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In vitro study of poly(lactic acid) pin degradation

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Abstract

An evaluation was made of pins of poly(lactic acid), an absorbable polymer, produced both with very little crystallinity (PLLA-A) and with extensive crystallinity (PLLA-C). These polymer pins were submitted to in vitro tests to evaluate the effects of degradation on mechanical, thermal, and structural properties, as well as molar mass variation. The pins were molded and immersed in a phosphate buffer solution (pH = 7.4) for 6 months. The results showed pins with greater crystallinity lost their mechanical properties more quickly, although an increase in the degree of crystallinity for both types of pins was observed over time. Structural analyses showed both superficial and internal erosion after two months of degradation. The greater retention of mechanical properties of the less-crystalline PLLA-A should prove useful in the production of implants where the stimulation of osteosynthesis is desired.

Keywords: Poly(lactic acid); Pins; Biodegradation

1. Introduction

Owing to their biocompatible and biodegradable nature, devices made of poly(alpha-hydroxy acids) have been used in the treatment of osteochondreal defects and small fractures, especially in maxilofacial and craniofacial surgery, i.e., in areas subject to limited strain [1,2]. These polymers are quite useful because their degradation occurs with simple hydrolysis of the ester bonds in an aqueous environment, and the degradation products (carbon dioxide and water) are metabolized by the organism, so that there is no need for subsequent surgery to remove the implant [3–5]; hence, biodegradable polyesters are indicated for various devices, including plates, pins, and screws in bone, as well as for membranes for cell cultures and guided regeneration in soft tissue [6–12]. Ideal materials for internal osteosynthesis should have enough initial rigidity to stabilize a bone for 6–12 weeks (depending on the specific bone concerned); moreover, they should not be much more resistant than bone. Once the bone has had time to heal, the mechanical stability should gradually decrease as the osteosynthesis increases, leading to a gradual transfer of load to the healing bone, thus preventing atrophy of the bone because of stress-shielding. Metals cannot be meet these demands, but polymers of the poly(alpha-hydroxy acids) such as poly(lactic acid) are beginning to do so [13].

Some in vivo experiments have shown that implants of poly(lactic acid), poly(glycolic acid) and their copolymers can cause inflammatory reactions as they are foreign bodies [2,14], as the type and intensity of inflammatory response is strongly influenced by the liberation of poly, oligo, and monomeric particles during in vivo degradation [15–20]. It is possible that amorphous and crystalline fragments generated during rapid or prolonged degradation provoke these inflammatory reactions by liberating acidic by-products in excessive quantities. Among the absorbable polymers, poly(lactic acid) is the one which requires the longest degradation time, longer than poly(glycolic acid), polydioxanone and the copolymers, as it can be found in the organism up to five years after the original implantation [15]. The time required for complete degradation and absorption of a polymer depends principally on the molar mass, its crystallinity, the size of the device implanted, its morphology, and the type of chain orientation [16,17]. The present article investigates the degradation process of poly(lactic acid) pins with two different degrees of crystallinity and evaluates the effect of this difference on mechanical, thermal, and morphological properties.

2. Experimental

Poly(lactic acid) supplied by MEDISORB was processed in a mini-injector (Mini-MaxCSC181MM) at 190°C, and

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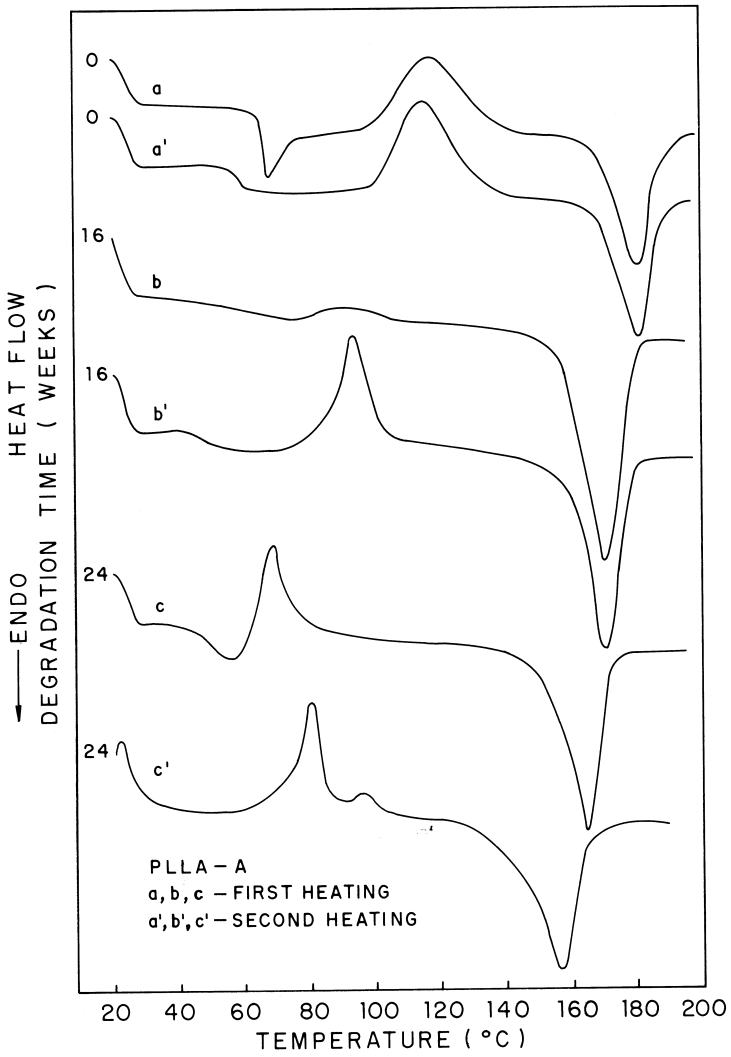

Fig. 1. Changes in the differential scanning calorimetry of the PLLA-A samples during 0, 16 and 24 weeks of degradation in phosphate buffer.

two different sample runs of 30 mm rods were obtained, the first consisting of 2 mm rods with extensive crystallinity (PLLA-C), and the second of 3 mm rods with very little crystallinity (PLLA-A). After molding, the 2 mm-rods were cooled for 30 min at room temperature, while the 3 mm ones were quenched at 20°C. The samples were sterilized with ethylene oxide and immersed in tubes containing a phosphate buffer solution (pH 7.4) in a thermally-controlled bath of 38°C ± 0.5°C; the samples were left for 1, 2, 4, 8, 12, 15, 20 and 24 weeks. The measurement of DSC (differential scanning calorimetry), (Du Pont) was made while heating the samples from 20°C to 200°C at a rate of 10°C min^{-1}, maintaining the final temperature for 5 min, and then cooling at the same rate; each sample was then re-heated. The samples were sealed in aluminium pans and the measurements were obtained under argon atmosphere. Tests of three-point bending of a 19 mm segment were made at 15°C using a MTS-810 (Materials Test System), (ASTM D790). The average molar mass in weight (M_w), in number (M_n) and viscosimetric (M_z) after in vitro study was determined by gel permeation chromatography (GPC, Waters) with three columns of Ultrastyragel 500, 1000 and 10 000 A, coupled to a refraction index detector. Samples of 200 μL were dissolved in 10 mL chloroform (Merck P.A.) and injected, with chloroform used as an eluent at a rate of 1 mL/min. Molar mass and rate of polydispersivity were calculated using polystyrene as a standard. For the measurement of scanning electron microscopy (MEV), (JEOL-300), the samples were fractionated in liquid nitrogen and coated with gold.

3. Results and discussion

The in vitro degradation of rods of poly(lactic acid), was studied in view of future application in the production of devices to promote osteosynthesis. Samples with two different degrees of crystallinity were used to verify the relationship between this parameter and the time of degradation so that implantation time can be adequately controlled. After

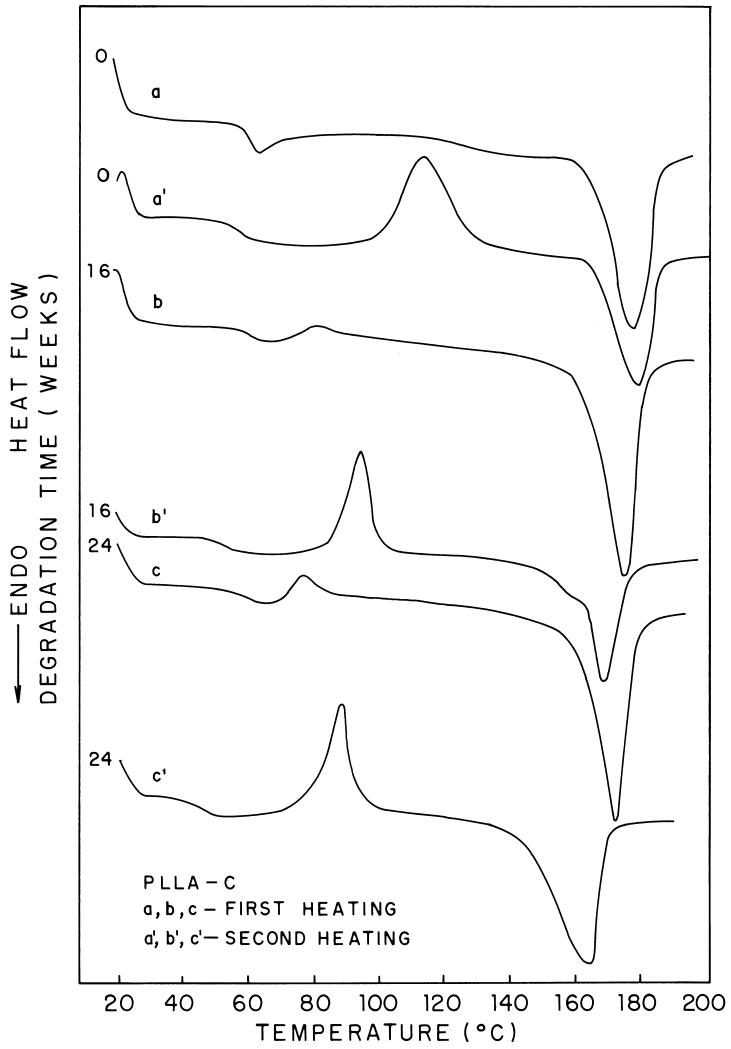

Fig. 2. Changes in the differential scanning calorimetry of the PLLA-C samples during 0, 16 and 24 weeks of degradation in phosphate buffer.

immersion in a phosphate buffer solution pH 7.4, simulating that of body fluids, the rods were periodically removed, washed with water to remove excess salt, and dried in a vacuum for 48 h at 50°C. Prior to degradation, DSC data showed that after the initial heating treatment, both samples revealed clear peaks of endothermic melting (T_m = 178°C and 189°C for PLLA-C and PLLA-A, respectively), but the glass transition temperature (T_g = 58°C and 60°C for PLLA-C and PLLA-A, respectively) was not well defined; PLLA-A samples showed a peak for exothermic crystallization (T_c = 116°C), which was expected, given the low degree of crystallinity, Figs. 1 and 2. After the second heating treatment, both samples presented distinct peaks in relation to crystallization, melting, and glass transition: T_c = 115°C, T_m = 180°C, and T_g = 58°C vs T_c = 116°C, T_m = 181°C, and T_g = 59°C, for the PLLA-C and PLLA-A samples, respectively. The appearance of a crystallization peak for the PLLA-C samples after the second heating phase suggests that the rate of cooling involved (10°C min^{-1}) is rapid enough to prevent slow nucleation and consequent crystal growth. This analysis of role of heat is presented for the PLLA-A (Tables 1 and 2) and PLLA-C samples (Tables 3 and 4).

During the 24 weeks in phosphate buffer, the crystallization temperature decreased for all PLLA-A samples, both for the initial heating phase (T_c = 69°C) and the subsequent one (T_c = 80°C). This decrease can be attributed to slow chain relaxations, and indicates an increase in crystallization, as randomly-oriented polymeric chains require more energy to crystallize under heating. A similar decrease in temperature was found for PLLA-C samples after the second heating phase (T_c = 88°C).

The degree of crystallinity was calculated from the enthalpy of melting, which is considered to be 93.7 J g^{-1} for 100% crystalline poly(lactic acid) [21]. The degree of crystallinity increased for both PLLA-A and PLLA-C samples, Table 1 and 3, respectively. This increase during degradation is frequently discussed in the literature [5,15,22,23,26], with most authors suggesting that it is because of a rearrangement of the shorter chains generated

Table 1
Differential scanning calorimetry of PLLA-A samples as function of degradation time for the first heating

Degradation time (weeks)	Melting temperature (°C)	Melting enthalpy (J/g)	Degree of crystallinity χ (%)	Crystallization temperature (°C)	Crystallization enthalpy (J/g)
0	181.20	42.30	—	116.70	−47.38
1	180.50	47.89	10.90	104.90	−37.63
2	179.50	58.30	26.80	101.30	−33.17
4	178.40	69.30	42.60	86.30	−29.50
8	175.90	69.80	41.80	79.94	−30.65
16	170.20	53.30	52.40	90.60	−4.14
20	167.60	58.40	55.60	89.00	−6.31
24	164.40	50.60	55.80	68.90	−4.30

by the degradation process itself, along with the consequent formation of new crystals, although some believe that the degradation of the amorphous part of the polymer merely results in a larger percentage of crystalline phase being left. This process is explained by Li et al. [22] and Leenslag et al. [23] as being owing to the hydrolysis of ester bonds occurring in the amorphous regions of the polymer, which would explain the increase in crystallinity observed. Li et al. [22] point out that the degradation process is more complex than merely the ratio between amorphous and crystalline parts. Using different plates of amorphous PDLA, they observed that the degradation process is heterogeneous, being more rapid in the center than on the surface when the plate is in contact with an aqueous medium. They suggest that an initially homogeneous sample in contact with an aqueous medium undergoes the initiation of hydrolysis, with consequent cleavage of the ester bonds, confirmed by a decrease in molar mass. At the beginning of the process, it is probable that the degradation occurs principally on the surface because of the absorption gradient of water, but as the concentration of carbonyl groups increases in the center, these serve as catalysts for the process. This self-catalyzing behavior was shown to occur in general during the degradation process of aliphatic polyesters. However, the process depends on the chemical structure and configuration of the polymeric chains, as well as the morphology of the device involved [22]. Lam et al. [24] confirmed such self-catalysis when they showed that non-porous membranes undergo degradation more rapidly than porous ones, because the latter facilitate dissolving and spread of the degradation products throughout the aqueous medium, thus discouraging self-catalysis.

The more rapid increase in degree of crystallinity in PLLA-A samples is a result of the more rapid degradation of the amorphous areas of the samples and the consequent increase in shorter chains, giving rise to more foci of crystallization. Although the PLLA-C was subject to the same process, the initial state already included more areas of crystallization, so the increase was not so accentuated. These data confirm the results of Li et al. [22], who found an increase in degree of crystallinity for initially amorphous PLA35.5/PGA25 co-polymers.

Another parameter to be considerate is enthalpy of crystallization. It decreased as degradation time increased, as less energy is necessary for the formation of crystals when the number of smaller chains, formed by degradation, increases. Prior to the first heating treatment, the polymer chains were basically randomly organized and quickly reached the T_c temperature of crystallization, whereas during the second heating treatment some crystals had already formed, thus requiring greater energy for crystallization; this would explain why the crystallization temperature for the second heating was higher.

During the process of degradation, the melting temperature decreased slightly for both PLLA-A and PLLA-C samples, probably because the degradation of the material

Table 2
Differential scanning calorimetry of PLLA-A samples as function of degradation time for the second heating

Degradation time (weeks)	Glass transition temperature T_g (°C)	Melting enthalpy (J/g)	Melting temperature (°C)	Crystallization temperature (°C)	Crystallization enthalpy (J/g)
0	58.88	44.96	181.52	115.73	−49.54
1	58.17	46.34	181.22	112.62	−46.91
2	56.82	53.11	179.38	110.89	−50.65
4	53.26	63.12	174.90	91.14	−37.09
8	50.73	59.24	172.69	97.62	−42.23
16	49.05	51.79	170.63	94.62	−30.90
20	45.78	56.01	166.43	89.47	−22.47
24	38.12	42.19	156.52	80.44	−23.24

led to the formation of crystals, which are resistant to further degradation.

Three-point mechanical bending tests (ASTM) showed that this polymer behaves like a hard and ductile material; when submitted to a constant tension, it initially suffered deformation, later elongation, and finally rupturing. Figs. 3–5, show the variation in the Young's modulus values, elongation at point of rupture, and maximal tension upon rupture, respectively, as a function of degradation time. The data obtained suggest that PLLA-C loses its mechanical bending properties more quickly than PLLA-A, with the latter thus being more appropriate for application in devices for osteosynthesis, as such devices will be able to withstand the stress to which they will be submitted until the bone recuperates. After 4 weeks, the samples of PLLA-C rupture without elongation, which confirms the fragility of the more crystalline substance, while the samples of PLLA-A ruptured only after 8 weeks. These results are comparable to those of other authors [13,25]. In an in vivo study, Pistner et al. [13] verified the prolonged mechanical stability of samples considered to be amorphous. Using bending tests, the authors reported a decrease in the Young's modulus for both amorphous and crystalline samples, although the crystalline ones decreased from 4227 to 2344 MPa after 8 weeks post-implant, while the amorphous ones which initially had a value of 3362 MPa retained this value for 12 weeks; only after 32 weeks did the value decrease to 2373 MPa. After 24 weeks, the crystalline samples decreased from 117 to 7 MPa, whereas for the amorphous ones this figure dropped from 118 to 51 MPa.

The mechanical stability of the PLLA-A samples suggests that they could be used as devices to promote osteosynthesis in small fractures. In such cases, their lifetime is sufficient to allow for bone recuperation; by the time the material is losing its mechanical properties, the recuperated bone will be able to take over its own functions.

Data on the variation of average molar mass for the PLLA-A and PLLA-C samples are shown in Table 5 and 6, respectively. This analysis confirms the degradation of the polymer as a function of time of immersion in the phosphate buffer. It was not possible to obtain continuous data as a function of immersion time, but measurements were made at the beginning, middle and end of the period (2, 12, and 24 weeks). The material obtained was analyzed after processing and sterilization with ethylene oxide. A certain preliminary degradation was observed immediately after the sterilization. In general, the samples with a greater degree of crystallinity underwent more rapid degradation during the first two weeks, while the PLLA-A samples underwent more drastic changes between the second and twelfth weeks. By the end of the study, the PLLA-A samples had undergone only slightly greater degradation than had the PLLA-C ones.

Visual analysis showed that the samples acquired a whitish color after 2 weeks of degradation, and the material became visibly cracked. The PLLA-C samples showed

Table 3
Differential scanning calorimetry of PLLA-C samples as function of degradation time for the first heating

Degradation time (weeks)	Glass transition temperature T_g (°C)	Melting enthalpy (J/g)	Melting temperature (°C)	Degree of crystallinity χ (%)
0	58.70	45.40	178.58	48.00
1	53.33	65.06	176.57	69.00
2	55.38	57.02	179.84	61.05
4	55.02	60.10	176.67	64.14
8	57.54	64.49	177.33	68.82
16	61.03	60.69	174.99	60.00
20	59.91	61.77	174.25	65.92
24	59.78	63.04	171.95	67.27

Table 4
Differential scanning calorimetry of PLLA-C samples as function of degradation time for the second heating

Degradation time (weeks)	Glass transition temperature T_g (°C)	Melting enthalpy (J/g)	Melting temperature (°C)	Crystallization temperature (°C)	Crystallization enthalpy (J/g)
0	58.23	46.14	180.22	114.98	−50.32
1	55.44	60.01	177.89	107.68	−49.22
2	53.53	60.22	176.21	101.43	−37.91
4	50.32	58.80	172.21	94.72	−34.84
8	52.67	58.19	172.46	96.11	−36.05
16	52.48	54.98	169.88	94.05	−35.20
20	50.37	55.00	167.46	90.78	−29.96
24	44.04	51.66	162.30	87.72	−25.83

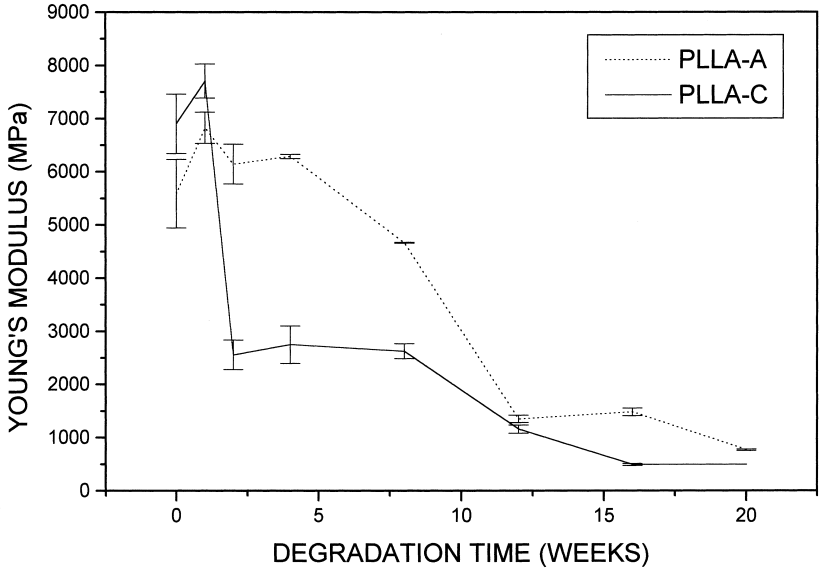

Fig. 3. Variation of Young's modulus as function of degradation time to PLLA-A and PLLA-C samples.

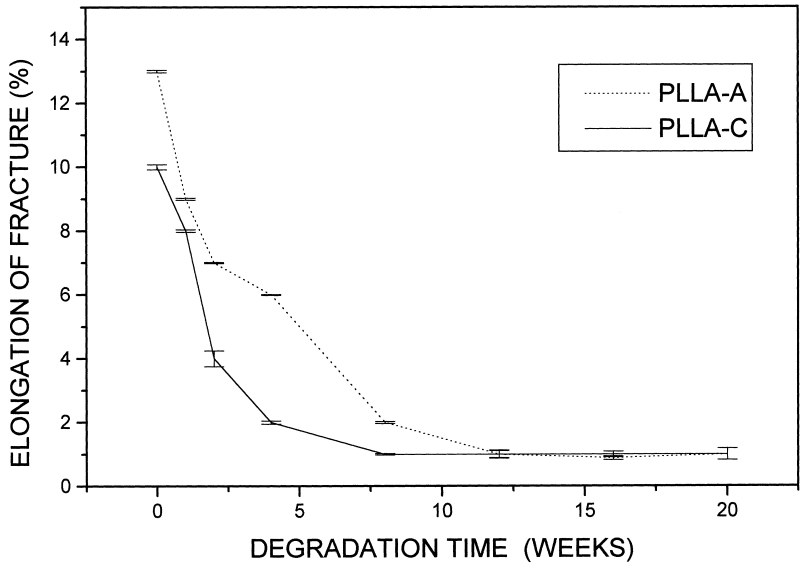

Fig. 4. Variation of elongation of fracture as function of degradation time to PLLA-A and PLLA-C samples.

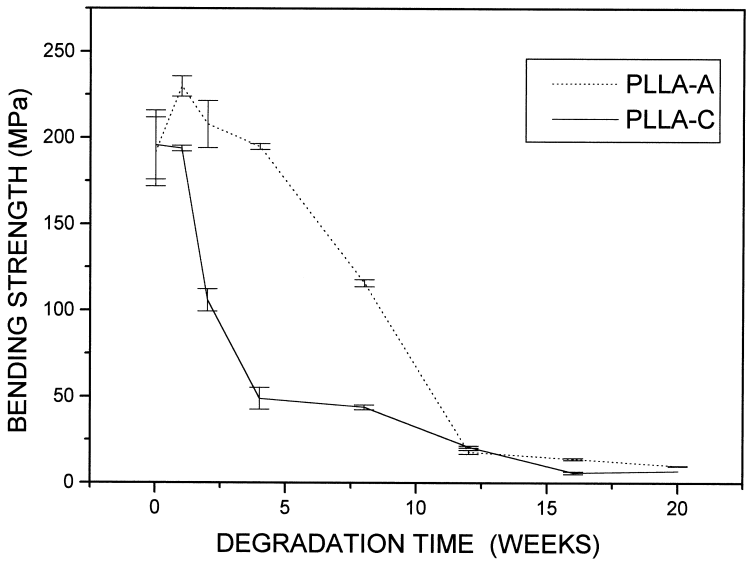

Fig. 5. Variation of bending strength as function of degradation time to PLLA-A and PLLA-C samples.

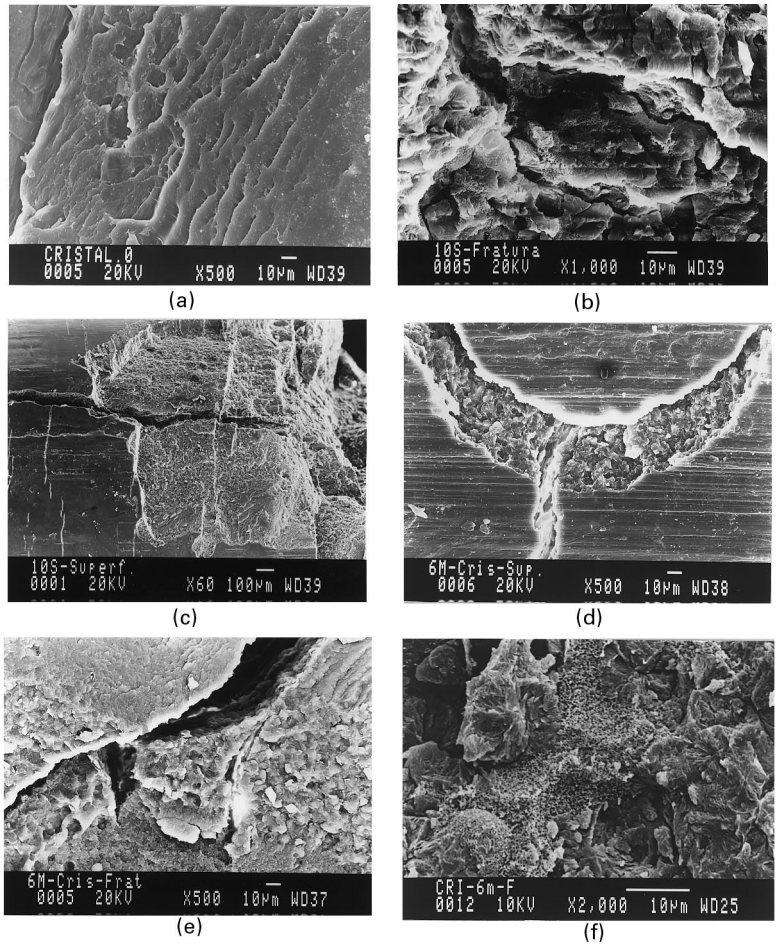

Fig. 6. Micrografs of PLLA-C samples: (a) $t = 0$, (b) $t = 10$ weeks (surface), (c) $t = 10$ weeks (surface of fracture), (d) $t = 24$ weeks (surface of fracture) and (e) $t = 24$ weeks (surface). Notice that on the first stages the samples shows a surface of fracture with crystalline agglomerations. Observe cracks and erosion as function of degradation time.

Table 5
Molar mass average in weight (M_w), in number (M_n), viscosimetric (M_z) and polydispersivity (M_w/M_n) as function of degradation time for PLLA-A samples

Degradation time (weeks)	M_w	M_n	M_z	M_w/M_n
Raw material	305 378	161 421	535 095	1.89
Injection-molded sterilized	303 383	151 818	608 260	2.00
2	243 381	139 848	396 397	1.74
12	53 469	24 792	82 869	2.15
24	35 091	15 117	56 176	2.32

Table 6
Molar mass average in weight (M_w), in number (M_n), viscosimetric (M_z) and polydispersivity (M_w/M_n) as function of degradation time for PLLA-C samples

Degradation time (weeks)	M_w	M_n	M_z	M_w/M_n
Raw material	305 378	161 421	535 095	1.89
Injection-molded sterilized	270 383	152 865	455 834	
2	150 410	83 178	231 815	1.80
12	61 980	28 076	98 001	2.20
24	37 220	13 433	73 412	2.77

more crystalline agglomerations initially Fig. 6a, with an increase in such agglomerations after 10 weeks, Fig. 6b, as well as the appearance of surface cracks Fig. 6c. After 16 weeks, in addition to the cracks, a small difference between the central region and the edges was observed, a difference which became more pronounced after 20 weeks of degradation. At this time, the cracks were more clearly defined, and the appearance of the central region was quite distinct from that of the edges.

These changes had increased after 24 weeks, as can be seen in Figs. 6d,e. In addition to the cracks, various regions show evidence of erosion, not only along the surface of the fractures, but also on the external surface of the rods. Fig. 6f shows the presence of well-defined spherical crystalline agglomerates, which prove the increase in crystal formation during the degradation. These data are in agreement with those in the literature [22,27], which suggest that degradation does not occur homogeneously, but rather more quickly in the interior than on the surface because of acidic self-catalysis. The

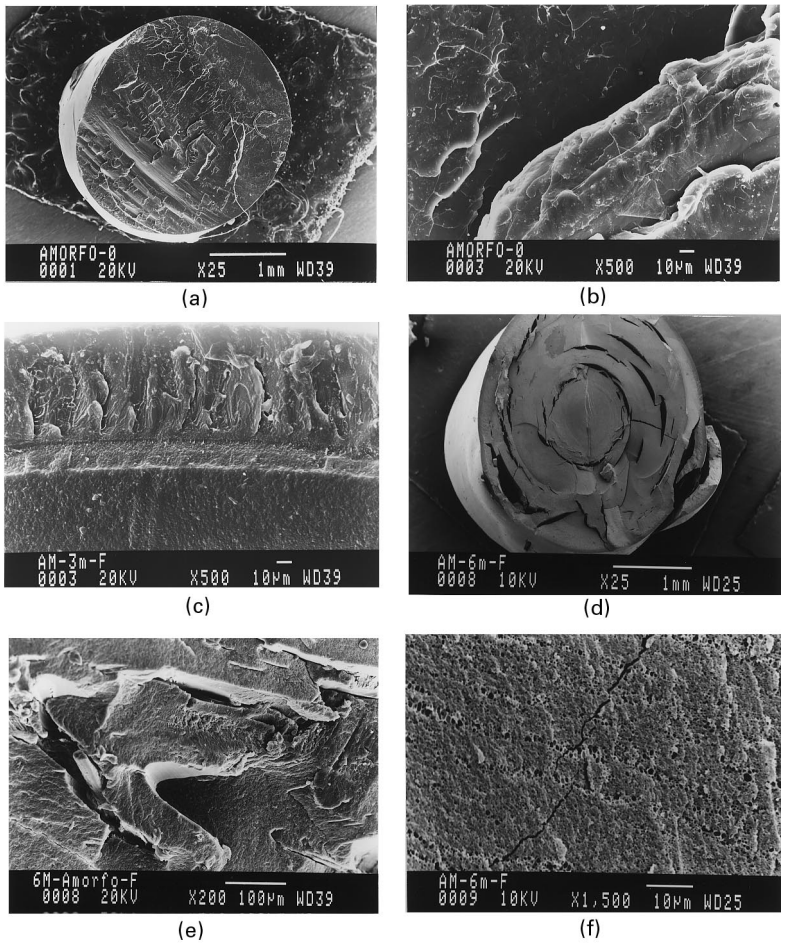

Fig. 7. Micrografs of PLLA-A samples: (a, e, b) $t = 0$ (surface of fracture), (c) $t = 12$ weeks (surface of fracture), (d) 24 weeks (surface of fracture), (e) 24 weeks (surface of fracture) and (f) 24 weeks (surface of fracture). Notice that before degradation the surface of samples was smooth. After 24 weeks the samples shows cracks and points of erosion.

present results show that the characteristics of degradation are dependent on the crystallinity of the material, with structural changes arising because of secondary effects such as chain relaxation.

Micrographs of the PLLA-A samples revealed surfaces is smoother than those of the PLLA-C samples, Figs. 7a,b. After 8 weeks of degradation, no significant morphological changes were observed, although after 12 weeks Fig. 7c distinct alterations such as the appearance of cracks occur, with visible differences between central and peripheral portions, as also reported in the literature [22,27]. After 24 weeks, an increase in the number of cracks and points of erosion were observed, and the samples had been completely destroyed, Figs. 7d–f, which explains the deterioration in mechanical properties observed.

4. Conclusions

Given the possible use of PLLA in the fabrication of implants to replace metallic devices for the promotion of osteosynthesis, the polymer was molded into rods to evaluate the importance of degree of crystallinity in degradation. These rods were produced with two different degrees of crystallinity. Data from DSC showed an increase in degree of crystallinity with increasing time of degradation. The more amorphous PLLA-A samples were more resistent to bending than the more crystalline PLLA-C ones; moreover, micrographs of the latter showed extensive crystalline agglomerations, while the former evidenced only a smattering of such agglomerates; after 10 weeks of degradation, these agglomerations had increased substantially in number. These data suggest that the delay in the reduction of the quality of the mechanical properties of the PLLA-A samples makes them more appropriate for use in devices to promote osteosynthesis.

Acknowledgements

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References

[1] Gogolewski S. Resorbable polymers for internal fixation. Clin Mater 1992;10:13–20.
[2] Bostman O, Paivarinta U, Manninen M, Rokkanen P. Polymeric debris from absorbable polyglycolide screws and pins. Acta Orthop Scand 1992;63:555–559.
[3] Engelberg I, Kohn J. Physico-mechanical properties of degradable polymers used in medical applications: a comparative study. Biomaterials 1991;12:292–304.
[4] Amecke B, Bendix D, Entenmann G. Resorbable polyesters: composition properties applications. Clin Mater 1992;10:47–50.
[5] Pistner H, Bendix DR, Muhling J, Reuther JF. Poly(L-Lactide): a long-term degradation study in vivo. Part III. Analytical characterization. Biomaterials 1993;14:291–298.
[6] Bostman , Makela EA, Tormala P, Rokkanen P. Transphyseal fracture fixation using biodegradable pins in children. J Bone Joint Surg 1989;17-B:706–707.
[7] Leeslag JW, Pennings AJ, Bos RRM, Rozema FR, Boering G. Resorbable materials of poly(L-lactide). VI. Plates and screws for internal fracture fixation. Biomaterials 1987;8:70–73.
[8] Bos RRM, Rozema FR, Boering G, Nijenhuis AJ, Pennings AJ, Jansen HWB. Bone plates and screws of bioabsorbable poly(L-lactide). An animal pilot study. Br J Oral Maxillofac Surg 1989;27:467–476.
[9] Wald HL, Sarakinos G, Lyman MD, Mikos AG, Vacanti JP, Langer R. Cell seeding in porous transplantation devices. Biomaterials 1993;14:270–278.
[10] Robert P, Mauduit J, Frank RM, Vert M. Biocompatibility and resorbability of a polylactic acid membrane for periodontal guided tissue regeneration. Biomaterials 1993;14:353–358.
[11] Trantolo DJ, Altobelli DE, Yaszemski MJ, Gresser JD. In: Wise DL, editor. Human biomaterials applications, New Jersey: Humana Press Inc, 1996.
[12] Dumitriu S. Polymeric Biomaterials. New York: Marcel Dekker Inc, 1994.
[13] Pistner H, Stallforth H, Gutwald R, Muhling J, Reuther J, Michael C. Poly(L-lactide): a long-term degradation study in vivo. Part II: physico-mechanical behaviour of implants. Biomaterials 1995;15:439–450.
[14] Bostman O. Osteolytic changes accompanying degradation of absorbable fracture fixation implants. J Bone Joint Surg 1991;73:679–682.
[15] Mainil-Varlet P, Rahn B, Gogolewiski S. Long-term in vivo degradation and bone reaction to various polylactides. 1. One year results. Biomaterials 1997;18:257–266.
[16] Offegeld H, Michaeli W, Menges G. The injection molding of resorbable implants. ANTEC 1989;35:1282–1286.
[17] von Oepen R. Injection molding of biodegradable implants 2, International workshop on Implant Materials, 1990, Frankfurt, Germany.
[18] Lam KH, Schakenraad JM, Esselbrugge H, Feijen J, Nieuwenhuis P. The effect of phagocytosis of poly(L-lactic acid) fragments on cellular morphology and viability. J Biomed Mater Res 1993;27:1569–1577.
[19] Lam KH, Schakenraad JM, Groen H, Esselbrugge H, Dijkstra PJ, Feijen J, Nieuwenhuis P. The influence of surface morphology and wettability on inflammatory response against poly(L-lactic acid): a semi-quantitative study with monoclonal antibodies. J Biomed Mater Res 1995;29:929–942.
[20] Hyon SH, Jamshidi K, Ikada Y. Melt spinning of poly-L-lactide and hydrolysis of the fiber in vitro. Polymers as biomaterials, Section A: materials and properties, Plenum Press, 1985. p. 51–65.
[21] Fisher EW, Sterzel HJ, Wegner G. Investigation of the structure of solution grown crystals of lactide copolymers by means of chemical reactions. Kolloid-Z Z Polymere 1973;251:980–990.
[22] Li SM, Garreau H, Vert M. Structure–property relationships in the case of the degradation of massive aliphatic poly(α-hydroxy acids) in aqueous media, Part 2: degradation of lactide–glicolide copolymers: PLa37.5Ga25 and PLA75Ga25. J Mater Sci: Mater in Med 1990;1:131–139.
[23] Leenslag JW, Pennings AJ, Bos RRM, Rozema FR, Boering G. Resorbable materials of poly(L-lactide) VIII. in vivo and in vitro degradation. Biomaterials 1987;8:311–314.
[24] Lam KH, Nieuwenhuis P, Molenaar I, Esselbrugge H, Feijen J, Dijkstra PJ, Schakeraad JM. Biodegradation of porous versus non porous poly(L-lactic acid) films. J Mater Sci: Mater in Med 1994;5:181–189.
[25] Li SM, Garreau H, e Vert M. Structure-property relationships in the case of the degradation of massive aliphatic poly((-hydroxy acids) in aqueous media, Part 3: Influence of the morphology of poly(L-lactic acid). J Mater Sci: Mater in Med 1990;1:198–206.
[26] Mainil-Varlet P, Gogolewski S, Nieuwenhuis P. Long-Term soft tissue reaction to various polylactides and their in vivo degradation. J Mater Sci Mater in Med 1996;7:713–721.
[27] Therin M, Cristel P, Li S, Garreau H, Vert M. In vivo degradation of massive poly(α-hydroxy acids): validation of in vitro findings. Biomaterials 1992;13:594.