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A Short Survey on Currently Used Experimental Setupsfor Testing Glaucoma Drainage Devices

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Abstract

Commonly used glaucoma drainage devices have many disadvantageouscircumstancesespecially in postoperative period such as hypotony, flammation, etc. There are great efforts to overcome these problems in literature. Researchershave investigated glaucoma drainage devicesby in-vivo, ex-vivo and in-vitro experimental setups and tried to overcome their disadvantages. In this study,one branch of them, in-vitro experimental setups currently usedin testing of glaucoma drainage devices are surveyed.

Keywords: Glaucoma drainage devices, in-vitro experimental setups, intraocular pressure, microfluidics.

1. INTRODUCTION

Glaucoma is an eye diseasein which optical nerve is damaged due to abnormal rise of intraocular pressure (IOP) by time. According to World Health Organization, Glaucoma is the second common reason for blindness.In a healthy eye, IOP is 2000 Pa varying between 1600 and 2666 Pa. However it may increase up to 8000 Pa in glaucomatous eyes[1].

IOP can be lowered by some methods such as; surgery (laser treatment, trabeculoctomy etc.), medical therapy, and glaucoma drainage devices (GDD). Although none of these methods gives definite results, GDDs are more preferable due to high success rates depending on design developments inthe last decade. First successful GDD in history was introduced by Molteno in1963 [2].Molteno's implant is comprised of a silicon tube and a plate end of the propylene tube. The tubeshunts anddischarges the flow by pressure differences on each side of plate. The other non-valved GDD is Baerveldt's device. Baerveldt's implant is comprised of a silicone rubber tube and a barium impregnated silicone end plate on which fenestrations allow fibrous bands to diminish bleb profile. After implantation of non-valved GDDs, hypotony occurs (IOP< 5 mmHg) because the bleb formation takes some time postoperatively. To prevent postoperative hypotony, valved GDDs were improved such as Krupin slit valve and Ahmed Glaucoma Valve (AGV). Krupin's valve consists of an anterior chamber tube and a slit valve which regulates the aqueous humour(AH) flow. AGV has thevalve at the end of the plate to restrict the flow until the flow pressure is boundedbetween8-12 mmHg [3]. The properties of mentioned GDDs are summarized in Table 1.

Table 1. Currently used GDDs and their properties [4]

GDD	SHAPE	MATERIAL	ADVANTAGES	DISADVANTAGES
MOLTENO	Round, dog dish shaped	Propylene	Simple Tube&Plate couple	Uncontrolled flow mechanism
				Small reduction in IOP
				Hypotony
BAERVELDT	Kidney shaped	Silicone	Easy to modify	Micromotion
			Flexible	Bulky device
			Low profile	Hypotony
			Fenestrations	Diplopia
				Scar deformation
KRUPIN	Oval	Silicone	Unidirectional slit valve	Bulky device
			Minimal contact with muscles	Valve malfunction
			Flexible	Small surface area
				High profile

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AHMED	Pearl shaped	PP&Silicone	Simple valve	Valve malfuntion
			Venturi flow	Micromotion
			Easy to implant	Inflammation
			Minimal contact with muscles	High profile

In the next chapter, experimental setups to examine the problems and superiorities of currently and commercially used GDDs (Table 1) are reviewed and summarized. In third chapter, comprehensive comparisons of GDDs will be discussed. Lastly, in discussion and conclusions chapter, common and differing points of experimental setups will be stated. Strong and weak approaches of them whilst testing the GDDs will be questioned.

2. EXPERIMENTAL STUDIES IN LITERATURE

In 2011, Moon et al. [2] designed a new GDD comprised of three layer and and a check valve. They mainly used PMDS material instead of propylene which is more flammatory than PMDS. Bottom layer is the fluidic channelin which fluid flows firstly. Valve seat and membraneact as check valve mechanisms when internal pressure is greater than external pressure,so that membrane is deformedand theflow initiates. They produced two types of GDDs; one is for humans (GDDH) and the other one is for animals (GDDA). They determined cracking pressure of GDDH and GDDA as 20 mmHg and 10-15 mmHg respectively. They examined it via subsequent experimental setup in Fig 1.

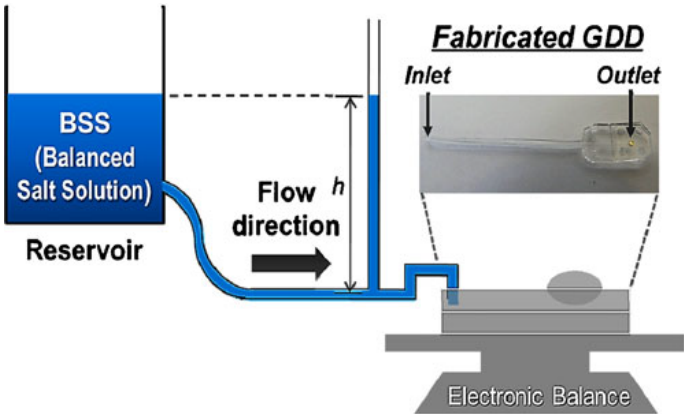

Figure 1. The experimental setup for GDDH and GDDA [2].

Because of the symmetry, they made their analysis in 2D and then they converted 2D flowrates to 3D for minimizing computational time.According to test results, mean value and standard deviation of cracking pressure was 18.33±0.66 mmHg (2444±87.79Pa) which was close to prescribed value of 20 mmHg (2666Pa)by 5 percent. In addition, they tested whether there were any flowrate when internal pressure is smaller than external pressure. They applied external pressure at valve orifice 22.5, 45, 67.5 and over 75 mmHg, respectively.

According to test results, GDDH showed good repeatability and consistent cracking pressure. GDDH showed nearly zero flowrates at 17.63 mmHg (2350 Pa) and 8.1±0.2 µl/min at 30 mmHg (4000 Pa). Finally, they repeated procedures for GDDA and applied it on rabbits for in-vivo tests. The cracking pressure for GDDA was found to be 12.46 mmHg (1656 Pa) within the range ofprescribed values 10-15 mmHg in-vitro. During in-vivo tests, GDDAs were implanted in rabbits suffered from IOP over 30 mmHg. At the end of these tests, there were shown regulation in IOP entire follow-up period 12 weeks. Hypotony was not encountered under 10 mmHg.

In 2011, Char DeCroos et al [5]compared classical AGVwith PRIME-AGV. They developed a prototype AGV enclosed in a porous membrane of ePTFE (Polytetrafluoroethylene) which provides to develop more vascularized and permeable capsule.They established an experimental setup which consists of a syringe pump, pressure transducer (±0.65 mmHg) and a GDD in saline or2.5% gelatin in Fig 2. They also connected a mercury manometer to calibrate the system.

Firstly, they tested seven AGV and seven PRIME-AGV in saline at variable flow rates (at 1,2,5,10,20 and 50 µl/min, and $p<0.05$). Then, seven AGV and seven PRIME-AGV were tested in 2.5% gelatin solution at the same flow rates.They concluded that AGV with porous membrane added resistance which decreased with increasing flow.They planned to investigate combined effects of the resistance added by the porous membrane while decreasing the resistance due to a thinner, more vascular capsule.

In 2012, Malekiet al [6] improved a biodegradable truncated-cone shaped plug filter to prevent postoperative hypotony in nonvalved GDDs. According to their hypothesis, plug filter inserted in a nonvalved GDDthatattenuates the AH flow and prevents postoperative hypotony until bleb formation progress. When the bleb formation progresses, the plug filter degrades. They usedHagen-Poiseuille equation in plug filter design.They produced two plug filters with different

materials; PLGA (with properties 50/50 mole ratio; 42-48 ˚C glass transition temperature; and 3-4 weeks degradation time) and PLA (with properties 100/0 mole ratio; 56-60 ˚C Glass transition temperature; and5-6 months degradation time), respectively. Glass transition/degradation time of polymers were adjusted by changing their molecular weight and end groups. They coated PLGA with a biocompatible polymer SU-8 to overcome low glass temperature. They inserted it in a Baerveldt GDD and tested it. Their experimental setup consisted of a syringe pump, pressure sensor and data acquisition system as in Fig 3.

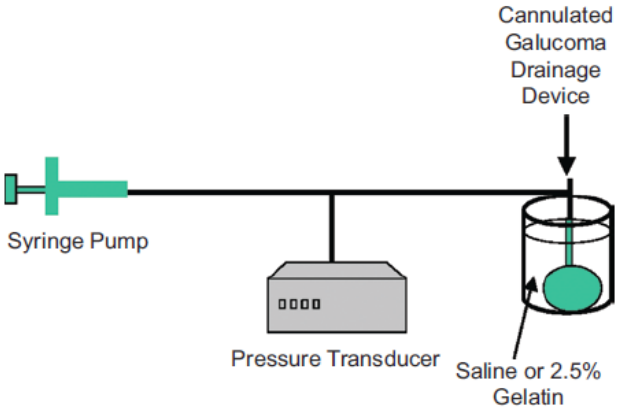

Figure 2.The experimental setupfor AGV and PRIME-AGV [5].

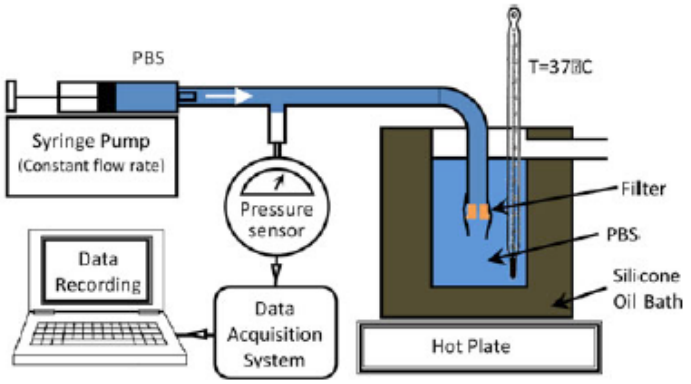

Figure 3.The experimental setupfor Baerveldt GDD[6].

Malekiet al [6]used PBS (phosphate buffered saline) solution in 37 ˚C oil bath to imitate the AH. Then, they pumped PBS into the GDD with plug filter at flowrate 2-3 µl/min and read the pressure from monitor. Firstly, they tested whether plug filter to slide in case of clogging. There wasn't seen any sliding with plug filter. They tested PLGA with two holes 40 and 85 µm diameters, respectively, but they could not attain desired results due to large hole size. They attained desired pressures (15-20 mmHg) at 30-40 µl/min. Next, they used plug filters in series. As expected, pressure drop increased a bit. According to these experiments, they determined effective hole diameter as 44 µm.Then, they pumped PBS at 37 ˚C at flow rate 3 µl/min and observed back pressure of PLGA with two holes. It was seen that pressure was highly increasing after some time later. They made various experiments with different type of cone to overcome this problem. As the result, they succeeded in regulating the pressure more than 15 days with PLA. PLGA filters coated by SU-8 or UV-curing adhesive regulated the pressure up to 45 day that was sufficient for bleb formation.

In 2012 Siewertet al [7] developeda valved GDD. They designed the GDD to provide AH flow from anterior chamber to suprachoroidal space as a distinct flow pathway from novel GDDs.Firstly they adjust their opening pressure and produced it from two different materials (PUR and SIL) with different wall thicknesses and valve lengths.They built an experimental setup to examine flow characteristics through the developed GDD as in Fig 4.

Their experimental setup was different from currently used syringe pump setups. Firstly, their pressure differences between in and out flow of the chamber (3), in whichGDD was tested, was constant due to two hydrostatic heads in the pressure chambers (1 and 2). Fluid was flowing from (1) through (3) into (2) and finally into the fluid reservoir (4). The fluid was continuously weighted by a scale (10). Measurements were made by two sensors (6) and (7) in combination with two magnetic valves (8,9). The valves were manipulating pressure as refilling the chambers from reservoir (5), the valveswere opened at when pressure in (1) decreases and pressure in (2) increases. For data recording and system controlling, a personal computer (12) with analog to digital converter (11) was used.They found difference between opening

and closing pressure of SIL material in the light of results. They thought thatit was due to an interaction of the valve with the current flow and could have been expected for micro-mechanical PUR valves as well.

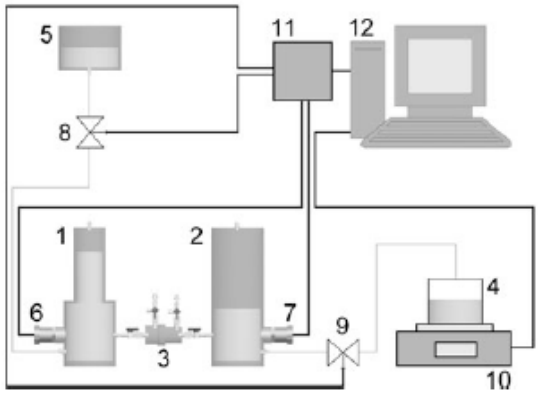

Figure 4. The experimental setup [7].

In 2012Schmidt et al [8] tested a GDD designed by Siewert et al. (in 2010) [9]with a different experimental setup. They designed micro-Particle Image Velocimetry (μPIV) setup to characterizethe flow mechanics of the valve. Their experimental setup is illustrated in Fig 5.

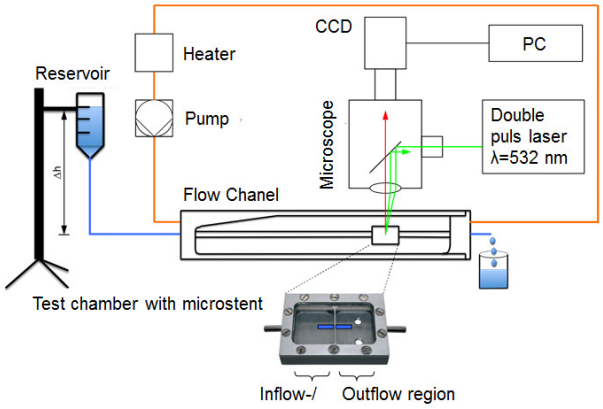

Figure. 5 μPIV setup [8]

Before the experiment, they matched refractivity of the test fluid (pure water and 1.5 μm rhodamine red-dyed tracer particles) to silicone by potassium thiocyanate. They measured the velocity at valve section at variable pressures differences (1, 4, 16 mmHg).The flow velocity ranged from 10^{-6} to $2.5x10^{-2}$m/s for different pressures according to experimental result.When they compared these results with detection of valve opening pressure by volumetric flow rate and pressure difference, they attained a good correlation. They could not compare mean flow velocity and volume flow quantitatively based on the presented μPIV because flow velocity measurement was performed in only one direction. They assumed that it was symmetric due to the geometry of the valve. Furthermore, their flowrate measurements inside the microstent failed due to accumulation of tracer particles on the implant surface. Consequently, they inferred that μPIV provided qualitative and quantitative information about current fields and would be a powerful tool for development and evaluation of micro-mechanical valves. And they consideredcoating the microstent surface including inner lumen with hydrophilic or hydrophobic materials to prevent tracer accumulation and design new GDDs for future work.

In 2013, Paschalis et al [10] designed a ferrovalve in which ferrofluidics prevented early hypotony. When the ferrofluidwas in magnetic field, it acted as a valve and blocked the flow. They used two magnets in this design. First magnet was used for fixation of ferrofluid and the second magnet was used for adjusting opening pressure of the valve. If the second magnet was closer, it's opening pressure was higherand vice-versa. When pressure exceeds opening pressure, flow begins.They tested their design and compared with AGV. The experimental setup consisted of "distilled H_2O" (dH_2O) reservoir and a manometer. Different test pressures was adjusted by changing the height of dH_2O reservoir. The opening and closing pressures had been calibrated as 10 mmHg and 7 mmHg respectively (with a variability ±0.5 mmHg) before the experiment. The experiment was performed at the pressures 7, 12, 16 and 21 mmHg over a period of 30 days. In consequence of the experiment, it was seen that the flow/pressure response of the valve showed increase of flow at higher pressures (1.8 μl/min at 12 mmHg; 4.3 μl/min at 16 mmHg; 7.6 μl/min at 21 mmHg with variations ±0.2 μl/min). They achieved 12.5 mmHg pressure at the AH production rate in normal eyes (~2.5 μl/min). They measured no closing

pressure at the outlet tip of the AGV because AGV requires subconjuntival implantation to achieve closing pressure. Because of this result, AGV should not be used extraocularly. On the other hand, they measured 3 mmHg differences between opening and closing pressures in ferrofluidic valve. The ferrovalve gave promising results in-vivo tests.

In 2013, Quang Minh Luong et al [11] modified an AGV to gain stable IOP for attenuation of the hypertensive phase after capsule formation while avoiding postoperative hypotony. They produced a valve from biodegradable polymer. They used classical syringe pump basedexperimental setup as it is seen in Fig 6 to compare normal AGV and modified AGV(mAGV). They tested three mAGV and three AGV and averaged their datas, compared their starting and ending pressures (pressures before and end of the degradation time average 7 weeks). According to their results, average starting and ending pressures of AGV was13.3±1.5 mmHg and 10.7±1 mmHg, respectively. Average starting and ending pressures of mAGV was10.7±1.8 mmHg and 1.9±1.8 mmHg.

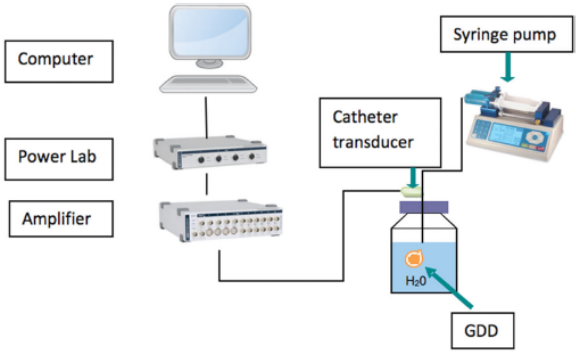

Figure 6. The experimental setupfor AGV and mAGV[11].

In 2014 Villamarin et al [12] designed an adjustable glaucoma drainage device. This device has a mechanism comprised of a mechanical disk around a shaft. The mechanical disk position is adjusted by the control unit (CU) which contains a compass at the one end. When disk angle becomes smaller, flow resistance becomes greater. This mechanism provides non-invasive adjusting IOP after implanting.They examined this GDD by in-vitro and ex-vivo experimental setups. In in-vitro setup, they used syringe pump and electronic manometer setup. They used saline solution to imitate AH at a physiological rate of 2µl/min. They measured pressure at inlet and oulet and found a relationship between pressure values and angular position of the disk. As a result, when the disk positionwas adjusted correctly, the GDDsprevented hypotony.

In 2015, Sheybani et al. [13]testeda non-valved GDD,XEN implant,and compared it with Ex-Press and Baerveldt implants.They measured XEN at5 mmHg initial pressure and1.2 µl/min flow rate before the experiment. They used syringe pump experimental setup in Fig 7.They used distilled water at 21 ˚C whose viscosity is 0.9778 centipoise (cP) and water at 37 ˚C with 0.6904 cP.They made experiment at several flowrates: 25, 50 and 74 µl/min, respectively. They measured these devices at high rates because the pressures weresmall when these devices were measured at physiologic flowrates, the measurement device read them as zero. However,they measured XEN implant at nearly physiologic flowrates (1, 2, 5 and 10 µl/min) and the pressures were measured as between 6.28 to 7.85 mmHg for XEN implant thus it can prevent hypotony. According to experimental results, Baerveldt and Ex-Press implants have so low pressure values at physiologic flow rates that is why they cannot prevent hypotony.

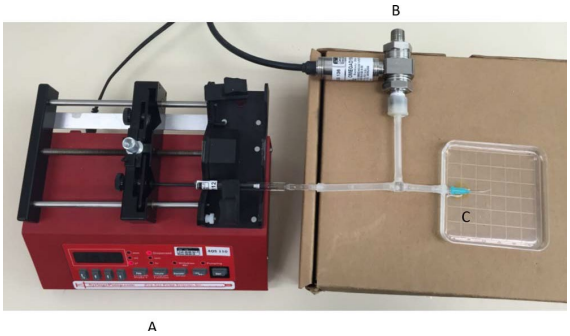

Figure 7. The experimental setupfor XEN implant [13].

3. GLAUCOMA DRAINAGE DEVICES

All of the glaucoma drainage devices have a tube providing AH flow into a plate at back of the eye. It is a silicon based tube usually has inner diameter 0.3 mm and outer diameter 0.64 mm. There are a few GDDs in market and they are

commonly used. It's hard to compare different GDDs objectively due to most of the GDD surveys in literature are based on long-term studies. Different criteria which are based on limited-time observations have been applied on various study populations and samples of all sizes to attain successful results in literature.

Commercially available GDDs are Molteno, Schocket, Krupin, Baerveldt, Ahmed and Optimed GDDs in chronological order [14]. These GDDs show design variety according to dimension, shape and plate material. Nevertheless, GDDs can be mainly classified in two separate categories as valved and non-valved. Their comparisons were given at table 1.

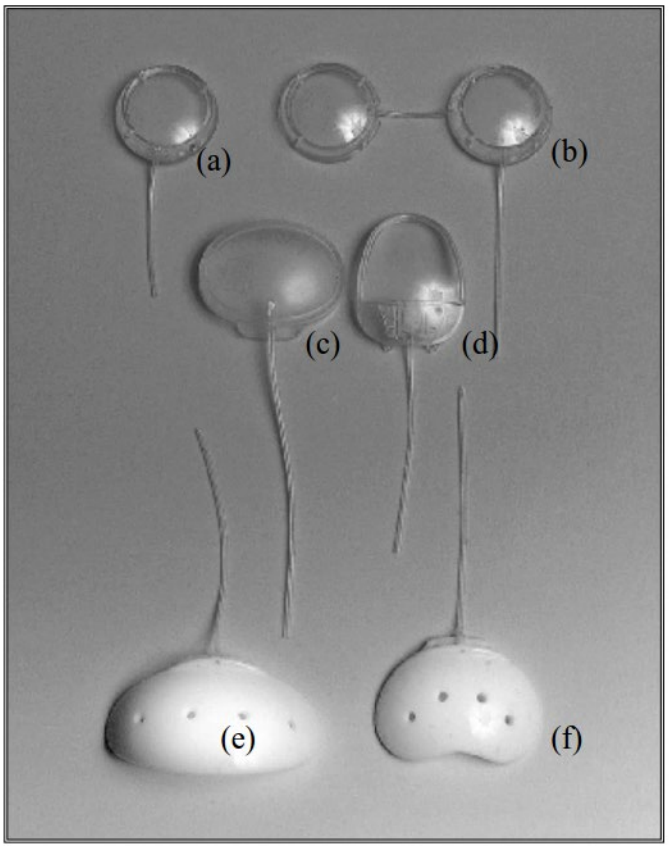

Figure 8. (a) One-plated Molteno implant (b) double-plated Molteno implant (c) Krupin slit valve (d) Ahmed Glaucoma Valve (d) Baerveldt implant with 350 outlet plate (e) Baerveldt implant with 250 outlet plate [3].

Molteno implant is comprised of a PP plate which is attached on long, non-valved silicon pipe in Fig 8a. Drainage is only provided by pressure difference between pipe and plate outlets [15]. Developed two-plate Molteno implants in 1980sas shown in Fig 8b, postoperatively controls IOP further at hypertensive phase and it's reported that two-plated Molteno implants generally were more effective in IOP reduction than one-plated implants. Another change is the design which splits outlet plate,also called as pressure protrusion, with V shaped protrusion into two pieces. This design was considered to prevent hypotony due to the reduction of drainage area which is possible at initial and to prevent excessive filtration but it is failed as intracellular studies show [16]. Postoperative hypotony is routinely observed at Molteno implants. Although many associated complications, Molteno implantis a design that other devices base it for comparison.

Krupin device in Fig 8c is formed by attaching a pipe which has the cross shaped slit at its tip to an expansion plate. The flaps which form the slit were designed for cracking even at a very small pressure increase.This design is considered as inadequate compared to non-valved Baerveldt and Molteno devices because flow resistance is merely ensured by the pipe [17].

Baerveldt implant was developed in the beginning of the 90s. It is comprised of a barium impregnated silicon outlet plate which is attached to a long silicon pipeas shown in Fig 8e and Fig 8f. It is the key fact of the design to implant big outlet plate into eye correctly. Moreover, although the plate of Baerveldt is very big, unlike the Molteno's design, it can be placed steadying into eye muscles due to its low profile. Wide outlet plate increases decrease of pressure and it ensures easy implantation than Molteno implant does[16, 18].

When literature was surveyed, it was seen that most of the novel implants cannot overcome the clogging problem. Therefore, newly improved devices aim patients to be more comfortable and aim to prevent clogging. One of the new devices is the Venturi valved device improved by Mateen Ahmed in Fig 8d. This device has some advantages such as occupying fewer places, durableness, superior ability in drainage etc. Although, ensuring high range in pressure control

is inadequacy of this device. Namely, it can create the risk of damage of eye nerves before the drainage of fluid due to the high IOP and it can be late to prevent outflow. Therefore, IOP can decrease extremely and cornea can collapse. As a result, a new and improved implant must be designed to overcome this wide range pressure control.

An ideal GDD must be implanted easily, must be consistent in operating pressure range, must not cause the complications, must be bio-inert, and must be functional throughout the patient's life.

An ideal GDD has not been produced yet. However, AGV can be accepted as the nearest GDD to ideal in terms of today's technology and practical approaches. As said before, although AGV should work like a real valve in a specified range, it works as a flow obstructer after a while.In theory, the valve closes when the IOP is greater than 1200 Pa and opens when IOP is greater than 2933 Pa to prevent hypotony. AGV does not perform as introduced; also it is not closed when IOP reaches desired value. When the valve opens for first time, the valve does not close again and stays as it is.

AGV was introduced in 1993 for the first time. The valved GDD design was improved to prevent hypotony. AGV is comprised of pear shaped oval hard polypropylene (PP) plate and a silicon pipe attached to the plate in Fig 9. AH flows through two thin silicon elastomer membranes on up surface of the plate.These membranes are located in the front of the implant and they open and close by the effect of "Venturi diaphragm" which is generated by AH flow on the silicon leaves. The pressures between 1067-1600 Pa are sufficient to open the leaves and transfer AH through the valve into reservoir. Velocity of a liquid which flows from large cross section area to small cross section area increases according to Bernoulli's hydrodynamic principle. The valve is comprised of venturi shaped chamber (bottleneck). As shown in Fig 9b, inlet width (2.11 mm) of the chamber is greater than outlet width (1.64 mm) and there is a pressure difference between anterior chamber in which flow initiates and AGV tip chamber. If flow rate increases, gap between trapezoidal shaped plates of the valve increases further. This valve opens when IOP is 1067 Pa to minimize early postoperative hypotony case [14].

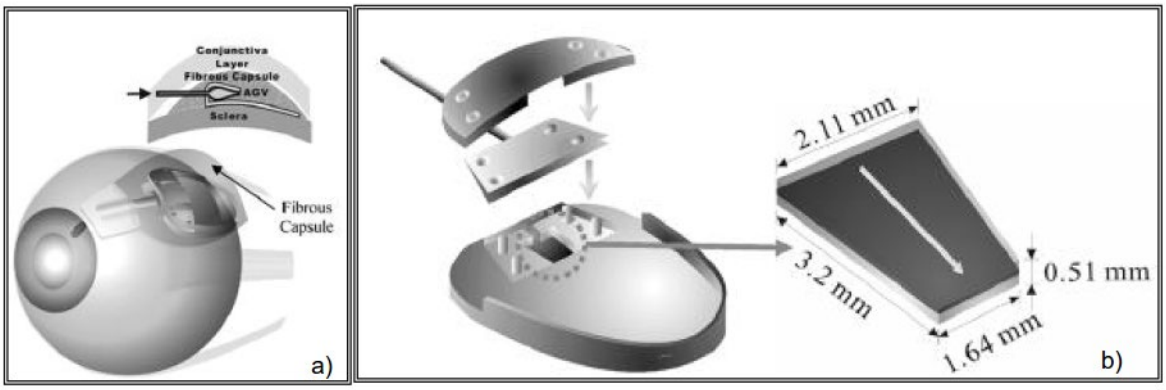

Figure 9 (a) A Side view of a standard AGV which is placed into eye and view of fibrous capsule (b) Parts of AGV S2 model and dimensions of chamber [19].

4. DISCUSSION AND CONCLUSIONS

4.1 Common and Differing Points of Experimental GDD Setups

As this short literature survey shows, almost all of theup-to-date experimental setupsused for GDD testingarenearly the same. Researchers generally use a syringe pump to provide flowrate and transducer to measure pressure and a computer for data acquisition.Second widely used experimental setup is comprised of an elevated reservoir, pressure measurement device and electronic balance. In this setup,the height of the reservoircreates a hydrostatic pressure and it is measured by a height gauge, while flowrate is measured by an electronic balance.Other than these, two different types of experimental setups (these are experimental setups by Siewert et al [7] and Schmidt et al [8]) are found in literature but they are not commonly used.

Although syringe pump setups most widely used experimental setups in GDD researches, they have big disadvantages. Firstly, they are open loop systemsthatmay affect precision adversely. Secondly, flexibility of the pipe systemandslow-response of syringe pumps may cause undesired vibrations.Stability and balancing responses of the syringe pumps may cause extended time of experiments and repeatability errors.

4.2 Proposal fora Noveland Original Experimental Setup for GDDs

During this literature review, any comprehensive study for a new experimental setup on GDDs is not encountered. The proper experimental setup for GDD testing should be more precise and have shorter response time than those of syringe pump setups.The experimental setup should be designed as it will ensure more than one GDDs to be tested

simultaneously. So, it will be possible to test differentGDDs at the same time and the same external conditions.

The experimental studies in literature investigated early postoperative IOP reduction. However, the main important point is whether the GDDs function well after a certain period of time on implantation. Again, it should be tested how the GDDs give effective response against to postoperative complications such as hypotony, diplopia etc. Especially, commonly encountered problems in GDDs as backflow, clogging, and high-pressure intervals should be testedmore sensitively. A new experimental setup could eliminate disadvantages of commonly used setups, could make it possible to comment more on design defects of GDDs.

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