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# Possible Mechanism on Enhanced Blood Compatibility, Biostability, and Anticalcification of Sulfonated Polyethyleneoxide-Grafted Polyurethane†

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= Abstract = **To investigate the correlation between blood compatibility and biostability as well as the calcification-resistance of polymers, the surface of polyurethane (PU) was grafted with hydrophilic polyethyleneoxide (PEO), and further negatively charged sulfonate groups ($SO_3$) to produce PU-PEO1000 and PU-PEO1000-$SO_3$, respectively. PEO-$SO_3$ grafted PU surface showed great smoothness and high hydrophilicity. PU-PEO1000-$SO_3$ was much more blood compatible than untreated PU and PU-PEO1000 from the results of in vitro platelet adhesion test and blood clotting times and ex vivo occlusion times. After 6 months implantation in rats, the degree of surface cracking and calcification on explanted PUs was decreased in the following order: PU 〉 PU-PEO1000 〉 PU-PEO1000-$SO_3$, meaning that PU-PEO1000-$SO_3$ is most promising as a biostable and calcification-resistant polymer. It is suggested that the more blood compatible modified PUs are, the more biostable and calcification-resistant. Such superior blood compatibility, biostability, and anticalcification of PU-PEO1000-$SO_3$ might be attributed to the synergistic effect of nonadhesive and mobile PEO and negative sulfonate acid groups. Therefore, surface-modified PU-PEO-$SO_3$ is expected to be useful for blood/tissue contacting biomedical material.**

Key Words: *Polyurethane, Surface modification, PU-PEO-$SO_3$, Smoothness, Hydrophilicity, Blood compatibility, Biostability, Anticalcification*

## INTRODUCTION

Biomedical polymers for surgical implants require proper physical and mechanical properties, in vivo stability, nontoxicity, sterilizability and biocompatibility to maintain the long-term safety and performance of biomaterials implanted in the biological environment.

Polyurethanes (PUs) have been widely used in biomedical devices due to their superior physical properties and relatively good biocompatibility. However, the inherent thrombogenicity of PU remains a problem and limits greater widespread application (Lelah and Cooper 1986). Also, in vitro and in vivo degradation and calcification of PUs have been recently

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reported by many investigators (Marchant *et al.* 1988; Stokes and Davis 1987; Takahara *et al.* 1991).

In order to develop blood compatible polymers, much research has been carried out on the basis of several hypotheses such as negative surface charge, surface or interfacial free energy, pharmacologically active surface, and surface motion (Andrade *et al.* 1987). It was reported that polymers grafted with hydrophilic polyethyleneoxide (PEO) showed less protein adsorption and platelet adhesion to improve antithrombogenicity significantly (Mori *et al.* 1982). Many polymers containing negative charges, especially sulfonate groups, have also received much attention. Grasel and Cooper (1989) have prepared sulfonated PUs and pointed out that these anionic PUs exhibited the enhanced thromboresistance which might ascribe to increased fibrinogen adsorption and decreased platelet adhesion. Santerre *et al.* (1992) have described the high adsorption of fibrinogen on sulfonated PUs as well.

It is known that biostability is closely related to calcification in implanted polymers. Calcification defined as the deposition of calcium compounds such as either some calcium phosphate minerals consisting of hydroxyapatite or the calcium salts results in the loss of the flexibility of biomaterials, thereby causing their mechanical failure and degradation (Schoen *et al.* 1988). Although the failure of artificial blood pumps and heart valves, especially bioprosthetic valves is often caused by calcification, no clinically effective therapy to inhibit such a calcification is presently available. However, it is suggested that modification of synthetic elastomers such as PU is desirable for preventing calcification (Schoen *et al.* 1988).

In our previous studies, surface-modified PUs grafted by hydrophilic PEO (PU-PEO) and further sulfonated by propane sultone (PU-PEO-$SO_3$) have showed improved antithrombogenicity (Han *et al.* 1989b & 1991). In particular, PU-PEO-$SO_3$ exhibited excellent blood compatibility by means of a synergistic effect of the dynamic mobility of pendant PEO chains and electrical repulsion of negatively charged sulfonate groups ($SO_3$).

In this work, in vitro and ex vivo blood compatibility and in vivo rat subcutaneous implantation of modified PUs was performed to examine the relationship between blood compatibility with biostability and calcification, and particularly, to study a possible synergistic effect of PEO and sulfonate groups.

## MATERIALS AND METHODS

### 1. Materials

Polyurethane (PU) sheet and bead (Pellethane 2363-80AE, thickness 1mm; Dow Chemical Co.) and tubing (Royalthene R-380 PNAT, ID 1.5 mm, OD 2.0 mm; Uniroyal Chemical Co.) were used after being extracted with methanol for 24 hrs at room temperature. Hexamethylene diisocyanate (HMDI; Aldrich Chemical Co.) and 1, 3-propane sultone (PST; Aldrich Chemical Co.) were purified by distillation under reduced pressure. Polyethyleneoxide (PEO, MW:1000; Wako Pure Chemical Inc.) was dehydrated under vacuum at 50 °C overnight. Toluene was employed after being dried with sodium metal, and stannous octoate (28 % Sn; Sigma Chemical Co.) and other reagents were utilized as purchased without further purification.

### 2. Surface modification of PUs

The methods of surface modification of hydrophilic PU-PEO, and negatively charged PU-PEO-$SO_3$ have been previously described in detail (Han *et al.* 1989a & 1992). Fig. 1 illustrates the reaction scheme for surface modification of PUs.

The surface of the PU sheet was treated with HMDI to introduce free isocyanate (-NCO) groups in toluene with stannous octoate at 40 °C for 1 hr under nitrogen (PU-HMDI). Consecutively, the PU-HMDI was grafted with the PEO1000 in benzene with stannous octoate for 24 hrs at 40 °C to yield PU-PEO1000. The hydroxyl end groups of grafted PEO1000 chains were further sulfonated by PST via sodium alcoholate in a mixture of isopropanol, sodium

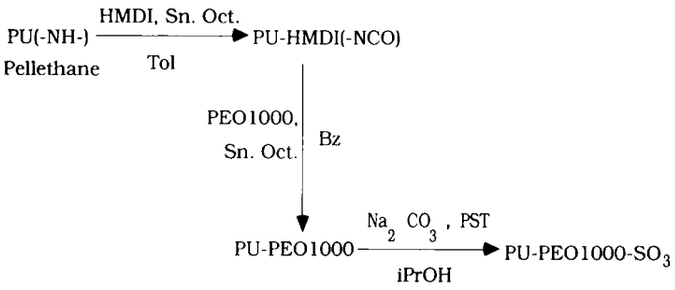


Fig. 1. Modification scheme of polyurethane surfaces.
HMDI = $OCN(CH_2)_6NCO$,
PEO1000 = $HO(CH_2CH_2O)_{22}H$,
PST = $(CH_2)_3SO_3$.

carbonate, and dimethyl sulfoxide for 20 hrs at 45 °C to produce PU-PEO1000-$SO_3$.

### 3. Surface characterization

The surface morphology of modified PUs was examined with a Hitachi S-510 scanning electron microscope (SEM) at an accelerating voltage of 15 kV. Samples were mounted and then sputter-coated with gold using an ion coater.

The dynamic advancing and receding contact angles of modified PU sheets were evaluated with a Wilhelmy plate contact angle apparatus (WET-TEK F100, Biomaterials Int.) in double-distilled water at constant temperature (20 °C) and humidity (30 % RH). The velocity of the translation stage was 20 mm/min.

### 4. In vitro blood compatibility

Platelet adhesion test was carried out with human platelet-rich plasma (PRP). Sample beads (2 g, 35 $cm^2$) were immersed in 4 ml of PRP and then mildly shaken for 1 hr at 37 °C. After the beads were withdrawn from PRP, adhered platelet number was counted using a Technicon H1 system (Technicon Instruments Corporation). Control sample without beads was incubated with PRP and used as a reference. Also, the platelet-adhered beads were rinsed with phosphate buffered saline (PBS), fixed with 2 % glutaraldehyde solution in PBS buffer for 2 hrs at room temperature, dehydrated with several dilutions of ethanol and water, and then lyophilized. The bead was coated with an evaporated gold layer and the morphology of adhered platelets was observed with SEM.

Activated partial thromboplastin time (APTT) was determined using the Fibrometer method (Mason *et al.* 1972). A sample sheet was incubated in 300 $\mu$l of control plasma (Control Plasma N, Behring Co., Germany) for 1 hr after which the plasma was separated. The partial thromboplastin (0.1 ml, Neothrombin) was preheated for 2 min and the obtained test plasma (0.1 ml, 37 °C) as mentioned above was added, followed by the addition of 0.025M $CaCl_2$ (0.1 ml) exactly 30 sec later. Then, the clotting time was measured using Fibrintimer (Behring Co.).

The determination of prothrombin time (PT) was conducted via one-stage prothrombin time method (Miale 1972). After treating the sheet in the same manner as in the APTT method, the mixture of 0.1 ml of thromboplastin (Sigma Chemical Co.) and 0.1 ml of 0.025M $CaCl_2$ solution was preheated to 37 °C. Test plasma (0.1 ml) was immediately added to the mixture and then the clotting time was measured using Fibrintimer.

### 5. Ex vivo blood compatibility

An arterio-arterial (A-A) shunt test (Nojiri *et al.* 1987), a new ex vivo model, was performed as the following: male rabbits (New Zealand White, 2-3 kg) were anesthetized with ketamine/urethane, and the right carotid arteries were carefully exposed surgically. Then, the modified PU tubings (2.0 mm OD x 1.5 mm ID, length 30 cm) equilibrated overnight with PBS were rinsed and carefully inserted into the clamped ligated carotid artery of the rabbit. The flow rate was controlled to 2.5 ml/min continuously using a suture tourniquet and measured with an ultrasonic flow meter (ES-4100Z, ARS Electric). The occlusion time was defined as the time that the blood flow decreases to zero.

### 6. In vivo biostability and calcification

An animal test was conducted by sub-

cutaneous implantation in male rats (60-80 g). A small intra-muscular pouch from the abdominal muscles was made and a 1 x 1 cm specimen sheet was inserted in the pouch. The skin incision was closed by suture. The rats were sacrificed at 6 months after implantation by an overdose of ketamine, and the implants were retrieved.

The surface morphology on explanted sheets was examined with energy dispersive analysis of X-ray (EDAX, Kevex Delta IV) having the quantum Si detector, coupled with a Hitachi 2500C SEM. Specimens were mounted and sputter-coated with carbon using an ion coater and observed at an accelerating voltage of 20 kV.

The quantitative analysis of calcium and phosphorus deposited on the sheets was carried out as follows: the retrieved sheets were slightly rinsed with deionized water and extracted individually with shaking for 5 days at 65 °C in 0.6N HCl of 5 ml. Then, these extract solutions were assayed by inductively coupled plasma atomic emission spectrometer (ICP, Plasmascan 710, Lattam Co.).

## RESULTS

The surface characteristics and blood compatibility of modified PUs have been described in detail elsewhere (Han *et al.* 1989a, b, 1991& 1992). Fig. 2 shows the surface morphology of modified PUs. The untreated PU surface was relatively smooth, while the PU-HMDI surface, reaction intermediate, was

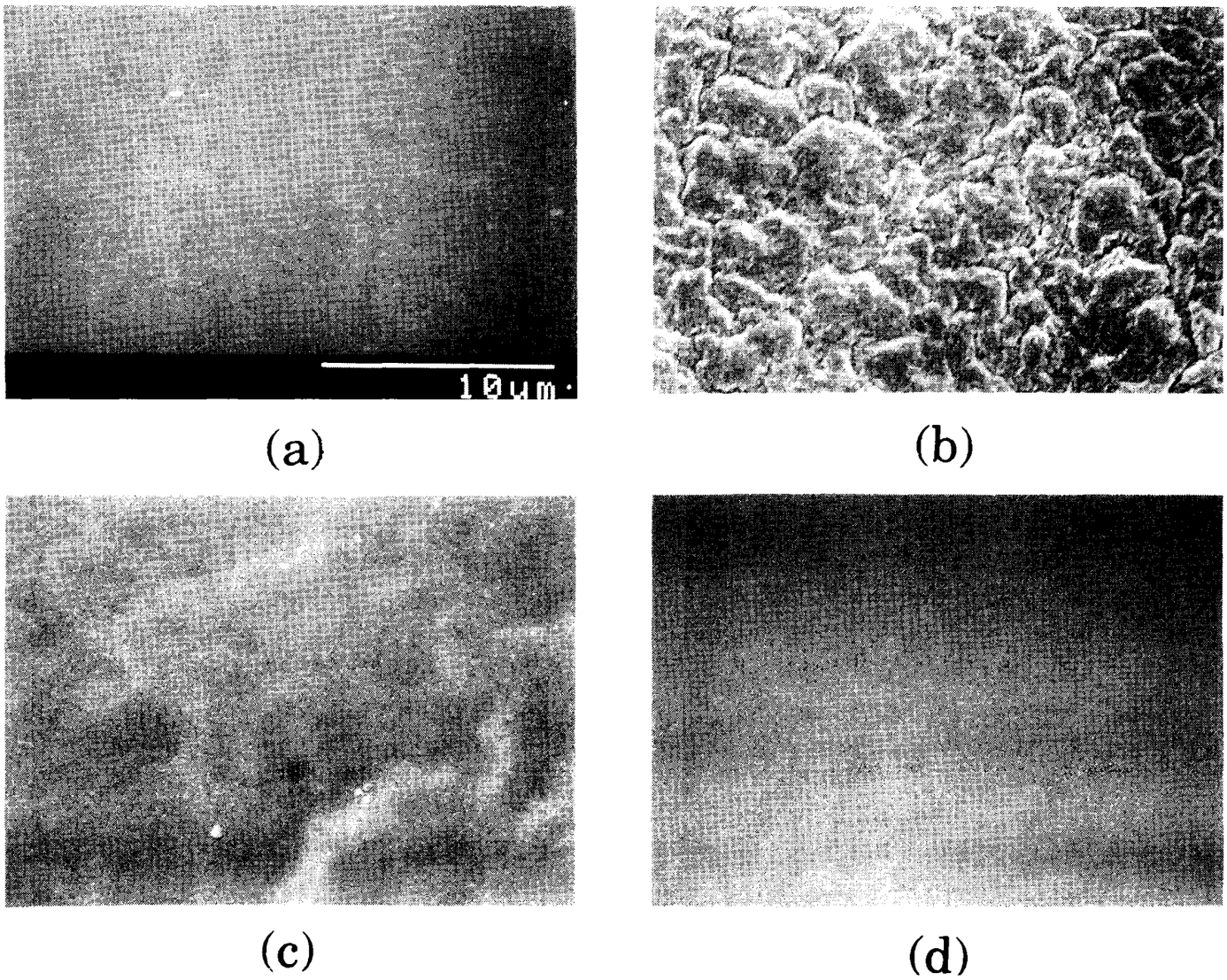


Fig. 2. SEM micrographs of modified PU surfaces : (a) PU, (b) PU-HMDI, (c) PU-PEO1000, (d) PU-PEO1000-$SO_3$.

not. However, the surface of PU-PEO1000 was fairly smooth and especially, that of PU-PEO1000-$SO_3$ showed high smoothness and homogeneity. As shown in Table 1, PEO1000 grafted PU showed lower receding angle (more hydrophilized surface) than untreated PU. In addition, PU-PEO1000-$SO_3$ surface exhibited complete wetting behavior which represents a much higher hydrophilic surface on account of negatively charged $SO_3$ groups. Such a PU-PEO1000 -$SO_3$ is thought to show a more favorable response to blood.

**Table 1.** Surface wettability and blood compatibility of modified PUs

| Material | Contact angle in water | | In vitro(sec) clotting time | | Ex vivo(min) A-A shunt |
|---|---|---|---|---|---|
| | $\theta$adv | $\theta$rec | APTT | PT | occlusion time |
| PU | 86 | 41 | 35.8 | 13.3 | 50 |
| PU-PEO1000 | 40 | 15 | 34.5 | 14.5 | 140 |
| PU-PEO1000-$SO_3$ | 45 | wet | 45.5 | 14.9 | 360 |

Fig. 3 shows the effect of modified PU surfaces on platelet adhesion. PEO grafted PU displayed less platelet adhesion than untreated PU. Moreover, PU-PEO1000-$SO_3$ exhibited a much lower degree of platelet adhesion compared to other PUs, demonstrating that PU-PEO1000-$SO_3$ may be the most blood compatible. The morphology of adhered platelets onto modified PU surfaces is shown in Fig. 4. It was found from SEM observation that PU-PEO1000-$SO_3$ showed the least adhesion and activation of platelets, which is consistent with the above results by platelet counting (Fig. 3).

Table 1 also lists the blood compatibility data of modified PUs. The APTT and PT, especially APTT, of sulfonated PEO1000-grafted PU were extended, while those of PU-PEO1000 did not show any significant change compared to untreated PU. This can be explained by an anticoagulant activity of grafted $SO_3$ groups, as reported in other sulfonated polymers (Jozefonvicz and Jozefowicz 1990).

As shown in Table 1, the ex vivo A-A shunt occlusion time of PU was just 50 min, but that

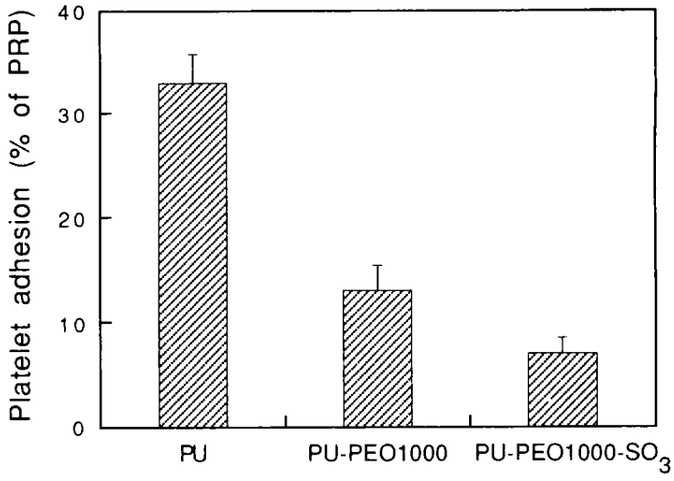


**Fig. 3.** Effect of modified PU surfaces on platelet adhesion (mean ± SD, n = 3).

of PEO1000 grafted PU was extended to 140 min. Furthermore, the occlusion time of PU-PEO1000-$SO_3$ was 360 min, indicating a synergistic effect of the hydrophilic PEO and negatively charged $SO_3$ groups. These occlusion time results agree with in vitro platelet adhesion and blood clotting time data: the less platelet adhesion and activation and the longer the APTT and PT, the more extended the ex vivo occlusion time.

Fig. 5 shows SEM photographs of modified PUs implanted for 6 months in rats. More extensive surface cracks were revealed on PU surface and these cracks were considerably covered all over the surface. The degree of crack formation after 6 months implantation decreased in the following order: PU 〉 PU-PEO1000 〉 PU-PEO1000-$SO_3$. It is suggested that PU-PEO1000-$SO_3$ has the least extent of cracks relative to other PUs.

The relationship between ex vivo A-A shunt occlusion time and in vivo calcification after 6 months implantation on modified PUs is illustrated in Fig. 6. The deposition amount of calcium decreased in the following order: PU 〉 PU-PEO1000 〉 PU-PEO1000-$SO_3$. This result also means that PU-PEO1000-$SO_3$ is the most calcification-resistant. Accordingly, from results of Fig. 6, the occlusion time is in inverse proportion to the amount of calcium deposition: the more blood compatibility in modified PUs,

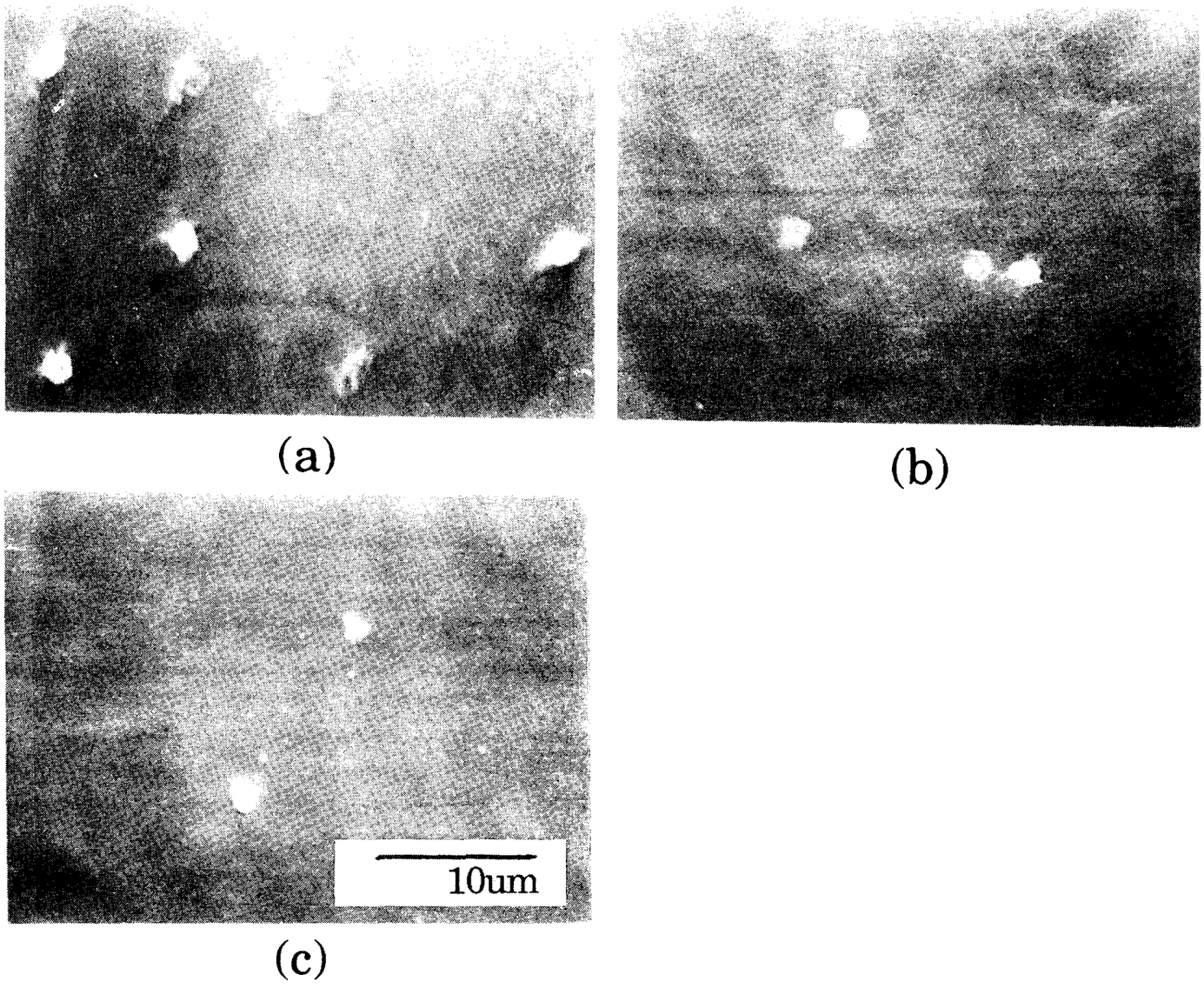


Fig. 4. SEM micrographs of platelet adhesion on modified PU surfaces : (a) PU, (b) PU-PEO1000, (c) PU-PEO1000-$SO_3$.

the more biostability and anticalcification.

## DISCUSSION

### 1. Blood compatibility of PU-PEO1000-$SO_3$

The introduction of sulfonate groups at the end of the PEO chain grafted onto a PU surface, such as PU-PEO-$SO_3$, enhanced blood compatibility enormously. It is thought that this result is ascribed to the synergistic effect of the hydrophilic and mobile PEO and negatively charged $SO_3$ groups, as can be explained by the "negative cilia" model as shown in Fig. 7 (Han *et al.* 1991).

In this model, the possible blood-material interactions are as follows; the hydrated flexible PEO chain motion suppresses protein adsorption and platelet adhesion, where the PEO chain motion might be increased by the electric repulsion between negative sulfonated end groups ($SO_3$). In addition, the sulfonated end groups of the PEO chain expel blood components including platelets further by electric repulsion, and moreover the sulfonate groups contribute to better blood compatibility by inhibiting blood coagulation factors.

Besides, PU-PEO-$SO_3$ exhibited the smoothest surface, and the hydrated water structure at the interface may be changed due to the hydrophilic PEO and the negative and wettable

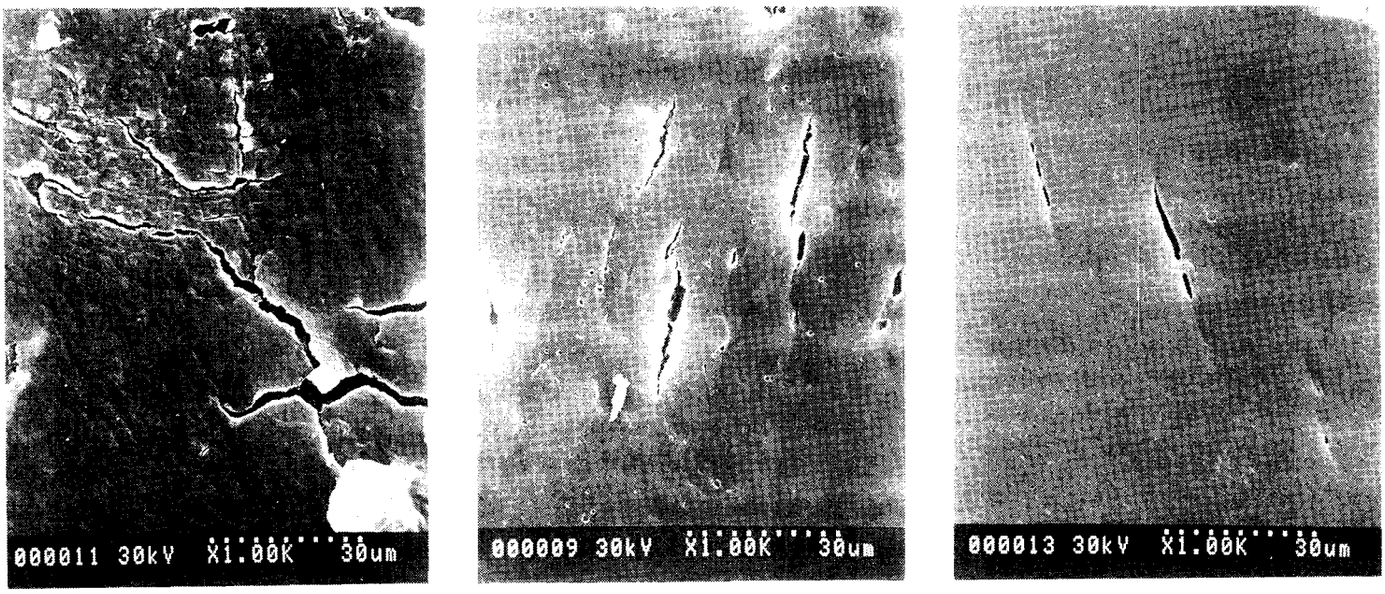


Fig. 5. SEM micrographs of modified PU surfaces implanted for 6 months in rats : (a) PU, (b) PU-PEO1000, (c) PU-PEO1000-$SO_3$.

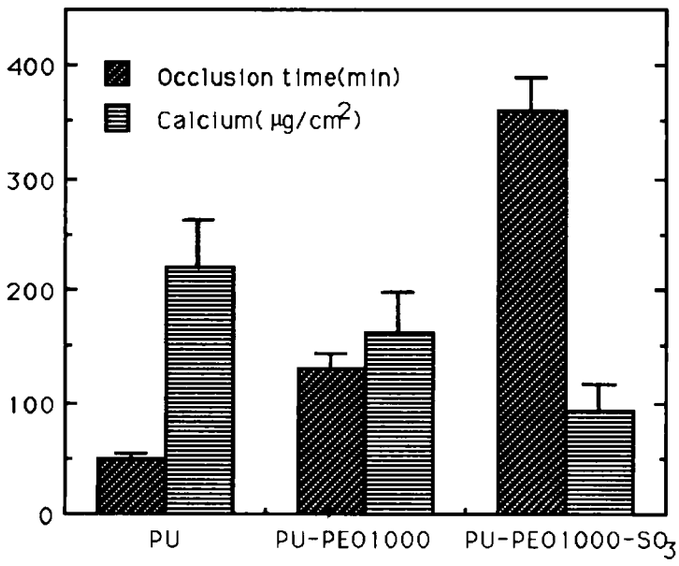


Fig. 6. Comparison between ex vivo A-A shunt occlusion time and in vivo calcium contents after 6 months implant of modified PUs.

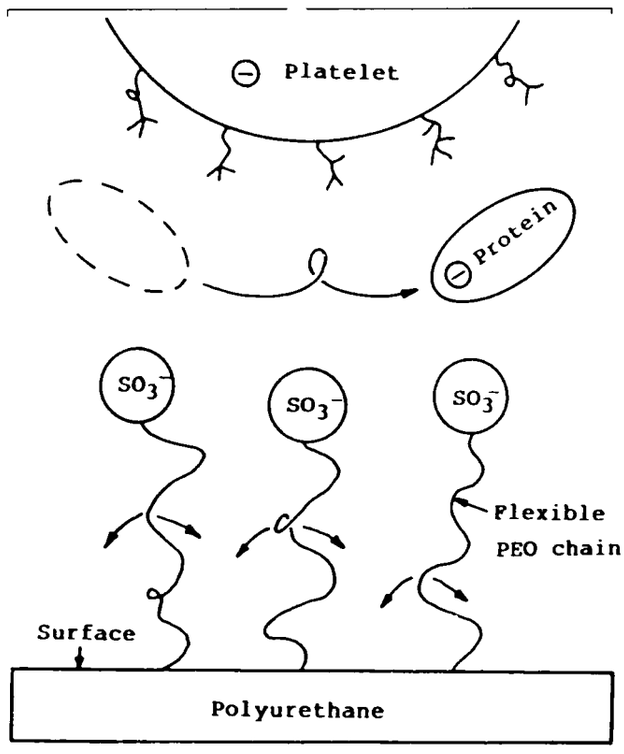


Fig. 7. "Negative cilia" model on PU-PEO-$SO_3$ system.

grafted $SO_3$ groups, that might also be responsible for improved blood compatibility.

## 2. Biostability of PU-PEO1000-$SO_3$

In general, cracks produced in implanted materials have been known to act as initiation sites for thrombus formation or calcification so that they enfeeble the material, then ultimately result in degradation. Therefore, recent investigations have drawn much attention to preventing the degradation of implanted polymers

including PUs.

The exact mechanism for crack formation has not been well established. However, various hypotheses on the degradation of polymers have been suggested based on the results of experiments: a) oxidation by metal ions, oxygen and hydrogen peroxide (Phillips and Thoma 1987; Takahara *et al.* 1991a), b) hydrolysis by lysosomal enzymes (Takahara *et al.* 1992b), c) environmental stress cracking (Stokes and Davis 1987), d) leaching out of additives and low molecular weight fractions (Ratner 1983), and e) calcification by calcium deposition (Schoen *et al.* 1988).

It was found that the surface of PU-PEO1000-$SO_3$ is the most biostable to show less crack formation (Fig. 5). The possible mechanism of biostability on PEO-$SO_3$ grafted PU may be thought of as follows: first, the surface has good smoothness and homogeneity, which can suppress the formation of surface crack by least defect. Second, the nonadhesive property of PEO decreases the adsorption and activation of phagocytic cells by its mobility. Also, the highly hydrophilic nature of the sulfonated PEO surface provides for rapid and firm hydration, thereby surrounding the surface with water and reducing the reaction of the tissue with foreign materials.

### 3. Anticalcification of PU-PEO1000-$SO_3$

It is known that most implanted medical devices lead to calcification. Such a calcification associated with biomaterials occurs very often in bioprosthetic heart valves, aortic homografts, polymeric blood pumps, and trileaflet valves, and also frequently in mechanical heart valves, vascular grafts, and subcutaneous implanted materials in rodents (Levy *et al.* 1991; Schoen *et al.* 1988). Therefore, in order to be utilized in modified PUs with long-term stability for artificial organs, especially the cardiovascular system of the artificial heart and its valves, the features of anticalcification as well as blood compatibility in the implants are demanded.

PU-PEO1000-$SO_3$ exhibited the least degree of calcification among PU implants probably due to the synergistic and cooperative effects of PEO and sulfonate groups. For PEO, a long side chain of PEO is grafted to the main PU backbone (as PU-PEO1000) and then it is more flexible and mobile enough to possibly reduce the calcium deposition on the surface. For sulfonated groups, grafted sulfonate acid groups ($SO_3^-$) cause lower local pH, resulting in dissolving deposited calcium compounds, thus inhibiting calcification.

In addition to each characteristic of PEO and sulfonate groups, the synergistic effects of them could be taken into consideration in anticalcification behavior. The excellent surface smoothness and homogeneity of PU-PEO1000-$SO_3$ result in the suppression of crack formation, thus preventing calcification. PEO-$SO_3$ grafted on PU surface might acts as diphosphonates (Fieisch 1989), a synthetic inhibitor of calcification and also acts as detergents (Jones *et al.* 1988) like sodium dodecyl sulfate (SDS), which have superior wetting and dispersing properties. In addition, its high hydrophilicity might cause a change in water structure hydrated at the interface and then reduce material-tissue interactions. Furthermore, as mentioned above, blood compatibility by synergistic effect of hydrophilic mobile PEO and negatively charged sulfonate groups might contribute to reduced calcification.

In summary, from the results of blood compatibility, biostability and calcification for several surface-modified PUs, the blood compatibility of the polymer was closely related to its biostability and calcification: the more blood compatible modified PUs are, the more biostable and calcification-resistant. To clarify further the mechanism of polymer-associated blood compatibility, biostability and calcification and to investigate the correlation among them, in vivo animal tests for total artificial heart (TAH), its polymer valves, and vascular graft system are in progress.

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