Surface Modification of Segmented Polyurethanes by Grafting Methacrylates and Phosphatidylcholine Polar Headgroups To Improve Hemocompatibility

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A new type of phosphatidylcholine-containing segmented polyurethane (SPU) surface was produced by grafting various methacrylates and phosphatidylcholine polar headgroups to a vinyl-group-containing segmented polyurethane (V-SPU) using α,α′-azobisisobutyronitrile (AIBN) as a radical initiator. 1,4-Butanediol (BD) as chain extender was used to synthesize the V-SPU, which is based on diphenylmethane diisocyanate (MDI) and vinyl-group-containing poly(butadiene) diol (PBD). Several methacrylates, such as methyl methacrylate (MMA), butyl methacrylate (BMA), stearyl methacrylate (SMA), and a phosphatidylcholine polar-headgroup-containing vinyl monomer, 2-(methacrylorloxy)ethyl-2-(trimethylammonium)ethyl phosphate (MTP), were grafted to the V-SPU. The bulk characteristics of the grafted V-SPUs were investigated by infrared (IR) spectroscopy, viscosity, and gel permeation chromatography (GPC) measurements. Mechanical properties of the typical SPU containing MMA were measured by dynamic viscoelasticity and tensile measurements. The phosphatidylcholine polar headgroups were oriented on the surface of these materials, as revealed by attenuated total reflectance-Fourier transform infrared spectroscopy (ATR−FTIR), electron spectroscopy for chemical analysis (ESCA), and contact angle measurements. The phosphatidylcholine polar-headgroup-grafted SPU surfaces showed slightly decreased water contact angles, also indicating that hydrophilic phosphatidylcholine polar headgroups are present at the surface. The hemocompatibility in vitro was evaluated with platelet-rich plasma (PRP) contact tests and viewed by scanning electron microscopy (SEM) using the ingrafted V-SPU as a reference. It was found that fewer platelets adhered to the modified surfaces and showed less shape variation than to the unmodified V-SPU. Platelet adhesion to phosphatidylcholine polar-headgroup-grafted polymers was inhibited 88−95% compared with unmodified V-SPU.

Introduction

Since the first paper on 2-(methacryloyloxy)ethyl-2-(trimethylammonium)ethyl phosphate (MTP) was published in 1982,[1] considerable attention has been paid to the MTP and its analogues because MTP has phosphatidylcholine polar headgroups and phosphatidylcholine groups attached to polymer surfaces are known to improve hemocompatibility.[2−4] Several groups also reported phosphatidylcholine-containing polyurethanes, polyurethane ionomers, and their hemocompatibilities.[5−7]

On the basis of the premise of achieving hemocompatibility through mimicking the chemical constituents of the biologically inert surface of the inactivated platelet membrane, recently we developed a series of new polyurethanes bearing phosphatidylcholine analogues on side chains[8−11] and main chains.[12−14] We also reported some new phospholipid segmented polyurethanes which showed excellent mechanical properties, significant hemocompatibilities,[15−20] and amphiphilic

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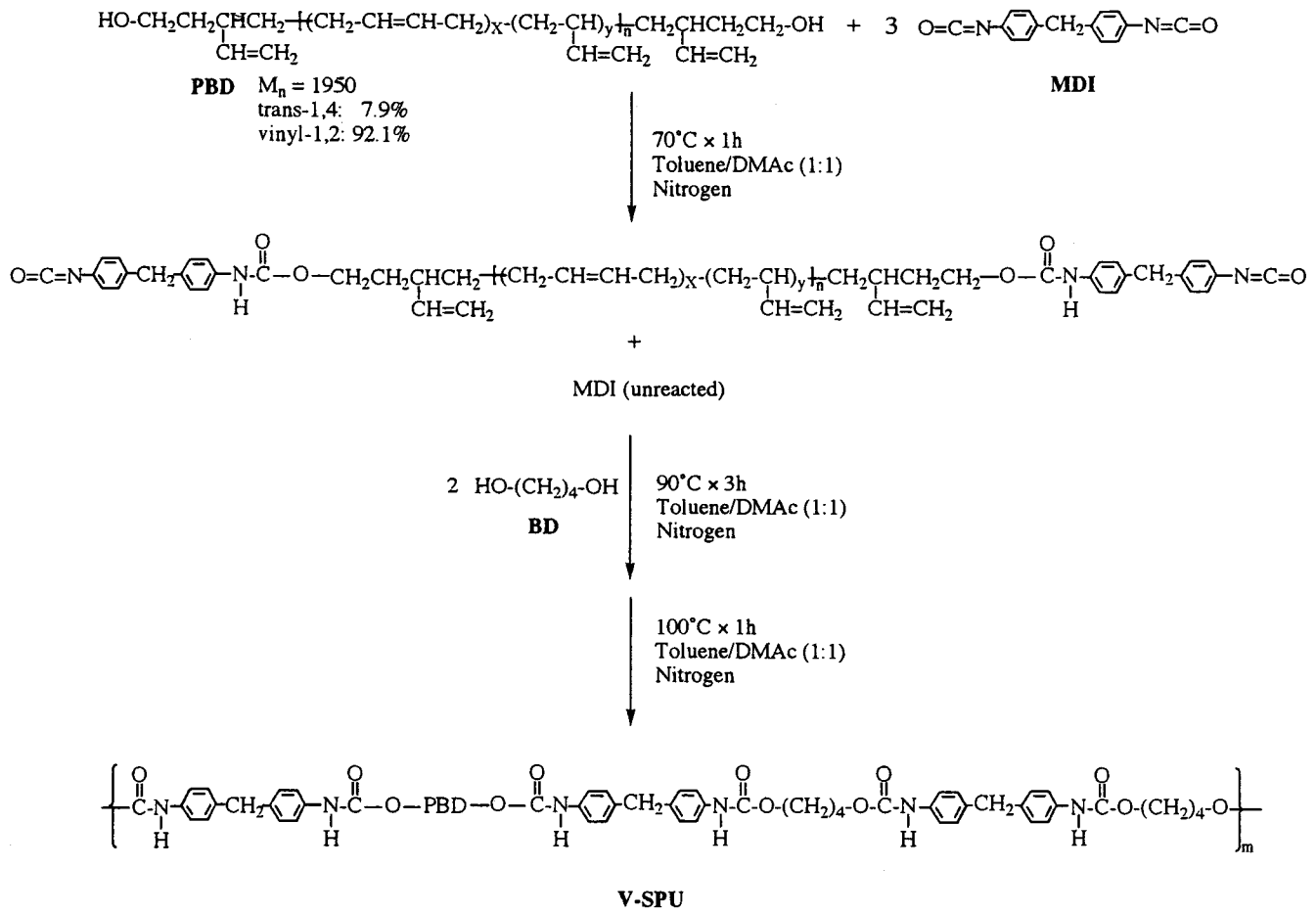
Scheme 1. Synthesis of Vinyl-Group-Containing SPU



V-SPU

microphase-separated domain structures.[21] More recently we successfully incorporated a phosphatidylcholine polar-headgroup-containing diol, [bis(2-hydroxymethyl)]propane-2-(trimethylammonio)ethyl phosphate, into segmented polyurethanes (SPUs) and found the resulting SPUs have important hemocompatibility.[22]

In this study, we incorporated vinyl monomer MTP into SPUs by using graft polymerization method. Various methacrylates and MTP were grafted to a vinyl-group-containing SPU (V-SPU) using α,α′-azobisisobutyronitrile (AIBN) as a radical initiator. The V-SPU was synthesized by reaction of MDI and vinyl group-containing poly(butadiene) diol (PBD) following addition of the chain extender 1,4-butanediol (BD). Several methacrylates, methyl methacrylate (MMA), butyl methacrylate (BMA), stearyl methacrylate (SMA), and a phosphatidylcholine polar headgroup-containing vinyl monomer, MTP, were grafted to the V-SPU. Bulk characterization of the polymers included IR spectroscopy, viscosity, and GPC measurements. The mechanical property investigation included dynamic viscoelasticity measurement and tensile measurements. Surface characterization was performed by attenuated total reflectance−Fourier transform infrared spectroscopy (ATR−FTIR) spectroscopy, electron spectroscopy for chemical analysis (ESCA), and contact angle measurements. The hemocompatibility of the polymers was evaluated by describing the platelet state and shape variation for the attached platelets.

Experimental Section

General Method. Cast films were prepared by the following method. After briefly drying under vacuum to remove residual methanol, the polymers were dissolved in toluene/DMAc (volume ratio 1/1) solution by using an ultrasonic generator. The polymer solutions (10% w/v) were cast onto a glass plate and dried in an oven at 55 °C for at least 24 h to remove most of the solvent. The final drying stage involved drying the sheet in a vacuum oven at 65 °C for 24 h to remove residual solvent. The IR spectral analyses of the polymers were taken on cast films using a Jasco A 202 spectrometer. Viscosity measurements were conducted with an Ubbelohde-type viscometer in a mixed solvent of toluene and DMAc (1:1, v/v) at 25 °C. For different concentrations, reduced specified viscosities η_{sp}/C were established and extrapolated to zero concentration. GPC measurements were performed on a HLC802UR GPC instrument with G4000H8 + G2000H8 columns; the samples were dissolved in DMAc/toluene (volume ratio 1:1), and narrow molecular weight polystyrene was used as standard. Temperature dependence of the dynamic viscoelasticity of the samples was obtained using a microprocessor-controlled Rheovibron DDV-01FP under a dry nitrogen purge. Typically, the sample (0.07−0.12 mm thick, 2 mm wide) 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

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Scheme 2. Synthesis of Methacrylates and Phosphatidylcholine Polar-Headgroup-Grafted SPUs

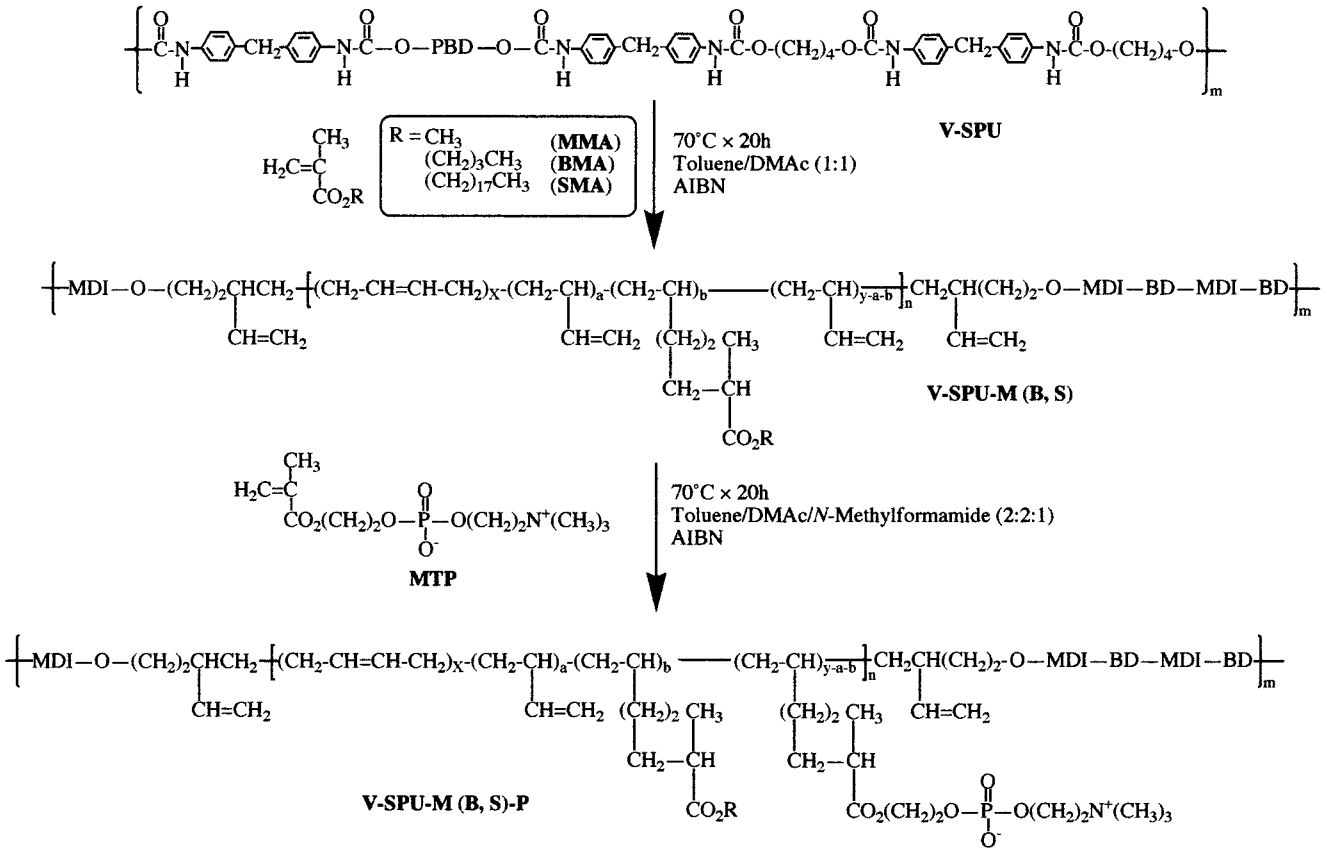

Table 1. Stoichiometry, Yield, IR Data, and Molecular Weight of the SPUs

				IR spectral data (cm^{-1})								GPC data	
polymers	compositions		yield (%)	NH	CH_2	NHCOO	C=C	arom C−H	COO	P=O	$POCH_2$	M_w $\times 10^4$	M_w/M_n
V-SPU	PBD1950:MDI:BD	1:3:2[a]	92.0	3300	2850	1710	1640	1600 1515	−	−	−	4.3	1.2
V-SPU-M	V−SPU:MMA	1:0.5	87.5	3300	2850	1740	1640	1600 1520	1160	−	−	9.4	1.9
V-SPU-M-P	V−SPU-M:MTP	1:0.2	78.1	3300	2850	1740	1640	1600 1520	1160	1240	1070	9.9	2.2
V-SPU-B-2	V-SPU:BMA	1:1	86.2	3300	2850	1740	1640	1600 1520	1160	−	−	8.6	1.8
V-SPU-B-2-P	V-SPU-B-2:MTP	1:0.2	72.3	3300	2850	1740	1640	1600 1520	1160	1240	1070	8.9	2.3
V-SPU-B-3	V-SPU:BMA	1:3	89.6	3300	2850	1740	1640	1600 1520	1160	−	−	9.0	1.6
V-SPU-B-3-P	V-SPU-B-3:MTP	1:0.2	75.8	3300	2850	1740	1640	1600 1520	1160	1240	1070	9.3	2.0
V-SPU-S	V-SPU:SMA	1:0.5	88.7	3300	2850	1740	1640	1600 1520	1150	−	−	6.1	1.5
V-SPU-S-P	V-SPU-S:MTP	1:0.2	76.6	3300	2850	1740	1640	1600 1520	1150	1240	1070	6.5	2.1

[a] Mole ratio for VSPU.

properties were measured by an Instron type tensile tester (Tenshiron Model UCT-5T) with a crosshead speed of 12 mm min^{-1} at 23 °C and 57% relatively humidity. The sample was cut into a dumbbell-shaped specimen using an ASTM D638 (Type V) standard die. ATR-FTIR spectroscopy was performed on surfaces of films cast from various solvents. The spectrum was 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. ESCA spectra were obtained on a Shimadzu ESCA 750 spectrometer using Mg Kα radiation. The cast films were peeled from the glass and mounted on the specimen holder. 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. In addition to taking survey scans (0−1000 eV) to determine the elemental composition of the various surfaces, elemental compositions were also determined on the basis of 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. Contact angles between polymer films and pure water were measured by using a Contact-Angle Meter Model CA-A (Kyowa Inter Face Science Co., LTD, Japan). The values quoted are the average of 12 measurements of each sample taken at 3 min contact of the water droplet on the air-exposed side. The procedure of hemocompatibility evaluation for blood platelet adhesion and

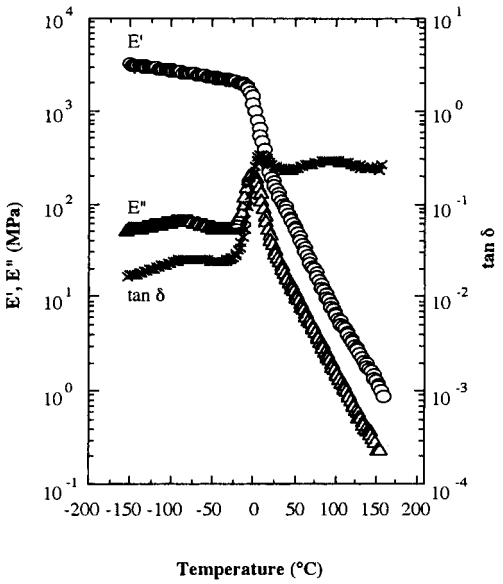

Figure 1. Temperature dependence of the storage modulus (E'), loss modulus (E''), and loss tangent (tan δ) for typical V-SPU-M-P at 11 Hz.

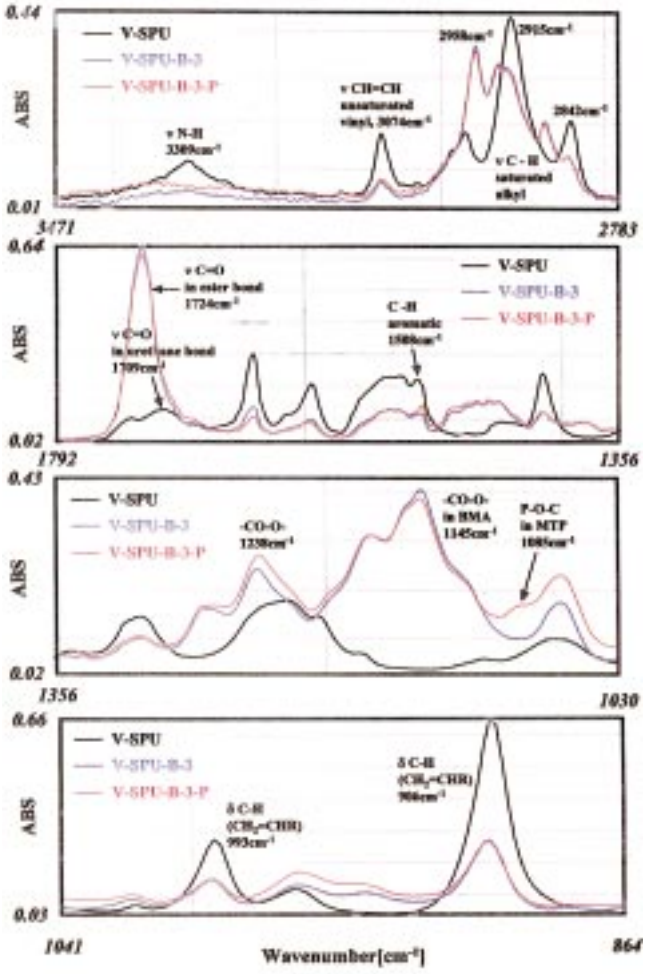

Figure 2. ATR−FTIR spectra of the V-SPU, V-SPU-B-3, and V-SPU-B-3-P.

shape variation was similar to that described previously.[9] Briefly, the films were washed with saline and incubated at 37 °C for 1 h with freshly prepared, platelet-rich plasma (PRP) obtained from the blood of Japanese male white rabbits (45 mL of blood and 5 mL of 3.8% sodium citrate aqueous solution)

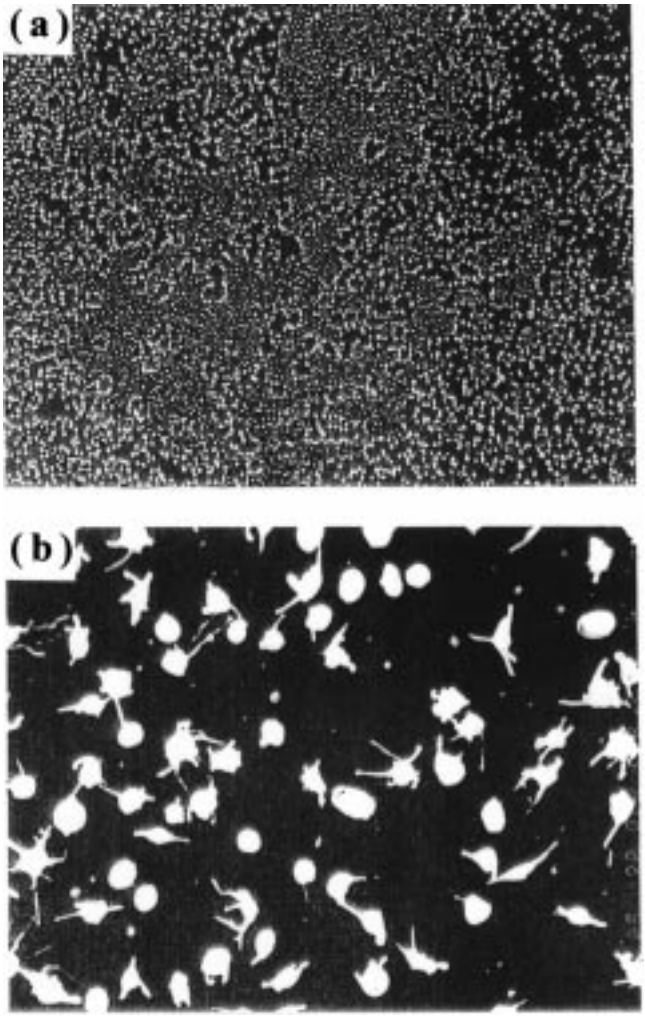

Figure 3. SEM photographs of the surface of V-SPU film after 60 min of PRP exposure. Actual magnification: (a) ×300 and (b) ×3000.

Table 2. ESCA Elemental Surface Composition (%) and Water Contact Angles of the SPUs

polymers	C_{1s}	O_{1s}	N_{1s}	P_{2p}	P_{2p}/C_{1s}	contact angle (deg)
V-SPU	87.73	9.84	1.64	0.00	0.0000	101.8 ± 2
V-SPU-M	90.29	6.72	2.80	0.00	0.0000	101.2 ± 2
V-SPU-M-P	87.37	10.57	1.24	0.38	0.0054	100.0 ± 3
V-SPU-B-2	86.88	11.30	1.45	0.00	0.0000	100.8 ± 4
V-SPU-B-2-P	85.99	12.26	1.25	0.50	0.0058	98.0 ± 3
V-SPU-B-3	82.51	15.96	1.19	0.00	0.0000	97.7 ± 2
V-SPU-B-3-P	83.98	13.85	1.82	0.35	0.0041	97.0 ± 4
V-SPU-S	89.62	8.96	1.20	0.00	0.0000	103.7 ± 2
V-SPU-S-P	87.71	10.82	1.11	0.36	0.0041	103.0 ± 3

by centrifugation at 1000*g* (rpm) for 20 min. Samples were rinsed with saline and treated with 2.5% glutaraldehyde in saline and kept at 4 °C overnight. The sample was rinsed with saline and dehydrated by systematic immersion in a series of ethanol−water solutions: 60, 70, 80, 90, 95, and 100% v/v, following soaking in a mixed solvent of ethanol and isoamyl acetate (volume ratio 1:1) and soaking in isoamyl acetate. The samples were dried by a critical-point-drying method with carbon dioxide and were coated with gold prior to being observed in an electron probe microanalyzer (EPM-810, Shimadzu) operated at an accelerating voltage of 20 kV. Ingrafted V-SPU was used as a control sample.

Materials. Vinyl-group-containing PBD with a number-average molecular weight of $M_n = 1950$ and 92.1% 1,2-vinyl and 7.9% 1,4-trans structure components was kindly provided

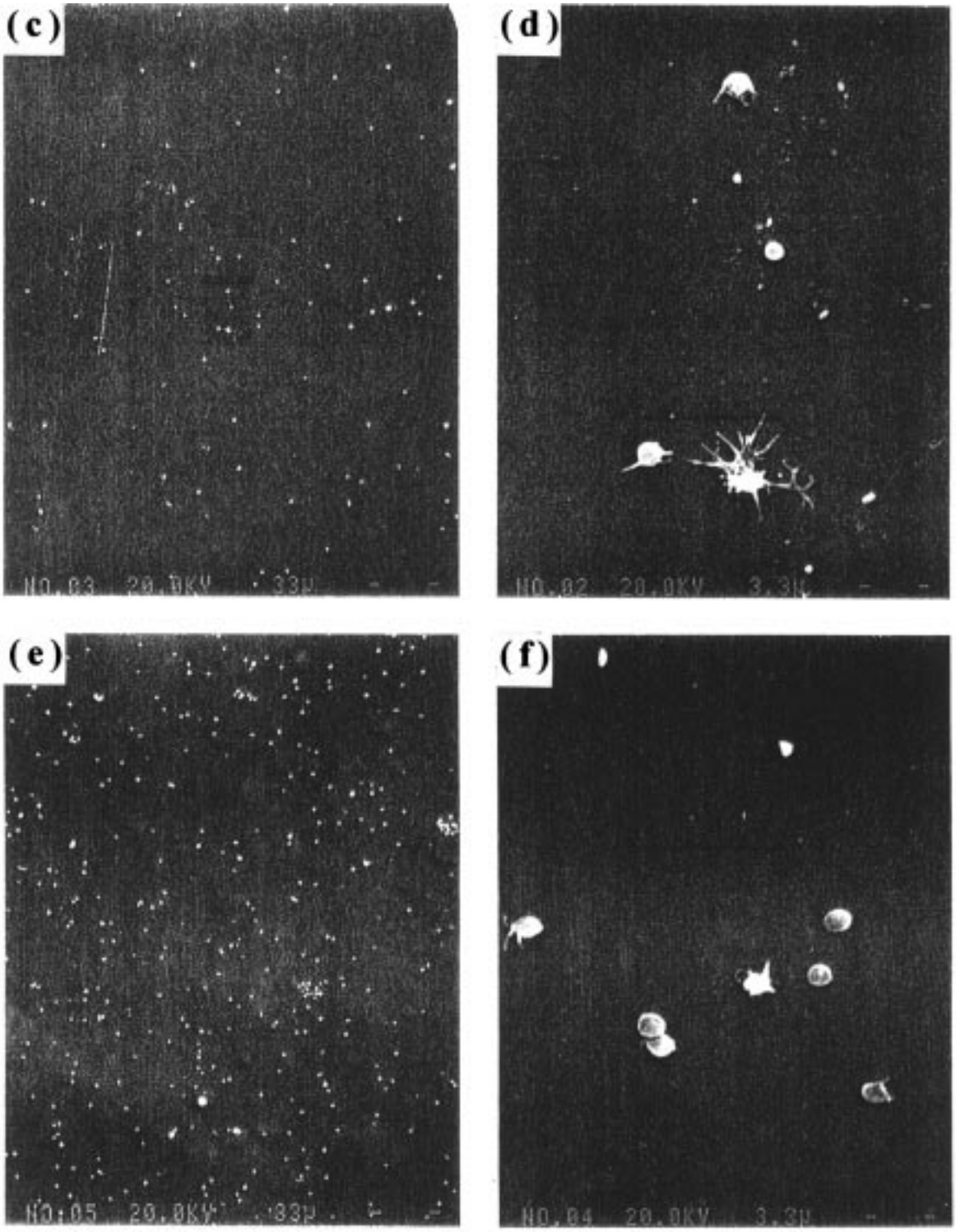

Figure 4. SEM photographs of the surfaces of MMA-grafted SPUs (V-SPU-M) and MMA and MTP-grafted SPU (V-SPU-M-P) films after 60 min of PRP exposure: (c and d) V-SPU-M and (e and f) V-SPU-M-P. Actual magnification: (c and e) ×300 and (d and f) ×3000.

by Nisso Kasei Co. Ltd. BD, MMA and BMA were commercially obtained from Nacalai Tesque, Inc., and purified by vacuum distillation. SMA was purified by recrystallization from methanol. Methanol was distilled in the presence of magnesium methoxide to ensure dryness. Acetone was distilled from anhydrous potassium carbonate. Toluene was distilled over phosphorus pentoxide. All other solvents were purchased as the best commercial grade and dried over 4A molecular sieves (Wako Pure Chemical Ind. Ltd.) prior to use.

Synthesis of MTP. The synthesis of MTP has been described in detail previously.[1]

Synthesis of V-SPU. As shown in Scheme 1, V-SPU based on vinyl-containing PBD and extended only with BD was synthesized according to a conventional two-step solution polymerization procedure under a nitrogen atmosphere.[23] 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 toluene:DMAc without catalyst. In the first step, 2.25 g (9.00 mmol) of MDI dissolved in 10 mL of the mixed solvent was added to a stirred

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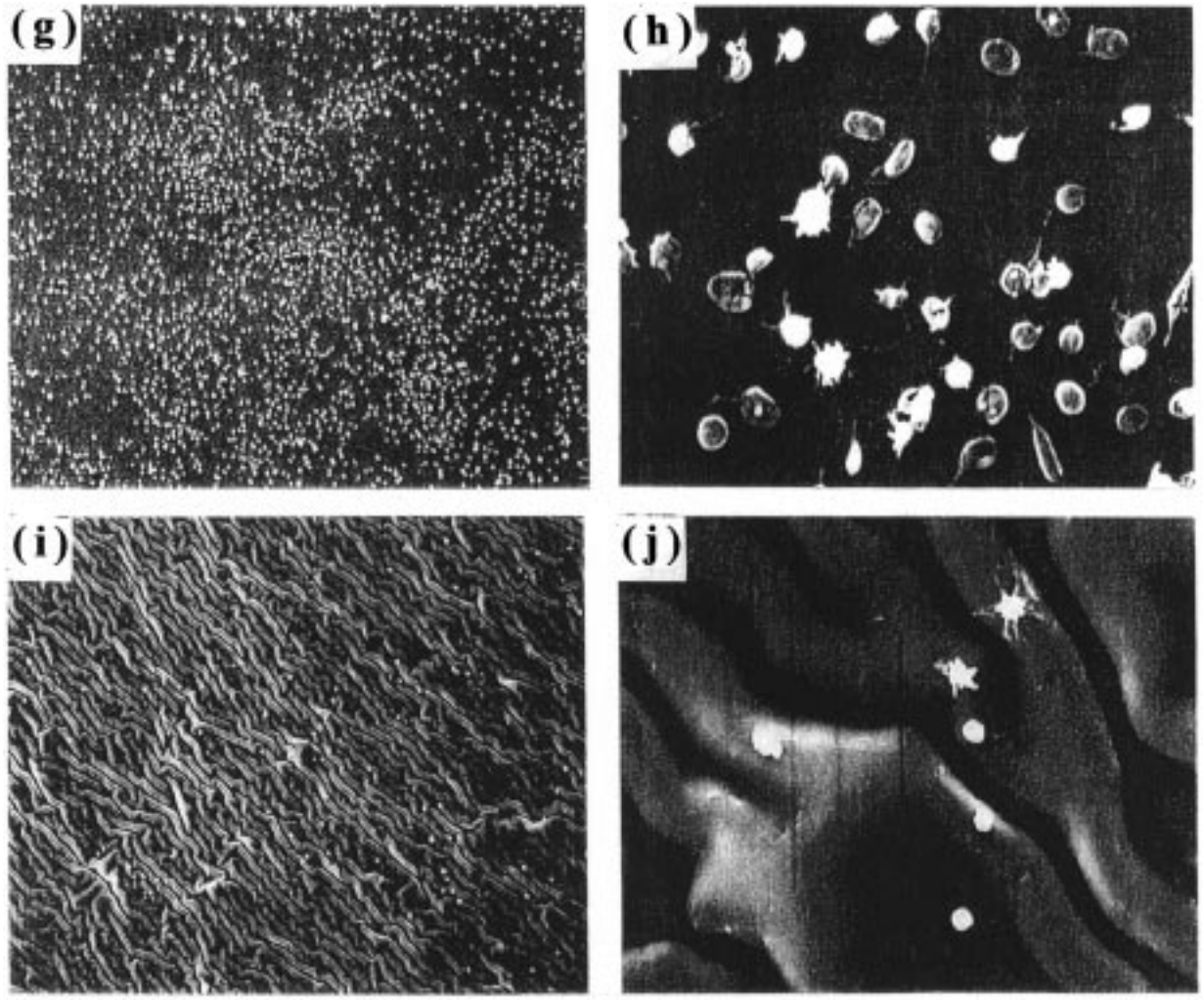

Figure 5. SEM photographs of the surfaces of BMA-grafted SPU (V-SPU-B-2) and BMA and MTP-grafted SPU (V-SPU-B-2-P) films after 60 min of PRP exposure: (g and h) V-SPU-B-2 and (i and j) V-SPU-B-2-P. Actual magnification: (g and i) ×300 and (h and j) ×3000.

solution of 5.85 g (3.00 mmol) of PBD (M_n = 1950) and 40 mL of the same mixed solvent under a dry nitrogen atmosphere. After stirring at 70 °C for 1 h, the solution was cooled to room temperature slowly. In the second step, 0.54 g (6.00 mmol) of BD, which was previously dissolved in 2 mL of the mixed solvent, was added dropwise over a 10-min period to the reaction mixture with stirring. Stirring was continued at 90 °C for 3 h, following stirring at 110 °C for another 1 h. The resulting V-SPU was precipitated in methanol. Then, the polymer was washed with methanol and the washing procedure was performed three additional times with methanol. The polymer was dried in a vacuum oven at 70 °C for at least 48 h. A pale yellow elastomer of V-SPU (8.0 g, 92%) was obtained: IR (film) 3300 (NH), 2900 (CH_3), 2850 (CH_2), 1710 (carbonyl of NHCOO), 1640 (C═C), 1600, 1515 cm^{-1} (aromatic CH). M_w = 43 000, M_n = 35 800, M_w/M_n = 1.2.

Grafting of Methacrylate Monomers MMA, BMA, SMA and Phosphatidylcholine Polar Headgroup Monomer MTP. As shown in Scheme 2, methacrylates and phosphatidylcholine polar headgroups were grafted onto V-SPU by two steps.

In the first step, V-SPU and methacrylate monomers MMA (or BMA, SMA) were dissolved into a 1:1 mixed solvent of anhydrous toluene and DMAc with 10% (wt/v) concentration, together with AIBN (1.0% mol of methacrylate monomer) as an initiator. The solutions were transferred into sealable ampules and were flushed with nitrogen under dry ice/methanol bath (−20 °C) for 10 min. Then the ampules were sealed and shaken at 70 °C for 20 h. After cooling to room temperature, the ampules were opened. The polymerization solutions were concentrated and poured into an amount of dry methanol to give pale yellow precipitates. The obtained precipitates were washed with dry acetone three times, and the precipitates were filtered off and then dried in a vacuum to afford grafted polymer V-SPU-M (or V-SPU-B or V-SPU-S) as white solids.

In the second step, MTP was grafted onto the synthesized V-SPU-M (or V-SPU-B or V-SPU-S) using the procedure similar to these described above. V-SPU-M (or V-SPU-B or V-SPU-S) and MTP were dissolved into a 2:2:1 mixed solvent of anhydrous toluene, DMAc and *N*-methylformamide with 10% (wt/v) concentration, together with AIBN (1.0% mol of MTP monomer) as an initiator. The solutions were sealed in the ampules and shaken at 70 °C for 20 h. The polymerization solutions were concentrated and poured into an amount of dry methanol to give pale yellow precipitates. The obtained precipitates were washed with dry methanol three times, and the precipitates were filtered off and then dried in a vacuum to afford grafted polymer V-SPU-M-P (or V-SPU-B-P or V-SPU-S-P) as white solids.

The grafted polymers were characterized by their IR (film), GPC, ATR-FTIR, ESCA spectral data, and contact angle measurements. The stoichiometry, yield, IR data, molecular weight, ESCA elemental surface composition (%), and water contact angles of the grafted SPUs are summarized in Tables 1 and 2.

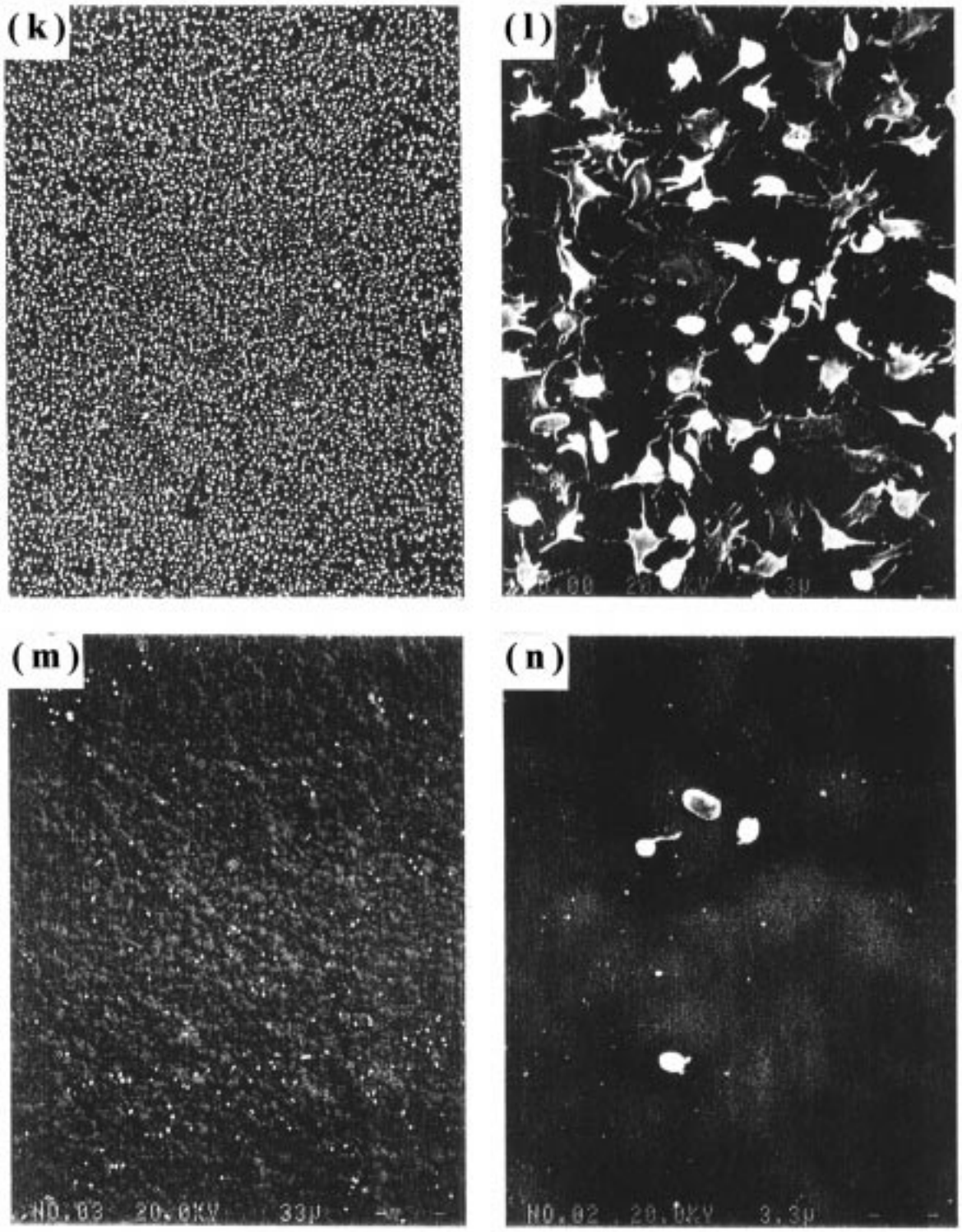

Figure 6. SEM photographs of the surfaces of SMA-grafted SPUs (V-SPU-S) and SMA and MTP-grafted SPU (V-SPU-S-P) films after 60 min of PRP exposure: (k and l) V-SPU-S and (m and n) V-SPU-S-P. Actual magnification: (k and m) ×300 and (l and n) ×3000.

Results and Discussion

Bulk Property Characterization. The IR spectral analyses of the polymers were taken on solvent-cast films. All of the phosphatidylcholine polar-headgroup-grafted polymers include both MDI and MTP, as is clear from the IR spectrum of each material. Adsorption bands due to NH stretches at 3300 cm^{-1}, C−H stretches at 2920 and 2850 cm^{-1}, urethane carbonyl stretch at 1740 cm^{-1}, C═C stretch 1640, aromatic C−H stretches at 1600 and 1520 cm^{-1}, ester ether CO−O at 1160 cm^{-1}, P═O at 1240 cm^{-1}, and P−O−CH_2− at 1070 cm^{-1} were observed.

The viscosity determination showed that the synthesized polymers had relatively high molecular weights and further proved by GPC characterization. From the relationship between retention time and molecular weights derived for narrow-distributed standard polystyrene, the weight-average molecular weights (M_w) and

corresponding polydispersities were derived. The results suggest that the grafted polymers increased their molecular weights.

The typical result of dynamic viscoelasticity experiment for the V-SPU-M-P film sample is displayed in Figure 1. The storage modulus (E') slowly decreased from 3.15×10^3 MPa at −150.3 °C to 1.2×10^3 MPa at 0 °C, following a rapid decrease with a 3-fold order of magnitude change. The elastomer region for the material was not clear. The peak of tan δ at 12 °C (T_g), together with the peak of loss modules (E'') at 2.1 °C, was also observed. Moreover, the tensile property of the V-SPU-M-P was also determined. This elastomer has an 8.74 MPa ultimate strength and an elongation at break of 53%. The Young's modules of this material was 8.6 MPa with elongation at 18%, although the data did not repeat, as the elongation reached around 860% for the second measurement while the film still did not break.

Surface Property Characterization. Surface properties of the polymer films were investigated by ATR-FTIR, ESCA, and contact angle measurements. The air-facing surface of the films were the blood-contacting surface; therefore, all surface and hemocompatible properties were related to the air-facing surface.

Figure 2 shows the ATR-FTIR spectra of the V-SPU, V-SPU-B-3, and V-SPU-B-3-P. The analyses for absorption bands are also shown in Figure 2. For V-SPU, unsaturated C═C stretches occur at 3074 cm^{-1}, trans 1,4-addition of C═C stretches at 964 cm^{-1}, and 1,2-addition of C═C stretches at 993 and 906 cm^{-1}. The NH stretches occur at 3309 cm^{-1}. The saturated C−H stretches occur at 2915 and 2842 cm^{-1}. The peak at 1709 cm^{-1} is assigned to carbonyl groups that are hydrogen bonded (presumably to the urethane hydrogens), and the peak at 1724 cm^{-1} is assigned to carbonyl groups that are not hydrogen-bonded. Moreover, the band at 1639 cm^{-1} of the amide I stretch and the peaks at 1597 and 1508 cm^{-1} due to aromatic C−H stretching were clearly observed.

Compared to V-SPU, V-SPU-B-3 and V-SPU-B-3-P displayed additional stretches at 1724, 1238, and 1145 cm^{-1} due to C═O and CO−O− bonds. Meanwhile 1,2-addition of C═C stretches at 993 and 906 cm^{-1} showed reduction. This indicates that BMA was successfully grafted onto the V-SPU.

Compared to V-SPU-B-3, V-SPU-B-3-P displayed additional stretches at 1085 cm^{-1} due to the P−O−CH_2− bond. This indicates that the phosphatidylcholine polar headgroup monomer MTP was successfully grafted onto the V-SPU-B-3.

Table 2 lists ESCA elemental surface compositions and the water contact angle of the grafted polymers. The ratio of the peak area of phosphorus to that of carbon (P_{2p}/C_{1s}) was also calculated and summarized in Table 2. ESCA measurements showed the presence of phosphorus, which is a strong indication of the presence of phosphatidylcholine polar headgroups. The phosphatidylcholine polar-headgroup-grafted SPUs surfaces showed slightly decreased water contact angles, also indicating that hydrophilic phosphatidylcholine polar headgroups are present at the surface.

Hemocompatibility Evaluation. The methacrylates (MMA, BMA, or SMA) and phosphatidylcholine polar headgroup monomer MTP grafted SPUs were assessed as biomaterials by the degree and nature of blood platelet adhesion resulting from exposure to platelet-rich plasma (PRP) for 60 min. The specimens incubated in PRP were viewed by SEM. The typical SEM photographs of V-SPU (a and b), V-SPU-M (c and d), V-SPU-M-P (e and f), V-SPU-B-2 (g and h), V-SPU-B-2-P (i and j), V-SPU-S (k and l), and V-SPU-S-P (m and n) are shown in Figures 3−6.

For grafted phosphatidylcholine polar-headgroup-containing SPUs, the hemocompatibilities of the materials were significantly improved. The grafted SPUs showed a relatively limited number of platelets adhered, and the cells remained rounded with no extensions formed relative to unmodified V-SPU. Generally, it seemed that the magnificence of the morphology changed in the following order: V-SPU > V-SPU-S > V-SPU-B > V-SPU-M > V-SPU-M-P > V-SPU-B-P > V-SPU-S-P.

The platelet density in 10 μm × 10 μm was 6.54, 6.10, 5.85, 0.75, 0.77, 0.53, and 0.34 for V-SPU, V-SPU-S, V-SPU-B, V-SPU-M, V-SPU-M-P, V-SPU-B-P, and V-SPU-S-P, respectively. These results indicated that the phosphatidylcholine polar-headgroup-grafted polymers did not support platelet adhesion.[24−26] Platelet adhesion to phosphatidylcholine polar-headgroup-grafted polymers V-SPU-M-P, V-SPU-B-P, and V-SPU-S-P was inhibited 88%, 92%, and 95% compared with unmodified V-SPU, respectively. Additionally, it was observed that the attached platelet density for V-SPU-M-P was slightly higher than that of V-SPU-M, but V-SPU-M-P greatly reduced the shape change of adhered platelets.

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