Implantable Microdevice for the Treatment of Hydrocephalus

A Thesis
Submitted to the faculty of Drexel University by Jonghyun Oh in partial fulfillment of the requirements for the degree of Doctor of philosophy

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ABSTRACT

Implantable Microdevice for the Treatment of Hydrocephalus

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We present a novel microdevice for the treatment of hydrocephalus. Hydrocephalus is a pathological condition in which excessive cerebrospinal fluid (CSF) is accumulated within the subarachnoid space of the brain due to deficient arachnoid granulations, resulting in the brain damage or death. Current treatment for hydrocephalus is to surgically implant a shunt device to drain the excessive fluid from the ventricles to peritoneal cavity or other parts of the body. This method has over 50% failure rate due to occlusions and mechanical failures of shunt components. The proposed microfabricated device can mimic the function of normal arachnoid granulations and thus can replace the deficient arachnoid granulations. The microfabricated arachnoid granulations (MAG) consist of arrays of microvalves and microneedles.

The microvalves are made of a PDMS/Parylene composite layer and have a 3-D dome petal shape. Such geometry enables the microvalve to rectify fluid flow in the forward and backward direction due to pressure differentials like normal arachnoid granulation. Microvalve design was optimized using 3-D numerical simulation. The microvalves were fabricated using three main microfabrication techniques: diffuser lithography for dome-shaped SU-8 mold fabrication, thin polymer film
deposition and reflow for PDMS/Parylene membrane formation, and excimer laser machining for valve opening. The pressure drop vs. flow rate characteristics of the fabricated microvalve was investigated through in-vitro flow tests using a bench-top CSF simulator. The results showed that a 10x10 microvalve array with combined opening shape is optimal for our application.

The microneedle array is to surgically pierce the dura mater membrane after being assembled with the microvalve. The microneedles were fabricated using three main techniques: diffraction photolithography for tapered SU-8 needle fabrication, RIE etching for needle sharpening, and excimer laser machining for through-hole creation. Puncture tests were conducted using pig’s dura mater and the microneedles coated with a Ti layer showed promising results (16 out of 100 needles pierced dura and the needles were not deformed). Blood adhesion tests were also carried out using human blood simulating the CSF dynamics and no significant platelet adhesion was observed at the microneedles. The MAG presented in this dissertation demonstrates a great potential for the treatment of hydrocephalus.
CHAPTER 1: INTRODUCTION

1.1 Background of hydrocephalus

1.1.1 Cerebrospinal fluid (CSF)

CSF is the acronym of Cerebrospinal fluid which is a clear and colorless fluid. This fluid contains small quantities of glucose and protein. CSF fills the ventricles of the brain and the central canal of the spinal cord.

Ependyma is an epithelial membrane in the central nervous system facing the ventricular system of the brain and spinal cord [1]. It is believed that this membrane is involved in the production of CSF at a rate of 0.3~0.5 ml/min [2]. Figure 1-1 shows the CSF circulation in the brain. CSF produced in the Ependyma of the Choroid plexus passes through third and fourth ventricles by diffusion and then CSF arrives in the subarachnoid space. It circulates around brain and spinal cord. Arachnoid granulations periodically permit CSF accumulated in the subarachnoid space to be diverted into the superior sagittal sinus. The average volume of intracranial CSF is 125 ml in an adult. The CSF pressure in the subarachnoid area varies according to the age group. The pressure is estimated to be 40~50 mmH$_2$O for infants and 40~100 mmH$_2$O for children. In adults, it remains constant at about 150 mmH$_2$O which is usually about 40~50 mmH$_2$O above the intracranial
Figure 1-1. CSF circulation in the brain. (Copyright © 1998, Lynne Larson, All rights reserved.). CSF flow: Choroid plexus $\rightarrow$ third ventricle $\rightarrow$ fourth ventricle $\rightarrow$ subarachnoid space $\rightarrow$ arachnoid granulation $\rightarrow$ sagittal sinus.
over the intracranial venous pressure. The total volume of CSF is turned over 4~5 times in a 24h period. The production and absorption of CSF maintains in a dynamic equilibrium that keeps the pressure constant [2].

CSF in the brain has three major roles. First, CSF surrounds the brain and cushions the brain and spinal cord from some shocks. Secondly, CSF serves to rinse the metabolic waste from the nervous system. Lastly, the constant presence of adequate levels of CSF maintains pressure balance in the brain. Failure to fulfill any of these major roles may cause serious damage to the nervous system, resulting in brain damage or death.
1.1.2 Arachnoid granulations

As shown in Figure 1-2, arachnoid granulations are small protrusions of the arachnoid (membranes covering the brain and spinal cord) through the dura mater. CSF is produced inside ventricles and then leaves to surround the whole brain and spinal cord. Arachnoid granulation enables excessively accumulated CSF to be drained into the superior sagittal sinus (blood stream), which keeps the balance of the intracranial pressure in the brain. The first exposure of the world to the arachnoid granulations was in the 16th and 17th century [3]. Pacchioni, in 1705, reported the clustering of arachnoid villi along the sagittal sinus [4]. Luschka and Trolard investigated the arachnoid structure penetrating a small space of the sagittal sinus in 19th century [5]. Later, Key and Retzius confirmed the role of villi as a natural valve [6]. In the twentieth century, a differential hydrostatic pressure as a working force of arachnoid granulation was reported by Davson [7]. Most research over the last century has focused on further characterizing the ultrastructure and functional attributes of AG, with less attention to its macroscopic anatomy, distribution, and total surface area [8].
Figure 1-2. Arachnoid meninges [8]: (a) schematic of cross-sectional view near AG, (b) coronal section of human brain, (c) appearance of human arachnoid granulations.
1.1.3 Hydrocephalus

Hydrocephalus can be defined as an excessive accumulation of CSF within the subarachnoid space of the brain. This accumulation causes high pressure difference above 200 mmH₂O in the brain, which results in central nervous system problems.

Hydrocephalus can be categorized into two types of communicating and non-communicating hydrocephalus according to the conditions. Non-communicating hydrocephalus occurs when the flow of CSF is blocked along the narrow channels between the ventricles. Communicating hydrocephalus occurs when the flow of CSF is blocked after passing through the ventricles [9]. The most common type is communicating hydrocephalus. Figure 1-3 shows a baby whose head swelling was caused by severe communicating hydrocephalus. Without proper medical care, this pediatric hydrocephalus results in developmental disabilities or death. Children and adults may experience the typical symptoms such as gait disturbance, balance problems, and headache [10].
Figure 1-3. A baby who is suffering from communicating hydrocephalus. This disease causes swelling of the brain. (an image from Wikimedia Commons)
1.2 Diagnosis, treatment, and problems

1.2.1 Diagnosis of hydrocephalus

Nowadays, hydrocephalus is characterized and diagnosed by clinical symptoms of dementia (a loss of brain function that occurs with certain diseases), urinary incontinence, and gait disturbance as well as analysis of neuroimaging by ultrasound, computed tomography (CT) and magnetic resonance imaging (MRI) coupled with mean value of intracranial pressure (ICP) measured by an epidural pressure sensor [11]. An ultrasound is a sophisticated method of outlining structures within the head using high frequency sound waves. It can be performed to examine the size of the ventricles especially for babies. However, once the skull bones have closed over the fontanels, this method cannot be done as ultrasound cannot go through bone. Normally a CT brain scan is a technique in which tiny beams of x-ray outline the skull, brain, ventricles, and subarachnoid space. In addition to visualizing the size and shape of the ventricles, abnormalities such as tumors, cysts, and other pathology can also be seen. A MRI is a non-invasive diagnostic tool that uses radio signals and a magnetic to form computer images of the brain, its ventricular system and coverings, and pathological lesions.
1.2.2 Review of treatment methods

a. Patents

From the middle of the 20th century onward, a lot of patents for the treatment of hydrocephalus have been introduced. Existing patents pertaining to hydrocephalus treatment can be focused on the shunt system.

Shunt system has been the fundamental treatment method for hydrocephalus for nearly 50 years. Samuel Schwartz (1963) acquired first patent about a ventricular-venous shunt device comprised of a catheter and two one-way check valves, which can drain cerebrospinal fluid into the circulatory system [12]. His apparatus design was focused on several key points: a small diameter to avoid providing space for hostile organisms, a simple concept to reduce the valve failure, and a hydraulic design to eliminate eddy flows. Figure 1-4 shows graphics of the invented apparatus. Figure 1-4(a) is one-way check valve, which is normally open under forward flow and normally closed under backward flow by deforming a flexible plastic (13 in Figure 1-4(a)). Richard H. Ames (1969) invented a two-way flushing device that consists of two chambers and a catheter with a check valve (17 in Figure 1-5) [13]. This device can easily check blockage of the shunt by tissue particles by compressing either of the two chambers Figure 1-5(a) shows a cross-sectional view of the shunt flushing device and (b) shows a schematic of the shunt system inserted in a patient.
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Figure 1-6. A ball type shunt valve invented by Salmon Hakim and Carlos A. Hakim. This valve is normally closed and open when a spherical ball is pushed by forward flow.
Salmon Hakim and Carlos A. Hakim (1983) invented a shunt system with ball type check valve, which can vent CSF from a cerebroventricular catheter to a drainage catheter [14]. This prevents brain debris or CSF proteins clogging a thin slit in the valve. Figure 1-6 shows the invented shunt valve, which is opened when a spherical ball is pushed by forward flow. Bernard Marion (1987) invented a ball type shunt valve with a rotating rotor [15]. This design avoids the siphon effect when the patient moves between vertical and horizontal positions, and it can be easily calibrated at any desired closing pressure for implantation. Figure 1-7 is a schematic of the cross-sectional view of the invented valve. When the body is moving, a spring blade (9 in Figure 1-7) fixed to the rotor (10) rotates along the cylindrical wall (6). Inlet flow results in a pressure differential, which pushes the ball (8) inward, and this pushing force deforms the blade simultaneously. This whole valve mechanism controls the CSF flow. Additionally, Alain Lecuyer (1994) invented an implantable drainage valve for the treatment of hydrocephalus [16]. This valve can avoid hyperdrainage under normal pressure differential when the patient rises from a lying or recumbent position to a standing position. As shown in Figure 1-8, the invented valve is implanted vertically when the patient’s head is upright. When the patient is in a recumbent position, the weight (24 in Figure 1-8) provides additional compressive force against the spring (22) to maintain the valve in a closed condition. Christoph Miethke (2005) invented a controllable hydrocephalus valve comprised of an electrical
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Figure 1-8. A ball type shunt valve with a rotating rotor invented by Bernard Marion. 10: valve, 12: valve body, 14: inlet, 16: outlet, 18: tapered valve seat, 20 spherical closure member, 22: spring, 24-26-28: weights, 32: upstream section, and 34: downstream section. The invented valve is implanted vertically when the patient's head is upright. When the patient is in a recumbent position, the weight (24 in Figure) provides additional compressive force against the spring (22) to maintain the valve in a closed condition.
Figure 1-9. A schematic of a hydrocephalus valve invented by Christoph Miethk. 1: electronic system, 2: coil, 3: slide, 4: sphere, 5: outlet, 6: blind hole, 7: spring, 8: battery, and 9: detector. An electronic system is supplied by a battery. A current of this system is applied to a coil which generates a magnetic field in order to move the slide. The detector can detect a slide position. This slide can move the sphere between rest position 1 and rest position 2 in order to open and close the valve. When the sphere is in the rest position 2, fluid can go outside. The control of the slide may take place from a time control or a control calculated by complex algorithm.
Figure 1-10. A self adjusting hydrocephalus valve invented by Meir Rosenberg. When the blocking member (46 in Figure) is seated against the valve seat (44), CSF cannot enter through the valve seat and into the chamber. When the blocking member is pushed toward bellows (52), bellows collapses and fluid can pass through the valve.
control system opening and closing the valve [17]. This system can improve adaptation to the specific circumstances of the patient. In Figure 1-9, it is shown that the system is supplied power from a battery. The current of this system is applied to a coil, which generates a magnetic field that can move the slide, and a detector can track this slide position. This slide can move the sphere between rest position 1 and rest position 2 in order to open and close the valve. When the sphere is in the rest position 2, fluid can flow outwards. The control of the slide may take place through a time control or a control calculated by a complex algorithm. Meir Rosenberg (2008) invented a self-adjusting hydrocephalus valve, which can continue to drain CSF at a rate proportional to the average pressure difference across the valve [18]. In the valve mechanism in Figure 1-10, when the blocking member (46 in Figure 1-10) is seated against the valve seat (44), CSF cannot enter through the valve seat and into the chamber. When the blocking member is pushed toward the bellows (52), the bellows collapses, and fluid can pass through the valve.
b. Journal papers

Even though the most appropriate treatment for hydrocephalus has been shunt surgery, significant problems such as occlusion, infection, and malfunction remain. Also, there have been no alternative treatments so far. However, the following journal papers present novel attempts at hydrocephalus treatment.

Yoon et al. (2004) reported a novel cerebrospinal fluid shunt system for the hydrocephalus patients as shown in Figure 1-11 [19]. The CSF shunt system consists of a micro telemetry pressure sensor, an electromagnetic micropump and a controller. The pressure sensor has a flexible p+ diaphragm and a planar copper coil that construct an LC resonant circuit. The cerebrospinal pressure is measured from the phase shift at the resonance frequency. The proposed telemetry pressure sensor can measure the intracranial pressure ranging from 0 to 120 mm H$_2$O. The micropump consists of an actuator diaphragm and a pair of passive valves. Each device is fabricated by micromachining technology and tested to obtain the characteristic. If the applied pressure is larger than 110mm H$_2$O, the fabricated micropump operates and drains. Fig. 18(d) shows the measurement system for the in-vitro test of the closed-loop shunt system. When the pressure is lower than 90mm H$_2$O by the water drainage, and the micropump stops operating. When the pressure is lower than 90mm H$_2$O by the water drainage, and the micropump stops operating. The
Figure 1-11. Micro devices for shunt system. (a) schematic view of a CSF shunt system, (b) micro pump part: flap valve, (c) micro pump: actuator, (d) the measurement system for the in-vitro test of the closed-loop shunt system.
feasibility of the proposed shunt system is evaluated with the in vitro performance test.

N. Al-Zubi et al. (2009) proposed a new approach to automate and improve the treatment and management of hydrocephalus through a cognitive system over a distributed network of hydrocephalus patients with intelligent shunt system [20]. As shown in Figure 1-12, the intelligent system specifically addresses the use of the valuable information in the ICP signal coupled with patient feedback and surgeon examination and enforced by the eShunt agent, to improve understanding and management of hydrocephalus. A requirement of a considerable amount of ICP analysis and treatment data is necessary to build a self-learning and robust classification system for ICP waveforms and hydrocephalus patients. This approach will tackle challenges in analysing, collecting and managing ICP data, by providing a distributed system of eShunt agents that manage patients autonomously, and share information between them. It can reduce treatment costs dramatically, and can potentially save lives.
Figure 1-12. Overview of the system
1.2.3 Shunt surgery as main treatment and problems after shunt surgery

a. Shunt surgery as main treatment

The most common treatment to manage hydrocephalus medically is insertion of the shunt system which consists of two catheters and an one-way valve as shown in Figure 1-13. The ends of the catheter connect a space within a ventricle and another space within the abdominal (or peritoneal) cavity in which negative pressure is generated. A valve along the catheter is a one way valve that drains excessive CSF from the brain, and the shunt regulates the flow or pressure of CSF from the ventricles. A reservoir is located in the shunt or added as a component, and this reservoir allows CSF to be extracted for testing purposes as shown in Figure 1-13(a). Valve types available are categorized according to the medical condition. The fixed pressure valves include a single valve mechanism that regulates the shunt flow rate. The valves are typically available in three pressure ranges: low, medium or high. The adjustable valve includes a mechanism that can be non-magnetic tools. This gives the doctor the ability to change the valve pressure setting in the office without using a surgical procedure.

Figure 1-14 shows how to implant the shunt system. In the surgical process, a U-shape surgical cut is made near the top of the head. Another cut is made in the belly. A small hole is drilled in the skull. A
Figure 1-13. A shunt system. (www.medtronic.com); (a) shunt components and valve functions, (b) fixed pressure valve with overdrainage protection and cutaway, and (c) adjustable valve that can be adjusted to difference pressure settings for surgery and cutaway.
Figure 1-14. VP shunt system and surgery process. (www.seattlechildrens.org/uploadedimagesSeatt...
Figure 1-15. Brain scanned images (CSF: dark color), of enlarged ventricles before shunt insertion and normal ventricles after shunt insertion; (a) CT images, (b) ultrasound images, and (c) MRI images. (www.hydroassoc.org)
catheter is passed into a ventricle. Another catheter is placed under the skin behind the ear and moved into the peritoneal cavity. A valve is placed underneath the skin behind the ear. The valve is attached to both catheters. Figure 1-15 shows brain scanned images taken from (a) CT, (b) ultrasound, and (c) MRI methods. Left images show enlarged ventricles before shunt insertion and right images show normal ventricles after shunt insertion. CSF enters the shunt system through small holes near the tip of the proximal catheter and flows into the peritoneal cavity. After inserting the shunt, it was examined that ventricles were normal.

b. Problems after shunt surgery

Over 40,000 shunt surgeries are performed every year in the US. Although the shunt systems have been evaluated by new technologies, the shunt system is not perfect in terms of the medical care. The inconvenience, financial cost, psychological problem, and shunt failure present major issues associated with the shunt system. The failure rate for all implanted shunts is as high as 40% by 1 year and 50% by 2 years. This failure rate stems from several shortcomings. The most common reasons for the failure of the shunt system are [22]:

1. Obstruction

2. Mechanical failure.

Obstruction is the flow interruption through the shunt due to occlusion of the shunt lumen. Mechanical failure is caused by one of the
following: a fracture of the distal tubing, disconnection of shunt components, migration of the intraventricular catheter after initial insertion, misplacement of a ventricular catheter, and misplacement of a distal catheter. Less common reasons are as follows [22]:

①. Overdrainage and underdrainage
②. Loculation (isolated segments of ventricle)
③. Abdominal complications (pseudocyst:loculated intra-abdominal fluid collection)

These problems after shunt surgery result in additional operation in half of all patients with the shunt system within two years and significant monetary cost.
1.3 Our approach for the treatment of hydrocephalus

Currently, hydrocephalus is treated by a surgical procedure, in which a tube/valve device shunts excess CSF from the intracranial compartment to another location. The shunt systems currently in use was initially developed in 1950’s and has remained essentially unchanged for over 50 years. Although the shunt systems have prevented death and disability from hydrocephalus, they still have persistent shortcomings. The current shunt systems have a very high failure rate (~50%) within two years after implantation mainly due to occlusion by debris, blood clot or infection. Other causes of failure include tubing breakage, kinking or shortening due to patient growth or movement. Another significant shortcoming of the shunt system is imprecise shunting such as over and under shunting. According to the National Inpatient Sample database for the year 2000, there were 5,574 patients who had a shunt either inserted, revised, or removed. The total cost was $1.1 billion in the United States. Ventricular shunts as primary procedures constitute a significant medical and economic problem [23].

We propose an innovative approach for the treatment of hydrocephalus which can address the problems of the current treatment as shown in Figure 1-16. The goal of this research is to develop an implantable microdevice that diverts excessive CSF from the subarachnoid space to the sagittal sinus. We are attempting to replace the deficient arachnoid granulations (AG) that produce the pathologic condition of
communicating hydrocephalus with an artificial device equivalent to restore the normal absorptive function. The implantable microfabricated arachnoid granulations (MAG) consist of an array of hollow microneedles and corresponding passive microvalves. The microneedle array will be surgically placed to pierce the dura mater to act as a one-way conduit for CSF. Microvalves attached to the microneedles regulate the CSF flow into the sagittal sinus in response to the pressure differential between the sinus and the subarachnoid space just like normally functioning AG. Therefore, the proposed device will more closely mimic the physiologic CSF dynamics. The proposed MAG will open a new era in the treatment of hydrocephalus.

We present an upgraded PDMS/Parylene microvalve that has a 3-D dome petal shape for the treatment of hydrocephalus. This valve design was inspired from a PDMS valve used in condiment bottles (e.g. French’s mustard source bottle). The thin PDMS valves have a dome shape with cross-cut opening such that the fluid cannot flow out until pressure is generated by squeezing the plastic bottle. Microfabrication techniques were applied to miniaturize the valve for our application. Previously we reported a Parylene micro valve [2]. However, the valve failed to prevent reverse flow and maintain its shape during flow test. This was mainly due to the relatively flat (non-hemispherical) geometry and the non-sticky nature of Parylene. Therefore, we present the use of a PDMS/Parylene...
Figure 1-16. Schematics of microfabricated arachnoid granulation (MAG)
Figure 1-17. A schematic diagram of opening and closing mechanism of the PDMS/Parylene microvalve with 3-D dome petal shape. (a) $P_1 > P_2$: close and (b) $P_1 < P_2$: open.
composite microvalve. By adding a PDMS layer, the self-sealing property of the valve membrane was greatly improved. Novel microfabrication techniques have been developed to build the proposed PDMS/Parylene microvalve that has 3-D dome shape geometry.

Figure 1-17 shows a schematic diagram of how the valve works. When the internal pressure ($P_2$) is greater than the external pressure ($P_1$), the pressure difference causes the microvalve to open. On the other hand, when $P_1$ is greater than $P_2$, the valve is closed and sealed.

Figure 1-18 shows to compare conventional shunt system and our microfabricated device. Shunt systems divert CSF from SAS to Peritoneal cavity but our MAG diverts CSF from SAS to SSS just like normal arachnoid granulations. Shunts consist of a single valve and two long catheters while our MAG consists of an array of 100 devices. Therefore, even if some of the devices experience occlusion, the system can still function and divert CSF. Also, since our MAG does not have long catheters and works based on the pressure difference between SAS and SSS, the problems of the shunt systems such as occlusion, infection, and mechanical failures can be minimized or eliminated. Finally, unlike the bulk shunt systems, our MAG is a tiny device.

To implant the device on the dura mater and build the channel for the flow of CSF through the dura mater, a microneedle with the channel should puncture the dura mater tissue. This microneedle is made of SU-8. SU-8 is commonly used as epoxy based negative photoresist. It is one of
the most biocompatible materials used in bio-MEMS. A major consideration is an optimal balance of sharpness and strength to puncture the dura mater.

This dissertation presents the design, fabrication, and testing of the implantable microdevice for the treatment of Hydrocephalus. Design optimization of the microvalve has been performed through numerical simulation study using COMSOL software. Prototype models were fabricated using microfabrication techniques such as photolithography, thin-film deposition, diffuser lithography, reactive-ion etching and excimer laser machining. A variety of tests including in vitro and in vivo tests with fabricated devices have been performed.
### Shunt vs. MAG

<table>
<thead>
<tr>
<th>Shunt</th>
<th>MAG</th>
</tr>
</thead>
<tbody>
<tr>
<td>From SAS to peritoneal cavity</td>
<td>From SAS to SSS (Physiological)</td>
</tr>
<tr>
<td>Implanted under the skin</td>
<td>Implanted under the skull</td>
</tr>
<tr>
<td>Single valve &amp; two long catheters</td>
<td>Array of 100 devices, no catheter</td>
</tr>
<tr>
<td>Problems (Occlusion, infection, mechanical failures)</td>
<td>Most of the problems of VP shunts are addressed</td>
</tr>
<tr>
<td>Bulky system</td>
<td>Small device</td>
</tr>
</tbody>
</table>

Figure 1-18. Shunt vs. MAG
1.4 Specific Aims

1.4.1 Aim 1: Design, simulate, fabricate, and test an array of one-way microvalves.

Comsol Multiphysics software was applied to the 3-D simulation of a microvalve for accurate prediction of valve performance and design optimization. Several microfabrication techniques such as dome-shaped SU-8 mold fabrication, PDMS/Parylene coating, and laser machining for valve opening were investigated to build the proposed microvalve with which the valve performance test was done. The pressure-drop vs. flow rate characteristics of the fabricated microvalve was investigated through in-vitro flow tests of a 10x10 microvalve array with each microvalve having a 210 \( \mu \text{m} \) diameter and three kinds of opening shapes. The simulated data was compared to experimental data to validate the design parameters. This work towards accomplishing Aim1 was described in Chapter 2.

1.4.2 Aim 2: Design, simulate, fabricate, and test an array of microneedles.

In order to design the channel size inside the microneedles, pressure drop through the channel was considered and calculated not to affect the valve performance using the comsol Multiphysics program. We
employed the SU-8 microneedle fabrication process reported by Choi et al. [2]. The microneedles were fabricated through a three-step process: UV light scattering in a thick SU-8 layer for generating a tapered microstructure, RIE process for sharpening the tapered microstructure, and Ti coating for improving the strength. In order to find an optimal balance of strength and sharpness, the puncture tests were performed on pig’s dura mater which is very similar to human’s dura mater and will be used in in-vivo test. The biocompatibility test was performed to check the channel blockage due to the platelets adhesion. This work for Aim 2 was described in Chapter 3.

1.4.3 Aim 3: Assemble an array of microvalves and an array of microneedles into MAG (Micro-fabricated arachnoid granulation), and perform in-vitro flow test and biocompatibility test.

A microvalve array will be aligned and bonded with a microneedle array. In-vitro flow test and biocompatibility test will be performed with fabricated MAG before in-vivo testing of this device in a pig. This work for Aim 3 was described in Chapter 4.
1.5 References


CHAPTER 2: AN ARRAY OF PDMS/PARYLENE MICROVALVES

2.1 Review of microvalve array for biomedical applications

The innovative treatment of hydrocephalus is to implant a biocompatible micro check valve mimicking the function of AG. The microvalve for this approach requires following conditions; biocompatible and nontoxic material, ease fabrication, and proper valving functions such as minimal cracking pressure, high backward flow resistances, and sufficient forward flow (~ 0.4 ml/min at CSF pressure of 1500 Pa).

Several implantable microvalves have been presented for biomedical applications. Chung et al. (2003) developed a MEMS-based CSF shunt microvalve consisting of flow nozzles with a 6 μm thick parylene membrane connected to an anchor by bridges [1, 2]. The function of this valve can be precisely controlled by the selection of the design parameters. The dimension of the assembled CSF shunt valve is 2.5x2.5x0.8 mm³. The pressure acting on the valve is generated by a finger pushing on the outer housing. A maximum displacement of 72 μm and maximum resistible pressure up to 4 kPa were observed. Figure 2-1 shows schematics of CSF shunt system in function. In pushing phase, CSF shunt valve is pumped down to abdominal cavity. In restoring phase, CSF is sucked from brain to the inner cavity of CSF shunt system. Since this microvalve should be operated using a finger, this valve can’t be implanted for our application. Chen et al. (2007) proposed surface-
Figure 2-1. Schematics of CSF shunt system in function. In pushing phase, CSF shunt valve is pumped down to abdominal cavity. In restoring phase, CSF is sucked from brain to the inner cavity of CSF shunt system.
Figure 2-2. Concept of dual-valved microflow regulation. (a) target flow regulation profile, (b) a back-to-back configuration of dual valves, and (c) regulation profile of dual-valved microfluidic system.
micromachined parylene dual valves for on-chip unpowered microflow regulation [3, 4]. This back-to-back dual-valved configuration requires only two in-channel check valves which consist of a normally closed valve in forward flow operation at the inlet and a normally open valve in backward flow operation at the outlet of a microchannel. The dual microsystem was able to regulate pressure in the range of 0~1 psi with measured flow rates of up to 0.7 mL/min for air flow and 1.3 μL/min for water flow. Figure 2-2 shows the concept of dual-valved microflow regulation. Figure 2-2 (a) is an ideal bandpass profile of dual valves, (b) is a schematic view of dual valves, and (c) is the regulation profile of dual-valved microfluidic system. A microvalve for our application should be working sensitively with the increase of intracranial pressure. This microvalve can’t be adapted to our application because a valve is closed in the pressure range over cut-off point by outlet NO valve as shown in Figure 2-2(c). Emam et al. (2008) presented an array of implantable one-way microvalves for the treatment of hydrocephalus [5]. This parylene microvalve can control flow based on pressure differential. Initial flow tests demonstrated the desired low cracking pressure of the valve and a sufficient mechanical stability. As this valve does not have a backward flow resistance, this microvalve can’t be applied to our application. Cheng et al. (2008) reported a transcutaneous controlled magnetic microvalve based on iron-powder filled polydimethylsiloxane (PDMS) for implantable drug delivery systems, which allows transcutaneous control when it is
Figure 2-3. Schematics of the magnetic microvalve closed normally and opened by a permanent magnetic.
Figure 2-4. (a) Full glaucoma drainage device (GDD) system consisting of a dual-valve microflow regulation system, a parylene tube carrier, and a rollable/foldable anchor (NO: Normally Open, NC: Norally Closed) and (b) Subconjunctival implantation concept of GDD.
implanted under the skin [6]. Only a magnet is required to work the microvalve for drug delivery. Figure 2-3 shows schematics of the magnetic valve closed normally when there is no magnetic force applied and opened by a permanent magnetic. This valve can’t be employed in our application because of an external force which can’t be acceptable for our application. Lin et al. (2009) presented a 20 μm thick parylene-enabled microvalved shunt implant for glaucoma drainage. This shunt has dual back-to-back microvalves (open at 20 mmHg and closed beyond 50 mmHg) inside the tube [7]. The dual-checkvalve operation enables this device to physically drain the extra intraocular fluid and regulate the intraocular pressure within the normal range (15~20 mmHg). This valve is the first implanted checkvalved glaucoma drainage device (GDD) for the treatment of glaucoma, which is passive, consumes no additional power, and functions without any circuit board involved to pursue its medical application. The working mechanism of this dual valve is the same as that of Cheng’s valve. Figure 2-4 shows that (a) is the glaucoma drainage device system consisting of a dual-valve microflow regulation system, a parylene tube carrier, and a rollable/ foldable anchor and (b) is a subconjunctival implantation concept of glaucoma drainage device. As the valve is closed beyond 50 mmHg this microvalve can’t be used for our application.
2.2 Design of an array of microvalves using 3D simulation

2.2.1 Design criteria for microvalve

1. It should be an array type for minimizing the chances of device failure.

2. It should be an one-way, passive valve which should function based on pressure differential.

3. It must have a very low cracking pressure (< 10 mmH$_2$O) and high backward flow resistance (no flow up to 200 mmH$_2$O): normally closed valve.

4. It needs to be small (< 5x5x1 mm$^3$) but not too small for surgical implantation.

5. The valve material needs to be biocompatible to minimize blood clotting and any damage to the tissue.

6. The device should be cost-effective and is preferably made of polymer.
2.2.2 Selected designs and materials

We have proposed two designs for microvalve. One is a dome-petal design and the other is a corrugated spring design. The dome-petal design uses its geometric effect to open and close. The corrugated spring design as shown in Figure 1-18. This idea came from silicon valves in condimental bottles such as French’s bottle. The corrugated spring design is a typical diaphragm valve. This design as adopted from literature review as an alternative design. The reason why we chose the dome-petal design as our primary valve design was not only because it was a unique design but because it requires only one photomask process.

In terms of valve material, we chose PDMS/Parylene composite. PDMS is polydimethylsiloxane. It is silicon elastomer. We picked it because its sticky nature can provide a good self-sealing ability and because it is biocompatible and micro-manufacturable. Parylene is polyparaxylylene. It is a thin film polymer deposited from gas phase. We picked it because it can provide mechanical rigidity to the valve. Parylene is also known to be biocompatible.
2.2.3 Design and simulation of an array of microvalves

In order to be capable of diverting cerebrospinal fluid equivalent to normally functioning arachnoid granulation, 3-D dome petal shape was employed as our check valve design. This shape enables the check valve to open and close easily. The normally open valves stay open until the pressure reaches a certain point which the membrane collapses and covers the orifice. With this reason, the normally closed valve design was chosen to minimize the backward flow. Thin polymer films, PDMS and Parylene were chosen as the valve material to achieve the low cracking pressure required for our application.

Multiple arachnoid granulations exist in the dura mata membrane of the brain. In order to mimic this design and also avoid device failure due to valve blockage, 7x7 and 10x10 arrays of microvalves were designed with an area of 5x5 mm$^2$. In order to simulate native arachnoid granulations, the valve must operate at relatively constant rate of 0.3~0.5 ml/min at a pressure range of 500 to 1500 Pa with no backward flow. The main design parameters that determined the valve performance are listed in Table 2-1. The thickness of Parylene C was fixed as 10 μm in order to provide the rigidity on a PDMS layer while the thickness of PDMS was varied. As minimum size of the laser beam is 6 μm, the opening gap was fixed as 6 μm. Two microvalves were designed. Five different opening shapes such as slit cut, cross cut, and combined cut were investigated for those microvalves. In order to validate and optimize design, 3-D
numerical simulation study was conducted. The COMSOL software was used to analyze the fluid-structure interaction with the coupling between fluid and a dynamic microvalve. Figure 2-5(a) is the three-dimensional simulation model. The size of the simulation space is 500 μm x 500 μm x 5 mm. A microvalve is located in the middle separating the space into two parts, superior sagittal sinus (top) and subarachnoid area (bottom). The dimension of the dome shaped microvalve is shown in Figure 2-5(b) and (c). In the simulation only a Parylene layer was considered because including a thin PDMS layer requires numerous meshes and consequently extremely high computation capacity. Since the Young’s modulus (3.2 GPa) of Parylene C (density=1310 kg/m³, Poisson’s ratio=0.4) is much higher than that (0.5 MPa) of PDMS, the motion of a microvalve depends primarily on the Parylene layer. For the fluid, the property of water (density=1000 kg/m³, dynamic viscosity=0.001 Pa·s) was used in the simulation.

Three multiphysics of Solid Stress-Strain, Moving Mesh, and Incompressible Navier-Stokes were coupled in the simulation. Fully developed laminar flow generated the force distribution on the microvalve resulting in the displacement of the microvalve. This motion had direct influence on the development of the flow again using the moving mesh method. In Solid Stress-Strain modeling, an elastic formulation and a nonlinear geometry formulation were applied for large deformation. The square edge boundaries of a microvalve were fixed to the wall. Other boundaries experience a fluid load as a force sum of pressure and viscous
flow. The governing equation is

\[ F = -n \cdot (-pI + \eta (\nabla u + (\nabla u)^T)) \]  \hspace{1cm} (1)

where \( n \) is the normal vector, \( p \) is the pressure, \( I \) is the unit diagonal matrix, \( \eta \) is the dynamic viscosity, and \( u \) is the velocity. In Moving Mesh modeling, the arbitrary Lagrangian-Eulerian (ALE) method handles the dynamics of the deforming microvalve and the moving boundaries with a virtual moving grid. It generated new mesh coordinates on the channel based on the movement of the boundaries of the microvalve. It reformulates the Incompressible Navier-Stokes equation to solve the flow as follows;

\[ -\nabla ((-\rho )I + \eta (\nabla u + (\nabla u)^T)) + \rho (u \cdot \nabla) u = F, \quad \nabla \cdot u = 0 \]  \hspace{1cm} (2)

where \( \rho \) is the fluid’s density and \( F \) is the volume force affecting the fluid. All wall boundary conditions are no slip except zero pressure at the outlet and positive pressure at the inlet.

In the mesh generation, predefined mesh size was set to Normal. Maximum element sizes for the microvalve and the fluid were set to 5e-6 m and 1e-4 m. GMRES and Incomplete LU were used as a parametric segregated solver.
Table 2-1. Design parameters of the microvalve.

<table>
<thead>
<tr>
<th>Design parameters</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dome diameter (D)</td>
<td>170 μm, 210 μm</td>
</tr>
<tr>
<td>Dome height (H)</td>
<td>80 μm, 100 μm</td>
</tr>
<tr>
<td>Parylene C thickness</td>
<td>10 μm</td>
</tr>
<tr>
<td>PDMS thickness</td>
<td>Variant range (Figure 2-7)</td>
</tr>
<tr>
<td>Opening gap (G)</td>
<td>3 μm (defined by laser)</td>
</tr>
<tr>
<td>Opening shape</td>
<td>Cross-cut, slit-cut, combined</td>
</tr>
</tbody>
</table>

Opening lengths (L1, L2)

- 170 μm, 210 μm (Cross-cut and Slit-cut)
- \( L_1 = 210 \, \mu m, L_2 = 30, 60 \, \mu m \) (Combined-cut)
Figure 2-5. 3D simulated geometry, dimensions, and boundary conditions: (a) total view, (b) top view of a microvalve, and (c) side view of a microvalve.
2.2.4 Results and discussion

Figure 2-6(a) and (b) show the 3-D plots for velocity, displacement, and von Mises stress when the gap and the inlet pressure are 3 μm and 1300 Pa. Maximum von Mises yield strength is 0.721 MPa at the corner of dome. This value is much lower than the yield strength (=65.5 MPa) of Parylene C. As PDMS is more flexible than Parylene, the maximum displacement of a microvalve is decided by Parylene. These results prove the safety and durability of a microvalve without mechanical failure. In Figure 2-6(a), the percentage rate of valve displacement to gap size at 1300 Pa is 4%. The valve displacement is very small against our expectation. Perhaps, the reason is why a stiff parylene layer is dominant in the valve displacement.

Average velocity (=2.56e-4 m/s) at 1300 Pa can be achieved by averaging all values from the slice plot for velocity in Figure 2-7. Flow rate (=0.0038 ml/min) for single microvalve can be calculated by multiplying average velocity and square area (500 μm x 500 μm) together. Multiplying this flow rate by 100 (total number of microvalves) becomes the flow rate (=0.38 ml/min) for an array of 10x10 microvalves. A plot of pressure difference vs. flow rate, as shown in Figure 2-7, was made by repeating this calculation based on the simulation of two microvalves with 3 and 4 μm gaps. The simulation result shows that the flow rate is apparently very sensitive to the gap size. Both valves with 3 and 4 μm gaps work in the desired working zone under forward flow. However, the
valve with 3 μm gap is expected to have higher resistance than that with 4 μm gap under backward flow due to smaller gap. Simulated data has a good agreement with experimental data at a 3 μm gap under forwardward flow. This result indicates the validation of this simulation which can be qualified as a tool for the microvalve design.
Figure 2-6. Simulated plots for: (a) velocity (slice and arrow) and displacement at $P_{in}=1300$ Pa and (b) von Mises stress and velocity (arrow) at $P_{in}=1300$ Pa.
Figure 2-7. Simulated plots for pressure difference vs. flow rate at 3 and 4μm gaps.
2.3 Fabrication of an array of microvalves

2.3.1 Fabrication process

Figure 2-8, 2-9, and 2-10 show the fabrication process flow of PDMS/Parylene dome petal microvalve. The three main fabrication processes are dome-shaped SU-8 mold fabrication, PDMS and Parylene coating on the mold, and Excimer laser machining for valve opening.

In Figure 2-8, first, a dome-shaped SU-8 mold was fabricated by diffuser lithography technique based on light scattering through diffuser glass. Initially, a thin SU-8 2002 layer was spin-coated on a Cr patterned glass plate and exposed to UV, effectively acting as an adhesion promoter for subsequent fabrication steps. Then a thick SU-8 2035 layer was spin-coated on top. This substrate was then flipped over and a diffuser glass with one side of Opal (NT43-719, Edmond Optics Co., Ltd, Barrington, NJ) as placed on the Cr plate followed by UV exposure, post-exposure bake, and developing. This process produced dome-shaped SU-8 molds as shown in Figure 2-8(a). The dome diameter on the fabricated SU-8 mold is a little larger than the diameter of Cr patterned circles due to the light scattering.

Then, the SU-8 mold was silanized prior to PDMS/Parylene deposition for easy release. PDMS was diluted with hexane (PDMS: Hexane=1:1) and was spin-coated on the SU-8 mold at 1000 rpm for 20 sec. The mold was then kept upside down at room temperature for
Figure 2-8. Fabrication process flow for dome-shaped SU-8 mold.
Figure 2-9. PDMS and Parylene deposition process.
Figure 2-10. Excimer laser machining process and microscopic images of fabricated microvalves: (a) D=170 μm & Cross cut (170 μm x 170 μm), (b) D=170 μm & Slit cut (170 μm), (c) D=210μm & Slit cut (200 μm), (d) D=210 μm & Combined cut (200 μm x 30 μm), (e) D=210 μm & Combined cut (200 μm x 60 μm), and (f) 10x10 array of microvalves with (e).
2.5 or 5 hours to induce PDMS reflow and to form a uniform layer prior to baking (70℃, 30 min). A 10 μm thick Parylene layer was then deposited on the PDMS coated with the SU-8 mold (Figure 2-9).

Finally, KrF excimer laser machining (RAPID X250; Resonetics Co, Ltd, Nashua, NH) was done to make valve opening with cross-cut and slit-cut shapes on the composite layer of PDMS and Parylene released from the SU-8 mold. A beam diameter of approximately 5 μm was used for this process. Dome diameters of array type were 170 and 210 μm (The original Cr pattern diameters were 150 and 200 μm, respectively). Five kinds of opening shapes listed in table 1 were generated. Figure 2-10(a) and (b) show opening shapes generated on the dome with 170 μm diameter. Figure 2-10(c)–(e) show opening shapes generated on the dome with 200 μm diameter. The ablation gap size of the valve was about 3 μm. Figure 2-10(f) is a finished 10x10 array of microvalves with (e) shape.
2.3.2 Results and discussion

Figure 2-11 shows a cross-sectional SEM picture of a microvalve which has a 210 μm diameter and experienced 5 hr PDMS reflow. This side view was generated by laser ablation with 5 μm beam diameter along each dome’s center across a 10x10 array. This dome shape is more spherical compared to the relatively flat shape which we suggested previously. The thickness of Parylene was found to be a uniform 10 μm in all areas. The thickness of PDMS varies according to the location of the dome. The thickness between corner and top is about 1.5 μm. The thickness near top area is about 3 μm. The PDMS thickness outside of the dome is about 70 μm.
Figure 2-11. SEM image: cross-sectional view of a microvalve (D=210 μm and 5hrs reflow).
2.4 Investigation for wrinkle phenomena

2.4.1 Sample preparation for wrinkle test

In the PDMS/Parylene composite layer, the Parylene layer provides the mechanical rigidity necessary for release process (thin PDMS layer without Parylene was torn during the release process) while PDMS can still maintain its surface properties such as observation is that lots of repeated wrinkles were observed on the PDMS/Parylene composite layer as shown in Figure 2-4.

The wrinkle size and frequency varied as a function of the ratio (PDMS: Parylene) of the thickness of the two layers. No wrinkle was observed on the dome membrane where PDMS and Parylene have comparable thicknesses while lots of wrinkles were found on the base membrane where PDMS is much thicker (70-100 µm) than Parylene (10 µm). The wrinkle formation seems to be due to the mechanical rigidity mismatch between elastic PDMS and rigid Parylene layers which likely created wrinkles to relieve the stress.

For better understanding of this wrinkle issue, ten samples listed on Table 2-2 have been prepared. Each sample has one or two layers coated on the 2x2 glass (1.65 mm thick) or thick PDMS blocks. The thickness of these layers varies. These samples were investigated under optical microscope.
Table 2-2. 10 kinds of samples prepared for the investigation of the wrinkle issue

<table>
<thead>
<tr>
<th>Sample #</th>
<th>Substrate</th>
<th>Middle layer</th>
<th>Parylene C</th>
<th>Wrinkle</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2x2 Glass</td>
<td>No</td>
<td>10 μm</td>
<td>None</td>
</tr>
<tr>
<td>2</td>
<td>2x2 Glass</td>
<td>Thin SU-8 2005 at 1000 rpm</td>
<td>10 μm</td>
<td>None</td>
</tr>
<tr>
<td>3</td>
<td>2x2 Glass</td>
<td>40 μm thick PDMS</td>
<td>10 μm</td>
<td>Wavy</td>
</tr>
<tr>
<td>4</td>
<td>2x2 Glass</td>
<td>20 μm thick PDMS</td>
<td>10 μm</td>
<td>Dots</td>
</tr>
<tr>
<td>5</td>
<td>PDMS block</td>
<td>No</td>
<td>10 μm</td>
<td>None</td>
</tr>
<tr>
<td>6</td>
<td>2x2 Glass</td>
<td>No</td>
<td>2 μm</td>
<td>None</td>
</tr>
<tr>
<td>7</td>
<td>2x2 Glass</td>
<td>Thin SU-8 2005 at 1000 rpm</td>
<td>2 μm</td>
<td>None</td>
</tr>
<tr>
<td>8</td>
<td>2x2 Glass</td>
<td>18 μm thick PDMS</td>
<td>2 μm</td>
<td>Dots</td>
</tr>
<tr>
<td>9</td>
<td>2x2 Glass</td>
<td>8 μm thick PDMS</td>
<td>2 μm</td>
<td>Wavy</td>
</tr>
<tr>
<td>10</td>
<td>PDMS block</td>
<td>No</td>
<td>2 μm</td>
<td>None</td>
</tr>
</tbody>
</table>
2.4.2 Results and discussion

Figure 2-12 shows repeated wrinkles without delamination which were observed on only the samples of #3, 4, 8, and 9. The reason is that wrinkles occur on a film which requires coherent deformation of a soft material. The proof is that these samples included a thin film of Parylene and a layer of soft material, PDMS on the glass.

Wave wrinkles were generated on sample #3 and sample #9 with the thickness ratio of 4:1 while dotted wrinkles were found on sample #4 (thickness ratio=2:1) and sample #8 (thickness ratio=9:1). This phenomenon may refer to the thickness ratio as main factor for wrinkle generation. However, even though sample #3 has the same thickness ratio as sample #9, the wrinkle width of sample #3 is twice as large as those of sample #9. This result may indicate that both of the thickness and the thickness ratio are related with wrinkle generation. Based on this relationship, the case of sample #3 and #4 can be explained with thicker PDMS layer which is vertically more compliant. Thicker PDMS enabled sample #3 to be developed further. In addition, as wrinkles were not developed fully on samples with the ratio out of 4:1 based on this investigation, the thickness ratio of 4:1 may be close to a critical point which causes maximum wrinkle generation.

From the literature review on this phenomena, we learned that if a rigid plate is subjected to stress and attached to a soft elastic medium, it is very likely that this stress is relieved by wrinkling: The composite plate
Figure 2-12. Wrinkles (20x magnification): (a) sample #3 (wave width=10 μm), (b) sample #4, (c) sample #8, and (d) sample #9 (wave width=5 μm).
buckles into a large number of waves and the pattern and size of the wrinkles depend on the thickness of the materials as well as the thickness ratio.
2.5 Flow characterization for the performance of the microvalve

2.5.1 Flow test

Flow tests were performed using deionized water in order to characterize the performance of the microvalves. Differential pressures between the top and bottom sides of the microvalve were measured under various flow rate conditions. The range of pressure difference measured in this test was between 0 and 8 kPa at a flow rate of up to 0.8 ml/min. Figure 2-13 shows the test set-up consisting of a PDMS flow chamber where an array of microvalves is placed, a pressure transducer (max. 1 psi, OMEGA Co., Ltd, Stamford, CT), a read-out, and a syringe pump. Both sides of the microvalve were tightly fixed to the test chamber using a PDMS gasket to ensure sealing. Pressure difference for forward and backward flows was measured after the flow reached steady-state. To obtain reverse flow data, the valve was simply switched to the opposite direction. It was found that this orientation change occasionally caused bubbles to form inside the tubing. These bubbles were found to have a profound influence on the flow characteristics and failure rates of the device and were removed prior to testing. The flow test was repeated five times for measuring the characteristics of each valve. All valves were not deformed after several tests.
Figure 2-13. Top: Schematic diagram of an experimental setup for the flow test, Bottom: picture of an experimental setup.
2.5.2 Results and discussion

Figure 2-14 shows the flow test results from three different kinds of microvalve array with 170 μm diameter:

(a) 5hr reflow and cross-cut opening (170 μm x 170 μm),
(b) 2.5hr reflow and cross-cut opening (170 μm x 170 μm),
(c) 5hr reflow and slit-cut opening (170 μm).

These were all from an array of 7x7 microvalves. The slope of the plot is inversely proportional to the flow resistance. In other words, a higher slope indicates a lower flow resistance. The flow slope of the case (b) was approximately 0.04 μl/Pa·min, which was about 32 times higher than a single microvalve (data not shown). Note that the single device had slightly larger diameter (210 μm) than the array valves (170 μm). By comparing curves (a) and (c), the effect of valve opening shape may be observed. Cross-cut opening provides more flexibility to the valve membrane than the slit-cut opening. Consequently, the microvalve with a cross-cut opening can be cracked open more easily under forward flows and have less flow resistance than slit-cut valve. It is also shown that slit-cut opening provides a better sealing and higher flow resistance under backward flows. Therefore, the slit-cut opening microvalve has better flow rectification performance while the cross-cut opening microvalve provides lower cracking pressure and more flow rates during forward flows.

The effect of PDMS reflow time can also be analyzed by
Figure 2-14. Flow test results for 7x7 array microvalves with 170 μm diameter: (a) 5hr reflow and cross-cut opening (170μm x170μm), (b) 2.5hr reflow and cross-cut opening (170μm x170μm), and (c) 5hr reflow and slit-cut opening (170 μm).
comparing curves (a) and (b). The microvalve made by 5 hr reflow shows a lower flow resistance than 2.5 hr reflow case in both forward and backward flow conditions. This is probably due to the thickness variation of PDMS layer as a function of reflow time. 5 hr reflow would be sufficient for the formation of a uniform PDMS layer while 2.5 hr may result in non-uniform thickness with thick layer at the bottom and thin layer at the top of the microvalve. This non-uniform PDMS layer may result in higher flow resistance for 2.5 hr reflow microvalves.

An ideal microvalve for the treatment of hydrocephalus needs to have a cracking pressure close to zero, a forward flow rate of 0.3~0.5 ml/min at pressure differences between 500 and 1500 Pa. Although none of the microvalves presented in Figure 2-14 met all the requirements, some insight could be obtained from the data. Basically, slit-cut opening provides a better flow rectification (better sealing in backward flows) and cross-cut opening provides a higher flow rate in forward flows. One way to increase the forward flow rate of the slit-cut valve without decreasing its self-sealing performance may be to increase the opening length. Another way is simply to increase the number of valves (e.g. 10x10 array instead of 7x7 array).

Above-mentioned recommendations such as larger diameter in valve size, more microvalves, and modified opening shape were applied to 10x10 array microvalves. The flow test results from three kinds of 10x10 array microvalves with 210 μm diameter are pictured in Figure 2-15:
Figure 2-15 Flow test results for 10x10 array microvalves with 210 μm diameter: (a) 5hr reflow and cross-cut opening (210μm x60μm), (b) 5hr reflow and cross-cut opening (210 μm x30μm), and (c) 5hr reflow and slit-cut opening (210μm).
(a) 5hr reflow and combined-cut opening (210 μm x 60 μm),
(b) 5hr reflow and combined-cut opening (210 μm x 30 μm),
(c) 5hr reflow and slit-cut opening (210 μm).

The slope of curves (a), (b), and (c) in Figure 2-15 were found to be 0.25, 0.15, and 0.02 μl/Pa·min respectively. The maximum error range of averaged difference pressure is about ±6% at low pressure differentials and about ±2% at high pressure differentials. Small variance of error range proves that the microvalves are mechanically stable during the flow test. By comparing (a), (b), and (c), the slopes of curves (a) and (b) are much larger as compared with curve (c). This means that a 10x10 array microvalve with slit-cut opening has much higher forward flow resistance than curves (a) and (b) types. As the cross opening length (60 μm) of curve (a) is larger than the combined opening length (30 μm) of curve (b), the flow slope of curve (a) is almost twice as large as that of curve (b) at the same pressure difference. The flow test was repeated five times for every microvalve. Additionally, the mechanical integrity of the microvalve array was maintained after flow testing without any plastic deformation, making them suitable for long term in vivo use.

In Figure 2-15, all opening shapes provide very high flow resistance to the backward flow in the range of zero to -2500 Pa. High flow resistance is due to short slit cut (0, 30, and 60 μm) crossing long slit cut (200 μm) and a PDMS layer on top area which makes better sealing.

As seen in Figure 2-14 and 15, all types of array microvalves have
been tested to characterize the valve performance at various operating conditions. Finally, curve (a) in Figure 2-15 can be selected as the best microvalve with the valve performance mimicking arachnoid granulations. The reason is that this valve has easy opening function under forward flow and better sealing effect under backward flow. Also, the flow slope (0.25 µl/Pa·min) of this array microvalve exists within the dashed line which means a working zone of arachnoid villi (forward flow rate of 0.3–0.5 ml/min at pressure difference between 500 and 1500 Pa) to be required for an ideal valve.
2.6 References


CHAPTER 3: AN ARRAY OF SU-8 MICRONEEDLES

3.1 Review of an array of microneedles for biological applications

A hypodermic syringe needle was a traditional route to inject drugs or extract bioliquids. This macro syringe had many shortcomings such as they were ineffectual, painful, and wasteful in terms of the volumes of bioliquids consumed. Since the introduction of Microelectromechanical Systems (MEMS) technology, conventional syringes could be replaced with microneedles for better treatment of patients. Delivering medication transdermally is one of the major applications of microneedles, which are usually made of silicon, metals or polymers. Xu et al. (2007) reported on an array of polymer microneedles with pyramid-shaped tips and titanium shield for transdermal drug or nanoparticle delivery [1]. Figure 3-1 shows the fabrication process. Pyramid-shaped holes are fabricated on a silicon wafer with a patterned oxide layer. A releasing layer was coated on this wafer. Then, first and second SU-8 layers were coated on the releasing layer and exposed using a mask with an array of clear circles to form microneedle arrays. AB glue or PDMS was solidified to form the needle’s base on the SU-8 layer. After removing the unexposed SU-8, Ti was sputtered to enhance biocompatibility and hardness. Roxhed et al. (2007) presented ultrasharp hollow microneedles for efficient transdermal drug delivery [2]. As shown in Figure 3-2, holes were formed for flow channels
Figure 3-1. Fabrication process flow: (a) The 4 in silicon wafer was oxidized double sides, (b) the pyramid shapes were generated on the wafer after KOH etching, (c) a releasing layer was coated, (d) The first SU-8 layer was spincoated, (e) 600 μm thick SU 8 layer was spincoated and exposed by defined mask to form needle shaft, (f) the exposed SU-8 polymer was heated, (g) AB glue or PDMS was solidified to form the needle’s base, (h) an array of microneedles was developed and separated from master, and (j) Ti was sputtered on it to enhance biocompatibility and hardness.
Figure 3-2. Fabrication process flow of side-opened hollow microneedles. Microneedles were made on 600 μm thick silicon wafer by alternating between anisotropic Deep Reactive Ion Etching (DRIE) and isotropic SF₆ plasma etching.
Figure 3-3. Process flow for fabrication of SU-8 hollow microneedle array.
through a 600 µm thick wafer using DRIE (Deep reactive ion etching). Then, a 5x5 microneedle array was made by alternating between anisotropic DRIE and isotropic SF₆ plasma etching. The oxidation on the needle through the oxide etch mask was used for sharpening the needle. Liquid delivery through the microneedles was successively tested through the skin. Choi et al. (2007) reported on a three-dimensional MEMS microfluidic perfusion system with a SU-8 microneedle array for thick brain slice cultures [3]. In figure 3-3, this needle array was fabricated by a sequence of three processes of photolithography for the SU-8 tower, reactive ion etching for sharpened tips, and laser ablation for microchannel definition inside the needles. Bhandari et al. (2008) presented a novel mask-less method of fabricating high aspect ratio microneedles for blood sampling [4]. The fabrication process is shown in Figure 3-4. A YAG laser with a wavelength of 1064 nm boredholes (diameter= 80 µm and height=450 µm) through the silicon wafer. Rectangular columns were then created by making orthogonal cuts in the x and y directions using a dicing saw. Wet isotropic etching was performed to form sharp microneedles. Wang et al. (2009) presented a hollow polymer microneedle array for drug delivery that was fabricated by a photolithography process combined with replica molding technique [5]. Figure 3-5 shows the fabrication flow. A SU-8 layer was spinecoated on a PDMS mold with a profile of pyramid tip. A vacuum process was performed to remove bubbles in the PDMS trenches. The SU-8 layer was then exposed to form the pyramid tips and
Figure 3-4. Process flow for fabrication of hollow microneedle array. A: 700 μm thick silicon wafer, B: hole formation (diameter=80 μm and height=450 μm) using YAG laser with a wavelength of 1064 nm, C: rectangular columns were created by making 0.5 mm deep cuts., and D: isotropic etching for sharp needle.
Figure 3-5. Process flow for fabrication of hollow microneedle array: (a) a PDMS mold with profile of pyramid tip was made., (b) a 800 μm thick SU 8 layer was spincoated and a backside vacuuming process was performed to remove bubbles in the PDMS trenches., (c) a SU 8 layer with a mask was exposed to form pyramid tips and shafts., (d) a SU 8 layer was exposed to form the microneedle base., (e) the PDMS mold was removed., and (f) unexposed SU 8 was removed.
shafts. The second exposure was applied to the SU-8 layer to form the needle base. Next, the PDMS mold was removed and unexposed SU-8 was developed away. Choi et al. (2010) demonstrated a polymethylmethacrylate (PMMA) microneedle array with electrical functionality for electroporating skin’s epidermal cells to increase their transfection by DNA vaccines [6]. Techniques used for the needle fabrication are PDMS micromolding, metal deposition, laser ablation for patterning, and electrodeposition. The first SU-8 was spincoated and exposed for the needle base, and the second SU-8 layer was spincoated and exposed to form the tapered geometry. RIE etching was applied to form the sharp needle. PDMS was then cast onto the SU-8 needle array to form an inverse PDMS mold and a replica PMMA microneedle array was formed. The Ti/Cu was sputtered on the PMMA microneedle array as a seed layer for electrodeposition of Ni, and the laser ablation of a metal layer was done to achieve electrical isolation. The next step was electrodeposition of Ni to enhance mechanical strength. This study demonstrated the mechanical and electrical functionalities of the first MEMS-fabricated microneedle array for electroporation designed for DNA vaccine delivery.
3.2  Design of an array of microneedles and simulation for the size decision of small channel inside the microneedle

3.2.1. Design criteria for microneedle

1. It must be an **array type** that can be assembled with a dome-petal microvalve array.

2. It must be **sharp and rigid** to be able to pierce dura mater.

3. **Needle height** needs to be **around 500 μm** because the thickness of dura mater is about 300 μm).

4. Hollow channel for CSF conduit:
   a. The hollow channel needs to be **off center** to maintain the sharpness of the microneedle.
   b. The channel diameter needs to be **less than 50 μm** to be able to pass through dura mater but not too small because the pressure drop across the channel should be minimized for proper valve performance.

5. The needle should be **small** and **biocompatible** (preferably polymer).
3.2.2. Design of an array of microneedles

Figure 3-6 shows the design of a 10x10 SU-8 microneedle array. The microneedles were designed to have a 500 μm-long conical shaped body with a sharp tip on a square base and a microchannel inside each microneedle to deliver CSF to the sagittal sinus. This long conical-shaped needle with a sharp tip is expected to puncture human dura mater with a thickness of 300 μm. In order to prevent the needles from being blocked by platelet adhesion and blood clotting, this microneedle array was designed as 10x 10 arrays on a base with an area of 5x5 mm² and a thickness of 200 μm. The height and bottom diameter of the conical-shaped body are 500 and 120 μm, respectively, and the distance between two adjacent cone centers is 400 μm. The microfluidic channels inside the microneedles consist of a small channel (H=300~350 μm) inside the needle and large channel (D=250 μm & H=150 μm) inside the base. Later, a 10x10 array of large holes inside the base will be aligned and bonded with a 10x10 array of microvalves for the MAG. In order to determine the diameter of the small channel, pressure drop through the channel will be calculated and visualized using 3D Comsol simulations. The strength and sharpness of the microneedles should be investigated through puncture testing with dura mater. The needle will be designed in order to achieve the optimal balance of strength and sharpness.
Figure 3-6. Schematic and dimensions of 10x10 conical shaped microneedle arrays.
3.2.3. Simulation for the size decision of small channel inside the microneedle to minimize pressure drop through the channel

The MAG can drain CSF from the subarachnoid space (SAS) to the superior sagittal sinus (SSS) after implantation. A pressure drop through the channels inside microneedles should not affect the valve performance as shown in Figure 2-14 and 15. In order to minimize the pressure drop through the channel, 3-D numerical simulation using the Comsol program can be applied for calculating and visualizing the pressure drop through the channel.

The geometry for this simulation was drawn based on the model for the microvalve simulation as shown in Figure 3-7. A small channel inside the needle was added in the geometry. A simulation procedure is very similar to the previous simulation for the microvalve. Three multiphysics modules of Solid Stress-Strain, Moving Mesh, and Incompressible Navier-Stokes were coupled in the simulation. Material properties and equations used in this simulation are shown in Chapter 2.2. All boundary conditions (BCs) necessary to determine a solution are the following: 1 is an inlet with an applied pressure, 2~11 are walls with a no-slip condition, 12 is an outlet with zero pressure, and the BC of a valve in this geometry is the same as the BC used in the microvalve simulation. In the mesh generation, the predefined mesh size was set to normal. Maximum element sizes for this geometry were set to 5e-6 and 1e-4 m.
Figure 3-7. 3-D simulated geometry, dimensions and boundary conditions; 1=inlet (BC=applied pressure), 2-11=wall (BC=no slip), 12= outlet (BC=zero pressure), and valve (BC=same as previous valve simulation)
The GMRES (Generalized Minimum Residual) solver with Incomplete LU was used as a parametric segregated solver.
3.2.4. Results and discussion

Figure 3-8 shows the 3-D simulation calculating the pressure drop through the channels at 1500 Pa to predict the pressure drop through microvalve and microfluidic channel inside the microneedle. Figure 3-9(a) is the result for pressure drop through channel with a diameter of 30 μm. Pressure drop through this channel at 1500 Pa is 600 Pa. This pressure drop affects the valve performance seriously. However, Figure 3-9(b) shows that the pressure drop through small channel with a diameter of 40 μm at 1500 Pa is less than 100 Pa which is acceptable. From above results, the channel diameter should be at least 40 μm. At the same time, current needle design limits the channel diameter to less than 50 μm. There are two reasons to limit the small channel diameter inside the needle. One is the channel location; the center of the channel should be located outside of the center of the microneedle to keep a sharp tip. The other is the limitation of the channel length. The height of the outlet should be over 300 μm from the bottom (diameter 120 μm) of the cone shape to puncture human dura mater with a thickness of 300 μm. These analysis results came to the conclusion that the channel diameter should be designed as 40 μm.
Figure 3-8. 3-D simulation results at 1500 Pa for optimization of channel size inside microneedle to predict the pressure drop through microvalve and channel inside microneedle: (a) $D_c = 30 \mu$m and (b) $D_c = 40 \mu$m.
Table 3-1. Pressure drop through small channel at 1500 Pa from numerical simulation and analytical solution.

\[ \Delta P = \frac{8 \mu L \bar{u}}{r^2} \quad \text{(For analytical solution)} \]

\( \bar{u} \) = average velocity, \( L \) = channel length, \( r \) = channel radius, \( \mu \) = dynamic viscosity, and \( \Delta P \) = Pressure drop

<table>
<thead>
<tr>
<th>Channel diameter (Dc, μm)</th>
<th>30</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Pressure drop (Pa)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>from Analytical solution</td>
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<td>105</td>
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<tr>
<td>Pressure drop (Pa)</td>
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<td>from Simulation</td>
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</tr>
<tr>
<td>Average velocity (m/s)</td>
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<tr>
<td>Channel length (μm)</td>
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<tr>
<td>Dynamic viscosity (Pa·s)</td>
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</tbody>
</table>
3.3 Fabrication of an array of microneedles

3.3.1 Fabrication process

In order to fabricate a 10x10 array of microneedles, four main fabrication processes are required as follows; microfabrication for tapered geometry, RIE (Reactive Ion Etching) for a sharpened microneedle, Excimer laser machining for the microfluidic channel inside the microneedle, and Metal (Al or Ti) & Parylene deposition on the microneedle for strength enhancement.

Figure 3-9 shows the fabrication process flow for the tapered SU-8 microstructure. First, a Cr layer on the 4x4 in glass plate is patterned. A dextrin solution (dextrin: DI water=1 g: 10 g) is then spin-coated on the Cr plate at 2000 rpm: 20s: 1000rps and baked at 120°C for 2 min. This dextrin layer is used for easy release of the array of microneedles from the glass plate. To form the base, SU-8 2035 is spin-coated at 500rpm: 10s: 300rps/ 500rpm: 30s: 300rps for 200 μm and baked at 65°C for 10 min and 95°C for 50min. It is exposed for 17.7 sec with a UV intensity of 21.2 mW/cm² and then baked at 65°C for 5 min and 95°C for 30 min. To form a tapered microstructure, SU-8 2150 is spin-coated at 500rpm: 10s: 100rps/ 1000rpm: 30s: 300rps for 550 μm and baked at 65°C for 5 min and 125°C for 4 hrs. It is exposed for 235.8 sec and then baked at 65°C for 1 min and 95°C for 2 hrs. Then, it is developed with SU-8 developer and rinsed with IPA (Isopropyl alcohol). The microneedles are separated from
Figure 3-9. Fabrication process for tapered SU-8 geometry [7].
the glass plate in water, melting the dextrin layer. A fabricated 10x10 array of microneedles is shown in Figure 3-9.

Figure 3-10 shows the fabricated 10x10 array of tapered microstructures with different diameters. Diameters patterned on the Cr plate are 50, 60, 80, and 100 μm. The bottom diameters of the tapered microstructures are larger than those generated on Cr plate due to the scattered light, but the top diameter of tapered microstructures are smaller than those of the Cr pattern. The height of all of the needles is 550 μm.

The second fabrication process is RIE, which is able to sharpen a microneedle using a plasma system (VITA; Femto Science Inc., Korea), as presented in Figure 3-11. Desirable operating conditions are as follows: gas ratio= CHF$_3$ (20 sccm): O$_2$ (180 sccm), pressure= 900~1500 mTorr, and power= RF 100 W. The power is kept constant to maintain a smooth surface. The optimized etch times for Figure 3-11(a), (b), (c), and (d) are 6 min, 6 min 15sec, 8 min 10 sec, and 9 min 20 sec. At longer etch times beyond these, the needle height decreases significantly.

As shown in Figure 3-10, the next process is KrF excimer laser machining (RAPID X250; Resonetics Co. Ltd, Nashua, NH) to make a microfluidic channel inside the microneedle. The excimer laser ablation is done in two steps to form a big channel inside the base and a small channel inside the cone-shaped body. First a 250 μm diameter laser beam is used to generate big channels from the backside and then, a 20 μm diameter laser beam is used to machine small channels, which are off-
center and parallel to the cone shape. The reason to machine from the backside is that it is easy to align the microneedle with a laser beam and much less debris is produced at the needle outlet.

The final process is the metal deposition on the SU-8 microneedle surface using the DC sputter system (T-M Vacuum Product, Inc., Riverton, NJ, USA) in Figure 3-10. The preferred metal is either Ni or Ti due to their biocompatibility and high strength. 1 μm thick Ti is deposited under the following conditions: Argon: 40 sccm and 30 mTorr, Power: DC 50W, Target temperature: room temperature, cycle: 5 min deposition & 5 min cooling, and total run time: 1hr 30 min. And then, 1 μm thick Parylene C was coated on the microneedle with a metal shield to reduce blood clots on the microneedle surface and to bond together using the diluted PDMS.
Figure 3-10. RIE, Excimer laser machining, and Metal & Parylene coating processes.
3.3.2 Results and discussion

Figure 3-11 shows the tapered SU-8 microstructures. They are different in appearance in terms of the Cr patterned masks, which were designed to have circular geometries with diameters of 50, 60, 80, and 100 µm at a constant spacing of 400 µm. Microstructures with diameters of less than 50 µm collapsed due to very high aspect ratio. The heights of all tapered microstructures are 550 µm. The bottom diameters of the tapered microstructures are larger than the Cr patterned diameters, and the top diameters are smaller. The tapered microstructures with high aspect ratio like these were created by a non-uniform UV dose between top and bottom of the SU-8 resist as shown Figure 3-9. This non-uniform UV dose means that the bottom layer is overexposed and the top layer is relatively underexposed. The sidewall of the tapered microstructures is fairly smooth, and the tapered angle of the microstructures ranges between 2.9 and 3.9º.

Figure 3-12 shows sharp microneedles after the RIE process. An isotropic reactive ion etching enables a tapered microstructure to be made as a very sharp microneedle with smooth surface. The etch time for each tapered microstructure with different diameters depends on the gas stabilization time in the chamber at the beginning of the RIE process for each single sample. When several samples were loaded for the process, the etch time was decreased significantly. This process can control the etch time to vary the needle sharpness and height.
Figure 3-11. Fabricated 10x10 array of tapered microstructures; (a) Cr patterned D 50 μm, (b) Cr patterned D 60 μm, (c) Cr patterned D 80 μm, and (d) Cr patterned D 100 μm.
Figure 3-12. 10x10 array of sharp microneedles after the RIE process. (Full scale range (0-100) in the images is 0-500 μm); (a) Cr patterned D 50 μm, (b) Cr patterned D 60 μm, (c) Cr patterned D 80 μm, and (d) Cr patterned D 100 μm
3.4 Young’s modulus measurement of pig’s dura mater

Pig is available animal with intracranial contents similar to a human. Therefore, the fabricated MAG will be implanted in the pig’s brain and monitored for in-vivo testing. In order to perform this test, it is necessary to puncture the pig’s dura mater with microneedles for implantation. The microneedles should be strong and sharp enough to puncture dura mater. As there is no information for pig’s dura mater, a method to estimate the strength of dura mater is to measure the Young’s modulus. Many methods exist to measure this value for isotropic materials, but it is difficult to measure the Young’s modulus of a thin membrane. One idea is that the Young’s modulus of pig’s dura mater can be calculated from a general characteristic equation for a flat diaphragm using the deflection measured by a photonic sensor, (MTI 1000 FOTONIC SENSOR, MTI Instruments Inc, Albany, New York, USA) which is a non-contact instrument with the fiber optics for transmitting and receiving.

First, output voltages were plotted as function of target displacement according to different light intensities (0.5k, 1k, and 2k) to make fiber optic sensor response curves to target motions as shown in Figure 3-13. The optical peak is a point of inflection on the performance curve, which means an area where the fiber optic sensor is not sensitive to small target displacements. A linear range between -1 and -5 V in the 1k curve was selected to precisely measure the position.
The second step is to measure the deflection of pig’s dura mater
within the linear range. Figure 3-14 shows the schematic of an
experimental setup, which consists of a syringe pump, a 1 psi pressure
sensor, a photonic sensor, and pig’s dura mater fixed along the circular
edge of a chamber. As dura mater is a little transparent, a small piece of
aluminum foil was put on the center of the dura mater for improving light
reflection. The probe of the optical sensor was moved to the effective
range. Applied water pressure by syringe pump generated some deflection
of dura mater and this deflection caused output voltage measured by the
photonic sensor. This voltage was converted to the deflection. Also, the
pressure was measured by the pressure sensor to control the deflection.
Deflection was increased with increasing pressure up to 230 Pa. This test
provided all of the values for the general characteristic equation for a flat
diaphragm.

The last step is to calculate Young’s modulus (E) using the general
characteristic equation for a flat diaphragm. This equation can be used for
a flat diaphragm at any deflection. Required values for this equation are as
follows: Poisson’s ratio (μ), radius (a) and thickness (h) of dura mater,
pressure (P), and deflection (y₀). In Table 3, all values measured and
calculated are listed. The averaged value of the Young’s modulus of pig’s
dura mater is 32 MPa. The correlation between Young’s modulus and
deflection of pig’s dura mater is that Young’s modulus was inversely
increased to deflection.
Figure 3-13. Fiber optic probe response curves to different intensities.
Young’s modulus ($E$)

General characteristic equation for a flat diaphragm at any deflection

$$E = \frac{P}{\frac{16 h^3 y_0}{3(1-\mu^2)\alpha^4} + \frac{(7-\mu)h y_0^3}{3(1-\mu)\alpha^4}}$$

$\mu$ (poisson’s ratio)=0.45
a (dura radius)=0.75 cm
h (dura thickness)=130 $\mu$m

Pressure ($P$) Membrane displacement ($y_0$)

Distance (1k graph)

Voltage ($V$)

Optical sensor (1k intensity) Moving

Light Distance Pig’s dura mater

Syringe pump Aluminium

Figure 3-14. An experimental setup schematic for Young’s modulus measurement of pig’s dura mater.
Table 3-2. Young’s modulus calculation of pig’s dura mater.

<table>
<thead>
<tr>
<th>Voltage_1k (V)</th>
<th>Pressure (Pa)</th>
<th>Distance_1k (mm)</th>
<th>( y_0 ) (mm)</th>
<th>Young’s modulus (MPa)</th>
</tr>
</thead>
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<tr>
<td>-1.8</td>
<td>0</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>-3.5</td>
<td>200</td>
<td>1.35</td>
<td>0.25</td>
<td>54</td>
</tr>
<tr>
<td>-4</td>
<td>220</td>
<td>1.25</td>
<td>0.35</td>
<td>25</td>
</tr>
<tr>
<td>-4.4</td>
<td>230</td>
<td>1.2</td>
<td>0.4</td>
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</tr>
<tr>
<td><strong>Average</strong></td>
<td><strong>32</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
3.5  Puncture test with pig’s dura mater

3.5.1  Preparation for puncture test

Figure 3-15 shows an experimental setup for a puncture test with pig’s dura mater. This setup consists of microneedle holder as a moving part, cap system for tension application to dura mater, and 1-axis stage driven by a micrometer (No. 263M, The L.S. STARRETT Co., Athol, MA, USA). An array of microneedles was placed and fixed on the microneedle holder, which is taped to the center of a moving block. In order to fix an array of needles on the needle holder, dextrin solution was used as temporary adhesive. To mimic the conditions of dura mater under constant tension in the brain, dura mater was fixed by cap system taped on the center of a fixed block. The horizontal movement of the microneedle on the 1-axis stage was controlled by the micrometer, which has a minimum resolution of 10 µm.

Sharp and tapered SU-8 microneedles without a metal shield were used in the puncture tests to check if the strength and sharpness of SU-8 microneedles without a metal shield are enough to puncture dura mater. Initially, an array of microneedles was moved toward dura mater until contact was made. This contact could be checked through the window shown in the schematic of Figure 3-15. The puncture test was performed with gradual, incremental movement of an array of microneedles after contact. Puncturing was checked under a stereo microscope at all locations.
Figure 3-15. An experimental setup for puncture test and a schematic diagram of working mechanism.
3.5.2 Results and discussion

Two 10×10 arrays of tapered microstructures and sharp microneedles with a diameter of 50 µm were used to demonstrate if any of them is strong and sharp enough to puncture pig’s dura mater. Figure 3-16 shows the puncture test results for tapered microstructures. This array of microstructures was moved up to 580 µm toward dura mater after the contact with dura mater. Dura mater was not punctured by this array of microstructures, which can be seen in the dura mater image of Figure 3-16. The microstructures after the puncture test were not deformed at all. This result proves that these microstructures need more sharpness.

Figure 3-17 shows the puncture test result for sharp microneedles. A movement of this array was made up to 590 µm toward dura mater after the contact with dura mater. The trace of microneedles, which did not puncture dura mater, is shown in the dura mater image of Figure 3-17. As a result of the test, all of the microneedles were bent due to low strength.

The reason for failure in the previous tests might come from the sharpness of the tip. In order to rectify this issue a 5-µm layer of Parylene was conformally coated on the surface to increase the thickness of the sharp tip for greater strength. Young’s modulus (2.1 GPa) of SU-8 is similar to that (3.1 GPa) of Parylene. Figure 3-19 shows the microneedle shapes before and after coating Parylene. After coating Parylene, the sharp tip was relatively blunted. The puncture test was repeated with this
microneedle, and the result was that even though the needles displayed greater strength, they were still not strong enough.

The aforementioned tests show that the tapered microstructures require more sharpness and the sharp microneedles need higher strength. In order to enhance the current strength of the microneedles, the only alternative is a metal (Ti or Ni) layer deposited on sharp microneedles using DC sputter, which prevents permanent deformation of SU-8 microneedles due to thermal stress.
Figure 3-16. Puncture test with tapered microstructures with a diameter of 50 µm. All needles were not bent after the test.
Figure 3-17. Puncture test with sharp microneedles with a diameter of 50 µm. All needles were bent after the test.
Figure 3-18. Puncture test with 5 µm Parylene coated sharp microneedles with a diameter of 50 µm. All needles were still bent after the test.
3.6 Titanium coating on SU-8 needle to improve the strength

Previous puncture test results proved that the current SU-8 needle is not strong enough to puncture the dura mater. A metal layer on the SU-8 needle is needed to improve the strength. A sputtering method should be used to deposit Ti on the side of the needle.

A DC sputter system (T-M Vacuum Product, Inc., Riverton, NJ, USA) at Rowan University has been used to deposit Ti. Initial conditions were Ar with 40 sccm and 10 mTorr, DC power with 150 W, room temperature as target temperature, and 30 min run time. These conditions caused the needle base to bend because of high thermal residual stresses inside the needle as shown in Figure 3-19(a). This bending created cracks in and delamination of the Ti layer on the needle base. In order to protect the base from bending, DC power was decreased to 100 W. This power required a 1-hr run time for a 1-μm thick layer of Ti. However, the base was still bent a little, and minor cracks were seen on the surface as shown in Figure 3-19(b).

In order to reduce the temperature during the process, power should be decreased and Ar pressure should be increased. Increased Ar pressure can increase neutral Ti particles, which can block the heat transfer to the samples inside the chamber. A disadvantage of this recipe is longer time (3 hrs) it takes due to the cooling cycle. The conditions are as follows; applied DC power of 50 W, each cycle of 5 min deposition and 5 min cooling, and Ar pressure of 30 mTorr. The total run time was 1 hr and
30 min. Figure 3-19(c) shows a Ti layer deposited without bending and cracks. Although the surface is not uniform due to high Ar pressure, Ti was deposited without a thermal problem. A small grain-like structure can be seen on the needle area. This structure may be caused by insufficient combination energy of atom to atom at room temperature.
Figure 3-19. Ti layer deposited at (a) 150 W, (b) 100 W, and (c) 50 W.
3.7 **Puncture test with a Ti coated SU-8 needle**

Based on previous puncture tests, the SU-8 needle required a metal layer to improve the strength. Therefore, a 1 μm thick Ti layer was coated on the SU-8 needle with a parylene shield that was used in the second puncture test. The second puncture test was the same as previous one. Figure 3-20 shows the results of the second puncture test. The 1100 μm movement of the needle toward the dura mater resulted in piercing by six out of 100 needles. Although a few needles were pierced, most of the needles after the puncture test were not bent, which proved that the needle is strong enough for our application. This problem was due to the elastic deformation of the dura mater. When the needle pushed the dura mater gradually, the dura mater was deformed elastically. This kind of deformation might disturb the piercing of all needles.

In order to develop the puncture technique, an impact force to the needle was employed before starting to deform. This idea was originated from installing the Utah array. They used some pressure gun to implant a metal needle array into the brain for the purpose of sending and receiving neural signals. There is no space in the brain to accommodate an additional device; therefore, this puncture test utilized some impact force generated by a finger. As shown in Figure 3-21, the result was that a third of a hundred needles pierced the dura matter. This puncture test still should be considered deeply for piercing of the dura mater.
Figure 3-20. Second puncture test. (a) contact with the dura mater, (b) after 1100 μm movement of the needle toward the dura mater, (c) pierced needle, and (d) the needle after the puncture test.
Figure 3-21. Third puncture test. (a) 10x10 needle array before the test, (b) needle array pierced through the dura mater using an impact force, and (c) pierced needles magnified.
3.8 In-vitro biocompatibility test using a 10x10 needle array

3.8.1 Objective of this test

Once the needle was designed and fabricated, it should be tested if it is biocompatible using blood samples prior to clinical trials. The in-vitro biocompatibility test serves two purposes:

1. To examine the device performance in more physically relevant conditions.
2. To predict the possibility of device blockage due to blood coagulation by investigating platelet adhesion characteristics.
3.8.2 Experiment procedure

Commercially available human blood containing an anti-coagulant K2 EDTA was used in this test. Platelet adhesion is not hindered by the anti-coagulant. The test was performed in the incubator in which blood cells can be viable during the test. Two chambers were designed based on the real volumes of SAS (Subarachnoid space) and SSS (Superior sagittal sinus). Chamber 1 (1x1x5 cm$^3$) was filled with whole blood pushed by a small syringe and chamber 2 (5x5x5 cm$^3$) was filled with saline solution pushed by a large syringe. Since both syringes have different sizes, this size difference generated pressure difference (1700 Pa at 0.333 ml/min) between chamber1 and chamber2. This pressure could make a forward flow from chamber2 to chamber1. The needle was placed between two chambers and the needle outlets were placed in the opposite direction of blood flow during the test. The needle was allowed to react with blood for 1hr. After the test, the needle was taken out of the experimental setup and investigated under the microscope. Then, it was rinsed with PBS (Phosphate buffered saline) several times. The needle was investigated again under the microscope. Later, more investigation will be done using SEM (Scanning electron microscopy) images which can provide better visualization of platelet adhesion.
Figure 3-22. Biocompatibility test setup in the incubator. This setup consists of syringe pump, pressure sensor, blood & saline chambers, and two syringes with different size.

Syringe pump
Pressure sensor

Chamber1: Blood
Chamber2: Saline

Sealing rubber
3.8.3 Results and discussion

Figure 3-23 shows the results of the biocompatibility test under a dynamic condition. (a) is the microscopic images of the needle right after the test. A lot of red blood cells reside on the needle surface. (b) is the microscopic images of the needle after rinsing with PBS (Phosphate-buffered saline) several times. Many cells were removed after rinsing. Still the needle has a light red color due to remaining red blood cells. (c) is the side view and the hole at the outlet of the needle. The objective of this test is to check the blockage of the holes caused by platelet adhesion. The right microscopic image of Figure 3-23(c) shows the outlet of the needle, which is not blocked by platelet adhesion based on the microscopic investigation. However, an inside channel could not be inspected under the microscope. A SEM image will be taken to see this channel in detail and calculate the number of platelets.
Figure 3-23. Biocompatibility test results. (a) right after the test, (b) after rinsing with PBS, and (c) Side view and hole of the needle after rinsing with PBS.
3.9 References


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*Biomedical Microdevices*, Vol.12, pp. 263-273, 2010

CHAPTER 4: CONCLUSIONS AND FUTURE WORK

4.1 Conclusions

The shunt systems, current main treatment of hydrocephalus, have over 50% failure rates due to occlusions, infection, and mechanical failures of shunt components. In order to address this need, we proposed an innovative treatment of hydrocephalus to replace deficient arachnoid granulation with “Microfabricated Arachnoid Granulation (MAG)”. This device can mimic the function (diverting CSF from Subarachnoid space to Superior sagittal sinus) of normal arachnoid granulation and consist of arrays of microvalves and microneedles.

Dome petal design was selected as proper design of the microvalve. Such geometry enables the microvalve to rectify fluid flow in the forward and backward direction due to pressure differentials like normal aracnoid granulation. PDMS/Parylene composite layer was chosen as materials of the microvalve considering biocompatibility and self-sealing property of PDMS. The design parameters of the microvalve were optimized using 3-D numerical simulation. The microvalves were fabricated using three main microfabrication techniques: diffuser lithography for dome-shaped SU-8 mold fabrication, thin polymer film deposition and reflow for PDMS/Parylene membrane formation, and excimer laser machining for valve opening. After parylene deposition on PDMS layer, lots of wrinkles only on the base of the microvalve were
observed. If a rigid plate is subjected to stress and attached to a soft elastic medium, it is very likely that this stress is relieved by wrinkling: The composite plate buckles into a large number of waves and the pattern and size of the wrinkles depend on the thickness of the materials as well as the thickness ratio. The pressure drop vs. flow rate characteristics of the fabricated microvalve was investigated through in-vitro flow tests using a bench-top CSF simulator. An ideal microvalve for the treatment of hydrocephalus needs to have a cracking pressure close to zero, a forward flow rate of 0.3–0.5 ml/min at pressure differences between 500 and 1500 Pa. The results showed that a 10x10 microvalve array with combined opening shape (200 μm x 60 μm) is optimal for our application.

The microneedles were designed to have a 500 μm-long conical shaped body with a sharp tip on a square base and a microchannel inside each microneedle to deliver CSF to the sagittal sinus. This long conical-shaped needle with a sharp tip is expected to puncture human dura mater with a thickness of 300 μm. In order to prevent the needles from being blocked by platelet adhesion and blood clotting, this microneedle array was designed as 10x 10 arrays on a base with an area of 5x5 mm² and a thickness of 200 μm. The height and bottom diameter of the conical–shaped body are 500 and 120 μm, respectively, and the distance between two adjacent cone centers is 400 μm. The microfluidic channels inside the microneedles consist of a small channel (H=300–350 μm) inside the needle and large channel (D=250 μm & H=150 μm) inside the base. The
microneedles were fabricated using three main techniques: diffraction photolithography for tapered SU-8 needle fabrication, RIE etching for needle sharpening, and excimer laser machining for through-hole creation. Puncture tests were conducted using pig’s dura mater under tension generated by capping system for mimicking in-vivo environment in the brain. As incremental insertion method caused dura mater to be deformed elastically, impact insertion method was adopted for better puncturing. The microneedles coated with a Ti layer showed promising results (16 out of 100 needles pierced dura and the needles were not deformed). Blood adhesion tests were also carried out using human blood simulating the CSF dynamics and no significant platelet adhesion was observed at the microneedles.

The MAG proposed for better treatment of hydrocephalus has been designed, simulated, fabricated, and tested successfully. It demonstrated a great potential for the treatment of hydrocephalus.
4.2 Future work

While we have been able to design, simulate, fabricate, and test the microvalve and the microneedle separately, we have yet to assemble the microneedle and the microvalve. In order to bond the microneedle with the microvalve together, diluted PDMS will be used as adhesive.

More in-vitro tests such as flow test, puncture test, and biocompatibility test will be performed using the assembled device (Microfabricated arachnoid granulation). Also, this device should be checked if current sterilization methods cause any damage to the MAG.

In-vitro test using pigs prior to clinical trial will also be performed to demonstrate the efficacy of the surgical techniques for implantation and to determine the short-term biocompatibility and acute toxicity related to the MAG.
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Patent
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2. Simulation of continuous flow microspotter for the deposition of high quality spots of DNA, proteins, cells, and biomolecules at University of Utah
3. Manipulation of micro-, nano-, and bioparticles using AC electrokinetics at Drexel University
4. A novel nanochannel construction technique and nanoscale fluid flows at Drexel University
5. Implantable microdevice for the treatment of Hydrocephalus at Drexel University (Ongoing project)