Phospholipid Component 를 함유한 가교된 Polyurethane Biomaterials의 제조와 물성

유혜진, 김한도
부산대학교 섬유공학과

Preparation and properties of crosslinked polyurethane containing phospholipid component for biomaterials

Hye-Jin Yoo and Han-Do Kim
Department of Textile Engineering, College of Engineering, Pusan National University, Busan 609-735, Korea

1. Introduction

Segmented polyurethanes have been widely used for various commercial and experimental blood-contacting and tissue-contacting applications such as vascular prostheses, blood pumps, heart valves, pacemaker lead wire insulation, catheters, artificial hearts, and cardiac assist devices due to their generally favorable physical and mechanical properties, as well as fairly good biocompatibility and antithrombogenicity characteristics.[1-3] Although many successful results have been obtained in the use of polyurethanes in different biomedical devices, the inherent thrombogenicity of segmented polyurethanes remains in trouble.4 Generally, blood coagulates and causes blood clotting when it encounters with the foreign solid surface. This phenomenon is assumed to begin with initial adsorption of blood proteins, and then followed by platelet adhesion and activation of coagulation pathway, leading to thrombus formation. Thus, several strategies have been proposed to improve the blood compatibility of biomaterials such as incorporation of ionic groups onto the polymeric surface,[6] alteration of the surface properties by grafting techniques[5] and immobilization of heparin, functionalized dextrans or biological compounds,[7] and introduction of phospholipid polymer.

Recently, considerable attention has been paid to phospholipids because they are known that they consist of hydrophilic and hydrophobic groups and forms the lipid bilayer and they are important building units of plasma membranes. It is believed that polymers containing the phospholipid moiety provide biomembrane mimicry and should be more compatible with the human body (re). Phosphorycholine which is an electrically neutral and zwitterionic head groups present on the external surface of blood cells is inert in coagulation assays. There is no doubt that the introduction of the phosphatidylcholine or its analogues into polymer is useful for improving blood compatibility. Also, it been reported that alkyl-grafted segmented polyreuthanes show a high affinity for albumin adsorption alkyl side chains onto a polyurethane has been shown to reduce platelet deposition and enahnce in vitro albumin adsorption. More recent studies suggestthat the blood compatibilities of the polyurejtnaes containing long-chain alkyl groups and phosphatidylcholine analogues are very exciting. Because no evidence of nay blood platelet

attachment was apparent from the PRP (Platelet-rich plasma) contact studies and from scanning electron microscopy evaluation for the phospholipid polyurethanes, the excellent blood compatibilities of the new phospholipid polyurethanes have become a very promising candidate for clinical trials. However, the mechanical strength of the films prepared from these polyurethanes is almost too weak to prepare real films.[8]

In this study, we synthesized a new phospholipid diol (2-[Bis(2-hydroxyethyl)methylammonio] ethylstearylphosphate, BESP). Then, a series of multiblock polyurethanes containing phospholipid component in their side chain were synthesized from HDI/PEO/PTMO/PBD/BESP. The BESP surfaces were prepared by the addition of multiblock polyurethanes containing various BESP contents to Pellethene followed by the crosslinking of them to enhance blood compatibility and to improve mechanical strength in this study. The chemical structure of multiblock polyurethane containing phospholipid component was examined using 1H NMR and FT-IR spectrometers. Surface properties of the crosslinked polyurethane films were investigated using ESCA and water contact angle measurements. The water absorption and tensile properties of the crosslinked polyurethane films were also investigated. The blood compatibility of the crosslinked polyurethane films was evaluated by platelet rich plasma (PRP) contacting experiments and the results were observed by scanning electron microscopy (SEM).

2. Experimental

2.1. Materials

A segmented biomedical grade polyurethane pellet (Pellethene 2363-80AE, Dow Chemical Co.) was used after washing with methanol for 3 days and dried in a vacuum oven overnight at 60C. Poly(ethylene oxide) (PEO, Mn=3400g/mol, Aldrich) and poly(tetramethylene oxide) (PTMO, Mn=2000g/mol, Aldrich) were dried for 24hrs. at 80C in vacuum before use. Hexamethylene diisocyanate (HDI, Aldrich), polybutadiene diol (PBD, Mn=3000g/mol, Aldrich), triethylamine (TEA) , steary alcohol, and 1,4-butanediol (BD, Aldrich) were used after dehydration with 4 Å molecular sieves for one day. Dicumyl peroxide (DCP, Aldrich) was used as provided.

2.2. Synthesis of 2-[Bis(2-hydroxyethyl)methylammonin]ethylstearylphosphate (BESP)

First, into a thoroughly dried flask were 0.037mol of steary alcohol and 0.041mol of triethylamine in dry tetrahydrofuran (THF). After cooling, 0.037mol of 2-chloro-2-oxo-1,3,2-dioxaphospholane (COP) was added slowly. The reaction mixture was maintained at 10℃ for 1h and then stirred at 15-20℃ for 2h. The obtained 2-stearyoxy-2-oxo-1,3,2-dioxaphospholane filtered off and washed with dry THF. Then 0.032mol of 2-stearyoxy-2-oxo-1,3,2-dioxaphospholane were dissolved in DMF and 0.048mol of N-methyldiethanolamine were rapidyl added to the solution. After the mixing solution was shaken in a thermostat maintained at 75℃ for 20h, the solvent was evaporated.

2.3. Synthesis of multiblock polyurethanes (modifying additives)

The appropriate amount of dried PEO (Mn=3400g mol-1) and three drops of dibutyltin diaurate as a catalyst were dissolved in THF. HDI was slowly added to the solution for 30 min. and the reaction mixture was stirred for 6hrs. at room temperature. Then PTMO, PBD, and BESP were added separately to the reaction mixture and reacted for 5, 3, and 1hr, respectively. The obtained

multiblock polyurethanes were precipitated in -hexane, after washing with an excess amount of distilled water to remove any unreacted components. They were dried for 2 days at 45C in a vacuum. The detailed compositions of the multiblock polyurethanes prepared in this study are summarized in Table 1.

2.4. Preparation of crosslinked Pellethene / multiblock polyurethane blends films

Pellethene were dissolved in tetrahydrofuran (THF) to form a 15wt% solution. The multiblock polyurethanes (about 40 wt% based on dry Pellethene pellet) and DCP (4wt% based on dry multiblock polyurethane containing phospholipid component) as a crosslinking agent were added to Pellethene solution. The solutions of polymer blends were agitated homogeneously. Films were prepared by the solution casted from the polymer blends solutions. The solvent was slowly evaporated at room temperature for 2 days in a desiccator cabinet followed by vacuum drying overnight at 60C. The crosslinking was performed by heating of the film in a vacuum oven at 120C for 3hrs.[7]

3. Results and discussion

The 1H NMR spectrum of the new phospholipid diol (2-[Bis(2-hydroxyethyl)methylammonin] ethylstearylphosphate, BESP) was presented in Figure 1. From the 1H NMR spectrum, the characteristic peaks corresponding to the CH_3 at 0.88ppm, $C\text{-}(CH_2)_{16}\text{-}C$ at 1.26ppm, $N^+\text{-}CH_3$ at 3.12ppm, and $OCH_2CH_2\text{-}N^+\text{-}CH_2$, $PO\text{-}CH_2CH_2\text{-}N^+$, and $PO\text{-}CH_2\text{-}C$ at 3.4-4.2ppm are observed, respectively, to confirm the structures of the phospholipid diol (BESP). As the blood make a contact with biomaterial surface, the hydrophilicity of biomaterials is very important for biocompatibility. The water contact angles of the crosslinked polyurethane film surfaces were shown in Figure 2. The water contact angles on the surfaces decreased with increasing BESP content. The hydrophilicity of samples was proportional to the BESP content of the crosslinked polyurethane films. This phenomenon may be due to the BESP chains extended into the water phase. Figure 3 was shows the relationship between water absorption (%, immersion time : 24 and 48 hrs.) and BESP content in the crosslinked polyurethane films. Generally, the interfacial free energy with water (or blood) is related to the hydrophilicity of biomaterial and its value is decreased with increasing hydrophilicity. Thus, the swelling property of biomaterial films may be important parameters in many applications. The swelling property of the crosslinked polyurethane films was examined by measuring the water absorption (%) after immersion in purified water for 24hrs. and 48hrs. The water absorption of the crosslinked polyurethane films increased remarkably with increasing BESP content. This is also attributed to the phospholipid component in the crosslinked polyurethane films.

4. References

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Table 1. Description of multiblock polyurethanes containing phospholipid component synthesized in this study.

Sample Designation	Composition of Multiblock Polyurethanes (mole ratio)	BESP content (Wt%)
A1	HDI/PEO/PTOM/BESP/PBD/BD (2.4 / 1 / 1 / 0 / 0.04 / 0.36)	0
A2	HDI/PEO/PTOM/BESP/PBD/BD (2.4 / 1 / 0.8 / 0.2 / 0.04 / 0.36)	1
A3	HDI/PEO/PTOM/BESP/PBD/BD (2.4 / 1 / 0.6 / 0.4 / 0.04 / 0.36)	3
A4	HDI/PEO/PTOM/BESP/PBD/BD (2.4 / 1 / 0.4 / 0.6 / 0.04 //0.36)	5
A5	HDI/PEO/PTOM/BESP/PBD/BD (2.4 / 1 / 0 / 1 / 0.04 / 0.36)	10

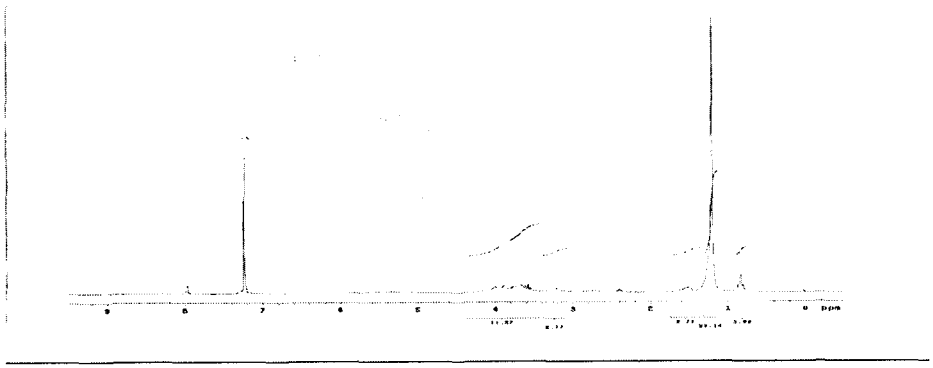

Figure 1. 1H NMR spectrum of typical phospholipid diol (BESP) .

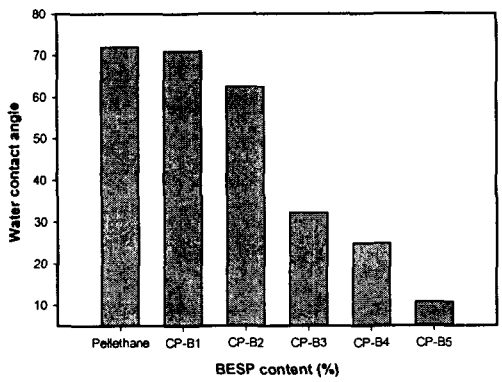

Figure. 2. Water contact angles of crosslinked polyurethane films.

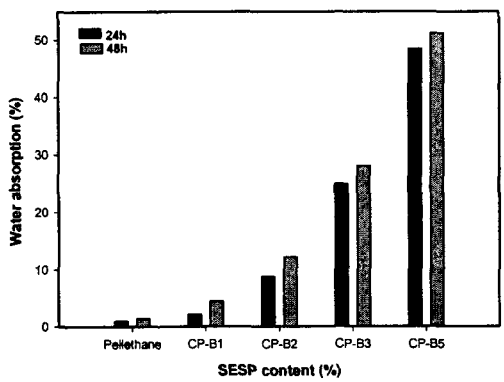

Figure 3. Water absorption of crosslinked polyurethane films after immersion in water for 24hrs. and 48hrs.