Opportunities to Topically Reduce Intraocular Pressure in Glaucoma

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Authors' contributions

This work was done in collaboration among all authors. Author OR conceptualized manuscript. Authors OR and AT drafted the manuscript. Author OR reviewed the literature. Author AT drew the figures. Authors MS and LH critically reviewed the manuscript. Authors JH and EV reviewed the final version of the manuscript. All authors read and approved the final manuscript.

Review Article

ABSTRACT

Since glaucoma is a serious health problem, numerous therapeutics are being developed to reduce Intraocular Pressure (IOP) as the only modifiable factor of all glaucoma symptoms. IOP-lowering agents are divided into six groups, each of which has a specific mechanism of action and side effects, which are the focus of this article and are explained in detail. All the mentioned agents are formulated as eye drops. However, as conventional topical eye drops have significant disadvantages, of which poor bioavailability and patient noncompliance are the main, novel approaches to designing their drug delivery systems were used and briefly presented in this review.

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Graphical Abstract

Glaucoma development

Therapeutic strategies for glaucoma
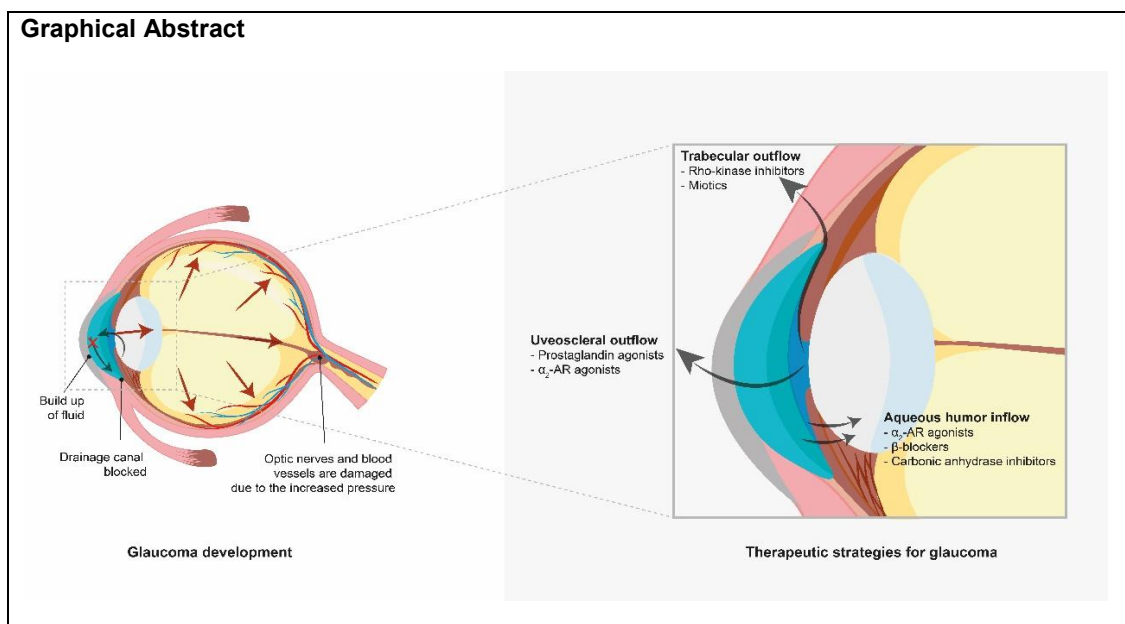
Keywords: Glaucoma; glaucoma treatment; intraocular pressure; novel drug delivery systems.

ABBREVIATIONS

AAs	-	*Adrenergic Agonists*
BBs	-	*Beta-adrenergic Blockers*
CAIs	-	*Carbonic Anhydrase Inhibitors*
CLs	-	*Contact Lenses*
IGS	-	*In situ Gel Systems*
IOP	-	*Intraocular Pressure*
MNs	-	*Microneedles*
PAs	-	*Prostaglandin Analogs*
PNIPAAm	-	*poly(N-isopropyl acrylamide)*
PP	-	*Punctal Plug*
RGC	-	*Retinal Ganglion Cell*
RK	-	*Rho-kinase*
RKIs	-	*Rho-kinase Inhibitors*
SLN	-	*Solid Lipid Nanoparticles*
TODDD	-	*Topical Ophthalmic Drug Delivery Device*

1. INTRODUCTION

Glaucoma is the most common cause of avoidable blindness worldwide. The health problem of glaucoma is its asymptomatic character in the early stages and patients' noncompliance [1–3]. Glaucoma comprises a group of neurodegenerative disorders characterized by changes in the optic nerve head due to damage to the retinal ganglion cell (RGC) axons. Damage to the RGC axons is at most the result of increased intraocular pressure (IOP). Increased IOP can occur either due to increased aqueous humor production or its impaired drainage. Damage to the RGC axons can be so severe that it can lead to the death of the RGC and thus to blindness [4,5].

Laser therapy, incisional surgery or drug therapy are options for glaucoma treatment. In most cases, initial treatment is drug therapy [6]. Although the IOP is not increased in all types of glaucoma, drugs that lower the IOP can delay or even stop the progression of the disease, even if the IOP is within physiological range [7,8].

There are numerous medical agents that reduce IOP and are currently in use that have different mechanisms of action, efficacy and side effects. Sometimes these represent their advantages and sometimes their disadvantages. In order to overcome their disadvantages, drugs should be integrated into improved novel drug delivery systems.

2. IOP LOWERING AGENTS

The groups of medications used in the treatment of glaucoma are [6]:

- Prostaglandin analogs (PAs);
- Beta-adrenergic blockers (BBs);
- Adrenergic agonists (AAs);
- Carbonic anhydrase inhibitors (CAIs);
- Miotics;

- Rho-kinase inhibitors (RKIs).

The most effective IOP lowering agents are PAs, as they reduce the IOP by 28–33%. Therefore, PAs are usually included in glaucoma treatment first. Slightly less reduction is induced by BBs, while AAs and CAIs reduce the IOP by 15–20% [9].

2.1 Prostaglandin Analogues

Prostaglandins are normally produced by the eye, but also by the prostate gland, after which they are named [10]. In animal studies during the 1960s and 1970s, IOP was found to be lower in inflamed eyes than in healthy eyes, which was caused by intraocular injection of prostaglandins. Camras et al. [11] demonstrated that IOP in the rabbit's eye was reduced after topical administration of prostaglandins. Nevertheless, natural prostaglandins, when administered to the human eye, caused significant side effects, such as conjunctival hyperemia, irritation and in some cases headache. Thus, PAs, also known as hypotensive lipids, were developed. They were equally effective in lowering IOP but showed fewer side effects [12].

The use of PAs in the therapy began in 1996 with latanoprost. Today, in addition to latanoprost, travoprost, bimatoprost, and unoprostone can be used in the treatment of glaucoma. Latanoprost and travoprost are selective agonists of prostaglandin receptors. Unoprostone differs structurally from latanoprost and travoprost and has the lowest affinity for prostaglandin receptors [12–14]. It is not as efficacious as other PAs in reducing IOP and must be taken twice daily [12]. Unoprostone is significantly different in the mechanism of action than other PAs as well. Studies have also shown that it can achieve its effect, at least partially, by activating potassium and chloride channels, thus leading to the relaxation of the trabecular meshwork and increased aqueous humor outflow via the conventional route. However, the exact mechanism of its action remains unknown. But its relatively weak affinity for prostaglandin receptors may be the reason for its advantageous local tolerability compared with other PAs. It should also be noted that it is effective both as a monotherapy and as an adjunctive therapy [15].

Although the structure of bimatoprost is similar to the other two PAs, it is indeed analogous to prostamides, which are a group of endogenous ocular hypotensives [14]. Bimatoprost is an amide prodrug. Its active form is latanoprost [16–18].

In contrast to other ocular hypotensives, PAs have almost no influence on aqueous humor production, but on uveoscleral outflow through the iris and ciliary body, which has been confirmed by many animal studies [19,20]. Similarly, other studies have confirmed that the exact mechanism of influencing the uveoscleral outflow is by facilitating it [19,21–24]. The aqueous humor drainage through the ciliary body may be increased by the relaxation of the ciliary muscle, as shown in studies conducted on monkeys [19–21,25]. Furthermore, PAs can potentiate the uveoscleral outflow by activating some enzymes, such as metalloproteinases that lead to collagen degradation. As a result, intercellular spaces open and the rate of uveoscleral drainage increases, leading to a decrease in IOP [20,26]. The same has been confirmed for humans in *in vitro* and *in vivo* studies [27–30]. To a certain extent, the trabecular meshwork plays role in enhancing aqueous humor drainage and lowering IOP [28–31].

Studies have confirmed that taking latanoprost [32–34], travoprost [33] and bimatoprost [35,36] twice daily is less effective than taking them once daily, preferably in the evening. Administration in the evening, rather than in the morning, seems to be more effective and can prevent the early morning surge in IOP that can be observed in many patients [13]. It is very important to be careful when adding bimatoprost to latanoprost in the treatment of glaucoma as the paradoxical increase in IOP can occur [37].

A great number of studies have confirmed the safety of using PAs either as a monotherapy or as a concomitant therapy to other ocular hypotensives. The most common local side effects are eye irritation, conjunctival hyperemia, and eyelash changes (lightening and darkening), as well as darkening of the iris and periocular skin pigmentation [12,13,38]. Systemic side effects include dyspnea, chronic and acute asthma [12,39].

In 2017, FDA approved a new PA in the United States, with a unique, dual mechanism of action, called latanoprostene bunod [40]. Latanoprostene bunod metabolizes to latanoprost, which increases uveoscleral outflow and the nitric oxide level, responsible for

intensifying the trabecular outflow. It is dosed once daily [41].

2.2 Beta-Adrenergic Blockers

The initial therapeutic application of BBs was in the treatment of various cardiovascular diseases, such as hypertension, angina pectoris and cardiac arrhythmias. The first BB ever administered to humans to lower IOP was propranolol in 1967 [42]. Propranolol is not used topically. However, it can cause damage to the cornea if taken for a long time. This effect is caused by its membrane-stabilizing properties [12,43].

The first BB formulated as an ophthalmic solution was timolol, the most frequently studied and used drug in glaucoma therapy. However, the use of BBs, even timolol, has been reduced since the introduction of PAs, because PAs lower IOP more effectively and have fewer systemic side effects [12,44].

Apart from timolol, other available BBs are betaxolol, levobunolol, metipranolol, and carteolol. They are administered once or twice daily. Since BBs bind competitively to beta-adrenergic receptors, they act antagonistically to adrenergic responses [12]. Timolol reduces IOP by reducing aqueous humor production and does not affect its drainage, whatsoever. The exact mechanism by which this is achieved is not yet undoubtedly determined [12,13,45].

It is believed that the underlying mechanism is binding to $beta_2$-adrenergic receptors in the ciliary epithelium, which in turn leads to antagonistic effects. The additional effect may be binding to $beta_2$-adrenergic receptors in ciliary arteries, leading to vasoconstriction and subsequently a decrease in aqueous humor production [12,13]. It may be interesting that it does not only lower IOP in the treated eye but also the contralateral eye without treatment. It is assumed that this bilateral effect of timolol occurs as a result of its systemic absorption [46].

Side effects of BBs are usually the result of beta-blocking action. Local or systemic side effects can occur. Local side effects are rare and include dry eyes or allergic reactions. However, since BBs are directly absorbed in venous circulation after topical administration and do not undergo first-pass metabolism in the liver, there is a risk of more significant systemic side effects compared with their oral administration. Systemic side effects include respiratory, cardiovascular, metabolic and central nervous system side effects [12,13].

2.3 Adrenergic Agonists

The AAs have been used in glaucoma medication therapy for a long time. Since the discovery of two different types of adrenergic receptors, alpha and beta, various approaches that include interaction with these receptors have been developed to produce the most significant IOP reduction possible. Some agonists of $alpha_1$, $alpha_2$ and imidazole receptors are powerful IOP reducers. Nowadays, clonidine and more frequently, its derivatives apraclonidine and brimonidine, are used. The exact location of their effect on IOP is uncertain. However, it is known that AAs can interact with adrenergic and imidazole receptors in the ciliary body, trabecular meshwork and brain. To some extent, they can reduce IOP bilaterally, although applied unilaterally [12,13].

In a study performed by Toris et al. [47], it has been proven that the effects of apraclonidine on IOP were achieved by facilitating the trabecular outflow, reducing aqueous humor production, and reducing episcleral venous pressure. On the other hand, brimonidine acts somewhat differently. It lowers aqueous humor flow and alters uveoscleral outflow [48].

Topically administered AAs cause some side effects, which typically consist of vasoconstriction in the conjunctiva, oral or nasal cavity, which leads to dryness in the nose and mouth. In combination with these, the conjunctiva can be blanched and eyelids slightly retracted. In contrast to brimonidine, apraclonidine has hardly any effect on the cardiovascular or central nervous system. However, the most annoying and alarming side effect of AAs is allergic reactions, which can be very severe [12,13].

2.4 Carbonic Anhydrase Inhibitors

Carbonic anhydrase (CA) in the eye plays a crucial role in aqueous humor production in the ciliary epithelium. If CA is inhibited, aqueous humor secretion decreases and as a result, IOP decreases. The CAIs are very efficient ocular hypotensives. Acetazolamide, methazolamide, and dichlorphenamide are systemic CAIs. Given their serious side effects, the question arose as to patients' adherence, so topical agents, such as brinzolamide and dorzolamide, were

developed [12,13,43]. Topical CAIs are more selective than systemic ones, but not as efficient in lowering IOP. In contrast to topical BBs, the duration of the effect of CAIs is 24 h [12].

The most troubling systemic side effect of CAIs is severe blood dyscrasia, which has been the cause of numerous fatal outcomes [49,50]. Other systemic side effects, such as fatigue, paresthesia, gastrointestinal problems and kidney stone formation, are common results of their long systemic administration, but rarely occur during the administration of topical CAIs. Ocular side effects include itching, blurred vision, allergic conjunctivitis, etc. and are more pronounced with dorzolamide than with brinzolamide [12].

2.5 Miotics

Miotics, also known as parasympathomimetics or cholinergic drugs, exhibit effects like acetylcholine and have been in use for more than a century. Miosis occurs as a result of a contraction of the ciliary muscle, which puts pressure on the trabecular meshwork, leading to an increase in outflow and a decrease in IOP [43].

There are two types of miotics: direct-acting ones such as pilocarpine, carbachol, and acetylcholine and indirect-acting ones, such as demecarium bromide and echothiopate iodide. Direct miotics directly affect the neuromuscular junction, while indirect miotics bind to acetylcholine esterase at the neuromuscular junction, thus inducing acetylcholine secretion and promoting the parasympathetic nervous system. Of all miotics, only pilocarpine is regularly used in glaucoma therapy. Others serve as a substitution in case of the occurrence of allergic reactions to pilocarpine [12,13].

Systemic side effects of pilocarpine include sweating, salivation, bradycardia, hypotension, bronchospasm and increased production of bronchial mucus. Pilocarpine affects various smooth muscles in the body and can cause nausea, vomiting and diarrhea [12,13].

2.6 Rho-kinase Inhibitors

The RKIs are a completely new class of drugs available for glaucoma therapy since 2017 when FDA approved netarsudil [51]. Rho-kinase (RK) is serine/threonine kinase and RKIs inhibit norepinephrine transporter in addition to inhibition of RK. Netarsudil enhances trabecular meshwork outflow and reduces episcleral venous pressure [52].

3. BARRIERS IN EFFECTIVE GLAUCOMA TREATMENT

3.1 Absorption and Distribution in Ocular Compartments

The application of a drug to the eye is a demanding process because of many factors that affect its absorption. The eye is a complex organ, consisting of several components that present barriers to drug absorption and distribution. The cornea and the anterior chamber are important for drug distribution inside the eye. Drug absorption begins with mixing a drug with tears, after its topical application. The quantity of a drug absorbed is directly proportional to its concentration in tears if it does not bind with other substances in the cornea. With eye blinking pushing a drug to go through the nasolacrimal duct, tears' evaporation, drug deposition on eyelid borders and binding to proteins and enzymes, a very limited amount of a drug can penetrate the eye (1–10% of the applied dose). Drug distribution inside the eye is impeded by the iris, lens and ciliary body [13].

If a sufficient amount of a drug is not present on the eye surface, then the absorbed dose will be too low to produce a therapeutic effect. By applying a larger amount of a drug to the eye, the excess amount will be removed from the eye surface through the lacrimal canals within a few minutes. Once again, there is no therapeutic effect. Therefore, it is necessary to develop drug formulations that will enable longer contact of a drug with the eye surface. Another undesirable way of losing a drug is its systemic absorption instead of the ocular one. A drug may be systemically absorbed from the conjunctival sac via blood capillaries or after a drug solution has been drained into the nasal cavity [53].

3.2 Flaws of Conventional Ophthalmic Topical Medications

More than 90% of all available ophthalmic drugs are administered in the form of eye drops, which is not surprising given the ease of their manufacture and the ease of use and application. Nevertheless, they have some flaws, of which the poor drug bioavailability of only up to 10% is the most important [54,55]. After administration, eye drops have a limited retention capacity in the

conjunctival sac of only 7-10 µL [54] on the one hand, followed by rapid drainage through the nasolacrimal duct [55] on the other, which leads to poor bioavailability.

3.3 Patients' (Non)Compliance

Regardless of how effective conventional eye drops may be in lowering IOP, the therapeutic outcome ultimately depends on the patient's ability to maintain the therapy. According to a study by Newman-Casey et al [56], the main reason for patient's noncompliance is their forgetfulness, either when refilling prescriptions or when omitting the dose. It is also important to mention the lack of self-efficacy in administering eye drops and the lack of patient education about glaucoma outcomes and the effectiveness of medications.

4. MORE EFFECTIVE APPROACHES IN GLAUCOMA TREATMENT

To solve the above problems, scientists have steered their research in the development of drug delivery systems in two parallel directions, either extending the contact time of the drug and the eye or slowing drug elimination [57]. In this way, a plethora of sustained drug delivery systems have been developed, many of which never reached preclinical trials but have been retained as a possible option for glaucoma treatment. On the other hand, few are commercially available. Fig. 1. shows novel drug delivery systems developed for the treatment of glaucoma, while Table 1 lists novel drug delivery systems for each specific IOP lowering drug, that provide additional data on their efficacy.
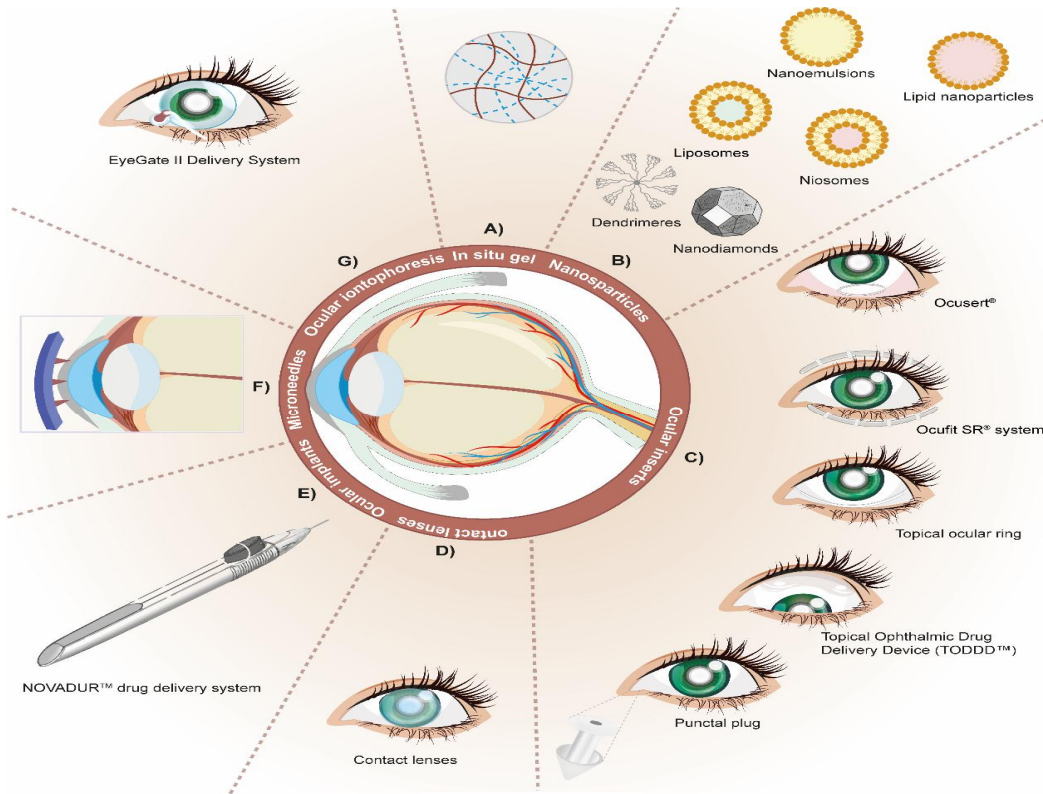

Fig. 1. Summary of drug delivery devices for glaucoma treatment. (A) In situ gel systems, (B) Nanoparticles: liposomes, niosomes, nanoparticles, lipid nanoparticles, dendrimers, nanodiamonds, (C) Ocular inserts: Ocusert®, Ocufit SR® system, topical ocular ring, Topical Ophthalmic Drug Delivery Device (TODDDTM), punctal plug, (D) Contact lenses, (E) Ocular implants: NovadurTM drug delivery system, (F) Microneedles, (G) Ocular iontophoresis: EyeGate II delivery system

Table 1. Summary of the groups of medications used in the treatment of glaucoma

Drug group	Active substance	Drug delivery system	Efficacy	Ref.
Prostaglandin analogs	Latanoprost	○ Latanoprost-loaded liposomes ○ Propylamino-β-cyclodextrin ○ Topical Ophthalmic Drug Delivery Device (TODDD) ○ L-shaped punctal plug (PP) ○ Latanoprost-eluting contact lenses (CLs) ○ Ocular implant	○ *In vivo* 90-day IOP reduction ○ *In vitro* stability tests, *in vivo* ocular irritation ○ *In vitro* 16-day release, *in vivo* 2-3-month IOP reduction ○ *In vitro* 90-day release, *in vivo* 3-month release ○ *In vitro / in vivo* 1-month release ○ *In vivo* 6-month release, phase Ib clinical trial	[58–65]
	Travoprost	○ Travoprost PP ○ iDose ocular implant	○ *In vitro* 3-month release, *in vivo* 6-month IOP reduction ○ *In vivo* 12-month IOP reduction	[62,63,66–68]
	Bimatoprost	○ Ocular inserts ○ Topical ocular ring ○ Bimatoprost SR - ocular implant	○ *In vivo* 4-week IOP reduction ○ *In vitro* 180-day release, *in vivo* 6-month IOP reduction ○ *In vivo* 6-month IOP reduction	[69–72]
Beta-adrenergic blockers	Timolol	○ *In situ* gel systems (IGS): Xyloglucan based PNIPAAm based ○ Solid lipid nanoparticles (SLN) ○ Timolol-loaded chitosan nanoparticles ○ Timolol-loaded liposomes ○ Timolol-loaded niosomes ○ Hybrid poly(amidoamine) (PAMAM)-dendrimer hydrogel-PLGA nanoparticles ○ Ocufit SR® - ocular insert ○ TODDD ○ Topical ocular ring	○ *In vivo* 24 h IOP reduction ○ *In vivo* 12 h IOP reduction ○ *In vitro* 3 h release ○ *In vitro* 24 h release, *in vivo* 8 h IOP reduction ○ *In vitro* 6 h release, *in vivo* 4 h IOP reduction ○ *In vitro* 10 h release, *in vivo* 8 h IOP reduction ○ *In vitro* 28-35-day release, *in vivo* 4-day IOP reduction ○ *In vitro* 8 h release, *in vivo* 14-day IOP retention ○ *In vivo* 3-month IOP reduction ○ *In vivo* 6-month IOP reduction, phase II clinical trial ○ *In vivo* 5-day IOP reduction	[70,73,74–76,77–84]

Drug group	Active substance		Drug delivery system		Efficacy	Ref.
		○	CLs			
	Betaxolol	○	IGS	○	*In vitro* 8 h release, *in vivo* 12 h IOP reduction	[85–87]
		○	Betaxolol-loaded montmorillonite/chitosan nanoparticles	○	*In vitro* 10 h release, *in vivo* 3 h IOP reduction	
		○	Betaxolol-loaded nanosuspension	○	*In vivo* 3-month IOP reduction	
	Carteolol	○	Carteolol-loaded dendrimers	○	Bioavailability 2.5 times higher compared with a solution	[88]
Adrenergic agonists	Clonidine	○	IGS	○	*In vitro* 6 h release	[89]
	Brimonidine	○	IGS	○	*In vitro* 28-day release	[80,90–97]
		○	Brimonidine tartarate-loaded Eudragit nanoparticle	○	*In vitro* 48–72 h release, *in vivo* 72 h IOP reduction	
		○	Brimonidine tartarate-filled chitosan nanoparticles	○	*In vitro* 4 h release, *in vivo* 8 h IOP reduction	
		○	PAMAM-dendrimer hydrogel-PLGA nanoparticles	○	*In vitro* 28–35-day release, *in vivo* 4-day IOP reduction	
		○	Ocular inserts	○	*In vitro* 24 h release, *in vivo* 24 h IOP reduction	
		○	CLs	○	*In vivo* 7-day IOP reduction	
		○	Ocular implant	○	*In vitro* 60-day release, *in vivo* 13-week IOP reduction	
		○	Hollow microneedles (MNs)	○	*In vitro* 35-day release, *in vivo* 1-month IOP reduction	
Carbonic anhydrase inhibitors	Acetazolamide	○	Acetazolamide-loaded Eudragit nanoparticles	○	*In vitro* 7 h release, *in vivo* 8 h IOP reduction	[98–103]
		○	Acetazolamide-filled cationic nanoemulsions	○	*In vitro* 90-minute release	
		○	Acetazolamide-loaded liposomes	○	*In vivo* 8 h IOP reduction	
		○	Acetazolamide-loaded niosomes			
		○	Acetazolamide-loaded carbosilane dendrimers	○	*In vivo* 6 h IOP reduction	
				○	*In vivo* 7 h IOP reduction	

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Drug group	Active substance	Drug delivery system		Efficacy		Ref.
	Methazolamide	○	Methazolamide-bound calcium phosphate nanoparticles	○	*In vivo* 18 h IOP reduction	[104,105]
		○	Methazolamide-filled SLNs	○	*In vitro* 8 h release, *in vivo* 8 h IOP reduction	
	Brinzolamide	○	IGS	○	*In vitro* 12 h release, *in vivo* 6 h IOP reduction	[106–108]
		○	Brinzolamide-loaded hydroxypropyl β-cyclodextrin liposomes	○	*In vitro* 9 h release, *in vivo* 12 h IOP reduction	
		○	Nanocrystals	○	*In vitro* immediate release, *in vivo* 1 h IOP reduction	
	Dorzolamide	○	IGS	○	*In vitro* 8 h release, *in vivo* 8 h IOP reduction	[109–116]
		○	Dorzolamide-loaded poly(D,L-lactide-co-glycolide) nanoparticles	○	*In vitro* 3-day release, *in vivo* 20 h IOP reduction	
				○	*In vivo* 6 h IOP reduction	
		○	Dorzolamide hydrochloride-filled nanoemulsions	○	*In vitro* 6 h release, *in vivo* 8 h IOP reduction	
				○	*In vivo* 24 h IOP reduction	
		○	Dorzolamide-loaded liposomes	○	*In vitro* 18 h release, *in vivo* 2-week IOP reduction	
		○	Dorzolamide with γ-cyclodextrin	○	*In vitro* 48 h release, *in vivo* 48 h IOP reduction	
		○	Ocular insert			
		○	ACUVUE® OASYS™ CLs			

Drug group	Active substance	Drug delivery system		Efficacy		Ref.
Miotics	Pilocarpine	○	Pilocarpine-loaded glutathione-PNIPAAm[1] IGS	○	*In vivo* 14-day IOP reduction	[117,118,119 –123,124– 131]
		○	Pilocarpine-loaded nanoparticles	○	*In vitro* 36-day release, *in vivo* 21-day IOP reduction	
		○	Pilocarpine-loaded liposomes	○	*In vivo* 9 h IOP reduction	
		○	Pilocarpine-loaded dendrimers	○	*In vivo* 5 h IOP reduction	
		○	β-cyclodextrin complex	○	Reduced the ocular irritation by preventing its rapid absorption and precipitation in the pre-corneal area	
		○	Pilocarpine-loaded nanocrystals	○	*In vitro* 20 h release	
		○	Ocusert® - ocular insert	○	*In vivo* 7-day IOP reduction, withdrawn from the market because of burst drug release and dislocation problems	
		○	CLs	○	*In vitro* 4 h release	
		○	Collagen corneal shields	○	*In vitro* 14-day release	
		○	Titanium MNs	○	*In vitro* 1-month release	
		○	Pilocarpine-coated MNs	○	With the excellent penetration of MNs into the sclera (up to 300µm) and a rapid dissolution rate of active substances, MNs caused fast and extensive constriction of a pupil	
		○	Dissolving MN ocular patch	○	Provided a deliver significantly higher flux of pilocarpine compared to pilocarpine solution	

PAs proved to be the most effective in IOP lowering, of which latanoprost is most frequently used as an active in the development of novel drug delivery systems. As can be seen in Table 1, different approaches were applied, of which ocular implant showed the longest IOP reduction effect *in vivo*. Nevertheless of all novel drug delivery systems containing PAs, the longest IOP reduction *in vivo* is clearly provided with travoprost iDose ocular implant, which is at the same time the longest-lasting effect of all novel drug delivery systems for treating glaucoma. Second in effectiveness are BBs, of which timolol formulated as an ocular ring achieved a 6-month IOP reduction as demonstrated in phase II clinical trial. Pilocarpine, the most commonly used miotic in glaucoma treatment is also present in numerous novel drug delivery systems, some of which are only available *in vitro* tests, as no *in vivo* tests have been performed. A large number of novel drug delivery systems are being tested for brimonidine, whose ocular ring showed a 13-week IOP reduction, the longest of all.

5. CONCLUSIONS

Although elevated IOP in glaucoma is treated with six different groups of drugs they all have different mechanisms of action, are not equally effective and cause more or less serious side effects. However, since glaucoma is recognized as a major health problem, scientists are trying to find a way to deal with it by developing novel drug delivery systems, which are different approaches with varying success and efficacy. However, since the results available are obtained using different methods, different tests and formulation approaches, it is very difficult to compare the effectiveness of novel drug delivery systems. However, considering the extent and number of available systems, we must be very optimistic that each patient will receive the most appropriate treatment for his glaucoma.

CONSENT

Not applicable.

ETHICAL APPROVAL

Not applicable

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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Peer-review history:
The peer review history for this paper can be accessed here:
http://www.sdiarticle4.com/review-history/66197