Sustained drug delivery for glaucoma: current data and future trends

Ahmad A. Aref

Purpose of review
Sustained drug delivery has been recognized as a need for patients with ocular hypertension or glaucomatos optic neuropathy. Several sustained drug delivery systems and devices are currently on the horizon. This review aims to summarize initial results with these platforms, as reported in the literature, and also provide insight into their possible role in the glaucoma treatment paradigm.

Recent findings
Sustained drug delivery systems currently on the horizon include the topical bimatoprost ocular insert, travoprost and latanoprost punctal plugs, latanoprost-eluting contact lenses, bimatoprost and travoprost intraocular implants, as well as several other therapies in earlier stages of development. Delivery strategies differ with respect to ocular site of implantation, ocular hypotensive agent, and duration of efficacy. Efficacy and safety outcomes with these devices are favorable thus far.

Summary
The glaucoma treatment paradigm is currently in a state of flux as sustained drug delivery systems bring promise to individuals suffering from ocular hypertension or glaucoma. Several options will likely become available in the near future to ease the burden of daily administration of chronic therapy with intraocular pressure-lowering agents.

Keywords
adherence, glaucoma, intraocular pressure, sustained drug delivery, sustained release

INTRODUCTION
Despite innovative advances in glaucoma laser and surgical techniques, medical intraocular pressure (IOP)-lowering remains the first-line therapeutic option in most cases [1]. However, medical therapy poses a unique set of challenges in the long-term care of glaucomatos individuals. For IOP-lowering medications to induce the desired effect, patients must purchase the medicine, successfully instill the drop into the eye, use the medication consistently, and dose at the appropriate time [2]. A study in the United Kingdom found that over half of 278 patients investigated in an observational study demonstrated poor adherence [3*].

Several strategies, including the use of financial incentives [4] and smartphone-based applications [5*], are currently under study with the goal of addressing glaucoma medical adherence challenges. Although promising, these methods will still require active instillation of the agents by glaucoma patients. Novel sustained drug delivery devices (Table 1) may relieve patients from this burden while providing for adequate IOP lowering and control of glaucomatos disease. This review aims to summarize initial results with these platforms, as reported in the literature, and also provide insight into their possible role in the glaucoma treatment paradigm.

TOPICAL BIMATOPROST OCULAR INSERT
The topical bimatoprost ocular insert (ForSight Vision5, Inc., Menlo Park, CA, USA) is an ocular ring composed of bimatoprost incorporated within a silicone matrix and supported by an inner polypropylene structure. The insert is manufactured in diameters ranging from 24 to 29 mm and designed for placement between the upper and lower

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fornices, with sizing dependent on one’s intercanthal distance. A scleral depressor may be used to assist with adequate insertion (Fig. 1). The device continuously elutes bimatoprost over a 6-month period. The rate of drug elution into the tear film is not constant over this time period and is dependent on properties of the silicone–drug matrix. This results in a descending dose of bimatoprost elution, ranging from 35 μg/day on day of insertion to 6 μg/day at 6 months. The device is replaced by the treating practitioner after 6 months of therapy.

The 6-month efficacy and safety results of the topical bimatoprost ocular insert were recently reported on by Brandt and colleagues [6**]. In this phase 2 noninferiority trial, performance of the bimatoprost insert was compared with timolol 0.5% ophthalmic solution, dosed twice daily. A double-dummy design was employed, which involved twice daily placebo artificial tear therapy to the group randomized to the bimatoprost insert and placebo nondrug eluting ring insertion in patients randomized to timolol. The primary efficacy outcome was the difference in mean baseline IOP change between the two treatment groups at each of three diurnal time points over 6 months of therapy. A noninferiority margin of 1.5 mmHg was declared prior to study initiation. Over 6 months of therapy, patients assigned to both the bimatoprost insert and timolol treatment groups experienced IOP reduction (3.2–6.4 and 4.2–6.4 mmHg, respectively, and greater than 20% for each group) compared with baseline. Although the difference in mean IOP change at each of the diurnal time points was within 1.5 mmHg, noninferiority of the bimatoprost insert was not reached because the upper boundary of the 95% confidence interval exceeded 1.5 mmHg at some of these time points. The bimatoprost insert was relatively well tolerated although 28 device dislodgments were noted to occur among 15 patients. All dislodgments were noted by the participants and brought to the attention of the investigators for immediate device replacement so that therapy could be maintained.

The study authors attribute the lack of noninferiority to inadequate sample size and also to possible paradoxical blunting in IOP-lowering efficacy because of agonist desensitization associated with continuous elution of a prostaglandin analogue. Indeed, IOP-lowering with the bimatoprost insert was less than predicted with topical drop therapy. However, one must also consider that patients under consideration for bimatoprost insert therapy would likely not be suitable candidates for drop therapy because of adherence issues.

### Table 1. Sustained drug delivery platforms currently in development

<table>
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<tr>
<th>Device</th>
<th>Implantation site</th>
<th>Stage of development</th>
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<tr>
<td>Travoprost punctum plug</td>
<td>Upper or lower canaliculus</td>
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Furthermore, an IOP reduction greater than 20% from baseline may be deemed adequate for patients with ocular hypertension.

A subset of patients that completed this phase 2 study went on to participate in an open-label single-arm study for 13 months of additional therapy [7]. The results after 6 months of additional therapy, with exchange of the original ocular insert for a new device, were reported in 75 study participants. Adverse events were noted to remain mild and self-limited in nature while continued IOP reduction (3.4–5.1 mmHg) was noted. This study suggests that beneficial IOP-lowering results may be maintained for up to 13 months with the topical bimatoprost ocular insert. A study (Clinicaltrials.gov Identifier: NCT02742649) to evaluate efficacy and safety with a fixed combination insert composed of both bimatoprost and timolol is currently underway. Superior efficacy with this device would potentially allow for adequate sustained release therapy with the topical bimatoprost insert in glaucomatous individuals.

**PROSTAGLANDIN PUNCTUM PLUGS**

The travoprost punctum plug (OTX-TP, Ocular Therapeutix, Inc., Bedford, MA, USA) is composed of travoprost encapsulated in polylactic acid microparticles suspended within a polyethylene glycol resorbable hydrogel rod. Upon exposure to the tear film, the rod swells to occupy the space within the upper or lower canaliculus. Hydrolysis of the polylactic acid microparticles takes place over a 90-day period, resulting in sustained release of the travoprost drug into the tear film. Fluorescein is also incorporated within the hydrogel rod to aid in visualization of the device (Fig. 2).

Clinical results with the OTX-TP device were reported on in a phase 2b clinical trial [8]. In this trial, 73 patients at 11 clinical sites were randomized to treatment with the OTX-TP device versus twice daily administration of topical timolol 0.5% eye drops. A double-dummy design was employed, which involved twice daily placebo artificial tear therapy to the group randomized to OTX-TP and placebo nondrug-eluting punctal plugs to patients randomized to timolol. At 90 days, a clinically meaningful IOP reduction (4.5–5.7 and 6.4–7.6 mmHg for the OTX-TP and timolol groups, respectively) was achieved in both treatment groups. Interestingly, the degree of IOP reduction achieved in patients randomized to timolol was greater than expected based on previously published data. The enhanced efficacy in the timolol group may have been related to greater contact time of the medicine with the ocular surface as a result of insertion of the placebo punctal plugs. No hyperemia-related adverse events were noted in any of the participants randomized to OTX-TP. The device retention rates were noted to be 91, 88, and 48% at days 60, 75, and 90, respectively.

Perera and colleagues [9] reported on shorter-term data with the OTX-TP device in a single-arm study involving 26 eyes of 17 Asian study participants over 30 days of therapy. In this study, IOP reductions of 24 and 15.6% were noted at days 10 and 30, respectively. The device’s retention rate was 42% after 30 days. The decrease in efficacy over the course of this study seems to be related to increasing rates of dislodgement through day 30. The intolerance rate was 1/17 as one study participant in the study required removal of the device because of epiphora. Otherwise, the device was well tolerated with low average hyperemia score (0.1 out of 30) noted by the investigators.
Phase 3 clinical trials investigating performance of the OTX-TP device are currently in the planning phase and will not include a timolol comparator or validation arm [10]. Rather, a placebo-controlled comparator arm using a nondrug-eluting punctal plug will be employed. This study design will bypass issues related to prolonged ocular surface contact time, and subsequent higher-than-expected efficacy, of timolol in participants undergoing placebo punctal plug placement. The trial will involve the use of an OTX-TP product designed for 75 days of active drug delivery.

Another prostaglandin punctual plug device is the latanoprost punctual plug delivery system (Latanoprost-PPDS, Mati Therapeutics, Inc., Austin, TX, USA). The device consists of a core of latanoprost–polymer matrix surrounded by silicone. The silicone plug is inserted using standard procedures at the slit lamp. A phase 2 study (Clinicaltrials.gov Identifier: NCT02014142) investigating the safety and efficacy of latanoprost-PPDS in comparison with timolol maleate ophthalmic gel forming solution dosed once a morning is ongoing.

**LATANOPROST-ELUTING CONTACT LENS**

Contact lenses are an attractive target for sustained drug delivery given their relatively large residence time in the eye [11]. Soft contact lenses may be impregnated with an IOP-lowering agent, which via diffusion into the tear film, can then be absorbed by the cornea in a continuous fashion.

Ciolino and colleagues [12**] recently reported on preclinical results using a novel latanoprost-eluting contact lens in glaucomatous monkeys. The contact lenses were produced in high (149 g latanoprost; \( \text{CL}_{\text{HI}} \)) and low (97 g latanoprost; \( \text{CL}_{\text{LO}} \)) dose variations. The IOP-lowering efficacy of the high and low-dose latanoprost-eluting contact lenses was compared with topical latanoprost therapy in four eyes of four adult glaucomatous monkeys using a cross-over design with a 3-week washout period between the consecutive treatments. Contact lens therapies were administered for 1 week, whereas topical latanoprost treatment was administered for 5 days. Mean baseline IOPs were 31 mmHg in each treatment group at the morning time point. On the last day of treatment, mean IOP reduction ranges throughout the diurnal period were \( 2.9 \pm 1.0 – 6.6 \pm 1.3 \), \( 4.0 \pm 1.1 – 7.8 \pm 3.8 \), and \( 6.0 \pm 4.4 – 10.2 \pm 2.5 \) mmHg in the topical latanoprost, \( \text{CL}_{\text{LO}} \), and \( \text{CL}_{\text{HI}} \) treatment groups, respectively. The differences in IOP reduction between the \( \text{CL}_{\text{HI}} \) and topical latanoprost groups were significant \( (P < .05) \) at the 9:30 AM, 1:30 PM, and 2:30 PM time points. Otherwise, no differences were detected in IOP reduction among the treatment groups. The authors conclude that IOP-lowering with the latanoprost-eluting contact lens may be at least as efficacious as topical latanoprost. Importantly, IOP-lowering achieved with the contact lens was more constant in nature compared with relative fluctuations observed in the topical latanoprost group. The study gives promise to contact lenses serving as vehicle for drug delivery in patients with glaucoma or ocular hypertension. However, one must consider potential challenges with long-term contact lens therapy in patients deemed to be nonadherent with a topical medical regimen.

**BIMATOPROST INTRAOCULAR IMPLANT**

The bimatoprost sustained release implant (Bimatoprost SR; Allergan plc, Dublin, Ireland) is a biodegradable implant designed for injection into the anterior chamber via a prefilled applicator. The agent is then continuously released over 4–6 months. In a phase 1/2 paired eye trial, 75 patients received Bimatoprost SR in one eye (6, 10, 15, or 20 µg dose) and topical bimatoprost 0.03% dosed daily in the fellow eye [13]. Through week 16, mean IOP reduction from baseline was 7.2, 7.4, 8.1, and 9.5 mmHg for eyes receiving the 6, 10, 15, and 20 µg doses of Bimatoprost SR, respectively. Mean IOP reduction from baseline among all eyes receiving topical bimatoprost was 8.4 mmHg. The Bimatoprost SR implant was relatively well tolerated and qualitative measures indicated patient acceptance of the device. A recent animal study with the device suggests that it may allow for episcleral venous pressure reduction via vasodilation of aqueous outflow venous vessels [14].

A benefit of intracameral devices for administration of sustained release therapies is that undocumented dislodgment or loss of the implant is not possible. The dramatic rise in the use of intravitreal injections for treatment of age-related macular degeneration [15] will likely foster greater acceptance of injection therapy in glaucomatous individuals.

**TRAVOPROST INTRAOCULAR IMPLANTS**

The Travoprost Extended Release implant (ENV515; Envisia Therapeutics, Morrisville, NC, USA) is a biodegradable device fabricated using novel particle replication in nonwetting templates microparticle engineering technology. The technology allows for the production of sterile nanoparticles containing an extended release formulation of travoprost [16]. In a preclinical study of six eyes of six normotensive Beagle dogs, intracameral implantation of ENV515...
resulted in a 35.3% (6.4 ± 0.6) mmHg IOP reduction from a baseline of 18.6 ± 0.2 mmHg (P < 0.001) over 8 months [17]. Implantation of the device was well tolerated with no adverse effects noted. Phase 2a human studies demonstrated an IOP reduction of 6.7 mmHg after 25 days that was comparable with a 6.6 mmHg reduction (P < 0.001) achieved with once daily dosing with travoprost ophthalmic solution administered to the fellow eye [18]. Baseline mean IOP was approximately 24 mmHg in each treatment group.

Another sustained release travoprost implant (iDose; Glaukos Corp., San Clemente CA, USA) designed for intracameral injection is currently under investigation in a phase 2 clinical trial (Clinicaltrials.gov Identifier: NCT02754596). The device is made of titanium and allows for continuous travoprost elution into the anterior chamber. When the device is depleted of active drug, removal and replacement with a new implant may be performed [19].

OTHER SUSTAINED RELEASE THERAPIES

In a study of normotensive Dutch rabbits, Fu and colleagues [20] reported on the sustained IOP-lowering of subconjunctival injection of dorzolamide-loaded polymer microparticles. Microparticles used in the study were synthesized by encapsulating the ion-paired carbonic anhydrase inhibitor and poly-lactic-co-glycolic-acid polymer into poly(ethylene glycol)-co-poly(sebacic acid). Subconjunctival delivery of the microparticles with a 27-gauge needle resulted in an IOP reduction of 4.06 ± 1.53 mmHg compared with fellow, untreated eyes (P < 0.0001) and continued for 35 days. Prior to therapy, the rabbit eyes were considered normotensive (mean baseline IOP not given) as no consistent method exists for experimental IOP elevation without affecting normal physiological state.

The efficacy of sustained IOP reduction by supraciliary delivery of brimonidine microspheres in New Zealand white rabbits was studied by Chiang and colleagues [21]. The microspheres were composed of brimonidine tartrate and polyactic acid polymer and delivered into the supraciliary space using a shortened 27-gauge hypodermic needle. Fellow eyes received topical brimonidine therapy as well as a ‘blank’ microsphere injection and served as controls. In the experiment, all rabbits that received a high-dose formulation (0.9 mg brimonidine) of microspheres experienced a sustained reduction in IOP, up to 6 mmHg, compared with controls for at least 3 weeks after injection (P = 0.017).

In a study investigating the potential use of collagen shields as a drug delivery platform, Agban and colleagues [22] successfully cross-linked polyvinylpyrrolidone-capped zinc oxide to pilocarpine hydrochloride. Using this method, pilocarpine was released from the shield over 14 days. The use of polyvinylpyrrolidone-capped zinc oxide nanoparticles in this study overcomes some of the limitations in transparency and safety noted in prior investigations of collagen shields for ocular drug delivery.

Lambert and colleagues [23] investigated an intravitreal route of drug delivery in ocular hypertensive mice using medication-loaded nanosponges. Nanosponges were synthesized to create a polymeric network to allow for entrapment of either brimonidine, travoprost, or bimatoprost. The respective drug-loaded nanosponges were then injected into the posterior segment of one eye of mice with microbead-induced ocular hypertension. The fellow eye served as a control and received an intravitreal injection of saline. Larger brimonidine and travoprost-loaded nanosponges lowered baseline IOP by 27% with an effect that persisted for 3 weeks postinjection. Larger sized bimatoprost-loaded sponges lowered baseline IOP by at least 4 mmHg for 4 weeks postinjection.

CONCLUSION

A clear need exists for sustained release therapies for the chronic treatment of glaucomatous optic neuropathy. An attempt to address this need was made with the introduction of pilocarpine inserts in 1975 [24]. However, tolerability issues and limited duration of efficacy led to its removal from the market. Since then, tremendous progress has been made and several drug delivery platforms show promise. Ideally, sustained drug delivery would not sacrifice the efficacy afforded with compliant eye drop therapy nor increase the need for more frequent outpatient visits. This will allow for consideration of these options beyond poorly adherent individuals or those not requiring maximal IOP control. Future areas of study include the investigations of fixed combination implants as well as the combined efficacy of multiple different implants. The glaucoma treatment paradigm is currently in a state of flux, for the benefit of patients, practitioners, and the healthcare delivery system.

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Glaucoma

Conflicts of interest
There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:
■ of special interest
■■ of outstanding interest


In this study analyzing computerized prescribing records, over half of patients demonstrated poor adherence to IOP-lowering therapy for glaucoma. These results are consistent with what has been previously reported in the literature and support the need for sustained drug delivery therapy.


The study employed a survey design to gauge patient interest in a novel smartphone-based and tablet-based glaucoma application. The proposed fee for the application limited patient interest.


The Willis Eye glaucoma app demonstrated poor adherence to IOP-lowering therapy for glaucoma. These results are consistent with what has been previously reported in the literature and support the need for sustained drug delivery therapy.


In this phase II randomized controlled study, a novel topical bimatoprost ocular insert was capable of reducing baseline IOP by 3.2–6.4 mmHg over a 6-month period. The study was underpowered to show noninferiority to timolol, but suggests a potential role for patients with ocular hypertension and/or patients experiencing medical adherence challenges.


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