JOURNAL OF Materials CHEMISTRY

Synthesis, characterization and blood compatibilities of novel segmented polyurethanes containing poly(butadiene) soft segments and phosphatidylcholine analogues in the main chains and long-chain alkyl groups in the side chains

Arata Korematsu,[a] Yu-Jun Li,[a,b] Takayuki Murakami,[a] Ikuko Sakurai,[c] Makoto Kodama[d] and Tadao Nakaya*[a]

[a]*Department of Bioapplied Chemistry, Faculty of Engineering, Osaka City University, 3-3-138 Sugimoto, Sumiyoshi-ku, Osaka 558–8585, Japan. E-mail: nakaya@bioa.eng.osaka-cu.ac.jp*
[b]*Present Address: Procter & Gamble Far East Inc., 17 Koyo-cho Naka 1-chome, Higashinada-ku, Kobe 658–0032, Japan*
[c]*The Institute of Physical and Chemical Research (RIKEN), 2–1 Hirosawa, Wako, Saitama 351–0198, Japan*
[d]*Bionic Design Group, National Institute for Advanced Interdisciplinary Research, 1–1-4 Higashi, Tsukuba, Ibaraki 305–0046, Japan*

Received 10th August 1998, Accepted 30th November 1998

New segmented polyurethanes (SPUs) containing poly(butadiene) (PBD) soft segments and phospholipid moieties in the main chains and long-chain alkyl groups in the side chains were synthesized. The phospholipid moieties include bis[2-(2-hydroxyethyldimethylammonio)ethyl] 2-octylpropane-1,3-diyl bis(phosphate) (OcPDP), bis[2-(2-hydroxyethyldimethylammonio)ethyl] 2-oleylpropane-1,3-diyl bis(phosphate) (OlPDP) and bis[2-(2-hydroxyethyldimethylammonio)ethyl] 2-cetylpropane-1,3-diyl bis(phosphate) (CPDP). The bulk characterization of synthesized SPUs was investigated by infrared (IR) spectroscopy and gel-permeation chromatography (GPC). The mechanical properties were evaluated by dynamic viscoelasticity and tensile measurements. The existence of phospholipid analogous groups on the surface of these SPUs was revealed by attenuated total reflection Fourier transform infrared spectroscopy (ATR-FTIR), X-ray photoelectron spectroscopy (XPS) and contact angle measurements. The blood compatibilities of the new polymers were evaluated by platelet rich plasma (PRP) contact studies and viewed by scanning electron microscopy (SEM) using medical grade BioSpan® and non-phospholipid polyurethane as references. These new materials have good surfaces in terms of platelet adhesion, and the morphology of adhered platelets undergoes a relatively low degree of variation.

Introduction

Heart valves and other synthetic prosthetic devices in contact with living tissue must be compatible with their biological host. To obtain polymers with biocompatible surfaces, many approaches have been explored. One of these approaches is to construct segmented polyurethanes (SPUs) that exhibit biostability. SPUs as biomaterials display certain favorable mechanical properties and biocompatibilities. However, some controversy still remains and limits their widespread application. The SPUs most frequency used today in biomedical applications are poly(ether urethane)s, which have good biostability[1–3] but which are subject to significant degradation under certain conditions of mechanical or chemical action of implanted devices.[4–6] One of the major cause of degradation is oxidation of the polyether chain. Oxidizing agents produced *in vivo* from inflammatory cells or metal corrosion products are associated with polyurethane degradation in implant devices.[4] It has been suggested that the major causes of degradation are calcification, environment, stress cracking, hydrolysis and oxidation.[4,7–11]

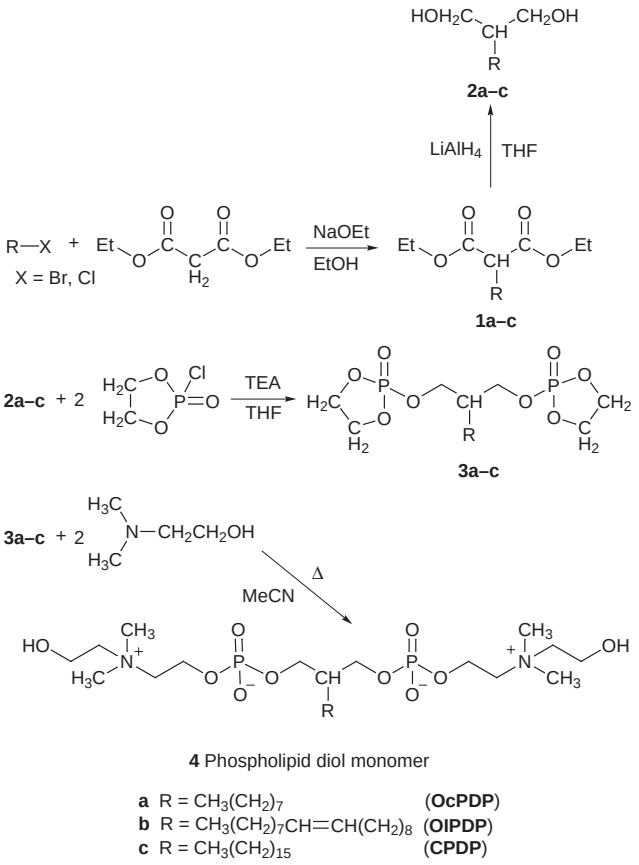
To develop polyurethane biomaterials which are more stable *in vivo*, it may be desirable to prepare SPUs without ether-containing polydiols. Takahara *et al.*[12] have used several non-ether polydiols such as poly(butadiene) (PBD), hydrogenated poly(butadiene) (HPBD) and poly(dimethylsiloxane) (PDMS) chain segments to synthesize segmented polyurethanes. They have demonstrated that segmented polyurethanes based on these hydrophobic polydiols showed distinct microphase separation between hard and soft segments. Moreover, these SPUs containing hydrophobic polydiols are also interesting for their interfacial chemistry. Due to the large difference in surface free energy between their hard and soft segments, the polydiol soft segments may be enriched at the air–solid interface. However, after immersing the specimen in water, surface reorganization may occur in response to the system's requirement to minimize its interfacial free energy. Moreover, a polyurethane containing a PBD soft-segmented component showed hardening due to the cross-linking of double bonds in the soft segment. It was concluded that polyurethanes with aliphatic hydrocarbon-based polydiol components are stable against oxidative degradation.

In order to develop segmented polyurethanes with surfaces that will not activate the blood coagulation system, a number of surface modification approaches have been taken.[12–14] Among them, an interesting and important observation is that albumin binds *via* hydrophobic bonds to molecules containing long alkyl chains, suggesting the synthesis of polymers containing alkyl chains of 16 or 18 carbon atoms[15–17] as side groups. These earlier studies suggest that improved blood compatibility might be attained by introducing hydrocarbon groups at the surface.

On the other hand, the possibility of utilizing polymers containing phospholipid molecular structures on their surface as biomaterials has been studied. Phospholipids consist of hydrophilic and hydrophobic groups and form the lipid bilayers of plasma membranes.[18] Phosphorylcholine, which is an electrically neutral and zwitterionic head group that rep-

resents the bulk of the phospholipid head groups present on the external surface of blood cells, is inert in coagulation assays.[19] In order to obtain biocompatible polymers in artificial organs, in 1986 we successfully synthesized phospholipid-like diols and polyurethanes.[20] In recent reports on our study of biocompatible phospholipid polymers, we described a series of polyurethanes containing phospholipid moieties in the side chains.[21–29] Moreover, it also seemed worthwhile to investigate the properties of polymers containing phospholipid analogues in the main chains.[30] In our previous papers,[31–34] we reported some polymers containing phosphatidylcholine analogues in the main chains. Recently, new polyurethanes bearing phosphatidylcholine analogues in the main chains[35–39] have been synthesized in this laboratory.

In this study, we have synthesized several new SPUs bearing non-ether soft segments and phospholipids in the main chains. Furthermore, the relationships between *in vitro* blood contacting properties and surface and bulk structure were evaluated before characterizing the polymers' stability in biological environments. The characterization tests for bulk characterization of the polyurethanes included IR, ^{1}H-NMR, gel permeation chromatography (GPC) and elemental analysis. Surface properties were investigated by contact angle measurements, attenuated total reflection Fourier transform infrared spectroscopy (ATR-FTIR) and X-ray photoelectron spectroscopy (XPS) analyses. The blood compatibility of the synthesized SPUs was evaluated by platelet rich plasma (PRP) contacting experiments and the results were observed by scanning electron microscopy (SEM). The state of platelet adhesion and shape variation for the attached platelets were described.



Scheme 1 Synthetic scheme for the preparation of the new phospholipid diols.

Experimental

Materials

Triethylamine (TEA), 2-dimethylaminoethanol (*N*,*N*-dimethylethanolamine), 4,4′-methylenediphenyl diisocyanate (MDI), and butane-1,4-diol (BD) were commercially obtained and purified by vacuum distillation. 1-Bromohexadecane, diethyl malonate, and lithium aluminum hydride were commercially obtained and used as received. Tetrahydrofuran (THF) and diethyl ether were dried by distillation from lithium aluminum hydride. *N*,*N*-Dimethylformamide (DMF) and *N*,*N*-dimethylacetamide (DMAc) were distilled from calcium hydride to ensure dryness. Methanol and ethanol were distilled in the presence of magnesium methoxide and magnesium ethoxide to ensure dryness. Acetone was dried by distillation from anhydrous potassium carbonate. Poly(butadiene) diol (PBD) with a number average molecular weight of 2840 and 60% 1,4-*trans*, 20% 1,4-*cis*, and 20% 1,2-vinyl structure components was kindly provided by Nippon Oil and Fats Co., Ltd.

2-Chloro-1,3,2-dioxaphospholane [bp 45.5–46.5 °C (15 mbar); lit.,[40] 45.5–47.0 °C (15 mbar)] was prepared in 66% yield by the reaction of ethylene glycol with phosphorus trichloride in dichloromethane, according to the method of Lucas *et al.*,[40] and oxidized to 2-chloro-2-oxo-1,3,2-dioxaphospholane [bp 103.5–105.0 °C (1 mbar); lit.,[41] 79 °C (0.4 mbar)] in 90% yield with oxygen, according to the procedure of Edmundson.[41] Synthesis of phospholipid diols bis[2-(2-hydroxyethyldimethylammonio)ethyl] 2-octylpropane-1,3-diyl bis(phosphate) (OcPDP) and bis[2-(2-hydroxyethyldimethylammonio)ethyl] 2-oleylpropane-1,3-diyl bis(phosphate) (OlPDP) have been described in detail previously.[37]

Synthesis of bis[2-(2-hydroxyethyldimethylammonio)ethyl] 2-cetylpropane-1,3-diyl bis(phosphate) (CPDP)

Using a procedure similar to that described for the preparation of OcPDP (**4a**) and OlPDP (**4b**),[37] diethyl 2-cetylmalonate (**1c**), 2-cetylpropane-1,3-diol (**2c**), 1,3-bis(2-oxo-1,3,2-dioxaphospholane-2-yloxy)-2-cetylpropane (**3c**) and bis[2-(2-hydroxyethyldimethylammonio)ethyl] 2-cetylpropane-1,3-diyl bis(phosphate) (CPDP) (**4c**) were prepared (Scheme 1). IR spectra of materials were recorded on a Jasco A 202 spectrometer and ^{1}H NMR spectra on a 400 MHz a FT NMR spectrometer JNM-A 400 using tetramethylsilane (TMS) as an internal standard.

1c: Colorless liquid; yield: 68.3%; bp 210–220 °C (8 mmHg); $\delta_H(CDCl_3)$ 0.86–0.88 (t, 3H, CH_3), 1.22–1.25 (m, 34H, $(CH_2)_{14}$, $CO_2CH_2CH_3$), 1.87 (m, 2H, CH_2CH), 3.30 (t, 1H, CH), 4.19 (m, 4H, $CO_2CH_2CH_3$); ν_{max}(neat)/cm^{-1} 2925, 2850, 1460, 720 (CH_2) and 1735 (C=O).

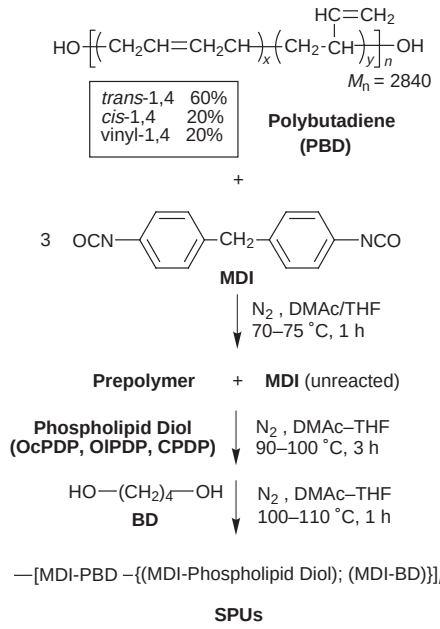
2c: White solid; yield: 79.6%; mp 45–47 °C; $\delta_H(CDCl_3)$ 0.86–0.88 (t, 3H, CH_3), 1.26 (s, 30H, CH_2), 1.78 (m, 1H, CH), 2.62 (s, 2H, OH), 3.63–3.83 (m, 4H, CH_2OH); ν_{max}(KBr)/cm^{-1} 3300, 1030 (OH), 2900, 2850, 1455 and 720 (CH_2).

3c: Pale yellow viscous solid; yield: 98%; $\delta_H(CDCl_3)$ 0.86–0.88 (t, 3H, CH_3), 1.26 (s, 30H, CH_2), 2.30 (m, 1H, CH), 3.71–3.84 (m, 4H, $POCH_2CH$), 4.04–4.50 (m, 8H, OCH_2CH_2OP); ν_{max}(neat)/cm^{-1} 2925, 2850, 1460, 720 (CH_2), 1260 (P=O), and 1020 ($POCH_2$).

4c: Pale yellow viscous solid; yield: 59.3%; $\delta_H(CDCl_3)$ 0.86–0.88 (t, 3H, CH_3), 1.26 (s, 30H, CH_2), 2.89 (s, 12H, N^+CH_3), 3.4–4.2 (m, 20H, OCH_2, N^+CH_2); ν_{max}(neat)/cm^{-1} 3350 (OH), 2925, 2850, 1480, 790 (CH_2), 1220 (P=O) and 1040 ($POCH_2$).

Synthesis of phospholipid SPUs

Phospholipid SPUs were synthesized by a three-step addition polymerization reaction outlined in Scheme 2. The polymer PBD1–OcPDP1 was based on 1:3:1:1 molar ratio of PBD:MDI:OcPDP:BD and the reaction was carried out in



Scheme 2 Three-step synthesis of the phospholipid SPUs.

a 1:1 mixture of DMAc–THF without catalyst. In the first step, 1.06 g (4.23 mmol) of MDI dissolved in 10 cm^3 of mixed solvent was added to the stirred solution of 4.0 g (1.41 mmol) of PBD and 10 cm^3 of the same mixed solvent under a dry nitrogen atmosphere. After stirring for 1 h at 70–75 °C, the solution was cooled to room temperature. In the second step, 0.81 g (1.41 mmol) of OcPDP, previously dissolved in 15 cm^3 of the mixed solvent, was slowly added to the reaction solution over 1 h. Stirring was continued at 90–100 °C for 3 h. For the last step, 0.13 g (1.41 mmol) of BD, previously dissolved in 15 cm^3 of the same mixed solvent, was slowly added into the reaction solution over 20 min. The stirring was continued at 100–110 °C for 1 h. The resulting phospholipid polymer was precipitated in methanol. The polymer was then washed with methanol and the washing procedure was performed three additional times with methanol. The polymer was dried under vacuum. The polymer PBD1–OcPDP1 was obtained in 96.5% yield as a pale yellow elastomer. Using a procedure similar to that described for the preparation of PBD1–OcPDP1, other new polyurethanes, PBD1–OlPDP1 and PBD1–CPDP1 were also synthesized. The polymer PBD1–OlPDP1 was obtained in 81.1% yield and PBD1–CPDP1 in 87.0% yield and both polymers were pale yellow elastomers.

To investigate the effect of the phospholipid component, a reference SPU based on PBD and extended only with BD was also synthesized, according to a conventional two-step solution polymerization procedure under nitrogen atmosphere.[42] This polymer was based on 1:3:2 molar ratio of PBD:MDI:BD and the reaction was carried out in a 1:1 mixture of THF–DMAc without catalyst (Table 1).

Preparation of cast films

After briefly drying under vacuum to remove residual methanol, the resulting polymers were dissolved in a casting solvent using an ultrasonic generator, and then cast onto glass plates to create films for bulk property testing or surface property experiments. In the casting procedure, the cast films were first dried in an oven at 70 °C for at least 24 h to remove most of the solvents. The final drying stage involved drying the sheet in a vacuum oven at 70 °C for at least 24 h to remove residual solvents.

Measurements

IR spectra were recorded on a Jasco A 202 spectrometer. GPC measurements were performed on a HLC802UR GPC instrument with G4000H8 + G2000H8 columns; the samples were dissolved in mixed solvent of THF and DMAc (volume ratio 1:1) and polystyrene was used as standard. The surface of the cast films was analyzed by XPS using a Shimadzu ESCA 750 spectrometer using Mg-Kα radiation. The cast films, after peeling from the glass, were mounted on the specimen holder. The typical operating conditions included maintaining the X-ray gun at 8 kV and 30 mA and reducing the pressure in the sample chamber to about 3×10^{-5} Pa. The take-off angle of the photoelectrons was 60°. The repeat times were once for carbon and oxygen, and five times for nitrogen and phosphorus, respectively. In addition to taking survey scans (0–1000 eV) with a view to determining the elemental composition of the various surfaces, elemental compositions were also determined on the basis of the peak areas from the C_{1s}, N_{1s}, O_{1s} and P_{2p} orbitals. Peak areas were calculated using standard Shimadzu ESPAC 100 software. The binding energy was referenced by setting the C_{1s} hydrocarbon peak to 285 eV. Contact angle measurements: the values quoted are the average of 10 measurements of each sample taken for the immediate contact of the water droplet, on the air exposed side, using a FACE contact angle meter. The temperature dependence of the dynamic viscoelasticity of the sample was obtained using a microprocessor-controlled Rheovibron DDV-01FP under a nitrogen purge. The sample (205 μm thick, 2 mm wide, 30 mm long) was cooled to −150 °C, and data were subsequently taken at a test frequency of 11 Hz and a heating rate of 3 °C min^{-1}. The stress–strain properties were measured using an Instron type tensile tester (Tenshiron Model UCT-30T) with a crosshead speed of 12 mm min^{-1} at room temperature. ATR-FTIR was performed on the surfaces of the cast films. The spectra were collected at 4 cm^{-1} resolution using a Jasco Micro FT/IR-200 microsampling spectrometer over 50 scans. The sampling area was 25 μm^2, coupled with an ATR accessory and 45° KRS-5 crystal. The procedure of blood compatibility evaluation for blood platelet adhesion and shape variation was the same as that described previously.[23,25–29,38,39,43] Briefly, the cast films were washed with saline and incubated at 37 °C for 1 h with freshly prepared PRP which was obtained from the centrifugation of the blood of rabbits. Samples were rinsed with saline and treated with 2.5% glutaraldehyde in

Table 1 Bulk property characterization of phospholipid SPUs and the reference SPU

SPUs	Stoichiometry[a] PBD:MDI:XPDP:BD	Hard segment (%)	Yield (%)	IR spectral data/cm^{-1} NH	CH_2	NHCOO	P=O	$POCH_2$	M_w[b]
PBD1–OcPDP1	1:3:1:1	33.3	96.5	3300	2925, 2850, 1460	1710	1220	1060	55000
PBD1–O1PDP1	1:3:1:1	35.4	81.1	3300	2925, 2850, 1460	1710	1220	1060	53000
PBD1–CPDP1	1:3:1:1	35.0	87.0	3300	2925, 2850, 1460	1710	1220	1060	70000
Reference SPU	1:3:0:2	24.7	98.1	3300	2925, 2850, 1460	1710	—	—	75000

[a]XPDP includes OcPDP (for PBD1–OcPDP1), O1PDP (for PBD1–O1PDP1), CPDP (for PBD1–CPDP1). [b]Determined by GPC using polystyrene as standard.

0.1 M cacodylate buffer at refrigerated temperatures overnight. The samples were rinsed with 0.1 M cacodylate buffer three times and dehydrated by systematic immersion in a series of ethanol–water solutions (60, 70, 80, 90, 95 and 100 vol%). Following critical point drying with carbon dioxide, the samples were coated with gold for analysis by SEM using a Shimidzu EPM-810.

Results and discussion

Synthesis of CPDP

The synthetic procedure is outlined in Scheme 1. According to the method of Hsu and Percec,[44] compound **1c** was obtained by the reaction of 1-bromooctadecane with diethyl malonate in ethanol in the presence of sodium ethoxide. Compound **2c** was obtained by reduction of **1c** in THF in the presence of $LiAlH_4$. The characterization of **1c** and **2c** was based on their IR and ^1H NMR spectral data and elemental analyses. The bifunctional intermediate **3c** was obtained by the reaction of **2c** with 2-chloro-2-oxo-1,3,2-dioxaphospholane in THF in the presence of TEA. It was characterized by IR and ^1H NMR spectral data. According to the method of Thuong and Chabrier,[45] the ring-opening reaction of **3c** was performed with 2-dimethylaminoethanol in acetonitrile at 70 °C for 20 h to afford new diol **4c** as a pale yellow viscous solid in good yield. The characterization of the new diol **4c** was based on its IR and ^1H NMR spectral data and elemental analysis. This diol was very hygroscopic and soluble in DMF at 70 °C, but almost insoluble in acetone and diethyl ether at room temperature.

Bulk property characterization

Bulk property characterization data are summarized in Table 1. The stoichiometry of the reaction was 1:3:1:1 for PBD:MDI:XPDP:BD. XPDP includes OcPDP (for PBD1–OcPDP1), OlPDP (for PBD1–OlPDP1) and CPDP (for PBD1–CPDP1). The designed hard segment was in the range 33.3–35.4%. The IR spectral analyses of the polymers were taken on cast films. All phospholipid polymers are related with the inclusion of PBD, MDI and phospholipid moieties. This is clear from the complete IR spectrum of each material, which shows absorption due to an NH band at 3300 cm^{-1}, an $NHCO_2$ band at 1710 cm^{-1}, CH_2 bands at 2925, 2850 and 1460 cm^{-1}, an aromatic linkage at 1600 cm^{-1}, a P=O at 1220 cm^{-1} and a $POCH_2$ at 1060 cm^{-1}. The molecular weights of the polymers were characterized by GPC based on a polystyrene standard. From the relationship between retention time and molecular weights derived for narrowly distributed standard polystyrene, the weight average molecular weights (M_w) of PBD1–OcPDP1, PBD1–OlPDP1, PBD1–CPDP1 and the reference SPU were 55000, 53000, 70000 and 75000. These molecular weights are sufficient for most biomedical applications.

The typical results of a dynamic viscoelasticity experiment for the PBD1–CPDP1 film sample are displayed in Fig. 1. For PBD1–CPDP1, the storage modulus (E′) slowly decreased from 4.51×10 MPa at −150 °C to 2.59×10^3 MPa at −80 °C, and then rapidly decreased by about two orders of magnitude. The material was followed into the elastomer region, giving 47 MPa near −50 °C. The peak of tan δ was observed at −64 °C, together with the peak of loss modulus (E'') at -78 °C. At 36.1 °C, 17.6 MPa, 1.21 MPa, and 0.0691 for E', E'' and tan δ were observed.

The tensile property data for the PBD1–CPDP1 film sample are summarized in Table 2. When the film sheet thickness was 205 μm, this elastomer had 3.26 MPa 100% modulus, and 5.46 MPa ultimate strength. Moreover, this elastomer had good mechanical strength with an elongation at break of 233%. However, the mechanical properties of these synthesized

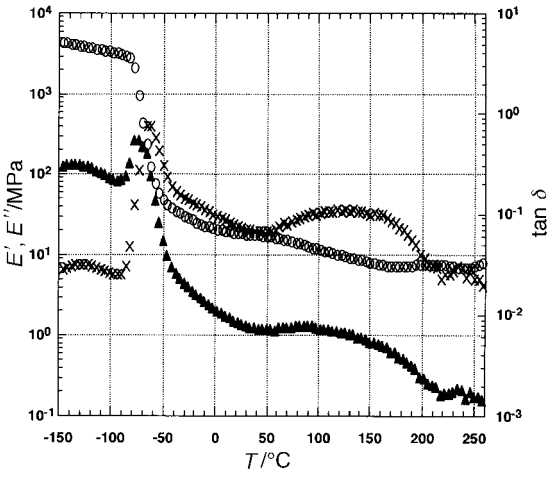


Fig. 1 Temperature dependence of the (○) storage modulus (E'), (▲) loss modulus (E'') and (×) loss tangent (tan δ) for the phospholipid segmented polyurethane PBD1–CPDP1 at 11 Hz.

Table 2 Mechanical properties of PBD1–CPDP1

Sheet thickness/ μm	Ultimate modulus/ MPa	100% Modulus/ MPa	Elongation at break (%)
205	5.46	3.26	233

phospholipid SPUs are, relatively, weaker than medical grade segmented polyurethane BioSpan®.[46]

Surface property characterization

The surface properties of the cast films of the resulting polymers were investigated by ATR-FTIR, XPS and contact angle measurements. In previous papers,[25,26,47] the surface properties and blood compatibilities of polymers were found to be different for the surfaces exposed either to air or to the mold substrate during the solvent casting process. In this study, the air-exposed surface of the phospholipid polymers was the blood contacting surface. Therefore, all surface and blood compatible properties were related to the air-exposed surface.

Fig. 2 shows the ATR-FTIR spectra of PBD1–CPDP1 and the reference SPU. The spectra of the polymers give evidence of unsaturated C=C double bonds, PO_4^-, NH, C=O bonds, nonbonded and bonded urethane, and unsaturated aromatic bonds. The analysis of PBD composition has been discussed in detail in our previous articles.[26,38] The peaks at 3075 cm^{-1} due to CH=CH unsaturated vinyl, at 964 due to *trans*-1,4 addition of CH=CH, at 680 owing to *cis*-1,4 addition of CH=CH and at 993 and 910 due to 1,2 addition of $CH=CH_2$ have been observed. The NH absorption band was found at 3311 cm^{-1}. The peak at 1708 cm^{-1} has been assigned to carbonyl groups that are hydrogen bonded (presumably to the urethane hydrogens) and the peak at 1730 cm^{-1} has been assigned to carbonyl groups that are not hydrogen-bonded. Moreover, a relatively weak band at 1641 cm^{-1} due to amide I and a peak at 1595 cm^{-1} due to aromatic stretching were clearly observed. Compared to the reference SPU without phospholipid analogous groups, PBD1–CPDP1 displays additional stretching at 1240 and 1050 cm^{-1} due to P=O and $PO–CH_2$ bonds.

Fig. 3 shows typical C_{1s}, O_{1s}, N_{1s} and P_{2p} spectra for PBD1–CPDP1 acquired at an 60° take-off angles. These spectra suggest a surface dominated by the PBD soft segment with urethane. The urethane (NH–COO) peak, when compared to the hydrocarbon (C–**C**–C) peak at 285.15 eV, is too small to allow accurate peak resolution. A Gaussian peak at 532.75 eV was used to fit the PBD1–CPDP1 O_{1s} peak. The

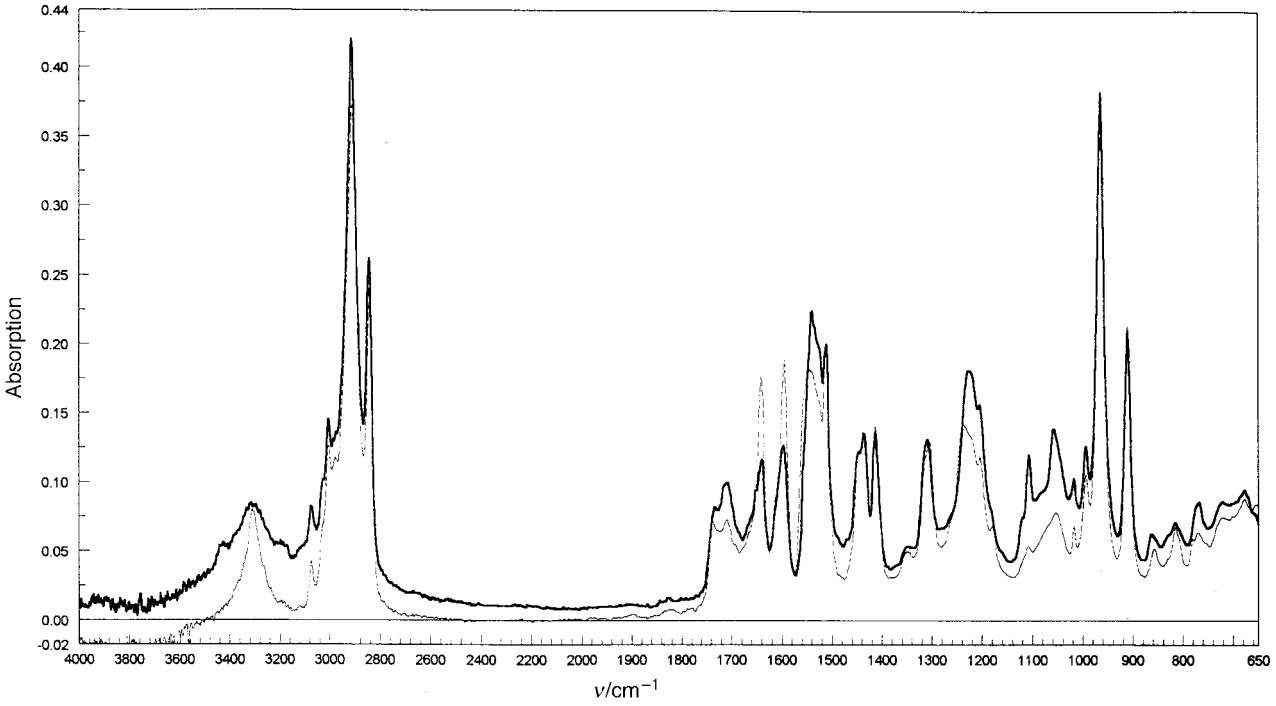


Fig. 2 ATR-FTIR spectra of PBD1–CPDP1 (solid line) and the reference SPU (dashed line).

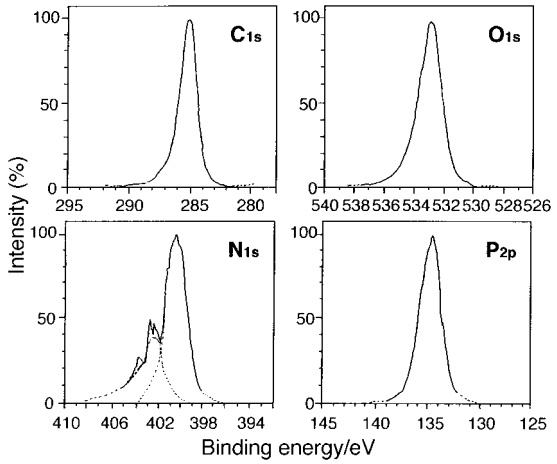


Fig. 3 XPS spectra of the cast film surface of PBD1–CPDP1.

high-energy and low-energy tailings on the O_{1s} peak reflect a combination of hole state lifetime broadening contributions from the urethane oxygens (N–CO**O** and N–C**O**O) and phosphorus oxygens ($\mathbf{PO_4}^-$). The high-energy and low-energy tailings on the N_{1s} peak also reflect a combination of hole state lifetime broadening contributions from the urethane nitrogen (**N**–COO) and phospholipid ammonium nitrogen [$\mathbf{N}^+(CH_3)_2$]. The nitrogen binding energy was 400.50 eV. A Gaussian peak at 134.30 eV was used to fit P_{2p} peak ($\mathbf{PO_4}^-$).

Table 3 lists XPS elemental surface composition of the synthesized polymers. All samples show a large amount of C_{1s} and a small amount of P_{2p} on the surface of the polymers. The ratio of elemental bulk composition of phosphorus is in the range of 1.56–1.61 and the ratio of elemental surface composition is in the range of 0.27–1.09. The ratios of the peak areas of oxygen, nitrogen and phosphorus to that of carbon (O_{1s}/C_{1s}, N_{1s}/C_{1s}, and P_{2p}/C_{1s}) were calculated and are also summarized in Table 3. The P_{2p}/C_{1s} values of the phospholipid SPUs were in the range of 0.0032–0.0144. The P_{2p} data suggest that phosphatidylcholine analogous groups are present on the surface of these synthesized phospholipid SPUs.

To investigate the hydrophilicity–hydrophobicity of the surfaces of the polymers, water contact angle measurements were carried out (Table 3). As expected, the relatively large contact angles indicated that these polymers had hydrophobic surfaces. PBD1–OcPDP1, PBD1–OlPDP1 and PBD1–CPDP1 exhibited contact angles of 92.1 ± 3, 90.1 ± 3 and $94.7\pm5^\circ$. These results agree with those of the XPS experiments, with samples having high carbon contents on the surface showing relatively strong hydrophobicity.

Blood compatibility evaluation

The synthesized phospholipid SPUs were assessed as biomaterials mainly by the degree and nature of blood platelet adhesion resulting from exposure to rabbit PRP for 60 min. The specimens incubated in PRP were viewed by SEM. This experiment was repeated twice and ten SEM photographs in various places were taken for each sample. Then, the mean values of the number of attached platelets and the platelet density were evaluated from these photographs. Typical SEM photographs of medical grade BioSpan®, PBD1–OcPDP1,

Table 3 XPS elemental surface composition (%) and water contact angle (°) of the phospholipid SPU[a]

SPU	C_{1s}	O_{1s}	N_{1s}	P_{2p}	O_{1s}/C_{1s}	N_{1s}/C_{1s}	P_{2p}/C_{1s}	$[\theta]_{(air)}$
PBD1–OcPDP1	84.47	13.93	1.33	0.27	0.1649	0.0157	0.0032	92.1 ($\pm$3.0)
	(87.17)	(8.31)	(2.91)	(1.61)				
PBD1–O1PDP1	81.86	16.66	1.13	0.35	0.2035	0.0138	0.0043	90.1 ($\pm$3.0)
	(87.56)	(8.06)	(2.82)	(1.56)				
PBD1–CPDP1	76.12	21.28	1.50	1.09	0.2796	0.0197	0.0144	94.7 ($\pm$5.5)
	(87.49)	(8.11)	(2.84)	(1.57)				

[a]Values in parentheses are expected theoretical elemental bulk compositions (%).

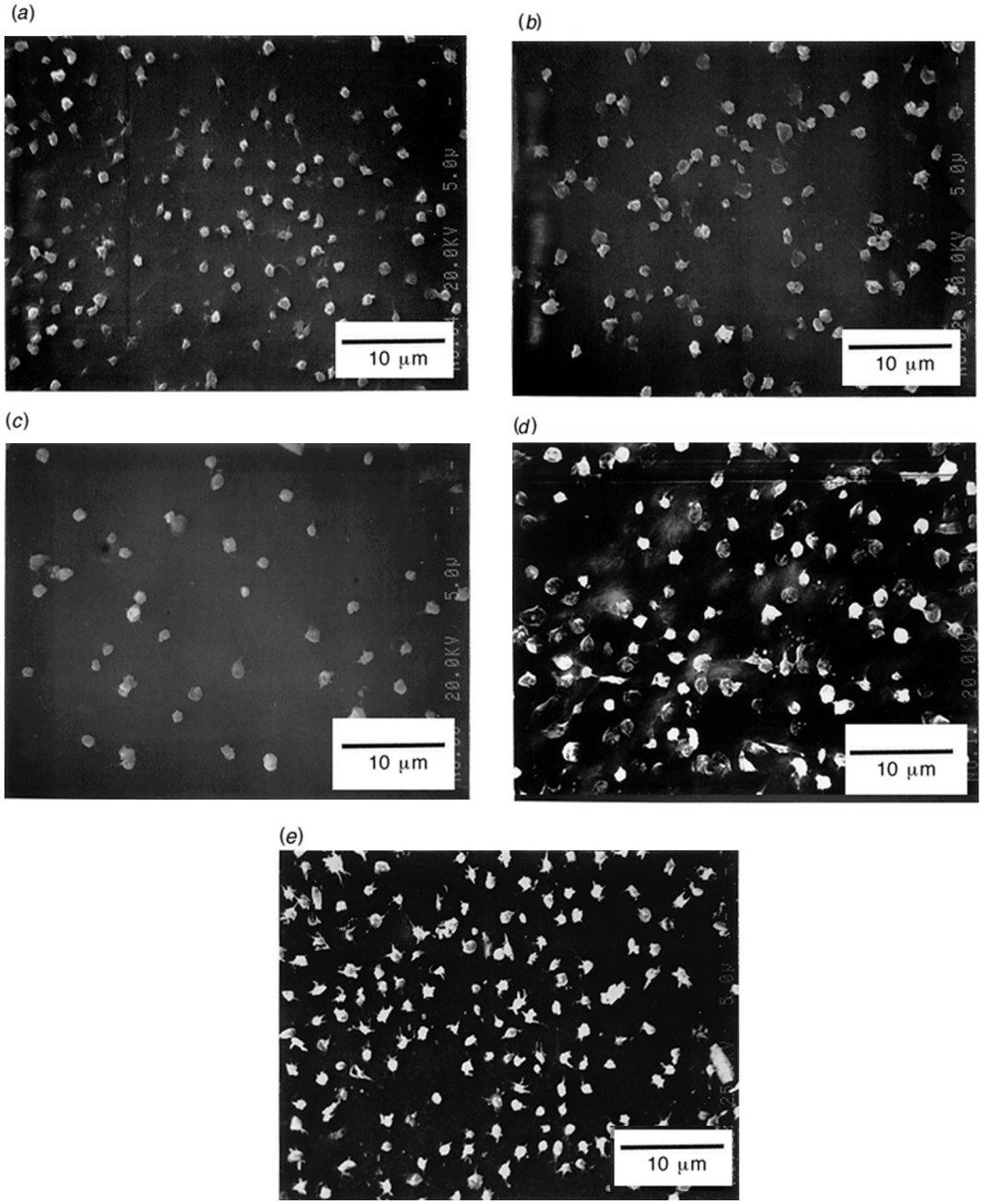


Fig. 4 SEM photographs of the surface of phospholipid SPUs, the reference SPU and medical grade BioSpan® films after 60 min of rabbit PRP exposure: (*a*) PBD1–OcPDP1, (*b*) PBD1–OlPDP1, (*c*) PBD1–CPDP1 (*d*) the reference SPU film cast from mixed THF and DMAc (volume ratio 1 : 1) solution and (*e*) medical grade BioSpan® film cast from DMAc solution (actual magnification: ×2000).

PBD1–OlPDP1, PBD1–CPDP1 and the reference SPU are shown in Fig. 4.

The surface of PBD1–CPDP1 did not show any substantial platelet attachment. Moreover, the shape variation of the adhered platelets, *i.e.* tail-forming or spreading, was very limited. On the other hand, the surfaces of PBD1–OcPDP1 and PBD1–OlPDP1 exhibited some attached platelets with some degree of shape variation. In contrast with phospholipid SPUs, medical grade segmented polyurethane BioSpan® and the reference SPU not only exhibited substantial platelet adherence, they also showed some degree of shape variation for the adhered platelets. Blood platelets were detected on all cast films exposed to PRP for 60 min, and the qualitative results of the PRP trials are summarized as follows:

The apparent 'number of attached platelets' was in the order:

BioSpan® and reference SPU > PBD1–OcPDP1 and PBD1–OlPDP1 > PBD1–CPDP1.

The apparent 'degree of shape variation of platelets' was in the order:

BioSpan® and reference SPU > PBD1–OlPDP1 > PBD1–OcPDP1 > PBD1–CPDP1.

On the basis of the SEM observations, the number of adhered platelets in an area of 10 × 10 μm was 0.69, 6.06, 7.48, 8.77 and 10.15 for PBD1–CPDP1, PBD1–OlPDP1, PBD1–OcPDP1, the reference SPU and BioSpan®, respectively. Although the shape variation of the adhered platelets may affect the accuracy of the estimated number of adhered platelets, it was apparent that the trend of blood compatibilities of the phospholipid SPUs are better than that of the reference SPU and BioSpan®.

As is seen from these results, the synthesized phospholipid polyurethanes, especially PBD1–CPDP1, have good surface properties in terms of platelet adhesion and the fact that the

morphology of platelets undergoes a relatively low degree of variation. The development of such blood-compatible phospholipid polyurethanes with good mechanical properties is ongoing in our group.

Acknowledgements

The authors are grateful to Professor T. Endo, Tokyo Institute of Technology, Yokohama (Japan), for helpful suggestions concerning the preparation of compounds **2a**, **2b** and **2c**.

References

1 J. W. Boretos and W. S. Pierce, *Science*, 1967, **158**, 1481.
2 J. W. Boretos, *J. Biomed. Mater. Res.*, 1972, **6**, 473.
3 J. W. Boretos, in *Proceeding of the 8th Annual Society of Biomaterials*, Wiley, Chichester, 1982, p. 24.
4 A. J. Coury, K. B. Stokes, P. T. Cahalan and P. C. Slaikeu, *Life Support Systems*, 1987, **5**, 25.
5 A. J. Coury, P. C. Slaikeu, P. T. Cahalan, K. B. Stokes and C. M. Hobot, *J. Biomater. Appl.*, 1988, **3**, 130.
6 A. Takahara, K. Takamori and T. Kajiyama, in *Artificial Heart 2*, ed. T. Akutsu, Spriger-Verlag, Tokyo, 1988, p. 19.
7 *Polyurethane in Biomedical Engineering II*, *Progress in Biomedical Engineering*, ed. H. Planck, I. Syryé, M. Dauner and G. Egbers, Elsevier Science, Amsterdam, 1987.
8 K. Stokes, A. Coury and P. Urbanski, *J. Biomater. Appl.*, 1987, **1**, 411.
9 K. Stokes and K. Cobian, *Biomaterials*, 1982, **3**, 225.
10 K. B. Stokes, P. Urbanski and J. Upton, *J. Biomater. Sci. Polym. Ed.*, 1990, **1**, 207.
11 K. B. Stokes, *J. Biomater. Appl.*, 1988, **3**, 228.
12 A. Takahara, A. Z. Okkema, S. L. Cooper and A. J. Coury, *Biomaterials*, 1991, **12**, 324.
13 W. Marconi, A. Martinelli, A. Piozzi and D. Zane, *Macromol. Chem. Phys.*, 1994, **195**, 875.
14 R. Rahman and B. D. Ratner, *J. Polym. Sci.*, *Part A*: *Polym. Chem.*, 1989, **27**, 2673.
15 R. C. Eberhart, M. S. Munro, G. B. Williams, P. V. Kulcarni, W. A. Shannon, B. E. Brink and W. J. Fly, *Artif. Organs*, 1987, **11**, 375.
16 T. G. Grasel, J. A. Pierce and S. L. Cooper, *J. Biomed. Mater. Res.*, 1987, **21**, 815.
17 I. Strizinar and M. Sefton, *J. Biomed. Mater. Res.*, 1992, **26**, 577.
18 K. Hara, in *Seirikasseishishitsu no Seikagaku to Ouyou* (in Japanese), Saiwai Shobo, Tokyo, 1993, p. 112.
19 A. A. Durrani, J. A. Hayward and D. Chapman, *Biomaterials*, 1986, **7**, 121.
20 T. Nakaya, M. Yamada and M. Imoto, Jpn. Pat. 61-207395, 1986 (*Chem. Abstr.*, 1987, **106**, 177059).
21 M. Yamada, Y.-J. Li and T. Nakaya, *J. Macromol. Sci. Pure Appl. Chem.*, 1995, **A32**, 1235.
22 Y.-J. Li, Y. Shibata and T. Nakaya, *Macromol. Chem.*, *Rapid Commun.*, 1995, **16**, 253.
23 Y.-J. Li, K. H. Matthews, M. Kodama and T. Nakaya, *Macromol. Chem. Phys.*, 1995, **196**, 3143.
24 Y.-J. Li, R. Bahulekar, T.-M. Chen, Y.-F. Wang, M. Kodama and T. Nakaya, *Macromol. Chem. Phys.*, 1996, **197**, 2827.
25 Y.-J. Li, T. Yokawa, K. H. Matthews, T.-M. Chen, Y.-F. Wang, M. Kodama and T. Nakaya, *Biomaterials*, 1996, **17**, 2179.
26 Y.-J. Li, K. H. Matthews, T.-M. Chen, Y.-F. Wang, M. Kodama and T. Nakaya, *Chem. Mater.*, 1996, **8**, 1441.
27 Y.-J. Li, R. Bahulekar, Y.-F. Wang, T.-M. Chen, M. Kitamura, M. Kodama and T. Nakaya, *J. Biomater. Sci. Polym. Ed.*, 1996, **7**, 893.
28 Y.-J. Li, K. H. Matthews, Y.-F. Wang, T.-M. Chen, M. Kodama and T. Nakaya, *J. Appl. Polym. Sci.*, 1996, **62**, 687.
29 Y.-J. Li, T. Tomita, K. Tanda and T. Nakaya, *Chem. Mater.*, 1998, **10**, 1596.
30 T. Nakaya and S. Nakai, *Kagaku* (in Japanese), 1987, **42**, 725.
31 T. Umeda, T. Nakaya and M. Imoto, *Makromol. Chem.*, *Rapid Commun.*, 1985, **6**, 285.
32 K. Sugiyama and T. Nakaya, *Makromol. Chem.*, *Rapid Commun.*, 1986, **7**, 679.
33 T. Nakaya, M. Yasuzawa and M. Imoto, *Macromolecules*, 1989, **22**, 3180.
34 M. Yamada, Y.-J. Li and T. Nakaya, *J. Macromol. Sci. Pure Appl. Chem.*, 1995, **A32**, 1723.
35 M. Yamada, Y.-J. Li and T. Nakaya, *Macromol. Chem.*, *Rapid Commun.*, 1995, **16**, 25.
36 Y.-J. Li, N. Nakamura, T. M. Chen, Y.-F. Wang, M. Kitamura and T. Nakaya, *Macromol. Chem.*, *Rapid Commun.*, 1996, **17**, 737.
37 A. Korematsu, Y.-J. Li and T. Nakaya, *Polym. Bull.*, 1997, **38**, 133.
38 Y.-J. Li, N. Nakamura, Y.-F. Wang, M. Kodama and T. Nakaya, *Chem. Mater.*, 1997, **9**, 1570.
39 Y.-J. Li, T. Nakaya, Z. Zhang and M. Kodama, *J. Biomater. Appl.*, 1997, **12**, 167.
40 H. J. Lucas, F. W. Mitchell and C. N. Scully, *J. Am. Chem. Soc.*, 1950, **72**, 5491.
41 R. S. Edmundson, *Chem. Ind.* (*London*), 1962, 1828.
42 J. H. Saunders and K. C. Frisch, in *Polyurethane Chemistry and Technology*: *Part 1.*: *Chemistry*, Interscience, New York, 1962.
43 Y.-J. Li and T. Nakaya, *Macromol. Symp.*, 1997, **122**, 363.
44 C. S. Hsu and V. Percec, *Makromol. Chem.*, *Rapid Commun.*, 1987, **8**, 331.
45 N. T. Thuong and P. Chabrier, *Bull. Soc. Chim. Fr.*, 1974, 667.
46 R. S. Ward and K. A. White, in *Proceedings From The Eighth Cimtec—Forum on New Materials Topical Symposium VIII*, *Materials in Clinical Applications*, *Florence*, Italy, July, 1994.
47 C. S. Paik Sung and C. B. Hu, *J. Biomed. Mater. Res.*, 1979, **13**, 161.

Paper 8/06279J