CHAPTER 1

INTRODUCTION

1.1 Introduction to Glaucoma

Aqueous humor is the fluid that is generated by eye's ciliary body. The production rate of the aqueous humor is about 2–3 μL/min and has a turnover time of 1.5–2 hours [1]. The aqueous humor consists of 99.1% water [2]. The generated aqueous humor flows from the posterior chamber, through the pupil, and then goes into the anterior chamber. It is believed that the function of the aqueous humor is to nourish the eye tissues around the anterior chamber. The aqueous humor is drained out from the trabecular meshwork into the channel of Schlemm, and eventually leads the fluid through the sclera into the venous system. As the aqueous humor stays in the anterior chamber for 1.5–2 hours, it manifests the normal average intraocular pressure (IOP) as 16 mmHg above the atmosphere pressure with standard deviation of 2.5 mmHg [1].

Primary open angle glaucoma is an eye disease where aqueous humor produced by the ciliary body cannot be drained out normally by patients' eyes' trabecular meshwork. 21 mmHg is deemed as the "upper limit of normal" IOP. Without successful aqueous humor drainage, the aqueous humor will accumulate in the anterior chamber of the eye and result in abnormally high intraocular pressure [3]. The elevated pressure will then be transmitted onto the retina in the back of the eye and continuously suppress and

damage the patient's optic nerves—causing visual field loss and eventual blindness if not treated sufficiently.

It is estimated that 60.5 million people worldwide have glaucoma in 2010, most of which is associated with abnormally high intraocular pressure [4], and the number may increase to almost 80 million by 2020 [5]. Statistics show that glaucoma is the second leading cause of blindness in the world (World Health Organization [6]). In the United States, it is also estimated that 2.2 million Americans have glaucoma but only half of them are aware of it, because glaucoma has virtually no symptoms. Glaucoma causes blindness in approximately 120,000 Americans, accounting for 9%–12% of all blindness in the United States. Glaucoma is five times more common in people of African-American descent than in Caucasians, and is the leading cause of blindness among African Americans. Unfortunately, 10% of glaucoma patients who receive proper treatment still experience loss of vision [6].

1.2 Current Treatment of Primary Open Angle Glaucoma

Current major clinical treatment of glaucoma includes traditional medication and glaucoma filtration surgery (GFS).

1.2.1 Medications for glaucoma

The typical medication for primary open angle glaucoma includes eye drops or oral medication, which function either to reduce the eye fluid production rate or help the drainage rate, depending on the form of the patient's glaucoma. However, eye drops and oral medications may have several side effects, such as blurred vision, low blood pressure, and fluctuation in heart rhythm [6]. Table 1-1 summarizes some current typical glaucoma medications and their corresponding possible side effects. The medication

treatment may also come with compliance issues: this type of medication requires patients to take eye drops regularly (every morning and evening), making it inconvenient and easily forgotten over continuous treatment. In addition, the medication may gradually lose its effect over a period of time, and hence some glaucoma patients may become resistant to all medications, called "refractory glaucoma" [7]. Refractory glaucoma is more stubborn and difficult to treat, and therefore some alternate approaches which physically drain away the aqueous humor are considered to treat these patients. Apart from the reasons mentioned above causing refractory glaucoma, problems with inefficient dosage style or glaucoma patients' allergic response to the drug composition also stimulate more research on alternative glaucoma treatments.

Table 1-1: Some current typical glaucoma medications and their corresponding possible side effects

Medication name	**Working mechanism**	**Possible side effects**
Timolol	Reduces aqueous humor production rate	Cardiac arrhythmias; Bronchospasm[8]
Travoprost (Travatan Z)	A prostaglandin that increases aqueous humor outflow rate	Blurred vision; Eyelid redness[9]
Latanoprost (Xalatan)	A prostaglandin that increases aqueous humor outflow rate	Blurred vision; Eyelid redness[10]
Pilocarpine	Increases aqueous humor outflow rate	Excessive sweating; Excessive salivation; Bronchospasm; Hypertension[11]

1.2.2 Glaucoma filtration surgery

Glaucoma filtration surgery (GFS) is an alternative glaucoma treatment which has been shown more effective at preventing glaucoma progression than other primary treatments in open-angle glaucoma [12]. Trabeculectomy, one of the most commonly used GFS, removes part of a patient's trabecular meshwork around the iris to create a pathway to improve the extraocular drainage of aqueous humor [2]. However, the biggest drawback of the surgery is that the incisions might heal after a period of time, and therefore repeated surgery is likely required. In addition, removing the trabecular meshwork leaves the IOP uncontrollable. The aqueous humor can flow away easily without any flow resistance and hence lead to hypotony—when IOP is lower than 5 mmHg. Ocular hypotony can lead to corneal decompensation or a flat anterior chamber with subsequent choroidal detachment or cataract formation [13].

1.3 Glaucoma Drainage Device

In order to have a reliable alternative in addressing those issues, a glaucoma drainage device (GDD)—with the intent of physically draining the excessive aqueous humor through the artificial drainage path so as to reduce the associated IOP—has been a persistent research goal. The drained-out excessive aqueous humor is redirected into a subconjunctival chamber, called a bleb [14]. The drained-out aqueous humor will be eventually absorbed by the human circulation system.

1.3.1 Active glaucoma drainage device

The development of GDD can be categorized into active and passive devices. For example, Neagu developed glaucoma drainage devices using the electrochemical actuating mechanism in 1998 [2]. The flow-rate is regulated by deformation of a

membrane micro valve actuated by electrolyzing the electrolyte underneath the micro valve. Besides the actuating system, the whole active eye-fluid regulating system also includes the pressure sensor, feedback control system, and an inductive coupling coil behaving as the power transmission system. In 2001, Bae also proposed another type of active glaucoma drainage device using a membrane micro valve similar to Neagu's [15–18]. Rather than being driven by electrochemical actuator, Bae's membrane micro valve is driven by an electromagnetical actuator. Bae's *in vitro/vivo* experiments demonstrated the device's capability to regulate fluid pressure to the desired pressure settings with the help of a proper feedback control system.

The advantage of the active GDD system is that it can control the flow-rate and the IOP according to the requirements of different patients. However, there are many disadvantages to this device. For example, power transmission is always one of the main concerns of the active devices. In addition, the necessity and the combination of actuating system, feedback control system, and the power transmission system makes the active GDD system much more complicated than passive GDD to fabricate, integrate, and implant. The conducting metal and the actuator used in the GDD usually come with a biocompatibility issue. Therefore, a passivation layer is normally needed to cover active devices, and the influence of those embedded electronic circuits on the human body is still unknown.

1.3.2 Passive glaucoma drainage device

Due to the complicated design and fabrication of the active GDD system, the GDD under development in this thesis focuses mainly on the passively driven approach. The GDD should have a micro check-valve that consumes no power, and can still

regulate the IOP within a normal pressure range (1020 mmHg), responding to different IOP situations. The material used must be biocompatible, to reduce the inflammatory response and prevent rejection of the device. The proposed GDD must also be easy to manufacture and surgically implant into the eye. The history and the development of the passive GDD will first be introduced in the following few sections.

1.3.2.1 History of the development of glaucoma drainage devices

The history of the development of the glaucoma drainage devices until 1997 is shown in Table 1-2. The earliest attempt at implanting a GDD can be dated back to 1907. Rollet first proposed the idea of implanting a horse-hair thread connecting anterior chamber to the subconjuctival space, trying to drain out the excess eye fluid [12, 19, 20]. Subsequently, other people tried many different kinds of materials, such as silk [21], gold [22], tantalum [23], glass rod [24], platinum [25], and polythene tube [26]. These previous hollow tubes were not successful because of bio-incompatibility and migration of the implants. In addition, the hollow tube, with neither threshold pressure constraint nor high-pressure protecting mechanism, causes excess fluid to leak out of the eye and leads to hypotony.

In 1969, Molteno introduced the GDD with the concept of utilizing an extra-thin plate with large surface area, based on his hypothesis that the previous filtration failure was primarily attributable to subconjunctival fibrosis [27]. Molteno's GDD has an acrylic tube attached to a thin acrylic plate implanted subconjunctivally. With no pressure regulating mechanism designed, the plate expands the conjunctival space to help distribute aqueous and prevent the "thinning of the bleb" [28]. With not too much success owing to plate exposure, tube erosion, and scar tissue formation, in 1973,

Molteno proposed a revised version of his previous GDD by placing the thin plate farther from the cornea with a longer acrylic tube to gain a higher success rate [29]. Although the Molteno GDD has no resistance valve embedded, the Molteno GDD utilized the deflection of the conjunctival layer to control the aqueous flow-rate and the final IOP.

With the higher success rate of the Molteno GDD, the tube-and-plate structure had become one of the benchmarks of GDD design. Since then, two major concepts have also been adopted for the GDD developments:

1. Built-in resistance, usually fulfilled by introducing a valve within the GDD, is introduced to GDD design to reduce postoperative hypotony. For example, in 1976, Krupin introduced the GDD with a slit valve to prevent early, postoperative hypotony [30]. The slit valve was designed to open at a pressure of 11 mmHg and close at a pressure of 9 mmHg. In 1993, Ahmed introduced a GDD with a valve utilizing Venturi's effect to reduce the friction within the valve system and help drain away the aqueous humor [31–34]. The Ahmed glaucoma valve (AGV) is designed to open at a pressure of 8 mmHg.
2. The large end plate or the explant becomes one of the paradigms. GDD developers tend to incorporate larger surface area to promote the bleb formation and therefore acquire lower IOP [35–39]. For example, Molteno introduced a double-plate GDD in 1981 [38] in contrast to the previous single-plate GDD in 1973. In 1992, Baerveldt also introduced a nonvalved silicone tube attached to a large barium-impregnated silicone end plate [40–42].

Table 1-2: History of glaucoma drainage device development [12]

Year	Investigator	Type	Material	Method	Flow control	Drainage site
1907	Rollet [43]	seton	Horse hair	Paracentesis	None	Anterior subconjunctival
1912	Zorab [21]	seton	Silk thread	Translimbal	None	Anterior subconjunctival
1925	Stefansson [22]	seton/tube	Gold	Translimbal	None	Anterior subconjunctival
1934	Row [44]	seton	Platinum	Cyclodialysis	None	Suprachoroidal
1940	Troncoso [23, 45]	seton	Magnesium	Cyclodialysis	None	Suprachoroidal
1942	Gibson [46]	tube	Lacrimal canaliculus	Transcleral	None	Anterior subconjunctival
1949	Bick [47]	seton/tube	Tantalum	Cyclodialysis	None	Suprachoroidal
1951	Muldoon [25]	seton	Platinum	Translimbal	None	Anterior subconjunctival
1952	Losche [48]	tube	Supramid	Cyclodialysis	None	Suprachoroidal
1955	Bietti [49]	tube	Polyethylene	Cyclodialysis	None	Suprachoroidal
1958	La Rocca [50]		Polyvinyl	Translimbal	None	Anterior subconjunctival
1960	Ellis [51]	tube	Silicone	Translimbal	None	Anterior subconjunctival
1967	Mascati [52]	tube	Plastic	Translimbal	None	Lacrimal sac
1969	Molteno [27]	tube-and-plate	Acrylic	Translimbal	None	Anterior subconjunctival
1974	Lee [53]	tube	Collagen	Translimbal	None	Vortex vein
1976	Krupin [30]	tube	Silicone and supramid	Translimbal	Slit valve	Anterior subconjunctival
1979	Honrubia [54]	tube	Silicone	Translimbal	None	Anterior subconjunctival
1982	Schocket [55]	tube and band	Silicone	Translimbal	None	Posterior subconjunctival
1985	White [56]	tube-and-plate	Silicone	Silicone	Valve and pump	Posterior subconjunctival
1986	Joseph [57]	tube and band	Silicone	Translimbal	Slit valve	Posterior subconjunctival
1990	Krupin [58]	tube-and-plate	Silicone	Translimbal	Slit valve	Posterior subconjunctival
1990	Baerveldt [59]	tube-and-plate	Silicone	Translimbal	None	Posterior subconjunctival
1993	Ahmed [32]	tube-and-plate	Silicone and polypropylene	Translimbal	Venturi valve	Posterior subconjunctival
1995	OptiMed [60]	tube-and-plate	Silicone and PMMA	Translimbal	Microtubules	Posterior subconjunctival
1995	Smith [61]	seton	Hydrogel	Translimbal	None	Intrascleral
1996	Pandya [62]	tube-and-plate	Silicone and hydroxylapatite	Translimbal	None	Posterior subconjunctival
1997	Glovinsky and Belkin [63]	tube	Stainless steel	Translimbal	None	Anterior subconjunctival
1997	Helies [64]	artificial meshwork	PTFE	Transcleral	None	Anterior subconjunctival

1.3.2.2 Contemporary passive glaucoma drainage device

Table 1-3 summarizes some of the current glaucoma drainage devices. The first category shows the commonly used tube-and-plate GDD design, which has dominated the GDD market since 1969. This type has an end plate located underneath the conjunctiva layer acting as the base for the bleb to form.

Table 1-3: Contemporary glaucoma drainage devices (GDDs) [12, 20]

Design	**Drainage location**	**Commercial available examples**
Tube-and-plate GDD	7–10 mm from limbus	Molteno, Baerveldt, Ahmed, Krupin, Optimed
Translimbal GDD	At the limbus	Ex-PRESS shunt
Trabecular bypass devices	Channel of Schlemm	GMP Eye pass, Glaukos trabecular bypass shunt
Trabecular bypass devices	Suprachoroidal space	SOLX system

The second type is translimbally implanted and drains the aqueous humor to the subconjunctiva. The most recently introduced GDD is EX-PRESS, made of stainless steel. The implantation concept of this type GDD resembles the concept of trabeculectomy surgery.

The third type involves implanting the GDD in such a way as to mimic the function of the trabecular meshwork, which helps drain away the aqueous humor through the channel of Schlemm. The GMP eye pass and Glaukos trabecular bypass shunt are examples of this type of GDD.

The fourth type of GDD drains the aqueous humor to the area of suprachoroidal space, and is still under clinical trials.

1.3.2.3 Glaucoma drainage devices with no resistance

Seen in Table 1-3, Molteno and Baerveldt are tube-and-plate GDDs with no resistance designed. This type of GDD has an end plate implanted underneath the conjunctival layer, which turns into the controlling membrane of the implants.

As for the translimbal GDD, Ex-PRESS shunt has no resistance designed as well. However, the small diameter (50 μm [20]) makes it still possible to have a pressure drop of 4.78 mmHg within in the tube while draining out the aqueous humor.

For the trabecular bypass type GDD, GMP Eye pass, and Glaukos trabecular bypass shunt are designed with no resistance incorporated. The main reason is likely due to the fact that their small tube sizes have already provided a certain amount of pressure resistance for the drainage devices. Because a proper flow resistance designed in the GDD system is required to prevent postoperative hypotony, the contemporary GDD usually comes with a mechanism designed to regulate the flow-rate and the IOP. To estimate the required flow resistance of the entire GDD, the flow resistance of a hollow tube is introduced in the following section.

1.3.2.3.1 Flow resistance of a hollow tube

The flow resistance is defined according to the relationship between the pressure drops versus the flow-rate. Assume that the volume flow-rate, Φ, is proportional to the pressure difference, Δp, then the relation can be expressed in a simple form as [65]:

$$\Delta p = R \cdot \Phi, \tag{1-1}$$

where R is defined as the channel flow resistance. If the liquid flow in the circular hollow tube is a laminar flow, the pressure difference, Δp, across a circular hollow tube can be calculated by Hagen–Poiseuille equation, which is expressed as:

$$\Delta p = \frac{128\mu l}{\pi d^4}\Phi, \tag{1-2}$$

where μ is the viscosity of the fluid, l is the tube length, d is the tube diameter.

Therefore, the flow resistance of a circular hollow tube can be found as:

$$R = \frac{128\mu l}{\pi d^4}. \tag{1-3}$$

The Reynolds number, *Re*, is used to identify whether the flow is a laminar flow. For a laminar flow, *Re* must be less than 2300. The Reynolds number is represented as:

$$Re = \frac{\rho \bar{v} d}{\mu}, \tag{1-4}$$

where ρ is the fluid density, and $\bar{v}$ is the average velocity of the fluid, which can be calculated by

$$\bar{v} = \frac{4\Phi}{\pi d^2}. \tag{1-5}$$

Take the Ex-PRESS shunt as an example. To calculate its pressure drop across the shunt, the Reynolds number is first calculated. The aqueous humor density is assumed to be 1000 kg/m^3, the volume flow-rate is taken as 2 µl/min = 3.3x10^{-11} m^3/sec, and the diameter of the Ex-PRESS shunt is reported as 50 µm [20]. The viscosity of the aqueous humor, μ, is found to be approximately similar to that of the saline, and therefore μ is equivalent to 1x10^{-3} Pa·s [2, 66, 67]. The Reynolds number is then calculated as 0.84, which is much smaller than 2300, and therefore the aqueous humor flow can be assumed as laminar flow in the shunt, and eqn. (1-2) can be applied to estimate the

pressure drop of the Ex-PRESS shunt. Because the length of the Ex-PRESS shunt is reported as 2.96×10^{-3} m [20], the pressure drop can be found as 636.77 Pa = 4.78 mmHg.

If the inner diameter of the Baerveldt and Molteno GDD shown in Table 1-4 as 0.635×10^{-3} m is considered, the length of the silicone tube is taken as 1×10^{-2} m, as shown in Table 1-3, the Reynolds number is obtained as 0.066, and the pressure drop is calculated as 0.0827 Pa=6.2×10^{-4} mmHg, which is relatively too small for practical GDD to use.

1.3.2.4 Glaucoma drainage devices with resistance

Two main tube-and-plate glaucoma drainage devices have been developed with micro valves as the flow resistance. The Ahmed glaucoma valve's silicone tube is connected to a silicone sheet valve, with the inlet section is made wider than the outlet. This special "Venturi shaped" chamber design introduces a pressure drop from inlet to outlet based on the Bernoulli principle. The Ahmed glaucoma valve is designed to open at 8 mmHg. Krupin developed another valved tube-and-plate GDD, with a silicone tube consisting of the cross-slit element. The Krupin GDD is designed to open at 11–14 mmHg. The other possible valved tube-and-plate GDD is the Optimed model-1014 GDD. The Optimed GDD is made of a "flow-restricting" unit consisting of multiple microtubules, each of which provides pressure drop governed by the Hagen–Poiseuille equation, as expressed in eqn. (1-2).

1.3.2.5 Comparison of current "tube-and-plate"-type glaucoma drainage devices

As the current dominant benchmark in the GDD development market, tube-and-plate structure are explored more and discussed at length in this section.

1.3.2.5.1 End plate size comparison

Table 1-4 shows the comparison of some geometry factors of the tube-and-plate. The GDD developers had been focusing on increasing the size of the end plates, as larger end plate size was believed to have more effective IOP regulating capabilities. However, the long-term implantation follow-up shows that there is no statistical difference between the surface areas ranging from 130 mm^2 (Molteno single plate) to 350 mm^2 (Baerveldt) among all different GDDs [19, 68, 69].

As for the comparison of the single-plate and double-plate Molteno GDD, although Heuer et al. concluded that the double-plate implants resulted in a statistically significant lower IOP and higher overall surgical success compared to single-plate GDD, the double-plate Molteno success and final IOP were only slightly better than the results with the single-plate implant [19, 36]. Lloyd et al. also found no statistical difference in the overall surgical success rate or IOP control comparing the Baerveldt's end plates' area with 350 mm^2 vs. 500 mm^2 [19, 40]. In addition, Smith et al. did a comparison of implantation results of 350 mm^2 Baerveldt GDD with 270 mm^2 double plate Molteno GDD. They found out that the mean IOP was similar at the 11.3 months of follow-up [19]. This may imply that end plate's area of 270 mm^2 might be large enough for the GDD and the improvement is not obvious once the area size is large than 270 mm^2. In summary, it is found by many researchers that the size of the end plate does influence the

IOP regulating capabilities to a certain point. However, the effect is not linear proportional and also not the overall success rate of the operation.

Table 1-4: A comparison of some of current commercially available "tube-and-plate"-type glaucoma drainage devices (GDDs) [12, 20]

Product name and Manufacturer	**Product**	**Year of first introduction**	**Tube dimension***	**Surface area (mm^2)**	**Biomaterial**	**Valved /nonvalved**
Ahmed Glaucoma Valve (New World Medical, CA, USA)	model S3	1993	0.635 mm OD 0.305 mm ID, [70]	96	Polypropylene	Valved
	model S2			184	Polypropylene	Valved
	model FP8			96	Silicone	Valved
	model FP7			184	Silicone	Valved
	model B1 (Bi-plate)			364	Silicone	Valved
Baerveldt Glaucoma Implant (Abbott Medical Optics, Inc.)	BG 103–250	1990	0.63 mm OD 0.30 mm ID, [71]	250	Silicone	Nonvalved
	BG 101–350			350	Silicone	Nonvalved
	BG 103–425			425	Silicone	Nonvalved
Molteno Glaucoma Implant (IOP Inc., CA, USA)	Molteno single plate	1979	0.64 mm OD 0.34 mm ID, [72]	135	Polypropylene	Nonvalved
	Molteno double plate			270	Polypropylene	Nonvalved
Hood Laboratories, Pembroke, MA	Kruping with disc	1990	0.58 mm OD 0.38 mm ID, [12]	180	Silicone	Slit valve
Optimed (Manufacturer not available)	Model-1014	1995	0.56 mm OD 0.30 mm ID, [12]	140	Silicone drainage tube with PMMA matrix	Microtubules

*OD: Outer diameter; ID: Inner diameter

1.3.2.5.2 Results of clinic trials comparison

Table 1-5 lists the results of five different GDDs' clinical trials summarizing from systematic literature reviews. The Pearson chi-square test was used to compare the incidence of surgical outcomes and complications among the GDDs. P value shown in Table 1-5 represents the paired *t*-test, which indicates how significantly different within a variable among the five GDDs. A two-tailed $p < 0.05$ was considered with statistically significant difference. As can be seen from the table, there is no statistically significant difference in the postoperative follow-up time among the five GDDs. The pre-op IOP shows a statistically significant difference as the pre-op IOP of Molteno with no modification shows a higher value. The post-op IOP and % change in IOP, which both can be deemed as the regulating capabilities of the GDD, show no statistically significant differences and therefore it implies that these five GDDs have very similar regulating capabilities. This is verified by the p-value of the surgical success as 0.94. As shown, all five GDD can lower IOP within the normal pressure range with successful rate between 72–79%.

There are no statistically significant differences found for the incidence of decrease in visual acuity (0.9), transient hypotony (0.17), chronic hypotony (0.51), and suprachoroidal hemorrhage (0.47). For the pre-op and post-op medication numbers, all five GDDs had no statistically significant differences, meaning five GDDs were all capable of reducing the post-op medication numbers. The diplopia occurrence of Baerveldt implant and Krupin valve show relatively high numbers compared to other three GDDs. Therefore $p = 0.01$ is obtained. The possible reason causing this high diplopia occurrence will be discussed in Section 1.3.2.6.2.

Table 1-5: Literature review of glaucoma drainage devices (GDDs) (1969–2002) [19, 20, 73, 74]

Variable	Molteno with no Modification	Molteno with surgical Modification (e.g., ligature)	Baerveldt Implant	Ahmed Glaucoma Valve	Krupin Valve	P value
Mean follow-up (Months)	23.1±10.8	27.1±14.2	18.6±7.8	16.0±7.5	21.3±11.2	0.72
Pre-op IOP, mmHg	42.1±2.1	34.1±4.8	30.8±4.2	33.9±4.5	36.3±1.5	0.02*
Post-op IOP, mmHg	17.1±1.3	16.6±2.1	14.3±1.8	16.6±1.8	13.8±1.6	0.32
% change in IOP	59±3	51±6	54±8	51±8	62±5	0.20
Surgical success, %	75±12	77±13	75±10	79±8	72±11	0.94
Decrease in visual acuity, %	33±18	30±13	27±10	24±7	28±4	0.90
Pre-op meds, no.	NR	2.3±0.3	2.2±0.3	2.7±0.3	2.7±0.3	0.40
Post-op meds, no.	1.5±1.0	1.1±0.6	0.8±0.2	1.0±0.3	1.0±0.2	0.86
Transient hypotony, %	26±14	12±7	15±8	14±8	17±12	0.17
Chronic hypotony, %	5±3	6±5	6±3	2±1	2±2	0.51
Diplopia, %	NR	2±2	9±5	3±1	7±5	0.01**
Suprachoroidal hemorrhage, %	NR	4±3	5±3	3±3	8±7	0.47

NR: Not reported

*Pre-op IOP was significantly higher in “Molteno with no modification” group

**Diplopia rate was significantly higher in Baerveldt group compared to Molteno and Ahmed glaucoma valve groups.

1.3.2.6 Postoperative complications of current glaucoma drainage devices

Table 1-5 reveals that these five GDDs can all successfully regulate the IOP and possibly treat the refractory glaucoma. However, several complications are generally found with GDDs.

1.3.2.6.1 Hypotony

It can be seen from Table 1-5 that the occurrence of post-op chronic hypotony of Ahmed glaucoma valve and Krupin Vale is obviously lower than the rest three GDDs. This implies the function of the incorporated valves of these two GDDs, which are claimed to close at the IOP of 8–9 mmHg. However, the transient hypotony occurrence

of these two GDDs does not show any impressive hypotony improvement as claimed by the manufacturers. It is likely due to the insertion site of the GDD's silicone tube that aqueous humor might leak through before the incision heals, causing the early hypotony. As for the nonvalved Molteno GDD, it clearly shows that the modified Molteno GDD has a better performance in terms of the early transient hypotony.

1.3.2.6.2 Diplopia

It is found from Table 1-5 that the occurrence of diplopia of Baerveldt is higher than the rest four GDDs. It is likely due to its special design that the device is implanted underneath the recti muscles. It is suggested that diplopia may be related to the height of the bleb or due to the adhesions to the recti muscles as the Baerveldt end plate is inserted under the muscle belly [40]. The problem is suggested to be solved by modifying the end plate such as fenestrating the end plate. However, the there is still no quantitative reports regarding this improvement yet [75].

In addition, it is also reported that up to 30% of the patients receiving GDD implantation surgery might have corneal decompensation [19]. The complexity of these complications proves the difficulties of developing a final successful glaucoma drainage device.

1.3.2.7 Long-term failure of the GDD: Bleb fibrosis

Apart from the immediate postoperative complications after the GDD implantation, the GDD could fail after a long-term operation. Bleb fibrosis is one of the major problems that lead to the GDD failure. The fibrous reaction around the end plate may encapsulate the end plate and eventually influence the final IOP.

The fibrosis is believed to happen due to the introduction of outside biomaterials such as the end plate of the GDD which could cause a fibrovascular response in the subconjunctival space [19]. In addition, the introduction of the aqueous humor into the subconjunctival space can stimulate fibrovascular proliferation in the episcleral tissue as well [26]. The intensity of the fibrous reaction may vary with respect to several factors such as the biomaterial, size, and/or design of the end plate and the individual patient's immune reaction to the operation, the GDD itself, and the presence of aqueous humor in the subconjunctival space, and also some factors that have not been understood.

Several suggestions are proposed to overcome the fibrosis problem. First of all, GDD made of more biocompatible material to reduce inflammation around the end plate, resulting in less scar tissue formation and promote longer GDD lifetime. The inert biomaterial should not attract fibroblast or protein deposits as well, which in turn could lead to cytokine release, chronic low-grade inflammation, and bleb failure [19]. The rigidity, flexibility, and shape design of the end plate is also believed to influence the fibrosis occurrence. The rigid plates might exhibit less to-and-fro micro motion with ocular movement leading to less chronic inflammation.

It is reported that the bleb fibrosis following the trebeculectomy operation can be successfully alleviated by medications such as mitomycin C and 5-fluorouracil. However, the effect of these medications on GDD implantation is still under debate and more clinical trials need to be done to get a clear picture.

1.3.3 Proposed glaucoma drainage device design

Summarizing all the advantages and disadvantages of current GDDs, an ideal GDD should have the following key elements:

1. There must be a micro valve designed in the GDD to provide the necessary resistance to regulate the IOP in a proper range. It is desirable to have a device to regulate the IOP to be in the range of 10–20 mmHg.
2. The biomaterial of the GDD must be totally inert so as to reduce the occurrence of the inflammation and the fibrosis reactions.
3. The GDD needs to have a reliable fixation anchor to prevent it from dislocation after it is implanted.
4. The previously developed GDD focused only on how to drain out the excessive aqueous humor to lower the IOP to a proper range. However, when at a sudden eye pressure increase such as bumping or rubbing the eyes, those GDDs cannot prevent the unwanted aqueous humor drainage. Therefore, an ideal GDD should have a protecting mechanism to prevent hypotony in the case of transient unexpectedly high eye pressure (e.g., > 50 mmHg).
5. An easy implantation procedure is needed to implant the GDD within 10 minutes, without cutting the conjunctival layers. Therefore, a translimbal type of GDD without an end plate is chosen.

Micromachined check-valves have long been used in microfluidic devices for flow controls in micro-total-analysis systems (μTAS) [76, 77]. Those check-valves are used for the control of flow direction, flow-rate, and even pressure distribution. Practically, micromachined check-valves can operate either actively or passively. In terms of human body applications, passive device are generally preferred due to the simpler structure design and no power consumption needed, that is, less complicated circuits embedded in the check-valves.

In our newly developed GDD, the key component of the GDD is one normally closed (NC) check-valve designed to open at 10–20 mmHg. The NC check-valve allows extraneous aqueous humor to flow out of anterior chamber when the IOP is higher than the designed cracking pressure. On the other hand, the NC check-valve remains closed as long as eye pressure is lower than the designed cracking pressure. It restricts eye fluid from leaking out of the anterior chamber to prevent hypotony. The NC check-valve will be introduced in chapter 2. To fulfill the concept that the GDD closes at a sudden unexpected high IOP, one normally open (NO) check-valve is also developed. This NO check-valve opens during the normal operation, but closes when it encounters a sudden high IOP. The NO check-valve will be introduced in Section 3.2. In addition, the development of the fixation anchors, the integration, *in vitro* characterization, and *ex vivo* experiments of the whole GDD system will all be introduced in chapter 3.

1.4 Intraocular Pressure Monitoring

Because there could be no symptoms of pain in open angle glaucoma and the human eye tends to compensate a small peripheral vision loss, open angle glaucoma patients are usually diagnosed in the late stage of the disease. Thus an early stage diagnostic becomes also important in glaucoma management.

1.4.1 Current clinical IOP monitoring approaches

One of the current clinical IOP monitoring approaches is implement applanation tonometry [78]. The fundamental working principle is by applying a force onto the corneal surface, which is flattened by the sensing probe surface. The applied force is balanced with the deflection of the corneal and IOP, and therefore the IOP can be calculated given the flattened cornea's mechanical properties and its surface area.

Goldmann applanation tonometry (GAT) and tono-pen (Reichert, Inc., Depew, NY) are two examples utilizing this contact approach to measure the IOP. The noncontact approaches such as pneumotonometry (i.e., air-puff tonometry) [79, 80], however, are currently more popular. The pneumotonometry blows an air-puff, which serves the applanation force in this case, onto the eye to flatten the corneal surface. The deformation of the corneal surface is measured by optical approach. Similar to the contact tonometry approach, the applanation force is balanced with IOP and the corneal surface, and therefore the IOP can be calculated given the measured flattened corneal surface and the applied force. Compared to contact tonometry, the pneumotonometry provides more accurate readouts as it has less refractory responses from the targets during the measurement.

1.4.2 Wireless telemetric sensing technology

Even though the applanation tonometry can provide quite useful information of patients' IOP, the readout, however, can be seriously affected by many unpredicted parameters such as the cornea thickness, the orientation of the instruments during the measurment, or variation in the corneal mechanical properties' from person to person [81–83]. Besides, the applanation tonometry requires skillful operation, which can only be performed by well-trained professionals such as ophthalmologists, making continuous IOP monitoring impractical.

Furthermore, it is reported that the IOP spikes that happen within the daily IOP fluctuations could also risk optic nerve damage [84–86], and therefore IOP is suggested to be monitored continuously with a long period of time. Nowadays, continuously monitoring of IOP still cannot be achieved *via* current applanation approach. Therefore,

a wireless IOP sensing technique is required to accomplish a direct, convenient and reliable continuous IOP sensing technology.

The concept of utilizing passive telemetric sensing technique to monitor IOP has been developed yearly to achieve the ideal sensors capable of noncontact and continuous in situ IOP measurement [87, 88]. A transensor is the key component of this technique that is implanted into the anterior chamber. The IOP signal is wirelessly obtained by an external coil reader which wirelessly interrogating the implanted sensor. Although the active devices were developed to demonstrate its capability of monitoring the IOP, its size and the power transfer are always the concerns and restrict them from practical usage [87, 89]. On the other hand, passive devices shows a more compact and flexible design which is more suitable for anterior chamber implantation [90].

The first passive device consisting of a capsulated electrical LC resonant circuit was reported in 1967 [91]. The transensor was implanted in the anterior chamber and the concept became the paradigm of current telemetric sensing technology. In recent years, many passive telemetric sensors were developed with the help of MEMS (microelectromechanical systems) technology [92–96]. However, those MEMS transensors usually used wafer bonding technique to create a chamber for the pressure-sensitive device. This process could increase the overall thickness of the device and make the implantation impractical due to the small space of the anterior chamber. In 2008 and 2010, Chen reported parylene-C-based passive IOP sensors featuring the biocompatibility and flexibility of parylene-C as the structural material [97, 98]. The variable capacitor of Chen's IOP sensor was monolithically fabricated by integrating the parylene-C fabrication techniques, and hence no wafer bonding is required. The

completed transensor is small enough for minimally invasive implantation into the anterior chamber.

Although Chen's IOP sensor has demonstrated its successful monitoring the IOP wirelessly, the quality factor reduces after the sensor implantation. This is attributed to the high loss tangent of the aqueous humor surrounding the device. The low quality factor degrades the performance of Chen's sensor, decreasing the sensing distance. In the thesis, two solutions are proposed to solve the problem. One is attaching a capillary tube on the bottom of the device serving as the pressure transducer connecting the anterior chamber and the variable capacitor. The other approach is to protect the sensing coil by covering protective materials with lower loss tangent than aqueous humor. These two new concepts provide new possibilities to skip or isolate the aqueous humor to preserve the quality factor of the sensor, and therefore make the passive IOP sensor implantation practical.

1.5 Biocompatible Material, Parylene-C, Usage

Parylene-C, poly(chloro-para-xylylene) is chosen to fabricate all the devices developed in this thesis. The molecular structure of parylene-C is shown in Figure 1-1. Parylene-C has been proved by Food and Drug Administration (FDA) to be the biocompatible material and complies with United States Pharmacopeia's (USP's) class VI plastics requirements, meaning it is totally implantable in the human body [99].

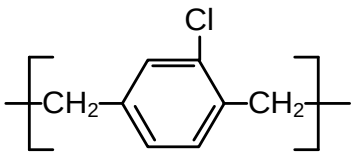

Figure 1-1: Molecular structure of parylene-C

Parylene-C is prepared by the vapor phase deposition at room temperature. To prepare the parylene-C film, the parylene-C dimer is first vaporized at 150°C to the gaseous dimer, and then pyrolyzed at 690°C, turning into the monomer gas. The monomer gas goes into the deposition chamber, conformally coating onto the targets. The deposition temperature is normally kept as room temperature (20°C), and the deposition pressure is in the range of 20–100 mTorr, which is unlike the metallic deposition chamber with deposition pressure as ~ 10^{-5} torr. In the pressure range of 20–100 mTorr, the mean free path is about 1 mm and therefore the monomer gas can uniformly distributed in the chamber and conformally coats the targets.

Parylene-C is a very good dielectric material with dielectric strength of 5600 V/mil and dielectric constant of about 3 [100]. Parylene-C has very low moisture permeability, and very inert to chemicals. In addition, parylene-C can be easily prepared in the clean room and can be patterned by normal oxygen plasma. Therefore, parylene-C fabrication is very compatible with CMOS/MEMS processes and has been widely used in BioMEMS research in recent days.

1.6 Characteristics of Parylene-C

Properties of parylene-C, such as mechanical, thermal and polymer properties, etc, have long been studied in the literature for years [101, 102]. The results are now very available and widely used in many aspects [100]. In many years, people have been using those numbers in designing the insulation layer of printed circuit boards, the modification of implantable medical devices, or any parylene-C-based biomedical devices. In the past few years of our experiences of fabrication of parylene-C film, however, several main concerns are raised.

Most of the properties' numbers were measured at parylene-C film as-deposited state, which means the parylene-C was never treated thermally, mechanically, or any other kinds of treatments, before it was tested. In our fabrication experiences, however, it showed that the mechanical property is seriously affected by its processing histories. For example, after a series of fabrication processes in the clean room, Young's modulus was obtained as 4.75 GPa as compared to 2.78 GPa provided by the vendor of parylene-C dimer [103]. Therefore, it is necessary to understand the final influences that every fabrication process could cause during the device manufacturing.

More specifically, parylene-C is one type of thermal plastic polymer and temperature is a key controlling parameters of its properties. Therefore parylene-C properties are different between room temperature and the human body temperature; i.e., 37°C. The current available parameters cannot ideally represent the behavior of parylene-C in human bodies and needs to be further studied and updated.

For all of the micro check-valves designed in chapter 2, a certain amount of residual tensile stress is always required to pre-stress the tethers so that the check-valves can behave as designed. Due to the natural property of the polymer, however, stress usually relaxes after a period of time, called stress relaxation. To predict the lifetime of these micro check-valves, the rheological properties, that is, creep and stress relaxation, of parylene-C need to be understood. On the other hand, it is also required to know the rheological properties of the parylene-C film to properly design the fabrication procedures. For example, in order to either make the parylene-C-based devices flat or mold it into a certain shape, the proper processing temperature and the information of the time constant of the stress relaxation is required. Viewing back several decades of

parylene-C research history, however, there is still a lack of the viscoelastic-viscoplastic properties of parylene-C film and it will be studied in the thesis.

In addition, MEMS process usually involves different elevated temperatures without the isolation of the oxygen. In such processes, the parylene-C film is likely to get oxidized without a proper treatment, and deteriorates the device properties and performance. Therefore, oxidation must be considered during the fabrication and its behavior is studied in this thesis to understand its influence after different thermal treatment.

Hassler et al. had done a series of uniaxial tensile tests to study the effect of annealing, steam sterilization, deposition pressure and saline soaking on parylene-C's mechanical effect [104]. The results showed that the mechanical properties are very temperature sensitive and seriously affected by the temperature-related process such as annealing and steam sterilization. After high temperature thermal treatment, the parylene-C became more rigid, more brittle, and harder. Hassler suggested that the parylene-C polymer chains grow to a crystal-like structure and make the parylene-C stronger. This is also confirmed in our uniaxial tensile and crystallinity tests.

1.7 Summary

A broad view of the motivations and contents of the whole thesis is introduced in this chapter. The histories of the GDD and the IOP sensors are explored, compared and discussed. It shows that the previously developed GDD leaded to many complications such as diplopia and hypotony. In addition, there was no mechanism among those GDD to prevent over drainage of the aqueous humor under the unexpected high IOP. As for IOP sensor review, previous telemetric IOP sensors experience a decreased quality factor

after implantation. New GDD design and IOP sensor improvement are therefore required to make glaucoma management efficient and practical.

Rheological properties of parylene-C play an important role in designing the medical devices, especially implantable ones. However, there are very few studies of the rheological properties of parylene-C can be found in the past decades of parylene-C research. In addition, parylene-C was reported as a very temperature-sensitive material. Therefore, a complete knowledge of parylene-C properties helps researchers use the materials properly and it will be discussed in the thesis.