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Hemocompatibility Evaluation of Polyurethane Film with Surface-Grafted Poly(ethylene glycol) and Carboxymethyl-Chitosan

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ABSTRACT: To improve the hemocompatibility and biocompatibility of polyurethanes (PUs), PU surface was firstly modified by poly(ethylene glycol) PEG through acryloyl chloride and subsequently grafted on carboxymethyl-chitosan (CMCS). Attenuated total reflection Fourier transform infrared spectroscopy and X-ray photoelectron spectroscopy analysis confirmed that carboxyl-chitosan was grafted onto PUs surface. The surface properties of unmodified and modified PU films were determined and compared by water contact angle assessment. After PEG and CMCS grafting, the surface energy of the PU film was increased. Furthermore, the hemocompatibility of the modified PU films was systematically evaluated by bovine serum albumin (BSA) adsorption, the dynamic blood clotting test, the platelet adhesion test, and the hemolytic test. It appears that BSA adsorption and platelet adhesion were significantly curtailed for the modified PU films. Therefore, the obtained results showed the modified PU film has better hemocompatibility.
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INTRODUCTION

Polyurethanes (PUs) are widely used in the medical devices, such as catheters, cardiac assisting devices, artificial heart, cardiovascular biomaterials, hemodialysis bloodline sets, center venous catheters, and intravenous bags, etc.[1–5] due to their excellent physic-mechanical properties[6,7] and relatively good biocompatibility.[4,5] However, microscopic thrombi and microemboli have been observed in some PU implants.[8] Hence, it is of great necessity to modify the surface of PU biomedical devices and therefore, enhance their hemocompatility.

To further improve their blood compatibility, lots of modification methods have been developed, such as plasma treatment, wet chemical treatment, ozonation treatment, and photochemical treatment.[9–12] Among these methods, graft copolymerization is one of the most effective methods to modify the physical, chemical, and hemocompatibility of PU with synthetic and natural polymers. A large number of materials have been grafted onto the surface of PU, such as poly(ethylene glycol) (PEG),[13,14] heparin,[14,15] phospholipid polymer,[16–18] natural materials (gelatin, collagen, chitosan), alginate, or biotin, etc.[19–23] Polyethylene glycol is considered to possess excellent blood compatibility of hydrophilic score. In previous studies, it has been proved that a single PEG grafted layer on PU surface could restrain the protein adsorption and then improve the blood-compatibility.[24] Moreover, based on the PEG-modified PU biomaterials, some special biomolecules were immobilized to the surface through a PEG layer to further enhance the biocompability.[25–27]

Chitosan (CS), a chitin's deacylated derivative, has good biological activity, including good biocompatibility, biodegradable no antigen, nontoxic.[23,28–30] Recent studies have focused on the surface modification of PU with natural CS to prepare new biomaterials with excellent mechanical property, good biocompatibility, increasing anticoagulation effect, and so on.[4,24,31,32] Some previous studies, both CS was immobilized onto the PU surface through poly(acrylic acid) spacer[31] and CS was grafted onto the surface of waterborne PU through the assembly of polyelectrolyte in aqueous emulsion,[32] prove better blood-compatility. Carboxymethyl-chitosan (CMCS) is one kind of blood-compatible chitosan derivative.[33] Yang et al.[34] argued that CMCS was better than the CS anti-clotting properties. Zhu et al.[35] discovered that the poly(ethylene terephtha) (PET) surface coupling CMCS shows excellent anti-clotting properties. Although CMCS has anticoagulation, its water solubility and weak mechanical properties limit its application in body biomaterial. However, it is able to be used as a surface anticoagulant for the other polymeric biomaterials with good mechanical property.

In this study, a new composite film was prepared by immobilizing CMCS onto the surface of PU through surface grafting PEG treated by chemical grafting. Because of the liquidity and hydrophilic of PEG, the formation of hydrated PEG can prevent protein and platelet adhesion. Meantime, the negative charge on the CMCS has played an electrostatic repulsion, thus demonstrated anticoagulant. This film reflects the synergistic effect of the exclusion of the PEG movement and CMCS. The surfaces were characterized by attenuated total reflection Fourier transform infrared spectroscopy (ATR-FTIR), X-ray photoelectron spectroscopy (XPS), and static contact angle measurements. Furthermore, surface hemocompatibility of the modified PU was examined by BOVINE serum albumin (BSA) adsorption, the dynamic blood clotting test, the platelet adhesion test, the hemolytic test.

EXPERIMENTAL

Materials

Thermoplastic polyether type PU particles were purchased by Shanghai Kindly Enterprise Development Group, China. CMCS was purchased by Qingdao Hereat Bio-tech Company, China. Hexamethylene diisocyanate (HMDI) and acryloyl chloride were purchased by J&K Scientific, China. Toluene, triethylamine were dried over 4 Å molecular sieves for 48 h before use. Other chemicals, including polyethylene glycol (PEG, $M_n = 2000$), formaldehyde, potassium persulfate were of analytical grade.

Sample Preparation

Preparation of PU Films. PU films were obtained by solvent evaporation. PU was dissolved in dimethylformamide (DMF) to form a clear solution (2.5%, w/v). This solution was poured into glass Petri plates. Then the Petri dishes were stored in an oven at 60°C for 48 h. Then remove the film from the culture dish. The films were purified by Soxhlet extractor with methanol and toluene for 24 h, followed by vacuum drying at 60°C for 24 h.

Grafting of PEG on the PU Film

PU films were immersed in a toluene solution containing 10% (w/v) HMDI and 2.5% (w/v) triethylamine. After stirring at 50°C for 2.5 h under N_2 atmosphere, the films were then washed in dry toluene to remove unreacted HMDI. Then they were reacted with 4 g of PEG in a toluene solution and 2.5% (w/v) of triethylamine for 24 h at 50°C. The samples were extracted in toluene for 18 h to remove unreacted PEG and were dried under vacuum at 40°C for 12 h.

Potassium Persulfate-Induced Graft Copolymerization on the PU Film

PU-PEG films were immersed in a toluene solution containing 6.25% (v/v) acryloyl chloride and 3.75% (w/v) triethylamine. After stirring at 5–10°C for 8 h under N_2 atmosphere, the films were extracted in toluene to remove unreacted reagents. The films were dried under vacuum at 40°C for 12 h. These films were immersed in an aqueous solution containing 0.5 g CMCS, 0.03 g $K_2S_2O_4$. The solution was purged with nitrogen gas for about 1 h at 60°C. At the end of the reaction, a 45% solution of formaldehyde was added into the reaction system to terminate the graft copolymerization. The grafted films were thoroughly rinsed in water and dried in a vacuum at 40°C for 24 h.

The degree of grafting (D_g) was calculated as

$$D_g(\%) = \frac{W_g - W_o}{S} \quad (1)$$

where, W_g is the vacuum dried membrane weight after potassium persulfate induced graft CMCS and W_o represents the vacuum dried membrane weight after grafting with PEG, S is the surface area of the film.

Characterization

ATR-IR. ATR-FTIR spectrometer (Nicolet-20DXB, Thermo Nicolet, USA) was used to study the chemical compositions original and modified PU membrane surfaces. The spectra were collected in the frequency region of 4000–700 cm^{-1}.

XPS. The original and modified PU films were analyzed using XPS (VG ESCALAB MK2, England). The elemental compositions were determined on the basis of peak areas and sensitivity factor from the C1s, N1s, and O1s peaks by advantage software. C, O, N elements ratio calculated by the following formula[36]

$$\frac{n_i}{n_j} = \frac{I_i}{I_j} \times \frac{\sigma_j}{\sigma_i} \times \frac{Ek_j^{0.5}}{Ek_i^{0.5}} \quad (2)$$

Ek = h−BE (AlK, h = 1486.6eV)

Atomic compositions were estimated using the following n: the number of surface atoms; I: XPS peak area; σ: C1s = 1.00, O1s = 2.93, N1s = 1.80.[37] All binding energy values were determined with reference to carbon, C1s = 285 eV.

Contact Angle and Surface Free Energy

Contact angles were measured by OCAH 200 contact angle goniometer. The surface free energies were calculated from the contact angle data at equilibrium by Fowkes' method.[38] The method divides the surface free energy into two components, dispersive (hydrophobic; γ^d) and polar (hydrophilic; γ^p) and uses geometric mean approach to combine their contributions. To measure the polar and dispersive surface free energy and interfacial energy,[39] the Owens-Wendt method using the extended Fowkes' equation was employed:

$$(1+\cos\theta)\frac{\gamma_L}{2(\gamma_L^d)^{1/2}} = (\gamma_S^d)^{1/2} + (\gamma_S^p)^{1/2}\left(\frac{\gamma_L^p}{\gamma_L^d}\right)^{1/2} \quad (3)$$

$$\gamma_{SL} = \left\{(\gamma_L^p)^{1/2} - (\gamma_S^p)^{1/2}\right\}^2 + \left\{(\gamma_L^d)^{1/2} - (\gamma_S^d)^{1/2}\right\}^2 \quad (4)$$

where, θ is the contact angle, γ_L is the surface free energy of the liquid, γ_S is the surface free energy of the surface γ_{SL} is the interfacial energy between surface and liquid. Table I shows the surface tensions of different liquids used in this study.

BSA Adsorption Evaluation

BSA was used as a model protein to evaluate the protein adsorption capacity of modified and original PU films. The BSA adsorption experiments were carried out by standard batch equilibrium adsorption studies at 37°C. BSA was added to phosphate buffered saline with concentrations varied as 200 μg/ml, and different PU samples were added into the BSA solutions. These samples were

Table I. Parameters of the Polar, γ^{p}, and Dispersive, γ^{d}, Components of the Surface Tensions of the Liquids

Liquids	γ^{p} (dyn/cm)	γ^{d} (dyn/cm)	γ^{S} (dyn/cm)
Distilled water	51.0	21.8	72.8
Diiodomethane	0	50.8	50.8
Blood	11.2	36.3	47.5
Human serum albumin (HAS)	33.6	31.4	65.0
Human fibrinogen (HFG)	40.3	24.7	65.0

incubated at 37°C for 4 h. After 4 h, the amount of protein in the solution was determined based on the absorbance at 595 nm using a UV spectroscope (756MC, Japan). The adsorbed amount was calculated from the differences of initial and final values.

Platelet Adhesion Test

In vitro platelet adhesion experiments and anticoagulation test were performed via human whole blood taken from a healthy donor. All films were cleaned and incubated in human platelet-rich plasma for 60 min at 37°C. After rinsing, fixing, and critical point drying, the quantity and morphology of the platelet adhered to the film's surface were examined using SEM.

Dynamic Clotting Test

For anticoagulation test, 0.1 mL of human blood anticoagulated by acid citrate dextrose was dripped on the sample surface in an open atmosphere at room temperature. Clotting was initiated by the addition of 10 μl of 0.2 M $CaCl_2$ solution. After 10, 20, 30, 40, 50 and 60 min, each sample was transferred into a beaker containing 50 mL of distilled water. Then the optical density of the supernatant was measured at 540 nm wavelengths using a UV spectrometer (756 MC, Japan).

Hemolytic Test

Each specimen was loaded into three tubes that contained 10 mL of physiological saline solution. And 10 mL of physiological saline solution used as a negative control group, 10 mL of deionized water as the positive control group. They were placed in the water bath of 37°C for 1 h. Then 0.2 mL of diluted human blood anticoagulated was dripped in these tubes and the

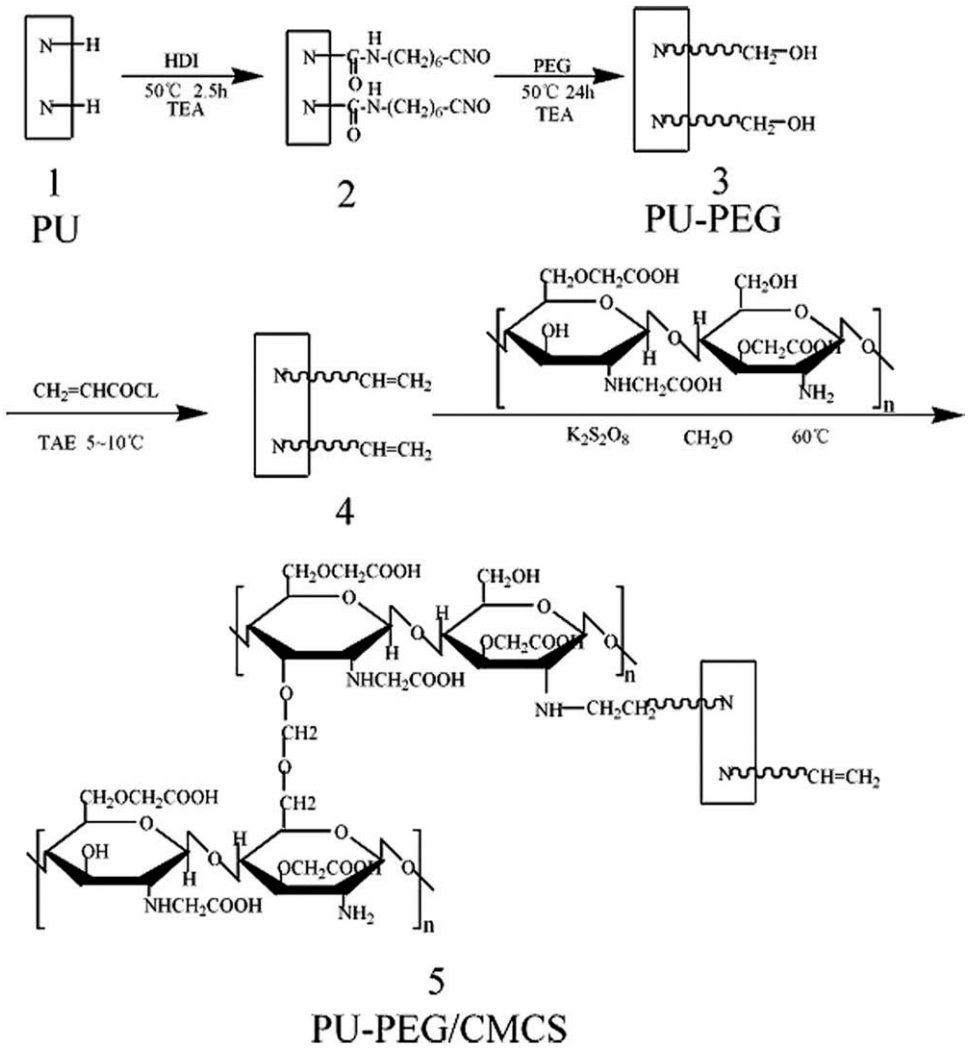

Figure 1. Procedure of grafting CMCS onto PU film surface.

tubes continued at 37°C water bath for 1 h, and centrifuged for 5 min at 2000 rpm. The upper clear solution of the blood mixture was characterized by the absorption spectrum.

Statistical Analysis

All quantitative experiments were run in quintuplicate unless specially stated and the resulting data were expressed as mean ± standard deviation. The experiment for MTP assay (SPSS software) was run in five replicates per experimental group ($n = 5$). The P value <0.005 between groups was considered highly statistically significant.

RESULTS AND DISCUSSION

PUs are widely used for implanted materials into human body due to their good physical and stabilized chemical properties. But the hemocompatibility of PUs can not meet the requirements of the clinical long-term implanted. To improve its hemocompatibility and biocompatibility, surface modification has been extensively investigated. In this study, PU surface was firstly modified by PEG through acryloyl chloride and subsequently grafted on CMCS, as shown in Figure 1.

Spectra Analysis

The ATR-FTIR spectra of PU-HMDI (b), PU-PEG (c), PU-acryloyl chloride (d), PU-PEG/CMCS (e) surfaces, as well as the unmodified PU (a) surface are shown in Figure 2. A new characteristic peak centered around 2272 cm^{-1} is observed in comparison Figure 2(a) with 2(b), which is assigned to stretching vibration of isocyanate (—NCO). It indicates that the PU film surface was successfully grafted with HMDI. Afterward, the —NCO peak disappear on the spectra, replaced by a broad —OH band which indicated the successfully grafted with PEG [Figure 2(c)]. In Figure 2(d), it exhibits a new peak at 1635 cm^{-1} compared with Figure 2(c), attributing to the CH_2=CH— existing in the structure of acryloyl chloride. Moreover, the peak at 1635cm^{-1} disappears on the spectrum [Figure 2(e)]. These generation and disappearance of new bands provide supporting evidence of the surface grafting of PEG and CMCS onto the PU film.

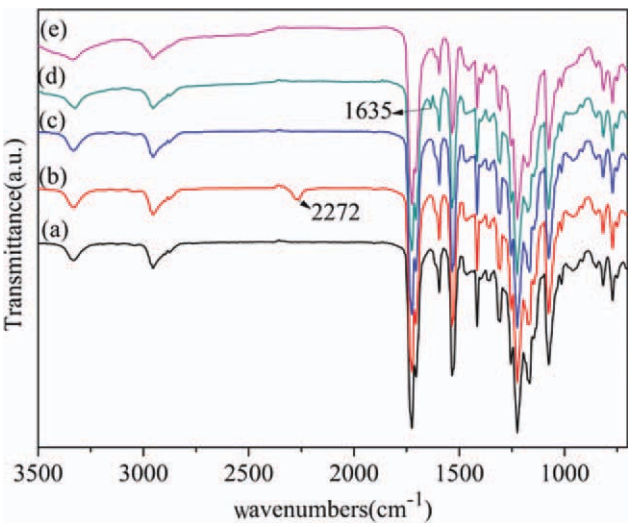

Figure 2. ATR-FT-IR spectra of PU film surfaces before and after each step of modification (a) PU control, (b) PU-HMDI, (c) PU-PEG, (d) PU-acryloyl chloride and (e) PU-PEG/CMCS. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

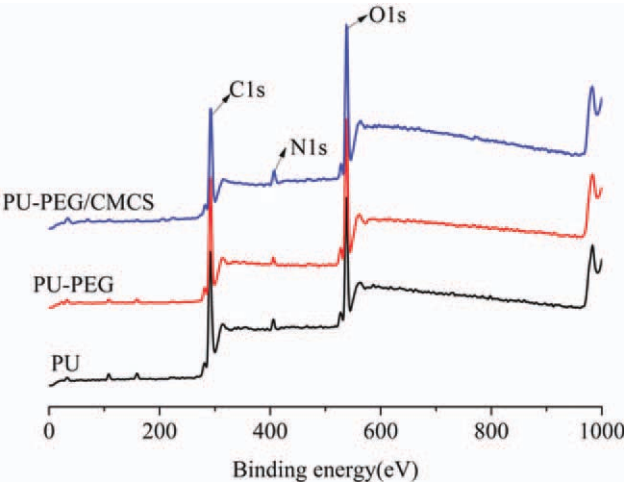

Figure 3. XPS survey scan spectra of the PU films, which represent relative intensity vs. binding energy (0–1000 eV). (a) PU control, (b) PU-PEG and (c) PU-PEG/CMCS. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Figure 3 shows the XPS spectra of PU, PU-PEG and PU-PEG/CMCS from a binding energy of 0 to 1000 eV. Table II summarizes the atomic percentage of modified surface measured by the XPS. The N/C ratios of the surface-modified and original PU films content were 4.6, 3.9, and 8.3, respectively. The O/C ratio of PU-PEG was 1.2 times greater than that of PU, and the O/C ratio of PU-PEG/CMCS was 1.46 times greater than that of PU. The above results confirmed that the obtained films were overlaid with PEG or CMCS.

Contact Angle and Surface Free Energy

It should be noted that the analysis of experimental data regarding the values of contact angle and surface free energy of PU is largely dependent on definition or the control of number of variables: fabrication technique, cleaning method, temperature, probe liquid purity, and etc. The results are listed in Table III. An analysis of experimental data in Table III indicates that water contact angle decreases from 83.5 to below 59.1 after grafted PEG and CMCS. Meantime, the surface free energy statistical comparison including γ_s, γ^d, and γ^p values show that the difference observed in total surface free energy γ_s is exclusively due to the difference of the polar component γ^p. It could be seen that the polar component of the surface free energy

Table II. Surface Elemental Composition from XPS Analysis (atom percent)

Samples	C (%)	O (%)	N (%)	N/C (%)	O/C (%)
PU matrix	71.2	25.5	3.3	4.6	35.8
PU-PEG	68.0	29.4	2.6	3.9	43.2
PU-PEG/CMCS	62.2	32.6	5.6	8.3	52.4

Table III. The Contact Angle and the Surface Energy of the Surface-Modified and Original PU Films

Samples	Contact angle (°)		γ_s(mJ m^{-2})	γ^p(mJ m^{-2})	γ^d(mJ m^{-2})	γ^p/γ^d
	H_2O	CH_2I_2				
PU matrix	83.5 ± 2.3	23.9 ± 2.8	48.0	1.5	46.5	0.032
PU-PEG	63.7 ± 1.7	33.8 ± 1.4	52.1	9.5	42.6	0.223
PU-PEG/CMCS	59.1 ± 2.9	35.8 ± 0.5	53.9	12.2	41.7	0.293

significantly increased for the modified PU films when compared to the unmodified PU film, and the polar component of the PU-PEG/CMCS is greater than the PU-PEG film. Previous studies confirmed that high polar components could improve the hydrophilic material. Niylas et al.[40] argued that γ^p/γ^d the material possesses excellent blood compatibility of the key. In the current study, there is a statistically significant difference between the fractional polarity γ^p/γ^d for different films. The value obtained for the modified PU films are higher than the unmodified PU film. Among them, the PU-PEG/CMCS film surface has the most value of γ^p/γ^d. The results shows the opposite trend with the water contact angle, which indicates that the PU-PEG/CMCS films possess better blood-compatibility, compared with both the control PU film and the PU-PEG film.

The evaluation results of the interfacial energy of the modified and unmodified PU surface are shown in Table IV. Those energies correspond to the energies of the interface between the surface and blood, plasma protein (human serum albumin, HSA; human fibrinogen, HFG; and immunoglobulin-G, lgG). It shows that the interfacial energy between the blood and the modified PU film is 5.13 dyn/cm, and after the interfacial energy of the modified PU films interfacial energy are 0.32, 0.21 dyn/cm. Similar results were obtained for the modified PU films and plasma proteins (HSA, HFG, and IgG) interface suggesting that surface modification is highly effective in reducing the plasma proteins adsorption. Being the smallest value of the interfacial energy with blood and plasma protein, the PU-PEG/CMCS film surface possesses excellent blood compatibility.

BSA Adsorption

In the blood-contacting application fields, the evaluation of plasma protein adsorption was one of the most important factors to determine the hemocompatibility of implanting materials.[41] In our work, the results of the adsorption of BSA to the surfaces are shown in Figure 4. The amount of protein decreased on the surface grafted with PEG or CMCS. Because of the PEG has a highly hydrophilic and flexible molecular chain, and when PEG bonding the water molecules to form hydrated PEG chains. The hydrated PEG chains on the materials interface can affect the fluid of blood, and the flexible PEG chain with the water flow could prevent the microsurface proteins in stagnation, adhesion, and deformation.[42] Moreover, CMCS carry a negative charge —COO— that would electrostatic repel and further reduce the fouling of the negatively charged proteins and other blood components. Therefore, grafting of the negatively charged CMCS is believed to improve the biocompatibility. In brief, the enhanced protein repelling ability of PU-PEG/CMCS surface is attributed to the synergistic effect of the hydrophilicity and the dynamic motion of PEG chains and negatively charged —COO— group of CMCS. These results are similar to those of the surface-modified and original PU films plasma proteins interfacial energy, PU-PEG/CMCS film surface adsorption of proteins at least.

Table IV. The Blood and Plasma Proteins Interfacial Energy of the Surface-Modified and Original PU Films

Samples	$\gamma^{S,}$ blood (dyn/cm)	$\gamma^{S,}$ HSA (dyn/cm)	$\gamma^{S,}$ HFG (dyn/cm)	$\gamma^{S,}$ lgG (dyn/cm)
PU matrix	5.13	22.38	29.67	24.21
PU-PEG	0.32	8.22	13.09	9.40
PU-PEG/CMCS	0.21	6.04	10.27	6.92

Platelet Adhesion

Platelet adhesion on the film is rather important for the blood compatibility of the blood-contacting materials. Less interaction between the platelet and the material surface would lead lower probability of thrombus. Therefore, suitable blood-implanting materials reveal lower platelet adhesion, activation, and aggregations.

As shown in Figure 5(a), the surface distribution of platelets on the unmodified PU surface was nonrandom, and platelet metamorphosis, born pseudopod. As shown in the Figure 5(b, c), the platelet adhesion was obviously reduced on the modified PU film surface and no obvious deformation of platelets were found. Few platelets adhesion on the modified PU-PEG and PU-CMCS films proved excellent anti-platelet adhesion. When

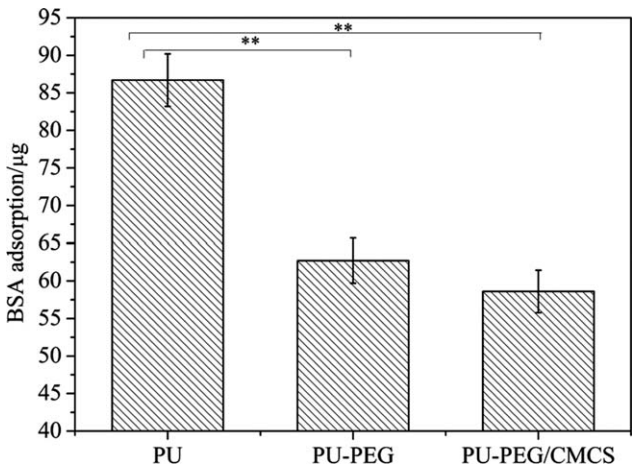

Figure 4. BSA adsorption of PU matrix, PU-PEG and PU-PEG/CMCS films (**$P < 0.005$).

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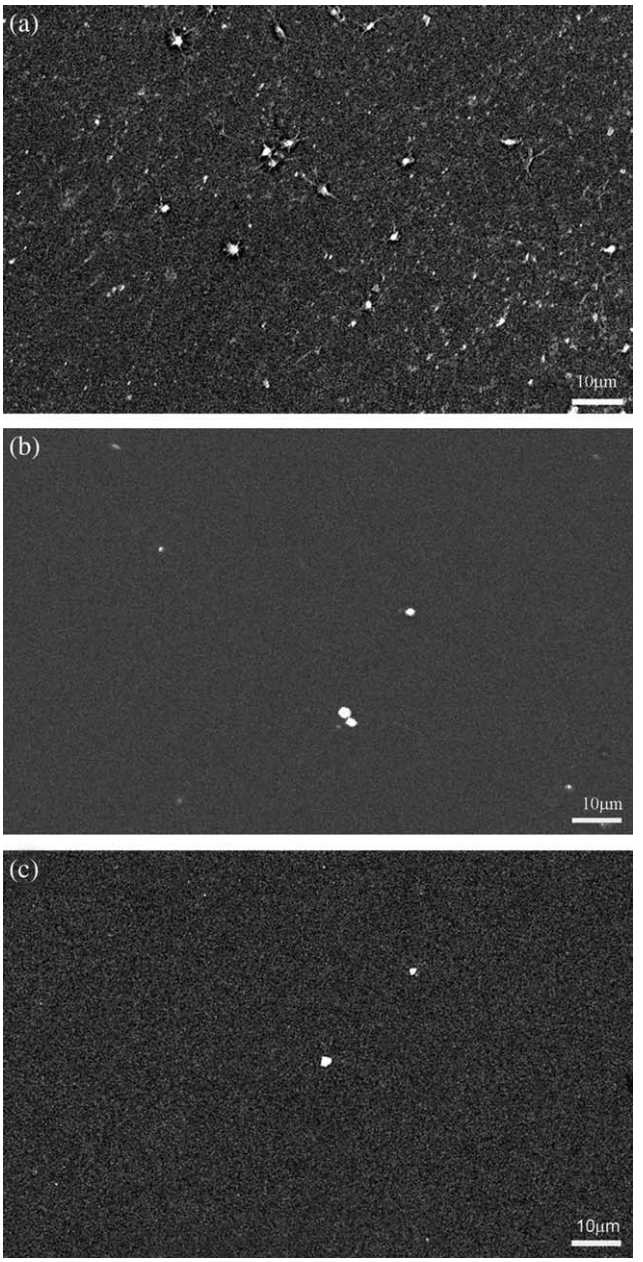

Figure 5. Platelet adhesion morphology of (a) PU control; (b) PU-PEG; (c)PU-PEG/CMCS.

blood is in contact with a foreign material surface, the adsorption of plasma proteins occurs, followed by platelet adhesion and deformation. After platelet adhesion, platelets release components such as 5-hydroxy tryptamine, adenosine diphosphate, and adenosine triphosphate, thereby inducing more platelet aggregation on the surface, and resulting in thrombosis. The modified PU-PEG/CMCS with platelet-rich plasma exposure, significantly reduced platelet adhesion, deformation decreases without causing a large gathering. The possible explanation for this excellent anti-platelet adhesion due to the contribution of low the blood and plasma proteins interfacial energy on the surface of the modified PU films.

Dynamic Clotting

Figure 6 shows the clotting time curves for the surface-modified and original PU films. The clotting time measurement is to test the activated degree of intrinsic coagulation factors. The slower the optical density (O.D.) value decreases with time, the longer the clotting time. As can be seen from Figure 6, the optical densities of the surface-modified PU films were bigger than the original PU films when the blood had been in contact with the materials for a long time. At the same time, Figure 6 also show the surface-modified PU films of the clotting time curves more gentle than the surface-unmodified PU films of the clotting time curves.

The point of O.D. equals 0.1 is defined as the initial clotting time which is also an important parameter to evaluate the anticoagulation quality of a biomaterial. It can be seen from Figure 6 that the O.D. values of the unmodified PU film has been less than 0.1 in 60 min, while the O.D. value of both PEG and PEG/CMCS modified PU film is greater than 0.1. The O.D. value of the PU-PEG was lower than 0.1 in 90 min, and that of PU-CMCS is higher than 0.1. It is shown that the modified PU films have better anticoagulation properties, and the anticoagulation property of the PU-PEG/CMCS is better than the PU-PEG film. This result is well in agreement with the results of PU-CMCS film, interfacial energy, and protein adhesion on the experimental materials.

Hemolysis

The absorbency at a wavelength of 540 nm of the samples was characterized with a spectrophotometer. The hemolysis percentage was calculated by following equation:

$$\text{hemolysis}(\%) = \frac{A - B}{C - B} \times 100\% \quad (5)$$

where A is A540 of test compound treated sample, B is A540 of physiological saline solution treated sample, and C is A540 of deionized water treated sample. The results are shown in Figure 7.

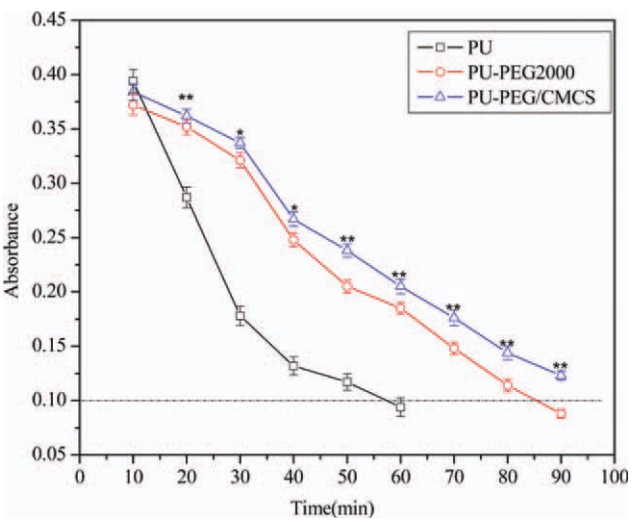

Figure 6. Dependence the optical density/time curves for the surface-modified and original PU films (*$P < 0.05$, **$P < 0.005$) [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.].

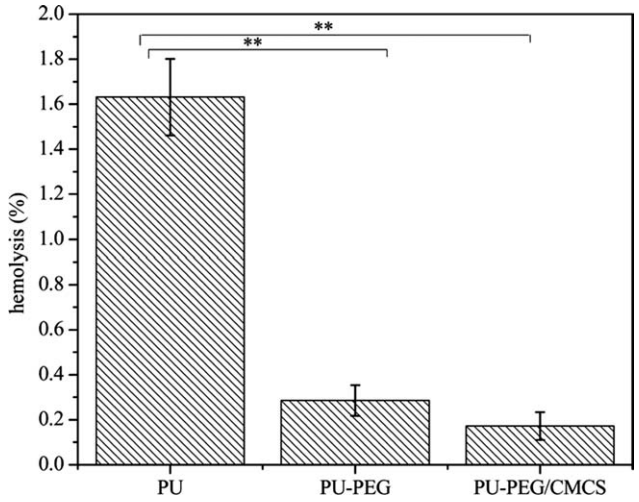

Figure 7. The hemolysis of the surface-modified and original PU films (**$P < 0.005$).

Hemolysis is which some of the red blood cells will be destroyed and the release of red blood protein when the blood contact with foreign surfaces. Good blood compatibility of materials should have low rates of hemolysis.[43] Figure 7 shows the hemolysis for the modified and unmodified PU films. The unmodified PU film of the highest rates of hemolysis, the modified PU films of hemolysis were significantly lower. The hemolysis of the PU-PEG/CMCS film is better than the PU-PEG film. The blood-compatibility of materials should be no hemolysis, but the truth is that in practice several medical devices cause hemolysis. This means that when the phenomenon of hemolysis happens, the most important is ensure that the material hemolysis rate control in the human body within the acceptable range. According to the American Society for Testing and Materials,[44] a material may be classified as hemolytic (>5% of hemolysis), slightly hemolytic (2–5% of hemolysis), and nonhemolytic (0–2% of hemolysis). It may be observed that hemolysis occur in <2% of the red cells, thus the PU-CMCS film is classified as a nonhemolytic material.

CONCLUSIONS

A simple and effective method for the coupling of CMCS onto PU surface was developed through surface grafting PEG treated by chemical grafting. In contrast to the PU surface, platelet adhesive and protein-adsorptive resistance of the PU-PEG/CMCS was greatly improved. The blood compatibility of PET-CMCS is believed to be related with the balance of hydrophilicity/hydrophobicity, the rates of hemolysis, dynamic clotting, low protein adsorption, and platelet adhesive. Thus, we believe that this modified PU film can be generally applied in a blood compatibility of biomedical devices.

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