

# Blends of Novel L-Tyrosine-Based Polyurethanes and Polyphosphate for Potential Biomedical Applications

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**ABSTRACT:** Elastomeric biodegradable polyurethanes and polyphosphate have been developed using an L-tyrosine-based diphenolic monomer desaminotyrosine-tyrosine hexyl ester (DTH). Soft segments, which are polycaprolactone diol (PCL) and polyethylene glycol (PEG) have been used for the synthesis of two biodegradable L-tyrosine polyurethanes (LTUs), which are PEG-C-DTH and PCL-C-DTH. An investigation of the physico-chemical properties shows that these polymers have dramatically different properties. By blending LTUs with L-tyrosine polyphosphate (LTP), we hope to produce a family of materials with a wide range of thermal, morphological, surface, and degradative properties. Examination of the blends shows a smooth surface morphology with a partially phase-separated structure. These findings are consistent with the results obtained from thermal

analysis of the blends. Hydrophilic nature of PEG imparts the PEG-based blends (PEG-C-DTH/LTP) with a significantly higher surface and bulk hydrophilicity compared with the PCL-based blends (PCL-C-DTH/LTP). Finally, the blends demonstrate a rapid initial hydrolytic degradation in phosphate buffered saline (PBS) followed by a significantly slower, prolonged degradation. The observed trend may occur due to the rapid hydrolytic degradation rate of the polyphosphate polymer followed by the degradation of the polyurethane component. Thus, tuning the physical properties by blending LTUs with LTP may be useful for drug delivery device and soft tissue engineering scaffold applications. © 2009 Wiley Periodicals, Inc. *J Appl Polym Sci* 114: 3235–3247, 2009

**Key words:** polyurethane; blends; hydrolytic degradation

## INTRODUCTION

Biodegradable polymeric materials have been extensively studied for development of various platforms for the delivery of therapeutic agents, as scaffolds for tissue engineering, and for other biomedical applications. A major advantage of using such degradable polymers for biomedical applications is the elimination of surgery for device retrieval at a later stage. A number of synthetic polymers such as aliphatic polyesters,<sup>1,2</sup> polyphosphazenes,<sup>3</sup> poly(orthoesters),<sup>4,5</sup> polyanhydrides,<sup>6,7</sup> polysaccharides,<sup>8,9</sup> poly(amino acids),<sup>10–12</sup> and “pseudo” poly(amino acids)<sup>13,14</sup> have been applied as biodegradable materials for biomedical applications. Moreover, the interactions of these polymeric materials with host tissues have been studied by various researchers.<sup>15,16</sup>

“Pseudo” poly(amino acids) are a class of polymeric materials that are obtained via structural modification of homo poly(amino acids) through the incorporation of hydrolytically degradable non-pep-

tide bonds along with the enzymatically degradable peptide bonds within the polymer backbone. These materials offer better processing properties, increased hydrolytic degradation, and predictable as well as tunable swelling properties as compared with their corresponding homo poly(amino acids).<sup>17,18</sup> Novel “pseudo” poly(amino acids) such as LTP<sup>19–21</sup> and LTUs<sup>22,23</sup> have been developed using an L-tyrosine-based diphenolic monomer desaminotyrosine-tyrosine hexyl ester (DTH). In case of the LTUs, the hard segments are composed of DTH as the chain extender and 4,4'-methylenebis(cyclohexyl isocyanate) (C) as the diisocyanate. The soft segments are comprised of either polycaprolactone diol (PCL) or polyethylene glycol (PEG).

The introduction of different functional groups into the polymeric backbone has varied effects on the physico-chemical properties of the final polymers. LTP is brittle and degrades completely over a period of 8 days due to the hydrolytic instability caused by the presence of the labile phosphate bonds within the polymeric backbone.<sup>19,21</sup> In case of polyurethanes, their physico-mechanical properties are found to be primarily dependent on the macrodiol chemical structure.<sup>22,23</sup> The LTUs containing the

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PCL soft segment (PCL-C-DTH) possesses high elastic modulus, ultimate tensile stress, and slow degradation rate *in vitro* as compared with PEG containing polyurethane (PEG-C-DTH).<sup>22,23</sup> The properties observed for these polymers suggest that LTP may be used for short-term drug delivery applications; whereas, the LTUs may be used for long-term drug delivery or soft tissue engineering applications.

Several applications pertaining to drug delivery may benefit from the use of a polymer with tunable material properties such as a combination of the fast degradation rate of polyphosphate and the mechanical properties of polyurethanes. Theoretically, a copolymer of LTUs and LTP may be obtained by chemical synthesis; however, a more practical approach is the blending of these two polymers to obtain a cohesive miscible blend with retention of the desirable properties of both parent polymers. This technique will provide a means to fabricate a family of materials with intermediate properties that may be controlled by altering the composition of the blends. Several examples of this technique to prepare novel biomaterials or for controlling material properties of biomaterials exist in literature.<sup>24–29</sup> Laurencin and coworkers<sup>24,25</sup> have investigated the miscibility of the polymeric components in blends of degradable polyphosphazenes/poly( $\alpha$ -hydroxyester), and the degradation rates of these blends with the primary aim of reducing the acidity of degradation products, which is currently a major problem associated with implants fabricated from aliphatic polyester type biomaterials such as polylactic acid, polyglycolic acid, and poly(lactic-co-glycolic) acid. Zhang and coworkers<sup>26</sup> have studied blends of collagen/polylactic acid and reported faster degradation rates for the blends compared with pure polylactic acid. However, the mechanical properties of these blends have been found to be compromised on incorporation of collagen. Woodhouse and coworkers<sup>27,28</sup> have synthesized a phenylalanine-based chain extender and diisocyanate and utilized the pendant side chains of these molecules as reaction sites for synthesis of elastomeric biodegradable polyurethanes. They have investigated blends of PCL-based polyurethane with PEG-based polyurethane for physico-mechanical properties and concluded that the blend properties and composition are intimately connected. Results obtained from their research also suggest that higher quantities of PEG-based polyurethane within the blends leads to increased hydrophilicity, faster degradation, and weaker mechanical properties.

In this work, biodegradable segmented LTUs are blended with LTP in systematic ratios via a solution casting-solvent evaporation technique to obtain six blends. These new blends have been extensively characterized for their physico-chemical properties

including morphological, thermal, surface, and degradative properties. We hypothesize that blending LTP with PCL-C-DTH or PEG-C-DTH will yield materials with properties that are intermediate between the two parent polymers.

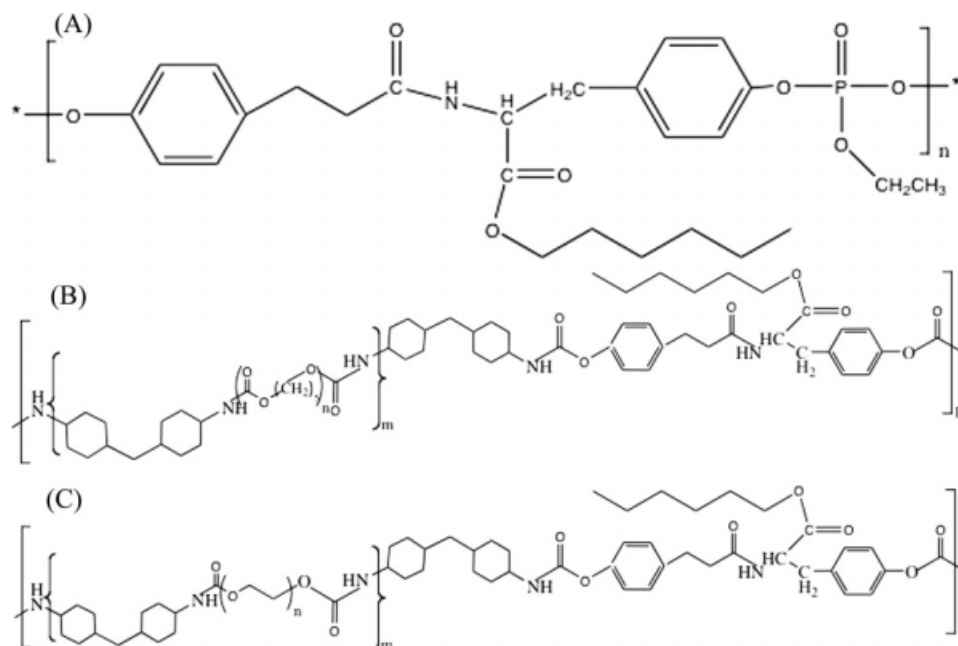
## MATERIALS AND METHODS

### Materials

L-Tyrosine, *n*-hexanol, thionyl chloride, diethyl ether, phloretic acid (also known as desaminotyrosine or DAT), *N*-ethyl-*N'*-dimethylaminopropyl carbodiimide hydrochloride (EDC-HCl), ethyl phosphodi-chloridate (EP), 4-dimethylaminopyridine (DMAP), dichloromethane (DCM), tetrahydrofuran (THF), dimethylformamide (DMF), polycaprolactone diol (PCL1250) (M.W. 1250), polyethylene glycol (PEG1000) (M.W. 1000), 4,4'-methylenebis(cyclohexyl isocyanate) (CHMDI), magnesium sulfate (MgSO<sub>4</sub>), stannous octoate, and hydrochloric acid (HCl) were obtained from Sigma-Aldrich Corporation (St. Louis, MO). All chemicals except dichloromethane and dimethylformamide were used without further purification. Dichloromethane was dehydrated by distilling it from a mixture with anhydrous calcium hydride to remove traces of moisture before each reaction step. Dimethylformamide was dehydrated by stirring with anhydrous calcium hydride and filtering before the reaction step.

### Fabrication of blends of polyphosphate and polyurethanes

The DTH monomer and LTP were synthesized according to the protocol developed by Sen Gupta and Lopina<sup>19,21</sup>; whereas, LTUs were synthesized according to Sarkar and Lopina's protocol.<sup>22,23</sup> LTP and LTUs synthesized using the above-mentioned protocols were characterized using NMR, FT-IR, and GPC, and the results were found to closely match the results in the literature.<sup>19,21–23</sup> The structure of LTP, PCL-C-DTH, and PEG-C-DTH polymers are shown in Figure 1(A–C), respectively. For each blend, the parent polyurethanes (PCL-C-DTH or PEG-C-DTH) and polyphosphate (LTP) were weighed according to the mass ratios described in Table I. The LTUs and LTP were then dissolved together in chloroform (for PCL based polyurethane) or dimethylformamide (for PEG based polyurethane) at a concentration of 5% w/v. Next, the polymer solution was cast into polytetrafluoroethylene dishes ( $\Phi = 25.4$  mm) and covered to allow for controlled evaporation of the solvent. Following 48 h of evaporation, the plates were placed in a vacuum oven at 40°C for 72 h to facilitate the removal of any residual



**Figure 1** Chemical structures of (A) LTP, (B) PCL-C-DTH, (C) PEG-C-DTH.

solvent. The films were then stored in a dessicator until use.

### Characterization of blends of polyphosphate and polyurethanes

Morphological analysis of the samples was performed using polarized optical microscopy (POM) and scanning electron microscopy (SEM). Discs ( $\Phi = 10$  mm) were obtained from pre-cast films using a cork-borer, placed on glasses slides, mounted under the cross-polarized filters of a Leitz Orthoplan Microscope, and viewed using a 10X objective. The images were captured using a CCD camera with a passive image capture (PCI) system. For SEM analysis, sections of the films were mounted on aluminum stubs, sputter coated with silver/palladium, and examined using a Hitachi S-2150 scanning electron microscope (SEM) at an accelerating voltage of 25

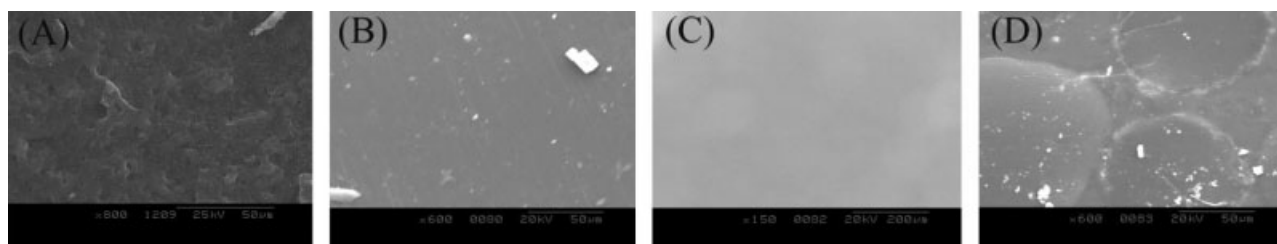
kV. The images were captured using a Quartz PCI system.

Differential scanning calorimetry (DSC, TA model 2910 instrument) was performed on the blends to determine glass transitions and the soft segment crystallinities. The samples used for DSC have identical processing histories before analysis and all the samples have been maintained at room temperature before analysis. The scans were performed from  $-100^{\circ}\text{C}$  to  $250^{\circ}\text{C}$  at a ramp rate of  $10^{\circ}\text{C}/\text{min}$ . The glass transitions on the scans were identified as the midpoints of the inflexion point on each spectrum. Thermal degradations of blends of polyphosphate and polyurethanes were studied using thermogravimetric analysis (TA model 2050 instrument). Approximately 10 mg of the blend was heated under a nitrogen atmosphere at a rate of  $10^{\circ}\text{C}/\text{min}$  to  $600^{\circ}\text{C}$  with a constant flow of nitrogen at a flow rate of 30 mL/min.

Contact angle studies were performed to correlate the relative surface hydrophilicity of the parent poly-

**TABLE I**  
Formulation of Blends of L-Tyrosine-Based Polyurethanes and Polyphosphate

Blend	10% Polyurethane solution (mL)	10% Polyphosphate solution (mL)	Solvent $\text{CHCl}_3$ or DMF (mL)	Polyurethane Mass (mg)	Polyphosphate Mass (mg)
PCL-C-DTH	5	0	5	500	0
90 : 10 PCL-C-DTH/LTP	4.5	0.5	5	450	50
70 : 30 PCL-C-DTH/LTP	3.5	1.5	5	350	150
50 : 50 PCL-C-DTH/LTP	2.5	2.5	5	250	250
PEG-C-DTH	5	0	5	500	0
90 : 10 PEG-C-DTH/LTP	4.5	0.5	5	450	50
70 : 30 PEG-C-DTH/LTP	3.5	1.5	5	350	150
50 : 50 PEG-C-DTH/LTP	2.5	2.5	5	250	250



**Figure 2** Scanning electron micrographs of PCL-based polyurethane and LTP blends. (A) PCL-C-DTH, (B) 90 : 10 PCL-C-DTH/LTP blend, (C) 70 : 30 PCL-C-DTH/LTP blend and (D) 50 : 50 PCL-C-DTH/LTP blend.

mer with increasing polyphosphate concentrations. The contact angle measurements were performed using a Ramè-Hart automated goniometer. Blended films were prepared by dissolving polymers in dichloromethane to obtain a 2% (w/v) solution. A clean glass coverslip was mounted onto a spin coater and held in position using vacuum, 3–4 drops of the polymer blend solution were placed onto the coverslip, and the spin coater was run at 2000 rpm for 30 seconds. The coverslip was dried under a flow of nitrogen and the surface was characterized by dynamic contact angle analysis using water as the liquid probe.

Swelling studies were performed using sterile distilled deionized water (DH<sub>2</sub>O). Pre-cast films were punched into 10 mm discs using a cork-borer and weighed to an accuracy of 0.1 mg on an analytical balance (Excellence Level, Mettler Toledo, Columbus, OH). Each sample was placed into an individual vial containing 20 mL of sterile DH<sub>2</sub>O and incubated at 37°C. The samples were removed from the incubator at pre-determined intervals, dabbed dry to remove any surface water, and weighed. The samples were then returned to their vials and re-incubated until the next sampling time. At the end of 78 h, the samples were removed from their vials and dried in a vacuum oven at 40°C for 4 days and reweighed. The degree of swelling was calculated by dividing weight of the swollen sample by the dry weight of the sample.

#### Degradation studies of blends

Degradation studies were performed using sterile phosphate buffered saline (PBS, pH = 7.4). Pre-cast

films were punched into 10 mm discs using a cork-borer and weighed to an accuracy of 0.1 mg on an analytical balance. Each sample was placed into an individual vial containing 15 mL of sterile PBS and incubated at 37°C. Three samples of each blend were removed from the buffer on days 1, 3, 7, 14, 21, 28, 42, and 56. After drying the samples in a vacuum oven at 37°C for 4 days, the samples were reweighed to determine the total amount of mass loss and calculate the percent total mass loss. The degraded samples were then analyzed using SEM as described previously in above section.

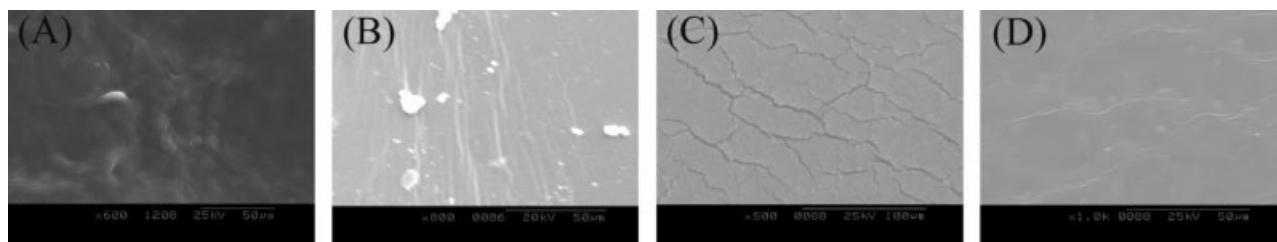
#### Statistics

All quantitative studies were performed in three replicates except for contact angle studies where four replicates were used. The Shapiro-Wilk test for normality was performed to determine if each sample group was normally distributed. Samples were considered normally distributed when  $P \leq 0.05$ . If no significant differences were found within a sample group, then the sample was considered normally distributed. Tukey's analysis of variance was then performed among the normally distributed sample groups. All results were considered significant if  $P \leq 0.05$ .

## RESULTS

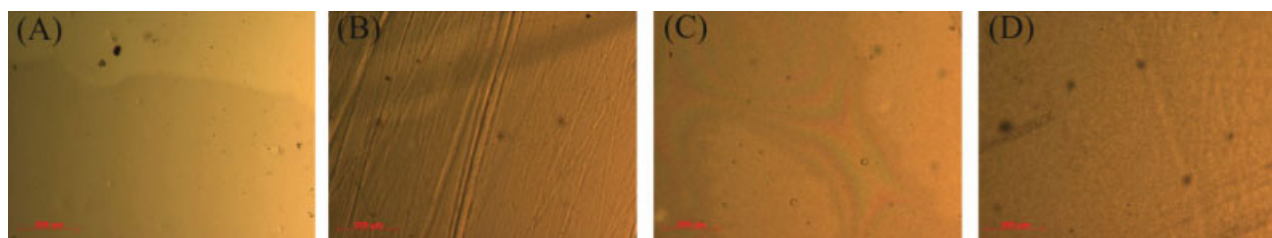
#### Microscopic characterization

Electron micrographs of films of PCL-C-DTH and its blends with LTP presented in Figure 2 show that the surface of both the pure PCL-C-DTH and PCL-C-



**Figure 3** Scanning electron micrographs of PEG-based polyurethane and LTP blends. (A) PEG-C-DTH, (B) 90 : 10 PEG-C-DTH/LTP blend, (C) 70 : 30 PEG-C-DTH/LTP blend and (D) 50 : 50 PEG-C-DTH/LTP blend.





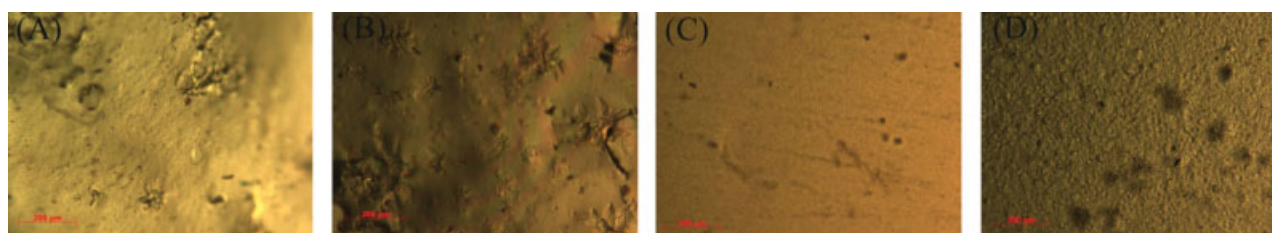
**Figure 4** Polarized optical micrographs of PCL-based polyurethane and LTP blends at 10 $\times$  magnification. (A) PCL-C-DTH, (B) 90 : 10 PCL-C-DTH/LTP blend, (C) 70 : 30 PCL-C-DTH/LTP blend and (D) 50 : 50 PCL-C-DTH/LTP blend. [Color figure can be viewed in the online issue, which is available at [www.interscience.wiley.com](http://www.interscience.wiley.com).]

DTH/LTP blended films have a slightly rough surface morphology. Similar results are also evident from Figure 3, which presents SEM images of surface of films of PEG-C-DTH polyurethane and its blends with LTP. POM images corroborate the surface morphology observed by SEM and in addition they indicate a minimal amount of phase separation for the pure LTU films (Figs. 4 and 5). Upon blending of LTP with LTUs, the formation of dark speckles on the surface of the films is observed. These speckles are distributed randomly on the surface of the film. Further, the examination of these films reveals the presence of an increasing amount of speckles with increasing LTP concentration within the blends. The speckles are also found to increase in dimension with increasing polyphosphate concentrations. These observations are suggestive of partial phase segregation between the blend constituents. Furthermore, the films do not show the presence of any distinct crystalline domains under cross-polarized filters during optical microscopy suggesting that the polymeric components are predominantly amorphous in nature.

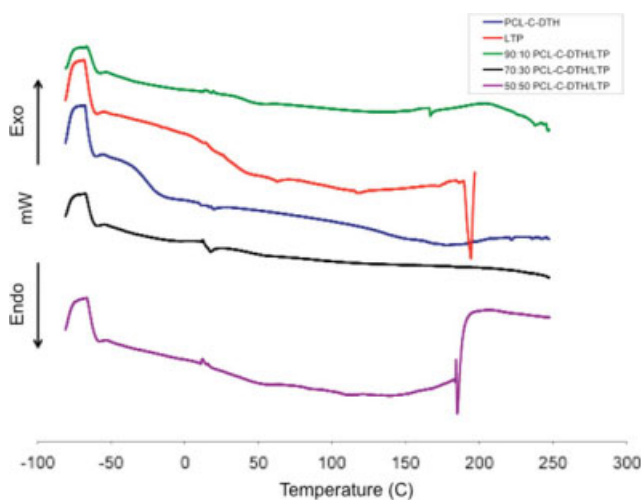
#### Thermal characterization

The thermal characteristics of pure polymers and blends have been assessed by differential scanning calorimetry (DSC) and the DSC thermograms of both pure polymers and blends are presented in Figures 6 and 7. The glass transition temperatures ( $T_g$ ) of PEG-C-DTH and PCL-C-DTH are approximately  $-32^\circ\text{C}$  and  $-26^\circ\text{C}$ , respectively, which corresponds

to the soft segment glass transitions of these polyurethanes. A small endotherm is observed at 10–15  $^\circ\text{C}$  for both LTUs, which probably arises from the disruption of the short-range order of the hard segments and/or H-bond interactions between the soft and the hard segments. Additionally, a broad endotherm is observed in case of the PCL-C-DTH polyurethane at 175 $^\circ\text{C}$  that can be attributed to the melting of the soft segment thus suggesting some soft segment crystallinity. The absence of the soft segment melting endotherm in case of PEG-C-DTH polyurethane indicates the amorphous nature of the PEG soft segment. No hard segment melting endotherms are visible on the thermal scans of polyurethanes indicating the amorphous nature of the hard segment with a phase mixing of the hard segment components. LTP shows a single glass transition temperature at approximately 35 $^\circ\text{C}$  indicating a completely amorphous nature of the polymer. This result is in agreement with the results obtained by Sen Gupta and Lopina.<sup>19</sup> The glass transitions for the PCL-C-DTH/LTP and PEG-C-DTH/LTP are dependent on the LTP concentration and are listed in Table II. Single  $T_g$ 's are observed for most polymer blends indicating a moderate to good phase mixing between the constituent polymers. For the 90 : 10, 70 : 30, and 50 : 50 PEG-C-DTH/LTP, the LTP glass transition cannot be distinguished; however, the PEG-C-DTH glass transitions are observed at approximately  $-23^\circ\text{C}$ ,  $-18^\circ\text{C}$ , and  $3^\circ\text{C}$ , respectively. Although it appears that 70 : 30 PEG-C-DTH/LTP has two  $T_g$ 's, it has been independently confirmed that the transition at 60–65 $^\circ\text{C}$  is actually an artifact.



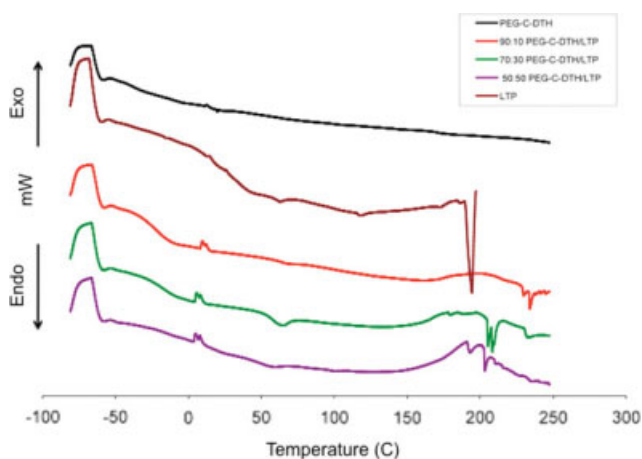
**Figure 5** Polarized optical micrographs of PEG-based polyurethane and LTP blends at 10 $\times$  magnification. (A) PEG-C-DTH, (B) 90 : 10 PEG-C-DTH/LTP blend, (C) 70 : 30 PEG-C-DTH/LTP blend and (D) 50 : 50 PEG-C-DTH/LTP blend. [Color figure can be viewed in the online issue, which is available at [www.interscience.wiley.com](http://www.interscience.wiley.com).]



**Figure 6** Representative thermal scans of PCL-C-DTH, LTP, and PCL-C-DTH/LTP blends as obtained through DSC. [Color figure can be viewed in the online issue, which is available at [www.interscience.wiley.com](http://www.interscience.wiley.com).]

In case of the PCL-C-DTH/LTP, only the LTP's  $T_g$ 's can be observed (Table II). For the 70 : 30 PCL-C-DTH/LTP, the lowering of the LTP's  $T_g$  ( $\sim 17^\circ\text{C}$ ) suggests a good miscibility between LTP and PCL-C-DTH. Finally, the absence of any melting endotherms on the thermal scans indicates that the blends are completely amorphous in nature.

TGA analyses results (Figs. 8 and 9) show that onset of thermal degradation for the pure PCL-C-DTH or PEG-C-DTH polyurethane occurs at approximately  $300^\circ\text{C}$ , and a complete degradation of these polyurethanes occurs by approximately  $500^\circ\text{C}$ . The thermal degradation (Figs. 8 and 9) of LTP begins at approximately  $250^\circ\text{C}$ . The polymer rapidly loses approximately 40% of its initial mass by  $350^\circ\text{C}$ . Subsequently, the mass loss is slower, and an additional



**Figure 7** Representative thermal scans of PEG-C-DTH, LTP and PEG-C-DTH/LTP blends as obtained through DSC. [Color figure can be viewed in the online issue, which is available at [www.interscience.wiley.com](http://www.interscience.wiley.com).]

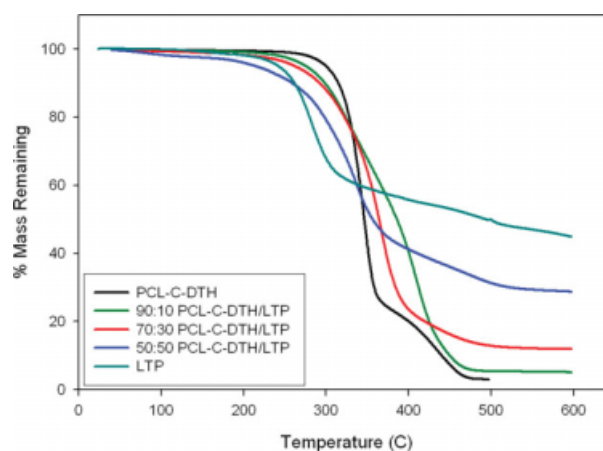
**TABLE II**  
Glass Transition Temperatures of Blends

LTP concentration	Glass transition temperature ( $^\circ\text{C}$ )			
	PCL-C-DTH/ LTP blends		PEG-C-DTH/ LTP blends	
0	-26	-	-32	-
10	-	38	-23	-
30	-	17	-17	-
50	-	39	3	-
100	-	35	-	35

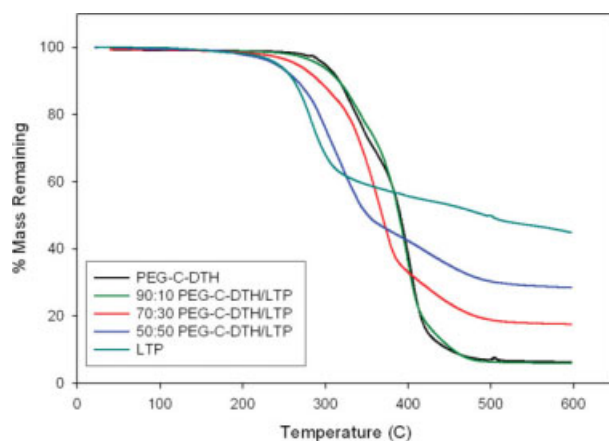
10–15% mass loss occurs by  $600^\circ\text{C}$ . Blending results in thermal degradation properties intermediate to the two parent polymers, and the onset of thermal degradation occurs at progressively lower temperatures as the LTP content of the blend increases. Another effect of LTP concentration on the thermal degradation properties of the blends is the increase in the char yield with increasing LTP concentrations. Despite the decrease in temperature at which thermal degradation occurs, the difference between the glass transition temperature(s) and the onset of thermal degradation temperature is large enough to make the thermal processing of these materials feasible.

#### Relative surface hydrophilicity characterization

The contact angle values in both advancing and receding mode for pure LTP, PCL-C-DTH, PEG-C-DTH, and their blends are shown in Table III. For pure LTP polymer, the average "advanced" and "receded" contact angle values suggest a moderately hydrophilic surface. The higher values of average "advanced" and "receded" contact angle values for the PCL-C-DTH compared with the PEG-C-DTH



**Figure 8** Representative thermal degradation profiles of PCL-C-DTH and PCL-C-DTH/LTP blends as obtained through TGA. [Color figure can be viewed in the online issue, which is available at [www.interscience.wiley.com](http://www.interscience.wiley.com).]



**Figure 9** Representative thermal degradation profiles of PEG-C-DTH and PEG-C-DTH/LTP blends as obtained through TGA. [Color figure can be viewed in the online issue, which is available at [www.interscience.wiley.com](http://www.interscience.wiley.com).]

and LTP suggests a relatively more hydrophobic surface for the PCL-C-DTH. Further, the soft segment of the polyurethanes also dictates the degree of surface hydrophilicity and the observed contact angles. A linear decrease in the contact angle values is observed with increasing LTP concentrations for PCL-C-DTH/LTP. This result indicates that the surface of the blends becomes progressively more hydrophilic with the addition of the LTP polymer. In contrast, this trend is not observed upon blending LTP with PEG-C-DTH. Instead, a maximal contact angle of  $65.41 \pm 2.16^\circ$  is observed for the 50 : 50, PEG-C-DTH/LTP (Table III). The “advanced” and “receded” contact angles are statistically different compared with the pure polymers (Table III).

### Swelling kinetics

The water uptake characteristics of pure LTUs and their blends are plotted in Figures 10 and 11. The PCL-C-DTH shows a very low degree of water

uptake ( $1.11 \pm 0.002$  at 24 h and  $1.13 \pm 0.01$  at 78 h). These observations are not found to be statistically significantly different ( $P = 0.99$ ). On the contrary, the swelling ratio observed for PEG-C-DTH is significantly higher at 78 h ( $2.64 \pm 0.03$ ) compared to 24 h ( $2.42 \pm 0.04$ ) ( $P < 0.05$ ). These data points suggest a much higher degree of bulk hydrophilicity for the PEG-C-DTH polyurethane.

The differences observed between the swelling behavior of PCL-C-DTH and PEG-C-DTH polyurethanes ( $P < 0.05$ ) are also reflected in the blends. Blends of PCL-C-DTH have a much lower degree of water uptake at both 24 and 78 h compared with the blends of PEG-C-DTH ( $P < 0.05$  for the comparison of 90 : 10, blends,  $P < 0.05$  for the comparison of 70 : 30, blends). Also, the PEG-C-DTH/LTP reach equilibrium swelling at  $\sim 20$  h as compared with  $\sim 60$  h for the PCL-C-DTH/LTP. The blending of LTP, in general, accelerates the water uptake and increases the bulk hydrophilicities compared to the parent polyurethanes.

For the 50 : 50 PCL-C-DTH/LTP and the 70 : 30 PEG-C-DTH/LTP, the experiments have been terminated at 10 h due to the rapid degradation of LTP. After 10 h, the masses of the films are found to decrease below the initial value, and the effects of polymer swelling and polymer degradation are difficult to distinguish. In case of the 50 : 50 PEG-C-DTH/LTP, the films are found to rapidly disintegrate on exposure to aqueous solutions making it impossible to collect experimental data. These observations affirm the higher bulk hydrophilicity of blends fabricated using PEG-C-DTH polyurethane compared to the blends fabricated from PCL-C-DTH polyurethane.

### Degradation studies

The hydrolytic degradation of LTUs and their blends has been evaluated using mass loss and changes in

**TABLE III**  
Contact Angle of Blend Samples ( $n = 4$ )

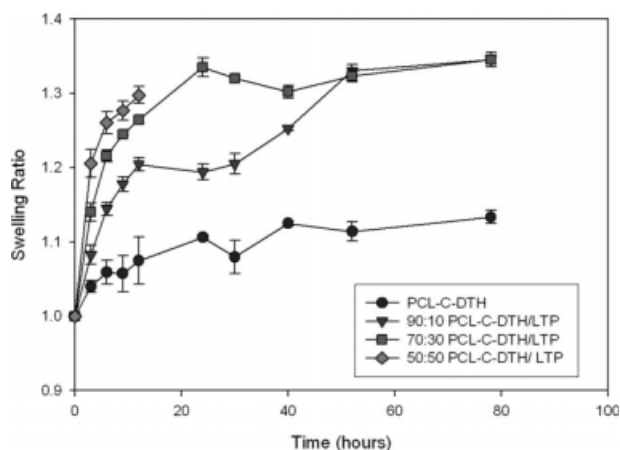
Blend	Advanced contact angle ( $a$ )	Receded contact angle ( $r$ )	Hysteresis ( $a-r$ )
PCL-C-DTH	$79.36 \pm 0.49$	$45.04 \pm 0.69$	$34.32 \pm 0.66$
90 : 10 PCL-C-DTH/LTP	$72.50 \pm 0.47$ ( $P = 0.52$ )	$29.26 \pm 1.35$ ( $P < 0.05$ )	$43.24 \pm 1.41$
70 : 30 PCL-C-DTH/LTP	$67.95 \pm 3.01$ ( $P = 0.02$ )	$28.68 \pm 2.42$ ( $P < 0.05$ )	$39.26 \pm 1.62$
50 : 50 PCL-C-DTH/LTP	$64.60 \pm 0.93$ ( $P < 0.05$ )	$19.46 \pm 0.78$ ( $P < 0.05$ )	$45.14 \pm 1.49$
PEG-C-DTH	$57.90 \pm 0.52$	$28.98 \pm 1.10$	$28.92 \pm 0.87$
90 : 10 PEG-C-DTH/LTP	$56.73 \pm 1.52$ ( $P = 1.00$ )	$23.24 \pm 0.65$ ( $P = 0.05$ )	$33.49 \pm 1.74$
70 : 30 PEG-C-DTH/LTP	$46.37 \pm 1.26$ ( $P < 0.05$ )	$21.58 \pm 1.11$ ( $P < 0.05$ )	$24.79 \pm 0.87$
50 : 50 PEG-C-DTH/LTP	$65.41 \pm 2.16$ ( $P = 0.05$ )	$40.25 \pm 2.33$ ( $P < 0.05$ )	$25.16 \pm 1.67$
LTP	$54.41 \pm 0.75$ ( $P < 0.05$ , <sup>a</sup> $P = 0.96$ <sup>b</sup> )	$21.52 \pm 0.34$ ( $P < 0.05$ , <sup>a</sup> $P = 0.03$ <sup>b</sup> )	$32.89 \pm 0.91$
Glass coverslips	$56.37 \pm 0.95$ ( $P < 0.05$ , <sup>a</sup> $P = 1.00$ <sup>b</sup> )	$28.33 \pm 0.63$ ( $P < 0.05$ , <sup>a</sup> $P = 1.00$ <sup>b</sup> )	$28.04 \pm 1.07$

<sup>a</sup> Statistical comparison between PCL-C-DTH and LTP or glass coverslips.

<sup>b</sup> Statistical comparison between PEG-C-DTH and LTP or glass coverslips.

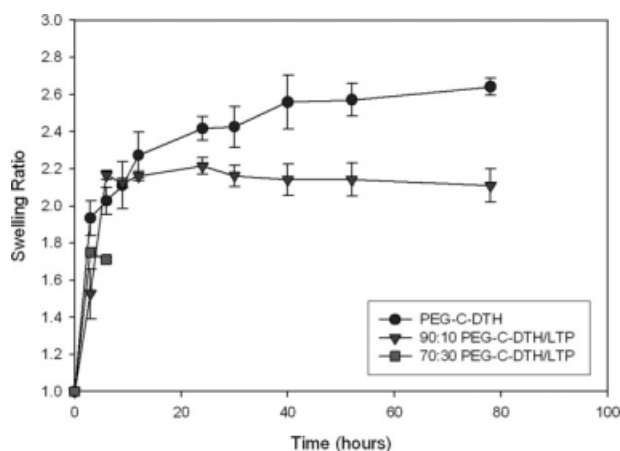
*P*-values presented in the Tables have been obtained by comparison of blends, LTP, and controls to the parent polyurethanes.



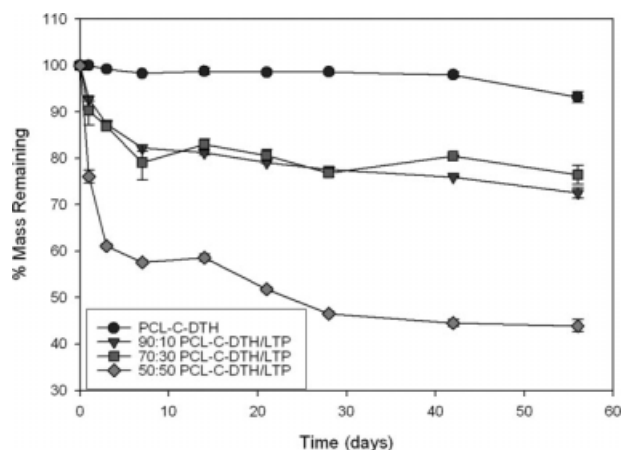


**Figure 10** Water absorption properties of PCL-C-DTH/LTP blends. Values represent mean  $\pm$  standard error for  $n = 3$ .

surface morphology as examined by SEM. As observed from Figure 12, the PCL-C-DTH shows a 4% mass loss over 8 weeks of incubation; whereas, the PEG-C-DTH shows approximately 15% mass loss over the same time frame. The mass loss for the blends is significantly higher than the parent polyurethanes, especially over the first 14 days of incubation. The hydrolytic degradation and the mass loss for the blends are a function of the LTP concentration. The PCL-C-DTH/LTP with a composition of 90 : 10 and 70 : 30 show approximately 15% mass loss over the first 14 days; whereas, the 50 : 50 blend loses nearly 45% mass over the same time period. After this initial rapid mass loss, the subsequent degradation is considerably slower, which is evident from the 8-week mass loss values. For the PEG-C-DTH/LTP (Fig. 13), approximately 20% mass loss is observed for the blend with a 90 : 10 composition over a period of 14 days of incubation; however, a



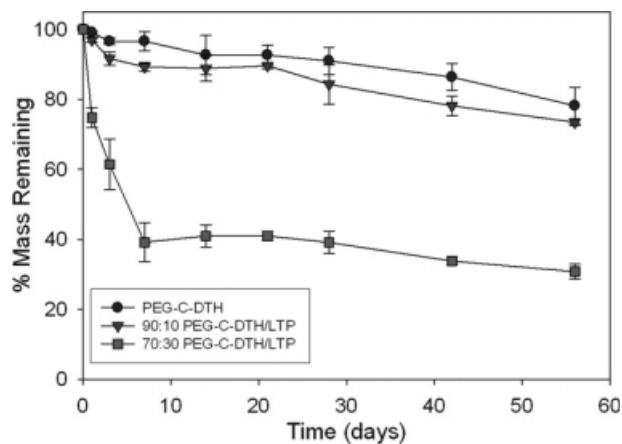
**Figure 11** Water absorption properties of PEG-C-DTH/LTP blends. Values represent mean  $\pm$  standard error for  $n = 3$ .



**Figure 12** Mass loss curves for blends of PCL based polyurethane and polyphosphate upon 8 weeks of incubation in phosphate buffered saline (PBS) at 37°C. Values represent mean  $\pm$  standard error for  $n = 3$ .

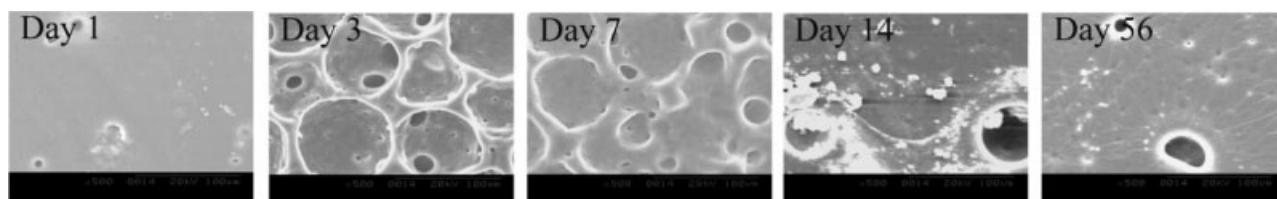
significantly higher mass loss of almost 60% is found to occur over the same time period for the blend with a composition of 70 : 30. The mass loss over subsequent 6 weeks of incubation is significantly slower for the PEG-C-DTH/LTP but faster compared to the PCL-C-DTH/LTP. Also, unlike the PCL-C-DTH/LTP with a 50 : 50 composition, the PEG-C-DTH blend of similar composition disintegrated within 24 h of incubation in buffer rendering further data collection impossible.

SEM analysis of pure LTU films presented in Figures 14 and 15 illustrates the hydrolytic degradation of these materials as a function of time. Before degradation, the LTU films have been found to be partially porous. The voids observed for PCL-C-DTH and PEG-C-DTH films before degradation are of the order of  $\sim 2$ –10 and 5–20  $\mu\text{m}$ , respectively. These voids are also much more widespread on the PEG-



**Figure 13** Mass loss curves for blends of PEG based polyurethane and polyphosphate upon 8 weeks of incubation in phosphate buffer saline (PBS) at 37°C. Values represent mean  $\pm$  standard error for  $n = 3$ .





**Figure 14** Surface morphology of degraded pure PCL-C-DTH films as a function of incubation time as observed by scanning electron microscopy.

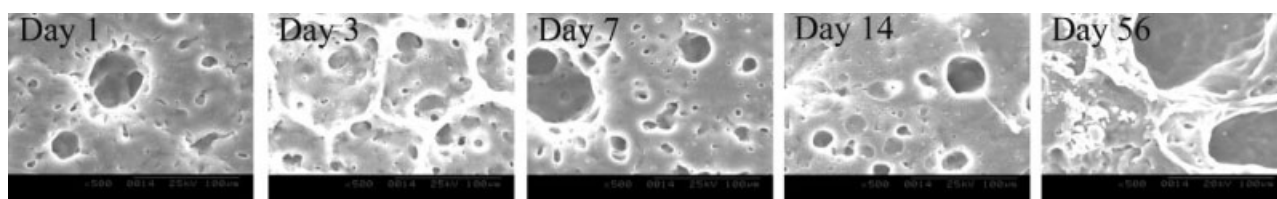
C-DTH film surface. A comparison of the degraded LTU films shows a higher frequency of holes for the PEG-C-DTH films. The number of holes per film sample is found to increase with increasing incubation times. As time increases, these voids enlarge and merge together to form larger crevices where the subsequent degradation may lead to the formation of new holes. Contrary to the behavior observed for PEG-C-DTH, numerous small pits are found to form on the PCL-C-DTH film, but the size of these voids does not change over time.

The morphology of degraded PCL-C-DTH/LTP and PEG-C-DTH/LTP with a mass ratio of 70 : 30 as examined by SEM has been presented in Figures 16 and 17. 70 : 30 PCL-C-DTH/LTP shows a smooth surface morphology without the presence of any pores before degradation (Fig. 2); however, the blended film shows a rough surface morphology by the third day of incubation along with the development of small pore-like structures (Fig. 16). As the incubation time progresses, the formation of cracks and pits can be observed on the film surface. In case of the 70 : 30 PEG-C-DTH/LTP films, the initial pre-degradation surface morphology is smooth and does not exhibit the presence of any pores or other surface defects (Fig. 3), but the film starts showing a rough surface morphology within a day of incubation. By the third day of incubation, numerous small pits and holes can be observed on the film surface which grow progressively bigger with incubation times. By the end of 8 weeks, the film shows a highly eroded surface with the presence of large surface defects such as holes and crevices that extends into the bulk of the polymer film.

## DISCUSSION

Novel polyurethanes and LTP have been developed for biomedical applications by using an L-tyrosine-based monomer desaminotyrosine-tyrosyl hexyl ester (DTH). These polymers have structurally common components within their backbone; however, the introduction of different functional groups during the final polymerization step imparts these polymers with chemical and structural diversity. The incorporation of a phosphoester functional group within the backbone (LTP polymer) leads to a highly rigid and brittle polymer with a moderately hydrophilic surface and a very rapid degradation rate.<sup>19–21</sup> However, the incorporation of urethane linkages into the polymer backbone leads to the formation of highly elastic materials.<sup>22,23,29</sup> As evidenced from the physico-chemical characterization results, properties such as thermal properties (section 3.2), surface properties (section 3.3), bulk properties (section 3.4), and degradation rates (section 3.5) can be adjusted. For the LTUs, the physico-chemical properties are a function of the macrodiols and diisocyanates.

The concept of polymer blends for biomaterial applications is progressively being employed as an alternative to copolymerization. Although both techniques are commonly used,<sup>30,31</sup> blending is easier and more cost-effective than the preparation of copolymers. If polymers are carefully chosen, blending could improve the mechanical and physical properties of the individual polymers while suppressing their undesirable characteristics.<sup>32,33,34</sup> With this rationale in mind, blends of LTUs with LTP have been developed to generate a family of materials with controllable properties.



**Figure 15** Surface morphology of degraded pure PEG-C-DTH films as a function of incubation time as observed by scanning electron microscopy.



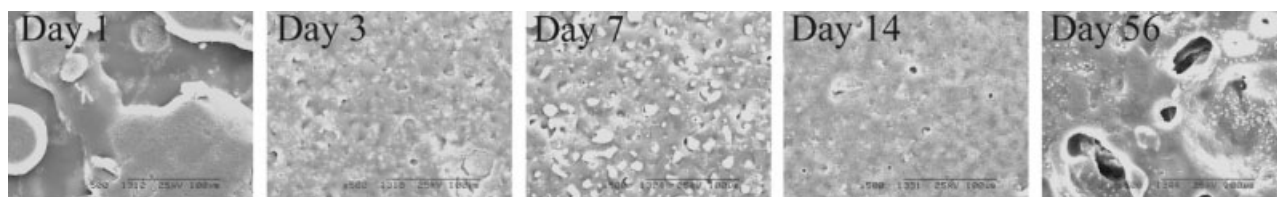
**Figure 16** Surface morphology of degraded 70 : 30 PCL-C-DTH/LTP blended films as a function of incubation time as observed by scanning electron microscopy.

When investigating phase separation of pure polyurethanes with POM (Figs. 4 and 5), the presence of few dark speckles is evident within the samples. This indicates a lack of complete phase mixing between the soft and the hard segment components within the polymeric backbone. This conclusion is supported by the DSC results presented in Figures 6 and 7. Between the two polyurethanes, improved phase mixing is expected in case of PCL-C-DTH due to the hydrophobic properties of the hard segments interacting with hydrophobic PCL and the higher affinity of PCL to form hydrogen bonds with the hard segments compared with the PEG molecules.

In case of the PCL-C-DTH, DSC indicates a broad but shallow endotherm at 175°C which can be correlated to the soft segment melting; however, the corroboration of crystal structure formation could not be obtained from POM data. Polyurethanes synthesized by Skarja and Woodhouse with a similar soft segment but different hard segment components exhibit crystallinity.<sup>28</sup> Further, the blends of their polyurethanes are also semi-crystalline.<sup>27</sup> Li et al. and others have argued that a PCL molecular weight between 2000 and 3000 Da is necessary for soft segment crystallization.<sup>35–37</sup> Additionally, the molecular weight of the soft segment necessary to achieve soft segment crystallization in segmented polyurethanes increases with increasing hard segment content.<sup>38–40</sup> Soft segment polyesters such as PCL, due to its ability to form hydrogen bonding, exhibit increased phase mixing with the hard segments, which may decrease the conformational mobility of the PCL chains, prevent their selective aggregation and ordering into crystals, and result in a primarily amorphous material.<sup>41</sup>

Blending of LTUs and LTP leads to the formation of dark speckles on the surface of the films indicating some phase separation (Figs. 4 and 5). The addition of LTP possibly leads to the disruption of the structured arrangement within the soft and the hard segment domains of the LTUs with the LTP molecules being randomly dispersed within the bulk of the polyurethane phase. However, DSC data shows single glass transition temperatures for most blends along with a broadened or indistinct  $T_g$ 's indicating a moderate to good phase miscibility of the polymeric constituents. These seemingly incongruous results suggest that polymers show mostly phase mixed behavior, but a complete miscibility of LTP with LTUs does not occur. Additionally, the applicability of  $T_g$  measurement as a tool for polymer miscibility and compatibility studies also depends on the differences between the  $T_g$  values of the parent polymers.<sup>40,41</sup> Usually, a larger difference in the  $T_g$  values of the constituent polymers is desirable for accurate results.<sup>40,41</sup> This requirement of the DSC method may be a drawback in this case considering the complexity in the determination of blend  $T_g$ 's for PEG-C-DTH/LTP and PCL-C-DTH/LTP. Consequently, a more sensitive method such as dynamic mechanical analysis (DMA) will be used for subsequent studies.

Surface properties such as wettability, chemistry, and roughness typically play an important role in determining the degree of cellular adhesion and proliferation on biomaterial surfaces. When investigating the parent polymers, larger contact angle values are observed for PCL-C-DTH because of the hydrophobic nature of PCL and the hard segments; whereas, PEG-C-DTH and LTP show comparable contact angles. Since PEG is hydrophilic, this result could be attributed to the presence of hard segments



**Figure 17** Surface morphology of degraded 70 : 30 PEG-C-DTH/LTP blended films as a function of incubation time as observed by scanning electron microscopy.

at the surface. Further, contact angle measurements show increases in surface hydrophilicity with the addition of LTP for most blends (Table III). These results are understandable considering the greater surface hydrophilicity of LTP. Additionally, they indicate the possibility of preferential migration of LTP to the surface of the blended film. However, the PEG-C-DTH/LTP did not show a conclusive trend similar to the PCL-C-DTH/LTP. The contact angle values are found to decrease initially as the LTP concentration increases from 0% to 30% and then a maximum value for contact angle is observed for the 50 : 50, PEG-C-DTH/LTP. Such a phenomenon may occur due to the presence of multiple functionalities on the blended film surface. Additionally, an interaction between PEG and LTP seems to occur, which possibly leads to the migration of PEG to the surface at lower LTP concentrations in response to the introduction of water droplet. Further examination of the films using a technique such as surface FTIR or X-ray photoelectron spectroscopy will be performed to explore these observations.

Bulk property such as water uptake plays an important role in the transport of nutrients and oxygen to the cells for polymeric scaffolds and in the release of the encapsulated therapeutic agents for drug delivery devices. Additionally, the water uptake process is important for the degradation of absorbable polymeric materials. When exposed to aqueous medium, PEG-C-DTH and its blends have greater tendency to swell as compared with PCL-C-DTH and its blends. Since the hard segments are the same, these differences can be directly attributed to the PCL and PEG functionalities. Since the PEG-C-DTH shows a higher degree of surface hydrophilicity, the interaction of water and its penetration through the surface of the polymer matrix are facile compared with the relatively hydrophobic PCL-C-DTH. Consequently, higher equilibrium swelling ratios and a rapid establishment of equilibrium swelling for PEG-C-DTH are observed. These differences observed in the swelling behavior of the LTUs are also reflected in the swelling behavior of their blends. The higher overall swelling ratios and the faster rate of swelling observed for the PEG-C-DTH blends (Figs. 10 and 11) can be attributed to the higher surface and bulk hydrophilicities of PEG and the completely amorphous nature of both the polyurethane and LTP. The composition of the blends also has a considerable effect on their swelling characteristics as evident from Figures 10 and 11. In case of PCL-C-DTH/LTP, the swelling ratio at 24 h increases from  $1.11 \pm 0.002$  to  $1.34 \pm 0.01$  as the LTP concentration increases from 0% to 30% and then declines to  $1.18 \pm 0.01$  in case of the 50 : 50 PCL-C-DTH/LTP; however, no such specific trends are observed in case of PEG-C-DTH/LTP. The increase in swelling ratio with

increasing LTP concentration possibly occurs due to the leaching out of the LTP polymer following its rapid degradation making the bulk of the blended film more accessible. However, under the current circumstances, isolating the contribution of swelling and mass loss is not possible.

Understanding the degradation properties of a biodegradable polymer is perhaps one of the most crucial aspects to its successful implementations for biomedical applications. The results obtained from hydrolytic degradation studies of L-tyrosine-based polyurethanes (Figs. 12 and 13) show significant differences exist between the rates and participating mechanisms of the LTU's degradation. The dissimilarity in degradation rates can be attributed to the variation in the soft segment chemistry of these polymers. Since the hard segment chemistry and composition are similar, the differences between hydrophilicities of PCL and PEG play a decisive role in determining the degradation rates. Cerrai and coworkers have shown that an increase in hydrophilicity can be directly correlated to an increased degradation rate.<sup>42,43</sup> Our results are in agreement. PEG-C-DTH has a higher hydrophilicity and exhibits a faster degradation rate compared to the hydrophobic PCL-C-DTH polymer. Additionally, the molecular weights of the soft segments also impacts degradation rates.<sup>44</sup> Since the chain lengths for the PCL and PEG blocks have been maintained constant, we expect this parameter to have similar effects on degradation rates of all samples.

SEM analysis of the polymeric materials shows the PEG containing materials degrade at a faster rate following hydration. Figures 14 and 15 illustrate the degradation of PCL-C-DTH and PEG-C-DTH as a function of time, respectively. It is evident from the representative images that polyurethane films exhibit a partially porous structure before degradation; however, the dimensions and density of pores on the PEG-C-DTH film surface ( $\sim 5\text{--}20\ \mu\text{m}$ ) are much higher compared with those on the PCL-C-DTH ( $\sim 2\text{--}10\ \mu\text{m}$ ). The overall observed effects pertaining to the progression of hydrolytic degradation are much more widespread for PEG-C-DTH films as compared with the PCL-C-DTH films as evident from both mass loss curves (Figs. 12 and 13) and surface morphology examinations (Figs. 14 and 15). PEG-C-DTH film shows holes and crevices on a uniformly eroded surface as a result of both surface and bulk degradation; whereas, PCL-C-DTH film shows a cracked and pitted non-uniformly eroded surface suggesting the predominant effects of surface erosion.

The rapid initial mass loss observed in case of the PCL-C-DTH/LTP and PEG-C-DTH/LTP (Figs. 12 and 13) can be attributed to the rapid degradation rate of LTP in aqueous medium. Although all blends



show a rapid initial degradation, the subsequent degradation rates of the polyurethanes are quite different. After the rapid initial degradation of LTP, the rate of degradation is dependent on the chemistry of the parent polyurethane. Since the polyurethanes have similar hard segment chemistry, the differences in the rates of degradation are attributed to the hydrophilicities of the soft segments. Due to the increased hydrophilicity of PEG-C-DTH, the swelling and hydrolysis rates are enhanced. Fromstein and Woodhouse also obtained similar results during their degradation studies on PEG- and PCL-based polyurethane blends.<sup>27</sup>

Figure 17 shows that the blend surface is initially free of surface defects; however, numerous pits are formed during the first 3 days of degradation. These defects grow progressively larger with time. The hydrolytic degradation of the hard segments of PEG-C-DTH could result in the release of PEG from the backbone, facilitate the mass transfer into and out of the solid, and lead to a rapid overall mass loss. Overall, the PCL-C-DTH/LTP blends are less susceptible to hydrolysis. Faster degradation rate induced by blending could be attributed to surface degradation of LTP, which makes the bulk of the polymer accessible for hydrolysis.

Finally, the rapid disintegration of the 50 : 50 PEG-C-DTH/LTP results in a gel-like phase. Such a phenomenon could occur by rapid and large uptake of water. Consequently, the degradation products of LTP and the PEG segment within the PEG-C-DTH may be partially solubilized. A similar phenomenon should also be expected for the 50 : 50 PCL-C-DTH/LTP; however, these films are stable over the complete time frame of degradation studies. We believe that the lower water uptake by these films provides a better stability to these films, prevents the solubilization of the polyurethane components, and preserves the physical structure during the degradation studies.

## CONCLUSION

Six blends of LTUs and LTP have been fabricated by a solution casting-solvent evaporation technique. LTUs and LTP have dramatically different physico-chemical properties, and materials with intermediate properties can be created by blending these polymers. This technique offers an easy means to tune the properties of the parent polymers. The material properties of the blends are dependent on their composition. Data obtained from characterization of the blends indicates that the polymers are amorphous, show partial phase segregation, and the degree of phase segregation is contingent on LTP concentration. Furthermore, LTP exhibits better blending with PCL-based polyurethanes compared with the PEG-

based polyurethanes. Additionally, the soft segment of the LTUs and LTP concentration influences the bulk properties such as water uptake, degradation rates, and hydrolytic stability. In summary, materials with a wide range of physico-chemical properties have been fabricated by a relatively simple fabrication technique, which entails the physical blending of two polymers. The physico-chemical properties of these materials are a function of the blend composition.

## References

1. Slomkowski, S. *Macromol Symp* 2007, 253, 47.
2. Jain, R. A. *Biomaterials* 2000, 21, 2475.
3. Lakshmi, S.; Katti, D. S.; Laurencin, C. T. *Adv Drug Delivery Rev* 2003, 55, 467.
4. Heller, J. *Adv Drug Delivery Rev* 1993, 10, 163.
5. Heller, J.; Barr, J.; Ng, S. Y.; Abdellauoi, K. S.; Gurny, R. *Adv Drug Delivery Rev* 2002, 54, 1015.
6. Kumar, N.; Langer, R. S.; Domb, A. J. *Adv Drug Delivery Rev* 2002, 54, 889.
7. Park, E. S.; Maniar, M.; Shah, J. C. *J Control Release* 1997, 48, 67.
8. Sinha, V. R.; Kumria, R. *Int J Pharm* 2001, 224, 19.
9. Friend, D. R. *Adv Drug Delivery Rev* 2005, 57, 247.
10. Miyamae, T.; Mori, S.; Takeda, Y. U.S. Pat. 3,371,069 (1968).
11. Spira, M.; Fissette, J.; Hall, C. W.; Hardy, S. B.; Gerow, F. J. *J Biomed Mater Res* 1969, 3, 213.
12. McCormick-Thomson, L. A.; Duncan, R. *J Bioact Compat Polym* 1989, 4, 242.
13. Choueka, J.; Charvet, J. L.; Koval, K. J.; Alexander, H.; James, K. S.; Hooper, K. A.; Kohn, J. *J Biomed Mater Res* 1996, 31, 35.
14. James, K.; Kohn, J. In: *Controlled Drug Delivery: Challenges and Strategies*, Park, K., Ed.; American Chemical Society: Washington D.C., 1997; p 389.
15. Peppas, N. A.; Langer, R. S. *Biopolymers I*; Springer: Heidelberg, 1993.
16. Hollinger, J. O. *Biomedical Application OF Synthetic Biodegradable Polymers*; CRC Press: Boca Raton, 1995.
17. Kohn, J.; Langer, R. *Chem Biol Proc Am Pept Symp* 1988, 10, 658.
18. Kohn, J. *Drugs Pharm Sci* 1990, 45, 195.
19. Sen Gupta, A.; Lopina, S. T. *Polymer* 2004, 45, 4563.
20. Sen Gupta, A.; Lopina, S. T. *J Polym Sci Part A: Polym Chem* 2004, 42, 1906.
21. Sen Gupta, A. Dissertation, The University of Akron: College of Engineering, 2003.
22. Sarkar, D.; Yang, J. C.; Sen Gupta, A.; Lopina, S. T. *J Biomed Mater Res* 2007, Accepted.
23. Sarkar, D.; Yang, J. C.; Lopina, S. T. *J Appl Polym Sci* 2008, 108, 2345.
24. Ambrosio, A. M. A.; Allcock, H. R.; Katti, D. S.; Laurencin, C. T. *Biomaterials* 2002, 23, 1667.
25. Ibim, S. E. M.; Ambrosio, A. M. A.; Kwon, M. S.; El-Amin, S. F.; Allcock, H. R.; Laurencin, C. T. *Biomaterials* 1997, 18, 1565.
26. Yang, X.; Yuan, M.; Li, W.; Zhang, G. *J Appl Polym Sci* 2004, 94, 1670.
27. Fromstein, J. D.; Woodhouse, K. A. *J Biomater Sci: Polym Ed* 2002, 13, 391.
28. Skarja, G. A.; Woodhouse, K. A. *J Appl Polym Sci* 2000, 75, 1522.
29. Dunn, A. S.; Campbell, P. G.; Marra, K. G. *J Mater Sci: Mater Med* 2001, 12, 673.
30. Sarkar, D.; Yang, J. C.; Klettlinger, N.; Lopina, S. T. *Express Polym Lett* 2007, 1, 724.



31. Buchanan, C. M.; Gedon, S. C.; White, A. W.; Wood, M. D. E. *Macromolecules* 1992, 25, 7373.
32. Shimamura, E.; Kashuya, K.; Kobayashi, C.; Shiotani, T.; Shima, Y.; Doi, Y. *Macromolecules* 1994, 27, 878.
33. Paul, D. R.; Newman, S. *Polymer Blends*; Academic Press: New York, 1978.
34. Iannace, S.; Ambrosio, L.; Huang, S. J.; Nicolais, L. *J Appl Polym Sci* 1994, 54, 1525.
35. Vasquez-Torres, H.; Cruz-Ramos, C. A. *J Appl Polym Sci* 1994, 54, 1141.
36. Li, Y.; Ren, Z.; Zhao, M.; Yang, H.; Chu, B. *Macromolecules* 1993, 26, 612.
37. Van Bogart, J. W. C.; Gibson, P. E.; Cooper, S. L. *J Polym Sci: Polym Phys Ed* 1983, 21, 65.
38. Hepburn, C. *Polyurethane Elastomers*; Elsevier Science: London, 1993.
39. Li, F.; Hou, J.; Zhu, W.; Zhang, X.; Mao, X.; Luo, X.; Ma, D.; Kim, B. K. *J Appl Polym Sci* 1996, 62, 631.
40. Maurer, J. J. In *Thermal Characterization of Polymeric Materials*; Turi, E. A., Ed. Academic Press: New York, 1981.
41. Bikiaris, D.; Prinos, J.; Botev, M.; Betchev, C.; Panayiotou, C. *J Appl Polym Sci* 2004, 93, 726.
42. Cerrai, P.; Tricoli, M.; Lelli, L.; Guerra, G. D.; Sbarbati Del Guerra, R.; Cascone, M. G.; Giusti, P. *J Mater Sci: Mater Med* 1994, 5, 308.
43. Sbarbati Del Guerra, R.; Cristallini, C.; Rizzi, N.; Barsacchi, R.; Guerra, G. D.; Tricoli, M.; Cerrai, P. *J Mater Sci: Mater Med* 1994, 5, 891.
44. Park, T. G.; Cohen, S.; Langer, R. *Macromolecules* 1992, 25, 116.