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Segmented Polyurethane / 2-Methacryloyloxyethyl Phosphorylcholine Polymer Alloy as Novel Biomaterials with Nano-scale Polymer Domains

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Segmented polyurethane (SPU)s with nano-scale polymer domains by phase separation of polymer segments are widely used as materials for making various medical devices. Their mechanical properties and processing abilities are efficient, however, the biocompatibility is not enough for implantable devices and blood-contacting devices. By blending of 2-methacryloyloxyethyl phosphorylcholine (MPC) polymer into the SPU to prepare new polymer alloys, they have excellent biocompatible surface. In this study, we attempted to control the polymer domain structures between SPU and MPC polymer. The evaluation of mechanical properties, thermal properties, surface characterization, and protein adsorption resistance of SPU / MPC polymer alloy were carried out with attention to the composition of blending MPC polymer and sonication time during blending. Young's modulus of the polymer alloy was almost the same level as that of SPU even when the MPC polymer composition was below 20 wt%. The polymer alloy was stable at 150 °C and it is possible to set with heat treatment. During the heat treatment, the phase separation structure of the polymer alloy altered. Since the MPC units existed on the surface at the polymer alloy, the protein adsorption on the surface from human plasma was suppressed. We concluded that the control of domain structure is important factor for the mechanical properties of SPU, and we could succeed to realize the biomaterial that has the desirable properties.
Key words: phospholipid polymer, polymer alloy, polyurethane, thermal property, domain structure

1. INTRODUCTION

Segmented polyurethane (SPU)s are block-type copolymer composed of polyether soft segment and polyurethane hard segment. These two polymer segments do not compatible each other and make unique microdomain structure.[1] Due to the microdomains of different properties, the SPU shows the desirable characteristics for biomedical materials. That is, good stability, high mechanical and physical properties, and the thermoplasticity of the SPUs, and thus the SPUs are used for catheters, diaphragms of artificial hearts, coating materials for leads for pace maker of heart, etc.[1] However, the biocompatibility and chemical stability of SPUs under biological condition are not satisfactory for long-term implantation. Therefore, it is necessary to suppress cell adhesion and activation to prevent degradation of the SPU. Many attempts concerned with the surface modification of SPU to obtain biocompatibility have been reported. Such modifications are covalent bonding of alkyl groups for the selective adsorption of albumin, [2] poly(ethylene oxide), PEO chains for the reduction of protein adsorption,[3] heparin molecules for preventing thrombin activation on the surface,[4] and introducing sulfonate groups in the SPU.[5,6] Coating of poly(2-hydroxyethyl methacrylate(HEMA)-*block*-styrene) on the SPU tubing was very effective method to inhibit occlusion even after a 1-year implantation period in dogs.[7]

We have been investigating the preparation and evaluation of phospholipid polymers having 2-methacryloyloxyethyl phosphorylcholine units as novel biomaterials.[8,9] The MPC polymers inhibited protein adsorption and cell adhesion, even when they contacted with human whole blood without anticoagulant.[10-12] The surface modification of conventional biomaterials with MPC polymers significantly improved their biocompatibility and antithrombogenicity. In our previous reports, the MPC polymers were blended into SPU to make the SPU/MPC polymer alloy. The microdomain with about 500 nm in diameter composed of the SPU and the MPC polymer was observed and these polymer alloy membranes showed antithrombogenicity.[13,14]

We hypothesized that when the polymer domain structures in nanometer scale can be controlled, the polymer alloys will show good mechanical properties, high fatigue resistance, and excellent biocompatibility. Therefore, our approach is important to develop the novel biomaterials through polymer alloy.

In this study, we attempted to regulate the three polymer domains of SPU/MPC polymer alloy. These domains in-

clude both soft and hard segments of SPU and MPC polymer. To regulate the domain structures, the composition of MPC polymer in the polymer alloy and sonication time during blending were controlled. We evaluated the mechanical properties and thermal properties of SPU/MPC polymer alloy. When the SPU/MPC polymer alloy can be thermoformed without any change in its excellent blood compatibility and its mechanical properties, it may be shaped into various devices with heat treatment and provide the novel thermoplastic materials for the biomedical devices. Moreover, protein adsorption was observed to confirm the blood compatibility of the polymer alloy.

2. MATERIALS AND METHOD

2.1. Materials

MPC was synthesized by a previously reported method[11] and purified by recrystallization from acetonitrile. 2-Ethylhexyl methacrylate (EHMA) was purified by distillation under reduced pressure in an argon atmosphere and the fraction of bp 56.0 °C / 1.0 mm Hg was used. 2,2'-Azobisisobutyronitrile (AIBN) was recrystallized from methanol. As a 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_2Cl_2) were purified by distillation. The other reagents were extra-pure reagent grade and used without further purification.

2.2. Synthesis of MPC Polymer

Poly (MPC-*co*-EHMA) (PMEH) was synthesized by conventional radical copolymerization of the corresponding monomers in EtOH using AIBN as an initiator.[14] The MPC polymer was purified using a reprecipitation technique. The synthesized MPC polymer has 30 mol% of MPC unit. The structure of the MPC polymer (Fig. 1) was confirmed by phosphorus analysis, the ^{1}H-NMR, and FT-IR, and the MPC unit composition in the polymer was determined by ^{1}H-NMR and phosphorous analysis.

2.3. Preparation of Polymer Alloy

Solutions containing 5 wt% SPU and 5 wt % MPC polymer were separately prepared. As a solvent, an EtOH / CH_2Cl_2 mixture (3 / 7 by volume) was used. The copolymer solutions were mixed with each other at given ratios, and then stirred for 30 min and sonicated for a given time 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 hours at room temperature, and the glass plate was used to control the rate of solvent evaporation. 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 another overnight. The polymer membranes formed in the dish were carefully peeled off. The SPU membranes without the MPC polymer were prepared by the same procedure.

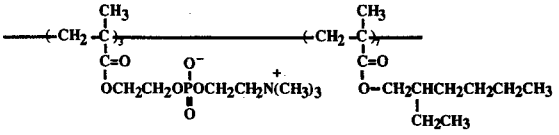

Fig. 1. Chemical stuctures of MPC polymer (PMEH).

2.4. Measurement of Mechanical Strength

As to polymer alloys tensile strength measurements were carried out using a STA-1150(ORIENTEC, Tokyo, Japan). The samples were cut into a dog bone shape (the size was 12.5 mm x 2.5 mm). The crosshead speed was 10 mm/min.

2.5. Evaluation of Thermal Properties

A differential scanning calorimetric analysis (DSC) was carried out using a DSC 6100 (SEIKO Industry, Chiba, Japan). The heating rate was 5 °C / min from -100°C to 250°C.

2.6. Surface Characterization

X-ray photoelectron spectra (XPS) were recorded using an ESCA-200 (Scienta, Uppsala, Sweden). The measurement was carried out at room temperature. The take-off angle of the photoelectron was 90 deg.

2.7. Protein Adsorption Test

Protein adsorption from human plasma on the polymer surfaces was evaluated using gold colloid labeled immunoassay as previously reported.[11] This method was qualitative, but it was reported that the number of gold colloid particles observed with a scanning electron microscope (SEM) corresponded to the number of proteins determined by radio immunoassay.

3. RESULTS AND DISCUSSION

3.1. Formation of SPU/MPC Polymer Alloy Membrane

The molecular weight of MPC polymer (PMEH) was 3.3 x 10^4. The MPC polymer was designed to have an affinity with soft segments of SPU. The MPC polymer was soluble into CH_2Cl_2 / EtOH (7/3 by volume). This solvent could also solve SPU easily. The common solvent enables to create SPU/MPC polymer alloy.

The blending compositions of the PMEH were 5, 10, and 20 wt%. All of SPU/MPC polymer alloys could form the thick membrane by the above method. The membrane thickness was about 200 μm.

In addition, we changed the sonication time during preparation of the polymer alloy membrane. The sonication times were 0 , 10 , 20, and 30 min. Except 0 min of sonication, the SPU/MPC polymer alloys formed fine membranes. In the case of 0 min sonicating polymer alloy, the large scale phase separation between SPU and PMEH was occurred, and did not form the membranes. Thus, it was

revealed that the sonication process was necessary for the preparation of the polymer alloy membrane.

3.2. Effect of MPC Polymer Composition on Mechanical Properties of Polymer Alloy

The mechanical properties of the polymer alloy are summarized in Table I. The Young's modulus of SPU/MPC polymer alloy was almost the same as that of SPU when the composition of the MPC polymer was 5 and 10 wt%, but maximum elongation and maximum strength were decreased 75-80% level of the SPU. In the case of polymer alloy with 20 wt% MPC polymer, every mechanical property was lowered drastically. When the MPC polymer chains interpenetrated into the microdomains composed of hard segment in SPU, the mechanical properties should be lowered. Though we designed the MPC polymer, PMEH, to interact with soft segment of the SPU to suppress the decrease of mechanical strength of the SPU, a large number of the PMEH chains affected the microdomain structure of hard segment. The polymer alloys with less MPC polymer compositions maintained the enough strength to apply as biomedical elastomer. To control the composition of MPC polymer in the polymer alloy, we achieved the domain structures, which had enough mechanical properties.

The effects of sonication on the mechanical properties were not so clear. However, without sonication, the polymer alloy membrane could not be prepared and we did not measure the mechanical properties. It is revealed that the sonication process is required to prepare the polymer alloy membrane, and the membrane with at least 10 min sonication had good mechanical strength even in comparison with the SPU membrane.

3.3. Thermal Properties of Polymer Alloy

Fig. 2 demonstrates DSC curve of SPU and SPU/MPC polymer alloy(10 wt% MPC polymer in the polymer alloy, sonication time; 30 min) with/without heat treatment. The SPU had two endothermic peaks around 70°C and 130°C, and glass transition point around - 25°C (Fig. 2-(1)). The peak around 70°C indicated the ordering of mixing phase composed of soft and hard segments. The peak around 130 °C was attributed to the melting of the ordered hard segments. The glass transition point was assigned to the soft segment of SPU. The phase separation of two segments in SPU provides good mechanical properties. According to the DSC curves, we tried to set the form of SPU at 150°C heat treatment. Under this temperature, the SPU can be easily processed into various shapes, such as flat membrane, particles, and fibers. The SPU/MPC polymer alloy indicated the similar DSC curve as that of SPU(Fig. 2-(3)). The glass transition point was slightly shifted to - 20°C. The interaction between SPU chains and MPC polymer chains induced this phenomena. However, the MPC polymer in this condition did not have an adverse effect on the mechanical properties as a whole. Thus, it is considered that the MPC polymer chains entangled with the soft segments of the SPU and interacted with the microdomain of hard segments very weakly.

With heat treatment at 150°C , the DSC curves of SPU and SPU/MPC polymer alloy changed. In both cases, the peak around 130°C was disappeared, and the peak around 70°C became much larger and broader than those of the SPU and polymer alloy before heat treatment. These results indicated that the amount of microdomains of hard segment of SPU was decreased, and mixing phases of soft and hard segments increased.

3.4. Existence of the MPC Units at the Surface of Polymer Alloy

When the MPC units exist at the surface of the SPU/MPC polymer alloy, the polymer alloy has the good antithrombogenicity.[13,14] Thus, the atomic components on the surface of the SPU/MPC polymer alloy were determined with XPS (XPS charts are not shown). At the surface of the polymer alloy, the phosphorus atoms and nitrogen atoms in ammonium ions were observed at 133 eV and 399 eV, respectively. SPU did not have such atom components, and these peaks were assigned to the phosphorylcholine group of the MPC unit. There is no significant difference between air side and glass side. This means that the MPC units were located at the surface of the SPU/ MPC polymer alloy even the MPC polymer composition was 10 wt %. The same peaks were observed on the SPU/MPC polymer alloy after heat treatment. It is revealed that the SPU/MPC polymer alloy can be set the form under 150°C heat treatment, and MPC units cover the surface of the polymer alloy. Therefore, it is expected that the SPU/MPC polymer alloy would have good biocompatibility even after heat treatment.

Table I. Mechanical Properties of the Polymer Alloy.

polymers	sonication time (min)	Young's modulus (MPa)	maximum elongation (Δl%)	maximum strength (MPa)
SPU	30	49.2±4.5	718±23	60.3±1.4
SPU / MPC polymer (95/5)	30	40.6±3.3	569±20	41.2±1.6
SPU / MPC polymer (90/10)	30	47.8±4.1	622±46	46.4±4.2
SPU / MPC polymer (90/10)	20	44.0±4.1	435±29	30.9±3.7
SPU / MPC polymer (90/10)	10	45.1±3.8	600±40	52.8±6.8
SPU / MPC polymer (80/20)	30	26.5±4.0	267±24	8.8±0.6

3.5. Protein Adsorption Resistance of the Polymer Alloy

The plasma protein adsorption on the SPU and SPU/MPC polymer alloy(10 wt% MPC polymer in the polymer alloy, sonication time; 30 min) was evaluated by

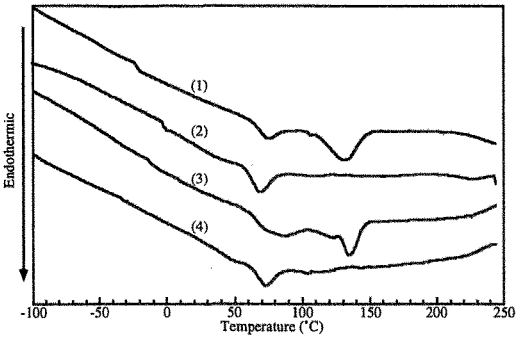

Fig. 2. Thermal properties of SPU and SPU/MPC polymer alloy. (1) SPU, (2) SPU with heat treatment, (3) SPU / MPC polymer alloy(MPC polymer composition: 10 wt%, sonication time: 30 min), (4) SPU / MPC polymer alloy with heat treatment.

gold-colloid labeled immunoassay.[11] In this study, fibrinogen at the plasma contacting surface were determined because it is a very considerable protein for clot formation. Fig. 3 shows the adsorption pattern of fibrinogen observed on the SPU and SPU/MPC polymer alloy. In this picture, white dots are corresponded to the fibrinogen adsorbed on the surface. A large amount of fibrinogen was observed on the SPU. On the other hand, the SPU/MPC polymer alloy dramatically reduced the fibrinogen adsorption on the surface. It has been reported that the MPC polymer can reduce protein adsorption and following clot formation.[10-12] The surface of the MPC polymer has much free water compared with the conventional polymers including SPU and poly(HEMA).[15] If the MPC units are covered with the SPU, the surface properties of the SPU should be changed to that of the MPC polymer. Therefore, it is very important to locate the MPC units at the surface to get biocompatibility.

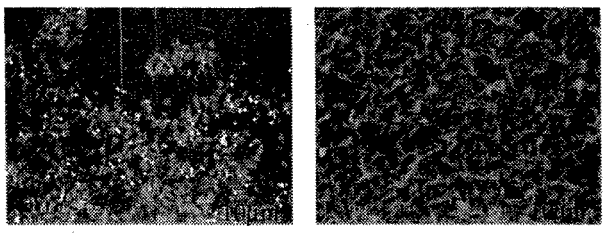

Fig. 3. Protein adsorption on the polymer surfaces. (1) SPU, (2) SPU / MPC polymer alloy(MPC polymer composition: 10 wt%, sonication time: 30 min).

CONCLUSION

We prepared the polymer alloy composed of SPU and MPC polymer to make new biomaterials. The microdomain structure of soft and hard segment of the SPU and the MPC polymer could be controlled by changing the composition of MPC polymer and sonication time during polymer blending. The SPU/MPC polymer alloy with 10 wt% MPC polymer showed good mechanical and biomedical properties. Also, the SPU/MPC polymer alloy could be set form into various shapes by heat treatment at 150°C and surface biocompatibility did not changed even after heat treatment because the MPC units existed at the surface of the polymer alloy. We concluded that the SPU/MPC polymer alloy can be applied to actual medical devices for long-term implantation such as the diaphragm and valve of artificial heart, artificial vascular prosthesis and implantable catethers.

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