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Polylactic Acid Macromonomer Radical Propagation Kinetics and Degradation Behaviour

Thomas R. Rooney,^a Davide Moscatelli,^b and Robin A. Hutchinson^{*a}

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Poly(lactic acid ethyl ester methacrylate) (PLA_nEMA) macromonomers are synthesized with $n=1, 5, 7,$ and 9 average number of polyester units. While propagation rate coefficients (k_p) determined by pulsed laser polymerization experiments for bulk PLA₁EMA and PLA₅EMA are not significantly different over the 40–100 °C temperature range, they are elevated by 60% compared to methyl methacrylate, indicating that the nature of substituents several units beyond the methacrylic group does not decisively impact bulk k_p measurements. Compared to bulk PLA₅EMA, the apparent k_p in 75 wt% *n*-butanol solution is enhanced due to hydrogen bonding, whereas in 75 wt% dimethylformamide solution it is reduced by 35% because of differences in macromonomer and solvent molar volumes. The PLA₅EMA macromonomers are used to produce nanoparticles (NP) by emulsion radical polymerization that degrade almost four times more slowly than NPs produced from their hydroxyl terminated macromonomer counterpart.

Introduction

Poly(lactic acid) (PLA) is a highly versatile material produced from 100% renewable resources with an auspicious outlook for a variety of commodity applications.¹ Indeed, packaging, disposable bottles, and biomedical applications benefit from one of PLA's most notable features: hydrolysis of the polyester backbone to yield non-toxic degradation products.^{2,3} Production of PLA can be accomplished via the polycondensation of lactic acid; however, difficulties associated with efficient removal of the liberated water limit the molecular weight (MW) that can be achieved by this route.⁴ Thus, most approaches focus on the ring-opening polymerization (ROP) of the cyclic lactide (LA) dimer which allows for better control over PLA's MW characteristics.⁵ In addition, functional ROP initiators can be implemented to impart customized features onto the final polyester material.^{6–8}

When 2-hydroxyethyl methacrylate (HEMA) is used as ROP initiator, the resulting HEMA-PLA_{2n} macromonomers, with average chain length $2n$ defined by the stoichiometric ratio of LA to HEMA, can be further polymerized via "grafting through" radical polymerization (RP) of the vinyl end-group to produce comb-polymers with well-defined polyester grafts affixed to a higher MW acrylic backbone.^{9–11} Such HEMA-PLA_{2n} macromonomers have been employed in radical miniemulsion polymerization,^{12,13} solution polymerization to make hydrogels,¹⁴ and emulsion polymerization to produce

degradable nanoparticles (NP) for drug delivery applications.^{15–17} In the case of NPs, degradation time is controllable by the type and average number n (typically $n = 1–5$) of grafted polyesters, a feature that causes distinct changes in material hydrophobicity which can be exploited for various applications.^{15,18} As bulk erosion can be assumed for PLA hydrolysis of nanoscale materials,¹⁹ degradation of the PLA grafts in NPs produced from macromonomers can be compared to the solution hydrolysis of PLA oligomers which is not only influenced by factors such as temperature and pH,^{20,21} but also chain length due to the difference in reactivity of backbone and terminal esters.²² Terminal ester hydrolysis, via preferential backbiting or chain-end scission mechanisms, is facilitated by the terminal hydroxyl group²³ and was found to be chain-length independent.²⁴ For backbiting (or preferential chain-end scission) to be effective, the terminal hydroxyl groups must be accessible to the aqueous environment;²⁰ in general, the balance of water diffusion and PLA degradation behaviour depends on material dimensions and topology (e.g., surface brushes, bulk, solution) which are governed by the intended application and method of production. Thus, to efficiently produce and to better predict degradation performance of polyester macromonomer based comb-(co)polymer materials, an understanding of the underlying macromonomer RP kinetics is required to track both hydroxyl end-group and macromonomer chain length incorporation behaviours.

To date, few works have addressed the RP kinetics of methacrylate type polyester macromonomers. Although studied under limited conditions, typical methacrylate/methacrylate relative reactivity – i.e., equal addition probabilities – was demonstrated for HEMA-PLA_{2n} and polycaprolactone (PCL) based HEMA-PCL_n macromonomer copolymerizations with methyl methacrylate (MMA),^{25–27} while

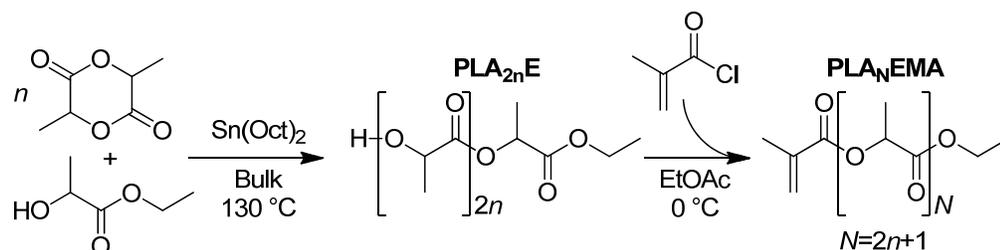
^a Department of Chemical Engineering, Dupuis Hall, Queen's University, Kingston, ON, K7L 3N6, Canada. E-mail: robin.hutchinson@queensu.ca

^b Department of Chemistry, Materials and Chemical Engineering "Giulio Natta", Politecnico di Milano, Via Luigi Mancinelli 7, 20131 Milano, Italy. E-mail: davide.moscatelli@polimi.it

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Scheme 1: Synthetic route for production of PLA_NEMA.

another study detailing the copolymerization of styrene (ST) with polyester methacrylate type macromonomers showed that the relative reactivity depends only on the chemical identity up to several units away from the methacryloyl end-group.²⁸ In terms of propagation rate behaviour, the pulsed laser polymerization coupled with size exclusion chromatography (PLP-SEC) technique is the most accurate and reliable method for determining propagation rate coefficients (k_p), as is described in comprehensive detail by Beuermann and Buback.²⁹ The k_p is calculated according to Eqn. 1 where MW_i is the MW of the i^{th} inflection point of a low-conversion PLP-generated molar mass distribution (MMD), ϕ_{mon} is the volume fraction of monomer in solution, ρ_{mon} is the monomer density, and t_0 is the time between pulses.

$$k_p = \frac{MW_i}{i \cdot \phi_{\text{mon}} \cdot \rho_{\text{mon}} \cdot t_0} \quad (1)$$

The IUPAC *subcommittee on "Modeling of Polymerization Kinetics and Processes"* has established family type behaviour for MMA, ethyl methacrylate (EMA), *n*-butyl methacrylate (BMA), and dodecyl methacrylate (DMA),^{30,31} where an increase in the length of the linear alkyl ester group correlates to an increase in the value of k_p measured for bulk monomer using the PLP-SEC technique; this trend is reported more recently to extend even up to behenyl methacrylate.³² A similar increase in bulk k_p with increasing ester side chain length was reported for polyethylene glycol ethyl ether methacrylate (PEGEEMA, 3 PEG units) compared to EEMA (1 PEG unit),³³ although another study found no additional increase in bulk k_p for polyethylene glycol methyl ether methacrylate (PEGMA, 7-8 PEG units) at similar temperatures.³⁴ For the polyester macromonomer systems of interest in this study, the estimation of k_p could not be completed for hydroxyl-terminated HEMA-PCL₃ because of the poor solubility of the resulting comb-polymer in tetrahydrofuran (THF), the SEC eluent; nonetheless, bulk copolymerizations with up to 50 wt% MMA indicated no significant differences in copolymer propagation rate

coefficient ($k_{p,\text{cop}}$) for HEMA-PCL_n with average chain length $n = 2$ and $n = 3$.²⁷

Since macromonomers are inherently viscous (some even solid at room temperature) their solution propagation behaviour is also of high practical and technical importance. The influences of solvent on propagation kinetics are extensive and can arise from both specific and non-specific interactions between monomer and solvent.³⁵ For example, at a monomer concentration of 0.8 mol·L⁻¹ in *n*-butanol (BuOH), the k_p of BMA is enhanced by as much as 85% because of the well-documented hydrogen bond formation between hydroxyl and methacryloyl carbonyl which reduces the electron density at the double bond, making BMA more reactive towards radical addition.³⁶ On the other hand, differences between the molar volumes of monomer and solvent ($V_{\text{mon}} - V_{\text{sol}}$) can manifest as a competition for positions at the radical chain-end leading to a lower than or greater than analytical local monomer concentration and corresponding increase or decrease in apparent k_p measured by PLP-SEC, respectively.³⁵ Beuermann and Garcia substantiated this concept by establishing a linear relationship between $V_{\text{mon}} - V_{\text{sol}}$ and the ratio of k_p at infinite dilution to bulk k_p (i.e., $k_{p,\infty}/k_{p,\text{bulk}}$) for a variety of monomer/solvent pairs contained within $-100 \text{ cm}^3 \cdot \text{mol}^{-1} < V_{\text{mon}} - V_{\text{sol}} < 150 \text{ cm}^3 \cdot \text{mol}^{-1}$.³⁷ In terms of macromonomers, this relationship was extended to PEGEEMA solution homopolymerizations in toluene ($V_{\text{mon}} - V_{\text{sol}} = 139 \text{ cm}^3 \cdot \text{mol}^{-1}$) and THF ($V_{\text{mon}} - V_{\text{sol}} = 164 \text{ cm}^3 \cdot \text{mol}^{-1}$), for which the apparent k_p at 25 °C in 80 vol% solvent was reduced by 32% and 53% compared to bulk, respectively.³³

In this work, polylactic acid ethyl ester methacrylate (PLA_NEMA, where N average PLA units corresponds to $2n+1$ cyclic LA monomers in the ROP step because the ethyl 2-hydroxypropionate initiator fragment contributes 1 PLA unit to each macromonomer chain), was synthesized according to Scheme 1. As the alkyl end-group of PLA_NEMA ensures the resulting comb-polymer is THF soluble, the determination of macromonomer k_p (an important parameter required to

efficiently produce comb-polymers with tailored properties) is not hindered by solubility limitations, as is the case for hydroxyl-terminated HEMA-PLA_n or HEMA-PLA_{2n} macromonomers. Another benefit of the alkyl end-group is that PLA_nEMA can be copolymerized with HEMA-PLA_{2n} to yield PLA-grafted comb-polymers with tunable hydroxyl group densities (an important design parameter for post-polymerization modifications such as esterification reactions); however, the influence of the ethyl ester end-group on the hydrolytic degradability of PLA must be assessed. Therefore, this work investigates both the production and hydrolysis performance of PLA_nEMA-based comb-polymers. Firstly, PLA_nEMA homopropagation kinetics are studied in BuOH, dimethylformamide (DMF) and xylenes solutions in addition to bulk, to examine the effects of hydrogen bonding and molar volumes on polyester macromonomer k_p . Secondly, PLA_nEMA macromonomers are used to produce NPs by emulsion radical polymerization in order to evaluate the influence of PLA_nEMA's ethyl ester end-group on the rate of NP hydrolytic degradation in comparison to NPs produced from hydroxyl-terminated HEMA-PLA_{2n} macromonomers.

Experimental

Materials

Methyl methacrylate (MMA, 99%), (3S)-cis-3,6-dimethyl-1,4-dioxane-2,5-dione (LA, 98%), ethyl 2-hydroxypropionate (ETL, ≥98%), 2-hydroxyethyl methacrylate (HEMA, 97%), tin(II) 2-ethylhexanoate (Sn(oct)₂, 92.5–100.0%), triethylamine (TEA, ≥99.5%), basic alumina (Brockmann 1), 2,2-dimethoxy-2-phenylacetophenone (DMPA, 99%), ammonium persulfate (APS, >98%), *n*-butanol (BuOH, 99%), and dimethylformamide (DMF, 99.8%) were purchased from Sigma Aldrich and used as received. Tetrahydrofuran (THF, >99%, ACP Chemicals), hexanes (reagent grade, ACP Chemicals), methanol (reagent grade, ACP Chemicals), ethyl acetate (EtOAc, reagent grade, ACP Chemicals), hydroquinone (reagent grade, Fisher Scientific), xylenes (99.9%, Fisher Chemical), dichloromethane (DCM, 99.9%, Fisher Chemical), sodium dodecyl sulfate (SDS, ~99%, MP Biomedicals), chloroform-d (CDCl₃, 99.8% D, Sigma Aldrich), and dimethylsulfoxide-d₆ (DMSO-d₆, 99.9% D, Cambridge Isotope Laboratories) were used as received. Methacryloyl chloride (MACI, 97%, Sigma Aldrich) was distilled immediately before use. All water used in this work was in-house distilled water that was further purified (18.2 MΩ·cm) using a Millipore Synergy water purification system equipped with SynergyPak purification cartridges.

Macromonomer Syntheses

All (macro)monomer and poly(macro)monomer ¹H NMR characterizations were performed on a Bruker Avance instrument operating at 400 MHz using the peak assignments and calculations presented in our previous copolymerization study.²⁸

Alkyl Terminated Monomer: The synthesis of PLA₁EMA was performed as previously reported,²⁸ with the exception that EtOAc was used as the methacrylation solvent instead of THF.

In a sealed 3 neck 100 mL round bottom flask, ETL (4.25 g, 36.0 mmol) was dissolved in 60 mL EtOAc to which 15 mL TEA (108.4 mmol) was added. The solution was cooled to 0 °C using an ice bath, bubbled with nitrogen for 10 min, and then 4.6 mL freshly distilled MACI (47.1 mmol) was fed over 20 min using a glass syringe. The reaction mixture was maintained at 0 °C for 3 hours, filtered to remove the TEA salt, and then passed through a column of basic alumina. Approximately 1 mg of hydroquinone was added to the product solution before the solvent was evaporated *in vacuo* to afford 4.51 g 1-ethoxy-1-oxopropan-2-yl methacrylate or poly(lactic acid ethyl ester (PLA₁EMA) with number average $N = 1$ in 67 % yield.

Alkyl Terminated Macromonomer: The syntheses of PLA_nEMA macromonomers were conducted as previously reported for $N = 5$,²⁸ except with EtOAc used as the methacrylation solvent instead of THF; synthesis characterization for $N = 7$ and $N = 9$ is detailed by Table S1 and SEC oligomeric molar mass distributions are shown in Figure S1. LA (5.27 g, 36.6 mmol) was loaded into a 50 mL sealed round bottom flask, purged with nitrogen, and then heated to 130 °C. A Sn(oct)₂/ETL mixture with molar ratio 1:400 was prepared separately (1:200 for the $N = 9$ synthesis), then 2.17 g of this mixture (corresponding to 18.3 mmol ETL) was added to the LA by syringe and allowed to react for 4 hours at 130 °C to afford poly(lactic acid ethyl ester (PLA_nE) with number average $n = 5.5$ and LA conversion ≈ 94 % (as determined by ¹H NMR).

Next, in a sealed 3 neck 100 mL round bottom flask, PLA_nE (7.44 g, 18.3 mmol -OH) was dissolved in 38 mL EtOAc to which 7 mL TEA (50.6 mmol) was then added. The solution was cooled to 0 °C using an ice bath, bubbled with nitrogen for 10 min, and then 2.3 mL freshly distilled MACI (23.6 mmol) was fed over 20 minutes using a glass syringe. The reaction mixture was maintained at 0 °C for 3 hours, filtered to remove the TEA salt, and then passed through a column of basic alumina. Approximately 1 mg of hydroquinone was added to the product solution before the solvent was evaporated *in vacuo* to afford 6.21 g poly(lactic acid ethyl ester methacrylate (PLA₅EMA) with number average $N = 5.3$ in 77 % yield.

Hydroxyl Terminated Macromonomer: The synthesis of hydroxyl terminated macromonomer HEMA-PLA₅ was achieved by bulk ROP of LA using a previously reported procedure.¹⁷ LA (5.68 g, 39.4 mmol) was loaded into a 50 mL sealed round bottom flask, purged with nitrogen, and then heated to 130 °C. Separately, a Sn(oct)₂/HEMA mixture with molar ratio 1:400 was prepared, then 2.05 g of this mixture (corresponding to 15.8 mmol HEMA) was added to the LA by syringe, and then allowed to react at 130 °C for 2 hours. The LA conversion was ≈ 96% for HEMA-LA₅ with $2n = 5.3$ (as determined by ¹H NMR).

It should be noted that although HEMA-PLA₅ and PLA₅EMA have similar average MW, the former are predominantly even numbered oligomers (i.e., $2n = 2, 4, 6$) while the latter are predominantly odd numbered oligomers (i.e., $N = 3, 5, 7$) because the ETL initiator fragment contributes a single PLA unit to each polyester chain.²⁸

Pulsed Laser Polymerization

Low-conversion MMA, PLA₁EMA, and PLA₅EMA homopolymerizations were conducted using a pulsed laser setup consisting of a Coherent Xantos XS-500 laser operating at the XeF line of 351 nm and capable of producing laser energy of 1–6 mJ per pulse at repetition rates up to 500 Hz. Bulk (macro)monomer as well as (macro)monomer diluted with 75 wt% DMF, xylenes, and BuOH mixtures were prepared with 5 mmol·L⁻¹ DMPA photoinitiator. Approximately 1 mL of the monomer mixture (0.5 g for PLA₁EMA and PLA₅EMA bulk homopolymerizations) was added to a Quartz cuvette of 10 mm pathlength (CV10Q3500S, Thorlabs), heated to reaction temperature using an external circulating oil bath, and exposed to laser energy while the temperature was monitored and controlled to within ± 0.5 °C. Experiments were conducted using laser repetition rates between 5 and 50 Hz (see Table S5–S9 of the Supporting Information for the exact operating conditions employed for each sample).

Following the PLP experiments, with pulsing time controlled to keep macromonomer conversion low, the residual solvent, MMA, or PLA₁EMA was removed under constant air stream. At –20 °C, poly(MMA) and poly(PLA₅EMA) samples were precipitated in methanol while poly(PLA₁EMA) samples were precipitated in hexanes. Samples were centrifuged at 6000 rpm for 10 minutes followed by decantation of the supernatant to collect the homopolymer precipitate, which was then dried under air stream and used to determine sample conversion by gravimetry. Parameters relevant to k_p determination are summarized by Table 1. The densities of MMA, PLA₁EMA, and xylenes were measured at temperatures between 25 and 70 °C using a Paar DMA 48 Density Meter, while the density of highly viscous PLA₅EMA was extrapolated from solution density measurements in xylenes, assuming volume additivity, as shown by Table S2 (and Table S3 for PLA₇EMA).

The oligomeric distributions of macromonomers (Figure S1) as well as molar mass distributions (MMD) of all PLP samples were assessed by size exclusion chromatography (SEC). Since PLA₅EMA is a distribution of macromonomers with an average

of $N = 5.3$ PLA units per chain, ¹H NMR analysis of several PLP-generated low-conversion poly(PLA₅EMA) comb-polymers was employed to confirm preservation of graft density into the comb-polymer (average $N = 5.0$). The SEC setup consists of a Waters 2960 separation module instrument with a Waters 410 differential refractometer (DRI) and a Wyatt Instruments Dawn EOS 690 nm laser photometer multiangle light scattering (LS) detector. Four Styragel columns (HR 0.5, 1, 3, 4) were maintained at 35 °C with distilled THF as eluent at 0.3 mL·min⁻¹. The DRI detector was calibrated using 14 narrow poly(MMA) standards (302–853,000 Da) and the LS detector was calibrated by toluene as recommended by the manufacturer. The LS output was interpreted using differential refractive index (dn/dc) measured for poly(PLA₁EMA) and poly(PLA₅EMA) homopolymers in THF at 35 °C by a Wyatt Optilab DSP refractometer at 690 nm calibrated with sodium chloride. Six homopolymer samples of 1–20 mg·mL⁻¹ were prepared in THF and injected sequentially to construct a curve with slope dn/dc , as summarized by Table 1. In addition, the dn/dc of PLA₅EMA macromonomer was measured as 0.040 mL·g⁻¹, while the dn/dc for comb-polymers with average graft lengths $N=7$ and $N=9$ plateaued at a value of 0.051 mL·g⁻¹, confirming that dn/dc becomes independent of the acrylic backbone length as well as the length of the polyester grafts.

SEC of low conversion polymers produced by PLP was also performed using a Viscotek 270 max separation module with a RI, viscosity (IV), and LS (low and LALS and right angle RALS) triple detector setup. A set of two porous PolyAnalytik columns with an exclusion limit molecular weight of 20·10⁶ g·mol⁻¹ was used in series at 40 °C with distilled THF as eluent at a flow rate of 1 mL·min⁻¹. The Mark-Houwink (MH) parameters for poly(PLA₁EMA) and poly(PLA₅EMA) homopolymers in Table 1 were estimated as an average of the output from the IV and LS detectors (using dn/dc summarized by Table 1) generated by several independent samples. The IV vs MW data for poly(PLA₁EMA) and poly(PLA₅EMA) are included as Figure S2 and S3 with global fits presented in Figure S4.

Table 1: Parameters for calculation of k_p from SEC analysis of PLP-generated samples of PLA_nEMA.

	ρ (g·mL ⁻¹)	$[M]$ at 25 °C (mol·L ⁻¹)	dn/dc (mL·g ⁻¹)	Mark-Houwink parameters	
				K (10 ⁻⁵ dL·g ⁻¹)	a
MMA	0.9671–0.001117· $T/^\circ\text{C}$	9.39	0.089 ³⁸	9.44	0.719 ³⁹
PLA ₁ EMA	1.0478–0.001048· $T/^\circ\text{C}$	5.49	0.069	24.4	0.581
PLA ₅ EMA	1.1892–0.000956· $T/^\circ\text{C}^a$	2.46	0.055	7.52	0.647
Xylenes	0.8833–0.000876· $T/^\circ\text{C}$	-	-	-	-
DMF ⁴⁰	0.9686–0.000958· $T/^\circ\text{C}^b$	-	-	-	-
BuOH ⁴¹	0.8267–0.000809· $T/^\circ\text{C}^b$	-	-	-	-

^a Pure species density extrapolated from xylenes solution assuming volume additivity ^b Independent regression of literature data.

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NP Synthesis and Degradation Study

NP synthesis was carried out following a previously reported procedure with minor modification.¹⁷ In a 50 mL 3 neck round bottom flask equipped with condenser, 0.2 g SDS surfactant was dissolved in 18 mL deionized water, heated to 70 °C, and further purged with nitrogen for 10 min. About 16 mg APS was dissolved in 2 mL deionized water and added to the purged solution. One gram of macromonomer was dissolved in one gram of DCM and then the mixture was fed over one hour at constant injection rate using syringe pump (PLA₁EMA was fed directly without DCM) under constant flow of nitrogen. The reaction was allowed to proceed for one additional hour (two additional hours for PLA₅EMA macromonomer systems). No coagulum was formed during the emulsion polymerization of PLA₁EMA; however, a coagulum less than 8 wt% (relative to macromonomer fed) was formed for the macromonomer systems, a result consistent with HEMA-PLA₅ NP synthesis reported elsewhere.¹⁷ While feeding the macromonomer over a one hour period gives starved conditions for HEMA-PLA₅ macromonomer, droplets were observed throughout the feeding period for the PLA₅EMA homopolymer and copolymer systems, an observation indicative of the increased hydrophobicity of PLA_NEMA in comparison to HEMA-PLA₅ macromonomers. The conversion of all systems was greater than 99% as estimated by concentrating 1 mL of latex under constant air stream overnight and dissolving the solids in DMSO-d₆ for ¹H NMR characterization.

The particle size distributions (PSD) for all four NP suspensions are presented in Figures S7-S10 where each PLA_NEMA (macro)monomer system exhibited a secondary peak near 4000 nm which continued to appear even after passing the latex multiple times through a 0.2 μm filter. Although less than 1% residual macromonomer was detected by ¹H NMR analysis of the final dried PLA₅EMA latex, longer reaction times as well as additional initiator and MMA shots at the end of the reaction were unsuccessful in removing the secondary peak. Despite its incomplete characterization or removal, this secondary peak accounts for less than 0.1 vol% of the PLA_NEMA NP systems, and therefore no further treatment was implemented. An accelerated degradation study was performed by maintaining NP latexes at 50 °C in an external water bath and periodically removing them for characterization, following procedures used previously.⁴² The solution pH was measured using a Mettler Toledo SevenExcellence pH meter, while NP size and polydispersity indices (PDI) were determined with a Malvern Zetasizer Nano ZS (size range 0.3 nm –10 μm) at 25 °C with backscattering optics (173°), using a 4 mW He-Ne (633 nm) laser. All samples were measured in DTS0012 disposable

cuvettes. The reported sizes represent an intensity average of at least 30 scans.

Results and Discussion

Bulk Homopropagation Kinetics

PLP experiments were performed for bulk homopolymerizations of MMA (equivalent to PLA₀EMA), PLA₁EMA, and PLA₅EMA over a temperature range of 40–100 °C, with specific conditions summarized by Tables S5, S6, and S8. As a highly viscous liquid, the PLA₅EMA macromonomer is characterized by the low-termination limit of the PLP-SEC technique;^{43,44} therefore, to maximize the success of bulk PLA₅EMA PLP experiments, relatively low pulse repetition rates (10–33 Hz) were employed^{43,44} and the total number of pulses was limited to 100.⁴⁵ In conjunction with Tables S6 and S8, the MMDs and corresponding first derivative plots in Figure 1 demonstrate that bulk PLA_NEMA (both $N = 1$ and $N = 5$) homopolymerizations fulfil the PLP-SEC consistency criteria: at least two inflection points separated by a MW factor of 2 as well as good agreement between k_p estimations made from a minimum of two different pulse repetition rates under otherwise identical conditions.

As shown by the poly(PLA₅EMA) MMDs interpreted by universal calibration, the consequence of PLP experiments with lower pulse repetition rates is that higher MW polymer is produced which may exceed the calibration range of the SEC instrument; fortunately, the inflection point positions for all poly(PLA₅EMA) samples were well within the polyMMA calibration range such that k_p determination was not impeded. Universal calibration is applied throughout this work using MH parameters (Table 1) for poly(PLA₁EMA) and poly(PLA₅EMA) estimated by the Viscotek SEC (see Figures S2 and S3, respectively) over a MW range of approximately 25,000–160,000 g·mol⁻¹ and 126,000–800,000 g·mol⁻¹, respectively. The intrinsic viscosity of the comb-like polymers at identical MW decreases as the graft length is increased from $N = 0$ (PMMA), to $N = 1$, and to $N = 5$ (Figure S4), following the trends seen for calibrations established for polyMMA to polyDMA.⁴⁶ Despite being estimated by calibrations established over a limited MW range, the k_p values for poly(PLA₁EMA) and poly(PLA₅EMA) based on the determined MH parameters are corroborated by the reasonable agreement (within 15%; see Tables S6-S9) with those estimated from light scattering.

In Figure 2, the k_p measured for bulk PLA₁EMA, and PLA₅EMA homopolymerizations over the temperature range of 40–100 °C are compared to values measured for bulk MMA, which are within 10% of the IUPAC benchmark values.³⁰

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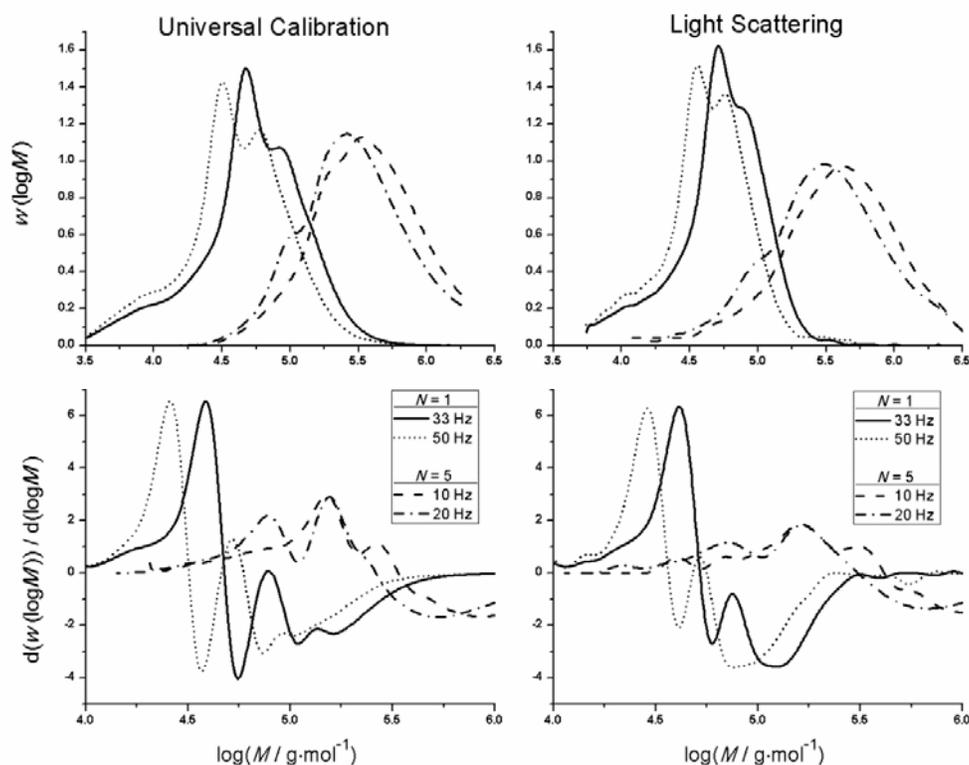


Figure 1: RI (left; interpreted by universal calibration) and LS (right) measures of MMDs (top) and corresponding first derivative plots (bottom) for polymer produced by PLP homopolymerization experiments of bulk PLA₁EMA ($N=1$) and PLA₅EMA ($N=5$) at 60 °C with 5 mmol·L⁻¹ DMPA, at pulse repetition rates as indicated in the legends.

Following family type behaviour,³¹ the k_p for an alkyl ester methacrylate with linear ester side chain length of 5 atoms (e.g., PLA₁EMA), is expected to be 20% greater than $k_{p,MMA}$ at 50 °C.³² However, the data in Figure 2 show that the k_p for PLA₁EMA is augmented by 60% compared to $k_{p,MMA}$ at 50 °C, with the difference maintained over the complete range of temperatures studied. The structure of PLA₁EMA is unique in that it comprises both branched methyl groups as well as polar ester functionalities in its ester side chain. A combination of these features is thought to contribute to the comparatively elevated k_p estimate for PLA₁EMA at 50 °C of 952 L·mol⁻¹·s⁻¹, which is in a similar range as other diverse non-hydroxylated and non-linear heteroatom-containing methacrylates.⁴⁷⁻⁵¹ In particular, similar values were established for four bulky tertiary amine substituted ethylmethacrylates,⁴⁸ with the k_p of 2-(N,N -

dimethylamino)ethyl methacrylate (DMAEMA) slightly higher, presumably related to its less encumbered tertiary amine, and the k_p for 3-(N,N -dimethylamino)propyl methacrylate (DMPMAE) clearly below the proposed family behaviour due to the additional methylene of its propyl spacer. Thus, an interpretation of bulk PLA₁EMA k_p behaviour is likely rooted in the proximity of its polar and steric substituents to the methacrylic group.

In the case of the PLA₅EMA macromonomer, inspection of Figure 2 reveals that the addition of 4 more PLA units into the ester side chain does not significantly alter its bulk k_p from that of PLA₁EMA, certainly not to the extent that the bulk k_p was increased from MMA ($N = 0$) to PLA₁EMA. Since the bulk k_p Arrhenius estimates for PLA₁EMA and PLA₅EMA in Table 2 encompass values typical of the alkyl ester methacrylate

family,³⁰⁻³¹ and the $N = 1$ and $N = 5$ bulk k_p data are reasonably well represented by fitting a pre-exponential using the bulk MMA IUPAC benchmarked activation energy (E_A) for k_p of 22.36 $\text{kJ}\cdot\text{mol}^{-1}$ (Figure S5), a combined Arrhenius fit is justified. Thus, the chemical features of the isobutyrate bridge adjacent to the methacrylic group must be solely responsible for the elevated PLA_1EMA k_p measurements in bulk. (As stated previously, ^1H NMR analysis of the low-conversion PLP-generated polymers showed that the average N of the PLA_5EMA macromonomer is preserved during the “grafting through” polymerization.) In other words, the presence of polar or steric groups further along the ester side chain does not decisively impact the bulk k_p of PLA_NEMA systems. In support of this claim, we found that polyester type, length, and end-group functionality did not contribute to the relative reactivity of various methacrylate macromonomers and ST copolymerization systems,²⁸ and other work showed that the influence of the N,N -dimethylamino substituent on bulk k_p is diluted from DMAEMA to DMAPMAE.⁴⁸ Furthermore, while Siegmann et al. measured a 50% increase in bulk k_p for PEGEEMA (3 PEG units) compared to EEMA (1 PEG unit) at 25 °C,³³ Smolne et al. found no further increase in the bulk k_p of PEGMA (7-8 PEG units) compared to that reported for PEGEEMA.³⁴ Interestingly, the values at which the PEGylated methacrylates appear to plateau (707 and 1954 $\text{L}\cdot\text{mol}^{-1}\cdot\text{s}^{-1}$ at 40 and 80 °C, respectively) are close to the values measured for PLA_1EMA (780 and 1978 $\text{L}\cdot\text{mol}^{-1}\cdot\text{s}^{-1}$ at 40 and 80 °C, respectively). Finally, we recall that the pre-exponential for k_p is largely governed by the degree to which the internal rotations of the transition state (TS) for propagation are hindered,⁵² and that Buback has explained the trend of increasing bulk k_p from MMA to DMA in terms of the longer aliphatic ester side chain which can better shield the dipolar interactions between methacrylic esters, causing less friction in the TS.⁵³ As the addition of 4 more “frictional” dipolar esters in the ester side chain did not cause a significant change in bulk k_p for PLA_NEMA , it seems that the nature of the substituents several units beyond the methacrylic ester does not decisively influence k_p .

Table 2: Arrhenius parameters estimated for bulk PLA_NEMA (macro)monomers with error margins for the 95% confidence intervals.

	$k_p^{70^\circ\text{C}}$ ($\text{L}\cdot\text{mol}^{-1}\cdot\text{s}^{-1}$)	E_A ($\text{kJ}\cdot\text{mol}^{-1}$)	\pm	A ($\text{L}\cdot\text{mol}^{-1}\cdot\text{s}^{-1}$)	\pm
MMA $N=0$	979	22.1	2.2	2.3×10^6	2.6×10^6 1.2×10^6
PLA_1EMA $N=1$	1744	21.6	1.6	3.1×10^6	2.3×10^6 1.3×10^6
PLA_5EMA $N=5$	1764	19.9	1.2	1.8×10^6	9.8×10^5 6.4×10^5
Combined $N=1,5$	-	21.1	1.3	2.7×10^6	1.5×10^6 9.8×10^5

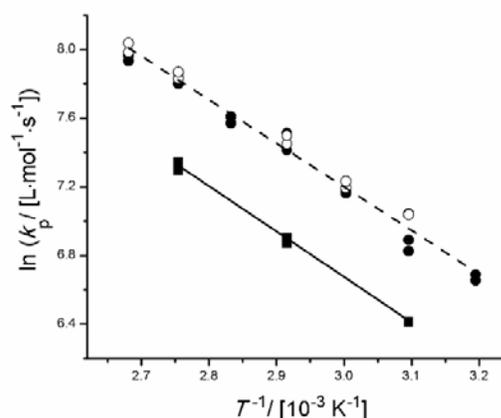


Figure 2: Arrhenius plot for k_p determined from bulk PLP experiments of MMA (■), PLA_1EMA (●), and PLA_5EMA (○) using universal calibration to interpret SEC output. Best fit lines for MMA (solid) and the combined $N = 1$ and $N = 5$ data sets (dashed) are provided.

Solution Homopropagation Kinetics

In order to investigate the influence of hydrogen bonding and (macro)monomer molar volume on PLA_NEMA homopropagation kinetics, the PLP-SEC study was extended to MMA, PLA_1EMA , and PLA_5EMA solution homopolymerizations in 75 wt% BuOH, DMF, and xylenes with conditions summarized by Tables S5, S7, and S9; additional experiments with MMA and PLA_1EMA were conducted at an equimolar ratio of BuOH to monomer. The resulting k_p estimates at 70 °C and 90 °C are presented in Figure 3 and Figure S6, respectively, to compare specific solvent influences on each system ($N = 0, 1$, and 5). However, due to the marked decrease in monomer molar concentration from $N = 0$ to $N = 5$ at constant solvent weight fraction (see bulk monomer concentrations in Table 1), direct comparison of solution k_p estimates from different N are not necessarily meaningful. In the case of MMA ($N = 0$), for which differences in monomer and solvent molar volumes ($V_{\text{mon}} - V_{\text{sol}}$) are not very large, there is no significant difference between the solution k_p measured in xylenes compared to bulk, the k_p is slightly elevated in DMF, and in BuOH the k_p of MMA is clearly enhanced because of the well-documented hydrogen bond formation between hydroxyl and methacryloyl carbonyl which reduces the electron density at the double bond making MMA more reactive towards radical addition.³⁵

The situation is different for the PLA_1EMA and PLA_5EMA systems, for which a reduction in k_p compared to bulk is measured (modest in xylenes and pronounced in DMF), even though no specific interaction between PLA_NEMA and either solvent is expected. This same trend in apparent k_p was reported in the PLP-SEC study of PEGEEMA in toluene ($V_{\text{mon}} - V_{\text{sol}} = 139 \text{ cm}^3\cdot\text{mol}^{-1}$) and THF ($V_{\text{mon}} - V_{\text{sol}} = 164 \text{ cm}^3\cdot\text{mol}^{-1}$),³³ solvents similar to xylenes and DMF (in terms of relative polarities and molar volumes), respectively, a result that was reconciled in terms of the previously established linear relationship between $V_{\text{mon}} - V_{\text{sol}}$ and $k_{p,\infty}/k_{p,\text{bulk}}$.³⁷ Although this correlation formally predicts that systems with very large $V_{\text{mon}} - V_{\text{sol}}$ (i.e., > 226

$\text{cm}^3\cdot\text{mol}^{-1}$) yield negative ratios of $k_{p,\infty}/k_{p,\text{bulk}}$, the logic can still be applied to explain the PLA_NEMA results: at 70 °C the molar volumes of PLA_1EMA ($191 \text{ cm}^3\cdot\text{mol}^{-1}$) and PLA_5EMA (average of $422 \text{ cm}^3\cdot\text{mol}^{-1}$) are larger than those of DMF ($81 \text{ cm}^3\cdot\text{mol}^{-1}$) and xylenes ($129 \text{ cm}^3\cdot\text{mol}^{-1}$) such that solvent molecules outcompete (macro)monomers for positions at the reaction site, leading to a lower than analytical local (macro)monomer concentration and corresponding reduction in apparent k_p measured by PLP-SEC. The fact that there is only a small difference in the apparent k_p (measured as 75 wt% solvent) for $0.50 \text{ mol}\cdot\text{L}^{-1}$ PLA_5EMA in DMF ($V_{\text{mon}}-V_{\text{sol}} = 341 \text{ cm}^3\cdot\text{mol}^{-1}$) and $1.23 \text{ mol}\cdot\text{L}^{-1}$ PLA_1EMA in DMF ($V_{\text{mon}}-V_{\text{sol}} = 110 \text{ cm}^3\cdot\text{mol}^{-1}$) at 70 and 90 °C (Figure 3 and Figure S6, respectively), indicates that there should exist a minimum $k_{p,\infty}/k_{p,\text{bulk}}$ which cannot be exceeded by further increases in $V_{\text{mon}}-V_{\text{sol}}$ of monomer/solvent pairings. The physical interpretation is that the volume around the chain-end radical which can be preferentially occupied by solvent molecules is finite. This reasoning is consistent with Buback's interpretation of linear alkyl acrylate homopropagation trends in toluene: a larger molar volume of the solvent (compared to monomer) allows for higher mobility of the TS structure and thus a higher k_p results from the lower entropic penalty.^{53,54}

Turning now to the PLA_NEMA homopolymerization experiments in 75 wt% BuOH, the k_p values in Figure 3 are increased compared to bulk PLA_5EMA and slightly decreased compared to bulk for the PLA_1EMA system. Since the effect of hydrogen bonding on the k_p of a generic methacrylate (xMA) is known to depend on the relative concentrations of alcohol and xMA,^{36,55} additional experiments were performed so that the k_p data estimated for MMA, PLA_1EMA , and PLA_5EMA in BuOH could be examined as a function of δ (molar ratio of alcohols to methacryloyl carbonyls; Eqn. 2) for solution homopolymerizations, as summarized at 70 °C in Table 3 and at 90 °C in Table S4, respectively.

$$\delta = \frac{[\text{BuOH}]}{[\text{xMA}]} \quad (2)$$

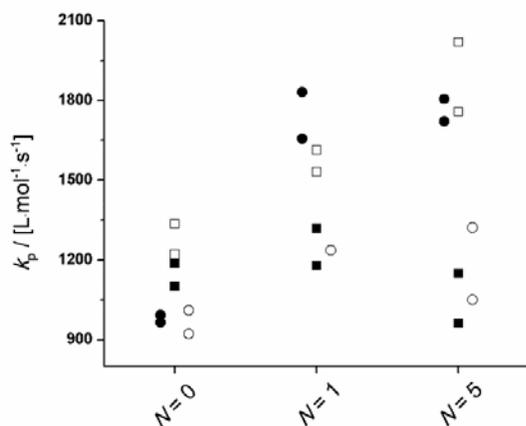


Figure 3: Plots for k_p of MMA, PLA_1EMA , and PLA_5EMA determined by universal calibration in bulk (●), 75 wt% xylenes (○), 75 wt% DMF (■), and 75 wt% BuOH (□) solutions at 70 °C with $5 \text{ mmol}\cdot\text{L}^{-1}$ DMPA.

As δ increases from 1.0 to 4.1, the ratio of $k_{p,\text{BuOH}}/k_{p,\text{bulk}}$ for MMA increases from 1.20 to 1.31 at 70 °C, in reasonable agreement with a 10% linear increase in k_p per δ up to $\delta = 6.1$ reported for MMA in benzyl alcohol at 30 °C.⁵⁵ A similar increase in k_p was observed at even greater dilutions (up to $\delta = 11.3$) for BMA in BuOH at 70 °C,³⁶ as also summarized by Table 3. In contrast, the ratio of $k_{p,\text{BuOH}}$ to $k_{p,\text{bulk}}$ decreases for PLA_1EMA , as the comparison is confounded by the effect of large $V_{\text{mon}}-V_{\text{sol}}$ on apparent k_p . Thus, it is more meaningful to compare the k_p in BuOH ($96 \text{ cm}^3\cdot\text{mol}^{-1}$) against the k_p measured in DMF ($81 \text{ cm}^3\cdot\text{mol}^{-1}$) because the corresponding $V_{\text{mon}}-V_{\text{sol}}$ for these solvents in PLA_NEMA systems are similar.

When the $k_{p,\text{BuOH}}/k_{p,\text{DMF}}$ ratios are computed, it is clear that the hydrogen bonding provided by BuOH also leads to augmented k_p for PLA_NEMA systems. The extent of the increase is quite significant, although the corresponding values of δ are also much higher (see Table 3), and the systems are complicated by the extra linkages in the methacrylate side chain: while for MMA and BMA, there is only a single methacryloyl carbonyl with which the alcohol's hydroxyl can interact, in PLA_NEMA systems there are $N+1$ carbonyls which can accept hydrogen bonding. As the measured increases in $k_{p,\text{BuOH}}/k_{p,\text{DMF}}$ for the limited $N = 1$ and $N = 5$ data sets can be reasonably accounted for by the proportionalities with δ estimated for BMA and MMA, it is unlikely that hydrogen bonding interactions with the N polyesters in the methacrylic ester side chain have any significant intrinsic kinetic effect on PLA_NEMA homopropagation, in agreement with our conclusion that the substituents several units beyond the methacrylic ester do not decisively influence the bulk k_p measurements for PLA_NEMA . Nevertheless, the extent to which system specific enhanced k_p via hydrogen bonding between hydroxyl and methacryloyl carbonyl is diluted by the repeating esters in the PLA_NEMA side chain should be further investigated by controlling for δ as a function of the $N+1$ carbonyls at various temperatures. Furthermore, since $V_{\text{mon}}-V_{\text{sol}}$ is an important parameter for PLA_NEMA homopolymerizations, future work should include the influence of macromonomer molar volume on apparent reactivity ratios as well as $k_{p,\text{cop}}$ measurements for PLA_NEMA bulk copolymerizations with smaller molar volume comonomers such as MMA.

Table 3: Ratio of k_p determined in BuOH to bulk or DMF at 70 °C with $5 \text{ mmol}\cdot\text{L}^{-1}$ DMPA at various δ for each (macro)monomer.

Monomer	δ	$\frac{k_{p,\text{BuOH}}}{k_{p,\text{bulk}}}$	$\frac{k_{p,\text{BuOH}}}{k_{p,\text{DMF}}}$
MMA	1.0	1.20	-
	4.1	1.31	1.12
	5.3	1.33	-
BMA ³⁶	11.3	1.47	-
	1.0	0.81	-
PLA_1EMA	7.5	0.90	1.26
PLA_5EMA	19.1	1.07	1.79

Nanoparticle Degradation Study

As previously mentioned, the ability to tune the degradation time of NPs produced from polyester macromonomers by specifying the average number and type of polyester units in the ROP step of the macromonomer synthesis has been demonstrated.^{15,18} However, whether the rate of NP degradation can be further controlled by end-group design needs to be evaluated, since the terminal hydroxyl of HEMA-PLA₅ and the terminal ethyl ester of PLA₅EMA distinguish macromonomers with the same average chain lengths by different hydrophobicities. To investigate the effect of PLA_NEMA's alkyl end-group on degradation, 5 wt% NP suspensions were prepared by semi-batch radical emulsion polymerizations at 70 °C with 1% SDS as surfactant using the following four (macro)monomer systems: PLA₁EMA, PLA₅EMA, HEMA-PLA₅, and a comonomer mixture of 50 wt% PLA₅EMA and 50 wt% HEMA-PLA₅, with PSDs presented in Figures S7, S8, S9, and S10, respectively.

An accelerated degradation test for each NP suspension was performed over several weeks at 50 °C with the progress of the degradative swelling mechanism monitored by periodically measuring the increase in average particle size, as shown in Figure 4; as degradation proceeds, the NPs become more hydrophilic leading to an increase in water absorption and apparent particle size at constant polydispersity index (PDI, pertaining to particle size), thus confirming that the increase in size is not due to coagulation.^{15,42} The corresponding PDI values from this study summarized by Figure S11 are near constant with time, only increasing slightly at the final stages of degradation to suggest the formation of a small quantity of aggregates late in the process. The important feature of the data in Figure 4 is the time at which the particle size begins to rapidly increase, as this indicates that the NPs have almost degraded to the final water-soluble material. For example, the rapidly increasing size of the HEMA-PLA₅ latex from days 7–9 leads to the complete hydrolysis of the PLA grafts by day 10 to yield a poly(HEMA) backbone (which is observed as a swollen polymer at room temperature that can be dissolved upon dilution), in close agreement with an 8 day degradation time measured for very similar HEMA-PLA₄ NPs.¹⁸ On the other hand, after 40 days the PLA₅EMA homopolymer latex has finally degraded while the PLA₁EMA latex is still observable.

The continual increase in NP sizes over 40 days indicates that hydrolytic degradation of the NPs produced from the hydrophobic alkyl-terminated macromonomer occurs at a much slower rate because of the added hydrophobicity of PLA_NEMA's ethyl ester end-group. For comparison, NPs produced from the PCL (more hydrophobic than PLA) based HEMA-PCL₃ macromonomer, with similar average MW as both PLA₅EMA and HEMA-PLA₅, were completely degraded after only 20 days under the same conditions.⁴² Furthermore, PLA_NEMA's lack of terminal hydroxyl precludes preferential chain-end scission hydrolysis, where protection of oligomeric PLA hydroxyl end-groups (through esterification or acetylation) has been shown to significantly reduce the rate of hydrolysis under both

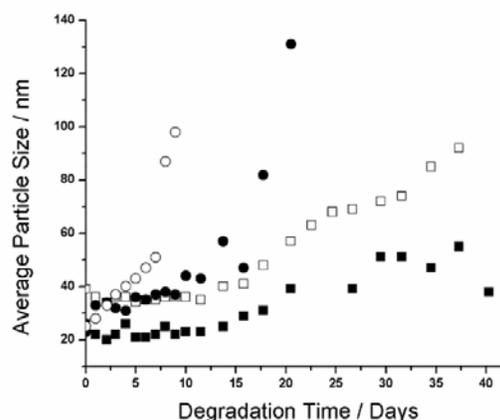


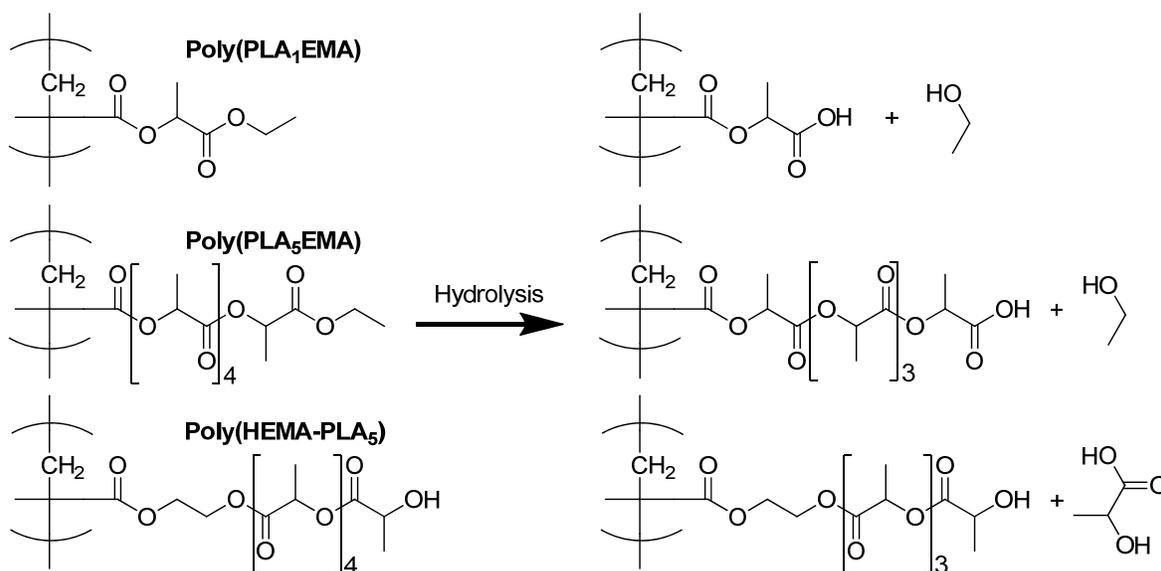
Figure 4: Intensity average size measurements at 25 °C for NPs produced from PLA₁EMA (■), PLA₅EMA (□), an equal mass copolymer of PLA₅EMA and HEMA-PLA₅ (●), and HEMA-PLA₅ (○) throughout the accelerated degradation study performed at 50 °C.

acidic and basic conditions.^{23,24} However, as illustrated by Scheme 2, any hydrolysis event in a PLA_NEMA chain yields a carboxyl-terminated graft. Since Codari et al. showed that preferential chain-end hydrolysis of bifunctional hydroxyl- and carboxyl- terminated oligomeric PLA can be ascribed to the increased end-group hydrophilicities,²² the slow hydrolysis of PLA_NEMA NPs must be due to the initial ethyl ester protection of PLA end-groups. Consideration must also be given to the pH of the NP environment because the terminal units of the hydrolysed PLA_NEMA grafts could exist as carboxylic acids or carboxylates which would certainly influence their degradability. Nevertheless, the delayed degradation (in comparison to HEMA-PLA₅ NPs) afforded by the initial ethyl ester protection should remain effective regardless of the pH.

In the case of PLA₁EMA NPs, the reduction in pH after 35 days of accelerated degradation (Table S10) indicates hydrolysis of the terminal ethyl ester to release ethanol; however, minimal increases in PLA₁EMA NP size measurements to 40 days suggests that hydrolysis of the single grafted PLA unit to yield a PMAA backbone is unfavourable such that complete degradation of PLA₁EMA homopolymer will not occur over a timescale typically associated with PLA based materials. As seen in Figure 4, the PLA₅EMA homopolymer latex degrades more quickly than the PLA₁EMA latex; although it seems counterintuitive that complete degradation of the PLA₅EMA homopolymer was observed before that of the PLA₁EMA homopolymer, the latter has roughly 2.5 times more esters attached to the methacrylic backbone per unit mass due to the macromonomer's larger MW. In support of the notion that these units are more difficult to hydrolyse than typical ester linkages in the polyester backbone, the release of ethylene glycol was not detected at the end of the polyester graft degradation for previous HEMA-PLA₃ NP degradation studies, indicating that the poly(HEMA) backbone did not degrade to PMAA.¹⁷

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Scheme 2: Proposed degradation products after one hydrolysis event at the terminal grafted unit of poly(PLA₁EMA), poly(PLA₅EMA), and poly(HEMA-PLA₅) comb-polymers.

Under unbuffered degradation conditions (i.e., acidic), the choice of macromonomer end-group affords a considerable range of NP degradation times from 10 to 40 days for HEMA-PLA₅ and PLA₅EMA homopolymer latexes, respectively; when 50 wt% PLA₅EMA is added to the HEMA-PLA₅ macromonomer recipe, an intermediate NP degradation time of 23 days is achieved (Figure 4). This finding verifies the successful copolymerization of the two macromonomers, despite their differences in water solubility, and also demonstrates that end-group choice can be used to tune NP degradation time in acidic environments. Depending on the intended application's pH and functional timescale, formulations could benefit by using PLA_NEMA as a comonomer to modify system hydrophobicity and degradation time while still maintaining the properties of aPLA based system. In addition, PLA_NEMA can be used to improve selectivity of post-polymerization esterification reactions through use as a comonomer spacer with hydroxyl or carboxyl functionalized monomers.

Conclusions

Poly(lactic acid based methacrylate (macro)monomers (PLA_NEMA) with $N = 1$ and $N = 5$ average polyester units per chain were synthesized and their homopropagation kinetics studied in bulk and solution using the PLP-SEC technique. Reasonable agreement (within 15%) was obtained for k_p

estimates from low-conversion PLP samples analysed by SEC coupled with light scattering and universal calibration, validating the dn/dc and Mark-Houwink parameters measured in this work for both $N = 1$ and $N = 5$ comb-polymers. No significant difference between PLA₁EMA and PLA₅EMA bulk k_p estimates was detected over the temperature range of 40–100 °C, indicating that polar and steric characteristics several units beyond the methacrylic group do not decisively influence k_p . Furthermore, the apparent solution k_p values measured for both PLA₁EMA and PLA₅EMA in DMF as well as in xylenes were markedly decreased compared to bulk due to differences in (macro)monomer and solvent molar volumes, while in BuOH the apparent k_p of both systems increased relative to in DMF because of hydrogen bonding.

PLA_NEMA (macro)monomers were used to produce NPs by semi batch radical emulsion polymerization. When an equal weight of PLA₅EMA is used as comonomer, the time for accelerated degradation at 50 °C of hydroxyl terminated HEMA-PLA₅ NPs is increased from 10 to 23 days, while the PLA₅EMA homopolymer NPs took 40 days to degrade. An explanation for the slow degradation is proposed in terms of PLA graft orientation relative to the methacrylic backbone; ethyl ester protection of poly(PLA_NEMA) grafts' carboxyl end-groups delays the onset of preferential chain-end hydrolysis. The ability to affect degradation time by copolymerizing PLA_NEMA with HEMA-PLA_{2n} provides further opportunities to tune the

performance characteristics of this family of degradable NPs according to specific application requirements.

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