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Zwitterionic monomer graft copolymerization onto polyurethane surface through a PEG spacer

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ABSTRACT

A new zwitterionic surface was obtained by a novel three-step grafting procedure. The zwitterionic monomer was introduced by cerium-induced graft copolymerization in the presence of N,N′-methylene bisacrylamide (MBAA) as cross-linking agent. Attenuated total reflection Fourier transform infrared spectroscopy (ATR-FTIR) and X-ray photoelectron spectroscopy (XPS) analysis confirmed the MBAA could stimulate zwitterionic monomer grafting onto the membrane surface. Surface properties were also determined by atomic force microscope (AFM) and water contact angle. The hemocompatibility of the modified PU membranes was evaluated by the activated partial thromboplastin time (APTT), thrombin time (TT) and prothrombin time (PT). The TT and APTT of PU were significantly prolonged by the zwitterion of sulfobetaine monomer grafting copolymerization. The new polyurethane membrane could have a great potential in biomedical applications.

1. Introduction

Polyurethane (PU) is popularly investigated in biomedical applications, such as artificial hearts, vascular grafts and pacemaker leads, because of its long-term bio-stability, excellent mechanical properties, and moderately good biocompatibility [1–5]. However, the hemocompatibility of PU is inadequate and needs to be improved.

Surface modification has been considered a useful method to tailor the surface characteristics of a material without detrimentally affecting the bulk properties. Over the past years, many attentions have been focused on the surface modification of PU [6–8]. A variety of surface modification methods such as plasma treatment, wet chemical treatment and photo-oxidization method have been used [9–11]. Among various methods, graft copolymerization is most attractive because it is a useful method for modifying the chemical and physical properties of the synthetic and natural polymers. A number of materials have been grafted onto the surface of PU to improve its hemocompatibility, such as poly(ethylene glycol) (PEG) [12,13], heparin [14,15], phospholipid polymer [16–18], and so on.

The zwitterion of sulfobetaine has received more and more attention because of the similar biocompatibility and interesting solution property as phosphobetaine and carboxybetaine. In the past years, Lin's group has successfully suggested that surface-modified polymer membranes tailoring of zwitterion of sulfobetaine show excellent blood compatibility because they can maintain normal conformation of biomacromolecules [19–26]. Over the last few years, PEG has been widely used in biomedical applications and has displayed superior biocompatibility due to its good biocompatible property, solubility, thermal and mechanical stability [27–29]. However, the problem of hemocompatibility has not been solved ultimately, the synthesis and modification of polyurethanes for improving biocompatibility are continuing. Keeping in mind the unique properties of PU, we expected to demonstrate a novel strategy for surface modification that builds a chemical reactive spacer PEG on the surface of PU allowed for the subsequent graft copolymerization of zwitterionic vinyl monomer. Though many studies have been reported on surface modification of PU, there are few reports in the literature combining the PEG and zwitterions of sulfobetaine into the PU surface.

In our study, a new PU film with sulfobetaine through a PEG spacer was prepared. The membrane was fully characterized by attenuated total reflection Fourier transform infrared spectroscopy (ATR-FTIR), X-ray photoelectron spectroscopy (XPS) analysis, atomic force microscope (AFM) and water contact angle. The

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surface hemocompatibility of the modified PU was examined by the activated partial thromboplastin time (APTT), thrombin time (TT) and prothrombin time (PT).

2. Experiments

2.1. Materials

Polyurethane, Pellethane®, was purchased from Dow Chemical Co. (Midland, MI, USA). Hexamethylenediisocyanate (HDI) was purchase from Aldrich Co. (Milwaukee, WI, USA) and was used without further purification. Polyethylene glycol (PEG, molecular weight 1000) was dried under vacuum at 60 °C over night. Toluene was dried over molecular sieves 4A prior to use. Dimethyl formide (DMF), ceric ammonium nitrate (CAN), nitric acid, di-n-butyl tin dilaurate (DBTDL) [2-(methacryloyloxy)ethyl]-dimethyl-(3-sulfopropyl)-ammonium hydroxide (MEDSA), N,N′-methylene bisacrylamide (MBAA) were used without further purification.

2.2. Preparation of polyurethane membrane

Pellets of the PU were extracted with ethanol for 24 h in order to remove processing agents and low-molecular weight components. The pellets were dried thoroughly in a vacuum at 40 °C and then dissolved in DMF to a 15% (w/w) solution. The solution was spread on cleaned glass plates to obtain transparent films. The plates were heated to 55 °C for 12 h in the airflow oven and vacuum dried at 50 °C for 24 h to remove solvent completely. The PU membranes were cut into strips of about 1 cm × 2 cm in size and subjected to the following experiments.

2.3. Reaction of HDI onto PU membrane surface

In order to functionalize the PU surface, PU membranes were immersed in a 40 mL toluene solution containing 3.7% (v/v) HDI and 0.5% (v/v) DBTDL as a catalyst. The reaction was allowed to stir at 50 °C for 2 h under N_2 atmosphere. The membranes were then washed in dry toluene to remove unreacted HDI.

2.4. Grafting of PEG on the PU membrane

PU-HDI membranes were reacted with 10 g of PEG in 40 mL of toluene and 0.5% (v/v) of DBTDL for 12 h at 70 °C. Then membranes were extracted in toluene for 18 h to remove unreacted PEG, and washed briefly with ethanol. The membranes were characterized after being dried under vacuum at 40 °C for 24 h.

2.5. Ce (IV)-induced graft copolymerization on the PU membrane

MEDSA and the cross-linking agent MBAA were grafted onto the membrane surface by using the method of Tomita et al. [30]. PU-PEG membranes were immersed in a 35 mL aqueous solution containing 0.25 M MEDSA, 0.4 M HNO_3, 0.05 M CAN and 20 mM MBAA. The solution was purged with nitrogen gas for about 30 min, and then the system was heated at 50 °C for 3 h. At the end of the reaction, a 2% solution of hydroquinone was added into the reaction system to terminate the graft copolymerization. The grafted membranes were thoroughly rinsed in water and dried in a vacuum at 50 °C for 24 h and weighted. Grafting was defined as follows:

$$\text{Grafting } (\%) = [(W - W_0)/W_0] \times 100$$

where W is the vacuum dried membrane weight after Ce (IV)-induced graft copolymerization and W_0 represents the vacuum dried membrane weight after grafting with PEG.

3. Characterization

3.1. Attenuated total reflection Fourier transform infrared spectroscopy (ATR-IR)

Attenuated total reflectance Fourier transform infrared spectroscopy (ATR-FTIR) measurements were carried out on a Nicolet Nexus FTIR equipped with an ATR accessory MUP with GeS crystal. Thirty-two scans were collected for each sample.

3.2. X-ray photoelectron spectroscopy (XPS)

XPS was used to determine the near-surface composition of the membrane. XPS analysis of the membrane surface was made on a VG Multilab 2000 with Al Kα source. The anode voltage was 15 kV and the anode current was 10 mA. The core-level signals were obtained at a photoelectron take-off angle of 90°. The elemental compositions were determined on the basis of peak areas and sensitivity factor from the C_{1s}, $N_{1s,}$ O_{1s}, and S_{2p} peaks by an Avantage software. All binding energy values were determined with reference to carbon, C_{1s} = 284.6 eV.

3.3. Atomic forced microscope (AFM)

Surface morphology was observed by atomic force microscope (AFM). The surface topographic feature of the PU and PU-MEDSA membranes was performed on DI Nanoscope IV scanning probe microscope (Digital Instrument Inc., USA) in air at ambient conditions using tapping mode probes with constant amplitude (200 mV).

3.4. Contact angle measurement

Dynamic contact angles were measured using the Wilhelmy plate technique [31] in a Krŭss K12 contact angle apparatus (KRüSS Corporation German). The films were immersed into and taken out from purified water with a rate of 10 cm min^{-1} to measure advancing and receding contact angles. Static contact angle measurements were performed on a JC2000Y stable contact angle analyzer at room temperature with distilled water as test liquid. With each specimen, both types of measurements were repeated at three different locations.

3.5. The measurement of TT, PT and APTT

Human venous blood samples were purchased from Wuhan Union Hospital, and the plasma was obtained by centrifugation at 2000 rpm for 15 min. The tested membranes were contacted with 200 μL of citrated plasma, and then incubated at 37 °C for 30 min. The PT was measured according to the following procedure. 50 μL of PT-S reactive was added to 25 μL incubated plasma samples, and then the mixture solution was tested with an automated blood coagulation instrument. The TT was tested using 200 μL of healthy human blood plasma and 200 μL of thrombin. For the detection of the APTT time, 25 μL of APTT reactive was added to 25 μL incubated plasma samples, and they were incubated at 37 °C for 5 min. The coagulation times were measured using an automatic coagulation instrument synchronously with the addition of a 2.5 mM calcium chloride solution to the tubes. The reported values are the average of three runs.

4. Results and discussion

In this study, a three-step grafting procedure was performed. The progress of modification was depicted in Scheme 1. In the first step, diisocyanates have been used for activating PU surfaces. In