Biodegradable Microfabricated Plug-Filters for Glaucoma Drainage Devices

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Biodegradable Microfabricated Plug-Filters
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Abstract—We report on the development of a batch fabricated biodegradable truncated-cone-shaped plug filter to overcome the postoperative hypotony in nonvalved glaucoma drainage devices. Plug filters are composed of biodegradable polymers that disappear once wound healing and bleb formation has progressed past the stage where hypotony from overfiltration may cause complications in the human eye. The biodegradable nature of device eliminates the risks associated with permanent valves that may become blocked or influence the aqueous fluid flow rate in the long term. The plug-filter geometry simplifies its integration with commercial shunts. Aqueous humor outflow regulation is achieved by controlling the diameter of a laser-drilled through-hole. The batch compatible fabrication involves a modified SU-8 molding to achieve truncated-cone-shaped pillars, polydimethylsiloxane micromolding, and hot embossing of biodegradable polymers. The developed plug filter is 500 μm long with base and apex plane diameters of 500 and 300 μm, respectively, and incorporates a laser-drilled through-hole with 44-μm effective diameter in the center.

Index Terms—Biodegradable plug-filter, glaucoma drainage device (GDD), hot embossing, laser drilling, micromolding.

I. INTRODUCTION

SEVERAL ocular diseases that cause increased intraocular pressure (IOP) and ultimately result in decreased visual field are collectively termed high-tension glaucoma. Elevated IOP (normal IOP is typically between 10 and 21 mmHg) may damage the optic nerve and result in permanent blindness. According to National Institutes of Health approximately 120,000 individuals are blind from glaucoma that accounts for 9% to 12% of all cases of blindness in the United States. The rate of glaucoma blindness is mainly attributed to the failure of early diagnosis and the limitations of the available treatment options.

The treatment provided for glaucoma is highly dependent on the progression of the disease. If the initial treatment with medication and/or laser surgery is not satisfactory, more invasive methods such as trabeculectomy and implantation of glaucoma drainage devices (GDDs) are performed [1]. The basic concept of all the GDDs currently available is very similar to the Molteno implant, first introduced in 1969 [2]. GDDs include a tube that is connected to an equatorial plate under the conjunctiva. This tube would create an alternate aqueous pathway from the anterior chamber (AC) that shunts the aqueous humor out of the eye to the end plate located in the equatorial region of the globe. The diverted aqueous humor is then removed through intercellular spaces and the lymphatic system. The use of GDDs as an alternative to trabeculectomy and cyclodepressive procedures in the management of glaucoma is increasing [3].

The GDDs currently used in glaucoma management can be classified into two main groups: 1) nonvalved devices that include Molteno (Molteno Ophthalmic Limited, Dunedin, New Zealand) and Baerveldt glaucoma implant (Abbott Medical Optics Inc., Abbott Park, IL). These devices contain a tube without any active resistance to regulate the outflow; and 2) valved devices that include the Ahmed glaucoma valve (New World Medical, Rancho Cucamonga, CA) and the Krupin slit valve (Hood Laboratories, Pembroke, MA). The second group incorporates a valve at the end of the tube that results in some restriction of outflow to the drainage plate [4]. It has been shown that the valved Ahmed glaucoma implant may not be as effective as the nonvalved devices (Molteno and Baerveldt) at lowering the IOP [5]–[8]. Goulet et al. demonstrated a significant rise in the IOP after 2 years with the Ahmed valve in spite of medications used to control the pressure. In the same time period, they also observed a higher failure rate with the Ahmed valve as compared to the Baerveldt shunts [5].

Nonvalved implants might be better in the long term but they inherently pose a higher risk of early postoperative hypotony due to excessive outflow since these implants rely on wound healing and fibrous bleb formation at the endplate to regulate the aqueous drainage. Once established, this fibrous capsulation provides sufficient resistance to outflow and control over IOP. The size of the end plate surface area and the thickness of the fibrous bleb determine the amount of fluidic resistance through the device. However, it takes a few weeks for the fibrous bleb to form. During this time period aqueous humor drains passively through the silicone tube without any measurable restriction. This problem of hypotony due to excessive drainage may lead...
Fig. 1. (a) Plug-filter inserted in a Baerveldt implant’s tube to regulate the outflow and (b) 3-D schematic of the microfabricated plug filter.

II. DESIGN AND FABRICATION PROCESS

A. Design

Fig. 1(a) shows a Baerveldt implant with a biodegradable filter plug inserted into its inlet silicone tube. It is instructive to calculate the pressure drop across the tube, if no flow restrictor is employed. Flow rates in the microtube are small enough to assume laminar flow, so the pressure drop due to friction for a cylindrical tube can be calculated by the Hagen–Poiseuille equation [14]:

\[ \Delta P = \frac{8\eta LQ}{\pi r^4} \]

where \( \Delta P \) is pressure drop across the tube, \( \eta \) is dynamic viscosity, \( L \) is length of the tube, \( Q \) is the flow rate, and \( r \) is the radius of the tube. Baerveldt implant contains a 0.30-mm inner diameter silicone tube that is 32 mm long [15]. When this device is implanted in the eye, unless the flow is restricted prior to the bleb formation, the pressure difference between the two sides of the tube (AC versus the atmosphere) will be 0.027 mmHg, causing severe hypotony (assuming a aqueous humor viscosity and flow rate of \( 6.92 \times 10^{-4} \text{ kg/m.s} \) [16] and 2 \( \mu\text{L/min} \) [17], respectively). Based on simple geometrical and fluid dynamics arguments, introducing a 500-\( \mu \text{m} \) long cylindrical plug with a 24-\( \mu \text{m} \) diameter through hole in the tube can reduce the pressure in the AC to the normal physiological range of 15–20 mmHg.

B. Fabrication Process

Fig. 1(b) demonstrates the 3-D schematic of the plug-filter. It has a truncated-cone-shaped geometry to facilitate insertion into the tube of commercial GDDs. The diameter and the length of the laser-drilled hole in the middle of the plug filter regulate the aqueous outflow after GDD implantation.

The fabrication process for the plug filter is depicted in Fig. 2. First, a truncated-cone-shaped micropillar array was fabricated using SU-8 (2100 series, Microchem Corporation, Newton, MA) photoresist. Since achieving 500-\( \mu \text{m} \) thickness with a single spin coat is challenging, three layers of repeated application followed by soft bake prior to the UV exposure were used to achieve the desired height [see Fig. 2(a)]. Then, the triple-layered SU-8 was overexposed from the backside through a 1-mm thick glass mask (6000 mJ/cm\(^2\) UV exposure dose) [see Fig. 2(b)]. This backside overexposure results in SU-8 pillars with a smooth sidewall at a certain angle [18] [see Fig. 2(c)]. The fabricated SU-8 mold was then treated with tridecafluoro-(1,1,2,2, tetrahydrooctyl)-1-trichlorosilane (United Chemical Technologies, Inc., PA) vapor to ease the removal of the subsequent polydimethylsiloxane (PDMS) layer. PDMS was next cast against the mold and cured at 110\( ^\circ \text{C} \) for 20 min [see Fig. 2(d)].

After peeling off the PDMS from the SU8 mold [see Fig. 2(e)] biodegradable plug-filters were fabricated by hot embossing. This was accomplished by pouring polymer powder on top of the mold and heating it up to 140\( ^\circ \text{C} \) in vacuum for 3 h [see Fig. 2(f)]. Due to the high viscosity of the biodegradable polymer, this vacuum heating is necessary to ensure that the polymer fills the holes completely and replaces the trapped air. Afterward, the PDMS mold was removed from the vacuum, placed on top of a hotplate (140\( ^\circ \text{C} \)), and biodegradable polymer was squeezed between the PDMS mold and another PDMS layer by applying 25-kPa pressure [see Fig. 2(g)]. This step is required for removing excess biodegradable polymer from the surface of the PDMS mold and separating individual plug filters [see Fig. 2(h)]. Finally, CO\(_2\) laser (Resonetics, Nashua, NH)
micromachining was used to drill a 24-μm diameter flow-regulating through-hole at the center of plug filter [see Fig. 2(i)].

Due to the high viscosity of biodegradable polymers, even at temperatures well above their glass transition (140–150 °C), both vacuum and high temperature are required to completely fill the PDMS mold. Fig. 3(a) shows an SEM image of a conical frustum-shaped SU-8 micropillar, with a base diameter of 500 μm and an apex diameter of 300 μm fabricated by the modified back-side exposure method [see Fig. 2(b) and (c)]. An optical image of an array of the microfabricated plug filters in the PDMS mold before laser drilling is shown in Fig. 3(b). The plug filters were laser drilled without removing them from the mold, so the PDMS mold acted as a package for the final device.

III. MATERIALS AND METHODS

We tested two different structural materials for fabrication of the biodegradable plug filter: PLGA (5050 DLG 4A, SurModics Pharmaceuticals Inc., AL) and poly-lactic-acid (PLA), (100 DL 7 E, SurModics Pharmaceuticals Inc., AL). It is instructive to compare the mechanical and degradation properties of these two structural materials that are summarized in...
Table I. As can be seen, by increasing the DL-lactide ratio in the PLGA, the glass transition temperature increased at the expense of longer degradation times. This is a well-known property of PLGA copolymers. For 100% PLA with a glass transition temperature of 56–60°C, the degradation time is about 5–6 months that is longer than what is required for the bleb formation. However, one can adjust the glass transition/degradation time of the biodegradable polymers by controlling their molecular weight and the end groups [19].

As will be discussed in Section IV, neither of these polymers can be used as the structural materials of the plug filter. One can use an alternative approach to overcome the low glass transition of the PLGA by coating the outer area of the plug filter with a biocompatible polymer such as SU-8, parylene, or an epoxy [see Fig. 4(a)]. This outer shell will provide mechanical support to the filter and prevent clogging of the holes. We coated the plug filter with SU-8 (UV-curing adhesive) by spinning the resist on a glass slide and rolling the plug filter against its surface (the shell thickness can be adjusted by controlling the spin rate).

However, to make the process batch compatible, a mold can be fabricated in silicon as depicted in Fig. 4(b). The mold can then be coated with PLA, SU-8, or UV-curing adhesive [see Fig. 4(c)] followed by stamping the plug filters against the coated mold [see Fig. 4(d)]. Fig. 4(e) and (f) shows optical images of the plug filter before and after coating with 50-μm thick UV-curable adhesive (Henkel, CT), respectively.

After fabrication, the plug filter was inserted into the open end side of a commercial Baerveldt implant silastic tube [see Fig. 5(a)]. Due to the conical shape of the plug filter, insertion can be simply done using a forceps [see Fig. 5(b)].

In vitro testing was conducted using phosphate buffered saline (PBS) (Sigma-Aldrich Company, MO) in a 37°C silicone oil bath to simulate the aqueous humor and body temperature. In this setting, the syringe pump acts as the aqueous humor inflow and the flask containing the valve serves as a sub-Tenon space. Fig. 6 shows the block diagram of the test setup. PBS solution was pumped into the GDD tube having a plug filter at constant
flow rate (2–3 μL/min) and backpressure was monitored using the MPX2010GP (Freescale, TX) pressure sensor. The pressure sensor was calibrated to account for the resulting hydraulic pressure caused by submerging the filter in the water. Labjack U12 (Labjack Corp. CO) was used for data acquisition. An optical photograph of the test setup is shown in Fig. 6(b). A magnified image is illustrated in Fig. 6(c), showing a needle connected to the GDD device floating in PBS solution. The upper left inset of this picture shows a closeup of the GDD device while the upper right inset shows the filter lodged inside the tube.

IV. RESULTS AND DISCUSSION

After successful fabrication of the plug filter, the first experiment was designed to confirm that the plug filter does not move inside the silastic tube at elevated pressures that can occur if the central hole is clogged. For this purpose, we inserted a PLGA plug filter with no hole in the silicone tube and PBS was pumped into the tube at the constant flow rate of 3 μL/min at 37 °C while the resulted pressure was monitored by computer. Fig. 7 demonstrates the resulted backpressure versus time. As depicted in the graph, pressure rose continuously until the point of a sudden drop due to pressure-created leaks in the test setup. We did not observe any movement during this period indicating that the plug filter can withstand pressures up to 160 mmHg. The slow rise time of the pressure in Fig. 7 is due to the air gap between the liquid and the pressure sensor. This is required since liquid cannot come into contact with the membrane of the pressure sensor.

In the next step, we calibrated the pressure versus flow rate of the plug filters using a room temperature setup. Fig. 8 shows flow rate versus pressure characteristics of plug filters made of PLGA having two holes, each with an apex and bases diameters of 40 and 85 μm, respectively.

Testing different filters resulted in similar characteristics showing the reproducibility of the experiment. However, as can be seen from the graph, flow rate at the pressure of interest (15–20 mmHg) is much higher than the expected value (30–40 μL/min as opposed to the physiological rate of 3 μL/min). This is mainly due to the large hole sizes of the plug filters. As illustrated in (1), flow rate is proportional to the fourth power of the hole’s diameter, which explains the resulted high flow rates in plug filters having holes with twice the diameter. In an effort to limit the flow rate, multiple plug filters can be used in series. As expected, this will increase the pressure drop in proportion to the number of devices (1). Based on these sets of experiments, we can define an effective hole diameter of 44 μm. This incorporates the effect of tapering due to laser microdrilling.

After calibration, we continued the characterization of the PLGA plug filter having two laser-drilled holes by inserting a plug filter into a silicone tube, pumping PBS with constant flow rate of 3 μL/min PBS at 37 °C, and monitoring the backpressure. The pressure versus time is shown in Fig. 9. As can be seen, the plug filter regulated the pressure for up to 2 days. However, the pressure started to rise after that, and elevated pressures above 600 mmHg popped out the plug filter from the tube. Observation of the filter under an optical microscope revealed that the plug filter was completely deformed and the holes were collapsed. This deformation can be explained by the low glass transition temperature of PLGA (42–48 °C, see Table I). Furthermore, PBS acted as a plasticizer and lowered the glass transition temperature even further, softening the PLGA at 37 °C. Since the diameter of the plug filter was chosen to be larger than the inner diameter of the GDD tube, a circumferential mechanical stress on the filter resulted in mechanical collapse of the holes in the softened PLGA.

One method to overcome the softening problem is to change the structural material of the plug filter. We explored other
commercially available biodegradable polymers with a higher glass transition temperature that can be used as the plug-filter’s structural material. As shown in Table I, PLA has a higher glass transition temperature (56–60°C). We also laser drilled only one hole in plug filters (rather than two holes in the previous samples) in an attempt to increase the flow resistance and raise the backpressure. Fig. 10 shows the pressure versus time graph of the new filter, when tested in similar condition and PBS flow rate was set to 2 μL/min. As can be seen, pressure was regulated and no increase in the pressure was observed for up to 15 days. However, pressure is lower than the desired value (15–20 mmHg) that is attributed to the larger hole size (effective diameter of 38 μm) than what was initially designed (24 μm).

V. CONCLUSION

In conclusion, a biodegradable plug filter was developed to test the feasibility of flow control in nonvalved glaucoma drainage devices. A batch-compatible fabrication process flow for fabrication of a self-packaged plug filter was discussed. A truncated-cone-shaped geometry was chosen to simplify the insertion of the plug filter into the GDD’s tube. In vitro results showed that plug filter made of PLA was capable of regulating the pressure for more than 15 days. However, plug filters made of 50/50 PLGA showed softening at body temperature resulting in the collapse of the through-hole after insertion into the tube. To address the softening issue in the PLGA plug filters, they were coated with SU-8 or UV-curing adhesive. These coated structures were capable of regulating the pressure up to 45 days that is long enough for bleb formation.

Although the degradation period of the selected biodegradable polymer (50/50 PLGA) is 3–4 weeks (see Table I) biodegradation kinetics can vary from few weeks to several months depending on numerous factors including device geometry. The degradation scheme of PLGA is bulk rather than surface erosion that means polymer breakdown takes place throughout the entire sample. This implies a sharp drop in pressure after plug-filter degradation rather than a continuous pressure loss throughout the process (see Figs. 10 and 11).

Further research is needed to optimize the size of the hole in order to achieve desirable IOP regulation. In addition, it is desirable to adjust the PLA/PGA composition to attain an appropriate glass transition/degradation time ratio. Finally, it is worth mentioning that inflammatory or red blood cells released into the aqueous humor after the operation could potentially clog the hole in the plug filter (although the possibility is low due to the large diameter of the hole, 24 μm). If clogging occurs during this period, eye drops or ablation of the plug filter with laser can be used to reduce the IOP and open the drainage path.

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REFERENCES


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