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Novel Triphosphorylation Polyurethane Nanoparticles for Blood-contacting Biomaterials' Coating†

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Improving blood compatibility of blood-contacting biomaterials and devices has been the subject of intensive research. In this study, we synthesized a novel excellent blood compatible polyurethane /sodium triphosphate nanoparticle (PU/STPP). The characterization of polyurethane /sodium triphosphate (PU/STPP) nanoparticles was carried out by transmission electron microscopy (TEM), scanning electron microscopy (SEM), dynamic light scattering (DLS), nuclear magnetic resonance (NMR), and energy dispersive spectroscopy (EDS). Blood compatibility assessment of PU/STPP nanoparticles was performed by in vitro coagulation time, plasma clotting time, hemolysis rate and red blood cell morphology tests. The cell compatibility evaluation of PU/STPP nanoparticles were obtained by MTT cell viability tests. The PU/STPP nanoparticles were also used to modify vascular prostheses with cosedimentation. Platelet adhesion tests showed that the blood compatibility of vascular prostheses coated with PU/STPP nanoparticles is better than that of pure vascular prostheses.

Introduction

Blood-contacting biomaterials and devices should be of excellent blood compatibility and cell compatibility. At present, blood clots of biological materials seriously restricted their use in blood-contacting medical devices. Therefore, the development of blood-contacting materials with anticoagulant activity has become one of the key issues in biomedical research.¹⁻⁴ Due to excellent mechanical properties of polyurethanes (PU),⁵⁻⁸ PU are frequently used as biomaterials and devices, surface coating of biomedical devices and drug carriers.⁹⁻¹³

However, the blood compatibility of PU is not sufficient to make them attractive materials for demanding applications in blood-contacting medical devices.^{14,15} And the blood compatibility of PU must be enhanced while it was used for blood-contacting materials. To overcome these problems, various materials have been developed to improve the blood compatibility of PU materials.¹⁶⁻¹⁸

Polymer modification is a important way to improve the blood compatibility of blood-contacting materials and devices based on the PU. Hydroxyethyl methacrylate, sulfobetaine etc. were used to improving the blood compatibility of PU by grafting modification.¹⁹⁻²³ In addition, You et al. has used

microwave-assisted functionalization method to improve blood compatibility of PU.²⁴ Morimoto et al. has used a phospholipid semi-interpenetrating polymer networks in modification blood compatibility of PU.²⁵ Some bioactive substances such as heparin, fungal glucan have also been used to improve the blood compatibility of PU.^{26,27}

Phosphorylation polyurethane is a good way to improve the blood compatibility of PU because of phosphorus salts in body fluids, the cell membrane and nucleic acids etc. as a key component of the human body. And not only sodium triphosphate (STPP) is one of the most widely used phosphate compounds as dispersants and surfactants, but also triphosphate has a high bonding strength to the PU matrix.

In this study, we synthesized the novel PU/STPP nanoparticles as the blood contacting materials' coating to improve their blood compatibility and cell compatibility. Transmission electron microscopy (TEM), scanning electron microscopy (SEM), dynamic light scattering (DLS), nuclear magnetic resonance (NMR) and energy dispersive spectroscopy (EDS) were used to characterize the morphology and structure of PU/STPP nanoparticles. The blood compatibility of the nanoparticles was evaluated by measurements of the activated partial thromboplastin time (APTT), prothrombin time (PT), thrombin time (TT), plasma recalcification time, hemolysis rate and red blood cell morphology. The cytotoxicity of the nanoparticles was evaluated by the MTT cell viability test. In addition, the experiment of blood compatibility of vascular prostheses with PU/STPP nanoparticles' coating was also done.

Experimental section

Materials

4,4'-Diphenylmethane diisocyanate (MDI), poly(tetramethylene ether glycol) (PTMG) and dimethylol propionic acid (DMPA) were purchased from Sigma-Aldrich

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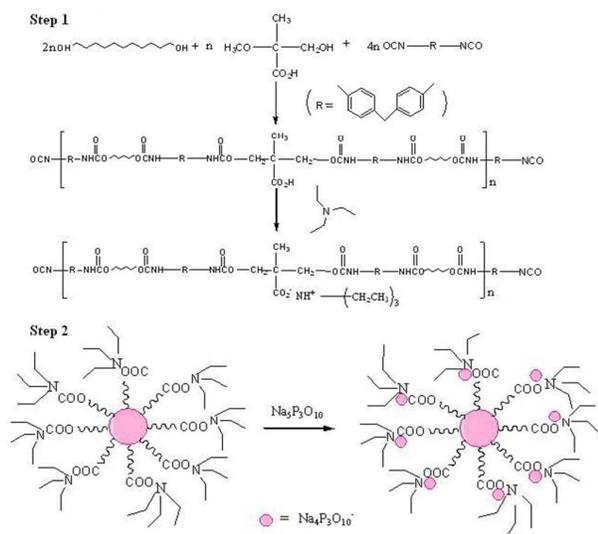
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China Inc. PTMG was dried in a vacuum oven for 12 h at 100 °C. DMPA was dried in air for 2 h at 100 °C. Sodium triphosphate (STPP), ethyl acetate and pyrrolidinone were provided by Aladdin Reagent Co. Ltd. (Shanghai, China). Ethyl acetate and pyrrolidinone were purified by distillation and dried over 4 Å molecular sieves. The vascular prosthesis was provided by the Gulou hospital in Nanjing.

Synthesis of PU/STPP Nanoparticles

As shown in the scheme 1, PTMG (17.6 g), MDI (8.5 g) and 1.0 μL dibutyl tin dilaurate (DBTL) were dissolved in 80 mL ethyl acetate. The resulting solution was added to a 500 mL four-necked round bottom flask and stirred at 70 °C under a nitrogen atmosphere. DMPA (1.76 g) in 10 mL pyrrolidinone was gradually added within 4 h. Subsequently, 5.5 mL isopropanol was added. The reaction was continued at 45 °C for 30 min. 2 mL Triethylamine was added and then the reaction was kept for an 15 min. The mixture was added to 100 mL of the sodium dodecyl sulfate solution (4 wt%) and further stirred for 30 min. Finally, the STPP solution (0.2 M) was added gradually to the reacting solution with a ultrasonic processing within 30 min.

The PU/STPP nanoparticles were collected by the centrifugation, dialyzed in distilled water for 7 days, and then dried by frozen.



Scheme 1. The synthesis steps of the PU-STPP nanoparticles.

Preparation of PU/STPP nanoparticle-modified vascular prostheses

An amount of PU/STPP nanoparticles was added into the 0.5 mg/mL PU ethanol solution and sonicated in a waterbath sonicator for 30 min. The suspension was dropped into the vascular prosthesis. The modified vascular prosthesis was dried in a vacuum at 60 °C for 4 h. The PU/STPP particles could be tightly fixed into the PU film when PU was sedimented into the porous of vascular prosthesis. The content of PU/STPP particles was 8.45×10^{-4} mg/cm² on the surface of the vascular prosthesis.

Morphology and element analyses

The TEM and SEM images of samples were obtained on a Hitachi-H-7650 TEM (Hitachi Co., Japan) and a JSM-7600F SEM (JEOL Co., Japan), respectively. The size distribution of PU/STPP nanoparticle and its zeta potential were measured in

water (pH, 7.2) at 25 °C by a Malvern Zetasizer Nano ZS90 dynamic light scattering instrument (Malvern Co., U.K.), and all measurements were repeated five times. The ³¹P-NMR of PU/STPP nanoparticles was carried on an AVANCE-400 Fourier transform spectrometer (Bruker Co., Switzerland) at 162 MHz. The EDS spectrum of PU/STPP nanoparticles was obtained on a Noran-Vantage EDS spectrometer (Thermo Noran Co., USA).

Quantum chemistry calculation of NH⁺(C₂H₅)₃-P₃O₁₀⁵⁻

A quantum chemistry calculation was carried out to understand the way in which the cationic quaternary ammonium salt interacts with a phosphoric acid anion or a triphosphoric acid anion. All the molecules were completely optimized using the DFT/B3LYP method with the 6-31+g(df,p) basis set. All the theoretical calculations were carried out using the GAUSSIAN 03 program package with the default convergence criteria.

Interaction energy is defined as $E_b = E_{(product)} - E_{(reactant)}$. In this study, $E_{(reactant)}$ is the sum energy of constituent molecules in a pair including the cationic quaternary ammonium salt NH⁺(C₂H₅)₃ and PO₄³⁻/or P₃O₁₀⁵⁻, each of which were previously optimized independently. Then, the pair of constituent molecules being placed together in a proper position was optimized to generate a final geometry, and the corresponding energy minima could be considered as $E_{(product)}$.

In vitro cytotoxicity measurements

The cell viability of endothelial progenitor cells (EPCs) was determined using an MTT assay, according to ISO 10993-5. The 1×10^4 cells/μL EBM-2 in culture medium were transferred to a 96-well plate and incubated under a 5% CO₂ humid atmosphere at 37 °C for 24 h. The culture medium was removed, and 100 μL/well of the various concentrations of PU/STPP nanoparticles in normal saline solution (5, 50, 500, 5000 μg/mL turbid liquid) were added to the 96-well plate. The normal saline solution was removed and 100 μL/well culture medium was added to the 96-well plate. The samples were incubated under a 5% CO₂ humid atmosphere at 37 °C. After 24 h or 72 h, the culture medium was removed and the cells were washed with 150 μL phosphate-buffered saline (PBS, pH = 7.4), followed by the addition of 20 μL/well tetrazolium salt (MTT) solution. After 4 h, the MTT solution was removed from the 96-well plate and 150 μL/well DMSO was added. The 96-well plate was gently shaken for 10 min at 37 °C. The O.D. was measured at 490 nm by an ELISA reader. All measurements were repeated eight times. The positive control was the MTT solution and the negative control was the culture medium.

Blood compatibility measurements

The blood samples were supplied by Nanjing Gulou hospital. And experiments' procedures were in agreement with the guidelines of the regional ethic committee for *in vitro* experiments.

In vitro coagulation time measurements. The nephelometry measurements of blood samples including APTT, PT and TT were performed with a coagulation instrument (Sysmex CA-1500 Sysmex Corp., Japan). And the concentrations of PU/STPP nanoparticle in blood were 5, 50, 500 μg/mL respectively.

Plasma clotting time measurements. The various concentrations of PU/STPP nanoparticle samples in saline (5, 50, 500 μg/mL) were added to a 96-well plate at 37 °C. And 0.1 mL platelet poor plasma (PPP) and 0.1 mL 0.025 M CaCl₂ solution were added to the wells.

The optical density (O.D.) was measured at 405 nm on a ELISA reader (BioTek synergy 2, BioTek Company, USA). The

optical density was measured every minute. All measurements were repeated three times.

Hemolysis rate measurements. 10 mL normal saline solution were added into 8 mL fresh adult whole blood with the sodium citrate anticoagulant. 200 μ L dilute blood were added to 10 mL PU/STPP nanoparticles saline (5, 50, 500, 5000 μ g/mL). All samples were incubated at 37 $^{\circ}$ C for 1 h and centrifuged at 1000 rpm for 10 min. The O.D. was measured at 545 nm by an ELISA reader. The positive control was the mixture of 10 mL distilled water and 0.2 mL dilute blood sample. The negative control was the mixture of 10 mL normal saline solution and 0.2 mL dilute blood sample. All measurements were carried out three times.

The degree of hemolysis was calculated as follows:

$$\text{Hemolysis}\% = \frac{D_t - D_{nc}}{D_{pc} - D_{nc}} \times 100\%$$

where D_t , D_{pc} and D_{nc} are the absorbances of the test sample, the positive control and the negative control, respectively.

Red blood cell morphology measurements. 4 mL red blood cell suspension were added into 5 mL normal saline solution. 200 μ L dilute red blood cell suspension were added into 10 mL PU/STPP nanoparticles saline (5, 50, 500, 5000 μ g/mL liquid). The samples were incubated at 37 $^{\circ}$ C for 1 h. After interacted with the different concentration of PU/STPP nanoparticles, the morphology of the red blood cells was observed on a inverted phase contrast microscope (CK40, Olympus Corp., Japan).

Platelet adhesion experiment. A pure vascular prosthesis and a modified vascular prosthesis were sterilized with 75% ethanol and washed with PBS. Fresh platelet-rich plasma (PRP) was added onto the pure vascular prosthesis sample and the modified vascular prosthesis sample. After a 1 h incubation at 37 $^{\circ}$ C, the samples were washed with PBS and fixed in 2.5% glutaraldehyde for 30 min. The samples were washed with PBS and dehydrated in a series of solvents with different ethanol concentrations (50%, 60%, 70%, 80%, 90% and 100%) and dried in air at room temperature. The images of the samples were taken on a JSM-7600F SEM (JEOL Co., Japan).

Results and discussion

Morphology and element analyses of PU/STPP nanoparticles

The TEM image of PU/STPP nanoparticles is shown in Figure 1(a). The average size of the PU/STPP nanoparticle was about 150 ± 10 nm with a uniform size distribution. Figure 1(b) is the SEM image of PU/STPP nanoparticles, and PU/STPP nanoparticles were orderly arranged on the glass matrix. The morphology of majority of the PU/STPP nanoparticles was the same as the ones with a 0.29 % deviation in the TEM image and SEM image. The size distribution of PU/STPP nanoparticles in saline by the dynamic light scattering showed that its average diameter was about 164 nm, and its PDI was 0.17 (Figure 1(c)). The zeta potential of the nanoparticles was -37.7 mV, which indicates that the PU/STPP nanoparticles were of high electronegativity and stability in saline.

The ^{31}P NMR spectroscopy of PU/STPP nanoparticles is shown in Figure 2(a). The 1D ^{31}P NMR resonance signals at $\delta - 1.142$ ppm was assigned to $\text{P}_3\text{O}_{10}^{5-}$. This signal indicated that STPP was self-assembled on the surface of the PU nanoparticles. The EDS spectrum of PU/STPP is shown in Figure 2(b). It revealed that the P element has been introduced to the surface of PU nanoparticles. The results of EDS are consistent with the ^{31}P NMR spectroscopy results shown in Figure 2(a).

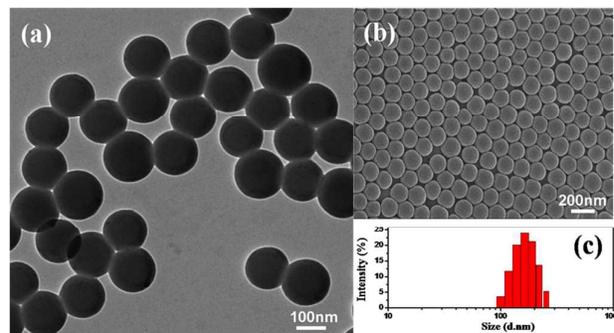


Figure 1. Morphology of PU/STPP nanoparticles (a) TEM image of PU/STPP nanoparticles; (b) SEM image of PU/STPP nanoparticles; (c) Size distribution of PU/STPP nanoparticles.

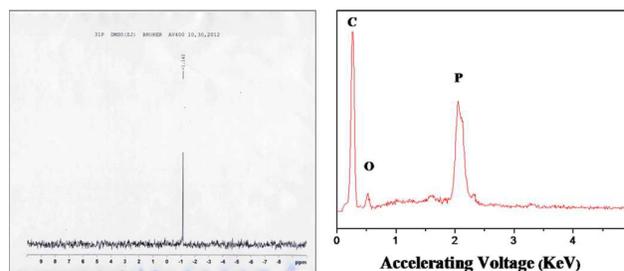


Figure 2. Element analyses of PU/STPP nanoparticles (a) ^{31}P NMR spectra of PU/STPP nanoparticles; (b) EDS spectra of PU/STPP nanoparticles.

A quantum chemistry calculation was carried out to understand the way in which the cationic quaternary ammonium salt interacts with a phosphoric acid anion or a triphosphoric acid anion. Quantum chemistry calculations showed that the decomposition tendency of $\text{P}_3\text{O}_{10}^{5-}$ upon receiving a proton was stronger than that of PO_4^{3-} (as supplementary Figure 1-3 and supplementary Table 1).

Blood compatibility of PU/STPP nanoparticles

In vitro coagulation time, plasma recalcification time, hemolysis rate and red blood cell morphology are the four most important parameters for blood compatibility of biomaterials as a blood-contacting material, especially for powder materials.

Coagulation time often detects abnormality in blood plasma clinically. And the coagulation time including ATPP, PT and TT has been used to evaluate the blood compatibility of blood-contacting biomaterials. The in vitro coagulation times of samples are shown in Figure 3 (a–c). The ATPP, PT and TT increased from 92 s to 115 s, from 15 s to 33 s and from 18 s to 28 s with increasing concentrations of PU/STPP nanoparticles from 0 to 500 μ g/mL, respectively. And the results of coagulation time indicated that the PU/STPP nanoparticles were of good antithrombogenicity.

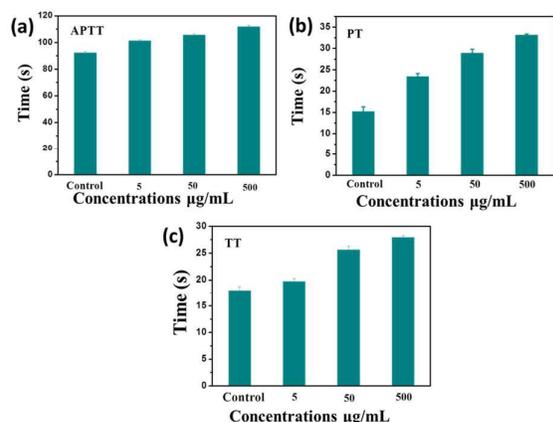


Figure 3. In vitro coagulation time of PU/STPP nanoparticles. (a) APTT; (b) PT; (c) TT.

To further evaluate the antithrombogenicity of the PU/STPP nanoparticles, the plasma recalcification time of nanoparticles was measured. In this study, the T1/2 max (the time to half saturate the absorbance) was recorded as the plasma clotting time.²⁸ The plasma clotting time of the different concentration of PU/STPP nanoparticles is shown in Figure 4. The plasma clotting time was significantly increased from 18 min to 23 min with the increase in the concentration of PU/STPP nanoparticles from 0 to 500 µg/mL. The increase in the plasma clotting time results in better antithrombogenicity.^{28,29} This result indicates that the PU/STPP nanoparticles were of good blood compatibility.

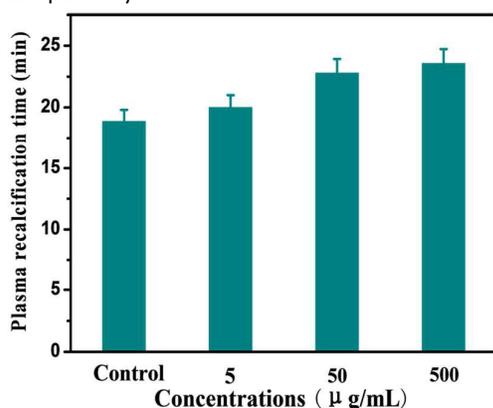


Figure 4. Recalcification time of PU/STPP nanoparticles.

The rate of hemolysis and red blood cell morphology can be used to evaluate the red blood cell damage of blood-contacting materials. The hemolysis rates of PU/STPP nanoparticles with the different concentrations were shown in Figure 5. The hemolysis rates were varied from 0.85% to 2.07% for different concentrations of PU/STPP nanoparticles (from 5 µg/mL to 5000 µg/mL), whereas the hemolysis rates of pure PU nanoparticles was ranged between 2.35 to 2.79. It demonstrates that the anti-hemolysis property of PU/STPP nanoparticle is better than that of pure PU nanoparticles. But the anti-hemolysis property of PU/STPP nanoparticles should be improved when it was used as an in vivo anti-hemolysis material future.³⁰

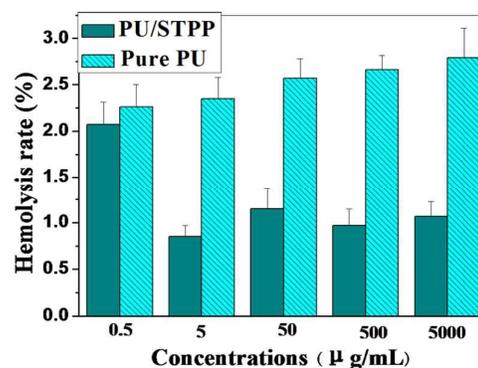


Figure 5. Hemolysis rate of PU/STPP nanoparticles.

Red blood morphology is examined often used to evaluate the damage that biomaterials cause in red blood cells. The images of red blood cells treated with different concentrations of PU/STPP nanoparticles are shown in Figure 6. The red blood cells retained the same circular morphology of the control group at various concentrations of PU/STPP nanoparticles (5, 50, 500, 5000 µg/mL). These results indicate that the PU/STPP nanoparticles do not damage red blood cells. Thus, the PU/STPP nanoparticles have good blood compatibility.

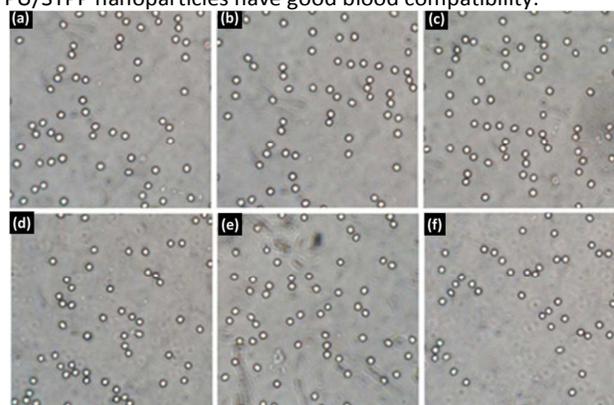


Figure 6. Red blood cell morphology treated with control or different concentration of PU/STPP nanoparticles. (a) The control group with 0.9% physiological saline solution; (b) 0.5 µg/mL; (c) 5 µg/mL; (d) 50 µg/mL; (e) 500 µg/mL; (f) 5000 µg/mL of PU/STPP nanoparticles).

In vitro cytotoxicity of PU/STPP nanoparticles

The MTT assay is commonly used to test in vitro cell cytotoxicity of materials. Figure 10 is the graph of the MTT assay results of PU/STPP nanoparticles with EPCs for 24 h and 72 h. Cell viability with different concentrations of PU/STPP nanoparticles (from 0.5 µg/mL to 5000 µg/mL) ranged between 94% and 101% after the 24 h treatment (Figure 7(a)). And the cell viability after a 72 h treatment (Figure 7(b)) was similar and ranged between 92% and 103%. The results of MTT assay indicated that PU/STPP nanoparticles are of low cytotoxicity. Therefore, the PU/STPP nanoparticles were of good cell compatibility.^{31,32}

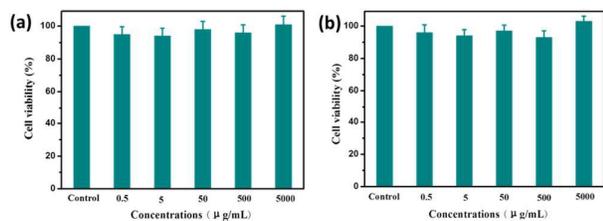


Figure 7. MTT assay results of EPCs treated with different concentration of PU/STPP nanoparticles. (a) 24h; (b) 72h.

Blood compatibility of the PU/STPP nanoparticle-modified vascular prosthesis

The platelet adhesion test is an important approach to evaluate the blood compatibility of blood-contacting biomaterials. The SEM images of platelet adhesion to the modified vascular prosthesis and the pure vascular prosthesis are shown in Figure 8. Platelets did not adhere to the modified vascular prosthesis obviously (Figure 8(a)). However for the pure vascular prosthesis, the platelets had extended pseudopodia and were fully spread out on the surface of the pure vascular prosthesis (Figure 8 (b)). And the number of platelets on the pure vascular prosthesis was about 5330/cm². These results demonstrate that the blood compatibility of vascular prostheses is improved significantly with the PU/STPP modification.

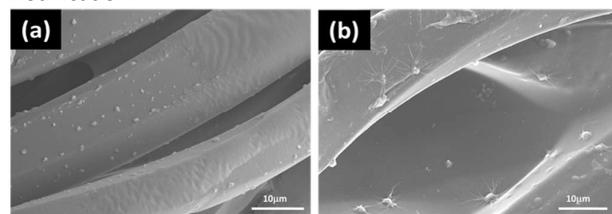


Figure 8. The SEM images of platelet adhesion on modified vascular prosthesis and pure vascular prosthesis after 60 min of human PRP exposure. (a) Modified vascular prosthesis; (b) Pure vascular prosthesis.

Conclusions

We successfully synthesized the monodispersed PU/STPP nanoparticles with the uniform morphology. The combined measurements of activated partial thromboplastin time (APTT), prothrombin time (PT), thrombin time (TT), plasma recalcification time, hemolysis rate and red blood cell morphology indicate that PU/STPP nanoparticles are of excellent blood compatibility. The MTT assay revealed that the PU/STPP nanoparticles are of low cytotoxicity with EPCs. And more, tests of platelet adhesion to PU/STPP nanoparticle-modified vascular prostheses show that the blood compatibility of the modified vascular prostheses is better than that of the pure vascular prostheses. Therefore, our work suggests that the PU/STPP nanoparticles could be used to improve blood compatibility of blood-contacting biomaterials.

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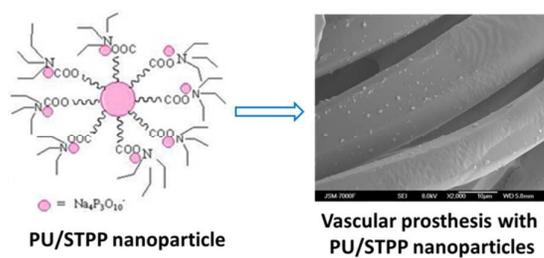
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