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Inorganic biodegradable devices for temporary implants

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INORGANIC BIODEGRADABLE DEVICES FOR TEMPORARY IMPLANTS

by

KASSAN UNDA

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Approved by

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Dr. Matthew J. O'Keefe

ABSTRACT

Implantable electronic devices have great potential to benefit many health care technologies. They comprise of two different categories. The first is permanent prosthetic devices like cardiac pacemakers or nerve stimulants. The other category includes temporary devices for interventional medical monitoring and control scenarios, which lose functionality and become unnecessary after their intended operational lifetime. This can cause serious electromagnetic and biomechanical safety concerns if not removed from the body by an additional surgical operation.

This thesis focuses on exploring the feasibility of implantable inorganic bioresorbable thin film resistive devices utilizing bioactive glass as the core structural material. This device will be fully functional inside the human body for a desired time period and then will completely dissolve without causing any safety issues. A bioactive borate glass wafer was used as the substrate for the devices. The chemical composition of bioactive glass can be varied to control the dissolution rate in biological environments. We built a test structure composed of an insulating layer (silicon oxide) and metal electrodes (gold-palladium). The insulating layers were deposited using two different methods. The first one being physical vapor deposition (radio frequency sputtering) and the other being chemical vapor deposition (plasma-enhanced chemical vapor deposition). They were then subsequently tested for their operation in simulated body fluids. This feasibility study is expected to lead to a variety of useful sensors and actuators (e.g. temperature, pressure, flow, metabolites and radiation dose, etc.) that can be applied to many areas (e.g. circulation, rehabilitation, diabetes, cardiology, drug delivery, radiation oncology) that can benefit temporary implantable devices.

ACKNOWLEDGMENTS

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I wish to my express sincere thanks to Dr. Delbert E. Day for his time deliberating on challenges, devising solutions, and his constant encouragement throughout this study. Dr. Day has been instrumental in providing bioactive glass for my experiments. I am indebted to Dr. Matthew J. O’Keefe for letting me use his lab for sputtering silicon dioxide. He has also been very supporting and encouraging throughout this study.

I am grateful for all the help from the technical staff of Material Research Center Eric Bohannan, Clarissa Wisner, Brian Porter and Ron Haas, PhD candidate Ali Mohammadkhah in Materials Science and Engineering for making bioactive glass samples for the experiments and my fellow lab mates Shihab Adnan and Altamash M Fakki.

I am thankful to God for all the opportunities. I wish to express my endless gratitude to my father Dr. Noor Mohammad Unda for his moral support and encouragement.

Appreciation is also extended to Ashwini Kumar Vaddadi and my other friends at Missouri University of Science and Technology.

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1. INTRODUCTION

Implantable electronic devices for temporary interventional medical monitoring and control scenarios lose their functionality and become unnecessary after their intended operational lifetime. They can cause serious safety concerns if not removed from the body by an additional surgical operation. The goal of this study was to explore the feasibility of potentially implantable inorganic biodegradable devices, which will be fully functional inside the human body for a desired time period and will then completely dissolve without causing any medical problems. Recently, biodegradable polymers have been utilized for this purpose. Most biodegradable polymers exhibit a short degradation time upon implantation [1]. An alternative approach is explored in this study using inorganic biodegradable materials for developing these bioresorbable devices. Developing this kind of device using inorganic biodegradable materials has been the primary focus of this study.

A bioactive glass is a material that undergoes specific surface reactions when implanted in the body. Varying the chemical composition can control the dissolution rate of inorganic bioactive glass material in biological environments and they leave no residue behind. Bioactive borate glass wafer was used as the substrate for the devices. Silicon oxides are key materials for dielectrics and encapsulation layers in a class of silicon-based electronics that has the ability to completely dissolve in a controlled fashion with programmable rates, when submerged in bio-fluids and/or relevant solutions[2]. The kinetics of hydrolysis of these materials depends on pH levels/ion concentrations of solutions and temperatures, morphology and chemistry of films[2]. The end product is silicic acid, which is biocompatible and environmentally benign at low concentrations.

Thus silicon oxide has been used as an insulation layer between the glass surface and the device area.

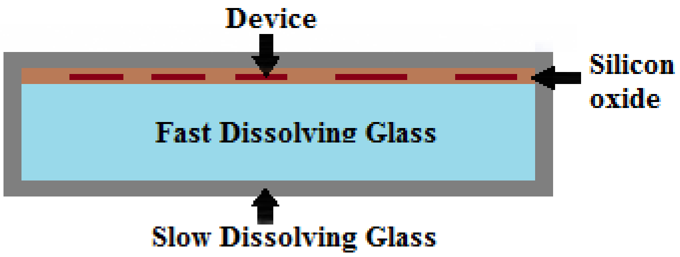
We built a test structure composed of an insulation layer (silicon oxide) and metal electrodes (gold-palladium). The insulation layers were deposited in two different ways using physical vapor deposition and chemical vapor deposition. The first kind had silicon oxide on all except one face. The other kind was entirely coated with silicon oxide. A pair of thin film metal electrodes was formed on the surface of silicon oxide. The electrode impedance was monitored during the dissolution process in simulated body fluid to test the concept. This approach is expected to lead to a variety of useful sensors and actuators (e.g. temperature, pressure, flow, metabolites and radiation dose, etc.) that can be applied to many areas (e.g. circulation, rehabilitation, diabetes, cardiology, drug delivery, radiation oncology) that can benefit temporary implantable devices.

1.1 BIODEGRADABLE DEVICES

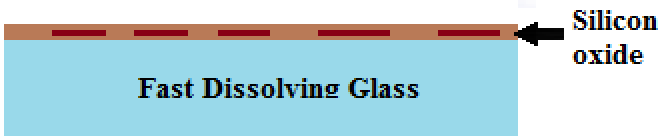
Some implanted electronic devices are required only for a limited period of time and can cause serious electromagnetic and biomechanical safety concerns if not removed from the body by an additional surgical operation after their intended operational life time. This calls for the development of bioresorbable devices. These devices dissolve inside the human body after serving their purpose without causing any safety issues. Recently biodegradable conducting polymers have been utilized for this purpose. An alternative approach is explored in this thesis using inorganic biodegradable materials for developing these bioresorbable devices.

1.2. DEVICE STRUCTURE

The device is formed on a thin film of silicon oxide deposited on a fast dissolving bioactive borate glass. The advantages of slow and fast reacting glasses can be combined to produce a two-layered composite glass having two different dissolution rates. The fast dissolving glass provides the mechanical support to the device. The device is insulated from its surrounding by coating it with silicon oxide. The whole structure is then encapsulated using a slow dissolving glass, which is mainly responsible for determining the operational lifetime of the device. The outer glass layer will slowly dissolve while protecting the inner glass layer from the body fluid. When the outer layer completely dissolves, the fast reacting inner layer will be contacted by the body fluid and will quickly dissolve. The fast dissolving glass can take anywhere between a couple of hours to a few days to dissolve and the slow dissolving glass can take anywhere between several months to a couple of years to dissolve. Figure 1.1 shows the conceptual biodegradation process of the proposed device.



(a) Initial structure of device



(b) Dissolution of slow dissolving glass

(c) Dissolution of slow dissolving glass

(d) Dissolution of remaining thin film crust

Figure 1.1. Device operation concept for bioresorbable device

To test the device concept a simplified test structure was used. Figure 1.2 shows the device preparation steps for single side coated wafer. A fast dissolving bioactive borate glass wafer is used as a substrate, which is then coated with silicon oxide. A simple resistive device is then formed on top of the silicon oxide layer. A nylon washer is glued using silicone to the bottom of the glass wafer to provide an equal area for contact of the glass wafer with the simulated body fluid. The whole structure is then encapsulated using a silicone paste. Silicone paste is a very good water resistant insulator and thus no additional coating of silicon oxide is used to cover the device from top.

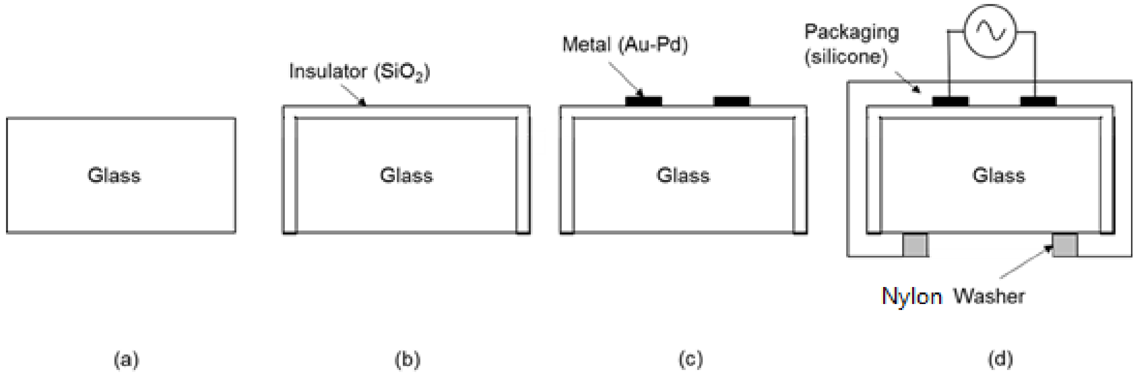


Figure 1.2. Overall device fabrication and packaging procedure of a single side coated device.

1.3 INORGANIC APPROACH

Most biodegradable polymers exhibit a short degradation time upon implantation [1]. The dissolution rate of inorganic biodegradable glass material in biological environments can be controlled by varying the chemical composition. This property can be exploited to develop bioresorbable devices with different lifetimes to suit different applications. The polymers have a limited surface modification strategy, while the functionalization of inorganic surfaces (e.g. grafting self-assembled monolayer on glass) has been extensively studied and commonly practiced [3]. Common inorganic semiconducting materials possess high electron mobilities compared to those of conducting polymers. This is critical to obtain the high frequency characteristics required for various electronic functions. Also, mechanical properties of organic materials, in general, are not as viable as those of inorganic materials for many mechanical applications where stiffness is required. Most polymers have a Young's modulus values below several GPa, while the modulus of ceramics and metals are in the order of several-ten to several-hundred GPa.

Many mechanical parameters (pressure, flow, strain, stress, etc.) can be detected by tailoring the common device structure of diaphragm-based pressure sensors prepared by such inorganic materials. Another path to detect strain is the resistance change due to mechanical deformation of metals (strain gauge, etc.). These advantages of inorganic biodegradable materials over their inorganic counterparts can be utilized to develop bioresorbable devices with much wider application range and with better performance.

1.4 BIOACTIVE GLASS

Bioactive glasses are the glassy materials that undergo specific surface reactions when introduced into the body and react with the fluids and form inorganic crystalline calcium phosphate such as hydroxyapatite (HA) depending on the glass composition [4]. The HA layer formed is very similar to the inorganic component of the bone and is responsible for the formation of a strong bond with hard and soft tissues and hence they elicit biological responses like promoting cell migration, cell differentiation and deliver ions for healing process. This property of forming a HA when immersed into a simulated body fluid (SBF) in vitro is an indication of bioactivity. Bioactive glasses forming HA require calcium as a component more the 10% of their weight [5].

Hench first discovered bioglasses with the well-known silicate-based composition in 1968 [6]. Silicon based bioglasses such as 45S5 and 13-93 have been widely used for bone and soft tissue applications, which include bones replacements in the middle ear, periodontal defects treatment and implants of the periodontal region [6]. Silicate bioactive glass is based on 3-D glass forming SiO_2 network in which Si is fourfold coordinated to oxygen. These key compositional features along with its low SiO_2 content are responsible for the bioactivity of 45S5 glass [7]. In the case of silicate glasses once the glass surface gets hydrated, the glass begins to dissolve, and a silica rich layer forms on the surface of the glass due to low solubility of silica in body fluids. Calcium ions from the glass diffuse through the silica rich layer forming chemical bonds with phosphates present in the body fluids [4]. This leads to the formation of amorphous calcium phosphate layer which crystallizes into HA over time. This property of HA allows tissues like bone to bond chemically to bioactive glasses [4].

1.5. BIOACTIVE BORATE GLASS

Certain works showed that other glass-forming systems, such as borate and phosphate bioactive glasses are also bioactive. These glasses degrade faster and have lower chemical durability and convert more completely to a hydroxyapatite-like material, compared to silicate bioactive glasses. The major glass former for borates is B_2O_3 as opposed to SiO_2, whose compositions can contain an array of alkali metals, alkaline earth metals and transition metals. Based on P_2O_5 glass forming network and CaO and Na_2O as modifiers, phosphate glasses has been developed for medical use [7]. These glasses have chemical affinity with bone as these ions constitute organic mineral phase of bone [7]. Hence these glasses may have additional chemical potential as resorbable materials.

It converts to HA through a similar process as silicate bioactive glass, but without the formation of SiO_2 rich layer [7]. This is due to the high solubility of borate in body fluids similar to the phosphate glasses. Due to the absence of diffusion layer, borate glasses react completely without a significant reduction in dissolution kinetics [5]. Figure 1.3 shows the SEM image of reacted borate bioactive glass converted to HA in vivo. It has been shown that borate bioactive glasses support cell proliferation and differentiation in vitro. They also serve as substrate for drug release. Administration of growth factors such as vascular endothelial growth factor (VEGF) was used for inducing vascular growth in bone implants which are quite expensive [8]. Copper generally regulates angiogenesis and the addition of this element to bioactive glasses adds to the advantage apart from faster release of growth factors coated on the implanted material [9]. These angiogenic properties of bioactive glass are also important for soft tissue regeneration and hence help in healing delayed or non-healing wounds which are vascular-deficient in diabetic patients [10]. Silicate and borate based bioactive glasses have been used in treating bone defects by stimulating gene expression in grafting materials [11].

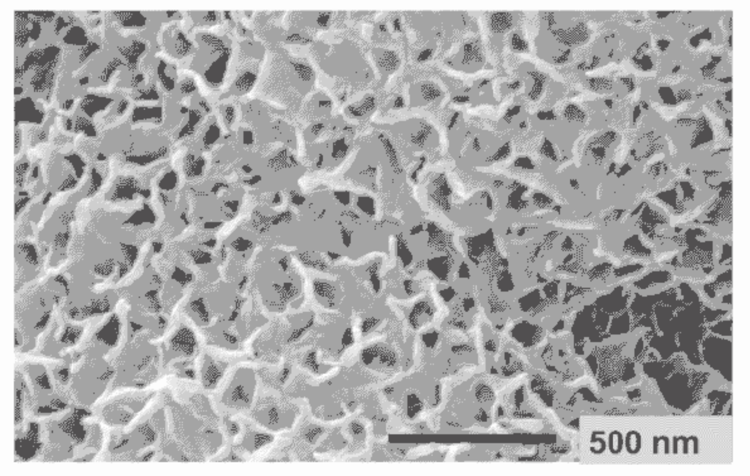


Figure 1.3. SEM image of reacted borate bioactive glass converted to hydroxyapatite (HA) in vivo [8]

Borate based bioactive glasses have controllable degradation rates by replacing the SiO_2 in silicate 45S5 or 13-93 glass with B_2O_3. This borate based bioactive glass serves as the main structural material for all the devices in the present experiments. The advantages of the slow reacting silicate bioactive glass and the fast reacting borate glasses can be combined to produce a two layered composite glass having two different dissolution rates. Since bioactive glasses exhibit high electrical resistivity ($\geq 10^{10}$ Ω·cm) it is possible for direct use as the substrate and packaging material.

1.6. INSULATION, PASSIVATION AND ENCAPSULATION

Silicon oxides are key materials for dielectrics and encapsulation layers in a class of silicon-based electronics that has the ability to completely dissolve in a controlled fashion with programmable rates, when submerged in bio-fluids and/or relevant solutions [12]. The kinetics of hydrolysis of these materials depends on pH levels/ion concentrations of solutions and temperatures, morphology and chemistry of films [12]. The end product is silicic acid, which is biocompatible and environmentally benign at low concentrations. Thus silicon oxide is the right fit and has been used as an insulation layer between the glass surface and the device area.

2. EXPERIMENTS

2.1. SUBSTRATE PREPARATION

2.1.1. Glass Rod Preparation. Bioactive borate glass is prepared by melting sodium tetraborate ($Na_2B_4O_7$) in a platinum crucible for 45 minutes at 1000˚ C, stirred every fifteen minutes using a pure silica rod, and poured into stainless steel cylindrical molds, annealed at 450˚ C for 30 minutes and then cooled slowly (furnace normal cooling rate) to room temperature to form a cylindrical glass rod approximately 1.5 cm diameter and 3cm length. Table 2.1 shows the borate glass composition used in this study.

Table 2.1. Glass Composition

Component	Wt %	Mol %
B_2O_3	69.2	66.7
Na_2O	30.8	33.3

2.1.2. Wafer Preparation. Circular bioactive borate glass wafers approximately 3-4 mm thick were prepared by slicing cylindrical glass rod using a low speed saw (Isomet, Buehler). The glass wafers were cleaned using acetone and then mounted on aluminum holders using a thermo plastic product, Brewerbond 220 (Brewer Science, Rolla, MO).The top surface of the aluminum holder is covered with a thin coating of Brewerbond 220. It was heated on a hot plate at 80^o C for 10 minutes, 130^o C for 10 minutes and at 200^o C for 2 hours followed by cooling. Once it reached room temperature, it was then again heated to 130^{o} C and the glass wafer was placed on top and slightly pressed followed by cooling. The bonding between the glass wafer and the aluminum holder was very strong at room temperature.

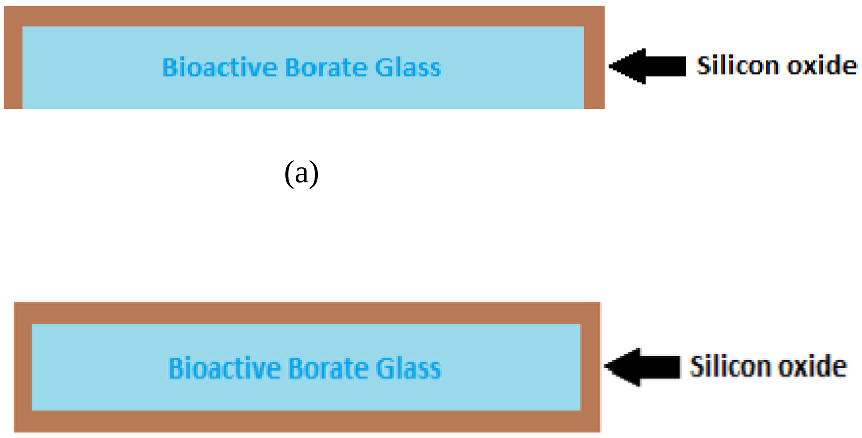
The next step was polishing and grinding with automatic polisher (Tegramin30, Struers). Table 2.2 shows the process steps of grinding and polishing conducted in this study. First step was to bring the top surface of all the mounted glass wafers to a level for which grinding is done using a SiC foil of grit size of 76 µm for 30 seconds using 50 N force. Similarly the remaining polishing steps are carried out down to the grit size of 12 micron as mentioned in the table. After the 12 micron step, alcohol based diamond polish is used to further bring down the surface roughness. The samples were polished using 3 micron diamond suspension for 3 minutes at using 50 N force. After 3 micron step the samples were polished using 1 micron diamond polish suspension keeping all the other parameters same and in the last step a diamond polish suspension of quarter micron is used keeping rest of the parameters same. The wafers are then demounted by heating the aluminum holders to a temperature of 130^{o} C and sliding the wafers off the holders. The wafers are then cleaned ultrasonically in 1-Dodecene for about 15 minutes, followed by one more ultrasonication step in isopropanol for 15 minutes. They are then sprayed with isopropanol and then blown dried using high purity nitrogen gas. The entire process mentioned above was repeated on the other face of the glass wafers. The final wafers after the last step were approximately 1-2 mm thick with a highly reflective surface.

Table 2.2. Polishing Steps

Step No.	**Grit Size (µm)**	**Polishing Agent**	**Force (N)**	**Time**
1	76	SiC foil	50	30 seconds
2	32.5~36	SiC foil	50	10 seconds
3	16.7~19.7	SiC foil	50	1 min
4	4.5~6.5	SiC foil	50	1 min
5	3	Diamond Suspension	50	3 min
6	1	Diamond Suspension	50	3 min
7	.25	Diamond Suspension	50	3 min

2.2. DEVICE PREPARATION

2.2.1. Thin Film Deposition. Bioactive borate glass wafers were coated with silicon oxide using two different processes. The first being physical vapor deposition (PVD) by RF sputtering and the other being plasma enhanced chemical vapor deposition (CVD) to form single side coated wafers and double side coated wafers. Figure 2.1 represents the conceptual structure of the single side and double side coated wafers. The thickness and refractive index of the silicon oxide film deposited were measured using various instruments including the profilometer, interferometer and ellipsometer.



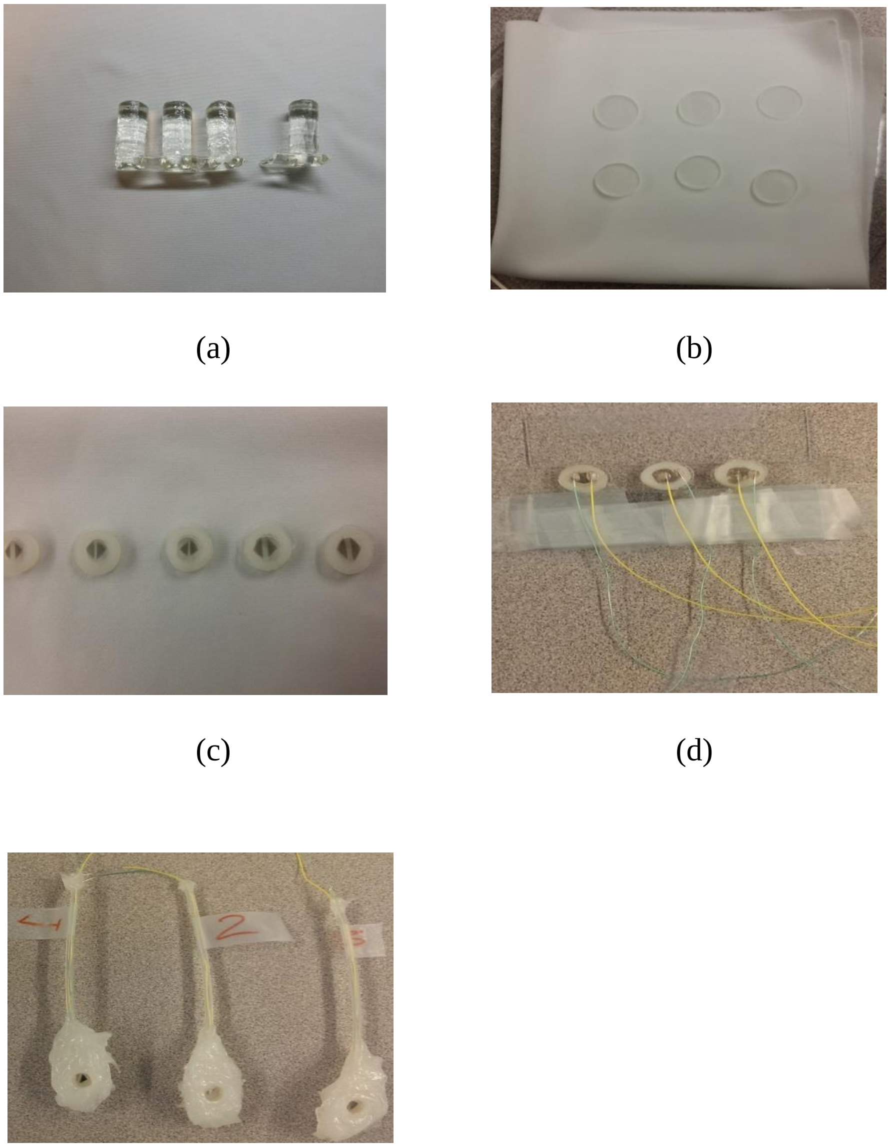
(a)

(b)

Figure 2.1. Conceptual representation of coated wafers. (a) Single side coated bioactive borate glass wafer (b) Double side coated bioactive borate glass wafer

Gold-palladium (1:1) thin film electrodes, 1mm apart, were sputtered on top of the silicon oxide using a silicone shadow mask with a flash coater (Hummer VI). Thickness of gold-palladium layer is approximately 50-100 angstrom. Single stranded wires of 30 AWG are then soldered to these contacts using silver paste.

2.2.2. Packaging. To provide an equal exposed area to the solution in all the devices a nylon washer (inner diameter 90 mm) was glued to the wafer bottom surface of the device where no electrodes were formed using silicone paste. This silicone formed a reliable water resistant bond with the wafer after curing. To prevent the wires from contacting water, they were encapsulated in a plastic tube which was then sealed on the top using silicone. Everywhere except the region defined inside the washer is coated with silicone paste including the junction between the tube and the wafer. The device was then left for four hours for the silicone to cure. If any holes or uncoated areas were observed after curing then an additional layer of silicone was applied and then cured. Figure 2.2 shows the various steps involved in the building device. For all the in-vivo operations in future slow dissolving glass will be used for encapsulation instead of silicone and there will be no nylon washer involved.



(a) (b)

(c) (d)

(e)

Figure 2.2. Device building. (a) Bioactive glass rods, (b) Bioactive Glass Wafers (c) Sputtered electrodes (d) Wires soldered to the electrodes, (e) Completed devices.

2.3. INSTRUMENTATION

2.3.1. Thermal Analysis of Bioactive Borate Glass. Differential thermal analysis (DTA) of bioactive borate glass is done using DTA7 PerkinElmer. The temperature was ramped at 10^{o} C per minute.

2.3.2. Surface Roughness of Bioactive Borate Glass. To determine the surface roughness of the final wafers after the grinding and polishing steps, an atomic force microscope (Nanoscope IIIa, Digital Instruments) was used. For each of the three samples, images of their surface at different magnifications were captured. Surface areas covered were100 μm^2 and 1 μm^2. 3D images of their surfaces were also recorded.

2.3.3. Dissolution Rate Measurement. The initial weight of bare bioactive glass wafers (no silicon oxide deposition), wafers coated on one side with silicon oxide and wafers completely coated with silicone oxide was measured using a balance (Analytical Balance AE240, Mettler). Each wafer was immersed in 1 L of SBF and weight loss measurements were taken every six hours till the glass wafer becomes completely dissolved. The SBF was stirred once every two hours. The containers with the wafers and the SBF were placed in an incubator (Heratherm IGS 100, Fischer Scientific) maintained at 37^{o} C during the test.

2.3.4. Optical Analysis of Surface. To observe the physical stability of silicon oxide film in SBF with time, three single side coated bioactive borate glass wafers were immersed in 50 ml SBF and one was used for as a reference and was stored as is. Sample 1 was stored as is, sample 2 was immersed in SBF for 3 hours, sample 3 was immersed in SBF for 6 hours and sample 4 was kept immersed in SBF for 12 hours. The surface of the glass samples was analyzed and recorded using an optical microscope (Hirox digital microscope KH-8700).

2.3.5. Elemental Analysis. The elemental composition of the surface of these samples was analyzed using x-ray photoelectron spectroscopy (Kratos Axis 165). Monochromatic Al X-Ray source (1486.6 eV) was used to excite the surface, and the standard slot was 700x300 microns (analysis area). On each sample three different locations was analyzed.

The elemental composition of the silicon oxide particles present in the SBF solution was studied using energy dispersive spectroscopy. Helios Nanolab 600 microscope, which was equipped with an Oxford X-Max EDS detector was used for this purpose. The solution was filtered using a nylon mesh of pore size of 0.45µm. Oxford INCA software was used for EDS. An accelerating voltage of 5 kV and a current of 0.17 nA was used. 20 seconds of live time was used for spectrum collection at a working distance of 5 mm. The nylon meshes were sputtered with gold palladium and three different locations was analyzed on each of them.

2.3.6. Elemental Analysis of Solution. The concentration of silicon oxide was measured in the respective SBF solutions to study the dissolution behavior of silicon oxide. This was determined with the help of inductively coupled plasma optical emission spectroscopy analysis (optima 2000 ICP-OES). The concentration of silicon oxide dissolved in SBF at different time intervals was determined. The solution was filtered using 0.22 µm nylon mesh prior to any measurements and was then diluted 10 times with 1% HNO_3. Wavelength used in this process was 251.611 nm. The instrument detection limit (IDL) was 0.1 ppm and method detection limit was 1 ppm.

2.3.7. Impedance Monitoring. For the impedance monitoring of devices, three devices at a time were immersed in a jar filled with 3 L of SBF constantly stirring at 50 rpm kept inside the incubator at 37 ^{o}C. Impedance monitoring was done using an electrochemical measurement system (PC4/750, Gamry). All the measurements were taken at 1.0 kHz. Readings were initially taken every 15 minutes for first two hours and then every two hours till the device dissolved.

3. RESULTS AND DISCUSSION

3.1. THERMAL ANALYSIS OF BIOACTIVE BORATE GLASS

Differential thermal analysis (DTA) of bioactive borate glass is done using DTA7 PerkinElmer. Figure 3.1 represents the results of the differential thermal analysis. The temperature is ramped at 10^{o} C per minute. DTA yields the following results, glass transition temp is 470^{o} C, glass crystallization temp is 597^{o} C and glass melting temp is 734^{o} C respectively. This implies that any additional device preparation process on the wafers should be done below the glass transition temperature. Otherwise, the softening of wafer is not acceptable to build the device structure.

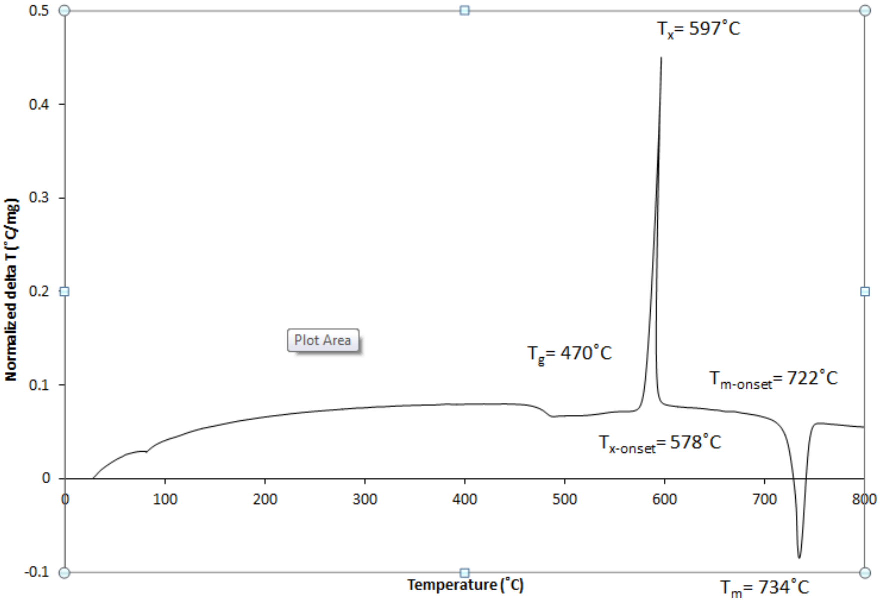
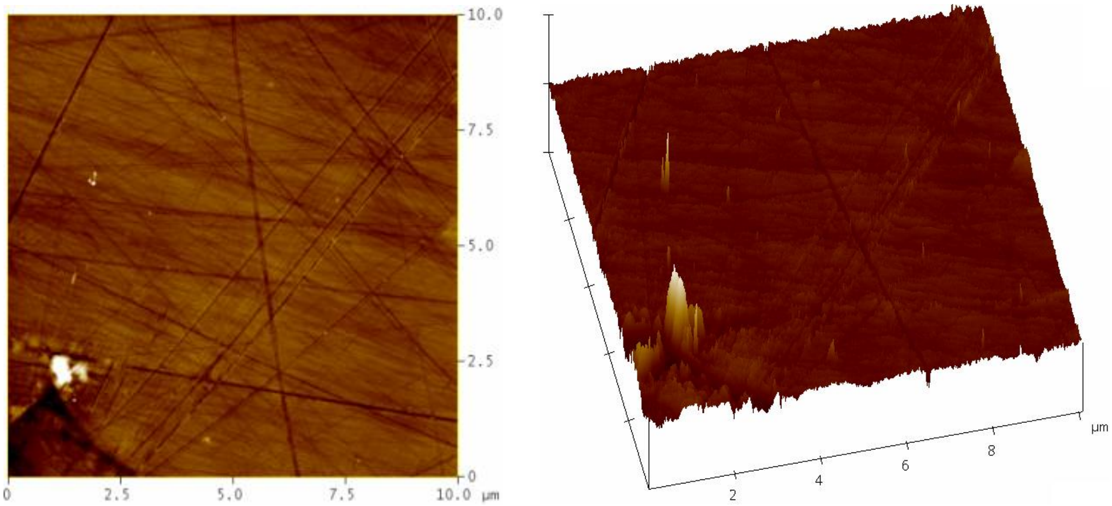


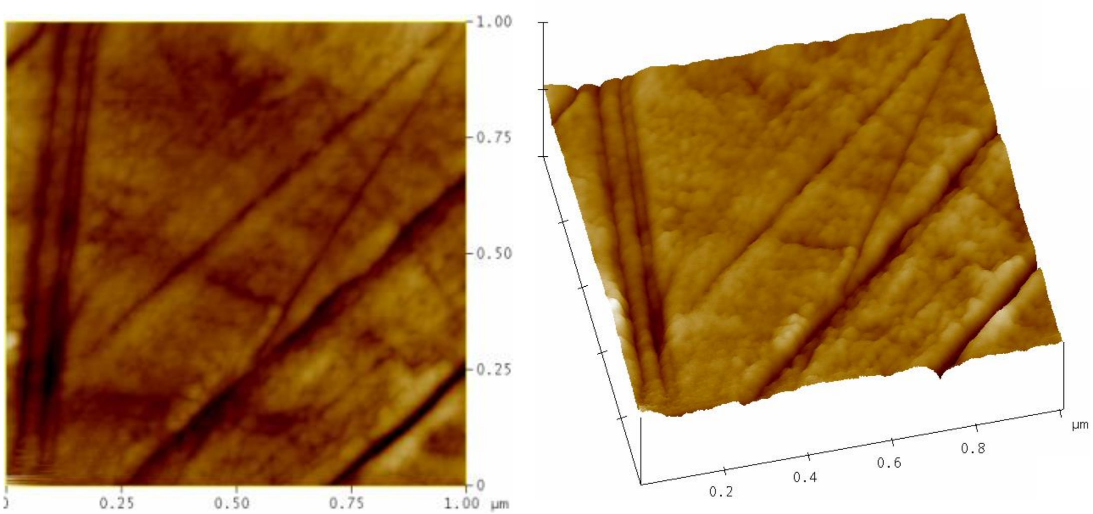
Figure 3.1. Differential thermal analysis of sodium tetraborate (T_g=glass transition temp, T_x=crystallization temp, T_m=melting temp).

3.2. SURFACE ROUGHNESS OF BIOACTIVE BORATE GLASS

Figure 3.2 shows the representative pictures of the surface of three different wafers including 2D and 3D images. Images of the polished surface of each sample at two different magnifications are shown. Surface areas covered were 100 μm^2 and 1 μm^2. Mean maximum peak to peak roughness of surface of each wafer is recorded in Table 3.1. Some areas of the wafer surface have higher surface roughness as seen in the 3D images (about 2 micron) and have not been recorded in Table 3.1 as it represented only a small portion of the overall surface area of the wafer. The mean maximum roughness values in Table 3.1 are less than half of the thickness of the silicon oxide film deposition done in the experiments (0.3 μm for PVD and 1.0 μm for CVD). This is expected be thick enough to cover except some highly rough local regions most of the bioactive glass wafer surface. The refractive indices (at 5459 Å) of thin film silicon dioxide films grown in steam and/or dry oxygen (atmosphere pressure) at 980° to 1200°C varied from 1.4610 to 1.4624 for 3500- to 6800-Å films [13]. The refractive index of the deposited oxide film using PVD was 1.484 and the one deposited using CVD had a refractive index of 1.480.

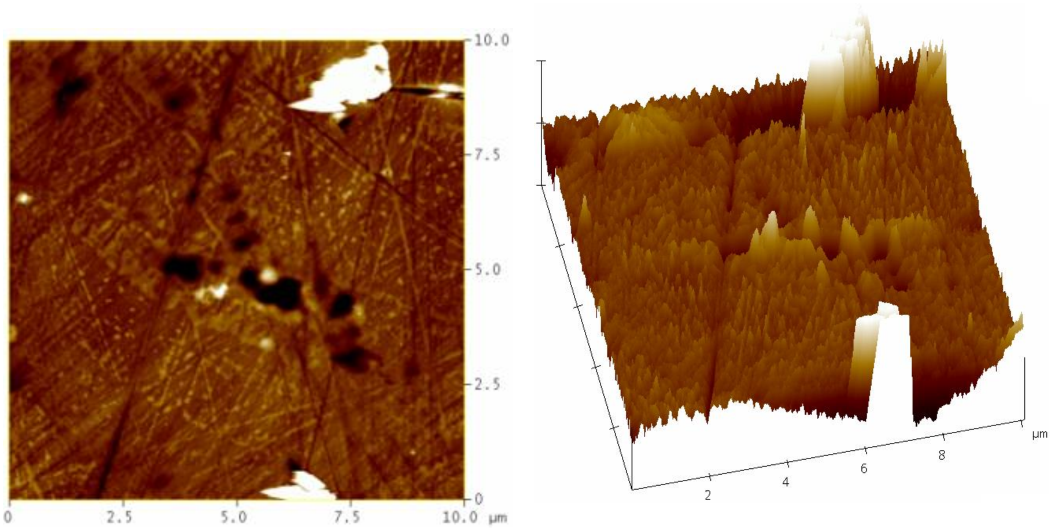


Sample1(a)

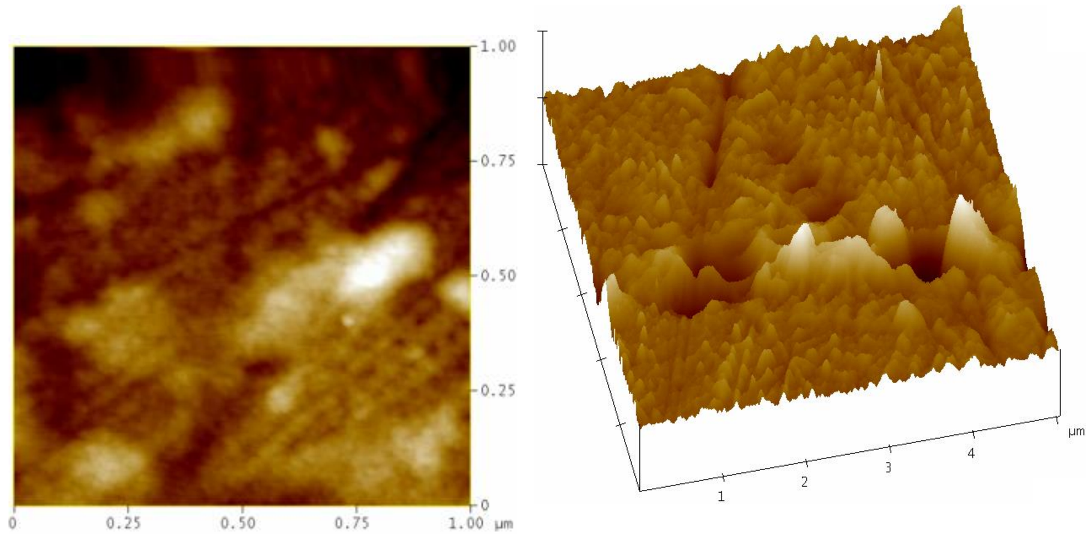


Sample1 (b)

Figure 3.2. AFM images of the surface of three bioactive glass wafers, sample1-3 with lower and higher magnifications (left - 2D image, right - 3D image)

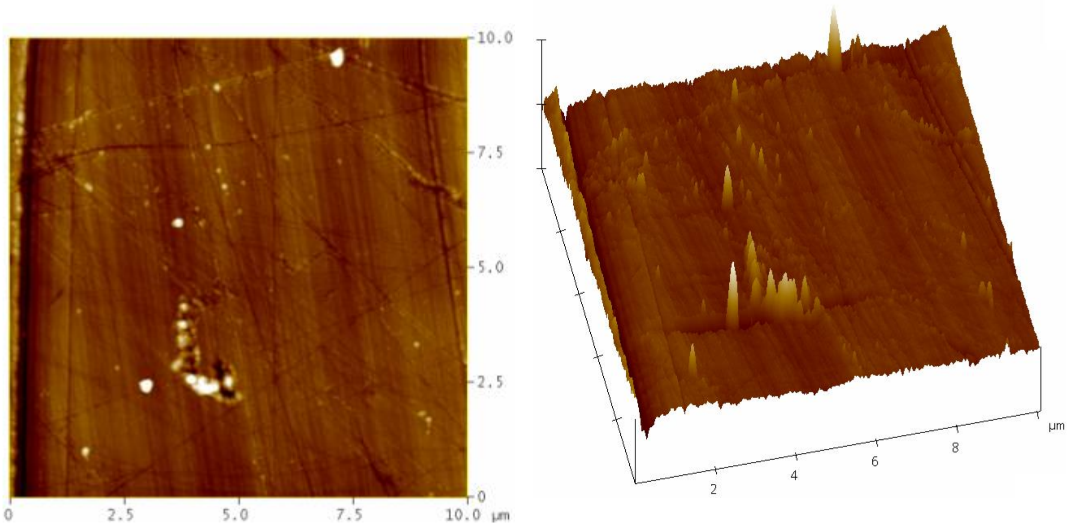


Sample2 (a)

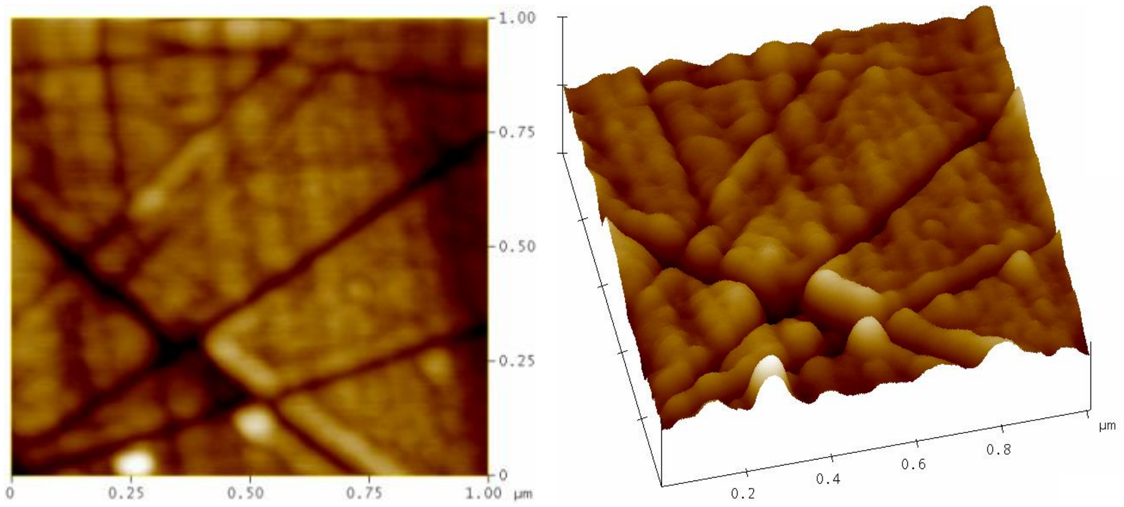


Sample2 (b)

Figure 3.2. AFM images of the surface of three bioactive glass wafers, sample 1-3 with lower and higher magnifications (left - 2D image, right - 3D image) (cont.)



Sample3 (a)



Sample 3 (b)

Figure 3.2. AFM images of the surface of three bioactive glass wafers, sample1-3 with lower and higher magnifications (left - 2D image, right - 3D image) (cont.)

Table 3.1. Mean maximum peak-to-peak roughness of borate glass wafers surface

Sample Number	Roughness (μm)
1	0.086
2	0.126
3	0.095
Mean / standard deviation	0.102 / 0.0210

3.3. CHARACTERIZATION OF SILICON OXIDE FILM

Table 3.2 represents the thickness of silicon oxide deposited using PVD and CVD. To determine the thickness of silicon oxide coating, three silicon wafer pieces as monitor were placed with the borate glass wafers during deposition. A portion of the top surface of these samples was masked to create a step. The height of the step size was measured using three instruments including the profilometer, interferometer and ellipsometer and the value came out to be approximately 0.29 micron for PVD. Similar steps were repeated for measuring the thickness of silicon oxide coating deposited using CVD. The thickness of CVD coating came out to be 0.99 micron. Normally refractive index for SiO_2 films deposited on glass substrates at a sputtering pressure of $6x10^{-3}$ is 1.453 ± 0.003 ($Ar:O_2$ is 9:1) [14], while that of SiO_2 films prepared by plasma enhanced chemical vapor deposition is approximately 1.51 (N_2O/SiH_4=20) [15]. The value of refractive indices reported in Table 3.3 is close to the respective standard values and thus indicate a good quality films.

Table 3.2. Thickness of silicon oxide deposited using PVD and CVD

	Instruments	**Profilometer (μm)**	**Interferometer (μm)**	**Ellipsometer (μm)**
PVD	Average (n=3)	0.2760	0.2915	0.2887
	Standard deviation	0.0272	0.0068	0.0068
CVD	Average (n=2)	-	-	0.9915
	Standard deviation	-	-	0.0137

Table 3.3. Refractive indices of the silicon oxide films

R.I.	**PVD (n=3)**	**CVD (n=3)**
Average	1.484	1.479
S.D.	0.007	0.001

3.4. DISSOLUTION BEHAVIOR OF WAFERS

The solubility of sodium tetraborate is 1.49 gms and 8.79 gms per 100 ml in cold and hot water respectively [16]. Thus the amount of SBF used in all the experiments is more than enough to completely dissolve the glass wafers.

The solubility of silica is relatively independent except when the amount of solid silica in the suspension except when its less than 0.1 %[17]. The solubility of silica in water at a pH of 7.4 (adjusted using NaOH) was approximately 0.01%[17]. Four main factors which affect the dissolution rate of silicon oxide are: temperature, pH, ionic content of the solutions and chemical /morphological properties of the films [2]. The dissolution rate is also dependent on film density [2]. Reduce density can enhance the ability of aqueous solutions to diffuse into the material, thereby to accelerate the hydrolysis reaction by increasing the reactive surface area [18,19,20]. Thus depending on the application the silicon oxide layer can be made to stay or to be gone after the desired time. In the experiments covered in the thesis it should stay for much longer period than the sodium tetraborate.

3.4.1. Dissolution Rate Measurement. Figure 3.3 shows the results for the dissolution rate measurement tests of bioactive glass without silicon oxide coating and its mean dissolution rates and their standard deviation are recorded in Table 3.4. Figure 3.4 shows the results for the dissolution rate measurement tests of bioactive glass with single side coating (PVD) and its mean dissolution rates and their standard deviation are recorded in Table 3.5. Figure 3.5 shows the results for the dissolution rate measurement tests of bioactive glass with double side coating (PVD) and its mean dissolution rates and their standard deviation are recorded in Table 3.6. Figure 3.6 shows the results for the dissolution rate measurement tests of bioactive glass with single side coating (CVD) and its mean dissolution rates and their standard deviation are recorded in Table 3.7. Figure 3.7 shows the results for the dissolution rate measurement tests of bioactive glass with double side coating (CVD) and its mean dissolution rates and their standard deviation are recorded in Table 3.8.The difference in weights of the wafers can be seen in all the figures can be seen and it varies from 0.3 to 0.78 this is because of the manual preparation of the wafers.

Practically, it is challenging to prepare wafer samples with same thickness, same surface roughness due to the manual preparation procedures of slicing and polishing, which causes the initial weight difference between each samples. Although the initial weight is different the dissolution rate is similar approximately same for single side coated wafers (PVD), double side coated wafer (PVD) and for bare glass wafer.

Ideally it is expected that single side coated wafer have about half dissolution rate of that of bare glass wafer as it has approximately half of the exposed area (1.53 cm^2 compared to the surface area of glass wafer 3.06 cm^2). Also double side wafer should have ideally no weight loss in the observed time frame. To determine the possible explanation for unexpected fast dissolution rates of silicon oxide film coated wafers more thorough investigation of the coated wafers during the dissolution in SBF was conducted.

The dissolution rates of coated bioactive glass wafers were almost same as the bare glass wafers because of flaking of the silicon oxide film in first few hours, as we found traces of silicon oxide particles in the material filtered from the SBF solution in which the coated wafer was kept immersed for as short as three hours. The ICP-OES analysis confirms partial dissolution of oxide film, but the film flakes off in first few hours of reaction with SBF which makes the dissolution rates of coated bioactive glass wafers and bare bioactive glass wafers almost equal. The possible reasons for flaking off of silicon oxide film could be the localized highly rough regions and needs to be explored more in future work.

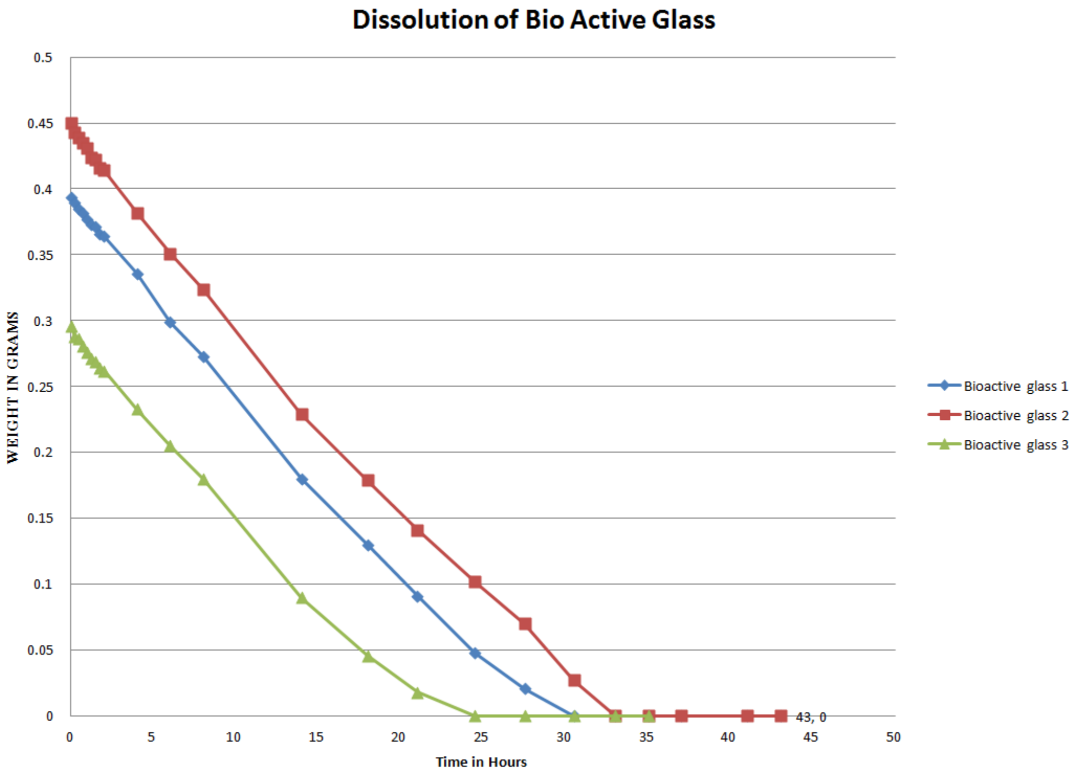


Figure 3.3. Loss in weight with time of bare bioactive borate glass in SBF at 37 ° C

Table 3.4. Dissolution rate of bare bioactive borate glass wafer

Sample no	Mean Dissolution Rate (mg/hr cm^2)
1	5.17
2	5.33
3	4.95
Mean/standard deviation	5.15 / 0.19

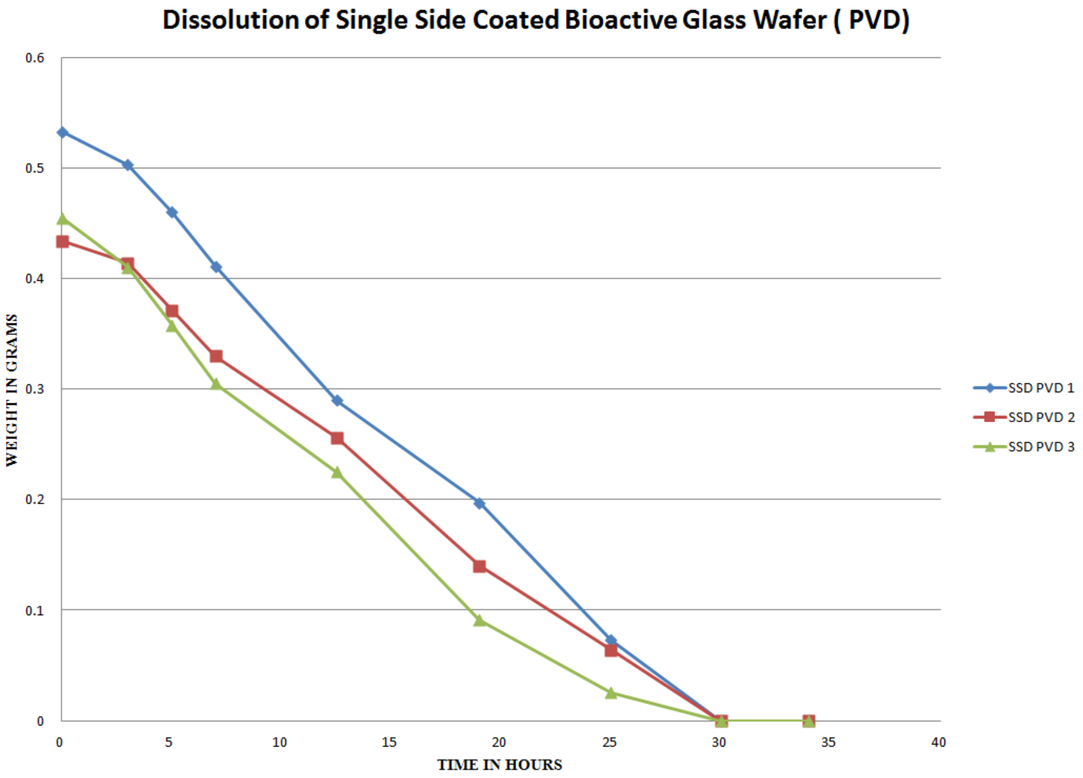


Figure 3.4. Loss in weight with time of single side coated (PVD) bioactive borate glass in SBF at 37 ° C

Table 3.5. Dissolution rate of single side coated (PVD) bioactive borate glass wafer

Sample no	Mean Dissolution Rate (mg/hr cm^2)
1	5.00
2	4.90
3	5.39
Mean/standard deviation	5.09 / 0.25

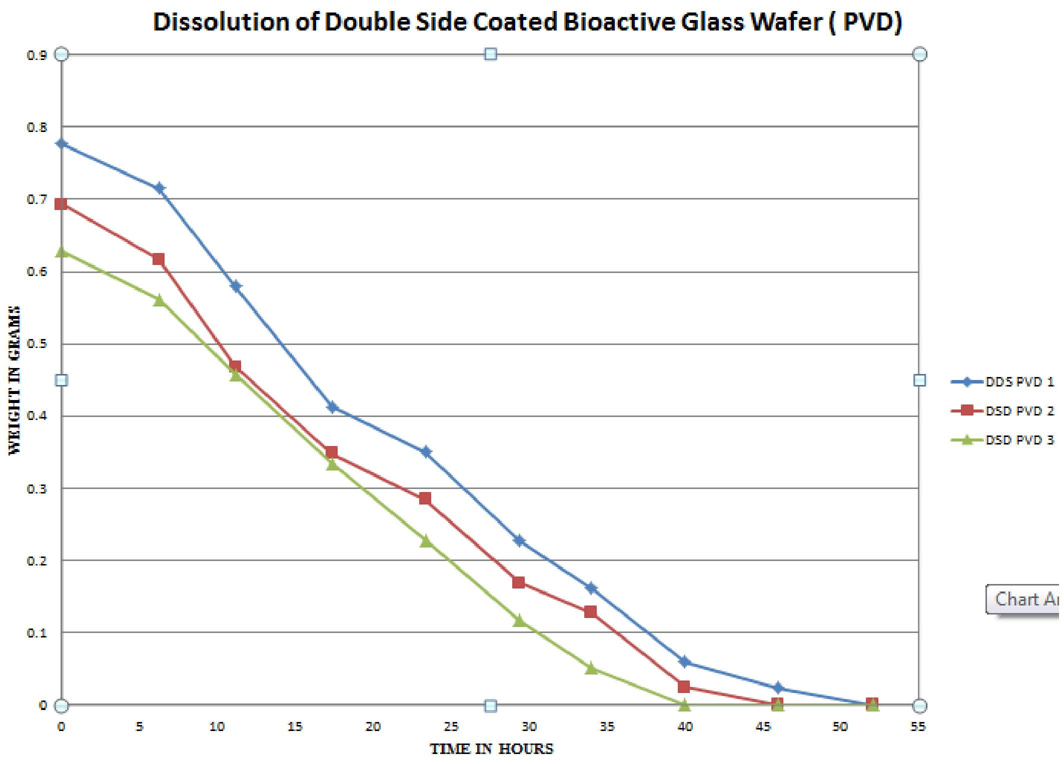


Figure 3.5. Loss in weight with time of double side coated (PVD) bioactive borate glass in SBF at 37 ° C

Table 3.6. Dissolution rate of double side coated (PVD) bioactive borate glass wafer

Sample no	Mean Dissolution Rate (mg/hr cm^2)
1	4.30
2	4.49
3	4.90
Mean/standard deviation	4.56 / 0.30

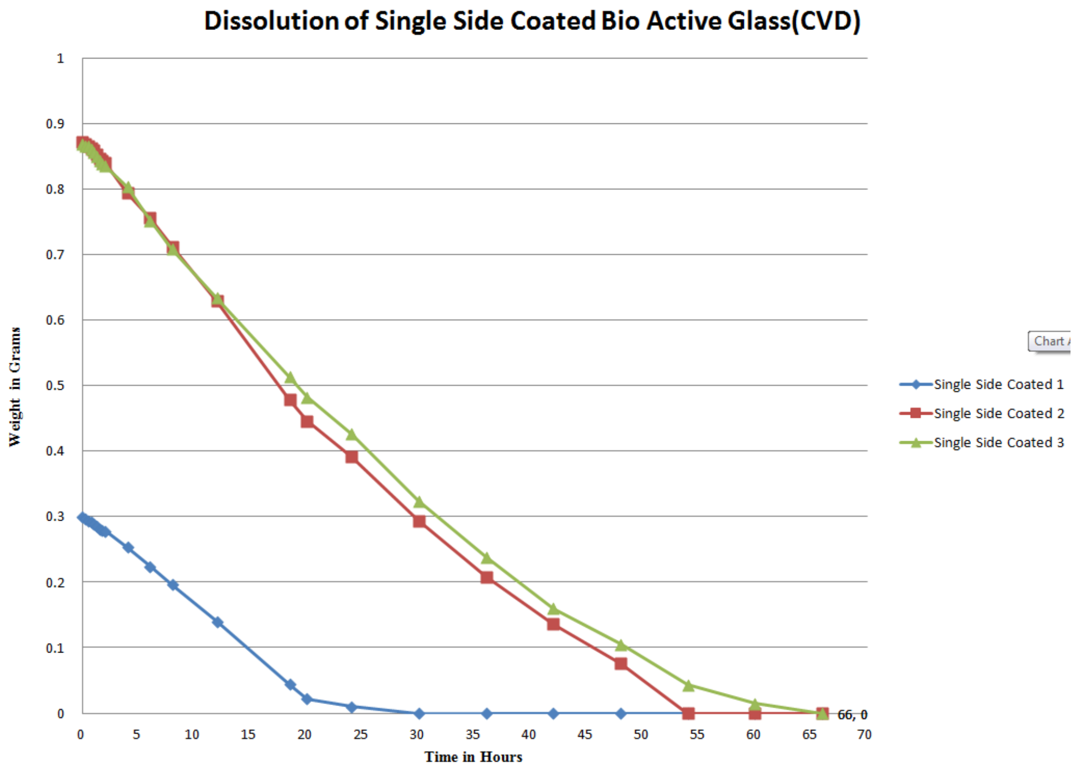


Figure 3.6. Loss in weight with time of single side coated (CVD) bioactive borate glass in SBF at 37 ° C

Table 3.7. Dissolution rate for single side coated (CVD) bioactive borate glass wafer

Sample no	Mean Dissolution Rate (mg/hr cm^2)
1	4.08
2	6.33
3	5.66
Mean/standard deviation	5.35/1.15

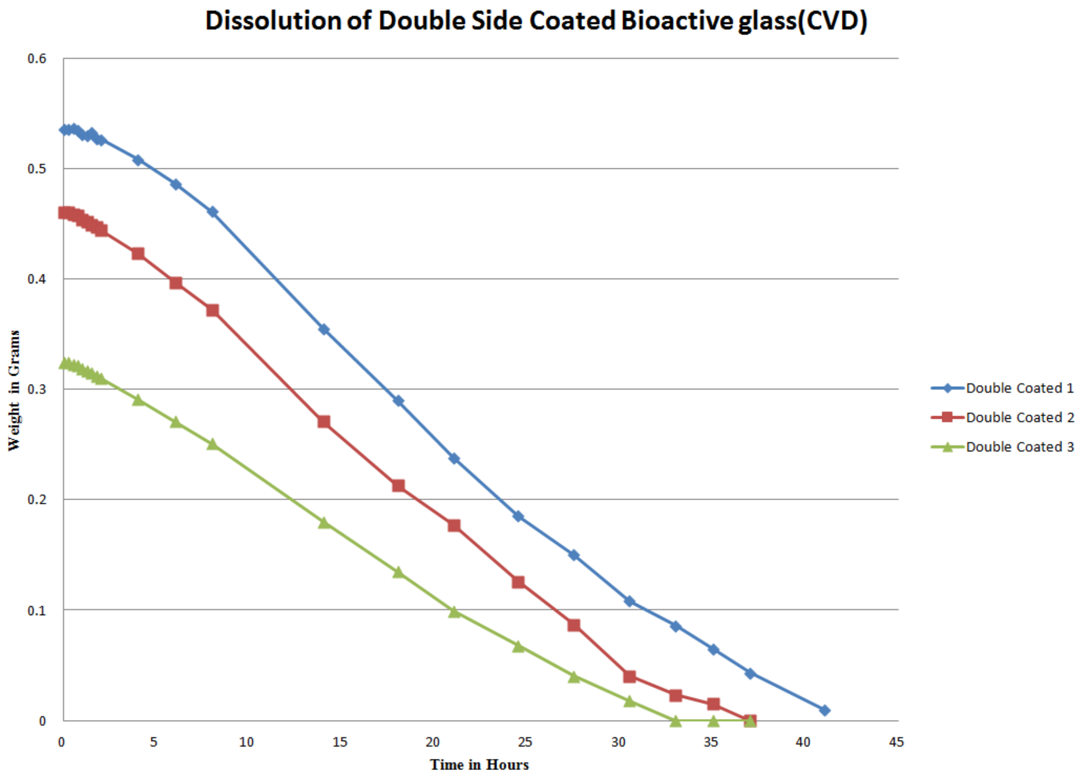


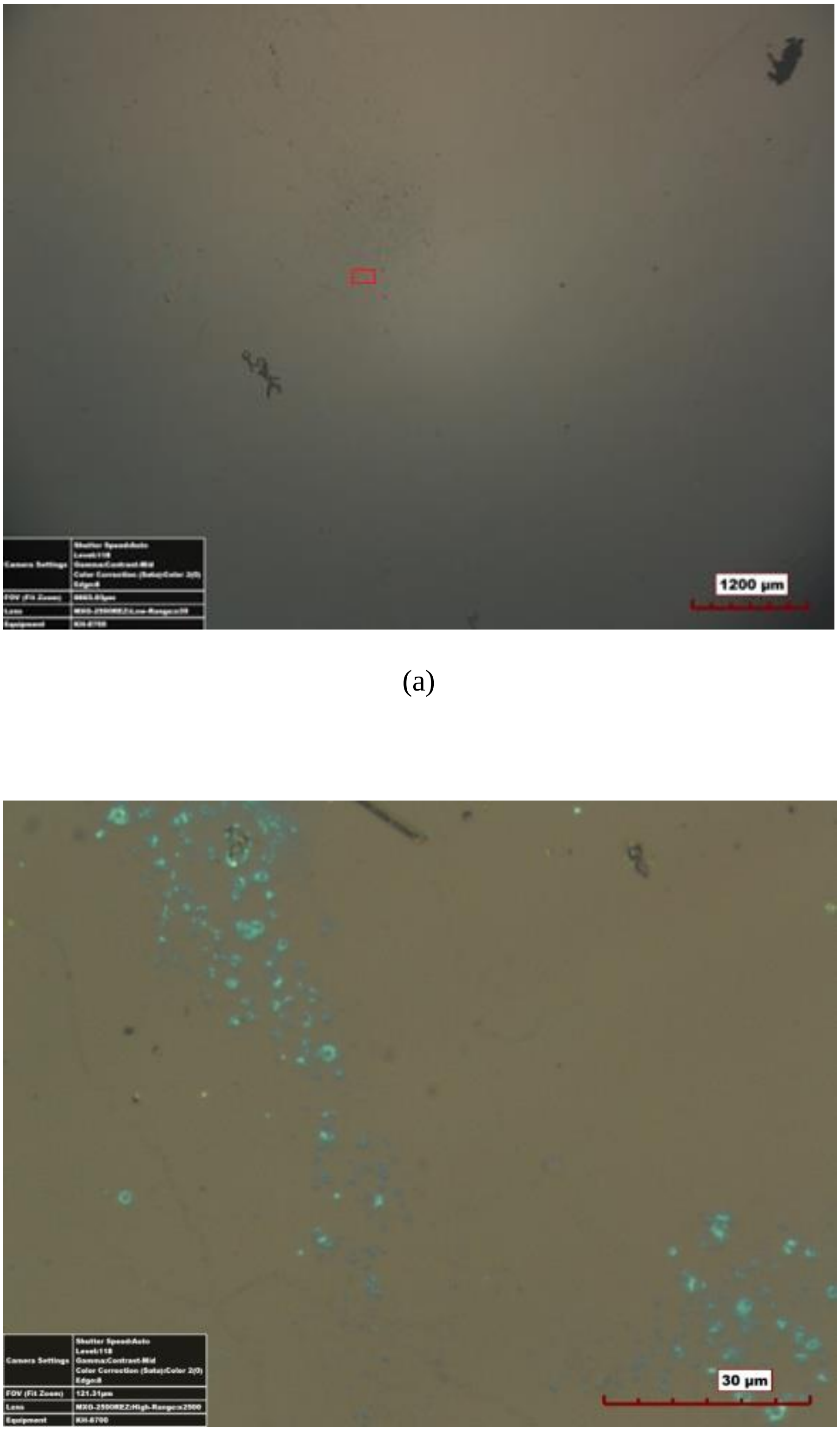
Figure 3.7. Loss in weight with time of double side coated (CVD) bioactive borate glass in SBF at 37 ° C

Table 3.8. Dissolution rate for double side coated (CVD) bioactive borate glass wafer

Sample no	Mean Dissolution Rate (mg/hr cm^2)
1	3.02
2	3.59
3	2.98
Mean/standard deviation	3.19/0.34

3.4.2. Surface Analysis. Pictures of the surface of one reference sample and three bioactive borate glasses after reacting with SBF over 3, 6 and 12 hrs are recorded in Figures 3.8-3.11. As seen in the figure after three hours majority of the silicon oxide coating is disappeared. The silicon oxide film left on the surface has a greenish appearance. After 6 hours most of the oxide coating is disappeared and after 12 hours there rarely any oxide coating is left on the surface.

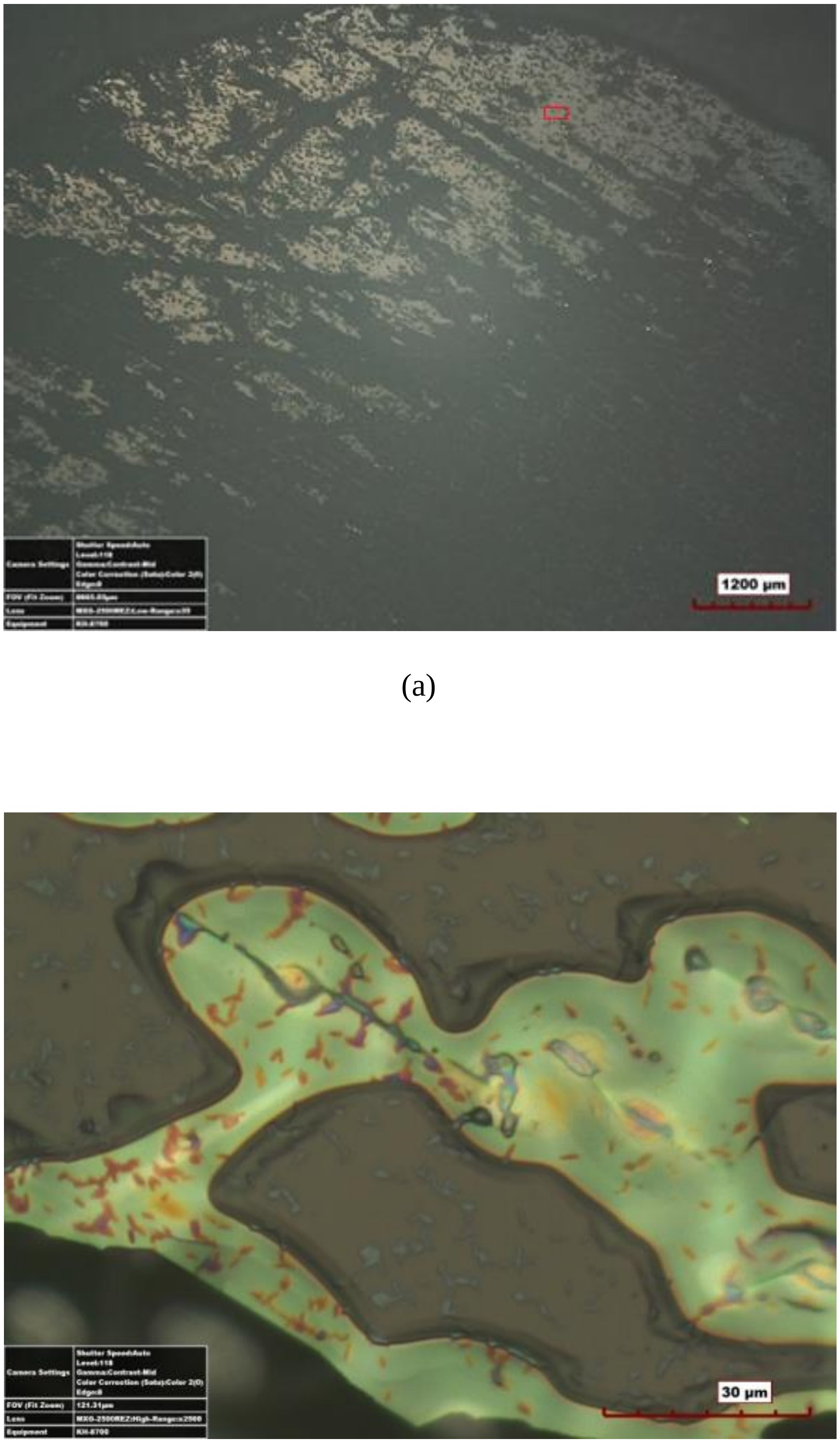
Results of the elemental analysis using energy-dispersive X-ray spectroscopy are recorded in Table 3.9. The results indicate that is a very steep decrease in silicon oxide content on the surface within 3 hours and this percentage keeps on falling down with time. There is negligible amount of silicon oxide if any on the surface after 12 hours. The initial ratio of Si/O is about 0.49, which indicates that the coated film is very close to SiO_2. Constant oxygen amount throughout the table means the emergence of sodium after immersing in SBF. This means that the sodium is exposed and its ratio keeps a steady value as expected from the original composition ($Na_2B_4O_7$). The elements included in the other category are Fluorine, Titanium, Nitrogen, Calcium, Carbon, Chlorine and Boron. The initial atomic concentration of elements in other category is from surface contamination and then its increase in later stage indicates emergence of Boron.



(a)

(b)

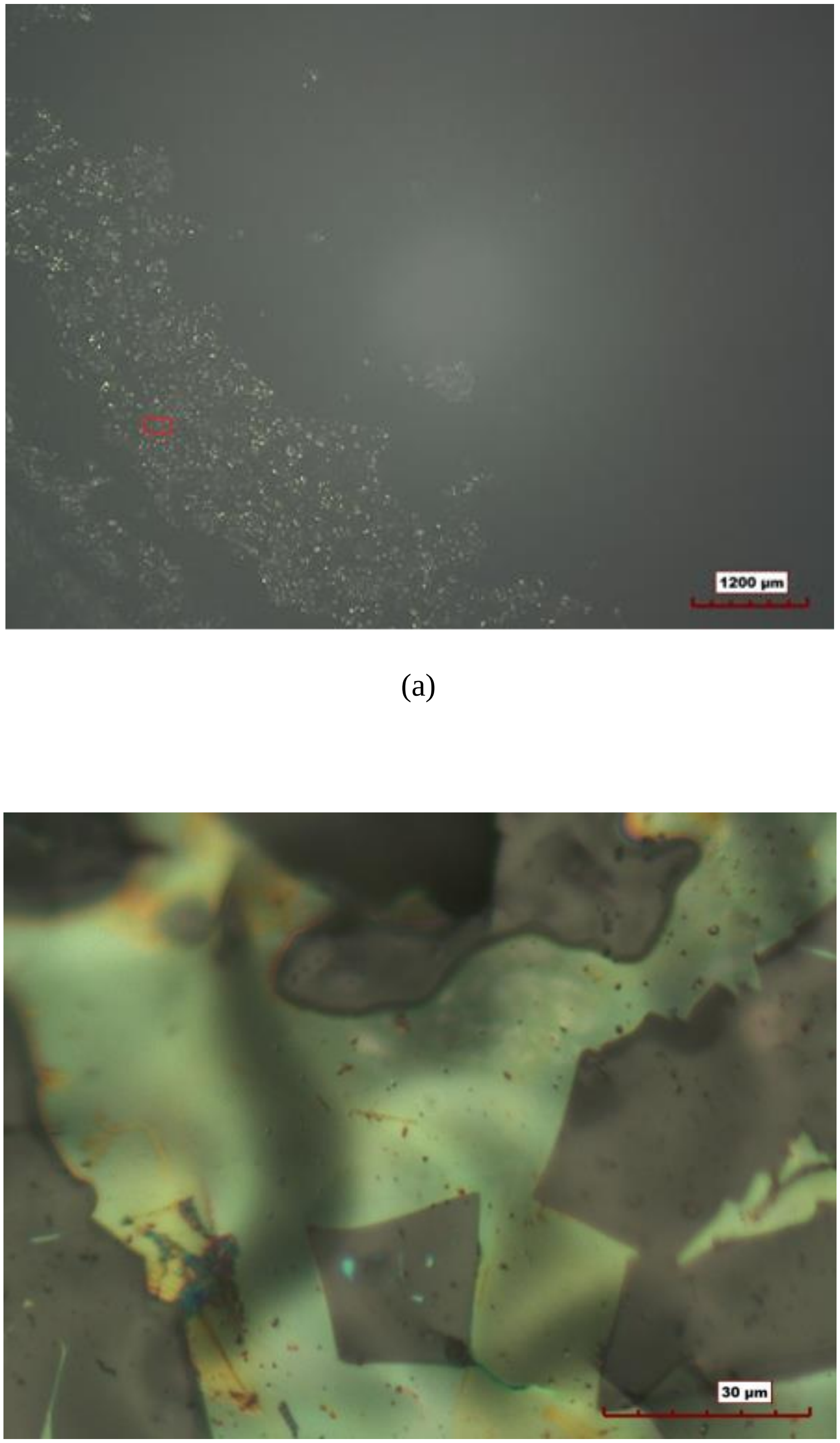
Figure 3.8. Optical microscope image of surface of wafer coated with silicon oxide. (a) Scale: 1200µm (b) Zoomed image of the area marked in Figure a, scale: 30µm



(a)

(b)

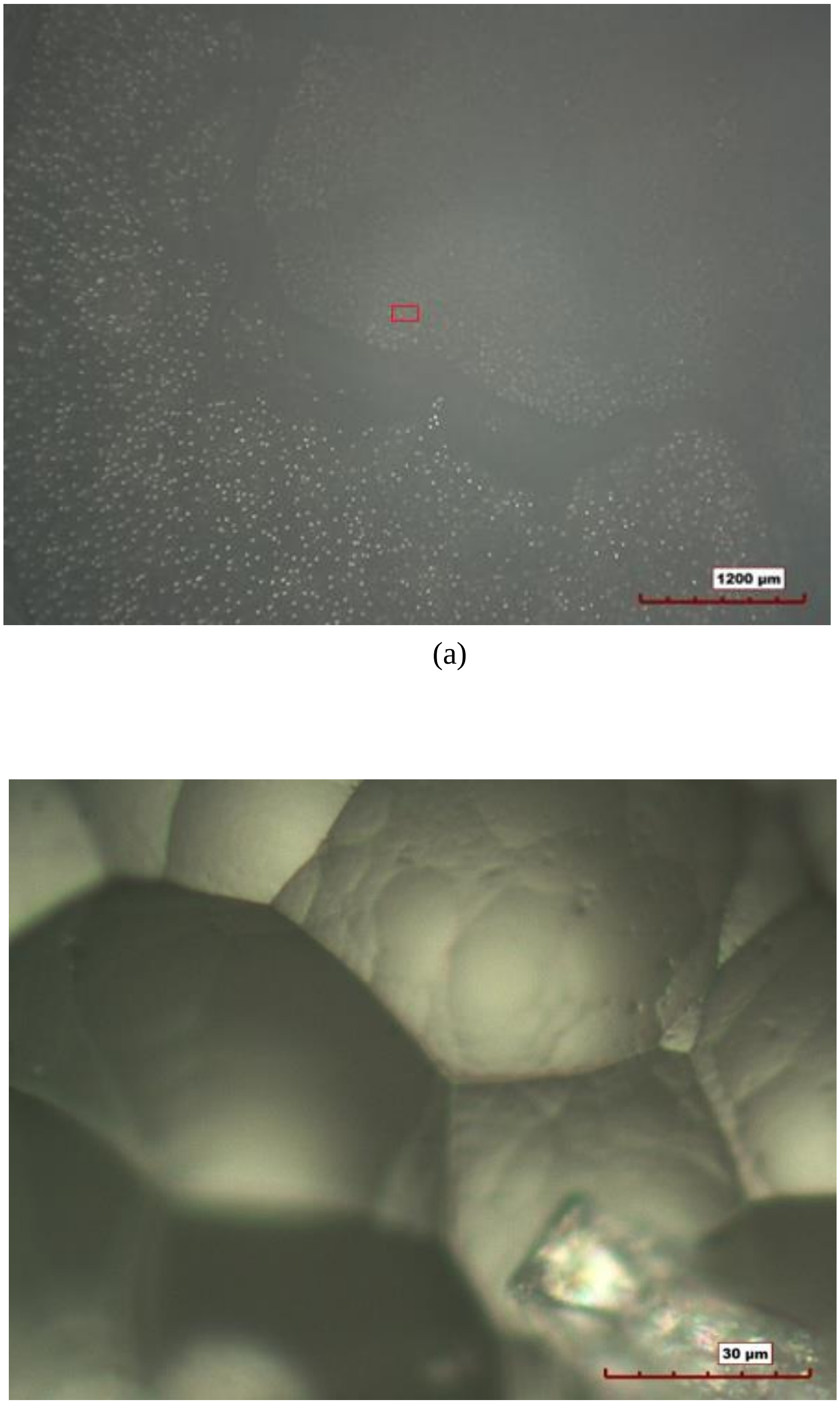
Figure 3.9. Optical microscope image of surface of wafer coated with silicon oxide (PVD) after immersing in SBF for 3 hours. (a) Scale: 1200µm (b) Zoomed image of the area marked in Figure a, scale: 30µm



(a)

(b)

Figure 3.10. Optical microscope image of surface of wafer coated with silicon oxide (PVD) after immersing in SBF for 6 hours. (a) Scale: 1200µm (b) Zoomed image of the area marked in Figure a, scale: 30µm



(a)

(b)

Figure 3.11. Optical microscope image of surface of wafer coated with silicon oxide (PVD) after immersing in SBF for 12 hours. (a) Scale: 1200µm (b) Zoomed image of the area marked in Figure a, scale: 30µm

Table 3.9. Variation in elemental composition of the surface of the silicon oxide coated (PVD) bioactive borate glass wafers over time on reaction with SBF determined using XPS

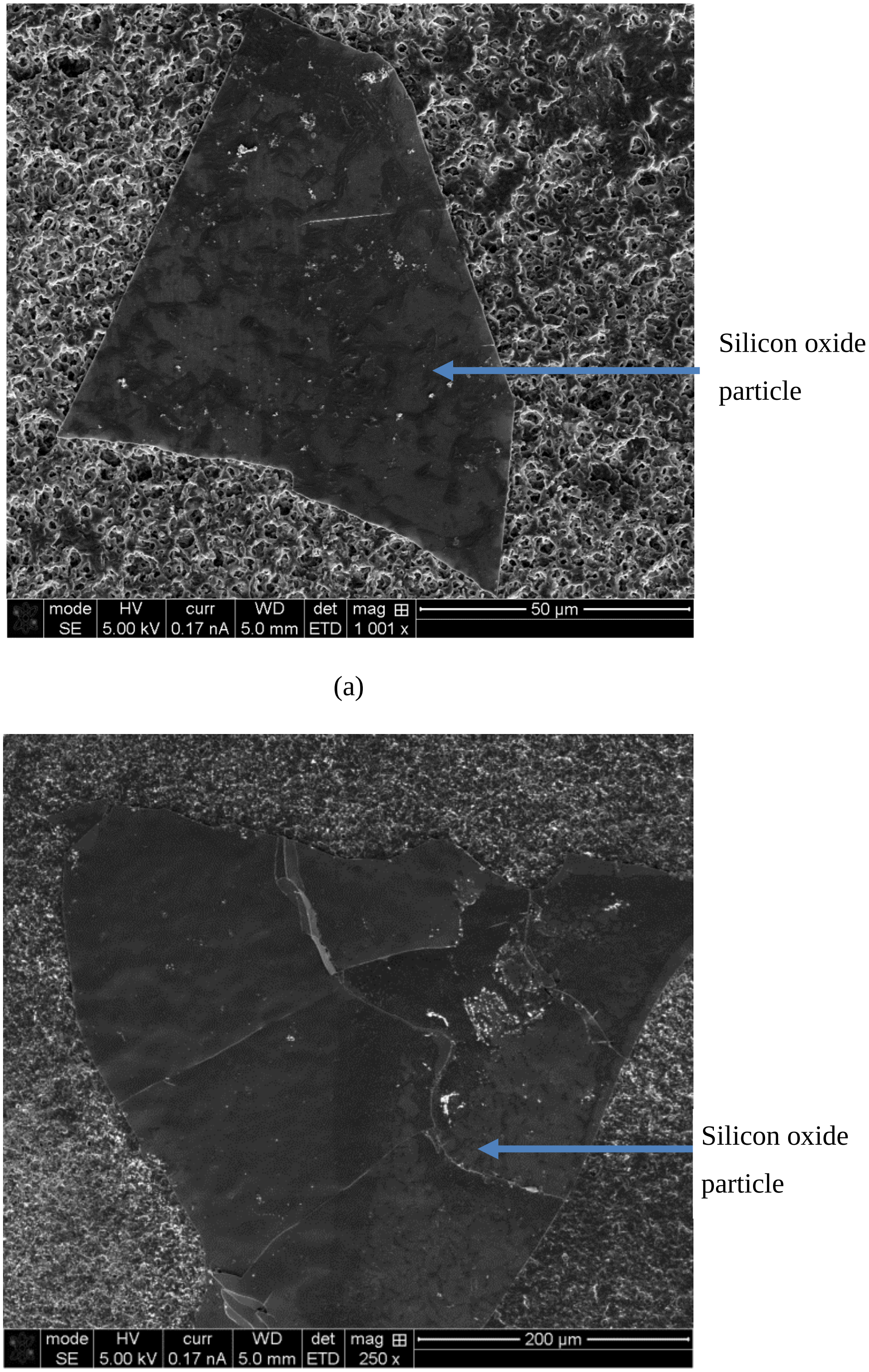
Sample	Location no	Na atomic conc %	O atomic conc %	Si atomic conc %	Others atomic conc%
As is	1	0.00	61.3	29.92	8.71
Immersed in SBF for 3 hrs	1	9.08	48.64	7.50	34.78
	2	13.36	49.05	0.45	37.14
	3	13.82	50.06	0.44	35.68
	Mean/SD	12.08/2.61	49.25/0.73	2.79/4.07	35.86/1.19
Immersed in SBF for 6 hrs	1	8.83	44.24	0.21	35.68
	2	11.81	50.41	0.45	37.33
	3	10.02	50.30	3.44	36.24
	Mean/SD	10.22/1.50	48.31/3.53	1.36/1.79	36.41/0.83
Immersed in SBF for 12 hrs	1	14.62	50.45	0.00	34.94
	2	16.9	49.67	0.00	33.41
	3	17.07	50.28	0.00	32.65
	Mean/SD	16.19/1.36	50.13/0.41	0.00/0.00	33.66/1.16

3.4.3. Solution and Particle Analysis of Silicon Oxide Coating (PVD). The ICP-OES analysis indicates the dissolution trend of silicon oxide in SBF over time. The concentration of silicon oxide in SBF in which no coated glass wafer was dissolved came out to be below the IDL (i.e. negligible amount of silicon oxide concentration). Table 3.10 indicates the concentration of silicon oxide in the solution at different intervals i.e. after 0, 3, 6 and 12 hours. There is an increasing trend in the concentration of silicon oxide in the solution as expected. The values however might have some errors.

Table 3.10. Concentration of silicon oxide (PVD) in the SBF at different time intervals

Time (in hours)	Concentration of silicon oxide (mg/l)
0	0.025 (< IDL)
3	0.98
6	1.19
12	3.61

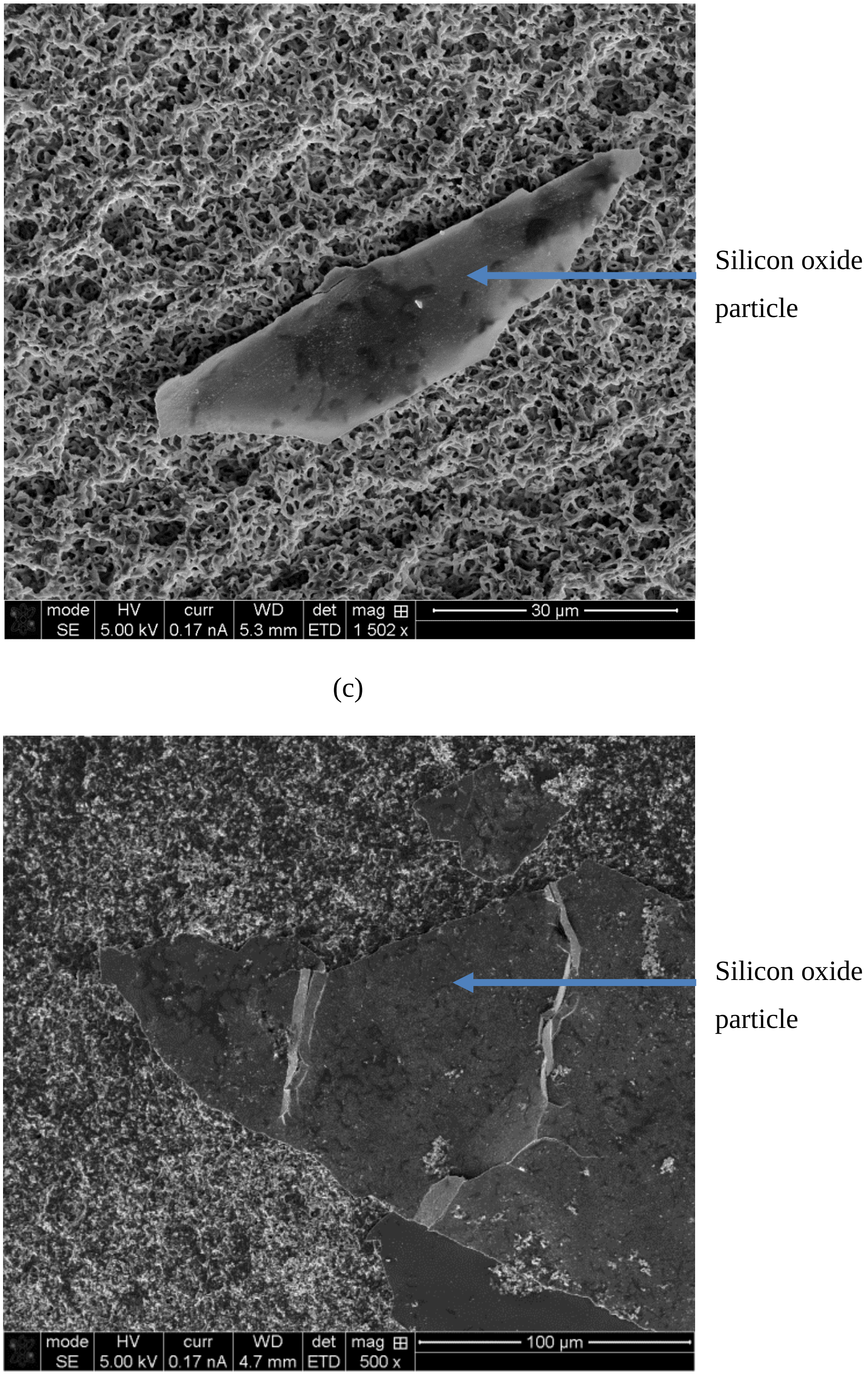
Flaking off of silicon oxide film started in first few hours of immersing the coated glass wafer in SBF as silicon oxide particles were present in the material filtered from all the SBF solutions. Figure 3.12 shows the pictures of the silicon oxide particles filtered from the SBF solution. Table 3.11, 3.12 and 3.13 indicates the elemental composition of the filtered particle from the SBF solutions in which single side coated bioactive borate glass wafers were immersed for 3, 6 and 12 hours, respectively. The other category in the respective tables includes following elements Carbon, Phosphorus, Aluminum and Magnesium.



(a)

(b)

Figure 3.12. Silicon oxide particles in the filtered material



(c)

(d)

Figure 3.12. Silicon oxide particles in the filtered material (cont.)

Table 3.11. Elemental composition of the particle filtered after 3 hours

Spectrum no	Na atomic %	O atomic %	Si atomic %	Other atomic %
1	1.99	61.41	15.20	21.39
2	1.00	65.56	27.6	6.84
3	2.38	61.03	27.31	21.68
Mean/SD	1.79/0.71	62.66/2.51	23.37,7.07	16.63/8.48

Table 3.12. Elemental composition of the particle filtered after 6 hours

Spectrum no	Na atomic %	O atomic %	Si atomic %	Other atomic %
1	1.65	67.52	24.89	5.94
2	2.66	67.88	20.77	8.69
3	0.71	65.33	25.24	8.72
Mean/SD	1.67/0.97	66.91/1.38	23.63/2.48	7.78/1.59

Table 3.13. Elemental composition of the particle filtered after 12 hours

Spectrum no	Na atomic %	O atomic %	Si atomic %	Other atomic %
1	1.61	61.92	36.99	13.21
2	1.55	60.40	19.19	18.86
3	1.63	61.31	22.08	14.98
Mean/SD	1.59/0.04	61.21/0.76	26.08/9.55	15.68/ 2.88

3.5 IMPEDANCE MEASUREMENT

Figure 3.13 shows the results of impedance measurements conducted with microslide glass device of similar size (Pyrex glass, diameter 10 mm and thickness .15 mm) with double side coating. Figure 3.14 and 3.15 shows the results of impedance measurements of bioactive glass devices with single side coating (PVD) and bioactive glass devices with double side coating (PVD). Figure 3.16 represents the operational lifetime of PVD coated bioactive glass wafers. Figures 3.17 and 3.18 shows the results of impedance measurements of bioactive glass devices with single side coating (CVD) and bioactive glass devices with double side coating (CVD). Figure 3.19 represents the operational lifetime of CVD coated bioactive glass wafers. The measurements were taken every 15 minutes for first two hours and then were taken every two hours till the device dissolves. The majority of microslide glass devices used as the reference devices for comparison showed stable behavior with their impedance readings being in the range of approximately 80 % of their initial impedance (approximately 30 mega ohms). None of the devices ever exhibited impedance below 40 % of their initial value (they never failed like other borate based devices whose impedance will fall down to a few hundred ohms when shorted).

The single side coated (PVD) bioactive glass devices show stable behavior for a length for approximately 15 hours with impedance readings being in the range of approximately 80 % of their initial impedance (20-23 mega ohms), mean being 13.5 hours and standard deviation being 4.44 . More stable behavior of the bioactive glass devices with double side coatings was observed for a length for average 24.6 hours maintaining 80% of the original impedance readings. It exhibited, however, a relatively large dispersion (mean = 21.16 hours, standard deviation = 10.94). The single side coated (CVD) bioactive glass devices show stable behavior for a length for approximately 7.2 hours with impedance readings being in the range of approximately 80 % of their initial impedance (20-28 mega ohms), mean being 18 mega ohms and standard deviation being 1.54919. More stable behavior of the bioactive glass devices with double side coatings was observed for a length for average 19.8 hours maintaining 80% of the original impedance (23-35) readings with mean being 21 mega ohms and standard deviation being 6.84.

It is considered that the large deviation of the initial stable period mainly comes from the difference of original weight of each glass wafers. The double side coated devices have a longer stable performance because of an additional silicon oxide film in the bottom. It appears that the silicon oxide layer delays breakdown by many hours and this adds to the increased initial stable time.

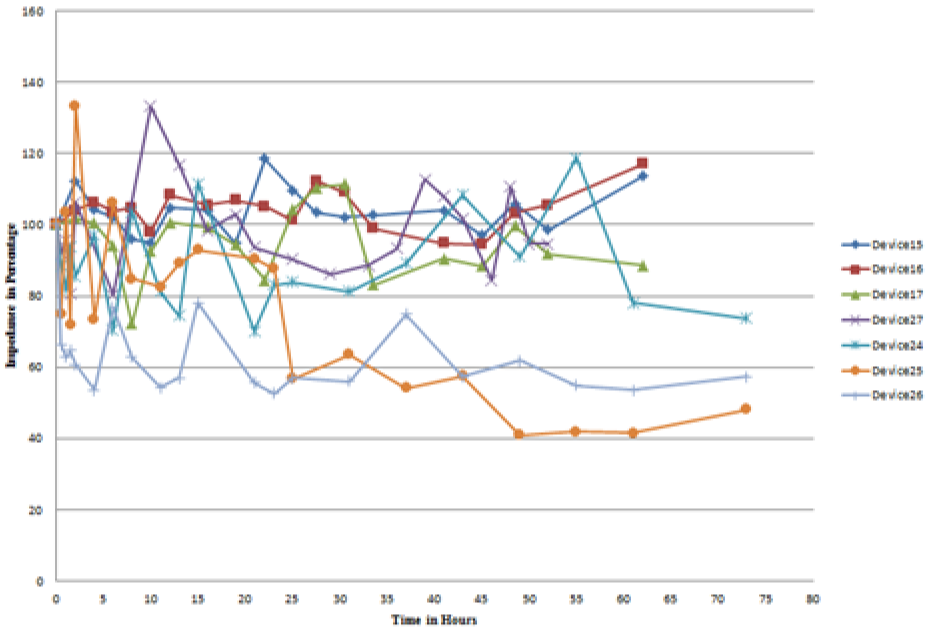


Figure 3.13. Impedance test of micro slide glass devices in SBF at 37 ° C

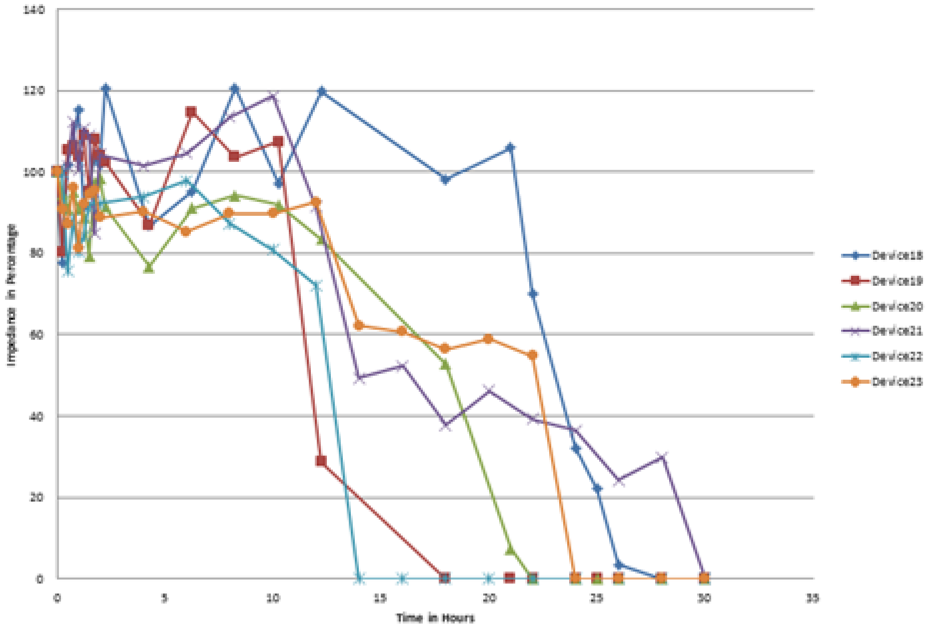


Figure 3.14. Impedance test of single side coated (PVD) bioactive borate glass devices in SBF at 37 ° C

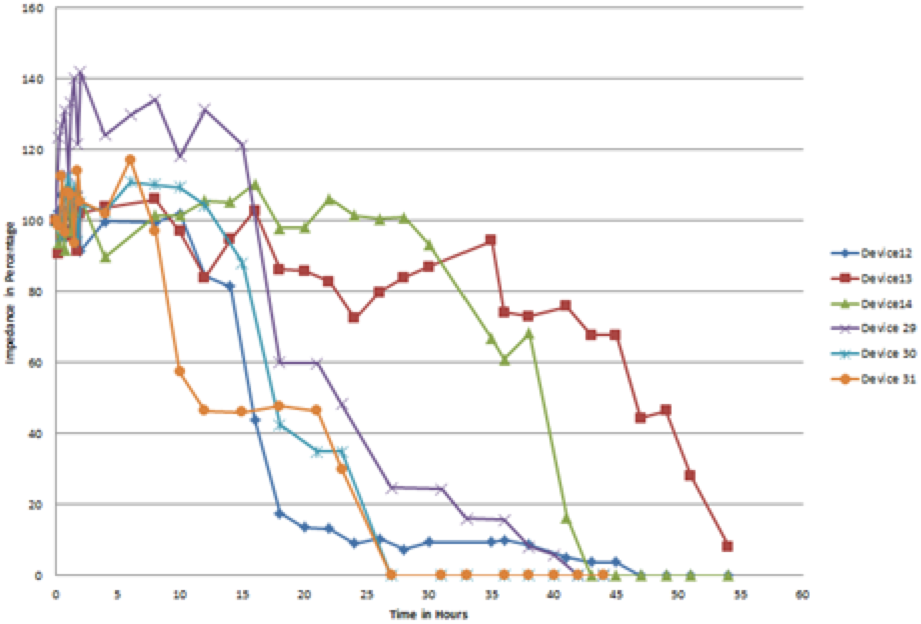


Figure 3.15. Impedance test of double side coated (PVD) bioactive borate glass devices in SBF at 37 ° C

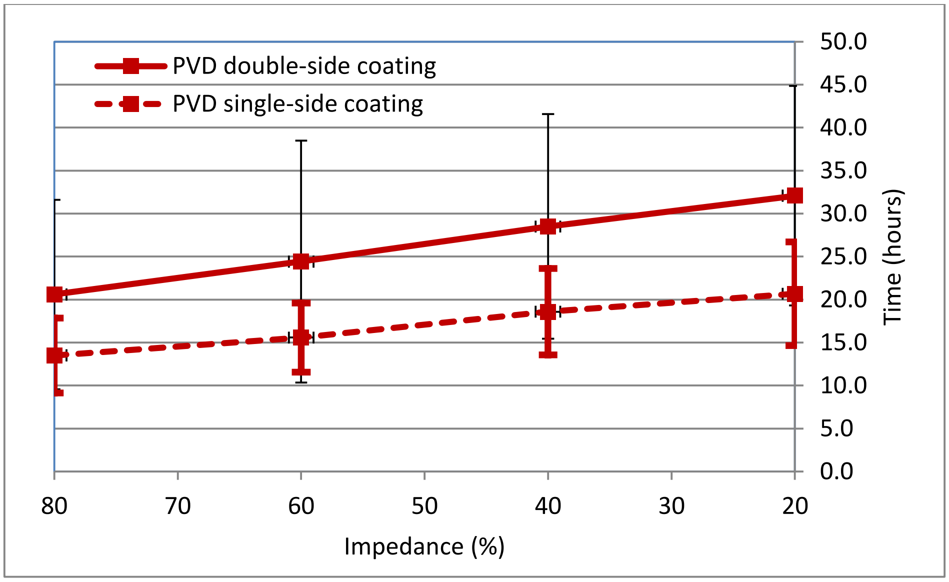


Figure 3.16. Operational lifetime of PVD coated bioactive borate glass devices

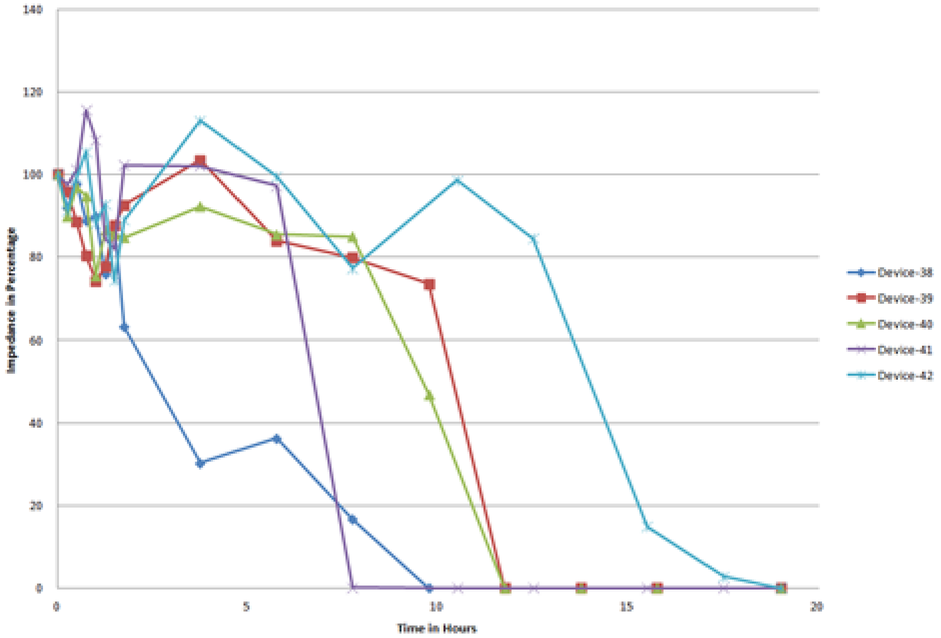


Figure 3.17. Impedance test of single side coated (CVD) bioactive borate glass devices in SBF at 37° C

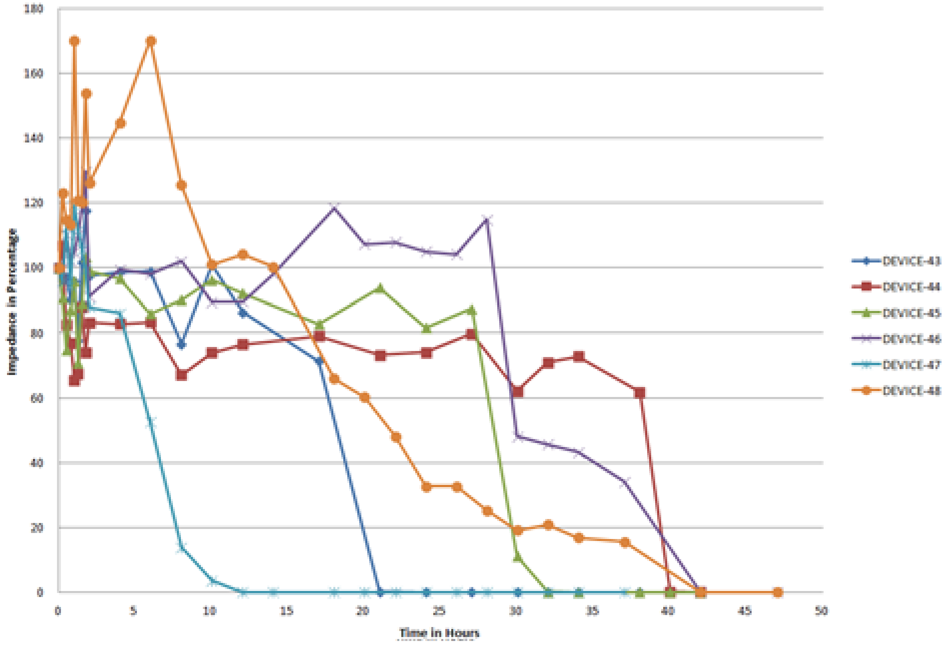


Figure 3.18. Impedance test of double side coated (CVD) bioactive borate glass devices in SBF at 37 ° C

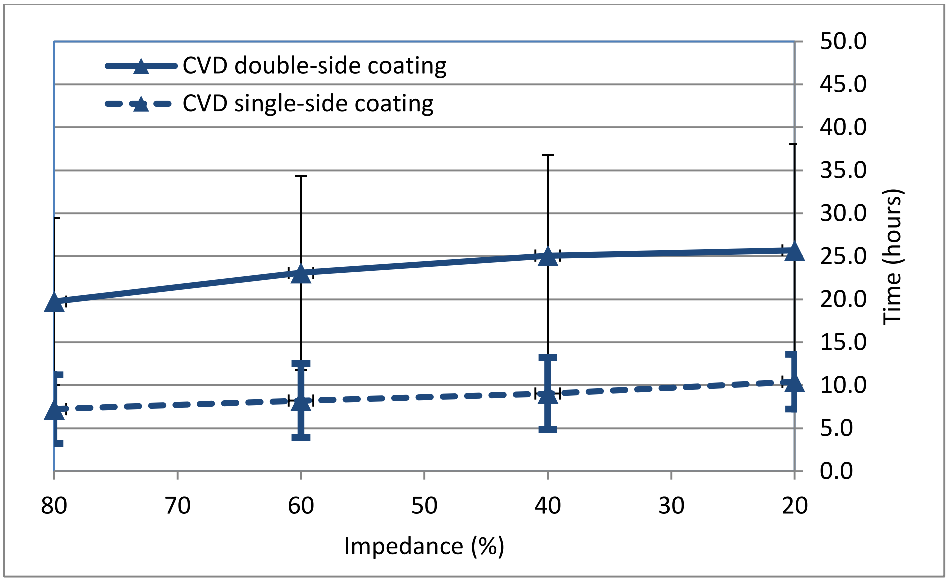


Figure 3.19. Operational lifetime of CVD coated bioactive glass devices

4. CONCLUSIONS

A test device structure to explore the concept of inorganic biodegradable devices were prepared and characterized. This is based on the impedance monitoring between two electrodes to estimate the disintegration of whole device structure during the dissolution process the simulated body fluids. A specially formulated borate-based bioactive glass was used as the core materials for this application. When the device was built on a double side coated bioactive glass wafer, the device exhibited a longer stable performance. Based on the results, it is highly feasible to implement a new class of device that is fully functional only for a limited operational lifetime after implantation.

The devices built using silicon oxide film deposited by PVD tend to work better than the devices built with silicon oxide film deposited using CVD. This was highly unexpected as the refractive index of CVD film was much closer to the standard reference value. However there is a difference in the thickness of both films (PVD-0.3 micron and CVD-0.998 micron). How film thickness affects the performance of the device needs to be studied. Getting rid of other variations such as surface roughness, wafer thickness and any possible contamination might help us to see clear differences in the performance of devices built using PVD and CVD coated silicon oxide films. More study needs to be done to able to do a better comparison between the performance of devices built using PVD and CVD coated silicon oxide films.

Most desirable applications of fully implantable biodegradable devices include biomedical sensors including pressure/flow monitoring for blood circulation problems, gastrointestinal tract disorders, head injuries, urinary problems and ocular diseases, to name but a few. Biomechanical monitoring, such as stress/strain along bone fractures or associated with spinal fusion surgery, is highly desirable for orthopedic repair and rehabilitation. Also temperature monitoring of prosthetic devices to prevent the early failure due to excessive friction will provide physicians with useful information. The outcome of this study is expected to lead to implementing a new class of implantable devices.

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APPENDIX A.

DETAILED PROCEDURE FOR PREPARING BIOACTIVE BORATE GLASS WAFERS

Bioactive borate glass wafer is prepared by first making glass rods and by then slicing it into wafers using a low speed saw (Isomet, Buehler). Preparation procedure for glass rods and wafers is described in Table A.1. The glass wafers were then mounted on an aluminum holder using a thermo plastic product, Brewerbond 220 (Brewer Science, Rolla, MO), so that they can be clamped into a specimen holder and then polished using an automatic polisher (Tegramin30, Struers). Mounting procedure is described in Table A.2. Table A.3 covers the detailed procedure polishing and grinding.

After the polishing the wafers were then demounted and cleaned. Table A.4 records the procedure for demounting and cleaning glass wafers.

Table A.1. Preparation procedure for glass rods and wafers

Sr. No.	Procedure
1	- Melting sodium tetraborate ($Na_2B_4O_7$) in a platinum crucible for 45 minutes at 1000˚C - Stirred every fifteen minutes using a pure silica rod
2	- Poured into stainless steel cylindrical molds - annealed at 450˚C for 30 minutes - Cooled slowly (furnace normal cooling rate) to room temperature
3	- Cylindrical glass rod of approximately 1.5 cm diameter and 3cm length was formed - Glass rod formed is then wrapped using an insulation tape and mounted on the saw - A small weight is applied on the saw arm and the instrument was setup at medium speed - Glass wafers formed were then cleaned using acetone

Table A.2 Mounting procedure for wafers

Sr. No.	Procedure
1	- Aluminum holder cleaned with acetone - Top surface of holder coated with a thin layer of Brewer Bond 220
2	- Holder heated on a hot plate - At 80^{o} C for 10 minutes - At 130^{o} C for 10 minutes - At 200^{o} C for 2 hours - Cooled to room temperature
3	- Holder again heated to 130^{o} C - Glass wafer was placed on top and slightly pressed - Cooled to room temperature - Very strong bonding between the glass wafer and the aluminum holder

Table A.3. Procedure for polishing and grinding glass wafer

Sr. No.	Procedure
1	- Six aluminum holders mounted with glass wafers were clamped in a specimen holder - Insert the holder in the automatic polisher(Tegramin30, Struers)
2	- Mount MD-Gekko (300 mm magnetic pad for attaching SiC foils) on MD-Disc (drive plate) - An alcohol based lubricant (DP-Lubricant Yellow, Struers) is used just enough to keep the surface moist through all the polishing and grinding steps
3	- Drive plate is set at 300 RPM - Head is set at 150 RPM - Co-rotation of both drive plate and head (drive plate 300rpm, head 150 rpm)*,** - To level the top surface of all the mounted glass wafers grinding is done using a SiC foil of grit size of 76 micron for 30 seconds using 50 N force

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Following steps are then carried out using SiC foil of grit sizes as mentioned below applying a force of 50 N.

<table>
<tr><th>Step No.</th><th>Grit size (microns)</th><th>Time</th></tr>
<tr><td>1</td><td>76</td><td>30 seconds</td></tr>
<tr><td>2</td><td>32.5~36</td><td>10 seconds</td></tr>
<tr><td>3</td><td>16.7~19.7</td><td>1 min</td></tr>
<tr><td>4</td><td>4.5~6.5</td><td>1 min</td></tr>
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To bring surface roughness further down from 4 micron, alcohol based polycrystalline diamond polish DP-Spray P (Struers) was used
DP-Spray P cans used nitrogen as a propellant
MD-Dur (Struers) polishing cloth was used
Can was sprayed for 2 seconds on the cloth, once every minute
Following steps are then carried out using DP-Spray P of different particle sizes as mentioned applying a force of 50 N.

<table>
<tr><th>Step No.</th><th>Particle size (microns)</th><th>Time</th></tr>
<tr><td>1</td><td>3</td><td>3 min</td></tr>
<tr><td>2</td><td>1</td><td>3 min</td></tr>
<tr><td>3</td><td>.25</td><td>3 min</td></tr>
</table>
</td>
</tr>
</table>

Table A.4. Procedure for demounting and cleaning glass wafer

Sr. No.	Procedure
1	- Aluminum holders heated to a temperature of 130^{o} C - Wafers were slided off the holders
2	- Wafers cleaned ultrasonically in 1-Dodecene for 15 minutes - Wafers were wiped clean using 100% continuous polyester wipes (TX 1009 Alpha Wipe) - Ultrasonication in isopropanol for 15 minutes - Wafers were wiped clean using 100% continuous polyester wipes (TX 1009 Alpha Wipe) - Wafers were sprayed with isopropanol and then blown dried using high purity nitrogen gas.

* Same rotation speed for drive plate and head might result in better polishing as it may damage the surface of the wafer less

** Less rotation speed about 150 Rpm for both drive plate and head might result in better polishing

APPENDIX B.

DETAILED PROCEDURE FOR THIN FILM COATING

Bioactive borate glass wafers were coated with silicon oxide using two different processes either PVD or CVD. For single side coating wafers were placed on surface on one face and then silicon oxide was deposited. To form double side coated wafers these wafers were then flipped (placed on the surface inside the deposition chamber on another face). Table B.1 describes the methods used for deposition of silicon oxide and gold-palladium. Gold-palladium (1:1) thin film electrodes, 1mm apart, were sputtered on top of the silicon oxide using a silicone shadow mask with a flash coater (Hummer VI)

Table B.1. Methods used for deposition of silicon oxide and the working parameters used

Method	Working parameters
Silicon oxide with PVD (RF sputtering)	- Deposition time: 3.5 hours (30 min's cleaning and 3 hours deposition) - Total working pressure: 8×10^{-3} torr (7.2×10^{-3} torr argon and 0.8×10^{-3} torr oxygen) - Ratio of argon to oxygen: 8:1
Silicon oxide with CVD (Plasma enhanced)	- RF Power: 125 W - RF Freq: 13.56 MHz - Deposition time: 72 seconds - Working pressure: 2.8 torr - Temperature: 400^{o} C - Gas: N_2OH 1200 SCCM and SiH_4 60 SCCM
Gold-Palladium (Hummer VI)	- Gas: Nitrogen - Working Pressure: 100 millitorr - DC Current: 10 mA - Deposition time: 5 minutes

APPENDIX C.

DETAILED PROCEDURE FOR DEVICE PACKAGING

Procedure for packaging of device is described in Table C.1.

Table C.1. Procedure for packaging of device

Sr. No.	Procedure
1	- Nylon washer (inner diameter 90 mm) was glued to the bottom surface of the device where no electrodes were formed using silicone paste (GE silicone II clear, Premium waterproof silicone) - Reliable water resistant bond with the wafer after curing
2	- Wires were encapsulated in a plastic tube - Everywhere except the region defined inside the washer is coated with silicone paste including the junction between the tube and the wafer
3	- Top end of the tube is sealed with silicone paste
4	- Device was then left for four hours for the silicone to cure
5	- If any holes or uncoated areas were observed after curing then an additional layer of silicone was applied and then cured

APPENDIX D.

SBF RECIPE

Table D.1 shows the recipe for preparing 1 L of SBF. The SBF solution prepared had a pH of approximately 7.4.

Ingredients	**Weight (gms)**
NaCl	7.996
$NaHCO_3$	0.35
KCl	0.244
$K_2HPO_4.3H_20$	0.228
$MgCl_2.6H_20$	0.305
1M HCl	40ml
$CaCl_2$	0.278
Na_2SO_4	0.071
$NH_2C(CH_2OH)_3$	6.057

VITA

Kassan Unda was born in Sambalpur, India. He received his Bachelor of Engineering degree from Rajiv Gandhi Prodyogiki Vishwa Vidhyalaya (India), in Electronics and Communication in 2011. He is pursuing his Master of Science in Computer Engineering from Missouri University of Science and Technology and will graduate in 2014.