Synthesis and Characterization of Radiopaque Poly(ether urethane) with Iodine-Containing Diol as Chain Extender

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ABSTRACT: Novel radiopaque iodinated poly(ether urethane) (IPEU) was prepared by using iodine-containing diol as chain extender in a normal two-step condensation polymerization process. This new iodine-containing diol was synthesized by iodination of terephthalic acid and then reaction with 3-aminopropanol. The chemical structure of the diol chain extender and IPEU was characterized, and the basic properties of IPEU were measured and compared with PEU. X-ray images showed that 15 wt % iodine-containing IPEUs were highly radiopaque, and radiopacity did not decrease after 6-week oxidative degradation treatment. Experimental results showed that IPEUs possessed good thermal stability, favorable mechanical properties, and noncytotoxicity. These results reveal that it is an effective route for the synthesis of biological polyurethane with radiopacity by using iodine-containing diol as chain extender. © 2011 Wiley Periodicals, Inc. J Polym Sci Part A: Polym Chem 49: 2191–2198, 2011

KEYWORDS: biomaterials; polycondensation; polyurethanes

INTRODUCTION Polyurethane (PU) is an important biomaterial used in implantable cardiovascular and orthopedic devices for the excellent mechanical properties including flexibility, strength, and wear resistance as well as favorable biocompatibility.[1–5] However, the radiolucent property of PU limits its further applications particularly in minimally invasive operation and the noninvasive evaluation of the implanted material or device. X-radiography is a simple, low cost technique, which is widely used in clinic operation. As a consequence, attempt to prepare the radiopaque PU is well desired.

Several approaches have been reported on the radiopaque PUs. One commonly used method is to blend some radiopaque additives such as barium sulfate, zirconium dioxide, or bismuth halides during the PU polymerization procedure.[6–8] Most of the commercial radiopaque PUs are prepared in such manner. However, these blends have some inherent disadvantages. For example, some additives would inevitably damage the mechanical properties of bulk PU, and some salt particles would be leached out of PU matrix and be absorbed by the body. A promising and feasible alternative is to incorporate heavy atoms such as iodine into PU through covalent bond. This method could offer PUs with radiopacity and maintain the excellent properties of PUs. However, it is not easy to incorporate iodine into PU in practical synthesis. Generally, PU is composed of hard segments of the reaction units of diisocyanates and linear difunctional chain extenders and soft segments of polydiols. As most of the iodination reaction is based on oxidation mechanism, incorporation of iodine in isocyanate-containing component and polydiol is not a feasible choice. Jayakrishnan and coworkers[9,10] once developed a coupling method to attach the tri- or penta-iodine-containing derivatives to PU based on the reaction of chloride with the active —NH— groups in PU backbone. Recently, this research group reported using a iodinated chain extender to synthesize radiopaque PU.[11] It is noteworthy that several patents have used bromine-containing diols as chain extenders to confer some degree of radiopacity on PU.[12,13] However, iodinated compound has more advantages than brominated one for X-ray imaging. First, iodine has greater mass attenuation coefficient than bromine, which makes iodine more effective in radiopacity. Second, the synthesis and the related toxicity of the iodinated aromatic molecules have been extensively investigated as modern X-ray contrast media and intermediates. Consequently, iodo-substituted polymer would presumably lessen the unknown risk for patient's health.

In this article, a new iodinated diol of *N*,*N*′-bis(3-hydroxypropxyl)-2,3,5,6-tetraiodoterephthalamide (HPTDP) was synthesized and used as chain extender to make PU radiopaque. Several tetraiodoterephthalic acid-based compounds have been investigated as X-ray contrast and these studies have

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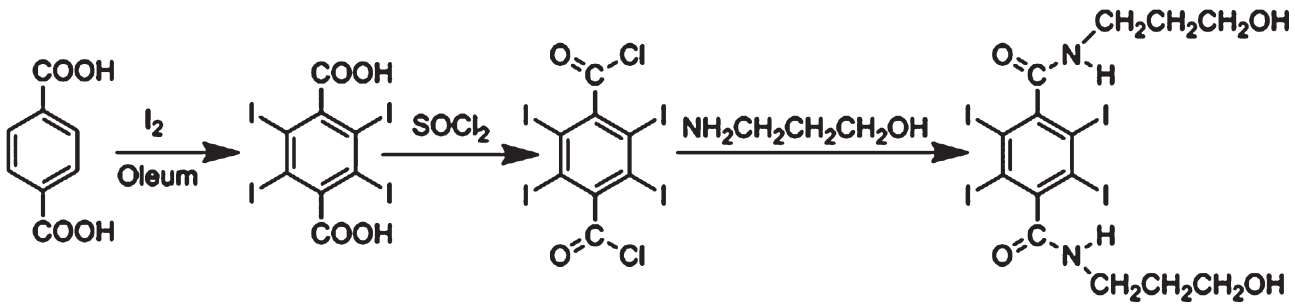


SCHEME 1 Synthesis of *N*,*N*′-bis(3-hydroxypropxyl)-2,3,5,6-tetraiodoterephthalamide.

demonstrated the medical safety of tetraiodoterephthalic acid-based compounds.[14,15] In this sense, using tetraiodoterephthalic acid-based diol as radiopaque medium in PU is a secure choice to patient's health. The whole synthesis procedure was characterized in detail, and the radiopacity of the iodine-containing PU were investigated briefly. Further, the biostability of the iodinated PU was briefly studied. Experimental results show that the iodinated PU is a promising material as X-ray opacifier with excellent mechanical properties and biostability.

EXPERIMENTAL

Materials

4,4′-Diphenylmethane diisocyanate (MDI; Sigma-Aldrich, St. Louis, MO) was purified by hot filtration; poly(tetramethylene glycol) (PTMG, M_n = 650, BASF China Co.) was dried for 24 h at 80°C under vacuum prior to use; tetrahydrofuran (THF), dimethylformamide (DMF), and dimethylacetamide (DMAC) (Tianjin Kermel Chemical Reagent Co.) were vacuum distilled and kept over 4 Å molecular sieves; 3-aminopropanol (Rizhao Lideshi Chemical Co.), terephthalic acid, iodine, sodium bisulfite, chloroform, triethylamine, thionyl chloride and other materials (Tianjin Kermel Chemical Reagent Co.) were used as received.

Preparation of *N*,*N*′-Bis(3-hydroxypropxyl)-2,3,5,6-tetraiodoterephthalamide

HPTDP was synthesized as follows (Scheme 1): 2,3,5,6-tetraiodobenzen-1,4-dioic acid was prepared from terephthalic acid by iodination, using 50% oleum as solvent, then acylated by thionyl chloride in the presence of DMF to obtain 2,3,5,6-tetraiodobenzene-1,4-dioyl dichloride,[16] which reacted with 3-aminopropanol using DMAC as solvent and triethylamine as acid binding agent to get the solid product HPTDP. ^{1}H nuclear magnetic resonance (NMR) (The spectrum was taken in DMSO-d_6, Fig. 1.): δ = 8.41 (NH), 4.42 (OH), 3.51 (CH_2O), 3.23 (CH_2N), 1.70 (CH_2). IR (thin film): 3420, 3290 cm^{-1} (NH, OH), 2925 cm^{-1} (CH_2), 1639 cm^{-1} (C=O), 1560 cm^{-1} (Ar), 1261 cm^{-1} (C—N), 1043 cm^{-1} (CH_2-OH).

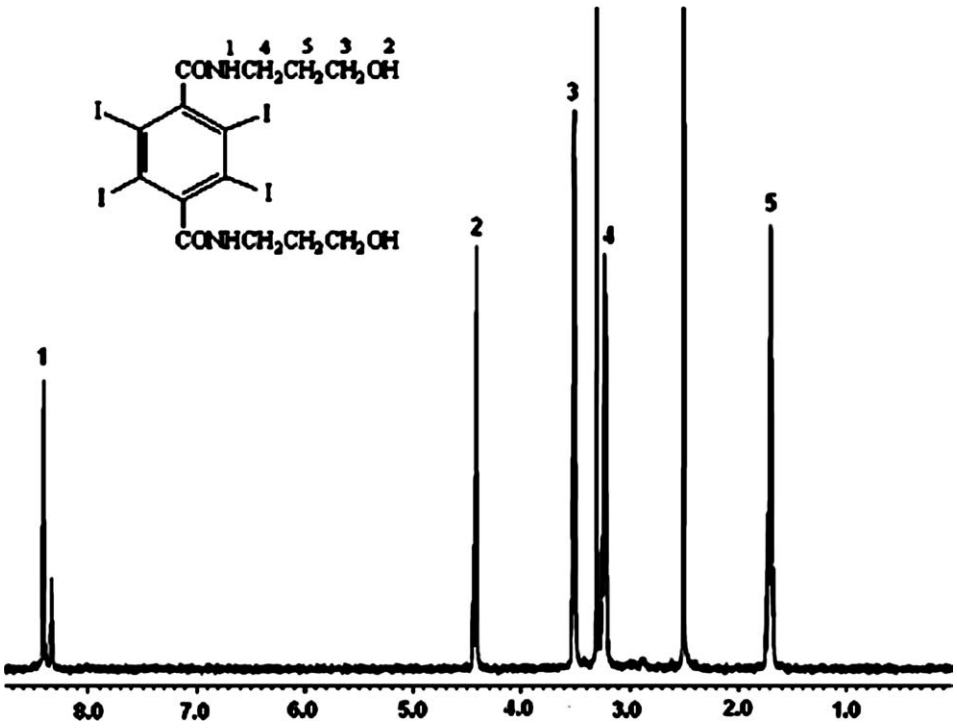
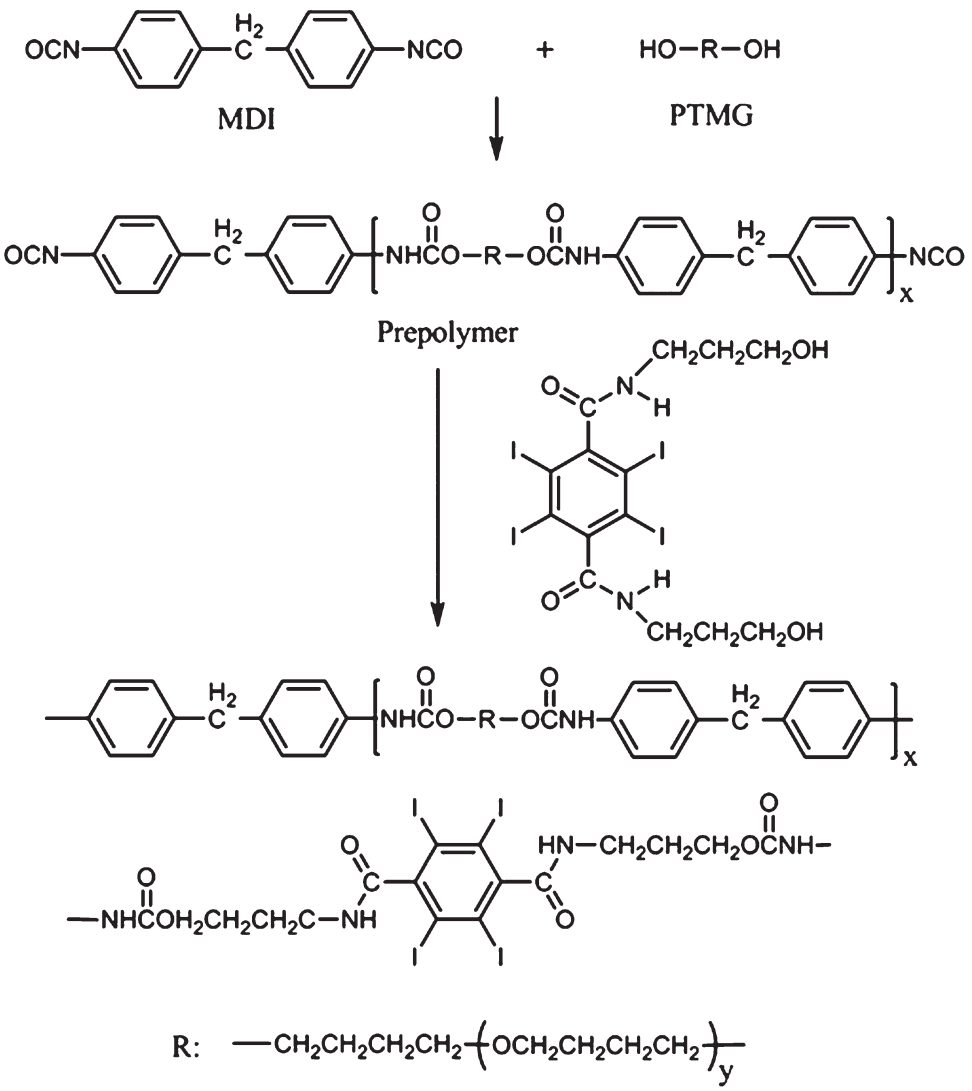


FIGURE 1 ^{1}H NMR spectrum of HPTDP.



SCHEME 2 Synthesis of iodine-containing poly(ether urethanes) (IPEUs).

Preparation of Iodine-Containing Poly(ether urethanes)

The product iodine-containing poly(ether urethane) (IPEUs) based on PTMG as soft segment and MDI/HPTDP as hard segment were synthesized using normal two-step process (Scheme 2). The MDI and PTMG were taken in a three-necked round-bottom flask. The reaction took place at 70–80 °C over 2.5 h in an inert atmosphere of nitrogen with a mechanical stirrer. Then HPTDP dissolved in anhydrous DMAC was added. The reaction mixture was stirred about 9–12 min at 90–100 °C. DMAC (15–20 mL) was added in batches during the process. The polymer was precipitated from methanol, washed with water. Then the viscous mixture was cast onto a Teflon plate and vacuum dried at 75 °C for 6–8 h and stored at room temperature in dark. IR (thin film, Fig. 2): 3277 cm^{-1} (NH), 2939cm^{-1} (CH_2), 1728 cm^{-1} (C=O), 1632 cm^{-1} (NH—C=O), 1099 cm^{-1} (C—O—C), 769 cm^{-1} (O=C—O).

In a similar manner, PEU was also prepared from the same reactants in the molar ratio of MDI/PTMG = 1/1, without chain extender for comparative studies.

Characterization

NMR spectra were measured on a JEOL JNM-ECA600 300 MHz instrument with tetramethylsilane as an internal standard at the ambient temperature. Fourier transform infrared spectra (FTIR) were traced with a Nicolet 560-IR spectrometer. The molecular weights and their distributions were determined by using a gel permeation chromatography (GPC) apparatus at room temperature with THF as eluent (1 mL/min). The instrument was equipped with a refractive index detector (Wyatt Optilab rEX) and fitted with a PLgel 5 μm mixed-D column. The column was calibrated with linear polystyrene standards. Overall surface morphology and energy dispersive spectrometer (EDS) analysis were characterized by emission scanning electron microscope (SEM). Samples of SEM were placed on brass disks and were sputter coated with a gold target under vacuum in an argon atmosphere. Coated specimens were examined on a JSM-6301F at an accelerating voltage of 5 kV. Differential scanning calorimetry (DSC) analyses were performed on a DSC-2910 (TA instruments, New Castle, DE) in nitrogen

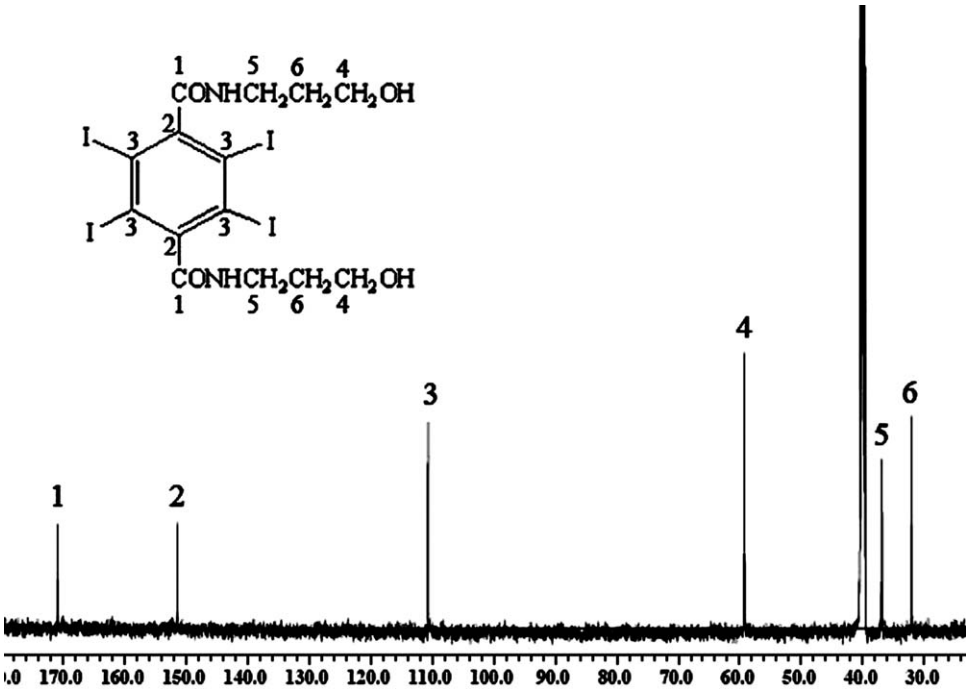


FIGURE 2 ^{13}C NMR spectrum of HPTDP.

atmosphere with a heating rate of 10 K/min. Thermogravimetric analyses (TGA) were performed on a Q5000 (TA Instruments) in nitrogen atmosphere with a heating rate of 10 K/min. Elemental analysis (EA) of HPTDP was performed by Service Institute of Chemistry, Chinese Academy of Sciences, Beijing, China.

Mechanical Properties

The mechanical properties of IPEUs were measured on a Universal Testing Machine (GT-TS-2000, Taiwan) according to GB528-76 with a speed of 50 mm/min at 25 °C to obtain the tensile strength and the breaking elongation. The samples were casted from THF solutions and shaped to dumbbell products. The thickness and width of the specimens were 3.0 and 3.2 mm, respectively. The length of the sample between the two pneumatic grips of Testing Machine was 12 mm. Five measurements were conducted for each sample, and the results were averaged to obtain a mean value.

In Vitro Degradation

The IPEUs were dissolved in THF and cast to a thickness of ~0.5 mm on Teflon substrates. Films were peeled from the substrates after being dried in a vacuum oven at 60 °C and were cut into pieces with a size ~1 × 5 cm^2. H_2O_2 (10%) and 0.05 M $CoCl_2$ were used as oxidants for our oxidative pretreatment. IPEU samples were immersed at 37 °C for 6 weeks. The solution was changed every 3 or 4 days. After the treatment, the specimens were removed, rinsed thoroughly in deionized water, and vacuum dried prior to examination. The transparency of the samples did not show apparent change visually, and the surface morphology was observed by SEM.

Cytotoxicity Studies

Cytotoxic evaluation of IPEU was carried out by the direct contact and test on extract assay with a monolayer of L929 mouse fiberblast cells as mentioned elsewhere. Cytotoxicity of IPEU was quantitatively assessed further by MTT (3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assay.[17]

Radiopaque Properties

X-radiographs were obtained using a standard clinical X-ray machine (General Electric, XR/A) equipped with 2.5 aluminum filtration set at 60 kV with 10 mA current for 0.2 s. The square IPEU samples with 2 mm thickness were cast from 30% THF solutions. PEU was used as control following the same method. The aluminum wedge with 2 mm thickness was kept as standard for visual comparison.

RESULTS AND DISCUSSION

Preparation of IPEUs

Terephthalic acid was iodinated according to the procedure reported elsewhere.[18] The method is based on electrophilic substitution of protons by iodide ions. In the typical experiment, when 4 g of terephthalic acid was reacted with 2.5 equiv. of iodine, the yield of the product was 14.5 g, which was the expected yield if tetra-iodination took place. NMR analysis confirmed that the reaction resulted in tetra-iodination of terephthalic acid. Further, the possible steric hindrance due to the presence of bulky iodine atoms in the ring might have limited the extent of iodination of the ring. EA of HPTDP showed about 65% of iodine content in the product, which corresponded to tetra-iodination. The melting point (obtained from DSC) of HPTDP was found to be 327 °C.

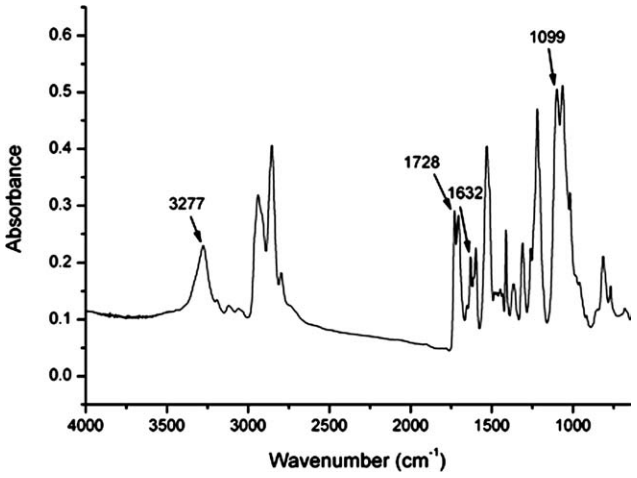


FIGURE 3 FTIR spectrum of IPEU-4.

^{1}H NMR spectrum of HPTDP is shown in Figure 1. The secondary amine group and hydroxyl group are indentified at $\delta = 8.41$ and 4.22 ppm, respectively. Three characteristic shifts for CH_2 protons appeared between $\delta = 1.70$ and 3.51 ppm. The singlet signal indicated the absence of protons on the benzene ring as a result of the successful substitution of the protons by iodine, which was also confirmed by ^{13}C NMR (Fig. 2). Thus, it can be safely stated that the reaction used here is leading to pure product isolation in excellent yield.

To achieve the goal of obtaining radiopaque PU with desirable properties for medical applications, the strategy adopted here was to incorporate the radiopacifying molecule as the chain extender in the PEU synthesis. We expected the resultant PEU to be sufficiently radiopaque with HPTDP as chain extender as it contained four iodine atoms per molecule.

IPEU was synthesized using MDI, PTMG and HPTDP as chain extender. The FTIR spectrum of IPEU is shown in Figure 3, which demonstrates the presence of the expected functional groups. The FTIR spectrum of IPEU shows —NH peak at 3277 cm^{-1}, C=O peak at 1728 cm^{-1}, C—O—C peak at 1099 cm^{-1}, respectively. The peak at 1632 cm^{-1} related to the NH—C=O stretching proves the successful incorporation of HPTDP to the PU backbone during copolymerization. IPEUs were obtained in 90% yield, typical for PU synthesis. HPTDP was incorporated into the prepolymer in the second stage of the two-step process. To study the influence of the addition of iodine-containing diol, four IPEUs were synthesized. The stoichiometry of the reactants used for reaction and the abbreviation of the resulting polymers were listed in Table 1. It could be observed that the molecular weight of IPEU slightly decreased with the addition of HPTDP, which is attributed to the rigidity of HPTDP in chemical structure.

Thermal Properties of IPEUs

Thermal characterization of PUs was studied by DSC and TGA. TGA curves of IPEUs showed two decomposition stages (Fig. 4). The first decomposition stage between 200 and 305 °C is a depolycondensation process that is associated with the urethane hard segment. The second decomposition stage between 305 and 450 °C is the decomposition of the soft segment by polyol depolycondensation (PTMG). Furthermore, segmented PU in the decomposition stage depends on the hard-segment content.[19] Figure 4 reveals that the TGA curves in the second decomposition stage shifted to higher weight remained region as hard-segment content was increased. PEU was stable up to 343°C and 50% weight loss occurred at 386 °C. Hence it was clear that the introduction of iodine-containing chain extender accelerated the advent of decomposition of IPEUs. However, IPEUs still possess good thermal properties as only 5% weight loss occurred at 300 °C, which is very meaningful for guiding the processing of the polymers.

The results of DSC studies are presented in Figure 5. PUs are known to exhibit two glass transitions in the hard and soft segment domains, respectively.[20] However, for all the samples, only one glass transition was detected. The results suggested that hard and soft segments in PEUs were well compatible in the amorphous phase. Compared with the glass transition temperature (T_g) of PEU, T_gs of IPEUs shifted to higher temperature region, as exhibited by DSC curves. MDI as hard segments usually formed densely packed regular structures close to a crystalline order.[21] Whereas, DSC curves did not display distinct cold crystallization and melting peaks, which should result from the disturbance of chain regularity of MDI molecules owing to the introduction of HPTDP as chain extender. This disturbance also suggests that IPEUs did not form microphase separation.

Mechanical Properties of IPEUs

Mechanical properties of polymer are also important with respect to practical applications. The tensile properties of the IPEU samples are summarized in Table 2. There were many factors which can affect the physical behaviors of the synthesized PEUs, such as molecular weight, chemical

TABLE 1 Composition and Molecular Weight of Resulting IPEUs

Sample	Molar Ratio of MDI/Chain Extender/PTMG	Hard Segment (wt %)	Feeded Chain Extender (wt %)	M_n ($\times 10^4$)	PDI
IPEU-1	1.1:0.1:1	35.24	7.81	4.61 ± 2.77	1.9 ± 0.2
IPEU-2	1.2:0.2:1	38.51	14.83	3.74 ± 2.25	2.0 ± 0.2
IPEU-3	1.3:0.3:1	46.30	19.43	3.19 ± 1.92	2.0 ± 0.2
IPEU-4	1.4:0.4:1	50.53	23.87	3.38 ± 2.03	2.1 ± 0.2

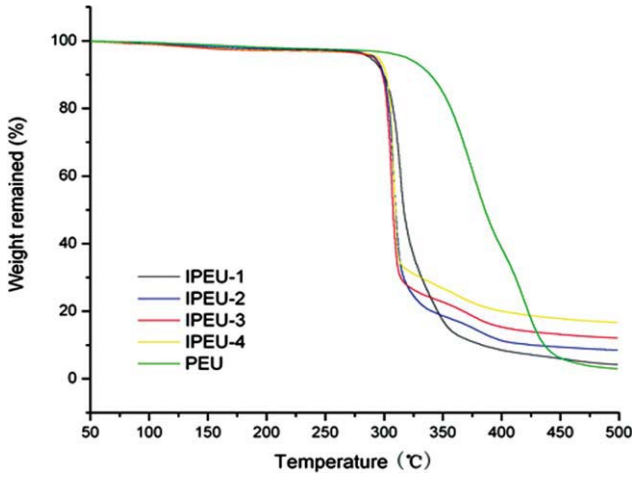


FIGURE 4 Thermogravimetric traces of IPEUs and PEU.

composition, and glass transition temperature. A trend of decreasing of breaking strength was observed with decrease of molecular weight, and the elongation at break exhibited reduction with the increase of HPTDP, which should result from the huge bulk of iodine-hindered molecular movement.

Cytotoxicity of IPEUs

To confirm the nontoxic nature of IPEU, a preliminary cytotoxicity evaluation using L929 mouse fibroblast cells was carried out. Neither IPEU nor its extract induced any morphological changes to the cells confirming its noncytotoxic response to fibroblast cells at an extract radio of 0.2 g/mL. The morphology of the cells growing on the surface (scored as zero) is depicted in Figure 6.

Radiopaque Properties of IPEUs

IPEUs and PEU were subjected to X-radiographic examination to compare their visibility in X-radiogram. Here, IPEUs and PEU were made into discs of 2 mm thickness, and the

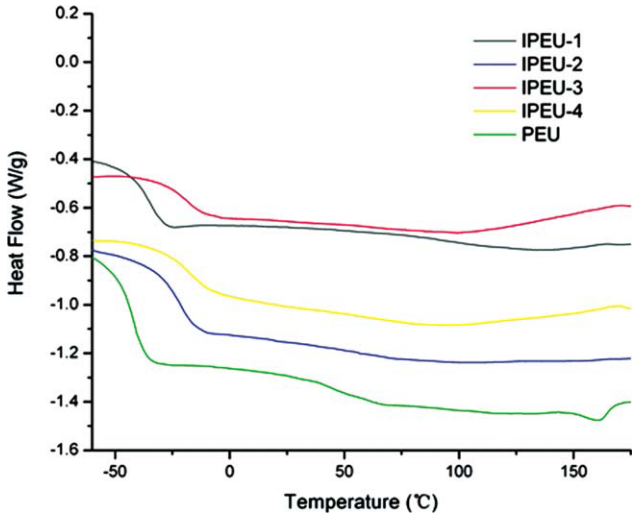


FIGURE 5 DSC traces of IPEUs and PEU.

TABLE 2 The Tensile Mechanical Properties of the Samples

Sample	Breaking Strength (MPa)	Breaking Elongation (%)
IPEU-1	28.8 ± 0.5	1670 ± 25
IPEU-2	26.6 ± 1.2	1334 ± 32
IPEU-3	24.0 ± 1.0	1450 ± 62
IPEU-4	25.1 ± 1.8	1150 ± 18

sharpness of the image was compared with aluminum wedge of 2 mm thickness (Fig. 7). It can be seen from the X-ray images that the images due to IPEUs were much sharper than the image of PEU. Increasing the iodine content from IPEU-1 to IPEU-4 clearly leads to improved contrast. Compared with aluminum wedge of same thickness, IPEU-4 showed image darker than that of aluminum wedge, which demonstrated good radiopaque property.

Biodegradation Research of IPEUs

As IPEUs obtain good radiopaque efficiency, desired thermal properties and mechanical properties, it is expected that the radiopacity acting under oxidative degradation treatment would stabilize. Also, this is the first time that radiopaque performance research of iodine-containing PU after biodegradation by this method is reported.

To study radiopacity change of IPEU after degradation, an *in vitro* oxidative treatment was involved. This degradation experiment used 10% H_2O_2 and 0.05 M $CoCl_2$ as oxidants, and the IPEU films were immersed at 37°C. After 6 weeks, the IPEU films were removed from the treatment solution and vacuum dried for 24 h prior to analysis. *In vivo*, the oxidative $H_2O_2/CoCl_2$ treatment accurately reproduced the 1-year effect within 24 days.[22] Other studies also have shown the use of the $H_2O_2/CoCl_2$ solution for simulating the

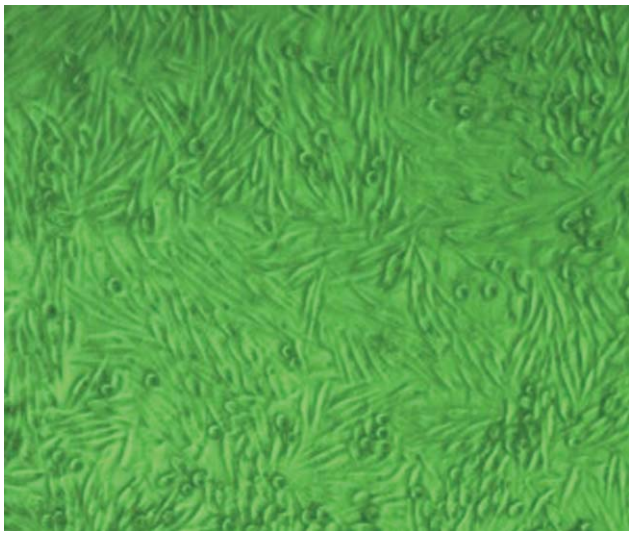


FIGURE 6 Fibroblast cells around IPEU-4. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

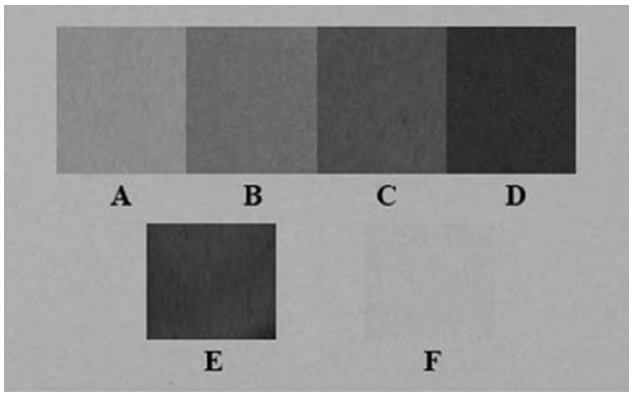


FIGURE 7 X-ray images of IPEU-1 (A), IPEU-2 (B), IPEU-3 (C), IPEU-4 (D), aluminum wedge (E), and PEU (F) discs.

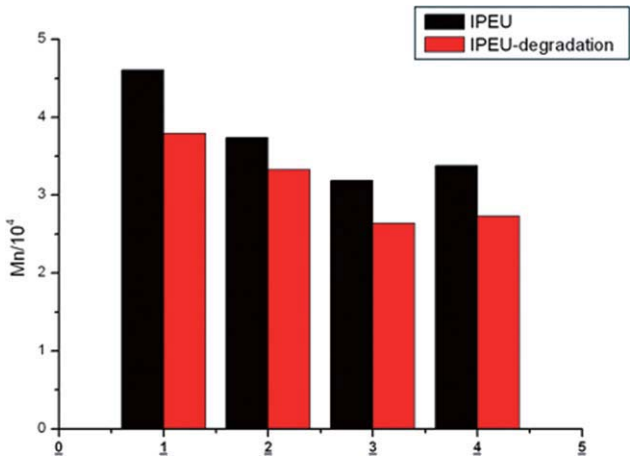


FIGURE 8 Histogram of molecular weight of IPEUs and IPEUs degradation. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

chemical and physical characteristics of *in vivo* degradation of PEU and for predicting long-term stability.[23–25] Moreover, *in vitro* studies provided the necessary data to elucidate the mechanism of soft segment oxidation of PEU.

The IPEU samples before and after oxidative treatment were measured by GPC chromatograms to detect the variety of the molecular weight and polydispersity. The visualized change of molecular weights of IPEUs was also shown in Figure 8. In contrast to corresponding IPEU, IPEU degradation showed significantly decreased molecular weight and increased polydispersity. Ebert et al.[26] also reported that PEU implanted in *vivo* for long periods have similar change of molecular weight and polydispersity. Compared to IPEU-1, both the number and weight average molar mass were less for IPEU-2, IPEU-3, and IPEU-4. This indicated that, the chain extending ability of HPTDP was slightly hampered, possibly due to the presence of bulky iodine atoms in HPTDP.

The SEM micrographs of the IPEU and IPEU degradation *in vitro* are shown in Figure 9. IPEU films displayed smooth

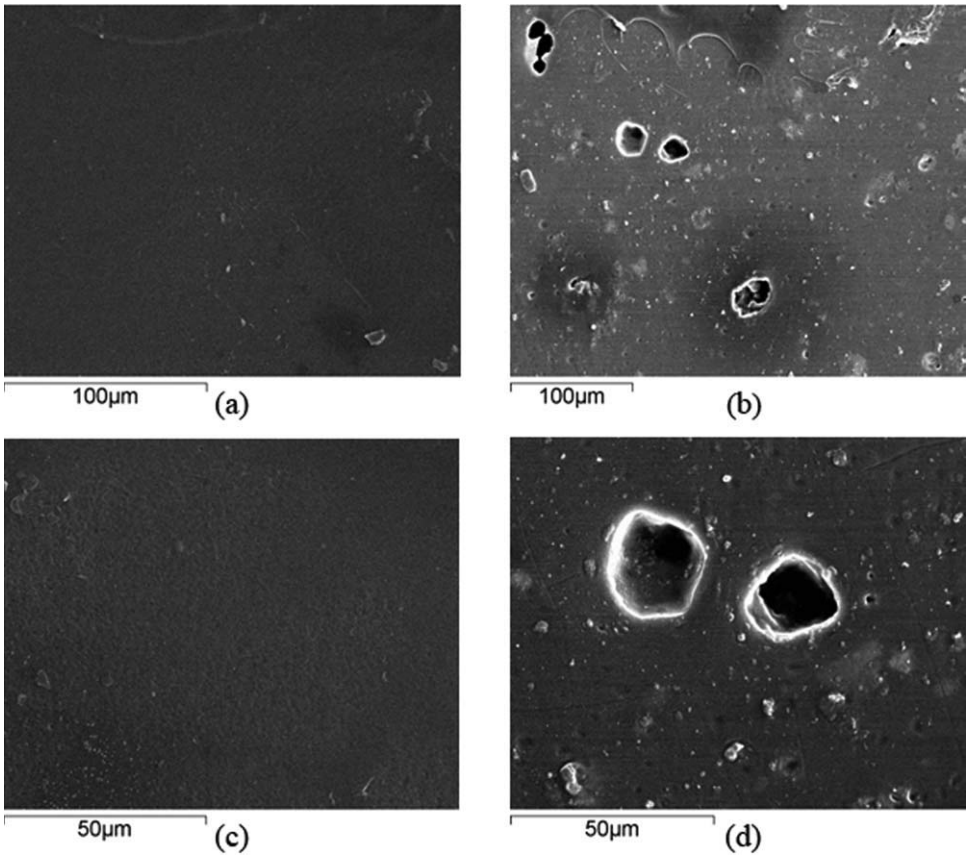


FIGURE 9 SEM micrographs of: (a) and (c) IPEUs and (b) and (d) IPEUs degradation.

and neat surface [Fig. 9(a)]. However, the overall surface of the IPEU degradation appears to be rougher than that of the IPEU substrate [Fig. 9(b)]. After 6 weeks, limited amount of large pits were observed on unstabilized IPEU degradation specimens. Previously, pitting of the surface was attributed to extraction of low-molecular weight degradation products that resulted from chain scission.[27]

The presence of iodine in the PEU could be elucidated by EDS. In the EDS spectrum, both IPEU and IPEU degradation showed peaks corresponding to carbon, oxygen, and iodine atoms. Thus the presence of iodine resulting from incorporation of HPTDP in the PEU and conservation of iodine after oxidative degradation treatment were confirmed. Comparing the X-ray absorption images of the IPEUs and IPEUs degradation it can be seen that IPEUs degradation do not show clearly visible change of sharpness, from which can be concluded that the radiopaque properties of IPEUs maintain good stability after oxidative degradation treatment *in vitro* for 6 weeks.

CONCLUSIONS

Novel PEU with radiopaque property was synthesized by a normal two-step process using MDI, PTMG, and chain extender HPTDP. FTIR spectra and GPC indicated that product IPEU was successfully synthesized. Moreover IPEU exhibited good radiopacity compared to the same thick aluminum wedge, and radiopacity did not decrease after oxidative degradation treatment. Also, it showed good thermal stability and mechanical properties. The cytotoxicity evaluation confirmed the nontoxicity of IPEU. The purpose of this work is to explore a new route for the synthesis of biological PU with radiopaque properties.

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REFERENCES AND NOTES

1 Hsu, S.; Tseng, H.; Lin, Y. Biomaterials 2010, 30, 6796–6808.

2 Belanger, M. C.; Marois, Y.; Roy, R.; Mehri, Y.; Wagner, E.; Zhang, Z.; King, M. W.; Yang, M.; Hahn, C.; Guidoin, R. Artif Organs 2000, 24, 879–888.

3 Del Rio, E.; Lligadas, G.; Ronda, J. C.; Galia, M.; Cadiz, V. J Polym Sci Part A: Polym Chem 2010, 48, 5009–5017.

4 Jovanovic, D.; Engels, G. E.; Plantinga, J. A.; Bruinsma, M.; van Oeveren, W.; Schouten, A. J.; van Luyn, M. J. A.; Harmsen, M. C. J Biomed Mater Res 2010, 95A, 198–208.

5 Pierce, B. F.; Brown, A. H.; Sheares, V. V. Macromolecules 2008, 41, 3866–3873.

6 Williams, D. F.; Roaf, R. Implants in Surgery; London: WB Saunders, 1993; pp 132–134.

7 Cabasso, I.; Smid, J.; Sahni, S. K. J Appl Polym Sci 1989, 38, 1653–1666.

8 Cabasso, I.; Smid, J.; Sahni, S. K. J Appl Polym Sci 1990, 41, 3025–3042.

9 James, N. R.; Philip, J.; Jayakrishnan, A. Biomaterials 2006, 27, 160–166.

10 James, N. R.; Jayakrishnan, A. Biomaterials 2007, 28, 3182–3187.

11 Kiran, S.; James, N. R.; Joseph, R.; Jayakrishnan, A. Biomaterials 2009, 30, 5552–5559.

12 Markusch, P. H.; Sarpeshkar, A. M. U.S. Patent 5177170, 1993.

13 Markusch, P. H.; Sarpeshkar, A. M. U.S. Patent 534698, 1994.

14 Suter, H.; Zutter, H.; Brunner, J. Helv Chim Acta 1971, 54, 2097–107.

15 Felder, E.; Pitre, D. U.S. Patent 4044048, 1977.

16 Petta, M.; Meyer, D.; Mayer, D. U.S. Patent 5693311, 1997.

17 Sylwester, G.; Katarzyna, G.; Ewa, Z.; Anna, C. J Biomed Mater Res A 2008, 85, 456–465.

18 Arotsky, J.; Butler, B.; Darby, A. C. J Chem Soc C: Org 1970, 10: 1480–1485.

19 Chuang, F. S. Polym Degrad Stabil 2007, 92, 1393–1407.

20 Nirmala, R. J.; Juby, P.; Jayakrishnan, A. Biomaterials 2006, 27, 160–166.

21 Bagdi, K.; Molnar, K.; Pukanszky, B. J Therm Anal Calorimetry 2009, 98, 825–832.

22 Elizabeth, M. C.; Sachin, P.; James, M. A.; Anne, H. Biomaterials 2006, 27, 3920–3926

23 Christenson, E. M.; Anderson, J. M.; Hiltner, A. J Biomed Mater Res 2004, 70A, 245–255.

24 Wiggins, M. J.; Anderson, J. M.; Hiltner, A. J Biomed Mater Res 2003, 65A, 524–535.

25 Wiggins, M. J.; MacEwan, M.; Anderson, J. M.; Hiltner, A. J Biomed Mater Res 2004, 68A, 668–683.

26 Ebert, M.; Ward, B.; Anderson, J.; McVenes, R.; Stokes, K. J Biomed Mater Res 2005, 75A, 175–84.

27 Renier, M.; Wu, Y.; Anderson, J.; Hiltner, A.; Lodoen, G.; Payet, C. J Biomed Mater Res 1994, 5, 511–529.