PII: S0032-3861(96)00711-2

Polymer Vol. 38 No. 8, pp. 1879–1884, 1997

0032-3861/97/$17.00+0.00

Influence of residual monomers and metals on poly (L-lactide) thermal stability

D. Cam* and M. Marucci
Centro Ricerche Ambientali, Montecatini-Ravenna, Via Ciro Menotti 48,
48023 Marina di Ravenna, Italy
(Received 15 May 1996; revised 18 June 1996)

Poly (L-lactide) (PLLA) with molecular weight ranging from 7600 to 700 000 has been purified from traces of residual metals and has then undergone thermal behaviour examination. The PLLA decomposition temperature obtained by thermogravimetric analysis was used as a measure of its thermal stability. It has been demonstrated that residual low molecular weight compounds such as moisture, lactic acid, lactide, etc. associated with PLLA can be removed without affecting the polymer thermal stability, while residual metals were revealed to be the principal parameter which causes drastic thermal degradative effect on the polymer. The decomposition temperature of pure PLLA at infinite molecular weight was 353°C. The thermal stability of PLLA has been studied as a function of the amount of added tin, zinc, aluminium and iron. Experimental results enable the comparison of their influence on PLLA thermal stability which follows a decreasing order: Fe > Al > Zn > Sn. The more selective the catalyst for PLLA polymerization, the less efficient is its depolymerization effect at high temperature. © 1997 Elsevier Science Ltd. All rights reserved.

(Keywords: poly (L-lactide); residual monomers; residual metals)

INTRODUCTION

In the last decades, medical devices made of polylactide have gained enormous interest in surgery applications due to their favourable chemical, biological and mechanical properties. The need to design materials able to degrade in a specific and controlled way, to develop a totally body absorbable internal fixation implant in order to eliminate the second surgical operation after the healing period consists nowadays a real comfort with respect to traditional metallic protheses. The simple chemical structure of poly (α-hydroxy acids) favours their compatibility with biological tissues involving a simple degradation mechanism with no complex end products and without causing adverse reactions. The simple structure of such an aliphatic polyester, on the other hand, turns out to be susceptible to thermohydrolysis which causes serious drawbacks concerning the degraded properties of the material after processing.

Although it is known that poly (L-lactides) (PLLAs) belong to a group of polymers with poor thermal stability[1], the main techniques used to process this material into medical devices are compression, extrusion and injection-moulding[2]. Many implants such as thread, cord, gauze, knitted and woven clothes, and tubes are constructed from PLLA fibres which have been obtained by melt-spinning[3–6]. In all cases the manufactured and sterilized products have been demonstrated to be partially degraded with respect to the starting material, so that the mechanical properties have been modified, and improvised degradation kinetics are revealed[7,8].

The parameters which have been reported to influence PLLA thermal stability include moisture, hydrolysed monomers and oligomers, molecular weight and residual metals. However, no literature has reported the relative significance of their contribution to the degradative reaction of the polymer. Understanding the influence of these parameters on the polymer thermal stability is relevant for providing the degradation property of the manufactured products.

The purpose of this work is to investigate the influence of all the individual parameters supposed to deal with the polymer thermal stability. The PLLA material was first purified and a known amount of the contaminant components were added in order to evaluate separately their influence on the polymer decomposition temperature. The degradative effect of tin, zinc, aluminium and iron on PLLAs at high temperature has been compared.

EXPERIMENTAL

All manipulations have been carried out rigorously under nitrogen atmosphere.

Reagents

L-Lactide (LA) was purchased from Purac, and was recrystallized twice from ethyl acetate and dried in a vacuum at 50°C just before the polymerization reaction.

Stannous 2-ethylhexanoate was purchased from Sigma-Aldrich, and was distilled under reduced pressure and stored under nitrogen atmosphere. A pentane solution of catalyst was freshly prepared for the polymerization reaction.

Standards based on inorganic salts of tin, zinc, aluminium and iron, of high purity, have been used as contaminant metals to the polymer.

The solvents ethyl acetate and pentane were dried over

---

* To whom correspondence should be addressed

$CaCl_2$ and CaH_2 respectively, and distilled under nitrogen atmosphere.

Polymer preparation

Polymerization. Freshly purified LA was mixed with a suitable amount of catalyst, the whole mass was introduced into a reactor and high vacuum was applied for 4–5 h at room temperature. The reactor was then disconnected from the vacuum line and heated to the polymerization temperature of 110°C with stirring. After a predetermined time the stirrer was stopped and the polymerization reaction was continued for 72 h. The polymer obtained was milled into small chips and stored in dry atmosphere.

Purification. Purified PLLA was obtained by three different methods:

1. The as-polymerized PLLA was milled into chips of dimensions 4–6 mm and these underwent extraction with boiling ethyl acetate in Soxhlet for 24 h under nitrogen atmosphere. The product was dried in high vacuum at room temperature for a week by means of a lyophilizer and stored in a desiccator over silica gel.
2. The polymer was dissolved in methylene chloride (2–3 wt%) and precipitated from methanol (three-fold volume of methanol to that of methylene chloride). The precipitated flakes of PLLA were filtered, washed with fresh methanol dried and stored as above.
3. The polymeric methylene chloride solution was stirred with an equal volume of a 5% (w/w) aqueous hydrochloric acid solution at room temperature. Thereafter, the methylene chloride solution was separated and washed with distilled water until neutral pH in a separatory funnel. The polymer was precipited from the resulting methylene chloride solution with methanol, and washed and dried as described above.

PLLA with added known amount of contaminants. PLLA containing a known amount of metal catalysts, L-lactic acid or L-lactide monomer was prepared as follows. The purified polymer (obtained from purification method 3) was checked to be free of every kind of impurity and dissolved in methylene chloride. Suitable amounts of standards or monomers were added. The solutions was stirred for 15 min at room temperature and the solvent was evaporated . The recuperated polymer was carefully dried by means of a lyophilizer and underwent thermogravimetric analysis (t.g.a.).

Characterization

Inductively coupled plasma-atomic emission spectroscopy (i.c.p.-a.e.s.). Determination of metallic residual in PLLA by i.c.p.-a.e.s. was performed with a Plasma Spectrometer, Varian-Liberty 200. An average of three to five sample measurements were performed for each datum value. About 0.25 g of PLLA sample were microwave-digested in concentrated mixture of H_2SO_4 and HNO_3 at 200°C. After cooling, the system was brought to suitable concentration for i.p.c.-a.e.s. measurement with dilute chloric acid. Standards were prepared by diluting 1000 ppm stock solutions purchased from Sigma-Aldrich to suitable concentrations.

Thermogravimetric analysis. The t.g.a. measurements were performed with a Perkin-Elmer instrument TGA-7 in nitrogen atmosphere. The furnace temperature was calibrated with pure nickel (magnetic transition temperature 354°C). The sample (*ca* 5 mg) initially underwent a 60 min isotherm at 150°C, followed by a heating rate of $10°C\,min^{-1}$ to 450°C where complete mass reduction of the sample had occurred. In this work the thermal stability of PLLA has been estimated as its decomposition temperature which was measured at the onset point of the thermogravimetric curve: the intersection of the isothermal line and the flex tangent of the t.g.a. curve. For coherence and comparability of t.g.a. data, the measurements were conducted rigorously in a continuous series to avoid experimental discrepancy.

RESULTS AND DISCUSSION

Thermal degradation of PLLA due to the thermal hydrolysis of main chain ester bonds has been noted to be influenced by various parameters such as: trace amounts of water; hydrolysed monomer/oligomers; residual catalyst[1]. Regarding the complex set of parameters involved, it is difficult to decide which dominates the thermal degradation of polylactide, since little information about the degradation mechanism is reported.

In order to obtain a better insight into the thermal degradation mechanism of PLLA, all the above-mentioned affecting parameters have been eliminated by rigorous purification of the polymer. Three different purification methods have been conducted on milled PLLA. The elemental analyses were performed with i.c.p.-a.e.s. since a preliminary study had demonstrated that this is the most suitable technique to reveal the presence of parts per million heavy metals in PLLA[9].

Table 1 shows the efficiency of three different attempts to remove residual catalysts from PLLA:

1) Extraction of the as-polymerized/milled PLLA with boiling ethyl acetate in Soxhlet under nitrogen atmosphere is the most convenient purification method but it succeeded only in removing most but not all of the iron and chromium released from the milling operation.
2) Dissolution of the same PLLA sample in methylene chloride and its precipitation from the methanol reduced most but did not eliminate all the metal in the polymer. Tin was particularly difficult to remove.
3) The most effective purification method to eliminate all kinds of residual metals from PLLA is treatment of the polymeric solution with dilute chloric acid, and this was the standard purification mode employed in this work in order to prepare PLLA samples completely free of impurities.

This last purification method is unlikely to be preferred by most authors due to the possibility of

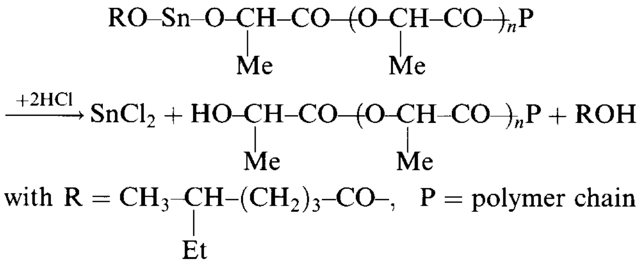
Table 1 Residual metals in purified PLLA

PLLA purification method	Sn (ppm)	Fe (ppm)	Cr (ppm)
As-polymerized/milled PLLA	138	867	92
Extraction in Soxhlet	135	43	4
Dissolution/precipitation	100	18	5
Dissolution/acid treatment/precipitation	3	5	4

Sn, Fe, Cr were determined by i.c.p.-a.e.s.

ester bond hydrolysis which could cause the molecular weight to decrease. However to minimize this drawback, the treatment should be at room temperature for a limited time, and the product should be rigorously washed until complete disappearance of trace acid which could damage drastically the polymer at high temperature.

According to the reported insertion mechanism of lactide ring-opening polymerization catalysed by tin ottoate[10,11], the as-polymerized PLLA should still contain active site with tin linked chemically to the polymer chain. The treatment of the PLLA methylene chloride solution with chloric acid favours the hydrolysis of Sn–O bonds and the formation of soluble salts which will be leached easily to the washing solvent. A representative reaction is proposed in equation (1):



$$\mathrm{RO{-}Sn{-}O{-}\underset{Me}{CH}{-}CO{-}(O{-}\underset{Me}{CH}{-}CO)_{n}P} \xrightarrow{+2HCl} \mathrm{SnCl_2 + HO{-}\underset{Me}{CH}{-}CO{-}(O{-}\underset{Me}{CH}{-}CO)_{n}P + ROH}$$

$$\text{with } \mathrm{R = CH_3{-}\underset{Et}{CH}{-}(CH_2)_3{-}CO{-}}, \quad \mathrm{P} = \text{polymer chain} \qquad (1)$$

The purified polymer was extensively dried in lyophilizer for a week at room temperature and underwent successive t.g.a. analyses. Storing the purified polymer was avoided because even if monomer had been completely removed from the product and was stored under nitrogen atmosphere, traces of moisture deposited on the surface of the polymer may again produce hydrolysed monomers or oligomers upon heating the sample. All purified polymers were verified to be free of residual metals by means of i.c.p.-a.e.s.

Figure 1 illustrates the t.g.a. curves of nickel and purified PLLA with M_v of 500 000 running in nitrogen atmosphere with an isotherm of 60 min at 150°C and a heating rate of 10°C min^{-1} until 450°C. The onset temperature of nickel was used for the furnace calibration (the magnetic transition temperature of nickel is 354°C) and that of PLLA was used as a measure of its decomposition temperature.

Effect of molecular weight on the PLLA decomposition temperature

Figure 2 illustrates the decomposition temperature (T_{dec}) values of purified PLLA plotted against the viscosimetric average molecular weight ($\overline{M}_v$). The intrinsic viscosity values $[\eta]$ of the starting polymers were measured with an Ubbelohde viscosimeter in chloroform at 25°C, and the viscosimetric average molecular weight ($\overline{M}_v$) was estimated from equation (2)[12]:

$$[\eta] = 5.45 \times 10^{-4} \times M^{0.73} \qquad (2)$$

The monomer LA has been used as a homologue of PLLA, with molecular weight of 144. T.g.a. measurements of the PLLA sample series have been performed with and without isothermal treatment, in order to demonstrate the high purity of the samples which lead to a good reproducibility and accuracy of the values. The curve in *Figure 2* shows a sharp slope decrease as the molecular weight rises above 140 000 g mol^{-1} and

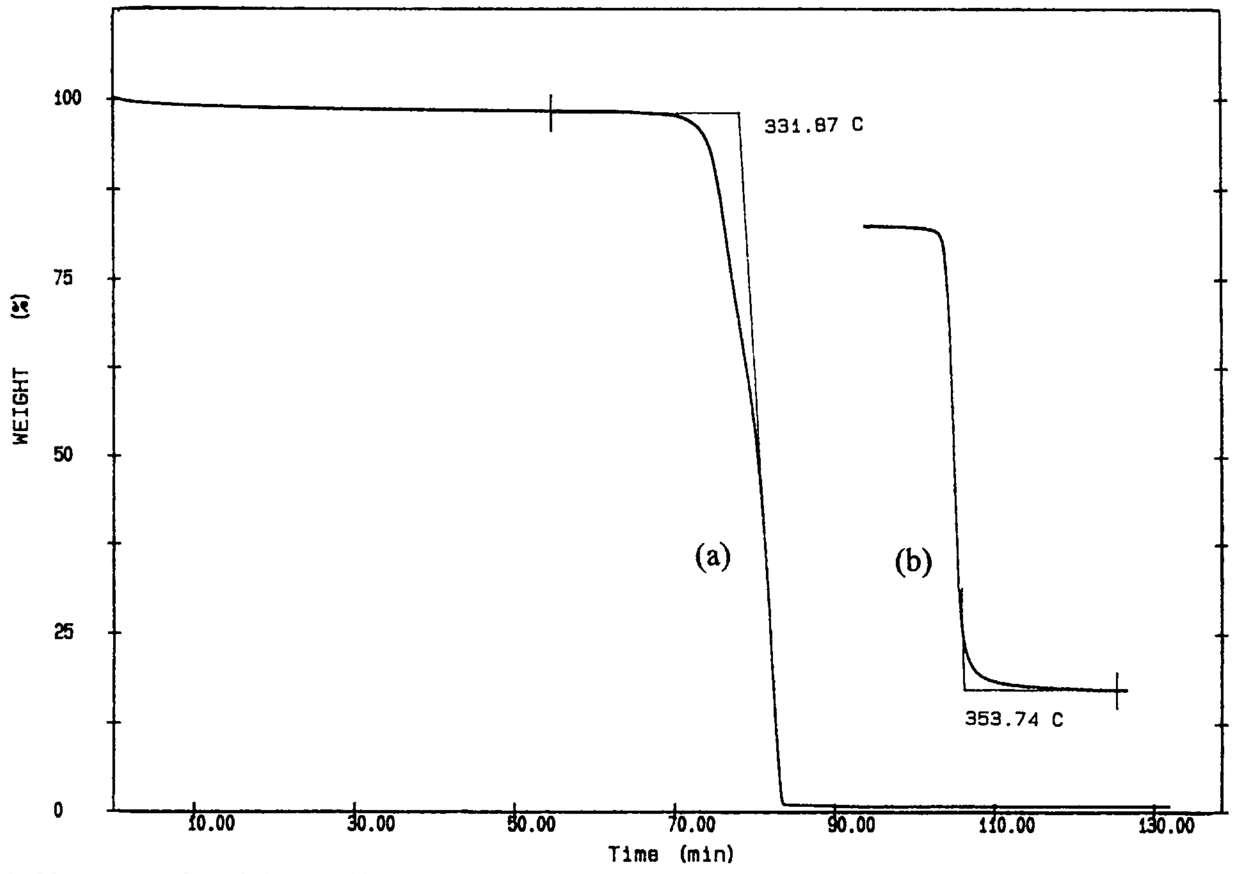


Figure 1 Measurement of PLLA decomposition temperature by t.g.a: (a) PLLA; (b) nickel

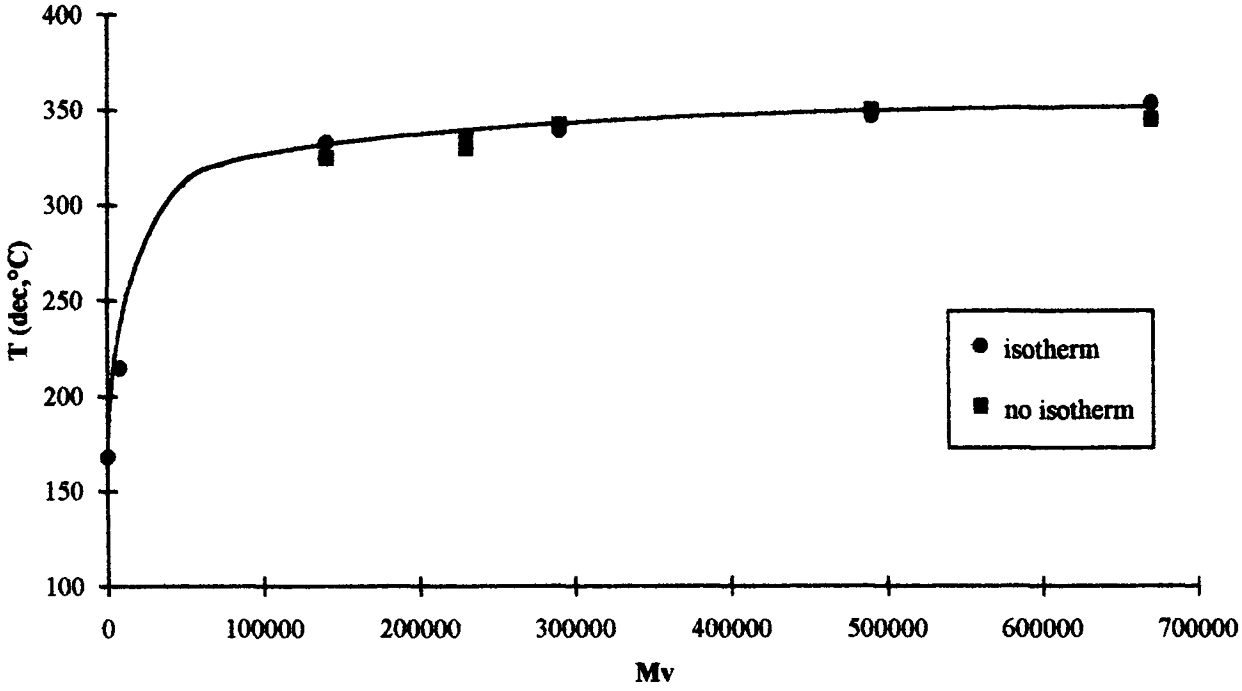
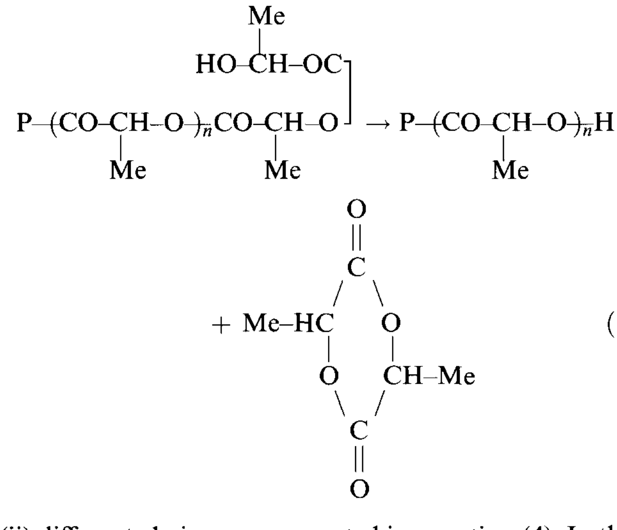
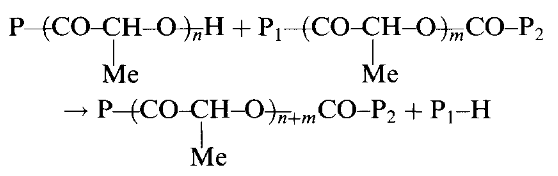


Figure 2 Effect of molecular weight of PLLA decomposition temperature

approaches 353°C as the molecular weight becomes infinite. This fact could be explained by the following. When excluding all parameters which can accelerate the thermal hydrolysis of PLLA (moisture, monomers, oligomers, residual catalyst) the degradation reaction should be brought about especially by the terminal hydroxyl groups of: (i) the same chain as proposed in equation (3) to form monomer and/or oligomer cyclic compounds:


(3)

(ii) different chains as represented in equation (4). In this case a random scission of the macromolecule should lead to a drop in molecular weight:



$$P{-}(CO{-}\underset{Me}{CH}{-}O)_{\bar{n}}H + P_1{-}(CO{-}\underset{Me}{CH}{-}O)_{\bar{m}}CO{-}P_2 \rightarrow P{-}(CO{-}\underset{Me}{CH}{-}O)_{\overline{n+m}}CO{-}P_2 + P_1{-}H \qquad (4)$$

with P, P_1, P_2 = polymer chains.

The lower molecular weight, the more concentrated are the terminal hydroxyl groups which accelerate equations (3) and (4). Hence resulting PLLA oligomers are thermally unresistant, and decomposed at low temperature. Over a certain range of molecular weight ($M_v > 140\,000\,\mathrm{g\,mol^{-1}}$) the terminal hydroxyl concentration becomes negligible with respect to that of the ester repeating units within the polymer chain, the PLLA decomposition temperature T_{dec} is then slightly influenced by their molecular weight; T_{dec} reached 330–340°C for infinitely high PLLA molecular weight (see *Figure 2*). This observation appears likely to be consistent with the high thermal stability of acetylated PLLA studied by Jamshidi *et al.*[1].

Effect of low molecular weight compounds on the PLLA decomposition temperature

Table 2 reports the decomposition temperature of purified PLLA sample ($M_v = 140\,000\,\mathrm{g\,mol^{-1}}$) as a function of added amounts of L-lactic acid and LA. The t.g.a. measurements have been performed without isothermal treatment, and a slight deflection of T_{dec} is evident with the increasing amount of added monomers, more so with lactic acid that with lactide.

The same PLLA series of samples containing known amounts of monomers have undergone an isothermal treatment at 150°C for 60 min inside the t.g.a. furnace

Table 2 Effect of monomers on PLLA decomposition temperature

Monomer wt%	T_{dec} (°C) of PLLA with added L-lactic acid	T_{dec} (°C) of PLLA with added L-lactide
0	324	324
1	322	323
5	321	322
10	319	319
20	316	317
50	308	309

T_{dec} were measured by t.g.a. running in nitrogen atmosphere without isotherm, heating rate 10°C min^{-1}

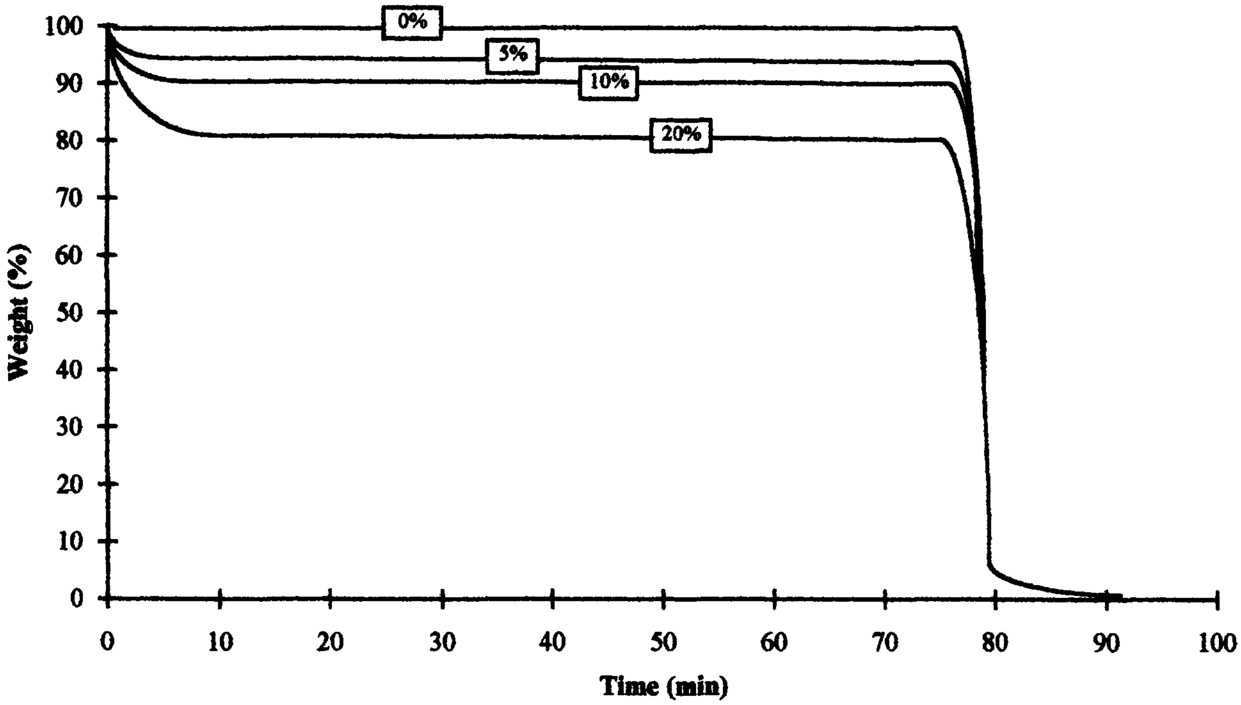


Figure 3 Effects of monomers on PLLA decomposition temperature: t.g.a. analyses running with isotherm at 150°C for 60 min, heating rate 10°C min^{-1} of samples containing 0, 5, 10, 20 wt% of L-lactide

under nitrogen atmosphere. The t.g.a curves are shown in *Figure 3*, respectively for samples contaminated with 0, 5, 10 and 20 wt% LA. It can be noticed that the samples lost their mass almost correspondingly to the added amount of monomer during the 60 min of isotherm at 150°C, but the T_{dec} appeared invariate. It seems that previous thermal treatment of PLLA succeed in removing low molecular weight compounds associated with the material without affecting its thermal stability.

The same behaviour can be noticed when adding L-lactic acid to the PLLA samples. Hence a pretreatment of PLLA in nitrogen atmosphere at 150°C for 60 min before processing proves to be useful in removing low molecular weight compounds.

Effect of residual metals of the PLLA decomposition temperature

To the purified PLLA sample having $M_{\mathrm{v}} = 230\,000\ \mathrm{g\,mol^{-1}}$, there was added respectively four different kinds of standards in the range 0–15 000 ppm. The resulting polymers underwent t.g.a. measurements; *Figure 4* illustrates the T_{dec} of PLLA as a function of

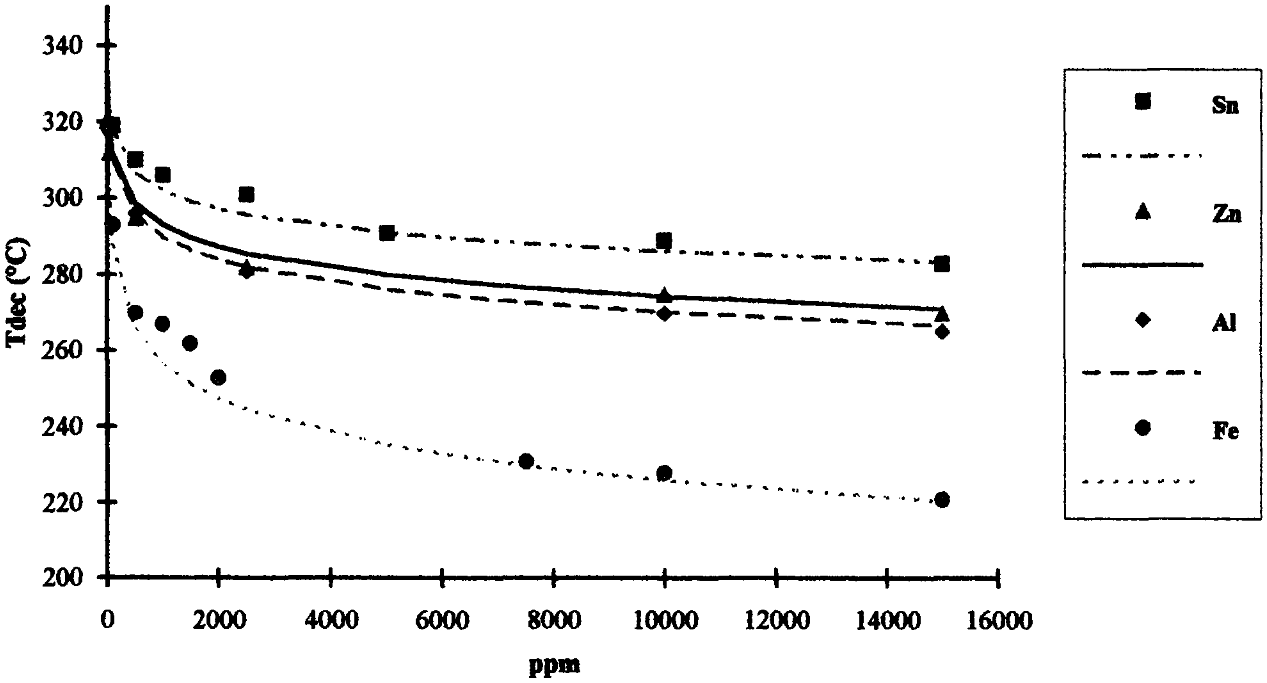


Figure 4 Effect of tin, zinc, aluminium and iron on PLLA decomposition temperature

tin, aluminium, iron content in the samples. The four series of symbols reported in *Figure 4* represent the experimental data, while the lines correspond to the best fit equations (5):

$$T_{\mathrm{dec}} = T_0 - N \ln (m) \qquad (5)$$

where T_0 (330°C) is the decomposition temperature of infinitely pure PLLA, m is the amount of metal (ppm) added to the polymer and N represents the factor with which the ionic metal affects the polymer degradative reaction. The data evaluation gives the following values: $N_{\mathrm{Sn}} = 6.8$, $N_{\mathrm{Zn}} = 8.1$, $N_{\mathrm{Al}} = 8.6$ and $N_{\mathrm{Fe}} = 13.4$. The degradative effect of tin, zinc, aluminium and iron on PLLA increases in the following order: $\mathrm{Sn} < \mathrm{Zn} < \mathrm{Al} < \mathrm{Fe}$.

The presence of residual catalytic metals in PLLA has been noted to accelerate the inter- and intra-molecular transesterification reactions at high temperature (over 240°C) which can be revealed by the evident change of the specific optical rotation[1,13,14]. It is obvious that compounds that can bring about the transesterification of the polymer can bring about their degradation by 'back-biting'. The very relevant degradative effect of iron on PLLA could be explained by the high capacity of transition metals to coordinate ester groups and accelerate the transesterification and depolymerization reactions at high temperature. *Figure 4* shows that Sn- and Zn-initiators can give rise to interchange and depolymerization at high temperature but more modestly with respect to aluminium and iron, since the former have been known as the most selective catalysts for the polymerization of lactide[13,15].

Comparing with other parameters such as moisture and hydrolysed monomers or oligomers, residual metals influence drastically the thermal stability of PLLA. In fact, the sample containing 1 wt% of monomers decomposed at a temperature 1–2°C lower than that of the pure one (*Table 2*), while the samples containing the same amount of metals (10 000 ppm of Sn, Zn, Al, Fe) decomposed respectively at 50, 60, 70 and 110°C lower than that of the pure polymer (*Figure 4*).

CONCLUSION

Thermal stability of PLLA has been investigated in detail. Low molecular weight compounds such as moisture, monomers, hydrolysed monomers and oligomers associated with the polymer, can be removed without affecting the thermal stability of the material. An isothermal pretreatment at 150°C for 60 min of the polymer in inert atmosphere should be useful to eliminate undesired volatile impurities.

The depolymerization of PLLA at high temperature is shown to be caused especially by the presence of residual metals which catalyse the chain transfer, intra- and inter-transesterification and depolymerization reactions. Regarding the various kinds of metals which can be found in the polymer (as contaminants or catalysts), a degradative effect has been demonstrated in the following order for tin, zinc, aluminium and iron: $\mathrm{Sn} < \mathrm{Zn} < \mathrm{Al} < \mathrm{Fe}$.

ACKNOWLEDGEMENTS

This work is financially supported by the 'Istituto Imobiliare Italiano S.p.A.' under requirement of the Italian Ministry of University and Science Technological Research. M.M. is very grateful to 'Tecnobiomedica' for the awarded fellowship. Dr M. Villani is gratefully acknowledged for the data evaluation.

REFERENCES

1 Jamshidi, K., Hyon, S. H. and Ikada, Y. *Polymer* 1988, **29**, 2229

2 Matsusue, Y., Yamamuro, T., Yoshii, S., Oka, M., Ikada, Y., Hyon, S. H. and Shikinami, Y. *J. Appl. Biomaterials* 1991, **2**, 1

3 Tunc, D. C. and Jadhav, B. in 'Progress in Biomedical Polymer' (Eds C. G. Gebelein and R. L. Dunn), Plenum Press, New York, 1990, p. 239

4 Adriano, K. P., Pohjonen, T. and Törmälä, P. *J. Appl. Biomaterials* 1994, **5**, 133

5 Eling, B., Gogolewski, S. and Pennings, A. J. *Polymer* 1982, **23**, 1587

6 Hoffman, A. S. *J. Appl. Polym. Sci., Appl. Polym. Symp.* 1977, **31**, 313

7 Paganetto, G., Mazzullo, S., De Lollis, A., Buscarolli, S., Rocca, M., Fini, M. and Giardino, R. *Biomateriali* 1991, **2**, 179

8 Migliaresi, C., Cohn, D., De Lollis, A. and Fambri, L. *J. Appl. Polym. Sci. 1991*, **43**, 83

9 Cam, D., Marucci, M., Fadel, M. and Goberti, P. 'Frontiers in the Medical Applications of Polymers', Technomic, Lancaster, PA, in press

10 Zhang, X., Macdonald, D. A., Goosen, M. F. A. and Mcauley, K. B. *J. Polym. Sci., Part A: Polym. Chem.* 1994, **32**, 2965

11 Kricheldorf, H. R., Kreiser-Saunders, I. and Boettcher, C. *Polymer* 1995, **36**, 1253

12 Schindler, A. and Harper, D. *J. Polym. Sci., Polym. Chem. Edn* 1979, **17**, 2593

13 Kricheldorf, H. R. and Serra, A. *Polym. Bull.* 1985, **14**, 497

14 Kricheldorf, H. R. and Kreiser, I. *J. Macromol. Sci., Chem.* 1987, **A24 11**, 1345

15 Nijenhuis, A. J., Gripjpma, D. W. and Pennings, A. J. *Macromolecules* 1992, **25**, 6419