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# Material properties and tissue reaction during degradation of poly (96L/4D-Lactide) – a study *in vitro* and in rats

F. W. CORDEWENER, F. R. ROZEMA, R. R. M. BOS, G. BOERING
*Department of Oral and Maxillofacial Surgery, University Hospital Groningen, The Netherlands*

To investigate the mechanical and physical properties of, and the histological reaction to, as-polymerized poly(96L/4D-lactide) (PLA96), a degradation study was performed *in vitro* and in rats. The PLA96 studied had a molecular weight ($\bar{M}_w$) of $1.5 \times 10^6$ g/mole. Test samples were implanted subcutaneously in the back of rats or put in phosphate-buffer. The mechanical and physical properties of PLA96 showed major changes during the first 3 weeks of degradation. Tensile strength ($\sigma_b$), impact strength and $\bar{M}_w$ decreased rapidly. The heat of fusion ($\Delta H_m$), a measure for crystallinity, increased whereas the melting temperature ($T_m$) remained almost constant. The mechanical properties were lost completely after 7 weeks of degradation. After 55 weeks, both water absorption and mass loss had reached approximately 30%, and $\bar{M}_w$ had decreased to $15 \times 10^3$ g/mole. $\Delta H_m$ had slightly increased further but $T_m$ remained unchanged. The measurements during degradation *in vitro* did not show significant ($p > 0.05$) differences from the measurements during degradation *in vivo*. The histological reaction to PLA96 could be characterized as a mild foreign body reaction without signs of inflammation.

## 1. Introduction

Poly(lactide) (PLA) has been the subject of many investigations in the search for biodegradable osteosynthesis materials [1–9]. PLA is a poly (α-hydroxy) acid and is considered to be a biocompatible material [5, 6, 10–12]. In our department, as-polymerized poly (L-lactide) (PLLA) has been the focus of research. Bone plate/screws osteosyntheses made of as-polymerized PLLA have been developed for the internal fixation of unstable zygomatic fractures. In a testgroup of 10 patients the osteosyntheses provided sufficient fracture stability during the bone healing period and all treated fractures healed without complications [4]. However, approximately 3 years after implantation, most of the patients developed swellings at the site of implantation. The physical nature of the highly crystalline particles still present in the tissues in large amounts in combination with the low degradation rate of PLLA may have been a causative factor of this late complication [13, 14]. In our opinion, this so-called late tissue response may be reduced or prevented by incorporating D-lactide units in the PLLA chain. Poly(L/D-lactide) will have smaller, less perfect crystalline domains and a lower overall crystallinity than PLLA [15]. In addition, an increased degradation rate can be expected as a consequence of the lower crystallinity [2, 11]. The altered crystalline structure in combination with the increased degradation rate may in our opinion facilitate the *in vivo* resorption of poly(L/D-lactide) and thereby reduce or prevent a late tissue response in the later phases of degradation. However, the incorporation of D-lactide units will in general reduce the mechanical properties of PLA [10, 16]. At concentrations higher than approximately 10% the initial mechanical properties obtained are reduced notably and, due to the increased degradation rate, lost rather rapidly [7, 10, 16]. Considering the aforementioned, we have decided to use a copolymer composed of 96% L-lactide and 4% D-lactide, so-called PLA96, for further studies on the usefulness of a L/D-lactide copolymer as a biodegradable osteosynthesis material. Aside from studies focused on the tissue response to PLA96 in the long term, attention should be directed towards the material properties of PLA96 during the earlier phases of degradation. It is important to realize that the material properties and degradation rate of PLA are not determined only by the ratio of L-lactide to D-lactide units. Other factors of influence are the molecular weight, residual monomer and processing conditions [10,16–19]. Regarding the complex set of factors involved it is important to extensively study the material properties of PLA, whenever compositional changes are made.

It was the aim of the present study to investigate the mechanical and physical properties of, and the histological reaction to, as-polymerized PLA96 during degradation *in vitro* and *in vivo*.

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## 2. Materials and methods

### 2.1. PLA

As-polymerized poly(96L/4D-lactide) (PLA96) was prepared by DSM-Research, Geleen, The Netherlands. Polymerization of L- and D-lactide (mole ratio 96/4) was performed in bulk under vacuum for 68 h at 120 °C. Stannous-octoate 0.02 wt % was used as a catalyst. The weight-average molecular weight ($\bar{M}_w$) of the PLA96 was $1.5 \times 10^6$ g/mole relative to polystyrene standards, with a residual monomer concentration of 1.8%. The melting temperature ($T_m$) and heat of fusion ($\Delta H_m$) were 156.5 °C and 27.4 J/g, respectively. Dumb-bells according to ISO 37 type 3 and plates measuring $10 \times 10 \times 1.6$ mm were machined from blocks of PLA96 (Fig. 1). Each test sample was weighed and separately packed in two paper/PE/PP laminate bags (P3 'DRG Hospital Supplies'). Subsequently, the test samples were sterilized with a specially designed ethylene-oxide (EO) gas sterilization procedure, exposing the test samples for 3 h to EO gas with a concentration of 715 mg/l at 40 °C and a pressure of $5.1 \times 10^4$ Pa. The residual EO concentration in the test samples was less than 1 ppm after an aeration time of 3 weeks.

### 2.2. Sterilization effects

To detect possible changes of the initial material properties of the test samples due to the applied EO sterilization procedure, five dumb-bells and five plates were used for material characterization before and after sterilization.

### 2.3. Degradation study

To study degradation *in vivo*, 35 adult male Wistar-Albino (Wistar-Hsd/Cpb:WU) rats with an average weight of 300 g were used. Two dumb-bells and two plates were implanted in the back of each rat in four positions (Fig. 2). The rats were anaesthetized with a nitrous-oxide–fluothane mixture and operated on under aseptic conditions. The backs of the rats were shaved and prepped with iodine solution. Pockets were created by blunt preparation after making a small skin incision of ± 10 mm. Following insertion of the test samples in the pockets the incisions were closed with resorbable sutures (Dexon® plus, Cyanamid Korea). Postoperatively the rats had free access to standard ratfood and water.

To study degradation *in vitro*, dumb-bells and plates were stored without stirring at 37 °C in phosphate-buffer (pH 7.4) to which an antimicrobial agent was added (0.13 M $NaH_2PO_4$ + 0.13 M $Na_2HPO_4$ + 0.02 wt % $NaN_3$).

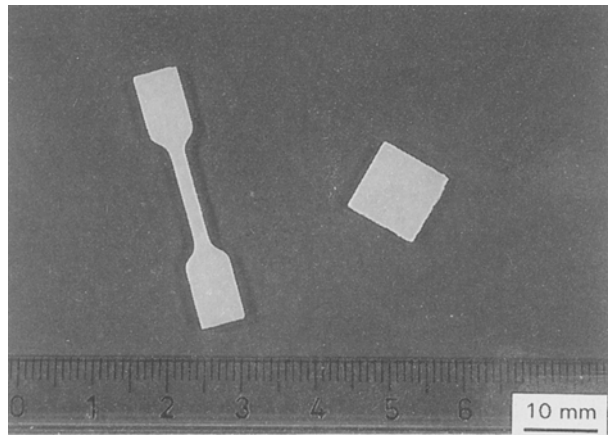


*Figure 1* Photograph of a dumb-bell and a plate.

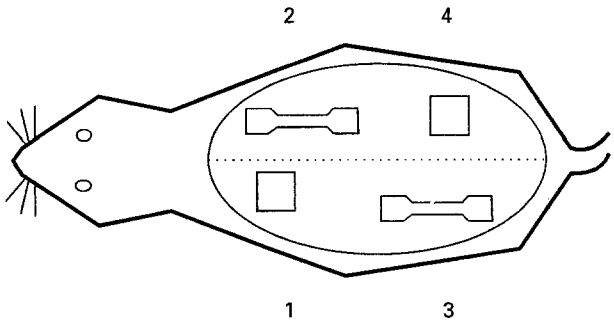


*Figure 2* Positions of the dumb-bells and plates in the back of the rats.

### 2.4. Implant retrieval

At weekly intervals up to 11 weeks and after 55 weeks from the onset of the study, five dumb-bells and five plates were retrieved from the rats and three dumb-bells and three plates were retrieved from the phosphate-buffer for material characterization.

At week 1 the five dumb-bells and the five plates were explanted from five rats (one dumb-bell and one plate per rat). At week 2 these rats were terminated and the remaining five dumb-bells and five plates explanted. From week 3 onward six dumb-bells and six plates were explanted from three rats. The sixth dumb-bell and plate explanted at week 4, 7, 9, 11 and 55 were excised *en bloc* with the surrounding tissue for light microscopic (LM) examination. The sixth dumb-bell and plate explanted at week 3, 5, 6, 8 and 10 were stored for future examination.

### 2.5. Material characterization

After visual examination of the retrieved samples, water absorption was calculated of the dumb-bells by weighing them separately after drying off the adherent moisture with a tissue ( $= m_{wet}$), using the formula: $\%H_2O_{absorbed} = 100\ (m_{wet} - m_{dry})/m_{dry}$, in which $m_{dry}$ is mass after drying to constant weight. Tensile strength ($\sigma_b$), elastic modulus ($E_b$) and elongation at break ($\varepsilon_b$) of the wet dumb-bells were measured at room temperature on a Zwick 1445 (Zwick GmbH., Ulm, Germany) operating at a crosshead speed of 10 mm/min. Impact strength of the wet plates was measured at room temperature on a Zwick 5102 equipped with a 2 Joule hammer according to Dynstat procedure. $\bar{M}_w$ and residual monomer concentration were determined by gel permeation chromatography

(GPC). GPC was performed at 26 °C on a HP1090 (Hewlett-Packard, Waldbronn, Germany), equipped with Waters ultra styra gel columns of $10^2$, $10^3$, $10^4$ and $10^5$ nm, on 0.2 wt % solution of PLA96 in dichloromethane. $T_m$ and $\Delta H_m$, a measure of the crystallinity, were determined by differential scanning calorimetry (DSC). DSC was performed on a Perkin Elmer DSC-7 over a range from 40 to 200 °C at a scanning rate of 20 °C/min. Change in mass ($\Delta m$) of the broken dumb-bells was calculated after drying them to constant weight at 30 °C and a pressure of $3 \times 10^4$ Pa in a Heraeus VTR-5036 (Heraeus Instruments GmbH., Hanau, Germany) drying-furnace, using the formula: $\Delta m = 100\,(m_{dry} - m_o)/m_o$, in which $m_o$ is initial dry mass before implantation. GPC and DSC analyses were performed on specimens of one dumb-bell at each time interval.

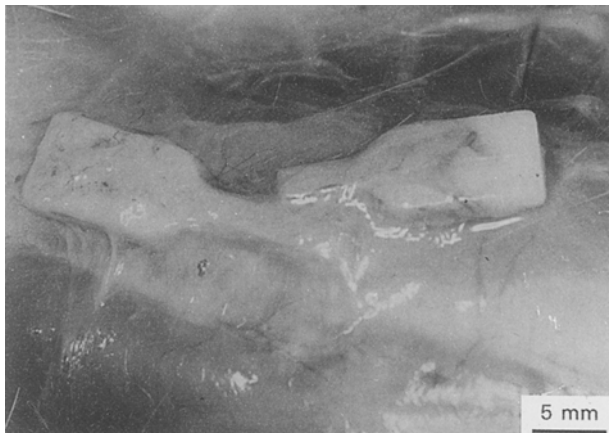


*Figure 3* Photograph of a broken dumb-bell *in situ* in the back of a rat.

## 2.6. Light microscopy

The specimens for light microscopic examination were fixed in 4% formaldehyde. After dehydration, decalcification and plastic embedding, 3 μm histological sections were cut with a Jung® 11-40 (R. Jung, Heidelberg, Germany) plastic microtome and stained with toluidine blue and basic fuchsin.

## 2.7. Analysis of data

Data are given as mean ± SD. For comparison of the *in vivo* and *in vitro* measurements 2-tail variance analysis was performed by means of the Student's *t*-test. The level of significance was preset on $p < 0.01$. To avoid random significances, *p*-values were adjusted for the number of tests performed. All analyses were performed with SPSS/PC$^{+TM}$.

# 3. Results

## 3.1. Sterilization effects

The applied EO sterilization procedure did not significantly ($p > 0.05$) change the inital material properties of the PLA96 test samples (Table I).

## 3.2. Degradation study

The rats recovered well from the implantation operation and wound-healing was uneventful in all cases. In the course of the study, the initial sample size ($n$) could not always be maintained. Some dumb-bells were found to be broken *in situ* and the test samples had become increasingly fragile at the later stages of the study. Due to the fragility it was not always possible to retrieve samples in one piece, or samples broke upon installation in the measuring equipment. In the case of loss of samples, actual sample sizes are given between brackets. For the same reason measuring of the mechanical properties was no longer performed after 7 weeks post-implantation.

Broken dumb-bells were found in the rats from week 5 onwards (Fig. 3). At week 5, one of the six dumb-bells explanted was broken. At week 8, three of the six and at week 11 and 55 all dumb-bells were found to be broken *in situ*. Seven of the eight dumb-bells found to be broken in the first 8 weeks were implanted at position 2. Some of the intact dumb-bells explanted were bent and/or twisted. The plates, however, all remained intact during the implantation period.

Visual examination of the explanted dumb-bells and plates showed a change in lucency from fairly translucent to whitish opaque. This change could already be noted from week 2 onward. Water absorption occurred at an almost constant rate during the first 6 weeks of implantation. After week 6, the water absorption rate slowed down but water absorption kept increasing to 30 ± 2.0% ($n = 2$) at week 55 (Fig. 4). Tensile strength ($\sigma_b$) decreased in a linear fashion during the first 7 weeks. Nearly 50% of the initial tensile strength was lost at week 3 (51.3 ± 2.0 MPa to 27.5 ± 5.7 MPa) (Fig. 5). Elastic modulus ($E_b$) gradually decreased almost 50% during the first 7 weeks from 3.4 ± 0.2 GPa to 1.8 ± 0.4 Gpa ($n = 3$). Elongation at break ($\varepsilon_b$) significantly decreased at week 3 to

TABLE I The initial material properties of as-polymerized PLA96 before and after the ethylene-oxide (EO) sterilization process

| PLA96 condition | Tensile strength (MPa) | Elastic modulus (GPa) | Elongation at break (%) | Impact strength (kJ/m$^2$) | Molecular[a] weight ($10^6$ g/mole) | Monomer[a] concentration (%) | Heat of[a] fusion (J/g) | Melting[a] temperature (°C) |
|---|---|---|---|---|---|---|---|---|
| Unsterilized | 50.6 ± 1.1 | 3.4 ± 0.4 | 5.4 ± 1.6 | 6.9 ± 3.0 | 1.5 | 1.8 | 27.4 | 156.5 |
| Sterilized | 51.3 ± 2.0 | 3.4 ± 0.2 | 5.8 ± 1.9 | 6.6 ± 1.3 | 1.3 | 1.8 | 27.2 | 157.1 |

Values are means ± SD for 5 samples
[a]Values for 1 sample

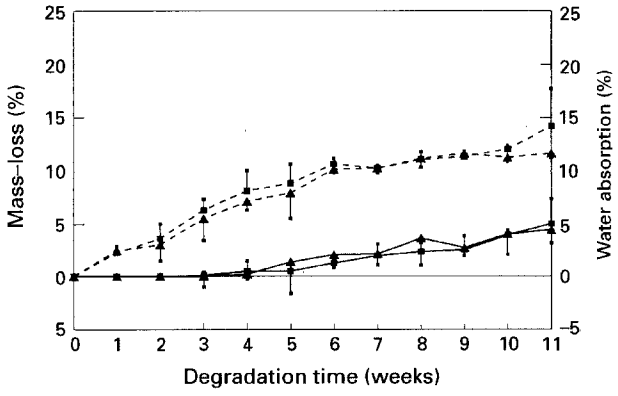


*Figure 4* Mass-loss (—) and water absorption (– – –) during degradation of as-polymerized PLA96 *in vitro* (▲) and in rats (■).

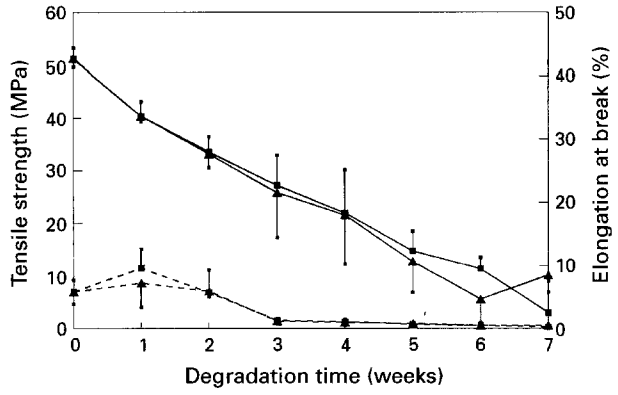


*Figure 5* Tensile strength (—) and elongation (– – –) at break during degradation of as-polymerized PLA96 *in vitro* (▲) and in rats (■).

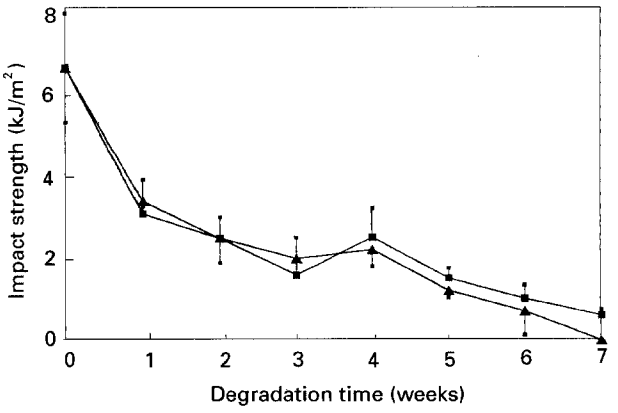


*Figure 6* Impact strength during degradation of as-polymerized PLA96 *in vitro* (▲) and in rats (■).

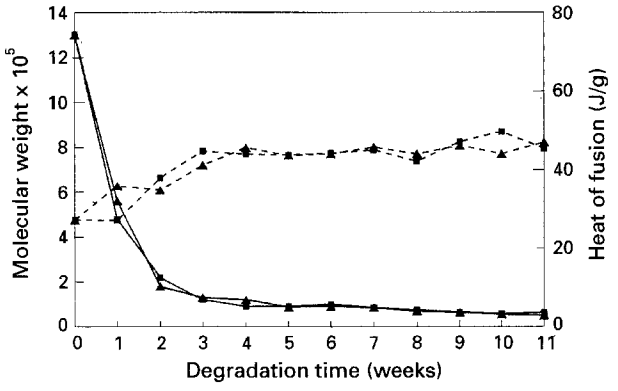


*Figure 7* Molecular weight (—) and heat of fusion (– – –) during degradation of as-polymerized PLA96 *in vitro* (▲) and in rats (■).

1.3 ± 0.1%. The changes from the initial value measured at week 1 and 2 were non-significant ($p > 0.05$) (Fig. 5). Impact strength rapidly decreased by a little over 50% during the first week from 6.6 ± 1.3 kJ/m$^2$ to 3.1 ± 0.8 kJ/m$^2$. The impact strength decrease was less pronounced thereafter, to 0.6 ± 0.1 kJ/m$^2$ ($n = 3$) at week 7 (Fig. 6). $\bar{M}_w$ dropped steeply during the first 2 weeks from $1.3 \times 10^6$ g/mole to $220 \times 10^3$ g/mole. Subsequently, $\bar{M}_w$ decreased more slowly to $64 \times 10^3$ g/mole at week 11 (Fig. 7) and to $15 \times 10^3$ g/mole at week 55. A residual monomer content of 0.4% was detected at week 1. No residual monomer was detected from the second week onwards. $T_m$ remained almost constant during the study. The lowest value was 156 °C at week 5, the highest 158 °C at week 8. $\Delta H_m$, a measure of the overall crystallinity, increased during the first 3 weeks from 27.2 J/g to 44.8 J/g. In the weeks following, a further slight increase of $\Delta H_m$ to 52.6 J/g was recorded at week 55 (Fig. 7). Significant mass-loss of the dumbbells was first recorded at week 6, being 1.3 ± 0.4%. Mass-loss increased to 5.1 ± 2.3% at week 11 (Fig. 4) and finally to 27.8 ± 2.1% ($n = 2$) at week 55.

The measurements during degradation *in vitro* did not show significant ($p > 0.05$) differences from the measurements during degradation *in vivo*. As in the case of the *in vivo* study, measurement of the mechanical properties was no longer performed after 7 weeks post-implantation (Figs 4 to 7).

## 3.4. Light microscopy

At week 4, a thin collagen capsule (thickness ± 40 μm) was observed surrounding the implant consisting of immature collagen fibres with fibroblasts in between oriented paralled to the implant surface. Surrounding the collagen capsule, a zone of well-vascularized loose connective tissue was observed. A cell layer (thickness ± 15 μm) was observed in direct contact with the implant surface, separating the implant from the collagen capsule. This layer predominantly consisted of macrophages and several foreign body giant cells. Few mast cells filled with histamine-like granules were seen in this tissue (Fig. 8).

At week 7, the collagen capsule appeared more mature and had become vascularized. In the cell layer in direct contact with the implant an increased number of macrophages and foreign body giant cells was observed (Fig. 9).

At week 9, the collagen capsule had become denser and showed increased vascularization. The distinction between the collagen capsule and the bordering loose connective tissue was more pronounced. The cell layer in direct contact with the implant looked more irregular and showed signs of increased activity. Ingrowth of macrophages into cracks in the surface of the implant was observed at some sites (Fig. 10).

At week 11, the histological image showed no apparent differences from the image observed at week 9.

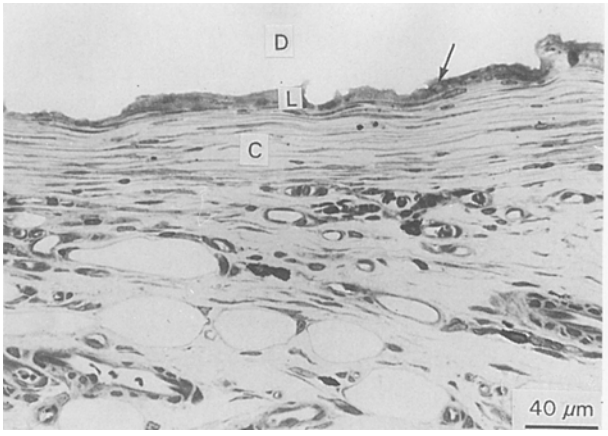


*Figure 8* Photomicrograph of a section of a dumb-bell 4 weeks after implantation. The dumb-bell (D) is surrounded by a thin collagen capsule (C). A layer of cells (L) is seen in direct contact with the implant, separating it from the collagen capsule. In this cell layer, macrophages (arrow) can be seen (toluidine blue and basic fuchsin stain).

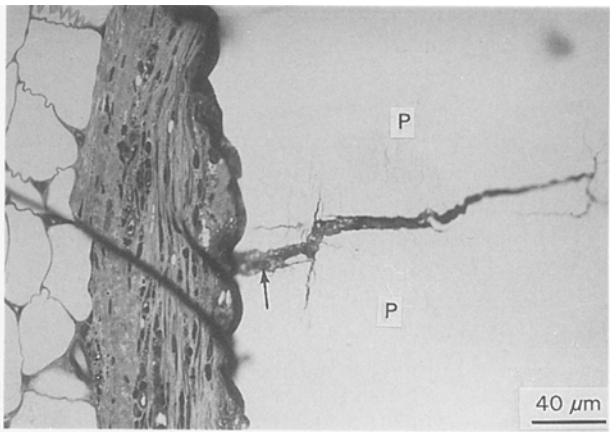


*Figure 10* Photomicrograph of a section of a plate after 9 weeks of implantation. Macrophages (arrow) can be seen growing into cracks in the surface of the plate (P) (toluidine blue and basic fuchsin stain).

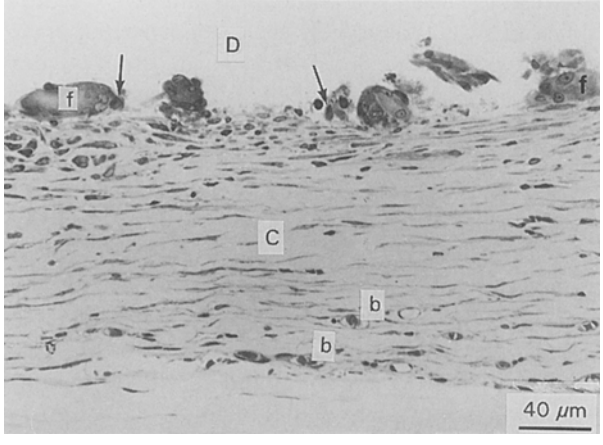


*Figure 9* Photomicrograph of a section of a dumb-bell 7 weeks after implantation. In the collagen capsule (C) surrounding the dumb-bell (D) blood vessels (b) are seen. Increased numbers of macrophages (arrows) and foreign body giant cells (f) are seen in the cell layer adjacent to the implant (toluidine blue and basic fuchsin stain).

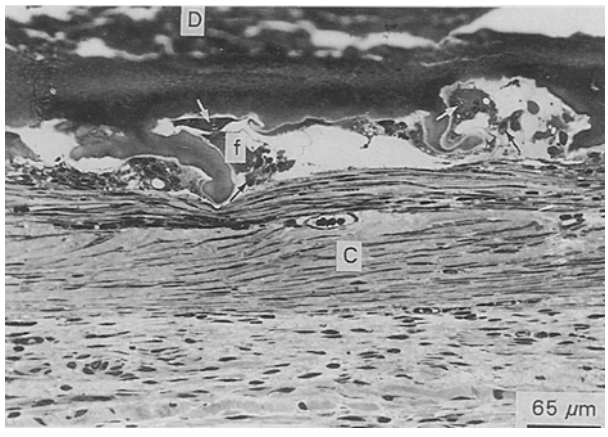


*Figure 11* Photomicrograph of a section of a dumb-bell (D) 55 weeks after implantation. The dumb-bell is surrounded by a dense, mature collagen capsule (C). Large numbers of macrophages (black arrows) and foreign body giant cells (f) are seen in close contact with the surface of the implant. The cytoplasm of some of these cells has a foamy appearance (white arrows) (toluidine blue and basic fuchsin stain).

At week 55, the collagen capsule (thickness $\pm$ 100 μm surrounding the implant consisted of densely packed, mature collagen fibres with fibrocytes in between oriented parallel to the implant surface. The capsule showed good vascularization. Surrounding the collagen capsule, a zone of well-vascularized loose connective tissue was observed. The cell layer (thickness $\pm$ 30 μm) in direct contact with the implant surface contained large numbers of macrophages and foreign body giant cells. Small, loose fragments of PLA (diameter 10–30 μm) were seen located in the collagen capsule, in the surrounding loose connective tissue at distances up to 300 μm away from the implant surface, and in the cell layer lining the implant surface. Conglomerates of mainly macrophages and foreign body giant cells were frequently observed at the implant surface and around the loose PLA fragments. The cytoplasm of some of these macrophages and foreign body giant cells had a foamy appearance (Fig. 11). Ingrowth of cellular material in the implant was occasionally observed. Birefringent material, apparently inside the cytoplasm of macrophages and foreign body giant cells, was observed in some areas when examined under crossed Nicol prisms.

Overall, the histological reaction to PLA96 could be characterized as a mild foreign body reaction without signs of inflammation.

## 4. Discussion

In this study it was found that the mechanical and physical properties of PLA96 showed major changes during the first 3 weeks of degradation. The mechanical properties were lost completely after 7 weeks. After 55 weeks, $\bar{M}_w$ had decreased to $15 \times 10^3$ g/mole and mass-loss had reached nearly 30%. $\Delta H_m$, increased, whereas $T_m$ remained constant. There were no significant differences between the measurements *in*

*vitro* and in the rats. Overall, the histological examination revealed a mild foreign body reaction without signs of inflammation.

No significant differences were found during degradation between the *in vitro* and *in vivo* measurements. The active involvement of enzymes in the *in vivo* degradation process of PLA96 therefore seems unlikely. The initial degradation of PLA96 appears to be a process of pure hydrolysis similar to that observed for biodegradable materials like poly(glycolic acid) (PGA), poly(ε-caprolactone) (PCL) and poly(L-lactide) (PLLA) [19–22]. The increase of $\Delta H_m$ during the first 3 weeks is a direct indication of an increase in the overall crystallinity of the PLA96. This process is visualized by the change of the test samples from fairly translucent to opaque. The increased crystallinity makes the PLA96 more brittle, which is reflected by the decrease in the measured impact strength and elongation at break. It is likely that, in similarity to what has been observed for PGA, PCL and PLLA, the hydrolysis of PLA96 starts in the amorphous zones [20, 23, 24]. Recrystallization of low molecular weight oligomers generated by hydrolysis in the amorphous zones can attribute to the increase in crystallinity [23]. An additional effect of hydrolysis in the amorphous zones is that interconnections between the crystalline regions, maintained by these amorphous zones, are lost. This can cause a decrease in tensile strength of PLA, even before the onset of mass-loss [10, 25]. As crystallinity increases, PLA becomes more resistant to hydrolysis, and the change in material properties will proceed at a slower rate. The results of this study suggest that the order of events described above may also apply for PLA96. The almost constant $T_m$ of PLA96 shows that, despite the increase in overall crystallinity, the crystalline domains do not actually change in dimension and quality during the degradation process.

The decrease of the mechanical properties of the PLA96 tested is quite rapid. This may be due to the low initial crystallinity of the PLA96. The degree of crystallinity determines the rate of water absorption [10, 11]; the lower the crystallinity, the faster the water absorption. In addition, it is known that lactide monomer or low molecular weight oligomers present in PLA cause rapid initial degradation [16, 17]. The monomer content in the PLA96 studied was quite low initially, however, the influence of residual monomer can be strong. Significant differences in the decrease of molecular and material weight, as well as in morphological changes have been observed between PLA samples with or without residual monomer [17]. It is supposed that the monomer, by diffusing out of the PLA sample, leaves a microporous structure that is easily permeable for water. In our study, no remaining monomer could be detected after 2 weeks of degradation. Regarding the rapid changes in the mechanical and physical properties during this period, it is likely that the residual monomer attributed considerably to the rapid initial degradation process.

Standard EO-sterilization can change the initial material properties of PLA, although the changes reported of are only minimal [7, 18]. To our knowledge, no studies of the effect of standard EO-sterilization on the course and character of the degradation of PLA have been published. It is generally assumed that it is a reliable sterilization method that does not affect the course and character of the degradation of PLA. However, PLA is a thermo- and moisture-labile polymer and hence should preferably not be exposed to high temperatures and humidity. Therefore, we used an EO sterilization procedure that was designed with the objective of minimizing the deteriorating effects on PLLA. The initial material properties of PLA96 were not significantly changed by this procedure. Considering the comparable values for $\bar{M}_w$ before and after sterilization, chain scissioning induced by the sterilization process is unlikely. These findings suggest that the course and character of the degradation process of PLA96 have not been influenced by the applied EO sterilization process.

The observation that several of the dumb-bells implanted at position 2 had spontaneously broken *in situ* might be related to the local tissue condition or to the anatomical situation. It seems unlikely that the local tissue condition has caused the dumb-bells at position 2 to degrade faster than the other samples because no differences were found between the *in vitro* and *in vivo* measurements. The local anatomical situation may have subjected the dumb-bells to relatively high dynamic loads. Dynamic loading can accelerate the decrease of mechanical properties of PLLA osteosyntheses during degradation [26]. Dynamic loading may either accelerate the degradation process or just be the cause of early breakage without affecting the degradation process itself. To what extent dynamic loads have actually interfered with the degradation process of the test samples in this study remains unclear.

The histological reaction to the PLA96 test samples was mild, without signs of inflammation. Based on our own experience and studies of others, we did not expect to see a histological reaction to PLA96 fundamentally different from the reaction to PLLA, PGA or their co-polymers during the degradation time under investigation in this study [5, 7, 8, 17]. The histological image of PLA96 after 55 weeks closely resembles the image that was observed for PLLA in rats after 143 weeks [5]. In both cases, disintegration of the PLA implants was observed, associated with the presence of large numbers of macrophages and, only in case of PLA96, foreign body giant cells. PLA96 apparently starts disintegrating considerably earlier than the PLLA used in our previous studies. In this respect, it is interesting to briefly consider the thermal behaviour of PLA96. During the study, $T_m$ remained almost constant at a temperature considerably lower than the also constant $T_m$ measured for the PLLA used in our previous studies [13]. This indicates that the crystalline domains of PLA96 remain smaller and less perfect than those of PLLA [15]. Furthermore, $\Delta H_m$ of PLA96 after 55 weeks was found to be still lower than the initial $\Delta H_m$ measured for PLLA [13]. Therefore, the overall crystallinity of PLA96 is still lower than that of PLLA initially and, consequently, PLA96 remains more susceptible to hydrolytic degradation. Regarding the histological observations and the

thermal behaviour, the supposed favourable conditions for a facilitated resorption in the long term still seem to be present. The validity of this assumption is under investigation in our department in a long-term *in vivo* study.

Regarding the relative rapid loss of mechanical properties, osteosyntheses made of PLA96 may be suitable only for applications under low biomechanical load. However, the performance of an osteosynthesis is not only dependent on the material it is manufactured of, but also on its design and dimensions. The design and dimensions of a biodegradable osteosynthesis will in part dictate the degradation process and hence the mechanical and clinical performance [11, 24, 27]. The optimal design and dimensions of an osteosynthesis should be developed on the basis of accurate information about material properties and functional demands.

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