Polymer 49 (2008) 4393–4398

Contents lists available at ScienceDirect

Polymer

journal homepage: www.elsevier.com/locate/polymer

Synthesis and characterization of novel biodegradable and biocompatible poly(ester-urethane) thin films prepared by homogeneous solution polymerization

Wenshou Wang [a], Yanlin Guo [b], Joshua U. Otaigbe [a,*]

[a] School of Polymers and High Performance Materials, The University of Southern Mississippi, Hattiesburg, MS 39406-0076, USA
[b] Department of Biological Sciences, The University of Southern Mississippi, Hattiesburg, MS 39406-0076, USA

ARTICLE INFO

Article history:
Received 5 May 2008
Received in revised form 19 July 2008
Accepted 26 July 2008
Available online 3 August 2008

Keywords:
Poly(ester-urethane)s' dispersion
Biodegradable
Biocompatibility

ABSTRACT

Novel biodegradable and biocompatible poly(ester-urethane)s were synthesized by *in situ* homogeneous solution polymerization of poly(ε-caprolactone) diol, dimethylolpropionic acid (DMPA), and methylene diphenyl diisocyanate in acetone followed by solvent exchange with water. The effects of the DMPA content and hard segment content on the properties of the polyurethanes were measured by DSC, TGA, and hydrolytic degradation measurements. The results showed that DMPA had a dramatic effect on the particle size; the particle size decreased rapidly with increasing DMPA content. The hydrolytic degradation test showed that the degradation rate was little affected by the DMPA content in the range investigated, but was observed to be influenced by the hard segment content. Cell toxicity analysis showed that the biodegradable poly(ester-urethane)s synthesized in this study did not exhibit any detectable toxicity to human umbilical vein endothelial cells and mouse embryonic stem cells. Both types of cells can effectively adhere to and spread on the surface of pure poly(ε-caprolactone) or poly(ester-urethane)s. The present study demonstrates the feasibility of a facile synthesis of biodegradable polyurethanes and of their aqueous dispersions with prescribed properties for biomedical applications.

1. Introduction

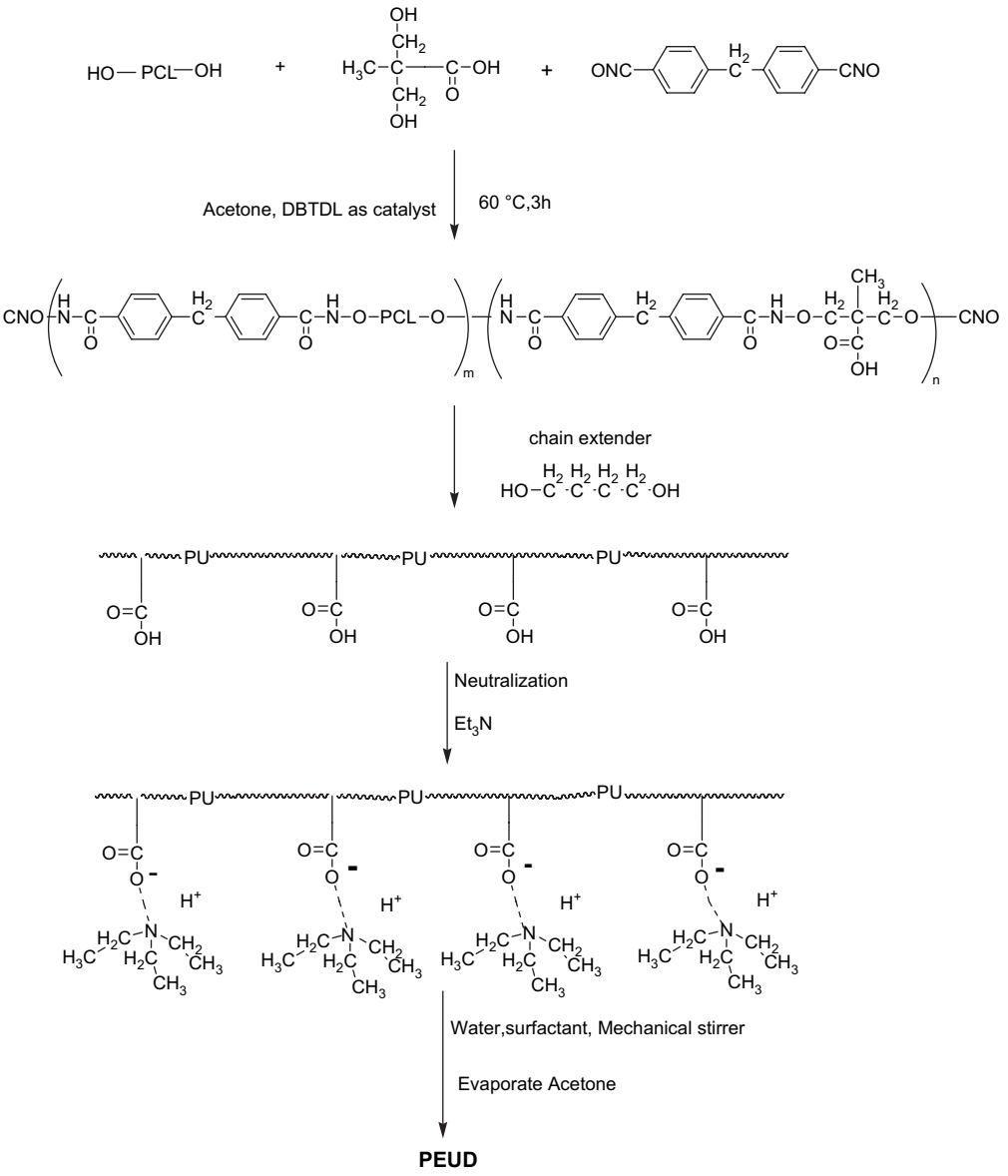
Aqueous polyurethane dispersions are of current interests because of stringent government environmental protection regulations and the potential cost reduction emanating from replacing traditional organic solvents from industrial formulations with an aqueous medium. In this context, polyurethane dispersions have found a number of useful industrial applications in diverse areas such as coatings, adhesives, sealants, defoamers, and textile dyes [1–10]. The synthesis and characterization of polyurethane ionomers have been extensively studied [11,12]. Typically, an ionomer type polyurethane dispersion is produced in two steps: (i) formation of a prepolymer of diisocyanate, polyols, and dimethylolpropionic acid and (ii) subsequent conversion of the prepolymer to high molecular weight polyurethane through the use of a suitable chain extender. The effects of ionic content, solid content, degree of neutralization and chain extension on aqueous polyurethane have been studied and recently reported in the literature [13–17].

In recent years, biodegradable materials are of active academic and industrial research interests for environmental reasons and for their potential uses in biomedical applications with enhanced benefits. In this area, biodegradable polymers such as polylactide, poly(ε-caprolactone), polycarbonate, poly(amino acid) have found interesting uses in biomedical application areas such as drug delivery, stent, packing materials, because of their relatively good mechanical properties, biodegradability, and biocompatibility [18–22]. Because of their desirable intrinsic elasticity, biodegradable polyurethanes have been explored for potential uses in tissue engineering [23–27]. Their potential uses in biomedical applications have been extensively reviewed by Cooper and coworkers [28]. However, relatively few studies have been reported for biodegradable polyurethane dispersions despite their advantages over traditional commercial polyurethane dispersions already mentioned. Consequently, there is a need for studies aimed at discovering facile synthesis routes to biodegradable polyurethanes from already existing raw materials and processes, as well as, optimizing key performance properties such as biocompatibility, thermal, mechanical and rate of biodegradation for biomedical applications.

In previous papers [7,29,30], we reported the synthesis and structure/property relations of pure aqueous polyurethane dispersions using homogeneous solution polymerizations in either NMP or acetone. In the present paper, we explore the feasibility of extending the previously reported methods to synthesize a series of

* Corresponding author. Tel.: +1 601 266 5596.
E-mail address: joshua.otaigbe@usm.edu (J.U. Otaigbe).

0032-3861/$ – see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.polymer.2008.07.057



Scheme 1. Synthesis route of the poly(ester-urethane) dispersions.

novel biodegradable and biocompatible poly(ester-urethane)s (PEU) via *in situ* homogeneous solution polymerization of poly(ε-caprolactone) diol, dimethylolpropionic acid (DMPA), and methylene diphenyl diisocyanate in acetone followed by solvent exchange with water. The effects of the DMPA content and the hard segment content on the biocompatibility, biodegradation rate, and thermomechanical properties will be discussed. The present study may stimulate a better understanding of the rational synthesis of biodegradable and biocompatible polyurethane materials with improved properties, making them widely applicable.

2. Experimental section

2.1. Materials

Poly(ε-caprolactone) diol (TONE® Polyol 5249) was purchased from Dow Chemical Company; and methylene diphenyl diisocyanate, acetone, dibutyltin dilaurate, 1,4-butanediol, dimethylolpropionic acid and triethyl amine were obtained from Aldrich. Ethoxylated nonylphenol ammonium sulfate (Abex® EP-110, Rhodia Chemicals, Cranbury, NJ) was used as an external surfactant to increase the storage stability of the dispersion. Phosphate buffer solution (1 M, pH = 7.4) was purchased from Sigma–Aldrich Company.

2.2. Polyurethane dispersion synthesis

A 250 ml round-bottomed three-necked flask equipped with a mechanical stirrer was used as a reactor vessel for the polymerization reaction whose temperature was controlled by using a constant temperature oil bath. Poly(ε-caprolactone) diol, dimethylolpropionic acid (DMPA), and methylene diphenyl diisocyanate were added to the flask prior to addition of the desired amount of acetone. The flask was then immersed in the oil bath maintained at 60 °C and its contents stirred. After the solid contents dissolved completely, dibutyltin dilaurate (1 wt% of the total solid weight) was added to the reaction system. After 3 h, 1,4-butanediol was added to the flask as chain extender. The reaction was allowed to continue for another 3 h prior to adding triethyl amine (DMPA equiv.) to the reaction system, and stirred for 30 min while maintaining the temperature at 60 °C. In this work, the ratio of

isocyanate group to total hydroxyl group (polyol, chain extender, DMPA) was kept at 1.05:1. A dispersion of the resulting polyurethane was obtained by adding a mixture of water and surfactant (4 wt% based on the total solid) over 10 min period. The dispersion was subsequently agitated for 1 h with the mechanical stirrer operating at 600 rpm. At the end of the reaction, acetone was removed from the system via a rotor evaporator to yield the aqueous poly(ester-urethane) dispersion (PEUD) that was used to cast the films used in this study. The thin films of polyurethanes were prepared by casting the aqueous PEUD onto a polypropylene plate followed by drying in a vacuum oven for 48 h at 50 °C. The films just mentioned were used for the DSC, TGA, degradation measurements, and cell toxicity analysis described in the following section.

2.3. Measurements

Particle sizes of the aqueous PEUD were determined with a Microtrac® UPA 150 light-scattering particle analyzer. Thermal analysis of the films was performed under a nitrogen atmosphere using a DSC (TA Q100®, TA Instruments) over a temperature range of −80 °C to 250 °C and a heating or cooling rate of 10 °C/min. The midpoint of the transition zone was taken as the glass transition temperature (T_g).

Mechanical tensile stress–strain measurements were conducted according to standard ASTM D882 method using a Material Testing System Alliance RT/10 and analyzed using an MTS Testworks 4 software package. The stretching rate is 20 mm/min at room temperature. Three dumbbell-shaped specimens with effective cross-sectional dimensions of $4 \times 0.7\ mm^2$ were tested and the mean values were similar to those reported in this paper. The degradation test was conducted in a buffer solution of pH = 7.4 at a degradation temperature of 37 °C following procedures reported elsewhere [31]. The poly(ester-urethane)s were cut into disks (diameter = 15 mm and thickness = 1 mm) and placed into the buffer solution (pH = 7.4) at 37 °C. The original weight of the sample was recorded as W_0. When the sample was taken out of the buffer solution and the excess water of the surface was removed with a tissue paper, its weight was recorded as W_1. The sample weight after drying in a vacuum oven at 30 °C for at least 48 h was recorded as W_2. The percent water absorbed (W_{ab}) was calculated from $100 \times (W_1 - W_2)/W_2$; and the weight loss ($W_{loss}$) was calculated from $100 \times (W_0 - W_2)/W_0$.

Cell toxicity evaluation was conducted as follows: human umbilical vein endothelial cells (HUVECs) and mouse embryonic stem cells (mESCs) were seeded on PCL or PEU coated cover glasses in 12-well cell culture dishes at a density of 3×10^4/ml. The HUVECs and mESCs were cultured in endothelial growth medium 2 (EGM-2, Lonza, Co.) and embryonic stem cell growth medium (ESGRO complete medium, Millipore, Co.), respectively. After incubation for 24 h at 37 °C in a humidified incubator (5% CO_2, 95% air), the cells were fixed and stained with 1% toluidine blue as previously reported elsewhere [32]. Cells were examined under an Olympus microscope with a phase contrast lens (CAch N40×) and photographed with a Cannon digital camera. The experimental samples were purified before the test by first dissolving them in DMF followed by precipitation in ethanol.

3. Results and discussion

3.1. Effect of DMPA content on particle size of the poly(ester-urethane) dispersion

It is well known that ionic functional groups are efficient stabilizers of polymer dispersions in water. In order to study the effect of DMPA on the PEUD particle size, four PEUDs with different DMPA contents were prepared following the procedure already described above. The elementary steps of the PEUD synthesis are presented in Scheme 1. The effect of DMPA content (wt% based on total solid content) on particle size is shown in Fig. 1. It is clear from Fig. 1 that when the other parameters were kept constant the particle size decreased sharply (from 190 nm to 37 nm) with increasing DMPA content ranging from 4 wt% to 5 wt% at first, and then followed by relatively slow decrease at higher DMPA content like others have previously reported for somewhat similar polyurethane dispersion systems [7,16]. It is worthy to note that 3 wt% DMPA content yields an unstable dispersion having a bimodal particle size distribution. The DMPA enhances the hydrophobicity of the poly(ester-urethane) so that increasing DMPA content leads to an improved PEUD, resulting in smaller particle sizes. It would appear from the results of this study that a minimum DMPA content of 4 wt% is required to achieve a relatively stable and uniform dispersion in the current PEUD system.

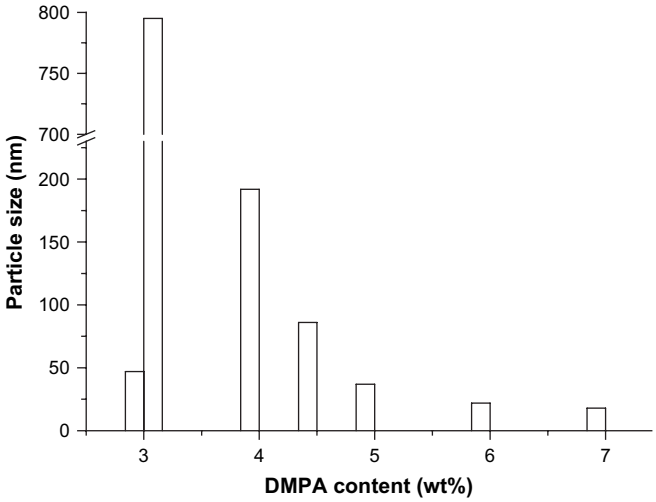


Fig. 1. The particle size of poly(ester-urethane) dispersions as a function of DMPA content.

3.2. Effect of PEU hard segment content on properties

In general, the nature and concentration of hard segment of polyurethanes strongly influence the dispersion particle sizes, as well as, the thermal and mechanical properties of polyurethane

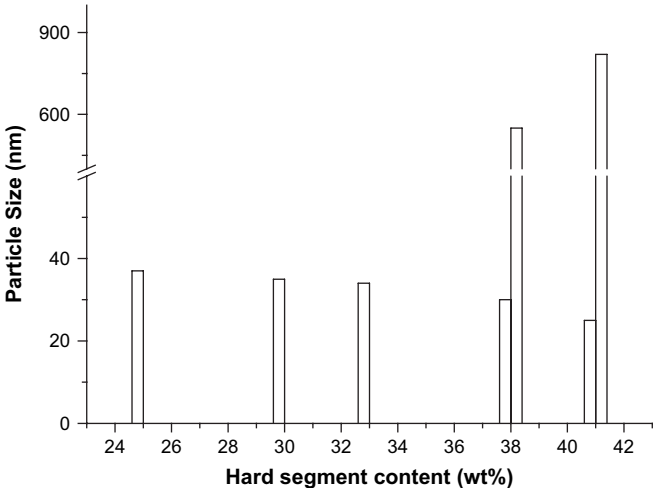


Fig. 2. The particle size of poly(ester-urethane) dispersions as a function of hard segment content.

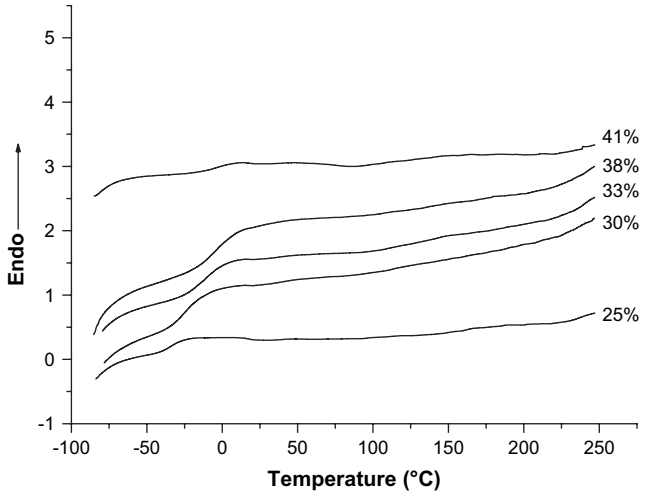


Fig. 3. The DSC curves of poly(ester-urethane)s with different hard segment contents indicated.

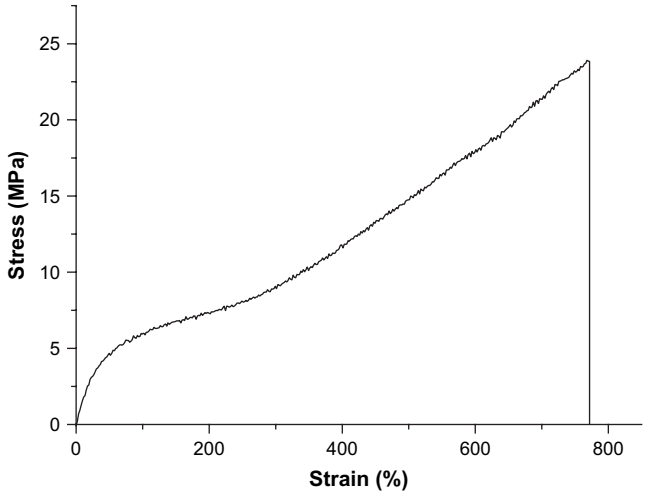


Fig. 4. Typical tensile stress–strain curve of the poly(ester-urethane).

elastomers. Fig. 2 shows the effect of hard segment content on the PEUD particle size. Here, the DMPA and solid contents were kept at 5 wt% and 26 wt%, respectively. Clearly Fig. 2 shows that the hard segment has little effect on the particle size until a hard segment content of about 33 wt% is achieved. At higher hard segment content (i.e., 38 wt% and 41 wt%) the PEUDs were observed to show a bimodal particle size distribution with the mean particle sizes shown in Fig. 2. The PEUDs just mentioned were relatively unstable showing evidence of polyurethane precipitation after 24 h. The reason for this remarkable result is not clear at this time but may be due to strong hydrogen bonding between the hard segments which leads to formation of the hydrophobic large particles. This hydrogen bonding is exacerbated at high hard segment content, making it difficult for the ionic functional groups in the PEUD to produce a stable dispersion. On the basis of the preceding results, a hard segment content of $\leq$33 wt% is recommended for preparing stable and homogeneously dispersed aqueous PEUDs.

The effect of hard segment content on the thermal properties of the PEUs is shown in Fig. 3. As expected, increasing hard segment content leads to an increase in the glass transition temperatures of the PEU elastomer due to restriction of the soft segment motions by the hard segments. It is worthy to note that the crystallizable PCL component of the PEU did not show a crystal melting peak in the DSC spectrum probably due to the hindering of the mobility of the PCL moieties [34]. The glass temperatures of the PEUs of this study are summarized in Table 1.

Fig. 4 shows a typical tensile stress–stain curve of poly(ester-urethane)s prepared from the PEUs with different hard segment contents as already described. The Young's modulus, strength, and elongation at break of the poly(ester-urethane)s just mentioned are summarized in Table 1. Expectedly, increasing hard segment content leads to higher tensile strength and modulus with a concurrent decrease in the elongation at break values. Because of the well known microphase separated structure in polyurethanes into hard and soft segments, the mechanical properties of the poly(ester-urethane)s at elevated temperatures (i.e., $>T_g$) should depend largely on the hard segment content, leading to relatively tough poly(ester-urethane)s at high hard segment content.

Table 1
Mechanical properties and T_g of the poly(ester-urethane)s

Sample code[a]	Tensile strength (MPa)	Modulus (MPa)	Elongation at break (%)	T_g (°C)
PEU25	21	1.9	1200	−32
PEU30	22	2.4	1086	−23
PEU33	24	2.8	987	−11
PEU38	25	3.0	856	−3.9
PEU41	27	3.2	545	−3.2

[a] Numbers denote percent hard segment content.

3.3. Hydrolytic degradation test

It is generally accepted that water absorption is a necessary condition for hydrolytic degradation of materials. Therefore, in a typical hydrolytic degradation test the rate of water absorption (or sample weight gain) can be correlated with sample weight loss. Here, we investigated the effects of DMPA content and hard segment content on the degradation rate of three poly(ester-urethane)s with varying DMPA and hard segment contents as indicated in Figs. 5 and 6. Fig. 5 shows the percent water absorption of poly(ester-urethane) versus time during the hydrolytic degradation test. It can be seen in this figure that the percent water absorption increases sharply in the first week of the test, rising to a plateau value of $15 \pm 2.5\%$.

Fig. 6 shows a small increase in percent weight loss in the first five weeks of the experiment that is ascribed to aqueous dissolution

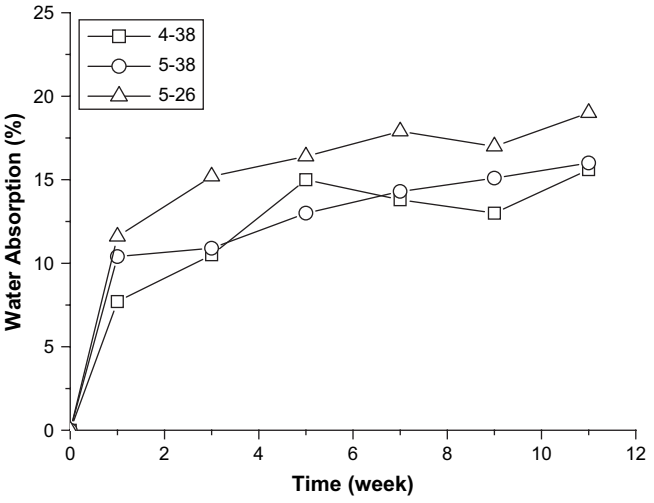


Fig. 5. The percent water absorption of poly(ester-urethane)s versus time. The figure legend shows DMPA content (first digit) and hard segment content (second two digits); e.g., 4–38 denotes 4% DMPA and 38% hard segment contents.

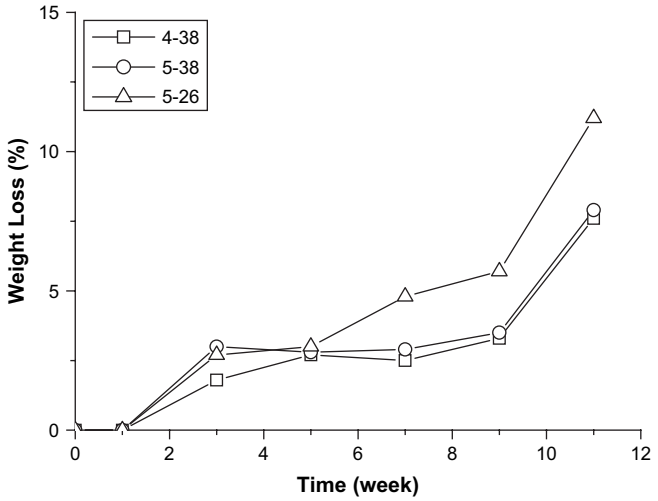


Fig. 6. The percent weight loss of poly(ester-urethane)s versus time. The figure legend shows DMPA content (first digit) and hard segment content (second two digits); e.g., 4–38 denotes 4% DMPA and 38% hard segment contents.

of small molecules such as unreacted monomers of poly(ester-urethane)s studied. After about seven weeks, the degradation rate increased sharply. The above results showed a relatively small influence of DMPA content compared to that of the hard segment content in the concentration range investigated. This observation is understandable because the degradation of polyurethane is known to be due to the degradation of the soft segment as already mentioned. In general, the degradation rate of the poly(ester-urethane) based on PCL was found to be slow (i.e., 15% weight loss in 11 weeks).

3.4. Cell toxicity evaluation

To evaluate suitability of the potential applications of the poly(ester-urethanes)s of this study in biomedical engineering, we investigated the PEU for its biological activity. Because PCL is a widely used biodegradable material in tissue engineering field due to its excellent biocompatibility, we used PCL as a control for our measurement of the cell toxicity of the PEUs synthesized in the present study. It is widely accepted that cell adhesion is an important cellular process that directly influences cell proliferation and survival. We analyzed two types of cells: human umbilical vein endothelial cells (HUVECs) and mouse embryonic stem cells (mESCs). Both HUVECs and mESCs effectively attached to polycaprolactone (PCL) or poly(ester-urethane) (PEU) coated glass plates within 3 h of cell seeding. Within a 24 h incubation period, the PCL and PEU did not show detectable toxicity to both HUVECs and mESCs (Fig. 7). The cells exhibited similar morphology as grown on biological matrices such as collagens and gelatin [32,33], indicating that the biodegradable poly(ester-urethane)s of this study may be suitable for a number of applications in the biomedical engineering field.

4. Conclusion

This paper describes the synthesis and characterization of a new kind of biodegradable and biocompatible poly(ester-urethane)s' dispersion and films with prescribed structure, properties and biocompatible function. The sample particle sizes varied with the DMPA content; and the glass transition temperatures and degradation rates can be tuned by varying the hard segment content. In addition, the materials showed excellent mechanical properties. Cell toxicity evaluation results showed that the poly(ester-urethane)s did not exhibit any detectable toxicity to HUVECs and

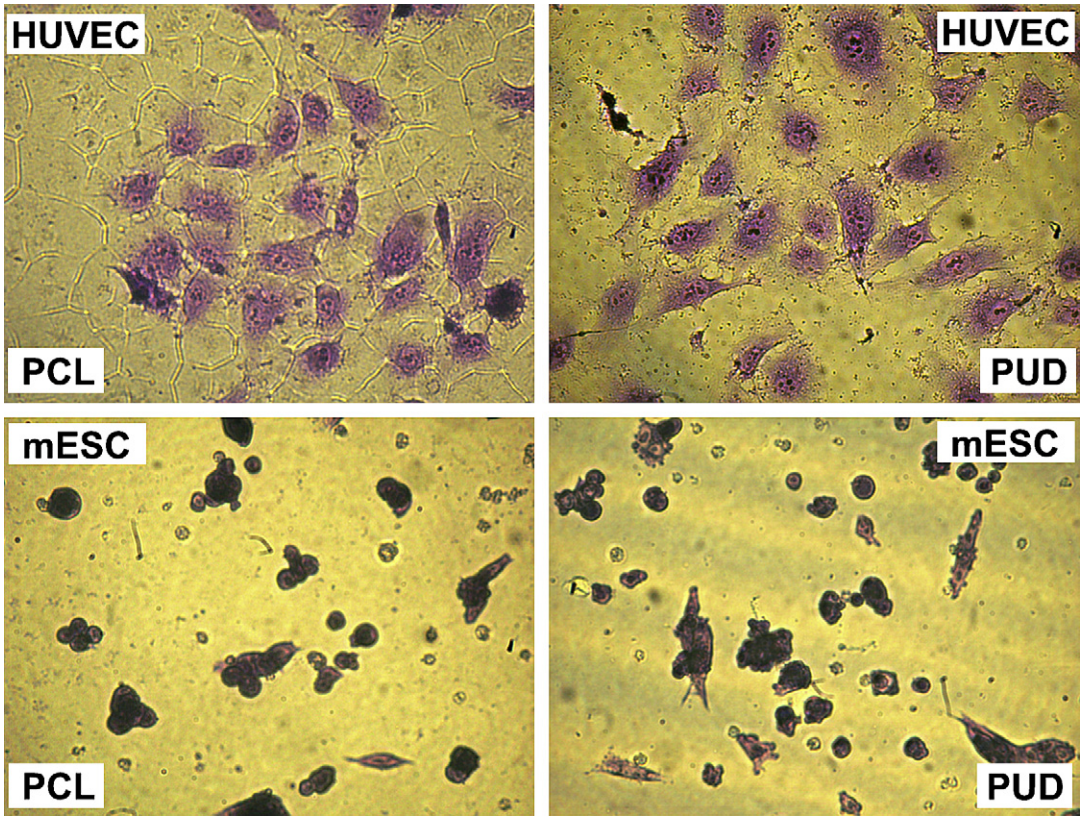


Fig. 7. Morphology of the cells adhered to the surface of the pure polycaprolactone (PCL) and poly(ester-urethane) (PEU) matrices.

mESCs. Both types of cells can effectively adhere to and spread on the surface of the poly(ester-urethane)s or pure PCL, suggesting their potential uses in biomedical applications.

Acknowledgments

This work was primarily supported by the Chemical, Bioengineering, Environmental, and Transport Systems Division of the National Science Foundation under award number CBET 0752150. J.U.O. acknowledges the research work of his former graduate students and postdocs.

References

[1] Dieterich D, Keberle W, Witt H. Angew Chem Int Ed 1970;9:40–50.
[2] Dieterich D. Prog Org Coat 1981;9:281–340.
[3] Wicks DA, Wicks ZW. Prog Org Coat 1999;36:148–72.
[4] US Patent 5,354,807; 1994.
[5] Subramani S, Choi SW, Lee JY, Kim JH. Polymer 2007;48:4691–703.
[6] Kim BS, Park SH, Kim BK. Colloid Polym Sci 2006;284:1067–72.
[7] Nanda AK, Wicks DA, Madbouly SA, Otaigbe JU. J Appl Polym Sci 2005;98:2514–20.
[8] Subramani S, Park YJ, Lee YS, Kim JH. Prog Org Coat 2003;48:71–9.
[9] Keyvani M. Adv Polym Technol 2003;22:218–24.
[10] Kim BK, Kim TK, Jeong HM. J Appl Polym Sci 1994;53:371–8.
[11] Wei X, Yu X. J Polym Sci Part B Polym Phys 1997;35:225–32.
[12] Visser SA, Cooper SL. Macromolecules 1991;24:2584–93.
[13] Kim BK, Lee JC. J Polym Sci Part A Polym Chem 1996;34:1095–104.
[14] Hourston DJ, Williams GD, Satguru R, padget JC, Pears D. J Appl Polym Sci 1999;74:556–66.
[15] Visar S, Cooper SL. Polymer 1992;33:3790–6.
[16] Huang SM, Chen TK. J Appl Polym Sci 2007;105:3794–801.
[17] Zhang S, Cheng L, Hu J. J Appl Polym Sci 2003;90:257–60.
[18] Tong HW, Wang M. J Nanosci Nanotechnol 2007;7:3834–40.
[19] Clapper JD, Guymon CA. Macromolecules 2007;40:7951–9.
[20] Gupta AP, Kumar V. Eur Polym J 2007;43:4053–74.
[21] Vasir JK, Labhasetwar V. Adv Drug Delivery Rev 2007;59:718–28.
[22] Zwingmann J, Mehlhorn AT, Sudkamp N, Stark B, Dauner M, Schmal H. Tissue Eng 2007;13:2335–43.
[23] Amsden B. Soft Matter 2007;3:1335–48.
[24] Takahara A, Hadano M, Yamaguchi T, Otsuka H, Kidoaki S, Matsuda T. Macromol Symp 2005;224:207–17.
[25] Barikani M, Ebrahimi MV, Mohaghegh SMS. J Appl Polym Sci 2007;104:3931–7.
[26] Ryynanen T, Nykanen A, Seppala JV. Polym Lett 2008;2:184–93.
[27] Kylma J, Seppala JV. Macromolecules 1997;30:2876–82.
[28] Lambda NMK, Woodhouse KA, Cooper SL. Polyurethanes in biomedical applications. CRC Press; 1998.
[29] Madbouly SA, Otaigbe JU, Nanda AK, Wicks DA. Macromolecules 2005;38:4014–23.
[30] Nanda AK, Wicks DA. Polymer 2006;47:1805–11.
[31] Bramfeldt H, Sarazin P, Vermette P. Polym Degrad Stab 2008;93:877–82.
[32] Yang BH, Cao DJ, Colman RW, Guo YL. J Cell Physiol 2004;200:360–9.
[33] Guo YL, Yang B. Stem Cells Dev 2006;15:655–64.
[34] Kloss J, Munaro M, De Souza GP, Gulmine JV, Wang SH, Zawadzki S, et al. J Polym Sci Part A Polym Chem 2002;40:4117–30.