Full Paper: A lower critical solution temperature (LCST) phase transition is reported for blends of the biodegradable polymers poly(D,L-lactide) (PDLA) and poly(ε-caprolactone) (PCL). From light scattering measurements the cloud point curve is determined to have a critical temperature of 86 °C and a critical concentration of mass fraction 36 wt.-% PCL. Optical microscopy of phase-separated films indicates a spinodal morphology at the critical concentration, and droplet phases at off-critical concentrations. After quenching phase separated blends below the melting temperature of PCL (60 °C), the crystallization of PCL is used to positively identify PCL-rich and PDLA-rich phases. When crystallization of PCL follows LCST phase separation, the size, shape, and distribution of crystalline regions can be adjusted by the degree of PCL/PDLA phase separation. Thus, the LCST phase separation offers a novel method to control microphase structure in biodegradable materials. Applications to control of mechanical and physical properties in tissue engineering scaffolds are discussed in light of the results.

LCST phase separation in biodegradable polymer blends: poly(D,L-lactide) and poly(ε-caprolactone)

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Introduction

Although few biological tissues are homogeneous, one-component materials, tissue engineering research to date has focused largely on pure aliphatic polyester scaffolds. The most popular biodegradable polymers, homopolymers or copolymers of poly(lactide) (PLA) and poly(glycolide) (PGA), are relatively stiff, brittle, and hard polymers. In contrast biological tissues like cartilage, skin, and tendon are often tough, flexible, or elastic. The unique mechanical properties of tissue are achieved through a multicomponent extracellular matrix composed of microphase-separated or network structures. Additionally some tissues contain oriented microstructures that lead to anisotropic mechanical properties.

<table>
<thead>
<tr>
<th>Polymer</th>
<th>Tensile modulus in GPa</th>
<th>Tensile strength in MPa</th>
<th>Elongation at break in %</th>
</tr>
</thead>
<tbody>
<tr>
<td>PLLA2)</td>
<td>3.1</td>
<td>48</td>
<td>2.8</td>
</tr>
<tr>
<td>PDLA24)</td>
<td>2.2</td>
<td>45</td>
<td>2.6</td>
</tr>
<tr>
<td>PGA2)</td>
<td>6.3</td>
<td>100</td>
<td>1.5</td>
</tr>
<tr>
<td>PCL25)</td>
<td>0.15</td>
<td>20.1</td>
<td>400</td>
</tr>
<tr>
<td>PLA(85)-b-PCL(15)2)</td>
<td>0.58</td>
<td>22</td>
<td>500</td>
</tr>
</tbody>
</table>

Tab. 1. Tensile properties of biodegradable polyesters
Tab. 2. Summary of pure polymer properties (according to the supplier, see text)

<table>
<thead>
<tr>
<th>Polymer</th>
<th>$M_w$ (Supplier)</th>
<th>$T_g$ [°C]</th>
<th>$T_m$ [°C]</th>
<th>$n$ (refractive index)</th>
<th>Polydispersity</th>
</tr>
</thead>
<tbody>
<tr>
<td>PDLA</td>
<td>127000</td>
<td>–60</td>
<td>60</td>
<td>1.50</td>
<td>1.50</td>
</tr>
<tr>
<td>PCL</td>
<td>114000</td>
<td></td>
<td></td>
<td>1.56</td>
<td>1.56</td>
</tr>
</tbody>
</table>

$M_w$ is the weight average molecular weight, and $T_g$ and $T_m$ are the glass transition and melting temperatures, respectively.

Ideally engineered tissue, consisting of live cells seeded into a synthetic degradable matrix, should have mechanical properties that match the natural tissue it is designed to replace. This is particularly important for load or tension bearing tissues like skin, bone, tendon, cartilage, and muscle, among others. Thus it is necessary to design synthetic degradable scaffolds with properties that more closely match those of native tissues than pure poly(lactides) and poly(ε-caprolactone) (PCL). An approach often successful with conventional engineered polymers is to strengthen or toughen brittle or stiff materials by incorporating a soft or elastomeric second component into the microstructure. When the softer (lower tensile modulus) component forms a second phase within the more brittle continuous phase, the second phase acts as a stress concentrator, enabling ductile yield mechanisms and preventing brittle fracture. This conventional approach to strengthening polymeric materials may also be applied to biodegradable polymers to develop materials with tissue-like properties. However, application of this method requires detailed knowledge of the phase behavior and microstructure of polymer mixtures. Although numerous studies examine room temperature miscibility of biodegradable blends, detailed studies of the temperature dependence of phase behavior and microstructure have not been reported for biodegradable polymers.

Poly(ε-caprolactone) (PCL) has a low glass transition temperature of about –60 °C (Tab. 2). PCL is a good candidate for toughening lactide-based polymers due to its lower tensile modulus and higher elongation at break than poly(lactide) (PLLA) and PDLA (Tab. 1). For example, biodegradable PLA–b–PCL block copolymers have been investigated and are found to range from soft to elastic depending on the PCL content (Tab. 1). However, these copolymers are generally more expensive and more difficult to prepare than their homopolymer counterparts. Blending may offer a cost-effective method of achieving a range of mechanical properties, although an ultimate solution may require some combination of both blending and copolymerization. A number of studies have examined the miscibility and mechanical properties of PLA with PCL, several of which are illustrated in Tab. 3. Each of these previous studies of PLA/PCL blends examined the miscibility at one temperature, either visually or with differential scanning calorimetry. However, the presence of crystalline PLA can obscure detection of liquid-liquid miscibility. Thus, some of the miscibility results are conflicting or incomplete. In addition, rubber toughening of PLA and PLA based urethanes has been achieved with some success by blending with PLA–b–PCL copolymers. These previous studies indicate that there is promise in toughening poly(lactides) by blending with soft or rubbery polymers like PCL or PLA–b–PCL. However, further progress requires knowledge of the phase behavior, such as the existence and location of the phase boundaries for an upper critical solution temperature (UCST) or a lower critical solution temperature (LCST). It is also necessary to understand the relationship between microstructure developed during phase separation and operating variables like temperature, composition, and time.

In this work, thermally induced phase separation in blends of poly(D,L-lactide) (PDLA) and PCL is evaluated as a means to control microstructure in biodegradable polymers. PCL is a crystalline polymer with a relatively low melting temperature near 60 °C. The D,L isomer of lactic acid is chosen to eliminate the added complexity of crystallization that occurs for PLLA. By using light scattering cloud point measurements, we present observation of an LCST phase boundary for this blend pair, previously unreported in the literature. The morphology of the phase-separated blends is characterized with optical microscopy following temperature jumps into the two-phase region. In addition, the distribution of PCL between each phase is identified by quenching below 60 °C after phase separation and monitoring the appearance of crystalline PCL.

**Experimental part**

**Blend preparation**

PDLA (Alkermes, Medisorb 100DL, Lot No. 7248-345, $M_w = 127000^{a,b}$) and PCL (Aldrich, Lot No. 07007DN, $M_w = 114000$) were used as obtained from the supplier. Properties of the pure PDLA and PCL are summarized in Tab. 2. Blends

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\(^a\) Certain equipment and instruments or materials are identified in the paper in order to adequately specify the experimental details. Such identification does not imply recommendation by the National Institute of Standards and Technology, nor does it imply the materials are necessarily the best available for the purpose.

\(^b\) According to ISO 31-8, the term “molecular weight” has been replaced by “relative molecular weight” $M_r$. For clarity, the conventional notation for number average ($M_n$) and weight average ($M_w$) molecular weight is utilized in the present paper.
were prepared by solvent casting from chloroform (Aldrich, ACS grade). Polymer solutions at a constant mass fraction of 10% were cast in Petri dishes and then dried under vacuum at 60°C for at least 4 d to remove residual solvent. A range of blend compositions from mass fraction 10% to 60% PCL was prepared in this manner. The resulting films were stored in a vacuum dessicator until experiments were performed.

Cloud point measurement
A laser light scattering apparatus was used to measure cloud points while scanning over temperatures of 80°C to 130°C at heating rates of 2.0°C/min, 1.0°C/min, and 0.5°C/min. The detector was positioned at an angle of 20° relative to the incident light. A computer interfaced heating stage (Mettler FP-82) controlled the temperature to within 0.1°C. For the cloud point measurements a 1 cm diameter polymer blend sample was placed in a 0.2 mm thick brass holder and pressed between a glass microscope slide and coverslip. The films were annealed at 75°C for one hour prior to each temperature scan to melt the PCL. This annealing temperature is in the one phase region for PDLA/PCL but above the 60°C melting temperature of PCL.

Optical microscopy
An optical microscope (Nikon Optiphot-2) coupled to a CCD camera (Kodak Model ES 1.0) and a vacuum heating stage were used to characterize the morphology of phase separated blends. Because the films were observed to dewet hydrophilic glass surfaces, samples were prepared by spin-casting (Headway Research, Model CB15) on silicon wafers (Semiconductor Processing Company) from chloroform solution (total polymer content mass fraction 10%). The silicon wafers were first acid-cleaned at 100°C for 1.5 h with a solution of mass fraction 70% H2SO4/30% H2O2. The hydrophobic silicon was prepared by etching acid-cleaned silicon wafers in a mass fraction 14% aqueous HF solution (J.T. Baker) for 3 min, followed by 5 min in a mass fraction mass fraction 40% NH4F solution (J.T. Baker). Films were spun at 2000 revolutions per min to yield thicknesses of approximately 20 μm. The films were imaged immediately after spin casting.

Results and discussion
Cloud point determination
Fig. 1 represents scattered intensity versus temperature data for a film containing mass fraction 22% PCL heated at a rate of 2.0°C/min. These data are typical of all compositions and heating rates. The error bars in Fig. 1 represent the standard deviation in scattered intensity over each 30 s (1°C) interval of data. As the heating begins, there is a gentle slope downward in scattered intensity as temperature increases, followed by a sharp rise in intensity at about 106°C. The sharp rise in scattered intensity is characteristic of an LCST phase transition, arising from an increase in concentration fluctuations near the phase boundary and growth of phase-separated domains.9 The cloud point is identified as the intersection of lines obtained by a linear least squares fit through the two slopes in the heating data, as shown in Fig. 1. In order to establish that the observed upturn in scattering is a thermodynamic phase transition, it is necessary that the scattering be reversible upon cooling, as is the case in Fig. 1. In fact, the heating and cooling cycle shown in Fig. 1 can be repeated many times, always yielding similar results.

It should be noted that for many of our samples, a hysteresis between the heating and cooling curves was
observed, as is often the case in polymer blends. For all concentrations, the cooling curve levels out to the “baseline” intensity an average of 3 °C lower than the upturn in the heating profile. This hysteresis, which can be minimized by reducing the heating or cooling rate, is indicative of differing kinetics during phase separation (heating) and remixing (cooling). In this paper, we use the upturn of scattered intensity in the heating profile as an operational definition of the cloud point.

The small downward slope in scattered intensity during heating below the cloud point temperature in Fig. 1 is most likely due to the temperature dependence of both refractive index and compressibility of the homogeneous polymer blend. For example, it is expected that refractive index, $n$, should decrease with increasing temperature (due to the density decrease), and that the isothermal compressibility, $\beta$, should increase with increasing temperature. For a homogeneous fluid, the scattered intensity, $I$, is related to $n$ and $\beta$ according to $I \propto n^2/\beta^{20}$. Thus a decrease in $n$ and increase in $\beta$ both contribute to a reduction in scattered intensity with increasing temperature in the homogeneous region. In addition, because of the crystalline nature of PCL, we can not rule out the possibility that some homogenization in the regions of melted PCL crystallites may give rise to the gentle downward slope in intensity prior to LCST phase separation. However, we annealed each sample at 75 °C for at least 30 min prior to each heating and cooling cycle, to provide for homogenization after melting of PCL.

The LCST cloud point curve is shown in Fig. 2. Two separate sets of solvent cast blends contribute to the data in Fig. 2. The critical point of the cloud point curve occurs at 86 °C and mass fraction 36% PCL. These results are relatively invariant for heating rates of 2 °C/min, 1 °C/min, and 0.5 °C/min. Despite the invariance to these heating rates, the observed cloud points may still reflect some shift to temperatures higher than the true thermodynamic phase boundary due to kinetic effects. Errors induced by kinetic effects, if any, are likely to be greatest at off-critical concentrations. At off-critical concentrations phase separation initially proceeds via nucleation and growth, and is usually slower than spinodal decomposition that occurs in the critical composition region.$^{21,22}$

Previous workers have reported both miscible and immiscible solvent cast blends of poly(lactic acid) and PCL at various temperatures, and those most relevant to the present work are described in Tab. 3.$^{6–8}$ The molecular weights of the polymers used in the studies in Tab. 3 are both higher$^{6,7}$ and lower$^{8}$ than $M_0$ in this study. For example, Yang et al. studied solution cast PLLA/PCL blends with $M_0$ values of 85 000 (PLLA) and 15 000 (PCL)$^{5}$. By using DSC and optical microscopy, they report evidence of partial miscibility in the melt at 200 °C for blends containing mass fractions between 10% to 50% PCL. Enhanced crystallization of PLLA in the phase separated blends was attributed to increased PLLA chain mobility due to PCL in PLLA-rich regions.$^{5}$ This PCL-enhanced crystallization of PLLA was independent of the overall PCL concentration. Hence changes in the overall PCL composition did not seem to effect the composition of PCL in the PLLA-rich phase. These observations are consistent with the existence of a phase boundary that intersects 200 °C (such as an LCST curve with critical point below 200 °C). Changes in the overall PCL concentration would thus affect the relative amounts of each phase, but not the distribution of PLLA and PCL between phases. The results of Yang et al. are consistent with the existence of the LCST phase boundary presented in this work, with the LCST shifted to higher temperatures due to the lower molecular weights. The amount of the shift of the LCST is unknown since miscibility was not examined at temperatures other than 200 °C. In addition it is not known how differences between the L-lactide and D,L-lactide isomers will affect the LCST phase boundary (PDLa was used in the present study).

The two other studies in Tab. 3 report phase separation in PLA/PCL blends with $M_0$ values higher than those in our study. One study investigated PLLA/PCL blends mixed in an extruder at 180 °C to 220 °C and report immiscibility for a blend containing mass fraction 20% PCL.$^{5}$ This conclusion was based on the observation of a bimodal distribution from size exclusion chromatography (SEC) in chloroform, as well as visual observations. However, it is unclear how the molar mass distribution from SEC in dilute solution relates to blend miscibility. Also, the crystallization of both PCL and PLLA hinders

<table>
<thead>
<tr>
<th>Reference</th>
<th>System$^a$</th>
<th>PCL composition mass fraction in %</th>
<th>Blending method</th>
<th>Miscibility</th>
</tr>
</thead>
<tbody>
<tr>
<td>6) PLLA (365 k, 849 k) PCL (160 k)</td>
<td>20</td>
<td>extrusion, 180–220 °C</td>
<td>immiscible, 25 °C</td>
<td></td>
</tr>
<tr>
<td>7) PDLa (325 k) PCL (266 k)</td>
<td>10 to 90</td>
<td>solution cast (CH$_2$Cl$_2$)</td>
<td>immiscible, 25 °C for 30 to 70% PCL</td>
<td></td>
</tr>
<tr>
<td>8) PLLA (85 k) PCL (15 k)</td>
<td>0 to 50</td>
<td>solution cast (CHCl$_3$)</td>
<td>immiscible, 200 °C</td>
<td></td>
</tr>
</tbody>
</table>

$^a$ Numbers in parentheses are polymer weight average molecular weights before processing. PLLA = poly(l-lactide); PDLa = poly(d,L-lactide).
LCST phase separation in biodegradable polymer blends: poly(D,L-lactide) and ...
Integration of the bright (PCL-rich phase) and dark areas (PDLA-rich phase) in Fig. 3d (NIH Image software) indicates that 49% of the area is occupied by the PCL phase. This agrees with the cloud point curve in Fig. 2 that shows a critical blend should split into two phases with roughly equal mass at 100°C (due to the symmetry of the cloud point curve). Here, we have made the assumption that the 2-dimensional surface projection represents the compositions present in the 3-dimensional blend. More quantitative determinations of composition in the surface and bulk of the blend film would require techniques beyond the scope of this work (e.g., XPS, SIMS, FTIR).

Fig. 4a presents an optical micrograph of a mass fraction 50% PCL blend 100 min after a temperature jump to 100°C. Although the approach to equilibrium is probably not complete at 100 min, it is clear that the blend has separated into droplets, approximately 20 to 30 μm in diameter. Using the cloud point curve as a guide, it is expected that the droplets are rich in PDLA, and the continuous phase is rich in PCL. This is confirmed by quenching the film to 30°C and observing the appearance of PCL spherulites over time, given in Fig. 4b, 4c, and 4d. Fig. 4b shows that after 3 min PCL spherulites are growing in the continuous phase regions and not in the droplets. Fig. 4c shows that after 5 min some of the spherulites begin to impinge upon one another and upon the PDLA droplets. After 30 min, Fig. 4d, spherulite growth is complete and PCL crystals do not penetrate into the droplet phase. These observations confirm that the droplets are rich in PDLA, in agreement with the cloud point curve (Fig. 3).

Fig. 5a presents an optical micrograph of a mass fraction 20% PCL/80% PDLA film spun-cast on silicon. (a) 115°C (two-phase region), 15 min. (b) 35 min after a quench to 30°C, under crossed polars.
properties of tissue. In addition, the interfacial adhesion at the microphase boundaries is crucial to mechanical strength. A useful way to enhance compatibility at the interface is to add small amounts of PDLA-b-PCL block copolymer, or to induce formation of copolymer at the interface by reactive compatibilization.

Conclusions

We report the existence of an LCST phase transition for PCL/PDLA blends. The significance of the LCST phase transition is that phase separation and microstructure can be controlled with both temperature and blend composition. The relationship between PCL/PDLA phase separation followed by PCL crystallization may allow detailed morphological control with programmed temperature jumps (above LCST) and quenches (below the \( T_m \) of PCL). For example, the size and distribution of micro-phase-separated structures can be controlled by adjusting the PCL concentration, temperature, and time inside the LCST two-phase region. Quenching into the one-phase region below the \( T_m \) of PCL will lead to PCL crystallization in one or possibly both phases. PCL crystallization should be sensitive to the distribution of PCL between the phases, as set by the LCST phase separation. One may thus achieve control of PDLA and PCL domain sizes as well as PCL crystal ordering by coupling LCST phase separation with crystallization steps. Experiments are planned to investigate the effect of microstructure developed during processing on the mechanical properties. The effect of copolymers on the LCST phase boundary and on mechanical properties will be accessed in future work.

Acknowledgement: J. C. M. gratefully recognizes support of the NRC/NIST Postdoctoral Research Fellowship.

17) R. G. Sinclair, Patent # 4045418, Gulf Oil Corporation, USA (1977)
23) L. Zhang, C. Xiong, X. Deng, Polymer 37, 235 (1996)
24) Product Specification for Medisorb 100DL, Polymer, Alkermes, Inc., USA