Effects of a Polymeric Additive in a Biomedical Poly(ether urethaneurea)

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SYNOPSIS

The biomedical poly(ether urethaneurea) Biomer has previously been shown to contain a standard antioxidant and a polymethacrylate additive with surface active properties. In the present communication, the latter additive has been shown to influence the morphology, mechanical properties, and surface chemistry of a poly(ether urethaneurea) with a composition similar to Biomer. It was shown that the *in vitro* blood compatibility of the poly(ether urethaneurea) was improved and that adsorption of fibrinogen from blood plasma decreased significantly due to the presence of the surface active polymethacrylate additive.

INTRODUCTION

Polymers are commonly used as materials for biomedical devices. It has been recognized that the polymers interact with living tissue and that severe body reactions can occur on implantation of plastic materials.[1] Acute and chronic inflammations in soft tissue are common. In blood contacting devices, polymeric materials induce blood clotting and cannot be used without systemic anticoagulants.[2] Research in the area of blood compatible materials is highly focused on the surface properties of synthetic polymers. It is well known that a foreign material when contacted with blood adsorbs within seconds a layer of blood proteins. The nature of the adsorbed protein layer is believed to influence the succeeding blood coagulation events, i.e., the surface can be either passivated or activated for blood clotting.[2] Different hypotheses have been put forward to explain the behavior of synthetic materials in relation to blood coagulation.[3-7] On the one hand, it is believed that hydrophilic surfaces will show less overall protein adsorption than will hydrophobic ones and, thus, will be less thrombogenic.[3] On the other hand, certain hydrophobic surfaces are believed to preferentially adsorb albumin, which passivates the surface for further interactions with the blood components.[8-10]

Linear poly(ether urethanes) and poly(ether urethaneureas) have excellent mechanical properties and relatively good blood compatibility. The reason for their blood compatibility is unclear. It has been suggested that the phase-separated morphology of the surface, i.e., the pattern of soft polyether domains and hard urethane or urea domains, would have influence on blood compatibility. Many studies have been carried out along these lines.[4-6,10]

Biomer is a biomedical grade poly(ether urethaneurea) manufactured by Ethicon, a subsidiary of Johnson & Johnson. The material is commonly used as a material for blood-contacting devices.[11] According to a report by Belisle et al.,[12] the monomers of Biomer are identified as 4,4′-methylene bis(phenyl isocyanate), poly(tetramethylene ether) glycol 1800, and ethylene diamine. In addition to the base poly(ether urethaneurea), Biomer was found to contain a standard antioxidant and a polymethacrylate additive, identified as poly(diisopropylaminoethyl methacrylate-*co*-decyl methacrylate).[12,13] In the present paper, we report on the effects of the latter additive on the properties of a poly(ether urethaneurea) with a composition similar to Biomer.

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EXPERIMENTAL

Equipment

Tensile testing was performed with film specimens (10 × 100 × 0.5 mm) at ambient temperature using a JJ Instruments T30K tensile testing machine. Dynamic mechanical measurements were made at 1 Hz with a Brabender Torsionautomat, Lonza system, using film specimens (10 × 50 mm) with thicknesses ranging from 0.8 to 2.1 mm. An AEI ES200B spectrometer was used for recording the ESCA spectra. SEM micrographs were obtained by using an ISI 100 instrument.

Polymer Materials

Two solutions in dimethyl acetamide of a poly(ether urethaneurea) (20% w/w) were provided by E. I. Du Pont de Nemours & Co. The poly(ether urethaneurea) was prepared from poly(tetramethylene ether)glycol (PTMG, M_w = 2000) and 4,4'-methylene bis(phenyl isocyanate) (MDI, capping ratio 1.6), and chain-extended with ethylene diamine (EDA).[14] The composition of the polymer was similar to that of Biomer.[14] One solution, designated PUUR, contained 0.5% w/w (based on dry polymer) of a standard antioxidant (Santowhite powder). The other solution, designated PUUR-A, contained a polymeric antifume additive (5% w/w based on dry polymer) in addition to the antioxidant. The antifume agent, Methacrol 2138F, is a methacrylic copolymer, i.e., poly(diisopropylaminoethyl methacrylate-*co*-decyl methacrylate), similar to that reported for Biomer.[12-14]

Pellets of a commercial poly(ether urethane), Pellethane 2363-80AE (Dow Chemical), was dissolved to a 10% solution at room temperature in dimethylformamide (Merck, *p.a.*) and kept at +4°C overnight before filtering through a 10 μm TEFLON† filter. A solution of Biomer was obtained from Johnson & Johnson, Stockholm, Sweden.

Film Preparation

Films used for tensile and dynamic mechanical testing were prepared by casting successive layers of polymer on clean glass plates from solutions diluted to 10%. The material was allowed to dry at 60°C for 24 h between castings. Final drying was done at 60°C for 24 h in air, followed by 24 h at 60°C in a vacuum oven. Films used for surface analyses were cast (single layer) on ultraclean glass plates and dried at 60°C for 24 h followed by curing at 60°C in a vacuum oven for 24 h. All surface analyses were made using the air-facing side of the films.

Contact Angle Measurements

Advancing and receding contact angles were determined from photographs taken from drops of doubly distilled water positioned on the polymer surface. The sizes of the drops could be increased (advancing angles) and decreased (receding angles) by a motor-driven syringe.

Blood and Antiserum

Citrated blood from one apparently healthy blood donor was centrifuged at 1500 g for 20 min and the collected plasma was stored at −80°C until use. Antisera for albumin and fibrinogen were obtained from Orion Diagnostica, Finland, and Dakopatts, Denmark, respectively. The antisera were used without further purification, diluted 1/20.

Blood Coagulation Tests

Thoroughly cleaned test tubes (10 × 70 mm) were coated by a single layer of polymer, dried, and cured as described above. To each tube, 0.25 mL of citrate-buffered human whole blood and 0.05 mL 0.1*M* $CaCl_2$ solution were added. The time for formation of a dense clot in the tube was measured. Clotting times reported are mean values for five measurements. The tests were performed at 37°C under agitation.

Platelet Adhesion

Film samples (diameter 10 mm) were contacted with citrated human whole blood at 37°C for 10 min. The samples were then treated for 2 h with a 2.5% solution of glutaraldehyde and rinsed thoroughly with a phosphate buffer solution (pH 7.2). The samples were then dehydrated by successive immersions in ethanol–H_2O solutions with increasing ethanol content, followed by immersion in ethanol/FREON12.‡ After 24 h in refrigerated FREON, the samples were dried by critical point drying with CO_2. The samples were analyzed by scanning electron microscopy (SEM) after sputtering with Pd/Au. The total number of adhering platelets/mm^2 was determined from micrographs obtained at a magnification of 400×.

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Ellipsometry

The polymers were deposited onto 0.2 mm-thick, polished silicon wafers from Wacker Chemie, Münich, Germany. The silicon wafers were washed in NH_4OH (25%), H_2O_2 (30%), and H_2O (1 : 1 : 5) at 80°C for 5 min, rinsed in deionized water, washed in HCl (37%), H_2O_2 (30%), and H_2O (1 : 1 : 6) at 80°C for 5 min, and rinsed in deionized water. The surfaces were dried in flowing N_2 and, finally, in an oven at 60°C. The clean wafers were transferred into a solution containing 1% by wt polymer dissolved in dimethylformamide. After 1 min of deposition time, the surfaces were dried in air at 50°C.

The thickness of the polymer layers were measured in air with an automatic AutoEll 2 Rudolph Research ellipsometer (λ = 632.8 nm, angle of incidence 70°) and found to vary between 100 Å and 700 Å. The adsorbed amount of organic material was calculated from ellipsometric data according to the method described in Ref. 15. Prior to plasma incubations, the samples were stored in 0.01 *M* phosphate-buffered saline (PBS) at pH 7.4 overnight. The wafers were transferred without delay into an ellipsometer glass cuvette filled with the PBS. The buffer was pumped out and citrated human plasma diluted to 10% in the PBS was immediately injected into the cuvette. After 10 min of incubation at room conditions, the plasma was pumped out and the cuvette was rinsed five times using the PBS, followed by injection of antisera diluted 1/20 in PBS. After 15 min, the cuvette was finally rinsed five times in PBS. After each procedure, the amount of adsorbed organic material was measured using the two-zone ellipsometer algoritm *in situ*. First, the thickness of the polymer film was determined in PBS. In the same spot, the thickness of polymer + total amount of adsorbed plasma was measured and, finally, the thickness of polymer + plasma + antisera was measured without moving the surface. Throughout the procedure, the refractive index n = 1.465 was assumed for both the polymer and adsorbed organic materia. The ambient refractive index used in aqueous solutions was 1.333.

RESULTS AND DISCUSSION

The polymethacrylate used as an additive in Biomer is basically a linear copolymer of isopropylaminoethyl methacrylate and decyl methacrylate.[12-14] In the present investigation, an additive with similar composition, Methacrol 2138F, was used. The polymer is not readily soluble in dimethylacetamide (DMAc), and when added to a DMAc solution of a poly(ether urethaneurea) phase separation occurs. Polymer films cast from such a solution become hazy due to the presence of the additive. The lack of compatibility of Methacrol 2138F with a poly(ether urethaneurea) has previously been noted by Wu et al.[14b] Tyler et al.[16] recently reported on significant differences in surface composition of two lots of Biomer, which were attributed to the presence of different amounts of the additive mentioned above.

In the present investigation, solutions in DMAc of a poly(ether urethaneurea) with a composition similar to Biomer were investigated. The material designated PUUR consisted of the pure poly(ether urethaneurea). PUUR-A also contained 5% of the Methacrol additive, based on the dry weight of the poly(ether urethaneurea).

The mechanical properties of the poly(ether urethaneurea) were affected to a certain extent by the Methacrol additive. At low strains, the stress–strain curves for PUUR and PUUR-A were identical within the limits of error (Fig. 1). However, at strains greater than 300%, PUUR-A was found to be stiffer than the material without the additive. The dynamic mechanical properties, as investigated by torsional pendulum measurements at 1 Hz on film specimens, were also found to be different. Similarly to Biomer [Fig. 2(A)], the material containing the additive (PUUR-A) exhibited an additional relaxation peak in the tan δ curve at approximately 25°C [Fig. 2(B)]. Since this peak was not present in the base polymer [Fig. 2(C)], it can unequivocally be ascribed to the presence of the additive. The extra relaxation peak has previously been observed in Biomer, but was not assigned to any

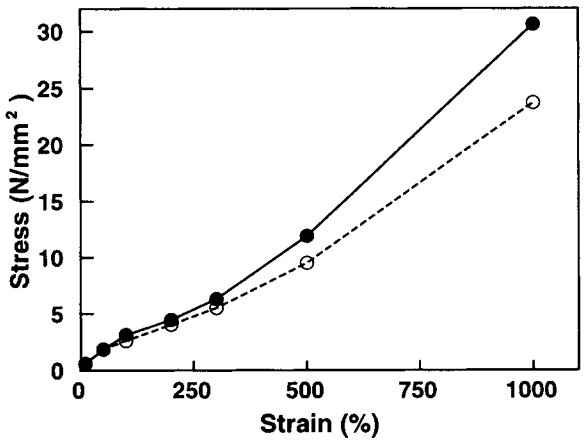

Figure 1 Stress–strain curves for (open circles) PUUR and (filled circles) PUUR-A. Crosshead speed: 50 mm/min.

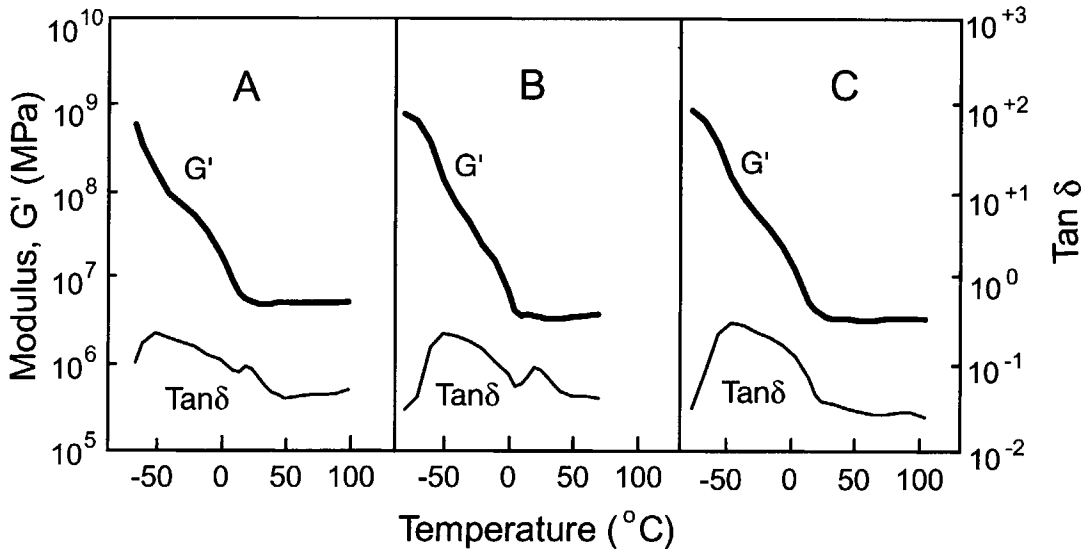

Figure 2 Torsional pendelum measurements at 1 Hz for (A) Biomer, (B) PUUR-A, and (C) PUUR. Heavy line, storage modulus G', thin line, loss tangent (tan δ).

particular structure.[17] The presence of a silicone impurity or a silicone processing aid has been noted,[10,18] but this has not been confirmed by Belisle et al.[12]

As mentioned above, the Methacrol additive contains tertiary amino groups. These groups can take part in hydrogen bonding with the urea blocks of the poly(ether urethaneurea). The morphology, and particularly the composition and the structure of the hard domains, is thus likely to be affected. Differences in morphology between PUUR and PUUR-A can explain the observed differences in their mechanical properties and in their physical appearance.

The additive can be regarded as a polymeric surfactant in the sense that it is enriched at the polymer/air interface, decreasing the interfacial free energy by introducing long alkyl chains of low polarity in the interface. This is clearly seen by comparing ESCA C1s spectra of PUUR and PUUR-A (Fig. 3). The air-facing sides of films cast from the two materials were found to be distinctly different, PUUR-A having a higher proportion of aliphatic C in the surface. The surface accumulation of the polyacrylate has also been observed in time-of-flight SIMS spectra[12] and in concentration depth profiles calculated for angle-dependent ESCA data.[16]

The wetting characteristics of PUUR and PUUR-A were quite different. Data on advancing and receding contact angles with water for PUUR, PUUR-A, Biomer, and Pellethane 2363-80AE are collected in Table I. Pellethane is a linear thermoplastic poly(ether urethane) marketed by Dow Chemical. As can be seen from the table, there is a large similarity between PUUR-A and Biomer in their wetting characteristics and their water-contact angles differ significantly from those of PUUR and Pellethane. Because of the presence of the additive, the PUUR-A material has a larger advancing contact angle. This was expected because of the higher proportion of hydrophobic alkyl groups present in the PUUR-A surface, as seen in the ESCA spectra. The contact-angle hysteresis was found to be much larger for PUUR-A and Biomer than for PUUR and Pellethane, and this indicates that the Methacrol additive has amphiphilic properties.

We have previously reported on the preparation and properties of amphiphilic graft copolymers based on hydrophobic polyacrylate backbones and hydrophilic poly(ethylene oxide) grafts.[19,20] We have also prepared amphiphilic segmented poly(ether urethanes) based on poly(ethylene oxide) and MDI, substituted in the hard blocks by long aliphatic chains, and studied their effects on surface properties when used as additives in poly(ether urethanes).[21] Because of the amphiphilic nature of these polymers, they tend to migrate to the surface of the matrix polymer, generating a contact-angle hysteresis on the order of 100°. The effects observed in the present investigation are smaller because of the pronounced hydrophobic character of the Methacrol additive.

The reason for the contact-angle hysteresis observed in the present case can be the following: Be-

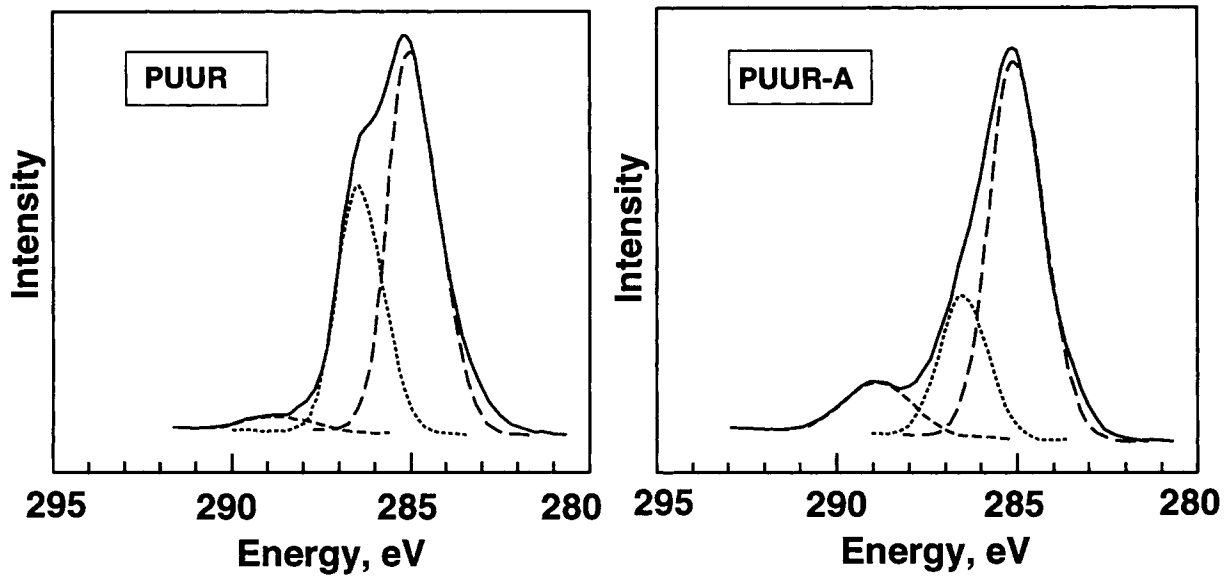

Figure 3 ESCA C1s spectra for (left curve) PUUR and (right curve) PUUR-A. The spectra were resolved into component peaks by computer simulation. Aliphatic C appears at 285 eV, ether C at 286.5 eV, and carbonyl C at 289 eV.

cause of the differences in morphology between PUUR and PUUR-A discussed above, the surfaces of PUUR-A and Biomer may be more distinctly segregated in hydrophilic and hydrophobic domains, as compared to the unmodified PUUR. By SEM analyses of freeze-fractured specimens, Wu et al.[14b] found that the Methacrol additive phase separated as discrete domain structures, approximately 0.5 μm in diameter. Although they found that the air-facing surfaces were quite featureless, formation of small pits after 5 weeks' implantation implied that the additive present at the surface leached out. The hysteresis observed in the present investigation should then be a measure of the phase segregation in the surface, i.e., the advancing wetting angles being characteristic of hydrophobic surface domains and the receding angles of hydrophilic domains.[22]

Table I Contact Angles with Water for Different Biomedical Polymers

	Contact Angles		
Material	θ_{Adv} (Deg)	θ_{Rec} (Deg)	Hysteresis (Deg)
PUUR	80 ± 3	55 ± 3	25 ± 3
PUUR-A	91 ± 3	22 ± 5	69 ± 4
BIOMER	83 ± 3	18 ± 2	64 ± 2
Pellethane 2362-80AE	77 ± 3	52 ± 5	25 ± 6

However, the domain structure of the surface may be quite different from that of the bulk of the material. For thermodynamic reasons, the additive accumulates at the air-facing surface, giving the surface a more homogeneously hydrophobic character.[10] Because of the low glass transition temperature of the material, the mobility of the polymer chains is high. On contact with water, the chains at the surface may rapidly rearrange to give a surface with a minimized interfacial free energy, i.e., a highly hydrated, hydrophilic surface with wetting characteristics quite different from the original one.[10,22] The hysteresis effect would then reflect the rearrangement of the surface and would be influenced by kinetic factors as well as by thermodynamic ones. This model is in accordance with ESCA results given by Tyler et al.[16]

We have previously noted that on addition of an amphiphilic polymer to a matrix polymer, the contact angle hysteresis was dependent on the amount added, reaching a constant value at a concentration of approximately 5% (w/w).[21] This effect is analogous to the behavior of a surfactant solution at the critical micelle concentration (cmc), i.e., the surface will be saturated by surfactant molecules before micelle formation, though aggregation takes place. In the present case, a phase separation in the bulk has occurred at 5% concentration, and the surface would then be saturated with the polymeric surface active additive.

Table II *In Vitro* Blood Clotting Times, Platelet Adhesion, and Protein Adsorption for Different Biomedical Polymers

Material	Clotting Time[a] (s)	Adhering Platelets[b] (No./mm^2)	Adsorbed Antisera (μg/cm^2)	
			α-Alb[c]	α-Fg[c]
PUUR	280 ± 10	2000 ± 300	0.07	0.65
PUUR-A	320 ± 15	1200 ± 300	< 0.02	< 0.02
Pellethane 2363-80AE	260 ± 10	2200 ± 300	—	—
Glass	210 ± 25	—	—	—

[a] Mean values of five measurements.
[b] Determined from SEM micrographs.
[c] Determined by ellipsometry (see Experimental section).

We may conclude that the additive significantly changes the surface properties of the PUUR matrix polymer. The surface chemistry and energetics are known to have pronounced effects on the blood contacting properties of a material, and one can suspect that blood compatibility as well as protein adsorption of PUUR and PUUR-A will differ. We have carried out *in vitro* blood compatibility tests with PUUR and PUUR-A, and the results from these tests substantiate this view. *In vitro* clotting times as well as platelet adhesion (Table II) are significantly different for the two materials, PUUR-A seemingly being the more blood compatible. It was noted that in the case of PUUR-A the platelets had a round shape, whereas the platelets adsorbed to a PUUR surface were slightly deformed and had developed pseudopodia.

Adsorption of plasma proteins at a surface is the first event that occurs on contacting the surface with blood, and the following events are believed to be determined by the adsorbed protein layer.[23] We determined the adsorption of albumin and fibrinogen from human blood plasma on PUUR and PUUR-A surfaces by means of antisera and ellipsometry (Table II). It is evident that the presence of the Methacrol additive at the surface of PUUR-A significantly decreases the adsorption of fibrinogen, which is indicative of a lower thrombogenicity of this surface, as compared to the unmodified PUUR.[23] A thorough study on the adsorption of plasma proteins to the present materials will be reported elsewhere.[24]

It may be noted that the idea of changing surface chemistry and blood compatibility of a material by means of surface active polymers has previously been put forward by Ward et al.[25] and Ratner et al.[26] Addition of siloxane block copolymers to a base polymer has been shown to cause large changes in its surface properties.[25]

CONCLUSIONS

In the present study, we have shown that the surface properties of a poly(ether urethaneurea) of a composition similar to Biomer to a large extent depend on the presence of a surface active polymeric additive. The additive, Methacrol 2138F, gives the surface amphiphilic properties and affects the bulk mechanical properties of the polyurethaneurea due to an increased phase separation. Protein adsorption and blood compatibility are greatly affected by the additive.

The PUUR and PUUR-A polymers used in this investigation were kindly put to our disposal by E. I. Du Pont de Nemours & Co., and we wish to express our thanks to Drs. C. R. Payet and G. A. Lodoen from the same company for their cooperation. The project was financially supported by NUTEK and ASTRA-TECH AB (a subsidiary of AB ASTRA), Sweden, which is gratefully acknowledged.

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