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# Synthesis of PLGA using a $C_3$-symmetric Zr (IV) amine tris(phenolate) alkoxide initiator and the effects of gamma radiation on its properties

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**Abstract** In this paper, we report the preparation and characterisation of poly(lactic-co-glycolic) acid (PLGA) using a $C_3$-symmetric Zr (IV) amine tris(phenolate) alkoxide initiator. Although the zirconium alkoxide initiator is slower than the most commonly used $Sn(Oct)_2$, relatively high molecular weights were obtained at a temperature of 130 °C, for a monomer to initiator ratio of 1000/1 (24 h) and 5000/1 (48 h). The degree of racemisation also depends on the initiator used. The reactions performed with the zirconium initiator showed a higher degree of racemisation when compared to those performed with $Sn(Oct)_2$. A slight increase in the racemisation with time was also observed. The effects of gamma radiation on PLGA were also studied. Doses commonly applied to sterilise materials for biomedical applications were employed—10, 18, 25 and 50 kGy. The molecular weight of all samples irradiated decreased in a dose-dependent fashion—up to 56 % loss for 10 kGy and 72 % for 50 kGy—but were less pronounced for higher doses. Changes in thermal properties, such as melting point, glass transition temperature and enthalpy of crystallisation and fusion, were also observed after irradiation.

**Keywords** PLGA · Synthesis · Zirconium · Gamma irradiation · Degradation

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# Introduction

According to the World Health Organization (WHO), cancer is a leading cause of death worldwide with 8.2 million deaths caused by cancer in 2012 [1]. Prostate cancer is the second most common cancer in men, with an estimated 1.1 million diagnoses in 2012 [1, 2]. The most applied treatments for prostate cancer are prostatectomy and radiotherapy [3]. A method of radiotherapy that has been increasingly used is brachytherapy with Iodine-125 [4], where encapsulated radioactive sources (seeds) are placed inside or very close to the area requiring treatment, reducing the propensity for unnecessary damage to surrounding healthy tissues [4, 5]. A further advantage is that brachytherapy with iodine-125 has low rates of urinary incontinence and sexual dysfunction, when compared with the traditional methods [6], with a return to normal activities within 1–3 days [4]. Research is ongoing for the development and production of iodine-125 seeds, to reduce costs and allow the distribution of seeds to public hospitals [5]. The seeds can be inserted loose or stranded in a bioresorbable material, most commonly poly(lactic-co-glycolic) acid (PLGA) [7]. The main role of the polymer is to reduce the chance of seed migration, which could potentially harm healthy tissues and organs [8–11]. For example, in Brazil, more than 90 % of the prostate brachytherapy procedures performed use stranded seeds [12]. For this reason, and to keep the costs of seeds low, we are developing new routes for the preparation of PLGA copolymers.

PLGA is a copolymer based on lactic and glycolic acid units and it is used for medicinal purposes due to its biocompatibility and absorbability [13–15]. PLGA can be synthesised through two different processes: (1) polycondensation of glycolic acid and lactic acid, resulting in a low molecular weight polymer; (2) ring-opening polymerisation (ROP) of the cyclic dimers of lactic acid (lactide-LA) and glycolic acid (glycolide-GA), in the presence of metal initiators, leading to the formation of controlled molecular weight polymers [14, 16, 17]. The industrial standard catalyst used in the synthesis of PLGA is tin (II) 2-ethylhexanoate $\{Sn(Oct)_2\}$, although other catalysts are applicable [18, 19]. ROP is preferred not only because it provides high molecular weight polymers, but it can also control the monomer sequence and polymer chain ends in a more suitable way [20, 21].

Lactide has three stereoforms: L-lactide, D-lactide and *meso*-lactide, in which one chiral centre has the R configuration and the other has the S configuration. An equimolar mixture of both L-lactide and D-lactide is called *rac*-lactide. PLGA prepared with different stereoforms of lactide will result in a material with different properties, since it directly affects the crystallinity of the polymer [22]. Depending on the ratio of lactide and glycolide used in the polymerisation, several forms of PLGA can also be obtained, ensuring great versatility to the product [21]. Most of the literature suggests that the degradation of PLGA is not enzymatic, but through hydrolysis of the ester linkages [23]. The time required for the degradation of PLGA is related to the ratio of monomers used in the synthesis: the higher the glycolic acid content, the less is the time required [24, 25]. The success of its absorbability lies in the fact that the two monomers produced by the hydrolysis, under normal

physiological conditions, are by-products of various metabolic processes in the body and are eliminated as carbon dioxide and water [25].

The most commonly used initiator for the industrial synthesis of PLGA via ROP is Sn(Oct)$_2$, because it is cheap, soluble in the monomers and most organic solvents and active [20, 26, 27]. Despite that it is approved by the Food and Drug Administration (FDA) as a food additive, the toxicity of tin compounds can be an obstacle for biomedical applications and its use remains questionable [26, 28–31]. The amount of residual tin found in commercial polylactides can be as high as 530 ppm, which is slowly incorporated into the bloodstream of the patient [29]. Tin compounds, even in trace amounts, are known to impair the functions of brain tissue, particularly in children [28, 32, 33]. Also, Mattos et al. reported that stannous ions are capable of forming reactive oxygen species, which could potentially interact with DNA [34].

To avoid the problems associated with organic tin compounds, several attempts to synthesise polymers for biomedical applications have been made, employing magnesium, iron, zinc, zirconium and lithium initiators [20, 29, 30, 35, 36]. Recently, Davidson and co-workers proposed the use of a $C_3$-symmetric Zr (IV) amine tris(phenolate) alkoxide for the synthesis of polylactide (PLA) using *rac*-lactide, yielding a highly heterotactic polymer with a high conversion, but it is yet to be tested for the synthesis of PLGA [37]. Zirconium compounds are reported to be 10–20 times less toxic than tin compounds and are allowed to be used in cosmetics and drugs [28, 29]. However, this does not take into account the toxicity of the ligand, which will need to be fully addressed for any industrially viable system. Further, the costs of the ligand/metal combination need to be fully investigated for scale-up applications.

Polymers designed for biomedical applications need to be sterilised to reduce the risk of infections and complications. Steam and dry heat sterilisation are not suitable for PLGA, since it could lead to deformation and/or hydrolytic degradation and melting of the polymer [13]. Chemical sterilisation by ethylene oxide can be used for heat- and moisture-sensitive polymers, but often leaves toxic residues even after a long period of time. Ethylene oxide is also a highly flammable gas and needs to be managed very carefully to avoid accidents [13, 38, 39].

Gamma irradiation sterilisation has been shown to be an efficient method to sterilise pharmaceuticals and medical devices [38–41]. It does not have toxicological issues due to remaining residues and it is a very rapid, safe and effective method [13, 38]. However, radiation generates free radicals in biodegradable polymers by chain scissions, which generally cause a decrease in the molecular weight. This molecular weight variation is normally dose dependent and may also affect other properties of the polymer, including degradation [39, 42–44]. A few papers report the influence of irradiation on PLGA using high doses of radiation, but there is a lack of information for lower doses (10–50 kGy), which are used to sterilise materials [40–42, 44].

This paper aims to investigate the use of a Zr(IV) amine tris(phenolate) alkoxide for the synthesis of PLGA films, and the influence of gamma radiation on the properties of the polymer produced and compare to PLGA prepared from Sn(Oct)$_2$.

## Experimental

### Materials

L-Lactide was prepared using L-lactic acid (85 %-Quimesp) and $Sn(Oct)_2$ as the initiator. The reaction was performed in two steps. The first was carried at 120 °C for 4 h, after which time the temperature was raised to 180 °C for a further 4 h, to remove the water and prepare the pre-polymer. In the second step, $Sn(Oct)_2$ was added (0.5 % w/w), the temperature was raised to 190 °C and the crude lactide was collected. This was recrystallised using dry toluene and sublimed twice prior to use. Glycolide was purchased from Sigma-Aldrich and recrystallised in dry toluene. The initiator $Sn(Oct)_2$ and co-initiator benzyl alcohol were also purchased from Sigma-Aldrich and used without further purification. The zirconium amine tris(phenolate) alkoxide was prepared as described in the literature [37]. The structure of the initiator is shown in Scheme 1. Simple alkoxides of Zr(IV) are known to polymerise lactide; however, these tend to afford polymers with relatively high dispersities due to multiple chains growing per metal centre. The addition of the tris(phenolate) ligand ensures that only one chain grows per metal centre. It is possible to prepare the tris(phenolate) with methyl groups in the ortho and para positions. However, this leads to the formation of zwitterionic Zr(IV) complexes; thus our study focused solely on the alkoxide initiator [45]. At a loading of 600:1, the maximum metal contamination in the film will be ca. 500 ppm (based on mass); this is too high for commercially applications. As is the common practise, the molecular weight is controlled by the addition of benzyl alcohol, and when this is performed the maximum metal content will be ca. 100 ppm.

### Polymerisation and characterisation

For all polymerisation reactions, monomers, initiator and co-initiator were added into a Schlenk tube inside the glove box. The ratio of lactide/glycolide added was 85:15 for all reactions. The ratio of initiator and co-initiator and time varied are shown in Table 1. The temperature used for all reactions was 130 °C. After the reaction time, a few drops of methanol were added to quench the reaction. The resulting polymers were dissolved in 50 mL of dichloromethane, which was removed under reduced pressure. The solid was analysed via $^1H$ NMR (CDCl$_3$) to determine the conversion. It was then washed with methanol twice and dried under

**Scheme 1** ChemDraw representation of the Zr(IV) initiator
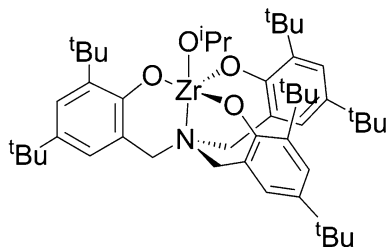
**Table 1** Parameters and results of the polymerisation reactions

| Entry | Initiator | [M]/[I] | Time (h) | Conversion (%)[d] | $M_n$ (Da)[e] | PDI[e] | LA/GA[d] | Racemisation (%)[g] | $L_L^g$ | $L_G^g$ |
|---|---|---|---|---|---|---|---|---|---|---|
| 1[a] | Zr Alk. | 600 | 4 | 72 | 34,700 | 1.29 | 76/24 | 29.1 | 16.05 | 5.41 |
| 2[a] | Zr Alk | 600 | 16 | 89 | 45,700 | 1.51 | 80/20 | 34.6 | 16.39 | 4.57 |
| 3[a] | Zr Alk | 600 | 24 | 87 | 49,200 | 1.57 | 81/19 | 34.2 | 15.75 | 4.25 |
| 4[a] | Zr Alk | 1000 | 8 | 52 | 29,700 | 1.18 | 65/35 | 32.0 | 10.09 | 5.54 |
| 5[a] | Zr Alk | 1000 | 24 | 94 | 96,800 | 1.36 | 82/18 | 31.0 | 15.82 | 3.50 |
| 6[b] | Zr Alk | 5000 | 24 | 68 | 28,000 | 1.21 | 72/28 | 28.1 | 9.28 | 3.50 |
| 7[b] | Zr Alk | 5000 | 36 | 72 | 30,600 | 1.21 | 77/23 | 30.1 | 10.34 | 2.92 |
| 8[c] | Zr Alk | 5000 | 48 | 92 | 98,400 | 1.28 | 82/18 | 26.5 | 14.57 | 3.12 |
| 9[c] | Zr Alk | 5000 | 72 | 93 | 55,100 | 1.41 | 82/18 | 26.5 | 12.23 | 2.56 |
| 10[b] | Sn(Oct)$_2$ | 5000 | 16 | 94 | 64,800 | 1.35 | 83/17 | 21.9 | 14.92 | 3.12 |
| 11[b] | Sn(Oct)$_2$ | 5000 | 24 | 96 | 35,700 | 1.27 | 85/15 | 22.5 | 12.93 | 2.64 |

[a] 130 °C, no co-initiator

[b] 130 °C, co-initiator benzyl alcohol [M]/[BnOH]: 600:1

[c] 130 °C, co-initiator benzyl alcohol [M]/[BnOH]: 1000:1

[d] Determined by $^1$H NMR spectroscopy

[e] Determined by gel permeation chromatography in THF relative to polystyrene

[g] Determined by $^1$H/$^{13}$C NMR spectroscopy

reduced pressure for 1 h. It was analysed again via $^1$H NMR (CDCl$_3$) to determine the LA/GA ratio. The molecular weight of polymers were determined via gel permeation chromatography (GPC), referenced to polystyrene standards, at a concentration of 2 mg/mL in THF.

**Preparation of the PLGA films**

PLGA films were prepared by the solvent-casting method. Briefly, 0.5 g of PLGA samples with different range of molecular weights (34,500, 45,700, 64,800, 82,900, 99,800 and 149,300 Da) were dissolved in 6 mL of chloroform (Sigma-Aldrich). The mixture was stirred at room temperature and casted onto a Petri dish. The solvent was evaporated at room temperature for 24 h.

**Gamma irradiation**

The films were irradiated at the multipurpose gamma irradiator at the Nuclear Energy Research Institute (SP/Brazil), loaded with cobalt-60 sources (model C-188, supplied by MDS Nordion—Canada). The total dose ranged from 10 to 50 kGy with a dose rate of 3.75 kGy/h. The industrial standard for sterilisation is debatable, but 25 kGy is considered to be more than sufficient to ensure sterile films [46]. The films were irradiated in the presence of air at room temperature. After the irradiation

process, the molecular weights of the samples were determined again via GPC, using the same procedure previously described.

## Thermal analysis

The DSC analyses were recorded on a TA Instruments DSC Q20. The sample was held at 10 °C for 1 min, heated to 200 °C at 10 °C/min and held at this temperature for 1 min, cooled to 10 °C at 10 °C/min and held at this temperature for 1 min and finally heated to 200 °C at 10 °C/min—the $T_m$ values are quoted for the second heating cycle and the $T_g$ from the cooling cycle.

## Results and discussion

The lactide synthesised for this work was characterised using ^{1}H NMR spectroscopy and DSC. The enantiomeric excess was determined by measuring the optical rotation of the as-prepared lactide monomer in chloroform (1 g/dm$^3$) using a polarimeter with a path length of 10 cm and a sodium D-line lamp (589 nm). The specific rotation was calculated using Eq. 1 [47]:

$$[\alpha]_\lambda = \frac{100 \times \alpha}{c \times l} \tag{1}$$

where $\alpha$ is the observed rotation (2.40), $c$ is the concentration in g/dm$^3$ and $l$ is the path length in decimetres.

The specific rotation obtained for the L-lactide prepared for this work was 240°. The reference optical rotation value for L-lactide is 260°, which leads to an enantiomeric excess of 92 %. Resonances observed for the produced L-lactide were a doublet at 1.68 (CH$_3$) and a quartet at 5.02 (CH). These resonances are comparable to those for commercial L-lactide and the literature [17].

The melting point of the synthesised L-lactide, determined from the DSC is 94 °C, which is close to the reference value (96 °C) [22].

From the results shown, we conclude that the produced L-lactide is very similar to the commercial monomer and suitable to carry out the proposed polymerisation reactions.

The effects of time, amount and type of initiator and co-initiator on the polymerisation of PLGA have been investigated. The temperature and monomer feed ratio remained constant. The results are summarised in Table 1. The conversion of the monomers was calculated through the comparison between methine (lactide) and methylene (glycolide) resonances from the monomer 5.05 ppm (LA) and 4.99 ppm (GA), and polymer 5.12–5.25 ppm (PLA) and 4.63–4.93 ppm (PGA) (Eq. 2):

$$\%\text{Conv.} = \frac{[\text{PLA}]}{[\text{PLA}] + [\text{LA}]} \times 0.85 + \frac{[\text{PGA}]}{[\text{PGA}] + [\text{GA}]} \times 0.15 \tag{2}$$

From the reactions performed, it is clear that the zirconium alkoxide initiator is slower than Sn(Oct)$_2$, for the polymerisation of L-lactide and glycolide, when the

same conditions are applied. A conversion of 96 % is achieved in 24 h using Sn(Oct)$_2$, whereas with the zirconium alkoxide the conversion is only 68 % for the same amount of time.

Relatively high molecular weights were obtained for the reaction using the zirconium alkoxide (Table 1 entry 5). The molecular weight can be controlled by the addition of benzyl alcohol (Table 1 entries 1 vs 7). As expected, a longer reaction time was necessary to achieve a high conversion for the 5000:1 reactions compared to 600:1 or 1000:1. Analysis of the $^1$H NMR spectra for the polymerisations involving benzyl alcohol all have small resonances in the aromatic region indicative of benzyl ester-terminated chains. These polymers have a molecular weight in the range suitable for the production of fibres used to make braided sutures. [48]. The LA/GA ratio was determined using the methine and methylene peaks found in the $^1$H NMR spectra (Fig. 1) from LA and GA (Eq. 3):

$$\text{LA/GA ratio} = \frac{2 \times [\text{PLA}]}{2 \times [\text{PLA}] + [\text{PGA}]} \tag{3}$$

With the exception of the entry 11, all LA/GA ratios determined were lower than the monomer feed. This is presumably due to the fact that the GA units are more reactive and tend to be consumed first. Long reaction times are needed to achieve a ratio close to the initial (85/15) when using the zirconium alkoxide initiator, and the closest ratio obtained with this initiator was 82/18.

The microstructure of the PLGA was determined by $^{13}$C{$^1$H} NMR spectra. Carbonyl resonances (166–170 ppm—Fig. 2) were used to determine the sequence length of LA and GA units, since they are more sensitive to sequence effects than other signals (Eq. 4). $I_{GG}$ was determined from the resonance at 166.4 ppm, $I_{L_G}$ from the resonance at 169.5 ppm and $I_{L_L}$ from the resonance at 169.6 ppm and 169.4–169.2 ppm [49–52]:
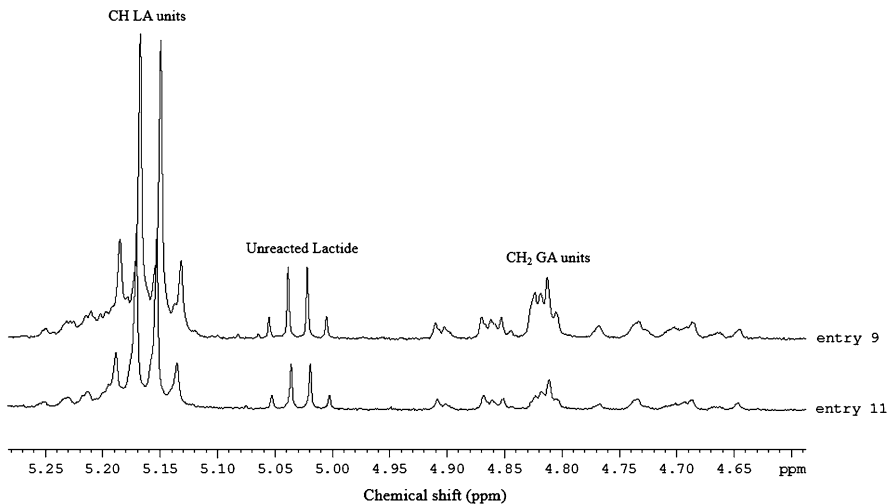


**Fig. 1** $^1$H NMR spectra of PLGA (400 MHz) in the CDCl$_3$ solution
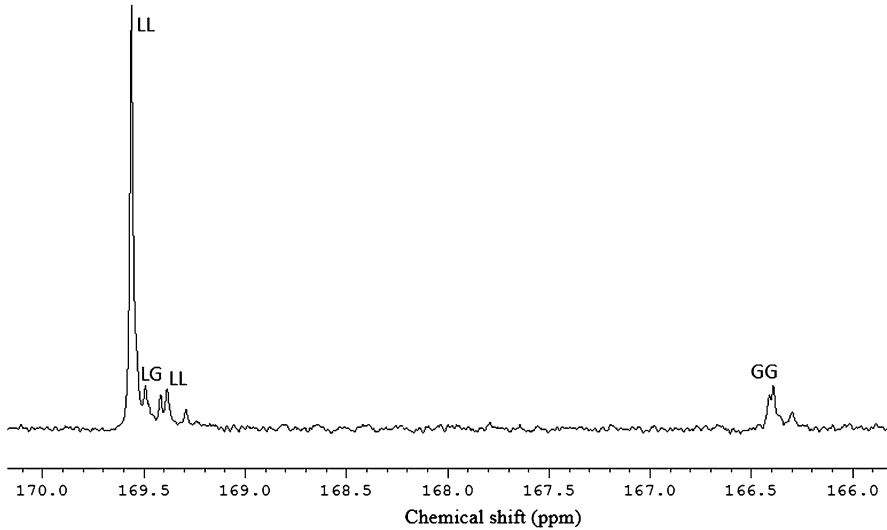
**Fig. 2** $^3C\{^1H\}$ NMR spectrum in the carbonyl region of PLGA in the CDCl$_3$ solution

$$L_{\mathrm{L}} = \frac{I_{L_\mathrm{G}} + I_{L_\mathrm{L}}}{I_{L_\mathrm{G}}}, \quad L_G = \frac{I_{L_\mathrm{G}} + I_{G_\mathrm{G}}}{I_{L_\mathrm{G}}} \tag{4}$$

The $L_\mathrm{L}$ and $L_\mathrm{G}$ calculated can also be used to explain the higher reactivity of GA units. For shorter reaction times, GA monomers are preferentially polymerised, forming longer GA blocks. This behaviour is quite evident in the entries 1–4 in Table 1. Upon increasing the reaction time, the remaining LA units are incorporated into the polymers chains and transesterification reactions start to take place. This leads to a reduction in the sequence length of both LA and GA units and a decrease in the molecular weight, as can be seen by comparing reactions 8–9 and 10–11. It was possible to conclude also that the polymerisation of LA and GA using the initiators proposed are not random, since it does not yield an $L_G$ equal to 2 [50]. However, transesterification reactions may have contributed to randomisation, particularly in the longer reactions.

Methine resonances (68.5–69.5 ppm) were used to calculate the degree of racemisation, as proposed by Gao and co-workers [52]. The value was obtained through the ratio of isotactic (69.0 ppm) and syndiotactic (69.1–69.3 ppm) sequences of LA (Fig. 3). According to the results obtained, the degree of racemisation depends on the type of initiator used. The reactions performed with Sn(Oct)$_2$ showed the lowest value of racemisation. A slight increase in the racemisation with time was observed in reactions 1–2, 6–7 and 10–11.

Relatively high values of racemisation were found; however, similar results were obtained in the literature [52]. One possible explanation could be that the use of GA can influence the racemisation of LA sequences [52].

The effects of gamma radiation on the molecular weight of the selected polymers are summarised in Table 2. It is evident, from the results shown, that there is a sharp
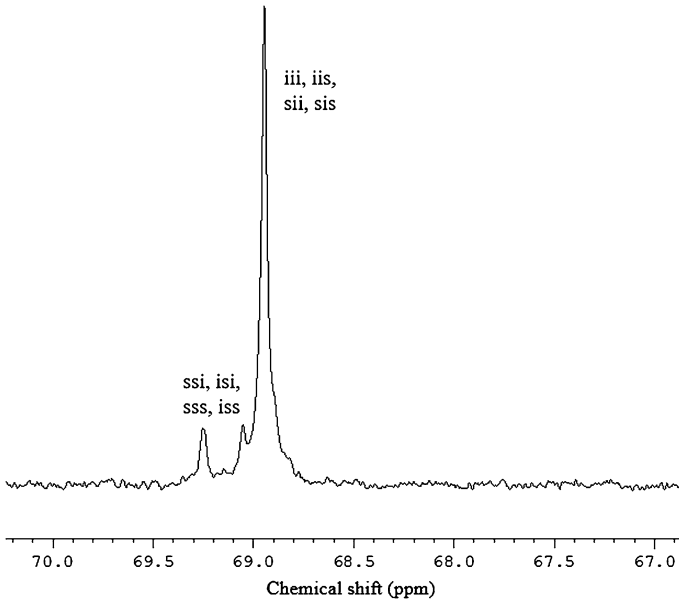
**Fig. 3** $^{13}C\{^1H\}$ NMR spectrum in the methine region of PLGA in the CDCl$_3$ solution

**Table 2** Molecular weight and PDI after irradiation

| Entry | Dose (kGy) | $M_n$ (Da)[a] | PDI[a] | $M_n$ retention (%) | $G_S$ | Entry | Dose | $M_n$ (Da)[a] | PDI[a] | $M_n$ retention (%) | $G_S$ |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 0 | 99,800 | 1.64 | 100.0 | – | 4 | 0 | 45,700 | 1.51 | 100.0 | – |
|   | 10 | 63,200 | 1.48 | 63.8 | 5.5 |   | 10 | 20,300 | 1.50 | 44.5 | 26.3 |
|   | 18 | 53,700 | 1.60 | 53.8 | 4.6 |   | 18 | 18,500 | 1.46 | 40.5 | 17.2 |
|   | 25 | 49,200 | 1.58 | 49.3 | 4.0 |   | 25 | 18,100 | 1.51 | 39.6 | 12.9 |
|   | 50 | 39,200 | 1.55 | 39.2 | 3.0 |   | 50 | 15,600 | 1.63 | 34.3 | 8.1 |
| 2 | 0 | 82,900 | 1.56 | 100.0 | – | 5 | 0 | 34,500 | 1.44 | 100.0 | – |
|   | 10 | 36,300 | 1.56 | 43.8 | 14.9 |   | 10 | 16,900 | 1.45 | 48.9 | 29.3 |
|   | 18 | 32,100 | 1.59 | 38.8 | 10.2 |   | 18 | 16,800 | 1.41 | 48.7 | 16.3 |
|   | 25 | 29,500 | 1.65 | 35.6 | 8.4 |   | 25 | 14,900 | 1.54 | 43.1 | 14.8 |
|   | 50 | 24,300 | 1.63 | 29.3 | 5.6 |   | 50 | 14,100 | 1.51 | 40.8 | 8.12 |
| 3 | 0 | 149,300 | 1.38 | 100.0 | – | 6 | 0 | 64,800 | 1.35 | 100.0 | – |
|   | 10 | 71,000 | 1.61 | 47.5 | 7.1 |   | 10 | 38,300 | 1.56 | 59.1 | 10.3 |
|   | 18 | 65,000 | 1.65 | 43.6 | 4.6 |   | 18 | 34,200 | 1.50 | 52.8 | 7.4 |
|   | 25 | 56,100 | 1.68 | 37.6 | 4.3 |   | 25 | 32,400 | 1.62 | 50.0 | 6.0 |
|   | 50 | 41,700 | 1.70 | 28.0 | 3.3 |   | 50 | 25,800 | 1.63 | 39.9 | 4.49 |

[a] Determined from gel permeation chromatography in THF relative to polystyrene
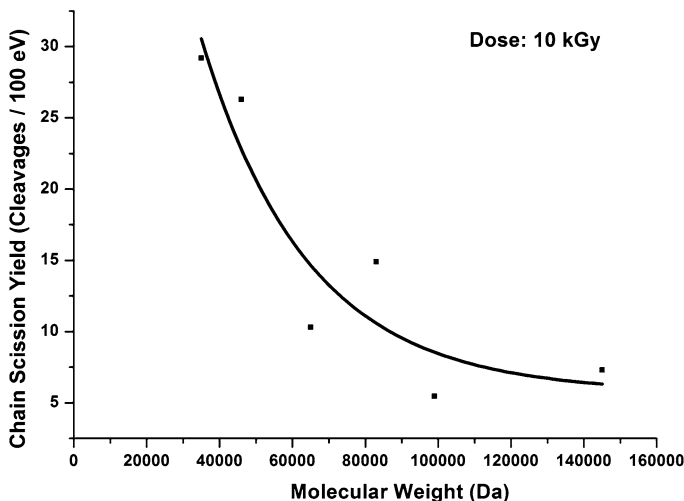
**Fig. 4** Variation of chain-scission yield ($G_s$) as a function of molecular weight when a radiation dose of 10 kGy is used

decrease in the molecular weight of all samples irradiated. The most drastic difference occurs in the lowest dose used (10 kGy), where the decrease of the molecular weight varied between 36 and 56 %, depending on the initial value. The decrease in the molecular weight is due to chain scission of the polymer backbone, since it dissipates the excess energy absorbed by breaking bonds, leading to the formation of shorter chains and free radicals. In the presence of oxygen, free radicals can be converted into peroxyl moieties, which in turn cause chain scission through hydrogen abstraction. This mechanism has a weaker effect on the decrease of the molecular weight [44, 53]. Also, a fast degradation occurs in the amorphous regions, whereas in the crystalline regions it is quite slow and requires higher doses of radiation [54].

The chain-scission yield ($G_S$), defined as the number of cleavages caused by the absorption of 100 eV, is a method to determine the relation between the decrease in the molecular weight and other parameters, such as dose and the initial molecular weight. It can be calculated using the following equation [55]:

$$G_s = \frac{N_A \left( \frac{1}{M_n} - \frac{1}{M_{n0}} \right)}{6.24 \times 10^{16} D} \qquad (5)$$

where $N_A$ is Avogadro's number, $M_n$ is the molecular weight after the irradiation, $M_{n,0}$ is the initial molecular weight and $D$ is the dose in kGy.

From the data presented in Table 2, it is evident that the chain-scission yield ($G_S$) is substantially influenced by the total dose absorbed and the initial molecular weight of the samples. The highest value of $G_S$ (29.3) was obtained for the sample with the lowest initial molecular weight (34,500 Da), when comparing the data for the same dose absorbed (10 kGy). This trend was observed in all the samples irradiated (Fig. 4). A similar behaviour was observed by Tahtah and co-workers,

when comparing the influence of the initial molecular weight and dose, in the chain-scission yield of gamma-irradiated chitosan [54].

When comparing the influence of dose in the $G_s$ in samples with the same initial molecular weight, we found that the higher the dose, the lower was the $G_S$ obtained. This can be explained by the fact that recombination of free radicals becomes more pronounced when higher doses are applied and can even become equal to chain-scission reactions when doses of 200 kGy or more are used.

DSC analysis was performed in two selected samples (entries 2 and 11—Table 1) for all doses used, to investigate the effect of radiation on the thermal properties of PLGA. The results obtained are summarised in Table 3. These two samples were chosen as they represented a high (entry 2) and a low (entry 11) racemisation system.

The glass transition temperature ($T_g$) of all samples decreased after irradiation, in a dose-dependent manner. In general, the higher the dose, the higher is the reduction for the PLGA prepared with both initiators. The melting temperature and crystallisation temperature could not be detected for the PLGA prepared with the zirconium alkoxide initiator. This might be attributed to the fact that the ratio of LA/GA units was 80/20, instead of 85/15, leading to the formation of an amorphous polymer. A further explanation might also be related to the degree of racemisation caused by the glycolide incorporation. This could potentially also affect crystallinity, resulting in no distinct $T_m$ in the DSC. In addition, the glass transition temperature was absent in the PLGA prepared with the same catalyst and submitted to a dose of 50 kGy. In the PLGA prepared with Sn(Oct)$_2$, two melting peaks and a crystallisation peak were found both in the unirradiated and the irradiated samples. The presence of two melting peaks can be explained by the fact that the molecular weight of PLGA in the amorphous regions are higher, since very long chains are harder to crystallise when compared to the shorter ones. Since the melting point ($T_m$) of the polymer is lower when the molecular weight decreases, a double peak may appear in the DSC [42].

**Table 3** Thermal properties of PLGA after irradiation

| Entry | Initiator | Dose (kGy) | $T_g$ (°C) | $T_c$ (°C)[d] | $\Delta H_c$ (J/g) | $T_{m1}$ (°C) | $\Delta H_{f1}$ (J/g) | $T_{m2}$ (°C) | $\Delta H_{f2}$ (J/g) |
|---|---|---|---|---|---|---|---|---|---|
| 1 | Zr alk | 0 | 44.2 | – | – | – | – | – | – |
| | | 10 | 36.7 | – | – | – | – | – | – |
| | | 18 | 33.7 | – | – | – | – | – | – |
| | | 25 | 32.1 | – | – | – | – | – | – |
| | | 50 | – | – | – | – | – | – | – |
| | | 0 | 50.4 | 129.3 | 18.4 | 159.7 | 7.0 | 151.1 | 5.3 |
| | | 10 | 43.5 | 114.1 | 27.6 | 155.8 | 13.8 | 142.1 | 1.5 |
| 2 | Sn(Oct)$_2$ | 18 | 46.6 | 118.3 | 27.6 | 156.3 | 10.6 | 145.2 | 4.6 |
| | | 25 | 44.2 | 113.9 | 26.2 | 155.7 | 9.9 | 141.3 | 1.6 |
| | | 50 | 42.5 | 110.9 | 27.5 | 154.6 | 9.8 | 141.1 | 1.4 |

The behaviour of the melting ($T_m$) and crystallisation temperatures ($T_c$) followed the same trend observed in the glass transition temperature—a reduction in a dose-dependent manner. The decrease in the $T_c$ is a consequence of re-orientation of shorter amorphous chains formed after the chain-scission events, which require less energy to crystallise [44].

The enthalpy of fusion of the first melting peak and the enthalpy of crystallisation increased after irradiation. As explained, shorter chains formed by chain scission orientate in the crystalline array more easily, leading to an increase in lamellar thickness. This effect is reported to be more pronounced in doses up to 50 kGy [53].

## Conclusions

Co-polymerisations of ʟ-lactide and glycolide using zirconium amine tris(phenolate) alkoxide as the initiator were investigated. High molecular weight polymers were obtained at 130 °C, for a monomer initiator/ratio of 1000:1 (24 h) and 5000:1 (48 h) with benzyl alcohol as co-initiator (monomer to co-initiator ratio of 1000:1). From the results, we conclude that zirconium alkoxide initiator is slower than the $Sn(Oct)_2$ for the reactions proposed. However, it is known to be far less toxic than tin, which is a great advantage for biomedical applications.

The effects of gamma irradiation on the PLGA were also studied. The molecular weight of samples decreased sharply after the irradiation process. The reduction is dose dependent, but less pronounced for higher doses. This is because recombination of free radicals becomes more evident when higher doses are applied, neutralising the effect of chain-scission reactions. The melting point, crystallisation temperature and glass temperature also decreased after irradiation. For commercial applications of these materials, we will need to fully investigate the sterilisation of the films.

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