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Inductively coupled passive resonance sensor for monitoring biodegradable polymers in vitro

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Abstract

Capacitive sensors can be used to monitor changes in materials by monitoring complex permittivity. Inductively coupled passive resonance sensors provide means to make short range wireless permittivity measurements if the sensors are embedded in the tested material. In this study, inductively coupled sensors were embedded in biodegradable polymers, which are important materials in regenerative medicine. However, it is challenging to observe their decay especially *in vivo*. After preparing the samples by compression moulding, the encapsulated sensors and a reference series were immersed in buffer solution. The signals from the passive resonance sensors were measured for eight weeks. In addition, mechanical and chemical testing was periodically carried out to monitor the state of the reference series. The wirelessly measured signals are compared with water absorption, flexural modulus, glass transition temperature and viscosity.

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1. Introduction

Biodegradable polymers are used as orthopedic implants in reconstructive surgery and as scaffolds in tissue engineering. Unlike conventional metallic implants, they eliminate the need for a removal operation and the related costs, infection risk and pain. Such polymers should maintain certain application-specific structural and mechanical properties for a designated period. Most of the conventional polymer characterization techniques like gel permeation chromatography (GPC) for molecular mass distribution, differential scanning calorimetry (DSC) for phase transition

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as well as mechanical tests are nevertheless destructive to the sample [1], leading to discontinuous sample monitoring even *in vitro*. As the degradation mechanics of some polymers are significantly different *in vivo* or show variation even between different patients, suitable methods are needed for online monitoring and material testing. Since inductively coupled passive resonance sensors can be used to monitor the complex permittivity of materials [2], we embedded specifically designed sensors into two types of biodegradable poly(lactide-co-glycolides). The aim was to test if the passive resonance sensors can be used to predict or indicate verifiable changes in biodegradable polymers.

2. Materials & methods

2.1. Sensor fabrication

The inductively coupled passive resonance circuits were specifically designed for the encapsulation process. The 20 mm by 20 mm by 1.60 mm circuits were fabricated using a four-layer circuit board design. A sensor consists of a finger-electrode sensing structure, a parallel-plate capacitor and a coil (Fig. 1a). The thickness of the copper layer was 35 μm .

2.2. Encapsulation

The two polymer types (both obtained from Purac Biochem B.V., Netherlands) used in the study were hydrolytically degradable poly(L-lactide-co-glycolide) [80:20] (PLGA) and poly(DL-lactide-co-glycolide) [85:15] (PDLGA). The materials were first dried in a vacuum chamber, after which polymer sheets (32 mm by 32 mm by 2 mm) were compression moulded from the polymer granules using a NIKE Hydraulics type ZB110 (Eskilstuna, Sweden) machine and a specifically designed metallic mould. The sensors were then encapsulated between two sheets that were also compression moulded around the circuits to form a seamless capsule (Fig. 1d).

2.3. Resonance measurements

Each encapsulated sensor was fixed on the bottom of a plastic container, after which 100 ml of Sørensen buffer solution was added. The samples were stored in an incubator at $+37^\circ\text{C}$ and the buffer solution was changed every other week. An inductive link was used to measure the encapsulated sensors wirelessly (Fig. 1b) through the bottom of the container by using a reader coil (35 mm in diameter) in a similar way as in [3]. Phase responses of the encapsulated sensors were measured with an in-house reader device at the frequency range from 20 MHz to 40 MHz. The baseline signal was removed. A sensor created a phase-dip in the measured data (Fig. 1c). The frequency (f_{md}) and the bandwidth (BW_p) of the dip were extracted by fitting a polynomial model to the phase-dip data and using the model to

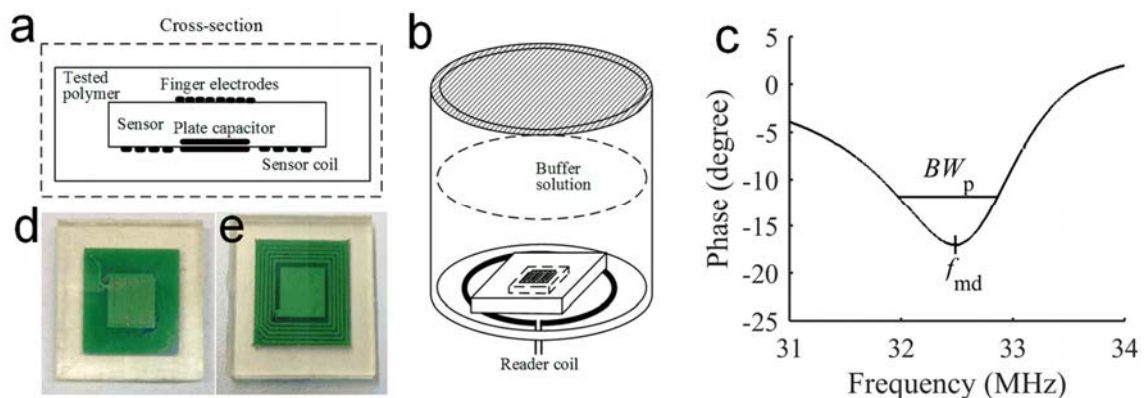


Fig. 1 (a) The cross-section of the encapsulated sensor; (b) The measurement setup; (c) A phase response and the extracted features; (d) A sensor in PLGA; (e) A sensor in PDLGA

interpolate the needed values. The measurements were carried out in the time period of eight weeks. The results measured one day after immersion were used as a comparison point to calculate the changes in the features. Two encapsulation of each tested polymer failed within the test period. This was detected as a sudden rise in the feature BW_p . Signals after that point were discarded.

2.4. Conventional polymer characterization methods

Reference test samples from both polymer types were immersed in Sørensen buffer solution at 37°C. The samples were tested at time points of 0, 2, 4, 6 and 8 weeks. Water absorption was measured by weighing the samples with an analytical scale immediately after taking them out from the buffer solution and comparing the resulting wet weights with the dry weights. The three-point bending test was done with an Instron 4411 (Instron Ltd., England) machine according to the SFS-EN ISO 178 Plastics – Determination of flexural properties standard. Glass transition temperatures (T_g) were measured using a Q1000 differential scanning calorimeter (TA Instruments, USA). An automated Ubbelohde viscometer (LAUDA, Germany) was used to determine the inherent viscosities of the samples.

3. Results & discussion

Biodegradable poly(lactide-co-glycolides) are formed by copolymerizing L-lactide or DL-lactide with glycolide. The different lactide forms originate from the optical activity of the molecule with L-lactide being the naturally occurring form. When comparing pure poly(DL-lactide) and poly(L-lactide), the latter has a slower degradation rate [4]. When it comes to poly(lactide-co-glycolides), generally an increased glycolide content leads to an accelerated decrease of molecular weight [5]. The used PLGA 80/20 and PDLGA 85/15 are both bulk degradable, which means that during the first few days, water absorbs to the polymer matrix until it is saturated. Next, the molecular weight of the polymer chains starts to decrease as water hydrolyzes the polymer bonds [6].

The results of the conventional polymer testing methods are shown in Fig. 2. Mechanical testing showed that the modulus of the PDLGA samples decreased significantly during the test period as opposed to the PLGA which retained its mechanical properties rather well. As shown in Fig. 2b, the PLGA absorbed water before the test point in second week. After that point, the water absorption level did not significantly increase. The water absorption level of PDLGA samples increased significantly during the test period. We also visually saw the PDLGA core softening after two weeks and eventually becoming a viscous liquid with a harder outer shell as the hydrolysis proceeded. We believe this phenomenon is a consequence of autocatalysis [6]. The viscosity, which represents the molecular size, indicated that the polymer chains in both sample types are continuously cleaved during the eight-weeks hydrolysis. This is in agreement with a previous report studying the degradation of PLGA 80/20 films [7]. The T_g of PDLGA samples decrease steeper compared with the T_g of PLGA samples during the first four weeks, after which the values of PDLGA diminished at a clearly faster rate. The reduction in T_g can be interpreted as the degraded polymer chains and fragments moving more easily around each compared with long polymer chains.

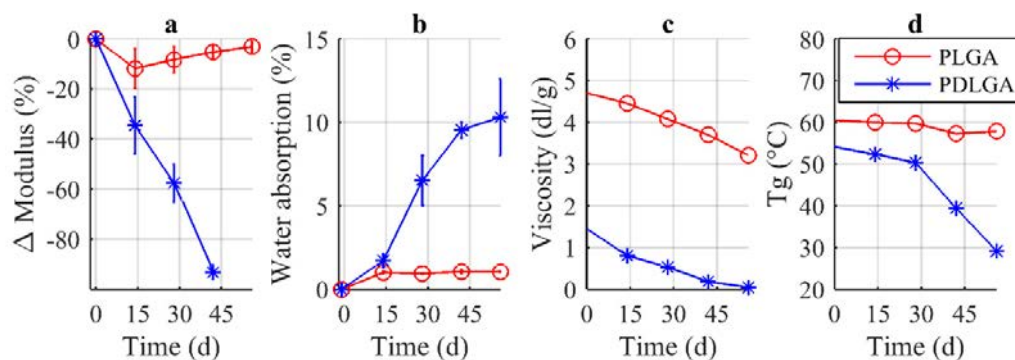


Fig. 2. (a) Modulus; (b) Water absorption; (c) Viscosity; (d) Glass transition temperature.

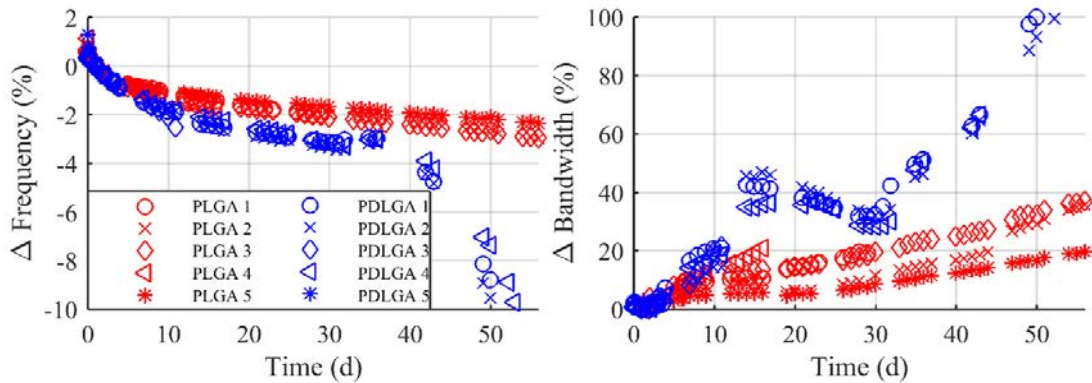


Fig. 3. The changes in the inductively measured frequency (f_{md}) and bandwidth (BW_p) of the phase-dip.

The changes in the frequency (f_{md}) and the bandwidth (BW_p) of the phase-dip are shown in Fig. 3. The initial drop of the feature f_{md} is expected to originate from water absorption into the polymer matrix. In the case of PLGA, the feature f_{md} continued to drift at a steady and slow rate. The measurement system was able to indicate differences that occurred within a day. This drift cannot be fully explained with water absorption into the polymer since the reference measurement showed that water absorption does not significantly increase in PLGA after the second week test point. In the case of PDLGA, the feature f_{md} started to drop significantly around the day 40. A possible connection between the conventional polymer characterization results and the inductively measured features was found between the feature f_{md} and the glass transition temperature measurement. Both signals dropped around six weeks in hydrolysis.

The BW_p of PLGA samples appeared to increase as the hydrolysis progressed. However, the BW_p of PDLGA samples had multiple phases. It increased first roughly two weeks. Then it decreased until the day 30 and after that it started to increase again. Such an up-and-down type of behavior is not seen in any of the PDLGA reference tests. Thus, the bandwidth measures material properties that cannot be directly coupled to the standard measurement. In the case of PDLGA material, the changes in the inductively measured features f_{md} and BW_p occurred at the different time frames. This indicates that the features can be linked to separate phenomena.

In conclusion, the PDLGA samples were noticed to degrade almost entirely during the tested period, while the PLGA samples showed reduced molecular size but hardly any other signs of degradation. An extended test period is needed to observe the degradation of PLGA samples. We suggest that the degradation of biodegradable polymers can be monitored wirelessly using inductive coupled passive resonance sensors. Linking the wirelessly measured features to any conventional measurements requires more extensive studies. The changes in the extracted feature f_{md} seemed to be partly connected with water absorption and decreased polymer chain length. Attaching sensors to polymers is still a challenging and time consuming process. Tests with different materials, extended test periods and possibly more frequent reference measurements are needed to get a deeper insight into the phenomena connecting the resonance measurements and polymer degradation.

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