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Degradation of thin poly(lactic acid) films: Characterization by capacitance–voltage, atomic force microscopy, scanning electron microscopy and contact-angle measurements

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ABSTRACT

For the development of new biopolymers and implantable biomedical devices with predicted biodegradability, simple, non-destructive, fast and inexpensive techniques capable for real-time *in situ* testing of the degradation kinetics of polymers are highly appreciated. In this work, a capacitive field-effect electrolyte–insulator–semiconductor (EIS) sensor has been applied for real-time *in situ* monitoring of degradation of thin poly(D,L-lactic acid) (PDLLA) films over a long-time period of one month. Generally, the polymer-modified EIS (PMEIS) sensor is capable of detecting any changes in the bulk, surface and interface properties of the polymer (*e.g.*, thickness, coverage, dielectric constant, surface potential) induced by degradation processes. The time-dependent capacitance–voltage (*C–V*) characteristics of PMEIS structures were used as an indicator of the polymer degradation. To accelerate the PDLLA degradation, experiments were performed in alkaline buffer solution of pH 10.6. The results of these degradation measurements with the EIS sensor were verified by the detection of lactic acid (product of the PDLLA degradation) in the degradation medium. In addition, the micro-structural and morphological changes of the polymer surface induced by the polymer degradation have been systematically studied by means of scanning-electron microscopy, atomic-force microscopy, optical microscopy, and contact-angle measurements.

1. Introduction

The ability of some polymers to degrade under physiological conditions has led to an enormous interest in these polymers for several medical applications ranging from resorbable implants [1,2] and orthopaedic devices [3] over scaffolds for tissue engineering [4,5] to biodegradable polymer particles (*e.g.*, microspheres [6,7], microcapsules [8]) and controllable carrier matrices for drug-delivery systems [9,10]). In the past decades several types of polymers have been investigated concerning their suitability for such applications [2]. The current tendencies are focused on the modification of approved biopolymers, in order to improve their functionality as well as on the search for new biodegradable materials with controlled degradability that can be easily removed from the body.

One aspect slowing down the technological progress of adapting the properties of those polymers to a specific application is due to the numerous factors influencing their degradation behaviour: starting from intrinsic properties, like the chemical composition [11,12] and the molecular weight [12] over additives such as drugs [12] or residual solvent [13] up to the surrounding medium [14]. *In vitro* studies of the degradation kinetics are thus not only essential for a fundamental understanding of the nature of the degradation process but also for the design and optimization of implantable biomedical devices with predicted and controlled biodegradability. Since common techniques to quantify polymer degradation are usually of destructive manner, such studies are laborious and limited in throughput so far, and therefore not suitable for real-time monitoring.

Recently, a capacitive field-effect electrolyte–insulator–semiconductor (EIS) sensor has been applied for the real-time *in situ* detection of polymer degradation (the benchmark polymer of poly(D,L-lactic acid) (PDLLA) was used as model system) for the first time by the authors [15]. Such EIS sensors are simple in

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layout, easy and low-cost in fabrication (usually no photolithographic process steps and complicated encapsulation procedures are required). In previous experiments, EIS sensors have been applied for the detection of pH [16], ion concentration [17,18], enzymatic reactions [19,20] and enzyme-logic gates [21], charged macromolecules [22] and nanoparticles [23]. In general, the functioning mechanism of field-effect (bio-)chemical sensors is based on the effect of charge or potential changes at the interface electrolyte/gate insulator induced by the particular analyte. However, other effects, such as the change in the dielectric constant or thickness of the gate material could modulate the effective gate capacitance and flatband voltage of an EIS structure [24] and therefore, can be also utilized as detection mechanism. Thus, if the gate surface of the EIS sensor is covered with a polymer film to be investigated, it can be expected that any changes in the bulk, surface and interface properties of the polymer (*e.g.*, thickness, coverage, dielectric constant, surface potential) induced by the degradation processes will modulate the global capacitance/impedance of the polymer-modified EIS (PMEIS) structure, which can be used as an indicator of the polymer degradation.

In this work, the degradation behaviour of thin PDLLA films has been monitored *in situ* and in real-time over a long-time period of one month by recording the time-dependent capacitance–voltage (*C*–*V*) characteristics of the PMEIS structures. In addition, parallel to these electrochemical measurements, the surface of the polymer films has been systematically characterized by means of scanning-electron microscopy (SEM) and atomic-force microscopy (AFM) as well as contact-angle method to provide a better understanding of the micro-structural and morphological changes in the polymer films during the degradation process. Moreover, a biochemical, enzyme-based assay was established to quantitatively detect the concentration of lactic acid–the product of PDLLA degradation–in the degradation medium. The results obtained from the diverse characterization methods were discussed and evaluated.

2. Experimental

The capacitive EIS sensors have a size of 10 mm × 10 mm and were cut from a wafer consisting of an Al–Si–SiO_2–Ta_2O_5 structure (p-Si, ρ = 5–10 Ωcm, 30 nm thermally grown SiO_2, 60 nm Ta_2O_5, 300 nm Al as rear-side contact layer). Thin films of the biodegradable polymer PDLLA (RESOMER® R 202 H, Evonik Röhm GmbH, Germany) were deposited on the surface of EIS chips from polymer solution by means of spin-coating method. RESOMER® R 202 H consists of a 50:50 ratio of D/L-lactic acid with a molecular weight in the range of Mw = 10,000–18,000 Da. The thickness of the polymer films was approximately 300 nm. A more detailed description of the deposition of the polymer film can be found in [15].

It is known, that PDLLA has a slow degradability in neutral pH solutions (the degradation time can be ~6 months and more) and shows a higher degradability in alkaline solutions [25]. Therefore, in order to accelerate the polymer degradation, in this study, proof-of-principle degradation experiments were performed in alkaline buffer solution of pH 10.6 at 37 °C. For the degradation experiments, a total number of N = 38 polymer-coated chips was exposed to a buffer solution. Two sensors were kept in contact to the degradation solution permanently and were electrochemically characterized investigating the functionality of the EIS sensors. After distinct exposure times, several sensor chips were removed from the degradation solution, carefully rinsed with deionized water and dried under an N_2 flow. These chips were used for surface-morphology analysis of the polymer films by means of optical microscopy, SEM and AFM as well as for contact-angle measurements, respectively. Moreover, a biochemical assay was applied that detects the formation of degradation products in the buffer solution and thereby, served as a quantitative measure for the degradation process.

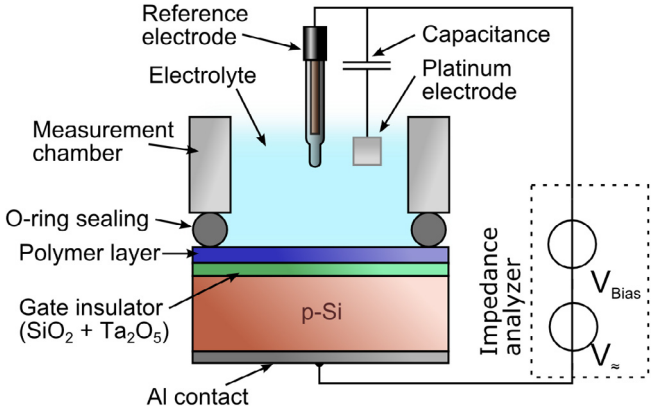

Fig. 1. Schematic of the PMEIS sensor and experimental setup for the monitoring of polymer degradation.

3. Results

3.1. Electrochemical characterization of the polymer films during degradation

A schematic of the PMEIS sensor and the measuring setup used for the electrical monitoring of the degradation kinetics of polymers is depicted in Fig. 1. For the electrochemical characterization, the PMEIS sensors were mounted in a home-made measurement cell, sealed by an O-ring, and contacted to an impedance analyzer (Zennium, Zahner Elektrik GmbH, Germany) *via* the aluminium contact at the backside of the EIS structure, and a liquid-junction Ag/AgCl reference electrode (Metrohm, filled with 3 M KCl, potential *vs* SHE: 198.5 mV) in contact to the degradation medium, respectively. The contact area of the polymer film is defined by the inner diameter of the O-ring and was about 0.5 cm^2.

As it has been demonstrated in previous experiments (see *e.g.*, [17,18,26,27], any series resistance (for example, resistance of the reference electrode) can lead to a frequency-dependent distortion of the *C*–*V* curves of the EIS sensor and even to practically flat curves at high frequencies, thus, resulting in inaccurate measurements of the sensor's capacitance as the measuring signal. Therefore, an additional current path in parallel to the reference electrode was added to the measuring setup to bypass the impedance of the reference electrode (typically in the range of a few 10 kΩ) by means of a platinum electrode in contact to the degradation medium. A capacitance of 330 nF prevents any DC current flow through this path. Using a bypass reduces the contribution of the serial resistance of the reference electrode in the *C*–*V* curves and impedance spectra. It does not affect the behaviour of the sensor but extends the frequency range in which the EIS-sensor signal can be measured accurately.

During the measurements, a DC bias voltage (V_{bias}) from −3 V to 2 V was applied between the Ag/AgCl reference electrode and the rear-side Al contact to force the PMEIS sensor to accumulation, depletion or inversion stage. An additional small AC voltage (20 mV, 120 Hz) is superimposed to the system in order to measure the capacitance of the PMEIS structure. All potential values are referred to the reference electrode.

The sensors were monitored over a time period of 30 days and the *C*–*V* curves were recorded sequentially every hour. Fig. 2 shows an example of the time-dependent *C*–*V* curves of the PMEIS sensor.

Due to the small capacitance of the polymer layer in series with the capacitance of the bare EIS sensor, at an early stage of polymer degradation (after 1 h; after 1 day) the recorded *C*–*V* curves were flat. With progressive degradation, the capacitance of the

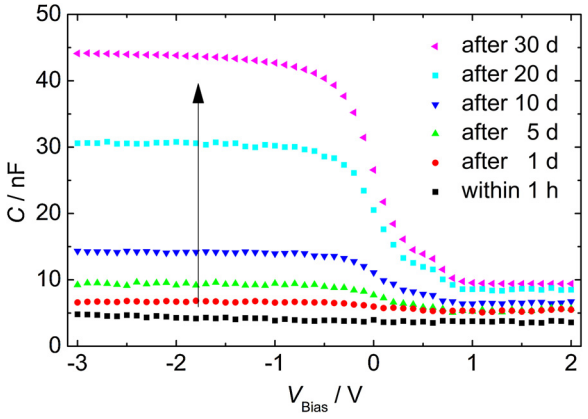

Fig. 2. *C–V* curves of a PMEIS sensor during erosion of polymer layer.

PMEIS sensor is increased and the *C–V* curves show a usual sigmoid-like shape with typical accumulation ($V_{bias} < -0.5$ V), depletion ($-0.5 < V_{bias} < 0.5$ V) and inversion ($V_{bias} > 0.5$ V) regions. This can be attributed to the thinning of the polymer layer and an increase of its permittivity due to an increasing fraction of water molecules inside the polymer layer (filling the pores with water), both resulting in a raise of the capacitance of the polymer film. Typically, PDLLAs absorbs about 1 wt% of water (see *e.g.*, [28]). The experiments performed in this study do not allow to distinguish the contribution of each factor in the capacitance change during the whole degradation process. However, since the polymers usually become saturated quickly when they get in contact with water, it can be suggested that the increase of the capacitance of the PMEIS sensor during the course of degradation is mostly due to the thinning and/or decomposition of the polymer layer.

The strongest dependence between the sensor capacitance and polymer degradation was observed in the accumulation region of the *C–V* curve. Thus, the increase of the capacitance in the accumulation region can be utilized to quantify the progress of the polymer degradation. Fig. 3 presents the chronological course of the capacitance at $V_{bias} = -2$ V for two investigated sensors. Even after 30 days of exposure of the PDLLA films to the alkaline medium, the capacitance of the PMEIS sensors was smaller than that of a bare EIS sensor (50–55 nF), indicating that the polymer films are not yet completely degraded.

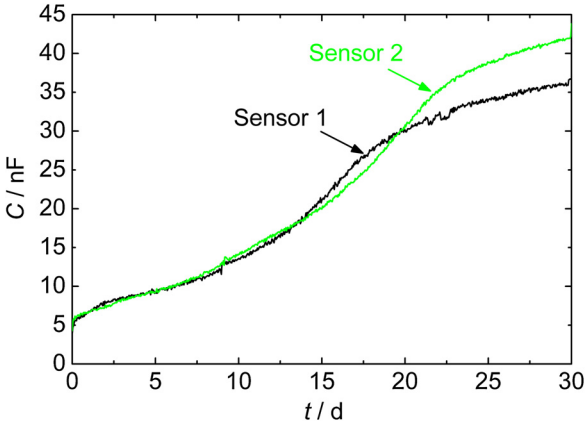

Fig. 3. Time-dependent changes of the capacitance of two PMEIS sensors in accumulation region.

Table 1
Surface roughness of PDLLA thin films evaluated from AFM characterization for different exposure times to buffer solution (pH 10.6, $T = 37\,^{\circ}C$).

Exposure time/day	RMS roughness/nm
1	7
3	16
6	27
8	79
10	45
16	31

3.2. Physical characterization of the polymer films during degradation

The morphology of the deposited polymer films was analyzed with optical microscopy (Keyence VHX II, Keyence, Japan), SEM (Magellan 400L XHR, FEI Company, USA) and AFM (BioMat Workstation, JPK Instruments, Germany). Tapping-mode AFM images were taken at ambient conditions using commercial silicon cantilevers (NCH Pointprobe, Nanoworld, Switzerland) with typical probe tip radii and spring constants of <8 nm and 42 N/m, respectively. The scanned areas were 20 μm × 20 μm.

The results of the morphological investigation are depicted in Fig. 4. Microscopic photographs of polymer-covered sensor chips at different stages of degradation are depicted in the top row. The middle row comprises images of the AFM-surface analysis of polymer samples immersed in buffer solution of pH 10.6 for one day (e), six days (f), 10 days (g) and 16 days (h), respectively. SEM images of polymer films after one day (i), six days (j), 10 days (k) and 16 days (l) exposure to buffer solution are summarized in the lower row. Fig. 4a depicts a PMEIS-sensor surface prior to the degradation experiments. The circular imprint in the microscopic images (Fig. 4b–d) is a result of the O-ring sealing. After ten days, macroscopic ruptures became visible in the PDLLA film (Fig. 4d). Detailed insight into the polymer degradation on the micro-scale level was gained by AFM and SEM analysis. Initially, AFM and SEM revealed a dense and homogenous polymer surface with shallow hollows. The surface appeared smooth, underlined by a root-mean-square (RMS) roughness of 7 nm (see also Table 1, after one day exposure). PDLLA films, which were exposed to buffer solution for six days appeared comparably smooth. However, especially the SEM characterization indicated the inset of micropore formation at the surface of the polymer film (Fig. 4j). After two weeks in buffer solution, the enduring hydrolytic degradation leads to a PDLLA film with a high degree of porosity (Fig. 4h and l). Quantitative information about the surface roughness is overviewed in Table 1. With prolonged exposure time to aqueous solution, the RMS roughness increased and reached a maximum value of 79 nm after eight days in solution. Afterwards, the RMS roughness decreased while, from the SEM images, the degree of porosity seems to continue to rise. Here, further studies are necessary to investigate this phenomenon in more detail.

3.3. Contact-angle measurements

The determination of the contact angle was done by the sessile drop technique using a standard contact-angle goniometer (OCA 15, Data Physics Instruments, Germany) and deionized water as probe liquid. The results of the characterization of the polymer film by means of contact-angle measurements are depicted in Fig. 5.

Prior to the exposure to the degradation medium, the polymer film exhibited a contact angle of 96° (data not shown) underlining its hydrophobic character, which is in good agreement to values reported in literature for non-degraded PDLLA films [29]. With prolonged exposure to the degradation medium a significant decrease of the measured contact angle within the first six days

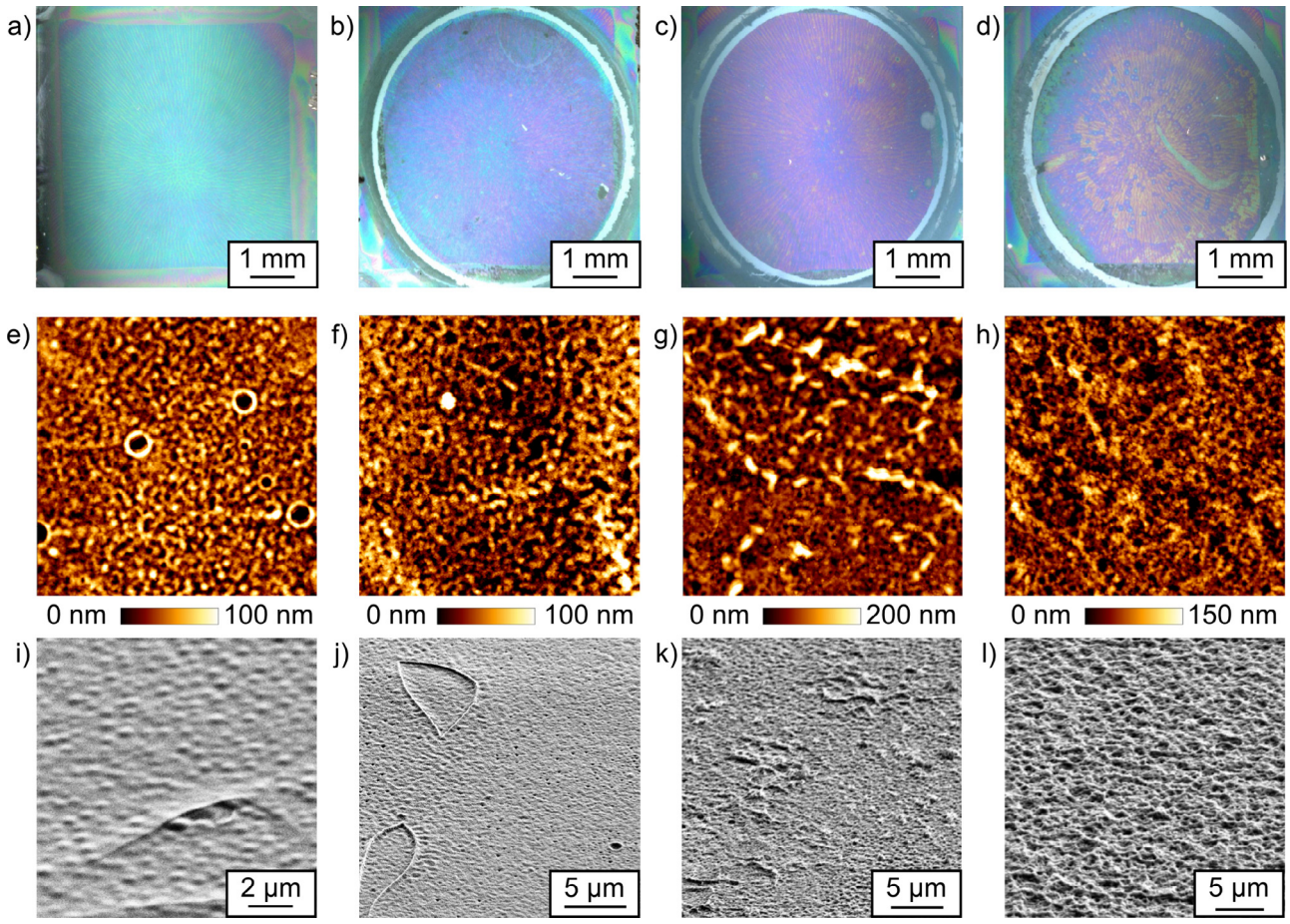

Fig. 4. Optical microscopy (top row), AFM (middle row) and SEM (bottom row) images of non-degraded (a) and degraded PDLLA samples after one day (e, i), three days (b), six days (f, j), eight days (c), 10 days (d, g, k) and 16 days (h, l) exposure to aqueous buffer solution (pH 10.6, $T = 37\,^{\circ}C$), respectively. The scanned area of the AFM images amounted to be 20 µm × 20 µm.

was observed. This could be attributed to both the increased wettability as well as the higher roughness (it has been shown that the contact angle of a hydrophobic surface increases with increasing surface roughness, whereas the contact angle of a hydrophilic surface decreases with increasing roughness [30] of the polymer surface as the degradation progresses. After six days in contact with the buffer solution, the contact angle was approximately 20° and then, remained in the range of 10–20° indicating a hydrophilic surface.

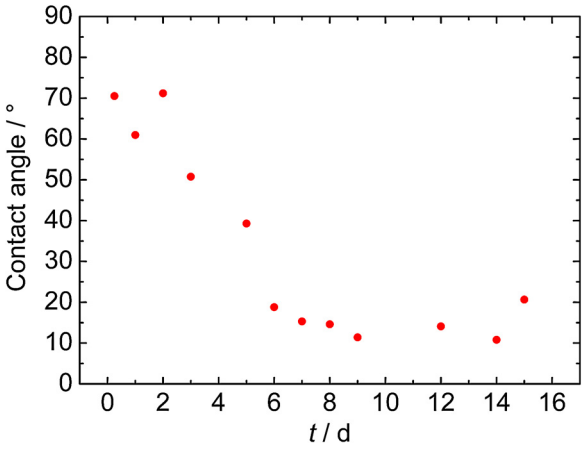

Fig. 5. Water contact angle on the polymer surface in dependence of the degradation time.

3.4. Determination of lactic acid formation

During the degradation and subsequent erosion of PDLLA on the chip surface, the long-chain polymer molecules are cleaved into low-molecular components. However, since PDLLA is only soluble in water below a certain critical molecular weight (1050–1150 Da; [31]), only monomers and oligomers contribute to the bioerosion: they are washed out from the bulk material and thus, can be detected in the degradation medium. Hence, the onset of the release and/or amount of monomers and oligomers washed out from the polymer bulk are also quantities indicating degradation and give information about the progress of the shortening of the chain length.

To determine the concentration of both enantiomers of lactic acid, namely D- and L-lactic acid, a specific enzyme-based assay (R-Biopharm, Germany) was applied. This assay is based on the enzymatic oxidation of lactic acid while the co-substrate nicotinamide adenine dinucleotide (NAD^+) is reduced to NADH. The oxidized and reduced forms of this co-substrate display different UV adsorption peaks. This difference in the adsorption spectra was photometrically quantified by a spectrophotometer (Xion 500, Dr. Bruno Lange, Germany) and thereby, used to determine the concentration of the lactic acid. In order to ensure that all oligomers washed out from the polymer bulk are split into their monomer

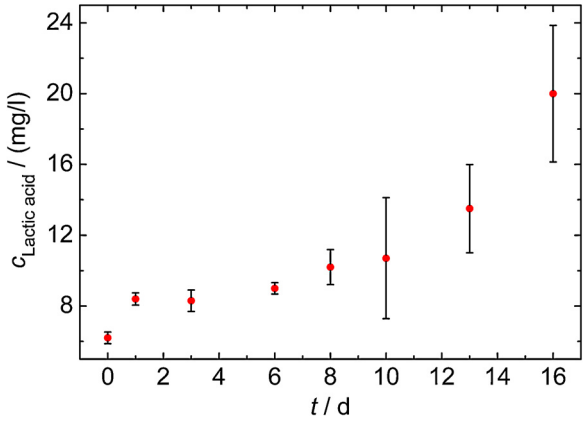

Fig. 6. Time-dependent concentration of lactic acid in the degradation medium measured by the biochemical assay. Each data point represents the average value of three samples. The error bars indicate the standard deviation.

units and,thus, contribute to the result of the assay, the degradation medium of each chip was further stored at 37 °C after it had been pipetted off. At the end of the degradation study, all 24 samples were analyzed at once.

Fig. 6 depicts the time-resolved concentration of the lactic acid monomers released from the polymer layer to the solution. Each data point represents the average value of three samples. The error bars indicate the standard deviation. As can be seen, during the degradation, the concentration of lactic acid increases from 8–9 mg/l to 20 ± 4 mg/l after 1–3 days and 16 days of exposure of the PDLLA to the degradation medium, respectively.

4. Discussion

During the degradation of the polymer film, the mean molecular weight and the amount of van der Waals forces of non-polar methyl groups decrease. At the same time, the amount of polar carboxylic groups increases. As a consequence, the surface of the polymer film becomes more hydrophilic [32]. In accordance, the contact angle decreased from 96° to a constant value in the range of 10–20° indicating a drastic change from a strong hydrophobic to a hydrophilic surface within the first six days of permanent exposure. During this time period, a slight increase of the capacitance of the PMEIS sensor has been observed. The further rising of the sensor signal can be attributed to the progressive erosion, resulting to the thinning and/or decomposition of the polymer layer. At the same time, the release of degradation products from the polymer bulk will result in the formation of pores inside the polymer bulk, which will be filled with water molecules. This process could also affect the global capacitance/impedance of the PMEIS sensor. The described erosion mechanism is supported by a continuous increase of the concentration of lactic acid in the surrounding solution after six days of degradation (see Fig. 6) and the decrease of surface roughness (see Table 1). Since bumps at the polymer surface feature a larger surface area, the release of degradation products to the solution, *i.e.*, the erosion of the polymer film can proceed more efficiently and finally causes a smoothing of the surface.

5. Conclusions and outlook

The use of capacitance–voltage measurements of polymer-covered EIS sensors has enabled real-time *in situ* monitoring of the (bio)degradation process of polymers. This has been successfully demonstrated by measuring the change of the accumulation capacitance as an indicator of the degradation of PDLLA. The polymer degradation induced capacitance changes of the PMEIS sensor were additionally verified by changes of the hydrophobicity, the surface morphology, and the increased concentration of lactic acid in the degradation medium. For the development of new biodegradable polymers, PMEIS sensors can gather information about the degradation behaviour of the polymers rapidly and under varying environmental conditions. Since EIS sensors are simple in layout, easy and low cost in fabrication, they are suitable for realizing multiplexed analyzing systems for “high throughput” degradation studies on multiple polymers and/or degradation conditions. It is conceivable that this technique can be advantageous for studies on the effect of additives (*e.g.*, drugs, residual solvents, polymerization initiator) on degradation kinetics, but also for a deeper understanding of degradation processes and erosion profiles, in general.

Of course, the processes inside the body are much more complicated that requires additional *in vivo* degradation studies in detail. Future experiments will be directed to test the feasibility of the proposed approach for a long-term (several months) degradation studies, where possible formation of biofilms on the polymer surface could affect signal behaviour of the sensor and lead to misinterpretation of the signal changes.

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