IMPLANTABLE PARYLENE MEMS FOR GLAUCOMA THERAPY

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Abstract-**An implantable glaucoma management system is presented for the first time. Glaucoma is an incurable disease characterized by gradual visual field loss that eventually results in blindness. Studies indicate that reduction of intraocular pressure reduces the rate of disease progress. A passive parylene MEMS pressure sensor and drainage shunt comprise a complete system for the detection and alleviation of elevated intraocular pressure. Tissue anchors for securing the pressure sensor to the iris have been developed to facilitate direct and convenient optical monitoring of intraocular pressure.**

***Keywords* – Glaucoma, glaucoma drainage devices, intraocular pressure sensor, parylene, tissue anchors**

I. INTRODUCTION

Millions of people worldwide are afflicted by irreversible vision loss attributed to glaucoma. There are often no signs or symptoms until vision loss is severe; estimates indicate that only half of the 3 million Americans with glaucoma are aware they have the disease [1]. The cause of the disease is not well understood and there is currently no cure. Glaucoma is a chronic disease and must be treated for life.

Glaucoma is characterized by pathological changes in the optic disc and nerve fiber layer of retina. Elevated IOP > 22 mmHg is known to be responsible for slowly killing the ganglion cell axons that comprise the optic nerve and is strongly implicated in the pathogenesis of glaucoma [2].

Evidence from large, prospective studies suggests that reducing IOP to normal levels (15.5±2.6 mmHg (mean±SD)) reduces the rate of disease progression [3, 4]. Glaucoma management options include medical therapy, laser surgery, incisional surgery, and glaucoma drainage devices (GDDs). Medical therapy lowers IOP by improving the outflow of aqueous humor (AH) or to reduce its production. Some surgical techniques attempt to stimulate AH outflow, however, the primary surgical strategy is to manage glaucoma by lowering the patients' IOP through removal of excess AH. Regardless of the technique that is employed, accurate real-time measurements of IOP and the ability to restore normal levels are critical in the treatment of this disease.

Glaucoma management typically starts from interventions that are the safest and least invasive. Inasmuch, medical therapy is the most widely used treatment initially. GDDs are used as a last resort in cases of refractory glaucoma or in patients who have not responded to previous treatment attempts. While GDDs can potentially lower IOP effectively, ophthalmologists are reluctant to use current GDDs due to high rates of complications.

II. CURRENT GLAUCOMA DRAINAGE DEVICES

All modern GDDs are based on the 1969 concept of the Molteno implant which consists of tube that shunts aqueous humor from anterior chamber to an external sub-conjunctival plate [5] . In the last 30-40 years, very few innovative advances in surgical operation or implant devices have occurred. Only two major modifications to GDDs have been introduced: (1) addition of a valve to resist outflow and reduce hypotony and (2) increase in the end-plate surface area to achieve lower IOPs.

GDDs are currently limited to the treatment of refractory glaucoma due to complications. The most significant complication of GDDs is postoperative hypotony (a condition where IOP is abnormally low, IOP <5 mmHg) [6]. During the early postoperative period, there is a lack of flow resistance prior to fibrous capsule formation around the end-plate resulting in hypotony, flat anterior chambers, choroidal effusions, and suprachoroidal hemorrhages. Strategies to avoid hypotony include performing the operation in two-stages to allow fibrous capsule formation, tube ligature, internal tube occlusion, and the development of valved GDDs. These solutions are not ideal and interestingly, current valved implants do not perform as advertised and do not eliminate the occurrence of these complications. Furthermore, the success rate of current GDDs decreases by 10-15% every year suggesting poor long term performance [2].

III. MEMS GLAUCOMA THERAPY

To the best of our knowledge, no one has fabricated a complete GDD or a passive IOP sensor using MEMS technology. MEMS technology offers several advantages over traditional approaches to glaucoma therapy including highly functional microfluidic systems that can be adapted to drug delivery and IOP management; miniaturized sensors suitable for implantation with precise and accurate readouts [7]; precision and batch fabrication.

The purpose of a GDD is to control and regulate IOP, however, current GDDs are lacking in function and in efficacy. These factors are partly attributed to suboptimal design and nonideal biomaterial selection. By leveraging polymer MEMS technology, all the components necessary for a GDD can be seamlessly integrated into a miniaturized, single-piece device that is biocompatible and minimizes complications. Our MEMS GDD is an implantable, passive parylene shunt to reduce and regulate IOP by controlling the removal of excess aqueous humor from the anterior chamber.

Until now, MEMS pressure sensors designed for the purpose of IOP sensing required electrical circuitry and hermetic sealing which severely limits their implementation. Also, tonometers fabricated using conventional techniques are not suitable for continuous IOP monitoring and cause a considerable amount of patient discomfort. They typically require contact with a patient's cornea, necessitating the use of anesthetics. We propose a new mechanical sensing paradigm for a passive and biocompatible parylene MEMS IOP sensor. Our sensor will be integrated with novel parylene/silicon tissue anchors such that the sensor platform will be implanted behind the cornea and attached to the iris without sutures. The mechanical structure has an integrated indicator tip that can be monitored through external optics to track changes in IOP.

Parylene is selected as the structural material for aforementioned components for its desirable properties, both as a biomaterial and a MEMS material. It is a USP Class VI material that is utilized for its biocompatibility, biostability, and low cytotoxicity. Parylene is a proven MEMS material [8-13] with excellent properties including low process temperature, low defect density, transparency, and chemical inertness. In addition, parylene technology accommodates multi-layer processing to produce highly functional structures and features. While biological environments are extremely corrosive to most MEMS materials, parylene is not affected as it cannot be degraded hydrolytically [14].

The combination of an implantable MEMS sensor and drain will make it possible to closely track a patient's IOP history and maintain IOP at normal levels. This constitutes a novel and complete diagnostic and therapeutic system for treating glaucoma.

IV. Parylene Glaucoma Drainage Device

GDDs must be designed to incorporate several physiological parameters. Aqueous humor is produced in the eye at 2.4±0.6 µL/min (mean±SD) and changes over the course of a day (morning: 3.0 µL/min; afternoon: 2.4 µL/min; evening: 1.5 µL/min). The resistance of conventional AH drainage tissues is ~3-4 mmHg/µL/min [3]. The minimal system requirements for a MEMS GDD are a shunt and pressure-sensitive valve to remove excess AH such that IOP is maintained between 5-22 mmHg.

A parylene shunt has been fabricated using a sacrificial silicon technology. A shunt mold is etched into a silicon wafer and parylene is deposited around the mold. Each shunt is removed from the master mold and the silicon is chemically removed. In Fig. 1, several types of shunts are shown with one end sealed off (~8×0.5×1 mm^3 and 10 µm thick wall). At the sealed-ends, remnants of the silicon mold are visible. This closed end is implanted into the anterior chamber of the eye where it comes into contact with AH. At this end of the shunt are several regions where the parylene has been etched down to 0.5 µm or less. When elevated IOP is detected these thinned regions can be punctured using a laser to allow excess AH to be released from the anterior chamber. Flow and pressure regulation is achieved by controlling the number of and time at which the punctures are made along the closed end of the shunt.

Like some commercially available GDDs, this parylene device does not prevent bi-directional flow; the laser puncture feature does allow flexibility in initiating treatment. Our next design will integrate a check valve to enforce one-way flow and mechanical barbs on the exterior of the tube to anchor the device and prevent slippage after implantation. Preliminary evaluation of these shunts by implantation into rabbit eyes also suggests the need for increased stiffness to facilitate handling and surgical insertion of these delicate tubes.

At physiological flow rates, pressure drops are negligible for the size of our shunt. Therefore, the majority of the pressure drop in the system will be concentrated at the valve. In order to promote drainage of AH out of the anterior chamber, the valve must be optimized to drain at a flow rate equal to the production of AH at elevated IOPs. It must open at IOP > 22 mmHg and close when IOP ≤ 22 mmHg to prevent hypotony. Current GDDs with valves have not performed as advertised and are unable to perform the shut-off function required after desired IOP levels are met. It is suspected that once the valves open, they never close and possibly account for some of the observed complications. Previously, we have demonstrated parylene valve that can be adapted to meet all the requirements for application to GDDs [15]. A new biocompatible, pressure-sensitive valve will based on this design will enable advanced glaucoma management by maintaining healthy IOP levels and achieving pressure-regulated shut-off.

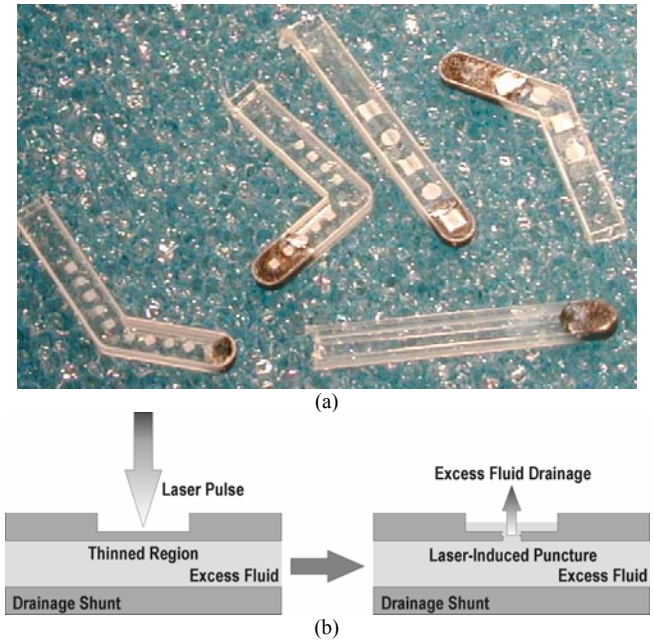

Fig. 1. (a) Parylene shunts with and without thinned regions. The dark region at the rounded tip is silicon that has been left to provide contrast for viewing. (b) Mechanism of AH release through laser-induced punctures in thinned regions.

V. Spiral-Tube Parylene IOP Sensor

Our mechanical pressure sensor is based on the principle of operation of a Bourdon tube [16] and consists of a centrally supported, free-standing parylene spiral-tube formed by a long, thin-walled toroidal channel (Fig. 2). An indicator tip is integrated at the end of the channel at the circumference of the spiral as a means for simple optical readout. A detailed report on the fabrication of the device is described in [17].

The hollow spiral channel forming the sensor is sealed at 1 atm as the gauge reference. When a uniform pressure difference is generated across the channel walls, a bending moment is created forcing an in-plane radial and angular deformation of the tube. When the external pressure is lower than the internal pressure in the channel, the spiral structure unwinds. When the external pressure exceeds the internal pressure, the spiral will further coil. This effect can be monitored by visually tracking the movement of the indicator tip. Deformation that results is linearly related to the applied pressure difference and can be correlated to environmental pressure, or in this case, IOP.

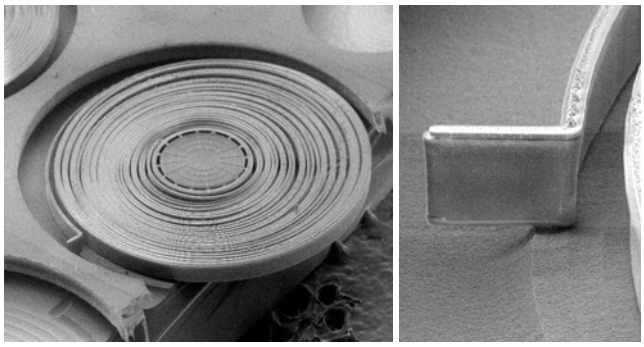

Fig. 2. SEM of passive, spiral-tube parylene IOP sensor (1 mm radius) and close-up of integrated indicator tip (6×100 μm)

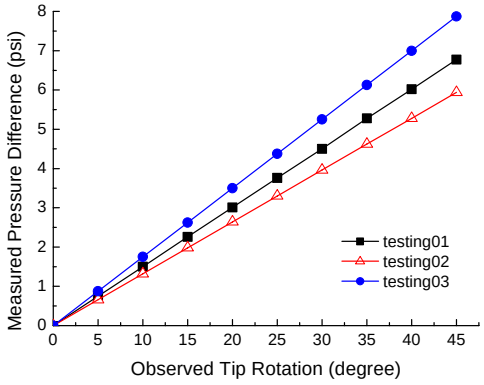

Fig. 3. Observed tip rotation in water under applied pressure.

Sensor operation has been verified in air, isopropyl alcohol (IPA), and water. Observed tip rotation is visually recorded with the aid of optical magnification as the environmental pressure is increased. The results for water are shown below (Fig. 3). Measured sensitivities are 0.22 °/mmHg (± 9% variation in rotation angles) in IPA and 0.13 °/mmHg in water (± 15% variation). Sensitivity of the pressure sensor can be tuned by changing the number of coil turns. Increased sensitivity can be achieved by increasing the number of coil turns, decreasing the thickness of the tube walls, and increasing the aspect-ratio profile of the tube.

Preliminary implantation studies in rabbits indicate that the spiral-tube structure lacks the necessary mechanical robustness to survive surgery. Currently, efforts to further reduce the overall device size and integration of a protective cap are underway to facilitate implantation. In addition to improving device reliability, design optimization is being investigated to increase sensitivity.

VI. Suture-less Tissue Anchors

Implantable devices require mechanical attachment to the biological environment. This is typically achieved by sutures, tacking, or stapling at the expense of increasing overall implant size through the addition of anchoring sites. Given the spatial constraints in the eye and to minimize damage, it is desirable to implant and secure our sensor and GDD without needing sutures.

The logical choice for placement of the IOP sensor to facilitate optical readout would be behind the transparent cornea on the iris. In order to monitor movement of the indicator tip, the sensor should be securely attached to the iris. The surface topology of the iris consists of numerous folds resembling hills and valleys that can accommodate alternative mechanical attachment methods. We fabricated and implanted two tissue anchoring prototypes consisting of Velcro-like arrays of parylene-covered silicon posts on the irises of rabbit eyes (Fig. 4).

Fabrication of the posts can be integrated with the IOP sensor process. To enhance the adhesion of parylene, anchors are patterned and etched at future post sites following [18]. Posts are then defined and etched using DRIE in a silicon substrate. Finally, the entire structure is coated with a biocompatible parylene layer.

The etched columnar anchors securely fastened silicon plates to rabbit irises. The plates remained fastened even after vigorous shaking imposed on the eye by the surgeon. The force required to dislodge anchored structures will be determined. Currently, these structures are being integrated on the backside of an IOP sensor substrate and will be used to hold the entire platform in place for visual inspection of IOP. Similar anchoring structures may also be applied to mechanically attach the GDDs.

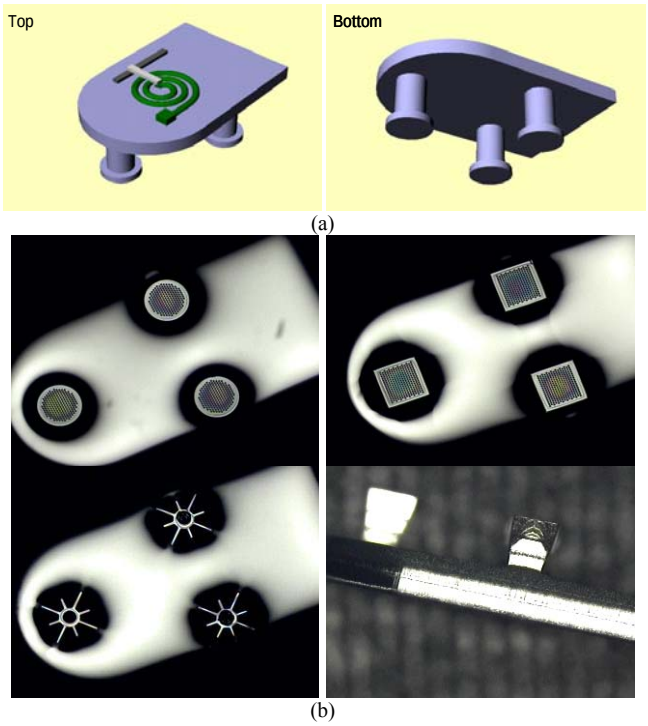

Fig. 4. (a) 3D illustration of IOP sensor on a silicon platform (1.5 mm × .75 mm) with integrated tissue anchors underneath. (b) Fabricated anchors showing different layouts and views (top and side). The circular anchor in the top left is 250 μm in diameter and 250 μm long. The square anchors measure 250 μm on a side and the radial arms in the lower left photo are 8 μm in width.

VII. Conclusion

Implantable parylene MEMS for complete management of glaucoma, including monitoring and therapy, are presented. Preliminary results of implanted system components into rabbits are extremely promising. Current work in progress includes careful examination of biocompatibility and implantation challenges and optimization of system components for application in humans.

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