Synthesis and Hemocompatibility Evaluation of Novel Segmented Polyurethanes with Phosphatidylcholine Polar Headgroups

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A new diol with a phosphatidylcholine polar headgroup, [bis(2-hydroxymethyl)]propane-2-(trimethylammonio)ethyl phosphate (BTEP), was synthesized and characterized. The BTEP, together with 1,4-butanediol (BD) as a chain extender, was used to synthesize segmented polyurethanes (SPUs) based on diphenylmethane diisocyanate (MDI) and various types of soft segments such as polycarbonate, polyether, polyester, and hydrocarbon diols. The bulk characteristics of the resulting SPUs were investigated by infrared (IR) spectroscopy, viscosity, and gel-permeation chromatography (GPC) measurements. Good mechanical properties of the typical SPU containing poly(butadiene) glycol (PBD) were indicated by dynamic viscoelasticity and tensile measurements. The phosphatidylcholine polar groups 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 hemocompatibilities of the new polymers were evaluated by platelet-rich plasma (PRP) contact studies and viewed by scanning electron microscopy (SEM) using medical BioSpan as a reference. The new materials have good surfaces in terms of platelet adhesion, and the morphology of adhered platelets undergoes a relatively low degree of variation. Suitably increasing percentages of phosphatidylcholine polar groups in the polymers and higher molecular weights of the soft segments of the polymers may further improve hemocompatibility.

Introduction

Recently, we reported new polyurethanes bearing phosphatidylcholine analogues in the side chains[1−4] and main chains.[5−7] We also reported a series of phospholipid-segmented polyurethanes which showed excellent mechanical properties, significant blood compatibilities,[8−12] and amphiphilic microphase-separated domain structures.[13] On the other hand, phosphatidylcholine polar headgroups have been shown to enhance hemocompatibility.[14−18] In this study, a new diol with phosphatidylcholine polar headgroups, [bis(2-hydroxymethyl)]propane-2-(trimethylammonio)ethyl phosphate (BTEP), was synthesized. Using 1,4-butanediol (BD) as a chain extender, BTEP was used to synthesize new SPUs based on diphenylmethane diisocyanate (MDI) as well as several types of soft segments such as a polycarbonate diol [poly(1,6-hexyl-1,2-ethylcarbonate) diol (PHEC)], a polyether diol [polytetramethylene glycol (PTMG) or poly(ethylene glycol) (PEG)], a polyester diol (N-4012), a hydrocarbon polydiol [poly(butadiene) glycol (PBD)], and a hydrogenated poly(butadiene) glycol (HPBD). Bulk characterization of the polymers included IR spectroscopy, viscosity, and GPC measurements. The mechanical property investigation included dynamic viscoelasticity measurements and tensile measurements. Surface characterization was performed by ATR−FTIR spectroscopy, ESCA, and contact angle measurements. The hemocompatibility of the polymers

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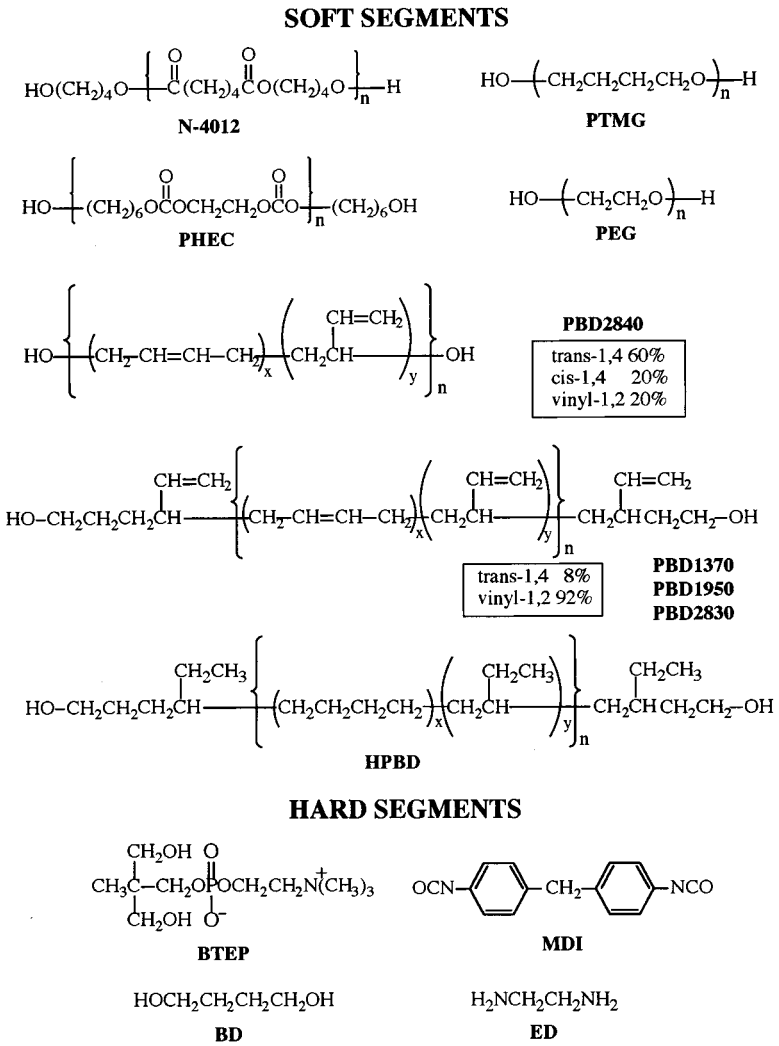

Figure 1. Chemical structures and abbreviations of the SPU and SPUU components.

Table 1. Stoichiometry, Yield, and Molecular Weights of the SPUs

polymer	stoichiometry polydiol:MDI:BTEP:BD	yield (%)	$M_w \times 10^4$	$M_n \times 10^4$	M_w/M_n
SPU_{PHEC}	1:3:1:1	69.7	1.90	0.95	2.0
SPU_{PEG}	1:3:1:1	68.3	3.66	1.74	2.1
SPU_{PTMG}	1:3:1:1	63.7	2.78	1.21	2.3
$SPU_{N-4012a}$	1:3:1:1	84.1	2.41	1.34	1.8
$SPU_{N-4012b}$	1:4:2:1	81.5	2.71	1.43	1.9
$SPU_{PBD2840}$	1:3:1:1	85.9	1.46	0.73	2.0
$SPUU_{PBD2840}$[a]	1:3:1:1	94.2	1.01	0.44	2.3
$SPU_{PBD1370}$	1:3:1:1	79.7	1.39	0.63	2.2
$SPU_{PBD1950}$	1:3:1:1	76.0	1.83	0.92	2.0
$SPU_{PBD2830}$	1:3:1:1	78.3	3.14	1.31	2.4
SPU_{HPBD}	1:3:1:1	83.4	1.02	0.48	2.1
$SPU_{control}$	1:3:0:2	95.0	4.05	3.95	1.0

[a] For $SPUU_{PBD2840}$ ED was used instead of BD.

was evaluated by describing the platelet state and shape variation for the attached platelets.

Experimental Section

General Methods. After briefly drying under vacuum to remove residual methanol, the polymers were dissolved in suitable solvents such as *N*,*N*-dimethylformamide (DMF), DMF/*N*,*N*-dimethylacetamide (DMAc) (volume ratio, 1/1), DMAc/tetrahydrofuran (THF)/*N*-methylformamide (NMF) (volume ratio, 1/1/0.1), and DMF/toluene/NMF (volume ratio, 8/3/0.1, 2/1/0.1, or 1/4/0.1, 1/4/0.1) by using an ultrasonic generator. The polymer solutions (10% w/v) were cast onto glass plates, and dried in an oven at 70 °C for at least 48 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 48 h to remove residual solvents. The IR spectral analyses of the polymers were taken on cast films using a Jasco A 202 spectrometer. GPC measurements were performed on an HLC802UR GPC instrument with G4000H8 + G2000H8 columns; the samples were dissolved in DMF, and narrow molecular weight poly(ethylene glycols) were used as standards. 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 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}. ATR−FTIR spectroscopy was performed on surfaces of films cast

Scheme 1. Synthesis of New Diol with Phosphatidylcholine Polar Group

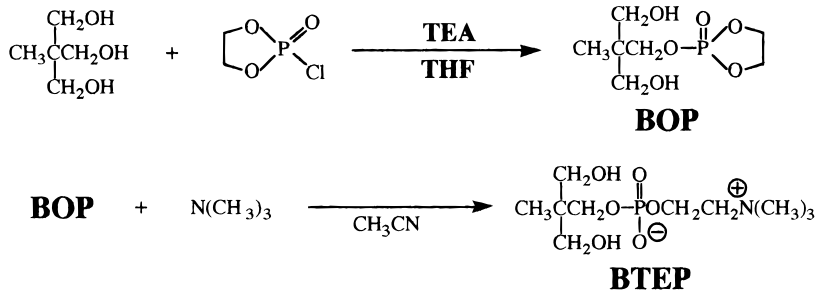

Table 2. ESCA Elemental Surface Composition (%) and Water Contact Angles of the SPUs[a]

polymer	C_{1s}	O_{1s}	N_{1s}	P_{2p}	P_{2p}/C_{1s}	contact angle (deg)
SPU_{PHEC}	76.42(56.04)	21.15(33.27)	2.02(3.13)	0.41(0.99)	0.0054	82.0 ± 3
SPU_{PEG}	68.07(57.19)	29.10(30.71)	2.39(3.13)	0.44(0.99)	0.0065	69.2 ± 2
SPU_{PTMG}	75.99(64.87)	21.67(22.01)	1.90(3.13)	0.44(0.99)	0.0057	81.8 ± 4
$SPU_{N-4012a}$	73.81(61.03)	24.91(27.64)	1.00(3.13)	0.29(0.99)	0.0038	77.7 ± 2
$SPU_{N-4012b}$	70.74(60.30)	27.09(27.09)	1.58(3.82)	0.59(1.69)	0.0085	77.1 ± 3
$SPU_{PBD2840}$	73.86(80.78)	24.39(6.45)	1.48(2.47)	0.38(0.78)	0.0044	94.0 ± 2
$SPUU_{PBD2840}$	79.80(80.79)	19.11(5.69)	0.88(3.20)	0.21(0.79)	0.0026	94.6 ± 4
$SPU_{PBD1370}$	82.63(76.44)	14.81(10.26)	2.03(3.92)	0.53(1.24)	0.0064	98.1 ± 3
$SPU_{PBD1950}$	79.04(78.41)	19.49(8.32)	1.15(3.18)	0.32(1.01)	0.0040	102.4 ± 2
$SPU_{PBD2830}$	80.01(80.68)	18.73(6.47)	1.07(2.47)	0.19(0.78)	0.0023	103.2 ± 3
SPU_{HPBD}	80.09(74.46)	18.50(10.05)	1.19(3.85)	0.21(1.22)	0.0026	105.5 ± 2

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

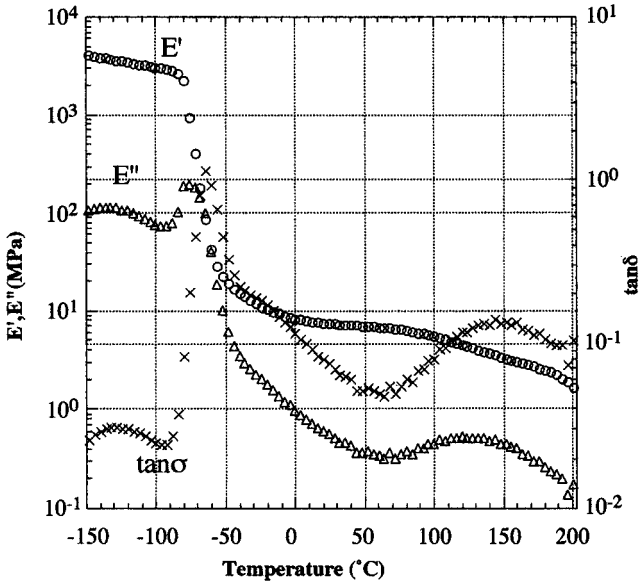

Figure 2. Temperature dependence of the storage modulus (E'), the loss modulus (E''), and the loss tangent (tan δ) for typical SPU_{2840} at 11 Hz.

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 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 shape variation was the same as that described previously.[2] 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) by centrifugation at 1000 rpm for 20 min. Samples were rinsed with saline, treated with 2.5% glutaraldehyde in saline, and kept at 5 °C overnight. The sample was rinsed with saline and dehydrated by systematic immersion in a series of ethanol−water solutions: 60, 70, 80, 90, and 100% ethanol, v/v. After critical-point drying with carbon dioxide, the samples were coated with gold prior to being observed in an electron probe microanalyzer (EPM-810, Shimadzu) operated at an accelerating voltage of 20 kV. Medical grade segmented polyurethanes (BioSpan) based on poly(tetramethylene) glycol (PTMG) were used as a control sample.

Materials. THF was distilled from lithium aluminum hydride to ensure dryness. DMF, DMAc, and NMF were dehydrated over calcium hydride for 2 days and then vacuum distilled. Methanol was distilled in the presence of magnesium methoxide to ensure dryness. BD was commercially obtained from Nacalai Tesque, Inc., Japan, and purified by vacuum distillation. All other solvents were purchased as the best commercial grade and dried over 4A molecular sieves (Wako Pure Chemical Ind., Ltd., Japan) prior to use. Polyester diol, N-4012 (M_n = 2000), was received from Nippon Polyurethane Industry Co., Ltd. PHEC (M_n = 2000) and BioSpan were received from Polymer Technology Group Inc. One PBD with a number-average molecular weight (M_n) of 2840 and comprising 20% 1,2-vinyl, 60% 1,4-trans, and 20% 1,4-cis structure components; three PBDs having 92% 1,2-vinyl and 8% 1,4-trans structure components and M_n's of 1370, 1950, and 2830; and one HPBD with an M_n of 1420 were kindly provided by Nippon Oil and Fats Co., Ltd.

Synthesis of BTEP. Trimethylolethane (10.0 g, 0.083 mol) was dissolved in dry tetrahydrofuran (250 mL); triethylamine (8.4 g, 0.083 mol) was added, and then at room temperature 2-chloro-2-oxo-1,3,2-dioxaphospholane[19] (9.55 g, 0.067 mol) was added dropwise over 30 min with stirring. After the addition was complete, the reaction was continued at room temperature with stirring overnight. The precipitated triethylamine hy-

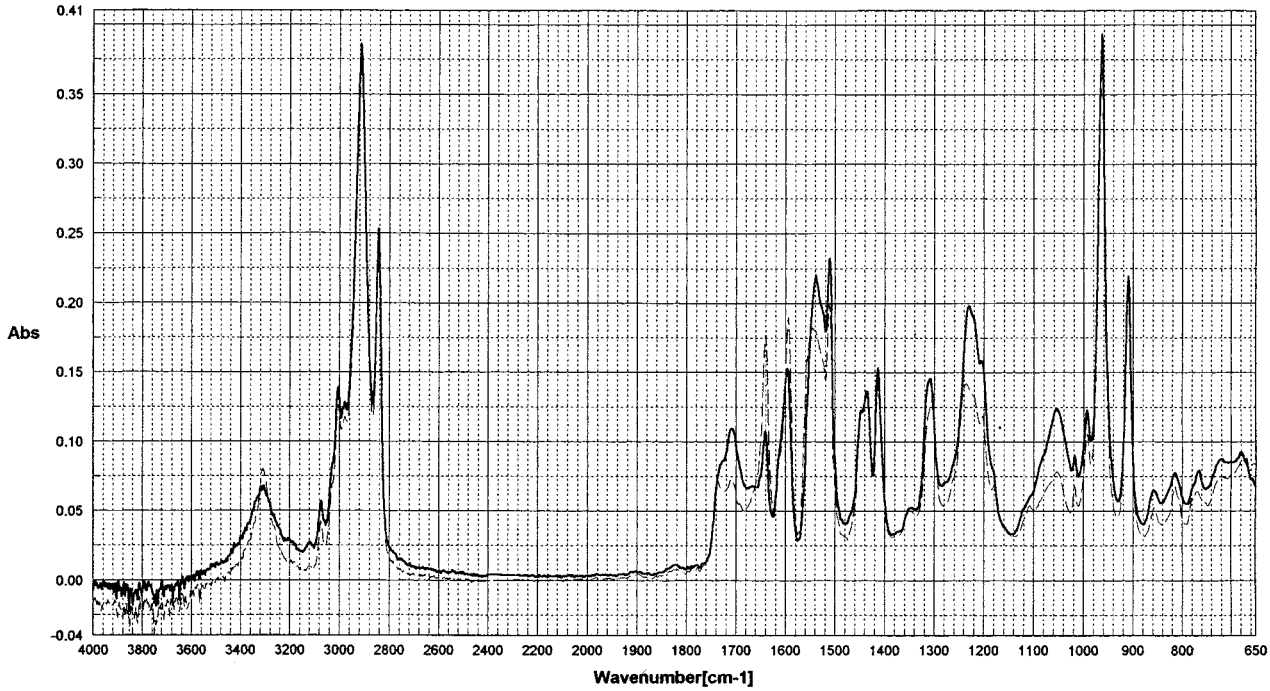

Figure 3. ATR−FTIR spectra of the SPU_{2840} (solid line) and $SPU_{control}$ (dashed line).

drochloride was filtered off, and the filtrate was concentrated under reduced pressure to remove solvent. The residual pale yellow viscous liquid was thoroughly washed with ethyl acetate to give the intermediate 2-[2-bis(hydroxymethyl)]propyloxy-2-oxo-1,3,2-dioxaphospholane. Which was then directly combined with acetonitrile (30 mL) and an excess of trimethylamine.[20] These compounds were placed in a pressure-resistant glass bottle, sealed, and reacted at 40−50 °C overnight. The acetonitrile was removed under reduced pressure. The residual liquid was washed with dry acetone and dried under vacuum to obtain BTEP (16.8 g, 63.2% yield). IR (neat) 3400 (OH), 2900 (CH_3), 1200 (P═O), 1050 ($POCH_2$) cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.65−0.7 (CCH_3, s, 3H), 3.3 [$N^+(CH_3)_3$, s, 9H], 3.6−3.75 [$C(CH_2OH)_2$, s, 4H), 3.9−4.3 (CCH_2OP, $POCH_2$-CH_2N^+, m, 6H). Anal. Calcd for $C_{10}H_{24}NO_6P{\cdot}2H_2O$: N, 4.4. Found: N, 4.6.

Synthesis of SPUs. The process of synthesizing SPUs was similar to that reported recently.[8−12] The polymers were based on a 1/3/1/1 molar ratio of polymeric diol/MDI/BTEP/BD. The reaction was carried out in a suitable solvent without catalyst. All SPUs were synthesized by similar methods; therefore, a representative synthesis is described below.

SPU_{PTMG} (PTMG−MDI−BTEP−BD). In the first step, a solution of 0.75 g (3.0 mmol) of MDI dissolved in 30 mL of DMF was added to 2.0 g (1.0 mmol) of PTMG (M_n = 2000) with stirring under a dry nitrogen atmosphere. After 1 h at 70−75 °C, the solution was cooled to room temperature slowly. In the second step, 0.285 g (1.0 mmol) of BTEP, which was previously dissolved in 5 mL of DMF, was slowly added into the reaction solution. Stirring was continued at 90−95 °C for 3 h. For the last step, using the same procedure, 0.09 g (1.0 mmol) of BD, which was previously dissolved in 1 mL of DMF, was added dropwise to the reaction mixture with stirring. The stirring was continued at 105−110 °C for 1 h. The resulting polyurethane was precipitated in methanol and washed with methaol. The polymer was dried in a vacuum oven at 70 °C for at least 48 h. A pale yellow elastomer of the SPU_{PTMG} (2.0 g, 63.7% yield) was obtained. IR (film) 3300 (NH), 2900 (CH_3), 1440 (CN stretch), 1710 (carbonyl of NHCOO), 1590 (aromatic CH), 1230 (P═O), 1050 cm^{-1} ($POCH_2$). M_w= 27 800, M_n= 12 100, M_w/M_n = 2.3.

The other phospholipid SPUs were synthesized using procedures similar to these described above. For segmented poly(urethane ureas) (SPUUs), only at the last step, ED was used instead of BD, and PHEC, PEG, N-4012, PBD, and HPBD were used instead of PTMG. The chemical structures of the SPU and SPUU components and detailed synthesis conditions for the synthesized phospholipid polymers are summarized in Figure 1 and Table 1.

Results and Discussion

Synthesis of a Novel Diol with a Phosphatidylcholine Polar Group. The new diol containing a phosphatidylcholine polar group was synthesized according to Scheme 1. The reaction of trimethylolethane with 2-chloro-2-oxo-1,3,2-dioxaphospholane was carried out in THF in the presence of triethylamine (TEA) at a 1/0.8 molar ratio to give 2-[2-bis(hydroxymethyl)]propyloxy-2-oxo-1,3,2-dioxaphospholane (BOP). BOP could be purified simply by washing thoroughly with ethyl acetate. On the basis of the ratio of C−CH_3 between BOP and 2,2-bis(methyloxy-2-oxo-1,3,2-dioxaphospholane)propanol in ^1H NMR spectra, it was determined that BOP was obtained with more than 90% purity. Successively, according to Thuong and Chabrier's method,[21] the ring-opening reaction of BOP was carried out by trimethylamine in dry acetonitrile to obtain BTEP.

Bulk Property Characterization. The IR spectral analyses of the polymers were taken on solvent-cast films. All of the phospholipid polymers include both MDI and phospatidylcholine moieties as is clear from the IR spectrum of each material. Adsorption bands due to NH stretches at 3300 cm^{-1}, a urethane carbonyl stretch at 1710 cm^{-1}, C−H stretches at 2900 cm^{-1}, a C−N stretch at 1440 cm^{-1}, aromatic C−H stretches at

(19) 2-Chloro-2-oxo-1,3,2-dioxaphospholane was synthesized according to Lucas and Edmundson's method. (a) Lucas, H. J.; Mitchell, F. W.; Scully, C. N. *J. Am. Chem. Soc.* **1950**, *72*, 5491. (b) Edmundson, R. S. *Chem. Ind. (London)* **1962**, 1828.

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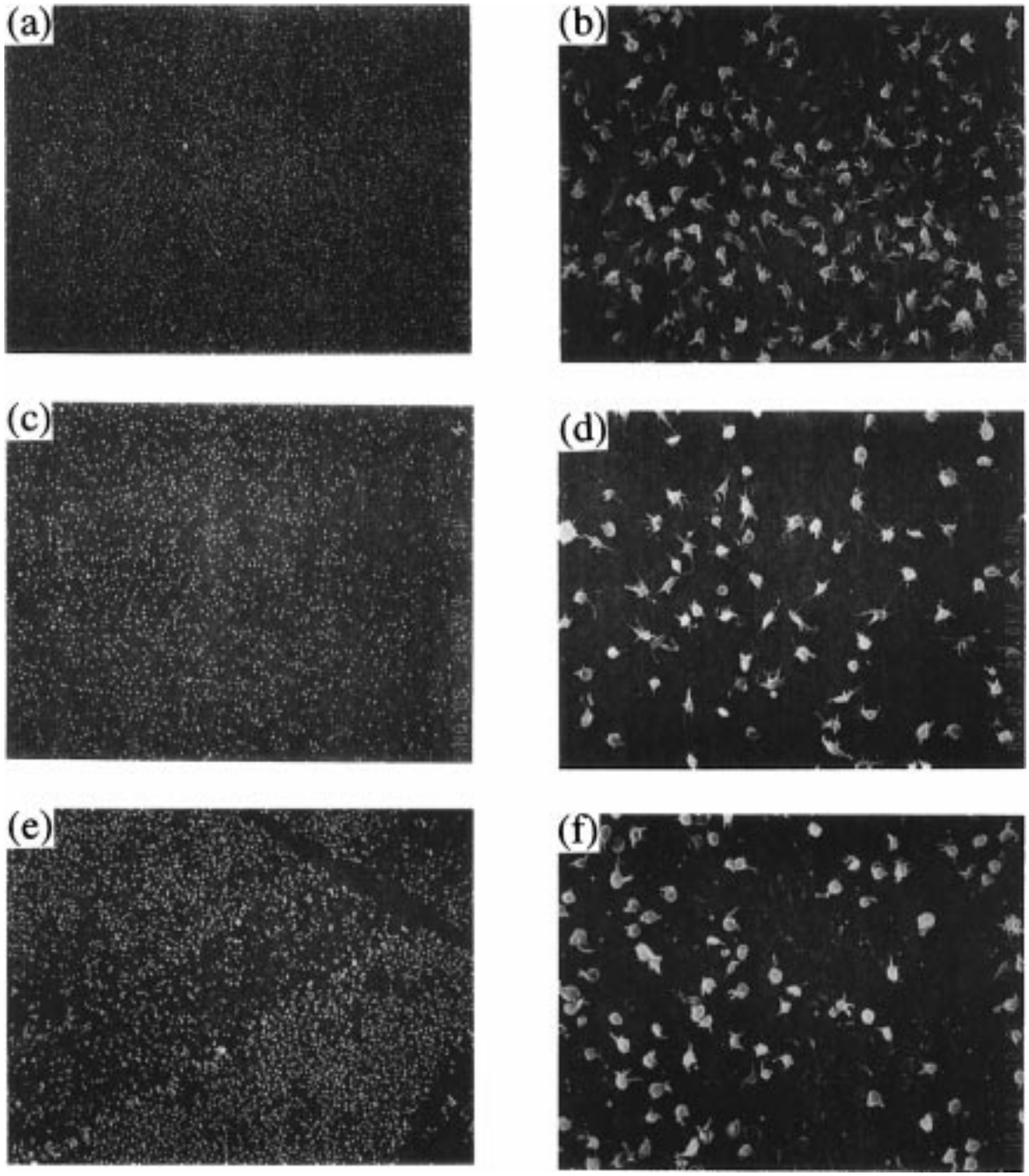

Figure 4. SEM photographs of the surface of phospholipid SPU films after 60 min of PRP exposure. (a and b) Medical grade BioSpan; (c and d) SPU_{PTMG}; (e and f) $SPU_{N-4012a}$. Actual magnification: a, c, and e, 270×; b, d, and f, 1800×.

1590 cm^{-1}, a P═O at 1230 cm^{-1}, and a P−O−CH_2− at 1050 cm^{-1} were observed.

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

Typical results of a dynamic viscoelasticity experiment for the $SPU_{PBD2840}$ film sample are displayed in Figure 2. The storage modulus (E') slowly decreased from 1.7 × 10^3 MPa at −150 °C to 1.3 × 10^3 MPa at −80 °C, following a rapid decrease with a 2-fold order of magnitude change. The material reached the elastomer region at 17 MPa near −45 °C. The peak of tan δ at −64 °C (T_g), together with the peak of the loss modulus (E'') at −75 °C was also observed. Moreover, the tensile properties of $SPU_{PBD2840}$ were also determined. This elastomer has a 3.40 MPa 100% modulus, a 4.40 MPa ultimate strength, and an elongation at break of 142%.

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 was the blood-contacting surface; therefore, all surface and hemocompatibility properties were related to the air-facing surface.

Figure 3 shows the ATR−FTIR spectra of the typical phospholipids $SPU_{PBD2840}$ and $SPU_{control}$ (PBD2840/MDI/BD = 1/3/2). The spectra of the polymers give evidence of unsaturated C═C bonds, PO_4^-, N−H, C═O, quater-

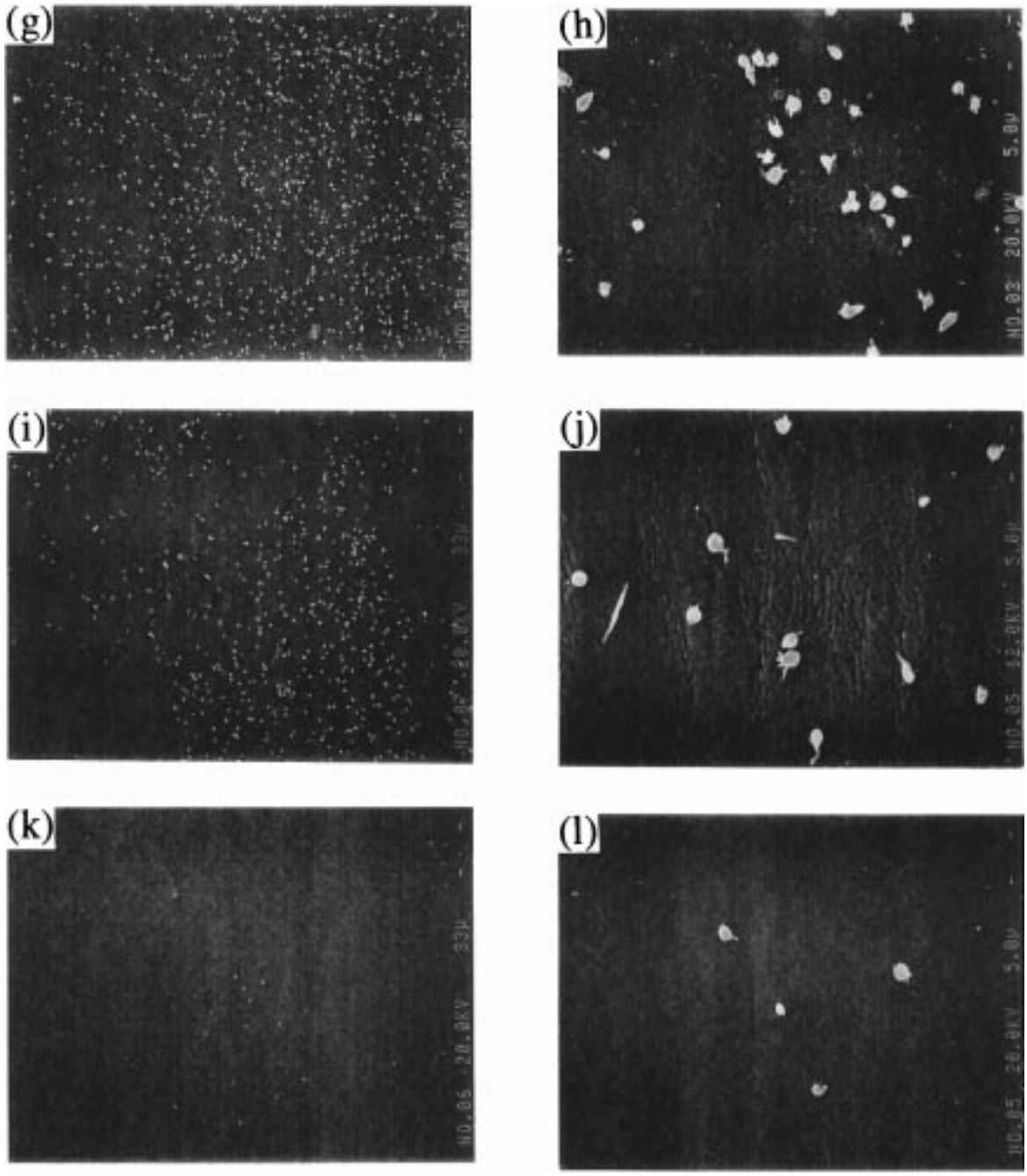

Figure 5. SEM photographs of the surface of phospholipid SPU films after 60 min of PRP exposure. (g and h) SPU_{PHEC}; (i and j) $SPU_{N-4012b}$; (k and l) SPU_{PEG}. Actual magnification: g, i, and k, 270×; h, j, and l, 1800×.

nary ammonium, nonbonded and bonded urethane, and unsaturated aromatic bonds. The analysis of PBD composition has been discussed in detail in a previous article.[8] Unsaturated C═C stretches occur at 3075 cm^{-1}; trans 1,4-addition of C═C stretches, at 964 cm^{-1}; cis 1,4-addition of C═C stretches, at 680 cm^{-1}; and 1,2-addition of C═C stretches, at 993 and 910 cm^{-1}. The NH stretches occur at 3311 cm^{-1}. The peak at 1710 cm^{-1} is assigned to carbonyl groups that are hydrogen bonded (presumably to the urethane hydrogens), and the peak at 1730 cm^{-1} is assigned to carbonyl groups that are not hydrogen bonded. Moreover, the relatively weaker band at 1641 cm^{-1} of the amide I stretch and the peak at 1595 cm^{-1} due to aromatic C−H stretching were clearly observed. Compared to a control sample ($SPU_{control}$) without the phosphatidylcholine moiety, $SPU_{PBD2840}$ displayed additional stretches at 1230 and 1050 cm^{-1} due to P═O and P−O−CH_2− bonds.

Table 2 lists ESCA elemental surface compositions and water contact angles of the synthesized polymers. The P_{2p} data suggest that phosphatidylcholine polar groups orient on the surface for relatively hydrophilic soft segments. The ratio of the peak area of phosphorus to that of carbon (P_{2p}/C_{1s}) was also calculated and is summarized in Table 2.

To investigate the hydrophilicity−hydrophobicity of the surface of the polymers, water contact angle measurements were carried out (Table 2). The large contact angles of the HPBD- and PBD-containing polymers indicated that these materials had extremely hydrophobic surfaces. As ESCA indicated, samples with the highest carbon content are the most hydrophobic.

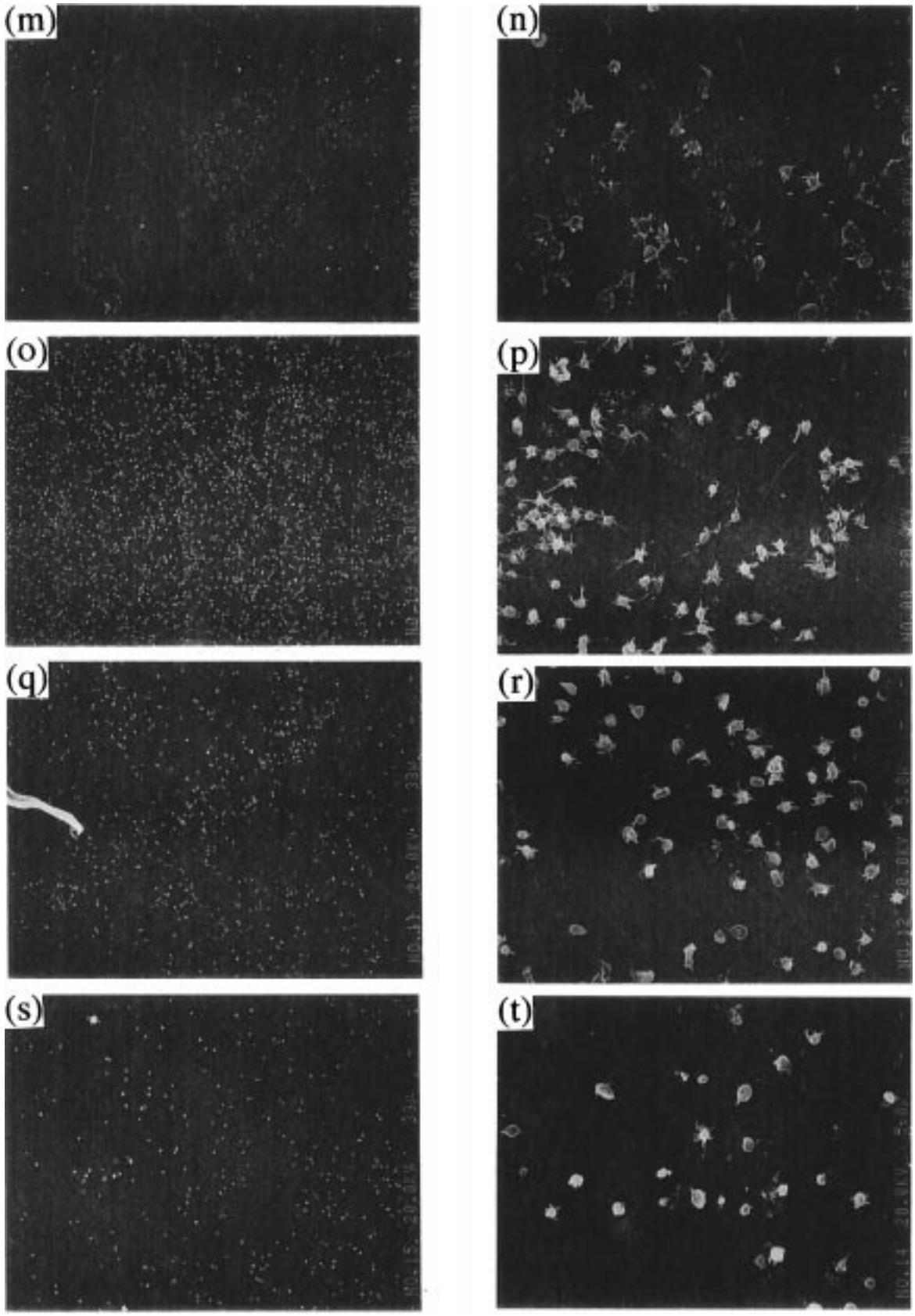

Figure 6. SEM photographs of the surface of phospholipid SPU films after 60 min of PRP exposure. (m and n) $SPU_{control}$; (o and p) $SPUU_{PBD2840}$; (q and r) $SPU_{PBD1370}$; (s and t) $SPU_{PBD1950}$. Actual magnification: m, o, q, and s, 270×; n, p, r, and t, 1800×.

Hemocompatibility Evaluation. The synthesized SPUs and SPUUs 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. Figures 4−7 show typical SEM photographs of medical grade BioSpan (a and b), SPU_{PTMG} (c and d), $SPU_{N-4012a}$ (e and f), SPU_{PHEC} (g and h), $SPU_{N-4012b}$ (i and j),

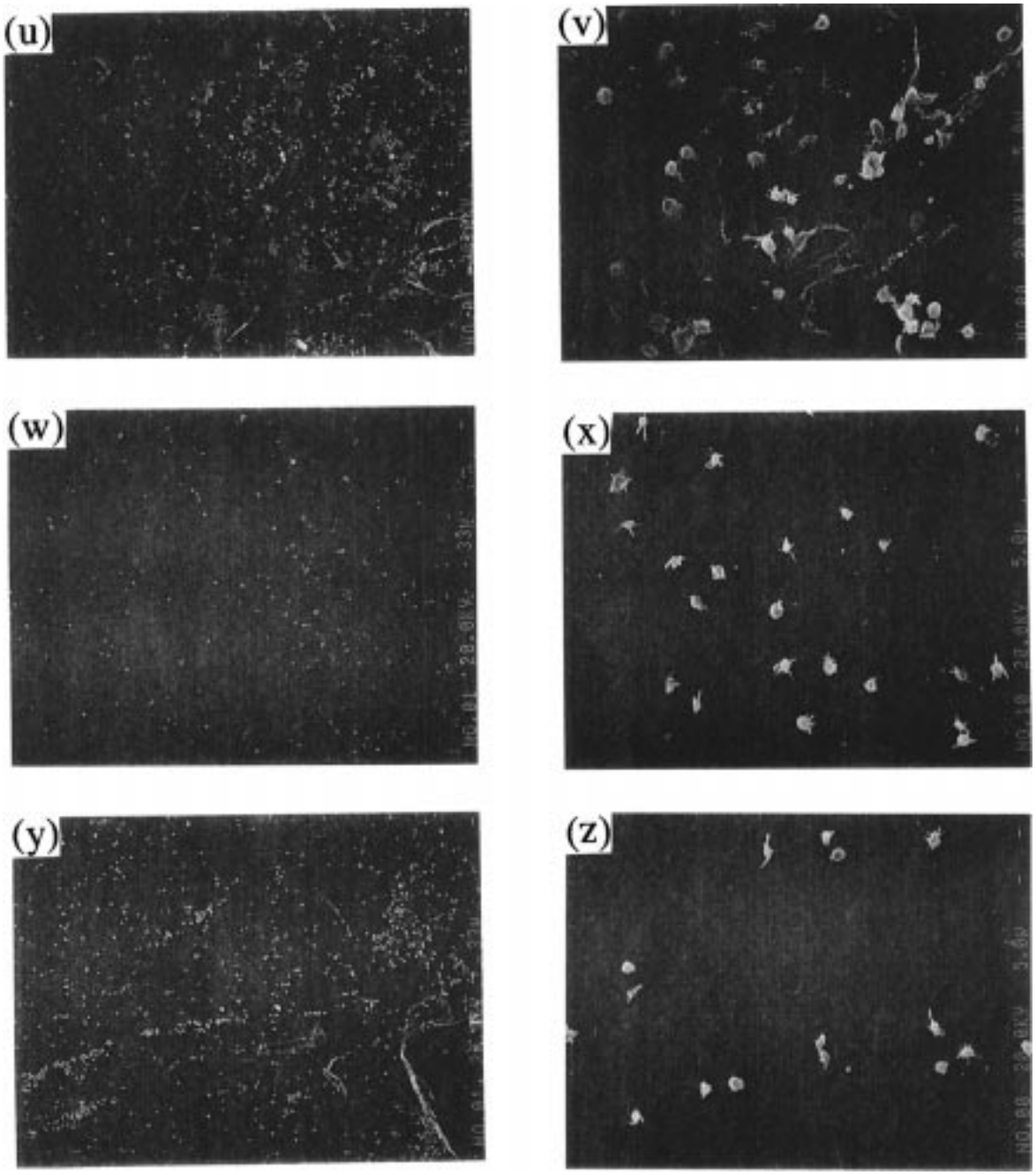

Figure 7. SEM photographs of the surface of phospholipid SPU films after 60 min of PRP exposure. (u and v) SPU_{HPBD}; (w and x) $SPU_{PBD2840}$; (y and z) $SPU_{PBD2830}$. Actual magnification: u, w, and y, 270×; v, x, and z, 1800×.

SPU_{PEG} (k and l), $SPU_{control}$ (m and n), $SPUU_{PBD2840}$ (o and p), $SPU_{PBD1370}$ (q and r), $SPU_{PBD1950}$ (s and t), SPU_{HPBD} (u and v), $SPU_{PBD2840}$ (w and x), and $SPU_{PBD2830}$ (y and z).

For synthesized phospholipid SPUs, a relatively limited number of platelets adhered and the cells remained rounded with no extensions formed relative to BioSpan. Generally, it seemed that the apparent degree platelet shape change of was in the order BioSpan > SPU_{PTMG} > $SPU_{N-4012a}$ > SPU_{PHEC} > $SPU_{N-4012b}$ > SPU_{PEG}. For hydrocarbon-based SPUs, the magnitude of morphology change was in the order $SPU_{control}$ > $SPUU_{PBD2840}$ > $SPU_{PBD1370}$ > $SPU_{PBD1950}$ > SPU_{HPBD}> $SPU_{PBD2840}$ > $SPUU_{PBD2830}$.

The platelet densities in 10 μm^2 were 7.61, 2.75, 3.4, 1.23, 0.4, 0.14, 1.81, 3.04, 2.5, 1.01, 1.3, 0.8, and 0.58 for BioSpan, SPU_{PTMG}, $SPU_{N-4012a}$, SPU_{PHEC}, $SPU_{N-4012b}$, SPU_{PEG}, $SPU_{control}$, $SPUU_{PBD2840}$, $SPU_{PBD1370}$, $SPU_{PBD1950}$, SPU_{HPBD}, $SPU_{PBD2840}$, and $SPU_{PBD2830}$, respectively. These results indicate that the hemocompatibility of the synthesized polymers is generally better than that of the medical grade segmented polyurethane BioSpan. It should be noted that for $SPU_{control}$, although the attached platelet density was not the highest among the hydrocarbon-based SPUs, the attached patelets showed the greatest shape change. Additionally, it seems that suitably increasing the phosphatidylcholine polar group percentage in the polymer and increasing the molecular weight of the soft segments may further improve the hemocompatibility.

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