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Thermal properties of amphiphilic biodegradable triblock copolymer of L,L-lactide and ethylene glycol

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Abstract Samples of poly(L,L-lactide)-block-poly(ethylene glycol)-block-poly(L,L-lactide) (PLLA-PEG-PLLA) were synthesized from L,L-lactide polymerization using stannous 2-ethylhexanoate, $Sn(Oct)_2$ as initiator and dihydroxy-terminated poly(ethylene glycol) (PEG) ($M_n = 4000$ g mol^{-1}) as co-initiator. The chemical linkage between the PEG segment and the PLA segments was characterized by Fourier transform infrared spectroscopy (FTIR). Thermogravimetry analysis (TG) revealed the copolymers composition and was capable to show the deleterious effect of an excess of $Sn(Oct)_2$ in the polymer thermal stability, while Differential Scanning Calorimetry (DSC) allowed the observation of the miscibility between the PLLA and PEG segments in the different copolymers.

Keywords PLLA-PEG-PLLA · Drug delivery systems · Amphiphilic copolymer · Thermal properties

Introduction

Amphiphilic polymers have received considerable attention as potential biomaterials in last decade [1]. In particular, materials capable of forming hydrogel remain in an active area of research due to application in drug delivery systems [2, 3]. Polymeric drug delivery systems have attracted the attention of the pharmaceutical industry due to its high capacity of drug incorporation and great stability in aqueous solution. Segmented copolymers consisting of hard polyester, A-block, and soft poly(ethylene glycol), B-block, form amphiphilic block copolymers and have the appropriate architecture of drug delivery systems and can be used as drug containers [4].

Polylactide (PLA) has been widely used in surgical repair, carriers in drug delivery, and temporary matrixes or scaffolds in tissue engineering due to its biodegradability, biocompatibility, high mechanical properties, and molding properties [5]. Poly(ethylene glycol) is often introduced for its hydrophilicity, biocompatibility, and nonimmunogenicity [6]. The introduction of PEG has been employed for rendering PLA resistant to cell or protein adsorption, thus reducing complications such as biofouling and thrombus formation in contact with biological fluids [7].

Recently, PLLA-PEG block copolymers have been prepared by ring-opening polymerization of lactides using PEG as macro-initiators with stannous octanoate [$Sn(Oct)_2$] as catalyst [8, 9]. This system is considered of particular importance for some reasons. It allows the union of the poly(L,L-lactide) block to the formed structures for example drugs, sorbitol and manitol, forming copolymers with different structures, presents high efficiency, the catalyst is accepted by the Food and Drugs Administration and is being used in commercial scale for the synthesis of the poly(L,L-lactide) in medical devices [10, 11].

Figure 1 shows the cyclic monomer insertion by coordination mechanism in two steps. In the first step, the $Sn(Oct)_2$ catalyst reacts with hydroxyl end groups of PEG, forming alkoxide containing a Sn–O–PEG bond that is considered the true starter of the reaction (a). In the second step, the cyclic monomer (lactide) is inserted between the Sn–O-linking, promoting the growth of the chain (stage of

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propagation) (b). As it is shown in Fig. 1, the PEG has double importance as true starter and transfer agent (c) [10–12].

In this article, a structure of poly(L,L-lactide)-b-poly (ethylene glycol)-b-poly(L,L-lactide) (PLLA-PEG-PLLA) triblock polymer was synthesized with PEG as a macroinitiator by ring-opening polymerization of L,L-lactide by a insertion-coordination mechanism [12].

Experimental

L,L-Lactide [(3S)-cis-3,6-dimethyl-1,4-dioxane-2,5-dione] and stannous 2-ethyl-hexanoate [$CH_3(CH_2)_3CH(C_2H_5)CO_2]_2Sn$ ($SnOct_2$) were purchased from Aldrich. Poly (ethylene glycol) (PEG), $M_n = 4000$ g mol^{-1} (25–31 mg KOH g^{-1}) (solid) was supplied by Oxiteno (Brazil). Chloroform, methanol, and hexane, all analytical grade, were supplied by Synth (Brazil). All these materials were used without further purification.

Three copolymers of PLLA-PEG-PLLA triblock were synthesized by bulk polymerization. In a glove box under dry nitrogen atmosphere, pre-weighed amount of PEG and stannous (II) 2-ethylhexanoate were introduced into a dry polymerization tube. The tube was sealed and placed in a silicon oil bath at 393 K for 20 min. After cooling to room temperature, a pre-weighed amount of L,L-lactide was inserted in the tube in the glove box. The tube was sealed and the polymerization was carried out under different experimental conditions [13]. Copolymer 1 was prepared using LA/EO/$Sn(Oct)_2$ molar ratio in feed of 2/1/1 and the temperature and the reaction time were 408 K and 144 h, respectively. Copolymer 2 was prepared by LA/EO/$Sn(Oct)_2$ ratio in feed of 1/1/0.05 and the temperature and the reaction time were 393 K and 148 h, respectively. Copolymer 3 was prepared by LA/EO/$Sn(Oct)_2$ ratio of 2/1/0.05 and the temperature and the reaction time were 120 °C and 148 h, respectively. The product was dissolved in chloroform and precipitated in hexane. The process of dissolution/reprecipitation was carried out three more times. Each copolymer was dried under reduced pressure at room temperature for 24 h.

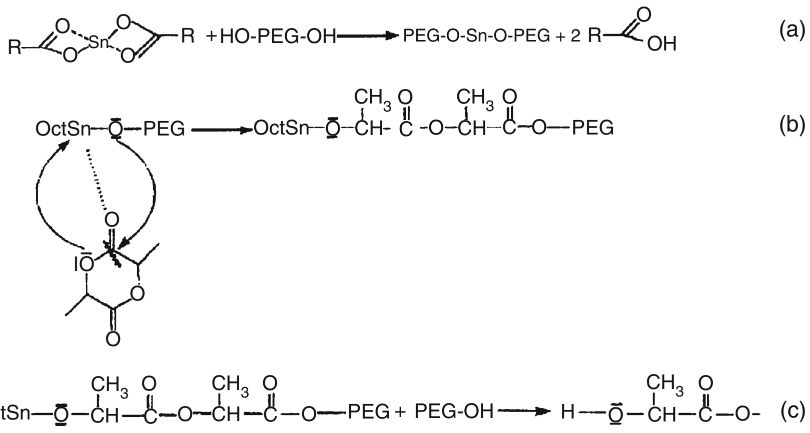
A Perkin Elmer spectrophotometer model, Spectrum One, was used. All spectra were recorded within a range of 4000–600 cm^{-1} with a 4 cm^{-1} resolution and co-addition of 128 scans. To reduce atmosphere effects, the sample detector was purged with N_2 before collected the background and each titration. All spectra were lead in duplicate and all experiments were carried out at room temperature at 298 ± 1 K.

Coupled Thermogravimetry–Differential Thermal Analysis (TG-DTA) was performed to achieve information on the nature of the interactions present in these copolymers. TG/DTG and DTA runs of these samples were performed in a TG-DTA Simultaneous Instrument, model SDT 2960, *TA Instruments*. The samples were heated at a rate of 10 K min^{-1} from 298 to 1073 K under nitrogen atmosphere. The thermal properties of these copolymers were measured with a Differential Scanning Calorimetry, model DSC 2010, *TA Instruments*. The samples were heated at a rate of 10 K min^{-1} from 298 to 473 K in a nitrogen atmosphere. For the DSC analysis, the copolymers were sealed in aluminum pans and the mass was about 10 mg.

Results and discussion

The IR spectra of the three copolymers are shown in Fig. 2. Compared with the spectrum of pure PEG [13], the band of the triblock copolymers in the hydroxyl region (about 3503 cm^{-1}) almost disappeared (except for the Fig. 2b), indicating that the hydroxyl end groups of PEG were consumed. The absorption peaks around at 2940 and 2880 cm^{-1} were attributed to the ν_{CH}, indicating that the co-initiator homopolymer PEG was modified. The peak around at 1756 cm^{-1} ($\nu_{C=O}$) was characteristic of the

Fig. 1 Synthesis of triblock copolymer



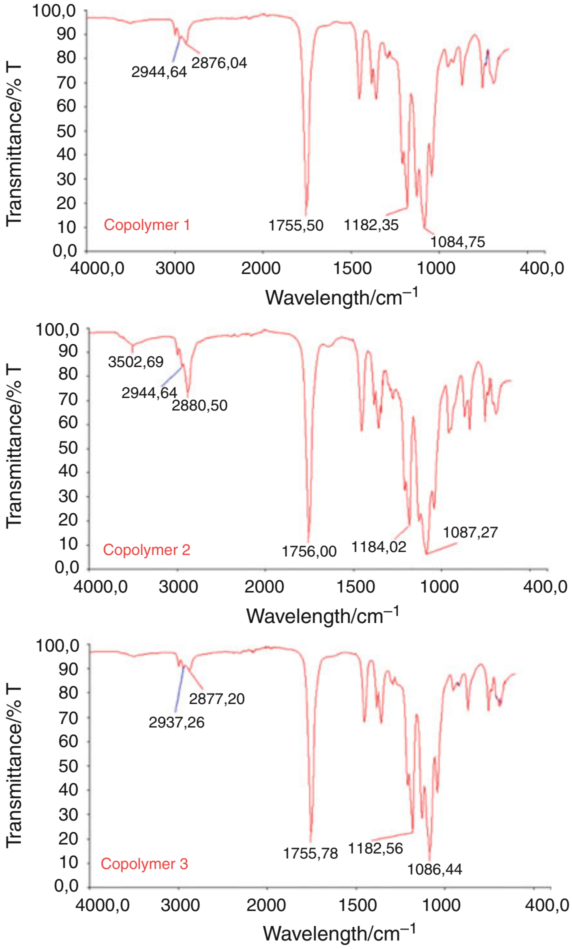


Fig. 2 FTIR spectra for the three copolymers

PLLA block. The peak around at 1183 cm^{-1} ($\nu_{\text{C–O–C sym}}$) belonged to the symmetric stretching and the peak around at 1086 cm^{-1} ($\nu_{\text{C–O–C asym}}$) was corresponding to the asymmetric stretching. The presence of the characteristic absorptions of each homopolymer in all spectra indicates the presence of the PEG and PLLA blocks and suggests the covalent bond between them [13].

The TG curves, Fig. 3, have shown that the copolymers are composed of two segments types with very distinct thermal stabilities that can be ascribed to the PLLA and PEG segments. These copolymers presented decreased thermostability when compared to PEG and PLLA homopolymers. These results are in accordance to those previously reported [14, 15]. All the copolymers have dual-step decomposition. In the first stage, which is the main transition, the copolymer degradation is related to the PLLA segment chain end "unzipping" mechanism [16]. And the second event, at a higher temperature, can be related to the thermal scission of the PEG main chain [15].

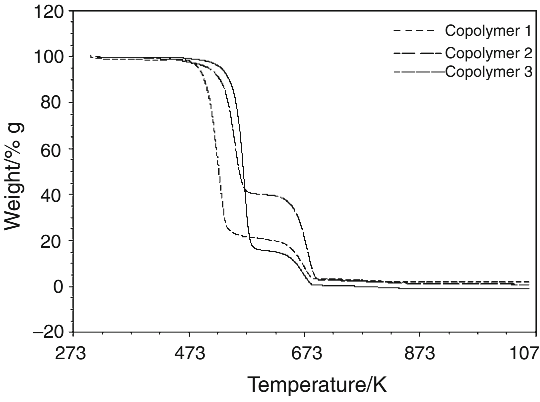


Fig. 3 Degradation profiles of the three copolymers by TG perform

In Fig. 3, copolymer 1 shows the first step at $T_i = 468$ K with approximately 77% of mass loss and the second event at $T_i = 593$ K with 20% of mass loss, after which a residue of 3% was observed. Copolymer 2 shows the first step at $T_i = 473$ K with 60% of mass loss and the second event at $T_i = 598$ K with approximately 38% of mass loss, after which a residue of almost 2% was observed. And copolymer 3 shows the first step at $T_i = 488$ K with 84% of mass loss and the second event at almost $T_i = 603$ K with approximately 16% of mass loss, after which no residue was observed. It is observed that copolymer 3 presented better thermal stability than the others. The TG quantitative mass loss is related to the composition of the samples [14, 17] and according to the observed results the content in PLLA and PEG of the samples are 80 and 20 wt% for the copolymer 1, 61 and 39 wt% for the copolymer 2 and 84 and 16 wt% for the copolymer 3, respectively. The experimental results are close to the compositions of the monomer feed in the polymerization reactions, specifically 62 and 38 wt% (copolymer 2) and 77 and 23 wt% (copolymers 1 and 3) for L,L-lactide and PEG, respectively.

The DTG curves provide better visual inspection of the two-step mechanism for the copolymers showed in Fig. 3. According to Fig. 4, for the first step of decomposition, copolymer 1 has a maximum decomposition rate (DTG peak) at 523 K. For the copolymers 2 and 3, the first-step decomposition peaks by DTG are at 563 K and 573 K, respectively. The second step of decomposition, for all three copolymers, the DTG peak is around 673 K. Moreover, the TG analysis revealed a decrease in thermal stability for the copolymer 1, which was definitely synthesized with an excess of Sn(Oct)$_2$, as the LA/EO/Sn(Oct)$_2$ molar ratio was 2/1/1. Although the copolymers were purified three times by dissolution and precipitation, it is possible that the copolymer 1 still has high residual amount of Sn(Oct)$_2$, which might influence the unzipping degradation reaction of PLLA segment, thus decreasing the degradation peak temperature to 313–323 K. However, deleterious plasticizing effects on the thermal stabilization of polylactides have also been reported previously.

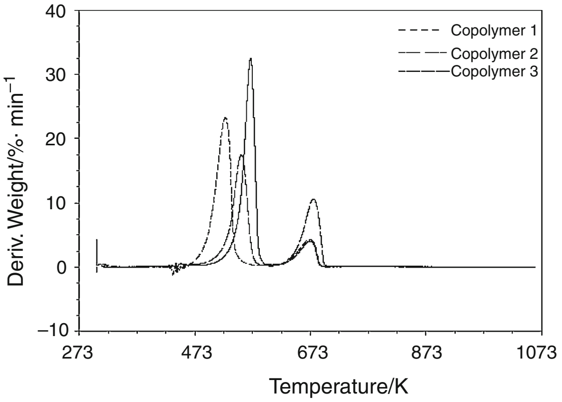


Fig. 4 DTG profiles of the three copolymers

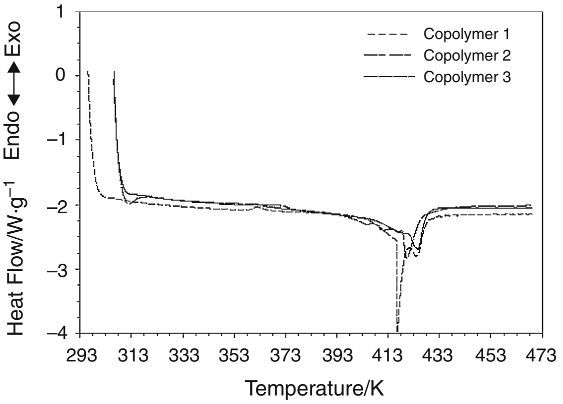


Fig. 6 DSC traces of the three copolymers

DTA results confirmed the TG results. The PEG segment is more thermally resistant than PLLA, as the degradation onset temperature observed by DTA is around 673 K, while the PLLA segment presented degradation peak at 523, 563, and 573 K, for the copolymers 1, 2, and 3, respectively (Fig. 5). Additionally, all copolymers presented an endothermic event with a maximum around 433 K, which is ascribed to a melt transition. The PLLA cycle depolymerization is characterized by a strong heat emission, while the PEG chain scission starts as a slightly endothermic event that becomes slightly exothermic.

DSC analyses, Fig. 6, allowed the confirmation of the crystalline melting, T_m of PLLA segments. The glass-transition temperature (T_g) for these copolymers varied from 363 to 373 K, according to the copolymer PLLA relative concentration (T_g for copolymers 1 and 3 around 363 K and for the copolymer 2 around 373 K). Copolymer 1 presented two melting endothermic peaks (T_m) around 417 and 425 K, respectively, which indicates a non-equilibrium crystalline melting followed by recrystallization and melting of more stable crystallites formed by PLLA segments.

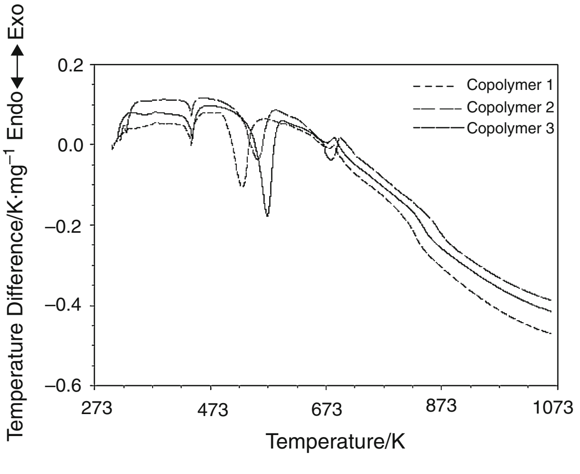


Fig. 5 DTA analyses of the three copolymers

Copolymer 2, which composition is 61 wt% of PLLA and 39 wt% of PEG, presented two melting endothermic peaks (T_m) around 313 and 421 K, respectively. The T_m' shift in conjunction with its broader temperature range indicates disturbance of the PEG crystalline structure due to segmental interactions with the PLLA fraction. Copolymer 3 shows only one melting endothermic peak around 426 K, which indicates that the PEG segments are completely dissolved in the amorphous phase and no crystalline melting was observed for PEG phase; the same occurred to copolymer 1.

Conclusions

The copolymers were characterized by FTIR spectroscopy and their thermal behavior was studied by DSC and simultaneous TG/DTA. The block structure inhibits the segmental motion of both components, causing the disturbance of the crystalline phases of PEG4000 segment as well as that of PLLA segment, so copolymers presenting 23 wt% of PEG and 77 wt% of PLLA do not show PEG crystalline melting, indicating total miscibility in the amorphous phase. Additionally, higher content of PEG in the copolymer (copolymer 2) allows the formation of PEG's crystalline phase; however, a decrease in the T_m of both crystalline phases (PEG and PLLA) is observed. TG analysis revealed the copolymers composition and was suitable to show the deleterious effect of $Sn(Oct)_2$ in the polymer thermal stability. These copolymers were obtained as solid polymeric materials and could find application in micro and nano encapsulation of drugs.

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