CHAPTER 3

INTEGRATION AND APPLICATIONS OF MICRO CHECK-VALVES FOR GLAUCOMA TREATMENT

Glaucoma drainage device (GDD) has been developed as an alternative solution to treat glaucoma patients who are resistant to normal glaucoma medications. This chapter presents the integrated parylene-C-tube-type micro-valved glaucoma drainage device incorporating micro-flow regulatory assembly, parylene-C protective tube and anchors. All components are designed to fit in a needle-implantable form factor for suture-less minimally invasive implantation through subconjunctival hypodermic needle injection.

A successful GDD can continuously drain out excess aqueous humor accumulated inside the anterior chamber and lower the intraocular pressure (IOP) to the range of 10–20 mmHg. On the other hand, to prevent hypotony happening, aqueous humor should be preserved inside the anterior chamber when a spike of high eye pressure happens (due to external impact). To accommodate these functions, a dual-valved GDD system capable of creating a “band-pass” pressure/flow-rate profile is proposed in this chapter. The parylene-C-tube-type GDD paradigm is developed to incorporate one normally closed (NC) and one normally-open (NO) valve that can regulate intraocular pressure (IOP) passively with no power consumption. The self-stiction-bonding NC check-valve which

has been introduced in Section 2.6 is adopted in this chapter to form the GDD due to its appropriate cracking pressure range. The NO valve will be further developed in Section 3.2 to complete the form factor of the proposed GDD system.

In addition, two types of "band-pass" micro-flow control assemblies are designed and developed to explore the different possibilities of the check-valve positions. The basic GDD type has both NC and NO valves fixed at the both ends of the parylene-C protective tube, while the modified GDD has a micro-flow regulating assembly which has adjustable distance of NC/NO valves. The adjustable NC/NO valves' distance enables ophthalmologists to optimize the check-valve positions in the GDD through *ex vivo*/*in vivo* implantation tests. In this section, a NO valve will be first introduced for later dual-valved GDD development.

In terms of the clinical implantation, the subconjunctival implantation with needle-inserted and suture-less surgical procedures is proposed for the new parylene-C-tube GDD. The biocompatible parylene-C-tube-type GDD can be minimally-invasively implanted under the conjunctiva using a #19-gauge hypodermic needle. A parylene-C fixation anchor is also developed to help the GDD anchor subconjunctivally after the implantation. The integrated GDD is first bench-top characterized and then delivered to the hospital for further *ex vivo* test to understand its biomedical feasibilities. Both bench-top *ex vivo* implantation results are shown and discussed in Sections 3.5 and 3.6, respectively.

3.1 Configuration of the "Band Pass" Flow-Rate Profile Dual-Valve GDD System

As shown in Figure 3-1, an ideal glaucoma drainage device should be capable of regulating the IOP to be below 20 mmHg while not causing hypotony (i.e., IOP < 5 mmHg) with time. Besides, the device should be closed if high IOP (e.g., > 50 mmHg) happens due to normal external interferences like eye rubbing or bumping. To realize the concept of this "band-pass" pressure/flow-rate profile, a dual-valve GDD system is proposed with an innovative micro-flow control design: one NC check-valve is chosen to achieve the necessary low-pressure-off response and one NO valve is chosen to behave as a high-pressure stopper.

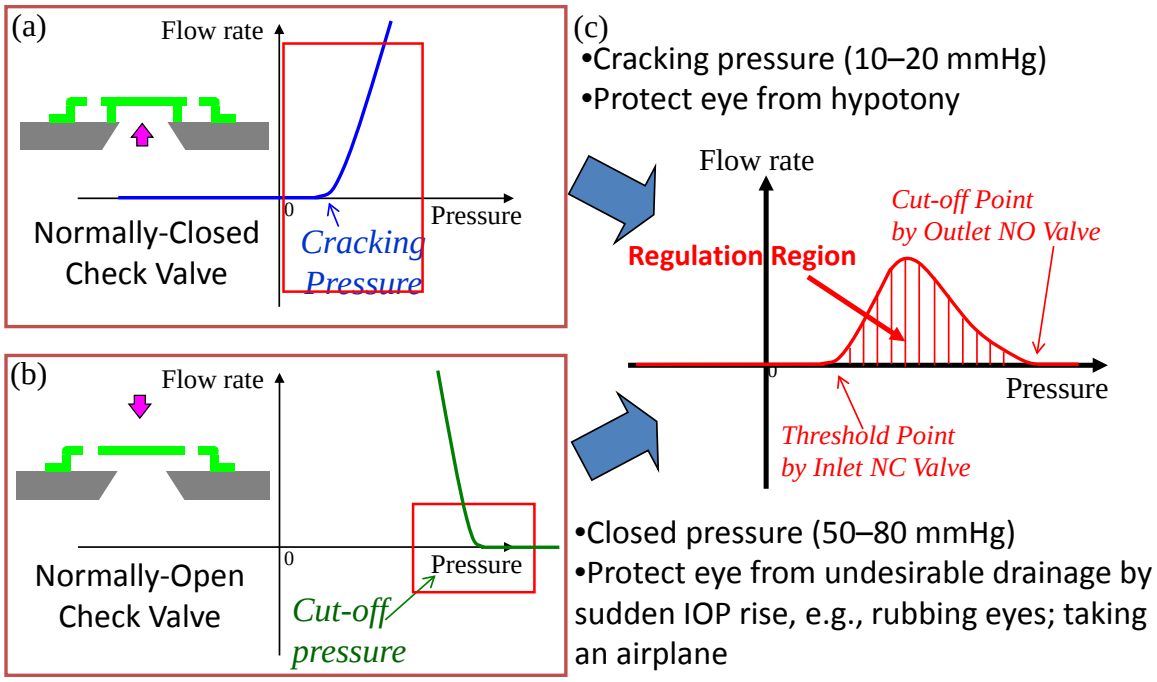

Figure 3-1: Concept of the "band pass" flow-rate profile of the proposed GDD system comprising (a) an NC check-valve, and (b) an NO valve to achieve (c) a band pass flow-rate profile

3.1.1 Dual back-to-back valves design

The dual NC/NO parylene-C-valves system artificially regulate the intraocular fluid drainage without any external power consumption, thus controling the IOP drainage profile of glaucoma patients. Therefore, it is ideal to have dual back-to-back valves consisting of an opened normally closed (NC) check-valve above 20 mmHg and a closed normally-open (NO) valve above 50 mmHg in series in order to realize the desirable pressure/band-pass flow regulation. The back-to-back configuration also prevents the GDD from water leakage if the fluid flows in the opposite direction.

To regulate the flow as a “band-pass” flow profile, Chen had demonstrated an on-chip surface-micromachined parylene-based dual-valve system which can achieve the flow regulation in the required ranges compatible with IOP regulation specification [139]. Besides, another approach also reported by Chen to regulate the flow as the same flow profile by a single parylene-C micro-valve adopting the floating-disk mechanism with a two level valve seat design [140]. However, these approaches required complicated processing. In the case of vacuum-collapsed sealing check-valve, the cracking pressure might drift with time because of gas permeation into the vacuum cavity. In addition, to accomplish a stand-alone implantable device, the micro check-valves must be extensively released and packaged into a capillary tube to become a real valve-in-tube system for real device implantation.

Furthermore, their integration with appropriate surgical components for fixation is also necessary for its practical applications. In 2007, Chen also reported the concept and successful experiments of using the surgical features in the proposed device in MicroTAS07 to anchor the biomedical device in human body tissue [141]. Therefore, the

new GDD system would attempt to integrate the dual-valved tube with the surgical features as the fixation anchor to address the dislodging problem after the device implantation.

3.1.2 Numerical simulation of the glaucoma drainage device

To define the geometry of the check-valves, the mechanical properties and the pressure/flow-rate characteristics of the check-valves were simulated using COMSOL Multiphysics™ to select the appropriate thickness and tether lengths of the NC check-valve. The check-valve outer diameter is restricted to be within 500 μm so that the overall GDD size can be fit into gauge #19 needle, which inner diameter is 690 μm. The cracking pressure of the NC check-valve is defined as 15 mmHg during the simulation. The flow-rate is also assigned as 2–3 μL/min to meet the required drainage rate of the aqueous humor [1].

The optimization of the check-valve flow characteristics is a complicated multiphysics simulation problem, which originally has to find out the linking equation between solid mechanics and fluidic dynamics. To overcome the problem, therefore, the simulation was separated to two easier simulations. One solid mechanics simulation is performed to understand the deflection of the covering plate versus the applied pressure, as shown in Figures 3-3 (a) and (c) for NC and NO valves, respectively. The other fluidic dynamics simulation was followed to understand the flow-rate versus different gap of covering plate openings, as shown in Figures 3-3 (b) and (d) for NC and NO valves, respectively. Once the geometry had been defined, the flow-rate of GDD system combining both NC and NO valves was simulated, as illustrated in Figure 3-3 (e). The simulations are iterated to verify the optimal geometry. The optimal design can be

selected for later fabrication based on the obtained simulation flow-rate results, as demonstrated in Figure 3-3 (f).

3.2 Design, Fabrication, and Test of the Normally Open Valve

3.2.1 Design of the NO valve

In this section, a NO valve is developed to accomplish the GDD's requirement of automatically off when the IOP is higher than the designed pressure.A cross section view of the NO valve design is shown in Figure 3-2. In NO valve design, the twisted-arm tether length is carefully designed while considering stiction to guarantee free-standing valve membrane after photoresist releasing [119–121]. The critical radius, r_{crit}, that the parylene-C membrane will not adhere to the substrate surface after the drying process can be predicted as:

$$r_{crit} = 1.7\sqrt[4]{\frac{3}{16}\frac{Et^3g^2}{\gamma_{la}cos\theta_c}}, \tag{3-1}$$

where E, and t is the Young's modulus and the thickness of the deflection material, respectively. g is the gap spacing; γ_{la} is the surface tension of the liquid–air interface, and θ_c is the contact angle between the drying liquid and the deflection material. In addition, sealing trenches are added in the free-standing membrane of the NO valves to avoid stiction and also to improve its high pressure sealing behavior.

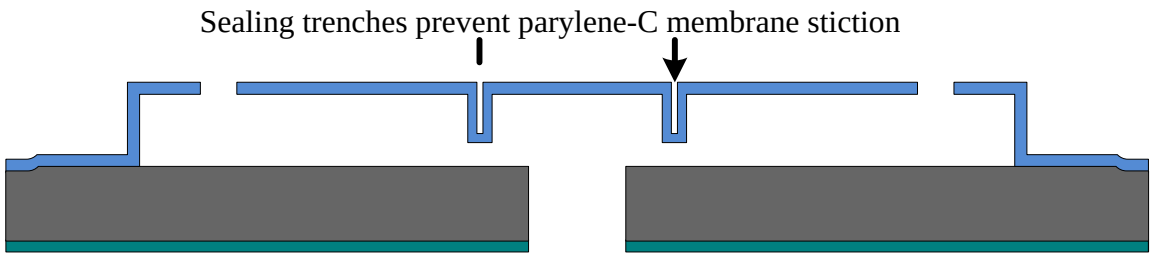

Figure 3-2: The cross section of a normally open check-valve

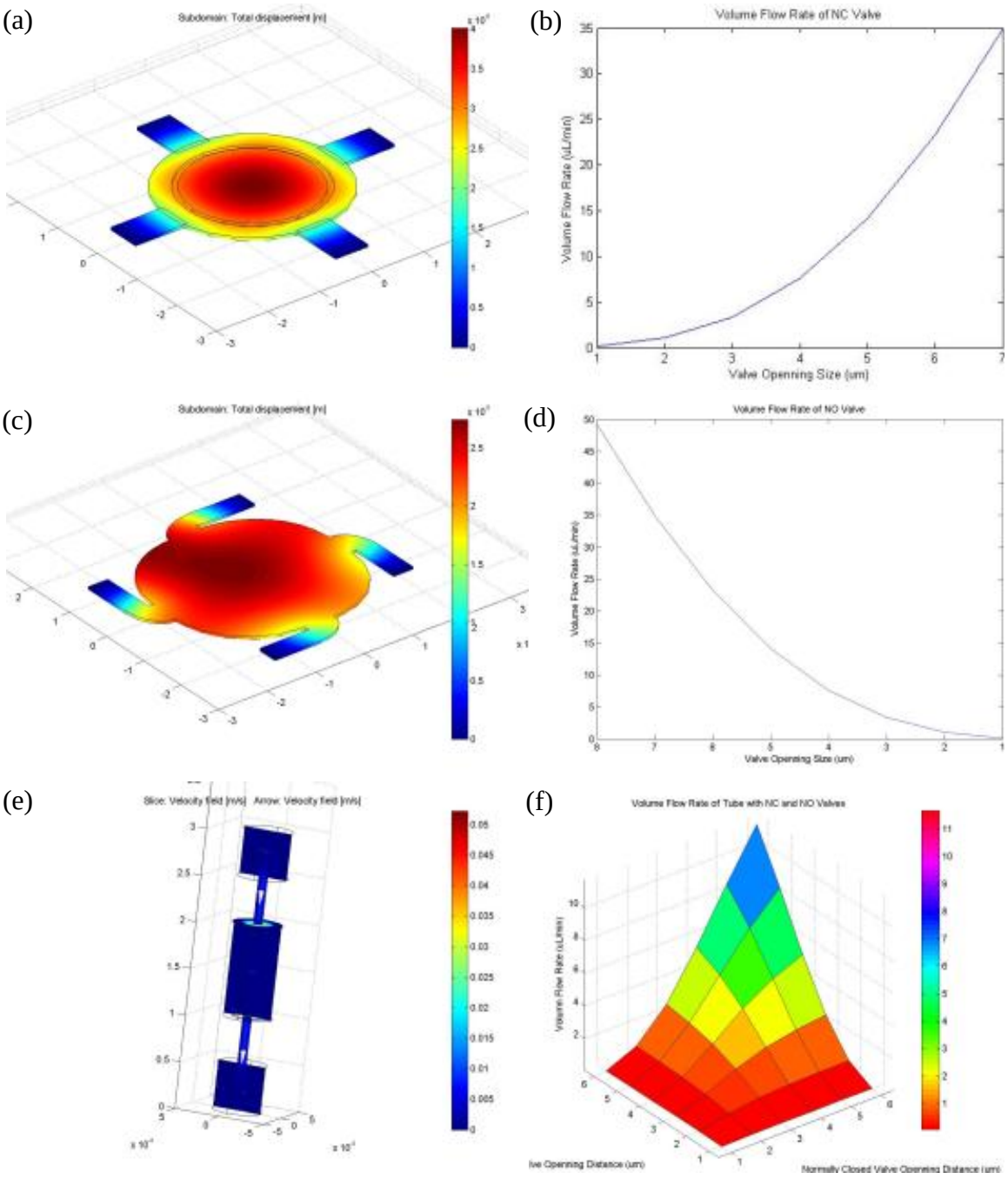

Figure 3-3: COMSOL Multiphysics™ simulation of the dual-valved GDD system: (a) deflection simulation of the NC check-valve, (b) flow-rate simulation results of the NC check-valve, (c) deflection simulation of the NO valve, (c) flow-rate simulation results of the NC check-valve, (e) flow-rate simulation of the dual-valved GDD system, (f) flow-rate simulation results of the dual-valved GDD system

3.2.2 Fabrication of the NO valve

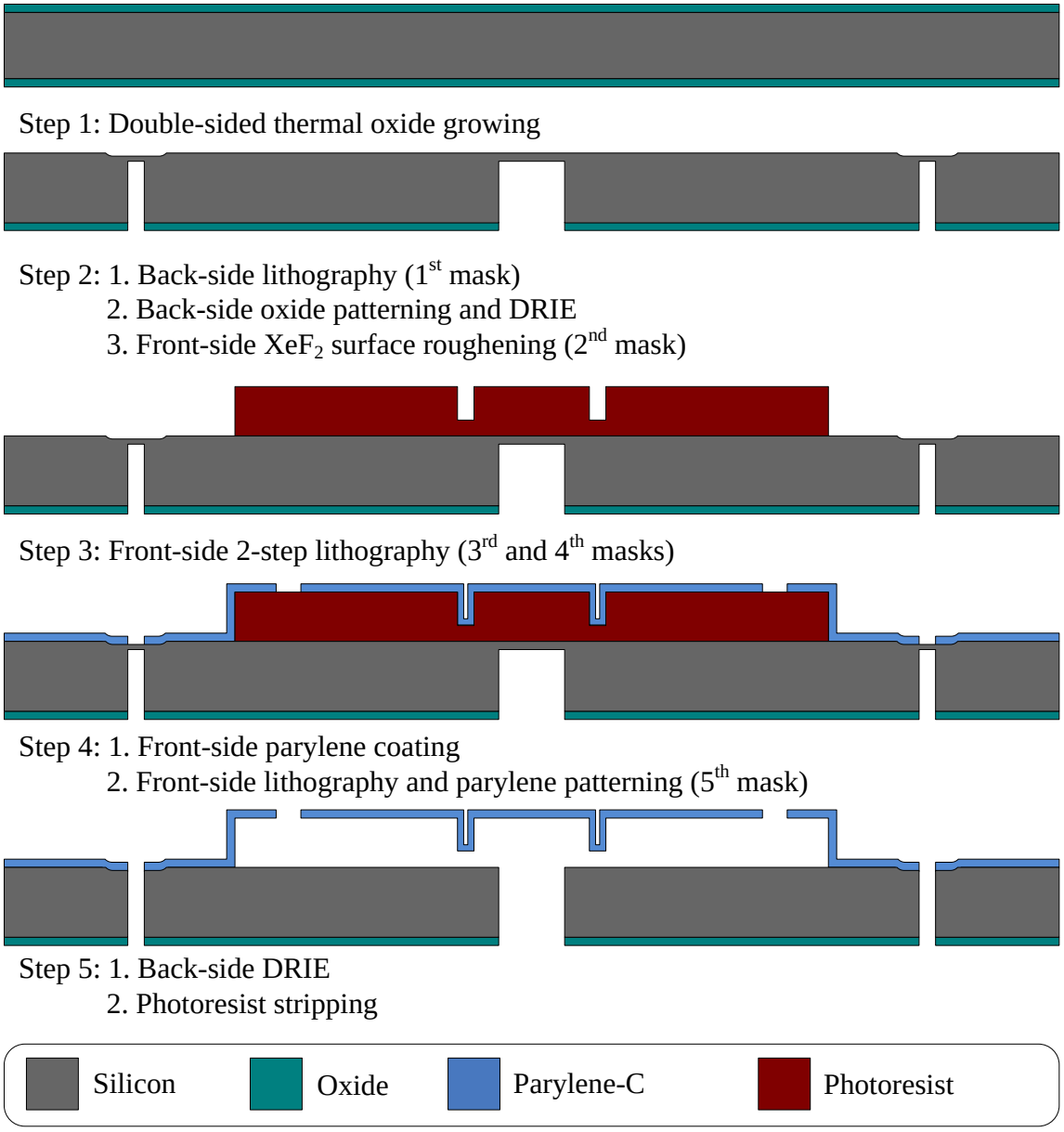

Figure 3-4: Fabrication procedures of the NO valve

The fabrication process started from growing thermal oxide on the silicon wafer surface, as shown in Figure 3-4. Through-wafer holes and releasing trenches of the check-valves were etched using backside DRIE until 50 µm silicon membranes was left. The circular boundary of the valve seats were defined here with diameter to be 500 µm,

which can be fit into parylene-C protective tube's I.D. smoothly. XeF_2 was used to roughen the front side surface to improve the adhesion between parylene-C and the silicon valve seat. Two-step exposure lithography was performed to create two different heights of sacrificial photoresist for the NO valve, where the lower photoresist was the location of the sealing trench of the parylene-C membrane. After parylene-C coating, RIE was used to pattern the coated parylene-C and then through holes and the releasing trenches were opened by completely etching away the remaining silicon membrane using DRIE to strip the sacrificial photoresist with acetone and IPA. The fabrication results are shown in Figure 3-5.

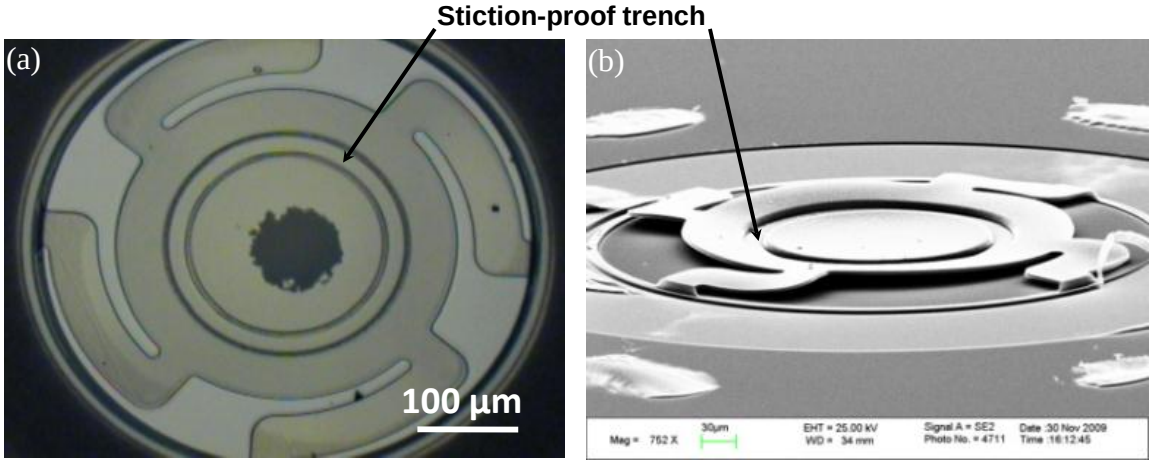

Figure 3-5: Fabrication results of the NO valve: (a) top view of the NO valve, and (b) SEM picture of the NO valve

3.2.3 Characterization of NO valve

Similar to the characterization procedures for the NC check-valves aforementioned in chapter 2, single NO valve was first packaged by the packaging procedure as Figure 2-12, and then characterized by the setup shown in Figure 2-13. The

pressure/flow-rate characteristic profile is demonstrated in Figure 3-6. It is found that no significant cracking pressure was obtained during tests, and fluid in NO valve flows smoothly before pressure reaches the high limit. The flow-rate starts to decrease when the pressure goes up to 0.5 psi (~ 25 mmHg) and almost closes after 1.12 psi (~ 56 mmHg). The leak rate is less than 5 µL/min. This result proves that the sealing trench designed on NO valve does seal the NO valve orifice. The small amount of leak rate may be due to the non-flat bottom under the sealing trench which comes from the top surface of the sacrificial photoresist layer.

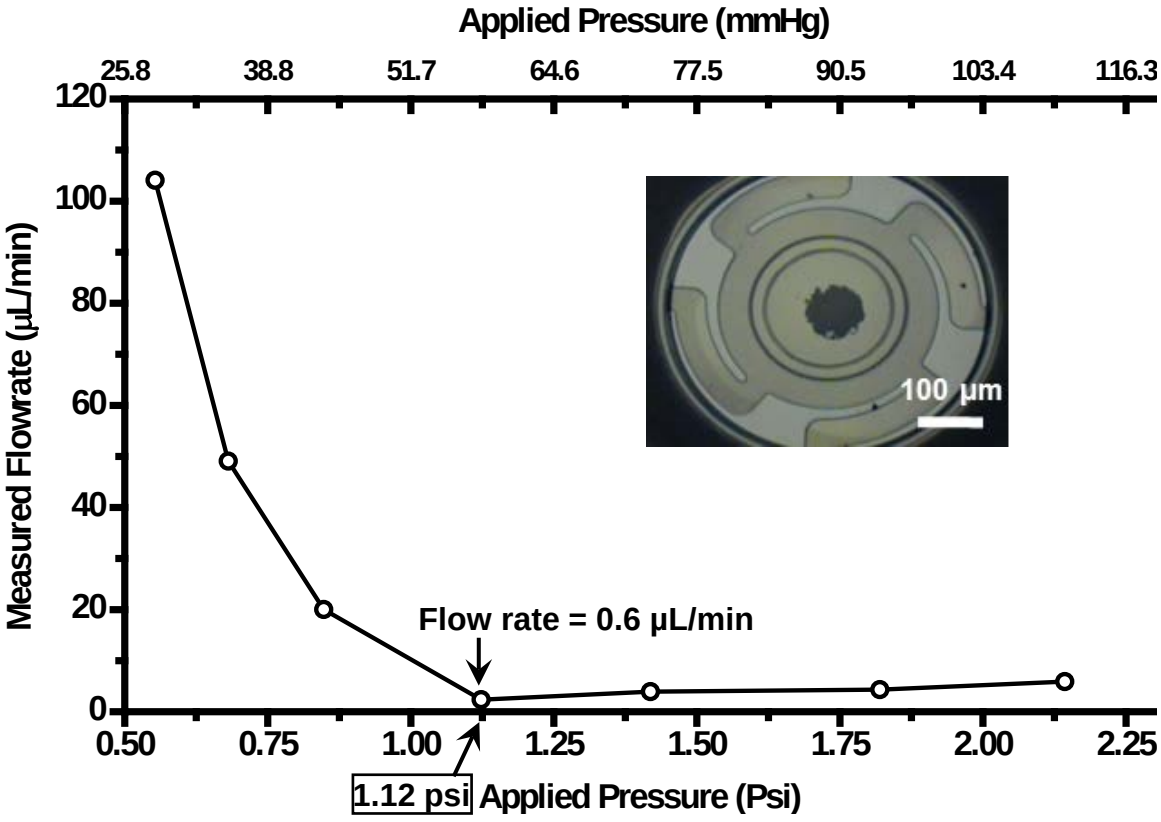

Figure 3-6: Pressure/flow-rate profile characterization results of the NO valve

3.3 Sutureless, Minimally Invasive Implantation of the Dual-Valved GDD

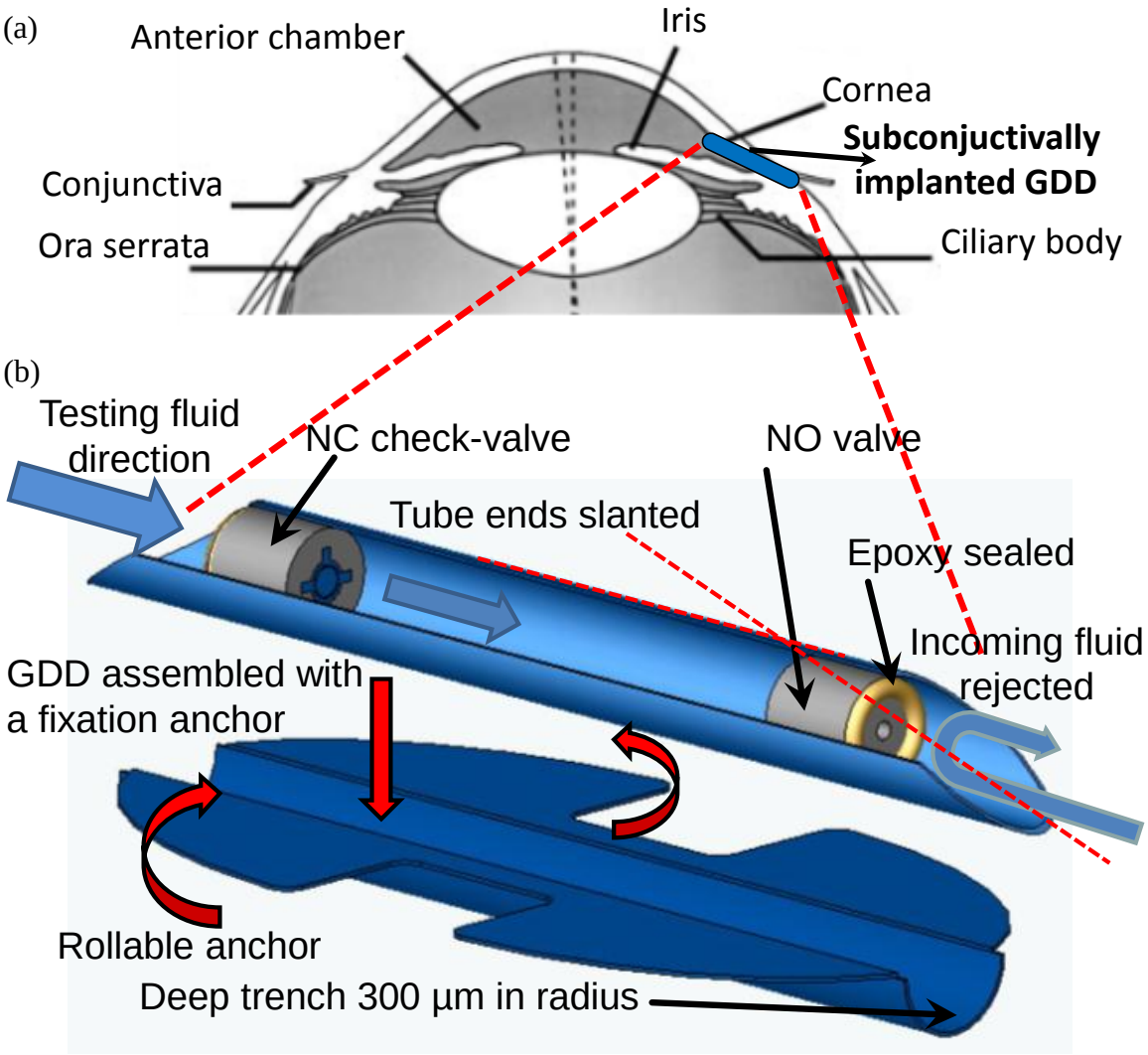

Figure 3-7: Concept of the minimally invasive implantation: (a) Subconjunctival implantation idea of the (GDD) implanted through the anterior chamber of the eye. (b) A complete GDD system consisting of a dual-valve micro-flow regulation system (one NC check-valve at one end of the tube and one NO valve on the other end of the tube), a parylene-C protective tube carrier, and a rollable/foldable anchor

3.3.1 Dual-valved GDD out-shape

A subconjunctival needle implantation would be executed to mimic the normal aqueous humor drainage pathway, as shown in Figure 3-7 (a). As such, the shape and length of the capillary tubes are carefully designed so that the implantation can be performed using a specific plunger-in-needle introducer setup. As aforementioned, the outer diameter of the GDD must be designed smaller than the inner diameter of the implantation hypodermic needle. The front end of the tube is tapered for convenient device placement after injection. The length is chosen so that the back end of the tube is observable through cornea during surgery. This surgical procedure can be completed within 10 min. In addition, no suture is required after implantation is done, greatly simplifying surgery process.

3.3.2 Dual back-to-back valve configuration

As shown in Figure 3-7 (b), a complete implant comprises a dual-valve micro-flow regulation system in a tube with integrated flexible tissue anchors. Dual back-to-back micro valves system with one check-valve normally closed but open at 20 mmHg and the other valve normally open (NO) but closed beyond 50 mmHg is designed to fulfill the concept of “band-pass” flow regulation described in Section 3.1. A stiction pre-stressed NC valve developed in Section 2.6 is adopted here for its appropriate cracking pressure range for the glaucoma treatment. Owing to the inherent structure of the NC check-valve, fluid coming from the opposite way will be rejected, protecting the anterior chamber from exterior contamination while the fluid can flow from NC check-valve to NO valve until the pressure reaches the limit of NO valve. Every parts of the GDD, (micro-valves, parylene-C protective tube, and parylene-C anchors), is fabricated

separately and eventually integrated into one system. Except for the micro valves which have been introduced in the previous sections, the parylene-C protective tube and the parylene-C fixation anchor are first introduced in Sections 3.3.3 and 3.3.4, respectively. The packaging procedures of the whole GDD system will be presented in Section 3.3.5.

3.3.3 Parylene-C protective tube carrier

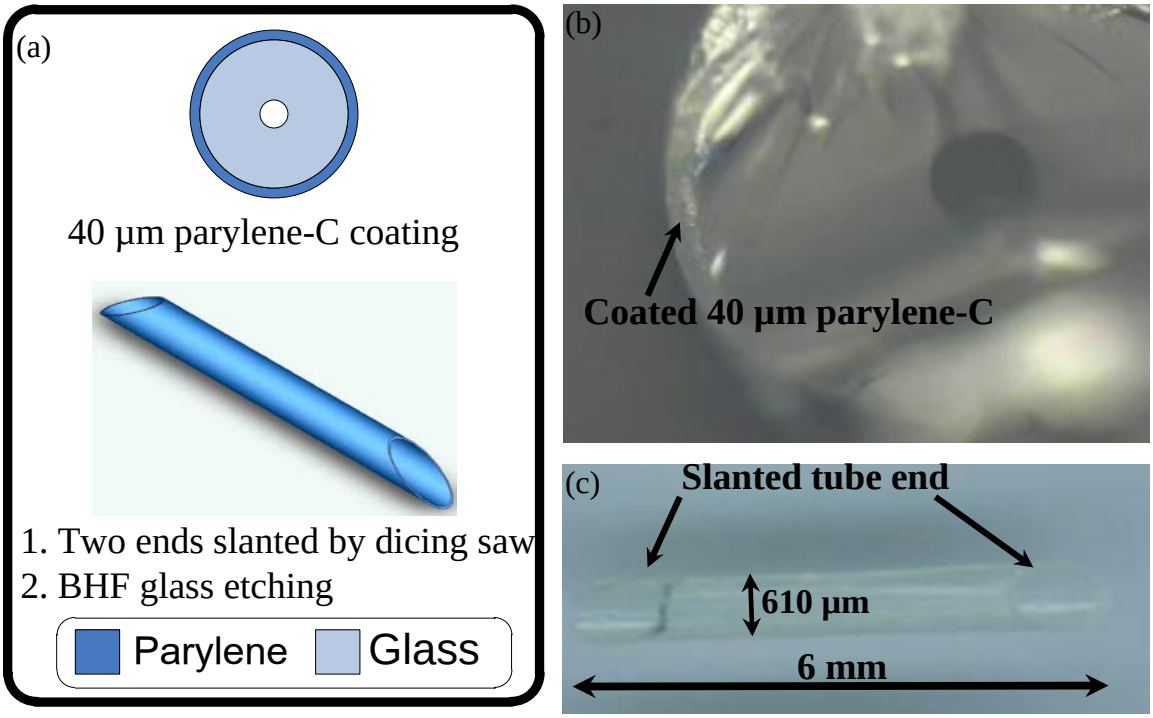

Figure 3-8: (a) Fabrication procedures of the parylene-C protective tube carrier, (b) coated 40 µm parylene-C on the sacrificial capillary glass tubing, (c) slanted and completed parylene-C protective tube carrier

As previously shown in Figure 3-7 (b), to accommodate two micro valves, a hollow tube made of thick parylene-C is utilized and the length is chosen as 6 mm long. Both ends of these parylene-C protective tube carriers are slanted at 30 degrees to facilitate the surgical implantation and guard the GDD against iris retraction.

The fabrication procedures of the parylene-C protective tube are shown in Figure 3-8 (a). Parylene-C protective tube carrier was made by coating 40 μm thick parylene-C onto capillary glass tubing with 530 μm in O.D., which were then cut into desired lengths of 6 mm with slanted ends on both sides and later free-released in BHF. Figure 3-8 (b) shows the coated 40 μm parylene-C on the capillary glass tubing while Figure 3-8 (d) shows the result of fabricated parylene-C protective tube carrier with two slanted ends.

3.3.4 Design and fabrication of the rollable/foldable parylene-C fixation anchors

To prevent the implanted GDD from dislodging, rollable/foldable anchors with hemispherical recesses are designed (Figure 3-7 (b)). The anchor has a wingspan larger than the O.D. of #19-gauge hypodermic needles and can stretch out after needle retraction for robust fixation. A parylene-C recess is also fabricated together with the fixation anchor to facilitate the integration of the valved GDD tube system with the fixation anchor. The radius of hemispherical recesses is 300 μm, fitting and covering the parylene-C protective tube carrier O.D. well during later integration.

During the fixation anchors' fabrication, the dry film photolithography technique was utilized to fabricate the connection between parylene-C recess and fixation anchor. The aluminum mask was patterned by Dry film photolithography prior to the parylene-C patterning to overcome the problem that regular liquid-based photoresist would not be possible to spin and cover over the recesses. Dry film photoresist is one kind of negative photoresist that is widely used in printed circuit board (PCB) industry. The process provides the capability of patterning circuit boards with small holes without any photoresist collapsing [142, 143]. Hence it becomes very useful in MEMS applications

to help pattern materials over cavities within the structures [144–146]. The high thickness of the dry film can also be transferred to the high aspect ratio sidewall fluidic channels in the microfluidics devices [147–151]. In our case, dry film was used to pattern the aluminum film on top of the parylene-C layer with a very deep trench. In addition, the dry film photoresist always comes as a large size sheet, rendering it a very good choice to fabricate large structures where regular liquid-based photoresist cannot be spun on, such as parylene-C MEMS wings [152, 153]. A laminator is required to laminate the dry film photoresist onto the parylene-C surface. The dry film photoresist is photo patternable by UV light with wavelength ranging from 360 to 420 nm, and developed by sodium carbonate ranging from 0.6% w.w to 1.2% w.w [154]. Being a polymer, the dry film photoresist can also be etched away during oxygen plasma etching, and can be stripped by potassium hydroxide after the entire process is completed.

Fabrication procedures for parylene-C fixation anchors are shown in Figure 3-9. The process started with growing thermal oxide layers on both sides of the silicon wafer. Front side oxide was first patterned for later XeF_2 etching. Then the silicon wafer was isotropically etched to create semispherical recesses with radius to be 300 μm in depth. A 20 μm-thick parylene-C layer was then coated onto the wafer. A layer of 2000 Å of aluminum, used as the oxygen-plasma etching mask, was deposited on top of the parylene-C film and then patterned by dry film photolithography. The parylene-C layer was then patterned by oxygen plasma and then released by soaking in DI water. Different fixation anchor shapes can be designed and patterned to fit different surgical requirements. Results of the fabricated anchors are shown in Figure 3-10 (f).

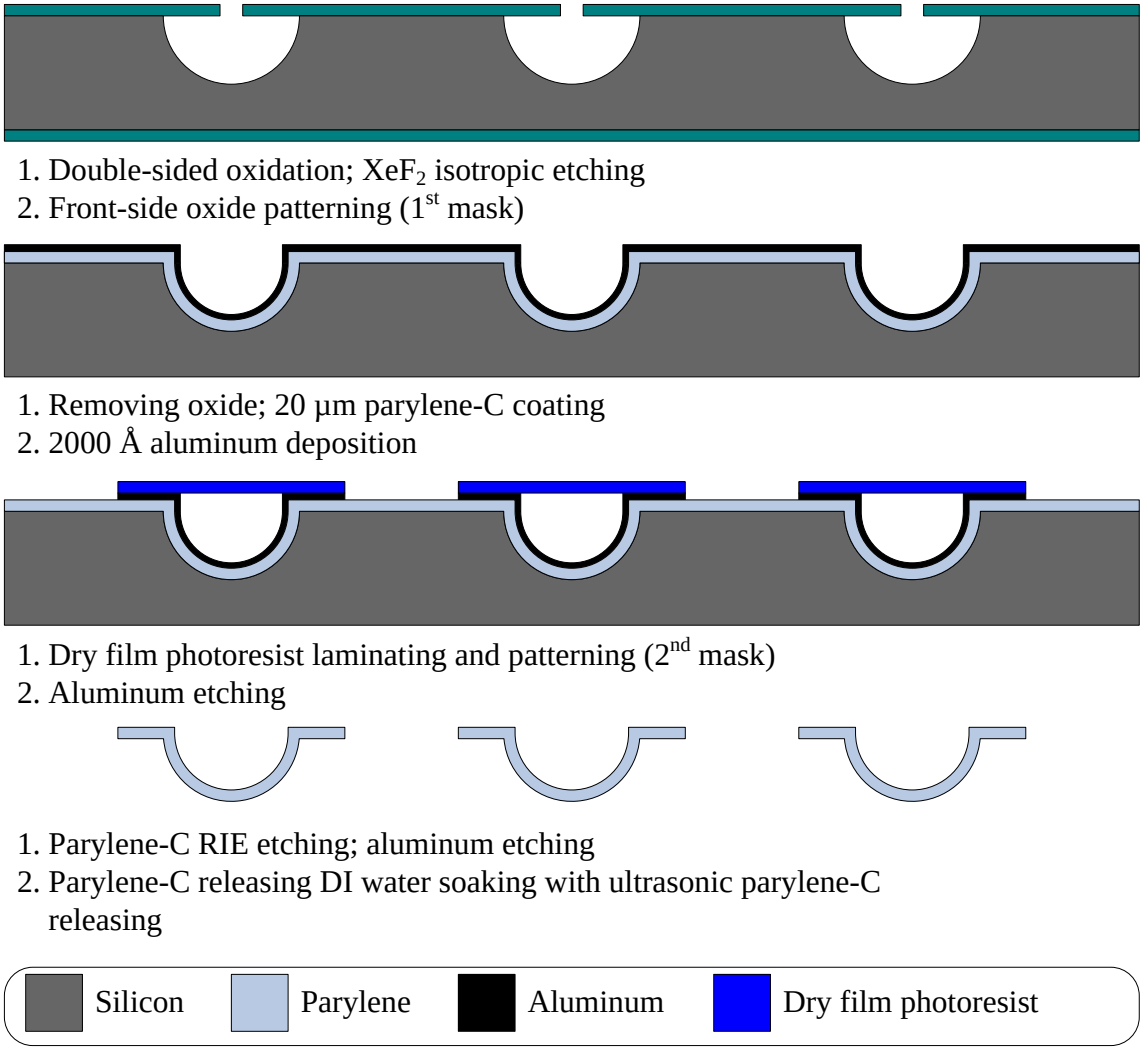

Figure 3-9: Fabrication procedures of the parylene-C fixation anchors

3.3.5 Dual-valved glaucoma drainage device packaging

The packaging procedure of the GDD is shown in Figure 3-10 (a) to (h). To package the entire GDD system, one NC check-valve and one NO valve were first released and then inserted into either ends of the parylene-C protective tube carrier, as demonstrated in Figure 3-10 (a) to (d). The NC check-valve is specifically manipulated by epoxy drops on the stiction-bonding area to enhance the anchoring adhesion, as illustrated in Figure 3-10 (b). The gap between the micro check-valves' seats and the

protective tube carrier inner wall was sealed by epoxy and the completed assembly is shown in Figure 3-10 (e). To mount the finished dual-valved tube onto parylene-C fixation anchors, tiny epoxy drops was first wiped on the semispherical recess. Then, the dual-valved tube was assembled onto the recess. Figure 3-10 (g) shows the final assembled GDD with different parylene-C fixation anchor shapes. Since the O.D. of the parylene-C protective tube carrier is 600 μm (530 μm + 70–80 μm parylene-C coating), it fits the recess of the parylene-C fixation anchor nicely after assembly. The anchor is flexible enough to be rolled/folded and insert into the testing Teflon tube thereafter, as shown in Figure 3-10 (h). The assembly is also suitable for the #19-gauge hypodermic needle implantation.

3.4 Valve-Position-Adjustable Dual-Valved GDD

Even though the design concept of the dual-valved GDD system proposed in section 3.3 is easy and straight forward, ophthalmologists are also interested in exploring the possibilities of adjustable check-valve positions within the parylene-C protective tube. The GDD in Section 3.3 has two position-fixed check-valves at the two ends. If the check-valves' position has to be modified, the parylene-C tube length needs to be altered and thus shortens the overall length of the GDD system and might cause the difficulties of the implantation. As a result, another novel post-micro-fabrication tube packaging technology using an auxiliary glass capillary tube as a coupling tube in this section is developed to help us assemble the micro-flow regulating system.

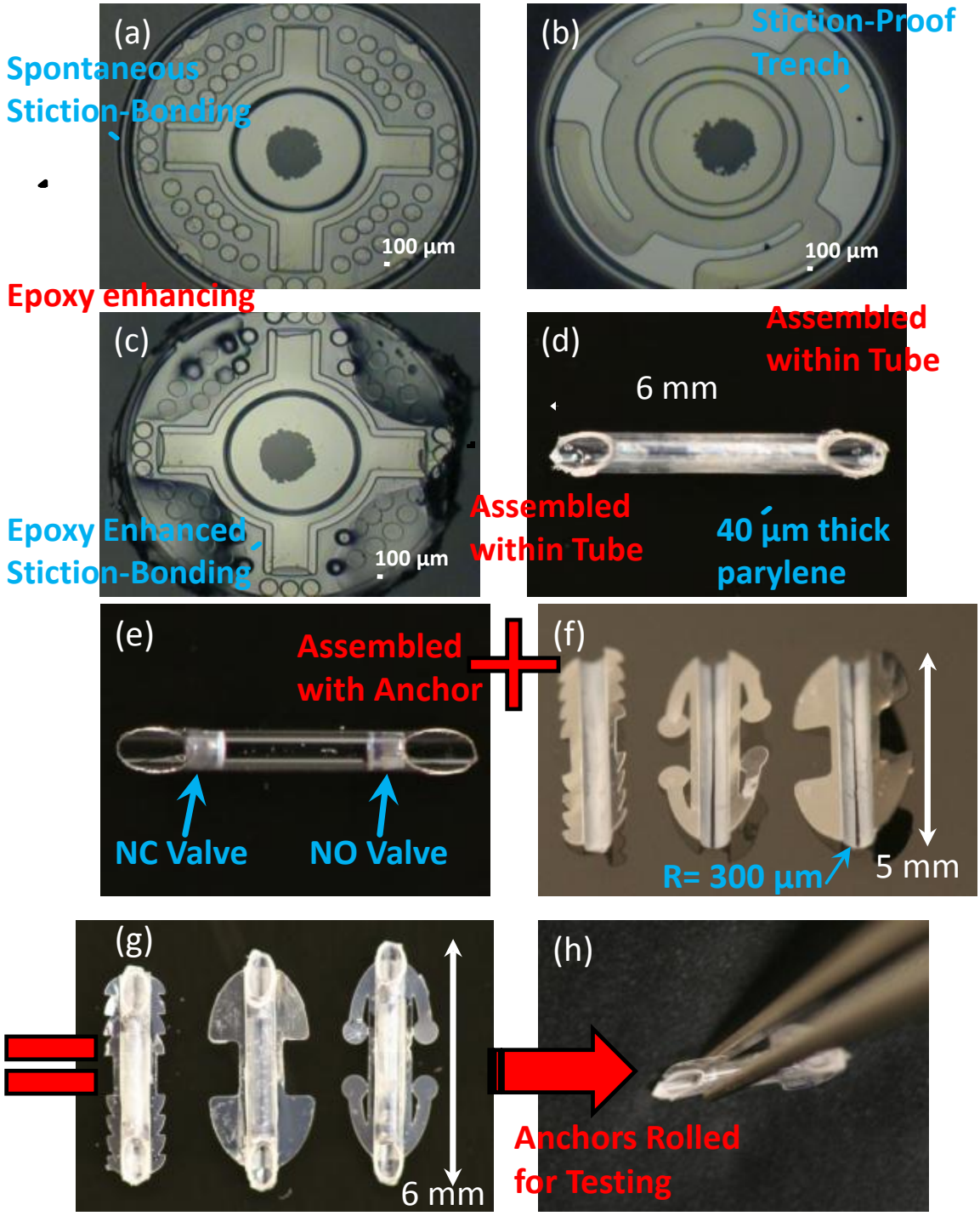

Figure 3-10: Packaging procedures of the dual-valved GDD system: (a) NC check-valve; (b) NO valve; (c) NC check-valve with stiction bonding enhanced by epoxy; (d) hollow parylene-C protective tube carrier; (e) one NC and one NO valve sealed in the parylene-C

protective tube carrier (transparent glass tube used here for clarity); (f) anchors with trenches of 300 μm in radius, different anchor shapes designed to facilitate the surgical convenience, and future GDD fixation (left: ragged anchor; middle: foldable anchor; right: rollable squeeze-tail anchor); (g) completed assembled GDD in top view; (h) anchors can be rolled/folded for testing and implantation convenience. Check-valves are first sealed in the carrier, which is then assembled onto anchors.

3.4.1 Configuration of the valve-position-adjustable dual-valved GDD

With the similar design concept described in Section 3.3, one NC check-valve and one NO valve are adopted here but attached to the two ends of the coupling tube with the valve surfaces facing to each other, as shown in Figure 3-11. The check-valves are fabricated with a ring groove for easier attachment. Both NC and NO valves are required to have smaller planar size than the inner diameter (I.D.) of the coupling tube so that the check-valves' surface can be inserted into the coupling tube and not be contaminated during packaging. The distance of the two micro check-valves can be adjusted by using different coupling tube with different lengths. In addition, the completed micro-flow regulating system makes it easier to load the check-valves into the protective tubes owing to its larger handling size. The parylene-C protective tube from Section 3.3.3 is still adopted in this design to accommodate the micro-flow regulating assembly and hence the finished GDD can still be perfectly fit into #19-gauge needle given its 610 μm O.D. which makes the minimally invasive hypodermic needle implantation feasible. The completed GDD has the same regulatory function as in Section 3.3, but with more flexible valve position choices.

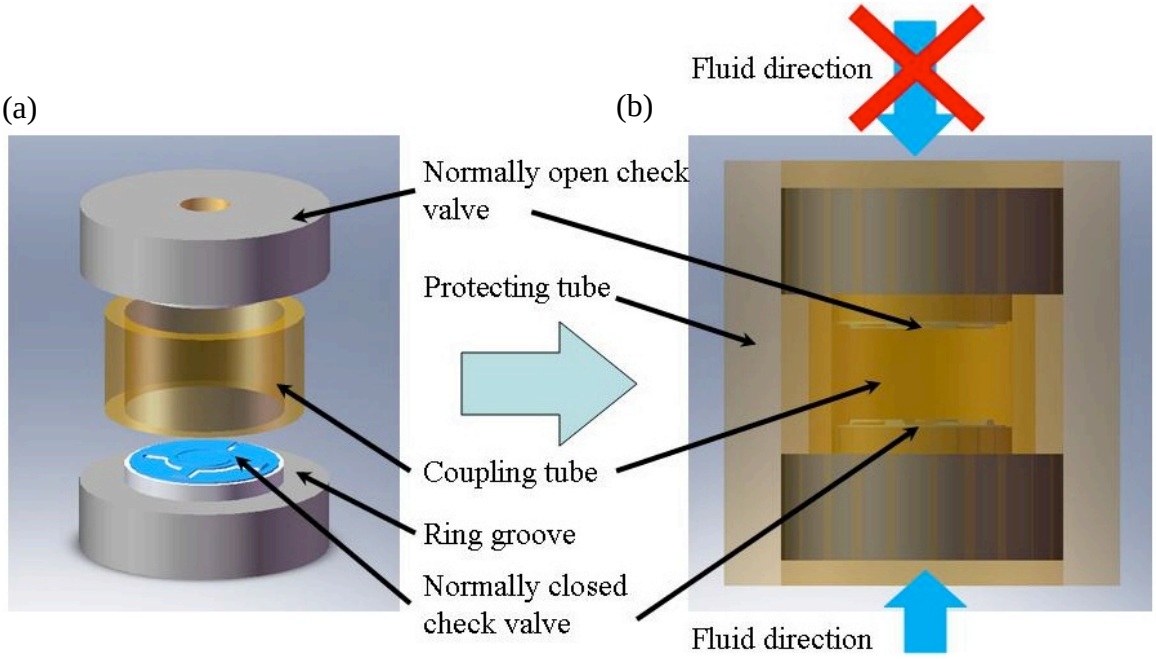

Figure 3-11: Schematics of valve-in-tube system: (a) Combination of one NC valve and one NO valve with a coupling tube to form the micro-flow regulating assembly. (b) Final finished valve-in-tube system

3.4.2 Grooved check-valves

As shown in Figure 3-12, in order to attached the check-valves onto the coupling tube, both NO and NC valves are further encircled by 65-μm-wide, 150-μm-deep grooves defined by DRIE on the top side for convenient assembly afterwards. The diameter of the valve's seat, however, is still designed as 500 μm. The I.D. of the coupling tube is 320 μm, which is slightly larger than the 300 μm check-valves' surface diameter. The outer diameter (O.D.) of the coupling tube is 400 μm, which is smaller than the I.D. of the outside parylene-C protective tube and can thus be packaged in the parylene-C protective tube.

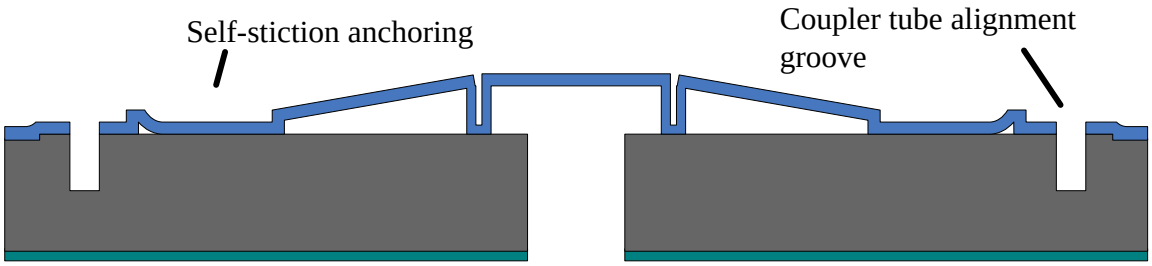

Figure 3-12: Cross section of the grooved self-stiction-bonding NC check-valve design

3.4.3 Grooved check-valve fabrication procedures

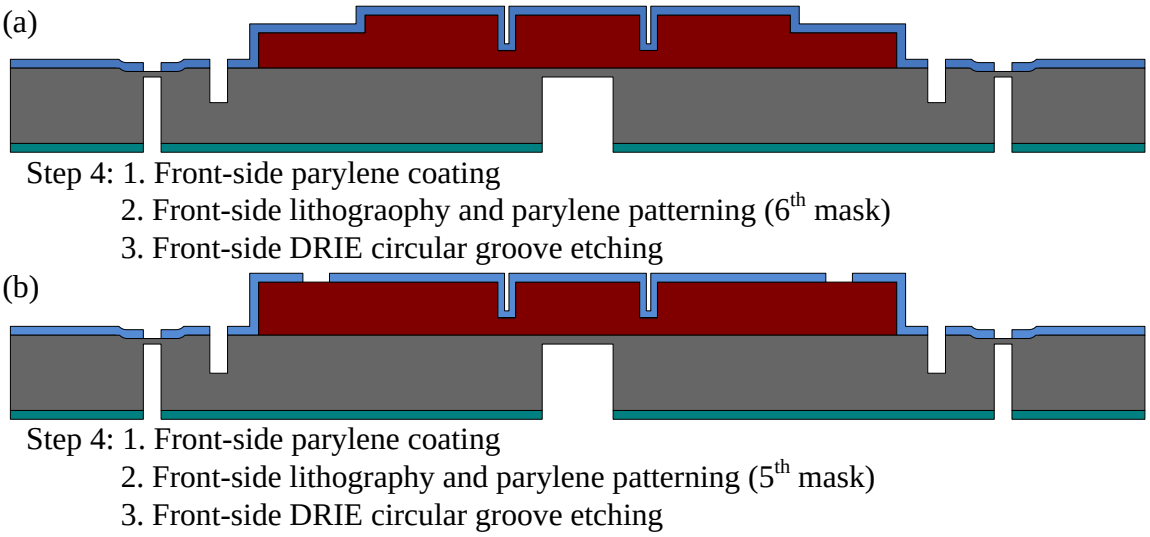

Figure 3-13: Modification of step 4 of the fabrication procedures of (a) NC check-valve and (b) NO valve by DRIE to incorporate a circular groove using the same photoresist mask for parylene-C patterning (photoresist mask not shown)

The grooved self-stiction-bonding NC check-valve and NO valve share very similar fabrication procedures shown in Figure 2-24 (NC check-valve) and Figure 3-4 (NO valve), respectively. However, in order to create the circular groove on top of check-valves, step four of the fabrication procedures in both Figure 2-24 and Figure 3-4 was modified to incorporate the usage of DRIE etching as shown in Figures 3-13 (a) (NC

check-valve) and (b) (NO valve). A 150-µm-deep groove was created encircling the check-valves using additional DRIE after parylene-C coating and patterning for convenient coupling tube packaging alignment afterwards. The stiction happens in NC check-valves as expected after the photoresist stripping and the drying process. The fabrication result of the grooved NC check-valve is shown in Figure 3-14 (a).

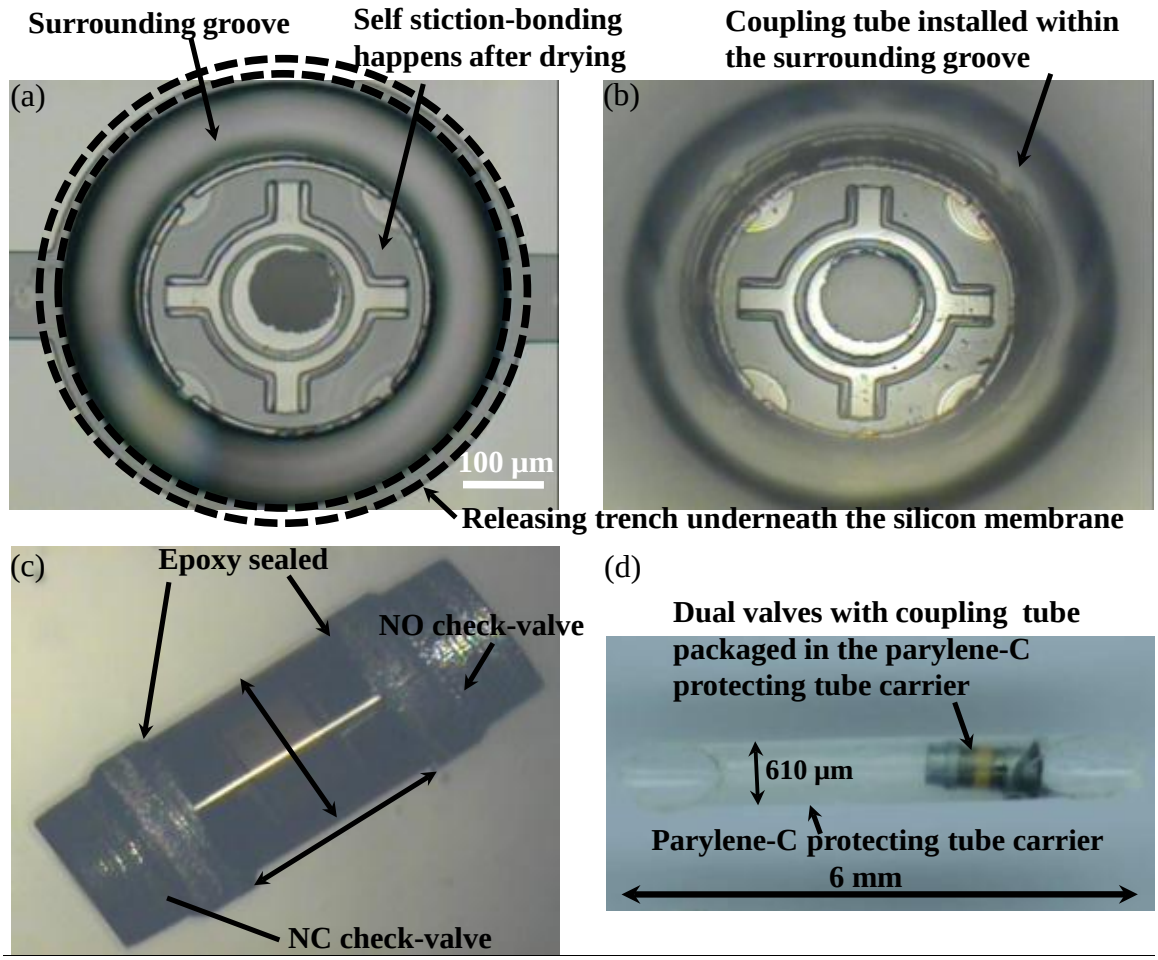

Figure 3-14: Micrographs of: (a) the fabrication result of an NC check-valve, (b) the top view of a NC check-valve packaged inside a coupling tube, (c) packaging results of the micro-flow regulating assembly, (d) the micro-flow regulating assembly packaged inside a tapered parylene-C protective tube carrier 610 µm in diameter, suitable for a #19-gauge hypodermic needle

3.4.4 Grooved check-valve packaging procedures

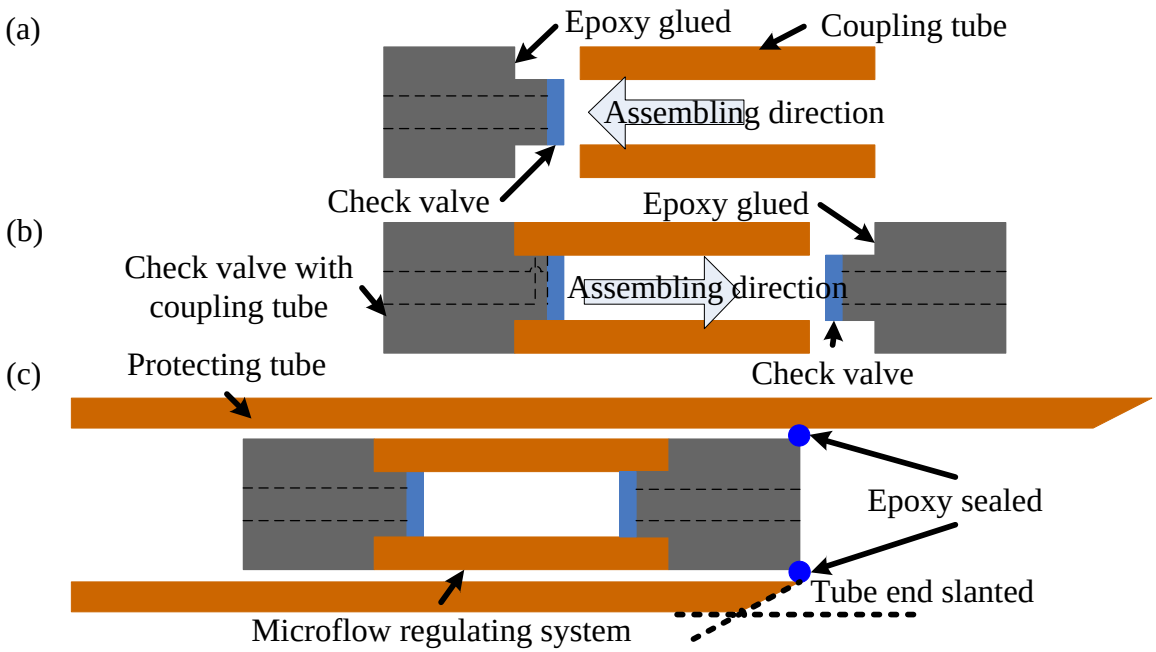

Figure 3-15: The packaging procedures: (a) one check-valve attached to one end of the coupling tube, (b) complete micro-flow regulating assembly, (c) final valve-in-tube system

As shown in Figure 3-15, the microfabricated valves were then packaged into a capillary protective tube to fulfill the valve-in-tube system. One microfabricated check-valve (NC or NO) was first attached to one end of the coupling tube with a tiny epoxy drop gently applied onto the alignment groove, as shown in Figure 3-15 (a). The other check-valve (NO or NC) was then attached on the other end of the coupling tube to form a micro-flow regulating assembly, as shown in Figure 3-15 (b). The micro-flow regulating assembly was then inserted into the protective tube which is first trimmed to 2–10 mm long and the entire tube-in-tube system was further secured by epoxy sealing, as shown in Figure 3-15 (c). The packaging results of the valve-in-tube system are

shown in Figure 3-14 (b) to (d). Figures 3-14 (b) and (c) shows the successful attachment of the check-valves onto the coupling tube with the help of the surrounding groove to form a micro-flow regulatory assembly. Figure 3-14 (d) demonstrates the complete valve-in-tube system which is suitable for #19-gauge needle implantation.

3.5 Bench-Top GDD Characterization

3.5.1 Bench-Top GDD characterization setup

The completed GDD was first characterized to verify that its behavior meets the standard IOP regulation requirements *via* the bench-top testing. The testing setup is adopted from Figure 2-13 with the same working fluid chosen and the Teflon tubing was connected to the pressure gauge with turning resolution up to 0.01 psi (~ 0.5 mmHg). Prior to characterize the completed GDD, the Teflon FET tubing was first cut into 2 inch segments in advance. Then one wingspan of the GDD was folded by tweezers and inserted into Teflon FET tubing, which has I.D. of 750 μm. The gap between the GDD and the Teflon tubing was sealed with photoresist and dried in the air, as illustrated in Figure 3-16. The characteristic curve of every assembly was generated and also filmed. In order to get a qualified working device, the result of the cracking pressure is required to fall in between 10–20 mmHg. It's also required that water drips should only be observed flowing out through the opening of valve-tubes, not the slits between valve-tubes and the FET tubing.

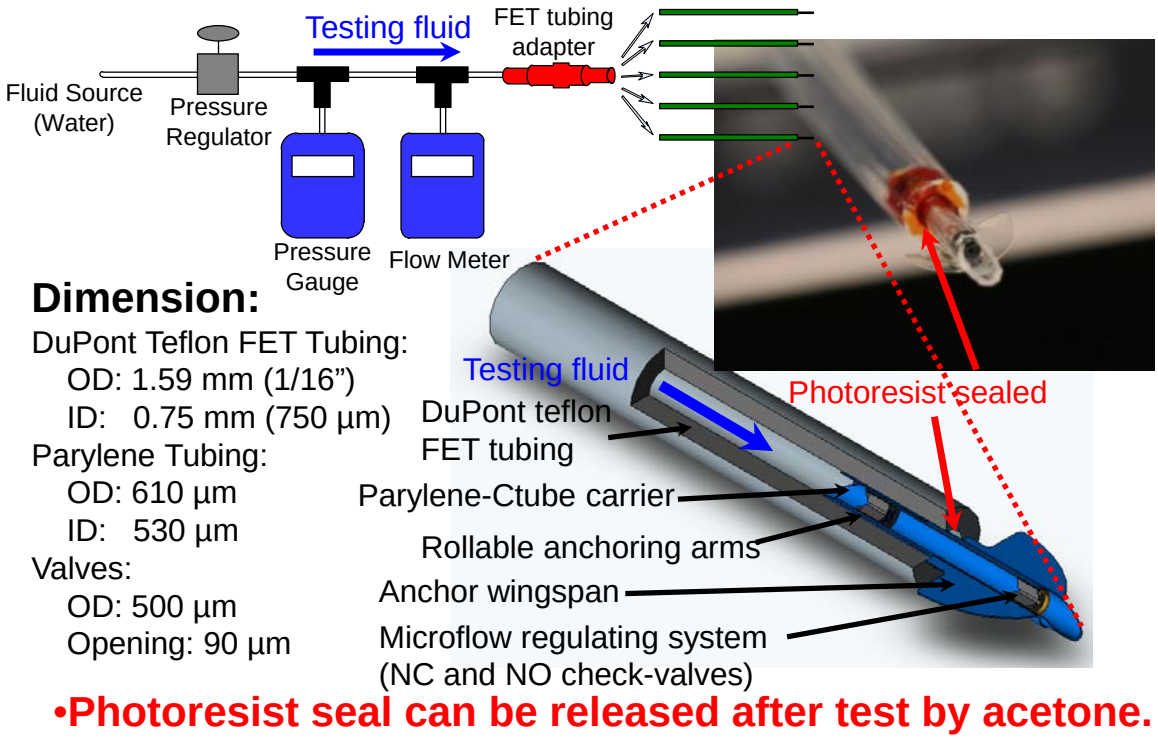

Figure 3-16: Testing setup of the GDD: Photoresist is painted in the gap between GDD and Teflon tubing for sealing.

3.5.2 Bench-Top GDD characterization results

Before every GDD is sent to animal surgical test, the devices are prepared and characterized first. One of the typical dual-valved GDD pressure/flow-rate profile characterization result is shown in Figure 3-17. The NC check-valve successfully opens at 0.33 psi (~ 17 mmHg) and NO valve starts to function at 1.1 psi (~ 57 mmHg), which is consistent with our simulation results. The off pressure of NO valve in the dual valve system is a bit larger than single NO valve system. It is likely due to the fact that part of the energy of the flowing fluid is consumed before the fluid reaching the NO valve by the friction and tether deformation of the NC check-valve. Therefore only part of the energy is left to push the NO valve membrane to close the valve orifice. This off pressure delay

makes the off pressure of the dual-valved GDD system right meet our design requirement to close after 50 mmHg. The testing flow-rate also show that our GDD system can perfectly satisfy the reported aqueous humor formation rate as 2–3 µL/min [1]. *In vitro* testing results of the cracking pressure are shown in Table 3-1. Tested and qualified GDD systems were then released by acetone and IPA for further *ex vivo* implantation test to study their biomedical feasibilities.

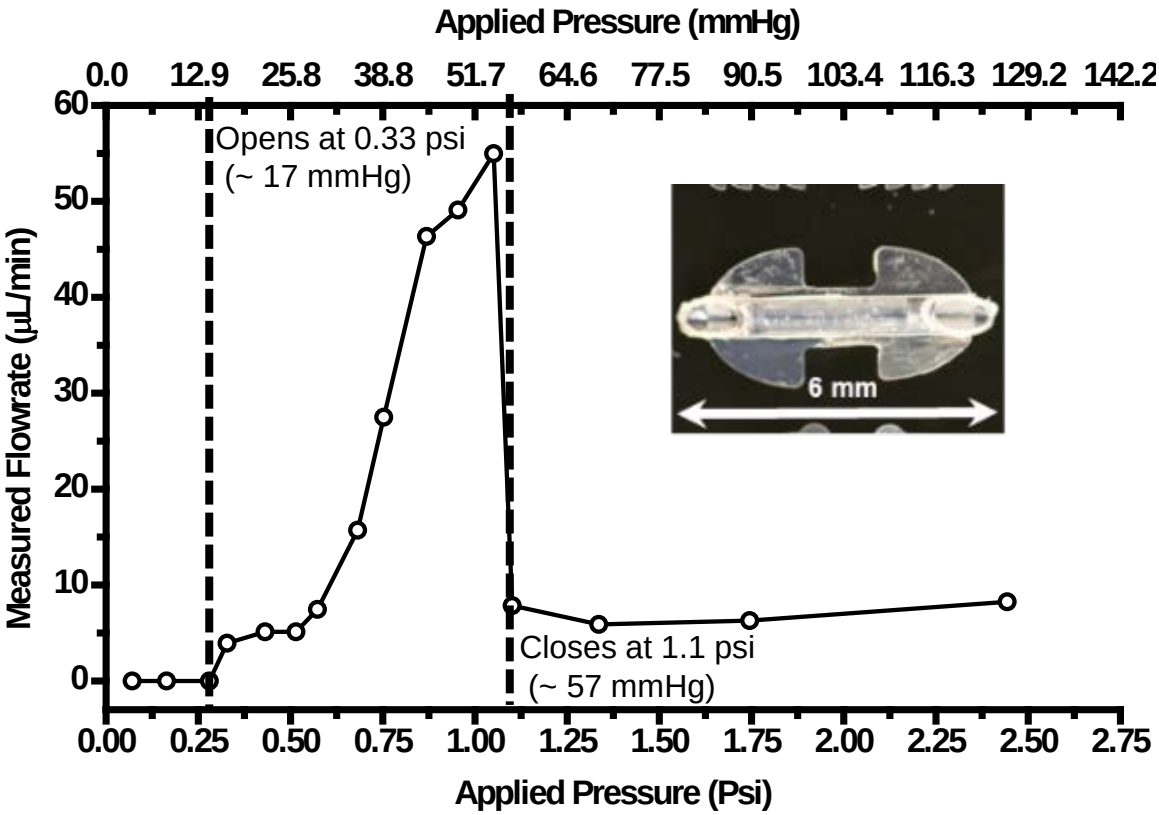

Figure 3-17: Dual-valved GDD characterization results: The fluid starts to flow after 0.33 psi (~ 17 mmHg) and closes at 1.1 psi (~ 57 mmHg). Water was chosen as the working fluid.

Table 3-1: Cracking pressures of two GDD systems obtained from *in vitro* and *ex vivo* tests

Measured Cracking Pressure (mmHg)	***In vitro***	***Ex vivo***
GDD in Section 3.3 (GDD 1)	17	15–25*
GDD in Section 3.4 (GDD 2)	12	24

*Number is obtained by estimation from video timeline.

3.6 GDD *Ex Vivo* Test and Discussion

The photoresist sealing the gap of the GDD system and the FET testing tube was dissolved during device soaking in the acetone and IPA. The GDD was pulled out from FET testing tube and its wingspan stretched back to its original shape. After characterization and GDD released, the working device was then delivered for sterilization in order to prepare it for later *ex vivo/in vivo* functionality verification. An enucleated porcine eye was used as our implantation model in the process and a height-adjustable saline bottle is used as the working fluid to mimic eye fluid and simulate different eye pressure situations, as shown in Figure 3-18.

A customized plunger-in-needle introducer using #19-gauge hypodermic needle and a blunt-end plunger with wire size as AWG-22 (644 μm) in diameter, as shown in Figure 3-19 (a), was developed to facilitate the minimally invasive needle incision and device injection. The introducer was designed to avoid the device's dislodging during introducer retraction within the gauge #19 hypodermic needle while the blunt-end plunger are used as the GDD carrier and deliverer. Figure 3-19 (b) demonstrates a GDD with the folded zigzag type parylene-C fixation anchor inserted into the #19-gauge hypodermic needle.

An experiment demonstrating this subconjunctivally implantation concept was performed by using a tapered hollow tube as shown in Figures 3-19 (c) and (d). After the implantation of the hollow tube, as shown in Figure 3-19 (c), testing dye was injected into the hollow tube and it can be seen from Figure 3-19 (d) that the dye successfully drained out to the diffusive subconjunctival location as expected.

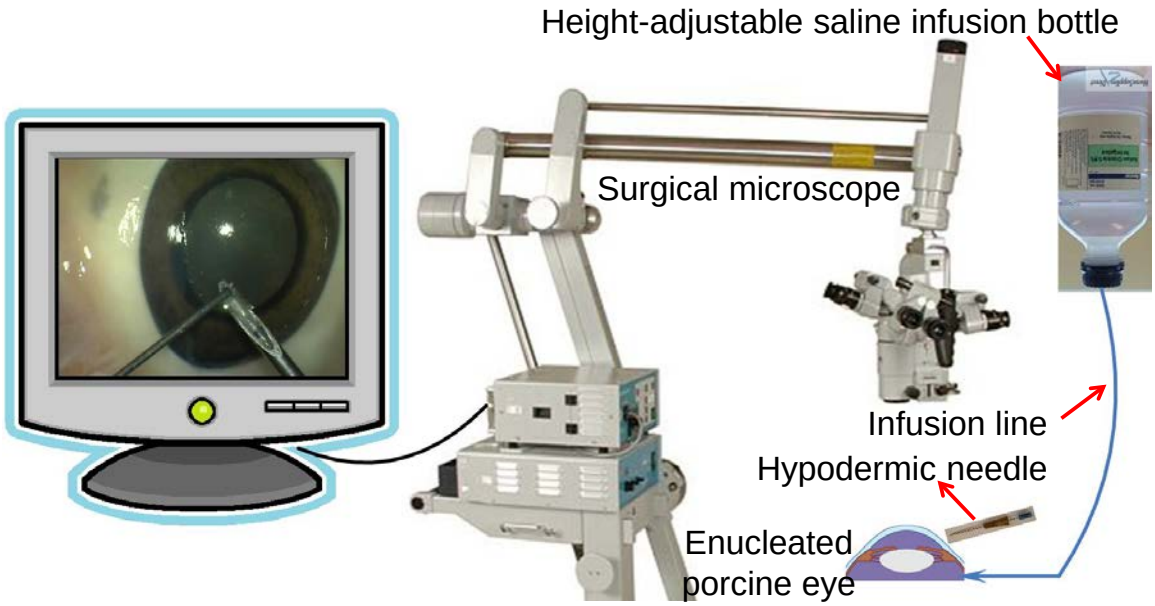

Figure 3-18: Testing setup of GDD *ex vivo* implantation test

3.6.1 GDD *ex vivo* implantation

Two *ex vivo* implantations are performed to understand the behavior of the two proposed integrated GDD systems implanted in enucleated porcine eyes and the function of the parylene-C fixation anchor. It can be shown Figure 3-20 (a) that the parylene-C fixation anchor helps the GDD stay firmly without moving successfully after needle retracted. Before the implantation started, the GDD was primed first, that is, inject saline through the GDD, to ensure no blockage within the tube.

3.6.2 Tapered hollow parylene-C protective tube mockup *ex vivo* implantation

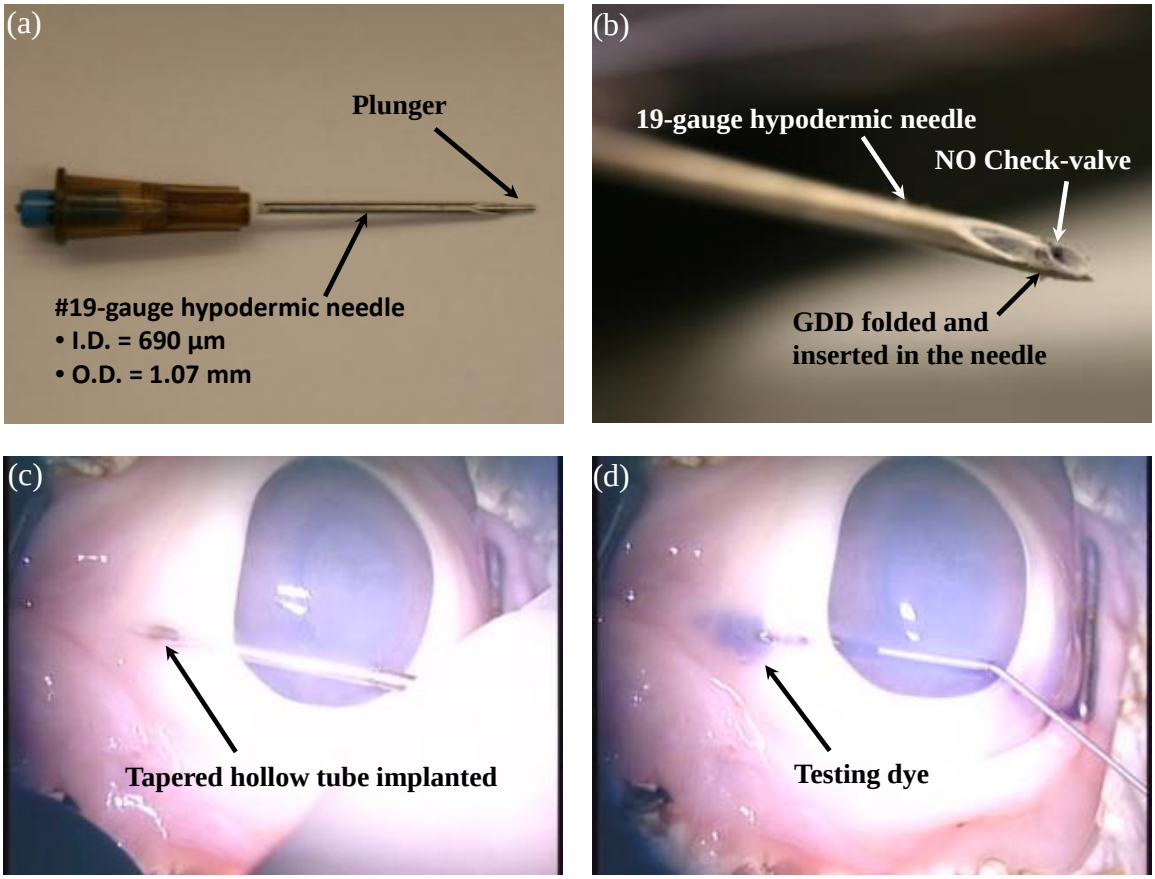

Figure 3-19: (a) The plunger in the needle introducer, (b) a GDD with folded zigzag type parylene-C fixation anchor inserted into a #19-gauge hypodermic needle, (c) a hollow parylene-C tube subconjunctivally implanted into an enucleated porcine eye, (d) testing dye shunted into the hollow tube. The drained-out testing dye is visible.

The *ex vivo* testing results of the first type of GDD developed in Section 3.3 are summarized in Table 3-1. The infusion line was connected to the vitreous chamber so that different pressures can be provided by raising the infusion bottle. After GDD implantation, a blue dye was injected into the anterior chamber, then the infusion bottle was raised up to increase the pressure. Soon after the infusion line was turned on, the dye

was seen to come out of the GDD, as shown in Figure 3-20 (a). After a few seconds, when the IOP reaches 52 mmHg, the infusion line is turned off. The video shows that GDD successfully opened to drain out testing dye well before the IOP reached its final 52 mmHg. From the timeline of the video, the turn-on pressure was around 15–25 mmHg.

Another implantation was also performed with the second type of GDD system introduced in Section 3.4. In this experiment, one end of the GDD was exposed to air in order to understand more about the behavior of the external end of the GDD. Unlike the previous setup, the infusion line and dye were both inserted and injected directly into anterior chamber to mimic the accumulation of aqueous humor during real glaucoma. Video recordings show that once saline and testing dye were both injected into the anterior chamber, GDD started to drain out the liquid due to the increased accumulated pressure, as shown in Figure 3-20 (b). We adjusted the saline flow-rate and observed that the GDD stopped to drain out fluids at 24 mmHg. The offset of the cracking pressure is possibly due to differences between *in vitro* and *ex vivo* testing environments. A hysteresis study was also executed at the end of the test to quantify the lowest pressure required to keep the GDD open. Using a cotton swab, capillary forces were introduced to continually pull eye fluids (saline, to be more accurate) out of the GDD. It was observed that the testing dye flow continued until the pressure reached 4 mmHg IOP for a few seconds. This result indicates that the response time of the valve's restoring force is in the order of several seconds.

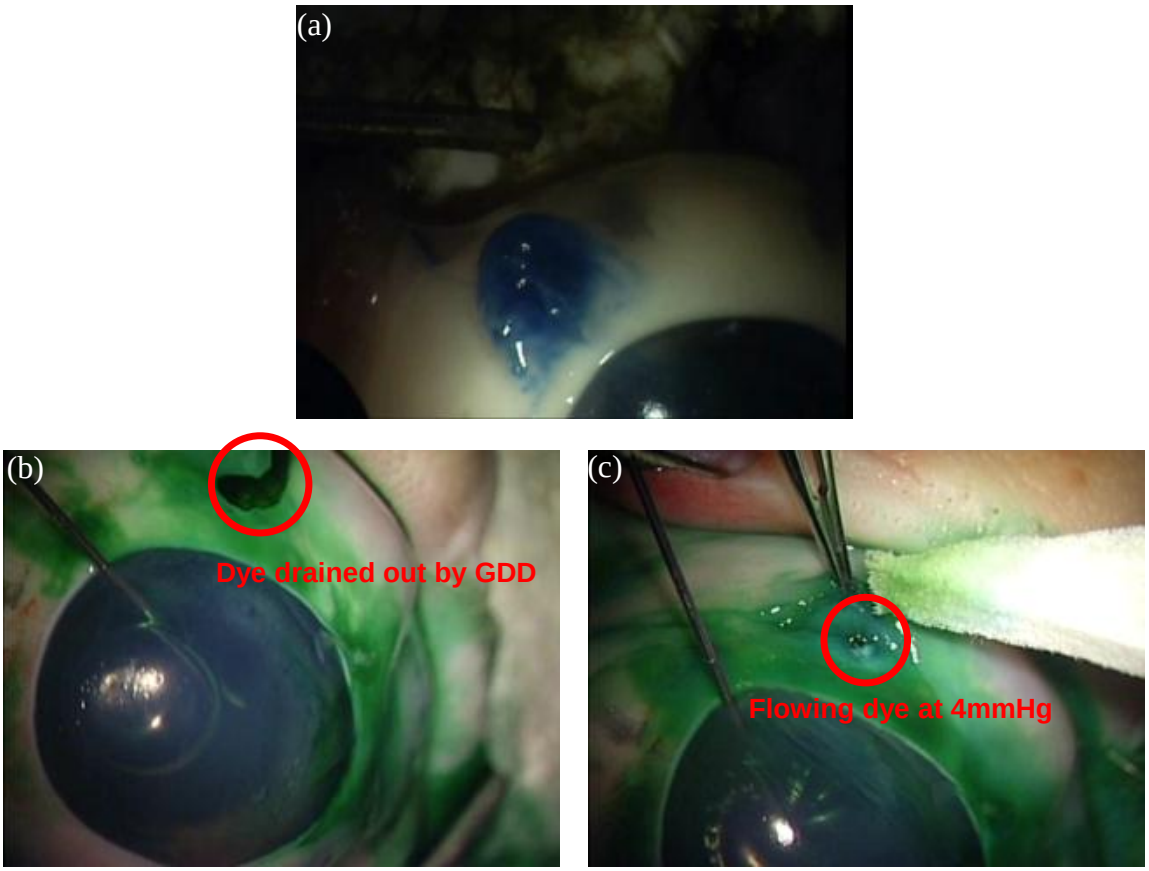

Figure 3-20: *Ex vivo* implantation results of: (a) GDD 1 and (b) GDD 2. The testing dye started to drain out after fluids were injected and stopped at 24 mmHg. (c) Residual dye kept flowing slightly at 4 mmHg.

After experimentation, the implanted GDD was retracted and investigated. Figure 3-21 (a) illustrates the situation of the NC check-valve retracted right after the implantation. Some residue is observed on top of the check-valve surface. The residue most likely comes from the eye fluid. After one week of soaking in DI water, the check-valve surface is cleaner, but some residues remained, as shown in Figure 3-21 (b). Future work would try to work out a solution to remove the residue and prevent GDD clogging after the implantion.

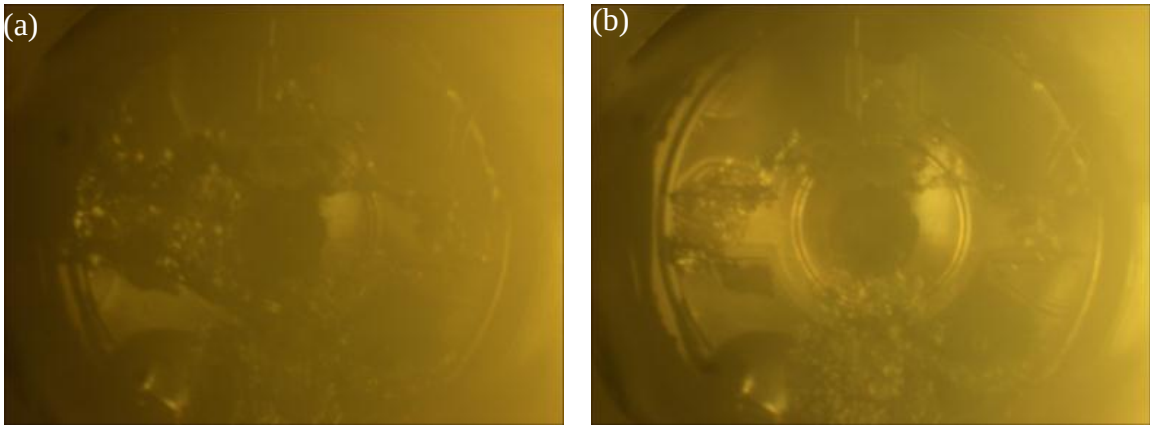

Figure 3-21: Inspection of the NC check-valve after *ex vivo* implantation: (a) right after the implantation, and (b) after one week of soaking in DI water

3.7 Summary and Conclusion

In this chapter, two types of glaucoma drainage devices are designed, developed, fabricated and tested: one has two valves integrated at both ends of the protective tube while the other allows position adjustments. Both GDD comprise of two types of valves (NC and NO) to accomplish the "band-pass" flow regulation. Two valves are packaged with valves' surfaces facing interior to each other to protect the valves' structure. For the selection of the NC check-valve, the self-stiction-bonding NC check-valve introduced in Section 2.6 is adopted here for the GDD system use due to its proper cracking pressure range. The NO valve is developed as the high-pressure stopper, which is one of the critical benefits of our GDD system. For the valve-position-adjustable GDD system, a coupling tube is involved into the system to realize the purpose of position-adjustable valve configuration. Aside from the valves development, the fabrication of the parylene-C protective tube is also developed. In addition, the parylene-C fixation anchors are fabricated by incorporating the dry film photolithography technique to overcome the

substrate recess problem. The packaging procedures of the entire GDD are developed to complete the final GDD system. Both bench-top characterization and *ex vivo* implantation test are performed to verify the functionality and the biomedical feasibility of the GDD. *Ex vivo* testing results show that the developed GDD can successfully regulate the eye fluid pressure down to ~ 24 mmHg. Some residues are found on top of the NC check-valve after the implantation. Future work would focus on the prevention of the accumulation of such residue.