Synthesis and Hemocompatibility of Biomembrane Mimicing Poly(carbonate urethane)s Containing Fluorinated Alkyl Phosphatidylcholine Side Groups

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In this article, we designed and synthesized biomembrane mimicing segmented poly(carbonate urethane)s containing fluorinated alkyl phosphatidylcholine (PC) side groups. To obtain these novel poly(carbonate urethane)s, a new diol with a long side chain fluorinated alkyl phosphatidylcholine polar headgroup (2-[2-2,2,3,3,4,4,5,5,6,6,7,7,8,8,9,9−hexadecafluoro−10−ethoxy−decyloxy-*N*-(2-hydroxy-1-hydroxymethyl-1-methyl-ethyl)-acetamide] phosphatidylcholine, HFDAPC) was first synthesized and characterized. Then a series of poly(carbonate urethane)s containing fluorinated alkyl phosphatidylcholine side groups were synthesized using methylenebis(phenylene isocyanate) (MDI), poly(1,6-hexyl-1,5-pentyl carbonate) diol (PHPCD), 1,4-butandiol (BDO), and HFDAPC. The obtained fluorinated phosphatidylcholine poly(carbonate urethane)s (FPCPCU) possessed high molecular weight, narrower molecular weight distribution, and good mechanical properties as characterized by GPC and Instron, showing an increased hydrophilicity and a possible arrangement of surface structure as characterized by water contact angle. XPS results indicated that the phosphatidylcholine polar headgroups have been indeed pulled out to the surface with the help of the migration of the fluorinated side chain that was directly connected with the phosphatidylcholine polar headgroup. A preliminary result by protein adsorption and platelet adhesion experiments suggested that only 5∼12.5 mol % phosphatidylcholine could be enough for good hemocompatibility. The current work demonstrates a new synthetic approach that can be used to bring the bioactive PC groups to the surface of the PC-containing polyurethanes more effectively.

1. Introduction

Polyurethanes (PU) have unique mechanical properties and fairly good biocompatibility that make them ideal materials for many implantable devices.[1−2] However, the long-term biostability and thromboresistance of polyurethanes are still major problems for in vivo application.[3,4] Poly(ester urethane)s are subject to hydrolytic degradation and are no longer used in devices designed for long-term implantation. Poly(ether urethane)s are prone to oxidative degradation under some conditions, including environmental stress cracking (ESC) and metal ion oxidation (MIO).[4,5] A poly(carbonate urethane), designed by Pinchuk et al.[5] to remove the susceptible ester and ether linkages in the soft segments, have shown excellent resistance to hydrolysis, ESC, and MIO as long-term biostable elastomers.[6] As the biocompatibility is concerned, on the other hand, some research results have shown that the biocompatibility of polyurethanes can be increased by introducing silicones, fluorinated alkyls, and poly(ethylene oxide)s group or grafting biological agents (such as RGD) to their surfaces.[7−13] Furthermore, it has been recently verified that the introduction of phosphatidylcholine or its derivatives into polymers is more efficient for improving of the biocompatibility and biostability due to their unique structure.[14−17] The large improvements in biocompatibility and biostability of the phosphatidylcholine polymer are considered due to its ability to suppress protein adsorption,[17−22] which limits other biological responses such as cell adhesive, complement activation, and inflammation.[17,23,24] Recently, some phospholipid polyurethanes have been reported.[25−31] Particularly, a series of comblike phospholipid diol and their polyurethanes with long alkyl groups remaining in the side chains and the phosphatidylcholine analogues in the polymer backbone were developed.[27−31] Nevertheless, these phosphatidylcholine monomers have only a short alkyl side chain; thus, the phosphatidylcholine polar headgroup cannot easily migrate to the surface. Thus, to achieve a phosphatidylcholine polar headgroups surface, one has to use a large amount of phosphatidylcholine chain extender to synthesize the polyurethanes that will cause high water adsorption in the bulk. More than 16 mol % phosphatidylcholine chain extender was reported to prepare phosphatidylcholine polyurethanes, and this, consequently, results in poor mechanical properties.[26,27] One way to solve this problem is to use a long side chain alkyl phosphatidylcholine polar headgroup instead of a short alkyl side chain. However, the effectiveness of biocompatibility was rather limited than can be achieved.[30]

In our previous work, surface mobility effects of fluorinated side chains attached to hard segments on the phase separation and surface topography of polyurethanes were studied to provide the probability that fluorinated side chains could migrate to the polymer surfaces.[32,33] On the other hand, polyurethanes covalently bonded to surface active endgroups that migrate to the surface to form biocompatible materials have also been reported in a U.S. patent.[34] In this study, to obtain polyurethanes with excellent biocompatibilities and biostability as well as good mechanical properties, a novel chain extender containing a long fluorinated phosphatidylcholine side group and a series of poly(carbonate urethane)s containing fluorinated phosphatidylcholine side groups were designed and synthesized. As is known, this

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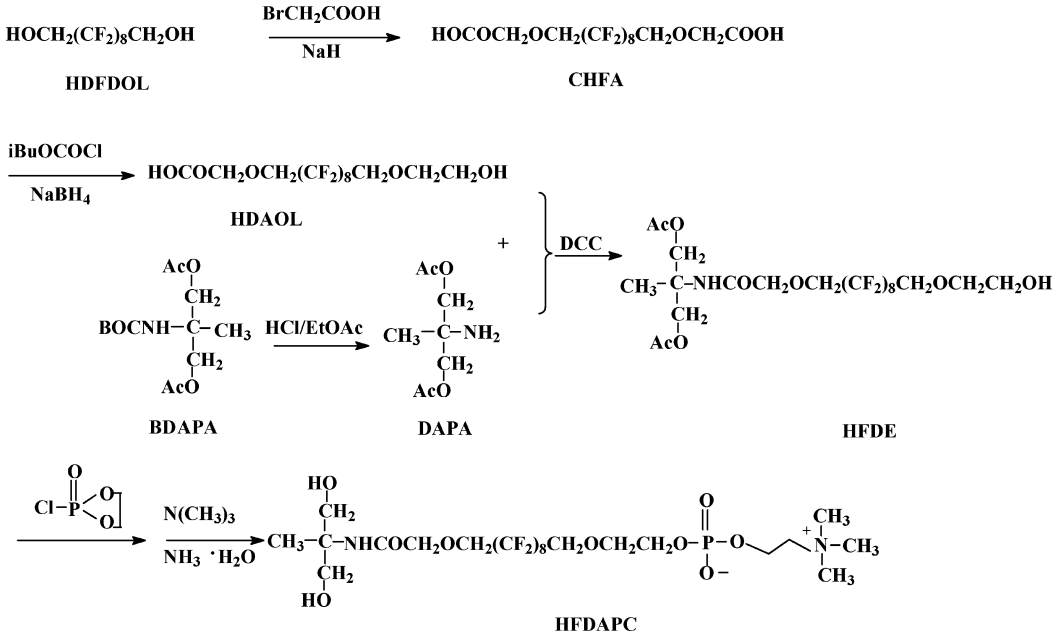

Figure 1. Synthesis route of HFDAPC.

zwitterionic compound containing polar headgroups and hydrocarbon chains does not adsorb protein.[18,19]

Our goal is to bring the phosphatidylcholine polar headgroups onto the surface or subsurfaces with the help of migration of the fluorinated side chain that is directly connected with the phosphatidylcholine polar headgroup. Thus, only a small amount of phosphorylcholine could be enough to improve hemocompatibility and biostability for polyurethanes. An overturn and rearrangement of the fluorinated phosphorylcholine side groups with phosphatidylcholine polar headgroups to relocate to the outermost surface area to provide biomembrane mimicry under water conditions has been verified in our previous studies.[35] In this work, we will report the synthesis and hemocompatibility of these novel segmented poly(carbonate urethane)s.

2. Experimental Section

2.1. Materials. 2,2,3,3,4,4,5,5,6,6,7,7,8,8,9,9-Hexadecafluoro-1,10-decandiol (HDFDOL) was purchased from Aldrich (97% purity). 2-Chloro-1,3,2-dioxaphospholane-2-oxide (COP, ACROS), sodium hydride (60%), DMSO, and dicyclohexylcarbodiimide (DCC) were used as received. Diphenyl methane diisocyanate (MDI) and 1,4-butanediol (BDO) were distilled under vacuum, and isobutyl chlorocarbonate (^{i}BuOCOCl) was distilled under normal pressure. *N*,*N*-Dimethylacetamide (DMAc) was dried over CaH_2 for 2 days at room temperature, distilled under vacuum, and stored in the presence of 4 Å molecular sieves. Poly(1,6-hexyl-1,5-pentyl carbonate) diol (PHPCD, $M_n = 1058$) was synthesized in our laboratory and dehydrated under reduced pressure at 100 °C for 4 hours.[32]

2.2. Synthesis of (10-Carboxymethoxy-2,2,3,3,4,4,5,5,6,6,7,7,8,8,9,9-hexadeca-fluorodecyloxy) Acetic Acid (CHFA). A solution of (HDFDOL) (1.94 g, 4.2 mmol) in 30 mL of DMSO was stirred under a nitrogen atmosphere. Sodium hydride (0.68 g, 16.80 mmol) was added slowly and stirred continuously at room temperature for 20 min. Then bromoacetic acid (1.17 g, 8.4 mmol) dissolved in anhydrous tetrahydrofuran (10 mL) was added dropwise to the stirred solution. After the reaction mixture was stirred for 2 h under a nitrogen atmosphere, distilled water (180 mL) was dropped into the reaction solution at ice bath temperature, and the solution was acidified to pH 3 with dilute hydrochloric acid. The solution was extracted three times with ethyl acetate (each time 35 mL). The accumulated extracts were washed with a saturated sodium chloride solution until the wash was neutral and then with water (one time), dried over anhydrous Mg_2SO_4 for 24 h, and concentrated in a vacuum to about 30 mL. The product was precipitated by the addition of petroleum ether (30∼60 °C), collected on a filter, washed with petroleum ether, and dried in a vacuum to yield 2.3 g of CHFA (94.7%). The synthesis route is shown in Figure 1. IR (KBr) 3424 (−OH), 3023, 2927 (−CH_2−), 1731 (C═O), 1208 (CF_2), 1146 (CF_2); APCIms (positive) *m*/*z* theoretical 578 g/mol, observed 579 g/mol; ^{1}H NMR (DMSO, TMS, 400 MHz) δppm: 4.32 (4H, s, −CH_2−COOH), 4.28 (4H, t, J = 19.4 Hz, CH_2−CF_2−), 12.91 (2H, brs, −COOH).

2.3. Synthesis of [2,2,3,3,4,4,5,5,6,6,7,7,8,8,9,9-Hexadecafluoro-10-(2-hydroxy-ethoxy)-decyloxy]Acetic Acid (HDAOL). A solution of CHFA (2.30 g, 3.98 mmol) and triethylamine (1.10 mL, 7.96 mmol) in anhydrous tetrahydrofuran (40 mL) was cooled to −15 °C, and isobutyl chlorocarbonate (0.74 mL, 5.0 mmol) was added. After the mixture was stirred for 15 min, $NaBH_4$ (0.19 g 5.0 mmol) was added. The reaction mixture was stirred for 2 h at room temperature, and then the excessive $NaBH_4$ was decomposed adding distilled water. The solution was concentrated under reduced pressure to give a solid residue, and the solid residue was dissolved in ethyl acetate. The solution was washed with dilute HCl, saturated NaCl, and H_2O; dried over Mg_2SO_4; filtered under vacuum; and evaporated in a vacuum to give crude HDAOL. The crude HDAOL was purified by silica gel column chromatography using gradient petroleum ether/EtOAc to yield 0.98 g of HDAOL (43.7%). The synthesis route is shown in Figure 1. IR (KBr) 3443 (−OH), 3020, 2927 (−CH_2-), 1754 (C═O), 1208 (CF_2), 1146 (CF_2, C−O−C); APCIms (positive) *m*/*z* theoretical 564 g/mol, observed 565 g/mol; ^{1}H NMR (DMSO, TMS, 400 MHz) δppm: 3.53 (2H, t, J = 4.8 Hz, −CH_2−OH), 3.62 (2H, m, −CH_2−O−), 4.16 ∼ 4.35 (4H, m, CH_2−CF_2−), 4.19 (2H, s, −CH_2−COOH), 4.74 (1H, brs, −OH). ^{13}C NMR (DMSO, TMS, 400 MHz) δppm: 60.4 (1C, s, CH_2−OH), 66.4∼67.7 (2C, m, 2CH_2−CF_2), 68.5 (1C, s, CH_2−CH_2OH), 74.2 (1C, s, CH2−COOH), 108.1 (m, C7, C8), 111.1 (m, C6, C9), 113.5 (m, C5, C10), 115.6 (m, C4), 118.1 (m, C11), 171.0 (1C, s, COOH). ^{19}F NMR (DMSO, TMS, 300 MHz) δppm: −119.0 ∼ −119.2 (4F, ^{4}C*F2*, ^{11}C*F2*), −121.8 (8F, 5CF_2, $^6CF_2$,$^9CF_2$, $^{10}CF_2$), 123.0 (4F, $^7CF_2$,$^8CF_2$) (Figure 2).

2.4. Synthesis of Acetic Acid 3-Acetoxy-2-{2-[2[2,2,3,3,4,4,5,5,6,6,7,7,-8,8,9,9-hexadecafluoro-10-(2-hydroxy-ethoxy)-decyloxy]-acetylamino]}-2-methyl-propyl Ester (HFDE). BDAPA (1.45 g, 5.0 mmol) was dissolved in 10 mL of ethyl acetate saturated with hydrogen chloride and left to stand at room temperature for 2 h.[36] The solution was concentrated under reduced pressure to give DAPA, and then DAPA,

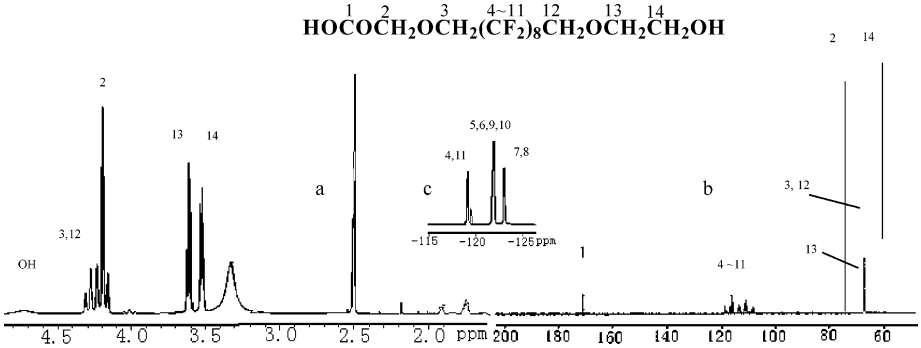

Figure 2. NMR spectra of HDAOL: (a) ^{1}H NMR spectrum, (b) ^{13}C NMR spectrum, and (c) ^{19}F NMR spectrum.

triethylamine (1.1 mL), and HDAOL (2.7 g, 4.8 mmol) were dissolved in a mixture of dimethylformamide (40 mL) and THF (30 mL). The solution was cooled to 0 °C, and dicyclohexylcarbodiimide (1.0 g, 4.8 mmol) was added. The reaction mixture was stored at room temperature for 24 h. The precipitate, *N*,*N*′-dicyclohexylurea, was removed by filtration, and the solvents were evaporated in a vacuum. The crude HFDE was purified by silica gel column chromatography using EtOAc/petroleum ether (1:2) to yield 1.8 g of HFDE (51.0%). The synthesis route is shown in Figure 1. IR (KBr) 3413 (−NH), 2937 (−CH_2−, CH_3), 1745 (C═O), 1685 (−CONH), 1219, 1150 (CF_2), 1047 (C−O−C); APCIms (positive) *m*/*z* theoretical 718 g/mol, observed 719 g/mol; ^{1}H NMR (DMSO, TMS, 200 MHz) δppm: 1.29 (3H, s, −CH_3), 2.01 (6H, s, 2CH_3CO), 3.52 (2H, m, −CH_2−OH), 3.60 (2H, m, −CH_2−O−), 4.05 (4H, s, 2CH_2OCO), 4.13 (2H, s, −CH2−CONH), 4.12∼4.34 (4H, m, CH_2−CF_2−), 7.46 (1H, s, NH).

2.5. Synthesis of 2-[2[2,2,3,3,4,4,5,5,6,6,7,7,8,8,9,9-Hexadecafluoro-10-ethoxy-decyloxy]-*N*-(2-hydroxy-1-hydroxymethyl-1-methyl-ethyl)-acetamide Phosphatidylcholine (HFDAPC). HFDE (8.1 g, 11.0 mmol) and triethylamine (1.6 mL, 11.0 mmol) were dissolved in a mixture of 100 mL of anhydrous diethyl ether and 30 mL of dry acetonitrile. After cooling the solution down to −20 °C, COP (1.6 g, 11.0 mmol) dissolved in anhydrous diethyl ether (10 mL) was added slowly to the stirred solution under nitrogen over 20 min. The temperature of the reaction mixture was maintained at −20 °C for 1 h and allowed to slowly warm to room temperature. Triethylammonium chloride precipitate was filtered off and washed with diethyl ether. The filtrate was evaporated under vacuum in a stream of nitrogen to give the residue as a colorless oil. Then the residue was dissolved in 60 mL of dry acetonitrile and transferred to a 100 mL glass pressure bottle. After the pressure bottle was cooled to −18 °C, excessive trimethylamine was rapidly added to the solution. The pressure bottle was then closed and maintained at 55 °C for 16 h, and subsequently, the solution was evaporated under vacuum to produce viscous liquid. The viscous liquid was dissolved in methanol and excessive ammonia was added with stirring for 24 h at room temperature. The solution was concentrated under reduced pressure to give crude HFDAPC. Finally, the crude HFDEAPC was purified by C18 reverse silica gel column chromatography using water/methanol to yield 8.6 g of HFDAPC (96.0%). The synthesis route and its structure are shown in Figure 1. IR (KBr) 3298 (−OH, −NH), 2941 (−CH_2−), 1677 (−CONH), 1204 (CF_2, P═O), 1147 (CF_2, C−O−C); APCIms (positive) *m*/*z* theoretical 816 g/mol, observed 817 g/mol; ^{1}H NMR (DMSO, TMS, 400 MHz) δppm: 1.17 (3H, s, −CH_3), 3.12 (9H, s, −$N(CH_3)_3$), 3.34∼3.41 (4H, m, 2CH_2−OH) 3.41∼3.51 (2H, m, −CH_2N), 3.60∼3.74 (4H, m, −CH_2−OP, PO−CH_2−), 4.03∼4.04 (4H, m, −CH_2O−CH_2−CF_2, CO−CH_2), 4.16∼4.34 (4H, m, 2CH_2−CF_2−), 4.92 (2H, m, −OH), 7.32 (1H, d, −NH). ^{13}C NMR (DMSO, TMS, 400 MHz) δppm: 18.4 (s, C1), 53.2 (s, 3C20), 58.2 (s, C3), 58.5 (d, C16), 63.4 (d, C18), 63.6 (s, 2C2), 65.6 (s, C19), 66.8∼67.3 (m, C6, C15), 71.0 (d, C5), 72.3 (d, C17), 108.2 (m, C10, C11), 110.8 (m, C9, C12), 113.5 (m, C8, C13), 115.9 (m, C7), 118.3 (m, C14), 168 (s, C4) (Figure 3b). ^{19}F NMR (DMSO, TMS, 300 MHz) δppm: −119.0 ∼ −119.2 (4F, $^{7}CF_2$, $^{14}CF_2$), −121.8 (8F,$^{8}CF_2$, $^{9}CF_2$, $^{12}CF_2$, $^{13}CF_2$), 123.0 (4F, $^{10}CF_2$,$^{11}CF_2$) (Figure 3).

2.6. Synthesis of Fluorinated Phosphatidylcholine Poly(carbonate urethane)s. Poly(carbonate urethane)s based on MDI, PHPCD, and chain extender were synthesized using two-step solution polymerization in DMAc. The feed ratios are shown in Table 1. MDI was added to the stirred DMAc solution of PHPCD under a dry nitrogen atmosphere at 50 °C and stirred for 1 h at 55∼60 °C. Chain extender (BDO, HFDAPC) and 1 ‰ stannous octoate were added to the reaction solution while the temperature was kept at 65∼70 °C for 20 min, followed by 5 h of continuous stirring at 80∼90 °C, and then at 100∼110 °C for 1 h. After the solution was cooled to room temperature, the polymer was precipitated in methanol and distilled water to remove the low molecular weight fraction, and dried under vacuum at 60 °C for 24 hours,[32] and the yield rate of these polymers is listed Table 2.

2.7. Characterization. *Instrumentation of Confirming the Intermediates and HFDAPC Chemical Structures.* ^{1}H NMR and ^{13}C NMR data were obtained with a Varian unity Inova-400 spectrometer (400 MHz) and Bulker-200 spectrometer (200 MHz). ^{19}F NMR data were obtained with BRUCK AC-P (300 MHz). Mass spectra of these compounds were obtained on an HP1100-LC/MSD with atmosphere pressure chemical ionization (positive mode). Infrared data was obtained with the Nicolet-560 spectrophotometer between 4000 and 600 cm^{-1} in the resolution of 4 cm^{-1}.

Molecular Weight Determination. Gel permeation chromatography was carried out on an HP1100 using two PLgel columns (10μ 10^4 Å, 10μ 500 Å). Molecular weights are relative to monodisperse polystyrene standards. The mobile phase was THF. The sample concentration was 1.000 g/L. The detector was RID, and the flow rate was 1.000 mL/min.

X-ray Photoelectron Spectroscopy (XPS). XPS was carried out on an XSAM-800 electron spectrometer. The spectrometer was equipped with a Mg Kα achromatic X-ray source (20 KV, 10 mA), and two takeoff angles of 30° and 90° were used with X-ray source. Each sample for XPS was prepared by casting the polymer solution onto a clean glass cover from 5% (w/v) DMAc. The samples were kept in an oven under vacuum at 40 °C for 24 h, 50 °C for 12 h, and 60 °C for 3 days.

Contact Angle Measurements. Contact angles were measured with an Eyma contact angle goniometer. Each sample for contact angle measurement was prepared by casting the polymer onto a clean glass cover from 5% (w/v) DMAc. The clean glass covers were kept in an oven at 40 °C for 24 h, 50 °C for 12 h, and 60 °C for 3 days under vacuum. Contact angles of samples air-facing side were measured on 3 μL of water at 20 °C, and the results reported are the mean values of five replicates.

Mechanical Testing. Mechanical testing was carried out with an Instron 4302 model Universal Testing machine at 23 °C and relative humidity of 50%. The crosshead speed was 500 mm/min. Each sample was cast to film from 5% (w/v) DMAc and put into an oven at 40 °C for 24 h, 50 °C for 12 h, and 60 °C for 3 days under vacuum. The results reported are the mean values of five replicates.

Protein Adsorption Experiments. The amount of proteins adsorbed on the air-facing surfaces of the polyurethane films (the films prepared according to XPS) was determined by the micro-BCA protein assay (Micro BCA Protein Assay, Pierce, Inc., Rockford, 1L) at 36.5 °C in

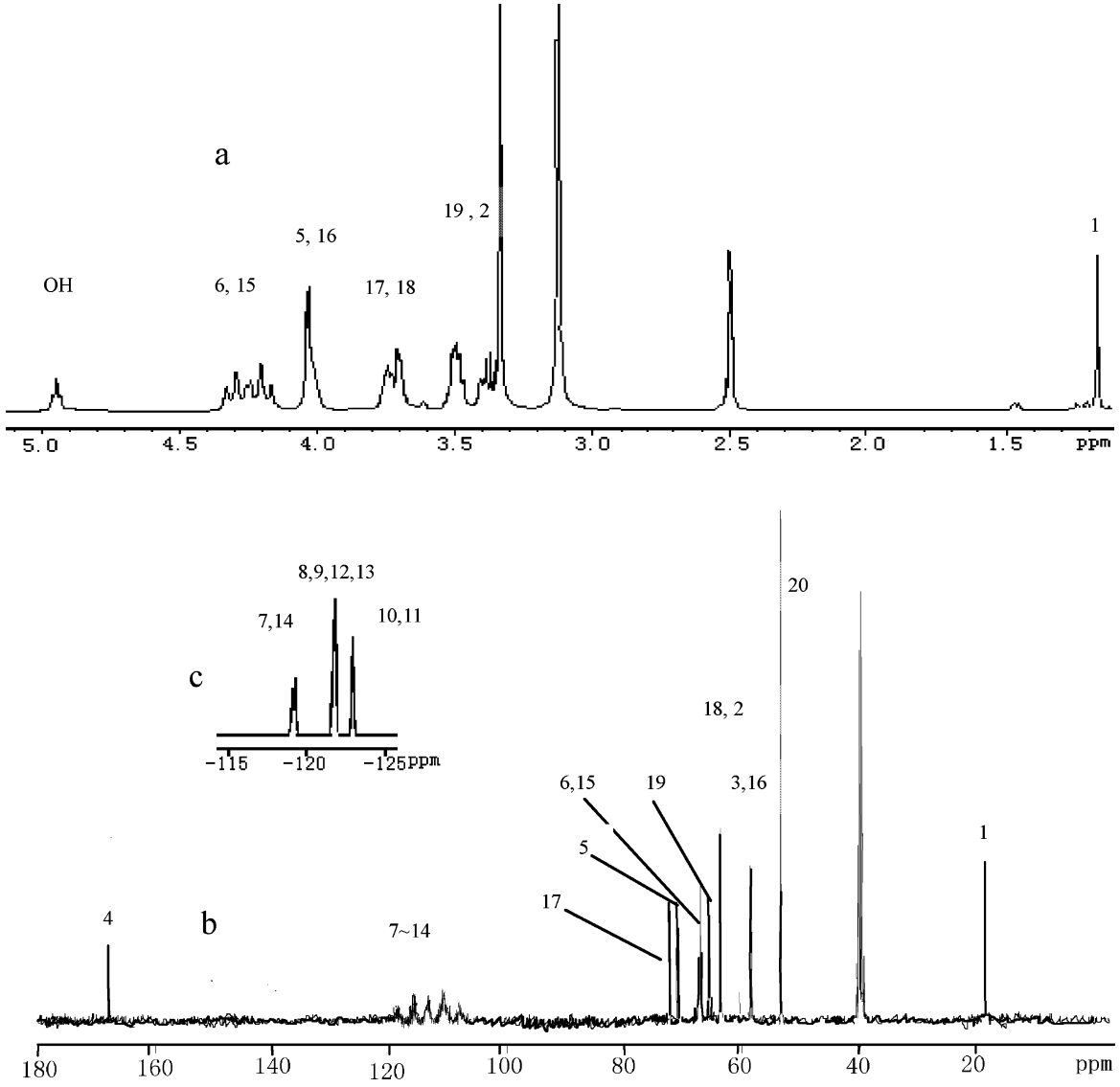

Figure 3. NMR spectra of HFDAPC: (a) ^{1}H NMR spectrum, (b) ^{13}C NMR spectrum, and (c) ^{19}F NMR spectrum.

Table 1. Theoretical Composition of Segmented Poly(carbonate urethane)s with Various Amounts of Fluorinated Phosphatidylcholine Diol Chain Extender

sample	molar ratio of MDI/ chain extender/ PHPCD	chain extender BDO, FPC[a] (mol)	fluorine atom %	phosphorus atom %
PCU	2:1:1	1.0, 0.0	0.0	0.00
FPCPCU5	2:1:1	0.95, 0.05	0.7	0.04
FPCPCU20	2:1:1	0.8, 0.2	2.5	0.16
FPCPCU50	2:1:1	0.5, 0.5	5.6	0.35

[a] FPC = HFDAPC.

PBS.[37,38] Bovine serum albumin (BSA) was purchased from Sanland Chemical Co. γ-Globulines (IgG) were purchased from the Sigma Chemical Co. Fibrinogen (Fbg) was purchased from the ICN Biomedicals, Inc. Fluorinated phosphatidylcholine poly(carbonate urethane)s films were kept in distilled water at 80 °C for 1 h and rinsed with ethanol and distilled water before use. The proteins adsorbed on the films were rinsed by ultrasonication in 1% SDS solution, and the amounts of proteins were determined at 562 nm with a 751-spectrophotometer. The mean value of triplicate samples for each film was calculated with the standard deviation, and statistical error was calculated by the Student's *t*-test ($p < 0.05$).

Table 2. Molecular Weights, Molecular Weight Distribution, and Yield Rate of Poly(carbonate urethane)s and Fluorinated Phosphatidylcholine Poly(carbonate urethane)s

sample	$M_n \times 10^{-4}$	$M_w \times 10^{-4}$	M_w/M_n	yield rate (%)
PCU	5.8264	9.9543	1.5249	99.0
FPCPCU5	1.2993	2.4842	1.9119	98.5
FPCPCU20	1.7834	3.6612	2.0529	90.3
FPCPCU50	1.8125	3.7415	2.0642	85.1

Evaluation of Platelet Adhesion. Fresh human whole blood was purchased from Blood Center of Chengdu City, and the platelet-rich plasma (PRP) was obtained with the blood centrifuged at 190*g* for 10 min. The poly(carbonate urethane)s films prepared according to XPS test were washed three times with distilled water and physiological saline and then soaked in PRP, where the platelet density was adjusted to $3.85 \times 10^5/\mu$L, for 1 h at 37 °C. After the PRP solution was removed, samples were rinsed with PBS (phosphate buffered saline, pH = 7.4) and treated with 2.5% glutaraldehyde at 4 °C overnight. Then, the samples were dehydrated by systematic immersion in a series of ethanol/water solutions (60, 70, 80, 90, 95, and 100 vol %) and later dehydrated by critical point drying using carbon dioxide as the transitional fluid. Finally, the samples were gold coated for the analysis of scanning electron microscope (SEM) with a Hitachi S-450 scanning electron microscope.

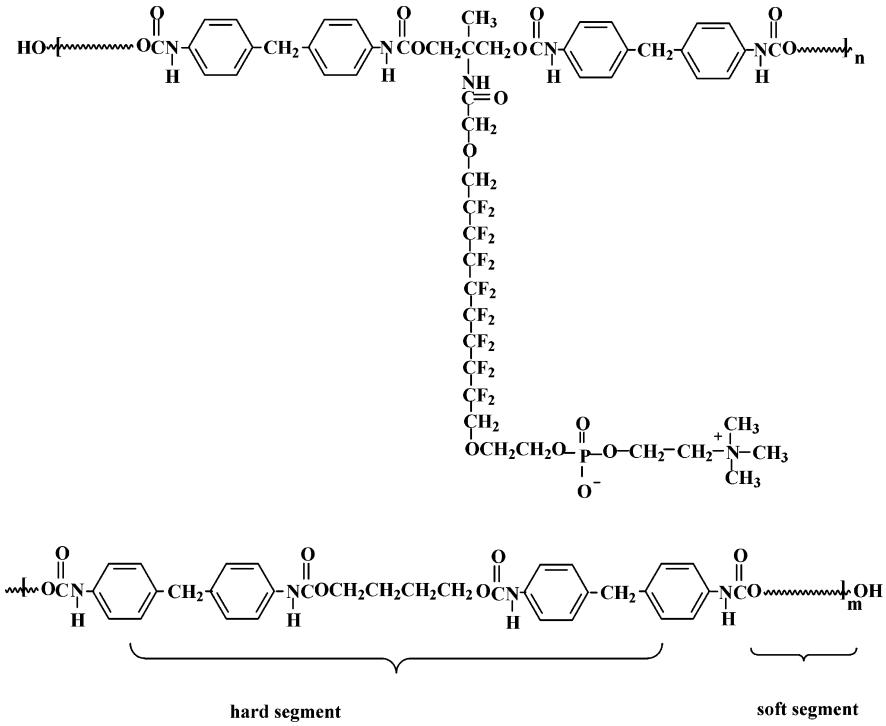

Figure 4. Schematic structure of fluorinated phosphatidylcholine polyurethanes, $n = 1, 2, 3, ..., m = 0, 1, 2, 3, ...$ Soft segment is PHPCD.

3. Results and Discussion

3.1. Synthesis of a Novel Diol with a Fluorinated Long Side Chain Phosphatidylcholine Polar Group. The new diol with a long side chain fluorinated alkyl phosphatidylcholine polar group was synthesized as illustrated in Figure 1. The long side chain fluorinated alkyl group has a low surface free energy so that the phosphatidylcholine polar group can be transferred to the surface of poly(carbonate urethane)s. To improve mobility of the novel diol containing a phosphatidylcholine polar group, the ether bond was designed to connect with the fluorinated side chain. In the synthesis route of the diol (Figure 1), HADOL and HFDAPC were the two key compounds; thus, their structures were thoroughly tested in our experiments to ensure the designed chemicals were synthesized. HADOL prepared from HDFDOL and bromoacetic acid was reacted with isobutyl chlorocarbonate in the presence of $NaBH_4$. Subsequently, the resultant novel diol HFDAPC synthesized from HADOL and DAPA was reacted with COP and trimethylamine. It should be mentioned that the method of HFDAPC synthesized with trimethylamine in dry acetonitrole is according to the Nakaya method.[39]

The ^{1}H NMR spectrum (Figure 2a) of the HADOL shows characteristic peaks of C*H*$_2$−OH, C*H*$_2$−CF$_2$−, and C*H*$_2$−COO at 3.53, 4.12∼4.34, and 4.19 ppm, respectively. Moreover, there are five complicated multiplets of signals due to carbon of (−CF$_2$−)$_8$ fraction arising from the fluorine atoms in the ^{13}C NMR spectrum (Figure 2b). Also the multiplet between 66.4∼67.7 ppm, the singlet at 60.4 ppm, and the singlet at 171.0 ppm should be attributed to −*C*H$_2$−CF$_2$,[40] −*C*H$_2$−OH, and −*C*OOH, respectively. Besides, the ^{19}F NMR spectrum of the HADOL (Figure 2c) shows the CH$_2$C*F*$_2$ signals between −119.1 and −119.3 ppm, the ^{5}C*F*$_2$, ^{6}C*F*$_2$,^{9}C*F*$_2$, and ^{10}C*F*$_2$ resonance at −121.8 ppm, and the ^{19}F signal (^{7}C*F*$_2$,^{8}C*F*$_2$) to the ^{19}F resonances at −123.0 ppm.[41] So these results suggested that the HADOL has been synthesized successfully. Figure 3a is a ^{1}H NMR spectrum of the HFDAPC, and there are multiplets at 4.16∼4.34 ppm due to C*H*$_2$−CF$_2$− originating from HDAOL and single at 3.12 ppm assigned to −N(C*H*$_3$)$_3$ of the phosphatidylcholine polar group. In addition, peaks of an *O*-methylene proton and *N*-methylene proton, both of which originated from the phosphatidylcholine group, were also observed at 3.60∼3.74 and at 3.41∼3.51 ppm, respectively. ^{13}C NMR spectrum (Figure 3b) of HFDAPC exhibited the same series of signals between 108.2 and 118.3 ppm due to C−F as that of HDAOL, thus confirming the presence of a fluorinated carbon chain in the molecular structure. The signals at 66.8∼67.3, 53.2, and 168 ppm were due to *C*H$_2$−CF$_2$−, −N(*C*H$_3$)$_3$, and *C*ONH, respectively. The ^{19}F signals of HFDAPC were almost at the same chemical shift position as that of HDAOL in the ^{19}F NMR spectrum (Figure 3c). Although the structures of CHFA and HFDE were simple and clear relative to those of HDAOL and HFDAPC, they were also measured with ^{1}H NMR, MS, and IR. The typical peaks between 4.16 and 4.35 ppm ascribed to C*H*$_2$−CF$_2$− were both exhibited in ^{1}H NMR spectra data of CHFA and HFDE, and the results of their Ms and IR indicated similarly that the CHFA and HFDE were also synthesized in this route.

3.2. Bulk Property Characterization. A series of fluorinated phosphatidylcholine poly(carbonate urethane)s with various amounts of chain extender containing a long side chain fluorinated alkyl phosphatidylcholine polar group were prepared using above the new diol with a long side chain fluorinated alkyl phosphatidylcholine polar group. The structures of the poly(carbonate urethane)s are shown in Figure 4. By changing the ratio of MDI/chain extender/PHPCD, the content of fluorine and phosphorus attached on the hard block can be controlled, as listed in Table 1. The chain extender without HFDAPC was also used to prepare conventional poly(carbonate urethane)s (PCU) for comparison. The fluorine contents are in the range of 0.7−5.6% (atomic percentage of fluorine), and the contents of phosphorus are from 0.04 to 0.35%. The ^{1}H NMR spectrum shows that the fluorinated phosphatidylcholine diol is copolymerized into the chain of the FPCPCU50 (Figure 5a). For FPCPCU50, there exists a single peak at $\delta = 3.12$ ppm ascribed

$$R_1O\overset{1}{C}H_2\overset{2}{C}F_2\overset{3}{C}F_2\overset{4}{C}F_2\overset{5}{C}F_2\overset{6}{C}F_2\overset{7}{C}F_2\overset{8}{C}F_2\overset{9}{C}F_2\overset{10}{C}H_2OR_2$$

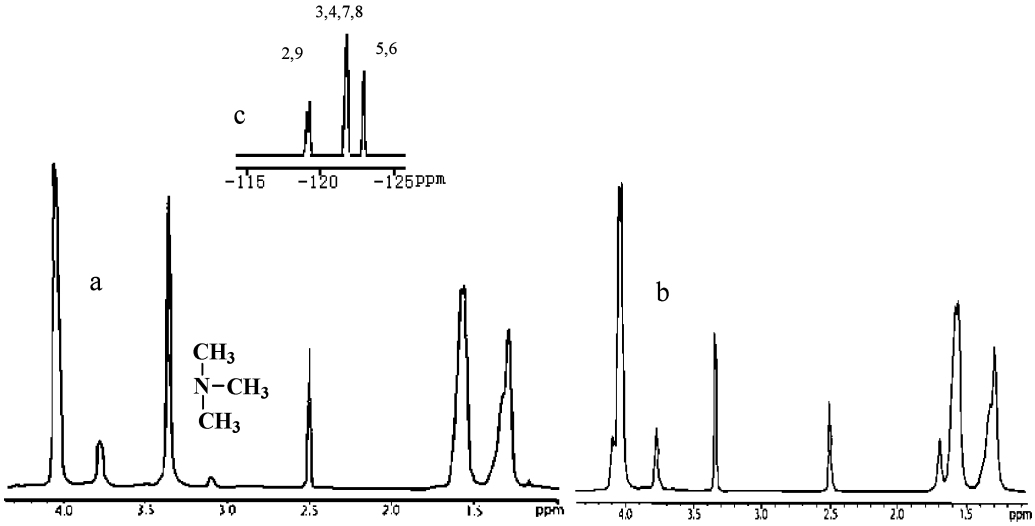

Figure 5. ^{1}HNMR spectra of FPCPCU50 (a) and PCU (b) at δ:1.0∼4.0 ppm, and ^{19}F NMR spectrum of FPCPCU50 (c).

Table 3. Strain−Stress Results of Fluorinated Phosphatidylcholine Poly(carbonate urethane)s and Poly(carbonate urethane)s

sample	ultimate tensile strength (MPa)	tensile modulus (MPa)	elongation at break (%)
PCU	57.9 ± 4.1	22.9 ± 2.2	369.7 ± 31.8
FPCPCU5	8.6 ± 0.6	18.9 ± 3.2	358.6 ± 77.5
FPCPCU20	24.5 ± 2.4	21.2 ± 3.9	472.8 ± 129.5
FPCPCU50	22.8 ± 4.1	35.5 ± 0.9	387.8 ± 45.1

to the methyl protons of the choline group (Figure 5a), compared with the ^{1}H NMR spectrum of the PCU (Figure 5b). The ^{19}F NMR spectrum (Figure 5c) of FPCPCU50 exhibits three strong singals among −119.0 ∼ −119.2, −121.7, and −122.9 ppm due to fluorine of CF_2 and these are unchanged compared with HFDAPC, thus, more confirming the novel chain extender covalently bonded to the polyurethanes chain. These molecular weights and molecular weight distributions were determined by GPC using polystyrene standards and THF as the mobile phase, and the result is listed in Table 2. It should be noted that the molecular weight of the PCU material is 3−5 times greater than that of the FPCUPCUs, and the reason is not clear so far. Since THF could not prevent the interaction between the zwitterionic phosphatidylcholine polar group and the column, the retained time on the column of fluorinated phosphatidylcholine poly(carbonate urethane)s could be delayed.[32] So the real molecular weight of phosphatidylcholine poly(carbonate urethane)s may be higher. This can be further proved by using the solution of $LiNO_3$ and DMAc (or DMF) instead of THF as the mobile phase, which shows a higher molecular weight than that with THF.[25] Another possible reason may be due to the fact that the diol with a long side chain fluorinated alkyl phosphatidylcholine polar group (HFDAPC) could not easily react with the isocyanate group compared with the normal chain extender (BDO). Tensile properties of the fluorinated phosphatidylcholine poly(carbonate urethane)s are summarized in Table 3. One observes a decreased ultimate tensile strength and modulus (the slope) but a increased elongation at break after introducing the fluorinated phosphatidylcholine side chain on the hard block of poly(carbonate urethane). The tendency in this case is the tensile strength and modulus decreases with an increase of the side chain content. Since there exists differences in molecular weight among the samples, tensile strengths cannot be compared directly. It should be noted that, although the tensile properties of the FPCPCUs is lower than that of normal PCUs, these tensile properties are good enough for FPCPCUs to find practical applications, especially, FCPCU20 and FPCPCU50 have 24.5 and 22.8 MPa ultimate tensile strengths, 21.2 and 35.5 MPa tensile moduli, and an elongation at breaks of 472.8% and 387.8%, respectively. The decreased tensile strength in the fluorinated phosphatidylcholine poly(carbonate urethane) series can be understood as being due to the increased phase mixing between hard blocks and soft blocks in these polyurethanes, as evidenced by DMA and DSC.[42] This is because the fraction of hydrogen-bonded carbonyl decreases and the fraction of free

Table 4. Atomic Percentage of Fluorine, Nitrogen, and Phosphorus in the Poly(carbonate urethanes) Seires

sample	takeoff angle	% N	%N bulk (theoretical)	% F	%F bulk (theoretical)	% P	% P bulk (theoretical)
PCU	30°	2.1	3.3	0.0	0.0	0.0	0.0
	90°	3.4	3.4	0.0	0.0	0.0	0.0
FPCPCU5	30°	1.2	3.3	1.1	0.7	0.0	0.04
	90°	2.4	2.4	0.8	0.8	0.0	0.0
FPCPCU20	30°	2.6	3.3	22.1	2.5	1.4	0.16
	90°	3.1	3.1	17.2	17.2	0.6	0.6
FPCPCU50	30°	2.2	3.2	16.1	5.7	1.2	0.35
	90°	2.4	2.4	14.5	14.5	0.9	0.9

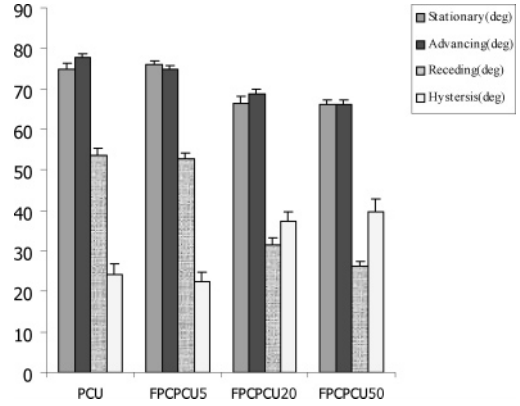

Figure 6. Contact angles measurement results of fluorinated phosphatidylcholine poly(carbonate urethane)s and poly(carbonate urethane)s.

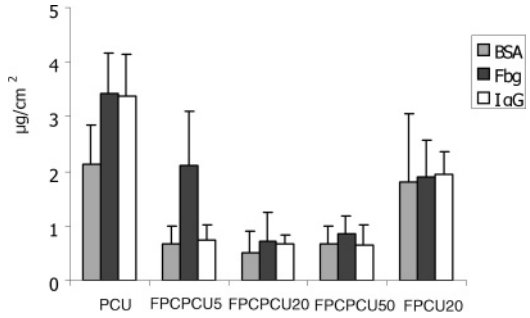

Figure 7. Amount of protein adsorbed on the surfaces of fluorinated phosphatidylcholine poly(carbonate urethane)s, poly(carbonate urethane), and fluorinated poly(carbonate urethane).

carbonyl in carbonate increases in this system, as suggested by FTIR analysis. For more detail, see ref 42.

3.3. Surface Property Characterization. For biomaterials, we are more concerned about the surface properties of the FPCPCUs. For an XPS measurement, the takeoff angle correlates to the depth that has been detected. At a takeoff angle of 30°, near surface (i.e., about 50 Å) structures are detected. At a takeoff angle of 90°, the sample depth is about 10 nm from the surface. The atomic concentrations of fluorine, phosphorus, and nitrogen at a depth of 5 nm (takeoff angle of 30°) and 10 nm (takeoff angle of 90°) away from the surface are listed in Table 4. The amount of elemental phosphorus and fluorine at the surface represents the amount of phosphatidylcholine polar groups and fluorinated side chains that migrate to the surface, respectively. As shown in Table 4, the amount of surface elemental phosphorus and fluorine on the surfaces of FPCPCU20 and FPCPCU50 is markedly higher than that in bulk and increases from subsurface (corresponding to a 90° takeoff angle) to the near surface (corresponding to a 30° takeoff angle). For example, the amount of fluorine is only 2.5% in bulk for FPCPCU20, whereas the amount of surface elemental fluorine reaches to 17.2% and 22.1% from the subsurface to the near surface, respectively. Here one observes a 7−9 times difference of fluorine content between the surface and the bulk. Similarly, the amount of phosphorus is only 0.16% for FPCPCU20, whereas the amount of surface elemental phosphorus reaches 0.6% and 1.4% from the subsurface to the near surface, respectively. Again a 4−9 times difference of phosphorus content between the surface and the bulk is achieved. This result indicates that the hard segments with phosphatidylcholine polar groups are indeed pulled out to the surfaces with the help of fluorinated side chains.

To further examine the surface of the FPCPCUs, water contact angle measurements were carried out. This is shown in Figure 6. One observes a much decreased stationary, advancing, and receding contact angle as the fluorinated phosphatidylcholine side chain is introduced into the hard block of PCUs. For example, the stationary, advancing, and receding contact angles for PCU are 75°, 77°, and 53°, respectively, but the corresponding stationary, advancing, and receding contact angles for FPCPCU50 are 66°, 66°, and 26°, respectively. This result indeed suggests that the surfaces of these novel poly(carbonate urethane)s be changeable with environmental change. A detailed investigation with contact angle measurement, X-ray photoelectron spectrum (XPS), and ATR experiments have suggested

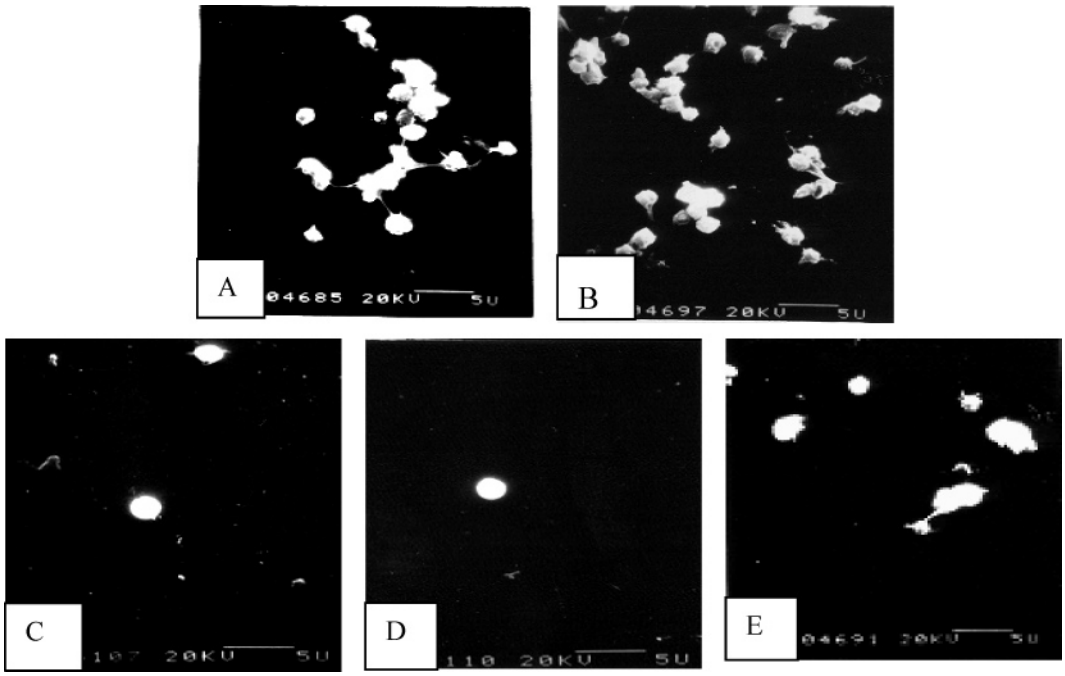

Figure 8. SEM of platelet adhesion to fluorinated phosphatidylcholine poly(carbonate urethane)s, poly(carbonate urethane), and fluorinated poly(carbonate urethane). A, PCU; B, FPCPCU5; C, FPCPCU20; D, FPCPCU50; E, FPCU20.

that the phosphatidylcholine groups may reversible turn over with the movement of the hydrophobic fluorinated alkyl groups when the samples were treated in dry air or water.[35]

3.4. Hemocompatibility Characterization. As blood contacting biomaterials, hemocompatibility is generally considered to be related to adsorbing protein on the materials surface and activate platelets to amplify coagulation. Thus, the hemocompatibility of the prepared fluorinated phosphatidylcholine poly(carbonate urethane)s was investigated by protein adsorption and platelet adhesion. The amount of BSA, IgG, and Fbg adsorption on the air-facing surface of the prepared fluorinated phosphatidylcholine poly(carbonate urethane)s is shown in Figure 7, together with PCU and fluorinated poly(carbonate urethane) (FPCU20) that the fluorine on the surface of FPCU20 is 26.4% (takeoff angle: 30°) for comparison.[32] The protein adsorption is obviously suppressed by the surface of the FPCPCUs compared with that of PCU and FPCU20. As can be seen, only 5% of fluorinated phosphatidylcholine chain extender results in a decrease of BSA from 2.14 μg/cm^2 to 0.67 μg/cm^2, Fbg from 3.43 μg/cm^2 to 2.10μg/cm^2, and IgG from 3.38 μg/cm^2 to 0.74 μg/cm^2 (Figure 7). In addition, the amount of Fbg adsorption on these polymers surfaces is higher than that of corresponding BSA and IgG on themselves surfaces because of Fbg having the greatest adhesion of 20.4 nN/m.[43] Figure 8 shows the SEM photographs of platelet adhesion to fluorinated phosphatidylcholine poly(carbonate urethane)s, together with PCU and fluorinated poly(carbonate urethane) (FPCU20) that the fluorine on the surface of FPCU20 is 26.4% (takeoff angle: 30°) for comparison.[32] One observes not only a substantial number of platelets adhered but also some deformed platelets on the surfaces of PCU and FPCU20. On the contrary, separated platelets on the surfaces of FPCPCUs are seen. Particularly for FPCPCU20 and FPCPCU50, platelets keep their original shape with a smooth surface. Moreover, the platelets look like they are standing-up on the surfaces of the FPCPCUs, again compared with lay-down on the surface of PCU and FPCU20, indicating a strong suppression of FPCPCU20 and FPCPCU50 to platelet adhesion. Thus the preliminary result obtained from protein adsorption and platelet adhesion experiment does suggest an improved hemocompatibility for the surface of the prepared fluorinated phosphatidylcholine poly(carbonate urethane)s. Further works are currently being carried out in an attempt to test the hemocompatibility of these fluorinated phosphatidylcholine poly(carbonate urethane)s.

4. Conclusions

In summary, we have successfully prepared a novel diol containing a fluorinated alkyl phosphatidylcholine polar headgroup and the corresponding poly(carbonate urethane)s with fluorinated phosphatidylcholine side chains attached to hard blocks, having high molecular weight, narrower molecular weight distribution, and good mechanical properties (FPCPCU20 and FPCPCU50). The result of water contact angle suggests an increased hydrophilic and a possible rearrangement of surface structure of these FPCPCUs when in contact with water. XPS result indicates that the phosphatidylcholine polar headgroups can be pulled out to the surface with the help of migration of fluorinated side chain that is directly connected with phosphatidylcholine polar headgroup. Thus only 5∼12.5% phosphorylcholine is needed to improve hemocompatibility for polyurethanes, and this is proved preliminarily by protein adsorption and platelet adhesion experiment. And the biostability for these polyurethanes will be verified more rigorously in future. The current work demonstrates a new synthetic approach that can be used to bring the bioactive PC groups to the surface of the PC-containing polyurethanes more effectively.

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Supporting Information Available. Additional ^{1}H, ^{13}C, and ^{19}F NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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