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Materials Chemistry and Physics 91 (2005) 484-489

MATERIALS CHEMISTRY AND PHYSICS

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Preparation and characterization of pH sensitive poly(*N*-vinyl-2-pyrrolidone/itaconic acid) copolymer hydrogels

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Received 21 May 2004; received in revised form 13 December 2004; accepted 20 December 2004

Abstract

Poly(N-vinyl-2-pyrrolidone) (PVP) is widely used in medicine due to its high biocompatibility. In this study, itaconic acid (IA) was co-polymerized with N-vinyl-2-pyrrolidone (NVP) monomer to prepare the pH sensitive hydrogels. These copolymer hydrogels were prepared using ultra-violet (UV) induced methods at ambient temperature. Monomer and cross-linking agent (N,N'-methylene-bisacrylamide (MBAAm)) concentration effects on preparation of this copolymer hydrogel were investigated using swelling, FT-IR, and SEM. The prepared copolymer hydrogel is highly pH sensitive. The percentage swell of the copolymer hydrogels was found to increase from 150 to 3011% as the pH value of the swelling solution varied from 4 to 10. These pH sensitive copolymer hydrogels present a promising approach for drug delivery applications.

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Keywords: pH sensitive; N-Vinyl-2-pyrrolidone; Itaconic acid; Hydrogel

1. Introduction

Hydrogels are cross-linked, three-dimensional hydrophilic polymer networks, which swell but do not dissolve when brought into contact with water [1–3]. The use of hydrogels as biomaterials has recently gained great importance in view of the low toxicity and high biocompatibility presented by many of them [4,5]. The main hydrogel application areas today include [6]: (i) topical applications as wound dressings, (ii) drug delivery systems, (iii) transdermal systems, (iv) dental applications, (v) injectable polymers, (vi) implants, (vii) ophthalmic applications, and (viii) stimuli-responsive systems. Volume changes in hydrogels occur in response to changing environmental conditions such as temperature, pH, solvent composition and electrical stimuli [7–10]. These materials have attracted much attention in medical and mechanical engineering fields. Among the drug delivery systems, hydrogels have been extensively exploited for biomedical applications due to their high water content and excellent biocompatibility. The pH sensitive hydrogels containing pendant acidic or basic groups such as carboxylic acids, sulphonic acids, primary amines, or ammonium salts which change ionization in response to change in the pH have become the subject matter of major interest for use as carriers in drug delivery research [11–13].

In this study itaconic acid (IA) was co-polymerized with *N*-vinyl-2-pyrrolidone (NVP) monomer to prepare pH sensitive hydrogels using ultra-violet (UV) induced methods. The equilibrium swelling behaviors are also investigated in response to changes in the pH of the swelling media.

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 $^{0254\}text{-}0584/\$$ – see front matter 02004 Elsevier B.V. All rights reserved. doi:10.1016/j.matchemphys.2004.12.037

2. Materials and methods

2.1. Materials

The *N*-vinyl-2-pyrrolidone (NVP) and itaconic acid (IA) reaction monomers are products of Acros Organics Co., USA, and Tokyo Kasei Kogyo Co. Ltd., Japan, respectively. Ammonium peroxodisulphate (APS, Wako Pure Chemical Industries Ltd.) was used as an initiator, N,N'-methylene-bisacrylamide (MBAAm, SIGMA Chemical Co.) as a cross-linking agent and Vitamin B₂ (Sigma Chemical Co.) to prevent oxidation. Carbonate pH standard solution (pH 4–10, ionic strength I=0.1) (Yakuri Pure Chemicals Co. Ltd.) was used as a buffer solution.

2.2. Ultra-violet (UV) induced poly(N-vinyl-2pyrrolidone/itaconic acid) composite hydrogels

Three components were used in the preparation of poly(Nvinyl-2-pyrrolidone/itaconic acid) (poly(NVP/IA)) copolymer hydrogels, namely N-vinyl-2-pyrrolidone (NVP), itaconic acid (IA), and distilled water. Aqueous NVP and IA monomer solutions were prepared in 70 wt.% distilled water in different compositions with 0.01 g l^{-1} riboflavin (B₂, C₁₇H₂₀N₄O₆) at a NVP/IA solution ratio:riboflavin=4:1. The feed composition is listed in Table 1. After the solution was stirred for 5 min, the photo-induced solution crosslinking and polymerization were carried out with UV-light irradiation in a Pyrex glass containing the solution for 1 h. The UV source was a high-pressure 1000 W mercury lamp (wavelength: 365 nm). The apparatus is schematically shown in Fig. 1. The copolymer hydrogels were washed for 24 h with distilled water to remove the unreacted monomers, dried in air for several days and dried again in a vacuum oven at 42 °C to constant weight.

2.3. Characterization of poly(NVP/IA) copolymer hydrogels

The chemical structure of the copolymer hydrogels was determined with Fourier transform infrared (FT-IR) spec-

Table 1 Feed composition of poly(NVP/IA) copolymer hydrogels

I I I I I I I I I I I I I I I I I I I					
Number	NVP (mmol)	IA (mmol)	APS (mol%)	MBAAm (mol%)	Distilled water (ml)
1*	81.0	2.3	0.9	3.0	13.3
2^{*}	81.0	4.6	0.9	3.0	13.6
3*	81.0	6.9	0.9	3.0	14.1
4**	81.0	2.3	0.9	4.0	13.3
5**	81.0	4.6	0.9	4.0	13.6
6**	81.0	6.9	0.9	4.0	14.1
7***	81.0	2.3	0.9	5.0	13.3
8***	81.0	4.6	0.9	5.0	13.6
9***	81.0	6.9	0.9	5.0	14.1

APS as an initiator; MBAAm as a cross-linker; numbers $1-3^*$ APS 0.9 mol% of monomers, MBAAm 3 mol% of monomers; numbers $4-6^{**}$ APS 0.9 mol% of monomers, MBAAm 4 mol% of monomers; numbers $7-9^{***}$ APS 0.9 mol% of monomers, MBAAm 5 mol% of monomers.



Fig. 1. Schematic diagram of UV-induced cross-linking and copolymerization equipment.

troscopy. The characteristic absorption peaks were detected using a JASCO FT/IR-300E spectrometer. For FT-IR measurement, spectra were obtained using the diffuse reflectance (DR) method.

The gelation percentage of the copolymer hydrogels was measured by extraction in distilled water and dried again in vacuum oven at 42 °C to constant weight. The gelation percentage was defined using Eq. (1), where W_d is the weight of the dried copolymer hydrogels after extraction, and W_i the initial weight of the monomer, initiator and cross-linking agent:

$$Gelation(\%) = (W_d/W_i) \times 100$$
(1)

The mass percentage of swelling was determined as follows: dried copolymer hydrogels were left to swell in distilled water and different pH solutions at 25 °C until equilibrium was attained. The swollen copolymer hydrogels were weighed periodically after removing the superficial water with filter paper. The measurements were continued until a stable weight was reached for each sample. The swelling ratio of each copolymer hydrogel was defined using Eq. (2); where M_t is the mass of the swollen copolymer hydrogel at time *t* and M_0 the initial mass of the copolymer hydrogels:

Swelling (%) =
$$((M_t - M_0)/M_0) \times 100$$
 (2)

A scanning electron microscope (SEM), JEQL JSM-6300, was used to observe the specimen morphologies. The swollen poly(NVP/IA) copolymer hydrogels were frozen in -20 and -80 °C in a refrigerator for 2–3 h, respectively. Specimens were then freeze-dried (-80 °C) to thoroughly dehydrate the samples. Other swollen poly(NVP/IA) copolymer hydrogels were dried in air.

3. Results and discussion

3.1. Percentage gelation of poly(NVP-co-IA) composite hydrogels

Radiation reactions utilize electron beams, gamma ray, X-ray or UV to excite a polymer and produce a cross-linked structure. Chemical cross-linking requires at least one difunctional, small molecular weight cross-linking agent. The



Fig. 2. The UV-irradiation time effect on the gelation percentage of the poly(NVP/IA) copolymer hydrogels.

UV-light irradiating cross-linking and polymerization can easily be adjusted by controlling the reaction time. Fig. 2 shows the percentage gelation behavior of the poly(NVP/IA) copolymer hydrogels. The copolymer hydrogel gelation percentages were in the 25–96% range. The gelation percentage increased as the UV induced reaction time increased. The poly(NVP/IA) copolymer hydrogel explains that cross-linking network between cross-linking agent (MBAAm) is formed by UV induction. The cross-linking polymerization reaction of poly(NVP/IA) copolymer hydrogels was determined as follows:



Fig. 3. The FT-IR spectra of: (a) itaconic acid, (b) *N*-vinyl-2-pyrrolidone, and (c) poly(NVP/IA) copolymer hydrogels.

are associated the –COOH group in the IA powder. As shown in Fig. 3(b), the absorption peak around 3500 cm⁻¹ can be ascribed to the C–N group. The absorption peak at 1721 cm⁻¹ is associated with the C=O group. Fig. 3(c) shows the absorption peak around 3010 cm⁻¹ ascribed to the –COOH and C=C overlap. The absorption peak at 1720 cm⁻¹ is associated with the C=O group. The absorption peaks at 3500 cm⁻¹ for the C–N group and 3000 cm⁻¹ for –COOH of NVP-co-IA



Poly(NVP/IA) copolymer hydrogels

3.2. FT-IR characterization of poly(NVP-co-IA) composite hydrogels

The DR-FT-IR spectra of IA and NVP are shown in Fig. 3(a) and (b). The presence of IA can be verified from the characteristic absorption peaks at $2800-3200 \text{ cm}^{-1}$, which

demonstrate that cross-linking and polymerization reactions were successfully achieved in the copolymer hydrogels.

3.3. Swelling characterization of poly(NVP/IA) copolymer hydrogels

The swelling behaviors of poly(NVP/IA) copolymer hydrogels in distilled water at different cross-linking agent



Fig. 4. Time effect on the swelling (%) of poly(NVP/IA) copolymer hydrogels at distilled water (MBAAm 3 mol% of monomers).

concentrations are plotted in Figs. 4-6. All swelling behavior is plotted based on the average of three trials. The poly(NVP/IA 0=1:0.09 mol) copolymer hydrogels had the highest swelling in time-dependent swelling behavior, while the swelling of poly(NVP/IA = 1:0.03 mol)copolymer hydrogels had the lowest. It is believed that poly(NVP/IA = 1:0.09 mol) copolymer hydrogels have denser and more tightened structure than other copolymer hydrogels at high NBAAm concentration. The effect of different IA contents on the photo-induced cross-linking and polymerization of copolymer hydrogels was examined using MBAAm contents varied from 3 to 5 mol% of the monomer solutions. The swelling for these copolymer hydrogels was decreased with increasing of cross-linking agent. The result implies that the structure of copolymer hydrogels would become denser and more tightened as the cross-linking agent was increased. The condensation would decrease the space between copolymer hydrogel networks, leading to a decrease in swelling [1]. Figs. 7-9 show that the percentage equilibrium swelling of poly(NVP/IA) copolymer hydrogels in-



Fig. 5. Time effect on the swelling (%) of poly(NVP/IA) copolymer hydrogels at distilled water (MBAAm 4 mol% of monomers).



Fig. 6. Time effect on the swelling (%) of poly(NVP/IA) copolymer hydrogels at distilled water (MBAAm 5 mol% of monomers).



Fig. 7. Equilibrium swelling (%) of the poly(NVP/IA) copolymer hydrogels in various pH solution.



Fig. 8. Equilibrium swelling (%) of the poly(NVP/IA) copolymer hydrogels in various pH solution.



Fig. 9. Equilibrium swelling (%) of the poly(NVP/IA) copolymer hydrogels in various pH solutions.

creased with decreasing cross-linking agent concentrations. This result is in agreement with other literatures, reported elsewhere [14,15]. The effect of different pH solution on swelling of poly(NVP/IA) copolymer hydrogels shown in Figs. 7–9 indicates that the swelling of copolymer hydrogels were increased as pH was increased. Poly(NVP/IA) copolymer hydrogels with swelling capabilities can reach as high as 3011%. An increase in pH from 4 to 10 caused a significant increase in the percentage equilibrium swelling of copolymer hydrogels with higher IA contents. In all compositions, maximum extents of swelling were reached, this being due to the complete dissociation of the IA acidic groups at this pH value. The first and second dissociation IA constants are $pK_{a1} = 3.85$, $pK_{a2} = 5.44$ [17]. However, the swelling capability decreases when more cross-linking agent is added. This is true for low concentration of IA, as in the case of 1:0.03 and 1:0.06 mol of NVP/IA concentration ratio shown in Figs. 7 and 8. However, as the concentration of NVP/IA increased to 1:0.09 mol, the data shows reverse results as indicated in Fig. 9 [16,17]. Note that, in general, the percentage equilibrium swelling of copolymer hydrogels is increased with increasing concentration of IA at each pH value.

3.4. SEM morphological observation

To investigate the morphology of the freeze-dried hydrogels, scanning electron microscopy was attempted. The porous structure of the material will be beneficial to the diversion the fluid when it applied in biomaterial. Different drying methods will greatly affect the inner structure of material especially for pore size and pore numbers. Fig. 10 shows the SEM photographs of a cross-sectional view of poly(NVP/IA) copolymer hydrogels. Fig. 10(a) shows that the surface was smooth and no open pores are found in the air-drying structure. However, as shown in Fig. 10(b) and (c), the structure of the composite hydrogels prepared at -20 and $-80^{\circ}C$ freeze-drying process was characterized by the large, open, channel-like appearance and highly porous structure with a







Fig. 10. The SEM micrographs of poly(NVP/IA) copolymer hydrogels: (a) air-dried, (b) cryofracture cross-section -20 °C freeze-dried and (c) cry-

ofracture cross-section of -80 °C freeze-dried.

mean pore size about $25-40 \,\mu\text{m}$. The differences in the pore size of poly(NVP/IA) copolymer hydrogels reflect the differences in heat transfer rates during the hydrogel freezing process. It is possible that at a higher freezing temperature, the number of nuclei of ice crystallization initially formed is smaller than that at a lower freezing temperature, leading to an increased final size of ice crystals. Because the larger ice crystals push to expand poly(NVP/IA) copolymer hydrogels chains to a greater extent, the pore size of the hydrogels will increase, while the structure will exhibit a large, open, channel-like appearance [18].

4. Conclusion

NVP was copolymerized into IA to prepare pH sensitive hydrogels using the ultra-violet (UV) induction method. The prepared copolymer hydrogel is highly pH sensitive. The swelling of copolymer hydrogels was found to increase from 150 to 3011% as the pH value of the swelling solution varied from 4 to 10. The equilibrium swelling of poly(NVP/IA) copolymer hydrogels decreased with increasing cross-linking agent concentrations. These poly(NVP/IA) copolymer hydrogels could be easily cut. The SEM revealed the freezedrying process could obtain a surface with the large, open, channel-like appearance and highly porous structure with a mean pore size about 25–40 μ m. These pH sensitive copolymer hydrogels present a promising approach for drug delivery applications.

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