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Statistical Copolymers of l,l-lactide and ε-caprolactone

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Summary

Copolymers of l,l-lactide with ε-caprolactone have been investigated in order to develop valuable biodegradable materials for medical applications. The syntheses of homopolymers and copolymers of l,l-lactide and ε-caprolactone by ring-opening bulk polymerization were performed using stannous octoate as initiator at 120 °C. The compositions of the copolymers were systematically varied by polymerization of monomer mixtures containing from 10 to 90 % of ε-caprolactone, at 10% step of variation. High polymerization conversions were observed for homopolymers and copolymers syntheses. Synthesized products were characterized by gel permeation chromatography (GPC) and nuclear magnetic resonance spectrometry (NMR). The analyses of the segment lengths by ^{13}C-NMR spectroscopy indicated the predominance of random copolymers formation and the transesterification reaction was not detected.

Introduction

The traditional applications of synthetic polymers are based on their relative inertness to biodegradation in contrast with the natural polymers, as cellulose and proteins. In these days, due to the increasing disposal volume of synthetic polymer products, the greater majority bio-resistant, the research and development of biodegradable polymers' products became an important question of strategy, due to the environmental implications. Besides, biodegradable polymers are useful in applications such as suture, chirurgical implants, controlled drug delivery implants, and (agricultural) chemicals delivery systems, among others. [1]

Poly(lactide) and its copolymers with others aliphatic hydroxyacids are used in many applications, such as sutures, bone fixation, bone replacement and solid matrix for the controlled drug release.[2] The main advantages of these aliphatic polyesters are biocompatibility and biodegradability to non toxic and readily excreted products.

The microstructure and architecture of copolymers, prepared by the ring opening polymerization of cyclic esters, result from the kinetics and thermodynamic of the polymerization systems and have been reported to be related to many variables; reaction medium, catalyst, nature of the co-initiator and temperature among the most important polymerization parameters. [3-10] Organic compounds of metals such as tin [7,11-9], aluminum [4-5,7,16-18], yttrium [19-20], zinc [7,11,13-14,18,21], and iron [22] have been included in the polymerization and copolymerization of l,l-lactide (LL), in order to develop low toxic active metal catalysts and to control the microstructure of the polymer, which affects its mechanical properties and biodegradability rate.

Polymers of l,l-lactide (LL) and ε-caprolactone (CL) have been usually prepared in bulk or in solution, and in addition in dispersion medium [17], using an organometallic initiator either in the presence or absence of a co-initiator containing active hydrogen(s). The initiator tin(II) octoate has been preferentially selected due to its acceptance in biomaterials applications. Recently, the mechanism involved in the initiation step of that reaction has been systematically studied and reviewed by Penczek et al.[24] The polymerization propagation step of the lactide/lactone-tin(II) octoate systems has been previously investigated and is believed to occur by a "coordination-insertion mechanism".[24-27]

The objectives of our study are to prepare biodegradable copolymers with a wide span of mechanical properties and to evaluate the influence of the microstructure in the biodegradation, in an on-going study. The copolymers were prepared by using extensive composition range in feed, tin(II) octoate initiator (no co-initiator added), bulk polymerization at moderate temperature (120 °C) and short time (3 hours) to avoid side transesterification reaction.

Experimental

Materials

l,l-Lactide [(3S)-cis-3,6-dimethyl-1,4-dioxane-2,5-dione] (LA), 98%, and stannous 2-ethyl-hexanoate ($SnOct_2$), and ε-caprolactone were supplied by Aldrich. Chloroform, methanol, hexane, toluene, tetrahydrofuran (THF) and acetone, analytical grade, were supplied by Synth (Brazil). All materials were used without further purification.

Synthesis of PLA-PCL copolymers

A series of copolymers and homopolymers was synthesized in bulk, using the monomer weight ratio, LL:CL, 10:90 to 90:10, at 10 percent step. The polymerization was carried out according to previously reported methods [24,27-28] with minor modification. In a glove box purged by dry nitrogen, pre-weighed amounts of ε-caprolactone, l,l-lactide and stannous 2-ethyl-hexanoate, at a proportion of 0,5 % per total monomers, were introduced in a dry tube. The tube was sealed and immersed into silicon oil bath, at 120 °C for 3 hrs. The copolymer thus obtained was purified by dissolution in chloroform and precipitation in methanol (three times). The white solid copolymer was filtered and dried under reduced pressure at room temperature for 24 hours.

Carbon-13 Nuclear Magnetic Resonance

The carbon-13 NMR spectra were obtained using a Bruker AC 200 spectrometer at 50MHz. The polymers were dissolved in deuterium chloroform and TMS was used as internal reference. The composition, the assignment of microstructure sequences and sequence lengths were performed based in the triad composition according to Kasperczyk and Bero[18], as follows:

$$L_{LL} = \frac{[LL-LL-LL]+[LL-LL-CL]+[CL-LL-LL]+[CL-LL-CL]}{[CL-LL-CL]+\frac{1}{2}([CL-LL-LL]+[LL-LL-CL])} \qquad \mathbf{(1)}$$

$$L_{CL} = \frac{[CL-CL-CL]+[LL-CL-CL]+[CL-CL-LL]+[LL-CL-LL]}{[LL-CL-LL]+\frac{1}{2}([CL-CL-LL]+[LL-CL-CL])} \qquad \mathbf{(2)}$$

Gel permeation chromatography (GPC)

The average molar masses and polydispersities of copolymers were determined by GPC, using a Waters model 150 apparatus, equipped with a differential refractometer detector. THF was used as the mobile phase at a flow rate of 1.0 ml/min and monodisperse polystyrenes were used as molar masses' standards.

Dynamic mechanical thermal analysis (DMTA)

A Rheometrics Scientific DMTA V was used to perform tension tests. The samples were cut from the bulk pressed sheets and had the following dimensions: length of 23 mm, width of 8mm and thickness of 2 mm. A strain limit of 0.1% and a frequency of 1 Hz were applied in the temperature range from – 100 to 100 °C at a heating rate of 2 °C/min.

Results and discussion

The monomer mixtures with tin(II) octoate were prepared and carefully introduced in reaction tubes under dry nitrogen atmosphere in a glove box. Before transfer to a thermostatic heating bath the reaction vials were screw-capped. No co-initiator was added to start polymerization reaction. In a separate set of experiments it was possible to get polymer yields over 95% after 12 hrs of reaction time, however a reaction time of 3 hrs was enough for a relative high yield of l,l-lactide in bulk polymerization at 120 °C, as expected from the pertinent homopolymerizations' results. The experimental conditions were chosen in order to achieve homogeneous copolymer samples, thus the mixtures of l,l-lactide and ε-caprolactone were deliberately copolymerized without complete conversion of monomers.

After polymerization, the formed polymer was diluted in chloroform to reduce the solution viscosity and then precipitated in methanol. The polymerization yields are shown in Fig. 1. A little inhibition in the polymerization rate was observed in the near equimolar mixtures and can be attributed to a comparative lower rate constant in the co-monomer cycloaddition reactions, thus polymer yields reduced from 80 to 60%.

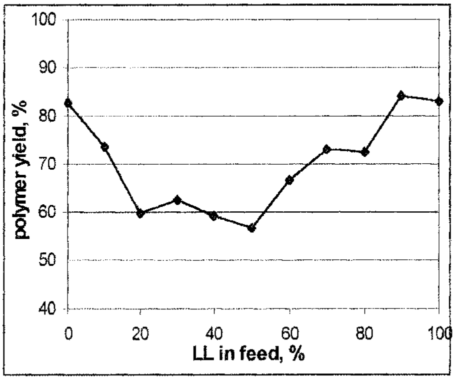

Figure 1 Polymer yield as a function of l,l-lactide concentration in monomers feed.

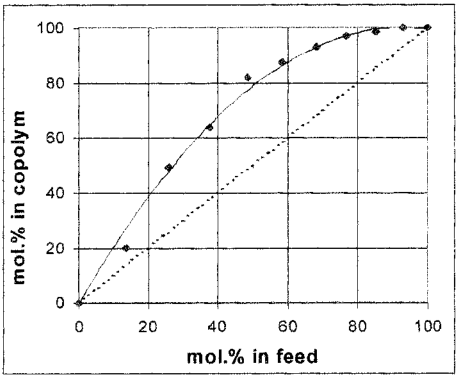

Figure 2 Lactate concentrations in copolymers in function of monomer feed.

The copolymers' relative molar compositions were determined by ^{13}C-NMR spectrometry. The compositions and characteristics of copolymers are shown in Table 1. The integration of each carbonyl signal in the ^{13}C-NMR spectra was taken as quantitatively proportional to the relative concentration of the caproyl unit, CL, and the lactidyl unit, LL, as well as to the relative amount of CL and LL in each type of triad.

Table 1 Compositions and molar masses of copolymers

Sample	Feed wt.%LL	Copolymer wt.% LL	Molar Mass Mw[a]	MWD[a]
Co 0	0	0	103,000	1.49
Co10	10	15.0	52,400	1.54
Co20	20	40.5	32,000	1.51
Co30	30	55.2	21,800	1.43
Co40	40	76.2	24,700	1.39
Co50	50	83.0	25,800	1.43
Co60	60	90.2	22,100	1.49
Co70	70	95.8	19,800	1.52
Co80	80	97.9	21,400	1.51
Co90	90	100	23,700	1.51
Co100	100	100	21,700	1.50

[a] GPC in THF, using monodisperse polystyrene standards

A predominance of LL incorporation in the copolymers was observed in all reactions (Table 1 and Figure 2), indicating that the probability of addition of the caprolactone to the lactidyl chain end is very low, however, the probability of the addition of the l,l-lactide to the caproyl chain end is high, in agreement with the previous results reported by Choi et al.[8]

The molar masses of copolymers were analyzed by GPC and by diluted solutions' viscometry. The copolymers molar masses by GPC are reported relative to the monodisperse polystyrene standards. The similar molar masses (Mw = 20,000-25,000 g/mol) and the moderate control of the polydispersity (around 1.50) revealed predominance of a *quasi-living* nature of the polymerization reaction, as well as the control of the transesterification reaction, which would broaden the molar masses polydispersity.

Table 2 Assignments of carbonyl chemical shifts due to different triads in copolymer.

Triad sequence[a]	Carbonyl chemical shift, ppm
CL-CL[b]-CL	173.504 ± 0.026
LL-CL-CL	173.434 ± 0.020
CL-CL-LL	172.852 ± 0.028
LL-CL-LL	172.796 ± 0.017
LL-LL[c]-CL	170.344 ± 0.012
CL-LL-CL	170.244 ± 0.013
CL-LL-LL	170.098 ± 0.012
LL-LL-CL	169.741 ± 0.012
LL-LL-LL	169.588 ± 0.010

[a] the correspondent carbonyl is underlined, [b] CL – caproyl, [c] LL– lactidyl

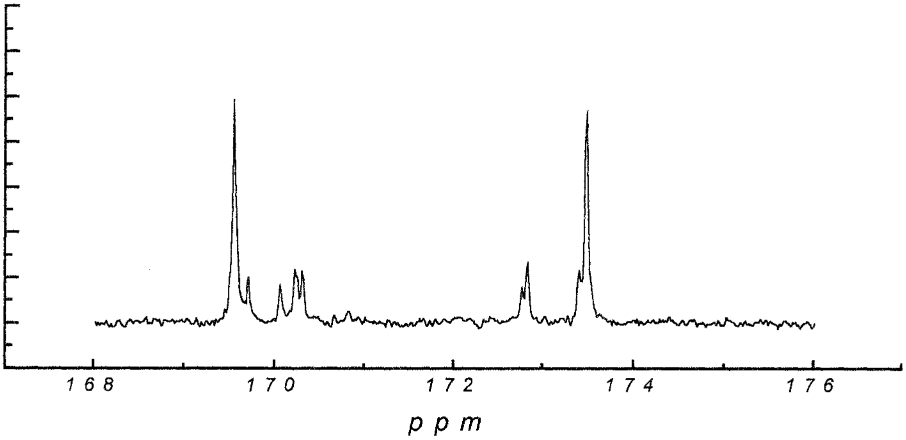

Figure 3 ^{13}C-NMR spectrum of copolymer Co30 in the carbonyl region.

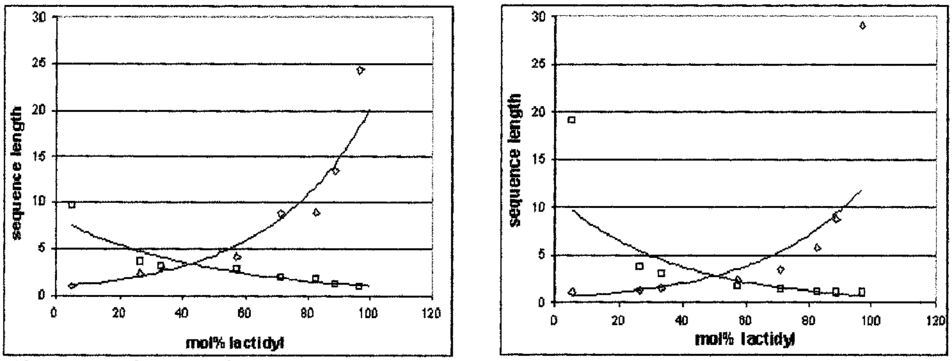

Figure 4. Influence of copolymer composition on the sequence lengths of (◊) lactidyl units and (□) caproyl units. (a) Experimental results; and (b) Bernoulli statistical distribution

The microstructure sequence lengths of copolymers were determined by analyzing the carbonyl signals in ^{13}C-NMR spectra in the region 168 - 174 ppm (Figure 3) and applying calculations according to Kasperczyk and Bero.[19] The calculations were based on the signals due to the eight possible triads formed by the two constitutive units, lactidyl (LL) and caproyl (CL). The observed carbonyl chemical shifts of the relevant triads are shown in Table 2 and are in accordance to those previously reported in the literature.[18]

The results are displayed in Fig. 4a and compared to statistical copolymers number average sequences lengths (L_{LLB} and L_{CLB}) expected for the observed copolymer composition, in terms of lactidyl unit concentration, [LL], and caproyl unit concentration, [CL], as determined by NMR (Fig. 4b). According to Bernoulli statistics, which considers a statistical distribution of both units, LL and CL, in the polymer, the average segment lengths are as follows:

$$L_{LLB} = \frac{\left(1+\frac{[CL]}{[LL]}\right)}{\frac{[CL]}{[LL]}} \tag{3}$$

and

$$L_{CLB} = 1+\frac{[CL]}{[LL]} \tag{4}$$

The copolymers' sequence lengths behaviors, both experimental and calculated, are quite similar, indicating predominance of random copolymers formation, nevertheless the experimental results revealed slightly longer lactidyl sequences, short blocks of poly(l,l-lactide) formation, except for copolymer Co80 and homopolymer structure for Co90. These results can be explained taking into account the relative reactivity data reported in the literature, indicating the higher reactivity of the l,l-lactide monomer toward both types of chain active end, lactidyl and caproyl, compared to the ε-caprolactone. The absence of the triad CL-LA-CL (LA, lactate, isolated half lactidyl unit) carbonyl peak at 171.0 ppm is also an evidence of the effective transesterification inhibition under the polymerization conditions, therefore favoring also random copolymers' formation.

The dynamic storage modulus (E') data for the copolymers Co10 and Co40 are shown in Fig. 5. The tests were carried out from samples cut from pressed sheets. Both copolymers have shown elastoplastic behavior; the vitreous-rubbery transition is clearly shown at –45 °C and –25 °C for Co10 and Co40, respectively. The rubbery plateau is observed for both copolymers throughout the polymer melt flow temperature, at 55 °C for Co10 and 70°C for Co40. The increase in the relative concentration of l,l-lactidyl unit caused the drop of the storage modulus in the temperature range 0-50 °C; and values of 300 MPa and 50 MPa at 25 °C are measured for Co10 and Co40, respectively. The copolymer storage modulus E' in function of temperature is strongly dependent on the composition and microstructure, which affect the crystallization ability. The detailed analyses of the structure-properties relationship in this copolymer series are underway.

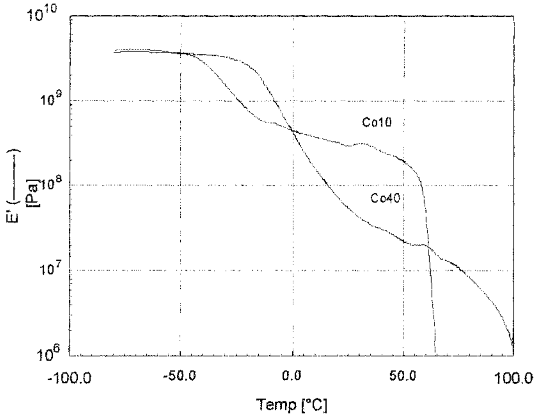

Fig. 5 Dynamic storage modulus (E') of copolymers Co10 and Co40 in function of temperature

Conclusions

Random copolymers of l,l-lactide and ε-caprolactone with wide composition range can be prepared by bulk polymerization under mild conditions, temperature of 120 °C and three hours, using stannous 2-ethyl-hexanoate as initiator.

The reaction conditions allowed the preparation of homopolymers and copolymers with moderate molar masses polydispersities (1.50 circa) and Mw of 20,000 to 25,000 g/mol. The absence of the transesterification reaction and the statistical nature of copolymers, were observed by the sequence lengths analyses using ^{13}C-NMR spectrometry.

The copolymers presented wide range of mechanical properties, from rubbery to stiff thermoplastics. The detailed mechanical properties evaluation and biodegradability behavior of these copolymers will be subjects of other communications.

Acknowledgements

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