# Construction of Hemocompatible Polycarbonate Urethane with Sulfoammonium Zwitterionic Polyethylene Glycol

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**ABSTRACT:** The novel hydrophilic sulfoammonium zwitterionic polyethylene glycol (SAPEG) macromolecule was designed and synthesized using polyethylene glycol (PEG, $M_w = 1000$) as the starting agent. The sulfoammonium zwitterionic PEG was grafted onto polycarbonate urethane (PCU) via two ways: (1) direct grafting of SAPEG onto PCU using diisocyanate as a spacer; (2) grafting of PEG mono(*N,N*-dimethyl glycine)ester (APEG) onto the PCU with diisocyanate, and then reacting with 1,3-propanesulfone via ring-opening reaction to form sulfoammonium zwitterionic structure. The X-ray photoelectron spectroscopy (XPS) was used to analyze the elements of the grafted materials. The results showed that the sulfur contents on the modified PCU were 0.5 and 0.9% for both grafting methods, respectively, indicating sulfoammonium zwitterionic PEG has successfully been grafted onto PCU chains. The low-water contact angle showed that the modified PCUs were higher hydrophilic than unmodified PCU. The results of hemolysis test and cytotoxicity test indicated that blood compatibility of the modified PCU was better than that of the unmodified PCU. The modified PCUs are preferred candidates for blood-contacting implants or devices due to the hemocompatibility and nontoxicity *in vitro*. © 2011 Wiley Periodicals, Inc. J Appl Polym Sci 122: 1084–1091, 2011

**Key words:** polyethylene glycol; sulfoammonium zwitterion; polycarbonate urethane; graft; blood compatibility; biomaterials

## INTRODUCTION

Polycarbonate urethanes (PCU) with excellent mechanical properties and biocompatibility have been applied for a wide range of biomedical applications, such as fibers, coatings, heart valve, blood pumps, and vascular protheses.[1–3] Some modified PCUs with super biostable property have been reported for long-term clinical application.[4–12] However, PCUs are not completely thromboresistant, as platelet adhesion/activation can still occur when PCUs contact with blood over extended period of time.[13,14] It is still a significant challenge to improve the blood compatibility of PCUs.[15] Many approaches have been developed to modify PCU as follows: polyethylene glycol (PEG) modification,[16–18] surface modification by photopolymerization,[19,20] endothelial cell seeding or tissue engineering, release nitrogen monoxide (NO),[21–23] and covalently bonding special molecular structures.[24–29]

According to Lin's hypothesis, the materials with zwitterionic groups should have excellently anticoagulant activity due to their substantially maintaining normal conformation.[24,27] Zhang et al.[30] hydroxylated segmented poly(ether urethane) by potassium peroxosulfate, and then grafted *N,N'*-dimethyl-*N*-(*p*-vinylbenzyl)-*N*-(3-sulfopropyl) ammonium chains onto the surface using ceric ammonium nitrate as initiator. Yuan et al.[24] used ozonization method to modify polyurethane by introducing hydroperoxide group, and then *N,N*-dimethyl-*N*-methacryloxyethyl-*N*-(3-sulfopropyl) ammonium was polymerized onto the surface. Yuan et al.[26] described the other approach to modify the polyurethane film with zwitterionic sulfobetaine by following three steps: first, the film was treated with hexamethylene diisocyanate (HDI) in toluene at 50°C in the presence of dibutyl tin dilaurate (DBTL) as a catalyst. Then, the primary amine groups of *N,N*-diethylethylenediamine and *N,N*-dimethylethylenediamine reacted with isocyanate groups bound on the surface.

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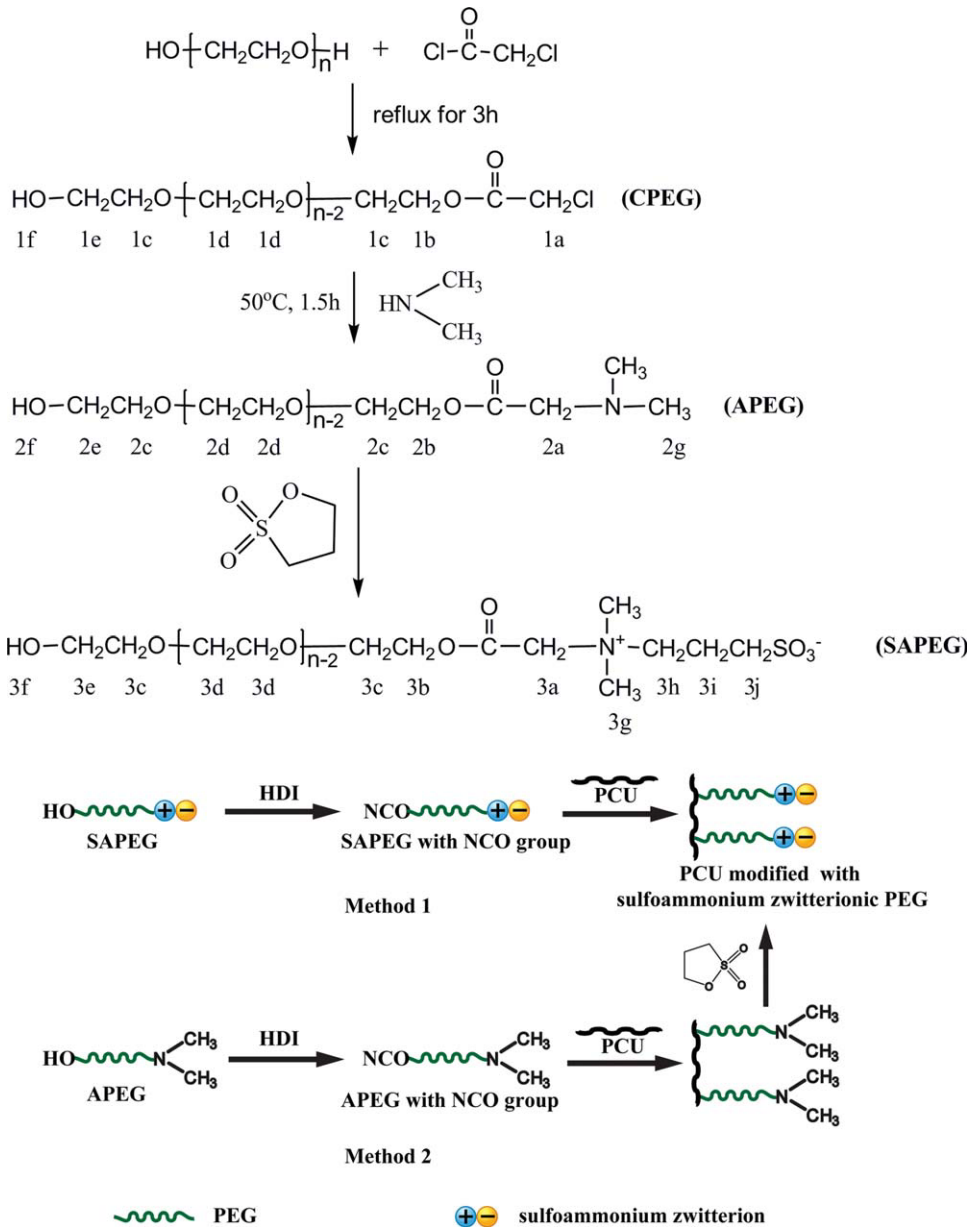


**Figure 1** Two synthesis routes of PCU-SAPEG. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Finally, the zwitterionic sulfobetaine groups were formed by the ring-opening reaction between tertiary amine and 1,3-propanesulfone (PS).[26]

Hydrophilic PEG is usually grafted onto biomaterial surfaces to provide a hemocompatible layer, which reduces the absorption of plasma albumen and red blood cells.[19,20,31,32] We aimed to improve the hemocompatibility of PCU with both PEG and sulfoammonium zwitterion. Herein, two novel methods were designed to graft sulfoammonium zwitterions onto PCU polymer chains using PEG as spacer (Fig. 1). For the first method, the ring-opening reaction of PEG mono(*N*,*N*-dimethyl glycine)ester (APEG) with PS was carried out and then grafted onto PCU chains. But, for the second method, APEG was first grafted onto PCU, then ring-opening reaction with PS. The modified PCUs were characterized by X-ray photoelectron spectroscopy (XPS). The results showed that both grafting methods have successfully introduced sulfoammonium zwitterionic PEG onto PCU chain to improve its hemocompatibility and hydrophilicity.

## EXPERIMENTAL

### Materials

4,4′-Methylene diphenyl diisocyanate (MDI, Mitsui Chemicals Corp.) was filtrated by G3 tundish after melting and then deposited in desiccators. Polycarbonate diol (PCN, $M_w$ = 1000, Beijing Santomer

Chemical Co.) was dried at 80°C for 24 h. 1,4-Butanediol (BD) was distilled at reduced pressure before use. PEG ($M_w = 1000$, Tianjin Damao Chemicals Co.) and chloroacetyl chloride (CAC, Shanghai Jinshan Tingxin Chemocals Co.) were used without further purification. Dimethylamine solution (33%) was provided by Shanghai Tianlian Fine Chemicals Company. PS was purchased from Suzhou Beike Fine Chemicals Company. HDI (Tianjin Petrochemical Corp.) was used as received. DBTL (Tianjin Ruijinte Chemicals Co.) was used as catalyst without further purification. All other chemicals were analytical grade and were commercially available.

### Synthesis of PCU

PCU was synthesized by melting polycondensation according to the procedures described in Ref. 33. Polycarbonate diol, MDI, and 1,4-butanediol with molar ratio of PCN : MDI : BD = 1 : 2 : 1 were heated to 120°C, poured the reaction mixture onto the polytetrafluoroethylene board, and then put into oven with the protection of nitrogen at 110°C for 8 h.

### Synthesis of PEG monochloroacetate (CPEG)

About 25.5 mL CAC was added into 40 g PEG and then stirred at 70°C for about 3 h. The melting mixture was dripped into anhydrous diethyl ether at room temperature. The mixture was transferred into separating funnel and the lower liquid was kept. The separation process was repeated three times, and then the lower liquid was dried under vacuum.

### Synthesis of PEG mono(*N,N*-dimethyl glycine)ester (APEG)

About 15 g CPEG and 5.6 mL 33% dimethylamine solution were reacted for about 1.5 h at 50°C. A certain amount of ethyl acetate was added to this reaction mixture, and the organic layer was separated. The organic solution was dried over anhydrous sodium sulfate for 24 h, and the solvent was evaporated to dryness to yield APEG.

### Synthesis of monohydroxyl PEG with sulfoammonium zwitterionic structure attached on other end (SAPEG)

About 16 mmol PS in THF solution (10%) was dripped into 10% APEG solution (8 mmol). The reaction was carried out at 50°C for 5 h. The reaction mixture was precipitated and washed with cooled THF and dried under vacuum at 50°C for 24 h.

### Grafting of Sapeg onto PCU (PCU-SAPEG, PCU1) (method 1)

A certain amount of sulfoammonium zwitterionic polyethylene glycol (SAPEG) was dissolved in *N,N*-dimethyl acetamide (DMAC) with excess amount of 10 mol % HDI and DBTL 0.1 wt %. The mixture was kept at 50°C for 5 h. In addition, 40 g 5% PCU in DMAC was added, and the reaction was continued for another 72 h. Methanol was added to the reaction mixture, and the precipitate PCU-SAPEG (PCU1) was collected by filtration. PCU-SAPEG was dried under vacuum at 50°C for 3 days.

### Grafting of APEG onto PCU and then ring-opening reaction with PS (method 2)

A 250-mL dry four-necked flask was equipped with stirrer, thermometer, and the nitrogen bubbler. APEG/DMAC solution (10%, w/v) with excess HDI and two droplets DBTL was added to the flask and then reacted at 50°C for 5 h. The 10% PCU/DMAC solution was added to the flask and kept at 50°C for another 48 h. The product was treated by similar means as PCU1.

The above product was added to another 250-mL dry four-necked flask with stirrer, thermometer, and reflux condenser. THF was added to the flask to prepare 10% solution. Ten percent PS solution in THF was added and then reacted at 50°C for 24 h. The same treatment as PCU1 was applied. The modified PCU was named as PCU2 by this method.

### Preparation of PCU, PCU1, and PCU2 films

A suitable amount of PCU, PCU1, and PCU2 was dissolved in THF to prepare 8 wt % solutions. The solutions were evenly spread on glass petri dishes, which were aligned perfectly horizontal to ensure the uniform thickness of films. The dishes were kept in a chemical hood for 48 h to allow THF to evaporate. The films were removed from the petri dishes and cleaned in ethanol by ultrasonic cleaner for 10 min; finally, the films were completely dried at 60°C for 6 h under vacuum.

### Measurements

The surface chemistry of compounds and polymer films was characterized with a Bio-Rad FTS-3000 transmission Fourier transform infrared spectrometer (Hercules, CA) over the range of 400–4000 $cm^{-1}$ with a 2 $cm^{-1}$ resolution and 50 scans. The chemical elements were analyzed with a PHI-1600 XPS (PerkinElmer, MA). $^1$H-NMR was done using $CDCl_3$ as solvent with a BRUKER AV400 apparatus (Bruker, Switzerland). Water contact angle of films was measured at 25°C by the sessile-drop method using a

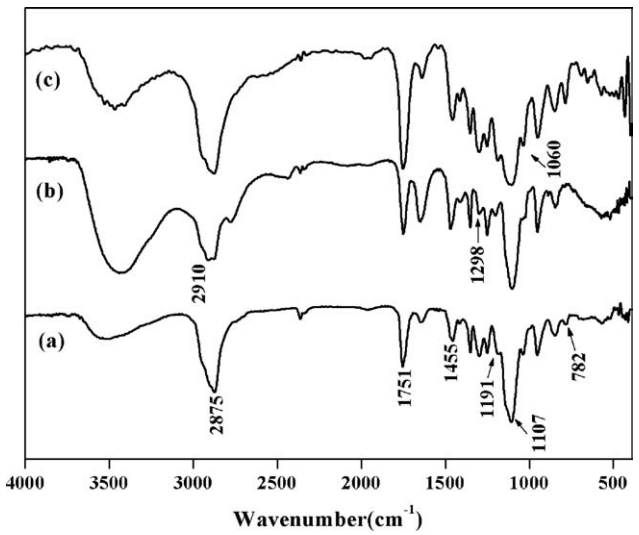


**Figure 2** Fourier transform infrared spectra of CPEG (a), APEG (b), and SAPEG (c).

contact angle goniometer (JC2000C1, Shanghai Zhongchen Digital Technical Equipment, China), and the reported results were the mean values of five measurements. The blood compatibility and biocompatibility of the materials were evaluated by hemolytic test and cytotoxicity test according to procedures described in Ref. 33.

The hemolytic rate was calculated according to the following formula:

$$\text{Hemolytic rate } (\%) = \frac{A - B}{C - B} \times 100\%$$

where A is the optical density (OD) at 545 nm of the solution with test materials, B the OD of negative control, and C the OD of positive control.

Platelet adhesion was carried out to evaluate the hemocompatibility by platelet-rich plasma (PRP) adhesion experiment.[34,35] The PRP was prepared by centrifugation from citrated whole rabbit blood. The PRP was in contact with the each of three films of PCU, PCU1, and PCU2 for 180 min at 37°C. Platelet adhesion *in vitro* was evaluated by Philip XL30 scanning electron microscopy (SEM; Eindhoven, Holland).

## RESULTS AND DISCUSSION

### Characterization of synthesized CPEG, APEG, and SAPEG

To graft sulfoammonium zwitterions onto PCU polymer chains, two novel methods were designed using PEG as spacer (Fig. 1). In the Method 1, CPEG, APEG, and SAPEG were synthesized according to routes shown in Figure 1. CPEG is a white or slight yellow solid when the synthesis was carried out under $N_2$ protection; otherwise, the product color was dark. As can be seen from FTIR spectrum of CPEG in Figure 2 (Curve a), a strong absorption was observed at 1751 $cm^{-1}$, corresponding to the stretching vibration of C=O, which indicated the existence of carbonyl group. Compared to carbonyl group of aliphatic ester at 1710–1740 $cm^{-1}$, the movement to the high frequency area may be due to the influence of the chloride on the α-C in CPEG. The peaks at 1107 and 1191 $cm^{-1}$ corresponded to the split of the stretching vibration of C—O.

The FTIR spectrum of APEG (Fig. 2, Curve b) showed that those characteristic peaks were close to those of CPEG. Moreover, the characteristic absorption peak of C—N at 1298 $cm^{-1}$ was overlapped with other peaks and could not be observed clearly. The bending vibration characteristic peak of C—Cl at 782 $cm^{-1}$ disappeared.

The FTIR of SAPEG (Fig. 2, Curve c) is similar to that of APEG, except for the new characteristic stretching vibration at 1060 $cm^{-1}$ for S=O in sulfonate. This indicated that the sulfoammonium zwitterionic structure was covalently conjugated to the end of PEG.

The $^1$H-NMR spectra of synthesized products were shown in Figure 3. In the $^1$H-NMR spectrum of CPEG, the corresponding resonance signals of the protons were as follows: splitting of the 1a peak, $\delta H_{1a} = 4.0–4.2$ ppm; splitting of 1b, 1c, and 1d peaks to triplets, $\delta H_{1b} = 4.3–4.4$ ppm, $\delta H_{1c} = 3.7–3.8$ ppm, $\delta H_{1d} = 3.7$ ppm, and $\delta H_{1f} = 6.2$ ppm. To further proof the chemical shift of $H_{1e}$, the raw material, PEG, was analyzed using $^1$H-NMR at the same conditions. The result showed that the chemical shift of $H_{1e}$ was similar to that of the $H_{1d}$, and some of those

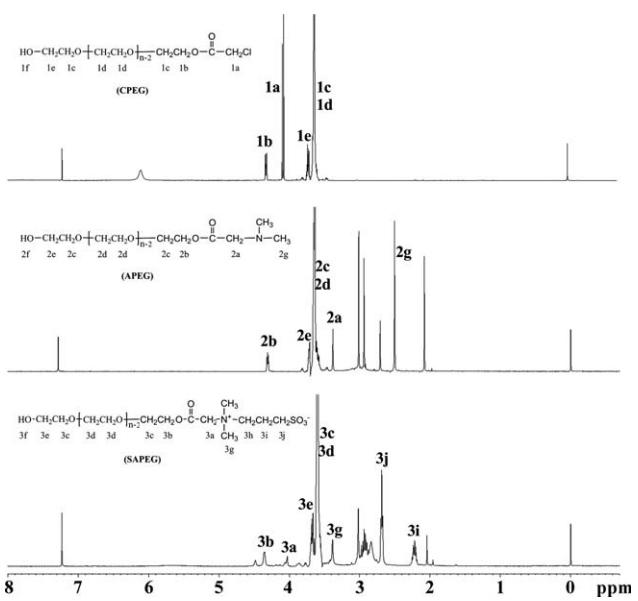


**Figure 3** $^1$H-NMR spectra of CPEG, APEG, and SAPEG using $CDCl_3$ as solvent.

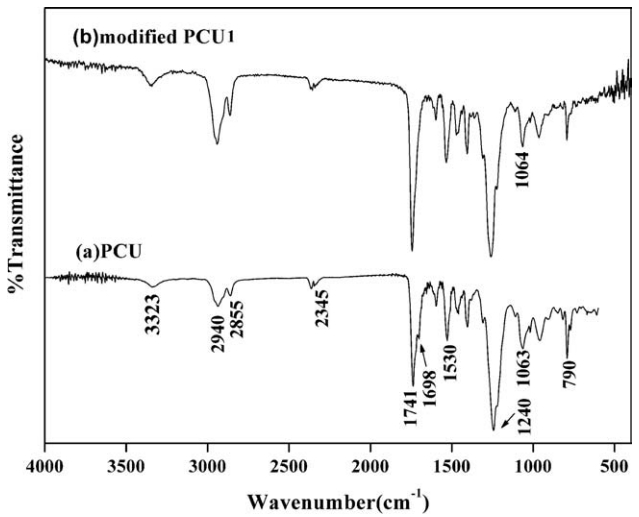


**Figure 4** FTIR spectra of PCU (a) and modified PCU1 (b).

peaks were overlapped, $\delta H_{1e} = 3.7$ ppm. If the compound was monoester, the ratio of the differentiated curve peaks of $H_{1a}$ and $H_{1f}$ should be 2 : 1, while the ratio was found to be about 1.2. The PEG esterification ratio was calculated as 60% from $^1$H-NMR spectrum. Liao[36] also reported that CPEG with monoester structure was the primary product when PEG ($M_n > 400$) reacted with CAC.

In the $^1$H-NMR spectrum of APEG, only single peak was observed for 2a and 2g without coupling effect. After the amination reaction, no proton peak at chemical shifting position of 4.1 ppm was observed, indicating the reaction was successful.

The characteristic resonance signals of 3i and 3j protons in SAPEG were found at $\delta H_{3i} = 2.2$–$2.3$ (quintet) and 2.6–2.7 ppm (multipeak), respectively. Combined with the above FTIR spectra, the ring-opening reaction was successful.

## Grafting of SAPEG onto PCU

Two methods were used to graft sulfoammonium zwitterionic structures on PCU to improve the hydrophilicity. The first one realized by grafting the SAPEG directly onto PCU polymer chains using an aliphatic diisocyanate as a spacer. In the second approach, APEG was first grafted onto PCU polymer chains using an aliphatic diisocyanate and then reacted with SP to form sulfoammonium zwitterion modified PCU. The advantage of the first method is that it can avoid the side reaction during the ring-opening reaction of SP with the tertiary amine groups of APEG.

Because the molecular weight of the PCU was higher than that of PEG, the grafting reaction as the first step in the second method resulted in the ring-opening reaction more difficult. Furthermore, NH groups in the carbamate of PCU chains might have the ring-opening ability to lead to side reactions. The SAPEG was grafted onto PCU by both methods and named as PCU1 and PCU2, respectively.

**TABLE I**
**ESCA Elemental Composition (%) of PCU, PCU1, and PCU2**

| Sample ID | C1s | O1s | N1s | S2p |
|---|---|---|---|---|
| PCU | 74.1 | 24.9 | 1.0 | 0 |
| PCU1 | 74.4 | 23.4 | 2.4 | 0.5 |
| PCU2 | 77.9 | 19.5 | 1.7 | 0.9 |

FTIR spectra of PCU and modified PCU1 by the first method were shown in Figure 4. The characteristic peaks of FTIR spectrum of PCU in Figure 4(a) were identified as follows: C—O—C, O—C=O, N—H, C=O, and NH at 1063, 1240, 1530, 1741, and 3323 $cm^{-1}$, respectively. The FTIR spectrum of the modified PCU1 as shown in Figure 4(b) was basically similar to that of the unmodified one. Because of the overlap of strength vibration peaks of C—O—C and S=O around 1060 $cm^{-1}$, the existence of sulfoammonium zwitterion can hardly be identified. Hence, XPS method was used to confirm the grafting reaction of SAPEG onto PCU.

The element contents of unmodified PCU and modified PCU1 and PCU2 films were listed in Table I. After grafting, the sulfur contents were 0.5% and 0.9% for PCU1 and PCU2, respectively. It indicated that the SAPEG chains were successfully grafted onto PCU chains. The higher sulfur content of PCU2 might attribute to the ring-opening reaction both by APEG and also by the secondary amine of PCU.

The XPS curves of the modified PCU were shown in Figure 5. The Gaussian function was used to simulate the C1s, N1s, O1s, and S2p spectra in PCU,

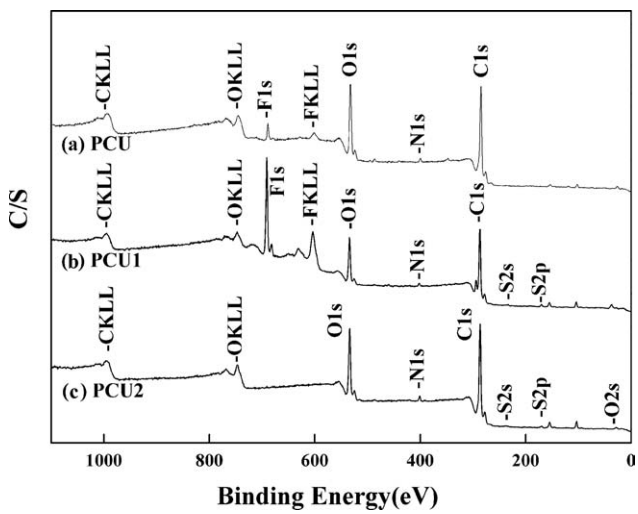


**Figure 5** XPS spectra of PCU (a), PCU1 (b), and PCU2 (c).

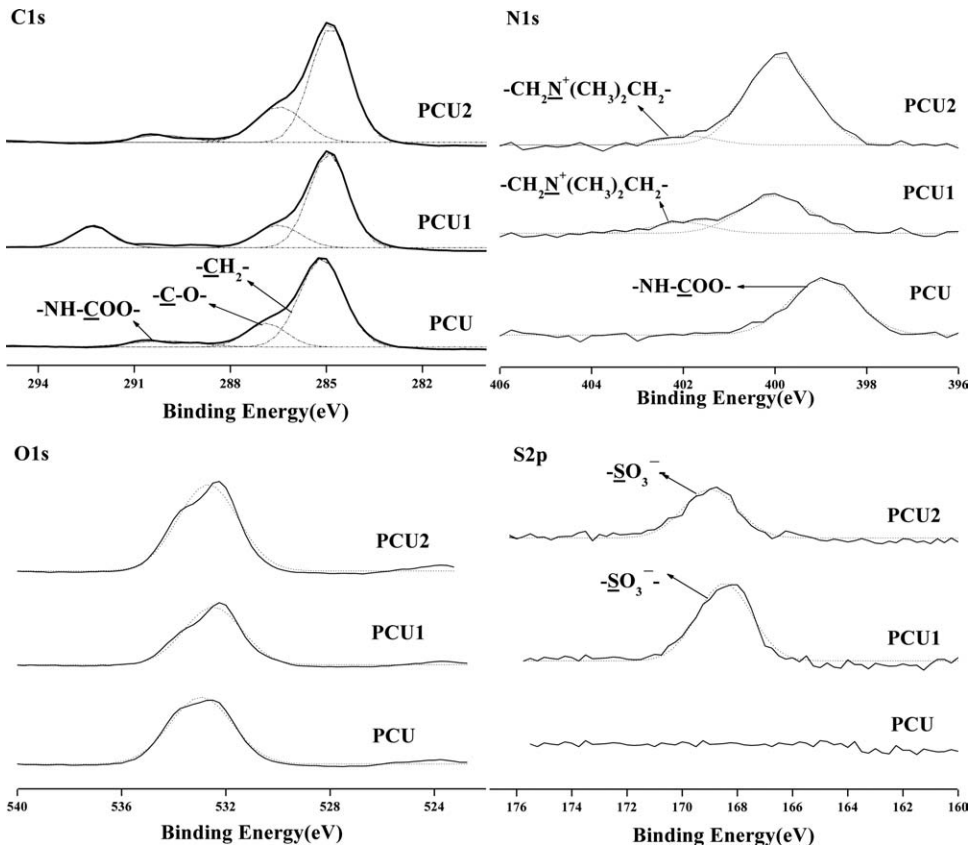


**Figure 6** XPS C1s, O1s, N1s, and S2p core-level spectra of PCU surface. Top: PCU2; middle: PCU1; bottom: PCU.

PCU1, and PCU2. The spectrum was calibrated by nuclear using the external standard method. The pollutant, saturate hydrocarbon, was used as the external standard material, and its binding energy of 285.00 eV of C1s was used as the standard. The binding energy of C1s in the PCU1 spectrum was 287.25 eV. Hence, all the binding energy positions were shifted to the left by 2.25 eV in the calibration. The binding energy for C1s in the PCU2 was 286.75 eV, and all the positions were shifted to the left by 1.75 eV to obtain the calibrated spectrum. The simulated curves were shown in Figure 6.

Three peaks existed in the C1s spectrum of PCU: the peaks at 285.14, 286.88, and 290.08 eV corresponded to the carbon of —$CH_2$—, —C—O—, and —COO—, respectively. There was only one peak for N1s at 398.95 eV, belonging to the nitrogen of —NH—COO—.

There were also three peaks for PCU1 in the C1s spectrum at 284.63 eV (—$CH_2$—), 285.63 eV (—C—O—), and 292.30 eV (—NH—COO—). Although two peaks for N1s were found at 400.00 eV for nitrogen of —NH—COO— and 402.02 eV for nitrogen of —$CH_2N^+(CH_3)_2CH_2$—, respectively. The peak at 168.45 eV in the S2p spectrum corresponded to the sulfur of $SO_3^-$, indicating SAPEG was successfully grafted onto PCU by first method.

Three peaks were also observed in the C1s spectrum of PCU2: 284.86 eV (—$CH_2$—), 286.47 eV (—C—O—), and 290.15 eV (—NH—COO—). Two peaks were observed in N1s: 399.90 eV for —NH—COO— and 401.87 eV for —$CH_2N^+(CH_3)_2$-$CH_2$—. The peak at 168.99 eV corresponded to the sulfur of $SO_3^-$. Except that peak position was slightly different from that of PCU1, the XPS curve was similar to that of PCU1, indicating that the second method could also graft SAPEG onto PCU chains.

When the first method was used to graft sulfoammonium zwitterion SAPEG onto PCU, the aliphatic diisocyanate HDI was used as spacer for introducing SAPEG. Considering lower reaction activity of HDI than MDI, the grafting reaction was easy to be controlled. The flexible property of PEG provided high chain mobility in solution and high hydrophilicity. In the grafting process, the first step was to react HDI with SAPEG to prepare the SAPEG with isocyanate functional group. However, the reaction product did not need to be separated and used for next step, because in the process of separation or storage, the side reactions of isocyanate groups might occur.

**TABLE II**
**Water Contact Angle of PCU, PCU1, and PCU2**

| Sample ID | PCU | PCU1 | PCU2 |
|---|---|---|---|
| Contact angle (°) | 82.1 ± 3.5 | 66.3 ± 1.7 | 62.9 ± 1.5 |

However, there was also a disadvantage for the unseparated product, that is, the excess isocyanate groups caused side reactions during the next reaction. Hence, in the experiment process in this work, only trace amount of the isocyanate was excess. Furthermore, SAPEG was added by drops to form the partially concentrated environment for promoting the complete reaction of SAPEG. Comparing to the reaction between small molecules, the reaction between polymers was more difficult due to the slow movement of macromolecules. Therefore, the longer time was desired for this reaction.

For the second method, APEG was first grafted onto PCU polymer chains and then introducing sulfoammonium zwitterion to PEG end by ring-opening reaction with PS. The influence factors for the first step were the same as in the preparation of PCU1. Some issues must be paid attention during the ring-opening reaction, for example, the carbamate groups of the PCU might open PS to form sulfoammonium zwitterion. This effect resulted in high-S content.

### Hydrophilicity of modified PCU

The SAPEG hydrophilic chains were grafted onto PCU chains to obtain high hydrophilic polymers due to the high extent of ionization. Water contact angle of the modified PCU was significantly lower than that of unmodified PCU. The results were listed in Table II. The modified PCU by the first method (PCU1) showed slightly higher water contact angle than PCU2 by the second method.

### Hemocompatibility and cytotoxicity of modified PCU

The results of hemolytic test and cytotoxicity test were listed in Table III and shown in Figure 7, respectively. Hemolytic test was a way to measure the degree of red cell dissolution and hemoglobin dissociation when blood contacted with materials. The hemolytic rates of all synthesized materials were less than 5%, which is the requirement of blood-contacting materials for medical applications

**TABLE III**
**Results of Hemolytic Test of PCU, PCU1, and PCU2**

| Sample ID | PCU | PCU1 | PCU2 |
|---|---|---|---|
| Hemolytic rate (%) | 1.4 ± 0.2 | 0.3 ± 0.1 | 0.2 ± 0.05 |

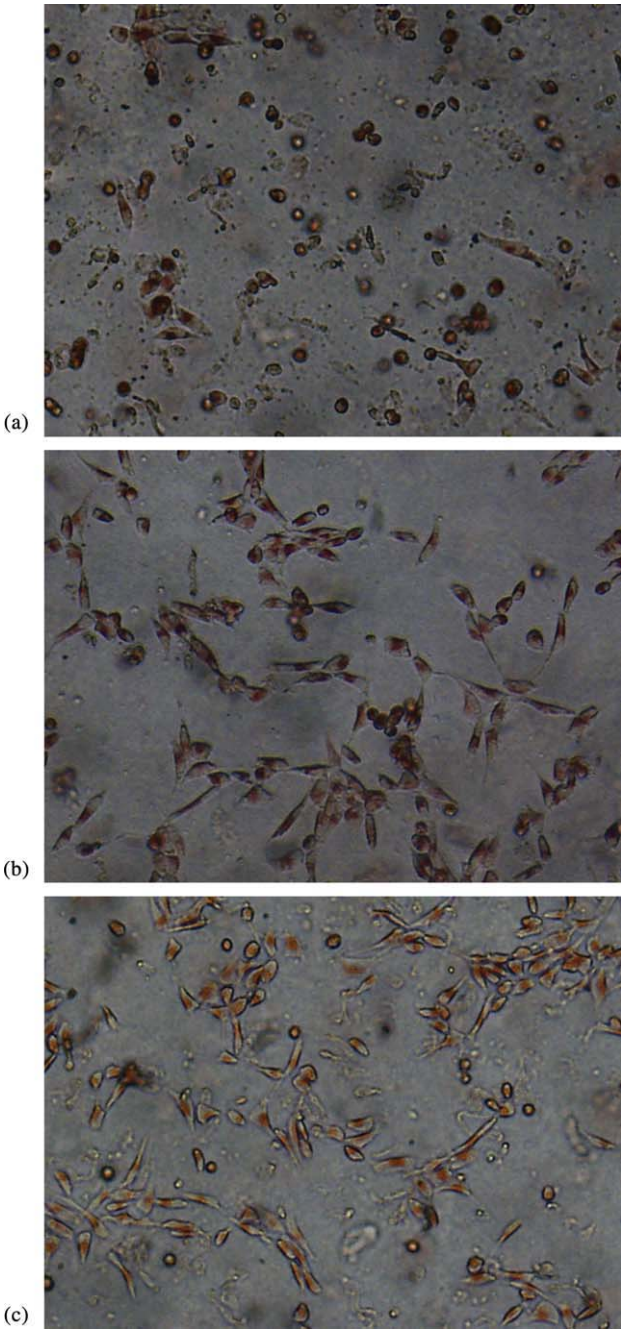


**Figure 7** Results of cytotoxicity test of PCU (a), PCU1 (b), and PCU2 (c). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

(Table III). Meanwhile, the hemolytic rate of the modified PCU was less than that of PCU, which indicated that the sulfoammonium zwitterionic structure and PEG spacer used in the modification improved the blood compatibility of PCU. Most of the adhered platelets on PCU were spread and deformed, which indicated that they might have been activated. However, platelets were rarely observed on PCU1 and PCU2 materials by SEM. The platelet adhesion results also demonstrated that

PCU grafted with zwitterions and PEG chains showed good blood compatibility.

To further prove the biocompatibility of the modified PCU and to compare with that of PCU, cytotoxicity test was carried out on the materials. Figure 7 showed that cell viability on the modified materials PCU1 and PCU2 was higher than that of PCU, which also proved that the modified PCU had better blood compatibility and biocompatibility than PCU.

## CONCLUSIONS

The hydrophilic SAPEG macromolecule was designed and synthesized to modify PCU. The sulfoammonium zwitterionic structure was grafted onto the PCU via two methods, that is, through direct grafting of SAPEG, and grafting of APEG followed by the ring-opening reaction. The sulfur contents of the modified PCU were found 0.5% and 0.9% for both grafting methods, respectively, indicating that SAPEG has been successfully grafted onto PCU. The modified PCU with PEG and sulfoammonium zwitterions had high hydrophilicity, blood compatibility than the unmodified PCU. The modified PCUs are preferred candidates as blood-contacting materials due to their *in vitro* high biocompatibility and nontoxicity.

The new compound SAPEG having isocyanate functional group will provide a way for material modification. Using SAPEG having isocyanate functional group can modify not only PCU materials, but also the other biomaterials with active hydrogen, such as chitosan, silk protein, and fibers. It can be used to synthesize functional copolymers constructed on some inorganic materials or directly coated on the material surfaces.

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