In vivo degradation and biocompatibility study of in vitro pre-degraded as-polymerized polylactide particles


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The degradation of high molecular weight as-polymerized poly(L-lactide) (PLLA) is very slow; it takes more than 5.6 yr for total resorption. Moreover, the degradation products of as-polymerized PLLA bone plates, consisting of numerous stable particles of high crystallinity, are related with a subcutaneous swelling in patients 3 yr postoperatively. In order to avoid these complications, polymers were developed that are anticipated to have comparable mechanical properties but a higher degradation rate and do not degrade into highly stable particles that can induce a subcutaneous swelling. On chemical grounds it can be expected that copolymerization of PLLA with 4% d-lactide (PLA96) or by modifying PLLA through cross-linking (CL-PLLA) will lead to less stable particles and a higher degradation rate. To evaluate the long-term suitability of these as-polymerized polymers, the biocompatibility of the degradation products should be studied. Considering the very slow degradation rate of as-polymerized PLLA, in vitro pre-degradation at elevated temperatures was used to shorten the in vivo follow-up periods. In this study, the biocompatibility and degradation of as-polymerized PLLA, PLA96 and CL-PLLA were investigated by implanting pre-degraded particulate materials subcutaneously in rats. Animals were killed after a postoperative period varying from 3 to 80 wk. Light and electron microscopical analysis and quantitative measurements were performed. The histological response of all three pre-degraded materials showed a good similarity with in vivo implanted material. Pre-degraded PLLA induced a mild foreign body reaction and showed a slow degradation rate. PLA96 and CL-PLLA had a substantially lower crystallinity, a smaller mean particle size and an enhanced degradation rate compared to PLLA. Based on the chemical and quantitative analysis, the degradation of PLA96 and CL-PLLA was much more enhanced and thus more favourable than the degradation of PLLA. Biomaterials (1995) 16 (4), 267-274

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Poly(L-lactide) (PLLA), a biodegradable poly α-hydroxy acid, has been tested extensively for the past decades1-4. Both in vivo and in vitro studies have shown that PLLA can be considered to be a biocompatible and biodegradable material5-8. At our department, as-polymerized high molecular weight PLLA has been successfully used for fracture fixation and orbital floor reconstructions9-11. As-polymerized PLLA has good mechanical properties compared to other biodegradable polymers but a disadvantage is that the degradation is very slow, it takes more than 5.6 yr for total resorption12. Moreover, the degradation products of these PLLA implants, numerous stable particles of high crystallinity, seem to be related with a subcutaneous swelling in patients 3 yr postoperatively12-14.

In order to avoid these complications, polymers should be developed that have comparable mechanical properties to the original as-polymerized PLLA but a higher degradation rate and a reduced crystallinity, to avoid long-lasting presence of particles as seen with PLLA. In this study an as-polymerized copolymer of 96% L-lactide and 4% d-lactide (PLA96) and as-polymerized cross-linked PLLA (CL-PLLA) were used. Copolymerization of L-lactide with 4% d-lactide units will cause a much lower initial crystallinity, smaller
and less perfect crystalline domains, which hopefully will result in an enhanced degradation rate. Bulk copolymerization of PLLA with 1% spiro-bis-dimethylene-carbonate leads to a CL-PLLA with a much lower initial crystallinity and melting temperature, but with improved mechanical properties.

For safe application of a newly developed biomaterial, the entire degradation and resorption should be examined before the implant is used. In many reports only the functioning of the implant is studied in a short-term experiment. The full process of degradation and resorption using a material in physiological settings has hardly been investigated, resulting in unexpected foreign body reactions such as sinus formation in bone or subcutaneous swellings. However, the assessment of the entire in vivo degradation and resorption of as-polymerized PLLA requires a follow-up of at least 6 or 7 yr due to the very slow degradation rate of as-polymerized PLLA. The as-polymerized PLAA6 and CL-PLLA copolymers are anticipated to have an increased degradation rate compared to PLLA, but to study the final degradation and disintegration, long-term in vivo studies again might be necessary. To avoid these long follow-up periods, in the present study in vitro pre-degradation at elevated temperatures as described by Rozema et al. was used to obtain an enhanced degradation rate. Based on the fact that hydrolysis is probably the only degradation mechanism for polylactides, in vitro pre-degradation at elevated temperatures is a good method to simulate physiologically degraded material.

The aim of this animal study was to evaluate qualitatively and quantitatively the degradation and biocompatibility of in vitro pre-degraded as-polymerized PLLA, PLAA6 and CL-PLLA.

MATERIALS AND METHODS

In this study three different types of high molecular weight as-polymerized polylactides were used for pre-degradation, PLLA, PLAA6 and CL-PLLA. The chemical properties of the non-degraded polylactides are shown in Table 1. All polymers were synthesized according to previously published protocols. Polymerization of L-lactide was performed after purification of the monomer (L- and D-lactide of CCA/Purac Biochem, the Netherlands) by recrystallization from toluene under an N2 atmosphere; the spiro-bis-dimethylene-carbonate was purified by washing with dichloromethane. The PLAs were as-polymerized under vacuum at temperatures of 110°C with 0.0015 wt% stannous-2-ethylhexanoate as a catalyst. To obtain pre-degraded material, thin chips of the polymers were hydrolytically degraded for 30 h in distilled water at 100°C. Molecular weight characterizations were carried out by gel permeation chromatography (GPC) at 35°C using a Waters ALC/GPC 150C, calibrated with polystyrene reference materials. Differential scanning calorimetry (DSC) measurements were performed on a Perkin–Elmer DSC-7. The sample size was 5 mg and the scan speed 10°C min⁻¹.

Animal study

To study the densely packed PLLA particles as seen in patients, 80 mg of each pre-degraded polymer was placed in No. 3 gelatine capsules. The filled capsules were sterilized with 1.8 Mrad gamma irradiation. A total of 20 male Wistar Albino rats, weighing 300 g, were used. The rats were anaesthetized with a nitrous oxide–oxygen–fluothane mixture. The dorsal hair was clipped and the skin was prepped with iodine. Subsequently, six incisions were made on the back of the rat and in bluntly created subcutaneous pockets, two capsules of each polymer were inserted. After implantation, the skin was closed with Dexon® resorbable sutures. After postoperative periods of 3, 5, 8, 12, 16, 32, 50, 60, 70 and 80 wk, two rats were killed. The tissues at the implantation sites and the area containing the brachial and axillary lymph nodes were generously excised and fixed in 1.5% (w/v) glutaraldehyde in 0.1 M phosphate buffer (pH 7.4) for 1 wk at 4°C. Two-millimetre-thick slices were cut perpendicular to the long axis of the excised tissue. Subsequently, the sections were dehydrated in graded series of ethanol. The sections were embedded in glycol methacrylate (GMA), polymerized for 24 h at -20°C. Sections of 2 μm were made (Jung microtome 1140/autocut), which were stained with toluidine blue and basic fuchsin. For transmission electron microscopy (TEM), half of the sections with the longest implantation period, 80 wk, were fixed in 2% (v/v) glutaraldehyde in 0.1 M phosphate buffer (pH 7.4) for at least 1 wk at 4°C. Post-fixation was performed with 1 wt% OsO₄ to which K₄Fe(CN)₆ 3H₂O was added to a final concentration of 0.05 M. The material was dehydrated in series of 70, 80, 90 and 100% acetone. The sections were embedded in LX 112 epoxy resin and polymerized for 24 h at 60°C. The ultrathin sections were stained with uranyl acetate–lead citrate. For TEM, a Zeiss EM 902 was used, operated at 80 kV.

Quantification of the pre-degraded material

Light microscopic sections of each polymer (N = 4) were used to determine the mean number of extracellular particles per frame area, the mean particle size and the polymer area fraction per frame area with a Quantimed 520 image analysis system (Cambridge Instruments, Cambridge, UK). All sections were analysed at ×100 magnification. To determine the statistical significance of a decrease in the mean particle size or polymer area fraction, the regression with implantation time was calculated.

RESULTS

The chemical characteristics of the pre-degraded materials prior to implantation are presented in Table
2. The loss of mass after pre-degradation of the PLLA96 was substantially higher than that of PLLA and CL-PLLA. During pre-degradation there was an increase in the heat of fusion for all three materials, from 62 to 83 J g⁻¹ for PLLA, 26 to 60 J g⁻¹ for PLA96 and 48 to 55 J g⁻¹ for CL-PLLA. The average weight molecular weight of the pre-degraded PLLA dropped from 16000 to 6000, the $M_w$ of the pre-degraded PLA96 decreased sharply to 2000. The degree of polydispersity was 4.4 and 6.1 for PLA 96 and PLLA, respectively.

The mean particle size and the area fraction of the three polymers with implantation time are presented in Table 3. The mean particle size of the pre-degraded PLLA at week 3 was a factor of 12 higher compared to the pre-degraded PLLA96 particles and a factor of 4.5 higher compared to the pre-degraded CL-PLLA. Between 3 and 80 wk, in PLLA implants the mean particle size and the area fraction showed a significant regression ($P < 0.01$ and $P < 0.05$, respectively) with implantation time. The mean PLA96 particle size decreased with implantation time, but at 32 wk there was an increase, while the total number of particles decreased. The area fraction of the PLLA96 particles showed a gradual and significant ($P < 0.05$) decrease, from 22.7% at 3 wk to 5.2% at 32 wk, which was the last measuring point. In the period from 3 to 80 wk, there was a significant ($P < 0.05$) decrease in the mean particle size of CL-PLLA particles. In the same period, the area fraction of the CL-PLLA particles decreased significantly ($P < 0.05$) from 27.4 to 6.4%.

**Histological analysis**

For all implants, at 21 days an acute inflammatory reaction due to the operation was no longer observed. Neutrophils, plasma cells or lymphocytes were rarely seen in any of the explants. At 3 wk, the PLLA particles were surrounded and individually embedded by young fibrous tissue with long slender fibrocytes, macrophages and foreign body giant cells (Figure 1). From 16 wk on, a mature and relatively hypocellular fibrous capsule was observed. Invagination of cells or collagen into the PLLA particles was rarely observed up to 50 wk of implantation (Figure 2). After 70 wk of implantation, fragmentation and the formation of smaller particles, which were internalized by phagocytizing cells, could be observed. The PLLA implanted rats showed only a small number of macrophages with internalized fragments, compared to the other materials, after 80 wk of implantation. Using TEM, the phagocytic macrophages had a normal appearance and were embedded in mature collagen (Figure 3). Non-electron-dense PLLA particles were present freely in the cytoplasm of the macrophages or in membrane-bound vacuoles. These PLLA particles had an irregular shape and some particles showed a lamellar or needle-like structure.

After 3 wk of implantation, the PLLA96 particles were embedded in young fibrous tissue which was infiltrated by cells, mainly macrophages, fibrocytes, foreign body giant cells and some lymphocytes (Figure 4). After 16 wk, the number of giant cells and fibrocytes had diminished but the number of macrophages, many with a large and foamy appearance, seemed to have increased. Under crossed Nicol prisms birefringent PLLA96 particles were observed intracellularly in these foamy macrophages. The surface of the remaining extracellular particles showed cracks and invasion by the cytoplasm of adjacent macrophages (Figure 5). From week 30, extracellularly positioned particles were no longer observed and the number of foamy macrophages had increased even further. At week 80, intra- or extracellular particles could no longer be observed using a light microscope. TEM images of the 80 wk PLLA96-implanted rats showed numerous macrophages with abundant amounts of lamellar PLLA96 material (Figure 6). The particles were packed in membrane-bound vacuoles that could be described as phagosomes. These highly packed macrophages did not show any signs of cell damage such as swollen mitochondria or rough endoplasmic reticulum.

The CL-PLLA particles showed a similar encapsulation by fibrous tissue compared with the PLLA particles after 3 wk of implantation (Figure 7). After 16 wk, the CL-PLLA particles showed fragmentation.

**Table 3** The mean particle size, polymer fraction and number of particles per frame area as a function of implantation time

<table>
<thead>
<tr>
<th>Weeks of implantation</th>
<th>PLLA area fraction (%)</th>
<th>Mean particle size (mm²)</th>
<th>PLGA area fraction (%)</th>
<th>Mean particle size (mm²)</th>
<th>Mean particle size (mm²)</th>
<th>CL-PLLA area fraction (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>4.61 ± 8.440²/250</td>
<td>47.1 ± 2.2³</td>
<td>0.369 ± 0.604/1208</td>
<td>22.7 ± 4.3³</td>
<td>1.027 ± 1.429/720</td>
<td>34.3 ± 1.6³</td>
</tr>
<tr>
<td>5</td>
<td>4.50 ± 8.904/274</td>
<td>48.6 ± 1.8</td>
<td>0.351 ± 0.905/1066</td>
<td>21.7 ± 3.9</td>
<td>0.935 ± 1.192/680</td>
<td>33.2 ± 2</td>
</tr>
<tr>
<td>8</td>
<td>4.37 ± 7.943/280</td>
<td>48.7 ± 2.4</td>
<td>0.313 ± 0.438/1193</td>
<td>16.9 ± 5.1</td>
<td>0.905 ± 1.165/676</td>
<td>33.8 ± 2.3</td>
</tr>
<tr>
<td>16</td>
<td>3.68 ± 10.729/292</td>
<td>49.1 ± 2.2</td>
<td>0.280 ± 0.364/1054</td>
<td>16.2 ± 2</td>
<td>0.887 ± 1.228/703</td>
<td>32.8 ± 2.1</td>
</tr>
<tr>
<td>32</td>
<td>3.65 ± 6.544/219</td>
<td>37.8 ± 9.1</td>
<td>0.615 ± 0.250/76</td>
<td>5.2 ± 2</td>
<td>0.782 ± 0.649/586</td>
<td>26 ± 2</td>
</tr>
<tr>
<td>50</td>
<td>2.73 ± 5.815/323</td>
<td>38.7 ± 6.3</td>
<td>no longer detectable</td>
<td>0.633 ± 0.828/570</td>
<td>27.4 ± 3</td>
<td></td>
</tr>
<tr>
<td>80</td>
<td>2.74 ± 5.719/267</td>
<td>32.8 ± 6</td>
<td></td>
<td>0.837 ± 0.594/109</td>
<td>6.4 ± 3.4</td>
<td></td>
</tr>
</tbody>
</table>

* is the number of measured particles per frame area.
² Significant regression ($P < 0.01$) of the mean PLLA particle size with implantation time.
³ Significant regression ($P < 0.05$) of the mean CL-PLLA particle size with implantation time.
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Figure 1. Light microscopic micrograph of PLLA particles (P) and connective tissue (C) after 3 wk of implantation. Toluidine blue, original magnification ×150.

Figure 2. PLLA particles (P) encapsulated by mature fibrous connective tissue after 50 wk of implantation. Toluidine blue, original magnification ×150.

Figure 3. Transmission electron microscopic (TEM) photograph, taken after 80 wk of implantation, of intracellular PLLA particles (P) in membrane-bound vacuoles (arrows). The endoplasmic reticulum (ER) has a normal appearance. At the bottom the nucleus (N) of the cell is visible. Bar = 1 μm.

Figure 4. Light microscopic micrograph, taken after 3 wk of implantation, of PLA96 particles (P) which are embedded in young fibrous tissue and cells. Toluidine blue, original magnification ×150.

Figure 5. After 30 wk of implantation, large fields with foamy macrophages are observed. Only a limited number of extracellular PLA96 particles (arrows) can be observed. Toluidine blue, original magnification ×150.

Figure 6. Transmission electron microscopic photograph of a highly packed macrophage with membrane-bound conglomerates (arrows) of PLA96 (P) particles. The cells are embedded by sheets of collagen (C). N, nucleus. Bar = 1 μm.

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Figure 7 Light microscopic micrograph of CL-PLLA particles (P) with young fibrous tissue and cells like macrophages, fibrocytes and foreign body giant cells (arrows) after 3 wk of implantation. Toluidine blue, original magnification × 150.

Figure 8 After 50 wk, the mean particle size and polymer fraction of CL-PLLA has decreased. Both intracellular (in macrophages) and extracellular CL-PLLA particles were observed (P). Toluidine blue, original magnification ×150.

Figure 9 Transmission electron microscopic photograph of fields of needle-like CL-PLLA particles (P), which are mostly located in membrane-bound vacuoles that can be described as phagosomes (arrows). Bar = 1 μm.

and ingrowth by cells and collagen. With longer implantation periods the total number and the mean particle size showed a gradual decrease. From 50 wk, fields of large particles were interlaced with collagen, macrophages and foreign body giant cells (Figure 8). Some of these macrophages had a foamy appearance and showed birefringent material under crossed Nicol prisms. After 80 wk of implantation, only a limited number of extracellularly positioned birefringent particles could be observed. Intracellularly in foamy macrophages, birefringent particles were clearly visible under crossed Nicol prisms. TEM analysis of the CL-PLLA after 80 wk of implantation showed numerous macrophages that were fully packed with phagosomes that contained particles with needle-like or lamellar structures (Figure 9). These macrophages and extracellularly positioned particles were surrounded by dense connective tissue. There were no clear signs of cell damage, although some mitochondria appeared to be swollen.

Light microscopy under crossed Nicol prisms of excised lymph nodes did not show any sign of the presence of polymer particles in any of the rats.

DISCUSSION

In this study, the final degradation and biocompatibility of the degradation products of as-polymerized PLLA and two newly developed polymers were evaluated using in vitro pre-degraded particles. Chemical characterization of the pre-degraded PLLA showed an increase in the heat of fusion from 65 to 85 J g⁻¹, which is indicative of an increase in crystallinity. This increase in the heat of fusion, which is due to recrystallization, clearly resembled the physiological degradation as seen with patient material. After pre-degradation, PLA96 and CL-PLLA particles also showed recrystallization and a slight decrease in melting temperature, but the heat of fusion, indicative of crystallinity, remained substantially lower when compared to PLLA. The incorporation of 4% D-lactide or cross-linking with 1% spiro-bis-DMC seems to be enough to cause smaller and less perfect crystalline domains and an increased rate of hydrolysis when compared to PLLA. Due to these factors, PLA96 and CL-PLLA had a higher degradation rate, a substantially higher loss of mass and the mean particle size was smaller when compared to PLLA. This conclusion is in agreement with results of a study of Zhang et al., where they describe that the molecular weight, strength and mass loss by PLA96 samples was much faster than by the homopolymer PLLA. The initial degree of polydispersity of PLA96 and PLLA was 2.5 and 2.6, respectively, which are normal values for a polyester prepared by ring opening. Both PLA96 and PLLA showed a steep decrease in average molecular weight, as might be expected, and due to the at-random chain scission caused by the hydrolytic degradation, the degree of polydispersity is also expected to increase.

All three polymers used in this study were high molecular weight as-polymerized and semi-crystalline. Factors like processing, molecular weight, residual
monomer and crystallinity all have a great influence on the degradation rate, mechanical and biological characteristics of a polymer. According to Chawla and Chang, PLLA samples with a low molecular weight degraded significantly faster than PLLA samples with relatively high molecular weights. The importance of the amount of residual monomer in a polymer was studied by Nakamura et al.; they concluded that polymers containing relatively high levels of monomer showed a much more enhanced degradation rate with significant differences in the decrease in molecular weight and material weight. Zhang et al. described that the as-polymerized PLLA and PLA96 used in their study had a low purity which caused a very rapid initial degradation rate, while melt processed polymers with a high degree of purity went through a lag phase and then showed a rapid degradation. They concluded that the degree of purity is the most critical factor affecting hydrolytic degradation. The as-polymerized polymers as used in the present study had a residual monomer concentration of about 1% and contained some residual catalyst. Indeed, the molecular weight and the mechanical properties of as-polymerized PLLA in aqueous solution showed a rapid initial decrease. However, after this initial phase of degradation, the crystallinity becomes an important factor influencing the degradation rate. A study with injection moulded PLLA and as-polymerized PLLA, Pistner et al., observed that the amorphous injection moulded PLLA had a more enhanced degradation and disintegration rate compared to the crystalline as-polymerized PLLA implants. After 90 wk of implantation, the amorphous PLLA had disintegrated into fragments while the as-polymerized crystalline PLLA still had its original shape. The injection moulded PLLA in the study of Pistner et al. evoked, after 1 yr of implantation, an increased cellular reaction, consisting mainly of foamy macrophages and foreign body cells. In another study of Pistner, the as-polymerized crystalline PLLA evoked a similar histological reaction with foamy macrophages, but only after 106 wk of implantation. It is therefore probable that the final degradation phase of a degradable polymer is accompanied by a similar histological reaction, characterized by an increase of cellular activity, although the onset and the intensity of this reaction depends on the polymers used.

The degradation and disintegration of the implants and histological changes they induce was monitored by a quantification of the mean particle size, the number of particles per area, and the polymer and tissue area fraction. For all particles types the standard deviation was high due to the high variation in the minimum and maximum size, which was probably caused by the at-random disintegration of the particles and by the fact that the histological sections run through the irregular shaped particles. PLA96 had the highest degradation and disintegration rates; the number of detecable extracellularly positioned particles per frame area decreased from 1208 at 3 wk to 76 at 32 wk. In this period, large numbers of small particles were internalized and could no longer be counted. The polymer fraction area of the remaining particles was still 5.2% at 32 wk, indicating that the remaining extracellular particles were relatively large, which may account for the increase in mean particle size between 16 and 32 wk. After 80 wk, a comparable decrease in the number of measured CL-PLLA particles and an increase in the mean particle size was observed.

In the period between 32 and 80 wk, the PLA96 particles and to a lesser extent the CL-PLLA particles had disintegrated into small particles that were internalized by large fields of foamy macrophages, thus evoking a final cellular response. The fields of macrophages with internalized particles greatly resembled the situation of the patients with physiologically degraded PLLA after 5.6 yr. These histological data suggest that there is little variation in the qualitative characteristics of the tissue reaction; the cell types appear to be the same for the three in vivo pre-degraded implants and for physiologically degraded PLLA. The absence of qualitative histological differences among the three pre-degraded polymers corresponds with a study of Behling and Spector with two chemically different polymers, polyethylene and polysulphone. Their study suggests that the factors which govern the type of cells seen at the implant site are the same, regardless of differences in chemistry or structure. This implies that when non-toxic particles are implanted, the chemical composition, the degradation rate, the size or surface area of the implanted particles do not have a significant influence on the kind of cells that are attracted.

However, quantitative measurements of the histological response indicates substantial differences among the three implant materials. After 3 wk of implantation, the PLA96 particles area fraction was 22% of the measured frame area, which implies that 78% of the surface area was occupied by cells and enveloping fibrous tissue. For CL-PLLA it was 34% particles and 66% cells and fibrous tissue per frame area, and for the PLLA particles it was respectively 50% particles and 50% cells and fibrous tissue. This suggests that the smaller PLA96 particles evoke a more intense histological response compared to PLLA. Maguire et al. suggest in an in vivo study with polyethylene and methylmethacrylate particles that the degree of biological reaction depends mainly on the size and surface of the particles. Sovatsjanova et al. described that the connective tissue reaction to an implant is influenced by a number of factors, one being its size. The PLA96 particles were a factor of 11 smaller and the CL-PLLA particles a factor of 4.5 compared to the PLLA particles, which seems to correlate with the intensity of the tissue reaction. The results of this study do not show which factor is the most dominant, but the mean particle size may have a great influence on the intensity of the tissue reaction. The pre-degradation in this study was similar for all implants, which implies that the mean particle size depended merely on the chemical composition. For a comparative quantitative and qualitative biocompatibility testing of chemically different materials, the mean particle size should be the same, since the tissue reaction is directly dependent on the size of the implant.

In a study on osteolytic changes accompanying the degradation of polyglycolide pins, Røstman described that specimens obtained from patients with
Whether these newly developed polymers will induce a clinically detectable foreign body reaction when used in clinical setting, for example as bone plates, they might induce a detectable foreign body reaction, as seen with PLLA plates used in patients. However, the moment of clinical manifestation, the intensity and duration of such a possible foreign body reaction are factors that are directly dependent on the chemical structure of the implant, since the rate of degradation and the intensity of the histological reaction vary among the three implants. Further studies are necessary to determine whether these newly developed polymers will induce clinically detectable foreign body reactions when used in physiological settings and, if so, what the most important factors influencing the intensity of this reaction are.

REFERENCES


