AN ELECTROCHEMICAL INTRAOCULAR DRUG DELIVERY DEVICE

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ABSTRACT

This paper presents the first implantable intraocular MEMS drug delivery device capable of being refilled. To avoid repetitive surgeries, a refillable reservoir constructed of silicone rubber is implanted and capable of withstanding multiple needle punctures necessary for drug refill. The device uses electrolysis-actuated pumping to provide long-term drug treatment at therapeutic levels, and a flexible parylene transscleral cannula for precise targeting of difficult-to-reach areas in the eye. This electrochemically driven micropump provides flow rates suitable for ocular drug delivery (pL/min to µL/min). An encapsulation packaging technique was developed for demonstrating device operation in acute surgical studies. Preliminary surgical results in ex vivo porcine eyes are presented.

INTRODUCTION

Precise and targeted drug therapy is critical in managing chronic intraocular diseases such as retinitis pigmentosa, age-related macular degeneration, diabetic retinopathy, and glaucoma [1]. Traditional routes of ocular drug administration include oral drugs, eye drops, and intraocular injection. With oral or topical methods, less than 5% of the medication is able to overcome physiological barriers to reach the intraocular space [2]. Intraocular injections achieve therapeutic concentrations by bypassing physiological barriers but suffer from low patient compliance. In addition, repeated intraocular injections required for long term therapy are associated with side effects such as hemorrhage, retinal detachment and cataracts [3]. Advanced ocular drug therapy is commercially available in the form of sustained-release implants. These implants contain a fixed amount of drug that is slowly released over time. Once the implant is depleted, it must be surgically removed and replaced. Due to the limitations of traditional methods of treatment, there is a need for advanced ocular drug delivery systems that are refillable, capable of targeted delivery, and provide accurate dosing.

Previously, we reported the first refillable, implantable, passive (un-powered) MEMS drug delivery device [4] showing the feasibility of implantable ocular drug delivery systems. This system contains a drug reservoir attached to a cannula that is implanted across the eye wall such that when the device is activated, drug is delivered directly to tissues in the vicinity of the outlet (Figure 1). Repeated activation eventually depletes the drug reservoir. Unlike conventional ocular drug delivery implants, this device was refillable, allowing long term therapy with only a single surgical intervention. Here, we present a drug delivery device in which an electrochemically-driven pump is integrated with the reservoir (Figure 2). In this configuration, programmable electronic control of drug delivery (intermittent or continuous) can be achieved.

Figure 1 Conceptual depiction of an implanted ocular drug delivery device (modified from [5]).

Figure 2 Cross section of drug delivery device depicting electrochemical pump operation.

DESIGN AND FABRICATION

The drug delivery device consists of an electrolysis pump, cannula, and drug reservoir (Figures 1-4). The drug is delivered through electrolysis actuation of aqueous pharmaceuticals stored in the reservoir. The electrochemically-induced phase change of water to hydrogen and oxygen gas increases pressure within the reservoir forcing drug through the cannula. Localized drug
delivery is achieved by inserting the flexible cannula into the eye and positioning the drug outlet at the site of therapy. Construction of the drug delivery system involves fabricating the pump and cannula on a silicon substrate and then combining it with the drug reservoir which was casted in silicone rubber.

Figure 3 Schematic diagram illustrating the components of the drug delivery device.

Figure 4 Drug delivery device shown without drug reservoir (1 mm wide cannula with 100x25 µm embedded microchannel).

Fabrication of the pump and cannula began with a silicon substrate with 4000Å of thermally grown SiO₂ (Figure 5). Then e-beam evaporated Pt/Ti (2000/200Å) was patterned to define interdigitated electrodes of the electrolysis pump (Figure 5A). The cannula footprint was defined by patterning the oxide layer and the exposed silicon was then roughend by XeF₂ etching. A sacrificial photoresist layer (5 µm) was applied to facilitate release of the cannula from the substrate (Figure 5B). To form the cannula structure, a layer of parylene C (7.5 µm) was deposited to form the base of the cannula (Figure 5C), then a photoresist sacrificial layer (25 µm) was deposited to define the channel height (Figure 5D), and a second parylene layer (7.5 µm) was applied to complete the cannula (Figure 5E). To pattern the final parylene/photoresist/parylene composite for the cannula, Cr/Au (200/2000Å) was used as a mask during oxygen plasma etching (Figure 5F) and later removed by wet etching. The entire wafer was cleaned in 5% HF dip and oxygen plasma. Then SU-8 was applied and patterned (70 µm) (Figure 5G). The sacrificial photoresist was then dissolved. The cannula was released and the remaining silicon beneath was removed by scribing and breaking the silicon away (Figure 5H).

Figure 5 Fabrication process flow for the pump and cannula substrate.

RESULTS AND DISCUSSION

Bench Top Testing
Flow rate and back pressure performance were obtained by using a custom laser-machined test fixture. Characterization of pump performance focused on the µL/min to µL/min flow rate range suitable for ocular drug delivery. 438 µL/min to 7 µL/min flow rates were measured under current-controlled electrolysis of 5 µA and 1.25 mA, respectively. Flow rate data was corrected to compensate for evaporation (~30 nL/min) (Figure 6). Normal intraocular pressure in humans range from 5-22 mmHg (15.5±2.6 mmHg (mean ± SD)) [6] whereas glaucoma patients suffer from elevated levels (>22 mmHg). Therefore, devices were evaluated while being subjected to physiologically relevant back pressures: 20 mmHg (normal) and 70 mmHg (abnormal) (Figure 7).
Figure 6 Current-controlled flow delivery after evaporation compensation (mean ± SE, n=4).

Figure 7 Flow performance under physiological back pressures (mean ± SE, n=4).

Pump efficiency, \( \eta \), for electrolysis actuation is defined as:

\[
\eta = \frac{V_{\text{experimental}}}{V_{\text{theoretical}}}
\]

where \( V_{\text{experimental}} \) is the total volume of the generated hydrogen and oxygen gases, and \( V_{\text{theoretical}} \) is the theoretical volume of the gas bubbles [7]. Pumping efficiency was observed to range from 24-49% and decreased with decreasing applied current (Figure 88). Overall, pumping efficiency was low due to gas recombination which was enhanced by exposure to platinum in the electrolysis electrodes. Pt catalysed recombination at a rate of 62 nL/min in this system (Figure 9).

Figure 8 Pump efficiency calculation.

Figure 9 Typical gas recombination behavior for platinum.

Device Assembly and Surgical Packaging

For surgical studies, the pump/cannula layer and drug reservoir were assembled into a complete device. A silicone rubber drug reservoir cap was bonded to the electrolysis pump by an encapsulation technique (Figure 1010). Silicone rubber was selected as the drug reservoir and packaging material because it is an effective adhesive sealing material [8] and can withstand multiple punctures by a non-corining syringe needle (30 gauge) [4].

Figure 10 Silicone drug reservoir (right) and packaged device with encapsulated drug reservoir and wires for electrolysis actuation (left).

The complete assembly process is shown in Figure 11. A silicone reservoir (Sylgard 184) was prepared by casting against a conventionally machined acrylic mold (cured at 65°C for 1 hour) (Figure 11A). The separated 6 mm x 6 mm silicone reservoir was aligned and placed on the pump/cannula chip. This stack is then placed on top of a silicone spacer. The pump/cannula chip also includes leads to supply current to drive the electrolysis reaction. The leads were attached to the electrode contact pads by using conductive epoxy. The assembly was placed in a Petri dish and the parylene cannula was immersed in DI water during device packaging to prevent it from being coated or clogged by silicone rubber during the encapsulation step. This assembly process exploits the hydrophobicity of silicone rubber. The stack was immersed in silicone and cured at
65°C for 1 hour. Finally, extraneous silicone material was cut from the device to complete the assembly (Figure 11G).

A

B

C

D

E

F

G

![Diagram](image)

Figure 11 Process flow for silicone reservoir fabrication and device assembly.

Surgical Testing

Preliminary \textit{ex vivo} surgical modeling in porcine eyes was performed in preparation for \textit{in vivo} device characterization. Surgical methods to insert the cannula and the effect of surgical handling on device integrity and operation were assessed. The cannula of an unassembled device was inserted through an incision at the limbus (between the cornea and the sclera) and directed into the anterior chamber (Figure 12) to determine ease of insertion. Future \textit{ex vivo} experiments are planned to verify device function prior to \textit{in vivo} demonstration of device operation in rabbit eyes.

![Image](image)

Figure 12 \textit{Ex vivo} testing of the device in porcine eye showing cannula inserted into anterior chamber of eye.

CONCLUSIONS

An electrochemically-driven implantable MEMS drug delivery device featuring integration of a pump with a drug reservoir and transcleral cannula was prototyped and tested. The bench top testing results demonstrate that this electrochemically-driven micropump can provide a wide operation range (pL/min to µL/min) suited to ocular drug delivery for the treatment of chronic diseases. Drug delivery under back pressures equivalent to normal and elevated intraocular pressures was also demonstrated. As expected, gas recombination decreased pumping efficiency. The encapsulation packaging technique developed completely seals the device and allows \textit{in vivo} and \textit{ex vivo} testing. Future work will focus on optimizing the electrolysis pump and the integration of a check valve to prevent back flow into the device.

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REFERENCES


