A refillable microfabricated drug delivery device for treatment of ocular diseases†

Ronalee Lo,[a] Po-Ying Li,[b] Saloomeh Saati,[c] Rajat Agrawal,[c] Mark S. Humayun[a,c] and Ellis Meng*[a]

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An implantable manually-actuated microfabricated drug delivery device was demonstrated as a new approach for delivering therapeutic compounds to ocular tissue in acute *in vitro*, *ex vivo*, and *in vivo* studies.

Delivering therapeutic compounds into the body in a precisely controlled and targeted manner is an ongoing challenge. Ocular drug delivery is necessary to slow disease progression but is especially difficult due to physiological barriers, space limitations in and surrounding the eye, and trauma to the eye resulting from invasive therapies. If left untreated, chronic retinal diseases such as glaucoma, age-related macular degeneration, diabetic retinopathy, and retinitis pigmentosa can lead to irreversible blindness.[1] Currently available treatment methods include topically and orally administered medications, intraocular injections, surgical intervention, and biodegradable implants. However, these treatments are limited by minimal drug diffusion to the target tissues, tissue trauma, and side effects.

We present the first microfabricated, all-polymer ocular drug delivery device.[2] This prototype features a refillable drug reservoir from which targeted delivery is provided to intraocular tissues *via* a valved flexible cannula (Fig. 1). The refillable reservoir offers key advantages over existing ocular drug delivery systems: (1) only a single surgical intervention is required; (2) functional lifetime of the device is extended without increasing the overall size; (3) in contrast to sustained delivery counterparts which need to be removed and replaced when the infused drug has been depleted, the refillable drug delivery device can be replenished without significant surgical intervention; and (4) the drug regimen can be altered on an as needed basis, including replacing the drug with new, advanced pharmaceutical solutions.

The drug delivery device was formed by assembling three layers of molded polydimethylsiloxane, or PDMS, (Sylgard 184, Dow Corning, Midland, MI, USA). Assembled devices consisted of a refillable reservoir, cannula, normally-closed check valve, support posts, and suture tabs (see electronic supplementary information, ESI, for device dimensions).† The

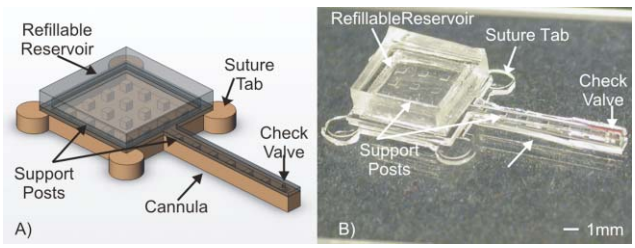

Fig. 1 (A) Device illustration and (B) assembled device photo. The main components (refillable reservoir, cannula, normally-closed check valve, support posts, and suture tabs) are indicated.

drug reservoir was placed beneath the conjuntiva and sutured to the sclera between the rectus muscles. The transscleral cannula was directed intraocularly *via* a surgical tunnel in the sclera (3 mm posterior to the limbus) and the cannula tip was placed into either the anterior or posterior segment of the eye in close proximity to the target treatment site associated with the disease being managed (Fig. 2). Sutures were used to close and seal the scleral tunnel opening around the cannula.

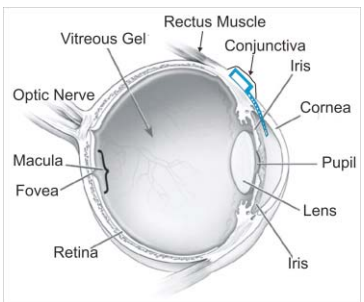

Fig. 2 Illustration of device placement on the eye; temporal placement provides easier access for refill and improves patient comfort. Here, the anterior segment configuration is shown (*i.e.* glaucoma treatment). Image modified using image courtesy of National Eye Institute, National Institutes of Health.

Drug solution was dispensed through the valved cannula following manual depression of the reservoir; the internal reservoir pressure must increase beyond the check valve cracking pressure to permit drug flow through the valve orifice. Flow ceased after the driving pressure was removed and the valve closed preventing bodily fluids from backflowing. Support posts were positioned along the length of the cannula and arrayed in the reservoir as a precaution to prevent the top and bottom walls from collapsing due to stiction between these surfaces.[3]

The PDMS components were molded using a soft-lithography process with silicon and acrylic masters. 4″ silicon wafers were

[a]*Department of Biomedical Engineering, Viterbi School of Engineering, University of Southern California, *1042 Downey Way- DRB-140, Los Angeles, CA, USA. E-mail: ellis.meng@usc.edu; Fax: +1-213-821-3897; Tel: +1-213-740-6952*
[b]*Ming Hsieh Department of Electrical Engineering, Viterbi School of Engineering, University of Southern California, Los Angeles, CA, USA*
[c]*Department of Ophthalmology, Doheny Eye Institute at the Keck School of Medicine, University of Southern California, Los Angeles, CA, USA*
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etched to create masters for the bottom and middle layer molds that form the base layers of the drug delivery platform. The top layer, or reservoir cap, was formed from a conventionally-machined acrylic master. An illustration of the fabrication process can be found in the ESI.†

Silicon masters were fabricated using deep reactive ion etching (PlasmaTherm SLR-770B, Unaxis Corporation, St. Petersburg, FL, USA) to create 100 μm and 250 μm deep features in the bottom and middle molds, respectively. PDMS mixed in a 10 : 1 base to curing agent ratio was poured into the silicon masters, degassed under vacuum, and cured (1 h at 70 °C). Molded PDMS sheets were carefully removed from the master and individual replicas were separated using a fine-tipped blade. The check valve was formed by cutting a hole, 305 μm in diameter, in the middle layer at the end of the cannula. This hole was aligned over the last support post of the bottom layer to create a normally-closed check valve.

The acrylic master for the top layer was made by securing Plexiglas squares onto a glass slide using epoxy (Loctite Professional Epoxy, Henkel Consumer Adhesives, Inc., Avon, OH, USA). The interior volume of the reservoir was defined by conventionally-machined Plexiglas squares; a target internal volume of 50 μL was obtained using 6 mm × 6 mm squares cut from a 1.59 mm thick Plexiglas sheet (actual volume 57.15 μL). PDMS was poured over the acrylic masters, degassed, and partially-cured for 30 min at 70 °C. Reservoirs were individually separated from the molded PDMS sheet.

The bottom and middle PDMS layers were aligned and irreversibly bonded by oxygen plasma surface modification. The partially-cured top layer was then assembled and the entire device was allowed to fully cure at room temperature (12 to 24 h). A layer of uncured PDMS was applied to the device perimeter to enhance bond strength between device layers and produce a mechanically robust structure able to survive surgical handling.[4,5] This reinforcing layer was cured (1 h at 70 °C) and excess PDMS was carefully removed.

The ocular drug delivery device was filled and refilled by piercing the reservoir membrane with a syringe needle. The device lifetime is dependent on the ability to repeatedly refill the device and on the integrity of the punctured membrane. A smaller needle diameter prolongs the lifetime of the reservoir; however, the needle must be stiff enough to puncture both the conjunctiva covering the device and reservoir membrane with ease. Given these tradeoffs, 30 G needles (305 μm outer diameter) were selected and two needle tip types (coring and non-coring) were investigated.

PDMS membranes were punctured *in vitro* with both needle types. The needle insertion points as well as the needle track cross-sections were compared. SEM images of both needle tips were taken to show the needle tip shape (Fig. 3A). The non-coring needle displaced material as it penetrated the membrane, whereas the coring needle removed a cylindrical plug from the membrane. After needle removal, the displaced material around the non-coring needle was restored to its original location, effectively re-sealing the tear, whereas a hole was left by the coring needle (Fig. 3B,C). Thus, the 30 G non-coring needle was selected as the refill needle.

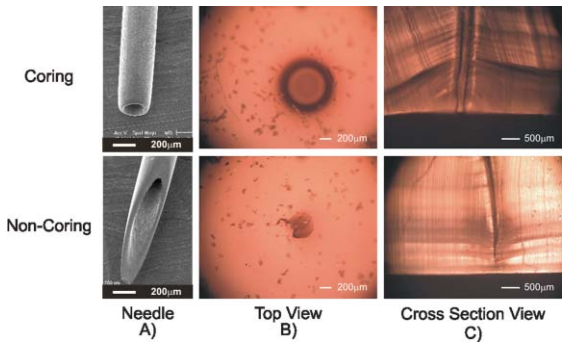

Fig. 3 Comparison of 30 G coring and non-coring needles. (A) SEM images of the needle tip, (B) top view of the needle puncture site in a PDMS slab and (C) cross sectional view of the needle track.

The puncture location on the refillable reservoir must be able to withstand a pressure gradient without leaking. Average intraocular pressure (IOP) is 15.5 ± 2.6 mmHg (mean ± SD), however, glaucoma patients can have elevated IOPs (typically 21 to 35 mmHg, higher values are possible due to temporal fluctuations or inflammation, such as glaucomacyclitic crisis).[6,7] The mechanical integrity of punctured PDMS was characterized by piercing PDMS membranes (250 μm and 670 μm thick) with a 30 G non-coring needle 8, 12, and 24 times. The punctured membrane was placed in a custom jig with pressurized water applied to one side of the membrane and a 50 μL calibrated pipette (Clay Adams, Parsippany, NJ, USA) attached to the other side. Pressure was increased in 0.1 psi (0.69 kPa, 5.17 mmHg) increments every 10 min until water leakage was observed by monitoring the pipette. A wide range of testing pressures well above normal and abnormal IOP values were applied.

The membranes were punctured repeatedly in the same location and evaluated. Puncture events through the same site represented the worst-case scenario where each subsequent puncture can cause further damage to the puncture location on the membrane. A summary of leakage pressures for both membrane

Table 1 Summary of leakage pressures for PDMS membranes punctured with a 30 G non-coring needle (mean ± SE, $N = 4$)

Number of punctures	250 μm membrane leakage pressure	670 μm membrane leakage pressure
8	1.01 ± 0.1 psi (6.96 ± 0.7 kPa, 52.23 ± 5.2 mmHg)	15.40 ± 1.5 psi (106.18 ± 10.3 kPa, 796.41 ± 77.6 mmHg)
12	0.93 ± 0.2 psi (6.41 ± 1.4 kPa, 48.09 ± 10.3 mmHg)	4.24 ± 0.6 psi (29.23 ± 4.1 kPa, 219.27 ± 31.0 mmHg)
24	0.64 ± 0.1 psi (4.41 ± 0.7 kPa, 33.10 ± 5.2 mmHg)	4.45 ± 1.4 psi (30.68 ± 9.7 kPa, 230.13 ± 72.4 mmHg)

thicknesses is presented in Table 1. The leakage pressure in both membranes decreased with additional punctures. The leakage pressure associated with the thicker membrane leveled out after 12 punctures, suggesting subsequent punctures did not induce further damage. As expected, higher pressures were necessary to induce leakage across the thicker membranes, however, the increase in leakage pressure was not linearly proportional to the increase in membrane thickness, suggesting a substantial improvement in mechanical integrity with additional thickness. In all but one setup, punctured membranes had leakage pressures higher than normal or abnormal IOPs. This experiment was conducted under laboratory conditions and the results may differ when the material is exposed to biological conditions. However, these results provide a baseline for estimating the necessary refill membrane dimensions to withstand IOP ranges.

The ability to refill the device significantly increases the device lifetime. Clinicians have suggested a practical refill frequency of no more than once every 3 months, with an associated 50 to 500 nL daily dosage volume to accommodate a wide range of possible drug regimens. A 50 μL reservoir can deliver 1000 doses of 50 nL or 100 doses of 500 nL, resulting in a refill rate of once every 33 or 3 months, respectively. A 3 month refill frequency with a maximum of 24 possible refills results in a device lifetime of 6 years.

In vitro, *ex vivo* and *in vivo* studies were conducted to demonstrate the feasibility of drug delivery into the eye. All animal procedures were approved by the Institutional Animal Care and Use Committee at the University of Southern California, Los Angeles and performed in conformance with the *Guide for Care and Use of Laboratory Animals* (National Institutes of Health).

Refill and device function were first verified *in vitro*. Then, enucleated porcine eyes were used to develop the appropriate surgical procedure for securing the device to the eye and placement of the cannula into the anterior chamber. Following the surgical procedure, device functionality was demonstrated *ex vivo* through repeated dispensation trials of dyed water followed by reservoir refill *via* a 30 G non-coring needle. Following several successful *ex vivo* trials, *in vivo* directed delivery of dyed water into the anterior chamber of male Dutch Belted pigmented rabbit eyes was confirmed.

Acute drug delivery was investigated using 10% phenylephrine solution; phenylephrine delivery enables real-time physiological verification of drug delivery by inducing rapid pupil dilation. Surgical sham devices were also fabricated and tested to aid in rapid prototyping of the device to incoporate improvements in device size, shape, or component placement. Identical 22.5 μL volumes were delivered by conventional intraocular injection (30 G needle and control eye) and our drug delivery device, and then pupil dilation for each case was compared.

The drug delivery device and surgical sham were secured to the sclera and the cannula was directed into the anterior chamber through a limbal incision or scleral tunnel, respectively (see ESI for description of surgical technique).† Baseline pupillary diameters (vertical and horizontal) measurements were taken prior to device dispensation. The phenylephrine was delivered into the eye by depressing the reservoir with surgical forceps or cotton swabs (see ESI for description of the experimental setup).† After dispensation, pupil diameter measurements were taken and compared to baseline values. A summary of resulting pupillary diameters is found in Table 2.

The control eye exhibited a greater pupillary diameter change compared to the other delivery mechanisms even when a smaller drug volume was used. Minimal leaking occurred during intraocular injection; it is well known that punctures <1 mm diameter are self-sealed. For both the device and the surgical sham, drug contact with the iris was diminshed due to the existence of leakage paths around the cannula. Sutures are unable to completely seal the limbal incision around the cannula in the device. A scleral tunnel reduces leakage around the cannula, however, in the unvalved surgical sham, drugs can backflow into the sham.

This manually-controlled drug delivery device enables targeted delivery of pharmaceuticals to intraocular sites. Here, successful delivery of phenylephrine to the anterior segment was demonstrated; anterior segment delivery is of particular interest in the management of glaucoma. However, precise control of delivered drug volume in this delivery platform is limited by variations in the duration and force applied during manual dispensation. The next generation device will utilize the same delivery paradigm but replace manual actuation with electrolysis actuation to precisely pump the desired dosage volume.[8–10] Automated delivery at the expense of a more complicated device may be preferred to further improve patient compliance.

In summary, a prototype, manually-actuated, refillable ocular drug delivery device capable of targeted delivery was designed, fabricated, and tested. Device functional lifetime was extended compared to conventional dissolving ocular drug delivery implants by incorporating a refillable drug reservoir accessible with a 30 G non-coring needle. The device feasibility and functionality was demonstrated *in vitro*, *ex vivo*, and *in vivo.* Real-time physiological evidence of drug delivery was obtained in acute studies of phenylephrine delivery. Electronically-controlled pumping for precise dosage control will be integrated into the next generation

Table 2 Summary of *in vivo* phenylephrine delivery studies in rabbits including vertical and horizontal pupillary diameter changes

	Control (syringe)		Drug delivery device		Surgical sham	
Volume	22.5 μL		~22.5 μL		~70 μL	
Delivery mode	Injected through limbus		Cannula (limbal incision)		Cannula (scleral tunnel)	
	Vertical	Horizontal	Vertical	Horizontal	Vertical	Horizontal
Baseline	5 mm	4 mm	6.5 mm	6 mm	4.5 mm	4.5 mm
Following delivery	9.5 mm	9 mm	8 mm	7 mm	7.5 mm	7.5 mm
Total change	4.5 mm (90%)	5 mm (125%)	1.5 mm (23%)	1 mm (16%)	3 mm (66%)	3 mm (66%)

device for chronic treatment of glaucoma and other chronic ocular diseases. Chronic *in vivo* studies are being conducted to determine long-term biocompatibility and functionality, as well as determining any biofouling that may occur during long-term implantation. These microfabricated drug delivery devices offer many advantages over existing ocular drug delivery therapies and enable a new mode of drug delivery not possible with conventional therapies.

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