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Research Paper

Hydrolytic Degradation and Drug Release of Ricinoleic Acid–Lactic Acid Copolyesters

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Abstract. A systematic study on the degradation and drug release from L-lactic acid and ricinoleic-acid-based copolyesters is reported. These copolyesters were synthesized by ring opening polymerization (ROP), melt condensation (COND) and transesterification (TRANS) of high molecular weight poly(lactic acid) (PLA) with ricinoleic acid (PLA-RA), and repolymerization by condensation to yield random and block copolymers of weight average molecular weights (Mw) between 3000 and 13,000. All polymers showed an almost zero-order weight loss, with a 20–40% loss after 60 days of incubation. Lactic acid release to the degradation solution is proportional to weight loss of the polymer samples. The main decrease in molecular weight was observed during the first 20 days, followed by a slow degradation phase, which kept the number average molecular weight (Mn) at 4000–2000 for another 40 days. Water-soluble 5FU was released from ricinoleic-acid-based polymers faster than slightly water-soluble triamcinolone. Drug release into phosphate-buffered saline (pH 7.4, 0.1 M) at 37°C from P(LA-RA) 60:40 prepared by condensation of the acids was faster than from pasty P(PLA-RA) 60:40 synthesized by transesterification for both drugs.

KEY WORDS: controlled drug release; degradable polymers; lactic acid; polyesters; ricinoleic acid.

INTRODUCTION

Polyesters are useful bioabsorbable materials for controlled drug release. They hydrolyze to hydroxy acid monomers when placed in aqueous medium. It has been reported that drug release and degradation of polyesters can be altered by using various composites of hydrophobic and hydrophilic monomers (1). D-, L-, and DL-poly(lactic acid) (PLA) are good candidates for the preparation of biodegradable copolymers.

Lactic-acid-based polymers have been prepared by direct polycondensation, ring opening polymerization (ROP), chain extension, or transesterification (2). Lactic acid can be condensed with other hydroxy acids, such as 6-hydroxycaproic acid, glycolic acid, and hydroxybutyric acid. Direct condensation usually resulted in low molecular weight copolymers that can then be further linked together to yield high molecular weight polymers. In the second step, linking molecules, such as diisocyanates, bis(amino-ethers), phosgene, phosphate, and anhydrides, have been applied (3–5).

Enantiomerically pure PLA is a semicrystalline polymer with T_g of about 55°C and T_m of about 180°C. The degree of crystallinity and melting temperature of PLA can be reduced by random copolymerization with other comonomers, leading to the incorporation of units disturbing the crystallization ability of the PLA segments. For example, glycolide, ε-caprolactone, δ-valerolactone, 1,5-dioxepan-2-one, and trimethylene carbonate were frequently used as comonomers to change thermal properties of PLA copolymers (6–9).

Fatty acids are suitable candidates for the preparation of biodegradable polymers (10–13), as they are considered safe and are hydrophobic and thus may retain an encapsulated drug for longer time periods when used as drug carriers. However, most fatty acids are monofunctional and cannot serve as monomers for polymerization. Ricinoleic acid is a common C18 fatty acid with a *cis*-configured double bond in the 9th position and a hydroxyl group in the 12th position (*cis*-12-hydroxyoctadeca-9-enoic acid). It is produced from the hydrolysis of castor oil (14).

Copolymerization of enantiomeric L-lactic acid with ricinoleic acid resulted in a low temperature melting biodegradable copolyesters having desired properties such as pliability, hydrophobicity, and softness (15).

Previous studies in our laboratory focused on the synthesis of ricinoleic-acid-based polyanhydrides (11,16). Polyanhydrides synthesized from ricinoleic acid maleate or succinate and sebacic acids possessed desired physicochemical properties, such as low melting temperature, hydrophobicity, and pliability, in addition to biocompatibility and biodegradability. The polymers were synthesized by melt

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condensation to yield film-forming polymers with molecular weights exceeding 100,000. In another study, fatty acid esters of ricinoleic acid were used as chain terminators of polyanhydrides based on sebacic acid (13). In addition, a systematic study on the synthesis and characterization of ricinoleic acid lactones (RAs), their homopolymerization, and ricinoleic acid-co-lactic acid polyesters synthesized by ROP was reported (15).

The objective of this study was to determine the hydrolytic degradation and drug release of polymers based on lactic acid and ricinoleic acid [P(LA-RA)s] for the potential use as drug carriers. The bifunctionality of ricinoleic acid allows its polymerization without any modifications. In a previous article, we reported on the copolymerization of PLA with ricinoleic acid, using different polymerization techniques that resulted in pliable, soft, or even liquid polymers, influenced by the polymer structure and ricinoleic acid content (15). In addition, P(LA-RA)s with initial PLA blocks with known length were synthesized. A systematic study on the degradation and drug release of ricinoleic acid-co-lactic acid polyesters is reported.

MATERIALS AND METHODS

Materials

Crude ricinoleic acid was purchased from Acros (85% pure; Geel, Belgium), and L-lactic acid (L-LA), and DL-lactic acid (DL-LA) were purchased from J.T. Baker (Deventer, Netherlands). D-Lactic acid was prepared from the hydrolysis of D-lactide in water; D-lactide was purchased from Purac Biochem (Gorinchem, Netherlands). $CDCl_3$, for nuclear magnetic resonance (NMR), was purchased from Sigma-Aldrich (Rehovot, Israel). All solvents and salts were of analytical grade and were obtained from Aldrich or Biolab (Jerusalem, Israel).

Instrumentation

Infrared (IR) spectra were performed on monomer and polymer samples cast on NaCl plates from CH_2Cl_2 solution on Bruker (Vector 22 System FT-IR). Ultraviolet (UV) spectra were taken on a Kontron Instruments Uvicon model 930 (Msscientific, Berlin, Germany). Thermal analysis was determined on a Mettler TA 4000-DSC differential scanning calorimeter (Mettler-Toledo, Schwerzzenbach, Switzerland), calibrated with Zn and In standards, at a heating rate of 10°C/min under nitrogen atmosphere. Melting temperatures of the copolyesters was determined also by Fisher Scientific melting point apparatus. Molecular weights of the copolyesters were estimated on a gel permeation chromatography (GPC) system consisting of a Waters 1515 Isocratic high-performance liquid chromatography (HPLC) pump, with 2410 refractive index detector (Waters, Milford, MA, USA) and a Rheodyne (Cotati, CA, USA) injection valve with a 20-μL loop. Samples were eluted with chloroform through a linear Styrogel column, 500-Å pore size (Waters), at a flow rate of 1 mL/min. The molecular weights were determined relative to polystyrene standards (Polyscience, Warrington, PA, USA) with a molecular weight range of 500–20,000 using BREEZE 3.20 version (copyright 2000, Waters Corporation computer program). The lactic and ricinoleic acids release was determined by HPLC using C18 reverse-phase column (LichroCart® 250-4, Lichrospher® 100, 5 μm). Lactic acid was eluted with a solution of 0.1% H_3PO_4 in double-distilled water (DDW) at a flow rate of 1 mL/min and UV detection at 210 nm. Ricinoleic acid was eluted with a solution of acetonitrile/0.1% H_3PO_4 in DDW 65:35 v/v at a flow rate of 1.4 mL/min and UV detection at 210 nm. The calibration curves were plot in the range 0.01–0.1 mg/mL (R^2 = 0.9998). The hydrolysis was conducted in 0.1 M phosphate buffer (pH 7.4) at 37°C with a constant shaking of 100 rpm. Triamcinolone and 5FU concentration in solution during drug release were determined by UV detection at 242 nm [calibration curve was plot in the range 0.01–0.05 mg/mL (R^2 = 0.9998)] and 267 nm [calibration curve was plot in the range 0.005–0.05 mg/mL (R^2 = 0.9998)], respectively. ^{1}H-NMR and ^{13}C-NMR spectra (in $CDCl_3$) were recorded on Varian 300- and 500-MHz spectrometers using TMS as internal standard (Varian Inc., Palo Alto, CA, USA). Optical rotations of polymers were determined on an Optical Activity LTD polarimeter (Cambridgeshire, England) using 10-mg/mL polymer in $CHCl_3$ solution. Viscosity of the polymers in dichloromethane was measured in Cannon-Ubbelohde 75-μm dilution viscometer. Afflux times were measured for four concentrations at 25°C; the data were analyzed for viscosity data by standard methods.

Polymer Synthesis

Copolymer Synthesis by ROP

Copolyesters of L-lactide (LA)–ricinoleic acid lactone (RA) with different LA/RA ratios were prepared by ROP as previously described (15). Briefly, toluene solution of LA and RA was dried by evaporating out the toluene over 4 h. Sn(Oct) (60 mg) was added as catalyst to the oily residue, and the mixture was left to react at 135°C. After 4 h, a sample was removed for molecular weight determination; the reaction was stopped after 24 h and the molecular weight was determined.

All polymers were characterized by ^{1}H-NMR, GPC, IR, differential scanning calorimetry (DSC), and specific optical rotation.

^{1}H-NMR (50% L-PLA-RA, δ): 5.45–5.33 (2H, m, C9, C10, –C**H**=C**H**–), 5.19–5.12 (1H, q, C**H**–CH_3, LA), 4.93–4.89 (1H, m, C12 **H**C–O–), 3.66–3.58 (1H, m, –C**H**–OH, RA), 2.28–2.227 (2H, m, C2 –C$\mathbf{H}_2$ and 2H, m, C11 –C$\mathbf{H}_2$), 2.01 (2H, m, C8 –C$\mathbf{H}_2$), 1.68–1.50 (2H, m, C3 –C$\mathbf{H}_2$, 2H, m, C13 –C$\mathbf{H}_2$, and 3H, d, –C**H**3, LA), 1.34–1.29 (16H, m, C4–7 and C14–17), and 0.865 (3H, t, C18 –C$\mathbf{H}_3$).

Copolymer Synthesis by Transesterification and Repolymerization by Polycondensation

Transesterification of PLA with ricinoleic acid was conducted as described elsewhere (15). Briefly, round-bottomed flask was charged with pure ricinoleic acid and PLA (L-PLA: Mn = 41,000; Mw = 91,000) in desired ratios (w/w total amount of both compounds was 10 g) and 100 mL toluene. The ingredients were dried with toluene and in bulk,

and transesterification was proceeded for 12 h at 150°C, followed by GPC and ^{1}H-NMR analysis. The reaction was stopped as soon as the product achieved minimal constant molecular weight. Repolymerization was carried out by thermal polycondensation followed by GPC.

^{1}H-NMR [P(LA-RA) 60:40, δ]: 5.47–5.29 (2H, m, C9–10, –CH=CH–), 5.20–5.00 (1H, q, CH–CH_3, LA), 4.90–4.87 (1H, m, C12 HC–O–), 2.38–2.24 (2H, m, C2 –CH_2 and 2H, m, C11 –CH_2), 1.99 (2H, m, C8 –CH_2), 1.66–1.40 (2H, m, C3 –CH_2, 2H, m, C13 –CH_2, and 3H, d, –CH_3, LA), 1.30–1.24 (16H, m, C4–7 and C14–17), and 0.866 (3H, t, C18 –CH_3).

Copolymer Synthesis by Thermal Polycondensation

Low molecular weight polyesters, PRA, L-, D-, and DL-PLA, P(L-LA:RA), P(D-LA:RA), and P(DL-LA:RA) with different LA/RA (w/w) ratios were prepared by thermal polycondensation as previously described (15). Briefly, round-bottomed flask was charged with pure ricinoleic acid and lyophilized lactic acid in appropriate ratios (total amount of both acids was 20 g) and 150 mL toluene. The acid mixture was dried overnight with refluxing toluene to remove water traces, and then toluene was removed and the temperature was raised gradually to 180°C. The acids were condensed for 3 h, and then the reaction flask was connected to an oil pump where the condensation was continued under a vacuum of 0.3 mm Hg for additional 12 h. Each step was followed by GPC analysis of samples to determine the molecular weight of the forming polymers at each time period. All polymers were characterized by GPC, ^{1}H-NMR, IR, DSC, m.p., Cannon-Ubbelohde 75 dilution viscometer, and specific optical rotation.

^{1}H-NMR [$CDCl_3$, P(LA-RA) 60:40, δ]: 5.45–5.30 (2H, m, C9–10, –CH=CH–), 5.20–5.02 (1H, q, CH–CH_3, LA), 4.94–4.86 (1H, m, C12 HC–O–), 2.38–2.24 (2H, m, C2 –CH_2 and 2H, m, C11 –CH_2), 2.01 (2H, m, C8 –CH_2), 1.68–1.50 (2H, m, C3 –CH_2, 2H, m, C13 –CH_2, and 3H, d, –CH_3, LA), 1.34–1.25 (16H, m, C4–7 and C14–17), and 0.868 (3H, t, C18 –CH_3) ppm.

^{1}H-NMR ($CDCl_3$, 100% PRA, δ): 5.44–5.30 (2H, m, C9–10, –CH=CH–), 4.873 (1H, m, C12 HC–O–), 2.309 (2H, t, C2 –CH_2), 2.194 (2H, t, C11 –CH_2), 2.01 (2H, m, C8 –CH_2), 1.603 (2H, m, C3 –CH_2), 1.446 (2H, m, C13 –CH_2), 1.291 (16H, m, C4–7 and C14–17), and 0.862 (3H, t, C18 –CH_3) ppm.

^{1}H-NMR ($CDCl_3$, PLA, δ): 5.16–5.15 (1H, q, CH–CH_3), 1.58–1.56 (3H, d, –CH_3, LA) ppm.

In Vitro Hydrolytic Degradation of the Polymers

Solid polymers were melted on a Teflon sheet and cast into a form. The hydrolysis of the copolyester was evaluated by placing cubic samples of each solid copolyester (3 × 3 × 3 mm, 70 mg) in 10 mL 0.1 M phosphate buffer pH 7.4 at 37°C with constant shaking (100 rpm). The liquid polymers were injected into the phosphate buffer solution (~70 mg of each polymer) for *in vitro* degradation studies. To avoid saturation of the solution, the phosphate buffer solution was replaced periodically with a fresh buffer solution. At each time point, a polymer sample was taken out of the buffer and vacuum-dried at room temperature overnight. The hydrolysis of the polymer was monitored by weight loss of the sample, change in polymer molecular weight as determined by GPC, and lactic acid and ricinoleic acid release by HPLC. All experiments were carried out in duplicates.

In Vitro Drug Release

Triamcinolone and 5FU (10 wt%) were incorporated in P(L-LA-RA)s and PRA by mixing the drug in the polymer melt and then injecting the viscous melt (~70 mg) into 100-mL phosphate buffer solution (0.1 M, pH 7.4). Drug release studies were conducted in phosphate buffer (0.1 M, pH 7.4) at 37°C with continuous shaking (100 rpm). At each time point, the solution was replaced with a fresh buffer, and drug analysis was performed. Triamcinolone and 5FU concentrations in the solution were determined by UV detection at 242 and 267 nm, respectively, whereas, as reference, the degradation solution of the blank polymer was used. Sink conditions were kept during the release study, and triamcinolone concentration in the releasing medium was not higher than 10% of its maximum solubility in water (solubility is approximately 0.05 mg/mL). All experiments were performed in duplicates.

RESULTS AND DISCUSSION

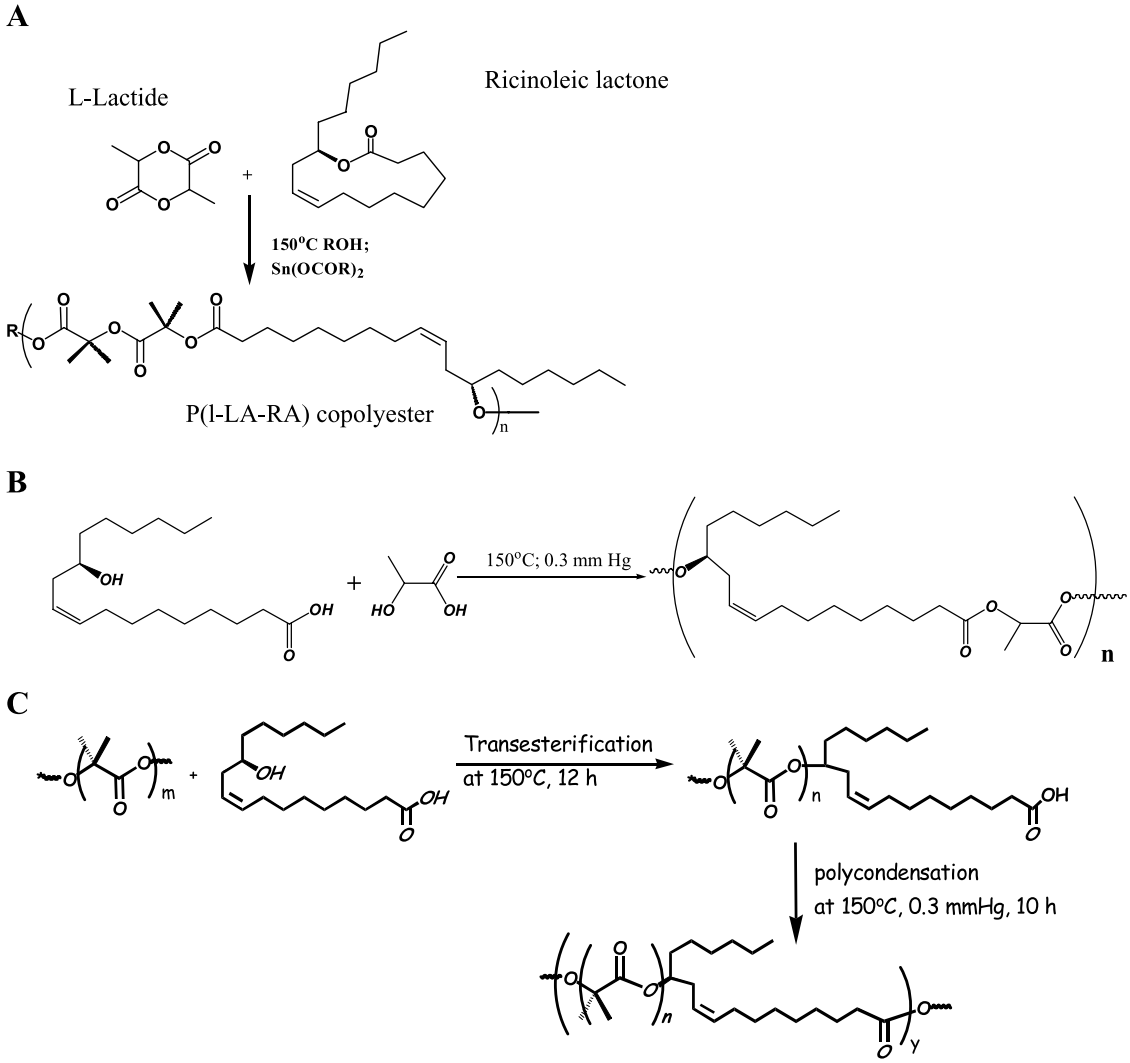
Polymer Synthesis

Polymers were synthesized according to Scheme 1.

Typical physical properties of various copolymers are given in Table I. Polymers with molecular weights in the range of 3000–16,000 were obtained. All polymers possess typical IR absorption at 1748 cm^{-1}, which corresponds to the ester carbonyl stretching bands. ^{1}H NMR spectra of the polymers fit their composition.

According to our previous report (15,17), thermal polycondensation resulted in random P(LA-RA) copolymers, whereas transesterification of high molecular weight PLA with pure ricinoleic acid and repolymerization of those oligomers by condensation resulted in multiblock P(PLA-RA) copolyesters.

^{1}H-NMR spectroscopy analysis coupled with information from DSC allowed determination of the polymer structure. Whereas NMR spectroscopy could identify statistical segments in the polymeric chain, DSC was used to determine the thermal properties and degree of crystallinity. Polymerization of pure RA by thermal polycondensation and transesterification kinetics were confirmed by ^{1}H-NMR (17). ^{1}H on C12 was relocated to lower field as a result of ester bond formation, and double-bond protons were slightly shifted to upper field upon polycondensation polymerization. Polymers prepared by thermal polycondensation are random polymers, whereas polymers prepared by transesterification have a multiblock character (15,17). Thermal analysis by DSC revealed crystalline structure for polyester synthesized by transesterification and ROP. In polyesters synthesized by random condensation, only P(LA-RA) 90:10 w/w contained crystalline domains (15,17). This information is correlated with the ^{1}H-NMR analyses where polymers containing relatively long LA blocks possess crystalline domains. In P(LA-RA)s, only



Scheme 1. Copolyester synthesis by: (A) ring opening polymerization(ROP); (B) random condensation of lactic acid (LA) and ricinoleic acid (RA); (C) transesterification (TRANS) of poly(lactic acid) (PLA) with RA and repolyesterification.

Table I. Chemical and Physical Properties of P(L-LA-RA) Copolyesters

Ricinoleic acid entry (%)[a]	Ring opening polymerization			Condensation			Transesterification		
	Melting temperatures (°C)[b]	Molecular weight[c]		Melting temperatures (°C)[b]	Molecular weight[c]		Melting temperatures (°C)[b]	Molecular weight[c]	
		Mn	Mw		Mn	Mw		Mn	Mw
10	130	14,000	16,200	80	4,100	5,800	147	11,000	14,000
30	112	8,400	11,100	Liquid at room temperature	5,800	7,800	111	5,500	8,100
40	107	10,060	14,000	Liquid at room temperature	4,200	5,300	93	5,000	7,000
50	105	7,300	9,800	Liquid at room temperature	3,500	4,500	Liquid at room temperature	5,600	8,200
100^{α}	–	–	–	Liquid at room temperature	3,600	3,400	–	–	–
0^{β}	150	30,000	11,000	–	–	–	–	–	–

($^{\alpha}$) Poly(ricinoleic acid); ($^{\beta}$) poly(L-lactic acid).
[a] Ricinoleic acid or lactone % according to w/w ratio of the monomers used for copolymerization.
[b] Melting temperature of the copolymers measured by Fisher apparatus.
[c] Molecular weight determined by gel permeation chromatography.

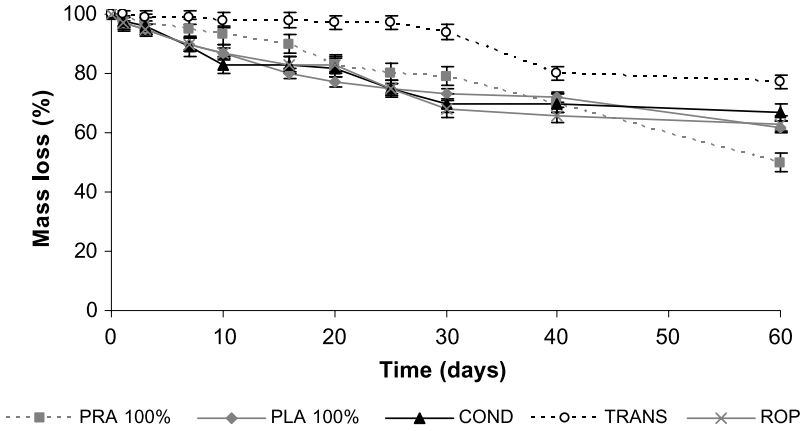


Fig. 1. Hydrolysis of polymers based on lactic acid and ricinoleic acid [P(LA-RA)s] 60:40 w/w monitored by specimen mass loss. The hydrolysis was conducted in 0.1 M phosphate buffer (pH 7.4) at 37°C.

LA blocks are able to crystallize. Ricinoleic acid structure is sterically hindered where RA blocks formed noncrystalline brush-like domains along the polymer chain. P(LA-RA) 8-0:20 prepared by polycondensation of LA and RA does not have LA blocks long enough to form detectable crystalline domains in the polymer. According to the ΔH, we can see that the longer the PLA block in the copolymer, the longer are the crystalline domains (15).

In Vitro Hydrolytic Degradation of Polymers

The hydrolysis of these copolyesters was monitored by weight loss of the specimens, changes in polymer molecular weight, and LA release from the polymer. P(LA-RA)s 60:40 w/w prepared by the three methods (ROP, thermal polycondensation, and transesterification) were compared.

All polymers showed an almost zero-order weight loss, with about 20% loss after 60 days of incubation (Fig. 1). All the polymers lost about 10% of their weight during the first 10 days. During this period, LA monomer was found in minute amounts in the degradation solution (Fig. 2). LA release to the degradation medium corresponds to weight loss of the polymer specimens.

Figure 2 shows that LA release from P(LA-RA), synthesized by condensation, is similar to LA release from pure PLA. L-PLA is a relatively hydrophilic crystalline polymer, whereas P(LA-RA) 60:40 w/w is a relatively hydrophobic noncrystalline polymer. In this case, hydrophobicity compensates for loss of crystallinity resulting in a similar degradation rate. LA release from P(LA-RA)s synthesized by transesterification and by ROP is also similar because of their block-like structure. During the first 25 days, these polymers release up to 5% of their LA content. After 25 days, the series of block-like polymers show a faster release of LA compared to the random P(LA-RA) prepared by polycondensation. These results are probably related to the different arrangement of [RA] and [LA] segments in the polymer. In the case of the block copolymers, there are amorphous domains of hydrophobic RA and hydrophilic domains of LA. In the case of the random copolymer, the segments of RA and LA are too short to create such domains. After 25 days of incubation, water penetrates inside

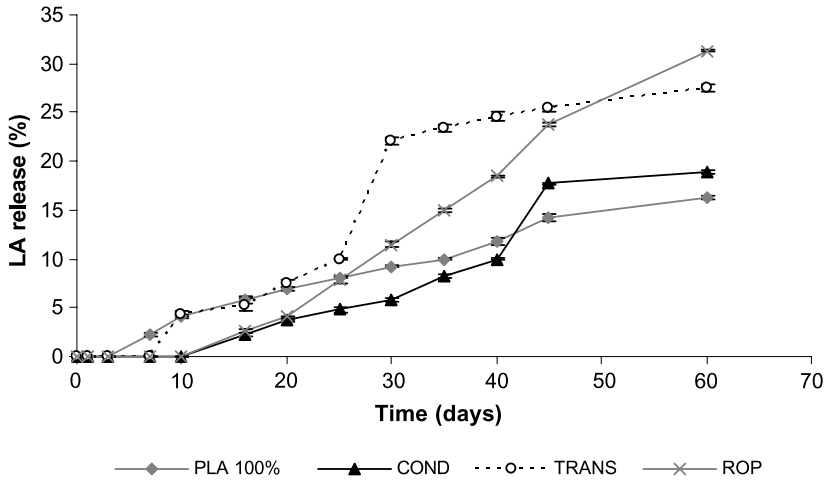


Fig. 2. Hydrolysis of P(LA-RA)s 60:40 w/w monitored by the release of lactic acid (LA) to the buffer medium, as determined by high-performance liquid chromatography.

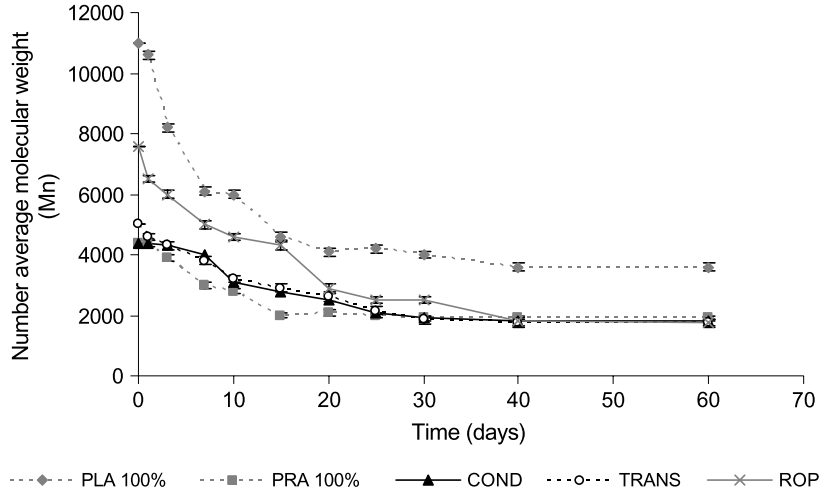


Fig. 3. Hydrolysis of P(LA-RA)s 60:40 w/w monitored by the Mn loss, determined by gel permeation chromatography. The hydrolysis was conducted in 0.1 M phosphate buffer (pH 7.4) at 37°C.

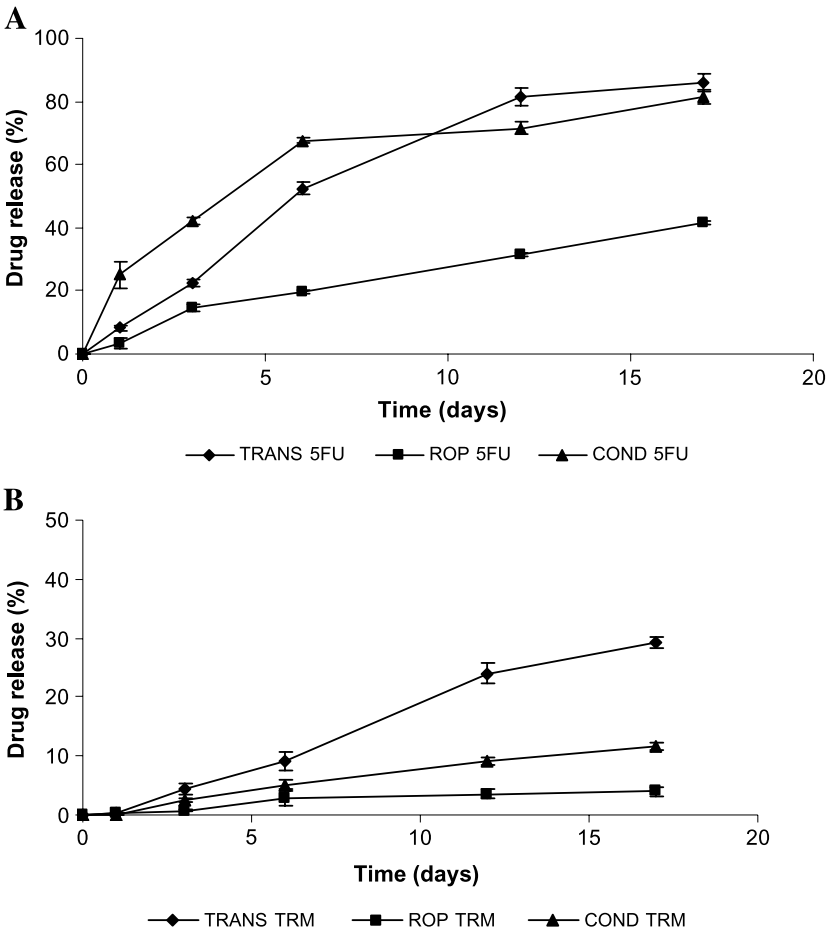


Fig. 4. *In vitro* release of 5FU (A) and triamcinalone (B) from P(LA-RA)s 60:40 prepared by different methods (TRANS—transesterification; COND—condensation; ROP—ring opening polymerization). The triamcinalone and 5FU release was conducted in a 0.1 M phosphate buffer (pH 7.4) at 37°C. The triamcinalone and 5FU content in the releasing medium was determined by ultraviolet detection at 242 and 267 nm, respectively.

the polymeric matrix. In the case of block copolymers, water penetrates into PLA domains and washes out large amounts of LA degradation products. For random copolyesters, only small LA amounts are being gradually washed out; this is because there are no PLA domains, only 1–2 LA units surrounded with hydrophobic RA units.

The number average molecular weight (Mn) loss was monitored by GPC (Fig. 3). Mn decreased to about 2000 Da during 60 days of incubation, regardless of the initial molecular weight and polymer structure. The main decrease in molecular weight was observed during the first 20 days, followed by a slow degradation phase, which kept the Mn at 4000–2000 for another 40 days. Little difference in the molecular weight loss for the different polymers was found.

Throughout the study, the samples of P(L-LA-RA) preserved original shape and did not crumble. During 60 days of the study, only partial polymer decomposition was observed.

In Vitro Drug Release from Polymers

The drug release characteristic from P(LA-RA)s prepared by transesterification was determined using triamcinalone as representative hydrophobic drug (very slightly soluble in water; Martindale, 30th ed.) and 5FU as representative hydrophilic drug (sparingly soluble in water; Martindale, 30th ed.). Triamcinolone is used to reduce the intensity of inflammatory reactions, and 5FU is a potent anticancer drug. The drugs were incorporated into the polymer by melt mixing. Triamcinolone and 5FU were constantly released from the copolymer for over 3 weeks (Fig. 4A, B).

The 5FU release from the polymers was much faster than the release of a slightly water-soluble triamcinolone. The total release of 5FU occurred during 17 days from polymers prepared by transesterification and thermal condensation. Slower release of 5FU was from polymer prepared by ROP (40% in 17 days; Fig. 4A). The same pattern was observed for triamcinolone release. The fastest release of triamcinolone was from the polymer prepared by transesterification—30% of the incorporated drug was released in 17 days—and the slowest release was from the polymer prepared by ROP—only 5% in 17 days (Fig. 4B). The drug release from polyesters depends on various physical and chemical parameters including hydrophobicity of monomers and polymer, crystallinity of polymer, water permeability of the polymer matrix, and the degradation medium and conditions. Polymers prepared by ROP are diblock copolymers and have the most crystalline nature and the highest melting point among the three polymers to be compared. Because of the high crystallinity of the polymer, the water hardly penetrates into the polymer matrix to diffuse the drug out. On the other hand, polymer prepared by transesterification has multiblock structure, lower melting point, and lower degree of crystallinity that allows water to penetrate and diffuse the drug out. The polymer prepared by polycondensation has a random noncrystalline structure. In this case, hydrophobicity compensates for loss of crystallinity resulting in a similar degradation rate, as what happened in the case of lactic acid release. Random occurrence of ricinoleic acid that is hydrophobic may cause water rejection and thus slower release than from the polymer prepared by transesterification.

CONCLUSIONS

Copolymers of LA and RA were synthesized by random condensation of RA and LA or by transesterification and repolymerization to yield solid and liquid polymers. Copolymers prepared by ring opening copolymerization resulted in solid LA-RA copolymer. The copolymers of similar RA-LA composition and molecular weights showed significant differences in thermal properties. Copolymers made by random condensation having more than 15% RA were liquid at room temperature. For copolymers made by transesterification followed by repolymerization by thermal condensation, only copolymer containing 50% ricinoleic acid was liquid at room temperature.

These polymers, particularly the liquid polymers, may be used as sealants and as injectable carriers of drugs.

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