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Tunable Degradation of Copolymers Prepared by Nitroxide-Mediated Radical Ring-Opening Polymerization and Point-by-Point Comparison with Traditional Polyesters

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Abstract

Two libraries of well-defined, degradable vinyl copolymers of opposite solubility, based either on methyl methacrylate (MMA) or on oligo(ethylene glycol) methyl ether methacrylate (OEGMA), and containing various amount of 2-methylene-4-phenyl-1,3-dioxolane (MPDL), were synthesized by nitroxide-mediated radical ring-opening polymerization. A comprehensive degradation study (long-term hydrolytic degradation, degradation of thick and thin films, water uptake, enzymatic degradation) was then performed and results were compared with those from traditional aliphatic polyesters (PLGA, PLA and PCL). It appeared that P(MMA-*co*-MPDL) copolymers slowly degraded in PBS with degradation kinetics slower than that of PCL whereas P(OEGMA-*co*-MPDL) copolymers led to significant degradation, in between that of PLA and PCL, depending on the amount of MPDL, but without leading to a dramatic drop of pH as for PLGA and PLA. Whereas P(MMA-*co*-MPDL) copolymers might be well-suited for biomaterials intended for long-term use (e.g., devices, implants), faster degrading P(OEGMA-*co*-MPDL) copolymers might be envisioned for short- or mid-term applications such as nanoscale drug-delivery systems and meet a need for hydrophilic degradable materials with tunable degradation kinetics.

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Tunable Degradation of Copolymers Prepared by Nitroxide-Mediated Radical Ring-Opening Polymerization and Point-by-Point Comparison with Traditional Polyesters

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Introduction

The development of (bio)degradable polymers is currently the focus of great attention given their use in a wide range of applications including (nano)medicine, microelectronics and environmental protection.¹⁻³ Polymers intended for biomedical applications are indeed of extreme importance for drug delivery or tissue engineering applications and should usually meet the following criteria: (i) biodegradability (mainly for administered materials) and biocompatibility (to avoid toxic side-effects); (ii) uniformity in polymer chain length and composition to ensure a reproducible biological response and (iii) functionalizability with biologically active (macro)molecules (e.g., drugs, targeting ligands) and fluorescent probes for therapeutic and diagnostic/tracing purposes, respectively.

Among the different classes of biodegradable polymers, aliphatic polyesters synthesized by ring-opening polymerization (ROP) of cyclic monomers (e.g., lactide, glycolide, caprolactone, etc.) are certainly the most studied materials for biomedical applications, including the manufacture of resorbable sutures, tissue engineering scaffolds and drug delivery systems.⁴ Importantly, polycaprolactone (PCL), polylactide (PLA), polyglycolide (PGA) and poly(lactide-*co*-glycolide) (PLGA) have gained Food and Drug Administration (FDA) approval for use in humans as a result of their biocompatibility and biodegradability.^{5,6} Other degradable polymers rapidly emerged as promising candidates such as synthetic polypeptides, polyanhydrides, poly(alkyl cyanoacrylates), poly(ortho esters), polyamides, etc.⁷

Vinyl polymers are very attractive materials and present numerous benefits compared to traditional polyesters owing to their ease of synthesis and their broad diversity of architectures, compositions and functionalities. For instance, these features have enabled the design of highly sophisticated and innovative polymer-protein/peptide bioconjugates or nanocarriers for drug delivery. These achievements were made possible in particular since the

advent of reversible deactivation radical polymerization (RDRP) techniques, such as nitroxide-mediated polymerization (NMP),⁸ atom-transfer radical polymerization (ATRP)⁹ and reversible addition-fragmentation chain transfer (RAFT) polymerization.¹⁰ However, given their carbon-carbon backbones, they are extremely resistant to degradation and this property strongly limits their application in the biomedical field because potential bioaccumulation in the organism may cause toxicity. This is unfortunate in regards to the massive amount of work devoted to vinyl polymer-based systems intended for biomedical applications.

This critical situation and the general need for more environmentally friendly plastic materials further stimulated the development of degradable vinyl polymers.¹¹ Among the different strategies, radical ring-opening polymerization (rROP) represents one of the most promising approaches because it combines the advantages of a radical mechanism, thus being fully compatible with free-radical polymerization and RDRP methods, and it enables insertion of labile groups (e.g., ester, disulfide, etc.) in the polymer backbone to ensure degradation.¹² Different classes of cyclic monomers undergoing a radical ring-opening mechanism have been developed and among them, cyclic ketene acetals (CKA),^{13,14} originally developed by Bailey in the 80's, are perhaps the most used monomers for rROP. Interestingly, CKA can be copolymerized with certain traditional vinyl monomers, mainly (meth)acrylic esters and vinyl acetate,¹⁵⁻²² allowing for tunable insertion of ester groups in the resulting copolymers. For instance, a variety of different copolymers based on 2-methylene-1,3-dioxepane (MDO) or 5,6-benzo-2-methylene-1,3-dioxepane (BMDO), which represent the two main CKA used in the literature, have been reported for potential applications in drug delivery, tissue engineering, hydrophobic coatings, or as other kinds of structural biomaterials.

Recently, our group revisited the use of 2-methylene-4-phenyl-1,3-dioxolane (MPDL) by optimizing its synthesis²³ and using it as a comonomer during the NMP of either

OEGMA²⁴ or MMA²³ to make degradable PEG-based or PMMA-rich materials, respectively (Figure 1). Even though NMP of methacrylic esters is known to be relatively difficult to achieve, the styrene-like open radical structure of MPDL allowed good control and high living chain fractions to be achieved during its copolymerization with methacrylic esters by acting as a so-called ‘controlling’ comonomer. Conversely to the use of BMDO or MDO under identical experimental conditions, MPDL enabled high monomer conversions to be reached and tunable insertion in the copolymers, thus leading to adjustable degradation; from moderate to nearly complete.²⁴ Also, neither the resulting P(OEGMA-*co*-MPDL) copolymers nor their degradation products were cytotoxic up to high concentration on three representative cell lines.²⁴ As for P(MMA-*co*-MPDL) copolymers, insertion of MPDL only moderately affected the glass transition temperature compared to pure PMMA, while giving low molar mass degradation products after hydrolysis.²³

Figure 1. Synthesis of degradable copolymers by nitroxide-mediated radical ring-opening copolymerization (NMrROP) between methacrylic esters and 2-methylene-4-phenyl-1,3-dioxolane (MPDL) as ester bound precursor in the copolymer backbone.

In these studies, copolymer degradation was performed under accelerated conditions to probe the presence of open CKA units; in aqueous 5% KOH for OEGMA-based copolymers and in THF/MeOH solution with 5% KOH for MMA-based counterparts. Degradation kinetics were rapid (from minutes to hours) and allowed to confirm the presence of labile groups in the copolymer backbones. However, even though these harsh degradation conditions are usually used for such a purpose, they do not reflect the physiological conditions and are thus poorly predictive of the materials fate in a biological environment. Also, to the best of our knowledge, degradation of CKA-based materials under physiological conditions have never been benchmarked with traditional aliphatic polyesters such as PLGA, PLA and PCL, which still represent gold standards in terms of degradable polymers for biomedical applications. Only degradation in the presence of enzymes are sometimes reported.^{16,25-27} This missing information is crucial for designing the right materials having the degradation pattern that match with the target application.

Herein, we performed a comprehensive degradation study of two distinct libraries of CKA-containing copolymers, namely hydrophilic P(OEGMA-*co*-MPDL) and hydrophobic P(MMA-*co*-MPDL) (Figure 2), under conditions mimicking the physiological environment. In particular, we simultaneously investigated: (i) the long term hydrolytic degradation in PBS at different pH; (ii) the physical erosion of thick and thin polymer films and (iii) the enzymatic degradation. A point-by-point comparison under identical conditions was also performed with the three representative aliphatic polyesters (i.e., PLGA, PLA and PCL, Figure 2), allowing the different materials to be compared and some preliminary structure-degradation relationships to be established.

Figure 2. Chemical structure of the different polyesters employed in this study: poly[(methyl methacrylate)-*co*-(2-methylene-4-phenyl-1,3-dioxolane)] (P(MMA-*co*-MPDL)), poly[(oligo(ethylene glycol) methyl ether methacrylate)-*co*-(2-methylene-4-phenyl-1,3-dioxolane)] (P(OEGMA-*co*-MPDL)), poly(D,L-lactide-*co*-glycolide) (PLGA), poly(D,L-lactide) (PLA) and polycaprolactone (PCL).

Experimental part

Materials

Oligo(ethylene glycol) methyl ether methacrylate (OEGMA, $M_n = 300 \text{ g.mol}^{-1}$), styrene (S, 99%), methyl methacrylate (MMA, 99%), anhydrous toluene (99.8%), lipase B from *Candida Antartica* immobilized on imobead (4019 U/g) were purchased from Sigma-Aldrich and used as received (except for MMA which was distilled under reduced pressure). BlocBuilder MATM alkoxyamine and the SG1 nitroxide were kindly provided by Arkema. Poly(D,L-lactide-*co*-glycolide) (Resomer[®] RG 503, lactide:glycolide 50:50, ester terminated, $M_w = 24\,000\text{--}38\,000 \text{ g.mol}^{-1}$), poly(D,L-lactide) (Resomer[®] R 203 S, ester terminated, $M_w = 18\,000\text{--}28\,000 \text{ g.mol}^{-1}$) and polycaprolactone (average $M_n = 45\,000 \text{ g.mol}^{-1}$) were obtained from

Sigma-Aldrich. 2-Methylene-4-phenyl-1,3-dioxolane (MPDL) monomer was prepared according to a previously published method (using the cyclic bromoacetal as an intermediate).²³ All other materials were purchased from Sigma-Aldrich at the highest available purity and used as received. Phosphate buffer saline (PBS 0.1 M, with 0.9 % NaCl and 0.02 % NaN₃, pH 7.4) and acetate buffer (0.1 M, with 0.02 % NaN₃, pH 5.5) were prepared in the lab. Deuterated chloroform (CDCl₃) was obtained from Eurisotop. All other solvents were purchased from Carlo-Erba.

Analytical methods

Nuclear Magnetic Resonance Spectroscopy (NMR). NMR spectroscopy was performed in 5 mm diameter tubes in CDCl₃ at 25 °C. ¹H spectroscopy was performed on a Bruker Avance 300 spectrometer at 300 MHz. The chemical shift scale was calibrated on the basis of the internal solvent signals.

Size exclusion chromatography (SEC). SEC was performed at 30 °C with two columns from Polymer Laboratories (PL-gel MIXED-D; 300 × 7.5 mm; bead diameter, 5 µm; linear part, 400–400 000 g.mol⁻¹) and a differential refractive index detector (Spectrasystem RI-150 from Thermo Electron Corp.), using chloroform as eluent, at a flow rate of 1 mL.min⁻¹, and toluene as a flow-rate marker. The conventional calibration curve was based on polymer standards from Polymer Laboratories; either poly(methyl methacrylate) (PMMA) standards (peak molar masses, $M_p = 625\text{--}625\,500\text{ g.mol}^{-1}$) for all polymethacrylate copolymers or polystyrene (PS) standards ($M_p = 162\text{--}523\,000\text{ g.mol}^{-1}$) for PLGA, PLA and PCL. This technique allowed M_n (number-average molar mass), M_w (weight-average molar mass), and M_w/M_n (dispersity, D) to be determined.

Atomic force microscopy (AFM). AFM experiments were performed using the Nanowizard 3 Ultra Speed from JPK Instruments (Berlin, Germany, www.jpk.com), installed on an air-buffered table coupled to a dynamic anti-vibration device, and enclosed in an acoustic box.

Imaging of the polymer thin film surface morphology was performed in air in AC or HyperDrive® mode, with gold-coated silicon cantilevers PPP-NCHAuD of $30 \pm 10 \text{ N.m}^{-1}$ spring constant and $290 \pm 5 \text{ kHz}$ resonance frequency (Nanosensors, Neuchatel, Switzerland). The pyramid-shaped tips had a radius of curvature less than 10 nm. A free amplitude oscillation of 15 nm (1 nm) was chosen in AC mode (in HyperDrive mode) allowing the best resolution of the imaged surface. In AC mode, setpoints ranging between 50% and 80% of the free amplitude were used depending on the polymer surface. Images were taken at scan rates of 1 or 2 Hz. Image processing (flatten, plane fit, edge and hole detection) was performed with the JPK Data Processing software (JPK Instruments). At least three different areas of each sample were scanned and typical images were presented. Average values of height and lateral dimensions of surface features were determined with all pictures.

Scanning electron microscopy (SEM). Scanning Electron Microscopy (SEM) was performed using a MERLIN microscope (Carl Zeiss) and operating at 3 kV with a filament current of about 0.5 mA. Liquid samples were deposited on a carbon conductive double-sided tape (Euromedex, France). They were coated with a palladium-platinum layer of about 3 nm using a Cressington sputter-coater 208HR with a rotary-planetary-tilt stage, equipped with a MTM-20 thickness controller.

Polymer synthesis

Synthesis of poly[(methyl methacrylate)-*co*-(styrene)] (P(MMA-*co*-S), P1). In a 20 mL vial, fitted with a rubber septum and a magnetic bar, a mixture of MMA (12.00 g, 1.20×10^{-1} mol), S (1.235 g, 1.19×10^{-2} mol) and the BlocBuilder MA alkoxyamine initiator (0.084 g, 2.20×10^{-4} mol) and free SG1 (0.002 g, 5.85×10^{-6} mol) was deoxygenated under stirring by nitrogen bubbling for 15 min at room temperature. The mixture was then immersed in a preheated oil bath at 90 °C, corresponding to the time zero of the reaction. After 2 h, the polymerization was stopped by cooling down to ambient temperature. The MMA conversion

was calculated by ^1H NMR spectroscopy and the macromolecular characteristics of the copolymer (M_n and $\bar{D}$) were determined by SEC (using a calibration based on PMMA standards). The copolymer was then precipitated once in cold MeOH and dried under high vacuum until constant weight.

Synthesis of poly[(methyl methacrylate)-*co*-(2-methylene-4-phenyl-1,3-dioxolane)] (P(MMA-*co*-MPDL), P2–P4). A typical solution copolymerization procedure (P2) is as follows. In a 40 mL vial, fitted with a rubber septum and a magnetic bar, a mixture of MMA (12.100 g, 1.21×10^{-1} mol), MPDL (4.900 g, 3.02×10^{-2} mol), the BlocBuilder MA alkoxyamine initiator (0.061 g, 1.60×10^{-4} mol) and anhydrous toluene (17.0 g, 19.61 mL) was deoxygenated under stirring by nitrogen bubbling for 15 min at room temperature. The mixture was then immersed in a preheated oil bath at 90 °C, corresponding to the time zero of the reaction. After 8 h, the polymerization was stopped by cooling down to ambient temperature. The MMA conversion was calculated by ^1H NMR spectroscopy and the macromolecular characteristics of the copolymer (M_n and $\bar{D}$) were determined by SEC (using a calibration based on PMMA standards). The copolymer was then precipitated once in cold MeOH and dried under high vacuum until constant weight. The same procedure was followed by adapting the amount of reactants for P3 [MMA (8.652 g, 8.65×10^{-2} mol), MPDL (9.348 g, 5.77×10^{-2} mol), BlocBuilder MA alkoxyamine initiator (0.0414 g, 1.09×10^{-4} mol)] and P4 [MMA (3.766 g, 3.77×10^{-2} mol), MPDL (14.234 g, 8.79×10^{-2} mol), BlocBuilder MA alkoxyamine initiator (0.020 g, 5.35×10^{-5} mol)]. Final compositions of the copolymers were determined by comparing the methyl protons in α -position to the ester group of MMA (at 3.7 ppm) to the aromatic protons of MPDL (at 7.2 ppm).

Synthesis of poly[(oligo(ethylene glycol) methyl ether methacrylate)-*co*-(styrene)] (P(OEGMA-*co*-S), P5). In a 20 mL vial, fitted with a rubber septum and a magnetic bar, a mixture of OEGMA (6.000 g, 2.00×10^{-2} mol), S (0.206 g, 1.98×10^{-3} mol), the BlocBuilder

MA alkoxyamine initiator (0.024 g, 6.23×10^{-5} mol) and free SG1 (0.002 g, 5.85×10^{-6} mol) was deoxygenated under stirring by nitrogen bubbling for 15 min at room temperature. The mixture was then immersed in a preheated oil bath at 90 °C, corresponding to the time zero of the reaction. After 30 min, polymerization was stopped by cooling down to ambient temperature. The OEGMA conversion was calculated by ^1H NMR spectroscopy and the macromolecular characteristics of the copolymer (M_n and $\bar{D}$) were determined by SEC (using a calibration based on PMMA standards). The copolymer was then precipitated once in a mixture of cold cyclohexane/petroleum ether (1/1, v/v) and dried under high vacuum until constant weight.

Synthesis of poly[(oligo(ethylene glycol) methyl ether methacrylate)-*co*-(2-methylene-4-phenyl-1,3-dioxolane)] (P(OEGMA-*co*-MPDL), P6–P8). A typical solution copolymerization procedure (**P6**) is as follows. In a 20 mL vial, fitted with a rubber septum and a magnetic bar, a mixture of OEGMA (2.643 g, 8.81×10^{-3} mol), MPDL (0.357 g, 2.20×10^{-3} mol), the BlocBuilder MA alkoxyamine initiator (0.014 g, 3.78×10^{-5} mol) and anhydrous toluene (3.0 g, 3.46 mL) was deoxygenated under stirring by nitrogen bubbling for 15 min at room temperature. The mixture was then immersed in a preheated oil bath at 90 °C, corresponding to the time zero of the reaction. After 8 h, the polymerization was stopped by cooling down to ambient temperature. The OEGMA conversion was calculated by ^1H NMR spectroscopy and the macromolecular characteristics of the copolymer (M_n and $\bar{D}$) were determined by SEC (using a calibration based on PMMA standards). The copolymer was then precipitated once in a mixture of cold cyclohexane/petroleum ether (1/1, v/v) and dried under high vacuum until constant weight. The same procedure was followed by adapting the amount of the reactants for **P7** [OEGMA (2.206 g, 7.35×10^{-3} mol), MPDL (0.794 g, 4.90×10^{-3} mol), BlocBuilder MA alkoxyamine initiator (0.012 g, 3.10×10^{-5} mol)] and **P8** [OEGMA (1.328 g, 4.43×10^{-3} mol), MPDL (1.673 g, 1.03×10^{-3} mol), BlocBuilder MA alkoxyamine

initiator (0.0085 g, 2.20×10^{-5} mol)]. Final compositions of the copolymers were determined by comparing the terminal methoxy protons of OEG (at 3.4 ppm) to the ester group of MMA (at 3.7 ppm) to the aromatic protons of MPDL (at 7.2 ppm).

Degradation experiments

All the degradation experiments were performed in an orbital shaker (IKA KS4000i control) oven set at 150 rpm and 37 °C.

Long-term hydrolytic degradation in PBS. 200 mg of copolymer was poured into 20 mL of 0.1 M PBS and mechanically stirred in an orbital shaker thermostated at 37 °C. Samples of 2 mL were withdrawn at different intervals (i.e., 4, 6 and 12 months) and lyophilized. 2 mL of chloroform were then added, allowing removal of buffer salts by filtration. Finally, the solvent was removed under reduced pressure and the degradation products were analyzed by SEC.

Hydrolytic degradation of thick polymer films. Films of ~1 mm thickness, 150 mg in mass and 1 cm² surface area were prepared using a solvent casting method. The copolymer was solubilized in chloroform at a concentration of 200 mg.mL⁻¹. 0.75 mL of copolymer solution was poured into plastic mold of 1 cm². The mold was covered with aluminum foil and the solvent was slowly evaporated in air at room temperature for 3 days to prevent bubble formation. The resulting copolymer film was then further dried under high vacuum for one day to evaporate remaining solvent. After weighing, films were placed in individual vials containing 10 mL of 0.1 M PBS and mechanically stirred in an orbital shaker thermostated at 37 °C. Films were withdrawn at different intervals (i.e., 4, 6 and 12 months). Water uptake and mass loss were evaluated by weighing using the following equation: water uptake $= \frac{m_w - m_d}{m_d}$ where m_d and m_w are the mass of the dried film after degradation and the mass of the wet film after degradation (quickly wiped with paper), respectively and mass loss $= \frac{m_d - m_0}{m_0}$ where m_0 is the initial mass.

Hydrolytic degradation of thin polymer films. Thin films of 10 mg in mass and $\sim 0.5 \text{ cm}^2$ surface area were prepared using a solvent casting method. The copolymer was solubilized in chloroform, with a concentration of 200 mg.mL^{-1} . 50 μL were dropped on a mica slide. The films were covered with aluminum foil and the solvent was evaporated slowly in air at room temperature for 2 days to prevent bubble formation. The resulting (co)polymer film was then annealed above the melting temperature of each (co)polymer; that is at 180°C , 115°C and 80°C for PMMA-based, PLA/PLGA and PCL films, respectively. When the annealing temperature was reached, thin films were dried under vacuum for 20 h. Films were then placed in 10 mL of 0.1 M PBS and mechanically stirred in an orbital shaker thermostated at 37°C . After selected intervals (i.e., 1, 6 and 12 months), films were withdrawn. Before imaging by SEM and AFM, they were washed with distilled water to remove salts that may be responsible for low image quality.

Enzymatic degradation. Copolymers were poured in 0.1 M PBS at a concentration of 0.5 mg.mL^{-1} by the nanoprecipitation technique. 50 mg of copolymer were solubilized in 2.5 mL of THF and added dropwise to 10 mL of 0.1 M PBS. THF was evaporated and lipase from *Candida Antartica* (100 U.mL^{-1}) was added to the mixture (250 mg). After one week of incubation under stirring at 40°C , the mixture was lyophilized and 2 mL of chloroform were added allowing removal of buffer salts by filtration. The degradation products were then analyzed by SEC.

Intravenous injections and preliminary toxicity to mice

Female athymic nude mice (6–8 weeks old) were purchased from Harlan Laboratory. All animals were housed in appropriate animal care facilities during the experimental period and handled according to the principles of laboratory animal care and legislation in force in France (authorization No. 03803.02). Mice ($\sim 20 \text{ g}$) were randomly divided into 7 groups of 5 mice and each group received a single injection in the tail vein with either copolymers (**P7** and **P8**) with concentrations from 0.8 to 2.4 g.kg^{-1} or 0.01 M PBS as control. The injected

volume was 10 μL per gram of body weight. Mice were regularly monitored for changes in weight and behavior, and were humanely sacrificed 20 days after the injection.

Results and Discussion

Synthesis and characterization of degradable copolymers

Two libraries of degradable copolymers with M_n of $\sim 23\,000$ – $35\,000\text{ g.mol}^{-1}$ and comprising variable amounts of MPDL units were prepared by NMrROP. Copolymerizations between MPDL and MMA (**P1–P4**) or OEGMA (**P5–P8**) were initiated by the BlocBuilder alkoxyamine to yield either degradable hydrophobic or hydrophilic copolymers, respectively (Figure 3, Table 1). For both libraries, the initial molar fraction of MPDL, $f_{\text{MPDL},0}$, was varied from 0.2 to 0.7 to adjust the amount of MPDL inserted in the copolymer and therefore its degree of degradation. Copolymers without MPDL were also synthesized by using styrene (S) as a ‘controlling’ comonomer, given the structural similarity of the styrenic radical with the open radical structure of MPDL (**P1** and **P5**).

Figure 3. Synthesis of (a) poly[(methyl methacrylate)-*co*-(2-methylene-4-phenyl-1,3-dioxolane)] (P(MMA-*co*-MPDL)) and (b) poly[(oligo(ethylene glycol) methyl ether methacrylate)-*co*-(2-methylene-4-phenyl-1,3-dioxolane)] (P(OEGMA-*co*-MPDL)) by nitroxide-mediated radical ring-opening copolymerization (NMrROP) of MMA (or OEGMA) and MPDL.

Table 1. Experimental Conditions and Macromolecular Characteristics of the Degradable Copolymers Used In This Study.

Expt.	Methacrylic ester	$f_{\text{MPDL},0}$	Conv. ^a (%) / time (h)	M_n^b (g/mol)	$\bar{D}^b$	F_{MPDL}^c
P1^d	MMA	0	40 / 2.5	32 500	1.19	0
P2	MMA	0.2	25 / 8	30 500	1.62	0.08
P3	MMA	0.4	35 / 8	32 600	1.55	0.12
P4	MMA	0.7	35 / 8	35 000	1.32	0.27
P5^d	OEGMA	0	29 / 0.5	22 900	1.24	0
P6	OEGMA	0.2	42 / 8	31 600	1.35	0.09
P7	OEGMA	0.4	46 / 8	33 100	1.32	0.15
P8	OEGMA	0.7	36 / 8	28 300	1.19	0.27

^aMethacrylic ester conversion determined by ¹H NMR spectroscopy. ^bDetermined by SEC after purification from PMMA standards. ^cDetermined by ¹H NMR spectroscopy. ^dStyrene was used as a controlling comonomer ($f_{\text{S},0} = 0.1$).

Because MPDL acts as a ‘controlling’ comonomer during the NMP of methacrylic esters, the higher $f_{\text{MPDL},0}$, the better the control of the copolymerization (Table 1). P(MMA-*co*-MPDL)

copolymers exhibited decreasing dispersities from 1.62 to 1.32 by gradually increasing the initial amount of MPDL from 0.2 to 0.7. A similar trend was observed with P(OEGMA-*co*-MPDL) copolymers whose dispersities ranged from 1.35 to 1.19 under identical experimental conditions.

The molar fraction of MPDL inserted in the copolymers was determined by ^1H NMR spectroscopy. Because of unfavorable reactivity ratios of MPDL/MMA ($r_{\text{MPDL}} = 0.01$ and $r_{\text{MMA}} = 4.0^{23}$) and MPDL/OEGMA ($r_{\text{MPDL}} = 0$ and $r_{\text{OEGMA}} = 6.95^{24}$) monomer pairs, the final amounts of MPDL in the copolymers, F_{MPDL} , were significantly lower than the initial amounts of MPDL in the comonomer feed. However, it was still possible to fine-tune F_{MPDL} by varying $f_{\text{MPDL},0}$. It led, on average, to copolymers containing ~8% (**P2** and **P6**), ~14% (**P3** and **P7**) and ~27% (**P4** and **P8**) for $f_{\text{MPDL},0} = 0.2, 0.4$ and 0.7 , respectively (Table 1). As for control P(MMA-*co*-S) **P1** and P(OEGMA-*co*-S) **P5** copolymers without MPDL, they were nicely controlled with low dispersities (1.19 and 1.24, respectively).

Long-term hydrolytic degradation in PBS

Long-term hydrolytic degradation of the different copolymers was first investigated in PBS (0.1 M, pH 7.4) at 37 °C to mimic physiological conditions. All copolymers were poured in PBS and incubated under orbital-shaking at 150 rpm and thermostated at 37°C. MMA-based copolymers and traditional aliphatic polyesters were insoluble in water and thus dispersed in PBS whereas OEGMA-based copolymers were soluble in water (Figure S1). The evolution of the M_n was monitored by SEC for 12 months by withdrawing samples at different intervals (i.e., 4, 6 and 12 months).

Degradation of P(MMA-*co*-MPDL) was very slow and led to a decrease in M_n of ~20 % after 12 months (Figure 4a and S2). Conversely to our expectations, no effect of the MPDL content was noticed on the degradation. Despite constant stirring by orbital shaking, P(MMA-

co-MPDL) copolymers poorly dispersed in water, leaving a persistent insoluble fraction at the water/air interface even after 12 months (Figure S1c). Conversely, P(OEGMA-*co*-MPDL) led to significant hydrolytic degradation under identical experimental conditions (Figure 4b and S3). The decrease in M_n was governed by the MPDL fraction in the copolymer; the higher F_{MPDL} , the more significant the degradation. After 12 months, the M_n decrease reached -38, -55 and -72 % for $F_{\text{MPDL}} = 0.09, 0.15$ and 0.27 , respectively.

The different degradation patterns of P(MMA-*co*-MPDL) and P(OEGMA-*co*-MPDL) copolymers can be explained by their different solubility in water. Whereas water-solubility of P(OEGMA-*co*-MPDL) is ensured by its OEG side chains, thus allowing water molecules to access to the ester groups in the main chain and cause degradation, P(MMA-*co*-MPDL) is too hydrophobic and exhibited poor water uptake that prevented significant degradation. This aspect will be further discussed in the *Hydrolytic degradation of polymer films* section. Both control copolymers **P1** and **P5** led to minimal degradation (~14 %) after 12 months, presumably because of partial hydrolysis of MMA and OEGMA units, respectively (note that such an artifact may also contribute to the decrease in M_n for copolymers **P2–P4**). Either hydrolysis is significant and the decrease in M_n is caused by loss of multiple methyl or OEG groups, or it is marginal but the few resulting carboxylic acid groups lead to interaction with SEC columns, thus affecting the retention time.²⁸ This last hypothesis seems predominant since ¹H NMR spectra of P(MMA-*co*-MPDL) and P(OEGMA-*co*-MPDL) did not show any noticeable change of integration for the peaks of the methyl/methylene protons in the α -position to the ester bond.

Figure 4. Evolution of the number-average molar mass, M_n , with time of the different copolymers during the hydrolytic degradation in PBS (0.1 M, pH 7.4, 37 °C). (a) P(MMA-*co*-MPDL): **P1** ($F_{\text{MPDL}} = 0$); **P2** ($F_{\text{MPDL}} = 0.08$); **P3** ($F_{\text{MPDL}} = 0.12$); **P4** ($F_{\text{MPDL}} = 0.27$). (b) P(OEGMA-*co*-MPDL): **P5** ($F_{\text{MPDL}} = 0$); **P6** ($F_{\text{MPDL}} = 0.09$); **P7** ($F_{\text{MPDL}} = 0.15$); **P8** ($F_{\text{MPDL}} = 0.27$). (c) Influence of the pH: **P4** (pH 7.4 or 5.5); **P8** (pH 7.4 or 5.5). (d) Aliphatic polyesters (pH 7.4).

Evolution with time of the M_n of P(OEGMA-*co*-MPDL), and in particular of the slope of the curves, suggested that even though hydrolytic degradation did not reach completion after 12 months, lower M_n will likely be obtained if the degradation is prolonged for a longer period of time (Figure 4b). However, the final theoretical M_n after complete degradation can be estimated from the final composition of the copolymers, providing nearly statistical incorporation of MPDL all along the copolymer chain. Given the unfavorable reactivity ratio of MPDL (MPDL/OEGMA: $r_{\text{MPDL}} = 0$ and $r_{\text{OEGMA}} = 6.95$;²⁴ MPDL/MMA: $r_{\text{MPDL}} = 0.1$ and

$r_{\text{MMA}} = 4$),²³ it was assumed that the number of consecutive MPDL units was negligible. Thus, the average number of OEGMA units between two MPDL units was calculated according to $1/F_{\text{MPDL}} - 1$ and was equal to 10, 6 and 3 for $F_{\text{MPDL}} = 0.09$ (**P6**), 0.15 (**P7**) and 0.27 (**P8**), respectively. It would correspond to a residual M_n of 3200 (**P6**), 1900 (**P7**) and 1000 g.mol⁻¹ (**P8**) and a final M_n decrease of 90, 94 and 96%, respectively.

Influence of pH on degradation was then investigated. One copolymer from each library, **P4** and **P8**, was subjected to degradation in acetate buffer (pH 5.5) for 12 months and the degradation pattern was compared to that obtained in PBS (0.1 M, pH 7.4). However, no noticeable effect was observed on the degradation rate as shown by a nearly perfect overlay of M_n values at each time point (Figure 4c).

A key aspect of the study was whether our materials could be competitive in terms of degradation under physiological conditions, with traditional aliphatic polyesters. The two series of MPDL-containing copolymers were therefore benchmarked with PLGA, PLA and PCL. Identical degradation conditions (PBS, 0.1 M, pH 7.4) were applied and evolution of M_n after different periods of time was reported on Figure 4d and S4. As previously reported, degradation of PLGA was the fastest, leading to complete degradation after 1 month.²⁹ As expected, since PLA is more sterically hindered than PLGA, its complete degradation took a longer time, approximately 12 months,³⁰ whereas degradation of PCL was the slowest leading to a decrease in M_n of only 36 % after 12 months.³¹ As for our MPDL-containing copolymers, P(MMA-*co*-MPDL) **P2–P4** exhibited slightly slower degradation rates than that of PCL. However, hydrolytic degradation of P(OEGMA-*co*-MPDL) **P6–P8** was comprised between that of PLA and PCL. It is a very important result showing that hydrolytic degradation of properly designed CKA-containing vinyl copolymers can be in the same order of magnitude than degradation of PCL and PLA, which are extensively used FDA-approved biodegradable polymers.

pH was monitored over time during hydrolytic degradation at pH 7.4 of OEGMA-based copolymers **P5–P8**, and of PLGA, PLA and PCL (Figure 5). Hydrolytic degradation of polyester leads to carboxylic acid chain-end frequently associated with a drop in pH.^{32,33} pH of PLGA and PLA dispersions decreased from 7.4 to 5.5 after 1 and 12 months, respectively.^{32,33} This drop in pH may be a strong limitation as it was shown that local acidification produced by the degradation products of PLGA/PLA usually resulted in detrimental local inflammatory response.^{32,33} Because of the minimal degradation of PCL over this period of time, no drop in pH was observed. Remarkably, pH of the different P(OEGMA-*co*-MPDL) solutions was stable and remain > 6.8 even after 1 year, as for P(OEGMA-*co*-S) used as a control copolymer. This high pH stability, related to a lower number of carboxylic acid moieties released from MPDL-containing copolymers during the degradation process, is very relevant and represents a meaningful advantage compared to aliphatic polyesters as their in vivo degradation may not lead to local acidification and probably to local toxicity.

Figure 5. Evolution of pH with time during hydrolytic degradation in PBS (0.1 M, pH 7.4, 37°C) of OEGMA-based copolymers: ●, **P5** ($F_{\text{MPDL}} = 0$); ■, **P6** ($F_{\text{MPDL}} = 0.09$); ▲, **P7** ($F_{\text{MPDL}} = 0.15$); ▼, **P8** ($F_{\text{MPDL}} = 0.27$) and aliphatic polyesters.

Hydrolytic degradation of polymer films

Films of approximatively 150 mg in mass, 1 mm thickness and 1 cm² surface area (Figure S5) were prepared by the solvent casting method from hydrophobic (co)polymers: P(MMA-*co*-S) **P1**, P(MMA-*co*-MPDL) **P2–P4**, PLA, PLGA, and PCL. Hydrolytic degradation was carried out in PBS (0.1 M, pH 7.4) stirred in an orbital shaker thermostated at 37 °C. Erosion of hydrophobic polymers occurs through surface or bulk erosion^{34,35} and the balance between the kinetics of diffusion of water inside the polymer matrix and the hydrolysis rate of the polymer's labile groups defines the erosion mechanism. If water diffusion is faster than the labile group hydrolysis, the material degrades through bulk erosion. On the contrary, if the chain cleavage is faster than water diffusion, the material undergoes surface erosion. Water uptake and mass loss were monitored for 12 months. In parallel, thin films (~10 mg in mass, 0.5 cm² surface area) were prepared on mica surface for further scanning electron microscopy (SEM) and atomic force microscopy (AFM) observations to gain some insight into the degradation mechanism of our copolymers.

The water uptake ability of thick polymer films was first determined by comparing their weight in wet and dry states (Figure 6a). Water uptake of PLGA and PLA films was fast and reached values as high as ~210 % after 1 month for PLGA and ~500 % after 4 months for PLA. This behavior confirmed that water significantly diffused inside PLGA/PLA matrix, in agreement with their relatively fast degradation rates (Figure 4d). PCL and P(MMA-*co*-MPDL) **P2–P4** films gave less than 8 % of water uptake. These results were consistent with long-term hydrolytic degradation experiments that showed very slow degradation of dispersed PCL and P(MMA-*co*-MPDL) copolymers.

Although the strong hydrophobicity of P(MMA-*co*-MPDL) copolymers may explain their poor water uptake, influence of their glass transition temperature (i.e., segmental mobility) cannot be ruled out. T_g s of PLGA and PLA are about 44–48 °C and 48–52 °C, respectively,³⁶ so relatively close to the experimental temperature (37 °C). Therefore,

although glassy, polymer chains still have some segmental flexibility, favoring water penetration in the polymer matrix.³⁷ For PCL, the situation was more complicated. Even if its T_g (-60 °C) is significantly lower than the experimental temperature, the crystallinity of the polymer strongly hampered water uptake.³⁸ Conversely, T_g of P(MMA-*co*-MPDL) is equal to 107 °C for **P1**, 100 °C for **P2**, 98 °C for **P3** and 74 °C for **P4**,²³ so much higher than those of PLGA and PLA. Consequently, not only P(MMA-*co*-MPDL) copolymers were hydrophobic but also very rigid and highly compact, thus preventing water molecules to extensively diffuse into the polymer matrix to induce degradation.^{37,39}

Figure 6. (a) Water uptake and (b) mass loss of thick films during hydrolytic degradation in PBS (0.1 M, pH 7.4, 37°C) of MMA-based copolymers: ●, **P1** ($F_{\text{MPDL}} = 0$); ■, **P2** ($F_{\text{MPDL}} = 0.08$); ▲, **P3** ($F_{\text{MPDL}} = 0.12$); ▼, **P4** ($F_{\text{MPDL}} = 0.27$) and aliphatic polyesters.

Similarly to water uptake, mass loss of PLGA and PLA thick films in 0.1 M PBS under identical degradation conditions was fast (Figure 6b). PLGA films lost ~75 % of their mass after 1 month and PLA lost ~63 % after 4 months. In contrast, MMA-based copolymers **P2**–**P4** and PCL had similar behavior, with a mass loss around ~10 % after 12 months (note that copolymer **P1** lost mass to the same extent as MPDL-containing copolymers, which might be assign to partial hydrolysis of MMA units). As water hardly entered into the polymer matrix,

only the surface of film was likely subjected to degradation, which left the bulk intact. Photographs of P(MMA-*co*-MPDL) **P4**, PLGA, PLA and PCL films before and after 12, 1, 4 and 12 months in 0.1 M PBS, respectively, further illustrated the rapid degradation of PLGA and PLA films as opposed to the nearly hydrolytic stability of films from **P4** and PCL (Figure S5). These data supported that P(MMA-*co*-MPDL) and PCL films³⁸ were degraded through a surface erosion mechanism.

SEM (Figure 7) and AFM (height images in Figure 8, cross section in Figure S6 and phase images in Figure S7) were then used to gain insight into surface erosion of thin polymer films from P(MMA-*co*-S) **P1**, P(MMA-*co*-MPDL) **P2–P4**, PLGA, PLA and PCL. Note that all thin film surfaces before hydrolysis (0 month) were not perfectly smooth at the nanometric scale and exhibited either several clusters of a few tens of nanometers high or roughness of the same range. Importantly, as the degree of hydrolysis reached an advanced stage (6 or 12 months), all films underwent drastic changes in their surface morphology with increased roughness or with the apparition of pores. The apparition of a tip effect on pictures was characteristic of degraded surface and meant that transfer of matter from the degraded surface to the AFM tip occurred during imaging. This matter modified the tip geometry and resulted in altered resolution in AFM imaging.

PLGA thin films were totally degraded after 1 month. SEM images showed highly porous micrometric cavities. This micrometric roughness added to a softening of the material prevented us from obtaining AFM pictures of PLGA film surface. For PLA film, erosion was slower and SEM pictures showed a PLA film surface of increasing porosity with time. Several micrometric holes were formed after 1-month hydrolysis, reaching tens of micrometers after 12 months. However, these porous structures were less visible by AFM. After 6 months, surface became rougher and small holes appeared, whereas after 12 months, the morphology of the surface drastically changed and large cavities of 30 nm deep appeared. For PCL, SEM

pictures showed numerous holes after 1 month which were turned into large and porous cavities after 12 months. By AFM, the surface of the film before hydrolysis was rough, with a difference in height of 50 nm. After 1 month, the surface seemed to flatten and for the 6-months hydrolysis, larger holes with a depth of 100 nm appeared. The 12 months film was too rough and porous to be observed by AFM with good resolution.

As expected, P(MMA-*co*-S) **P1** did not show drastic modification of morphology. By AFM, clusters seemed to erode with time, although this was less obvious by SEM. AFM observation of the copolymer with the lowest MPDL content (**P2**, $F_{\text{MPDL}} = 0.08$) showed a surface becoming more rugged and the clusters disappeared after 1 month. After 6 months, porosity started with a depth of 10 to 20 nm and after 12 months, holes became more numerous and their size and deep increased. The AFM pictures after 12 months of hydrolysis showed a drastic change in morphology, associated with advanced hydrolysis of the material. SEM images confirmed the apparition of numerous small holes on the surface of the films. For MPDL molar fraction of 0.12 (**P3**), the material became porous (20 to 40 nm deep) within only 1 month and the size and number of pores increased with time. The modification in morphology characteristic of film erosion was observed by AFM after 12 months. By SEM, many small holes similar to those observed by AFM were observed and bigger cavities of few micrometers appeared after 6 months. For the highest MPDL content (**P4**, $F_{\text{MPDL}} = 0.27$), several holes appeared on the surface after one month and the change in morphology occurred after only 6 months. After 12 months, large (few hundreds of nm) and deep (few tens nm) holes were observed on the surface by SEM. One can note that in all cases, AFM phase imaging pointed out the softening of the material with time (Figure S6), which became more viscoelastic while hydrolysis proceeded.

Altogether, these data indicated that films composed of P(MMA-*co*-MPDL) undergo surface erosion, similarly to PCL films. Because of the strong hydrophobicity and rigidity of

the copolymers, water uptake was rather modest ($< 10\%$), thus preventing bulk hydrolysis. Although slow, surface erosion was confirmed by both AFM and SEM and the kinetic of porosity formation on the surface of the film was affected by the MPDL content: the higher the MPDL content, the earlier the holes formation.

Figure 7. SEM images (Mag = 5 KX) showing the evolution of thin film surfaces of MMA-based copolymers **P1–P4**, PLGA, PLA and PCL during hydrolytic degradation in PBS (0.1 M, pH 7.4, 37 °C). Scale bar = 5 μ m.

Figure 8. AFM height images obtained in AC mode during hydrolytic degradation in PBS (0.1 M, pH 7.4, 37 °C) of MMA-based copolymers **P1–P4**, PLGA, PLA and PCL (5 μm × 5 μm, except for PLA at 12 months, 2 μm × 2 μm). The z-scale is indicated on the right side of each image (colored bar).

Enzymatic degradation

Hydrolytic degradation is of utmost importance while considering polyester family, as it is considered to be the main degradation mechanism in vivo.⁴⁰ However, since they are also susceptible to enzymatic degradation,⁴¹ the sensitivity of P(MMA-*co*-MPDL) and P(OEGMA-*co*-MPDL) copolymers to the action of lipases, a sub-class of the esterases, was studied. Incubation of the different copolymers was performed in 0.1 M PBS at 37 °C for one week in presence of lipases from *Candida Antartica*, one enzyme already used in the literature for such a purpose.^{16,27,42} Enzymatic cleavage is known to be specific and to catalyze hydrolysis, enzymes need to interact with their substrate (i.e., the ester bond of the polymer).⁴³⁻⁴⁵ Consequently, the affinity between the polymer main chain and the enzyme as well as the environment of the ester bond strongly affect the efficacy of the enzyme.

Negligible degradation was observed with P(MMA-*co*-MPDL) copolymers (**P1–P4**, Table 2), as illustrated by nearly perfect overlay of the SEC chromatograms all along the experiment (Figure S8). Conversely, P(OEGMA-*co*-MPDL) (**P4–P8**) displayed moderate degradation (-6–15%) while the control copolymer without MPDL (**P5**) was perfectly inert (Table 2, Figure S9).

Table 2. Evolution Of The Number-Average Molar Mass (M_n) Of P(MMA-*co*-MPDL) and P(OEGMA-*co*-MPDL) Copolymers After Enzymatic Degradation.

Expt.	Methacrylic ester	F_{MPDL}^a (mol. %)	M_n decrease ^b (%)
P1	MMA	0	-2
P2	MMA	8	-3
P3	MMA	12	-2
P4	MMA	27	-1
P5	OEGMA	0	< -1
P6	OEGMA	9	-15
P7	OEGMA	15	-13
P8	OEGMA	27	-6

^aDetermined by ¹H NMR spectroscopy. ^bDetermined by SEC using PMMA standards.

We assumed that hydrophobicity of the P(MMA-*co*-MPDL) copolymer backbone prevented interaction between the enzyme active site and ester functions, whereas the relatively water-solubility of P(OEGMA-*co*-MPDL) copolymers enabled at least partial enzymatic cleavage. However, we suspected the detrimental influence of hydrophobic MPDL units on enzyme accessibility to ester moieties as the higher the MPDL content in the copolymer, the lower the M_n decrease: -15 % for **P6** ($F_{\text{MPDL}} = 0.09$), -13 % for **P7** ($F_{\text{MPDL}} = 0.15$) and -6 % for **P8** ($F_{\text{MPDL}} = 0.27$). This trend should however be taken with care given the error of measurement from SEC. In addition, high aromatic group contents may result in interaction between aromatic rings (π -stacking) from MPDL units and induce specific conformation of the polymer chains,^{4,46} that would further reduce accessibility to ester functions. Also, given PEG is known to induce steric repulsion of proteins, one can question, even though they are relatively small, the adverse effect of OEG side chains on enzyme accessibility to the ester groups. Although enzymatic degradation was modest, it could likely be improved as it has been shown that performing the degradation on a longer timescale (35 days) and replacing the degradation medium every 24 h enabled extensive degradation of MPDL-containing materials.⁴⁷

Preliminary in vivo toxicity

Although OEGMA-based materials are considered to be non-toxic and potentially stealth,^{16,48-57} inserting multiple MPDL units group could modify the toxicity of the resulting copolymers. Even though innocuousness of P(OEGMA-*co*-MPDL) copolymers was previously demonstrated on two representative mammalian cell types,²⁴ in vivo toxicity has never been investigated.

P(OEGMA-*co*-MPDL) copolymers containing 15 and 27 % MPDL (**P7** and **P8**, respectively) were injected intravenously (single injection) in mice with concentrations

ranging from 0.8 to 2.4 g.kg⁻¹. The body weight and the mice behavior were monitored for 20 days. In all cases, despite a slight weight decrease during the first 6 days (ranging from -0.5 to -5 %), in general for the highest copolymer concentrations, evolution of body weight was nearly constant with time, similarly to untreated mice (Figure 9). Except for **P8** at 0.8 mg.kg⁻¹, the higher the copolymer concentration, the higher the body weight loss. However, neither mortality nor noticeable modification in terms of feeding and behavior was observed, suggesting the safety of the treatment.

Figure 9. Relative body weight change of mice, as a function of time after intravenous injections of PBS (0.01 M) or P(OEGMA-*co*-MPDL) (a) **P7** and (b) **P8**. The error bars represent the standard deviation (SD, n = 5).

Interestingly, the median lethal dose (LD₅₀) of traditional hydrophobic polyesters was equal to 0.22 g.kg⁻¹ for PLGA nanoparticles⁵⁸ and 1.47 g.kg⁻¹ for PEG-*b*-PCL nanoparticles⁵⁹ and PEG-*b*-PLA nanoparticles were well tolerated up to 0.44 g.kg⁻¹.⁶⁰ Despite the fact that P(OEGMA-*co*-MPDL) copolymers are water-soluble and not under the form of nanoparticles, their innocuousness in vivo, even at high concentration (2.4 g.kg⁻¹), makes them promising building block for the design of biocompatible and biodegradable polymers. Also, in vivo

toxicity of non-degradable, hydrophilic polymers, such as PEG, was also weak and LD₅₀ ranged from 8.6 g.kg⁻¹ for $M_{n,PEG} = 400 \text{ g.mol}^{-1}$ to 16.0 g.kg⁻¹ for $M_{n,PEG} = 4000 \text{ g.mol}^{-1}$.^{61,62}

Conclusion

Comprehensive degradation study of well-defined MPDL-containing polymethacrylates copolymers of opposite solubility (either based on MMA or OEGMA) synthesized by NMrROP, by means of long-term hydrolytic degradation, degradation of thick and thin films together with enzymatic degradation, all achieved in PBS (0.1 M, pH 7.4, 37 °C), was performed and point-by-point comparison with traditional aliphatic polyesters (PLGA, PLA and PCL) was established for benchmarking purposes.

It was shown that P(MMA-*co*-MPDL) copolymers slowly degraded in PBS with degradation kinetics slower than that of PCL. P(MMA-*co*-MPDL) film erosion suggested that combination of copolymer hydrophobicity and rigidity prevented bulk erosion and thus a slow surface erosion was observed by SEM and AFM. As expected, no decrease in M_n was obtained after enzymatic degradation.

Conversely, water-soluble P(OEGMA-*co*-MPDL) copolymers led to significant degradation under long term hydrolysis in PBS. The degradation kinetics was finely tuned by varying the MPDL content, which enabled to obtain degradation performances in between those of PLA and PCL, thus representing an important result. However, P(OEGMA-*co*-MPDL) copolymers were only moderately degraded by enzymes, likely because of a combination between a too high hydrophobicity of MPDL units, potential conformation of the copolymer chain because of hydrophobic interaction and steric repulsion of OEG side chains, thus preventing optimal cleavage by the enzyme.

On one hand, as they remained rather stable under hydrolytic and enzymatic conditions, P(MMA-*co*-MPDL) copolymers might be well-suited for biomaterials intended for long-term use, such as devices or implants.^{7,46,63,64} On the other hand, P(OEGMA-*co*-MPDL) demonstrated promising degradation rate under hydrolytic conditions and might thus be envisioned for short- or mid-term applications such as nanoscale drug-delivery systems and meet a need for hydrophilic degradable materials with tunable degradation kinetics.

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Supporting Information

Pictures of the copolymer solutions or dispersion in PBS during hydrolytic degradation, evolution of the SEC chromatograms of MPDL-containing copolymers and polyesters during hydrolytic and enzymatic degradations, pictures of the polymer films during hydrolytic degradation, AFM cross sections and phase images during hydrolytic degradation.

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