



Preparation of poly(glycolide-co-lactide)s through a green process: Analysis of structural, thermal, and barrier properties



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ABSTRACT

We have successfully synthesized poly(lactide), poly(glycolide), and poly(lactide-co-glycolide) copolymers in bulk by ring-opening homo- and copolymerization of glycolide and L-lactide, using sodium hydride as the environmentally friendly and nontoxic initiator. Random copolymers were obtained, and the microstructure was characterized by nuclear magnetic resonance (¹H and ¹³C NMR) and matrix-assisted laser desorption/ionization mass spectrometry (MALDI MS). The mechanism of reaction was elucidated by analysis of the polymer end groups. Homopolymer and copolymers films and their blends were obtained, and structure and physical properties analyzed. Thermal degradation analysis showed superior characteristics of copolymers with respect to the blends. Transport properties of water vapor were also evaluated and correlated to the copolymer composition.

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1. Introduction

Aliphatic polyesters such as poly(lactide) (PLA) and poly(glycolide) (PGA) are a viable degradable alternative to the petrochemical-based polymers and their diffusion is constantly increasing worldwide. Aliphatic poly(ester)s have attracted much attention because of their highly desirable sustainable development, and they are being increasingly used in all areas of everyday life. These polymers have found a broad range of practical applications from packaging for industrial products to films in agriculture [1] and represent, by far, the most used class of polymeric materials for biomedical application [2]. They can be synthesized by ring-opening polymerization (ROP) of the related cyclic esters such as lactide (LA) and glycolide (GA) by different enzymatic, cationic, anionic, or coordination-insertion polymerization mechanisms [2–3]. The most frequently used initiator is tin (II) 2-ethylhexanoate (Sn(Oct)₂) [2–3]. Although the Food and Drug Administration (FDA) has approved its use with a limit of 20 ppm of residual tin in commercially used medical polymers, its cytotoxicity has raised several issues [4]. Therefore, academic research is currently searching for more biologically and environmentally friendly initiators, with cost-efficient catalytic process. Several nontoxic catalysts or initiators such as magnesium, calcium, zinc, and iron complexes or enzymes have already

been evaluated [2–3]. We have recently reported the polymerization of ε-caprolactone promoted by sodium hydride (NaH), both in bulk and in solution [5]. NaH was also found to be active in the ROP of other cyclic esters such as rac-β-butyrolactone [6]. It is worth noting that its use in the polymerization of cyclic diesters, such as GA and LA, has not been reported thus far. Notably, NaH is not only a commercially available, economical and easy-to-handle initiator, but it is also made on a nontoxic metal. More importantly, sodium and potassium are essential to animal and human life [7].

Copolymerization of GA and LA has been widely used to engineer the properties of PGA and PLA. Poly(glycolide-co-lactide)s (PLGAs) are less stiff than the parent homopolymers, and they form amorphous polymers in the composition range of 25–75%. Copolymers with different ratios of the two monomers have been commercially developed and are being investigated for a wide range of biomedical applications [2–3, 8–10]. In detail, they have been used in medical products such as sutures, bone screws, tissue engineering scaffolds, and drug delivery systems. In this study, we describe the use of NaH as the only initiator in the ring-opening homo- and copolymerization of L-lactide and glycolide. Notably, polymerization processes have been performed in bulk, thus avoiding the utilization of solvents, and therefore adding even more value to the used process as an “environmentally friendly” method.

Here, we present the synthesis, microstructural and thermal analysis of PLGA copolymers at different compositions of LA and GA (i.e., 37% and 64% of GA). The homopolymers (PLA and PGA) were also synthesized

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using the same *green* experimental conditions. The obtained copolyesters and the homopolymers were characterized by nuclear magnetic resonance (NMR), size exclusion chromatography (SEC), thermogravimetric analysis (TGA) and matrix-assisted laser desorption ionization (MALDI) mass spectrometry analysis. Mechanical mixing of products with the same copolymer composition was also carried out using the synthesized pure polymers, and their thermal properties were compared. Finally, transport properties of water vapor (sorption and diffusion) and contact angle to water were evaluated and correlated to the copolymer composition.

2. Experimental section

2.1. General procedures

Moisture- and air-sensitive materials were manipulated under nitrogen using Schlenk techniques or MBraun Labmaster glovebox. Before use, glassware was dried overnight in an oven at 120 °C. Monomers (Sigma-Aldrich) were purified as follows: L-lactide was dried in vacuo with P₂O₅ for 72 h, and then stored at –30 °C in glovebox; glycolide was recrystallized from tetrahydrofuran (Delchimica, solvent distilled under N₂ over Na/benzophenone). Deuterated solvents (dimethyl sulfoxide d₆ (DMSO-d₆) and CDCl₃) were purchased from Euriso-top and used as received. MALDI matrices were provided by Sigma-Aldrich and used as supplied. All other reagents and solvents were commercially available and used as received.

2.2. Instruments and measurements

NMR spectra of polymers (Supporting Information S4–S9) were recorded in DMSO-d₆ at 100 °C and in CDCl₃ at 25 °C on a Bruker Avance 300 spectrometer (¹H, 300.13 MHz; ¹³C, 75.47 MHz). The resonances are reported in parts per million (δ) and coupling constants in Hertz (J), and they are referenced to the residual solvent peak versus Si(CH₃)₄: DMSO-d₆ at δ 2.50 (¹H) and δ 39.5 (¹³C), CDCl₃ at δ 7.26 (¹H).

SEC analyses were carried out at room temperature, in CHCl₃ with a Waters 515 HPLC pump, equipped with four Ultrastaygel HR columns (in the order HR4, HR3, HR2, and HR1) connected in series, and a Waters 2414 differential refractive index detector. Polymer solutions (200 μL, 5 mg/mL) were injected and eluted at a flow rate of 1 mL/min. Polymer Lab Caliber software was used to compute the average molar masses of the samples by the calibration curve obtained using a set of primary polystyrene standards.

MALDI mass spectra were recorded in reflector mode using a 4800 MALDI TOF/TOF™ Analyzer (Applied Biosystem, Framingham, MA, USA), equipped with a Nd:YAG laser (λ = 355 nm) and working in positive-ion mode. This matrix-assisted laser desorption time of flight mass spectrometry (MALDI-TOF MS) instrument is equipped with a laser having wavelength of <500 ps pulse and 200 Hz repetition rate. The

laser irradiance was set slightly above threshold. For PLLA and PLGA₃₇ (see Table 1), trans-3-indoleacrylic acid (IAA) (10 mg/mL in THF) was selected as matrix. 2-(4-Hydroxyphenylazo)benzoic acid (HABA, 0.1 M) in 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) was used as matrix for PGA and PLGA₆₄ (see Table 1). Appropriate volumes of the polymer solution (5–10 mg/mL in HFIP or THF) and matrix solution were mixed to obtain ratios of 1:1, 1:2, and 1:3 (sample/matrix v/v). A small volume of 2 μL of each sample–matrix mixture was spotted on the MALDI sample holder and slowly dried to allow matrix crystallization. The resolution of the MALDI spectra reported in the text is about 10,000 (FWHM), and the mass accuracy was 5–20 ppm for masses in the range of 1000–2000 Da.

X-ray powder diffraction (XRD) measurements were performed using a Bruker diffractometer (equipped with a continuous scan attachment and a proportional counter) with Ni-filtered Cu Kα radiation (λ = 1.54050 Å).

TGA was performed using a Mettler TC-10 thermobalance. Dynamic measurements were performed from 30 to 800 °C at the step of 10 °C/min, under a nitrogen atmosphere or in air (flow rate 60 mL/min). Sample weights were approximately 4–5 mg. The weight loss percent and its derivative (DTG) were recorded as a function of temperature.

Differential scanning calorimetry (DSC) was performed using approximately 6 mg of samples under nitrogen flow with a TA Q100 DSC thermal analysis instrument. Three scans for each sample, in the temperature range of 50–260 °C were performed. In the initial scan, the samples were heated at 10 °C/min through fusion and left in the melt for 3 min, and cooled at 50 °C/min. Finally, a second heating at 10 °C/min was carried out. The glass transition temperatures (T_g) were calculated as the midpoint of the heat capacity change in the third scan.

Static contact angles calculated using the sessile drop method were recorded and analyzed using an OCA 15 pro contact angle meter from Data Physics Instruments GmbH with SCA20 software (version 3.4.6 build 79). Water droplets of 1 μL were gently deposited on the substrate and quickly captured by a high-resolution camera. All measurements were conducted at 35 ± 2 °C and 50 ± 5% RH. The reported contact angles are the average of at least five measurements.

Transport properties (sorption and diffusion) of water vapor were measured using the microgravimetric method through a conventional McBain spring balance system, which consists of a glass water-jacketed chamber serviced by a high-vacuum line for sample degassing and vapor removal [11]. Inside the chamber, the samples were suspended to a helical quartz spring supplied by Ruska Industries (Houston, TX, USA) having a spring constant of 1.52 cm/mg. The temperature was controlled at 35 ± 0.1 °C by a constant temperature water bath. The samples were exposed to the water vapor at fixed pressures, P. The spring position was recorded as a function of time using a cathetometer. The spring position data were converted to mass uptake data using the spring constant, and the process was followed to a constant value of

Table 1
Homo- and copolymerization of glycolide and L-lactide.^a

Run	<i>f</i> _{GA} ^b	Yield [%]	<i>F</i> _{GA} ^c	<i>L</i> _{GG} ^d	<i>L</i> _{LL} ^d	<i>T</i> _{LGL} ^e	<i>T</i> _{GLG} ^e	<i>M</i> _n ^f [kDa]	<i>Đ</i> ^f
(1) PGA	100	19	100	–	–	–	–	/	/
(2) PLGA ₆₄	33	57	64	1.21	0.68	1.39	1.02	/	/
(3) PLGA ₃₇	11	39	37	1.54	2.62	0.36	2.68	10.8	1.5
(4) PLLA	0	53	–	–	–	–	–	6.1	1.4

^a Polymerization conditions: NaH = 50 μmol, T = 140 °C, t = 180 min (90 min in the case of PGA), [monomer(s)]/[NaH] = 180.

^b *f*_{GA}, molar percentage of glycolide in the feed.

^c *F*_{GA}, molar percentage of glycolide in the copolymer, as determined by ¹H NMR.

^d Average length of glycolidyl (GG) and lactidyl (LL) blocks in the copolymer, calculated from ¹³C NMR (DMSO-d₆, 100 °C).

^e Yield of the second mode of transesterification (%) of glycolidyl (LGL) and lactidyl (GLG) sequences, calculated respectively from ¹H NMR (CDCl₃, RT) and ¹³C NMR (DMSO-d₆, 100 °C).

^f Molar masses and dispersity assessed via SEC.

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