



ISSN: 2230-9926

Available online at <http://www.journalijdr.com>

IJDR

International Journal of Development Research

Vol. 11, Issue, 04, pp. 46401-46405, April, 2021

<https://doi.org/10.37118/ijdr.21622.04.2021>



RESEARCH ARTICLE

OPEN ACCESS

PREPARATION OF STATISTICAL COPOLYMERS OF TRIMETHYLENE CARBONATE AND LACTIDE: CANDIDATE MATERIALS FOR MEDICAL APPLICATIONS

Alexandre Carneiro Silvino*, André Luiz Chuwarten Rodrigues, Katherine Fernandes de Jesus and Marcos Lopes Dias

Universidade Federal do Rio de Janeiro, Instituto de Macromoléculas Professora Eloisa Mano, Av. Horácio Macedo 2030, CT, Bloco J, Ilha do Fundão CEP 21941-598, Rio de Janeiro, RJ, Brazil

ARTICLE INFO

Article History:

Received 20th January, 2021

Received in revised form

07th February, 2021

Accepted 18th March, 2021

Published online 28th April, 2021

Key Words:

Lactide, Trimethylene Carbonate, Medical Applications, Copolymers, Biocompatible.

*Corresponding author:

Dayse Christina Rodrigues Pereira

ABSTRACT

Copolymers of trimethylene carbonate (TMC) and L-lactide (LA) with distinct compositions were prepared in solution employing $[Mg(OEt)_2]_2 \cdot [Ti(OBu)_4]$ as initiator. Our results showed that the reactions in solution are considerably slower compared with the same copolymerizations carried out in bulk, however the copolymer ratios observed by NMR tracks the feed ratio excellently when the reactions were performed in toluene at 90°C. The values of degree of randomness (R) calculated for the copolymers were always lower than 1, confirming the preference for L-lactide incorporation, with LA microblocks slightly larger than expected. The effect of the composition in the thermal properties of the copolymer was also investigated by DSC

Copyright © 2021, Alexandre Carneiro Silvino et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Citation: Alexandre Carneiro Silvino, André Luiz Chuwarten Rodrigues, Katherine Fernandes de Jesus and Marcos Lopes Dias. "Preparation of Statistical Copolymers of Trimethylene Carbonate and Lactide: Candidate Materials for Medical Applications", *International Journal of Development Research*, 11, (04), 46401-46405.

INTRODUCTION

The design of materials for biomedical applications has been one the major motivations for the development of synthetic strategies to prepare biocompatible polyesters and polycarbonates with tailored structures. Among the most studied polymers, polylactide (PLA) is of particular interest in the manufacture of tissue engineering scaffolds, drug delivery systems and diagnosis tools due to its well known biocompatibility and *bioresorption* properties (Nair & Laurencin, 2007; Middleton & Tipton, 2000; Lasprilla et al. 2012; Saini et al., 2016; Schmidmaier et al., 2001). Nevertheless, the polylactide is considered a rigid thermoplastic, restricting its use in situations where flexibility is desirable, especially when the polymer is thought to mimic some parts of human tissue. Therefore, a common way to diminish the PLA stiffness is the copolymerization with monomers whose homopolymers have low glass transition temperatures e.g. 1,3-trimethylene carbonate (TMC). The use of TMC in copolymerizations with lactide (LA) has gained more attention due to the combination of soft and hard segments in the copolymer structure which allows

the fine tuning of important characteristics like drug permeability, thermal properties and degradation rate (Dargaville et al., 2001; Jelonek et al., 2011). Consequently, the subject has been covered by many authors, including the preparation of statistical, gradient and (multi)block TMC/LA copolymers with distinct compositions (Leng et al., 2016; Coulembier et al., 2012; Pospiech et al., 2005). Taking into account these facts, it is clear that the role of the initiator or catalyst in the resultant copolymer is a crucial factor as the preference for LA or TMC will regulate the monomer incorporation, furnishing products with different properties. Albeit growing efforts have been devoted to the development and exploratory activity screening of many metal-based catalysts, the tin(II) octoate and aluminum compounds are still considered the most efficient species for the ring opening copolymerization of TMC and LA. However, the safety of long-term use of these metals is still under debate and their presence in medical devices is discouraged (Kricheldorf et al., 2004; Kawahara & Kato-Negishi, 2011).

These limitations have prompted several research groups to explore the activity of compounds comprising less toxic metals, such as Zn, Fe, Ca and Mg on the polymerization and copolymerization of LA (Pastusiak *et al.*, 2016; Biernesser *et al.*, 2013; Dias *et al.*, 2011; Huang *et al.*, 2015). Some of us have already reported studies of biocompatible catalysts and initiators for LA polymerization and LA and TMC copolymerization (Silvino *et al.*, 2013; Silvino *et al.*, 2014; Silvino *et al.*, 2014b). More specifically, we have been exploring the activity of $[\text{Mg}(\text{OEt})_2]_2[\text{Ti}(\text{OBu})_4]$ (commercially known as Catylen[®] S200) as a replacement for tin and aluminum based catalysts/initiators for the preparation of polymers with medically oriented purposes. In this work we wish to report our results employing $[\text{Mg}(\text{OEt})_2]_2[\text{Ti}(\text{OBu})_4]$ as initiator for random copolymerization in solution of L-lactide (LLA) and TMC.

Experimental

Materials: All experiments were carried out under purified nitrogen using standard Schlenk techniques or in a glove-bag. Toluene and tetrahydrofuran (THF) were distilled from Na/benzophenone under nitrogen. Dichloromethane (CH_2Cl_2) was distilled from CaH_2 under nitrogen. Ethyl acetate was dried over MgSO_4 and distilled under nitrogen. Ethanol and methanol were obtained from Vetec[®] Brazil and used as received. The L-lactide was purchased from Purac[®] and recrystallized from dry toluene before use. 1,3-Trimethylene carbonate was purchased from ZMC China and recrystallized from ethyl acetate. The Mg/Ti initiator solution (Catylen[®] S200) was supplied by Evonik Industries and was used as received.

Homopolymerizations: In a typical polymerization procedure a Schlenk flask previously dried in oven at 100 °C for 24 hours was charged with 2.5 g of monomer (L-lactide or 1,3-trimethylene carbonate) and 20 mL of dry toluene. The Schlenk flask was then immersed in oil bath at the selected temperature. After the complete dissolution of the monomer the desired amount of initiator (0.5 wt %) was added via syringe and the polymerization was carried out for the desired reaction time. The polymer was immediately precipitated in an excess of cold ethanol, filtered and dried in oven at 50 °C for 24 hours.

Synthesis of Statistical Copolymers: In a Schlenk flask previously dried in oven at 100 °C for 24 hours was charged with L-lactide and 1,3-trimethylene carbonate in distinct LLA/TMC feeds (10:90, 30:70, 50:50, 70:30 or 90:10 mol %) and 20 mL of dry solvent. The Schlenk flask was then immersed in oil bath at selected temperature under magnetic stirring. After the complete dissolution of the monomers the desired amount of initiator (0.5 wt %) was added via syringe and the copolymerization was carried out for the desired reaction time. The product was immediately precipitated in cold ethanol, filtered and dried in oven at 50 °C for 24 hours.

Characterization: WAXD analyses were performed in a Rigaku Miniflex (model DMAX 2200) X-ray diffractometer (generator of 3kW, a graphite monochromator, $\text{CuK}\alpha$ radiation (wavelength, $\lambda = 0.154 \text{ nm}$), operated at 30 kV/15mA. Samples were scanned with a counting time of 1 s under a diffraction angle of 2θ in the range of 2.0 to 50.0°. Number-average (M_n) and weight-average (M_w) molecular weight of PLAs were determined by means of Gel Permeation Chromatography in an Agilent 1200 Series GPC-SEC Analysis System, Agilent Technologies, (Santa Clara, CA 95051 United States) fitted with PLgel 5 μm MIXED-C Columns (Agilent Technologies, USA) using polystyrene standards for the calibration and chloroform (CHCl_3) as the solvent at 30 °C with a flow rate of 1.0 mL/min. The glass transition (T_g), the crystallization (T_c) and the melting (T_m) temperatures of the samples were determined using a DSC-7 calorimeter (Perkin Elmer Inc., Wellesley, MA, USA) with a heating and cooling ramp of 10 °C/min under nitrogen flow from -30 to 200 °C for the statistical copolymers, from -80 to 50 for the polycarbonate sample and from 25 to 200 °C for the polylactide sample. All the values were taken during second scans unless otherwise stated.

The $^1\text{H-NMR}$ spectra were recorded at room temperature with a Varian Mercury VX-300FT-NMR spectrometer operating at 300 MHz (^1H) using tetramethylsilane (TMS) as an internal reference. Polymers were analyzed in CDCl_3 solution. Chemical shifts (δ) were given in ppm. Composition of the copolymers were determined from the $^1\text{H-NMR}$ spectra by taking the ratio of the peak areas corresponding to the LA methyl protons at $\delta = 1.4\text{--}1.6 \text{ ppm}$ and the TMC α -methylene protons at $\delta = 4.0\text{--}4.2 \text{ ppm}$. The average block lengths of lactyl units were obtained from the relative peak intensities of the lactide methine resonances of LA-LA ($\delta 5.17 \text{ ppm}$) and LA-TMC ($\delta 5.00 \text{ ppm}$) diads using the following equation (Pêgo *et al.*, 2003):

$$\bar{L}_{LA} = \frac{I_{LA-LA}}{I_{LA-TMC}} + 1 \quad (\text{Eq. 1})$$

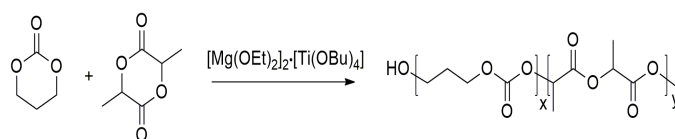
The degree of randomness (R) is given by the following equation (Dobrzynski & Kasprczyk, 2006)

$$R = \frac{\bar{L}_{LA}^R}{\bar{L}_{LA}} \quad (\text{Eq. 2})$$

Where \bar{L}_{LA}^R is the theoretical block length of lactyl units calculated using standard copolymer equations for a completely random copolymer ($r_{LA} = r_{TMC} = 1$, where r_{LA} and r_{TMC} are the reactivity ratios respectively) and \bar{L}_{LA} is the average length of lactyl blocks calculated using $^1\text{H-NMR}$.

RESULTS AND DISCUSSION

Copolymerizations: The random P(LLA-TMC) copolymers with distinct compositions were prepared in solution using Catylen[®] S200 as initiator system (Scheme 1). Catylen[®] S200 is a commercial product designed to be employed as support for Ziegler-Natta-type olefin polymerization catalysts composed of a 30 wt% solution of magnesium-ethanolate and titanium-n-butanolate in hexane forming a soluble complex with molecular formula $[\text{Mg}(\text{OEt})_2]_2[\text{Ti}(\text{OBu})_4]$ (Rauleder *et al.*, 2001). The initiator was tested in distinct reaction conditions in order to establish the best parameters for the copolymerizations in solution. The results are summarized in Table 1.



Scheme 1. Synthesis of the P(LLA-TMC) copolymers

The GPC data in Table 1 show that the polymers obtained had number-average molecular weights (M_n) between 4700 and 6400 g/mol with polydispersity indexes (PDI) varying from 1.12 to 2.80. All GPC elution curves showed monomodal patterns indicating the two metals are not independent initiation centers, which might simultaneously generate polymers with distinct molecular weights. These results agree with previously reported data employing the same initiator (Silvino *et al.*, 2014; Silvino *et al.*, 2014b). Remarkable differences in the Mg/Ti system activity can be observed depending on the selected conditions. Comparing the reactions performed at the same temperature, it is possible to observe the negative effect of CH_2Cl_2 and THF on the copolymer yield. Additionally, it seems that the use of more polar solvents favors the LA ROP, with almost no incorporation of TMC. Not surprisingly, these samples have the lowest PDI values, attesting the preferential formation of lactyl segments during the copolymerization.

Table 1. L-lactide and 1,3-trimethylene carbonate random copolymerization data

Entry	Feed Ratio (LLA:TMC)	Obs. Ratio ^a (LLA:TMC)	T (°C)	time (h)	Solvent	Yield ^b (%)	<i>Mn</i> ^c (g/mol)	PDI ^c
1	90:10	91:9	90	72	Toluene	80.2	6200	2.12
2	70:30	69:31	90	72	Toluene	77.4	4900	2.15
3	50:50	51:49	90	72	Toluene	76.0	4700	2.80
4	50:50	51:49	90	96	Toluene	73.5	3900	2.60
5	50:50	62:38	25	72	Toluene	73.8	5500	1.30
6	50:50	56:44	50	72	Toluene	59.0	6100	1.29
7	50:50	93:7	25	72	CH ₂ Cl ₂	49.4	4600	1.14
8	50:50	100:0	25	72	THF	34.6	3300	1.12
9	50:50	76:24	50	72	THF	40.6	5200	1.21
10	30:70	30:70	90	72	Toluene	68.1	5300	2.06
11	10:90	9:91	90	72	Toluene	72.8	6400	2.11

a: Determined by ¹H-NMR

b: Isolated polymer yield

c: Determined by GPC

Table 2. Feed ratio and average lactide block length calculated from ¹H-NMR data

Entry	Feed Ratio (LLA:TMC)	Obs. Ratio ^a (LLA:TMC)	Av. Block length of lactyl units		<i>R</i> ^d
			Calc. ^b	Obs. ^c	
1	90:10	91:9	10.0	17.7	0.6
2	70:30	69:31	3.3	5.2	0.6
3	50:50	51:49	2.0	3.0	0.7
4	50:50	51:49	2.0	3.1	0.6
5	50:50	62:38	2.0	13.5	0.1
6	50:50	56:44	2.0	6.0	0.3
7	50:50	93:7	2.0	ND	ND
8	50:50	100:0	2.0	∞	0
9	50:50	76:24	2.0	10.1	0.2
10	30:70	30:70	1.4	1.7	0.8
11	10:90	9:91	1.1	1.2	0.9

a: Determined by ¹H-NMR

b: Calculated using random copolymer equation

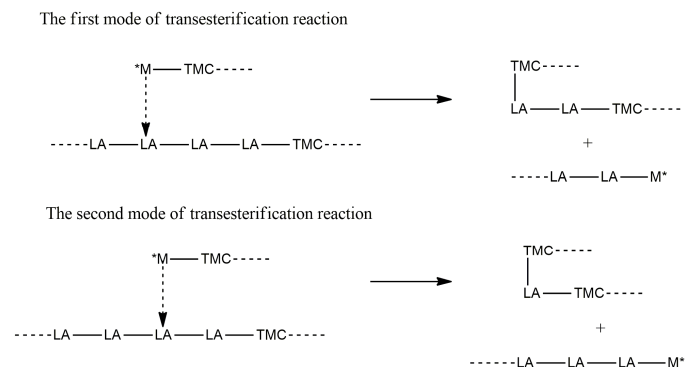
c: Determined by ¹H-NMR employing eq. 1

d: Randomness of the chain calculated according to eq. 2

The decrease in the PDI values when the copolymerizations were carried out at 25°C and 50°C stress the influence of the temperature on the Catylen[®] S200 reactivity ratio, resulting in LA-rich polymers, as determined by the ¹H-NMR analyses. It is interesting to note the changes in the reactivity of Catylen[®] S200 towards TMC and LA incorporation with the temperature. The copolymer compositions determined by ¹H-NMR suggest the increasing preference for LA at lower temperatures can be modulated from an almost true random copolymer to a blocky structure. The preferential incorporation of LA at lower temperatures is also corroborated by the observed average block lengths of lactyl units calculated by ¹H-NMR which were much greater than the theoretical lengths (Table 2). We think that under optimized conditions this route can be explored for one-pot synthesis of TMC-LA diblock copolymers. When the reactions were performed in toluene at 90°C, the best results referring to polymer yield and *feed/composition fidelity* are achieved, however, the polydispersity indexes were comparatively higher (> 2.0) probably due to the slow TMC ROP kinetics, which increases the significance of transesterification side reactions in the final molecular weight distribution. The influence of TMC on the rate of enchainment LA in solution was discussed by Darenbourg *et al.* They employed tridentate Schiff base calcium complexes to prepare copolymers from TMC and LA and they stated that the TMC ROP is much slower during copolymerization reactions (Darenbourg *et al.*, 2008). After an investigation of the kinetic of the copolymerization they also noted that the rate of enchainment of TMC is increased after consumption of LA which means that the two ring opening reactions compete with each other and influence the other's reactivity which agrees with our results. Previously published results of our group (not shown) exploring the copolymerization of TMC and LA employing the same initiator have indicated that the copolymerizations in bulk are much faster when compared to the ones performed in solution (Silvino *et al.*, 2014).

Nevertheless, the deviations in the copolymer compositions are comparatively lower and the observed average block lengths of lactyl units are in general slightly higher than the theoretical lengths calculated using standard equation for statistical copolymers. These results indicate that the structures of these copolymers are closer to random distribution than to microblock segments. Moreover, it was possible to determine the degree of randomness (*R*) employing the average block length of the copolymer using equation 2: The closer the calculated value of *R* is to 1 the closer the copolymer is to possess a totally random chain microstructure (Dobrzynski & Kasperczyk, 2006). One can note that with increasing TMC content in the polymer composition, the closer the degree of randomness is to 1. Nevertheless, the statistical nature of the structure may become accurately ascribed to the high degree of transesterification reactions which take place during the polymerization. As our group already discussed in our previous paper about lactide and TMC ROP with Catylen[®] S200 in bulk, we wish to extrapolate Dobrzynski *et al.* considerations about the distinction of the transesterification modes seen in lactide and glycolide copolymerizations to explain the structure of TMC and lactide random copolymers prepared in this work (Dobrzynski *et al.*, 2002). The authors stated that when lactidyl (LA-LA) and glycolidyl (Gli-Gli) exchange reaction takes place, the transesterification can be considered of first mode (*T*₁). On the other hand, when lactide and glycolidyl groups undergo bond cleavage resulting in Gli-LA-Gli or LA-Gli-LA sequences, the intermolecular transesterification can be considered as a second mode transesterification reaction (*T*₂). A description of the two transesterification modes is shown in Scheme 2. Thus the TMC-LA-TMC units produced during copolymerization are due to transesterification of second mode, which may turn the chain microblock segments into a randomized structure. These sequences are present in the copolymers due to the transesterification caused by the presence of high amounts of TMC during the copolymerization reaction and this finding agrees with our previously reported results

using the same initiator in bulk copolymerizations of LLA and TMC.¹⁷ It is interesting to note that, according to Jelonek *et al.*, highly randomized copolymers ($R \rightarrow 1$) are good candidates for regular drug release process because they are less likely to crystallize during degradation (Jelonek *et al.*, 2011).



Scheme 2. Transesterification of first and second modes occurred during copolymerizations (Adapted from Dobrzynski *et al.*)

WAXD Analysis: The P(LLA-TMC) copolymers and the PLLA sample prepared at 90 °C and 72 hours of reaction time were analyzed by WAXD. Only the diffraction patterns of samples containing a minimum of 50 % of L-lactide content in their compositions (Table 1, entries 1, 2, and 3) are shown in Figure 1 due to the amorphous characteristic of TMC/PLLA random copolymers when the TMC content exceeds 50 mol% .

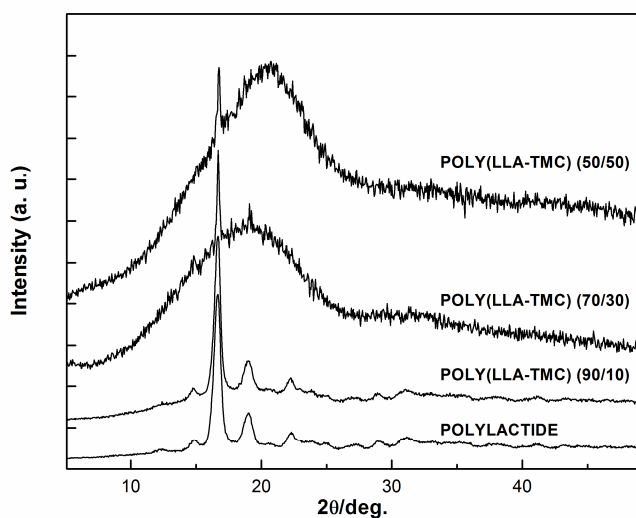


Figure 1. X ray diffraction patterns of PLLA and selected L-lactide/trimethylene carbonate copolymers

The sample P(LLA-TMC) (90/10) shows the characteristic reflections of PLLA at $2\theta = 14.8, 16.7, 18.9$ and 22.3° , confirming its semi-crystalline structure (Ikada *et al.*, 1987). The low content of TMC has only slightly reduced the intensity of crystalline peaks causing a discrete increase in the amorphous halo intensity. Conversely, samples P(LLA-TMC) (70/30) and P(LLA-TMC) (50/50) are clearly less crystalline, showing only a distinct reflection around $2\theta = 23^\circ$, attesting the presence of an amorphous structure for the copolymers with increasing content of TMC.

Thermal Analysis: The thermal properties of the copolymers prepared in toluene at 90 °C with distinct compositions were investigated by differential scanning calorimetry (DSC). To enable them to be compared, all samples had identical thermal histories. The second heating curves of copolymers prepared are shown in Figure 2 (selected data of the homopolymers were added for comparison). In all cases, the copolymer samples displayed unique glass transition temperature (T_g) with values intermediate between -29.6°C of PTMC

and 46.5°C of poly(lactide). As can be seen in Figure 3, the T_g values of the copolymers decrease linearly with the increase of TMC content attesting the random structure of the copolymers (Cai *et al.*, 2010).

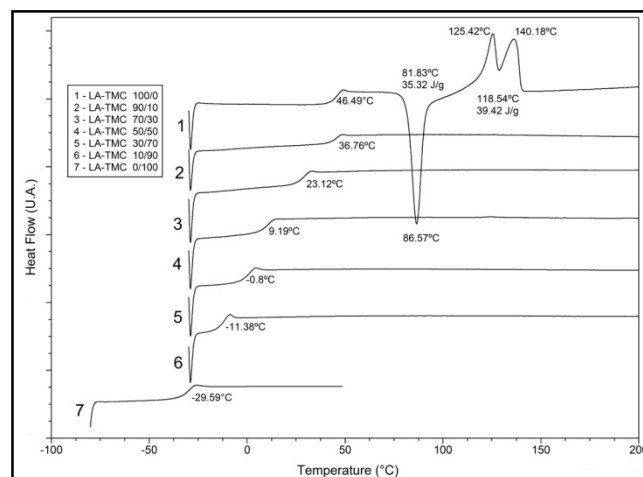


Figure 2. DSC curves of the random copolymers and homopolymers prepared using $[\text{Mg}(\text{OEt})_2]_2 \cdot [\text{Ti}(\text{OBu})_4]$ as initiator

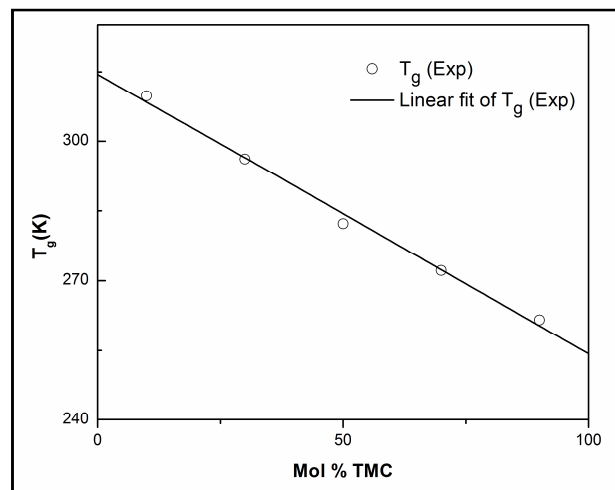


Figure 3. Behavior of glass transition temperature (T_g) of the copolymer with TMC content in the copolymers

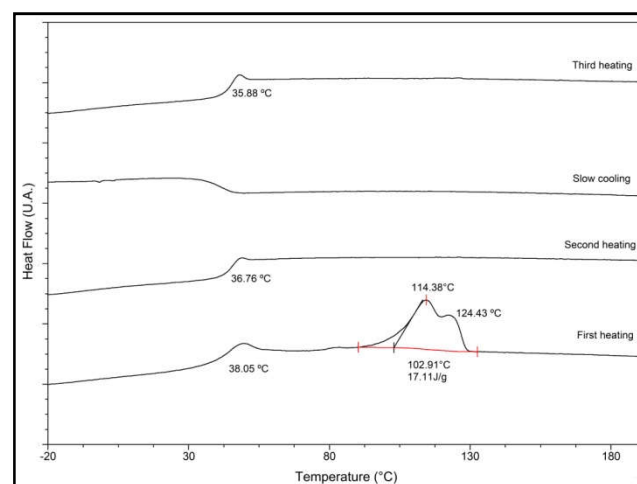


Figure 4. DSC heating curves and slow cooling curve of sample P(LLA-TMC) (90/10).

Although the PLLA second heating scan exhibit an exothermic event at 86.6°C assigned to crystallization and a bimodal endothermic event seen at 125.4 and 140.2°C , no evidence of crystallization or

crystal melting was detected during the second heating scan of the copolymers, even with higher contents of LA. However, a bimodal crystal melting profile was observed in the first DSC scan of the sample comprising 90 mol % of LA, which agrees with the narrow and intense peaks observed in the WAXD curve (Figure 4). It seems that the incorporated unities of TMC affect negatively the crystallization rate of the copolymer under our analysis conditions thus explaining the absence of melting peaks in the second heating scan.

CONCLUSIONS

Statistic copolymers of L-lactide and 1,3-trimethylene carbonate with distinct compositions were successfully prepared in solution using the complex $[Mg(OEt)_2]_2[Ti(OBu)_4]$ (Catalen® S200) as initiator. Comparing with reactions using the same initiator in bulk polymerizations, the reactions in solution are considerably slower, however the copolymer ratios observed by NMR tracks the feed ratio excellently when the reactions were performed in toluene at 90° C. When the reactions were carried out in THF or CH_2Cl_2 or at lower temperatures the copolymers composition deviations from the monomers feeds are significant, furnishing lactide-rich copolymers. The average block lengths of lactyl units calculated by NMR are in general slightly higher than the theoretical lengths calculated using standard equation for statistical copolymers corroborating the preference of the initiator for L-lactide incorporation. Whereas it is possible to detect crystalline peaks in the WAXD analysis of the copolymer with 10 % of TMC content, the DSC scans related to the second heating process showed no endothermic events attributed to crystal melting. Nevertheless, the first heating curve of the same sample showed two endothermic events at 114,3 and 124,4 °C. These results indicate that the presence of TMC, even at low concentration, has a negative effect on the rate of crystallization of copolymers. The values of R calculated for the copolymers prepared in this work were always lower than 1, confirming the preference for L-lactide incorporation, with LA microblocks larger than expected. Nevertheless, in the case of the copolymer comprising 10 % mol of LA the transesterification reactions changed the enchainment close to a total random structure.

Acknowledgments

The authors would like to thank the Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) and the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES) for the financial support

REFERENCES

Biernesser AB, Li B, Byers JA, *J. Am. Chem. Soc.* 2013, 135(44) 16553.

- Cai Z, Harada R, Nakayama Y, Shiono T, *Macromolecules* 2010, 43, 4527.
- Coulember O, Lemaure V, Josse T, Minoia A, Cornil J, Dubois P, *Chem. Sci.* 2012, 3, 723.
- Darensbourg DJ, Choi W, Karroonnirun O, Bhuvanesh N, *Macromolecules*, 2008, 41, 3493-3502.
- Dargaville BL, Vaquette C, Peng H, Rasoul F, Chau YQ, Cooper-White JJ, Campbell JH, Whittaker AK *Biomacromolecules* 2011, 12, 3856.
- Dias ML, Palermo LC, Silvino AC, *Macromolecular Symposia* 2011, 299-300, 156.
- Dobrzynski P, Kasperczyk J, Janeczek H, Bero M, *Polymer* 2002, 43, 2595.
- Dobrzynski P, Kasperczyk J, *Journal of Polymer Science: Part A: Polymer Chemistry* 2006, 44, 3184.
- Huang M, Pan C, Ma H, *Dalton Transactions* 2015, 44(27), 12420
- Ikada Y, Jamshidi K, Tsuji H, Hyon SH, *Macromolecules* 1987, 20, 904.
- Jelonek K, Kasperczyk J, Li S, Dobrzynski P, Jarzabek B, *International Journal of Pharmaceutics* 2011, 414, 203.
- Kawahara M, Kato-Negishi M, *International Journal of Alzheimer's Disease* 2011, 2011, 1.
- Kricheldorf HR, Hachmann-Thiessen, H, Schwarz G, *Biomacromolecules* 2004, 5:492-496
- Lasprilla AJR, Martinez GAR, Lunelli BH, Jardim AL Filho RM *Biotechnology Advances* 2012, 30, 321.
- Leng X, Wei Z, Ren Y, Bian Y, Wang Q, Li Y, *RSC Advances* 2016, 46, 40371.
- Middleton JC, Tipton AJ *Biomaterials* 2000, 2335.
- Nair LS, Laurencin CT *Prog. Polym. Sci.* 2007, 32, 762.
- Pastusiak M, Dobrzynski P, Janeczek H, Kaczmarczyk B, Kasperczyk J, *Materials Today Communications* 2016, 7, 140.
- Pêgo AP, Poot AA, Grijpma DW, Feijen J, *Journal of Materials Science: Materials in Medicine* 2003, 14, 767.
- Pospiech D, Komber H, Jehnichen D, Häussler L, Eckstein K, Scheibner H, Janke A, Kricheldorf HR, Petermann O, *Biomacromolecules* 2005, 6, 439.
- Rauleder H, Standke B, Horn M, Kotzsch H.-J, Srebny, H.-G. 2001, Patent No: US 6,294,682 B1
- Saini P, Arora M, RaviKumar MNV. *Advanced Drug Delivery Reviews* 2016, 107, 47
- Schmidmaier G, Wildemann B, Stemberger A, Haas NP, Raschke M.J *Biomed. Mater. Res.* 2001, 58 449.
- Silvino AC, Corrêa PS, Dias ML, *Journal of Applied Polymer Science* 2014, 131, 40771,
- Silvino AC, Martins DBAT, Rodrigues AC, Dias ML, *Journal of Polymers and the Environment* 2013, 21, 1002.
- Silvino AC, Rodrigues ALC, Jesus KF, Dias ML, *European Polymer Journal* 2014, 57, 66.
