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A facile preparation of poly(ethylene oxide)-modified medical polyurethane to improve hemocompatibility

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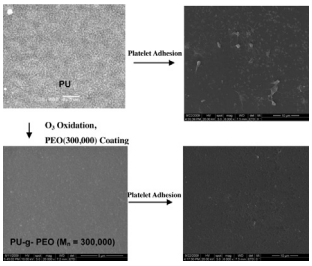
HIGHLIGHTS

- PU films were modified with PEO by a facile, environment-friendly approach.
- The hemocompatibility of the PEO-coated PU was significantly improved.
- PEO-coated PU films were very hydrophilic.
- The higher molecular weight of PEO shows better hemocompatibility.

GRAPHICAL ABSTRACT



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ABSTRACT

Poly(ethylene oxide) (PEO) has been widely applied in the modification of biomaterials because it shows high hydrophilicity and excellent biocompatibility. In the current study, the surface of medical polyurethane (PU) films was modified to improve hydrophilicity and hemocompatibility by a facile method without catalyst. PU films were modified directly using poly(ethylene oxide) (PEO) with various molecular weights. The existence, morphology, hydrophilicity and hemocompatibility were approved and studied respectively by attenuated total reflectance infrared spectroscopy (ATR-IR), atomic force microscopy (AFM), scanning electron microscopy (SEM), contact angel measurement and platelet-rich plasma adhesion study. Compared with the raw counterpart, the PEO-modified PU films have significant improved hydrophilicity and reduced platelet adhesion, as well as less shape deformation, especially for the one modified by the PEO (M_n = 300,000). These substantial improvements indicate potential application as blood-contacting coating in medical device.

1. Introduction

Various strategies of surface chemical modification have been developed because the surface properties of biomaterials can control the interaction between a living system and implanted materials [1–3]. In a biological setting, surface modification can reduce thrombogenicity, and control the adhesion of proteins or cells [4,5]. One approach involves surface modification by grafting a hydrophilic component, such as poly(ethylene oxide) (PEO), polyethylene glycol (PEG), poly(acrylic acid), poly(2-hydroxyethyl methacrylate) (PHEMA), poly(*N*-vinylpyrrolidone) (PVP) and chitosan [6–10]. Among hydrophilic polymers, PEO is a particularly effective polymer preventing protein adsorption and platelet adhesion, as the result of low interfacial free energy with water, unique solution properties, hydrophilicity, high chain mobility, and steric stabilization effect. Hence, the modification of polymeric materials by PEO has attracted considerable interests [11–13].

Polyurethanes (PU) have been extensively used in blood-contacting materials, such as a coating for cardiac pacemaker leads,

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breast implants, vascular devices, artificial heart implants, and heart valves [14–16]. This is due to the fact that polyurethanes show both relatively well-biocompatibility and excellent mechanical properties. However, the surface of medical PU is, to some extent, hydrophobic, not completely thromboresisitant, and needs to be improved for more applications [17]. PU modified by PEO and its derivates have been investigated intensively. The methods to prepare PEO surfaces include covalent coupling [18], interpenetration [19], adsorption, and graft copolymerization of PEO or PEO derivatives to substrates [20], which create permanent PEO surfaces. Generally, PU were first treated with diisocyanate as the coupling agent in toluene using stannous octoate ($Sn(Oct)_2$) as catalyst to introduce free isocyanate groups on the PU surface, and subsequently chemically grafted with PEO (or PEO derivatives) using the reaction between the terminal isocyanate groups and the hydroxyl groups of PEO in benzene in the presence of the same catalyst [21–23]. Another strategy is that PEO (or PEG) is used as the functional branched chains or parts and its derivates react with PU [14,24,25]. However, diisocyanate and stannous octoate are highly toxic, and the derivates of PEO (or PEG) are very expensive. These disadvantages may induce low-quality and high-cost of products. Recently, surface ozone oxidation has been largely applied in medical polymer modification because it could not only introduce uniform peroxides, but also is easily controlled and inexpensive [26,27].

In this report, the coating of PEO on the PU films activated using ozone was prepared by a simple method without catalyst. The effects of molecular weight of PEO (M_n = 1000, 10,000, 100,000 and 300,000, respectively) on the morphologies, hydrophilicty and platelet adhesion on the modified PU were studied. The surface properties were characterized by using attenuated total reflectance Fourier transform infrared spectroscopy (ATR FT-IR) and water contact angle. The effect of modification on the bulk of PU was assayed by gel permeation chromatography (GPC). The morphology and structure of modified PU films were observed by atomic force microscopy (AFM) and scanning electron microscopy (SEM). In addition, the hemocompatibility of PEO-coated PU was evaluated by *in vitro* platelet adhesion.

2. Material and methods

2.1. Materials

Polyurethane (Tecoflex®) was obtained from Lubrizol Specialty Chemicals (Shanghai) Co., Ltd, China. Tetrahydrofuran and methanol (AR, SCRC, China) are used as supplied. PEO (M_n = 1000, 10,000, 100,000 and 300,000) (Alfa Aesar, MA, USA) were used after vacuum drying at 60 °C for 24 h.

2.2. The pretreatment of PU films

The polyurethane was extracted with methanol at 60 °C for 24 h to remove low molecular weight components. PU films were prepared by casting thin films from 10% tetrahydrofuran (THF) solutions onto round glass dishes. Solvent was removed by drying at room temperature for at least 1 week, prior to another 24 h at 60 °C drying under vacuum. The formed films were approx. 0.3 mm thick and quite smooth. The peroxides groups of PU were introduced by ozone oxidation. Ozone was generated when dried oxygen of 300 L h^{-1} passed through an ozone generator (Sankang Ozone, China). And the operation condition was set at 0.25 A for 40 min. The concentration of ozone was about 25 mg L^{-1}. After the ozonization, it was degassed by purging O_2 to remove ozone adsorbed in the specimen. The ozonized PU samples were denoted as PU(O_3).

2.3. Surface coating of PU films with PEO

After pretreatment with ozone, the ozonized PU films were immersed immediately into a toluene solution of 6 wt% PEO. The reaction was carried out at 60 °C for 24 h with stirring under nitrogen atmosphere. A non-ozone treated surface was included in the same process as a control.

To remove the homopolymer or physically adsorbed polymer, the modified PU films were rinsed with hot water (80 °C, exchanged water every one hour) for 24 h, and subsequently dried in vacuum at 60 °C for 24 h. The PU films modified by PEO with molecular weights of 1000, 10,000, 100,000, and 300,000 were denoted as PU-*g*-PEO_{1k}, PU-*g*-PEO_{10k}, PU-*g*-PEO_{100k} and PU-*g*-PEO_{300k}, respectively.

2.4. Characterization

Molecular weights and molecular weight distribution of polymer were measured by gel permeation chromatography (GPC) system, equipped with a Waters 1515 Isocratic HPLC pump, a Waters 2414 refractive index detector, a Waters 2487 dual-wavelength absorbance detector, and a set of Waters Styragel columns. Tetrahydrofuran (THF) was used as the eluent with a flow rate of 1 mL min^{-1}. The temperature was maintained at 35 °C. And molecular weight of the sample polymer was calibrated with narrow molecular weight distribution polystyrene standards.

Surface functional groups were measured by attenuated total reflectance infrared spectroscopy (ATR-IR) spectra on a FTIR spectrophotometer from Nicolet 6700, coupled with omni-ATR accessory. 32 scans were collected with a solution of 4 cm^{-1}.

Surface morphology and structure of PU and modified PU films were characterized by SEM (LEO, 1530VP, Germany) and AFM (Veeco, Dimension 3100, USA) in tapping mode. The AFM topographic and phase images were obtained at the same time.

To characterize the wettability, the sessile drop method was used for contact angle measurements at 20 ± 1.5 °C using a commercial contact angle meter (Solon Tech. Shanghai, China). The diameter of droplet used for the measurement was *ca.* 2 mm. Ultra pure water droplets were placed at eight different positions for one sample. Then the average value was obtained. The experimental error of the measurements was ±1°.

2.5. Platelet adhesion

The adhesion and activation of the platelets on the surface of PEO-coated PU were observed. After equilibration with phosphate buffer saline (PBS, pH 7.4) overnight, samples (10 mm × 10 mm) were immersed in platelet-rich plasma (PRP) at 37 °C with mild shaking in an incubator. 500 mL of human blood from a healthy male volunteer was collected and mixed with 20 mL of 3.8% (v/v) sodium citrate PBS solution as an anticoagulant, and PRP was obtained by centrifuging the whole blood at 1300 rpm for 10 min. The number of platelets in PRP was adjusted to 3.5×10^{10} mL^{-1}. After a 10 h incubation the samples were taken out from the solution and rinsed five times with PBS to remove weakly adsorbed platelets. Then the strongly adsorbed platelets were fixed on the surfaces by immersing the sample in 2% (v/v) glutaraldehyde PBS solution at room temperature for 2 h. After fixation, the samples were dehydrated with a series of ethanol solutions (50%, 60%, 70%, 80%, 90% and 100%, v/v) for 15 min per step. Then they were dried in atmosphere overnight and under vacuum for 5 h in turn. The dried samples were coated with evaporated gold and the adhered platelets were observed with a SEM (LEO, 1530VP, Germany). The average number of adherent platelet was counted by SEM images in three different domains.