

Structure-Property Relationship of L-Tyrosine-Based Polyurethanes for Biomaterial Applications

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ABSTRACT: The structure-property relationship of L-tyrosine-based polyurethanes was demonstrated by using different polyols and diisocyanates. L-tyrosine-based chain extender, desaminotyrosyl tyrosine hexyl ester (DTH), was used to synthesize a series of polyurethanes. Polyethylene glycol (PEG) or poly caprolactone diol (PCL) was used as the soft segment and hexamethylene diisocyanate (HDI) or dicyclohexylmethane 4,4'-diisocyanate (HMDI) was used with DTH as the hard segment. The polyurethanes were characterized to investigate the effect of structure on different polyurethane properties. From FTIR and DSC, these polyurethanes exhibit a wide range of morphology from phase-mixed to phase-separated structure. The decreasing molecular weight of the PEG soft segment leads to relatively more phase mixed morphology whereas for PCL-

based polyurethanes the extent of phase mixing is less with decreasing PCL molecular weight. Results show that PCL-based polyurethanes are mechanically stronger than PEG-based polyurethanes but PCL-based polyurethanes degrade slower and absorb less water compared with PEG-based polyurethanes. The HMDI-based polyurethanes are less crystalline and comparatively more hydrophobic than HDI-based polyurethanes. The characterization results show that the polyurethane properties are directly related to the structure and can be varied easily for a different set of properties that are pertinent for biomaterial applications. © 2008 Wiley Periodicals, Inc. *J Appl Polym Sci* 108: 2345–2355, 2008

Key words: polyurethane; L-tyrosine; FTIR; hydrolytic degradation; morphology

INTRODUCTION

Polyurethanes are extensively used for various biomaterial applications because of their wide range of properties.^{1–3} Segmented polyurethanes are a unique class of block copolymers of alternating “soft” segment and “hard” segments.⁴ The soft segment of the polyurethanes consists of polydiol (moderately high-molecular weight diol) which is relatively amorphous and rubbery in nature. The hard segment usually consists of the diisocyanate and a low-molecular weight diol or diamine chain extender, which is relatively crystalline and glassy. Depending on the physical and chemical nature of the segments, polyurethanes exhibit dual phase structure and, therefore, have an unmatched combination of different properties. The biphasic nature of the segmented polyurethanes arises from the difference in structure, morphology, and distribution of the segments.⁴ A variety of polydiols, diisocyanates, and chain extenders has been used in the synthesis of polyurethanes and their effects on the properties have also been investigated.^{4–6}

Polyurethanes are becoming an increasingly important biomaterial for tissue engineering applica-

tions.^{7,8} Degradable polymers are used for fabrication of 3D scaffolds for tissue engineering. By altering the structure, polyurethanes with different properties are developed for tissue engineering application. Degradable polyurethanes are developed by introducing hydrolysable linkages in the polyurethane structures. The use of hydrolysable soft segments, e.g., polylactides,⁹ poly(ϵ -caprolactones),¹⁰ is the most common way of developing degradable polyurethanes. An amino acid-based chain extender has been used to incorporate degradable linkages in the polyurethane backbones.¹¹ The diisocyanates used are mainly aliphatic or amino acid based to avoid the toxic effect of aromatic degradation products.¹² Apart from degradability, these polyurethanes have shown to possess physicomechanical properties that are pertinent to tissue engineering applications.^{11,12} Investigation of the structure-property relationship of polymers for biomaterial applications has been studied for several polymers.^{12–14} The polyurethane morphology and properties are strongly dependent on the type, composition, and distribution of the components, which forms soft segment and hard segment of the polymer. The morphology and properties of the polyurethanes are controlled by the soft segment's molecular weight, amorphousness/crystallizability, concentration etc; for example with increasing molecular weight of PCL soft segment the polyurethanes are more crys-

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TABLE I
Composition of Polyurethanes

Code	Polyol (MW)	Diisocyanate	Soft Segment (wt %)	Hard Segment (wt %)	
				Diisocyanate	Chain Extender (DTH)
PU1	PEG (400)	HDI	35.4	29.7	34.9
PU2	PEG (600)	HDI	44.5	25.0	30.5
PU3	PEG (1000)	HDI	57.5	19.3	23.2
PU4	PCL (530)	HDI	41.5	26.3	32.2
PU5	PCL (1250)	HDI	62.6	16.9	20.5
PU6	PEG (1000)	HMDI	51.6	27.1	21.3
PU7	PCL (1250)	HMDI	57.1	24.0	18.9

talline in nature and, therefore, have better mechanical and thermal characteristics.^{4,12} The hard segment characteristics are also important factor in controlling the polyurethane properties, e.g., polyurethanes with 2,4 TDI as diisocyanate forms a relatively amorphous hard segment compared with 2,6 TDI.⁴ The structure-property relationships of the polyurethanes show that the properties of the material can be changed by altering the soft and hard segment of the polyurethanes.

In this work, we report a detailed analysis of structure-property relationship of a series of L-tyrosine-based polyurethanes with different soft and hard segments. The polyurethanes are based on L-tyrosine-based chain extender, desaminotyrosyl tyrosine hexyl ester (DTH). The use of amino acid-based chain extender ensures the biocompatibility of the polyurethanes for different biomaterial applications. The soft segments of these polyurethanes are either polyethylene glycol (PEG) or polycaprolactone diol (PCL) of different molecular weights. The molecular weights of PEG used in this study are 400, 600, and 1000, and the molecular weights for the PCL are 530 and 1250. Two different aliphatic diisocyanates are used: hexamethylene diisocyanate (HDI), a linear diisocyanate, and dicyclohexylmethane 4,4'-diisocyanate (HMDI), a cyclic diisocyanate. DTH is used as chain extender for all the polyurethanes. The properties of all the polyurethanes are characterized and compared from the structure-property relationship point of view. Since polyurethanes exhibit complex phase behavior, it is reasonable to assume that use of different soft and hard segments will impact the physicochemical properties of the polyurethanes. This work aims to relate the effect of structural variation on the properties of L-tyrosine-based polyurethane for selection of appropriate biomaterial.

MATERIALS AND METHODS

Materials

Polyethylene glycol (PEG; M_w = 400, 600, 1000) and polycaprolactone diol (PCL; M_w = 530, 1250) was purchased from Sigma Aldrich (Milwaukee, WI) and

was dried in vacuum oven at 50°C for 2 days to remove any entrapped water. The diisocyanates, HDI and HMDI, were also purchased from Sigma Aldrich and used as received. *N,N'*-dimethyl formamide (DMF) from EMD Chemicals, NJ, was used after drying over calcium hydride followed by molecular sieve. DTH was prepared from the hexyl ester of L-tyrosine and desaminotyrosine through carbodiimide coupling reaction.¹⁵ Deionized water was used for all other purposes.

Synthesis of polyurethane and casting of films

The polyurethanes were synthesized by conventional two step method. The details of the synthetic process are described elsewhere.¹⁶ Briefly, polydiol and diisocyanate were added to 50 mL dry DMF (solvent) in the molar ratio of 1 : 2 and were allowed to react for 3 h at 110°C in the presence of 0.1% stannous octoate¹¹ as catalyst and subsequently cooled down to room temperature. DTH was added to the solution in the molar ratio of 1 : 1 to the polydiol and the reaction was allowed to continue at 80°C for another 12 h. After 12 h the reaction was quenched by precipitating the polyurethanes in concentrated aqueous solution of sodium chloride. Depending on the nature of the final polymer, the polyurethane was either filtered or centrifuged and washed for several times. The polyurethanes were dried in vacuum at 40°C for 3 days prior to any characterization.

The detailed compositions and codes of the polyurethanes are shown in Table I. The weight percentage of the components is based on the actual weights of the components used for the synthesis of the polyurethanes.

The polyurethane films were cast from 5 wt % solution of the polymers in chloroform as the solvent. The solutions were cast in polytetrafluoroethylene petridish and the solvent was allowed to evaporate at room temperature for 24 h followed by drying in vacuum oven at 40°C to remove residual solvent. The polymer films obtained by this process were used for all characterizations except mechanical testing. 10 wt % solutions were used to cast polyurethane films for mechanical testing.

Polyurethane characterization

The molecular weights of polyurethanes were determined by gel permeation chromatography using tetrahydrofuran as solvent and polystyrene as internal standard. FTIR analysis of the polyurethanes was performed with a Nicolet NEXUS 870 FT spectrometer for neat samples.

The thermal characteristics of the polyurethanes were examined by differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA). DSC was performed with a DSC Q100V7.0 Build 244 (Universal V3. 7A TA) instrument at a scanning rate of 10°C/min from -80 to 250°C. TGA was performed with a TGA Q50V5.0 Build 164 (Universal V3. 7A TA) instrument from 0 to 600°C under nitrogen at a rate of 20°C/min. An average of 10 mg of solid sample was used for both the experiments.

The tensile properties of the films were measured by Instron Tensile Testing Machine with a load cell of 100 N and cross-head speed of 100 mm/min at room temperature. The sample dimension was 20 mm × 6 mm × ~ 0.3 mm with free length of 10 mm.

For contact angle measurement, thin films of polyurethanes were prepared on thoroughly cleaned and dried glass slides by dip coating the slides into the 5 wt % solution of polyurethanes for 12 h. The films were initially dried at room temperature for 24 h followed by vacuum drying at 50°C for another 48 h to remove the residual solvents. Static water contact angle was measured by sessile method using Ramé-Hart goniometer at room temperature in an air atmosphere both in advancing and receding modes.

The water vapor permeability of the polyurethanes was measured by calculating water vapor permeance [WVP in mg/(h mm² mm of Hg)] and water vapor permeability coefficient [WVPc in mg/(h mm mm of Hg)] using three replicates for each sample. Discs of polymer films were cut and placed on open vials containing 5 g of silica gel (mesh size 6–16) with a screw lid having a diameter of 2 cm (test area: 1.33 cm²) and then placed in desiccator maintained at constant relative humidity (R.H.: ~ 75%, 21°C). The moisture transmitted through the polymeric films was determined gravimetrically over 48 h period. The rate of water vapor transmitted was calculated from the slope of the linear curve for water vapor transmitted versus time plot. The WVP and WVPc were calculated from the following equations:

$$\text{WVP} = \frac{W}{A\Delta P} \quad (1)$$

$$\text{WVPc} = \frac{Wt}{A\Delta P} \quad (2)$$

where, W is the rate of water vapor transmitted per unit time, A is the cross-sectional area of the film,

ΔP is the vapor pressure difference, and t is the thickness of the film. The results reported are average of three values for each polymer film.

To measure water absorption, circular samples were cut from dried films (diameter: 1.5 cm and thickness: 0.15 mm) and immersed in 20 mL of deionized water. After 12 h, the hydrated samples were taken out and weighed after the surface water was blotted with Kimwipes. The water absorption was calculated on the basis of the weight difference of the film before and after swelling. The percentage of water absorption was calculated using the following equation:

$$\text{Water Absorption (\%)} = \frac{w_2 - w_1}{w_1} \times 100 \quad (3)$$

where, w_2 and w_1 are the weight of sample films after and before being immersed in water, respectively. The time period of 12 h was chosen because the polyurethanes exhibit substantial hydrolytic degradation after 12 h.

For hydrolytic degradation, similar circular samples (diameter: 1.0 cm and thickness: 0.15 mm) were cut from dried films. The samples were incubated at 37°C ± 1°C in 10 mL of phosphate-buffered saline (PBS; 0.1M, pH 7.4) containing 200 mg L⁻¹ of sodium azide to inhibit bacterial growth in a sealed vial placed within a constant temperature water bath. Samples were taken at intervals, weighed for mass loss after drying under vacuum at 40°C for 2 days. The hydrolytic degradation was calculated from the weight loss (%) using the following equation:

$$\text{Weight Loss (\%)} = \frac{w_2 - w_1}{w_1} \times 100 \quad (4)$$

where, w_2 and w_1 are the weight of sample films after and before degradation, respectively.

Release of a model hydrophobic drug *p*-nitroaniline from the polymer films was studied. Accurately weighed amount of *p*-nitroaniline and the polymer was dissolved in 10 mL of solvent (chloroform) such that a 20 : 1 weight ratio of polymer to *p*-nitroaniline was obtained. These polymer-*p*-nitroaniline solutions were used for solvent casting to obtain polymer films. Circular disk samples (diameter: 10 mm and weight: 30–40 mg) were cut from the films and immersed in 15 mL of phosphate buffer saline (PBS: 0.1M; pH 7.4) and incubated at 37°C. The release of *p*-nitroaniline was measured spectrophotometrically at 410 nm with 1 mL aliquots and the volume was maintained constant at 15 mL by adding PBS. The fractional cumulative release of the *p*-nitroaniline was measured over a 30-day-period using the following equation:

TABLE II
Representative Molecular Weight of Polyurethanes

Polyurethane	M_n	M_w	Poly Dispersity Index
PU1	4,710	11,260	2.39
PU2	7,520	12,790	1.70
PU3	78,980	98,100	1.24
PU4	12,530	25,640	2.05
PU5	150,370	246,120	1.64
PU6	93,640	119,900	1.28
PU7	64,670	75,430	1.17

$$R_i = \left(\frac{M_i}{L} \right) \quad (5)$$

where, R_i is the fraction of cumulative release on i^{th} day, M_i is the cumulative amount of *p*-nitroaniline released on i^{th} day, and L is the theoretical loading of *p*-nitroaniline. The fractional release of *p*-nitroaniline (R_i) is plotted against the square-root of time ($t^{1/2}$).

RESULTS AND DISCUSSION

Effect of polyurethane structure

Molecular weight

The molecular weights of the polyurethanes are shown in Table II. The results show that PCL-based polyurethanes are of comparatively higher molecular weight than the PEG-based polyurethanes. This is mainly due to the presence of water with PEG that leads to low molecular weight.¹¹ Lower soft segment's molecular weight results in low-molecular weight polyurethane in spite of having higher hard segment content.¹² This indicates that chain extension through DTH is random and the hard segment length is comparatively smaller in PU3, PU4, and PU5 compared with the other polyurethanes. The higher polydispersity index of PU1, PU2, and PU4 is also an indication of uncontrolled polymerization reaction. The effect of structural variation of the diisocyanate is not evident from the molecular weight, which indicates that the diisocyanate structures have practically no effect on the molecular weight. But the molecular weight of PU7 is low (compared with PU3, PU5, and PU6) because of the difficulties encountered in filtering the polymer solution while determining molecular weight. In general, PEG-based polyurethanes are tacky and soft compared with PCL-based polyurethanes, which are relatively stronger.

FTIR analysis

The FTIR spectra of the polyurethanes are shown in Figure 1. Figure 1(A,B) shows the effect of soft segment while Figure 1(C) shows the effect of different diisocyanates. The characteristic soft segment peak

for PEG-based polyurethanes is around 1100 cm^{-1} representing the aliphatic ether group (of PEG) and for PCL-based polyurethane is around $1730\text{--}1725 \text{ cm}^{-1}$ representing the ester carbonyl group (of PCL). The effect of soft segment's molecular weight for PEG-based polyurethanes shows that increasing molecular weight leads to increasing H-bonding of the urethane carbonyl within the hard segment domain leading to a cohesive and ordered hard segment.

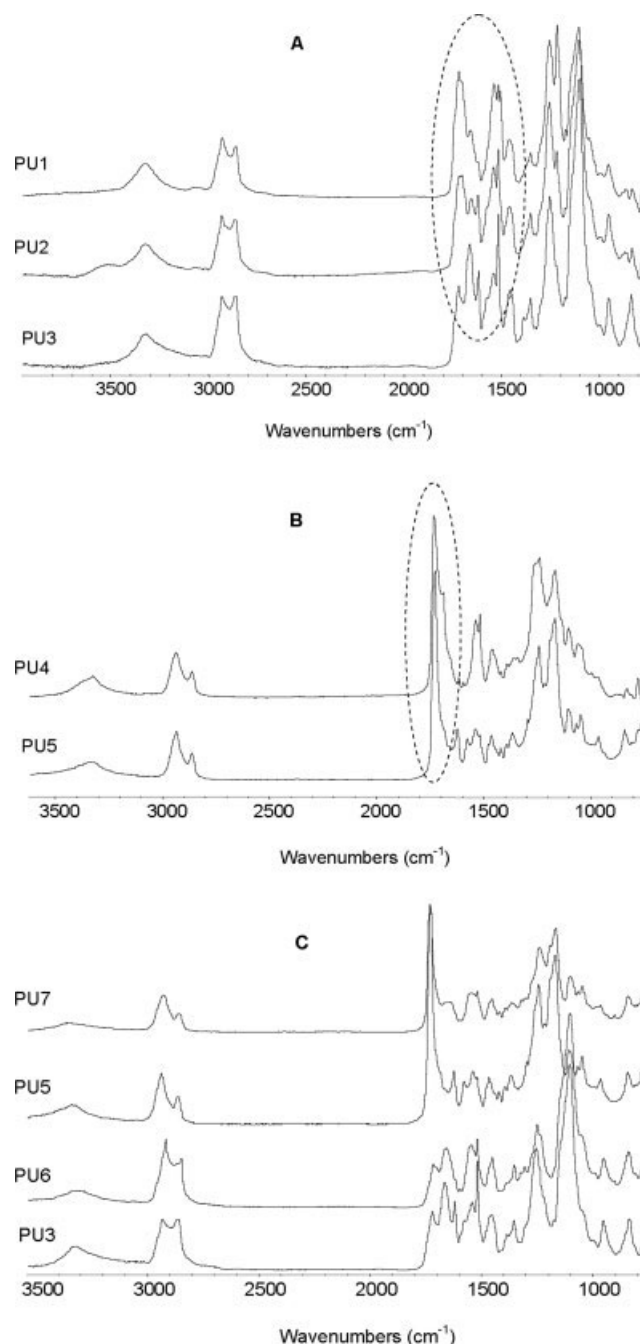


Figure 1 FTIR absorbance spectra of polyurethanes. (A) Series based on different molecular weight of PEG, (B) series based on different molecular weight of PCL, and (C) series based on different diisocyanates.

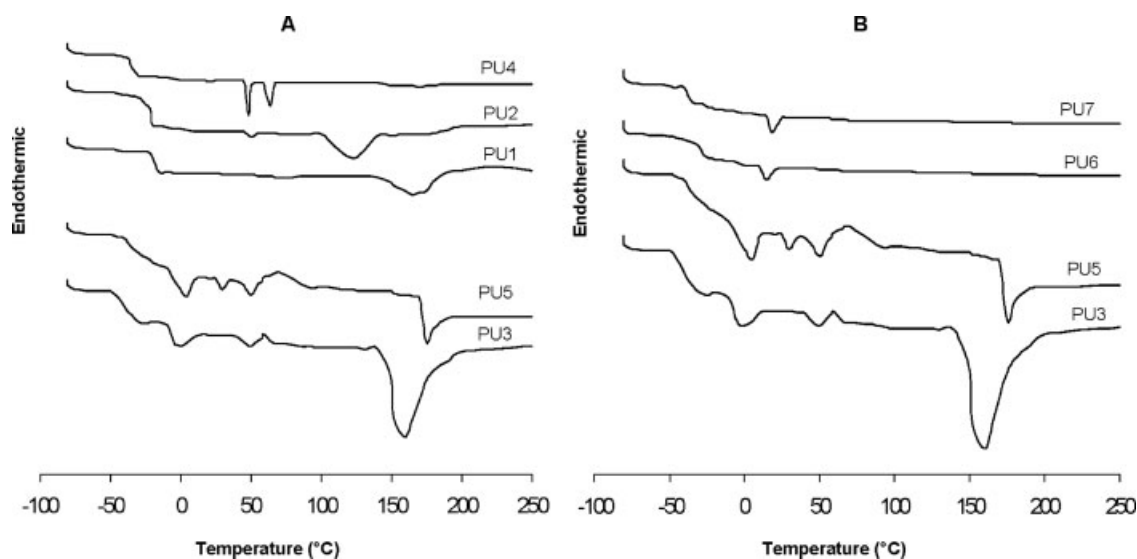


Figure 2 DSC thermograms of polyurethanes. (A) Series based on different molecular weight of PEG and PCL and (B) series based different diisocyanates.

The appearance of a peak at 1702 cm^{-1} in PU1 and PU2 in addition to 1718 cm^{-1} compared with the single peak at 1715 cm^{-1} in PU3 shows that a fraction of urethane carbonyl is non H-bonded in PU1 and PU2. However, no significant shift of N—H peaks around 3320 cm^{-1} indicates that the ether linkages are H-bonded and that leads to certain degree of phase mixing in PU1 and PU2, which is relatively less in PU3. The shorter soft segment probably leads to a shorter hard segment as evident from the molecular weight. This characteristic leads to random orientation of the polymer chain and therefore lesser H-bonding in the hard segment domain. For PEG-based polyurethanes considerable phase-mixed morphology is obtained with low-molecular weight soft segment, which is comparable to observations made by other researchers.^{6,12} The molecular weight of PCL soft segment has a similar, though less pronounced, effect. The presence of a strong ester carbonyl overlaps the peak due to urethane carbonyl group. However, in PU4 a peak around 1690 cm^{-1} is observed which might represent an H-bonded carbonyl group. This peak is either absent or merged with the strong ester carbonyl absorbance at 1726 cm^{-1} . This indicates that a fraction of ester carbonyl is H bonded in PU4 because of phase mixing between the hard and soft segment. In general, the shift of the ester carbonyl peak for PCL-based polyurethane from 1730 cm^{-1} in PU5 to 1726 cm^{-1} in PU4 is attributed to the more crystalline nature of high-molecular weight PCL and lattice effects.^{12,17} The effect of cyclic diisocyanate on the polyurethane morphology is not evident from FTIR analysis [Fig. 1(C)] but most likely cyclic structure of HMDI leads to more amorphous hard segment due to less packing and less number H-bonds.

Differential scanning calorimetry

The thermal characteristics (DSC) of the polyurethanes are shown in Figure 2. Figure 2(A) shows the effect of soft segment while Figure 2(B) shows the effect of different diisocyanate. Comparison of thermograms for PU1, PU2, and PU3 shows that the molecular weight of the PEG soft segment has significant effect on the thermal properties and morphology of the polyurethanes. The soft segment T_g (glass transition temperature) increases with decreasing molecular weight of PEG. The T_g values for the soft segment are -15 , -26 , and -40°C in PU1, PU2, and PU3, respectively. The increase in soft segment T_g indicates that decreasing molecular weight of PEG soft segment leads to more phase mixing between the hard and soft segment of the polyurethanes. Similar results have been observed for other polyurethanes with different molecular weight soft segments.^{12,18} The presence of three endotherms in PU3 corresponds to disruption of short range and long range order of hard segments and melting of the crystalline hard segment. These additional endotherms are different in PU1 and PU2. For PU1 only one broad endotherm was observed around 150°C representing the melting of the polyurethane whereas two endothermic transitions are observed for PU2 around 48°C and a broad one around 118°C . The first endothermic transition is probably due to disruption of ordered hard segments and/or H-bonding interactions between hard and soft segments. The second endotherm indicates melting of the polyurethane. This indicates that even with high hard segment content of PU1 and PU2, the hard segment is relatively less ordered and shows considerable phase mixing. The hard segments of PU1 and PU2 are relatively more amorphous. Thus the

increasing molecular weight of the PEG soft segment leads to more phase segregated morphology with a relatively ordered hard segment. The molecular weight of the PCL soft segment has less of an effect on thermal characteristics as compared to PEG. The soft segment T_g for PU4 is at -35°C compared with -37°C of PU5. This shows that there is significant phase mixing but it is practically unaffected by the change in molecular weight of PCL. This is in contrast to the observations made on polyurethanes based on PCL of molecular weight 530 by Skarja and Woodhouse¹² This is probably due to the unsymmetrical lysine-based diisocyanate and the pendant group of the phenylalanine-based chain extender used in that work. But the effect of PCL's molecular weight is consistent with other observations where the PCL soft segment beyond 2000–3000 molecular weight range is mostly phase separated.¹⁹ However, two endothermic transitions are observed for PU4 at 48°C and 66°C in comparison to four in PU5 at 0°C , 31°C , 52°C , and 173°C . The endotherms of PU4 correspond to disruption of interactions between hard and soft segments and within the hard segment. The additional endotherms of PU5 represent soft segment and hard segment melting.¹⁶ Comparison of endotherms for PU4 and PU5 shows that PCL soft segment with higher molecular weight exhibits soft segment crystallinity and also leads to a more crystalline and ordered hard segment. Although the change in soft segment T_g is not appreciable, the phase mixed morphology of PU4 is evident from the absence of melting endotherms. Comparison of PU3 and PU5 thermograms shows that at comparable molecular weight PCL-based polyurethanes exhibits soft segment crystallinity compared with PEG-based polyurethane.¹² Similarly comparison of PU2 and PU4 shows that interaction between the soft and hard segment is much stronger in PCL-based polyurethanes where H-bonding with ester carbonyl is stronger than H-bonding with ether oxygen of PEG soft segment.²⁰ The effect of diisocyanate structure has significant impact on the polyurethane morphology.²¹ Comparison of thermograms of PU6 to PU3 and of PU7 to PU5 shows that changing from linear to cyclic structure changes the hard segment morphology. The soft segment T_g of PU3 is -40°C and that of PU6 is -28°C . This shows the extent of phase mixing is more in PU6. However, the soft segment's T_g for PU7 is -39°C , which is very similar to PU5, indicating similar extent of phase mixing. This is probably due to the crystalline nature of PCL compared with PEG. But PU6 exhibits a small endotherm at 7°C compared with three endotherms of PU3. The absence of a melting endotherm in addition to the other endotherm (around 50°C) in PU6 shows that with cyclic diisocyanate the hard segment is relatively less ordered and more amorphous

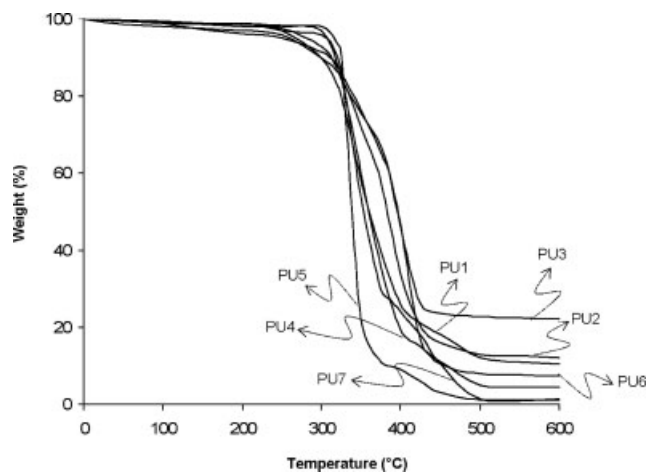


Figure 3 TGA analysis of polyurethanes.

in nature. The cyclic structure of the diisocyanate and the chain extender (DTH) prevents close packing of the hard segment leading to a relatively amorphous nature. The small endotherm around 7°C is due to disruption of some order of the hard segment and the interactions between the soft and hard segment. The similar comparison of thermograms of PU5 and PU7 show that cyclic diisocyanate prevents hard segment crystallization leading to a nearly completely amorphous hard segment. The TGA analysis of all the polyurethanes shows a very similar pattern, as shown in Figure 3. For PEG-based polyurethanes the initial 30% of weight is lost slowly followed by relatively faster degradation and for PCL-based polyurethanes the initial 70% of weight is lost slowly followed by relatively faster degradation. This is probably indicative of two phase structure of the polyurethanes. But, in general all the polyurethanes show the onset of degradation around 300°C indicating the stability of the polyurethane up to a temperature of 300°C .

Effect on polyurethane properties

Tensile properties

The mechanical properties of the polyurethanes are summarized in Table III. The results show that PEG-based polyurethanes are relatively weaker in mechanical properties compared with PCL-based polyurethanes because of relative crystallinity.^{11,12,16} The effect of soft segment's molecular weight can be seen for both PEG- and PCL-based polyurethanes. For PU1, PU2, and PU3, increasing PEG's molecular weight shows increased mechanical properties although the hard segment content of the polyurethanes is decreasing. Phase mixed morphology and lack of an ordered hard segment, as indicated by FTIR and DSC, results in poorer mechanical strength

TABLE III
Mechanical Properties of Polyurethanes (mean \pm SD, $n = 5$)

Polyurethane	Ultimate Tensile Strength (MPa)	Modulus of Elasticity (MPa)	Elongation at Break (%)
PU1	0.47 \pm 0.04	1.57 \pm 0.31	59.6 \pm 7.6
PU2	0.93 \pm 0.11	2.51 \pm 0.28	49.6 \pm 0.8
PU3	2.81 \pm 0.11	3.75 \pm 0.21	214 \pm 9
PU4	0.53 \pm 0.09	2.04 \pm 0.15	60.1 \pm 11.3
PU5	7.05 \pm 0.6	17.98 \pm 0.68	643 \pm 87
PU6	3.73 \pm 0.37	0.94 \pm 0.23	1513 \pm 95
PU7	18.60 \pm 1.54	3.15 \pm 0.28	725 \pm 29

in low-molecular-weight PEG-based polyurethanes. Moreover, the molecular weight of polyurethanes with lower molecular weight PEG is also low. Skarja and Woodhouse were not able to determine the tensile properties of the PEG-based polyurethanes, which indicate that PEG-based polyurethanes exhibit lower mechanical properties.¹² Similar explanations are applicable for the mechanical properties of PU4 and PU5 with different molecular weight of PCL soft segment. In addition, increasing PCL's molecular weight shows an increasing crystalline nature of the soft segment, which tends to improve the mechanical property of PU5 compared with PU4.^{4,12} The apparently lower tensile properties of PCL-based polyurethanes can be due to the unsymmetrical structure and distribution of the DTH chain extender in the polymer chain. But in general, the tensile strength of PCL-based polyurethanes is comparable but any direct comparison with other polyurethane is not possible because of the difference in the structure, composition, and molecular weight of the polymers. These results show the importance of phase segregated morphology (resulting from ordered and crystalline hard segment) in the mechanical property of the polyurethane. The diisocyanate structure has a significant impact on the mechanical properties of the polyurethanes. Both for PEG- and PCL-based polyurethanes, changing the diisocyanate from linear to cyclic structure improves the ultimate tensile strength and elongation but significantly reduces the modulus. Both PU6 and PU7 exhibit higher ultimate strength and very high elongation but reduced modulus of elasticity compared with PU3 and PU5, respectively. In general, cyclic structure improves the mechanical properties because of ordered and crystalline hard segment.²¹ But DSC and FTIR indicate considerable phase mixing and a disordered hard segment in PU6 and PU7. This explains the low modulus of elasticity of PU6 and PU7 compared with linear diisocyanate-based polyurethane. Therefore, increase in ultimate tensile strength and elongation is contrary to the general trend. This can be explained by the stain-induced crystallization and/or finite extensibility of the polyurethanes.²² Although the cyclic structure of HMDI is symmetri-

cal, it prevents close packing of the polymer chains. Therefore, at higher strain the molecular chains of the polyurethanes are either able to reorient to form crystalline structures or change the conformation to absorb higher energy.²²

Water contact angle

The water contact angle values of the polyurethanes both in advancing and receding mode are shown in Figure 4. The contact angle of PEG-based polyurethanes is lower because of the hydrophilic PEG soft segment. As expected, with increasing molecular weight of PEG the contact angle values are lowered because of more hydrophilicity whereas for PCL-based polyurethanes the contact angle increases with increasing molecular weight of PCL. The contact angle hysteresis (difference between advancing and receding contact angle) is higher in low-molecular-weight soft segments. This indicates that the surfaces of these polyurethanes are reoriented with more polar hard segment toward the surface.¹¹ Moreover, the contact angle of low-molecular-weight PEG-based polyurethanes are similar to the contact angle of PCL-based polyurethanes. These features indicate that the surface of the low-molecular weight polyurethanes are relatively heterogeneous with mixed hard and soft segments. The change of diisocyanate from linear to cyclic structure leads to a more hydro-

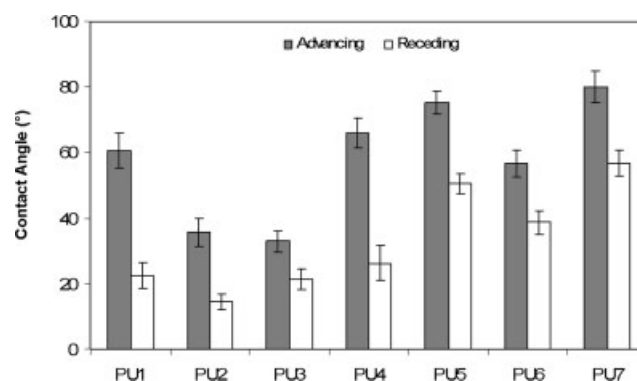


Figure 4 Advancing and receding water contact angle of polyurethanes (mean \pm SD, $n = 15$).

TABLE IV
Water Vapor Permeability of Polyurethanes (mean \pm SD, $n = 3$)

Polyurethane	Water Vapor Permeance [10^6 mg/h mm ² mm of Hg]	Water Vapor Permeability Coefficient [10^6 mg/h mm mm of Hg]
PU1	8.50 \pm 1.52	1.08 \pm 0.12
PU2	18.21 \pm 2.18	2.43 \pm 0.98
PU3	25.37 \pm 1.34	6.0 \pm 1.14
PU4	8.74 \pm 1.93	1.79 \pm 0.74
PU5	9.11 \pm 1.32	2.44 \pm 0.44
PU6	22.15 \pm 2.36	3.45 \pm 0.37
PU7	7.73 \pm 0.77	1.24 \pm 0.18

phobic surface as indicated by high contact angles and high hysteresis values. This is also indicative of a heterogeneous pattern of polyurethane surfaces with HMDI as diisocyanate.

Water vapor permeability

The water vapor permeability of the polyurethanes is shown in Table IV. Water vapor permeance (WVP) and water vapor permeability coefficient (WVPc) of PEG-based polyurethanes are higher for the hydrophilic PEG soft segment. Both the values of WVP and WVPc increases with increasing molecular weight of PEG because of higher hydrophilicity and heterogeneous phase mixed behavior whereas the trends are less significant in case of PCL-based polyurethanes. The presence of cyclic diisocyanate decreases the values of WVP and WVPc, which is mainly due to heterogeneous phase mixed characteristic of the polyurethanes.

Water absorption

The water absorption of the polyurethanes is shown in Figure 5. PEG-based polyurethanes absorb more water than PCL-based polyurethanes because of hydrophilicity of the soft segment. However, water absorption decreases with a decrease in PEG's molecular weight because of a relative decrease in the hydrophilic nature of the polyurethane. Moreover, polyurethanes with low-molecular-weight PEG exhibit phase mixed morphology due to which hydrophilicity of the soft segment is reduced. For PCL-based polyurethanes, the effect of molecular weight of PCL soft segment is not significant as observed by the water absorption of PU4 and PU5. Comparison of PU6 with PU3 shows that changing of diisocyanate from linear to cyclic structure leads to more water absorption. This is attributed mainly to the phase mixed morphology and relative amorphous hard segment of the polyurethanes. Similar feature, although in lesser extent, is observed for PCL-based polyurethane as seen by the water absorption of PU5 and PU7.

Hydrolytic degradation

The hydrolytic degradation of the polyurethanes is shown in Figure 6. The role of polymer morphology is important for polymer degradation.^{23,24} Figure 6(A) shows the effect of soft segment and its molecular weight on the hydrolytic degradation. PEG-based polyurethanes degrade at a faster rate compared with PCL-based polyurethanes.^{7,11,16} Since PEG is hydrophilic and absorbs more water, the degradation rate in PEG-based polyurethanes is faster than PCL polyurethane. Moreover, PCL is relatively crystalline compared with PEG. The extent of degradation decreases with decreasing molecular weight of PEG because of more hydrophobic nature of the polyurethane. Similar degradation characteristics were observed for PCL-based polyurethanes where PU4 (low-molecular-weight PCL-based polyurethane) degraded at a slower rate compared with PU5 (high-molecular-weight PCL-based polyurethane). But this is contrary to the expectation since PU4 is less hydrophobic and more amorphous compared with PU5. The phase mixed morphology of PU4, as seen from DSC and FTIR, indicates that PU4 is more hydrophobic and thus shows relatively slower rate of degradation. The effect of diisocyanate structure on the degradation characteristics is shown in Figure 6(B). The change of diisocyanate slows down the degradation rate for PEG-based polyurethane whereas in PCL-

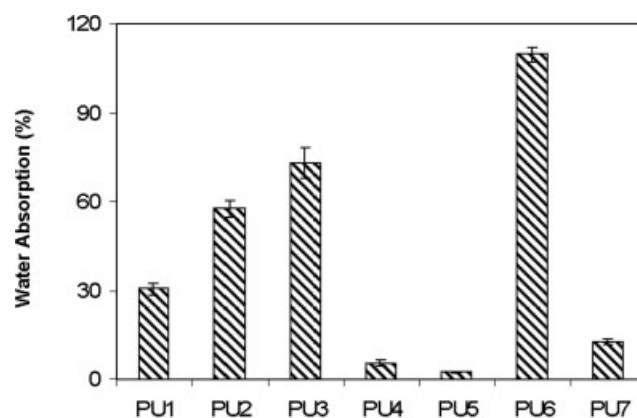


Figure 5 Water absorption characteristics of polyurethanes (mean \pm SD, $n = 4$).

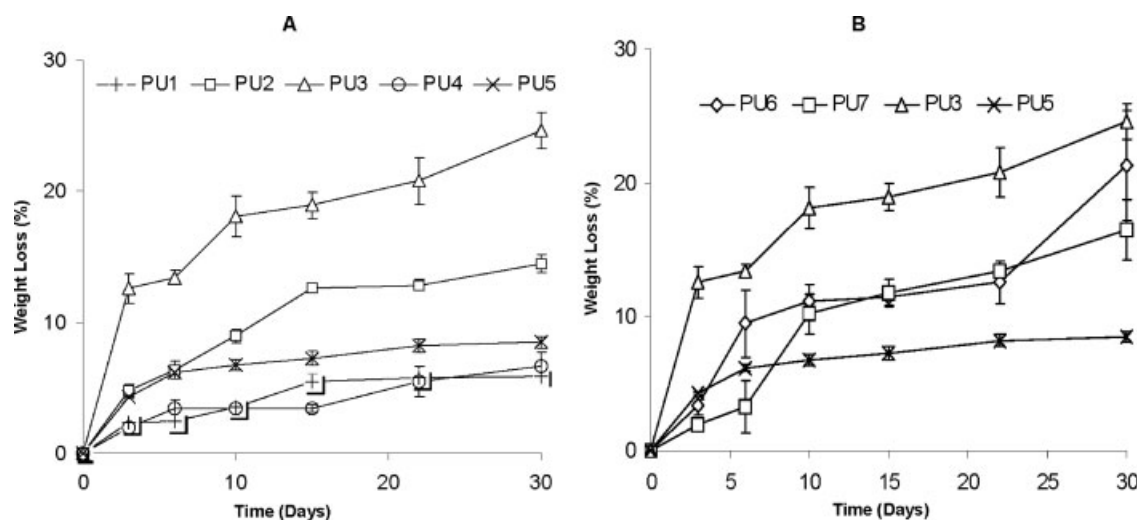


Figure 6 Hydrolytic degradation of polyurethanes in PBS (pH 7.4, 37°C). (A) Series based on different molecular weight of PEG and PCL and (B) series based on different diisocyanates (mean \pm SD, $n = 4$).

based polyurethanes it enhances the rate. This anomalous nature in degradation characteristics is due to the morphology of the polyurethanes. PU6 is relatively amorphous and absorbs more water than PU3 and, therefore, is expected to degrade faster compared with PU3. In addition, PU6 exhibits considerable phase mixing, which indicates that urethane linkages are H-bonded with the soft segment. This lowers the number of urethane linkages available for hydrolytic degradation. The soft segment PEG in PU3 is comparatively phase separated and, therefore, is readily dissolved after degradation. Since the hard segment in PU3 is ordered and relatively crystalline, the urethane linkages present at the interphase are degraded initially and rapid mass loss is experienced by PU3 because of easy extraction of degraded PEG in water. However, the opposite trend is observed in PU6. In PU6, the H-bonding interaction between the hard and soft segment prevents the dissolution of PEG after degradation, which results in a relatively smaller amount of mass loss. However, in case of PCL-based polyurethanes, PU7 degrades at a faster rate compared with PU5. The cyclic structured diisocyanate leads to relatively less ordered hard segment. The interactions between the hard and soft segment leads to a phase mixed morphology due to which the crystallinity of PCL soft segment is lower substantially. This enables water to approach more urethane linkages compared with PU3 and hydrolytically cleave the polymer chain. This shows that hard segment structure and morphology controls the degradation of the polyurethane.

Release characteristics

The release of *p*-nitroaniline, a model hydrophobic drug, was studied to investigate the effect of polyur-

ethane structure on the release pattern of the drug. The structure and morphology of the polymers are important controlling factors in the release of drugs.^{25,26} Figure 7 shows the release pattern of *p*-nitroaniline from polyurethane matrices where the fractional release is plotted against the square root of time. Figure 7(A) shows the effect of different soft segments with variable molecular weight. The series of polyurethanes based on PEG soft segment shows that more drug is released for low-molecular-weight PEG soft segment. For PU1 and PU2 more than 80% of the drug is released compared with only 43% released from PU3. *p*-nitroaniline, being a hydrophobic drug, is mainly dispersed in the hard segment of the polyurethanes rather than in the hydrophilic PEG soft segment. Since considerable phase mixing is observed in PU1 and PU2, the hydrophobic drug is uniformly distributed throughout the polymer matrix in PU1 and PU2. In PU3 the drug is mainly located in phase separated hard segment domains only. The extent of degradation is highest for PU3 but the percentage release of the drug is lowest for the series of PEG-based polyurethanes. This shows that release of *p*-nitroaniline is largely diffusion controlled. Similar observations are made for PU4 and PU5 for the effect of variable molecular weight of PCL soft segment. But in comparison to PU5 where release becomes constant after 2 days, PU4 continues to release drug till the end of the 30-day period. Moreover, phase mixed morphology and low-molecular-weight PCL soft segment has reduced the crystallinity of the soft segment in PU4, which improved the release of the drug. The release pattern of the drug is significantly changed by the structure of the diisocyanate as shown in Figure 7(B). For PEG-based polyurethanes changing the diisocyanate from linear to cyclic structure increased the release of *p*-nitroani-

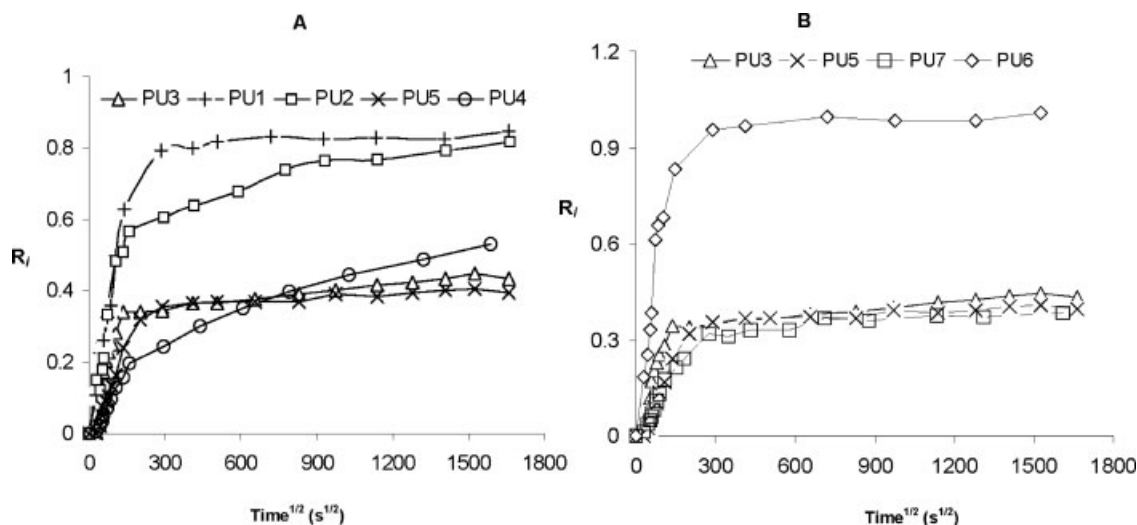


Figure 7 Release of *p*-nitroaniline from polyurethane matrices in PBS (pH 7.4, 37°C). (A) Series based on different molecular weight of PEG and PCL and (B) series based on different diisocyanates ($n = 4$).

line from 43% (in PU3) to 100% (PU6). This is due to uniform dispersion of the drug in mixed phase structure of PU6 where soft and hard segment intermixed. This allows the drug to be uniformly dispersed throughout the matrix resulting in substantially higher release. However, for PCL-based polyurethanes there was no change in the release pattern because of a change in the diisocyanate structure. Both PU5 and PU7 show about 39% release of *p*-nitroaniline in a 30-day period. PU7 shows phase mixed morphology and relatively amorphous hard segment, which is expected to increase the release of *p*-nitroaniline. The lower release in PU7 indicates that amount of water absorbed is not sufficient to diffuse out the poorly water soluble drug. This implies that the amount of water absorption is important for diffusion of the drug from the polyurethane matrices. Moreover, the hydrophobic drug mainly interacts with the relatively hydrophobic domains of the polyurethane.²⁷

CONCLUSIONS

A series of polyurethanes based on *L*-tyrosine derived chain extender was synthesized by using different polyols and diisocyanates. The effect of this structural variation on the physicochemical properties of the polyurethanes was characterized by different techniques. The characterization results show that the structure of the polyurethanes is directly related to the properties and properties of the polyurethane can be altered by changing the polyurethane structure. These structural variations led to the development of *L*-tyrosine-based polyurethanes with wide range of properties. In general two polyols, PEG and PCL with variable molecular weights

were used to investigate the structure property-relationship. Low-molecular-weight polyols as soft segment led to phase mixed morphology of polyurethanes because of significant interaction between the hard and soft segment. PEG-based polyurethanes are soft and weaker compared with PCL-based polyurethanes but degradation and water absorption properties are significantly higher in PEG-based polyurethanes. The molecular weight variation of the soft segment has a significant effect on the mechanical properties, surface characteristics, water absorption, release characteristics, and hydrolytic degradation. For PEG-based polyurethanes the decreasing molecular weight of PEG leads to more phase mixed morphology and higher hydrophobic characteristics. Decreasing molecular weight of PCL-based polyurethanes has less significant effect in the morphology of the polyurethane. Polyurethanes with low-molecular-weight PEG exhibit lower tensile properties, less water absorption, and slower rate of hydrolytic degradation whereas low-molecular-weight PCL does not affect the water absorption and degradation characteristics. The effect of diisocyanate structure was investigated with linear and cyclic aliphatic diisocyanate. Structural variation of diisocyanate significantly influences the morphology of the polyurethanes and, therefore, changes the tensile properties, water absorption, degradation rate, and release characteristics. The wide range of properties was achieved by easy and simple alteration of the polyurethane structure. In general, controlling mechanical properties, surface characteristics, degradation rate, and release pattern has significant impact on using the *L*-tyrosine-based polyurethanes for different biomaterial applications, including tissue engineering.

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