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Quantifying the Biodegradation of Packaging Thin Films Intended for Medical Micro Devices

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Abstract– Miniaturized medical devices represent a hot growing segment in the market of medical devices. They enable minimally invasive surgery in addition to new treatment and monitoring capabilities to the medical profession. They also improve portability and ease of use to patients. Successful examples include micro pacemakers, micro cochlear implants and ex-situ micro glucose sensors. Implantable medical micro devices using packaging technologies other than metallic canisters remain to be seen. Physiological monitors such as in-situ pressure sensors and BioMEMS could benefit greatly from advances in materials for the thin hermetic packaging of microelectronic components. Thin packaging materials that stop the diffusion and permeation of harmful substances are necessary to protect both the patient and the micro device. Ceramic films deposited by chemical vapor deposition are good candidates for this task due to their low permeability to gases, relatively low chemical reactivity and high conformal deposition. However, few studies are available about the degradation rates of packaging films in representative biological environments. This paper reports on a method to quantify the biodegradation rate of packaging films in a biological medium. Ten materials reported in the literature as biocompatible were studied: Al_2O_3, BN, DLC, HfO_2, SiC, SiN, SiO_2, SiOC, TiO_2 and ZnO. Biodegradation tests were performed for four weeks at 37°C in a saline solution supplemented with Fetal Bovine Serum, as well as in phosphate buffer saline at 37°C and 57°C. Changes in thickness and chemical composition were monitored by variable angle spectroscopic ellipsometry and x-ray photon electron spectroscopy. Six of these materials were chemically stable in both mediums, while the other four materials had degradation rates ranging from 1.5 to 150 nm per week, depending on the biological medium.

***Keywords*:** Biocompatible – Biodegradation – Biostable – Packaging Film –Silicon – Medical Device

1. Introduction

Minimally invasive medical devices and instruments enable new treatment and monitoring capabilities thanks to their miniaturized size, and reduce convalescence times and risk of infections post-surgery (Kilger et al., 2001). They also improve ease of use and cosmetic appeal of active medical implants for patients. Successful examples include micro pacemakers, micro cochlear implants and micro cameras (Jung, 2014). However, implantable medical micro devices using packaging technologies different to metallic enclosures are rare, especially for prolonged (>1 day) and chronic implants (>30 days). Such metallic canisters are expensive and can make up to 80% of the volume of the final medical device. Sensing applications like in-situ physiological monitors (e.g. pressure and glucose sensors) could significantly profit from advances in materials for the hermetic thin packaging of silicon microsystems (Yu et al., 2014). Silicon 3D integration of ASICs (Application-Specific Integrated Circuits) and MEMS (Micro Electro- Mechanical Systems) could further enhance the miniaturization and diversification of medical micro devices (Souriau et al., 2014)(Lamy and Simon, 2013). The integration of such advanced silicon devices in physiological monitors and biosensors needs the development of reliable biocompatible thin packaging films.

Thin packaging materials that stop the diffusion and permeation of harmful substances are necessary to protect both the patient and the micro device. Ceramic films deposited by chemical vapor deposition

are good candidates for this task due to their low permeability to gases (Greenhouse et al., 2012), high conformal deposition and relatively low chemical reactivity (Franssila, 2010). However, few studies are available about the degradation rates of biomaterials in representative biological environments (Hedberg, 2012). This paper proposes a method to quantify the degradation rate of packaging thin films in a biological medium.

2. Materials And Methods

Ten materials reported in the literature as compatible with biological applications (Kotzar et al., 2002)(Lousinian et al., 2008)(Zhuo et al., 2005)(Arya et al., 2012)(Matero et al., 1999) were studied: Al_2O_3, BN, Diamond Like Carbon, HfO_2, SiC, SiN, SiO_2, SiOC, TiO_2 and ZnO. Thin films of these materials were deposited on wafers of polished p-type silicon (100). Coupons of size 20x15 mm^2 were diced from these wafers. We found that all coupons coated with these films, except for ZnO, are non-cytotoxic according to the norm ISO 10993-5 for the biological evaluation of in-vitro cytotoxicity (Morales et al., 2014).

Table 1 resumes the different films deposited by either Atomic Layer Chemical Vapor Deposition (ALCVD) in a Fiji F200 machine from Cambridge Nanotech Inc. or Plasma-Enhanced Chemical Vapor Deposition (PECVD) in a Centura 5200 machine from Applied Materials Inc. Samples were kept inside a nitrogen chamber until the biodegradation tests were performed.

Table 1. Thin films deposited on silicon substrates.

Material	Avg. thickness /nm	Fabrication
Al_2O_3	20	ALCVD 250°C
HfO_2	20	ALCVD 250°C
TiO_2	20	ALCVD 250°C
ZnO	20	ALCVD 250°C
SiN:H	100	PECVD 400°C
SiO_2	500	PEVCD 400°C
SiOC	450	PECVD 400°C
SiC	100	PECVD 350°C
DLC (a-CH [a])	100	PECVD 400°C
BN	50	PECVD 400°C

[a] Amorphous Hydrogenated Carbon, a type of Diamond Like Carbon (DLC).

Prior to the biodegradation tests, coupons were submitted to a typical cleaning protocol with ethanol and a common detergent soap used in biological laboratories, Triton X-100. Next, coupons underwent a standard cycle of sterilization with Ethylene Oxide (EtO) consisting of 180 min of preconditioning at 50% relative humidity and 240 min of exposure.

Biodegradation tests were performed for four weeks at 37°C in a NaCl solution (0.9 wt%) supplemented with 10% volume of Fetal Bovine Serum (FBS). This biological medium was changed every 48 hours. Coupons were sterilized by immersion in ethanol at 70°C, De-Ionized (DI) water and irradiation with UV light (250 nm) before being re-immersed in a new saline FBS medium.

In addition, sample coupons as deposited were submitted to degradation tests for four weeks in Phosphate Buffer Saline (PBS) at 37°C and 57°C. PBS solutions (pH 7.4) are commonly used to simulate the ionic concentrations of blood plasma. The PBS solution was supplied by Euromedex Inc. as a 0.2 µm-filtered 10X solution containing KH_2PO_4 10.6 mM, $Na_2HPO_4 \cdot 2H_2O$ 30.0 mM, NaCl 1.54 M and dissolved to 1X with DI water of 18.2 MΩ•cm.

Changes in thickness and chemical composition were monitored before and after each test by Variable Angle Spectroscopic Ellipsometry (VASE) and X-ray Photon electron Spectroscopy (XPS). Prior to measurements, sample coupons were rinsed sequentially with DI water, acetone, isopropyl

alcohol and DI water. A nitrogen blow gun was used to remove the excess of water from coupons, before being dehydrated on a hot plate at 125°C for 15 min.

The film thickness of each coupon was determined by using a computer-controlled variable angle of incidence spectroscopic ellipsometer of the rotating analyzer type by J.A. Woollam Co., Inc. The measurement area of 6x4 mm^2 was always taken at the center of the coupon with the help of a paper support with alignment marks (Fig. 1). The software WVASE32 (version 3.774) was used for data fitting of optical parameters. Data fitting was made using the Cauchy model for transparent materials in the wavelength range of 400–1700 nm and incident angle of 55°, 65° and 75°. The Mean Squared Error (MSE) of the thickness estimated this way was smaller than 5 for measured coupons, which indicated a good data fitting. Experimental errors of ±1 nm were expected for the thickness measurements due to the difficulty of locating exactly the same spot on the coupon.

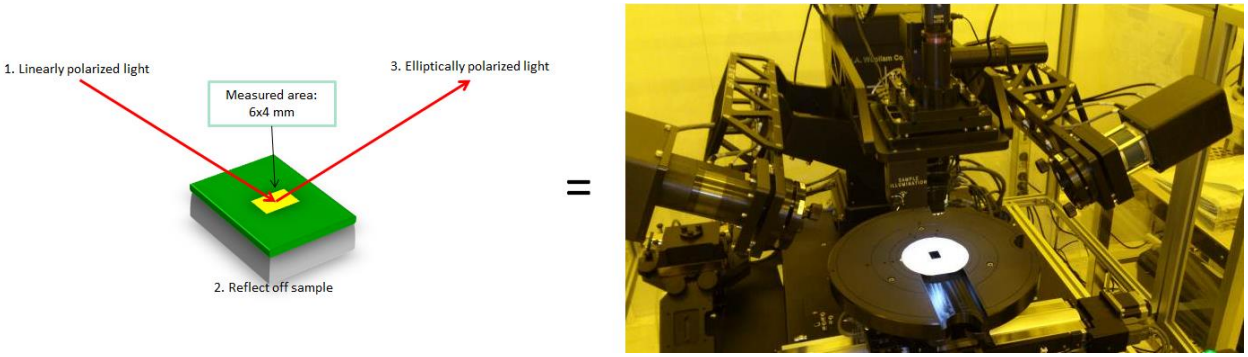

Fig. 1. Measurement of coupon film thickness by variable angle spectroscopic ellipsometry (VASE).

XPS measurements were performed with Ka1 radiation of Aluminum (excitation 1486.6 eV, spot size 100 µm) at a collection angle of 45° relative to the surface normal vector, giving a penetration depth of 6.4 nm in SiO_2. 63% of the intensity was emitted below 3 nm.

3. Results And Discussion

The variation of film thickness for the different materials is presented in Table 2. Each value is the average change of thickness of three coupons rounded to the nearest unit.

Table 2. Change of thickness (nm) in comparison to initial states after different degradation tests on coupons.

Film	After cleaning with ethanol and soap	After sterilization with EtO	After 4 weeks in 37°C NaCl/FBS	After 4 weeks in 37°C PBS	After 4 weeks in 57°C PBS
20 nm TiO_2	0	0	0	0	0
50 nm BN	0	0	0	0	0
100 nm DLC	0	0	0	0	0
20 nm HfO_2	0	0	0	0	0
100 nm SiC	0	0	0	0	0
450 nm SiOC	0	0	0	0	0
500 nm SiO_2	0	0	-15	-6	-10
100 nm SiN:H	0	0	-50	-59	[a]
20 nm Al_2O_3	0	0	-20	0	0
20 nm ZnO	-7	-7	[b]	[b]	[b]

[a] Film disappeared after two weeks of test. [b] Film disappeared after one day of test.

3. 1. After Cleaning

All films, except ZnO, were stable to the cleaning protocol with ethanol and detergent. A change of thickness of 7 nm was detected for the ZnO coupons after this cleaning procedure. This loss of thickness is probably due to the amphoteric behavior of zinc oxide that produces soluble ions in alkali and acid solutions (Housecroft and Sharpe, 2005) :

$$ZnO + 2H^{+} \rightarrow Zn^{2+} + H_2O \quad (1)$$

In acid solution

$$ZnO + H_2O + 2OH^{-} \rightarrow [Zn(OH)_4]^{2-} \quad (2)$$

In alkali solution

3. 2. After Sterilization With Eto

The sterilization procedure with EtO did not produce a significant change of thickness or chemical composition of coupons; even for coupons of ZnO. Parameters psi and delta of ellipsometry spectroscopic are very sensitive to changes of thickness and morphological structure of thin films (Ron Synowicki, 2010). These parameters did not change after the sterilization procedure with EtO, indicating the films were not affected by this procedure. One example of a film unchanged after sterilization with EtO is shown in Fig.2.

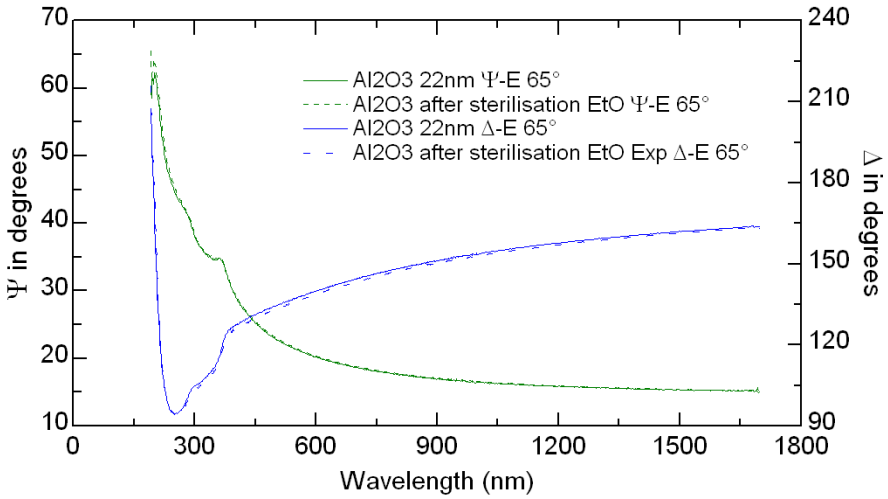

Fig. 2. VASE spectra of one Al_2O_3 film before and after sterilization with EtO.

3. 3. After Immersion In Nacl/PBS

Biodegradation tests in saline solution supplemented with FBS had a negative impact on coupons of Al_2O_3, SiN:H, SiO_2, and ZnO. Especially for Al_2O_3 and ZnO films that disappeared completely (Fig. 3 and 4). By linear extrapolation from degradation data in the NaCl/FBS medium, annual dissolution rates of deposited films are 8 µm/yr for ZnO, 0.7 µm/yr for SiN:H, 0.3 µm/yr for Al_2O_3, and 0.2 µm/yr for SiO_2 films. Similar values have been reported for in vivo degradation tests of PECVD silicon nitride (Maloney et al., 2005) and silicon oxide (Hämmerle et al., 2002).

These film dissolution rates, although apparently small, are problematic for the corrosion protection of metallic redistribution layers in microelectronic components with openings in the packaging film (e.g. biosensors), because they allow infiltration of corrosive liquid mediums inside the silicon device and device failure occurs as consequence (Greenhouse et al., 2012). For implants where the life of the patient

depends on the correct functioning of the medical device, these dissolution rates are not acceptable as the chemical inertness of the packaging film must be guaranteed.

3. 4. After Immersion In PBS

Results of accelerated degradation tests in 57°C PBS are misleading. On one hand, they overestimate greatly the degradation rates of SiN:H films. On the other hand, they fail to predict the decomposition of Al_2O_3 films in complex biological environments like the NaCl/FBS medium. Therefore, extrapolation of results of accelerated degradation tests in PBS should be taken carefully, especially when predicting the aging behavior of chronic implants.

XPS measurements confirmed the decomposition of Al_2O_3, SiN:H, SiO_2, and ZnO films in NaCl/FBS and PBS at 37°C. In general, a surface enrichment in Na, Cl and Si atoms was recorded after the degradation tests in both biological mediums. The XPS lines of Zn (Fig. 4) and Al disappeared after one day and 28 days immersed in the NaCl/FBS medium, respectively.

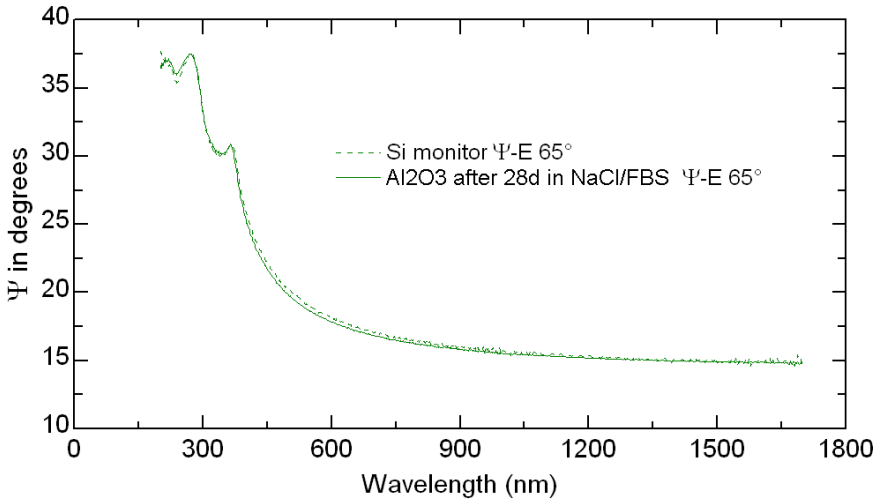

Fig. 3. VASE spectra of Al_2O_3 coupon and control (Si monitor) after 28 days in NaCl/FBS medium.

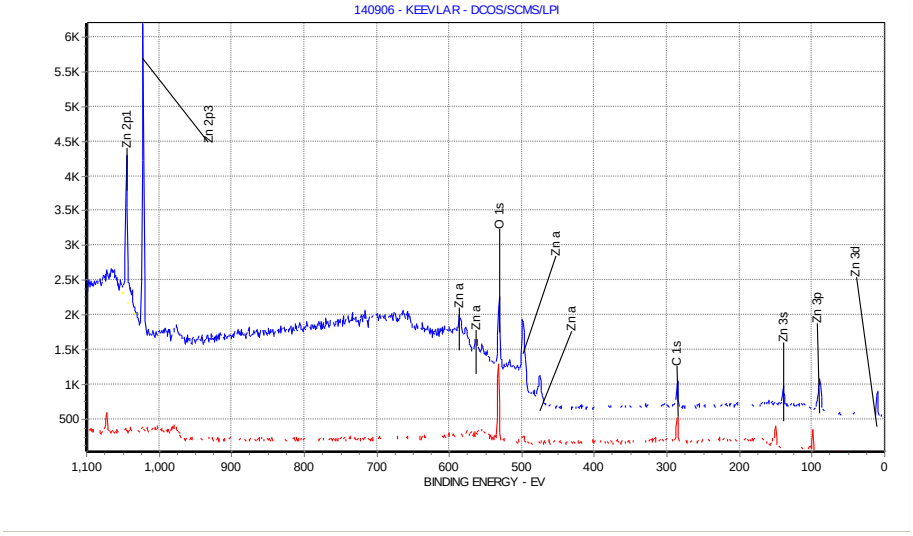

Fig. 4. XPS spectra of a ZnO film before (blue line) and after (red line) one day in NaCl/FBS medium.

4. Conclusions

Six thin films (BN, DLC, HfO_2, SiC, SiOC, and TiO_2) were chemically stable after standard biomedical procedures of cleaning, sterilization with EtO and biodegradation tests in PBS and NaCl/FBS. Other three films (SiN:H, SiO_2, and ZnO) were not stable in PBS and had degradation rates ranging from 6 to 600 nm after four weeks of testing. Although Al_2O_3 films were stable in PBS, they were not stable and dissolved in the NaCl/FBS medium, which is in good agreement with the response in vivo of aluminum oxide implants (Williams, 1981). Films of Al_2O_3, SiN:H, SiO_2, and ZnO as fabricated here are not recommended to be used alone for packaging silicon devices as part of biosensors or BioMEMS in direct contact with the body.

We believe that biodegradation tests in complex biological environments like the NaCl/FBS medium are more pertinent to predict the aging behavior of biocompatible films used for encapsulating implantable medical micro devices.

More research is needed to determine the efficiency of BN, DLC, HfO_2, SiC, SiOC, and TiO_2 films as diffusion barriers of toxic substances. Different substrates like copper and aluminum should be tested as well to assess the adhesion strength and compatibility with these films.

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