Transactions of the Materials Research Society of Japan. Vol. 20

Synthesis of Novel Aromatic Polyimide for Biomaterials

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The authors have synthesized fluorinated polyimides derived from 2, 2'-bis(3,4-dicarboxyphenyl)hexafluoropropane dianhydride (6FDA) and aromatic diamines to develop novel biomaterials. The polyimides were all soluble in polar solvents. For the evaluation of *in vitro* blood compatibility, the platelet adhesion and the plasma protein adsorption on polyimide membranes were measured by an amino acid analyzer and observed by using scanning electron microscopy. The amount of plasma protein absorbed on the membranes was approximately 0.3 - 0.4 ($\mu g/cm^2$), which was 1/4 less than the value measured in polydimethylsiloxane (PDMS). The deformation and aggregation of platelets adhered on the polyimides were not observed, while the surface of PDMS was found to be fully covered with spread and aggregated platelets. For *in vivo* evaluation, the polymers were implanted in the femoral vein of the mongrel dog for 7 days. Thrombus formation and fibrins were found on the surface of PDMS. The formation, however, was not observed on the polyimides.

1. INTRODUCTION

The designs of the surface with blood compatibility are one of the most important terms in biomaterial science. Many efforts have been directed toward modifications of the polymer surface such as hydrophilicity, hydrophobicity, microdomain structure, and steric hinderance by polymer chain. The successful design of surface intended for use as biomaterials is to bind the antithrombo-genic substance such as heparin onto the polymer surface.

We describe herein a novel biomedical polymer, which is derived from 6FDA dianhydride and aromatic diamines. The interactions between the surfaces of polyimides and platelet-rich and platelet-poor plasma are discussed. *In vivo* experiment for evaluation of blood compatibility has been carried out by insertion of the polymer into the peripheral vein.

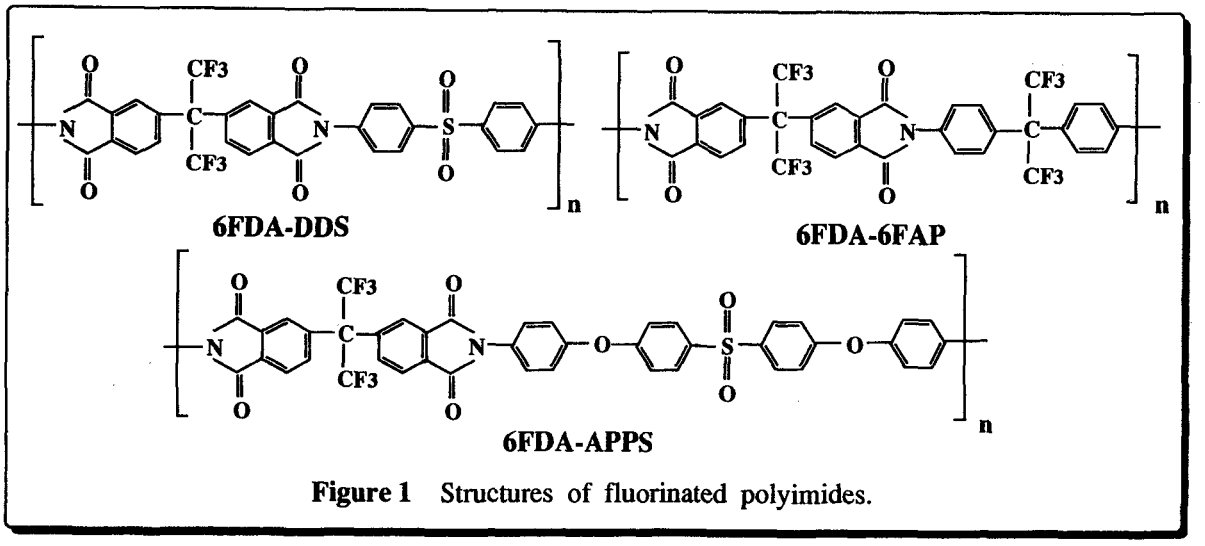

Figure 1 Structures of fluorinated polyimides.

Table 1
Characteristics of Fluorinated Polyimides

Polyimide	Mw	Mw/Mn	Tg (℃)	Contact Angle against Water (deg.)
6FDA-DDS	44700	1.5	325	93
6FDA-APPS	64800	1.4	267	96
6FDA-6FAP	92000	1.1	320	93

2. EXPERIMENT

2.1. Syntheses of 6FDA Polyimides

Fluorinated polyimides have been synthesized with a chemical imidization of the poly(amic acid) precursors.[1-4] The poly(amic acid)s derived from 2, 2'-bis(3,4-dicarboxyphenyl)hexafluoropropane dianhydride (6FDA) and aromatic diamines were prepared by solution condensation polymerization and were converted into the corresponding polyimides by a chemical imidization with seven-equimolar of acetic anhydride and triethylamine. The diamine monomers used were 3,3'-diaminodiphenylsulfone (DDS), bis[4-(4-aminophenoxy)phenyl]sulfone (APPS), and 2,2'-bis(4-aminophenyl)hexafluoropropane (6FAP)). The structures of fluorinated polyimides are presented in Figure 1.

2.2. Characteristics of Polyimides

The molecular weights (Mw and Mn) of the polyimides were determined by gel-permeation chromatography (detector: Jasco 830-RI monitor) with tetrahydrofuran as the solvent. The glass transition temperature (Tg) was determined by differential scanning calorimetry (DSC: Seiko DSC200, SSC/5200H). The surfaces of polyimides were characterized by a contact angle measurement using a drop of water.

The results of characteristics of the polyimides are listed in Table 1. The polyimides had a narrow molecular weight distribution (Mw/Mn) and showed a hydrophobicity.

2.3. *In Vitro* and *In Vivo* Experiment

The blood was withdrawn from the carotid of a mongrel dog into the siliconized glass tube containing 3.8 % trisodium citrate aqueous solution. Platelet rich plasma (PRP) and platelet poor plasma (PPP) were prepared from the blood by centrifugation. The platelet counts (approximately $2x10^5$ /μL) in PRP were adjusted by diluting the PRP with the PPP and determined by a coulter counter (Coulter Electronics Inc.).The polyimides and polydimethylsiloxane (PDMS)[5] membranes were soaked in PRP suspension and incubated at 37 ℃ for 2 hours. After being rinsed with a phosphate buffered saline, the sample membranes were fixed with 3 % glutaraldehyde saline solution for 2 days. The morphological deformation of platelet adhesion on the membranes were observed by scanning electron microscopy (SEM: JEOL JXP-6100P), and the amounts of adhered platelet and adsorbed plasma protein were measured by an amino acid analyzer (HITACHI 835). The amount of adhered platelet was expressed by the platelet protein adhered on

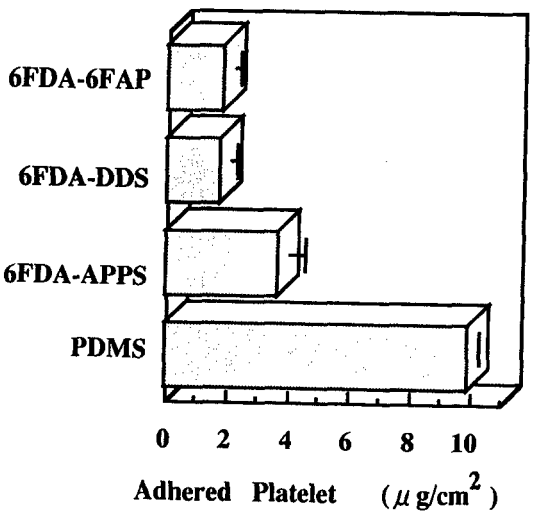

Figure 2 The amount of platelet adhered on polymer membranes. (Mean± S.D., n=3)

substrate ($\mu g/cm^2$), because a close correlation between them has been clarified.[6]

In vivo experiment was carried out by method as reported in the literatures.[7,8] The polyimides and PDMS tubes were implanted in the femoral vein of the mongrel dog for 7 days. The structure and cross section of the implanted specimens were observed by SEM.

3. RESULTS AND DISCUSSION

Figure 2 presents the amount of platelet adhered on 6FDA-6FAP, 6FDA-DDS, 6FDA-APPS and PDMS after contact with PRP for 2 hours. The amount of platelet adhered on the surface of fluorinated polyimides was effectively reduced as compared with those measured on PDMS surface. Although the number of platelets adhered on 6FDA-APPS was slightly enhanced than the values obtained of 6FDA-6FAP or 6FDA-DDS, these fluorinated polyimides showed the excellent *in vitro* blood compatibility.

Figure 3 presents the scanning electron micrograph of platelet adhered onto 6FDA-DDS and PDMS. Surface of PDMS was found to be fully covered with spread and aggregated platelets (Figure 3 (a)). Formation of pseudoponds was clearly visible and the platelets were activated. On the other hand, adhered platelets on the surface of 6FDA-DDS were isolated, without aggregation and showed no morphology changes (Figure 3 (b)). It is well known that aggregation and deformation of platelet adhesion on surface play a major role in the in vivo initiation of thrombus formation on foreign surfaces. However, it is also important to elucidate the interaction between the polymer surface and the plasma proteins, because the adsorption of plasma protein as fibrinogen governs the adhesion of platelet to polymer surface and is a contributor to thrombosis.

Figure 4 shows the amount of plasma

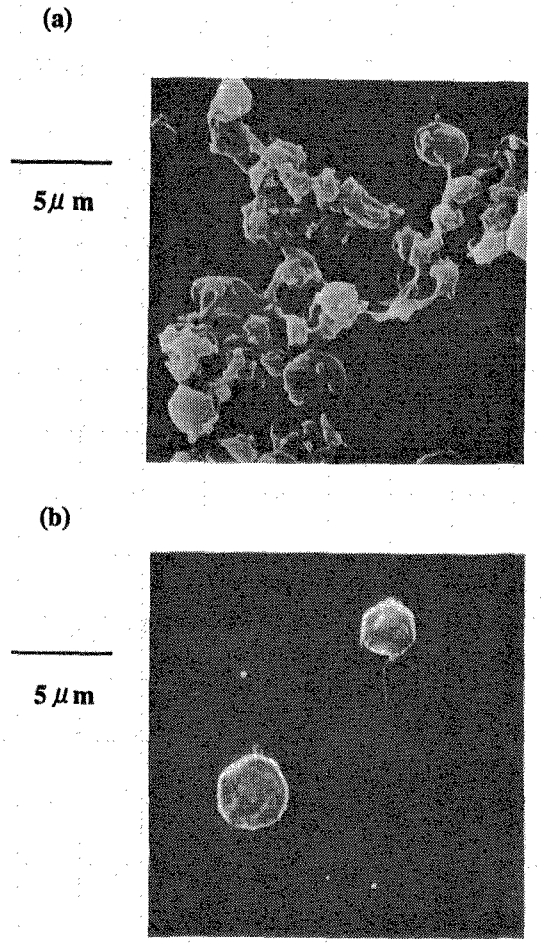

Figure 3 Scanning electron micrographs of platelet on (a) PDMS and (b) 6FDA-APPS (Magnification: x 3500)

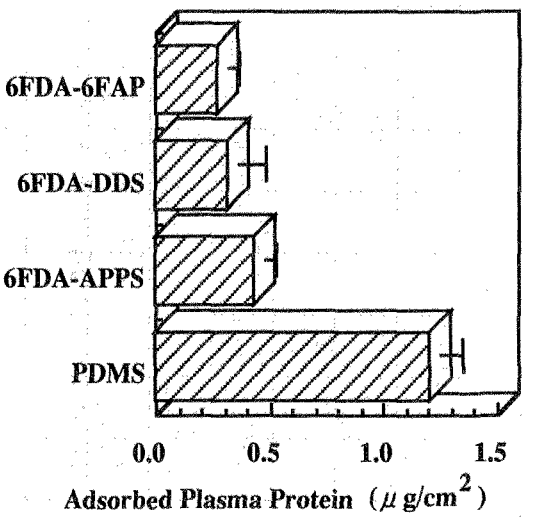

Figure 4 The amount of plasma protein adsorbed on polymer membranes . (Mean±S.D. , n=3)

protein adsorbed onto the polyimides after contact with PPP for 2 hours. The polyimides leaded to a marked decrease of plasma protein adsorption and showed the protein adsorption of 0.3 - 0.4 ($\mu g/cm^2$), which was 1/4 less than the values measured in PDMS. It may be considered that this decrease of plasma protein on the polyimides depresses the facilitation of platelet adhesion and activation.

Figure 5 presents the result of *in vivo* evaluation to the 6FDA-APPS polyimide, which was implanted in the femoral vein of the mongrel dog for 7 days. Red thrombus formation incorporating red blood corpuscles and fibrins were found on the surface of PDMS. However, no thrombus formation and fibrin precipitation were not observed on the polyimide, as shown in Figure 5.

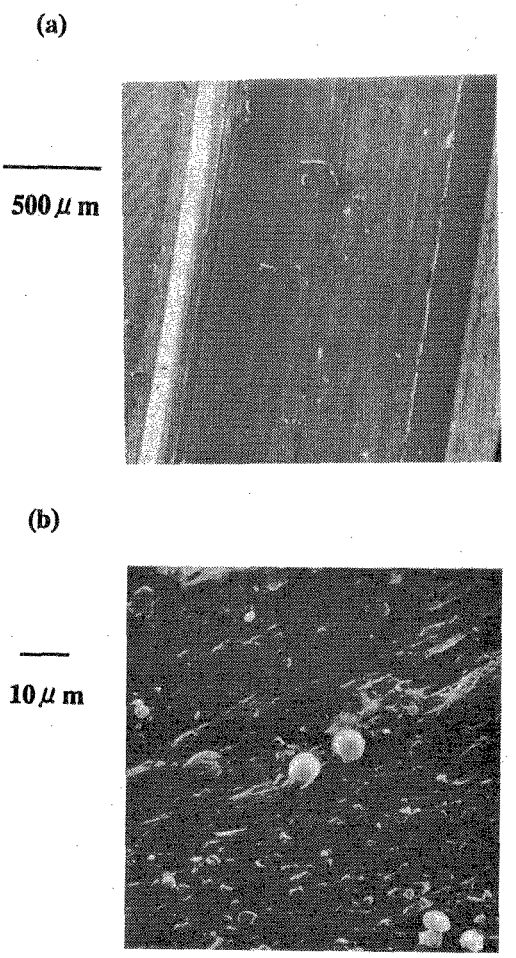

Figure 5 Scanning electron micrographs of blood components on 6FDA-APPS
(a) x 35 (b) x 1000

4. CONCLUSIONS

Fluorinated polyimides were synthesized and evaluated in *in vitro* and *in vivo* experiment for development of novel biomaterial. The polyimides showed good blood compatibility in *in vitro* evaluation by suppressing platelet adhesion and activation. Thrombus formation and fibrin precipitation were not also observed on the polyimides, which were implanted in the femoral vein of the mongrel dog for 7 days. These results indicate that the fluorinated polyimides are promising polymer for biomaterial. It should be noted, however, that our *in vitro* and *in vivo* analyses do not provide conclusive evidence for the effect of the chemical structure of polyimides on the blood compatibility. Our future study will be concentrated on a good understanding of the interactions between the physicochemical structure of polyimides and the plasma proteins and cellulars.

5. REFERENCES

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