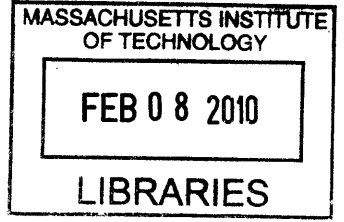


Polymer Substrates with Microneedles for Epidermis Injection

by  
John R Pavlish



Submitted to the Department of Material Science  
Engineering in Partial Fulfillment of the Requirements for the  
Department of

Bachelor of Science in Material Science & Engineering

at the

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Massachusetts Institute of Technology

June 2009

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## Polymer Substrates with Microneedles for Epidermis Injection

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Submitted to the Department of Material Science  
Engineering on May 8, 2009 in Partial Fulfillment of the  
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### **ABSTRACT**

Injections of medicine into the body are commonplace, whether they be intravenous or capsules. The benefit of using a macroneedle for injecting cargo into the circulatory system is its simplicity. However, introduction of the needle intravenously can also include foreign matter if the needle is unsterile. Due to macroneedles ability to pierce skin and veins for effortless insertion, it can also damage unintentional areas if a patient resists the needle, or if it is poorly inserted. Thus the body can be subjected to undesirable materials beyond the intension medicine cargo.

Current research reevaluates methods of introducing cargo medicine into the body. Popular models consider polymer substrates with different surface designs and medicine release. Thin polymer substrates allow flexible construction for adhering to tissue while specific polymers with high Young's modulus create strength for rigidity. Cargo can be placed within or on top of the substrate itself for release to the epidermis or dermis in stages, which is difficult for both oral medicine and macroneedles.

A specific substrate system with microneedles can prevent inflammation or tear of the epidermis but still puncture for cargo release. Depending on the substrate contact surface area, a larger microneedle array can be utilized, for a higher success rate of release beyond individual microneedles.

Microneedles can carry and release medicine either internally or externally through the epidermis. In the latter, Langerhans cells can be utilized for activating the immune system by releasing antigenes.

Aims of this thesis show the effects of polymer microneedle substrates with methods for constructing the substrate arrays that are flexible adherent to the epidermis, rigid enough for puncturing the stratum corneum, but not weak enough to buckle or be brittle.

Thesis Supervisor: Darrell Irvine

Title: Professor of Material Science Engineering, & Biological Engineering

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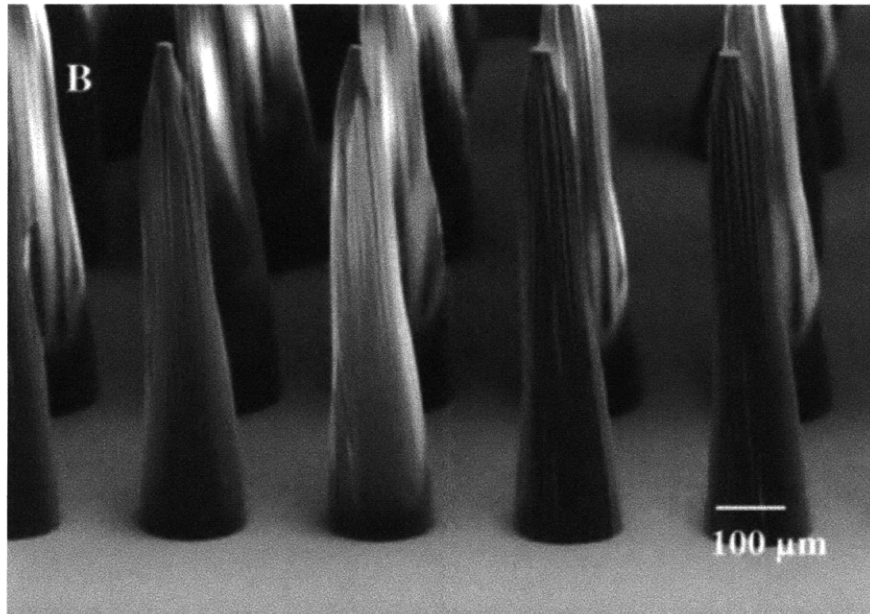
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**INTRODUCTION 1.0**

### *1.1 Introducing Medicine Into the Body*

There are a wide array of methods for introducing medicine into the body. Typical ways of releasing medicine are *via* oral delivery and intravenous macroneedles. Patients prefer medicine in capsule forms rather than needles for many reasons. Simplistic and individual administration makes oral medicine ideal. Despite these advantages, medicine in oral form takes more time to be activated internally as it navigates within the digestive system. More importantly, some drugs or proteins simply cannot be delivered orally in capsules because they are degraded in the digestive system or poorly transported across the gut epithelium into the tissues. Macroneedles are ideal for introducing medicine to specific areas of the body or for quick release. Benefits arise from the possibility of piercing through skin tissue directly into veins in the circulatory system; thus the medicine can be an adjunct to the body's immune system. But there are limitations to using macroneedles intravenously. If the patient is afraid, or if the injection itself is poorly administered [2], then the benefits of administering the medicine through intravenous needles cannot be achieved.

Due to the limitations of macroneedles and oral capsules, engineers are interested in other methods of introducing medication into the body. One alternative is through individual patches being combined with microneedles. Microneedles possess some of the advantages of both macroneedles and oral capsals. In addition, microneedles are able to relay vaccines, proteins, or medicine cargos to specific areas, such as the mucosal immunity in the epidermis or dermis directly to pathogens.



**Figure 1** | A PLGA microneedle array under SEM from a PDMS mold from the work of J.H. Park and M.R. Prausnitz [9]

The interest in microneedles stems from their ability to combine the benefits of both capsules and macroneedles. Microneedles are able to pierce the epidermis and introduce medicine directly to target areas, just like their macroneedle kin. Specific microneedles can prevent piercing through the hypodermis, or only the epidermis. The ejective of the microneedles is to deliver its cargo to a specific area of the body. Instead, microneedles deliver their cargo to the Langerhans cells, which are a type of dendritic cells, in the stratum spinosum layer of the epidermis. These dendritic cells are not to be confused with the same name in neuron cells. "Dendritic" simply refers to the ability of the cell to grow additional appendages. When foreign material invades the epidermis, Langerhans cells capture antigens as antigen-processing cells, or APC's. APC Langerhans cells travel through the lymphatic system and deliver the antigens to T-cells for the remaining immune system. Once the entire immune system becomes activated, it then eradicates the foreign matter. Thus microneedle insertion of medicine into the body is as simple as a shot for preventing the flu.

Furthermore, microneedle substrates can be easily administered individually like capsules and reduce opportunities for failure by either the patient or the injection. Since microneedles do not pierce below the epidermis, patients do not see blood and the microneedles themselves are difficult to see with the naked eye. Different microneedle arrays consist of different release and removal techniques, from ease of peeling, dissolving the microneedle substrate or a combination of both, with the substrate ejecting dissolvable microneedles onto the epidermis. Along these lines, one way consists of dissolving the substrate after certain durations of time, while another could eject the microneedles from the substrate, then dissolved instantaneously.

Regardless of the methods, the design goals for the substrates are simplicity, extended release, high rate of success, and patient comfort. To achieve these aims, engineers construct polymer solid state film substrates over most other materials, such as steel and silicon, even though they have higher moduli and extensive research support in the growing computer industry [10]. Polymer substrates incorporate both flexible and rigid structures for puncturing the stratum corneum and allowing delicate removal. Other considerations are water solubility and multi-composed polymers for the microneedles. Both qualities can control the intake of medicine, but the former controls the release of medicine through the body pH levels while the latter can dissolve in specific release. Multi-composite polymers can pierce the epidermis to release the cargo medicine. By combining the polymer substrate with a liquid solution, its viscosity can allow a release of the medicine in stages, while a porous polymer would quickly release the medicine without being hindered. Either cases allow multiple medicine degrees or types of medicine than a single release like macroneedle syringes. The microneedle substrate array is determined by the mold it is cast in. Current mold materials have a range of elastic moduli and range from rubber-based polymers to aluminum. Within the molds themselves, the impressions of the microneedles can be

formed in a range of techniques, common methods are nanoindentation, UV lithography [2] or laser stenciling. After the molds are prepared, the substrates can be formed. Once the resin for the substrate is placed into the mold, the substrate solidifies into the ideal substrate-microneedle structure.

### *1.2 Previous Microneedle Substrate Work*

Microneedle substrates have been applied since the 1980's with metal and silicon during the growing computer industry [10]. M.R. Prausnitz showed the idea of constructing a substrate of microneedles in the 1990's on micro level dimensions with polymers instead of metals and silicon. 3M's research currently creates polymer substrates with the circumference of a pencil eraser [3]. Depending on the microneedle array, the medication can be released into the body based in variable dosages. With a single substrate, multiple types of medicine could activate in separate time increments from one to four minutes. Cargoes the size of 20-40 kDa with proteins, peptides, or molecular salts have been released into swine and humans.

Polymer substrates have been available in the past for some medicine release into the body, such as patches with nicotine [9]. Many of these previous substrates only introduce the vehicle in an ointment or cream form rather than a liquid form. One of the benefits of polymer substrates is slow release over a long period of time, just like the extended release of medicine from intravenous needles. The ointment-based drug delivery is limited by the absorption past the stratum corneum of the epidermis, while the use of microneedles would allow the medication to enter the body with ease.

Polymers that are used for microstructure substrates are designed by two novel methods: one is by physical restraints of the polymer while the other is the chemical structure of the substrate itself. An ideal substrate cannot be constructed without either of these parameters. J.W. Lee revealed the difference of both a conical *versus*

pyramidal and CMC/BSA (carboxy-methylcellulose/bovine serum albumin) mixtures in PLA (polylactic acid) amylopectin [6].

This thesis examines the polymers for, and chemical methods of, constructing proper substrates with microneedles to introduce cargo into the body. There are several physical restraints on the polymer being cast into the mold. An ideal substrate needs to have a suitable modulus to be flexible for adhering to skin, but to contain microneedles for piercing the stratum corneum. If a substrate's microneedles were too resistant, the needles could break before introduction or be lodged in the skin against intension. Microneedles can also be damaged by either removal from the mold, or transportation into the skin. One of these limitations for the microneedles is the mold itself, as it could be formed incorrectly and prevent or reduce the effects of releasing the cargo into the body.



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**MATERIALS & METHODOLOGY 2.0**

### 2.1.1 Polymer Substrates & Microneedles

Polyglycolic acid (PLGA) with a lactide:glycolide 50:50 ratio, polyglutamic acid (PGA), poly(methyl methacrylate) (PMMA) at a 15,000 molecular weight ( $M_w$ ), and polystyrene (PS) were polymers chosen to be substrates and microneedles due to their biocompatibility, ease of use, and high modulus strength. All methods were tested with PLGA, in addition, PLGA was also tested with 0.1  $\mu\text{m}$  silica solutions and microparticles, while PGA, PMMA and PS were exclusively tested in the vacuum oven 2.2.2 only. The polymers were heated to their glass and melting temperatures then cooled back to room temperature at different rates. When PGA was used under the vacuum oven, it was mixed with chloroform or trichloroform (TCM) at a 0.10g/100 $\mu\text{l}$  ratio before the heating process. Glass and melting temperatures of the polymers are displayed in Table 1.

| Polymer      | T(g)  | T(m)  | E (GPa) | Manufacturer |
|--------------|-------|-------|---------|--------------|
| PLGA [5][12] | 60°C  | 180°C | 1.5-2.0 | Depot        |
| PGA [7]      | 40°C  | 230°C | 7.0     | Polyscience  |
| PMMA [1][12] | 104°C | 140°C | 3.2     | Aldrich      |
| PS [12]      | 95°C  | 240°C | 3.5-3.9 | Polyscience  |

**Table 1** | Modulus, glass and melting temperatures of the polymers used for the microneedle substrates

In the PLGA case, the silica was chosen to aid strength of the microneedles during the vacuum oven process. The silica solution, with 10 $\mu\text{m}$  particle, was combined with a 50:50 water and ethanol ratio. Both the silicon solution and the water ethanol ratio were then placed into the molds. When combined, the silicon water-ethanol mixture produced 100-150ml for each mold. Once in the molds, the solution was prepared at room temperature for 1-2 hours before applying the PLGA particles. Then

the PLGA-silica was processed for use.

For use of PLGA smaller than a millimeter, a different approach was provided. Microparticles of PLGA with 50 calcein were prepared in a 15ml of phosphate buffered saline (PBS) and heated in a 37°C water bath. Once the particles of the calcein suspended in the PBS solution, the suspension was gathered by a 0.2µm syringe filter. The solution was then kept in a 4°C environment with no light outside of use. This calcein solution would be used in the first emulsion for the microparticle PLGA solution.

Original granules of 30mg PLGA were dissolved in dichloromethane (DCM) for 10-15 minutes for a first emulsion, then 200µm calcein was added during one minute of sonication at 7W. A second emulsion was then prepared by inserting the first emulsion into 6ml of 2% polyvinyl alcohol (PVA) at 12W for 5 minutes. After the samples were sonicated, they were placed in a LabLine shaker of a frequency at three for 5-12 hours to dissolve the remaining DCM. All the liquid samples were measured with glass pipets to prevent corrosion into the sample. Both sample emulsions during sonication were placed within a beaker with ice.

Once the DCM was removed from the PLGA-PVA, the samples were filtered again through a [cell strainer] then 1.5ml of the sample was placed into three 2ml eppendorf tubes for centrifuging at 1800g for 10 minutes. The supernatant was then discarded and replaced with 1.5ml of water and centrifuged again; this process was repeated by removing the previous water supernatant and placing a new dosage of water at 1.5ml. Both water emulsions would centrifuged again at the same frequencies and time. After the second water rinse, the PLGA pellets were suspended in 0.2ml of water per eppendorf tube and all three tubes were combined together and stored in a 4°C environment with no light. The samples were then transferred in liquid nitrogen to a lyophilizer at 500kP for 48 hours. To filter the water and PVA from the PLGA, 2-3 layers of Kimwipes covered the eppendorf tube ends.

### *2.1.2 Molds & Cavity Designs*

Originally, aluminum, silicon and polydimethylsiloxane (PDMS) were chosen due to the work of Prausnitz [9]. Vax Design, the company that produced the molds, suggested silicone as it is similar to PDMS, and it has a higher elastic modulus than PDMS alone, thus preventing imperfections or tears on the substrate or mold. For all of the aluminum, silicone, and PDMS arrays, there were five rows and eight columns spaced at 600 $\mu\text{m}$  apart horizontally and vertically. All of the microneedle cavities had 100 $\mu\text{m}$  radii with either 400 $\mu\text{m}$ , 600 $\mu\text{m}$ , or 800 $\mu\text{m}$  lengths. Laser etching made one to two 5-10 $\mu\text{m}$  offset passes for the microneedle impressions with a frequency at 80-110mW. A second PDMS mold consisted of four arrays: two conical and two pyramidal designs. Height, spacing and numbering of the secondary PDMS microneedles were the same specifications as in the first molds. Both of the conical second mold arrays had higher surface areas than the first mold arrays with different hypotenuses.

### *2.2.1 Melt Press Fabrication of Microneedle Arrays*

One of the techniques that Prausnitz suggested was to use a melt press on an aluminum mold. The solid polymer is placed within a gasket barrier to direct it during formation of the melt press process in the microneedle cavities. Various gaskets were used: generic rubber, silicone from GRAPE Biolabs, Teflon, and generic steel. When the aluminum sample was set on the metal plates between the stainless steel plates, these plates exerted a force for 60 minutes at the polymer melting temperature. Then the sample temperature was dropped back to 0-40 $^{\circ}\text{C}$  with a water cooling system for 5-10 minutes. Once the temperature was returned to room temperature, the force was then reduced to allow removal of the sample. PLGA was the only polymer substrate used in this method.

All experiments of PLGA samples were consistent with a 25-50N force from a 0.30m<sup>2</sup> stainless steel plate for 5-10 minutes, then held at the maximum force for 30-60 minutes at 180°C. After this duration, the force was relaxed for 5-10 minutes, then the cooling system was applied. The PLGA was then left at room temperature before it was removed from the aluminum mold and gaskets.

### *2.2.2 Vacuum Oven Fabrication of Microneedle Arrays*

PDMS was the exclusive mold used in the vacuum oven method for all of the polymers substrates. PLGA, PMMA, and PGA were the tested polymer substrates. There were three variations of forming the microneedles in the molds: extending the time process, the point at activating the vacuum, and the rate of the temperature cooling process. Times were held in the vacuum oven from 1-24 hours. There were two points of activating the vacuum. One was starting the vacuum before the polymer samples were heated, while the other was activating the temperature in tangent with the vacuum itself. Cooling temperatures were either through the vacuum oven at [5°C per minute], while the other was turning off the vacuum oven at the melting temperature and naturally letting the temperature return to the room environment. Maximum temperatures for the polymers were based off of Table 1. Constants of the vacuum oven process were a vacuum of -15-25kPa and the melting temperature of each polymer. Once all polymers were removed from the vacuum oven, they were immediately placed into a -20°C environment for 1-24 hours, then returned to room temperature.

When prepared for the vacuum oven, the molds were cleaned with DCM, ethanol, and water bath for 3 minutes per bath. If previous samples remained on the molds, the molds were sonicated in the previous baths for 1-2 minutes. One mold contained 100-200µg of a polymer aside from the microparticle-sized polymers, which was mixed with a 80:20 water ratio. Parts of PLGA were processed for microparticles,

some was applied directly, while the rest was prepared with silica solvent at 0.10mg with 50:50 ratio of water-ethanol at 100-150 $\mu$ l. Both polymer sets had silicone gasket to contain the polymer on the mold.

For use with PGA in the vacuum oven, 100-150 $\mu$ l TCM was placed into the mold cavities before the PGA was applied. There were two methods of implementing the TCM into the molds. One was adding the TCM before the PGA was applied, and allow it to dissolve by 30-60 minutes. The second method was applying the TCM in tangent with the PGA, and allowing the TCM to dissolve over the same 30-60 minutes. The final step placed the PGA substrate into the vacuum oven.

### *2.2.3 Imaging*

Two different methods of visually inspecting the polymer substrate microneedle designs were used. One was a visual wavelength Olympus BX50 microscope with lenses from 2-20x zoom with a DXM1200 Nikon digital camera using the ACT-1 software for the visual spectrum. The other images were taken by the Phillips XL30 Scanning Electrical Microscope (SEM) for higher quality resolutions.

For SEM images, the samples were held at a 67-133kP environment of nitrogen with no Pressure Limited Apparatus (PLA) on a 1000 $\mu$ m area. There were two electron resolutions from the microscope, one was with the Gaseous Secondary Electron (GSE), while the other using the full Everhard-Thornley high vacuum secondary electron (SE). Samples were calibrated in the nitrogen environment using a chamber camera detector (CCD). All of the polymers substrates that were imaged with the SE detector were prepared beforehand with a 20nm surface of gold. Electron beams were held at 3-5kV for the GSE detector and 12-15kV frequency for the SE detector. The software used with the SEM was from EMLab P&K.

#### *2.2.4 Skin Insertion*

The most ideal microneedle substrates were tested on the skin of mice ears. The ears of the mice were removed and prepared with a 30 mL PVA solution to prevent degradation of the skin. After 30-60 minutes and having the PVA solution removed by Kimwipes, a proper substrate was selected for applying to the skin. The substrate was held firmly by the hand for 5 minutes and then the force from the hand was slowly relaxed. The substrate was then removed to allow 30 $\mu$ l of a blue dye onto the ear that was punctured by the substrate area. Another 5 minutes were allowed for the dye to seep into the skin, and then the dye was wiped off with Kimwipes, then cleaned with water and dried again. After this process, the skin and substrate were inspected in the optical microscope described in method 2.2.3. If the sample was kept for further study, it was placed in a no light 5 $^{\circ}$ C environment with water applied on the ear.

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**RESULTS 3.0**

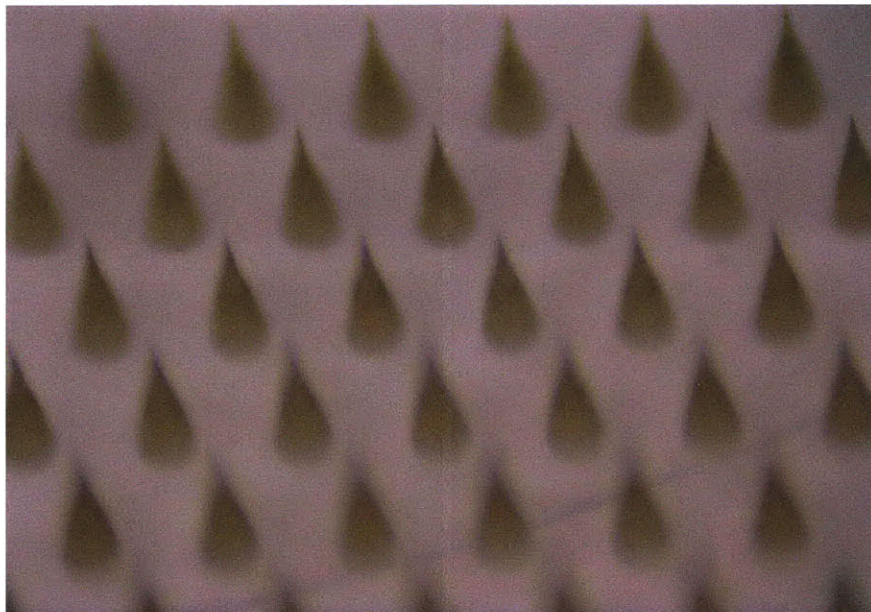
### *3.1 Mold Applications*

Originally, the aluminum plate had two molds for forming different substrates. Initially, both molds were used in the melt press, but the force exerted on the sheets caused the rubber and Teflon gaskets to warp and allowed the PLGA to move beyond the mold design itself. Since the second mold was at one of the corners of the aluminum plate, part of the substrate would flow out of the mold and gasket. This test was repeated with gaskets of Teflon and steel to prevent any movement outside of the mold, and the same results occurred.

In the case of the PDMS molds with the silicone gaskets, the smaller plates, which had little surface area for the gasket, caused some of the PLGA to spill off the PDMS in the vacuum oven. After the initial PDMS substrates were constructed, most of the samples were damaged by removal from the molds. It did not matter whether the PLGA was removed from the PDMS molds, which also happened to the silicone molds, preventing them from being used. The largest results of damage were either from tearing the substrate off the mold and leaving the microneedles embedded in the mold or from tearing pieces of the PDMS off the mold itself. PLGA and PGA were prone to cause this effect on the PDMS molds. All molds were held in a vacuum at -50kPa. J.H. Park had similar results, and suggested a vacuum at -70kPa [9]. After the vacuum oven process, only DCM and VWR tape were able to clean the molds for further use. After several uses of a particular mold, the PDMS molds would become brittle and break, requiring delicate removal of the substrates from the molds.

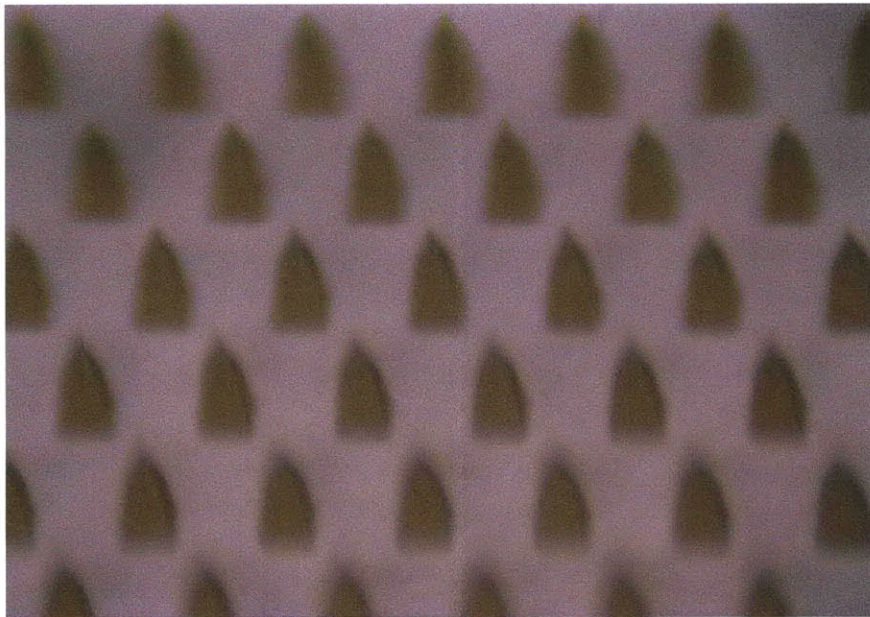
PLGA and PGA were the most prolific substrate arrays that were created on the PDMS molds. Conical dimensions for microneedles at 400 $\mu$ m and 600 $\mu$ m prevented damage from either the mold or the substrate. Nevertheless, there were some PLGA or

PGA microneedles that were unable to be removed from the molds, or the substrates were unsuccessful in completing the microneedle cavities in the molds. Instead, when these samples were removed from the molds, they revealed mounds of resin over the array impressions. A third case of the PLGA or PGA substrates tore off pieces of the mold during removal.



**Figure 2** | A PDMS conical mold design before being cast with a polymer substrate

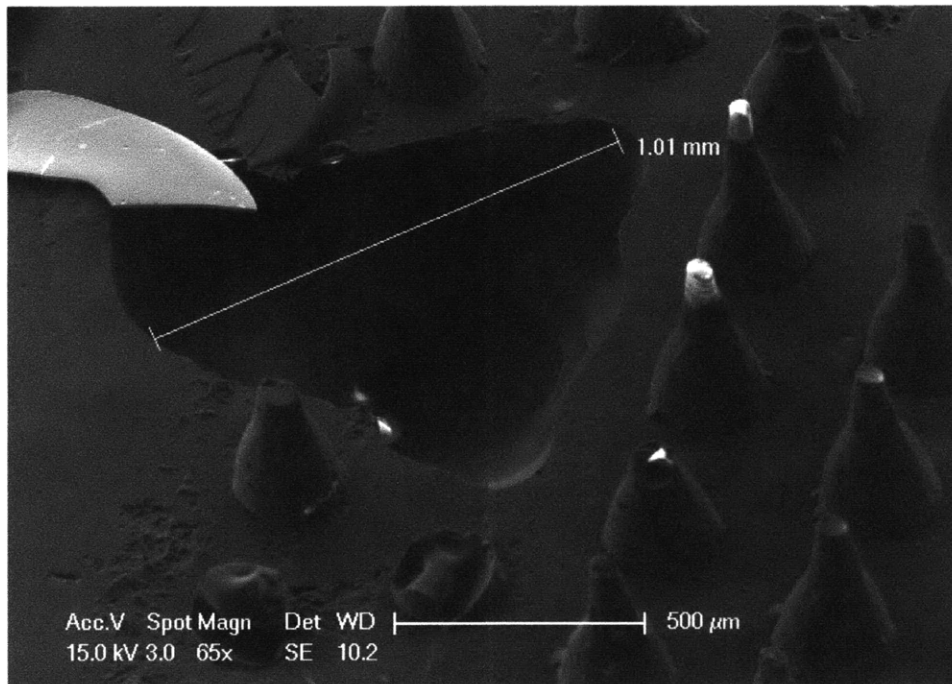




**Figure 3** | Pyramidal PDMS mold before being applied

### *3.2 Substrates*

For all of the polymers that were tested with the vacuum oven in 2.2.1 was the most successful method that was able to produce consistent uniform substrates. However, depending on the vacuum status that was held for the formation of the substrates, some of the polymer formed void pockets during the heating process, which was removing the remaining air in the vacuum oven. These pockets tended to be within the substrate, or within the cavities, which prevented formation of the microneedles. Figure 4 shows the dimensions of the pockets that formed within the substrates.



**Figure 4** | PGA substrate under SEM SE with a surface pocket

PLGA was the only polymer that went through all of the methods explained in 2.2. With the PLGA substrates formed from the melt press, no tool could remove the PLGA from the aluminum mold. When a tool was used, the entire PLGA substrate became damaged. Various techniques were applied on the aluminum-PLGA substrate for removal: sonication at 30°C for 20-30 minutes, cleaning the aluminum-PLGA substrate with Si soap 1g/100ml concentration in water during sonication, placement under a vacuum oven to the glass transition temperature, and then freezing at -20°C for 1-24 hours. None of these attempts separated the substrate from the mold more than using the original PLGA made right after the melt press. All of the PLGA microparticles that were fabricated in method 2.1.3 produced flakes. Applying the microparticles to the PDMS molds with a gasket was difficult regardless of the apparatus being used. The microparticles did not fill the cavities in the mold or up to the layer of the gasket. However, the second batch of PLGA microparticles, made with an 80:20 ratio with water

during the filtering process, could easily be added onto the molds. This concentration allowed the PLGA to flow into the cavities, but the concentration was not enough to fill an entire mold.

PGA with TCM allowed the polymer to form directly into the mold cavities as opposed to PGA alone. PGA alone tended to leave the microneedles within the mold, rather than keeping them on the substrate itself. The time duration of applying the DCM with the PGA did not prevent the formation of the microneedles, but instead produced consistent arrays. Under Figure 14, the PGA was uniform, aside from the perimeter ends.

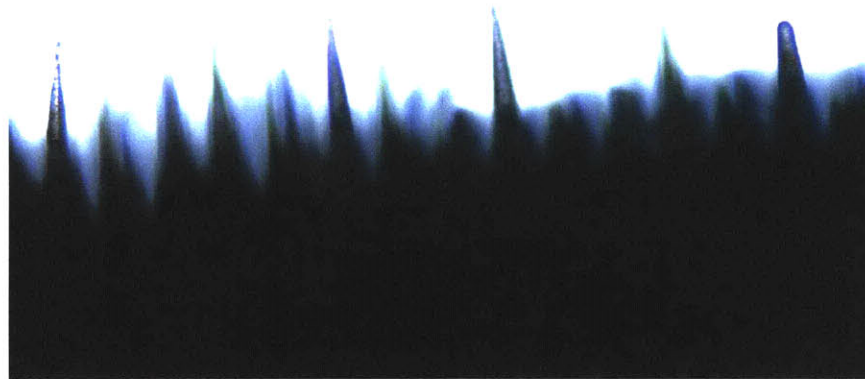
Both PMMA and PS were not successful in making microneedles consistently. While PMMA with the PDMS mold formed microneedles in the vacuum oven process 2.2.1, the array was more brittle than the PLGA and PGA substrates at the same constraints of method. PMMA could not be removed from the molds without damaging the microneedles. In addition, the PMMA sample was damaged under the imaging process, despite it being operated as delicate as the other substrate microneedle arrays. PS under the vacuum oven method 2.2.1 was unable to fill the microneedle cavities of the PDMS molds and could not make a stable substrate; rather the PS samples clearly were not melted uniformly into the molds, even though the PS was melted to its melting temperature and held there at an extended period of time, which made no difference.

### *3.3 Microneedles*

With the PLGA, PMMA and PGA substrates testing in a vacuum oven, the microneedles were either embedded within the mold cavities, or parts of microneedles were sheered off at the end from their intended height of 400-600 $\mu$ m. In the case of the microneedles formed in the PDMS molds, PLGA, PMMA and PGA all had some

examples of separation of the microneedles from the substrates during removal. DCM, ethanol, acetone, and water were used for used for removal of the residual microneedle fragments from the PDMS mold, but were not effective even after 24 hours of dissolving. These substrates which did not have their microneedles instead had only mound shaped surfaces on the same array area. However, if the molds were used again under a vacuum oven trial with their previous polymer substrate, the existing microneedles were able to adhere to the new substrate. In addition, VWR tape to removed the microneedles from the cavities with ease.

With the substrates that maintained their microneedles aside from those which were sheered, there were no remaining polymers within the mold cavities. Furthermore, there was no uniform length of the microneedles which were damaged within the same substrate. Instead, the damaged microneedles broke in varied lengths as illustrated in Figure 5.

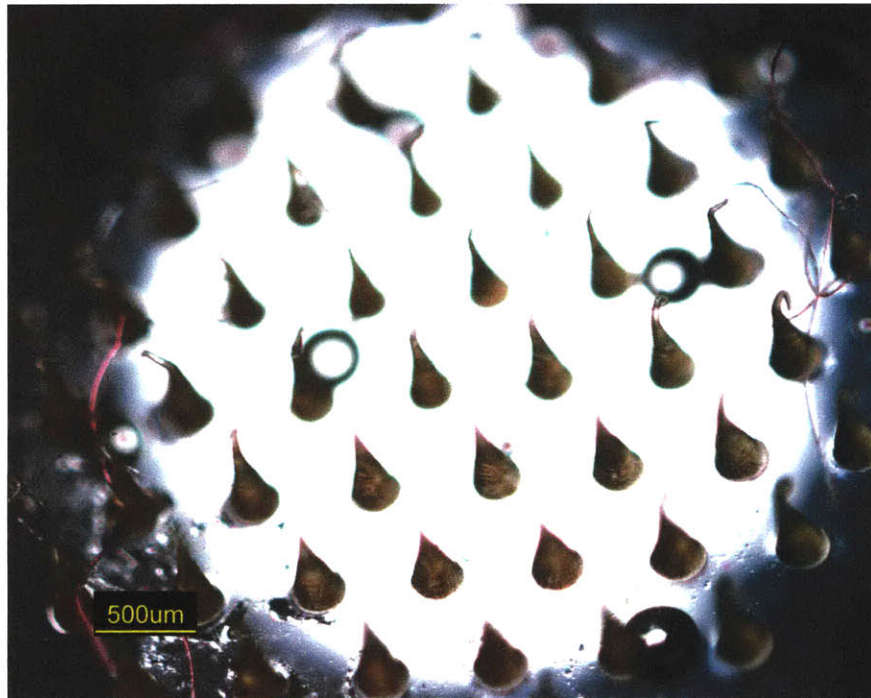


**Figure 5** | PGA microneedles under 4x resolution. There are both fully formed and sheered microneedles.

The optical microscope displayed the pure PLGA and PLGA-silica microneedles in Figure 6, , Figure 11 and Figure 12. PLGA microneedles created by the silica appeared in different colors in Figure 8. Two PLGA-silica samples were created under the vacuum oven process, and both created needles in different color bands. One sample contained bands of brown and orange uniformly across the substrate array while the second set had a light silver blue color in addition to the same brown band as illustrated in Figure 9. Despite the different color bands, both PLGA silica microneedles were created with the same amount of silica; the only difference was in their time durations. In spite of the silica particles in the PLGA, the microneedles were still able to bend as pure PLGA microneedles, aside from buckling at 400 $\mu$ m for the 600 $\mu$ m microneedles in Figure 12.



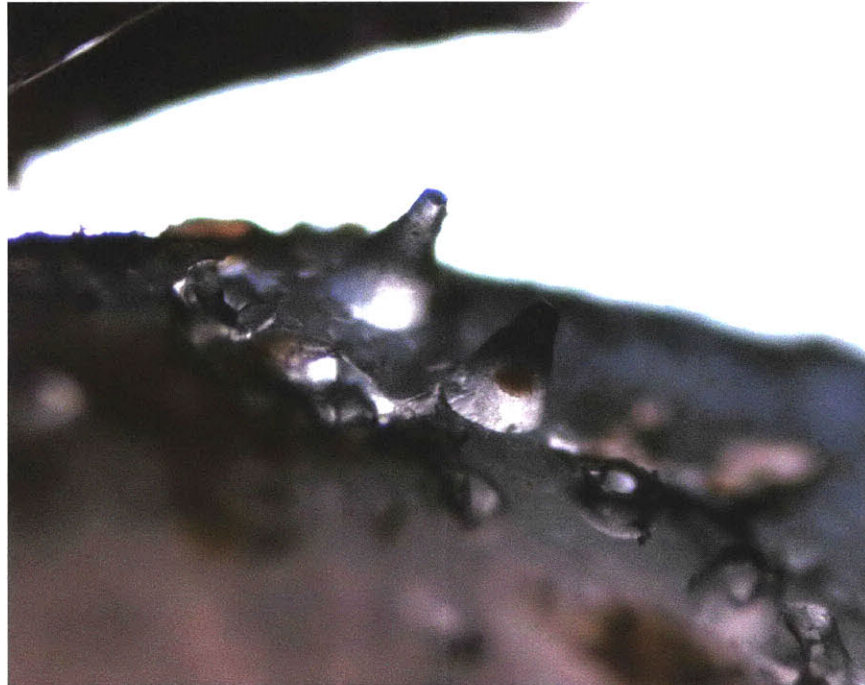
**Figure 6** | PLGA microneedle at 20 $\mu$ m point after removal from the first conical PDMS mold



**Figure 7** | PLGA microneedles immediately after removed from the PDMS mold with nonuniform bending at the apexes

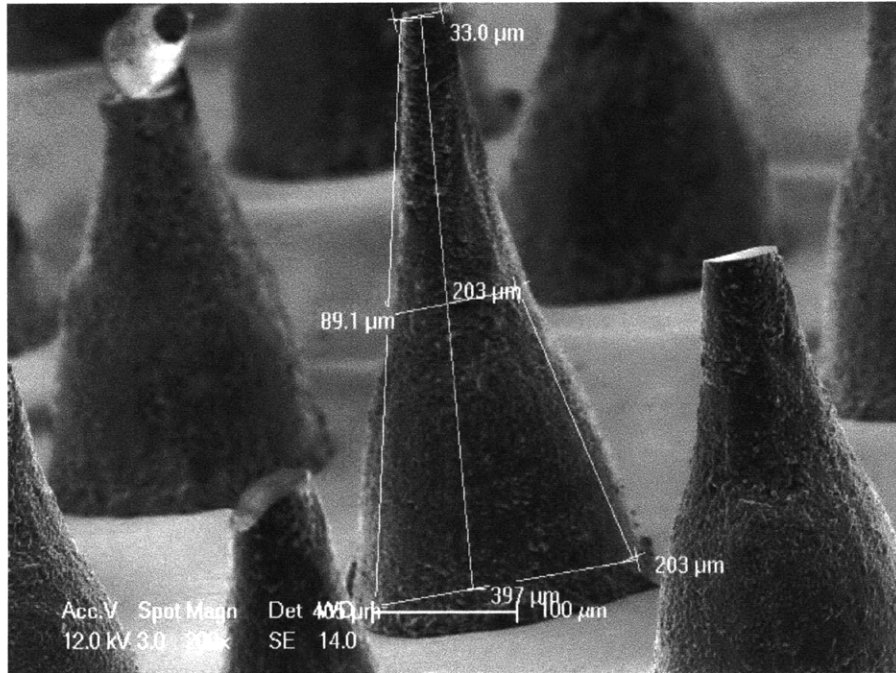


**Figure 8** | PLGA with 0.10µm silica. The entire array consisted of repeating bands starting along the microneedles

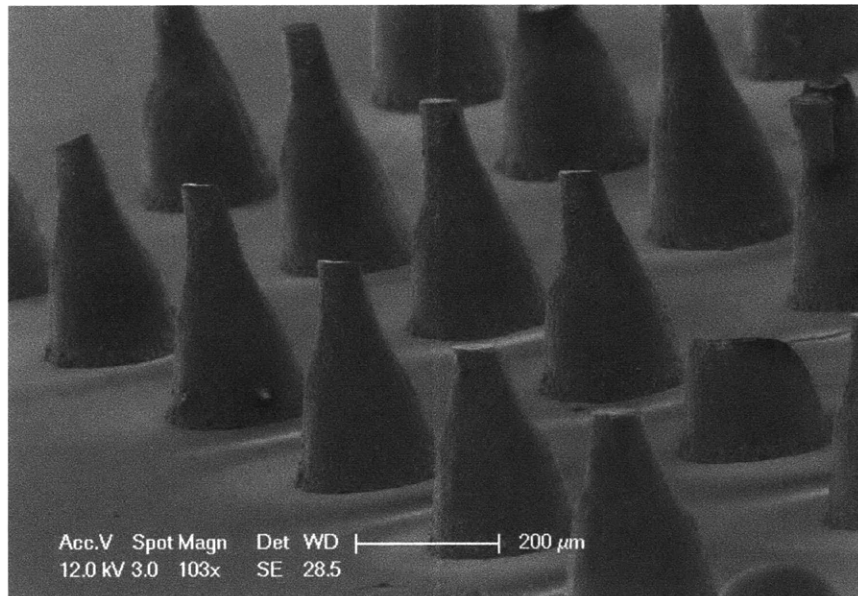


**Figure 9** | PLGA-silica microneedles with color bands of silver and brown

The SEM revealed finer details of the microneedles after they completed the vacuum oven process. With the PLGA, the microneedles were around the same 500 $\mu\text{m}$  height. Shorter needles were around the edges of the arrays. PGA microneedles tended to be truncated around 500-550 $\mu\text{m}$  for the 600 $\mu\text{m}$  needles with the tips being around a 15-25 $\mu\text{m}$  radius. Parts of the PGA surface area were not completed as mentioned in Figure 4. With the substrates that were produced in a vacuum oven leaving void pockets, the areas of the pockets were 50-75 $\mu\text{m}$  radii. Neither PGA and PLGA forms formed precise conical dimensions; the largest volume area of the microneedle tended to be at a 400 $\mu\text{m}$  height, where the apex area had different dimensions. This was the cause with PLGA as well, illustrated with Figure 10. This figure shows a diameter of the PGA at 89.1 $\mu\text{m}$  at approximate 200 $\mu\text{m}$  height for a 400 $\mu\text{m}$  needle.

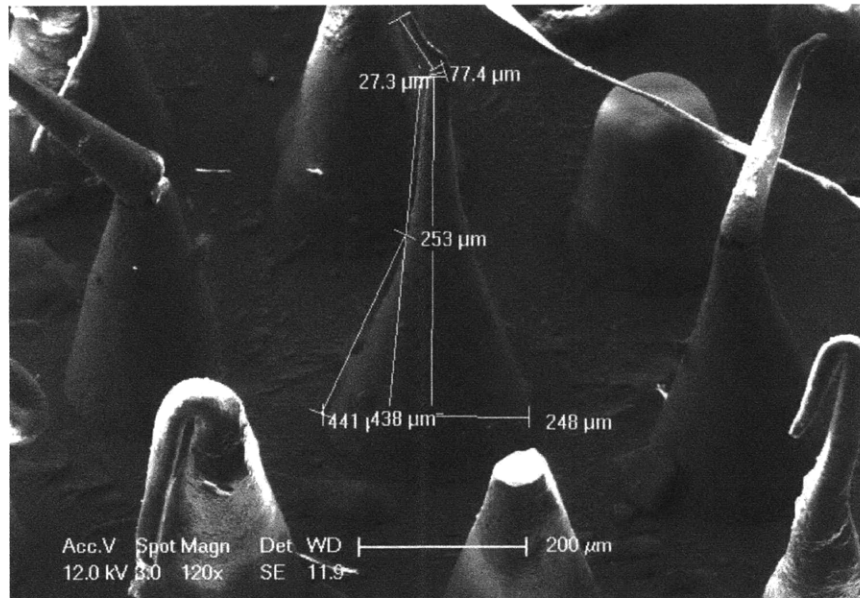


**Figure 10** | PLGA microneedle dimensions under SE mold of the SEM



**Figure 11** | PLGA array with nonuniform hypotenuses between the base and apex

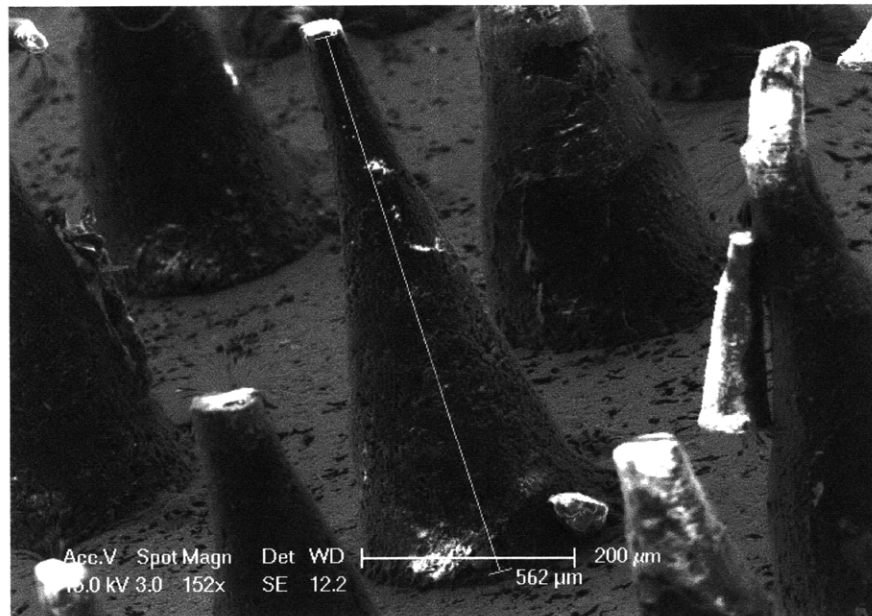




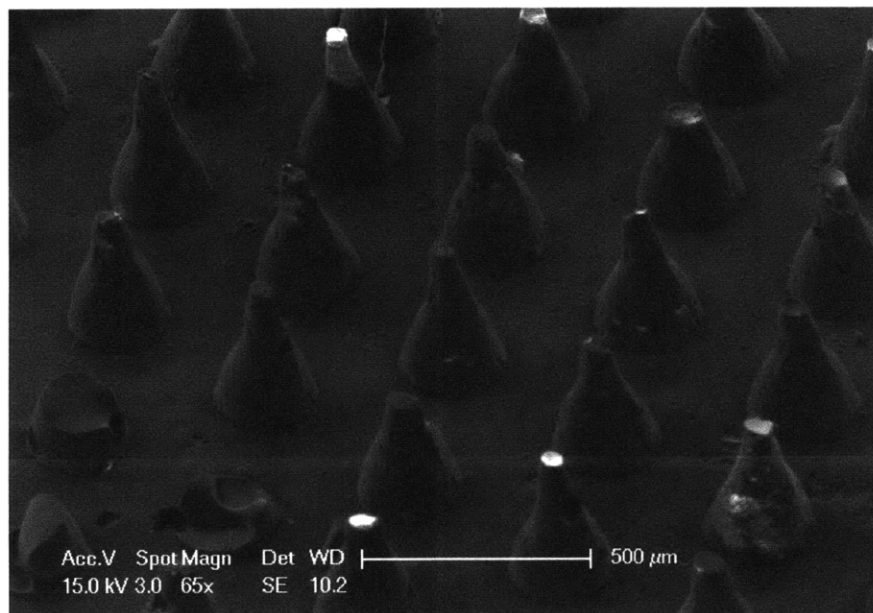
**Figure 12** | PLGA-silica array under SEM SE with bent and sheered microneedles after removal from a PDMS mold

The PLGA-silica microneedles had characteristics of both the pure PLGA and the PGA microneedles. In Figure 12, the microneedles tended to be bent, truncated, or a combination of both; while in the case of the non-silica PLGA, microneedles tended to be uniformly bent as illustrated in Figure 7.

PGA microneedles formed from the PDMS molds in the vacuum oven of 2.2.2 were consistent of formation, regardless of the mold dimensions. However, PGA was prone to void pockets and sheered needles like PLGA microneedles. The difference was that PGA never contained any bent microneedles.



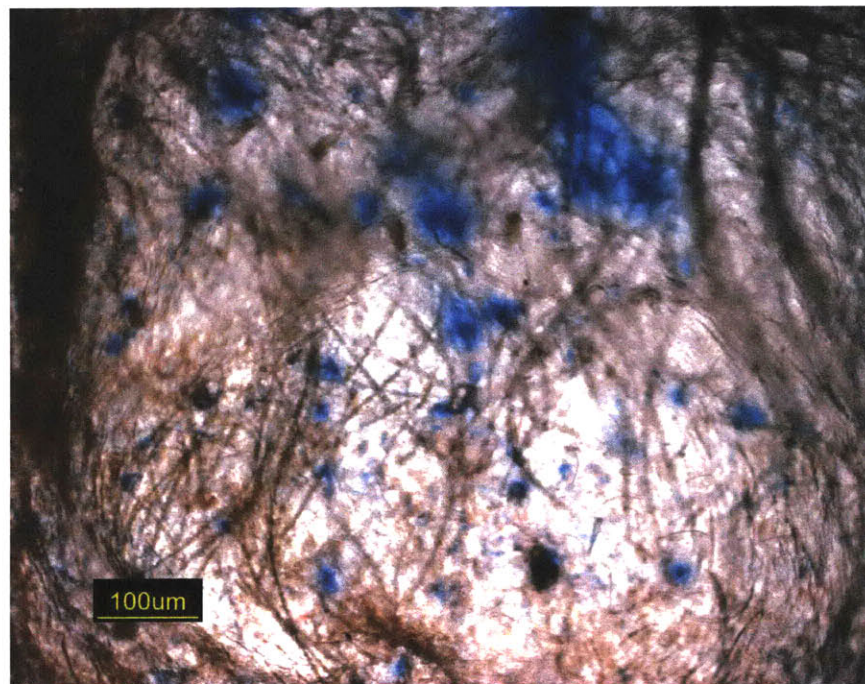
**Figure 13** | A PGA microneedle that is sheared at 562μm



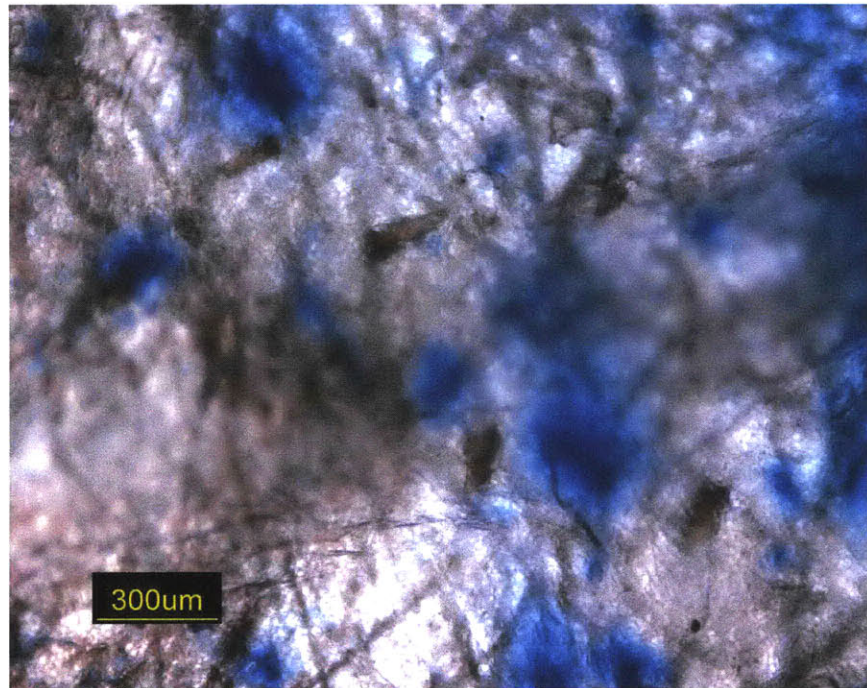
**Figure 14** | PGA array under SEM with uniform microneedle lengths after processed in a vacuum oven

PLGA and PGA were the only substrate microneedle arrays used for skin insertion. For the PLGA needles that were unable to pierce the skin, the needles either

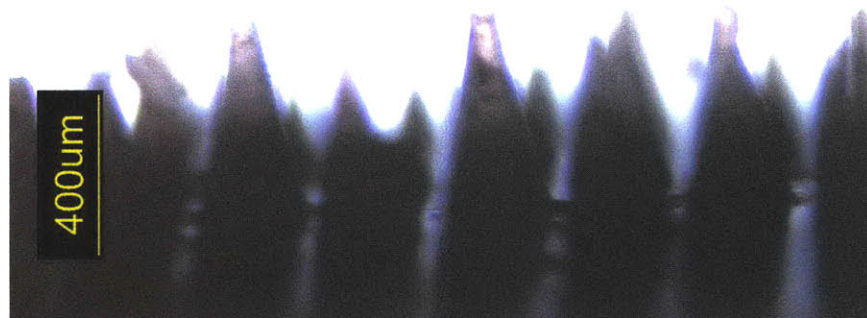
retained original dimensions or became bent. One PLGA microneedle array could not puncture more than 1-6 holes on the skin, with the same finger-hand force as PGA, even though the array had a total of 48 microneedles. Granted, not all of these 48 microneedles were complete, as some were unformed, torn, or bent as revealed by SEM imaging, but there were more microneedles which were in the proper dimensions to puncture the skin. In the case of the PGA, some of the needles would be imbedded within the skin, seen in Figure 15 and Figure 16. When the substrate array was removed from the skin, truncated needles around 400 $\mu$ m in length were left, illustrated in Figure 17. Further, Figure 16 shows that the dye is around the truncated microneedle end and around holes in other areas.



**Figure 15** | Mouse ear under 2x resolution after being punctured with a PGA array and dyed



**Figure 16** | Mouse ear under 4x resolution where remaining PGA microneedles had remained in the ear



**Figure 17** | The PGA array that punctured the ear skin under 4x resolution

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## CONCLUSIONS & DISCUSSION 4.0

### *4.1 Conclusions*

PDMS was the most successful mold, being able to produce the most amount of substrate arrays, in addition to the most type of polymer use. One of the benefits of the PDMS mold was its ability to allow the mold to be bent or torqued at a light enough force to maintain the mold's form, but aid in removal of the substrate from the mold. Aluminum nor any other metal could only require larger forces which could destroy the substrate before removal. This was also one of the positive qualities of the silicone gaskets as well for similar force removal. However, over use caused the same mold to eventually degrade, causing the mold to become brittle, which either broke the mold itself or the polymer substrate.

Microneedles made through the PDMS molds were more consistent in formation of substrate arrays, producing PLGA, PMMA, and PGA microneedles. Both PLGA and PMMA were able to form microneedles on PDMS molds. However, when PLGA substrates were removed off the PDMS molds, bent needles ensued. In the case of PMMA, the microneedles sheered off at the end to a 25 $\mu$ m radius. Regardless of the mold material, it seemed that an ideal force was needed for removal of the PLGA and PMMA for maintaining the microneedle surface on the substrate itself. With the PLGA on PDMS, it did not matter what type of force was applied on the substrate; the microneedles would still be torn off the substrate. While the silica solution that was applied to PLGA did increase the resilience of the PLGA, it became too brittle in parts, and the modulus was not high enough to pierce skin. The bands of the PLGA-silica seem to illustrate two types of bands: a pure PLGA, in addition to the PLGA-silica composite. Which describes why the PLGA-silica microneedles would become bent and truncated.

Aluminum was not entirely able to produce substrate arrays with microneedles, even though it had the same dimensions as the PDMS molds produced by Vax Design. Several methods of encouraging the PLGA substrates to be removed off the aluminum mold did not warrant enough use, compared to the PDMS molds. Since none of the removal techniques did not allow ease of the melt press process required. A different approach needed to be used. If a direct force from the melt press was exerted on only the mold array, the melt press would have produced similar results as the work from Prausnitz [2]. As the PLGA was only removable brittle shards, less pressure or temperature would produce similar arrays like the PDMS molds. The melt press stainless steel sheets had a larger surface area,  $0.30\text{m}^2$ , than the aluminum mold,  $0.0026\text{m}^2$ . This prevented all of the force from the melt press being exerted onto the mold. All of the PLGA samples formed on aluminum mold consistently produced solid state substrates above the glass transition temperature that flowed beyond the mold itself. Aluminum as a mold for PLGA would not be suitable for use. If aluminum was to be a candidate of a mold for microneedles, then it would need an easier removal technique for the substrates. For the use of melt pressing for microneedle substrate creation, a force would need to be on the surface area of the mold or substrate itself. Even if the force would be exerted on the substrate, enough of the substrate material above the mold needs to be accessible for removal, if polymer substrates were to be used in a mass production.

#### *4.2 Discussion*

In respect to the microparticle PLGA, an additional semicrystalline could aid the physical structure of the needles with a higher modulus. While silica was able to due such a process, it was not able to completely mix with the PLGA, causing the bands of the microneedles. A revision of the PLGA a network of a amorphous state could

maintain microneedles strength, but also still have flexibility to prevent the needles being brittle. Only a 0.10 $\mu\text{m}$  microparticle batch of silica was applied on the PLGA. Other monocular sizes of the silica would aid the PLGA. With the PLGA that remained in PDMS cavities after removal, a second vacuum oven process would be ideal, as it creates a multi-structured substrate to microneedle ratio. This process could then be attempted for cargo ejection off the substrate and past the epidermis similar as the examples of the PGA microneedles being applied on the skin. Since the microneedles are biodegradable, less effort of the patient would still be a possibility.

In the end, the PLGA substrates were consistent with their microneedles bending before being removed; while the PGA substrates were steady in the formation of the microneedles with different PDMS molds by heights and radii. Both polymers still produced nonuniform hypotenuses, suggesting that the vacuum oven process was preventing the polymers to fill the PDMS mold cavities. Even though various parameters of time and temperature were applied on the vacuum oven process, the PLGA and PGA microneedles still were not able to complete the intended cavities. This also describes the sheering of the microneedles with radii less than 30 $\mu\text{m}$ , as they were produced in a different way than the truncated microneedles around 50-100 $\mu\text{m}$  for the 400 $\mu\text{m}$  needles, and 100-150 $\mu\text{m}$  for the 600 $\mu\text{m}$  needles. Thus a uniform process with the vacuum oven would help forming uniform microneedles, as the substrate microneedle voids are sporadic.

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