The best glaucoma drops in the world are effective only when the patient takes them. Patients often grossly overstate their compliance, and two-thirds of newly treated patients discontinue their use of drops after 1 year. To make matters worse, some patients demonstrate their best compliance just before an appointment, a form of white coat syndrome used to achieve a positive result for their visit. However, this serves only to create a false sense of security for the patient and the physician.

Sustained-release drug delivery options come in many varieties, but they are all founded on a common principle: A single application of drug should last for a prolonged period of time. Depending on the option, sustained-release drug delivery can last from weeks, to months, to even a year. A staggering number of sustained-release drug delivery innovations are in various stages of development (Figure 1). This article presents an overview of the overarching categories and a few promising options within each.

**GEL-FORMING DROPS**

Pentablock copolymer gels can be used as drug carriers. The SoliDrop (Otero Therapeutics) is one such gel-forming drop. When the drop comes into contact with the ocular surface, heat causes it to become a viscous gel that sits in the lower fornix and releases drug over weeks. Preclinical investigations using brimonidine in a rabbit model suggest that a single SoliDrop can sustain levels of drug similar to standard topical brimonidine for 28 days. (Editor’s Note: For more on the SoliDrop, see pg 66.)

Some gel-forming drops release 30% to 40% of drug upon instillation and then trail off. This burst effect and variable drug release remains one of the challenges in the development of viable gel-forming drug options.

**SURFACE IMPLANTS**

Surface implants can be inserted or removed by the patient or a technician, and they have the advantage that a patient will generally be aware if the device becomes dislodged. These implants must be large enough to carry an adequate supply of drug, and this, in turn, can lead to symptoms of irritation. In addition to mechanical side effects from the implant, one must also expect the usual side effect profile from the drugs released: for example, conjunctival injection with a prostaglandin analogue.

Latanoprost-eluting contact lenses are continuous-wear contact lenses with an embedded membrane containing latanoprost. In a study in monkey eyes, these lenses delivered levels of latanoprost that exceeded those of topical therapy at 1 month after instillation. Latanoprost-eluting contact lenses are designed to be worn overnight, and drug levels show a rapid trail-off if they are removed.

The Topical Ophthalmic Drug Delivery Device (TODDD, Amorphex Therapeutics) is a soft surface implant placed in the upper fornix. The TODDD can be loaded with a drug in polymer form that can be released over a prolonged period of time. Early clinical investigation in five patients demonstrated that a TODDD containing timolol could sustain therapeutic levels for 180 days.

The Bimatoprost Ring (Allergan; formerly Healis, ForSight) is a 1-mm–thick ring with a diameter of 24 to 29 mm. It is placed in the fornix and releases bimatoprost over 6 months. In a phase 2 trial in 130 patients, the Bimatoprost Ring demonstrated 20% IOP reduction and 89% retention at 6 months, which was not noninferior to timolol. The device was generally well tolerated, although 21% of patients noted mucus production and 7% complained of irritation.

**PUNCTAL PLUGS**

Drug-eluting punctal plugs are more comfortable than surface implants. However, their small size means less drug can be carried, and, therefore, their IOP lowering effect tends to be more modest.
with a shorter duration of action, usually 3 months. Additionally, a patient might not realize if a punctal plug falls out.

The OTX-TP (Ocular Therapeutix) is a cylindrical punctal plug that contains preservative-free travoprost. It expands when hydrated after implantation and releases drug over 3 months. Eventually, the plug is resorbed and drains into the nasolacrimal duct. Although the OTX-TP sits below the punctum, it contains fluorescein to allow visualization at the slit lamp. Phase 2 studies demonstrated 88% retention at 75 days and slightly less IOP lowering than timolol at 90 days. (Many of the plugs had dissolved by 90 days.)

The Evolute (Mati Therapeutics) is an L-shaped punctal plug with a latanoprost core; it is designed to create unidirectional flow into the tear film and therefore reduce systemic absorption. Phase 2 studies showed a 20% reduction in IOP at 3 months with 92% retention.

**Subconjunctival Implants**

Durasert (EyePoint Pharmaceuticals) is a 3 mm x 0.3 mm biodegradable implant that can be placed in the subconjunctival space at the slit lamp. It is based on the same platform as the Iluvien fluocinolone acetonide intravitreal implant (Alimera Sciences), with a transparent polymer tube that releases latanoprost over 12 months. Phase 1 and 2 trials are under way.

**Injectables**

Sustained-release compounds can be injected into a variety of locations, including the subconjunctival, suprachoroidal, and intravitreal spaces. Injectable sustained-release compounds are slightly different from injectable devices in that there is no solid reservoir for the drug. With injection, these compounds bypass the ocular surface; therefore, less drug is required to reach therapeutic concentrations, and side effects are minimized. They can last up to 6 months.

IBI-60089 (EyePoint Pharmaceuticals) is a subconjunctival injection of sustained-release latanoprost housed in the company’s biodegradable Verisome platform carrier. IBI-60089 may provide 6 months’ duration from one injection. Its sister product for uveitis (IBI-10090) is being evaluated in a phase 3 trial.

Clearside Biomedical has developed a microneedle injector designed to pass through the sclera and deliver drugs directly into the supraciliary space. The company has teamed up with Santen to produce a sustained-release compound designed for injection into the supraciliary space using this microneedle technology. A rabbit study of a single supraciliary injection of brimonidine using a microsphere vehicle demonstrated a 6 mm Hg IOP drop sustained over 1 month. Prostaglandin analogues, which target the ciliary body, may pair particularly well with supraciliary microneedle injection.

Graybug Vision is developing a drug-encapsulated microparticle that could be injected subconjunctivally or intravitreally. Once inside the eye, the microparticle coalesces into a visible implant that can then deliver medication. The carrier has the potential to release drug over a 6-month period and may be able to deliver combination therapies.

**Intracameral Implants**

Intracameral implants release drug from a physical reservoir. Although implantation of these devices requires an ophthalmologist and is more invasive than some of the aforementioned options, they are attractive because of their favorable side effect profiles. Surface therapies must pass through layers of tissue before reaching their target and therefore require a large concentration of drug; in contrast, intracameral implants bypass the surface and can work with lower drug amounts, resulting in fewer drug-related side effects. Patients require monitoring after injection because the drug action trails off at varying rates in different people. Some implants biodegrade slowly, leaving behind residual material in the anterior chamber for months or years.

Bimatoprost SR (Allergan) is a biodegradable implant injected into the anterior chamber using a 27-gauge needle. In phase 1 and 2 studies, a single Bimatoprost SR implant showed similar efficacy to topical bimatoprost 0.03% at 4 months, and in 71% of patients this effect lasted 6 months. Phase 3 trials are under way.

Travoprost XR (Envisia Therapeutics) is another biodegradable anterior chamber implant. In a phase 2 study, the implant demonstrated 25% IOP reduction and noninferiority to timolol for 11 months after a single injection.

The iDose (Glaukos) is an implantable reservoir housed on a titanium implant secured in the angle. The reservoir releases travoprost through a membrane over 1 year, and the reservoir portion of the implant can be removed and replaced. A phase 2 study of the iDose demonstrated 30% IOP reduction for 12 months, and a phase 3 study is being planned.

**Intrascлярal Implants**

The Ophthalmic MicroPump (Replenish) is a device that is surgically implanted onto the sclera and resembles the plate of a tube shunt. It contains a reservoir and small computer. Connected to the plate is a small intra-
scleral tube that delivers nanoliter doses of medication into the eye. A one-way valve prevents retrograde flow back into the reservoir. The device is wirelessly chargeable and programmable, and the reservoir can be refilled. Development is currently preclinical. (Editor’s Note: For more on the Ophthalmic MicroPump System, see pg 67.)

**SUMMARY**

A wide spectrum of sustained-release drug delivery options are in development. Minimally invasive classes of devices such as gel-forming drops, surface implants, and drug-eluting punctal plugs offer convenience but shorter durations of action, side effect profiles similar to those of topical drops, and less efficacy than some of their more invasive counterparts. Moderately invasive options such as subconjunctival implants and injectables reduce the side effect profile and provide more efficacy, but they cannot be instilled by the patient. More invasive options including intracameral implants and intrascleral implants may provide longer-lasting and more efficacious therapy but must be implanted by an ophthalmologist.

Many great technologies never make it into surgeons’ hands due to factors beyond their clinical promise. A large number of devices discussed in this article have completed successful phase 2 trials and have earned support for the phase 3 trials required for their approval and commercialization. We can therefore be hopeful that several of these technologies will emerge as part of the glaucoma treatment paradigm in the future.

These technologies can help address compliance and adherence issues that have hindered our success in preventing blindness from glaucoma. Although there is no doubt that microinvasive glaucoma surgery technologies are shaping the glaucoma treatment landscape today, it is possible that drug delivery technologies will be a main driver shaping glaucoma treatment tomorrow.


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