Novel Biocompatible Waterborne Polyurethane Using L-Lysine as an Extender

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ABSTRACT: Polyurethane (PU) prepolymers based on isophorone diisocyanates, dimethylolpropionic acid, and polycaprolactone were prepared and chain-extended in water using L-lysine (PU–L), ethylenediamine (PU–E), and their mixture (PU–L–E) as extenders, respectively. The produced emulsion exhibited satisfactory freeze/thaw stability. Films cast from emulsions exhibited excellent mechanical properties and good antiblood coagulation character. Although the water-swelling ratio for 24 h for PU–L was higher than those of PU–L–E and PU–E, it possessed the smallest hydrolysis rate among the three samples. © 2002 Wiley Periodicals, Inc. J Appl Polym Sci 84: 2474–2480, 2002

Key words: waterborne polyurethane; extender; L-lysine; biocompatibility; polyurethanes; functionalization of polymers

INTRODUCTION

Polyurethane (PU) block copolymers, as an important class of biomaterials, have drawn the attention of many scientists worldwide due to their unusual mechanical properties and blood compatibility.[1] Their unique mechanical properties can be attributed to their specific microphase-separated morphology, which consists of hard-segment-rich and soft-segment-rich domains.[2] In segmented PU, soft segments contribute to the elasticity and low-temperature properties, whereas the hard segments contribute to the modulus, strength, and elevated temperature properties. Thus, the ratio of the hard segment to the soft segment, the extent of microphase separation, could adjust the mechanical properties in very wide ranges.

Waterborne PU systems permit the application of PUs into an aqueous medium. Only water is evolved during the drying process; thus, these systems are especially safe to the environment. In addition, another advantage of waterborne PU is the fact that the molecular weight can be adjusted to any extent, without changing the viscosity properties.[3] In the last 50 years, much literature has appeared and thousands of patents issued, which has led to quick improvement of waterborne PU.[4,5]

Natural material may be expected to be used in the synthesis of biomaterials. It is well known that L-lysine, as a natural amino acid, has two amino and one carboxyl group. Many amino acid derivatives[6] have been used as chain extenders for PU synthesis in bulk or in organic medium; however, L-lysine, itself, only can be dissolved in water, and, thus, it should be the good candidate for an extender of waterborne PU. Some advantages should be expected: One is that the two

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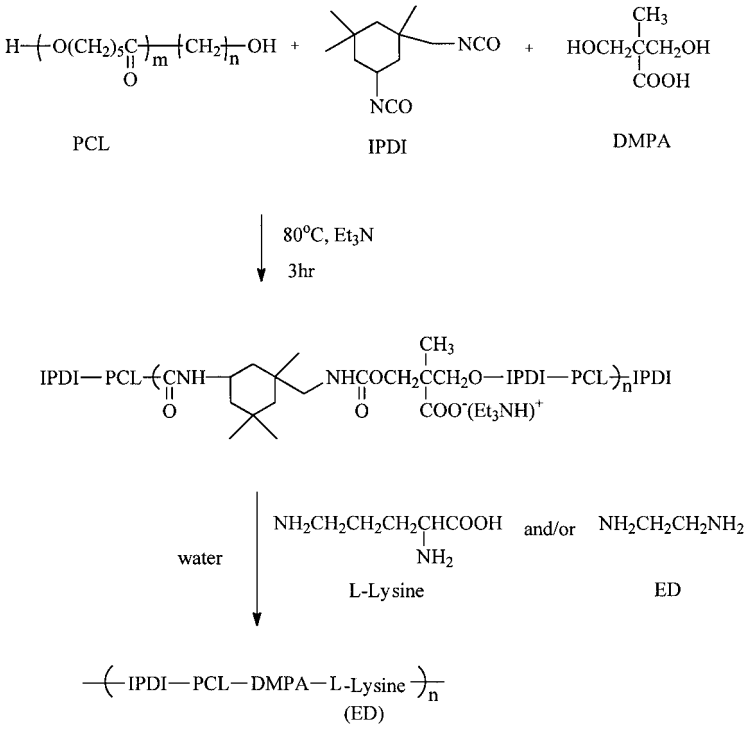

Scheme 1 Synthesis of PU urea emulsion with L-lysine as the chain extender: (a) theoretical value; (b) experimental value.

primary aminos in L-lysine molecules can be reacted with isocyano much more quickly than can those of the reaction between water and diisocyanate. Another advantage is that the carboxyl in the L-lysine molecules would be of benefit to the stability of waterborne PU. Third, of course, L-lysine would add safety to *in vivo* biodegradation.

In this article, a PU prepolymer based on isophorone diisocyanates, dimethylolpropionic acid, and polycaprolactone, which is known for its good biocompatibility, was prepared and chain-extended in water using ethylenediamine, L-lysine, and their mixture as extenders, respectively, as shown in Scheme 1. The produced emulsion exhibited satisfactory freeze/thaw stability. Films cast from these emulsions exhibited excellent mechanical properties and good antiblood coagulating character. The water swellability and hydrolysis properties of PU films were also investigated in this article.

EXPERIMENTAL

Materials

Polycaprolactone (PCL; M_n = 1000) and isophorone diisocyanate (IPDI) were commercial products from Aldrich (Milwaukee, WI). L-Lysine was a biochemical reagent. Dimethylolpropionic acid (DMPA), triethylamine (TEA), ethylenediamine (EDA), and *N,N*-dimethylformamide (DMF) were A.R. grade.

Synthesis

The basic formulations are given in Table I. PCL (15 g) and IPDI (6.67 g) were charged into a four-neck flask equipped with a mechanical stirrer, a thermometer, and a condenser. The solution was stirred at 80–85°C for 3 h, followed by adding DMPA (0.99 g) to the mixture. The mixture was kept at 80–85°C for another 2 h. The prepolymers were cooled, followed by adding triethylamine to neutralize the solution. Then, the prepolymers were chain-extended in the water using EDA, L-lysine, and the mixture of EDA and L-lysine (1:1) as the extenders. The polymers were designated as PU–E, PU–L, and PU–L–E, respectively. The resulting products were stable emulsions with a solids content of about 25%. The emulsions of the polymers were cast into Teflon disks and kept at room temperature for 3 days. Then, the disks were kept in a vacuum oven for 1 week at 60°C to obtain films of the polymers.

Characterization

The polymer films were dissolved in DMF and titrated by a standard solution of NaOH (0.01 mol/mL) to determine the content of the carboxyl group in the polymers using phenolphthalein as an indicator. The freeze–thaw stability of the emulsions was measured as follows: First, 2 mL of the emulsion was sealed in a weighing bottle and placed in an air oven at 90°C for 5 h. Then, it was immediately transferred to a refrigerator at 0°C for 5 h, which concludes a typical testing cycle. At least 10 testing cycles were performed for each sample to observe whether any system heterogeneity (e.g., phase separation or precipitation) could be detected in response to temperature mutations.

Differential scanning calorimetry (DSC) thermograms were recorded over a temperature range beginning at 203 K and terminating at 453 K. Samples were run at a heating rate of 20 K/min

The mechanical properties were determined on a table model Instron testing machine. An ASTM 1708 standard die was used for the samples and they were dried under a vacuum for a minimum of 48 h before testing. The samples were tested at room temperature using a crosshead speed of 50 mm/min.

Hydrolysis Stability of the Samples

The samples were weighed (W_1) and kept in deionized water at 37°C for 48 days, followed by drying and weighing (W_2). The hydrolysis weight loss was computed as follows:

$$\text{Hydrolysis weight loss (HWL)} = (W_1 - W_2)/W_1 \times 100\%$$

The water-swelling ratio of the films was studied as follows: A preweighed dry slab was immersed in ion-depleted water at 25°C. After equilibrium for 24 h, the sample was blotted with laboratory tissue and weighed. The water swelling ratio (SR) was expressed as the weight percentage of water in the swollen sample:

$$\text{SR} = (W_S - W_D)/W_D \times 100\%$$

where W_S is the weight of the swollen sample, and W_D, the weight of the dry sample.

Determination of the Blood Coagulation Time

Pieces of clean ground slides were coated with emulsions of the samples. After being dried, 0.2 mL fresh rabbit blood was added onto each piece of the slides, followed by adding a 20 μL solution of $CaCl_2$ (0.2 mol/L) onto each slide. A series of ground slides was put into distilled water (50 mL). After the hemoglobin was diffused into the water, the solution was tested by a spectrophotometer at 540 nm. The results were compared with those of the same ground slide without coatings.

Determination of Recalcification Time

A series of dried tubes was coated with emulsions and dried. Fresh rabbit blood (0.1 mL) containing sodium citrate and a solution of $CaCl_2$ (0.025 mol/L, 20.1 mL) were added into each tube. The time of the emergence of a milky white flocculate was recorded. The results were compared with those of blank tubes and the tubes coated with silicon oil.

RESULTS AND DISCUSSION

Analysis of the Carboxyl Group Content

The results of the carboxyl group content in the polymers by titration are consistent with the theoretical values, indicating that the reaction proceeded as expected and was processed completely (Table I). In other words, the chain extension in water was successful. The results of the experiment also could suggest that, although water and carboxylic acid can be reacted with isocyano in the prepolymers, the reaction rate was very slow at a low temperature compared to the reaction between isocyano and primary amine in that the reaction can be completed in a very short time.

Emulsion Stability

The emulsions all exhibited satisfactory stability in the whole range of the testing temperature and the transparency of the emulsions increased in the order of PU–E < PU–L–E < PU–L. Generally, the transparency reflects the particle size of the emulsion and the particle size of the emulsion is mostly governed by the concentration of solubilizing groups.[7] The solubilizing groups in this system are carboxylate anions, which were contained

Table I Synthesis and Properties of Waterborne PUs

Sample	Lysine (g)	TEA (g)	EDA (g)	Carboxyl Content (wt %)[a]	Carboxyl Content (wt %)[b]	T_g (°C)	Stress (MPa)	Strain (%)
PU–E	0	0.75	0.46	1.39	1.36	−21.0	42	756
PU–L–E	0.55	1.13	0.23	2.05	1.90	−24.4	51	877
PU–L	1	1.45	0	2.55	2.41	−31.3	78	924

[a] Theoretical value.
[b] Experimental value.

in DMPA as well as L-lysine. The ionic content increased in the above order due to the increase of the L-lysine content, so that the particle size decreases as the transparence increases in the same order.

Differential Scanning Calorimetry (DSC)

DSC traces are shown in Figure 1. The data are listed in Table I, where T_g is defined as the midpoint of the transition. As was noted, the soft-segments' glass transition temperatures (T_g's) decreased with an increasing L-lysine content. In other words, the glass transition temperature increased in the order of PU–L < PU–L–E < PU–E. In PU, the changing of the T_g's may be closely related to the compatibility between two phases: Higher phase-mixing will induce a higher T_g of the soft phase. With an increasing ion content, better phase-separated morphology will often be induced, because the ions could improve the cohesive energy in the hard domains and enhance the polarity difference between the hard and soft domains. In this system, the ionic content increased with an increased L-lysine content and a decreased EDA content, so the glass transition temperature changed according to the above tendency.

Endotherms, which appear at approximately 50–60°C in all of the DSC traces, can be seen.

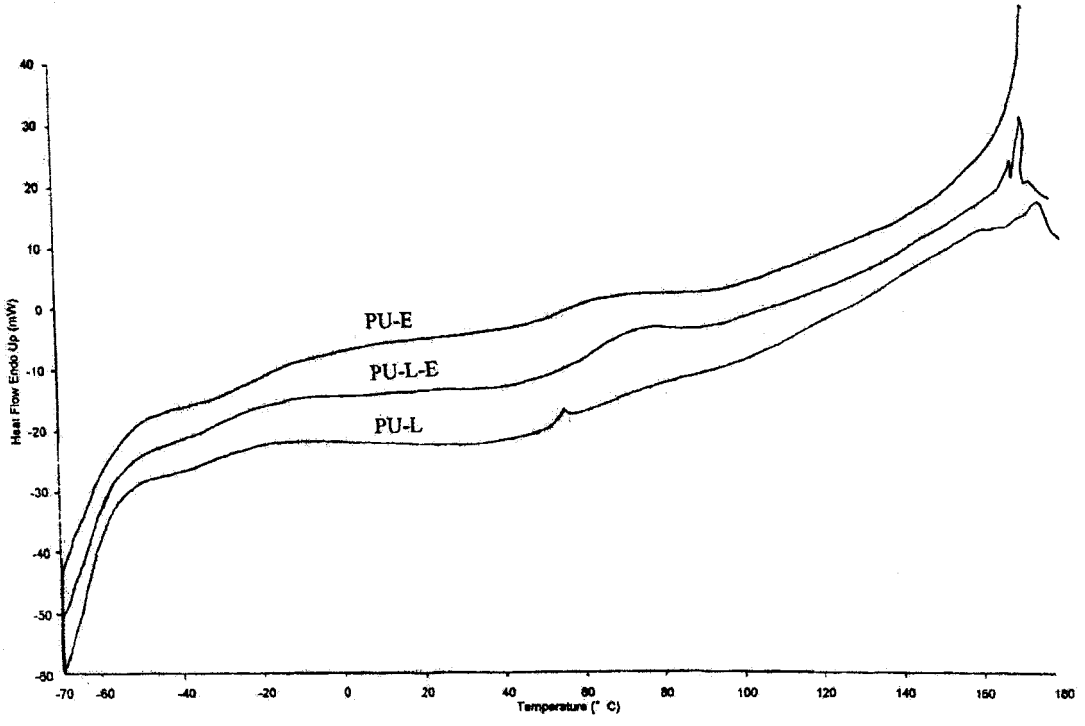

Figure 1 DSC parameters of waterborne PUs.

Some investigators previously reported this type of transition in many PUs, giving different interpretations. Some suggested a bimodal distribution of hard-segment lengths.[8,9] Lunardon et al.[10] attributed it to a β-transition of a mixed phase, while Curvé et al.[11] suggested a mixed interfacial region. However, Frontini et al.[12] indicated that the idea of a mixed phase of a mixed interfacial region could be ruled out since the 100% hard material also displays this transition. They also thought that it did not exhibit a typical secondary transition behavior. To understand this transition, they investigated the influence of thermal treatments on this transition and concluded that the transition observed in the DSC corresponds to a viscoelastic relaxation, which appears to be dependent on the thermal history. Other researchers also described similar transitions in PCL-based PUs containing different hard segments. Van Bogart et al. attributed the transitions in this region to the disruption of ordered, noncrystalline hard-segment aggregates.[13] However, Skarja and Woodhouse found that the transition noted at 60°C for PCL-based PU was not present in PEO-based PU. So, they suggested that this transition results from hard-segment/soft-segment ester interaction.[14] In our system, the samples all have the PCL soft segment and similar hard-segment contents, and the only difference was the extenders. It can be noted that the transition range became broader with decreasing carboxyl contents contained in the extender. It may be expected that interphase molecular interaction would be reduced with higher carboxyl contents in the extender because of the enhancement of intraphase molecular interaction. So, we suggest that the transition may be associated to the dissociation of urethane/urea soft-segment hydrogen bonds.

Mechanical Properties

Stress–strain curves are shown in Figure 2. The tensile strength and elongation at break of the PUs are listed in Table I. The values of the tensile strength and elongation at break were also found to depend on the content of L-lysine. It is well known that PU is a kind of material with microphase separation. The degree of microphase separation influences the mechanical properties of materials directly. Normally, a certain extent of microphase separation may promote the mechanical properties of materials. The stress increased in the order of PU–E < PU–L–E < PU–L due to the extent of the microphase separation increase, which resulted from the ionic content, which increased in the same order. This was consistent with the DSC results. However, the fact that the strain also increased in the same order is somewhat surprising because other researchers have indicated that the strain decreased with an increasing degree of phase separation which resulted from the higher ionic contents.[7] Yen and Cheng[15] showed that increased polyester soft-segment crystalline resulted in both increased ultimate tensile strength and ultimate elongation, as also seen by Skarja et al.,[14] while no crystallization was observed in the DSC for any of the samples in our system. It may be suggested that a higher degree of phase separation is of benefit to the soft-segment crystallization in the strain process, which resulted in increased ultimate elongation.

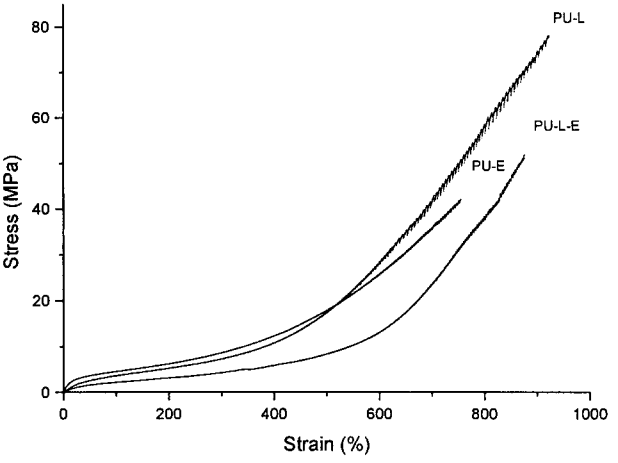

Figure 2 Stress–strain curves of waterborne PUs.

Water Swellability and Hydrolysis Properties

As a long-term implantable PU biomaterial, many researchers have paid more attention to its biostability. PU can undergo several types of degradation: mechanical degradation, biofouling, hydrolysis, oxidation, and so on. In polyether-based PUs, the ether linkages are easy to oxidize and calcify, while the ester linkages in polyester-based PUs are facilitated by an attack by water. In this kind of PCL-based waterborne PU, it can be noted from Table II that the water-swelling ratio after 24 h was changed from 9.8 to 44.8% when the L-lysine content was increased, that is,

Table II Water-Swelling Ratios and Hydrolysis Properties and Mechanical Properties (Saturated with Water for 24 h) of Waterborne PU

Sample	RS (%; 24 h)	HWL (%; 48 Days)	Strain (%) (Saturated with Water for 24 h)	Stress (MPa) (Saturated with Water for 24 h)
PU–L	44.8	2.47	1776	0.247
PU–L–E	21.1	4.78	1572	1.295
PU–E	9.8	7.56	1313	3.744

the water-swelling ratio can be adjusted to a very broad range by changing the L-lysine content. Moreover, those materials in the hydrogel state also exhibited reasonable mechanical properties.

It can also be noted from Table II that all the samples displayed a modest weight loss after 48 days. The better hydrolysis stability of PU with amine as an extender may be due to the higher cohesive energy of hard segments containing ureas. Although the 24-h water-swelling ratio for PU–L was higher than were those of PU–L–E and PU–E, it possessed the smallest hydrolysis weight loss among the three samples. This could be attributed to the higher phase-separation degree of PU–L that resulted in "purer" hard segments, which were not attacked by water easily, and to that PU–L contained more carboxylic groups, which were inhibited by the hydrolysis of PU.[16]

Blood Compatibility

Blood compatibility was evaluated by the free hemoglobin concentration in water and the recalcification time. The relationship between the test times and the A_{540nm} of the hemoglobin solution is shown in Figure 3. The higher absorption intensity represents the greater free hemoglobin concentration and indicates better blood compatibility. According to Figure 3, the three samples obviously have an antiblood coagulation character. The blood compatibility increases in the order of PU–E > PU–L > PU–L–E. The recalcification times of the blank tube and the tubes coated with silicon oil and with the samples were measured. The recalcification time of the blank tube is 29 s and the recalcification time of tube coated with silicon oil is 43 s. The recalcification time ratios of the tube coated with the samples to the blank tube and to the tube coated with silicon oil are shown in Table III. It is shown that the blood compatibility also increased in the order of PU–E > PU–L > PU–L–E, which is consistent with the result of the hemoglobin method. It can also been seen that the blood compatibility of PU–L and PU–E are better than those of silicon oil. The better blood compatibility of PU may be associated with the microphase-separation structure and the hydrophilic property of carboxylic acid.

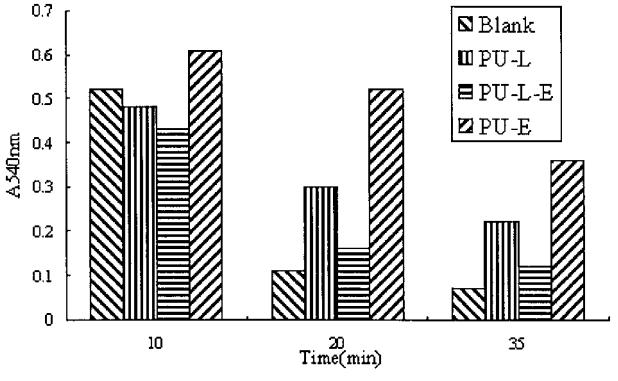

Figure 3 Relationship between test times and A_{540nm} of the hemoglobin solution.

CONCLUSIONS

A novel series of PU emulsions was synthesized successfully by an urethane prepolymer extended in water using L-lysine, ethylenediamine, and

Table III Recalcification Time Ratios of Tube Coated with Samples to Blank Tube and to the Tube Coated with Silicon Oil

Sample	Sample/Blank	Sample/Silicon Oil
PU–L	1.94	1.30
PU–L–E	1.42	0.96
PU–E	2.10	1.42

their mixture as extenders. The prepared emulsions exhibited satisfactory freeze/thaw stability and the films cast from the emulsions possessed excellent mechanical properties. Although the 24-h water-swelling ratio for PU–L was higher than those of PU–L–E and PU–E, it possessed the smallest hydrolysis weight loss among the three samples. The samples have an obvious antiblood coagulation character *in vitro*, and the antiblood coagulation character increased in the order of PU–E > PU–L > PU–L–E.

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