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Copolymerization of acrylonitrile with *N*-vinyl-2-pyrrolidone to improve the hemocompatibility of polyacrylonitrile

Ling-Shu Wan[a], Zhi-Kang Xu[a,*], Xiao-Jun Huang[a], Zhen-Gang Wang[a], Jian-Li Wang[b]

[a]*Department of Polymer Science and Engineering, Institute of Polymer Science, Zhejiang University, Yu Gu Road 38#, Hangzhou 310027, People's Republic of China*
[b]*College of Chemical Engineering and Materials, Zhejiang University of Technology, Hangzhou 310014, People's Republic of China*

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Abstract

Poly(acrylonitrile-*co*-*N*-vinyl-2-pyrrolidone)s (PANCNVP) were synthesized by water-phase precipitation copolymerization (WPPCP) with sodium chlorate–sodium metabisulfite as an oxidant/reducer initiator system. The copolymers were also synthesized by a solution copolymerization (SCP) initiated with azobis(isobutyronitrile) for comparison. Fourier transform infrared spectroscopy (FT-IR), nuclear magnetic resonance (^{1}H NMR), and differential scanning calorimetry (DSC) were used to characterize the copolymers. It was found that the copolymerization yield, the molecular weight of the copolymers, and the *N*-vinyl-2-pyrrolidone (NVP) conversion for WPPCP were much higher than those for SCP. Results indicated that WPPCP was a 'green' and effective method to incorporate NVP into polyacrylonitrile. The surface properties of the copolymer dense membranes were studied by water contact angle, protein adsorption, and platelet adhesion measurements. Typical results demonstrated that the introduction of NVP had little influence on the static, advancing, and receding contact angles of the dense membrane surface. However, the bovine serum albumin adsorption and the platelet adhesion were remarkably suppressed with the increase in NVP content in the copolymers. When the mole fraction of NVP in the copolymers reached 14.6%, little platelet adhesion took place. These results revealed that the hemocompatibility of polyacrylonitrile could be greatly improved by the incorporation of NVP.

Keywords: Acrylonitrile-based copolymer; *N*-Vinyl-2-pyrrolidone; Biocompatibility

1. Introduction

Since polymeric membranes were introduced in blood-contacting biomedical devices, significant efforts have been made to develop membranes with better blood compatibility [1]. Polyacrylonitrile (PAN) and acrylonitrile-based copolymers have been successfully applied as membrane materials for hemodialysis [2], ultrafiltration [3], enzyme-immobilization [4], and pervaporation [5]. However, due to the relatively poor hydrophilicity and/or biocompatibility for this type of membrane, some additional processes, such as chemical modification, biomacromolecule tethering (e.g. heparin), and cell seeding techniques must be taken to reduce protein adsorption and prevent blood clotting in hemodialysis [6]. Because both good blood compatibility and suitable flux are required for hemodialysis membrane, it is important to minimize the membrane–protein interactions which will irreversibly induce the membrane fouling as well as stimulate the blood coagulation process. These interactions are related to the chemical structure, the hydrophilicity/hydrophobicity balance, the morphology (i.e. the domain structure of a multi-component system), and the topography (i.e. the surface roughness) of the membrane surface [6].

As a versatile polymer soluble in both water and organic solvents, poly(*N*-vinyl-2-pyrrolidone) (PVP) has been the focus of numerous applications including additives, cosmetics, coatings and biomedicines [7]. The coating of PVP can evidently result in improved blood compatibility with no need to invoke tissue engineering techniques including endothelial cell seeding [7a]. For example, Robinson and Williams [8] reported that PVP could be simply adsorbed on silica particles to inhibit protein adsorption and even to remove adsorbed proteins from the

* Corresponding author. Tel.: +86 571 8795 2605; fax: +86 571 8795 1773.
E-mail address: xuzk@ipsm.zju.edu.cn (Z.-K. Xu).

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particle surface. This versatile polymer was most recently immobilized on poly(ethylene terephthalate) (PET) film by Meinhold et al. [9] to fabricate supported-hydrogels. The principal reason for successful PVP applications is its excellent biocompatibility with living tissues and extremely low cytotoxicity. PVP has also been used to modify the surface properties of polymeric membranes. By low-temperature plasma treatment, *N*-vinyl-2-pyrrolidone (NVP) was graft polymerized on poly(ether sulfone) ultrafiltration membrane, which resulted in higher filtration performance with less total and irreversible fouling [10]. Belfort et al. [11] had also successfully photochemically modified poly(ether sulfone) ultrafiltration membrane with NVP to increase the surface wettability and decrease the adsorptive fouling. On the other hand, Higuchi et al. [12] covalently conjugated PVP on the surface of polysulfone membrane with a multiple chemical process. It was reported that PVP-modified polysulfone membrane gave lower protein adsorption from a plasma solution and much suppressed number of adhering platelets than original polysulfone and other surface-modified membranes. Most recently, Kang et al. [13] cross-linked PVP on microporous chlorinated poly(vinyl chloride) membranes to improve their hydraulic permeation behavior. However, among them, grafting polymerization induced by plasma, electron beam, γ-radiation, and ultraviolet may result in a significant amount of homopolymer or cross-linked polymer. It is also difficult to control and quantify the grafting density and the chain length of the tethering polymer. Moreover, one of the serious disadvantages of some modification methods, such as blending, is the elution of the modification agent into the blood fluid during hemodialysis [12], which will not only decrease the membrane properties gradually but also pollute the blood.

N-Vinyl-2-pyrrolidone is a potential monomer for the chemical modification of polymeric membranes by copolymerization. Incorporating NVP into PAN by copolymerization may avoid the problems mentioned above because the content of NVP in the copolymer can be accurately tuned to achieve desired properties for the corresponding membrane and the NVP molecules integrated in the polymer main chain can not be easily eluted into the blood fluid. Copolymer membranes fabricated from poly(acrylonitrile-*co*-*N*-vinyl-2-pyrollidone) (PANCNVP) were recently described to attach hepatocytes in an artificial liver support system [14,15]. However, the copolymerizations of acrylonitrile with vinyl monomer including NVP were normally carried out in bulk, solution, and suspension processes [14–17]. The main problem for these processes may be of low molecular weight for the copolymers, which, as is well known, is unfavorable to the mechanical strength of the corresponding membranes. In our previous work [18–21], water-soluble monomers, such as α-allyl glucoside and maleic acid, were effectively incorporated into polyacrylonitrile by water-phase precipitation copolymerization (WPPCP) initiated with potassium persulfate ($K_2S_2O_8$)-anhydrous sodium sulfite (Na_2SO_3) to improve the antifouling property and the biocompatibility of polyacrylonitrile-based membranes. In these cases, water was used as the reaction medium, thus the copolymerization can be considered as 'green' chemistry. In light of the good water solubility of NVP, one can envisage that WPPCP should be a facile and a 'green' process that affords the advantages of increasing the molecular weight of PANCNVP and the NVP content in the copolymers, which, in turn, benefit the mechanical and biocompatible properties of the corresponding membranes. Nevertheless, the persulfate-based redox initiator system usually used for the synthesis of polyacrylonitrile-based homo- and copolymers will cross-link pyrrolidone seriously [22]. In this work, therefore, PANCNVPs were synthesized by WPPCP method initiated with sodium chlorate–sodium metabisulfite ($NaClO_3$–$Na_2S_2O_5$) and the blood compatibility of the copolymer dense membranes was evaluated by protein adsorption and platelet adhesion measurements.

2. Experimental section

2.1. Materials

Acrylonitrile (AN), dimethyl sulfoxide (DMSO), and NVP were commercially obtained from Shanghai Chemical Agent Co. (China) and were distilled at reduced pressure before use. Azobis(isobutyronitrile) (AIBN) was recrystallized in ethanol at 40 °C. Bovine serum albumin (BSA, pI = 4.8, M_w = 66 kDa) was purchased from Sino-American Biotechnology Co. and used as received. Sodium chlorate ($NaClO_3$), sodium metabisulfite ($Na_2S_2O_5$), and other chemicals were analytical grade and used as received without further purification.

2.2. Copolymerization of AN and NVP

Copolymerization of AN and NVP initiated with $NaClO_3$–$Na_2S_2O_5$ was performed by WPPCP method. De-ionized water (50 ml), AN (10.06 ml), NVP (1.82 ml), and the initiator system (20 mg of $NaClO_3$, 45.6 mg of $Na_2S_2O_5$) were added into a round flask with mechanical agitation at 60 °C under nitrogen atmosphere. The copolymerization was continued for a designated period of time (3 h), and then the precipitated copolymer was filtered and washed three times with de-ionized water and ethanol respectively. The resultant copolymer was dried under vacuum for at least 6 h at 60 °C. Solution copolymerization (SCP) was initiated by AIBN in DMSO at 70 °C with the usual procedure for comparison. The yield (conversion of the total monomers) was calculated with the mass ratio of the copolymer to the total monomers in the feed. The NVP content in the copolymer was determined from ^{1}H NMR spectrum and the conversion of NVP was calculated with

the mass ratio of the NVP units existing in the copolymer to the monomer in the feed.

2.3. Characterization

IR spectra were recorded with a Brucker Vector 22 spectrometer and ^{1}H NMR spectra were measured in DMSO-d_6 on a Brucker (Advance DMX500) nuclear magnetic resonance spectrometer. The homopolymer of NVP was removed completely by elution before these measurements. Differential scanning calorimetry (DSC) analysis was conducted by a STA409PC thermal analysis system at a heating rate of 10 °C/min from 50 to 350 °C. The intrinsic viscosity [η] was measured in DMSO at 30 ± 0.05 °C using an Ubbelchde viscometer. Copolymer was dissolved in DMSO that had been exhaustively dried over molecular sieves. For each copolymer, the viscosity of five concentrations was measured. The [η] was obtained by the extrapolation of a plot of specific viscosity/concentration versus concentration to infinite dilution using linear least squares. Estimates of the copolymer molecular weight were made according the following relationship for PAN in DMSO at 30 °C [23]:

$$[\eta] = 2.865 \times 10^{-2} M_v^{0.768}$$

where M_v is the viscosity-average molecular weight and the dimension for [η] is of ml/g.

2.4. Dense membrane fabrication

PANCNVP dense membranes were prepared by casting the DMSO solution of the copolymers (8 wt%) onto clean glass plates. The dense membranes were dried for 24 h at 100 °C under vacuum to remove the residual solvent and then immersed in pure water for 24 h. The resultant dense membranes were finally dried for another 24 h at 60 °C under vacuum. All dense membranes for contact angle, protein adsorption, and platelet adhesion measurements were treated according to the same procedure. The thickness of the dense membranes was approximately 18 ± 2 μm.

2.5. Contact angle measurements

Static contact angle (SCA) was measured by sessile drop method at room temperature with a contact angle goniometer (Dataphysics, OCA20, Germany) equipped with video camera. In a typical sessile drop method, a water drop (~5 μl) was added on a dry dense membrane sample in air, the image was recorded immediately and a static water contact angle was determined from the image with the imaging software. Advancing (ACA) and receding contact angle (RCA) were also measured following the static contact angle measurement by adding/withdrawing of pure water (~5 μl) to/from the water drop. At least ten measurements of different water drops were averaged to get a reliable value.

2.6. BSA adsorption

BSA adsorption was performed by the following method. The protein solutions with the concentration of 2.0 and 5.0 g/l were prepared by carefully dissolving desired amount of BSA powder in phosphate-buffer solution (PBS, 19.1008 g Na_2HPO_4 and 1.8145 g KH_2PO_4 for 1000 ml of buffer solution, pH = 7.4) at room temperature. Copolymer dense membrane with about 90 cm^2 of external surface area was introduced into a tube containing 10 ml BSA solution. Then the mixture was incubated at 30 °C for 24 h to reach adsorption equilibrium. The amount of adsorbed BSA was determined by measuring spectro-photo-metrically the difference between the concentration of BSA in the solution before and after contact with the dense membrane. The reported data were the mean value of triplicate samples for each copolymer dense membrane. Standard curve was also plotted with the same procedure.

2.7. Platelet adhesion

Experiments were carried out with fresh platelet rich plasma (PRP) bought from the Blood Center of Hangzhou, China. First, the dense membrane was placed onto a piece of flat glass. Then, a sample of 20 μl PRP was carefully dropped on the dense membrane center. After incubation for 30 min at room temperature, the dense membrane was carefully rinsed several times by phosphate buffer solution (pH = 7.4). Adhered platelets on the dense membrane were fixed with 2.5% glutaraldehyde/PBS solution for 30 min, followed by dehydration procedure using a series of ethanol-water mixtures (0, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100 volume% of ethanol) for 30 min, respectively. Samples were then air-dried and investigated with a scanning electron microscope (Cambridge S-260, UK) after gold sputtering.

3. Results and discussion

3.1. Copolymerization behaviors of AN and NVP

The copolymerization of AN and NVP in water medium was studied using a 90/10 AN/NVP monomer feed ratio. The homopolymer of NVP must be removed completely to obtain the purified copolymer. Therefore, concerning the high water solubility of PVP, the precipitate was eluted with hot water at least three times and filtrated under a reduced pressure to remove PVP and residual monomers. Then the resultant copolymer were washed by ethanol and dried under vacuum.

Fig. 1 shows the effects of initiator concentration ([I]), total monomer concentration ([M]), reaction temperature,

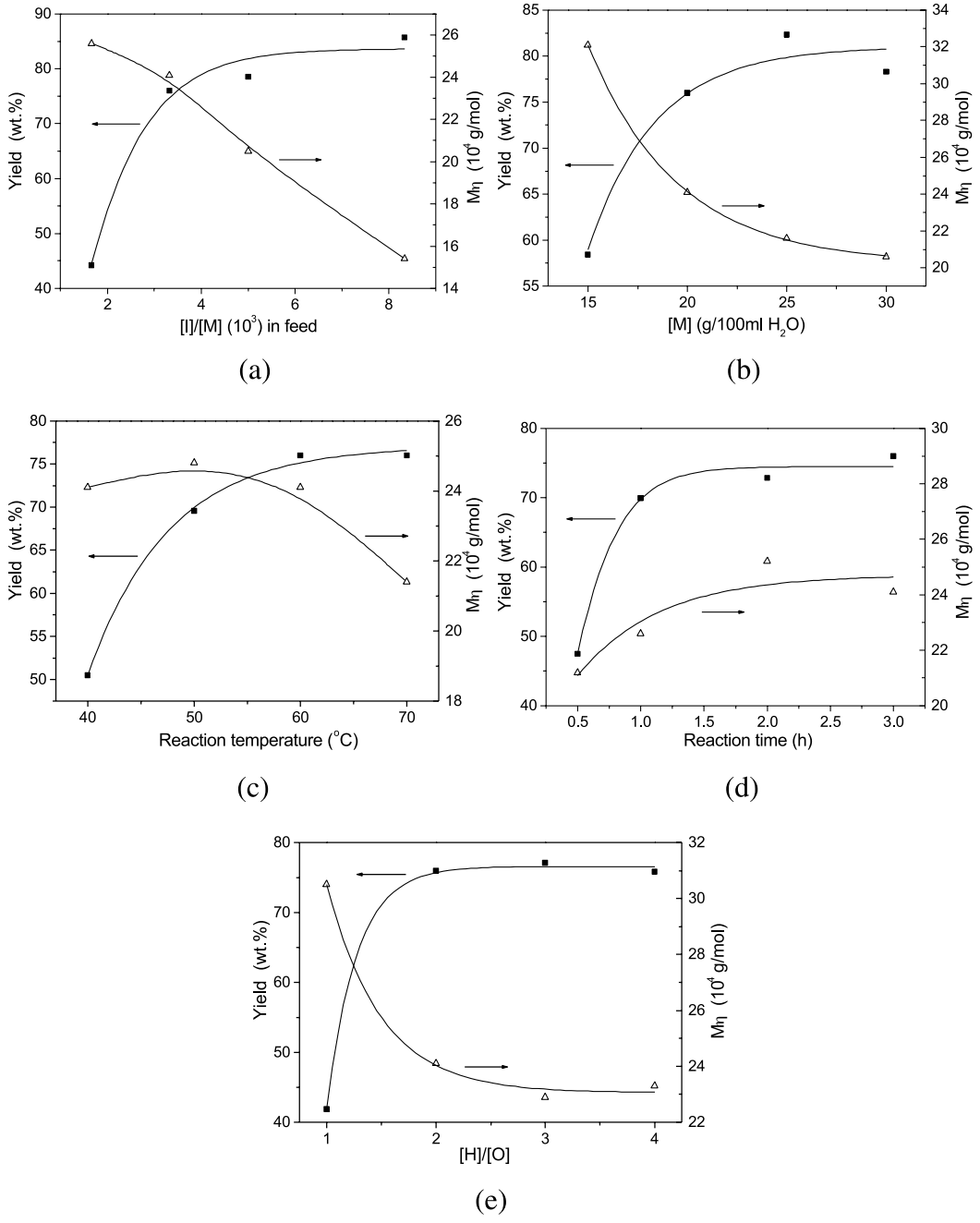

Fig. 1. Effects of (a) initiator, (b) total monomer concentration, (c) reaction temperature, (d) reaction time, and (e) inducer/oxidant ratio on the copolymerization yield (black square) and the M_η (white triangle). The copolymerization condition is as follows: AN/NVP mole ratio in feed, 90/10; total monomer concentration ([*M*]), 20 g/100 ml water; initiator/monomer ratio ([*I*]/[*M*]), 1/300; inducer/oxidant ratio ([*I*]/[*O*]), 2; reaction temperature, 60 °C; reaction time, 3 h.

reaction time, and inducer/oxidant ratio ([*H*]/[*O*]) on the copolymerization yield and the copolymer viscosity-average molecular weight (M_η). It can be seen from Fig. 1 that, with the increase in initiator concentration, total monomer concentration, reaction temperature, and inducer/oxidant ratio, the copolymerization yield increases while the M_η decreases correspondingly. It is apparent that the increase in initiator concentration generates more radicals (active regions) during unit time, which facilitates the copolymerization and decreases the molecular weight. Since more energy per time is received for the reaction system, the initiator decomposition rate is accelerated with the increase in the reaction temperature. Concerning the decrease in M_η caused by the increase in the inducer/oxidant ratio, it could be partly due to the chain-transfer from the propagating radicals to HSO_3^- derived from $Na_2S_2O_5$. With the extension of the reaction time, both the yield and the M_η rise at first and level off later on. However, the M_η can be

considered as changeless and it consists with the radical chain polymerization mechanism [24]. Following these results, the optimum condition for AN/NVP (90/10) copolymerization in water is obtained as follows: total monomer concentration, 20 g/100 ml water; initiator/monomer ratio, 1/300; inducer/oxidant ratio, 2; reaction temperature, 60 °C; reaction time, 3 h.

The influences of monomer feed ratio on the copolymer yield and the M_η are shown in Fig. 2. The results of solution copolymerization (SCP) performed in DMSO using AIBN as initiator are also compiled for comparison. It can be seen that both the yield and the M_η for WPPCP are higher than those for SCP. As the unique chain propagation and termination mechanism, WPPCP affords the advantage of increasing the molecular weight of the polyacrylonitrile-based polymer [25]. At the first period, the polymerization reaction of WPPCP takes place in water because of the water-solubility of the redox pair. When grew big enough, the propagating chains will be precipitated; therefore, the polymerization takes place both in water and on the surface of the precipitated microparticles. In other words, the copolymerization is changed from homogeneous to heterogeneous reaction. In such cases, both the chain termination and the chain transfer become relatively more difficult, which result in high yield and high molecular weight for the copolymer. As shown in Fig. 2, it is interesting that the introduction of NVP remarkably decreases the M_η of the copolymer from WPPCP, which might be attributed to the relatively larger side group of NVP and the stabilization of the radicals by this side group of NVP.

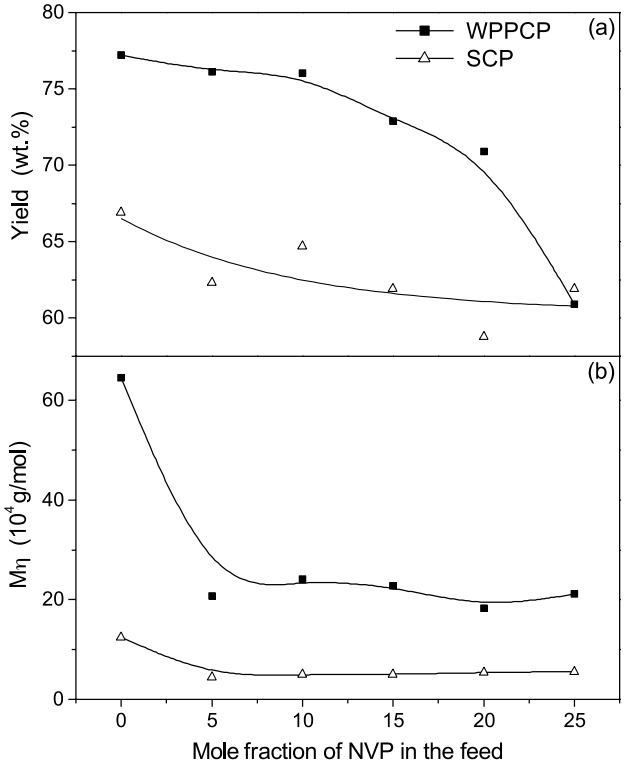

Fig. 2. Effect of NVP mole fraction in the feed on (a) the yield of AN/NVP copolymerization and (b) the [η] of the copolymer.

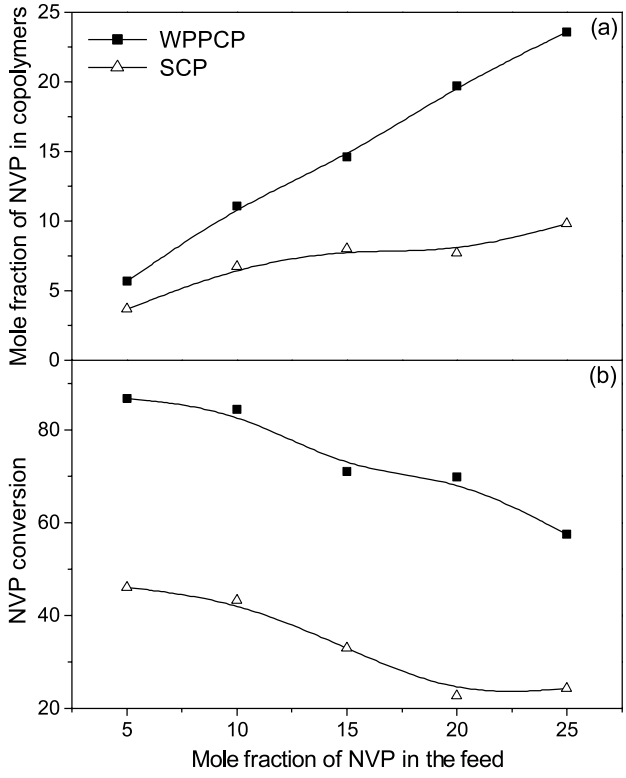

Fig. 3. Relations between (a) the NVP content in copolymers (b) the NVP conversion for the copolymerizations and the AN/NVP feed ratio.

It can be seen from Fig. 3, WPPCP is a process that not only results in copolymers with higher molecular weight but also increases the comonomer conversion for the copolymerization in comparison with SCP. In general, monomer

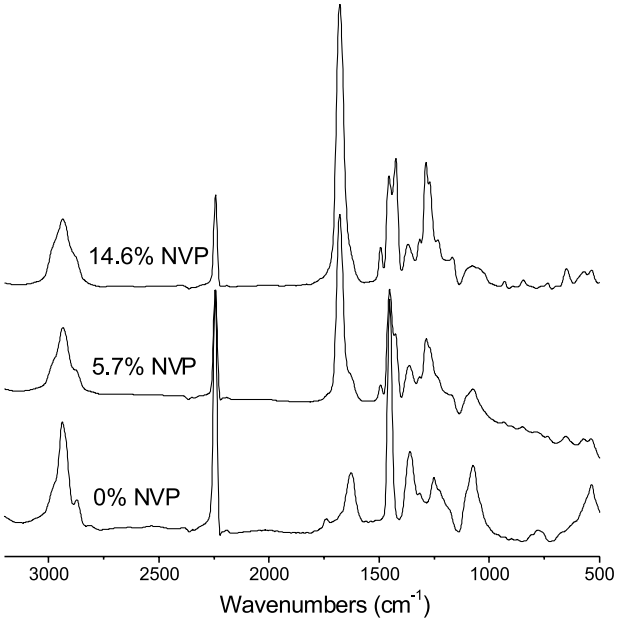

Fig. 4. IR spectra of polyacrylonitrile and PANCNVPs.

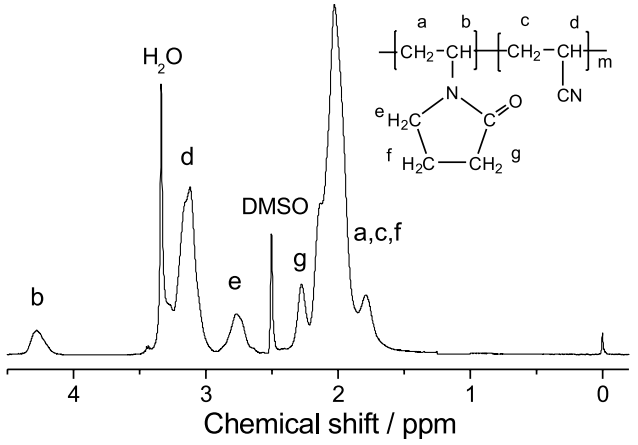

Fig. 5. Typical ^{1}H NMR spectrum of PANCNVP.

reactivity ratios can give some information about the composition of the corresponding copolymer, and one can obtain the monomer reactivity based on the results with copolymer yields of less than about 10% or by the integration method for higher copolymer yields. However, it is known that the reactivity of a monomer toward a radical depends on the reactivities of both the monomer and the radical. It was also mentioned by Kelen et al. [26] that, if more than four chain propagation elementary reactions (i.e. more than two independent monomers and/or radicals) must be taken into account, the equation describing the composition of the copolymer will be a more complex relationship and the reactivity ratios can not be rightly obtained from general equations. They had also pointed out the influence factors upon the radicals; which including the secondary valency forces. As the mechanism mentioned above, our WPPCP is a heterogeneous reaction. Therefore, it is apparent that the reactivity ratios of AN and NVP cannot be rightly obtained by general method and thus it is difficult to evaluate the difference of the reactivity of NVP between WPPCP and SCP directly. However, according to

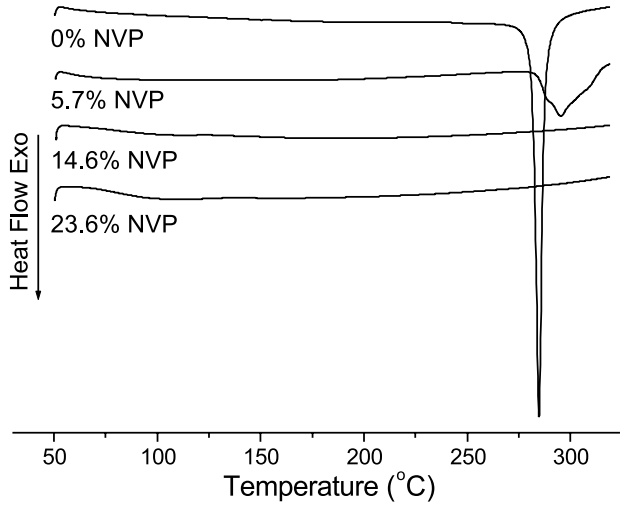

Fig. 6. DSC curves of polyacrylonitrile and PANCNVPs.

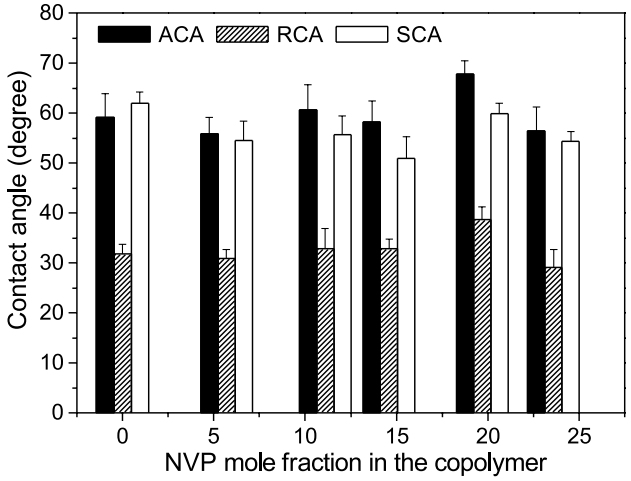

Fig. 7. Static (white columns), advancing (black columns), and receding (shaded columns) water contact angles of PANCNVP dense membranes with various NVP content.

the results shown in Fig. 3, it can be qualitatively concluded that the WPPCP method facilitates the incorporation of NVP into polyacrylonitrile compared with SCP. This may be reasonable based on the following fact. The solubility of AN in water at 60 °C is about 9 wt%, which means that AN is a slightly water-soluble monomer; whereas the comonomer, NVP, is highly water-soluble. Therefore, with the WPPCP method in which initiator presents in water, NVP has great chance to be initiated and polymerized compared with that in SCP. In conclusion, WPPCP is a facile and effective method to incorporate NVP into polyacrylonitrile.

3.2. Characterization of the copolymers

The PANCNVPs were characterized by IR and ^{1}H NMR spectra. Compared with the IR spectrum of polyacrylonitrile, a strong absorption at 1678 cm^{-1} associated with the carbonyl group appears for the copolymers. The absorption

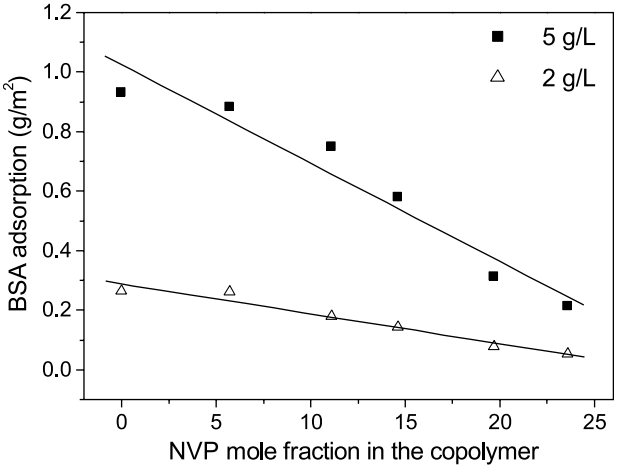

Fig. 8. BSA adsorption behavior in different concentrations on PANCNVP dense membranes with various NVP content.

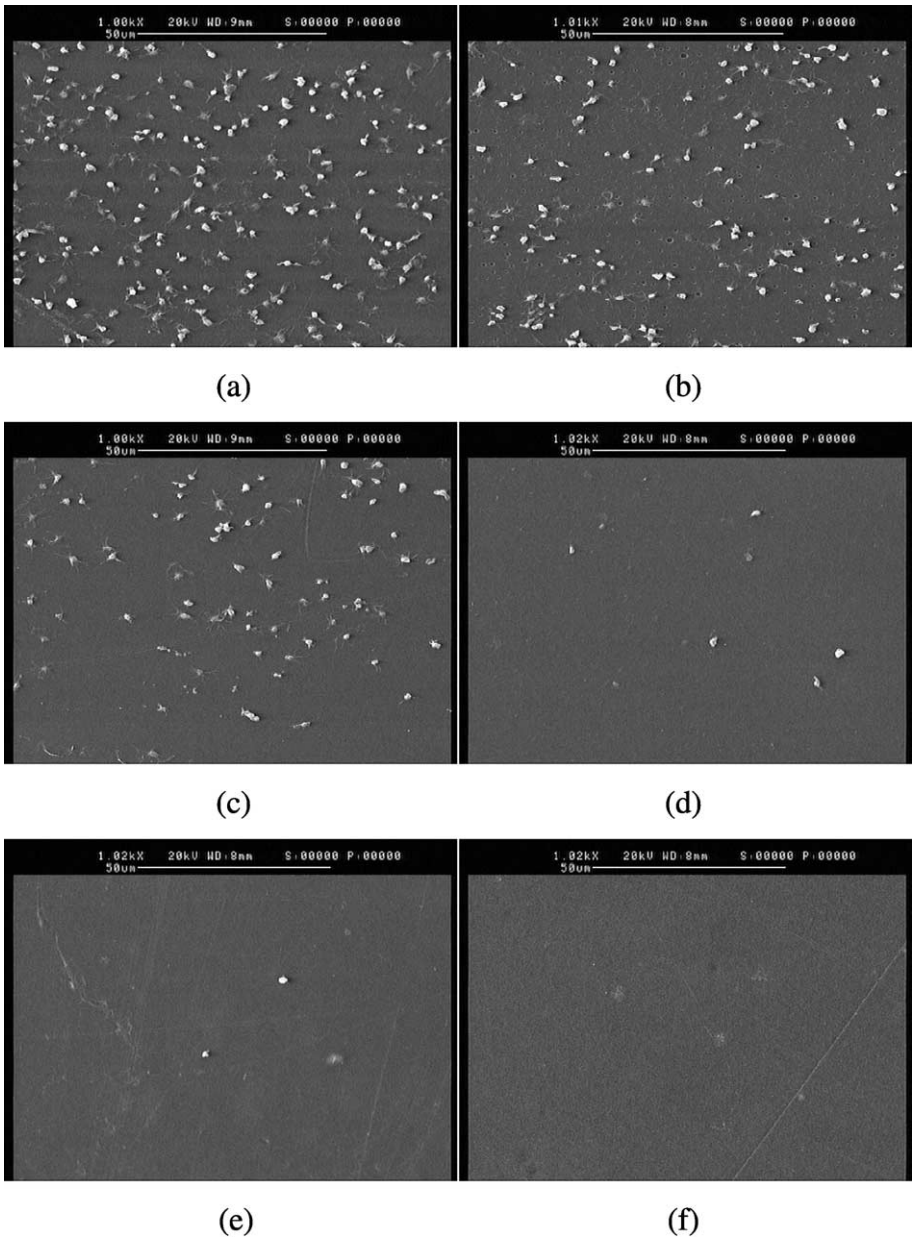

Fig. 9. Adhesion of platelets on the copolymer dense membrane surface. The NVP mole fraction in the copolymer is (a) 0; (b) 5.7; (c) 11.1; (d) 14.6; (e) 19.7; (f) 23.6.

at 1288 cm^{-1} due to the stretching vibration of the C–N bond can also be observed. It can also be seen from Fig. 4 that, with the increase in the NVP content in the copolymers, the absorption intensity ratios for carbonyl group to nitrile group increases correspondingly. Fig. 5 is the ^1H NMR spectrum of a typical PANCNVP in DMSO-d_6. The signals were assigned as shown in Fig. 5 [27,28]. Although the spectrum is overlapped to some extent, it is clear that the peaks at 4.2–4.4 (H_b) and 3.0–3.2 ppm (H_d) provide the quantitative information about the NVP content in the copolymers. The mole fraction of NVP in the copolymers can be calculated according to the following equation:

$$\mathrm{NVP}(\%) = I_b/(I_b + I_d) \times 100$$

where I is the intensity of the peaks in the NMR spectrum. The NVP content can also be calculated from the single peak of H_b and the overlapped peaks of $H_{a,c,f}$. The equation is as follows:

$$\mathrm{NVP}(\%) = 2I_b/(I_{a,c,f} - 2I_b) \times 100$$

In fact, the NVP content calculated from these two methods well agrees with each other and the data shown in Fig. 3 are the average from these two methods.

DSC curves are shown in Fig. 6. No clear T_g for the copolymers can be observed in this DSC conditions, while PAN and PANCNVP containing 5.7 mol% NVP show exothermic peak at 284.8 and 295.6 °C, respectively. This exotherm is related to the cyclization reaction of nitrile groups [29]. As the introduction of NVP encumbers the cyclization

reaction, the exothermic peak disappears below 350 °C when increasing the NVP content to 14.6% in the copolymer.

3.3. Surface properties of the copolymer membranes

It is well known that knowledge of the interfacial interaction of materials with plasma proteins and blood is important in establishing their blood compatibility. The surface properties of materials may be responsible for this interaction to a great extent. Therefore, the PANCNVPs synthesized by WPPCP were fabricated into dense membranes to evaluate the surface properties by pure water contact angle, protein adsorption, and platelet adhesion measurements.

It can be seen from Fig. 7 that the introduction of NVP results in a small influence on the static, advancing and receding contact angles. This might be ascribed to the moderate wettability of NVP and the dense membrane formation process in which the hydrophobic segments of the polymer chains tend to arrange outside to decrease the surface energy. Similar results were reported by Groth et al. [12] for the copolymers synthesized by SCP.

However, as shown in Figs. 8 and 9, it is obvious that, with the increase in NVP content in the copolymers, the BSA adsorption and the platelet adhesion on the membrane surface are suppressed remarkably. When the mole fraction of NVP in the copolymers reached 14.6%, little platelet adhesion takes place. All these results indicate that the hemocompatibility of polyacrylonitrile can be greatly improved by the incorporation of NVP. It also can be deduced that the biofouling phenomena of the corresponding separation membrane will be eliminated effectively.

4. Conclusions

Water-phase precipitation copolymerization is a ‘green’ and effective process to incorporate NVP into polyacrylonitrile. WPPCP can afford both higher molecular weight and NVP conversion compared with solution copolymerization. In addition, the content of NVP in the copolymer can be accurately tuned. Dense membranes were fabricated from these copolymers with various NVP content. Results from the protein adsorption and the platelet adhesion measurements show that the hemocompatibility of the dense membrane is greatly improved and one can envisage that this copolymer membrane has the perspective as a hemodialysis membrane material. Further work concerning the fabrication, separation properties, biocompatibility, and the potential applications of the PANCNVP asymmetric membranes has been carrying out in our laboratory.

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Copolymerization of acrylonitrile with *N*-vinyl-2-pyrrolidone to improve the hemocompatibility of polyacrylonitrile

Ling-Shu Wan[a], Zhi-Kang Xu[a,*], Xiao-Jun Huang[a], Zhen-Gang Wang[a] and Jian-Li Wang[b]

[a]*Department of Polymer Science and Engineering, Institute of Polymer Science, Zhejiang University, Yu Gu Road 38#, Hangzhou 310027, People's Republic of China*
[b]*College of Chemical Engineering and Materials, Zhejiang University of Technology, Hangzhou 310014, People's Republic of China*

Poly(acrylonitrile-*co*-*N*-vinyl-2-pyrrolidone)s (PANCNVP) were synthesized by water-phase precipitation copolymerization (WPPCP) with sodium chlorate–sodium metabisulfite as an oxidant/reducer initiator system for the first time. Results indicated that WPPCP was a 'green' and effective method to incorporate *N*-vinyl-2-pyrrolidone into polyacrylonitrile. The surface properties of the copolymer dense membranes on the basis of water contact angles, protein adsorption, and platelet adhesion revealed that the hemocompatibility of polyacrylonitrile could be greatly improved by the incorporation of *N*-vinyl-2-pyrrolidone.Poly(acrylonitrile-*co*-*N*-vinyl-2-pyrrolidone)s (PANCNVP) were synthesized by water-phase precipitation copolymerization (WPPCP) with sodium chlorate–sodium metabisulfite as an oxidant/reducer initiator system for the first time. Results indicated that WPPCP was a 'green' and effective method to incorporate *N*-vinyl-2-pyrrolidone into polyacrylonitrile. The surface properties of the copolymer dense membranes on the basis of water contact angles, protein adsorption, and platelet adhesion revealed that the hemocompatibility of polyacrylonitrile could be greatly improved by the incorporation of *N*-vinyl-2-pyrrolidone.