is dependent on the particular chemistry of the drug. Hydrophobic molecules have a tendency to accumulate more in the vitreous, whereas hydrophilic molecules tend to show greater concentrations in the aqueous humor.[45]

To reduce the number of doses per day, several gel formulations have been developed for topical medications. Timolol can be delivered using once daily gel-forming solutions (0.5% Timoptic-XE (Merck & Co., Whitehouse, NJ, USA) and Nyogel (Novartis AG, Basel, Switzerland)).[46,47] These gels are essentially timolol plus water soluble polymers that increase the viscosity of the solution. These formulations have been shown to reduce dosing (from twice a day to once a day) and may reduce the side effects associated with timolol. However, they can lead to blurred vision.[48]

Inserts

Ocular inserts have been developed that can deliver drugs over multiple days. One of the best known and most widely studied is the Ocusert system, which consists of two membranes of poly(ethylene-co-vinyl acetate) and a ring of the same material filled with pilocarpine.[49] The insert is designed to be placed in the inferior fornix and deliver the medication for 7 days. Although it is effective, some patients complained that the device would fall out or cause discomfort.[50] There have been subsequent design changes to the original insert that fit better and is less likely to fall out.[51] Similar inserts have also been developed to deliver other glaucoma medications such as timolol.[52] However, these improvements do not address fundamental limitations in the design. Inserts require patient education to use the device successfully as well as manual dexterity to manipulate and place the insert appropriately. Consequently, younger glaucoma patients were more likely to utilize and achieve efficacy with the device than older patients.[53]

Surgical implants

Surgical implants have the potential to deliver drugs for very long period in the eye. Implants for long-term steroid delivery are already clinically available. They include Ozurdex (Allergan, Irvine, CA, USA), a dexamethasone implant that delivers the steroid intravitreally for 6 months,[54] and Retisert (Bausch and Lomb, Rochester, NY, USA), an intravitreal implant that delivers fluocinolone acetonide for up to 30 months for chronic uveitis.[28] In addition, the Surmodics (Eden Prairie, MN, USA) I-vation implant, a helical screw coated with triamcinolone acetonide that delivers the drug intravitreally for 36 months has undergone Phase I clinical trial.[28] Although surgical implants can be effective for a long period, disadvantages include cost and invasiveness of initial surgery, as well as any subsequent surgery to remove the implant should an adverse reaction occur. For the majority of glaucoma patients who maintain their vision, associated surgical risks may deter widespread use.

For neuroprotective drugs, however, surgical implants may provide an attractive delivery option. They can facilitate the delivery of the neuroprotective drug to the retina for a prolonged period of time. For example, CNTF can be delivered from a rice-sized implant via encapsulated cell technology for up to a year.[55] The implant has been studied in a Phase I trial for retinitis pigmentosa; the patients tolerated it well and some showed improvements in visual acuity.[56]

An ideal drug delivery system for glaucoma would offer sustained release of the drug for 3–4 months from a single application that can be performed in an office setting (rather than surgical theater). The 3–4 months drug release period would work well with recommended intervals for glaucoma follow-up evaluations. Using one or more of the existing IOP-lowering medications, such slow-release ocular delivery systems that circumvent patient adherence factors may offer an attractive alternative to traditional topical eye drops for many elderly patients.

Novel delivery systems

Liposomes and nanospheres: improving topical formulations

Although pilocarpine is no longer used commonly, it has been used in the development of novel drop formulations. It has been encapsulated in liposomes and delivered in solution as an eye drop.[57] Monem *et al*[57] studied the effect of the charge on the surface of the liposomes on IOP reduction in rabbits. Neutrally charged liposomes resulted in similar IOP reduction but lasted twice as long as the conventional eye drop, suggesting that the liposomes increased the residence time of the drug.[57] This would reduce dosing of pilocarpine from four times daily to twice daily. However, prostaglandin analogs are still easier to use because of its once a day dosing.

DeCampos *et al*[58] have studied the role of charge on colloidal solutions of nanocapsules administered as drops in the eye. They reported that neutral particles showed greater delivery of the drug (rhodamine used as a model drug) than negatively charged particles. Interestingly, relatively uniform intracellular rhodamine content was observed when the nanocapsules were imaged at different time points after topical administration. They suggested that the nanocapsules are taking an intracellular route through the corneal epithelium. Alternatively, the nanocapsules, consisting of a diblock copolymer with a hydrophilic component (poly(ethylene glycol)) and a hydrophobic block (polycaprolactone) are releasing their payload very quickly or fusing with the cell membranes.[59]

The strategy of providing the drug with a carrier that allows it to stay longer on the surface of the cornea is an effective approach to reduce dosing frequency. However, this technology does not eliminate the fundamental problems of patient adherence and proper administration of topical eye drops.

Contact lenses as delivery vehicles

At least 38 million people in the United States wear contact lenses.[60] There has been a great deal of interest in

using contact lenses as the delivery device because of its familiarity with clinical practices and patient experiences.[61] Soft contact lenses are hydrogels, water-soluble polymers that are crosslinked to form networks. Hydrogels have a tremendous number of biomedical applications including drug delivery.[62] One of the greatest challenges with using hydrogels for drug delivery is that water-soluble drugs, such as those likely to be used in glaucoma, tend to elute very quickly from the highly hydrated polymer networks.[63] However, soft contact lenses, consisting of polymers of *N*,*N*-diethylacrylamide and methacrylic acid, have been shown to deliver timolol for longer periods (approximately 24 h).[64] A pilot study of contact lenses delivering timolol (on three patients) demonstrated that contact lenses delivering timolol can effectively lower IOP.[65] This suggests that lenses may be an attractive alternative to eye drops for delivering drugs for glaucoma. One obvious limitation of contact lens delivery system is that it requires patients to wear the contact lens at all times. Another potential limitation is that lenses are generally stored in a hydrated state, which has the potential for the drug to leach out of the lens over time.

Sophisticated surgical implants

As noted above, surgical implants have the potential to deliver drugs for a very long period in the eye. Beyond those currently available, more sophisticated implants for ocular delivery are on the horizon.

Ideally, one would like a system in which one could administer the medication to lower IOP in the ophthalmologist's office in a minimally invasive manner in a way that allowed the medication to last for 3–4 months until the patient returned for a regular visit. One novel approach is to implant a reservoir system in the subconjunctival space. The microelectromechanical system (MEMS) uses electrolysis to create bubbles that push the drug out of the reservoir of the device, which has a port that allows multiple loading of the drug.[66] Surgical steps required would be similar to currently available glaucoma drainage devices. It can be reloaded several times and has been well tolerated in initial rabbit studies.[67] Such a system has the potential for delivering both small and large neuroprotective molecules such as growth factors.[68]

Another advantage of a MEMS-based system is that one can regulate the rate of drug release from the device by controlling the electrolysis. An active delivery system can allow the clinician to change the rate of delivery, based on the clinical assessment. It also has the potential for intravitreal administration or the administration of multiple drugs with minor modification. Long-term studies are needed to evaluate the stability and sustained function of the device. A main disadvantage is that it must be surgically implanted in the eye with associated short-term and long-term risks.

Injectable systems

It is possible to develop a long-term release (eg, 3–4 months) formulation of a glaucoma medication that can be injected in an office setting. Subconjunctival administration of glaucoma medications in extended-release formulations can avoid the patient adherence issue. Unlike MEMS devices, they are passive delivery systems, capable of sustained, long-term delivery of medications.

Injection of existing drugs into the subconjunctival space can lead to prolonged delivery compared with simple topical application, in the order of hours or days.[69] To achieve more prolonged delivery over weeks or months in the subconjunctival space, a delivery vehicle, based on a polymer, is an attractive alternative. Both degradable and nondegradable polymers have been studied for injectable systems for ocular delivery.[70] Non-degradable polymers such as poly(ethylene-co-vinyl acetate) exhibit long term, constant rates of delivery for a number of drugs;[71] however, their disadvantage is the continued presence of a foreign body with a resulting immune response. Degradable polymers such as poly(lactic acid) or poly(lactic-co-glycolic acid) are an appealing alternative. They can exhibit nonlinear release kinetics with a large initial burst of drug.[72] The burst is particularly more pronounced for hydrophilic drugs because the drug interacts poorly with degradable polymers that tend be hydrophobic.[73] Fortunately, creative formulation using suitable excipients or additives can greatly reduce the burst effect and lead to greater polymer–drug interaction, resulting in drug delivery at a rate that correlates with the polymer degradation.[73] These polymers degrade by hydrolysis. The rate of degradation is controlled by the ratio of lactic acid to glycolic acid subunits, the molecular weight of the polymers, and, in the case of poly(L-lactic acid), the crystallinity of the polymer. The FDA has approved a number of devices using these materials and much research has been carried out by evaluating these polymers for ocular use.[74]

The use of degradable polymer systems is well suited for subconjunctival injection, which is an office-based procedure. Sustained delivery of drugs from degradable polyesters has been studied for subconjunctival administration, including antibiotics after cataract surgery,[75] carboplatin for murine retinoblastoma,[76] and celecoxib to reduce oxidative stress in the rat.[77] Unfortunately, sustained delivery from degradable polymers have been more difficult to achieve for the

traditional IOP-lowering glaucoma medications. One reason for this is the poor drug–polymer interaction. Another reason is that the injectable formulations typically contain particles with very high surface to volume ratios, and the large surface area results in rapid diffusion of the drug from the polymer.[78] However, by carefully tailoring the polymer formulation one can control the encapsulation and delivery of the drug. One formulation of polyester microspheres encapsulating timolol has been shown to deliver the drug for greater than 90 days *in vitro*. These microspheres can be injected subconjunctivally through a small gauge needle.[79]

For large molecules that may offer neuroprotection (eg, growth factors), additional challenges remain beyond the polymer–drug interaction and high surface area of injectable formulations. The challenges include retaining the bioactivity of the drug once delivered and poor transport to target tissues, specifically the retina and optic nerve.[80] However, intravitreal administration through a small gauge needle can overcome some of these issues. In addition to the CNTF-secreting implant that is currently in clinical trials, there have been efforts to develop cell-free injectable formulations of brain-derived neurotrophic factor (BDNF) and GDNF. The PLGA microspheres delivering BDNF have been shown to improve the survival of transplanted retinal progenitor cells[81] and improve functional recovery, following an ischemic retinal injury when administered intravitreally[82] in animals. Similarly, PLGA microspheres of BDNF can protect the retina in the DBA/2J mouse model of pigmentary glaucoma[83] and in large animal retinal ischemic injury models.[84]

In summary, any injectable slow-release (over several months) delivery system needs to consider the following issues. First, one must consider the effective dose of the drug. There are limits to the amount of drug that can be formulated with a polymer and limits on the amount that can be delivered to the eye. Several studies indicate that both the IOP-lowering medications and potential neuroprotective agents have a low enough effective concentration to be suitable for sustained delivery.[24] Second, one must consider the drug's stability and its interaction with, what is most likely, a hydrophobic polymer environment. Stronger association between a drug and polymer increases the likelihood for long-term, sustained delivery. Third, one must determine whether the drug, especially a complex large molecule such as a growth factor, is bioactive after being released from the polymer carrier. Formulations that overcome these three challenges have great clinical potential as a viable alternative to conventional eye drops.

Conclusions

There are many effective topical medications currently available for treating glaucoma. However, their clinical efficacy is limited by inefficient delivery systems, resulting in poor target bioavailability, increased systemic absorption/side effects, and poor patient adherence. Novel, more efficient delivery systems are on the horizon with potential to improve patient care by eliminating patient adherence factor and reducing side effects. Ultimately, these novel delivery systems for both IOP-lowering and potential neuroprotective drugs can lead to greater treatment options and preservation of vision in glaucoma.

Methods

Two search engines, PubMed and ISI Science Citation Index were used in this review.

Search terms included: polymer and drug and eye, glaucoma and polymer, glaucoma and drug, eye and drug delivery, glaucoma neuroprotection, and IOP and drug delivery.

Conflict of interest

Dr Lavik, Dr Kuehn, and Dr Kwon have filed a patent on the delivery of timolol from microspheres in the eye.

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