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Surface Characterization of Biocompatible Polysulfone Membranes Modified with Poly(ethylene glycol) Derivatives

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Abstract−Self-transformable and blood compatible devices of sulfonated poly(ethylene glycol) acrylate diblock copolymer (PEG-SO_3A/OA) with hydrophilic and hydrophobic block entrapped to polysulfone membrane surface were investigated in terms of the degree of hydrophilicity. The asymmetric membrane was formed by phase inversion process, and the induced hydrophilicity by reorientation of diblock copolymer at interface was verified with contact angle measurement, electron spectroscopy for chemical analysis (ESCA) depth profiling with ion sputtering and platelet adhesion test. Molecular dynamics (MD) simulations for the interface of hydration layer were also performed with various hydrophilic copolymer densities to gain optimum interfacial structure information. The dependency of water clustering behavior around diblock copolymers as a hydrophilicity parameter was described in terms of atom-atom radial distribution function (RDF). The results showed that the diblock copolymer entrapped surfaces demonstrated less platelet adhesion than control or copolymers having no hydrophobic blocks. In addition, oxygen composition significantly began to decrease deeper into the membrane, indicating the reorientation of diblock chains. Copolymer entrapped surfaces significantly induced the degree of water clustering, and the resulting equilibrium rearrangement of interfacial structures was distinctly dependent upon the density of copolymer. Taken together, the results show that the novel concept of *in situ* self-transformable surface modification strategy was successfully developed for biocompatible ultrathin biomedical membrane device.

Key words: Blood Compatibility, Phase Inversion, Molecular Dynamics, Radial Distribution Function, Water Clustering

INTRODUCTION

Biocompatible polymers are a critical functional element in a variety of bioartificial areas such as implants, diagnostics, bioprocessing and therapeutics. However, adverse reactions of cellular response caused by polymeric foreign materials are major subjects related to fundamental biomedical polymer research [Gristina et al., 1987], leading to a great deal of effort on the interaction of blood and artificial surfaces as applying this delicate control to biomaterials would lead to superior enhancement of the property of biomedical devices.

Many studies have been performed to get PEO (polyethylene oxide) to repel proteins under changing PEO conditions, showing more protein rejection and a higher grafting density for unbranched (linear) PEO [Gombotz et al., 1991; Su and Liu, 2003]. Also, the stretched-out polymers due to the high attachment density so-called polymer brushes have been reported [Milner, 1991]. Even though copolymers with one end attached to a surface are more restricted than free polymers, as the density of attachment points increases, the interaction between neighboring polymers increases and attached polymers begin to stretch out to prevent chain overlapping [Bergstrom et al., 1994]. That is, if once densities high enough to achieve polymer brushes are reached, PEOs are known to have the polymer brush effect. It has been accepted that PEO on surfaces will increase the hydrodynamic volume in water, and then reduce protein adsorption and immune reaction [Watanabe et al., 2002; Park et al., 2002]. However, in spite of the broad range of application of PEO, the optimum PEO conditions with dissociation-resistant, long-term durability and inapplicability of chemical grafting to miniaturized biomedical devices have not been established, as the optimum conditions should depend on the application field and methods. Moreover, the mechanisms of biocompatibility on the foreign surface have not yet been fully understood due to much more complicated biomedical interfacial structure. To overcome the complexity of interfacial chemistry, the interfacial phenomena such as the configurations and dynamics of polymer brushes have been studied by using a Monte Carlo simulation model [Cosgrove et al., 1987; Chun and Baig, 2001], as well as molecular dynamics simulations with varying grafting densities, monomer repeating units, and solvents. However, most computational approaches have concerned small molecules with unrealistic assumptions and it was difficult to generalize the models into real field.

In this study, we used an advanced self-transformable in situ fabrication method to enhance the biocompatibility of asymmetric polysulfone (PSf) biomedical membrane having ultrathin skin layer, in which an entrapped diblock copolymer contains hydrophilic block of PEG-SO_3 acrylate and hydrophobic block of octadecylacrylate (OA), as shown in Fig. 1a. Entrapping of block copolymers can be achieved by different solubility at the interface between solvents and polymer melts. That is, in aqueous solution, the copolymer will reside in a water/PSf interface and then its chain having a hydrophobic block is to entrap into membrane matrix by hydrophobic force and a sulfonated hydrophilic PEG block is to orient towards water phase, resulting in the modification of surface into having a hydrophilic nature, as shown in Fig. 1b. The self-transformed biocompatibility was verified with several experiments such as con-

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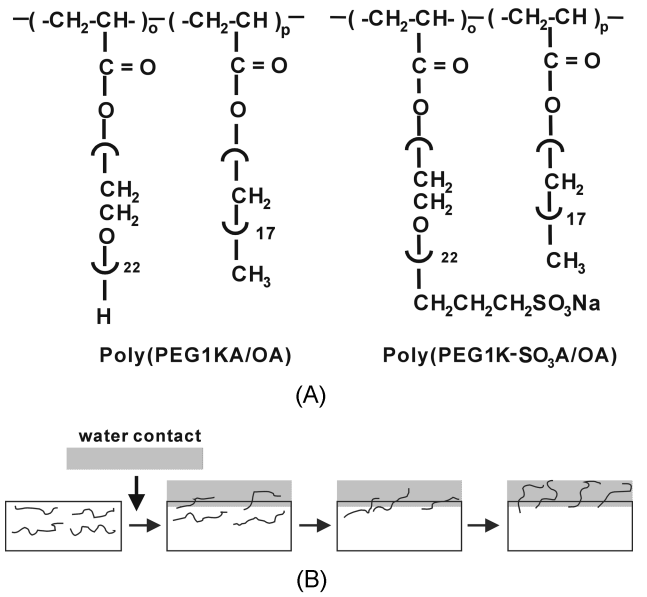

Fig. 1. (a) Structures of the synthesized copolymers. (b) Schematic diagram of self-transformable device with time course. After contacting with water, hydrophilic block starts to reorient from arbitrary conformation towards water phase, whereas hydrophobic block is to be anchored in membrane matrix by hydrophobic force.

tact angle measurement, ESCA depth profiling, and platelet adhesion test.

In addition, a molecular dynamics (MD) simulation study was undertaken to investigate the effect of interfacial structuring processes leading to the biocompatibility. Chain density profiles and water clustering patterns at the interface with or without copolymer were investigated by using the radial distribution function (RDF), *g(r)*, which is the most common statistical correlation function used in characterizing statistically isotropic particle systems. Evidence for a number of water-association modes is available from the radial distribution function plots [Bopp and Heinzinger, 1998]. The quantity $\rho 2\pi r g(r) dr$ gives the average number of water molecule centers in annulus of thickness *dr* at a radial distance of *r* from the center of a molecule (where ρ is the number density). The water clustering that affects the hydrophilic nature includes the number of water molecules around the copolymer. We now let the number of water molecule around the copolymer be quantitatively measured by radial distribution function by attempting to recreate the interfacial structure with various entrapped copolymer number.

This study involves the complete magnitudes and descriptions of the mechanism of interaction between blood and biomedical surface. Water structuring is a relevant parameter that is open to optimization. From the simulation and experimental results, water-PEO block copolymer configuration models dependent on optimum density were described and intuitively essential features for the dynamical behaviors of self-transformed blood compatible surfaces were suggested.

MATERIALS AND METHODS

1. Materials

Polysulfone (PSf, average Mw 30,000) (Udel P3500) supplied by Amoco was used as a membrane material. Unless otherwise specified, all chemicals were purchased from Aldrich and Sigma Chemical. N,N'-dimethylacetamide (DMAc) as a solvent for polysulfone was used without further purification. PEG mono-acrylates (PEGA, Monomer-Polymer and Dajac Lab., Feasterville, PA, USA) were dissolved in chloroform, precipitated in diethyl ether, and dried under vacuum at room temperature. OA was purified by vacuum distillation and α,α'-azobisisobutyronitrile (AIBN) was purified with recrystallization by using methanol. Polyvinylpyrrolidone (PVP, average Mw 55,000) was used as non-solvent additives in PSf/DMAc solution to control its miscibility with non-solvent water. Pure water was used as a nonsolvent (coagulant).

2. Synthesis of Poly(PEG-SO_3A/OA)

Sulfonation of PEGA monomer (M.wt of PEG, 1000) was carried out by using Na metal and then propane sultone to obtain sulfonated PEGA (PEG-SO_3A). Briefly, PEGA was reacted with Na metal at 50 °C for overnight and unreacted Na splices were eliminated by filtering process. Then, propane sultone was added to reaction solution and it was stirred at 50 °C for 24 h. PEG-SO_3A solution was precipitated in excess diethyl ether. After filtering, the precipitate was dried at room temperature in a vacuum oven. Copolymers were synthesized through free radical polymerization of PEGA/OA and PEG-SO_3A/OA monomers at 70 °C for 48 h in toluene using AIBN as an initiator, respectively. Molar ratio of hydrophilic monomer (PEGA or PEG-SO_3A) to hydrophobic monomer (OA) was 7 : 3. The polymerization mixture of 20 wt% monomer mixtures, 0.15 wt% AIBN and 80 wt% toluene, was bubbled with nitrogen for 30 min and reacted in a three-necked flask equipped with a condenser, thermo-controller, and magnetic stirrer. After the polymerization was finished, the reaction volume was reduced to about 60% by solvent evaporation under reduced pressure and precipitated in n-hexane or diethyl ether and finally dried in vacuum at room temperature for 2 days. The copolymers were characterized by Fourier Transform Infrared Spectrometer (FTIR, Mattson Alpha Centauri, Bucks, Eng-land) and Nuclear Magnetic Resonance Spectrometer (^{1}H-NMR, ^{13}C-NMR, Jeol JNM-PMX 60NMR, Tokyo, Japan).

3. Preparation of PSf Membrane

Concentrated polymer solutions for membrane fabrication were prepared by weighing the appropriate constituents in a glass container. The solutions were mixed until a homogeneous solution was obtained as judged by optical clarity. PSf was diluted in DMAc solution and then precipitated in non-solvent methanol. The precipitate PSf was dried under vacuum for 2 days to remove residual solvent. Polysulfone flat sheet membranes were prepared via the phase inversion process from casting solutions containing PSf, PVP, DMAc and various types of copolymers. The mixture was poured onto a glass plate and then the plate was evenly coated by drawing a retractable doctor blade across it. The plate was then immersed in a deionized water bath at 25 °C. The formed membranes were removed and placed in a deionized water bath for additional 2 h, then heat-treated for 16 h in an 80 °C water bath. The membranes were subsequently dried in a convection oven at 65 °C for at least 12 h.

4. Analysis of Membrane Surface

The PSf surfaces were examined by electron spectroscopy for chemical analysis (ESCA 2803-S, Surface Science Instruments) equipped with a monochromatic AlKα source, hemispherical ana-

lyzer, and a multichannel detector. The measurements were performed in the CAE (constant analyzer energy) mode and argon ions were used for sputtering. First, a survey spectrum of each sample was recorded. Therefore, a multiplex spectrum was recorded for every element detected on the surface after each sputtering step of 2 min. The total sputtering time was varied for depth profiles. Typically, spectra were collected with the analyzer at 35° with reference to the sample surface normal, and the operating pressure was approximately 3×10^{-9} Torr. The sputtering was performed by 3 kV argon ions with a sputtering current of about 2.7 μA. The ion beam was rastered over an area of 5 mm×5 mm. The binding energy scales for all spectra were referenced to the C1s signal at 285.0 eV. Peak fitting of the high-resolution spectra was done with Gaussian peak shapes by use of commercial software supplied by Surface Science Instruments.

Static contact angles were measured by using the VillHelmy100 video contact angle system. It used purified (Millipore 18 MΩ·cm resistivity) water drops (2 μL) on seven separate spots on each film surface in a controlled environment (100% relative humidity). Measurements were taken on both sides of water drops at ambient temperature 10-20 s after drops were applied to surfaces. Contact angle data report the average of drops at different surface locations.

5. Platelet Adhesion Test

Human whole blood, which was treated with citric acid, was centrifuged at 800 g for 10 min at 25 °C to prepare plate-rich plasma (PRP). Control and copolymer membranes (1×1 cm^2) were hydrated by placing them in phosphate-buffered saline (PBS, pH 7.4, 0.15 M)-filled 5 ml syringes for overnight. Prior to adhesion studies, the buffer was removed from the syringe and 2 ml of human PRP (platelet number 5.2×10^5 cells/μl) was introduced into the syringe. The syringe was then tapped to remove air bubbles, sealed, and rotated in a shaking incubator at 37 °C. By this method, the membranes were constantly exposed to PRP. Therefore, only surface/platelet interactive influences were observed. A set of syringes was arranged for adhesion times of 20, 40, 60 and 120 min PRP incubation. At each time point, the syringes were quickly removed from the shaking incubator, and counted immediately depleted platelets in the PRP with the coulter counter or hematocytometer. The amount of platelets was calculated as previously described [Ko et al., 2001].

6. MD Simulation Study

The Cerius^2 package (Molecular simulation Inc., CA) was used for all the MD simulations in the preparation and data collection. All calculations were performed using O_2 Workstation-R5000 (Silicon Graphics, Inc., CA). The PSf surface model was created from Surface builder. A diblock copolymer comprising the PEG1K, $(CH_2\text{-}CH_2\text{-}O)_{22}$, was obtained from polymer builder. One side of the hydrophilic chain was sulfonated and the other side was fixed to the PSf surface chain. Hydrogen was added to terminate the copolymer chains. In the first stage, the geometry of PSf and diblock copolymers was minimized from 300 K to 1,000 K and then 50 K to 300 K with 50 K increment.

The rectangular box for the MD simulation is a cubic lattice (i.e., a cubic box with periodic boundary conditions) containing PSf surface, water, and diblock copolymer according to its surface density. The cell parameters are a, b=30 Å, c=120 Å (c is the coordinate perpendicular to the surface). With these box dimensions, the cell density was measured at 0.98 g/cm^3. Parameters for potentials involving PSf and copolymer were calculated by using the PCFF valence force field commonly used in polymer simulations [Neelov et al., 1998]. All of the simulations were run by starting from optimized structures with 2000 steps of steepest descent followed by 20 ps (pico-seconds) equilibration at 298 K. A time step 1 fs (femto-seconds) was employed for the simulation of the equation of motion with a sampling interval of 0.1 ps. The system was allowed to relax during 400 ps using NVT ensembles, in which the temperature was kept constant as 298 K with a Nose-Hoover thermostat with a relaxation time of 0.1 ps. Numbers of atoms, volume and temperature were monitored throughout the simulation as a means of assessing the validity of the model used. Temporal interfacial information was obtained as if we were focusing on one block copolymer with a water molecule moving around it; we then took a snapshot at every fixed simulation step. We are thus able to obtain the interfacial change as well as the state of hydration at various simulation steps. The effects of copolymer density profiles on hydration state were also analyzed. Finally, we quantitatively calculated the RDF from the radius of hydration state. We focused on hydrophilic chains in suspension and kept its end of chain position stationary by using relative coordinates, describing mainly the geometrical description of the clustering. The validity of the simulation results was verified by previous reports, as shown in results.

RESULTS

1. Characterization of Copolymers

Sulfonation of PEGA monomer was performed with sodium metal and subsequently propane sultone. Sulfonation was confirmed by the presence of SO_2 at 1,030 cm^{-1} in the IR spectrum (Fig. 2). Poly(PEG-SO_3A/OA) copolymer was synthesized by conventional radical polymerization. The typical NMR spectrum of poly(PEG-SO_3A/OA) copolymer is shown in Fig. 3. The copolymer composition of PEGA/OA and PEG-SO_3A/OA is 8.1/1.9 and 8.7/1.3, respectively.

2. Surface and Bulk Property

The structure of the asymmetric membrane fabricated by phase inversion process showed an ultrathin skin layer (<1,000 nm) and

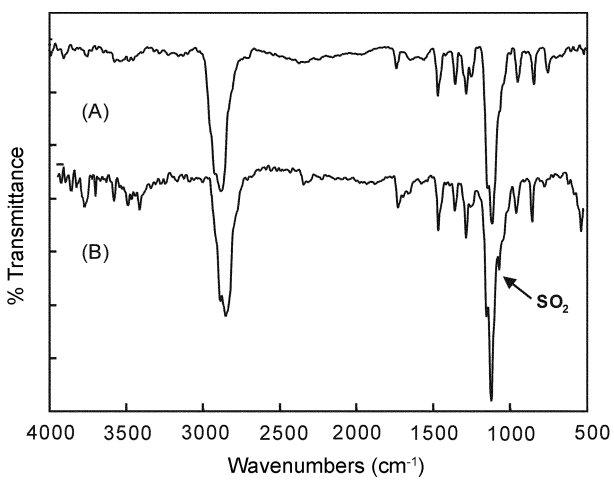

Fig. 2. FT-IR spectra of copolymers; (a) poly(PEG1k/OA) (b) poly (PEG1k-SO_3A/OA).

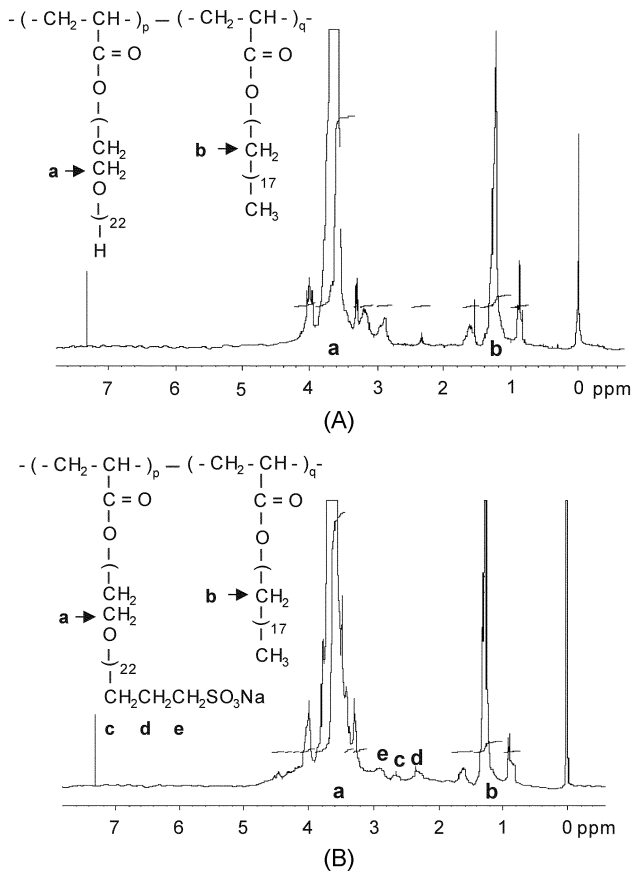

Fig. 3. ^{1}H-NMR spectra of copolymers; (a) poly(PEG1k/OA) (b) poly(PEG1k-SO_3A/OA).

Table 1. Contact angle data of copolymer-treated membranes[a]

Surfaces	θ^b	θ^c
PSf control	73±2.1	71±2.8
PEGA	68±1.8	65±4.3
PEGA/OA	51±3.4	49±5.1
PEG-SO_3A	69±2.1	66±3.7
PEG-SO_3A/OA	48±2.5	47±3.3

[a]Unit, degree, mean±S.D., n=7.
[b]no hydration time used.
[c]7 days hydration at room temperature.

sponge-like substructure characterized by the presence of macrovoids. It is well known that the optimum biocompatible nature of the asymmetric membrane depends on the surface skin layer, which is due to the fact that the surface skin layer of the membrane forms a more complicated interfacial structure after all. The following analyses were restricted to the ultrathin skin layer.

Table 1 summarizes the results of the contact angle measurements of ultrathin membrane prepared by using various kinds of copolymers. The results show that sulfonation served to enhance its hydrophilicity (i.e., contact angle decreased) as compared to control PSf. Intriguingly, the sulfonation effect is not notable in comparing the contact angle data for PEGA/OA vs. PEG-SO_3A/OA, probably resulting from the higher solubility of sulfonated copolymer followed by a little desorption from the membrane surface, or the difficulty of migration out through the membrane for sulfonated group in surface segregation process. The hydrophilicity of either PEGA or PEG-SO_3A treated membrane was close to the one of bare PSf, resulting from the no anchoring state with membrane surface. The copolymers with no hydrophobic block were expected to elute from the membrane matrix during fabrication process due to hot water treatment. After seven days in hydration, the hydrophilicity was strongly maintained, indicating long-term stability of diblock copolymer-anchored ultrathin PSf membrane. The sulfonation effects of diblock copolymer on surface hydrophilicity were not confirmed due to the data limitation in copolymer density on the asymmetric membrane surfaces. Taken together, the diblock copolymer was well anchored to its ultrathin membrane surface, which is due to the interface reorientation resulting from the extension of hydrophilic PEG chain into the water phase and the anchoring of hydrophobic chain into membrane matrix.

Table 2. ESCA data of PEG1K-SO_3A/OA entrapped PSf membrane[a]

Sputtering time	O	N	C	S
0	16.469	1.705	79.149	2.677
20	1.586	0.106	95.806	2.501
40	1.747	0.208	95.704	2.341
60	1.443	0.249	96.031	2.277
PSf	3.9*	2.0*	91.6*	2.6*

[a]depth profiling was used in ESCA.
*ESCA data of homogeneous PSf of nonsputtered membrane.

The diblock copolymer surface enrichment was verified with ESCA by depth profiling. Atomic percentage values along with surface depth are summarized in Table 2. The depth profiling was treated with an interval of 20 min. Surprisingly, there was a notable excess of oxygen composition and a corresponding increase in sulfur composition on the surface, as compared to the polysulfone membrane itself with no depth profiling, indicating that much more hydrophilic PEG blocks were driven to reside in the skin layer of the asymmetric membrane. In contrast, more hydrophobic blocks existed in the membrane matrix, as sampling depth moves from deep within the matrix. Stronger surface enrichment of oxygen composition was consistent with the results of the static contact angle measurements, indicating the reorientation of the diblock copolymer. Again, the depth-dependent difference in each element spectrum strongly supports the formation of reoriented copolymer at the interface. Taken together, whereas the polysulfone membrane surface has a strong character of hydrophobicity, the diblock copolymer entrapped to the membrane enhances the hydrophilicity, leading to high blood-compatibility. Also, diblock copolymer demonstrated no significant amount of elution after long period hydration, leading to long-term stability of the ultrathin membrane.

3. Platelet Adhesion

The results of in vitro platelet adhesion on PSf surfaces treated with PEGA, poly(PEGA/OA), PEG-SO_3A and poly(PEG-SO_3A/OA) are shown in Fig. 4, respectively. Less platelet adhesion on two diblock copolymers-anchored surfaces was consistent with the result of contact angle measurement. In addition, platelet adhesion on the diblock copolymer surfaces showed no significant differ-

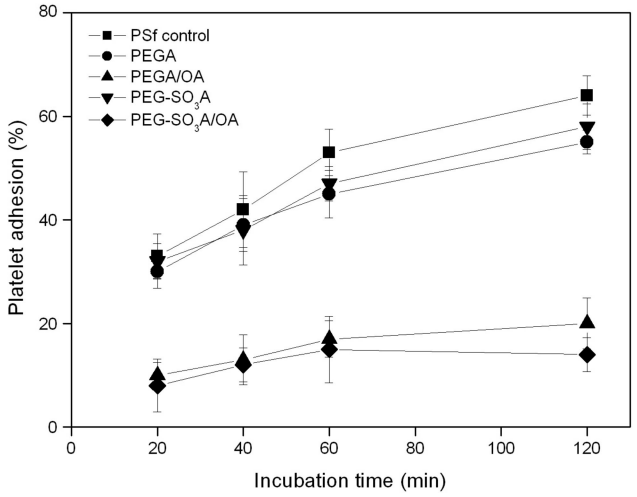

Fig. 4. Platelet adhesion on PSf membranes with copolymers (The data are expressed as % of the number of adhered platelet with respect to the total number of platelets).

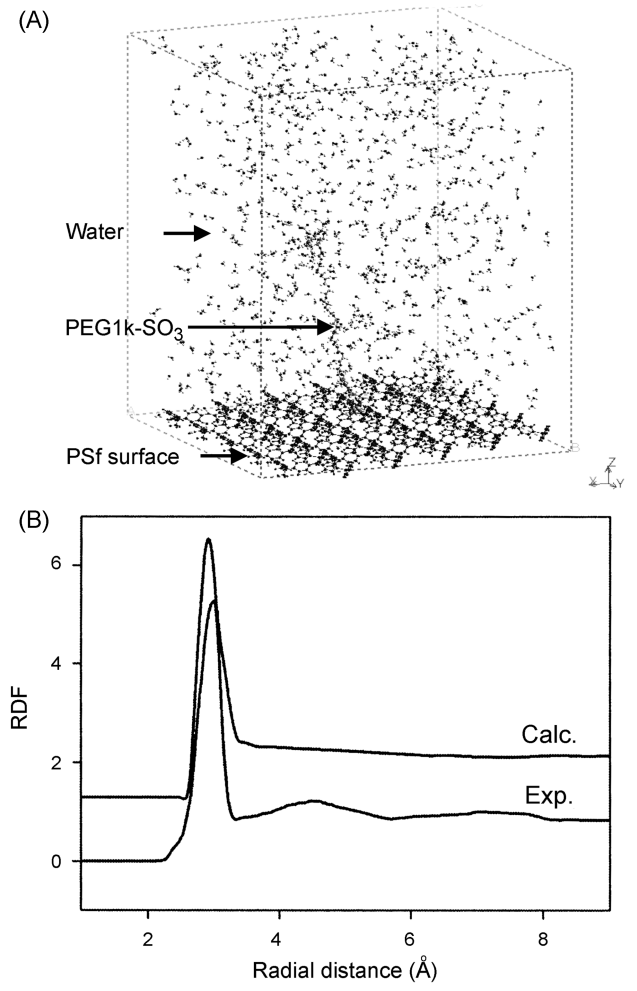

Fig. 5. (a) Snapshot of simulated model system of initial simulation configuration in a three dimensional periodic box at low density. (b) Computed and experimental oxygen-oxygen radial distribution functions for liquid water at 25 ℃ and 1 atm. Successive curves are offset 1.3 units along the ordinate.

ence with each other. That is, poly(PEG-SO_3A/OA)-anchored surface showed slightly lower platelet adhesion than poly(PEGA/OA)-anchored surface. And, as discussed above, the effect of PEGA or PEG-SO_3A with no hydrophobic chain on platelet adhesion was not observed due to the elution during the membrane fabrication process. Taken together, in the case of poly(PEG-SO_3A/OA) diblock copolymer-entrapped ultrathin membrane surface, the hydrophilic mobile segments served to exhibit less platelet adhesion, resulting in the enhanced biocompatibility.

4. Molecule-molecule Radial Distribution Functions

In order to investigate the behavior of water clustering around

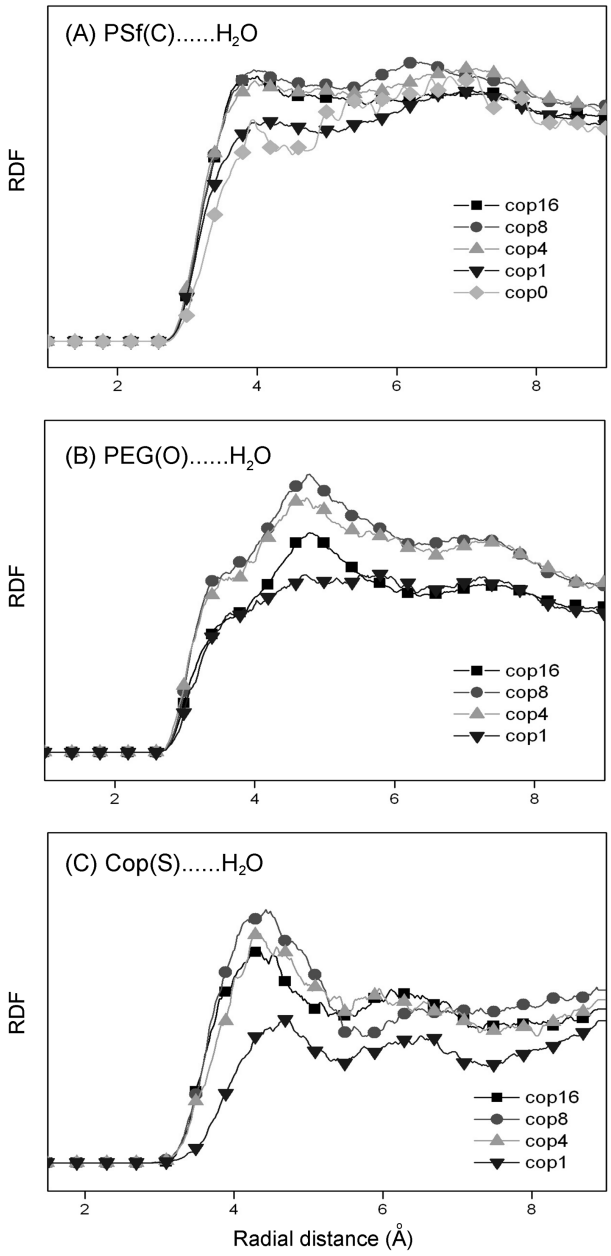

Fig. 6. Computed radial distribution functions at 25 ℃ and 1 atm. (a) Radial distribution function of carbon (PSf membrane) - oxygen (water). (b) Radial distribution function of oxygen (PEO) - oxygen (water). (c) Radial distribution function of sulfur (copolymer) - oxygen (water).

hydrophilic copolymers, we chose the initial simulation configuration as briefly shown in Fig. 5a, in which PSf surface, entrapped PEG1K-SO_3A chain and water molecules are shown in a three dimensional periodic box. In simulating water structure, the entrapped copolymer numbers were varied from one to sixteen in solution. In Fig. 5b, the experimental data of liquid water RDF and simulated water RDF, as a local water clustering parameter with equilibrium configuration of dynamic simulation at density 0.98 g/cm^3, were compared to estimate the validation of simulation model. In real water, the experimental results showed that the oxygen-oxygen radial distribution function has clear first and second peaks near 3 Å and 4.5 Å [Soper and Philips, 1985]. In comparison, the model used in this study showed good consistency around the first peak. According to these data, predictions of the water clustering patterns by the proposed model in this study are in good agreement with the experimental data. The results of MD simulation are shown in Fig. 6. The densities used in this study were similar to real systems at the cost of simulation time. As shown in Fig. 6, all RDFs manifest the different tendency of water clustering around PEG-SO_3 chain, as the RDF is quite sensitive to the distance from PSf surface or copolymer chain. It is obvious that the water clustering is preferentially oriented to the closer in proximity of surfaces. This preference decreases with increasing distance from the interface. The increased clustering state is a consequence of the water-PEG chain interactions, which are mainly hydrogen bonding in solution. Also, a long-range ordering was pronounced for the presence of copolymer. That is, the optimum water structuring state showed strong dependence upon the density of copolymer, which showed no copolymer aggregation. At longer distance above 10, water clustering was equilibrated and the RDF no longer changed as a function of distance.

In Fig. 6a, the first maximum in SO_3water RDF in term of S in SO_3 and O in H_2O was at 4.5 Å in the case of 8 copolymers entrapped than any other density. That is, it was possible to identify the high level of SO_3 coordination modes with water. S atoms strongly situated up to 9 Å with water, showing a long range ordering state. Especially, in the case of 16 copolymers, it can be suggested that relatively less water clustering than in the 8 copolymers resulted from the existence of electrostatic repulsion between copolymers due to high density. In Fig. 6b, the broader maximum in PEGwater RDF was at 4.8 Å in 8 copolymers. The positions of the peak maximum in RDF were found at slightly larger distance than SO_3-water, because of relatively lower electrostatic attraction. The results show that at high density, the hydration layer was narrower than the one at low density, as the water molecules near PEG chains are pushed back from packed structure significantly. Even though long-range repulsions exist mainly due to hydrophobic nature of PSf, more water molecules could be substantially resided on the membrane at 4 Å, as shown in Fig. 6c. As the copolymer density increases, the hydration effect of PSf surface could lead to more blood compatibility.

Taken together, RDF reproduces the interfacial structure fairly well, suggesting that an optimum copolymer state above a certain entrapped number exists. Also, the changed hydrophilic nature was consistent with the experimental results discussed above. The effects can be qualitatively concluded as the increase of hydrophilic nature of membrane surface.

DISCUSSION

It is well known that PEG grafted surface repels protein adsorption and platelet adhesion and the resultant biological behaviors are dependent on the PEG chain length and density. The current explanations for longer PEG chains include low interfacial free energy with water, hydrophilicity, dynamic motion of PEG, extended chain conformation of PEG, and unique solution properties of PEG [Kim et al., 1992]. The unique solution properties of PEO in water have been attributed to its structural similarity with water and the strong hydrogen bonding to the ether oxygen atoms [Tadokoro et al., 1984]. PEO molecules can occupy the spaces in the water structure with minimal perturbation of the structure. This arrangement of water molecules around PEO is thought to be the reason for its interesting biological properties. The molecular motion of PEO has been studied extensively, indicating its highly flexible nature depending on the PEO MW [Murat and Grest, 1989]. In dipole relaxation studies demonstrating the high freedom of reorientation of PEO in water, the chain segment mobility depends on the flexibility of the polymer chain. Flexibility and high mobility in aqueous solution are other special characteristics of PEO, because it reduces the protein contact time, thus providing less chance of protein interaction.

Though all its characteristics taken together give the biocompatible nature of PEO, the optimal conditions calculated and obtained were not consistent, nor well-defined. Furthermore, these theories deal with generalized models of large repeating units, which cannot predict the low molecular weight polymer case where the polymer end effect is dominant. PEO has its own peculiar properties that cannot be described with usual generalized polymer models such as the freely rotational model. It is essential to uncover well-defined optimal conditions for PEO, considering its numerous applications. High levels of hydration reported as two or three water molecules with each monomer may similarly explain the passive nature of PEO in not being recognizable by proteins [Antonsen and Hoffman, 1992]. Increasing coordination with water, or hydration state, suggested to be effective in reducing protein adsorption is a consequence of these passive characteristics [Llanos and Sefton, 1993], yet for reasons not entirely understood on interfacial phenomena.

Water clustering increases due to the hydrogen bond as the copolymer density increases, causing the hydrophilicity of the surface to increase fast. To rephrase these phenomena in our MD simulation, radial distribution function, *g(r)*, was applied to the system. It gives the probability associated with finding any water molecule at radial distance r from the center of another water molecule. And RDF can be ascertained from scattering experiments, which makes it a likely candidate for the reflection of structural clustering properties [Chang and Kim, 1998]. The RDF is clearly an adequate parameter to characterize the interfacial structural information, in which there was the variation of coordination mode with copolymer density. To obtain the time dependency of the interface structuring, we assume that if water is located closer to the copolymer, it is more likely to form a hydration layer. The water molecules are allowed to make an optimal energy state from a randomly started local minimum energy on the shell. The general features of water clustering patterns are consistent with the experimental data, although several assumptions are made in our simulation. The water clustering is due to the fact that the interfacial structure tends to cluster the water molecules together in order to get the required contact volumes. Since this is the case of unusual water clustering around copolymer

entrapped to surface, a copolymer may have a better pack structure than a colloidal dispersion. If there were significant aggregation of the copolymers, the aberrant RDF would result. The compactness of copolymer has not been discussed, nor experimentally verified until now. Considering long-term biocompatibility or brush effect, this could be important. A better-packed copolymer was described with the RDF of between copolymer and PSf, indicating the continual distance from the surface without aggregation of copolymer.

Hydration state around the copolymer increases due to the hydrogen bonded reaction as time progresses. The results show that the dependency of water structuring on the number of copolymer is strong for a high copolymer density and the quantitative change of water molecule is diminished for a low copolymer density, because most water molecules would be well clustered above a certain number of copolymer, while the water structuring would be not sensitively changed with the PSf surface having no copolymers. In our model system, we took into account a parameter such as water structuring after self-transformation was activated, promoting the understanding of interfacial structure patterning as the material contacts blood. Our simulations correspond to in vitro experiments, which is consistent with the reports that amphiphilic copolymers are surface-active, and when these copolymers are blended with polymer matrix they may diffuse and accumulate to surfaces [Wesslen et al., 1994; Kim et al., 1994]. It seems that polysulfone is a rigid polymer and is not easy for migration or reorientation of polymer chains in PSf during contact with water. However, it has been reported that block copolymer architectures favor surface segregation of the relatively hydrophilic block copolymer, and, in a phase inversion process of surface segregation, PEO segments are driven to the PSf membrane surface by their solubility in the aqueous coagulant [Hancock et al., 2000]. Also, although the amphiphilic polymer migration may be mainly occurring during the PSf membrane fabrication step, PEO segments in the water contacting step after polysulfone membrane fabrication will form a re-extended chain conformation, allowing highly dynamic motions at the interface. That is, during water contact angle measurement, the hydrophilic chain segment can be reoriented into water from dried membrane surface state. However, during ESCA measurement within such a short time course, it is impossible for the entrapped hydrophobic chain segment to exist more on the surface layer than the hydrophilic segment to reduce surface free energy, as the surface free energy is not enough driving force to migrate the hydrophobic segments to the interface, as compared to the hot water used in the reorientation of PEO blocks for the membrane fabrication process. The change of oxygen atom compositions resulting from the reoriented PEO segments was significantly observed by ESCA depth profiling despite several artifacts in ion sputtering with ions [Robert and Joseph, 2002; Jeon et al., 1999]. Also, the entrapping of hydrophobic block into membrane matrix was confirmed, although the density of hydrophilic chain formed by phase inversion process was expected to be lower than the one by chemical grafting. In this study, the effect of sulfonated PEG on hydrophilicity was verified, allowing PEG segments to have highly dynamic motions and extended chain conformation at the water-material interface.

An understanding of the phase inversion process is important because it determines the structure of ultrathin membrane devices such as morphology, pore size, and density of copolymer, which affect its enhanced biocompatibilities [Kim et al., 1999]. In this lab, many experiments have attempted to control the asymmetric membrane morphology by adjusting the exchange rate of solvent and non-solvent [Kim et al., 1998], developing a process producing optimum wet phase inversion membranes consisting of PSf, PVP, PEG, and diblock copolymer. (Detailed data not shown) Especially, in order to obtain optimum molar ratio of hydrophilic monomer to hydrophobic monomer, we have attempted several model systems with polyurethanes, where the various chain lengths and molar ratio of PEG-SO3 containing acrylate copolymers have been characterized, leading to the results that the water-soluble copolymers were available with the molar ratio of above 7 : 3 [Lee et al., 2000]. It has been known that substantially an ultrathin skin layer (<1,000 nm) can be formed because of enhanced coagulation kinetics due to the extremely rapid dissociation of the solvent complex in the aqueous quench medium [Lee et al., 2000]. Also, a sponge-like sub-microstructure is formed as well by the process. Variations of the process parameters such as type of solvent, composition, temperature and evaporation time result in different microstructures [Park and Seo, 2002]. As this fabrication process is based on a macromixing rather than a micromixing, the observational error can result from aberrant mixed granule distribution. If a more advanced strategy in mixing could be used, the gap between the microscopic nature of polymers at interfaces and the macroscopic behavior of the experimental results could be reduced.

In summary, the novel system was shown with blood-contacting application with a more superior in situ fabrication concept, in which the biocompatibility by reorientation of diblock copolymer entrapped on an ultrathin surface was successfully achieved by using self-transformable fabrication process. Also, the structural and dynamical properties in terms of RDF were analyzed to probe interfacial structure properties at each copolymer density. MD simulations are an important complement to get a valuable insight into interfacial surface chemistry in a macroscopic experimental investigation. And the water clustering behavior from RDF can be used as a key tool for interpreting the interfacial chemistry. Better-simulated real time correlations would take cluster-cluster interactions into consideration. Further research into correlations between in vitro studies and in vivo results are also needed and appropriate animal models are essential for biomedical applications.

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