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Hydrolytic degradation of PCL-PLLA semi-IPNs exhibiting rapid, tunable degradation

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Abstract

Accelerating the rate of polyester hydrolytic degradation is of interest for numerous biomedical applications. Poly(ϵ -caprolactone) (PCL) and poly(L-lactic acid) (PLLA) have been extensively studied as thermoplastic homo- and copolymers as well as PCL-PLLA blends. PCL-PLLA semi-interpenetrating networks (semi-IPN) prepared with thermoplastic PLLA embedded in a cross-linked PCL diacrylate (PCL-DA) network were previously shown to exhibit uniquely accelerated degradation behavior that increased with PLLA content. Herein, their properties before and during degradation were further investigated to reveal the origin of this behavior and to better understand the semi-IPNs' degradation mechanism. Initially, semi-IPNs exhibited restricted spherulite size and irregularity, as well as a phase-separated morphology and PLLA-rich surface. Under accelerated conditions (1 M NaOH, 37 °C), degradation was revealed to be initiated in PLLA regions. It was also found that the PCL-DA crosslinking and PCL-PLLA phase separation played the largest roles in degradation rates and that semi-IPNs underwent faster rates of degradation than an analogous blend largely due to the reduced crystallinity of PCL-DA. Non-accelerated conditions (PBS [pH = 7.4], 37 °C) up to 56 weeks, which had never before been studied for polyester semi-IPNs, revealed similar trends in degradation rates.

Keywords

Semi-interpenetrating networks; poly(ϵ -caprolactone); poly(L-lactic acid); degradation

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Supporting Information Available: The following files are available free of charge.

Initial film PCL and PLLA crystallinity values (%X_c) as determined from DSC; cross-sectional SEM images for initial PCL-DA (n = 45) and semi-IPN (75:25; n = 45) films; contact angle measurements for initial PCL-DA and semi-IPN films; cross-sectional SEM images of PCL-DA (n = 25) and semi-IPN (75:25; n = 25) films throughout accelerated (1 M NaOH, 37 °C) degradation; images of PCL-DA and semi-IPN films after accelerated (1 M NaOH, 37 °C) degradation; ATR-FTIR spectra of semi-IPN film surfaces upon accelerated (1 M NaOH, 37 °C) degradation; visual comparison of semi-IPN versus blend control films (75:25; n = 25) at 24 h accelerated (1 M NaOH, 37 °C) degradation; visual comparison of PCL-DA versus PCL control films (n = 25) at 24 h accelerated (1 M NaOH, 37 °C) degradation; mass loss and visual accelerated (1 M NaOH, 37 °C) degradation of PLLA control films (PDF).

INTRODUCTION

Aliphatic polyesters are extensively utilized in and explored for a variety of biomedical applications such as medical devices, drug delivery carriers and regenerative engineering scaffolds.^{1–5} The rate of biodegradation is critical to application performance and, as such, has been the subject of extensive study. Highly complex, polymer biodegradation is generally influenced by a combination of properties, including: (1) bond chemistry⁶, (2) molecular weight⁷, (3) crystallinity⁸ and (4) phase microstructure.⁹ Biodegradation of aliphatic polyesters occurs via hydrolysis of labile ester bonds.⁵ Their biodegradation rates ultimately depend on access of water to the esters bonds, which can also be influenced by additional material properties such as hydrophobicity.^{10–12} In addition, observed degradation behavior can be affected by the testing conditions (e.g. base catalyzed), and other factors such as sample thickness.^{13–14}

Poly(ϵ -caprolactone) (PCL) is a biodegradable aliphatic polyester extensively used for biomedical applications.^{1–5} It is also a thermoresponsive shape memory polymer (SMP) in which the crystalline lamellae serve as “switching segments” that actuate shape recovery and fixity when heated above or cooled below its melt transition temperature (T_m).¹⁵ Chemically cross-linked SMP networks have been formed from PCL dimethacrylates,¹⁶ and we have reported those formed from solvent-casted PCL diacrylate (PCL-DA).¹⁷ We have also previously described “self-fitting” PCL-DA SMP scaffolds with the potential to treat irregularly shaped craniomaxillofacial (CMF) bone defects.¹⁸ Following exposure to warm saline at $T > T_{trans}$ ($T_{trans} = T_m$ of PCL), the scaffold becomes malleable and can be readily press-fitted into an irregular defect. Subsequent cooling to $T < T_{trans}$ causes the scaffold to return to its original rigid state, locking in its new shape within the defect. However, the slow degradation of PCL, requiring 2+ years for complete resorption,^{9, 19–21} may limit bone regeneration using PCL scaffolds²² as well as other biomedical applications.

To accelerate the rate of PCL degradation, poly(L-lactic acid) (PLLA), another hydrolytically-degradable polyester, is often incorporated via copolymerization or blending.²³ Such materials typically exhibit increased rates of degradation over PCL alone as well as enhanced mechanical strength.^{24–27} The accelerated degradation has been attributed to the immiscibility and subsequent phase separation of PCL and PLLA that ultimately leads to increased water permeability.²⁸ We recently reported PCL-PLLA semi-interpenetrating networks (semi-IPNs), both solid films²⁹ and porous scaffolds,³⁰ comprised of cross-linked PCL-DA and thermoplastic PLLA. For these PCL-PLLA semi-IPNs, the PCL:PLLA wt% ratios were systematically tuned (100:0 [PCL-DA control], 90:10, 75:25, 60:40). The semi-IPN structure was confirmed to enable the formation of both PCL and PLLA crystalline domains. This favorably contributed to not only retention of shape memory behavior but also to the observed increased strength and rigidity for the “75:25” PCL-PLLA semi-IPNs. Also in these initial studies, PCL-PLLA semi-IPNs unexpectedly exhibited substantially accelerated rates of degradation *in vitro* versus the PCL-DA controls. The unique degradation behavior of such semi-IPNs had not been previously reported. While PCL-PLLA semi-IPNs prepared by cross-linking diisocyanate-bridged 4-arm star PCL oligomers in the presence of PLLA have also been reported,³¹ the degradation behavior was not characterized.

Given the unique and unexplored accelerated degradation behavior of PCL-PLLA semi-IPNs, herein, we sought to probe this by evaluating properties such as % crystallinity, crystalline morphology, wettability and surface composition before and during degradation. Moreover, whereas our previous studies were limited to base-catalyzed conditions, neutral conditions were also employed in this work. Thus, semi-IPNs of varied PCL:PLLA wt % ratios (100:0 [PCL-DA control], 90:10, 75:25, 60:40) and PCL-DA average degree of polymerization (n ; $n = 25, 45$) were prepared (Figure 1). For the semi-IPNs, the PLLA average degree of polymerization (m) was kept constant at $m = 90$. Additional thermoplastic homopolymers and blend controls utilized included: (1) PLLA ($m = 90, 850$), (2) 75:25 PCL:PLLA wt% blends ($n = 25, 45$) and (3) PCL ($n = 25, 45$).

EXPERIMENTAL SECTION

Materials

Polycaprolactone diol (PCL₉₀-diol; $M_n \sim 10,000$ g/mol), poly(L-lactic acid) (PLLA₁₇₀₀; $M_n \sim 123,000$ g/mol), ϵ -caprolactone, L-lactide, stannous 2-ethylhexanoate, triethylamine (Et₃N), acryloyl chloride, 4-dimethylaminopyridine (DMAP), 2,2-dimethoxy-2-phenylacetophenone (DMP), 1-vinyl-2-pyrrolidinone (NVP), potassium carbonate (K₂CO₃), sodium hydroxide (NaOH), phosphate-buffered saline (PBS; 1X, pH = 7.4), ethylene glycol and solvents were obtained from Sigma-Aldrich. Anhydrous magnesium sulfate (MgSO₄) was obtained from Fisher. Reagent-grade CH₂Cl₂ and NMR-grade CDCl₃ and D₂O were dried over 4 Å molecular sieves prior to use.

Material Synthesis

PCL_{2n}-diol ($n = 25$) and PLLA_{2m}-diol ($m = 90$) were synthesized as previously reported.²⁹ Briefly, PCL_{2n}-diol and PLLA_{2m}-diol were prepared by the ring-opening polymerization of ϵ -caprolactone or L-lactide, respectively, with ethylene glycol as the initiator and stannous 2-ethylhexanoate catalyst. The terminal hydroxyl groups of PCL_{2n}-diol ($n = 25, 45$) were subsequently reacted with acryloyl chloride, resulting in photo-crosslinkable acrylate (OAc) groups. The number average molecular weights (M_n) and degrees of acrylation were determined by proton nuclear magnetic resonance (¹H NMR) and were in agreement with those previously reported.

Film Fabrication

Solutions (25 wt% in CH₂Cl₂) of PCL:PLLA (100:0 [PCL-DA control], 90:10, 75:25, 60:40 wt% ratio; $n = 25, 45$ and $m = 90$) were prepared with 15 vol% of a photoinitiator solution (10 wt% DMP in NVP). The solution was transferred to a circular silicone mold (45 mm x 2 mm; McMaster-Carr) secured between glass slides and exposed to UV light (UV-Transilluminator, 6 mW cm⁻², 365 nm) for 3 min per side. The solvent-swollen film was sequentially removed from the mold, air dried (room temperature [RT], 12 h), dried *in vacuo* (36 in.Hg, RT, 4 h), soaked in ethanol (3 h) and air dried. The semi-IPN film was finally annealed (36 in.Hg, 85 °C, 1 h) and allowed to set at RT (48 h) before testing. For a control film, an annealing temperature of 160 °C was also used.

Thermoplastic PLLA ($m = 90, 850$), 75:25 PCL:PLLA wt% blend ($n = 25, 45$; $m = 90$) and PCL ($n = 25, 45$) controls were prepared via melt casting into ~ 5 mm x ~ 1.1 mm molds. Polymers containing PLLA ($T_m = \sim 155$ °C) were melted at ~ 160 °C whereas the thermoplastic PCL polymers ($T_m = \sim 55$ °C) were melted at ~ 85 °C. Film samples were allowed to set at RT (48 h) prior to testing.

Film Characterization

Thermal Properties—Differential scanning calorimetry (DSC, TA Instruments Q100) was used to determine T_m and the weight-adjusted % crystallinity of PCL and PLLA components in each semi-IPN composition. Film samples (~ 10 mg; $N = 1$, per time point) were sealed in hermetic pans and heated from RT to 200 °C at a heating rate of 5 °C min⁻¹. From the endothermic PCL and PLLA melting peaks, T_m and enthalpy change (ΔH_m) were measured. As in similar reports,^{32–33} adjusted percent crystallinity (% χ_c) was calculated via Equation (1):

$$\% \chi_c = \frac{\Delta H_m}{w_f \Delta H_m^\circ} \times 100, \quad (1)$$

where ΔH_m was calculated by the area of the melting peak, w_f is the component weight fraction (PCL:PLLA wt% ratio) within the semi-IPN and ΔH_m° is the enthalpy of fusion of 100% crystalline PCL (139.5 J g⁻¹)³⁴ or PLLA (93.0 J g⁻¹).³⁵

Polarized Optical Microscopy (POM)—Thin films for POM evaluation were fabricated on microscope slides, secured under a thin cover slip (0.15 mm). A Zeiss Axiophot microscope equipped with a polarizer and a digital camera (Nikon DXM1200) was used for characterizing the spherulitic morphology of the samples. Samples ($N = 1$) were visualized with a 20X objective, and image acquisition was controlled via Nikon ACT-1 software. Spherulite size was determined from the images with ImageJ software.

Scanning Electron Microscopy (SEM)—Film surfaces and cross-sections were evaluated via SEM. Samples ($N = 1$) were subjected to Au-Pt coating (~ 4 nm) prior to imaging. A Tescan Vega 3 SEM with an accelerating voltage of 10 kV was used to obtain the magnifications necessary to observe initial film surfaces. A JEOL 6400 SEM with an accelerating voltage of 10 kV was used to obtain other film images.

Attenuated Total Reflectance (ATR-FTIR)—An ALPHA interferometer (Bruker) equipped with a Platinum ATR module – diamond crystal with a 1.66 μ m depth of penetration at 45° – was used to determine film surface composition ($N = 1$). Each spectra was obtained in the region of 4000–500 cm⁻¹ via 32 scans at a resolution of 4 cm⁻¹.

Contact Angle Goniometry—Static water contact angle (θ) measurements were taken using a CAM 200 goniometer (KSV Instruments) equipped with an autodispenser, video camera and analysis software (Attension Theta). A 5 μ l deionized (DI) water droplet was placed on the film surface ($d = \sim 9$ mm; $N = 3$), and θ was iteratively measured over 120 s. θ values are reported at 15 s and 120 s.

Mass Loss – Accelerated and Non-accelerated Conditions—Discs (~ 5 mm x ~ 1.1 mm; $N = 4$, per time point) were immersed in 10 mL of media (“accelerated conditions”: 1 M NaOH solution, “non-accelerated conditions”: PBS) in sealed glass vials maintained at 37 °C. At each time point, the corresponding samples were taken from media, thoroughly rinsed with DI water and dried *in vacuo* (36 in.Hg, RT, ~ 16 h). The mass of the dried samples was then gravimetrically determined. Discs utilized for a given time point measurement were *not* utilized for further time points by returning to NaOH solution or PBS.

Degradation By-product Composition— ^1H NMR spectroscopy was used to determine the chemical composition of degradation by-products in the degradation media. Film discs (~ 5 mm x ~ 1.1 mm; $N = 1$, per time point) were immersed in ~ 1 mL of a 1 M NaOH D_2O solution in a sealed glass vial maintained at 37 °C. At 1, 4, 8, 24, 48 and 72 h, the solution was extracted for analysis. Spectra were recorded on a Mercury 300 MHz spectrometer. Peaks utilized for mol % comparison/analysis included: PCL-DA: [δ_{H} (D_2O): 1.95 (m, $-\text{COCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2-$)] and PLLA: [δ_{H} (D_2O): 3.88 (m, $-\text{COCH}(\text{CH}_3)\text{O}-$)].

Water Uptake with Non-accelerated Conditions—Discs (~ 5 mm x ~ 1.1 mm; $N = 4$) were immersed in 10 mL of PBS in sealed glass vials maintained at 37 °C. After 56 weeks, the samples were taken from media, rinsed with DI water, and the film surfaces were blotted dry. The mass of the samples was then gravimetrically determined before and after subsequent drying *in vacuo* (36 in.Hg, RT, ~ 16 h). The amount of water that had been absorbed was calculated with Equation (2):

$$\text{Water Update(\%)} = \frac{m_{\text{wet}} - m_{\text{dry}}}{m_{\text{dry}}} \times 100$$

(2)

Statistical Analysis—Data was reported as the mean $\pm$ standard deviation. Values were compared using ANOVA with Sidak or Dunnett post-hoc to determine p -values.

RESULTS

Initial Semi-IPN Properties

Semi-IPNs films comprised of cross-linked PCL-DA and thermoplastic PLLA at varying PCL:PLLA wt% ratios were prepared. Previous investigation confirmed that the resulting PCL-PLLA semi-IPN films contained the PCL:PLLA wt% ratios used in the fabrication as

well as PCL-DA cross-linking.²⁹ Given their ability to influence degradation behavior³⁶, the % crystallinity, morphology and surface properties were investigated prior to degradation conditions (Figure 2, Figure 3; Figure S1, Figure S2, Figure S3 Supporting Information).

Crystallinity—When adjusted for constituent weight (i.e. PCL:PLLA wt% ratio) within the semi-IPN, PCL % crystallinity remained consistent upon the inclusion and increase of PLLA within the semi-IPN films (Figure S1, Supporting Information). Semi-IPN crystallinity values were found to be ~35% and ~43% for films based on PCL-DA (n = 25) and PCL-DA (n = 45), respectively. Similarly, PCL-PLLA semi-IPN PLLA % crystallinity was found undergo minimal change with greater PLLA content, with values remaining at ~62%. In comparison, a thermoplastic PLLA control film exhibited similar crystallinity (~61%). Compared to corresponding thermoplastic PCL controls which exhibited crystallinity of ~80 % (PCL; n = 25) and ~65 % (PCL; n = 45), the crystallinity of cross-linked PCL-DA controls was significantly reduced to ~34% (PCL-DA; n = 25) and ~44% (PCL-DA; n = 45).

Crystalline Morphology—POM was utilized to observe differences in the films' semi-crystalline spherulites (Figure 2). POM images of the PCL-DA controls showed fairly regular arrays of small spherulites (up to ~15 μm in diameter) that were somewhat smaller for PCL-DA (n = 25). In contrast, the thermoplastic PLLA control revealed regularly-distributed, large spherulites (~60–160 μm in diameter). For the PCL-PLLA semi-IPNs with significant amounts of PLLA (i.e. 75:25 and 60:40 PCL:PLLA wt%), both PCL- and PLLA-like spherulitic morphologies were observed.

Surface Morphology—SEM imaging of film surfaces was employed to observe differences in surface features (Figure 3a). While PCL-DA films were homogeneous in appearance, the PCL-PLLA semi-IPN film surfaces were characterized by phase separation and heterogeneity. Cross-sectioned films confirmed that this extended beyond the surface and into the bulk (Figure S2, Supporting Information).

Surface Properties—Surface chemical composition was evaluated using ATR-FTIR spectroscopy (Figure 3b). Spectra of PCL-DA control films revealed a band at 1727 cm^{-1} , characteristic of carbonyl stretching within PCL's ester bond.³⁷ In contrast, semi-IPN surfaces displayed a PLLA-enriched surface due to the presence of an additional, larger band at 1760 cm^{-1} , characteristic of PLLA.³⁸

Film surface hydrophobicity was characterized by contact angle measurements of water droplets taken at 15 s and 120 s following deposition (Figure S3, Supporting Information). It was observed that PCL-PLLA semi-IPNs consistently exhibited greater surface contact angles (~62–80 °) versus corresponding PCL-DA controls (~45–54 °).

Accelerated Hydrolytic Degradation

Mass Loss—Under accelerated conditions (1 M NaOH, 37 °C), PCL-PLLA semi-IPN films underwent more rapid mass loss than the corresponding PCL-DA controls (~17–93% vs ~3–6% mass loss at 24 h) (Figure 4a, Figure 4c). In addition, the rate of degradation within semi-IPN compositions was generally more pronounced with greater PLLA content where 60:40 (PCL:PLLA wt%) semi-IPNs exhibited the greatest mass loss (~93% at 24 h).

Semi-IPN films based on PCL-DA ($n = 25$) generally degraded more rapidly than analogous semi-IPNs based on PCL-DA $n = 45$.

Mass Loss and Erosion—The appearance of films throughout accelerated degradation was also observed visually and via SEM imaging (Figure 4b, Figure 4d, Figure 4e). As observed previously,²⁹ PCL-PLLA semi-IPN films exhibited progressive dimensional loss (i.e. decrease in diameter and thickness). Under the same conditions, the PCL-DA control films experienced more degradation throughout the interior (Figure 4e; Figure S4, Figure S5, Supporting Information). SEM images show the difference for a control and a semi-IPN film of similar mass loss (~71–81%, “white boxes”).

Compositional Changes—Degradation of 75:25 (PCL:PLLA wt%) semi-IPNs was carried out in D₂O under accelerated conditions (1 M NaOH, 37 °C) and NMR analysis was used to determine the composition of degradation products over time (Figure 5). Based on the characteristic spectra peaks for PLLA and PCL components, the relative mol% of each was determined at each time point. After just 1 h, PLLA dominated the contents of the degradation media at (90–100 mol%). PCL was also found in the degradation media at time points as early as 4 h. While relative solubility of PCL versus PLLA may have contributed to these results, generally, the semi-IPN showed evidence of both PCL and PLLA degradation at early time points. By 24 h, essentially equimolar amounts of PCL and PLLA were present, and, thereafter, PCL was present in a majority. By 72 h (i.e. 85–92% mass loss), the solution compositions were 69:31 and 66:34 PCL:PLLA mol% when prepared with PCL-DA ($n = 25$, $n = 45$; respectively).

ATR-FTIR analysis was used to monitor changes in surface chemical composition during degradation. Spectra of representative 75:25 (PCL:PLLA wt%) semi-IPNs at 1, 4, 8, 24, 48 and 72 h indicated that the initially PLLA-rich surfaces of the PCL-PLLA semi-IPNs quickly become rich in PCL (Figure S6, Supporting Information). This occurred for semi-IPNs based on both PCL-DA ($n = 25$) and ($n = 45$).

Thermal Property Changes—For two representative semi-IPNs, 75:25 (PCL:PLLA wt %) based on PCL-DA ($n = 25$) and ($n = 45$), DSC was utilized to observe the thermal properties the PCL-PLLA semi-IPN films during degradation (Figure 6). The spectra revealed T_m peaks for both PCL and PLLA crystalline domains whose values generally remained constant (Figure 6a, Figure 6b). A $T_{m, PLLA}$ was still observed even at late stages of degradation (71+% mass loss; 48 h). Only at ~72 h, corresponding to a mass loss of ~88%, did appreciable reductions in $T_{m, PCL}$ and $T_{m, PLLA}$ values appear (Figure 6c). Changes in weight-adjusted % crystallinity of PCL and PLLA were unable to be determined due to the limitations in determining the weight fraction (w_f) of each constituent remaining at the specified time points.

Non-accelerated Hydrolytic Degradation

Degradation was also studied under non-accelerated conditions (PBS [1X, pH = 7.4], 37 °C), for a period of 56 weeks, in terms of mass loss, water uptake and visual features of erosion (Figure 7). As observed under alkaline conditions, the semi-IPNs underwent relatively-fast

degradation versus the corresponding PCL-DA control with ~9–15% and ~10–14% mass loss at 56 weeks versus ~5% and ~6% for the PCL-DA controls for films based on PCL-DA (n = 25) and (n = 45), respectively (Figure 7a, Figure 7b, Figure 7c). Degradation rate was also dependent on PLLA content, where 60:40 (PCL:PLLA wt%) semi-IPN films underwent the greatest mass losses at 56 weeks. Measurements of water uptake revealed similar trends (Figure 7d). All PCL-PLLA semi-IPN films absorbed significantly more water during degradation than the PCL-DA control films. This, too, generally increased with PLLA content. Lastly, at the observed mass loss, features more characteristic of bulk erosion (e.g. pores, cracks) were apparent in film cross-section images (Figure 7e).

DISCUSSION

As reported above, the degradation behavior of PCL-PLLA semi-IPNs was thoroughly investigated by: (1) extensive characterization of initial film properties and (2) the evolution of film properties during degradation, under both accelerated and non-accelerated conditions. In particular, the role of crystallinity, surface hydrophilicity and phase separation was considered. Crystallinity is known to decrease the rate of hydrolytic degradation due to restricted water diffusion.^{39–40} Both PCL % crystallinity and PLLA % crystallinity were similar between the PCL-DA control and PCL-PLLA semi-IPN films (Figure S1, Supporting Information). However, PCL % crystallinity was significantly reduced when compared to respective PCL thermoplastic control films. In addition, despite an initially PLLA-rich surface (as confirmed by FTIR), contact angle measurements revealed greater surface hydrophobicity of semi-IPNs versus PCL-DA controls (Figure 3b; Figure S3, Supporting Information). This is unexpected based on the relative hydrophilicity of PLLA.⁴¹ Thus, the increase may be a result of either semi-crystalline effects or phase separation-induced topography (Figure 3).^{42–43} Finally, with increasing PLLA content, PCL-PLLA semi-IPNs exhibited increasingly bi-phasic morphologies (Figure 2, Figure 3). Interestingly, annealing films at a higher temperature of 160 °C versus 85 °C was found to significantly reduce surface phase separation, as shown for representative 75:25 (PCL:PLLA wt%) semi-IPNs (Figure 8). As a result, the degradation rate decreased under accelerated conditions, with mass loss at 24 h reduced from ~41–44% (annealed at 85 °C) to ~7–25% (annealed at 160 °C). PCL crystallinity was shown to increase for films annealed at 160 °C compared to at 85 °C, but PLLA crystallinity was significantly reduced in films annealed at 160 °C (Figure S7, Supporting Information); a similar total crystallinity (i.e. combined PCL and PLLA crystallinity values) in films annealed at 85 and 160 °C was noted. Based on these results, a phase-separated morphology was concluded to have a significant role in the observed degradation of PCL-PLLA semi-IPNs. Under accelerated conditions, the semi-IPNs exhibited a faster rate of degradation versus the PCL-DA controls, with the rate increasing with PLLA content (Figure 4). Degradation by-products, observed via NMR, showed immediate evidence of PLLA degradation, and PCL degradation was also shown to begin at early time points of degradation (Figure 5). ATR-FTIR revealed that the semi-IPNs were initially PLLA-rich, but also that PLLA remained present throughout degradation (Figure S6, Supporting Information). Also, observed via DSC, T_m peaks for both PCL and PLLA within semi-IPNs were observed throughout all stages of degradation (Figure 6). These analyses confirmed that the accelerated degradation observed could be attributed to

the degradation of the combined PCL-PLLA semi-IPN system, and not to the exclusive degradation of the thermoplastic PLLA.

Enhanced degradation rates have also been observed in other PCL-PLLA systems, including blended and block copolymer strategies.^{23, 44–45} Thus, to evaluate potential differences in degradation rates, these semi-IPNs were compared to analogous blends and thermoplastic controls (Figure 9a; Figure S9, Supporting Information). POM images revealed that the PCL-PLLA blend controls (75:25 PCL:PLLA wt%) contained larger, more-regular spherulites while semi-IPNs exhibited restricted spherulite growth (i.e. reduced spherulite size and regularity) (Figure 9a). Crystallinity was also examined quantitatively for PCL $n = 45$ compositions, and it was found that the semi-IPNs exhibited a significantly lower PCL % crystallinity compared to analogous blends (Figure S8, Supporting Information).

Interestingly, PLLA crystallinity was significantly reduced in blends which were fabricated via melt-casting. Notably, the rate of degradation was substantially accelerated for the semi-IPNs versus the blends. Mass loss at 24 h was ~11–15% for the blend versus ~41–44% for semi-IPNs. In contrast to the semi-IPNs (Figure 4), SEM images of the blend show this relative lack of mass loss (Figure S9, Supporting Information). As the primary structural difference between the blend control and semi-IPN films is the cross-linked nature of PCL-DA, additional thermoplastic PCL controls ($n = 25, 45$) were investigated. POM imaging revealed that the thermoplastic PCL controls contained large, regular spherulites compared to the granular appearance for PCL-DA controls (Figure 9b). Quantitative crystallinity analysis also showed a significant reduction in crystallinity for the PCL-DA controls compared to the uncross-linked PCL controls (Figure S8, Supporting Information). After 24 h in accelerated conditions, the thermoplastics underwent only <1.5 wt% mass loss.

However, for the corresponding PCL-DA ($n = 25, 45$) control films, somewhat greater loss (~3–6% mass loss) was observed. At this minimal mass loss, the PCL thermoplastic did not exhibit visible erosion (Figure S10, Supporting Information). These additional blend and thermoplastic controls reveal the contributions of the disruption in PCL crystallinity upon cross-linking in the faster degradation rates for PCL-PLLA semi-IPNs. Lastly, to determine if there was a contrast in degradation behavior versus PCL-PLLA semi-IPNs, thermoplastic PLLA ($m = 90, 850$) controls were also analyzed (Figure S11, Supporting Information). PLLA ($m = 90$) represented PLLA having a degree of polymerization (m) equal to that of the PLLA within the semi-IPNs, whereas PLLA ($m = 850$) represented PLLA with a greater 'm.' At 24 h degradation under accelerated conditions, mass loss was somewhat similar between PLLA ($m = 90$) and PLLA ($m = 850$) (~30% mass loss). However, as noted, this mass loss was similar to or less than that determined for the PCL-PLLA semi-IPNs (Figure S12, Supporting Information).

Finally, under accelerated degradation conditions, the PCL-PLLA semi-IPNs exhibit surface-like erosion whereas the PCL-DA controls exhibited more characteristic bulk erosion (Figure 4e, Figure S4, Figure S5, Supporting Information). While aliphatic polyesters are known to undergo bulk erosion,¹³ surface erosion is often observed under highly basic testing conditions, including for thermoplastic PCL and PLLA.^{36, 46} When tested in non-accelerated conditions (PBS, 37 °C) for a period of 56 weeks, PCL-PLLA semi-IPNs still degraded at a greater rate with increasing PLLA content (Figure 7).

However, the nature of their physical mass loss, while still somewhat limited, was consistent with bulk erosion.

CONCLUSIONS

We previously reported PCL-PLLA semi-IPNs, prepared with thermoplastic PLLA embedded in a cross-linked PCL-DA network, having uniquely accelerated degradation rates.^{29–30} While accelerated degradation rates of PCL-PLLA copolymers and blends have been described, this had not yet been reported for semi-IPNs and so merited further investigation. Semi-IPN films were prepared with varied PCL:PLLA wt% ratios (90:10, 75:25 and 60:40). Prior to degradation, semi-IPNs exhibited a phase-separated morphology and a PLLA-rich surface. When subjected to accelerated conditions and non-accelerated test conditions, the rate of semi-IPN mass loss increased with PLLA content. Characterization revealed that the accelerated degradation of the semi-IPNs could not be attributed to the exclusively degradation of the thermoplastic PLLA. The accelerated degradation of the semi-IPNs was shown to be unique versus analogous thermoplastic PCL, PLLA and even PCL-PLLA blend controls, which can be attributed to the phase separation of PCL and PLLA phases/domains and to the reduction of PCL % crystallinity when cross-linked. This accelerated degradation behavior is expected to be valuable towards improving the performance of biodegradable polyesters in various applications such as tissue engineering scaffolds.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Film compositions investigated: (top) PCL-DA control and PCL-PLLA semi-IPNs and (bottom) PLLA thermoplastic (m = 90 and 850), 75:25 PCL:PLLA blend (n = 25, 45; m = 90), and PCL thermoplastic (n = 25 and 45) control films.

Figure 2.
POM micrographs of a) PCL-DA control and PCL-PLLA semi-IPN films and b) PLLA control films indicating crystalline morphologies.

Figure 3.

a) SEM images of PCL-DA control and PCL-PLLA semi-IPN film surfaces indicating phase morphology. b) Representative FTIR spectra of PCL-DA ($n = 45$) control and PCL-PLLA semi-IPN (75:25 [PCL:PLLA wt%]; $n = 45$) film surfaces highlighting a PLLA-rich semi-IPN surface.

Figure 4.

Mass loss and visual degradation under accelerated conditions (1 M NaOH, 37 °C) for PCL-DA control and PCL-PLLA semi-IPN films based on a,b) PCL-DA (n = 25) and c,d) PCL-DA (n = 45). e) SEM images of film cross-sections during accelerated degradation for PCL-DA (n = 45) control and PCL-PLLA (75:25 [PCL:PLLA wt%]; n = 45) semi-IPN films. Films of similar mass loss (~71–81%) are boxed for comparison.

Figure 5.

^1H NMR spectra of accelerated (1 M NaOH [D_2O], 37 °C) degradation media upon PCL-PLLA (75:25 [PCL:PLLA wt%]) semi-IPN film degradation for films based on a) PCL-DA (n = 25) and b) PCL-DA (n = 45).

Figure 6. Thermal properties of PCL-PLLA (75:25 [PCL:PLLA wt%]) semi-IPN films throughout accelerated (1 M NaOH, 37 °C) degradation. DSC curves for films based on a) PCL-DA (n = 25) and b) PCL-DA (n = 45), and c) quantified values throughout degradation for PCL and PLLA T_m.

Figure 7.

Mass loss under non-accelerated conditions (PBS [1x, pH = 7.4], 37 °C) for PCL-DA control and PCL-PLLA semi-IPN films based on a) PCL-DA (n = 25) and b) PCL-DA (n = 45). c) Quantified mass loss at 56 weeks non-accelerated degradation for PCL-DA control and PCL-PLLA semi-IPN films (*p < 0.01 vs corresponding PCL-DA control). c) Water uptake after 56 weeks non-accelerated degradation for PCL-DA control and PCL-PLLA semi-IPN films (*p < 0.05, **p < 0.01 vs corresponding PCL-DA control; +p < 0.05 vs corresponding PCL-DA (n = 25) film). e) SEM images of film cross-sections upon 56 weeks non-accelerated degradation for PCL-PLLA (60:40 [PCL:PLLA wt%]) semi-IPN films.

Figure 8.

Data for the representative PCL-PLLA (75:25, PCL:PLLA wt.%) semi-IPN is shown. SEM images of non-degraded film surfaces show a reduction in phase separation when annealed at 160 °C. Mass loss at 24 h under accelerated conditions (1 M NaOH, 37 °C) shows that films annealed at 160 °C degrade significantly slower than films annealed at 85 °C (** $p < 0.01$ vs corresponding film). Degradation was visualized at each time point further demonstrating that films annealed at 160 °C exhibit slower degradation than films annealed at 85 °C.

Figure 9.

a) POM micrographs, mass loss at 24 h under accelerated conditions (1 M NaOH, 37 °C) and the visual degradation of PCL-PLLA (75:25 [PCL:PLLA wt%]) blend control and PCL-PLLA (75:25 [PCL:PLLA wt%]) semi-IPN films (**p < 0.01 vs corresponding PCL-PLLA blend control). Results indicated the rapid, unique degradation of semi-IPNs. b) POM micrographs, mass loss at 24 h under accelerated conditions (1 M NaOH, 37 °C) and the visual degradation of PCL and PCL-DA control film (**p < 0.01 vs corresponding PCL control). Results revealed the effects of cross-linking on degradation.