Domain-controlled polymer alloy composed of segmented polyurethane and phospholipid polymer for biomedical applications

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Abstract

Segmented polyurethane (SPU)s are block polymers which have a good elastic property and thermoplasticity. However, the biocompatibility of SPU is not sufficient, and a living organism rejects the SPU as a foreign material. Thus, some modification is needed to provide excellent biocompatibility and retain the good physical characteristics of the SPUs. In this study, we blended the 2-methacryloyloxyethyl phosphorylcholine (MPC) polymer with SPU to prepare an SPU/MPC polymer alloy. We investigated the effects of the molecular weight ($M_w$) of the MPC polymer on the microdomain structure and mechanical property of the polymer alloy. When the MPC polymer with a higher $M_w$ was blended with SPU, the polymer alloy underwent a reduction in mechanical strength. On the other hand, even when the lower $M_w$ of the MPC polymer was blended with SPU, differential scanning calorimetric analysis revealed that the MPC polymer chains did not disrupt the crystallinity of the hard segments of SPU and the polymer alloy could maintain its physical properties the same as that of the original SPU. We investigated the adsorption of immunoglobulin (IgG) on the surface of the polymer alloy for evaluation of its fundamental biocompatibility. The SPU/MPC polymer alloy lowered the amount of adsorbed IgG compared to that on SPU. This means that the blending of the MPC polymer significantly improved the biocompatibility of the SPU. We succeeded in preparing an SPU/MPC polymer alloy that possesses both the good mechanical property of SPU and the improved biocompatibility using MPC polymers.

Keywords: 2-Methacryloyloxyethyl phosphorylcholine polymer; Segmented polyurethane; Polymer alloy; Phase separation; Thermal analysis; Blood compatibility

1. Introduction

Segmented polyurethane (SPU)s have elastic properties, thermoplasticity, and durability. These properties of the SPUs are the result of soft segments that mainly consist of polyether chains and hard segments that are primarily composed of polyurethane blocks [1]. The characteristics of the SPUs depend on the microdomain structure of these SPU polymer segments. The structures of the SPUs play an important role in obtaining good mechanical property and the processability into various shapes. The SPUs have been used for biomedical devices such as cardiovascular catheters, diaphragms of blood pumps, coating materials for implantable pacemakers, etc. [1]. However, when SPUs are used for long-term implantation in living organisms, some serious problems occur concerning in the biocompatibility and chemical stability. Anderson and co-workers reported that degradation and cracking are initiated by activated macrophages that come in contact with the SPU surface [2–4]. The polyether soft segments in the SPU are attacked by the oxygen radicals produced by the macrophages, and the degradation of SPU is induced. When the SPU is used in vivo for long periods, it is necessary to suppress the activation of the adherent cell at the surface in order to prevent degradation of the SPU. The activation and adhesion of cells result from protein adsorptions on the material surface. Thus, it is important to pay attention to the protein adsorption when the surface modification is performed. The surface modifications of the SPU to obtain biocompatibility have been attempted in various studies [5–7]. Also, another serious problem for SPU exists. When SPU contacts blood, plasma proteins adsorb on the surface of the SPU, and platelet adhesion and clot formation occur [8–13]. To prevent this thrombogenicity, many surface modifications studies have been carried out. They included the covalent bonding of alkyl groups for the selective
adsorption of albumin [8], poly(ethylene oxide), PEO, chains for the reduction of protein adsorption [9], and heparin molecules for preventing thrombin activation on the surface [10]. Moreover, sulfonate groups were introduced in the SPU to reduce platelet adhesion or protein adsorption [11,12]. Coating of a blood-compatible polymer such as poly(2-hydroxyethyl methacrylate-block-styrene) on the SPU was an effective method to inhibit occlusion even after a 1-year implantation period in dogs [10]. We have investigated the preparation and evaluation of phospholipid polymers as novel biomaterials [14,15]. The phospholipid polymers contained the 2-methacryloyloxyethyl phosphorylcholine (MPC) unit. The MPC has a phosphorylcholine group originating from phospholipids in the side chain, and the methacrylate in the main chain enables easy copolymerization with various monomers. The MPC polymers inhibited protein adsorption and cell adhesion even when they contacted human whole blood without an anticoagulant [16–18]. The surface modification of conventional biomaterials with MPC polymers significantly improved their biocompatibility and antithrombogenicity. As the modification methods, a simple coating, grafting, cross-linking, chemical reacting, and blending have been attempted [19–22]. In our previous reports, MPC polymers, which have an affinity with SPU on a molecular level, were blended into the SPU to produce the SPU/MPC polymer alloy, and these polymer alloy membranes showed excellent blood compatibility [23,24]. By using the SPU/MPC polymer alloy, polymer tubing with a 2-mm diameter was prepared and the antithrombogenicity of the SPU/MPC polymer alloy was investigated in vivo. When the polymer alloy tubing was implanted into an artery of a rabbit, no thrombus was observed even after a 30-day implantation. On the other hand, the tubing made from only SPU induced clot formation and occluded only after a 90-min implantation [25]. Also, the SPU/MPC polymer alloy could be processed with heat treatment at 150 °C, and the excellent biocompatibility of the polymer alloy was maintained even after heat treatment [26].

In this study, we focused on the domain structures of the SPU/MPC polymer alloy in order to prepare the new polymer materials for various medical devices. We considered that the microdomain structure of the SPU and MPC polymers was important regarding the properties of the SPU/MPC polymer alloy. We also attempted to control the microdomain structure of the SPU/MPC polymer alloy by changing the molecular weight ($M_w$) of the MPC polymer.

2. Materials and methods

2.1. Materials

MPC was synthesized by a previously reported method [14] and purified by recrystallization from acetonitrile. 2-Ethylhexyl methacrylate (EHMA) was purified by distillation under reduced pressure in an argon atmosphere, and the bp 56.0 °C/1.0 mm Hg fraction was used. 2,2'-Azobisisobutyronitrile (AIBN) was recrystallized from methanol. As an SPU, Tecoflex® EG-60D was obtained from Thermedics, Inc., MA, USA, and purified by a reprecipitation technique to remove all additives. Ethanol (EtOH) and methylene dichloride (CH$_2$Cl$_2$) were purified by distillation. For the protein adsorption test, we used IgG ($\gamma$-globulin from bovine blood, G5009, SIGMA). The other reagents were extra-pure reagent grade and used without further purification.

2.2. Preparation of MPC polymer

As the MPC polymers, poly(MPC-co-EHMA), PMEH, was synthesized by conventional radical copolymerization of the corresponding monomers in EtOH using AIBN as the initiator [21]. The concentration of AIBN in the feed was varied to obtain the PMEH with various $M_w$s. The PMEH was purified using a reprecipitation technique. That is, the polymerization solution was dropwise added to put into an excess amount of diethyl ether/chloroform (9/1) mixture. The PMEH precipitated was collected and dried. The structure of the PMEH was confirmed by $^1$H NMR, and FT-IR, and the MPC unit composition in the polymer was determined by $^1$H NMR and phosphorous analysis. The $M_w$ of the PMEH was evaluated by gel-permeation chromatography (GPC). The eluent was a methanol/water mixture (7/3). Calibration was carried out from the elution time of the GPC curve using poly(ethylene oxide) standards. The chemical structures of the PMEH and SPU are shown in Fig. 1.

2.3. Preparation of membrane from SPU/MPC polymer alloy

Solutions containing 5 wt% SPU and 5 wt% PMEH were separately prepared. As a solvent, an EtOH/CH$_2$Cl$_2$ mixture (3/7 by volume) was used. These solutions were mixed with each other at the SPU/PMEH ratio of 9/1 by weight, and then stirred for 30 min and sonicated for another 30 min at room temperature. The solutions (20 ml) were cast on a 20-cm$^2$ glass dish. To evaporate the solvent, the dish was kept for 5 h at room temperature (25 °C), and a glass plate that covered the glass dish was used to control the evaporation rate of the solvents. After this process, the dishes were kept at 60 °C in air overnight. To completely evaporate the remaining solvents, the dishes were then dried in a vacuum at 60 °C for another overnight period. The SPU/MPC polymer alloy membranes formed in the dish were then carefully peeled off. The SPU membranes without the PMEH were prepared using the same procedure. The thickness of the membranes were 200 μm. This ratio was good in order to reduce the adverse effect on the mechanical properties of the SPU/PMEH polymer alloy [26].
2.4. Tensile strength measurement

The tensile strength measurements were carried out using an STA-1150 (ORIENTEC, Tokyo, Japan). The samples were cut into a dog bone shape (the size was 12.5 mm × 2.5 mm). The crosshead speed was 10 mm/min. The number of specimens tested was three. Within the region of elongation from 0 to 5%, the strain–stress curves were completely linear. Thus, Young’s modulus was obtained from this initial elastic region.

2.5. Osmium tetroxide staining

The polymer alloy was embedded in epoxy resin, and then immersed in osmium tetroxide (OsO₄) aqua for 3 days to stain the domains of the MPC polymer. The specimens were cut off as thin sections to be observed by a transmission electron microscope (TEM, H-600, Hitachi, Tokyo, Japan). The juxta-surface of the polymer alloy was observed by TEM as cross sectional pictures.

2.6. Thermal analysis

A differential scanning calorimetric analysis (DSC) was carried out using a DSC 6100 (Seiko Industry, Chiba, Japan). The sample was cut into a round shape with a 5-mm in diameter. About 10 mg of each sample was sealed in separate aluminum pans. The heating rate was 5 °C/min from −100 to 250 °C.

2.7. State analyses of hydrogen bonding of hard segments using FT-IR spectra

The IR spectra were obtained using an FT-IR (FT-IR615, Jasco, Tokyo, JAPAN) equipped with the attenuated total reflectance (ATR) apparatus, ATR-300/H (Jasco), and having an incident angle of 45°. The polymer alloy was cut into a rectangular shape of 6.5 × 58 mm², and set in the sample holder of the ATR apparatus. A peak of the hydrogen form the bonded C=O of urethane bonds of the SPUs appeared at different wavenumbers from the free C=O, and we estimated the crystallinity of the hard segments based on these results. The peak splitting was carried out to estimate the amount of stretching vibration, using the Gaussian curve fitting.

2.8. Surface analysis with X-ray photoelectron spectroscopy

X-ray photoelectron spectra (XPS) were recorded using an ESCA-200 (AXIS His 165, Shimadzu/Kratos, Kyoto, Japan). The measurements were carried out at room temperature. The take-off angles of the photoelectron were changed from 90 to 15°. To evaluate the localization of PMEH after immersion in water, the samples were immersed in water for one week and then freeze-dried before the XPS measurement.

2.9. Protein adsorption test

To evaluate the amount of protein adsorption on the surface, 15-mm diameter membranes were contacted with IgG using a 1.6 g/dl concentration in PBS at 37 °C for 60 min. After the membrane was rinsed with PBS, the remaining IgG adsorbed on the surfaces was removed with a 1 wt% aqueous solution of sodium dodecylsulfate (SDS). The amount of proteins in the SDS solution was then determined by the micro-BCA method using a clinical test kit (micro BCA protein assay reagent kit, #23235, Pierce, Rockford, IL, USA).

3. Results

3.1. Formation of SPU/MPC polymer alloy membrane

In this study, we used PMEH as the MPC polymer to blend into the SPU. The PMEH was designed to have an affinity with the SPU, since the EHMA units in PMEH are compatible with the soft segments of the SPU. The synthetic result is shown in Table 1. The composition of the MPC unit in the obtained PMEH was around 30 mol%. It was the same level as that in the monomer feed. The $M_w$ of the PMEH was increased as the concentration of initiators decreased. The structure of
PMEH was confirmed by the FT-IR absorptions at 950, 1050, and 1260 cm\(^{-1}\) attributed to the phosphate group. The homopolymer of MPC, poly(MPC), is soluble in water and EtOH. However, when the PMEH has about a 0.7 mole fraction of hydrophobic EHMA units in the polymer chain, the PMEH is then insoluble in water. Therefore, the PMEH can be used without elution under biological conditions. The SPU and PMEH were soluble in a mixed solvent of EtOH/CH\(_2\)Cl\(_2\) (3/7 by volume). Thus we selected this mixed solvent as the solvent for polymer blending procedure.

The PMEH could be blended with SPU by the simple mixing of these 5 wt\% polymer solutions. After the solvent was evaporated, the SPU/MPC polymer alloy membrane with a 200 \(\mu\)m thickness was formed, but it was slightly opaque compared to the SPU membrane.

In this study, we used PMEHs of various molecular weights. The polymer alloy composed of SPU and PMEH (\(M_w\) 3.0 \(\times\) 10\(^4\)) was identified as SE30K. In the case of PMEH (\(M_w\) 7.0 \(\times\) 10\(^4\)), the polymer alloy is called SE70K. These membranes prepared from the polymer alloy did not show any significant differences in the appearances.

3.2. Mechanical properties of the SPU/MPC polymer alloy

The tensile strength measurement was carried out to determine the mechanical properties of the SPU, SE30K and SE70K (Table 2). SPU and SE30K showed the Young’s modulus of 49.2 and 50.2 MPa, respectively. There are no significant differences between SPU and SE30K (\(p > 0.05\)). However, the Young’s modulus of SE70K was 42.0 MPa; this value decreased compared to SPU and SE30K (\(p < 0.05\)). These results indicated that molecular weights of the PMEHs affect the mechanical properties.

3.3. Morphology of PMEH domain in the polymer alloy

The phase separations of SPU and PMEH in SE30K and SE70K were observed by TEM (Fig. 2). The black regions were stained PMEH domains. These pictures revealed that some of the PMEHs formed domains mainly composed of the MPC polymers. The phase separation would be varied by \(M_w\). In the case of SE70K, the domain size of PMEH was from 3 to 5 \(\mu\)m, but the size decreased to about 500 nm in the case of SE30K. The \(M_w\) of PMEH was higher, and PMEH chains tended to aggregate on a large scale.

3.4. Thermal properties of polymer alloy

The various thermal properties of the polymers are summarized in Table 3, and the DSC charts are shown in Fig. 3. In this table, \(T_g\) and \(T_m\) denote the glass transition temperature and the melting temperature, respectively. The SPU showed two endothermic peaks, and lower one is referred to as \(T_m1\) and the higher one is referred to as \(T_m2\). The \(T_m\) of SPU appeared at \(-25^\circ\)C. The lower peak (\(T_m1\)) of the SPU was observed at 74 \(^\circ\)C, and the higher one (\(T_m2\)) appeared at 130 \(^\circ\)C. By blending PMEH into SPU, the distinctive peaks of PMEH were not observed.

3.5. Bonding state of C=O in urethane bonds in SPU

The ATR/FT-IR results are shown in Fig. 4. The C=O of the urethane bond of SPU shows peak shifts by hydrogen bonds. The peak of the bonded C=O appeared at 1690 cm\(^{-1}\), and the peak of the free C=O appeared at 1715 cm\(^{-1}\). The ratios of the free and bonded C=O were evaluated by a peak splitting. The percentage of the free C=O of SPU was 9.6\%, that of SE30K was 12.5\%, and that of SE70K was 16.2\%. These results revealed that the bonded C=O of SE70K decreased compared to SE30K.

3.6. Surface properties

The chemical compositions of the polymer alloys were analyzed by XPS. The representative XPS charts of these polymer samples are indicated in Fig. 5. The SPU showed

| Samples | Young’s modulus (MPa) | Maximum elongation (%) | Breaking strength (MPa) |
|---------|----------------------|------------------------|------------------------|
| SPU     | 49.2 ± 4.5           | 718 ± 23               | 60.3 ± 1.4             |
| SE30K   | 50.9 ± 3.5           | 862 ± 39               | 54.1 ± 3.7             |
| SE70K   | 42.0 ± 1.4           | 826 ± 96               | 53.4 ± 10              |

\(p < 0.05\) against SPU and SE30K.
the XPS signals, which were attributed to carbon in the CH3– or –CH2–, –COC–, –C(=O)– groups, and nitrogen in the urethane bond were observed at 285.0, 286.2, 288.9, and 399.9 eV, respectively. The same signals were also observed in the SE30K and SE70K. In addition to these signals, XPS signals were observed at 402.2 and 132.9 eV, which were attributed to the nitrogen atom in the choline group in the MPC unit and the phosphorus atom in the MPC unit, respectively.

The take-off angle of XPS was related to the depth of the analyzing that was approximately from 5 to 20 nm. To evaluate the MPC polymer concentration on the surface, the phosphorus atom concentration divided by the carbon atom concentration (P/C) were calculated with the intensity of the signal ratios. The results are shown in Fig. 6. The result guaranteed that the MPC polymers existed on the juxta-surface. If the MPC units completely cover the surfaces, the P/C value will be 0.091. The P/Cs of SE30K and SE70K approximately ranged from 0.01 to 0.02. The blended PMEH was only 10 wt%, but this result indicated that PMEH chains were rich near the surface of the polymer alloy.

The P/C values of the polymer alloy that were immersed in water before the XPS measurement are shown in Fig. 6. The P/C values of SE30K and SE70K did not change after immersion. The poly(MPC) are soluble in water, but 70 mol% of the EHMA units could inhibit PMEH from eluting into water.

3.7. Inhibition of protein adsorption on the surface of SPU/MPC polymer alloy

The plasma protein adsorption on the polymer alloy was evaluated by a micro-BCA method. In this study, the adsorption of IgG (one of plasma proteins) was tested. The protein adsorption amounts on the surface are shown in Fig. 7. SE30K and SE70K inhibited the protein adsorption on the surfaces when compared to SPU. The adsorption and denaturation of the plasma proteins was the main factor to incur inflammatory response on the surface of implanted material. IgG is one of the plasma proteins and the polymer alloy proved to have the potential to avoid foreign body responses in the case of implantation.

| Table 3 | Thermal properties of polymers |
|---------|-------------------------------|
| Samples | $T_g$ ($^\circ$C) | $T_m1$ ($^\circ$C) | $T_m2$ ($^\circ$C) |
| SPU     | $-25$ | $74$ | $130$ |
| SE30K   | $-2$  | $69$ | $135$ |
| SE70K   | $-15$ | ND  | ND   |

Fig. 2. Phase separation states observed by TEM. Black regions are MPC polymer domain stained by $\text{OsO}_4$.

Fig. 3. DSC charts of polymer alloys.
4. Discussion

When different polymers are blended, the polymer alloy undergoes a phase separation and forms a microdomain structure. The phase separation is the main factor that changes the bulk and surface properties of the polymer alloy. There are possibilities that the blended polymer would have adverse effects on SPU. Thus, it is necessary to control the microdomain and to retain the original structure of SPU that provides the desirable properties for biomaterials. Also, it was reported that SPU of low crystallinity like Tecoflex® EG-60D (aliphatic polyurethane) cracked due to the hard segments [27]. Regarding this point, it is very important to control the blending conditions. Thus it is important to know the domain structures of the SPU/MPC polymer alloy and control the phase separation between the SPU and MPC polymer. We attempted the control of domain structure by varying the molecular weight of the MPC polymers.

The large-scale phase separation might incur a reduction in the mechanical properties, and the Young’s the SE70K underwent a reduction in Young’s modulus in the previous experiment. In the case of this study, the phase mixing is a main factor of this reduction because of good affinity of PMEH with SPU. However, the PMEH with higher molecular weight incurred the large-scale phase separation a little. Thus, to guarantee the possibility of reduction in mechanical properties, the PMEH with lower molecular weight is better than the higher one in consideration for possibility of reducing mechanical properties.

The DSC charts indicated a glass transition around \(-20^\circ C\). This glass transition was attributed to the domain composed of soft segments of SPU. The soft segments were mixed with the hard segments, and then the temperature was higher than the glass transition temperature of the poly(tetramethylene oxide) \((-88^\circ C\). The \(T_m\) of SPU was assigned to the microdomain mixing of the noncrystalline hard and soft segments. \(T_m\) was attributed to melting of the microcrystalline hard segments [28]. The distinctive peaks of PMEH were not observed in the polymer alloy. Thus, the microdomain structure of the polymer alloy that was observed by TEM was not a dominant factor concerning the phase separation of the polymer alloy. However, the DSC charts showed some differences between SPU and SE, and the differences were considered to be due to the mixing of SPU and PMEH. The first difference was the shift in the \(T_g\): The mixing of PMEH and the soft segments of SPU triggered the rise in the \(T_g\). The second one was a new peak due to acceleration of mixing between the hard segments and soft segments by PMEH. This new peak appeared around \(100^\circ C\). The PMEH mainly interacted with the soft segments of SPU. However, some parts of PMEH simultaneously interacted with the hard segments and

![Fig. 4. FT-IR spectra of polymer alloys.](image)

![Fig. 5. XPS charts of polymer alloys. Take-off angle of photoelectron was 90°.](image)
soft segments and accelerated the mixing of the soft segments and hard segments. Thus, SE30K showed three endothermic peaks in the DSC chart. In the case of SE70K, $T_{m1}$ and $T_{m2}$ completely disappeared. Also only the mid peak existed. This effect was due to the effect of the molecular weight. It was revealed that the increase in the molecular weight was due to the mixing of the soft segments and hard segments. This inhibited the crystallizing of the hard segments. Also, the ATR/FTIR results proved that the crystallinity of the hard segments was disordered in the case of SE70K compared to SE30K. This result was consistent with the DSC analyses. The crystallinity of the hard segments was important especially for stress cracking. It was reported that the weak crystallinity of the hard segments lead to surface cracking under biological conditions [27]. The blending state of SE30K was preferable in the view of stress cracking. These results showed that SE30K could be used for such devices as leads for pacemakers that have some problems concerning cracking.

The XPS analysis of the polymer alloy revealed that the PMEH was located on the surface and did not elute into water. With this surface composition, the polymer alloy inhibited the adsorption of IgG that is one of the plasma proteins, and can be expected to be used as a biomedical device material.

5. Conclusion

The phospholipid polymer, PMEH, was compatible with SPU by blending from a homogeneous solution containing SPU and PMEH. The blending state of SPU and PMEH could be controlled by the $M_w$ of PMEH. The SE70K disturbed the crystallinity of the hard segments, and will lead to a reduction in the mechanical properties of the polymer alloy. For SE30K, the crystallinity of the hard segments was retained, and the polymer alloy would have mechanical properties similar to those of SPU.

It is concluded that we could succeed in making a new polymer alloy composed of the MPC polymer and SPU without having any adverse effects on the significant properties of SPU. Moreover, the SPU/MPC polymer alloy could inhibit the adsorption of plasma proteins. This novel polymer alloy can be considered appropriate for biomedical devices.

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