

REVIEW ARTICLE

Sustained drug delivery platforms – A new era for glaucoma treatment

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Compliance, delayed-action preparations, drug delivery systems, glaucoma, intraocular pressure

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Received: 21-05-2019;
Accepted: 17-06-2019
doi: 10.15713/ins.clever.24

**Abstract**

Glaucoma is a leading cause of blindness worldwide. Treatment typically consists of the chronic administration of topical eye drops. However, fluctuations in intraocular pressure, local and systemic side effects, and low patient compliance have prompted the development of various sustained drug delivery platforms, both extraocular and intraocular, over the last decade. Some are currently undergoing advanced clinical trials. Extraocular platforms include wearable ocular surface devices (such as ocular insert rings, topical ocular drug delivery devices, gel-forming eye drops, collagen shields, and contact lenses), punctal plugs (such as the OTX-TP and Latanoprost punctal plug delivery system), and subconjunctival injections (such as the Eye-D VS-101, POLAT-001, GB-6249-103, IBI-60089, and dorzolamide-loaded polymer microparticles). Intraocular platforms include mainly intracameral implants (such as the Bimatoprost SR, ENV515 Travoprost XR, iDose, OTX-TIC, PAS108, and DE-117-loaded PLC), although other devices are drawing attention as potential treatment alternatives (such as intravitreal nanospheres and supraciliary implants). The purpose of this review is to describe these emerging sustained drug delivery systems for the treatment of glaucoma and ocular hypertension.

Introduction

Glaucoma is a chronic progressive optic neuropathy and the second most common cause of blindness worldwide.^[1] In 2013, approximately 64.3 million people were suffering from glaucoma worldwide, and it is estimated that this number will reach 111.8 million people by 2040.^[2] High intraocular pressure (IOP) is a modifiable risk factor of glaucoma and its progression and therefore serves as the target of current treatment modalities. Chronic administration of topical IOP-lowering eye drops has been the mainstay of glaucoma treatment for over a century. In recent years, laser procedures have been included in the treatment paradigm, while surgical options are usually reserved for patients who cannot or are unwilling to comply with topical therapy or have progressing uncontrolled disease.

Topical treatment offers significant advantages: Low initial cost, noninvasiveness, and ease of use. However, it is also associated with important drawbacks, mainly diurnal IOP

fluctuations, which pose a major risk for disease progression, and local and systemic side effects.^[3-5] Furthermore, compliance is often poor, especially because of the numerous types of drops and multiple daily dosages that are often necessary for adequate IOP maintenance.^[6-8] This problem is exacerbated in the elderly population, comprising the majority of patients with glaucoma, in whom deterioration in fine motor skills and mental capacity can hinder daily topical drop administration.

In the past decade, innovative research studies have begun to address these disadvantages of topical eye drops, leading to the emergence of various sustained drug delivery platforms as alternative means of treatment of glaucoma and ocular hypertension (OHT). Given the growing population of patients with glaucoma and OHT, it is important that ophthalmologists be familiar with current and novel drug-delivery platforms, both intraocular and extraocular. This article reviews the available sustained drug delivery devices as well as those under preclinical and clinical investigation.

Extraocular Drug Delivery Platforms

Extraocular drug delivery devices enable the gradual release of IOP-lowering medication, promoting a more stable diurnal IOP with fewer side effects than traditional chronic topical eye drop administration. Extraocular sustained drug delivery platforms are divided into surface devices, which lie on the anterior ocular surface, punctal plugs, which are placed within the punctum or canaliculi, and subconjunctival devices. All are designed to adhere comfortably with minimal ocular irritation while providing a continuous therapeutic effect.

Surface Devices

Bimatoprost ocular insert

The Bimatoprost ocular insert (Allergan plc, Dublin, Ireland) is a ring-shaped device containing Bimatoprost embedded in a silicone matrix which allows for its sustained release and an inner polypropylene structural support [Figure 1]. The ring ranges in diameter from 24 mm to 29 mm; the optimal size for use is determined by the intercanthal distance on a case-by-case basis. The device is placed in the upper and lower fornices by the treating practitioner and replaced after 6 months of continuous therapy [Figure 2]. Drug release into the tear film decreases over time, from 35 µg/day to 6 µg/day at 6 months.

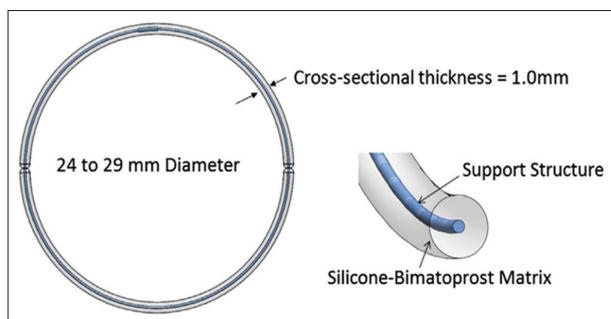


Figure 1: Bimatoprost ocular insert. Schematic representation. An inner polypropylene structural ring covered with a silicone-bimatoprost matrix for slow release of bimatoprost. Figure is adapted with permission from “Brandt JD, DuBiner HB, Benza R, Sall KN, Walker GA, Semba CP, *et al.* Long-term Safety and Efficacy of a Sustained-Release Bimatoprost Ocular Ring. *Ophthalmology.* 2017;124(10):1565–6”



Figure 2: Bimatoprost ocular insert. A step-by-step photographed instruction for correct placement of the bimatoprost ocular insert by the physician. (a) The insert outside the eye, (b) Insert the upper half of the ring to the upper fornix. (c) Retract the lower lid, (d) Place the bottom part of the ring in the lower fornix. (e) When the insert is in place make sure a small part of it is visible in the medial canthus. Figure is adapted with permission from “Brandt JD, DuBiner HB, Benza R, Sall KN, Walker GA, Semba CP, *et al.* Long-term Safety and Efficacy of a Sustained-Release Bimatoprost Ocular Ring. *Ophthalmology.* 2017;124(10):1565–6”

The results of a randomized double-blind noninferiority Phase II trial with the Bimatoprost SR in 130 patients with open-angle glaucoma (OAG) or OHT were published in 2016.^[9] Patients were assigned to receive either a 13-mg Bimatoprost ocular insert and artificial tears twice daily or a placebo ocular insert and timolol 0.5% ophthalmic solution twice daily, for 6 months. At the end of the study period, IOP was reduced by 3.2 mmHg to 6.4 mmHg in the Bimatoprost group and 4.2 mmHg to 6.4 mmHg in the timolol group. However, the predetermined noninferiority margin of 1.5 mmHg was not statistically demonstrated, possibly because of the small sample size. Retention rates were high, 93.1% at 3 months and 88.5% at 6 months, and the main adverse events were ocular discharge (19%), conjunctival hyperemia (12%), and punctate keratitis (12%).

Sixty-three patients from the Phase II study were subsequently enrolled in an open-label extension study to receive two more cycles of treatment with the Bimatoprost SR over 13 months.^[10] Patients proceeded in the same arm as in the original Phase II study and IOP decreased by approximately 4 mmHg, with no difference in response between the treatment and control arm. The overall reduction was similar to that of the past 3 months of the original study. Retention rates and adverse events were similar as well, except for a higher rate of ocular discharge (21%). The gradual decrease in the effect of Bimatoprost over the long term was in line with findings in previous studies of high-dose prostaglandins. The reason for the decline is unknown. A Phase Ib study evaluating the efficacy and safety of an ocular insert with a fixed combination of Bimatoprost and timolol for greater IOP reduction was recently completed, but the results have not yet been published.^[11]

Topical ocular drug delivery device (TODDD)

The TODDD (Amorphex Therapeutics, Andover, MA, USA) is a topical ophthalmic device made of a soft clear elastomeric material that is worn under the upper eyelid [Figure 3]. It is designed for the sustained delivery of different drugs over the long term. Preclinical trials with the TODDD containing timolol, prostaglandins, or their combination have been reported. Leahy *et al.* evaluated the efficacy of the TODDD containing 3 mg of timolol in normotensive rabbits.^[12] They found a maximal reduction in IOP of 5.5 mmHg, constituting a 37% difference from baseline, which was maintained for the entire 3-month trial period. Another preclinical trial in

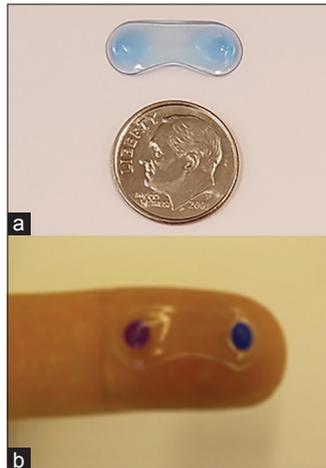


Figure 3: Topical ocular drug delivery device. (a) The clear elastic matrix of the device. (b) The purple and blue circles mark the drug depot cavities. Courtesy of Amorphex Therapeutics LLC

eight beagle dogs using the TODDD containing 600 μg of latanoprost yielded a decrease in IOP of 3 mmHg on days 4–8 and of 7 mmHg on day 16, for the same 37% reduction from baseline as in the earlier study.^[13] However, retention rates were low, and only three devices were still in place at the end of the study period (16 days). Both studies reported undetectable systemic drug levels. In humans, one safety and feasibility study of the TODDD (without a drug) showed a 75% retention rate with a suitable safety profile, and another clinical study showed continuous and uninterrupted timolol delivery with a therapeutic response for 6 months.^[14]

Gel-forming drops

SoliDrop

The *SoliDrop* (Otero Therapeutics, Pittsburgh, PA, USA) is a drug-loaded eye drop that is transformed into a hardened gel following contact with the ocular surface. The gel is retained under the lower eyelid and continuously releases the desired drug. When the treatment period is over, the gel is removed by washing the lower fornix with a little saline.^[15] In a preclinical study conducted in rabbits, Fedorchak *et al.* found that the reduction in IOP induced by one drop of a brimonidine-loaded gel-forming eye drop was comparable to that of standard brimonidine drops administered twice daily.^[16] Drug release and gel retention were maintained throughout the 28-day study period in all rabbits.

DuraSite ISV-215

The *DuraSite ISV-215* (InSite Vision, Alameda, CA, USA) consists of a stable mucoadhesive matrix of Bimatoprost 0.03% embedded in a *DuraSite*® delivery system. In a preclinical study in 32 pigmented rabbits, the *DuraSite ISV-215* was associated with better drug distribution in the aqueous humor and iris-ciliary body than Bimatoprost 0.03% ophthalmic solution.^[17]

Collagen shields

Agban *et al.* described a novel polyvinylpyrrolidone-capped zinc oxide (ZnO/PVP) collagen shield cross-linked with pilocarpine hydrochloride (PHCL).^[18] They tested three different nanoparticles: Titanium dioxide, ZnO, and the ZnO/PVP, and compared various parameters essential for safe ocular use: Size, cytotoxicity, mechanical strength, transparency, swelling capacity, bioadhesive properties and concentration of ions released. They have shown that the ZnO/PVP, when prepared with a ratio of 1:1 between collagen to ZnO/PVP nanoparticles, was the leading candidate. Besides its small size (6 nm) and a slightly lower cytotoxic effect (expressed by a higher viability of corneal epithelial cells and retinal pigment epithelium), the ZnO/PVP showed a 79.3% transparency rate compared to water and evaluated with a Ultraviolet–visible spectrophotometer (Libra323PC, Biochrom, UK) at 600 nm) and a continuous release of PHCL over 14 days.

Contact lenses

Ciolino *et al.* tested the effect of latanoprost-eluting contact lenses in a preclinical study with a 3-arm cross-over design.^[19] Glaucoma was induced in 4 eyes of female cynomolgus monkeys by repeated argon laser trabeculoplasty. Each monkey wore a continuous-wear low-dose (97 μg) latanoprost-eluting contact lens for 1 week, followed by a washout period of 3 weeks and 5 days of latanoprost topical drops. After another washout period of 3 weeks, the animals wore a continuous-wear high-dose (149 μg) latanoprost-eluting contact lens for 1 week. Use of the drug-eluting contact lenses at either dose was associated with a statistically significant decrease from baseline in most IOP measurements. The difference in the decrease in IOP between the high-dose latanoprost-eluting lens and latanoprost topical drops was statistically significant at most time points. The authors concluded that contact lenses can be at least as effective as ophthalmic solutions, with less fluctuation of IOP measurements and more stable IOP reduction.

Punctal Plugs

OTX-TP

The OTX-TP (Ocular Therapeutix, Bedford, MA, USA) is a rod-shaped hydrogel intracanalicular insert. When exposed to the tear film, it swells inside the canaliculus for adequate fixation. As the insert is invisible, fluorescein is incorporated within it for visualization under the slit-lamp. The insert contains travoprost encapsulated in polylactic acid microparticles for gradual sustained release to the tear film over 90 days. The device was tested in a double-blinded Phase IIb study wherein 73 patients were allocated to receive either the OTX-TP plug with placebo artificial tears twice daily or a placebo non-eluting plug with timolol (0.5% ophthalmic solution) twice daily.^[20] The results showed that IOP was reduced by 4.5–5.7 mmHg in the OTX-TP group and 6.4–7.6 mmHg in the timolol group. The reduction in

the timolol group was greater than expected, probably because the presence of the placebo punctal plug led to more contact time of the solution with the ocular surface. Retention rates were 91% on day 60, 88% on day 75, and 48% on day 90. No hyperemia-related adverse events were documented in any of the patients in the OTX-TP group. In another efficacy and safety single-arm study, OTX-TP plugs were inserted into 26 eyes of 17 patients with OAG or OHT.^[21] IOP was reduced by 24% on day 10 and 15.6% on day 30. The corresponding retention rates were 100% and 42%. One patient required removal of the plugs on the 1st day due to epiphora. On day 3, 38.5% of patients complained of mild ocular pain, but the rate dropped to zero by day 20. Other adverse events included excessive tearing in 3.85% of patients and itching in 11.5%. The average hyperemia score was low (0.1 out of 3). A Phase III clinical trial to evaluate the efficacy of OTX-TP plugs without validation arms is planned.^[22]

Latanoprost punctal plug delivery system (L-PPDS)

The L-PPDS (Mati Therapeutics, Austin, TX, USA) is an L-shaped punctal plug with a core of latanoprost-polymer matrix that is surrounded by silicone [Figure 4]. Two open-label Phase II studies designed to evaluate the safety and preliminary efficacy of different L-PPDS formulas have been reported.^[23,24] The first included two cohorts treated with two dosages of latanoprost, 44 μ g (66 patients, cohort 1) and 81 μ g (44 patients, cohort 2), for 6 weeks. Retention rates were high: About 77% in cohort 1 and 94% in cohort 2. Discontinuation of treatment was due to either loss of the plug or inadequate IOP control. Rates of adverse events ranged from 1.7% to 11.7% in cohort 1 and from 1.9% to 22.6% in cohort 2. The most common adverse events in both cohorts were itching and foreign body sensation. Conjunctival hyperemia was reported exclusively in cohort 2. The second study evaluated two different 95 μ g latanoprost formulas for 12 weeks. Results showed a 20% reduction in IOP from baseline and high retention rates (92% and 96%). A randomized multi-

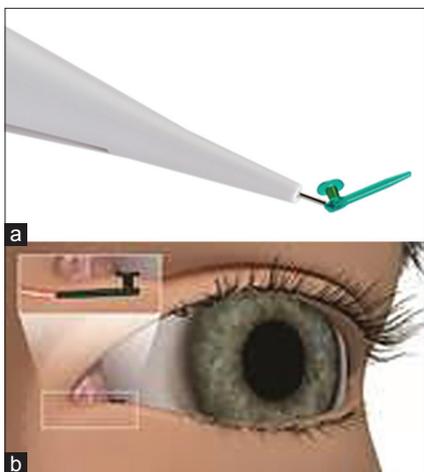


Figure 4: Latanoprost punctal plug delivery system. (a) Illustration of the device. (b) The device placed in the lower canaliculus. Courtesy of Mati Therapeutics Inc

center Phase II study evaluating the safety and efficacy of L-PPDS versus timolol eye drops for up to 14 weeks is ongoing.^[25]

Subconjunctival Devices

Eye-D VS-101

The Eye-D VS-101 (BioLight Life Sciences, Tel Aviv, Israel) is a latanoprost-loaded device that is inserted into the lower bulbar conjunctiva in an in-office procedure. A multicenter, randomized, controlled, and double-blinded Phase I/IIa study was completed in July 2017.^[26,27] Thirty-nine patients were allocated to receive latanoprost with the Eye-D VS-101 at high, medium, or low elution rates, and ten patients were treated with latanoprost 0.005% eye drops (control group). All groups were followed for 3 months. A reduction of 24% in mean IOP was found in the high-dose treatment arm (from a baseline of 23.5–17.9 mmHg); however, the company has not yet specified the latanoprost dosage of the insert. According to the company's statement, the inserts were well tolerated, and more than 90% of the adverse events were mild and transient; no severe adverse events were reported. A Phase IIb clinical study is pending.

Dorzolamide-loaded polymer microparticles

Fu *et al.* evaluated the IOP-lowering efficacy of injectable microparticles containing an ion-paired dorzolamide (carbonic anhydrase inhibitor) and polylactic-co-glycolic-acid polymer encapsulated into poly(ethylene glycol)-co-poly(sebacic acid).^[28] Injection of the microparticles using a 27 gauge needle to the subconjunctival space of the superior temporal region of the eye of normotensive Dutch rabbits resulted in a mean IOP reduction of 4.0 ± 1.5 mmHg compared to the untreated eye ($P = 0.0001$). The response was maintained for 35 days. Placebo microparticle injections had no effect on IOP ($P = 0.9$).

POLAT-001

The POLAT-001 (Peregrine Ophthalmic Pte Ltd, Singapore) is a 100 nm-long nanoliposome containing latanoprost. An open-label safety and efficacy study of a single subconjunctival injection of POLAT-001 in 6 patients with OHT reported an IOP reduction of more than 20% at each study visit ($P = 0.001$ – $P = 0.049$), 3 months after injection.^[29] An open-label Phase II clinical study comparing the POLAT-001 implant to latanoprost ophthalmic solution is currently underway.^[30]

GB-6249-103

Graybug Vision (Redwood City, CA, USA) is developing a drug-encapsulated microparticle containing different new molecular entities (NME) based on prodrugs of approved IOP-lowering agents. One such prodrug (GB-6249-103) was associated with an IOP reduction of about 20% over a 2-month period in a preclinical study in pigmented rabbits.^[31] Other NME (GB-201/202/203) are currently under preclinical study.^[32]

IBI- 60089

The IBI-60089 (Icon Bioscience, Sunnyvale, CA, USA) is a subconjunctival liquid injection containing latanoprost on a carrier platform called Verisome™. The device is currently under development. The goal is to enable the release of latanoprost in therapeutic doses for a 6-month period with a single injection. The company's most progressive device, the IBI-10090 (currently in Phase III study), contains dexamethasone for the treatment of inflammation following cataract surgery.^[33]

Intraocular Drug Delivery Platforms

Intraocular sustained-release devices for glaucoma treatment have been under development in recent years. Unlike extraocular devices, they involve surgical manipulation for device implantation. They offer a continuous controlled release of therapeutic agents without surface irritation and may be used in patients intolerant of topical agents or devices. There are three types: Intraocular implants, nanospheres, and supraciliary delivery of microspheres.

Intraocular Implants**Bimatoprost SR implant**

The Bimatoprost SR (Allergan plc, Dublin, Ireland) is a biodegradable implant injected into the anterior chamber through a prefilled injector for the sustained release of Bimatoprost to the eye over 4–6 months [Figure 5]. In a paired-eye controlled Phase I/II trial, after a washout period, 75 patients with OAG underwent implantation of the Bimatoprost SR (at doses of 6 µg, 10 µg, 15 µg, or 20 µg) in one eye and treatment with topical Bimatoprost 0.03% once daily to the fellow eye.^[34] Rescue topical medication, or a single repeated implant was allowed. After 16 weeks' follow-up, IOP was reduced by 7.2 mmHg (6 µg), 7.4 mmHg (10 µg), 8.1 mmHg (15 µg), and 9.5 mmHg (20 µg) compared to 8.4 mmHg in the fellow eye. There was no need for rescue or repeated treatment in 91% of patients at 16 weeks and 71% at 6 months. Adverse events were mild and transient (mostly limited to 2 days from injection); the most common were conjunctival hyperemia (24%) and foreign body sensation (16%). When asked at the 12-week time point if they would recommend the implant to others, 59.7% of patients stated it was extremely likely and 23.6%, that it was very likely. An ongoing noninferiority, multicenter, randomized, double-blinded, and parallel-group Phase III study of 528 patients with OAG or OHT is evaluating the safety and efficacy of the Bimatoprost SR (in 2 dose strengths) over topical timolol drops.^[35] The 3-month results are promising: The study apparently met its noninferiority criteria, with an IOP reduction of more than 30%. Another ongoing randomized, quadruple-blind, and parallel assignment Phase III trial aims to enroll 160 participants and is designed to evaluate the efficacy of Bimatoprost SR over selective laser trabeculoplasty (SLT).^[36] The study eye will undergo a sham SLT on day 1 followed by either three injections of Bimatoprost

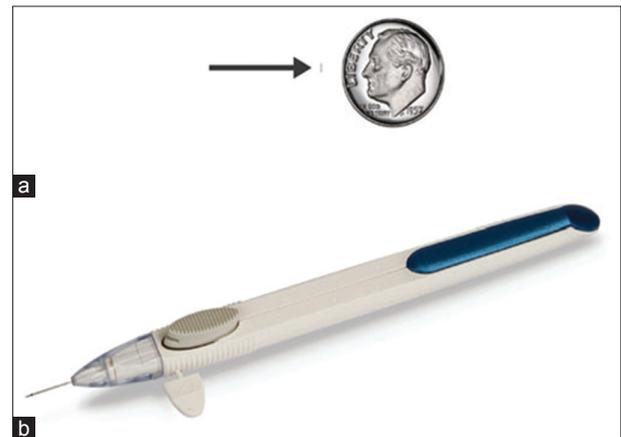


Figure 5: Bimatoprost Sustained Release (Bimatoprost SR) implant. (a) The implant (arrow) next to a dime coin for compression of size. (b) Implant injector system. Figure is adapted with permission from “Seal JR, Robinson MR, Burke J, Bejanian M, Coote M, Attar M. Intracameral Sustained-Release Bimatoprost Implant Delivers Bimatoprost to Target Tissues with Reduced Drug Exposure to Off-Target Tissues. *J Ocul Pharmacol Ther Off J Assoc Ocul Pharmacol Ther.* 2019 Feb;35(1):50–7”

SR on day 4, weeks 16 and 32 or only two injections on day 4 and week 16. The contralateral eye will undergo SLT on day 1 followed by either 2 or 3 sham Bimatoprost SR injection on the same time points as the study eye.

ENV515 Travoprost XR

The ENV515 Travoprost XR (Envisia Therapeutics, Morrisville, NC, USA) is an implant injected to the anterior chamber for extended release of travoprost through a biodegradable polymer drug delivery system. In a Phase IIa, clinical study including patients with OAG who were treated previously with prostaglandins, after a washout period, the ENV515 Travoprost XR was administered to the study eye and topical timolol ophthalmic solution 0.5% once daily to the fellow eye.^[37] At 11 months after a single dose, there was a mean reduction in IOP of 6.7 ± 3.7 mmHg (25% from baseline). The most common adverse event was dose-related transient hyperemia or eye redness. No serious adverse events were reported.

iDose Travoprost

The iDose Travoprost (Glaukos, San Clemente, CA, USA) is a titanium travoprost-containing implant measuring 1.8 mm × 0.5 mm that is placed in the anterior chamber through a small corneal incision and held there by a scleral anchor [Figure 6]. The implant is covered with a membrane that controls the release of travoprost so that it elutes continuously at therapeutic levels for long periods of time.^[38] A multicenter, randomized, and double-masked Phase II clinical trial was conducted to evaluate the safety and efficacy of the device at two travoprost elution rates. Findings were compared with topical timolol

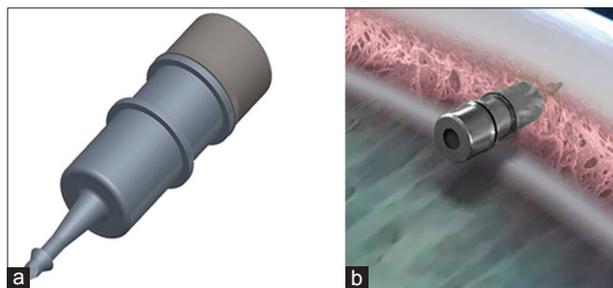


Figure 6: iDose travoprost. (a) The iDose device magnified. (b) Device anchored to the sclera. Courtesy of Glaukos UK, Ltd.

ophthalmic solution 0.5%. The interim 12-month results from 74 patients (49 iDose groups and 25 timolol groups) showed an IOP reduction of approximately 30% from baseline (7.9–8.5 mmHg). Mean glaucoma medication numbers in the iDose group ranged from 0.54 (fast eluting) to 0.56 (slow eluting) compared to 0.72 in the timolol group. There were no cases of hyperemia. A prospective, multicenter, randomized, and double-blinded Phase III trial is pending.^[39]

OTX-TIC

The OTX-TIC (Ocular Therapeutix, Bedford, MA, USA) is a bioresorbable implant containing micronized travoprost. The implant is injected intracamerally into the anterior chamber and is designed to release the drug over a period of 4–6 months. Preclinical studies in beagle dogs demonstrated an appropriate safety profile, maintenance of therapeutic drug levels in the aqueous humor, and IOP reduction. The first patient was enrolled to the open-label, proof-of-concept Phase I clinical trial in May 2018.^[40]

PA5108

The PA5108 (PolyActiva, Melbourne, Australia) is a rod-shaped implant placed in the anterior chamber through a clear corneal injection with a 27G needle. It contains latanoprost free acid (LFE) that is continuously eluted for at least 6 months. The PA5108 is designed to biodegrade to non-toxic products as soon as the treatment period is over.^[41] In a preclinical study in dogs of 3 LFE implant models, including the PA5108, IOP was found to be reduced at 10, 19, and 34 weeks compared with latanoprost 0.005% ophthalmic solution and placebo implants. The implants were well tolerated.^[42] A Phase I safety and tolerability clinical trial are ongoing.^[43,44]

DE-117

In 2016, Kim *et al.* were the first to report success with an intracameral DE-117-loaded polycaprolactone (PCL) implant, inserted to the anterior chamber (AC) through a clear corneal incision, for the treatment of glaucoma.^[45] In a more recent study in 16 normotensive rabbits, the same group found a statistically significant IOP reduction in eyes implanted with the DE-117 PLC compared with untreated eyes and placebo PCL devices.^[46]

Tolerability was good and rates of iris trauma and hyphema during the implantation procedure were lower (19%) than in the previous study (29%). One DE-117 implant migrated to the angle, but this had no obvious effect on its activity. One rabbit in the placebo group acquired partial corneal opacification and neovascularization in the treated eye.

Nanosponges

Nanosponges are nano-sized particles in the shape of red blood cells that are loaded with a drug and injected into the body. Most research on the use of nanosponges has focused on infectious diseases. In 2015, Lambert *et al.* compared intravitreally injected saline to intravitreally injected brimonidine-loaded or travoprost-loaded nanosponges in the eyes of hypertensive mice.^[47] IOP was reduced by 12–30% for 6 days in the brimonidine-loaded nanosponges arm ($P < 0.02$) and by 19–29% for 4 days in the travoprost-loaded nanosponges arm ($P < 0.02$). The nanosponges released the drugs in a linear, continuous pattern for 32 days.

Supraciliary Microsphere Delivery

In 2016, Chiang *et al.* published the results of their preclinical study of supraciliary injection of brimonidine-loaded poly(lactic acid) microspheres in New Zealand white rabbits.^[48] Two formulations of brimonidine microspheres (high and low dose) were administered, and there were two control groups: One received topical brimonidine in the form of eye drops (Alphagan®; positive controls) and the other was injected with an empty microsphere (negative controls). The results showed an IOP reduction of 6 mmHg in the study groups compared with 2 mmHg in the positive control group and no reduction in the negative control group. The reduction in IOP continued for 14 days in the rabbits given the low-dose formulation and 33 days in the rabbits given the high-dose formulation.

Discussion

The development of sustained drug delivery platforms marks the beginning of a new exciting era in the treatment of glaucoma for both patients and caregivers. The release of therapeutic levels of anti-glaucoma drugs over several months is intended to provide continuous stable drug levels in the eye over a relatively long period of time. This offers several advantages over the administration of topical IOP-lowering drugs, the current mainstay of glaucoma treatment: Slowing or preventing disease progression; lessening the need for strict patient compliance required with topical eye drops; and reducing the number of clinic appointments for patients. In addition, some of the devices are biodegenerative and do not require removal at the end of the treatment period. Thus, overall, these devices have the potential to improve both the preservation of vision and general patient well-being.

The novel platforms described in this article are in different stages of research – from *in vitro* evaluations to preclinical animal models and up to Phase III clinical studies. Some devices that are in the more advanced stages of research, such as the Bimatoprost SR, may be launched as early as 2020.^[49] They are expected to be a game changer in both the clinical management and prognosis of glaucoma as we know it today.

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How to cite this article: Shouchane-Blum K, Geffen N, Zahavi A. Sustained drug delivery platforms – A new era for glaucoma treatment. *Cli Exp Vis Eye Res J* 2019;2(1):22-29.

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