Surface Modification of Poly(vinyl chloride) for Antithrombogenicity Study

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ABSTRACT: A process was established to conduct heparinization on the surface of poly(vinyl chloride) for antithrombogenicity utilization. A bifunctional monomer, glycidyl methacrylate (GMA), was grafted onto the surface of PVC by gas-phase photografting polymerization without degassing first; then heparin was immobilized onto the poly(glycidyl methacrylate) segments. The branch structure of GMA and heparin were characterized by Fourier transfer infrared (FTIR) spectroscopy and electron spectroscopy (ESCA). It was confirmed that the bifunctional monomer GMA and heparin were grafted successfully onto the surface of PVC. The antithrombogenicity of the samples was tested both *in vitro* and *in vivo*, respectively. Results indicated that the blood compatibility of those products was improved greatly. © 2002 Wiley Periodicals, Inc. J Appl Polym Sci 85: 1013–1018, 2002

Key words: medical poly(vinyl chloride) (PVC); surface modification; antithrombogenicity; heparin

INTRODUCTION

Poly(vinyl chloride) (PVC) was widely used in medical devices because of its excellent mechanical and anti-aging properties. It was used as a medical catheter, artificial blood vessels, and some blood-contacting materials in extracorporeal circulation equipment during operations. However, a major problem with such articles is that their working surfaces are foreign to blood and tend to initiate red-cell destruction and coagulation, and as a result, to form clots. Much work[1–4] had been done to find ways to impart nonthrombogenicity on the surface of these synthetic articles. Surface heparinization is one of the most important ways to realize it. The surface of PVC is inert and needs to be modified before heparinization. Surface modification of PVC is a crucial solution to this problem. Methods for surface modification include chemical oxidation, corona discharge treatment, plasma treatment, ozonization, and photoinitiated graft polymerization.[5–11] Among these methods, photoinitiated graft polymerization is very suitable for surface modification because of less expensive equipment, easily controlling the reaction and the thin modified layers on the substrate surface.

The purpose of this article is to apply the heparinization method by Ranby et al.[1] to the PVC sample. It presents a two-step procedure to enhance the blood compatibility of PVC. A bifunctional monomer (glycidyl methacrylate, GMA) was grafted onto the surface of medical PVC, and then heparin was immobilized in poly(glycidyl methacrylate) branches. To date, no report has been found involving immobilization of heparin onto surface PVC materials by this method.

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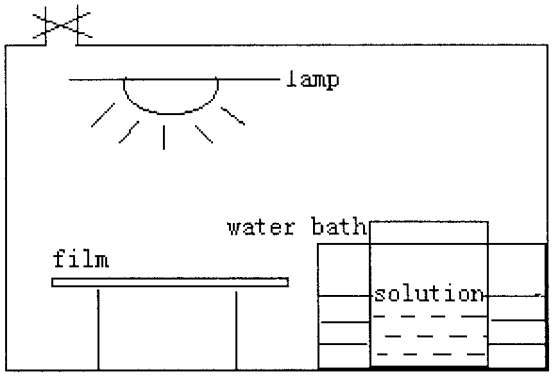

Figure 1 Gas-phase surface photografting device.

EXPERIMENTAL

Materials

PVC films (made in this laboratory) with a thickness of 0.04 mm were extracted for 24 h in ethanol and then dried at room temperature. PVC catheter (outer diam., 4 mm; inner diam., 3 mm) was supplied by Hongda Medical Devices Co., Ltd., Jiangxi, China. GMA, supplied by HengGuang Chemical Co., Luoyang, China, was used as received. Heparin sodium, supplied by AoBoXing Biochemistry Technique Co., Ltd., Beijing, China, was used as received. Benzophone (BP), ethanol, and acetone used were graded analytical reagents (AR).

Apparatus

The ultraviolet light source used for irradiation is a 400 W lamp which emits light in the near UV ($\lambda \geq 300$ nm; characterized wavelength, 340–360 nm). The photografting device is schematically shown in Figure 1.

Photografting and Immobilization

PVC materials to be grafted were placed in a small reactor together with a beaker containing a solution of 2*M* GMA and 0.2*M* BP in ethanol. The solution was heated to 80°C in a water bath and then irradiated for some time. After irradiation, the grafted materials were extracted with acetone for 24 h to remove monomer, initiator, and homopolymer formed during grafting polymerization. After that, the grafted materials were washed with distilled water and then dried at 50°C. Heparin was immobilized onto the grafted surface by placing the grafted material in a flask with 50 mL H_2O and 2 g heparin and stirring for 24 h at 50°C. After reaction, the film was washed with distilled water for 24 h and then dried at 50°C.

Measurements

FTIR Measurement

FTIR analysis was performed with a WQF-310 FTIR spectrometer with 2 cm^{-1} resolution and 16 scanning times.

ESCA Measurement

The ESCA spectra were recorded on a Perkin–Elmer PHI5400 ESCA System, with an AIK_α X-

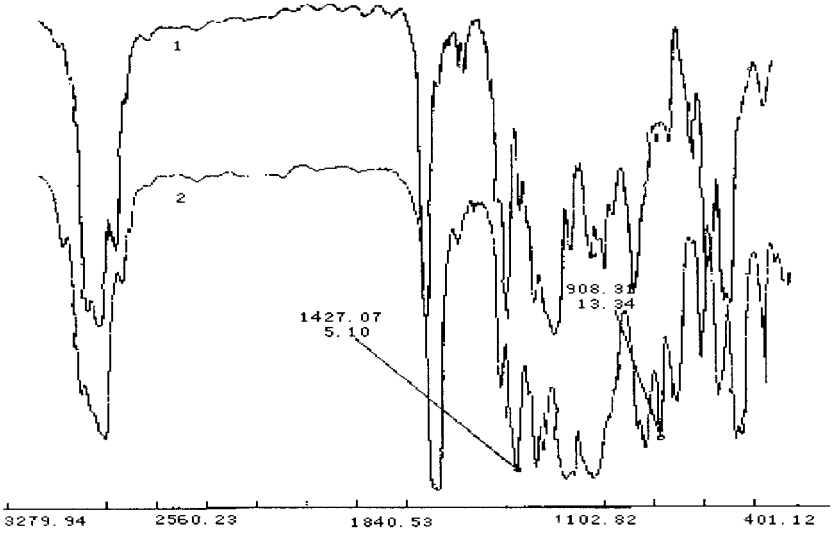

Figure 2 FTIR of pure and GMA-grafted PVC (1, pure PVC; 2, GMA-grafted PVC; GMA, 2*M*; BP, 0.2*M*; irradiation time, 20 min; temperature, 80°C).

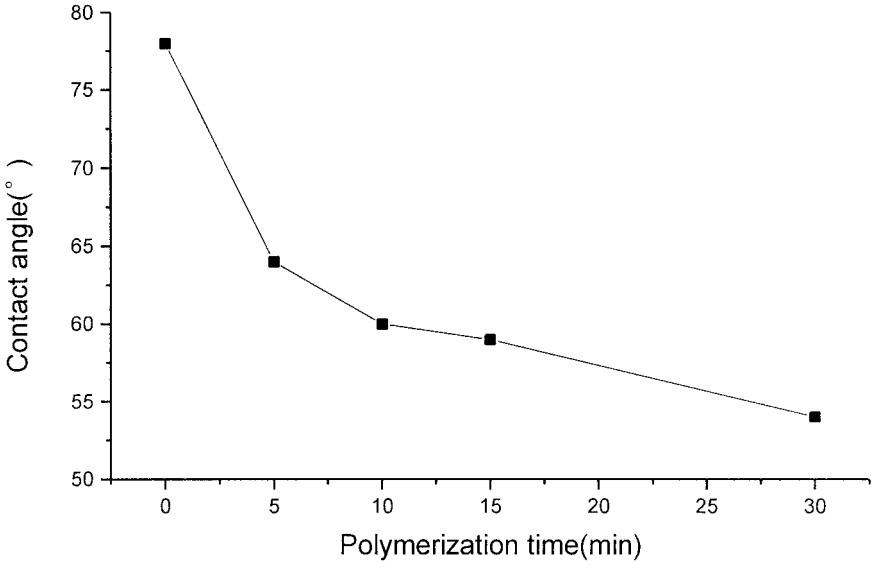

Figure 3 Contact angle against water on GMA-grafted PVC during different UV-irradiation times.

ray radiation source of 15 kV, 250 W. The vacuum degree is $1–4 \times 10^{-8}$ τ; input angle is 45°, and the contaminated C_{1s} (E_b = 285.0 eV) peak was used as a standard.

Contact Angle Measurement

The contact angles to water of the GMA-grafted samples were measured on a JY-82 contact angle goniometer (made in Jilin, China) at ambient humidity and temperature; measurements were carried out three times for each sample.

Antithrombogenicity Test In Vitro

By using modified Lee–White method,[12] the whole-blood clotting time (WBCT) was measured to evaluate the primary nonthromobogenic property of samples. About 0.5 mL fresh blood was injected into catheter samples, and then the initial time was recorded. Samples were kept static for 5 min and then vibrated softly every minute (within 30 min) until the blood was completely clotted. The time was recorded.

RESULTS AND DISCUSSION

Photografting with GMA

It is well known that the epoxy group can react with a lot of different functional groups. When GMA is grafted onto the surface, a reactive polymer surface containing epoxy groups is formed. To this surface, some substances can be attached through reaction with the epoxy group; its surface property can be further modified.

The grafting process studied here is based on the ability of excited BP to abstract a hydrogen from the substrate and then to form a surface macroradical. When benzophenone absorbs a UV quantum, it is excited to the singlet state of short lifetime and then rapidly relaxed to the more stable triple state through intersystem crossing (ISC). BP in the triplet state can abstract hydrogen from the polymer substrate (PH) and create active sites for graft polymerization. To this macroradical, with the addition of monomer, a poly-

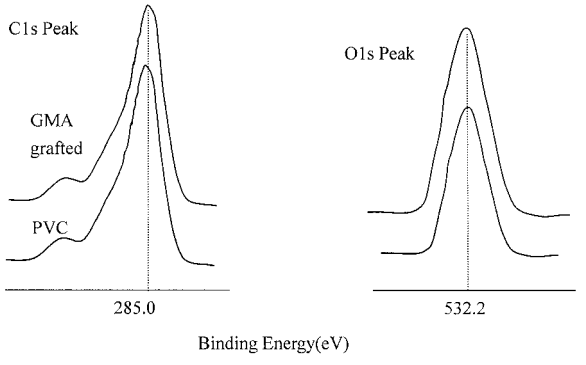

Figure 4 ESCA spectra of pure and GMA-grafted PVC (GMA, 2*M*; BP, 0.2*M*; irradiation time, 10 min; temperature, 80°C).

Table I Data of ESCA (GMA:2M, BP:0.2M, irradiation time:10min, temperature:80°C)

	Pure PVC		GMA-Grafted PVC		Heparinized PVC	
Element	eV	Conc. (%)	EV	Conc.(%)	EV	Conc.(%)
C_{1s}	285.0	84.58	284.0	81.95	285.0	78.66
O_{1s}	532.3	12.17	532.5	17.21	532.1	17.27
CI_{1s}	200.3	3.26	200.2	0.83	199.6	0.40
N_{1s}					400.1	3.38
S_{1s}					168.9	0.29

mer chain will grow out to form a graft copolymer on the surface.

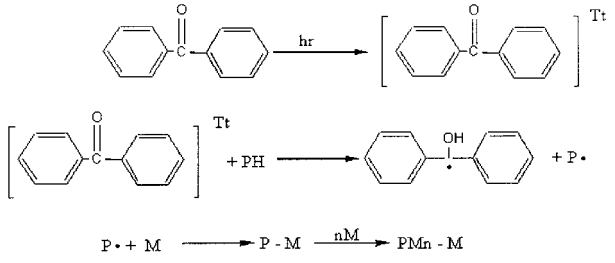

Figure 2 shows the FTIR spectra of pure PVC and GMA-grafted PVC. As can be seen, the characteristic bands of glycidyl ethers (about 910 cm^{-1}) appear in the spectrum of GMA-grafted PVC, and some peaks of PVC are strengthened (such as 849,750 cm^{-1}) accordingly. The new band of 908 cm^{-1} is induced by the epoxy groups of grafted GMA. Those strengthened peaks are also induced by it. It is proven that GMA was grafted onto the surface of PVC.

Figure 3 shows the results of the contact angle measurement. After 10 min of irradiation, the contact angle against water decreased from 78 to 60°. As epoxy groups of GMA are hydrophilic, it probably contributes to the decrease in the contact angle.

It can be found that with the wide scan, ESCA measurement on the grafted sample presents much higher amounts of oxygen than that of the pure sample. It may be attributed to the grafted GMA; the results can also be seen in Table I.

Table I gives the data of binding energy and concentration of elements on the surface of pure PVC, GMA-grafted PVC, and heparinized PVC. Clearly, the GMA-grafted PVC has higher oxygen fraction on the surface than that of pure PVC, which can be attributed to the surface grafting of GMA.

In Table I, it can also be seen that the ratio of carbon to oxygen is about 7 on the surface of pure PVC materials. After grafting, the ratio decreases to 4.8, which can be attributed to the grafted GMA (the ratio of GMA is 2). It can be concluded that GMA was grafted partially onto the PVC surface. However, it cannot cover the full surface because the grafting is effected by surface morphology of the substrate.

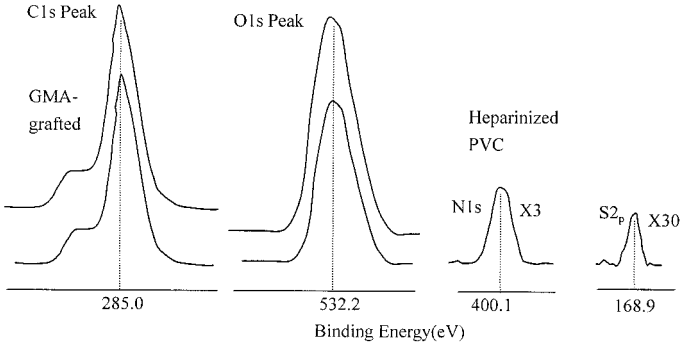

Figure 5 ESCA spectra of GMA-grafted PVC and heparinized PVC (photografting-GMA, 2*M*; BP, 0.2*M*; irradiation time, 10 min; temperature, 80°C; heparinization, 2 g heparin, 50 mL H_2O, stirring for 24 h at 50°C).

Table II WBCT during Antithrombogenicity Test In Vitro[a]

Dealt Method	WBCT (min)	Blood Compatibility Evaluation
Blank	3	Bad blood compatibility
Covalent[b]	>8 days	Better blood compatibility than blank sample, bad initial antithrombogenicity but better scouring durability
Ironic[13]	>9 days	Good initial antithrombogenicity, bad scouring durability
Covalent + Ironic[c]	>10 days	Best blood compatibility

[a] Rabbit blood.
[b] Photografting, GMA, 2 M; BP; 0.2 M; irradiation time, 10min; temperature; 80°C; heparinization, 2 g heparin, 50ml H_2O, stirring for 24 h at 50°C.
[c] Sample was dealt with covalent method first and then with ironic method.

The concentration of chloride decreases sharply, which may contribute to some decomposition reactions during photografting polymerization. Therefore, GMA is indeed grafted onto PVC surface on the basis of the analysis results of FTIR and ESCA.

Immobilization of Heparin

Heparin is a polysaccharide; it is also regarded as an important anticoagulant agent. Heparin is more effective in the free and mobile state; however, it is desired to immobilize heparin onto the polymer surface for a relatively long period of time. Heparin contains acid, amine, and alcohol groups, which can react with epoxy groups.[1] To prevent destruction of its anticoagulant properties, heparin must be attached under mild conditions and should preferably retain some flexibility after being grafted.

Figure 5 showed that after reaction, traces of sulfur and nitrogen which belong to the heparin are detected in ESCA spectra. Data in Table I also indicated traces of nitrogen and sulfur. Heparin is indeed immobilized onto the grafted material surface.

Blood Compatibility

Antithrombogenicity Test In Vitro

Antithrombogenicity test *in vitro* is an easy way to optimize the samples. Table II listed the WBCT result of samples via different methods during a antithrombogenic test *in vitro*.

From Table II, it can be seen that the sample related to both covalent and ironic method presents the best blood compatibility in addition to initial antithrombogenicity and scouring durability. Early work[13] portrays that sample via ironic method has good initial antithrombogenicity but bad scouring durability, whereas sample via covalent method is reverse to it. However, sample via both ironic and covalent method can combine the merits of the two methods.

Animal Test

To evaluate the blood compatibility and durability of heparin during application, both blank and heparinized PVC samples were implanted into the femoral artery of a dog to substitute a section of vein so that blood could be observed clearly.

The samples were taken out after10 h. Results indicated that heparinized samples possess much better blood compatibility than that of blank samples. There is little thrombogenesis on the surface of the heparinized samples, whereas the blank sample was completely clotted. The sample bonded with heparin presented excellent durability during the experiment.

CONCLUSION

GMA, as a bifunctional monomer, was successfully photografted onto the surface of PVC material and was confirmed by FTIR and ESCA measurements. Through the reaction of GMA with heparin, heparin was immobilized onto the PVC surface. The WBCT of optimized samples reached more than 1 week in the antithrombogenic test *in vitro*. Animal tests indicated that the property of antithrombogenicity and the scouring durability of heparin on PVC material greatly improved. Via both ironic and covalent method, products with good initial antithrombogenicity and scouring durability can be obtained.

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