In vitro evaluation of the long-term stability of polyimide as a material for neural implants

Birthe Rubehn a, b, *, Thomas Stieglitz a, b

a Laboratory for Biomedical Microtechnology, Department of Microsystems Engineering – IMTEK, University of Freiburg, Georges-Koehler-Allee 102, 79110 Freiburg, Germany
b Bernstein Focus Neurotechnology – Freiburg/Tuebingen, Freiburg, Germany

ARTICLE INFO

Article history:
Received 6 November 2009
Accepted 12 January 2010
Available online 9 February 2010

Keywords:
Neural prostheses
Polyimide degradation
Accelerated aging
Mechanical properties
Phosphate buffered saline

ABSTRACT

In order to be used as a material for neural prostheses, polyimide has to withstand the body environment over years. To obtain more information about the long-term stability of this material, we tested three commercially available polyimides (PI2611 – HD-Microsystems (type: BPDA-PPD), U-Varnish-S – UBE (type: BPDA-PDD), Durimide 7510 – Fujifilm (type: information not provided)). Specimens were stored in phosphate buffered saline (PBS) at 37 °C to simulate body temperature and at elevated temperatures of 60 °C and 85 °C to accelerate aging. During the course of 20 months, stress-strain curves were measured monthly by tensile testing. From these curves the Young’s modulus, the stress and strain at break, the fracture energy were extracted and used to characterize and to statistically evaluate the mechanical material properties. Mass loss was determined by weighing polyimide foils (Upilex25S - UBE) and optical measurements were conducted to examine changes in chemical structure and crystallinity. At 37 °C and 60 °C no change in material behavior could be observed, except for an increase of the Young’s modulus of the BPDA-PPD type stored at 60 °C. This demonstrates the long-term stability of all tested polyimides with respect to PBS. All extracted quantities mentioned above, as well as the mass, decreased in specimens stored in PBS at 85 °C. As a comparison, BPDA-PDD type specimens stored at 85 °C in deionized water showed no change in any property but behaved similarly to the reference material.

1. Introduction

For the past three decades polyimide (PI) has been used successfully as a substrate and insulation material for neural implants, and has therefore been proposed for long-term applications [1–4]. Interfacing with complex and sensitive neural tissue requires small and flexible implants. Polymers are well suited to this purpose. They act as a mechanical substrate to support the conductor paths and electrically insulate them against the body liquid. PI is used due to its chemical and mechanical durability, and because it can be processed in a standard clean room facility, whereby large numbers of electrodes and feature sizes in the micrometer range can be implemented.

The term “polyimide” does not only refer to one chemical structure but stands for a whole group of polymers. The best known PI type is poly(4,4-oxydiphenylene-pyromellitimide) or PMDA-ODA, (tradename: Kapton, DuPont, Wilmington, DE, USA) and a lot of research was done on it [5–8]. Kapton is known to be affected by humidity and was therefore disapproved as an implant material. The PI types used in this study belong to a newer generation of PIs with improved properties such as lower water uptake and hydrolytic stability [9]. Especially the PI type biphenyltetra-carboxylic dianhydride/para-phenylenediamine or BPDA-PPD (tradename: U-Varnish-S (UBE) or PI2611 (HD-MicroSystems)) was successfully used in neural implants [3,4,10] and hence is studied in this work.

Although PI has not yet been approved by the United States Food and Drug Administration (FDA), its biocompatibility in animal models is well documented [11–14]. Nevertheless, knowledge of the improved PI types’ long-term degradation behavior in biological tissue remains poor and has to be evaluated. While some studies present data dealing with the degradation of PI in a high temperature and/or humid environment [5,7,15,16], little is known about the long-term behavior of PI stored in body tissue or at least saline solution. In in vivo studies up to 12 months, no electrical failures could be observed [17,18]. But a decrease in tensile strength was reported on PI electrodes after 11 months in vivo [19]. In the
current study, we used phosphate buffered saline (PBS) in which the PI specimens could be stored at elevated temperatures to accelerate aging. We found that PBS provided a better model of body fluid than water, and had an altogether different effect on the degradation behavior of PI.

In this study we investigated the mechanical properties of the PI foils to evaluate their applicability as a substrate material. After storing the material at 37°C and at elevated temperatures (60°C and 85°C), the mechanical properties were examined with tensile tests, weighing tests and optical measurements in order to obtain information on the degradation behavior. While the tensile testing showed changes in the mechanical properties like Young's modulus, stress and strain at break, or the fracture energy to determine the onset of mechanical material failures. The weighing test was used to gain information about mass loss, water uptake and the change of water uptake over time to detect the material degradation. Optical analysis methods like Fourier transform infrared spectroscopy (FTIR), X-Ray Diffractometry (XRD), and X-ray photoelectron spectroscopy (XPS) gave information about changes in the chemical structure, crystallinity, and chemical composition, respectively.

2. Materials and methods

2.1. Tensile tests

The tensile test with a uniaxial load is easy to conduct and provides a stress-strain curve as the standard parameter which is common and often used in engineering.

2.1.1. Specimen layout

The rectangular layout of the PI specimens met the requirements of ASTM D882-02[20] but the dimensions were scaled down to make the specimens comparable to PI-based micro-implants. Specimens were made of MEMS-processed foils with a thickness of 6.4 μm–7.6 μm, length 40 mm and width 1 mm.

2.1.2. MEMS-processing

Since PI comprises a group of different polymers with different material properties, we chose three PIs from three different manufacturers. We purchased the fluid precursors PI2611 (HD Microsystems LLC, Parlin; NJ, USA), Durimide 7510 (Fujifilm Electronic Materials Co., Ltd., Tokyo, Japan) and U-Varnish-S (UBE Industries Ltd., Tokyo, Japan). PI2611 is well established in neural prostheses research due to its low water uptake. U-Varnish-S has the same chemical structure (BPOA-PPD) as PI2611. Durimide 7510 has a different chemical structure and contains a photo-initiator and an adhesion promoter.

The PI precursors were spin coated on silicon wafers for 30 s at 2400 rpm (Durimide) and 2000 rpm, respectively (PI2611, U-Varnish-S). To enable detachment of the specimens from the wafer after processing, the wafers were cleaned in hydrofluoric acid for 15 s before spin coating (PI2611, U-Varnish-S). Since Durimide contains an adhesion promoter, the wafers had to be coated with a passivation layer of CaF2 which inhibited the adhesion of the PI to the silicon. After spin coating, the wafers were put on a hotplate for 2 min at 120°C (PI2611, U-Varnish-S) and at 100°C (Durimide) respectively. Subsequently, Durimide was exposed to UV-light for 15 s at 9 mW/cm². The PI layers were cured under nitrogen atmosphere (furnace: YES-459PB-2PE-CP, Yield Engineering Systems Inc., San Jose, CA, USA). For Durimide and PI2611, the temperature was ramped up to 60 min and then hold for 60 min at 350°C. For U-Varnish-S, the temperature was ramped up to 170 min and held for 10 min at 450°C. Two layers of the photore sist AZ9260 (MicroChemicals GmbH, Ulm, Germany) were spin coated at 1600 rpm for 30 s to form a layer of 28 μm. A mask aligner (MM, Süss Microtec AG, Garchingen, Germany) was used to expose the photoset on a chromium photomask; this defined the peripherals of the specimens. After developing (developer solution: AZ400K, MicroChemicals GmbH, Ulm, Germany), the structured photoset protected the underlying PI in the following etching step. The PI was etched for 25 min in an O2-plasma (200 W, 30 mTorr, 50 sccm O2, RIE Multiplex, STS, Newport, UK). After stripping the photoset on aceton, the specimens were pulled off the wafer by tweezers.

2.1.3. Specimen storing

After detaching from the wafer, the specimens were stored in phosphate buffered saline (PBS; 0.138 M NaCl, 0.0027 M KCl) with a pH-value of 7.4 ([F913, Sigma-Aldrich Chemie GmbH, Steinheim, Germany]) at 37°C, 60°C and 85°C, respectively. The temperature of 37°C corresponds to the temperature of the human body, while 60°C is said to be the upper limit for plastics in accelerated lifetime testing, under the assumption of ageing of the material due to Arrhenius behavior [21,22]. The highest temperature of 85°C was chosen because of its standard use in moisture testing of electronic devices. (For example, to investigate the influence of moisture in electronic packaging, specimens are stored at 85°C and 85% relative humidity for 168 h–5000 h [23,24]). Additionally, a group of specimens made of PI2611 was stored in deionized water at 85°C. For each material, some specimens remained on the wafer and were stored as a reference at room temperature in an evacuated exci sator to keep them dry.

2.1.4. Test procedure

The first measurement was conducted two weeks after immersing the specimens in solution and was then repeated every four weeks. During one measurement, 60 specimens were taken per material (15 per each temperature and 15 as reference, for PI2611 15 were additionally measured that were stored in deionized water to compare the influence of water and saline solution on the PI degradation). The specimens were taken out of the solution and allowed to dry on a sheet of paper for some minutes while cooling down to room temperature. Each specimen was clamped between the clamp jaws of a tensile tester (HZW-Zwick-Line, Zwick/Roell, Ulm, Germany). The clamp jaws moved apart and when the initial load of 2 MPa was reached, the software started the measurement and the stress-strain curve was recorded until the specimen ruptured. The test velocity of the clamp jaws with respect to each other was 50 mm/min. The force acting on the specimens was measured with a 50 N load cell (KAP-TC, A.S.T. GmbH, Wolnzach, Germany). The stress-strain curve showed the stress (force per initial cross section) plotted over the strain (length difference between the initial length of the specimen and the elongated length, divided by the initial length). All statistic tests were conducted in GNU octave, version 3.0.1 [25].

2.2. Gravimetric analysis

A standard PI foil (210 mm by 300 mm by 25 μm, ca. 2.4 g, Upilex255, UBE Europe) was purchased from the manufacturer. Upilex255 is the trade name of a foil made of the precursor resin U-Varnish-S. The foil was cleaned with acetone and isopropanol, cut into pieces of approximately 50 by 50 mm², and stored in the same PBS solution as the tensile test specimens. Every 4 weeks the pieces were rinsed with deionized water and dried with a cloth. After allowing the pieces to dry at room temperature and pressure for 5 min, they were weighed on a standard laboratory weighing scale (TE64, Satorius, Göttingen, Germany). Subsequently, the foil was dried in a furnace at 85°C for 24 h, weighed again to determine the dry mass without water, and put back into PBS at 85°C.

2.3. Optical analysis

To evaluate whether the chemical or crystalline structure of the PI changed during the long-term test, the foils of the gravimetric analysis were tested with optical analysis methods.

2.3.1. Fourier transform infrared spectroscopy (FTIR)

A Upilex255 sample and a reference foil were measured with FTIR. The sample foil was stored in PBS at 85°C for 17 months and the reference was obtained from the manufacturer and stored at normal ambient atmosphere. Both foils were dried for 24 h in an excisator and subsequently measured by FTIR using an attenuated total reflectance (ATR) unit. On each specimen 10 measurements were conducted each at a different position on the foil.

2.3.2. X-Ray Diffractometry (XRD)

XRD can be used to detect whether the polymer is crystalline and whether the crystallinity changes during storage. Upilex255 foils were measured after 7 months (in PBS at 37°C and 60°C, in deionized water at 85°C) and after 23 months (in PBS at 85°C). The reference was a non-treated foil stored at normal ambient atmosphere. The specimens were taken out of solution, rinsed with deionized water, and dried for 24 h in an excisator at room temperature. Wide angle X-ray diffraction (WAXD) measurements were conducted with a Siemens D5000 (Siemens AG, Munich, Germany) in reflection mode.

2.3.3. X-ray photoelectron spectroscopy (XPS)

To check whether ions of the PBS diffused into the polymer during storage, XPS measurements were conducted. Upilex255 foils were measured after 22 months (PBS at 85°C) and 6 months (DI at 85°C, PBS at 37°C and PBS at 60°C) of storing in solution. A non-treated foil stored at normal ambient conditions was used as a reference. After taking the foils out of solution, they were rinsed in deionized water for 3 min and dried for 24 h in a vacuum of 2 × 10⁻⁷ mbar. Measurements were performed with a Perkin Elmer PHI 5600 ESCA (Perkin Elmer, Waltham, MA, USA) using a magnesium X-ray source emitting photons with 1253.6 eV. The survey was measured with a step size of ~0.8 eV and the detail with ~0.025 eV.

3. Results

3.1. Tensile tests

A stress-strain curve was obtained from every tested specimen. A typical stress-strain curve with the specific values used to
characterize the material behavior is depicted in Fig. 1. The Young's modulus \( E \) (in GPa) is the gradient of the straight line representing the elastic behavior of the material. The tensile strength \( \sigma_{\text{max}} \) in MPa coincided with the tensile stress at break. The strain maximum is the strain at break \( \varepsilon_{\text{max}} \) in % relating to the initial length. To characterize the plastic behavior of the specimen at values far below strain at break, the stress at a strain value of 10% was chosen \( \sigma_{10} \) in MPa. As a measure of ductility, the fracture energy was calculated as the area under the stress-strain curve [26]. Fig. 2 shows the development of the stress-strain curves for PI2611 over 17 months, stored in PBS at 85 °C. Each plot shows the curves of 15 specimens measured in one session. Curve (a) shows a dry reference stored at room temperature in a dry atmosphere. Curves (b), (c) and (d) show the tensile behavior of specimens stored in PBS after 8, 12, and 14 months respectively. The plot also contains a sample measured after 17 months in PBS with a maximum stress at break of 25 MPa and a maximum stain at break of 2% and therefore is concealed by the other sample curves. To give an overview over the long-term behavior, the values of \( E, \sigma_{\text{max}}, \varepsilon_{\text{max}}, \sigma_{10} \) and fracture energy of every temperature and material are plotted over time of storage in PBS (Fig. 3). Each column depicts one specific value measured with each of the three PIs. Each row shows the different specific values of one PI: PI2611 (Fig. 3(a)), U-Varnish-S (Fig. 3(b)), and Durimide 7510 (Fig. 3(c)). Each point represents the mean of the values derived from one sample i.e. 10–15 tested specimens; error bars show +/- standard deviation. Each curve shows the development of one specific value derived from specimens stored at a certain temperature. Not all displayed values could be calculated from the data of 15 specimens due to measurement failures but represent at least 10 specimens. The stress-strain curve of every specimen was plotted and examined. Data that did not show a straight line directly at the beginning of the measurement were rejected, due to the fact that the raw data record of these specimens started before the stress reached the initial value of 2 MPa, resulting in erroneous specific values. This led to 531 samples out of a total of 3968 (13%) being rejected, giving an average of 13 specimens per test sample. By comparing the data plots without the rejected data to those plots containing all data, no differences of the specific values and their development could be observed. However, the standard deviation was less when rejecting the erroneous data (Fig. 3).

The mechanical properties \( (E, \sigma_{\text{max}}, \varepsilon_{\text{max}}, \sigma_{10} \) and fracture energy) of each test sample were then tested for normality with the Anderson-Darling-Test. 66% of the samples were normally distributed (95% confidence interval); we therefore used the nonparametric two-sample Kolmogorov–Smirnov test to check whether the mechanical properties of the test samples differed significantly from those of the reference samples stored at room temperature and pressure. Probability \( p \) values less than 0.05 led us to reject the null hypothesis that the test sample and the reference sample derived from the same distribution.

Each comparison is depicted as a field in the color bar above each plot. The horizontal bar shows the development of the value of the reference sample stored at a certain temperature compared to the reference sample. Its color indicates the size of the corresponding \( p \)-values: values larger than 0.05 are depicted in yellow, values less than or equal to 0.05 and larger than 0.01 are in orange, values less than or equal to 0.01 and larger than 0.001 are in red, and values less than or equal to 0.001 are in dark red. Each field of the color bar corresponds to a point of the development curves in the plot below the color bar.

The Young’s Modulus shown in these plots was calculated by fitting a straight line to the measured values between 0.25% and 0.5% of strain. The standard values for calculating the Young’s Modulus are between 0.05% and 0.25% of strain [27]. As mentioned above, due to the low value of 2 MPa as the starting point for the measurement, most of the measured stress-strain curves were inaccurate in this strain range. At larger strain values, the standard deviation of the Young’s Modulus decreased, while the mean value and the development over time remained the same. The measured values of the reference samples correspond to values provided by the manufacturers (U-Varnish-S: \( E = 9.3 \text{ GPa}; \) PI2611: \( E = 8.45 \text{ GPa}; \) Durimide: \( E = 2.5 \text{ GPa} \)). Our method for calculating the Young’s Modulus is consistent with the standard method of drawing a tangent to the initial linear portion of the load-extension curve and calculating the gradient [20].

The stress at 10% strain values were only calculated for specimens that reached the 10% strain value. Specimens that broke before this point had a stress of 0 MPa at 10% strain and thus increased the standard deviation of the sample, thus the data of these specimens were not taken into account when calculating the mean and the standard deviation of the stress at 10% strain (Fig. 3). For comparison we produced a similar plot including specimens that broke below 10% the trend was identical, but with a higher standard deviation (data not shown).

Over the course of 20 months, the mechanical properties of all three PI types stored in PBS at 37 °C did not change with respect to
Fig. 3. Overview of the tensile test results: each column depicts one specific value measured with each of the three PIs. Each row shows the different specific values of one PI: (a) PI2611, (b) U-Varnish-S, and (c) Durimide 7510. The color bar over each diagram represents the development of the p-value over time. Each field represents the p-value resulted from the Kolmogorov–Smirnov test. Values larger than 0.05 (yellow) show that there is no difference between sample and reference. Values less or equal 0.05 (0.05 ≥ p-value > 0.01 in orange; 0.01 ≥ p-value > 0.001 in red, 0.001 ≥ p-value in dark red) stand for a significant difference between the sample and the reference sample.
the reference. This also applied to the specimens stored at 60 °C excluding the Young’s modulus of PI2611 and U-Varnish-S. All data points showed a large standard deviation and a large day-to-day variation. Nevertheless, three significant changes could be observed. Specimens stored in PBS at 85 °C showed a decrease in all monitored specific values (Fig. 3, red dots). This was found for all three materials. The first samples that showed this trend and significantly differed from the reference samples were measured at the earliest in month number 2 (stress at 10% strain of PI2611) and at the latest in month number 14 (strain at break of Durimide 7510), respectively. The second trend was only observed for the Young’s modulus of specimens made of PI2611 and U-Varnish-S, namely: the properties of PI2611 specimens stored at 85 °C started to split into pieces during rinsing with deionized water or significant mechanical stress, these foils developed creases and reaching a limit at 95% of the initial dry value. After replacing the PBS with new solution in month number 18, the mass loss continued. A second stop of the mass loss could be observed after month number 22 when \( m_{\text{dry}} \) reached 92.5% of the initial value. Fig. 5 displays the mass of differently stored foils after drying. Compared to the foil stored in PBS at 85 °C (diamonds) that already lost mass after 2 months, the foils stored in PBS at 37 °C (triangles) and 60 °C (dots), and the sample stored in deionized water at 85 °C (squares) showed no mass loss after 9 months. The water absorption of the unchanged samples was constant over time at 11%. The water uptake of 1.46% in samples stored in PBS at 85 °C corresponds with the information given by the manufacturer, which reports a water absorption of 1.4% after immersing the sample in water at 23 °C for 24 h.

The foils stored in PBS at 85 °C also changed its macroscopic behavior over time. Despite the fact that they were not subject to significant mechanical stress, these foils developed creases and started to split into pieces during rinsing with deionized water or while being handled during the monthly weighing process (Fig. 6, left).

### 3.2. Gravimetric analysis

By storing the PI foil Upilex25S in PBS at 85 °C, a decline in foil mass could be observed by measuring the foil directly after taking it out of solution (Fig. 4, squares) as well as after subsequent drying for 24 h at 85 °C in an oven (Fig. 4, dots). The values were normalized by the initial mass value of the foil at month 0. After immersing the foil for 25 months, it had lost approximately 7.5% of its initial mass while the water absorption remained stable over time with a mean value of 1.46%. The water absorption was calculated according to:

\[
A = \frac{m_{\text{im}} - m_{\text{dry}}}{m_{\text{dry}}} \times 100
\]  

where \( A \) is the water absorption in %, \( m_{\text{im}} \) is the foil mass after immersion and \( m_{\text{dry}} \) the foil mass after drying for 24 h at 85 °C. In the first months the mass was significantly decreasing until}

![Fig. 4](image-url)  

**Fig. 4.** The development of the mass of a PI film (Upilex25S, UBE) stored in PBS at 85 °C measured directly after taking the film out of solution (squares) and after subsequent drying for 24 h at 85 °C (dots). The values are normalized by the initial mass value of the foil at month 0.

For FTIR spectroscopy, two foils were measured at 10 different positions each. The mean of the 10 measurements is shown in Fig. 7. No changes in light absorption could be observed.

The XRD measurement (Fig. 8) revealed a semi-crystalline structure of the polymer material. Two broad peaks could be observed at the angles of \( 2\theta = 18^\circ \) and \( 2\theta = 25.4^\circ \), corresponding to a lattice spacing of the crystal regions of 4.7 Å and 3.4 Å respectively. The foils stored in PBS at 37 °C and 60 °C as well as in deionized water at 85 °C showed no change with respect to the reference, whereas the foil stored in PBS at 85 °C showed a decrease in crystallinity and a change in the crystal structure (the peak at 18° decreased and split up in two peaks at 18° and 19°). A detailed measurement was conducted to determine whether the peak decreased or just changed to a higher one with less width and was concealed due to the measurement resolution. But even with a smaller angle step size, no peak was found (Fig. 8, detail).

XPS measurements (Fig. 9) gave no indication of contamination by sodium, potassium, chloride or phosphorous ions, for foils stored...
in deionized water, PBS, or for the reference. It is possible that the limited resolution of the survey spectrum would allow the significant carbon peak to conceal a potassium peak in the K2p2/3 region. Therefore we conducted a more detailed spectral measurement with a step size of \(0.025\) eV (Fig. 9(b)). Even at this higher resolution, no potassium could be observed. In contrast, a significant presence of calcium was observed in the test foils, as evidenced by a Ca2p peak at 350 eV in the survey spectrum, which was not observed in the references (Fig. 9(a)).

4. Discussion

Both the large standard deviation and the day-to-day variation of the mechanical properties (Fig. 1) can be explained by the dimensions of the tensile test specimens. The ASTM 882-02 test specifications [20] describe the test procedure for foils using a minimum foil thickness of 625 \(\mu\)m and a width of 5 mm. In contrast, we used specimens with a thickness of 7 \(\mu\)m and a width of 1 mm. According to ASTM 882-02 this would be expected to enhance the effects of edge flaws. Notches at the edge have a higher influence on the measured properties of narrow and thin specimens than on ASTM-conforming specimens [20]. Under a light microscope, the edges of the specimens were smooth, while scanning electron microscope images revealed a rough surface with ridges in the submicrometer range (Fig. 10) which could have contributed to the high standard deviation of values at break \((\tau_{\text{max}}\) and \(\sigma_{\text{max}}\)). This is consistent with a previous observation that the tensile strain at break shows high statistical scatter [27]. Nevertheless, the small dimensions of our test samples are in the range of those for micromachined PI-based neural implants. Thus, this tensile test is more of a structural test than a purely materials-based analysis. Furthermore, a specimen made of a thin foil of spin-coated PI has different material properties from thicker, bulk material. Anisotropy can occur due to the forces that affect the precursor during spin coating, and due to the solvent loss and imidization of a thin film from a precursor solution which can in turn lead to a higher degree of molecular orientation of the preferential chain axis parallel to the foil surface [28–31]. It was found that spin-coated PI material in the vicinity of the surface has a different morphology than in the bulk material, by nature of a higher degree of crystallinity [32]. Hence, the dimensions of the tensile test specimens we used and their manufacture are in close correspondence to the processing of PI for neural implants, and could provide useful insights into the behavior of these materials during long-term implantation.

No difference in behavior between the reference group and the group stored at 37 \(^\circ\)C could be observed for any of the tested materials or monitored specific values. Additionally, no mass loss and no change in optically measured properties could be detected in Upilex25S at the same temperature. Based on these results, we conclude that the materials can be used at body temperature for a minimum time of 20 months. This is in agreement with the observation that PI sieve electrodes still function after 12 months implantation in vivo [17,18]. However, neither of these studies looked at possible changes in material properties of the implants. In contrast, Schuettler et al. [19] reported on sieve electrodes made of PI2611. Examined after 11 months in vivo, these electrodes showed a decrease by 30% of the initial stress at break as well as delamination of metal and PI. This could be due to a factor that was not included in our in vitro tests, namely the effect of enzymes on polymeric degradation, which has been described for other polymers like poly(ether urethanes) [33]. Thus, although PBS, by containing the same composition of ions and having the same pH
value as body fluid, is a more accurate model of body fluid than water, it is not definite that the material shows equal behavior in vivo and in PBS.

For specimens stored at 60°C, the mechanical properties did not degrade over time. This demonstrates a high durability of all three types of PI in the presence of PBS. In addition, the measurements conducted with BPDA-PPD foils showed that over time, there was neither a decrease in mass nor a change in material properties measured optically. These results strengthen the hypothesis that the tested PIs are stable in vivo over a period of 20 months or more. The tests showed that the three PIs are superior to PMDA-ODA type PI which already degrades after 30 days in distilled water at room temperature [5].

An anomaly was found in the Young’s modulus of BPDA-PPD type PIs at 60°C. The Young’s modulus increased constantly, starting at an initial value of 9 GPa and rising to 16 GPa after 20 months in solution. A possible explanation of this behavior of the polymer could be that there was a redistribution of the constituent crystals due to the higher storage temperature. While the overall number of crystals did not vary (Fig. 8), the adhesion between neighboring grains sliding over each other and the distribution of crystalline regions could have changed [26]. This theory is supported by the observation that only the Young's modulus increased, while the properties at break remained constant (Fig. 3(a,b)), which would correspond to a change in the crystal arrangement. In the elastic section of the stress-strain curve, the crystallinity and the arrangement of crystallites affect the Young’s modulus. After reaching the yield point in the part of the plastic deformation (Fig. 1), crystallites slide upon each other and change their arrangements due to the increasing strain forgetting the initial crystallite arrangement in which they were positioned by the tempering at 60°C. Hence, the Young’s modulus increases while the properties at break remain at the same values as the reference. However, it remains unclear why the Young’s modulus did not increase in deionized water at 85°C. At this higher temperature, the crystallites should have even more energy to rearrange. Further studies will be needed in order to examine in more detail the changes in the underlying crystal structure of PI during long-term storage at different temperatures.

The increasing Young’s modulus at 60°C could be also explained with a theory described as antiplasticization [34]. In general, plasticizers are known to cause an increase in elongation, decrease in tensile strength and Young’s modulus. But a plasticizer in a polymer can sometimes increase the Young’s modulus. Such a stiffening effect was also found in PI immersed in water. Harper and Rao [35] stored PI (PMDA-ODA) in distilled water at room temperature and at 90°C, respectively, and found a significant increase in stiffness over time up to 270 days of immersion. This effect was stronger for specimens stored at 90°C than for those stored at room temperature. Our results at 60°C are in good agreement with these findings. A water uptake of 1.1% could act as a plasticizer [28,36] and stiffen the material. Note that this model also fails to account for the constant values of specimens stored in PBS and deionized water at 37°C and 85°C respectively. However, these samples also have a water uptake of 1.1% which would lead to a stiffening according to the antiplasticization theory.

Despite the fact that the Upilex255S foil showed a decreasing mass over time, no change in the light absorption of this foil could be observed with FTIR measurements (Fig. 7). This indicates that there were no breakages of chemical bonds in the material and that the changes in material properties were not due to changes in the chemical structure of the polymer. A first hypothesis explains the decline of the mechanical properties with the decrease of crystallinity (Fig. 8). A loss of crystal regions in the polymer can also be deduced from the stress-strain curves in Fig. 2. While the Young’s modulus and therefore the stress at yield were decreasing over time, the strain at yield remained on a constant value of about 4%. This is a specific behavior of semi-crystalline polymers with a decrease in crystallinity [26]. The decrease and the change of the crystalline structure can have a strong influence on the mechanical properties of the polymer and also on the diffusion rates of molecules like water and oxygen which contribute to the degradation of PIs [36]. The two broad peaks in the XRD spectrum show that the
Fig. 9. XPS measurement of the Upilex25S foils after 6 months (in PBS at 37 °C and 60 °C respectively, in deionized water at 85 °C) and after 22 months in PBS at 85 °C. The reference represents a dry foil as received from the manufacturer. The survey spectrum was measured with a step size of ~0.8 eV (a). (b) shows a close up of the K2p3/2 peak region which is concealed in (a) by the C1s peak. This detailed spectrum was measured with a step size of ~0.025 eV. The sample data are shifted in steps of 15000 counts per second (survey) and 4000 counts per second (detail) with respect to the reference to show the samples without overlapping each other.

Fig. 10. SEM photograph of the edge of a tensile test specimen structured with an oxygen plasma.
Upilex25S foil has crystal regions with a Bragg spacing of about 5 Å and 3.5 Å. This is consistent with results found in the literature giving peaks at 2θ = 18°, 2θ = 22°, and 2θ = 25° for a BPDA-PPD type PI which corresponds to Bragg spacings of 5 Å, 4 Å, and 3.5 Å, respectively [28,37]. The change of crystallinity could be due to alkaline metal ions having enough energy to penetrate into the crystal lattice. With 2.8 Å for potassium, 2 Å for sodium and 3.6 Å for chloride, the ionic diameter of alkaline metal ions are in the same order of magnitude as the lattice spacing of the PI. This hypothesis conflicts with the results found in the XPS measurement (Fig. 9) where no alkalai salt ions could be detected in any of the foils.

An alternative hypothesis could explain the decrease of mechanical properties of specimens stored in PBS at 85 °C in terms of the leaching of low molecular weight components out of the foil. These components could either be additives added by the manufacturer to adjust the polymer properties, or unreacted molecules of the polyamic acid precursor not bound to the PI backbone. This could not only explain the decrease in mechanical properties but also the mass loss over time. Assuming that not all of the polyamic acid is converted to PI while curing, some percentage of the precursor molecule would therefore remain in the polymer. When exposed to PBS, amic acid molecules could be washed out, promoting the change in mechanical properties and mass [5]. This change would not be observed in the IR spectrum due to a very strong amide peak at 1720 cm⁻¹, which would conceal the weaker amide peak at 1660 cm⁻¹. The second amide peak at 1550 cm⁻¹ only has a medium amplitude [38] and changes to it would be covered by other smaller peaks of the spectrum.

This second hypothesis is only valid if, after a certain time, a constant mass is reached which represents the actual PI backbone. During the weighing measurements lasting over 25 months, the mass loss stopped after 22 months at a value of 95% reached after 15 months can be explained with the saturation of the PBS in which the foil was stored. In month 18, the PBS was replaced with new solution and the mass loss continued. The constant value after 22 months was not due to PBS saturation because the PBS was replaced after each measurement. That some parts of the material are soluble to PBS at higher temperatures was found not only in the mass loss but also in the surface structure of the Upilex25S foil (Fig. 6). In some areas the material dissolved inhomogeneously, revealing a certain structure in the remaining polymer.

Reasons given for PI degradation in the literature usually include elevated temperature and/or humidity [5,7,15,16]. Delasi [5] found a decrease of stress and strain at break of about 35% and 85% respectively in Kapton foil after two weeks of immersion in distilled water at 80 °C. It was found that Kapton hydrolyzes when immersed in water [5,15]. Our results do not show such behavior for PI2611 and Upilex25S. PI2611 specimens stored in deionized water at elevated temperature of 85 °C did not show any decline in the tested mechanical properties. The Upilex25S foils did not show any decline in mass or change in optical properties. With a test period of 20 months for the tensile tests and 25 months for the gravimetric measurements, we examined BPDA-PPD type PIs considerably longer than was reported for Kapton foil in the literature [5,7,15,16]. In contrast to specimens immersed in deionized water at 85 °C, specimens stored in PBS at 85 °C showed a rapid decrease in all quantities. Thus, it was not the combination of water and a temperature of 85 °C that led to a significant change in the mechanical properties, but rather the combination of a storage temperature of 85 °C with an immersion in PBS. This corresponds to the finding that PIs decompose in the presence of alkalai metal salts at elevated temperatures [36]. Examples of these salts are potassium chloride and sodium chloride, both of which are found in significant concentrations in body fluids. With this work we could confirm that in comparison to Kapton, PIs based on the precursor molecules BPDA-PPD show a much higher stability with regard to water and temperature which corresponds to other studies [37,39,40]. These results imply that much research done on Kapton might not be representative of the whole group of PIs; by the same token, not all results found with PMDA-ODA type PI can be applied to BPDA-PPD PIs.

The sample stored at 85 °C in PBS had a constant water absorption over time of 1.46%, whereas the samples showing no mass change seemed to swell less, with a constant water absorption of 1.1%. In comparison, Kapton foils that show a stronger deterioration in water have a larger water uptake than the PIs tested in this work [37]. The manufacturer specifies a water uptake of 2.8% after an immersion of 24 h at 23 °C in water for Kapton HN and VSN foils with a thickness of 25 μm.

As the XRD-measurement showed (Fig. 8), the crystalline structure of the PI in PBS at 85 °C changed. This implies that the temperature of 85 °C cannot be used to conduct accelerated aging tests. Due to the structural change, it is not possible to infer the long-term stability of the material at 37 °C from the results at 85 °C. Although the 85/85 test (1000 h at 85 °C and 85% relative humidity) is used for testing polymer material (epoxy) in chip packaging [24,25], temperatures above 60 °C are not recommended for accelerated shelf-life testing of polymers used in medical devices. Hemmerich [21] stated that the lifetime prediction methods based on the Arrhenius model become inaccurate at temperatures in excess of 60 °C, due to the large difference between the temperature during normal use and the elevated temperature while testing. This is consistent with the results presented in this work. While no changes in material behavior could be observed at 37 °C and at 60 °C respectively, the deterioration of the material at 85 °C in PBS was drastic. But the behavior at 85 °C does not necessarily give useful information about the long-term behavior at 37 °C [22], as demonstrated by the following example. The stress at 10% strain of PI2611 is reduced by 1/4 after 4.5 months in PBS at 85 °C. Applying the Hemmerich method [21], one can calculate the time duration needed to reach the same behavior in specimens stored at 60 °C in PBS:

\[
time_{el} = \frac{10 \cdot \text{time}_{at}}{Q_{10} \cdot \left(T_{el} - T_{at}\right)}
\]

Where time_{at} is the time duration of the test at the elevated temperature T_{el} and time_{at} is the time duration of the usage at the ambient temperature T_{at} (37 °C in the case of implanted materials). The reaction rate coefficient was found to be Q_{10} = 2 for medical polymers [21]. That implies a doubling of the reaction rate for each 10 K. Based on the data of the specimens stored in PBS at 85 °C, the Hemmerich method predicts a decrease of 1/4 of the initial stress value after a period of 22.5 months for specimens stored in PBS at 60 °C. As our results show (Fig. 3) the stress at 10% strain at 60 °C did not decrease over 20 months but remained stable at the initial value. This indicates that at higher storage temperatures, degradation processes take place that do not develop at 37 °C or 60 °C. This becomes more clear when attempting to graph these values in an Arrhenius plot [41]. The material stored at 37 °C, 60 °C, and at reference conditions, did not change over time, thus the reaction rate is zero for all three temperatures. The reaction rate of the material stored at 85 °C in PBS is 17 MPa/month (PI2611, stress at 10% strain). Drawing an Arrhenius plot with these values does not result in a linear relationship of temperature and reaction rate. Hence, the values found at 85 °C are not linked to the values at 37 °C by an Arrhenius equation, which in turn indicates that findings gathered from testing PIs at temperatures greater than 60 °C are not necessarily able to predict the long-term behavior of these materials at 37 °C.
5. Conclusion

Over the course of 20 months, the three tested PIs were stable in PBS at body temperature and even at 85 °C. No decrease of the measured properties with respect to the reference could be found which showed the long-term stability of the tested materials. A significant difference in behavior of BPDAPPD type PI stored in PBS compared to specimens stored in deionized water could be observed. While this PI type was even stable in water at 85 °C it was sensitive to salt ions in an aqueous solution like PBS at 85 °C. The tested PIs showed a loss in mass (Uplex255S) and a decrease in the measured mechanical properties (P12611, U-Varnish-S, Durimide 7510) when stored in PBS at 85 °C. However, no changes in the chemical structure of the polymer molecules could be observed in FTIR measurements. The values found with PBS at 85 °C could not be used to predict the long-term behavior of the material at body temperature.

Acknowledgements

This work was supported by the German Federal Ministry of Education and Research (BMBF grant 01GQ0830). The first author wants to thank Xian Ha Cai, Lorenzo Bresolin, and Jose Maria Forner for their help conducting the tensile and weighing tests, Christina Haßler for helping with the XRD measurement, Young-Hyun Jin for helping with the FTIR measurement, Dennis Plachta for tips regarding statistics, Juan Ordonez for fruitful discussions and literature hints, Benjamin Townsend for correcting the language (all IMTEK, Laboratory for Biomedical Microtechnology, Markus Hankeln (UBE Europe) for providing the Uplex255 foil samples, Sebastian Gutschen (IMTEK Laboratory for Nanotechnology) SEM imaging presented in Fig. 6, Daniela Mössner (IMTEK Laboratory for Chemistry and Physics of Interfaces) for conducting the XPS measurements, Jan Roden (Max Planck Institute for the Physics of Complex Systems, Dresden) for helpful discussions and programming tips, and Oswald Prucker (IMTEK Laboratory for Chemistry and Physics of Interfaces), Falk Barnikol (FUJIFILM Electronic Materials), and Gert Strobi (Chair of Polymer Physics, University of Freiburg) for very helpful discussions.

Appendix

Figure with essential colour discrimination. Fig. 9 of this article are difficult to interpret in black and white. The full colour images can be found in the online version, at doi:10.1016/j.biomaterials.2010.01.053.

References