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DEVELOPMENT OF A MICROELECTRONIC DEVICE FOR MEASURING CORROSION IN-VIVO

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ABSTRACT

There is an absence, in published literature, of the corrosion rate of titanium in the body. However, titanium is one of the most common materials used in the body. The aim of this research is to present a way to measure corrosion rates in the body through the development and evaluation of a three-electrode microelectronic device.

Previous research in the group has produced a microelectronic device that measures the corrosion rate. Thus far, the device has only been tested in-vitro, and requires a new microelectronic connection that enables the device to be connected to a potentiostat post-implantation. The connection must be insulated and safe with respect to the environment and not place undue stress on the animal. After the device connection is designed and prepared, it must be proven not to affect the results of the testing.
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Chapter 1

Introduction

Medical implants have been around since the ancient Egyptians used dental implants. Today, ceramics, metals and polymers are implanted into the body to treat a variety of issues. Rapid technological development has increased the variety of materials implanted into the body; however, the long term consequences are unknown. As a result, implants can fail, needing replacement, or implants can have side effects, requiring removal.

Metals are used in the human body to repair bones, tendons, ligaments and blood vessels. These metals can and do degrade in the body environment, it is important to understand the degradation so that better implants can be designed and used. This research represents a step in this process; the step of getting corrosion rate date on a metal implant in-vivo using electrochemical techniques. These electrochemical techniques allow instantaneous measurement of the corrosion rate as a function of time.

Since physiological changes occur in the body following surgery it would be useful to see how corrosion rate changes with time. Once a useful electrochemical device is designed and proven viable for measuring corrosion rates in-vitro the working electrode material on the device could be adapted to measure the corrosion rates of different implant metals. Ultimately the device designed in this research will be used, in this group, to measure the corrosion rate of resorbable magnesium alloys.

Metals are used frequently in the body for the same reason that they are used frequently in everyday objects, because they are versatile. However, metals are susceptible to
corrosion which can lead to failure and the presence of corrosion products in the body. The corrosion rate of these metals is critical to studying the lifetime of metal implants and the suitability for use in the body.

Corrosion testing in-vivo has several problems: placing the metal in the environment, making electrical connections for real time corrosion measurements, and corrosion by-products. Corrosion measurements have been made by placing a sample in the body and measuring the average corrosion rate through weight loss after removal. However, weight loss experiments will not give information about corrosion rate as a function of time. This leads to the development of a microelectronic device for corrosion measurement. The three electrode microelectronic device is small enough to be placed in-vivo without disturbance and with few by-products. The device also creates a position for electrical leads to be placed so that connections to measurement devices can be made externally.

The device used in this research uses titanium as the working electrode in order to determine the corrosion rate. Titanium is tested because it is a widely used metal for implantation. Although titanium has been used in implants for years, the corrosion rate in-vivo has not been extensively reported in the literature using electrochemical methods. Titanium is chosen for its material strength, and corrosion resistance due to an oxide layer. The corrosion rate will determine whether or not titanium can be used for a human lifetime without significant damage.

Once it has been shown that the microelectronic device provides useful results, it can also be used for corrosion testing of other metals. For example, the group’s long term goal is the development of a resorbable magnesium alloy, one that the body is able to break down and
eliminate without harmful effects, for use in stents. The device is useful because it can determine the instantaneous corrosion rate in-vivo of metals.
Objectives

This thesis was intended to focus on being able to test the in-vivo corrosion rate of titanium. The measurements of corrosion rate will come from an implantable device with three electrodes. For in-vivo testing, the microelectronic device was designed to be compact in order to be implanted in Sprague Dawley rats. The corrosion measurements using the new electrical connection will be compared to the corrosion measurements on evaporated titanium using a SCE reference and carbon counter electrode in Hank’s simulated body fluid at normal human, and rat, body temperature (37° C) [1]. Due to processing issues, the objectives changed from implanting the device to designing and testing the electrical connection.

The corrosive properties of titanium will be evaluated in several ways. Open circuit potential testing will evaluate the tendency of titanium to corrode and will be tested over an extended period of time. Polarization resistance will be used in order to determine how fast corrosion is occurring. EIS, electrochemical impedance spectroscopy, will be used as an additional way to determine corrosion rate, but also solution resistance and surface characteristics. Experiments to be run include:

- Open circuit potential vs. time
- Polarization Resistance
- Electrochemical Impedance Spectroscopy
- Experiments will be duplicated to test the microelectronic connection
The microelectronic connection is the focus of this research. The connection allows for electrochemical testing while the implant is in the test subject. Constraints include: insulation of everything except the working, counter and reference electrodes from the environment, protection from damage throughout the testing period and the ability to conduct tests without placing undue stress on the subject. Additional requirements include: compatibility with the existing device, suitability for implantation in the body, capability of being sterilized and robust enough for implantation and use over a period of several weeks.
Chapter 2

Literature Review

The research is aimed at finding the corrosion rate of titanium in-vivo by using an implantable microelectronic device. This information will be valuable because titanium has been used for years as an implant material. In addition, the research will lead the way to being able to test magnesium alloys in-vivo.

Medical implants are chosen for their ability to resist corrosion. However, this leads to the use of metals that are not found naturally in the body and therefore their effect is unknown. Titanium is one of the most widely used metals for medical implants due to its corrosion resistance and ability to support bone growth. Many research groups have been interested in the corrosion of metals in the body, including titanium and those that are resorbable, able to be eliminated from the body.

Corrosion

Corrosion is the destruction of a metal through electrochemical reactions. The requirements for corrosion include: an anode, cathode, electrolyte and electrical connection. The anodic reaction involves oxidation, the loss of electrons, and in general is the metal dissolving into ions in solution. The cathodic reaction involves reduction, the gain of electrons, in water this is either hydrogen or oxygen reduction. The electrolyte acts as an intermediate to accept the dissolved metal ions and provide the species being reduced. The rate of corrosion is largely dependent on the electrolyte. In addition to the movement of
ions, electrons must flow between the anode and cathode; this can be in the form of a solid connection or conduction through the solution.

Corrosion reactions are written as half-cell reactions occurring at the anode and cathode. For titanium in water this results in equations 1 and 2. Equation 1 is the anodic metal dissolution and equation 2 is the hydrogen evolution reaction. However, corrosion reactions will change according to the solution in which the metal is immersed. The corrosion of titanium will vary with environment, but is low compared to other pure metals. The uniform corrosion rate of titanium is accepted to be less than 40 µm/yr according to *Titanium: A Technical Guide* as long as it is in the passive state.

Passivity is the formation of an oxide film on the surface of a metal. The oxide film limits the interaction of ions due to diffusion rates. The metal oxide layer film forms whenever it is insoluble in the solution, but can usually be disturbed by mechanical means. Passive films lower the corrosion rate by orders of magnitude and are responsible for the corrosion resistance of the active metal aluminum. Passivity is one of the most important considerations in alloying. Corrosion resistant alloys take advantage of the passive films formed by some metals. For example, stainless steels are a solid solution of chromium, among other things, in iron. Chromium is known for the formation of an oxide layer under a wide range of conditions and effectively creates a barrier for the rest of the substituents in the alloy. In addition, many other metals exhibit the formation of an oxide layer such as titanium and magnesium.

**In-vivo corrosion**

Metals have been used in the body for thousands of years, dating to Egyptians using metals for various implants, such as gold teeth. Metals are evaluated for factors such as biocompatibility, mechanical properties and manufacturability. According to Fleck et al., biocompatibility is the “ability of a material to perform with an appropriate host response in a specific application” [2]. This includes considering factors such as cytotoxicity of the metal and possible long term effects of the metal such as carcinogenesis.
Mechanical properties are important because many implants are used as structural support such as in screws, plates or stents. If these implants were to fail, the existing injury would not be fixed, or could worsen. The manufacturability of the metal is also important. Some metals have very useful properties such as strength or corrosion resistance, but are too expensive to use in pure form. These metals can be used in alloys so that the useful properties can be used, while the cost remains lower.

In order to test the corrosion properties of prospective metals for implantation, metals are first tested in-vitro and subsequently in-vivo. However, in-vitro experiments ran according to ASTM standards do not produce corrosion rates similar to in-vivo testing according to Witte et al. [3]. This difference is thought to be due to the presence of organic molecules and effects caused by the biofilm that forms on the surface of the metal, specifically the inability of most organic molecules to be conductive. Biofilm is a general term, but in the body is the formation of tissue around the object which is foreign to the body. It is unknown whether this tissue layer will increase or decrease the corrosion rate. Organic molecules are carbon based molecules which can be ions or highly polar and can have the potential to affect the corrosion rate.

The main metals used in medical implants include: titanium, stainless steel, cobalt, tantalum and nitinol. Titanium is one of the most useful metals for implantation and is alloyed to improve properties; however, it is more expensive than the alternative, stainless steel. Stainless steel is an iron alloy of nickel, chromium and molybdenum. Stainless steel can be used in bone repair and as components of artificial heart valves. Cobalt is a metal that has recently been in the news as part of the metal on metal hip implant recall. Tantalum is an active metal protected by an oxide film; it is used in the repair of bone injury, stents and dental implants. Nitinol is an alloy of nickel and titanium which has two special properties: superelasticity and shape memory. Nitinol is growing as a stent material due to the ease of manufacturing.

Titanium is a transition metal known for its low density, corrosion resistance and bone response. Implants made from titanium are used for hard tissue replacement, such as dental or orthopedic...
applications and in cardiovascular applications such as heart valves. Titanium’s use is due to the corrosion resistance caused by the oxide layer. However, the oxide layer can be disturbed mechanically.

Rodrigues et al. found that the corrosion of Ti in hip replacements was significant [4]. This study chose three samples from a larger group of removed hip implants. The samples chosen were then viewed under scanning electron microscope in order to examine the effects of corrosion. In addition, the samples were tested for hydrogen. The study found that the implant underwent pitting and crevice corrosion following the mechanical erosion of the oxide layer. Figure 2-1 shows a pit which is approximately 200 \( \mu m \) in diameter. The samples also were affected by hydrogen embrittlement. This study is significant because titanium is generally assumed to be immune to corrosion in the body.

Figure 2-1 Titanium hip implant and SEM image (160x) showing pits from Rodrigues et al. [4].

The passive film on titanium is the crux of its corrosion resistance. According to Fleck et al., the oxide layer on titanium is spontaneously 2-10 nm thick [2]. The oxide layer is TiO\(_2\) which is an insulator. A study by Lamolle et al. shows that the surface of the titanium can be altered by hydrofluoric acid and hydride concentrations [5]. The results of the study show that the roughness of the surface increases the osseointegration. The graph and table in Figure 2-2 indicate the relationship between roughness and metal-bone adhesion. In addition, surface treatments on the titanium can increase the thickness of the oxide layer which also improves the bone-metal adhesion. The surfaces were examined using an SEM and the osseointegration is based on the force required to remove the metal. The study is significant because osseointegration will affect the success of bone repair implants and because the corrosion rate could be reduced by increasing the thickness of the film.
Figure 2-2 Data from Lamole et al. shows the relation between surface properties and the force required to pull the implant from the bone after implantation in rabbits [5].

**Medical Implant Materials**

Recently, issues have arisen over the release of ions by metal-metal hip implants. Certain metals have caused side effects in patients and have been related to pain. This leads to the removal of implants and addition risk for patients and increases the cost. This issue and lack of knowledge about the long term effects of metals on the body have led to the development of materials which will be short-lived in the body so that the long term effects are not an issue. These resorbable materials can use either polymers or metals.

Originally, bioabsorbable polymers were only able to be used for sutures due to the lack of strength. However, advances in the technology have allowed for successful use in pins, screws, plates and drug delivery devices. Some bioabsorbable materials for surgical applications include: dexon, vicryl, PDS and maxon. The low strength of polymers has the advantage of requiring bone growth in order to support the body. In comparison, some metals reduce the stress on the bones which can lead to decreased bone growth. This is because of Young’s Modulus, the metal carries more load for an equal change in
dimension. This means that the metal will carry the load that the bone should be holding, leading to reduced bone growth.

Metal implants generally have higher strength than polymers and some dissolved metal ions might be useful in bone growth and other functions. According to Bowen et al., primarily two metals have been investigated for use in resorbable stents [6]. These metals are iron and magnesium; however, iron corrodes too slowly and magnesium corrodes too readily. Bowen et al. placed wires in the arteries of rats in order to determine their corrosion. In addition, an attempt was made to develop an in-vitro experiment that obtained the same results as the in-vivo test.

Bowen et al. state that iron is most likely not suitable for use in stents because the corrosion products have been shown to accumulate locally. Figure 2-3 shows the increase in diameter of the iron sample in both the SEM image and the image of the iron wire taken from the arterial wall. In addition to this, the iron showed pitting which causes failures that can be difficult to predict. Magnesium showed promise because it corroded uniformly and the corrosion products dissolved and were removed from the area. After three months’ time, the AZ91 sample showed a 41% reduction in area. These results support the idea of a magnesium based bioabsorbable material.
Figure 2-3 SEM of Iron showing the voluminous growth of the iron oxide layer. Iron (above) and Magnesium (below) after 9 months in the artery lumen and wall (left and right respectively). From Bowen et al. [6].

**Corrosion Rate Determination In-Vivo**

Many researchers have acknowledged the need for in-vivo corrosion testing, however many seem to be developing their own methods. In-vivo measurements are important because the environment inside the body is very complex. The ions and organic molecules present will vary depending on where the implant is going to be used. In addition, a miscalculation in design or material choice will potentially affect the health of the patient. The methods used to estimate corrosion in-vivo can be classified as: implant/explant, real time measurements or in-vitro comparisons.

The first method implants a material into the region of the body where it will be used. After a period of time, the implant is removed and then studied in order to determine the corrosion that occurred. This method is simple to implement, however it yields only a corroded specimen which has to be analyzed by weight loss or imaging. This means that the corrosion rate that is measured is approximated
as an average rate over weeks or months or is described qualitatively. The problem with this is that the body’s response to the implant is not a constant response; the body will initially treat the implant as a foreign object and increase blood flow to the region causing inflammation. The increased ion exchange due to blood flow will likely increase the corrosion following implantation and then decrease over time.

In 2012, Pierson et al. conducted an experiment which implanted both iron and magnesium wires into the aorta of a rat [7]. In order to see the progression of corrosion, the wires were explanted at periods of 22 days, 45 days, 90 days or 270 days. The study showed qualitatively through SEM imaging that the corrosion of either material was increased with the wire in the arterial wall rather than the lumen. Using a SEM, the surfaces of the wires were inspected for visible signs of pitting in the iron sample. The study successfully used wire implants to compare corrosion of magnesium and iron in the two regions.

![Figure 2-4 SEM images from Pierson et al. of the initial iron wire (left) and the iron wire that was implanted in the arterial wall for 22 days showing pitting (right) [7].](image)

In 2012, Walker et al. implanted magnesium alloys into a rat and compared the weight loss of the materials to the weight loss while in three different solutions [8]. Alloys include: 99.99% pure Mg, Mg-0.8Ca, Mg-1Zn, Mg-1Mn, and Mg-1.34Ca-3Zn (wt %) and AZ31. This method obtained average corrosion rates for the samples in each solution, Earle’s Balanced Salt Solution (EBSS), Minimum Essential Media (MEM) and MEM with bovine serum albumin, which is useful for comparison and design. However, the solutions were unsuccessful in predicting the corrosion rate; the in-vivo sample
produced the lowest corrosion rate for every sample. Additionally, the samples were viewed using an SEM to analyze the surface.

Figure 2-5 Graphs from Walker et al. comparing corrosion in different solutions [8].

Figure 2-6 SEM image from Walker et al. indicating the deep (a) and superficial (b) corrosion layers as well as corrosion product (c) [8].

In 2012, Jorgenson et al. used EAAS, electrothermal atomic absorption spectroscopy, to measure the amount of titanium present near a titanium plate [9]. The craniofacial plates were removed after two years along with a tissue sample from the region. Toxicologists are interested in the levels of metal in the body because this will combine corrosion rate with the rate of elimination from the body. Jorgenson
found that the local levels of titanium were 8-32 \( \mu g/g \), meaning micrograms of titanium per gram of tissue. This relatively low result indicates that the titatnium levels are the result of corrosion. A similar study by Agins et al. studied the area around failed hip implants. This second study found levels near 1000 \( \mu g/g \) due mostly to the mechanical removal of titanium from the hip implant. The mechanical erosion of the hip implant is termed metallosis and is associated with an inflammatory response and generally pain. Although research has shown titanium to be biologically inert, there have been cases of hypersensitivity.

The second type of study records corrosion values by making electrical connections to the implant while in the body. Musa et al. created this device to measure corrosion of a neural probe, shown in the picture below, that allowed for electrochemical experiments to be run in the brain of anesthetized rats [10]. The device allowed open circuit potential, electrochemical impedance spectroscopy and cyclic voltammetry tests to be completed in the brain environment. These results were compared to the results obtained in phosphate buffered solution with and without bovine serum albumin. The results showed a lowered OCP and higher resistance to corrosion in the body of platinum using a Ag/AgCl reference.

Figure 2-7 from Musa et al. [10], showing different aspects of the novel device, A shows views of the entire device, B shows views of the custom reference electrodes and C is the custom reference electrode alone.
In Brazil in 2007 Pertile et al., ran OCP tests on Nitinol in the environment of human arteries [11]. This study is important because it ran tests on the human body which is very rare. Arteries used were the abdominal aorta, common iliac artery and femoral artery. The OCP measurements taken were similar to the measurements in-vitro, using Ringer’s, artificial urine and a simulated body fluid. The values for OCP ranged from -0.226 to -0.334 V, with the in-vivo measurement being the most noble. This type of study would be very useful in stent design because it gives values found in an artery.
Nearly all in-vivo studies compare their results to in-vitro experiments as a control or to improve in-vitro conditions so that they will be more representative. The familiar solutions are simulated body fluids such as Hank’s; other solutions such as Ringer’s, PBS and artificial urine are also used for comparison because they are similar. In addition to these, some studies have investigated adding bovine serum albumin, whole blood, plasma, and Dulbecco’s Modified Eagle Medium. However, research has not found a solution that is a good predictor of in-vivo corrosion across a range of materials. Because of the lack of representative solution, tests must be conducted in the body in order to obtain useful results concerning corrosion rate.

Although in-vivo testing is important in developing a material for use as a medical implant, there is a lack of published studies. The studies that have explored in-vivo corrosion have not produced the corrosion rate as a function of time. The development of a microelectronic device for in-vivo testing is useful because it will allow the development of alloys for medical applications, provide corrosion rates as a function of time and will impact aspects of life unrelated to materials.
The research conducted in this thesis will clear the way for future alloy testing in the body. In this group, this means the testing of magnesium alloys, however many other alloys could be tested in a similar manner. The research in medical alloys will allow improvement of medical equipment and implants which will save lives and money. Patients who need to receive multiple arterial stents will be able to if resorbable materials are developed. If resorbable materials are used in bone fixation plates, it could resolve issues where patients need to have multiple surgeries in order to remove a problematic implant and the cost and risk associated with that.
Chapter 3

Experimental Design and Methods

*In-Vitro Corrosion Experiments*

Rigorous in-vitro testing is necessary in order to continue with in-vivo experiments. Tests must show that the electrical connection provides results that are identical to the control, which is the testing of evaporated titanium specimens prior to processing. In order to continue with in-vivo testing, the results from the final design must agree with the evaporated Ti specimen, the design must be robust and the results must confirm the corrosion measurements taken on the evaporated titanium.

In-vitro testing was conducted on the prototype device, with the finished microelectrical connection, and on the evaporated titanium as a comparison in order to evaluate the electrical connection. The corrosion experiments were conducted in Hank’s SBF at 37°C in order to simulate the conditions in-vivo. However, the devices used were from a prior student’s research due to processing issues in the Fall of 2012.

Tests conducted included: open circuit potential, polarization resistance and electrochemical impedance spectroscopy. The tests were run in 8 hour cycles until 24 hours and then on a 24 hour cycle. The tests generally began with an hour of OCP followed by PR in order to evaluate the initial corrosion rate. An “8 hour” cycle is OCP run for 7 hours then PR run and then an hour of OCP until EIS is run. In reality, EIS measurements take a significant amount of time; most cycles last about 8 and a half hours. For this research the largest difference in quoted length of time and actual length of time that occurs is a “48 hour” test that obtains corrosion values at 49 hours for polarization resistance and 50 hours for electrochemical impedance spectroscopy.
The evaporated Ti specimen used as a control was prepared for testing by first attaching an insulated wire to the surface with the use of silver epoxy. The epoxy was cured at 65°C for two hours; next, the sample was then coated with PMMA, poly-methyl methacrylate, on all surfaces except for an area on the front, as shown in Figure 3-1 below. The PMMA was used as an electrically insulating coating that would prevent surfaces other than the test area of the silicon wafer or wire from being exposed to the electrolyte. The surface area of the test region was determined using MOTIC Images software which drew images from an optical microscope. The tests were run using a saturated calomel electrode as the reference and a graphite rod as the counter electrode. In order to keep the saturated KCL solution in the SCE saturated, the reference was replaced every 24 hours of testing with another electrode that was already at temperature (37°C).

Figure 3-1 The pure titanium sample was tested as shown before any processing of the 3-electrode device. Note the square test area in the center of the sample (the area not coated with the clear PMMA)

Testing on the prototype device was run in a similar manner; however, the sputtered platinum reference and counter electrodes on the device were used. The devices were tested using a Gamry Reference 600 potentiostat and the accompanying Gamry Frameworks and Gamry EChem Analyst
software packages. Figure 3-2 depicts the prototype device in solution during testing with the full connection made to the back of the device. The connection must be made from the back of the device for implantation; so that the cable connection can be made.

![Figure 3-2](image)

Figure 3-2 The prototype device with electrical connection used for testing made from the backside of the device

**Preparation of the Microelectronic Connection**

The purpose of the microelectronic connection is to allow the cable connection to the potentiostat to be made from the backside of the device so the device can be placed in-vivo. The connection was prepared in accordance with the requirements set in the objectives. These include: insulation from the environment for all surfaces except the three electrodes, protection from damage throughout the testing period and the ability to conduct tests without placing undue stress on the subject. Additional electrical connection requirements include: compatibility of the connection with the
of being sterilized and robust enough for implantation and use over a period of several weeks.

The final design of the prototype device was chosen based on discussion with Dr. Gluckman, and his prior experience with neural implantation. This was chosen because of the ease and security of cable attachment, inability for the animal to damage the connection, and the simplicity of the connection. The final design includes the use of cylindrical plastic molds and pins which are shown in Figure 3-3. These molds house the male and female pins in order to protect them from damage and secure the connection. Threading allows the two ends to be secured during in-vivo testing when the subject is free to move around. These pins are connected to the electrodes via 50µm wires which are stainless steel plated with gold and insulated by a polyimide coating.
The first step in creating the connection involves securing the wires to the front of the device with a conductive silver epoxy, this is shown in Figure 3-4. Once this bond was cured at 65°C, the polyimide coated wires were attached to the pins with the same silver epoxy and again cured. At this point, the conductive portion of the connection was finished and checked using a multimeter; the rest is for structural support. The next step used Devcon H2-Hold waterproof epoxy to secure the pins in the plastic housing (cured at room temperature) and then to attach the plastic housing to the back of the device. The finished product can be seen in Figure 3-5; the epoxy is visible as the white surface on the back of the device (before threading begins).
The final step in the process is coating all surfaces of the device with PMMA, other than the three electrodes used for corrosion measurements. The edges on all sides of the device were coated with PMMA, including the silver epoxy and wires in addition to coating the sides and rear of the device. Figure 3-5 shows the final product with the male cable adapter connected.
Several issues were encountered during the building of the prototype device. The original design used ordinary electronics pins similar to IC pins shown in Figure 3-6, depicting the first concept in the design process. The problem with this was the tendency for the pins to get bent, a potential difficulty in forming the connection and maintaining the connection while the animal moves around. In addition, the standard Gamry cable is relatively heavy compared to the amount of force that the Sprague-Dawley rat can withstand. The cable is heavy due to the need for driven shielding within the cable to allow for very low current measurements. Driving the shielding prevents power loss to the insulation surrounding the wires [12].
The need for driven shielding presented a problem for creating a lightweight cable that could be used for testing. The shielding must be driven at the same potential as the wire in order to prevent current loss inherent in measuring very high impedances. In addition to this, Gamry calibrates every cable used so that the impedance of the cable can be accounted for during testing. After consulting the manual, the complexity of the cable was better understood and Gamry was able to create and calibrate a cable that could be used for in-vivo testing, the resulting lightweight cable is shown in Figure 3-7.
Lightweight Cable

Figure 3-7 The lighter cable prevents stress on the animal while maintaining accuracy of the measurements.
Chapter 4

Results and Discussion

Testing Evaporated Titanium

E-beam evaporated titanium is the working electrode that is being tested in the implantable device, therefore, the prototype device was compared to a specimen that contained only the deposited titanium layer. The implantable device and the evaporated Ti specimen were tested through OCP, PR and EIS measurements. Polarization resistance measurements taken during the first 24 hours after first being placed in solution for the evaporated Ti specimen are shown in Figure 4-1. The slope of the curve gives a value of resistance which, when normalized to the area, can be converted into polarization resistance. The polarization resistance test showed that corrosion rate decreased from 0.917 mpy (at 1 hour) to 0.249 mpy (at the 24 hour mark). This corrosion rate was calculated from the Faraday and Stern-Geary equation using polarization resistance values of 16360 Ωcm (1 hr) through 60200 Ωcm (24 hr).
Figure 4-1 Polarization Resistance curves of the evaporated Ti specimen (TiPt-8) at 37°C in Hank’s Solution show the slope increasing as a function of time, indicating a decrease in corrosion rate (sample area is 0.32 cm²).

Additionally, Figure 4-2 shows a replicate experiment, which only tested the sample after 48 hours in solution. In this replicate experiment, the polarization resistance plot had a slope of 33656 Ωcm. The corrosion calculated from this slope was 0.446 mpy which is slightly higher than the experiment at 24 hours (shown in Figure 4-1). However, as seen in Figure 4-2, the current does not reach 0 A as it should which means that the experiments did not test both the anodic and cathodic polarization curves and the polarization resistance value may not be accurate if the plot does not pass through zero.
Figure 4-2 Polarization resistance of TiPt-8 wafer after 48 hours in Hank’s solution at 37°C shows a corrosion rate of 0.446 mpy (sample area is 0.32 cm²)

EIS measurements taken over a 48 hour period, shown in Figures 4-3 and 4-4, give polarization resistance values ranging from 50,214 Ωcm at 9 hours to 305,920 Ωcm at 49 hours. These values were obtained by extrapolating the Nyquist plot to its intersection with 0 Ω imaginary and subtracting the solution resistance. The specimen used in this portion of experiments (Figures 4-1 through 4-4) was given the name TiPt8; the corrosion rates measured from EIS range from 0.299 mpy at 9 hours to 49.0 x 10⁻³ mpy at 48 hours.
Figure 4-3 Bode plot of TiPt8 over a 48 hour period in Hank’s solution at 37°C, sample area is 0.32 cm²

Figure 4-4 The Nyquist plot of TiPt8 in Hank’s solution at 37°C over a 48 hour period

Table 4-1 shows all the measured electrochemical corrosion rate values from the evaporated Ti specimen. The corrosion rate tends to decrease as a function of immersion time;
from 0.917 mpy after an hour to 49.0 x 10\textsuperscript{3} mpy at 48 hours. The corrosion rate decreases by more than an order of magnitude which is likely due to an oxide layer formation. The polarization resistance measurement at 48 hours seems to be erroneous because it does not agree with other measurements, including the EIS measurement taken only an hour later. This error is likely due to a change in open circuit potential as the test was continuing because the current does not pass through zero and the curve is not visibly linear in the measured data points.

Table 4-1 Corrosion rates and Polarization resistance of the evaporated Ti specimen in Hank’s solution at 37°C

<table>
<thead>
<tr>
<th>TiPt8</th>
<th>Hour</th>
<th>PR (Ωcm\textsuperscript{2})</th>
<th>Rate (mpy)</th>
<th>EIS (Ωcm\textsuperscript{2})</th>
<th>Rate (mpy)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>16360</td>
<td>0.917</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>43272</td>
<td>0.347</td>
<td>50214</td>
<td>0.299</td>
</tr>
<tr>
<td></td>
<td>16</td>
<td>52452</td>
<td>0.286</td>
<td>57901</td>
<td>0.259</td>
</tr>
<tr>
<td></td>
<td>24</td>
<td>60203</td>
<td>0.249</td>
<td>76544</td>
<td>0.196</td>
</tr>
<tr>
<td></td>
<td>48</td>
<td>33656</td>
<td>0.446</td>
<td>305920</td>
<td>0.049</td>
</tr>
</tbody>
</table>

**Testing of the Implantable Device after Attachment of the Electrical Connection Assembly**

After the electrical connection was made on the prototype device, Figure 3-5, it was tested under the same conditions as the evaporated Ti specimen (Hank’s solution at 37°C). The implantable device differed from the evaporated Ti specimen in the electrical connection, lightweight potentiostat cable, and processing steps involved in patterning the device. All these changes were made with the thought that they should not affect the results. Figure 4-5 shows the polarization resistance curves for 96 hours of testing of the implantable device. As with the evaporated Ti specimen, the corrosion rate decreases with time, as the polarization resistance
increases. In this case the corrosion rate at 1 hour is 1.67 mpy and the polarization rate at 96 hours drops to 0.156 mpy. This drop is very similar to the evaporated Ti specimen and the values are comparable. This result is expected; it signifies that the electrical connection did not affect the corrosion measurements due to precautions taken to avoid interference with measurements.

![Polarization Resistance Curves](image)

Figure 4-5 Shows the polarization resistance curves for TCD1-2 at 37°C in Hank’s solution (area is 0.08 cm²) with the implantable electrical connection.

EIS data from the implantable device confirms the corrosion rates of the implantable device as seen in Figures 4-6 and 4-7. At 24 hours, the corrosion rate was 1.05 mpy which dropped to only 0.164 mpy after 96 hours in solution. The polarization resistances at these lengths of time were 14304 Ωcm to 91200 Ωcm, respectively. These values come from three experiments run on the same device; the first was consisted of three “8 hour” cycles, another was a measurement only at 48 hours and a third was taken only at 96 hours. These results show similar corrosion rates as those for the evaporated Ti specimen and the polarization resistance curves.
Figure 4-6 The Bode plot of the implantable device in Hank’s solution at 37°C.

Figure 4-7 Nyquist plot of the implantable device at 37°C in Hank’s Solution, the area is 0.08 cm²
Table 4-2 the results of the test on the prototype device, TCD1-2. The corrosion rate is slightly higher than the evaporated Ti specimen throughout the test. The results indicate a similar reduction in corrosion rate over time as compared to the evaporated Ti sample. This is due to a protective oxide film forming on the surface during immersion in the electrolyte. The results are similar for the prototype device and the sample titanium deposited wafer indicating a reliable connection has been made. In addition, the sample was tested separately for each time period and in total was in and out solution for a period of a week. The ability of the specimen to provide consistent results over this period of time signifies its robustness.

Table 4-2 Corrosion rate results of TCD1-2, the implantable device (using the new microelectronic connection) in Hank’s solution at 37°C

<table>
<thead>
<tr>
<th>TCD1-2</th>
<th>PR (Ωcm²)</th>
<th>Rate (mpy)</th>
<th>EIS (Ωcm²)</th>
<th>Rate (mpy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>9005</td>
<td>1.67</td>
<td></td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>13017</td>
<td>1.15</td>
<td>14304</td>
<td>1.05</td>
</tr>
<tr>
<td>48</td>
<td>30840</td>
<td>0.486</td>
<td>25152</td>
<td>0.596</td>
</tr>
<tr>
<td>96</td>
<td>96182</td>
<td>0.156</td>
<td>91200</td>
<td>0.164</td>
</tr>
</tbody>
</table>

The results in Table 4-1 and 4-2 indicate that the prototype device does replicate the results of testing the titanium deposited wafer, which is the ideal case. The corrosion rates of the prototype range from 1.67 mpy to 0.156 mpy over 4 days; the corrosion rate of the TiPt-8, corrosion of the evaporated Ti specimen ranged from 0.917 mpy to 0.049 mpy over 2 days. The samples were tested in several experiments at body temperature in Hank’s solution to simulate the in-vivo environment. With over a week in and out of solution, the sample has shown its
robustness through the stability of the corrosion rate with respect to repetitive testing and continuing to provide useful results.

The measured corrosion rates shown above in Tables 4-1 and 4-2 are similar to values obtained by Alves in a study of bulk titanium corrosion rates in Hank’s solution at body temperature [13]. The polarization resistance values of bulk Ti obtained in one test in Hank’s at body temperature were 29900 \( \Omega \) cm\(^2\) after 5 minutes in solution and 489000 \( \Omega \) cm\(^2\) after 168 hours. These polarization resistance values indicate a corrosion rate of 0.502 and 0.0301 mpy respectively.

**Sample Calculation:**

For polarization resistance tests \( R_p \) is the slope of the voltage vs current curve normalized to the sample area; for electrochemical impedance spectroscopy, \( R_p \) was obtained by extrapolating the Nyquist curve to 0 \( \Omega_{\text{imaginary}} \) and subtracting the solution resistance.

\[
i_{\text{corr}} = \frac{1}{2.303}\left(\frac{b_a \cdot b_c}{(b_a + b_c) \cdot R_p}\right) = 2.303 \cdot \frac{(0.1 \cdot 0.1)}{(0.1 + 0.1) \cdot 91200} = 0.238 \, \mu\text{A/cm}^2
\]

Corrosion Rate = \( K \cdot i_{\text{corr}} \cdot EW / \rho \) = 0.129 \((1.26 \, \mu\text{A/cm}^2) \cdot (23.9 \, \text{g/mol}) / (4.51 \, \text{g/cm}^3)\) = 0.164
Chapter 5

Conclusions

The data collected supports the goal of this research project, which was to develop the microelectronic connections between the 3-electrode device and the Gamry potentiostat. The data shows that the corrosion rates measured from the implantable device and the evaporated Ti specimen were similar, slowing to 0.164 and 0.049 mpy after several days respectively. The design of the device included using pins housed in a plastic mold, which are able to be threaded together in order to maintain the connection during testing. The actual conducting portion of this included the 50 micron wire which was bonded to the three electrodes and to the metal pins with silver epoxy. The wire therefore bends around from the front to the rear of the device, creating a point that places stress on the imine coating which should be redesigned for future improvements.

The project showed that corrosion rates of the implantable device and evaporated Ti specimen were similar. The e-beam evaporated titanium wafer had similar corrosion kinetics to that of the prototype device. Although the prototype device had been processed, had the new electrical connection and been tested with the new lightweight cable, the corrosion rates were consistent with each other, proving successful completion of the electrical connection. The corrosion rates of the prototype range from 1.67 mpy to 0.156 mpy over 4 days; the corrosion rate of the evaporated Ti specimen ranged from 0.917 mpy to 0.049 mpy over 2 days.
Chapter 6

Future Work

Now that the electrical connection between the potentiostat and the microelectronic 3-electrode device has been established, the next step is to move on to implanting the device. Some preliminary work for this involves sterilizing the whole unit as it will be used in order to retest the corrosion measurements made. In addition, the design could possibly be improved where the wires bend around the edge of the device. This point could become a weakness for long term testing because the wire is stressed. Once a solution is found testing would need to verify how some sterilization techniques could affect the titanium directly or the other materials involved in the connection.

Once the device has been approved for sterilization; then the device could be implanted and compared to the in-vitro results. This comparison would be able to show the differences or similarities in between the in-vitro and in-vivo corrosion rates and study the effectiveness of in-vitro studies for in-vivo corrosion. Additionally, in-vivo testing could show that the device is working effectively which would allow more devices to be made with the magnesium alloy as the working electrode.

This is ultimately the goal of the research group, because there has been interest in magnesium alloys as resorbable materials for biomedical applications. If the 3-electrode microelectronic device proves useful, then the working electrode could be altered into many alloy materials while the other processing steps remain the same. This would be useful to test any alloy used in the body.
Appendix A

Device Manufacture details

The procedure for creating an implantable microelectronic device was derived from a master’s thesis titled “Study of Magnesium Corrosion for Biomedical Devices: An Investigation Involving Microelectronic Processing” by Anna Hartsock. This thesis should be consulted for more complete details. The procedure that is presented in this thesis is a paraphrased version of what is contained in the thesis by Anna Hartsock.

Mask One

A photoresist assist (LOR2A) and a photoresist (S1813) are spun onto a six inch wafer. The phototresist assist was spun for 45 seconds at 3000 rpm and baked at 180°C for five minutes. The photoresist is spun at 4000 rpm for 45 seconds and baked at 95°C for one minute.

The mask size left large unused area; to make better use of the wafer area, the wafers were cleaved into quarters. A Karl Suss MA BA6 mask aligner was used to align Mask One. The wafer is then exposed (hard contact exposure) to UV light at 8 kW/cm² for ten seconds. Exposure to UV light will break the chemical bonds in the photoresist, allowing the exposed resist to be removed easier. The developer to remove the photoresist is CD-26. The quarters were immersed for about one minute, or until the exposed photoresist was completely removed. The wafers were then rinsed in DI water and dried with nitrogen.

The wafers were loaded into the Kurt J. Lesker CMS System at the Materials Research Lab (MRL). First, a cleaning recipe was used to remove any dust particles and phototresist. Then titanium and platinum were sputtered onto the wafer. Titanium was sputtered for 120 seconds at 100Å and the platinum was sputtered at 1000Å for 400 seconds on top of the titanium layer. The
quarters were then immersed in an acetone bath and ultrasonicated, to remove the platinum and
titanium that was on top of the photoresist.

Mask Two
The quarters were then transferred to the EB-PVD system at the Earth-Engineering Sciences Building. The working electrode was deposited on the wafer. Phototresist (S1813) was spun on the quarter wafer for 45 seconds at 4000 rpm and baked at 110°C for one minute. Mask Two was aligned and UV light was exposed to the system for seven seconds. The quarter was placed in a developer bath (CD-26) for about one minute to remove the photoresist.

A bath of HNO3 :H2O (ratio of 20 to 180 mL) was then utilized to remove the exposed working electrode. The quarter was immersed for roughly 50 seconds. A rinse of acetone and IPA insured that all of the excess deposited working electrode was removed before the next step.

Mask Three
The quarter wafers were loaded into the deposition chamber of the parylene evaporator. A recipe for evaporating parylene to obtain a desired thickness of 0.5μm was utilized. Actual thickness, when tested later, determined that the thickness was not uniform, but was between 0.56μm and 0.67μm. Photoresist (S1813) was spun on at a rate of 4000 rpm for 45 seconds. UV light was exposed for ten seconds and immersed in a developer bath (CD-26) for about one minute.

An oxygen plasma etcher was used to remove the exposed parylene coating on the electrode and the connection pads of the electrical leads. The PT720 plasma machine used an oxygen plasma composed of 90% O2 and 10% Ar. The quarters were exposed in 30 second increments until the exposed parylene was removed [14].
Appendix B

Components of Hank’s solution

Table 6-1 Hank’s Recipe taken from Bimber [14]

<table>
<thead>
<tr>
<th>Component</th>
<th>Concentration (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CaCl₂·2H₂O</td>
<td>186</td>
</tr>
<tr>
<td>KCl</td>
<td>400</td>
</tr>
<tr>
<td>KH₂PO₄</td>
<td>60</td>
</tr>
<tr>
<td>MgSO₄</td>
<td>98</td>
</tr>
<tr>
<td>NaCl</td>
<td>8000</td>
</tr>
<tr>
<td>NaHCO₃</td>
<td>350</td>
</tr>
<tr>
<td>Na₂HPO₄·7H₂O</td>
<td>90</td>
</tr>
<tr>
<td>Glucose</td>
<td>1000</td>
</tr>
</tbody>
</table>
REFERENCES


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________________________________________

Education

B.S., Engineering Science, 2013, The Pennsylvania State University, University Park, PA
Honors through the Schreyer Honors College
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Professional Experience

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Summer Intern in the Engineering Department at Volvo Powertrain, Hagerstown, MD
Summer Intern in the Maintenance Department at Volvo Powertrain, Hagerstown, MD

Association Memberships/Activities

Tutor at the Engineering Academic Excellence Center

Research Interests

I have broad interests in mechanical and bioengineering, especially in biomedical materials. My specific area of research includes the corrosion of metal alloys in-vivo