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Preparation, characterization and controlled release investigation of interpenetrating polymer networks of poly(acrylic acid)/triazole modified poly(vinyl alcohol)

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Abstract

A series of interpenetrating polymer networks of poly(acrylic acid) (PAA)/triazole modified poly(vinyl alcohol) (TMIPNs) were synthesized by radical polymerization in methanol at room temperature with L-ascorbic acid (Vc) and peroxide hydrogen (H_2O_2) as initiators and trihydroxymethyl propane glycidol ether (6360) as a crosslinker. The structures of the gels were characterized by Fourier transform infrared spectroscopy (FTIR) and differential scanning calorimetry (DSC). The swelling/deswelling behavior of hydrogels was studied in different pH and different concentrations of NaCl aqueous solutions. The results showed that the TMIPNs hydrogels had excellent pH- and salt-sensitivity in the range of the investigation. The mechanism of the swelling and the deswelling was discussed and the results were confirmed further by scanning electron microscope (SEM). In addition, the controlled release behavior of TMIPNs in vitro was also studied. The effects of physical stimulus (ultraviolet ray and ultrasonic wave), salt concentration, pH value and the swelling/deswelling on the controlled released behavior were also explored.

Keywords: Interpenetrating polymer network (IPN); Triazole; Swelling/deswelling behavior; Salt and pH sensitivity; Controlled release

1. Introduction

During the past decades, a diversity of polymer-based pharmaceutical carrier systems have been developed as new means of the controlling temporal or distributional (site-specific) drug delivery. Pharmaceutical controlling delivery systems offer numerous advantages in comparison with conventionally administrated drugs in dosage forms, such as improved efficiency and reduced toxicity. Polymeric crosslinked carrier matrices, such as hydrogels and supramolecular polymer aggregates as well as different types of microencapsulation vehicles are typical examples of common drug delivery devices (Guse et al., 2006a,b; Klose et al., 2006; El-Sherbiny et al., 2005; Liu et al., 2006).

Hydrogels have attracted wide research interest as controlled release devices due to their tunable chemical and three-dimensional physical structures, high water content, good mechanical properties, and biocompatibility. Bioresponsive, "intelligent" or "smart" hydrogels can regulate drug release through responding to environmental stimuli by the swelling and the deswelling (Liu and Sheardown, 2005; Zhang et al., 2004). Depending on their formulation, hydrogels can exhibit a variety of drug release profiles determined by the release environment. Thermosensitive and pH-sensitive hydrogels are the most extensively studied gels because of their special-responsive characteristics (Alvarez-Lorenzo et al., 2005; Liu et al., 2006).

Recently, many studies focused on poly(vinyl alcohol) (PVA) and PAA based hydrogels because of the highly hydrophilic, nontoxic, biocompatible and biodegradable properties (Barbani et al., 2005; Wu et al., 2006). Besides, PVA could also be used as an excellent water-soluble matrix polymer for making IPN hydrogels with poly(acrylic acid) (PAA) (De La Rosa et al.,

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2002; Hernández et al., 2005). It is well known that PAA is a pH-responsive polymer due to large variations in physiological pH at various body sites in normal as well as pathological conditions. The original pH-dependent release characteristic could be modified by varying the composition of polymers. Therefore, pH-responsive polymeric networks have been extensively studied (Kurkuri and Aminabhavi, 2004; Jin et al., 2006; Peniche et al., 1999).

The triazole derivatives are always chosen as model hydrophobic drugs because of the extensive bioactivities. For example, 1,2,3-triazole has been reported as antibacterials (Tian et al., 2005), antifungals (Zhao et al., 2006), antivirals, anti-inflammatories, analgesics, inhibit tumor proliferation, invasion, metastasis and anti-HIV drug (Kim et al., 2004; Holla et al., 2005). However, we have not found the report of it as a high molecular weight drug and with controlled release fashion in vitro.

In this work, we developed a novel smart hydrogel of IPN PAA/triazole modified PVA (TMIPN) with PAA as an essential material of gel forming, followed by interpenetration with triazole modified PVA, which was characterized by FTIR, DSC and SEM. The swelling/deswelling and controlled release behavior in vitro of TMIPN hydrogels were studied in detail. The results showed that TMIPNs had excellent pH, salt-sensitive and physical stimuli-response characteristics.

2. Experimental

2.1. Materials

Acrylic acid (AA, Beijing Eastern Chemical Works, China) was distilled at reduced pressure (b.p. 20–21 °C/0.5 mmHg) before use. Poly(vinyl alcohol) (PVA) (88% hydrolyzed, average molecular weight 70,000–80,000) was used as received. Trihydroxymethyl propane glycidol ether (6360), sodium chloride (NaCl), sodium azide (NaN_3), sodium nitrite ($NaNO_2$), sulfurous oxychloride ($SOCl_2$) purchased from Xi'an Chemical Reagent Plant (China). *p*-Methoxyphenylamine (PMPA), L-ascorbic acid (Vc), peroxide hydrogen (H_2O_2), dimethyl sulphoxide (DMSO), absolute diethyl ether ($C_2H_5OC_2H_5$), ethyl acetoacetate ($CH_3COCH_2COOC_2H_5$) and other organic chemicals purchased from Tianjin Chemical Reagent Company (China). The chemicals used in this work were analytical grade and used directly without further purification.

2.2. Synthesis

2.2.1. Synthesis of 1-(4-methoxyphenyl)-5-methyl-1,2,3-triazol-4-carboxylic acid (MMTCA)

The compound of l-(4-methoxyphenyl)-5-methyl-l,2,3-triazol-4-carboxylic acid (MMTCA) was synthesized as our previous work (Dong and Wang, 2005). The white solid was obtained and the yield (m.p. l85–186 °C) was 82.0 wt.%. ^{1}H NMR ($CDC1_3$, δ ppm): 13.15(broad peak, 1H,–COOH), 7.45(d, 2H, J = 8.1 Hz, Ar-2,6), 7.11(d, 2H, J = 8.1 Hz, Ar-3,5), 3.91(s, 3H, $ArOCH_3$), 2.77(s, 3H, TRZ–CH_3).

2.2.2. Preparation of triazole modified PVA (TMPVA)

The compound l-(4-methoxyphenyl)-5-methyl-l,2,3-triazol-4-carboxylic acid (MMTCA) 23.3 g (0.1 mol) was placed in a 150 mL round bottomed flask and 10.9 mL (0.15 mol) of sulfurous oxychloride was added dropwise in an ice-bath. The reaction mixture was stirred for 5 h at 0 °C and then stirred for 10 h at room temperature. The redundant sulfurous oxychloride was removed with absolute diethyl ether (5 × 20 mL) under reduced pressure. The crude product was a straw-colored solid and used directly without further purification. The yield was 95.0 wt.%. Then the crude product (0.5 g) was added into the solution of 10.0 mL DMSO containing 1.0 g PVA. The reaction mixture was stirred for 6 h at room temperature and then stirred for 8 h at 80 °C. The straw-colored ropy liquid, TMPVA, was obtained.

2.2.3. Preparation of hydrogels

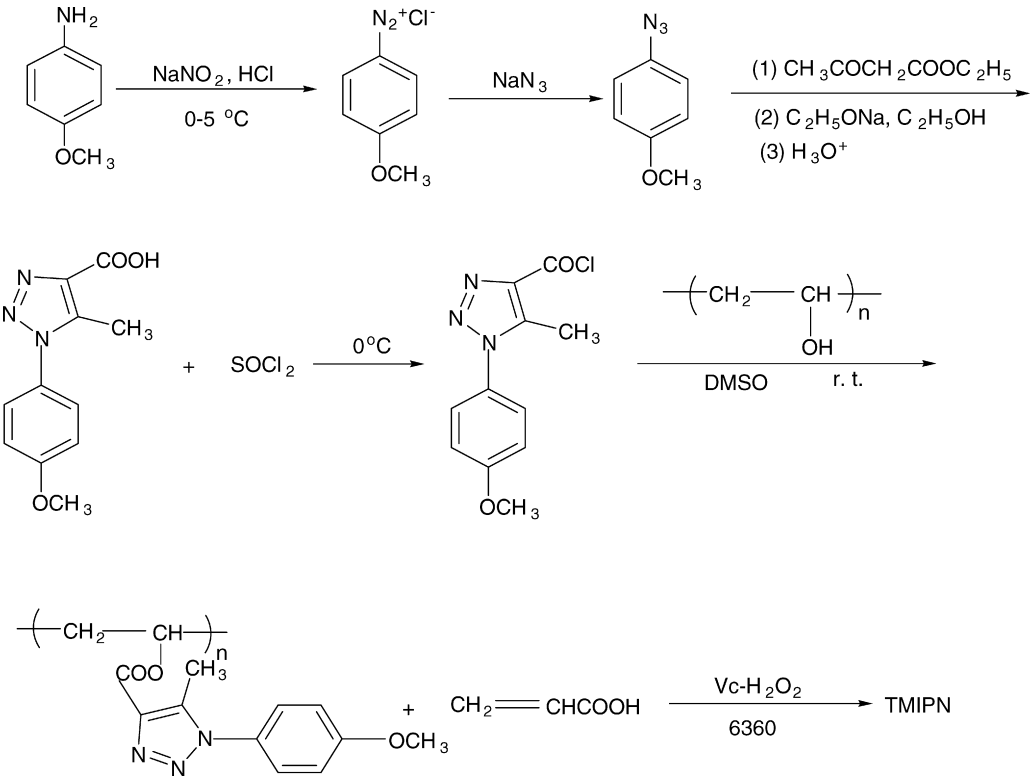
The preparation process of interpenetrating networks of PAA/TMPVA (TMIPNs) was as follows: 8.0 mL of freshly distilled AA (partly neutralized by 9.1 mol L^{-1} NaOH before use and the neutralization degree was about 70%), 6.0 mL of distilled water and 10 mL of TMPVA dissolved in DMSO were sequently added into a four-necked flask equipped with a stirrer, a thermometer and a gas inlet tube. After that, a crosslinker (6360), in comparison to AA at a molar ratio of 2.5×10^{-4}, was added to the system. Then, the mixture was cooled to about 20 °C, H_2O_2 (0.10 mol L^{-1}) and Vc (0.028 mol L^{-1}) in equal volumes were introduced into the mixture. The reactive system had been triggered immediately and the temperature rised sharply. When the reactive system cooled to 56 °C naturally, the flask was put into a water bath with constant temperature of 56 °C for 8 h. During all the above processes, nitrogen atmosphere should be operated continually. The crude product was immerged in distilled water for 3 days (changing water for every 8 h). Then it was dried under vacuum oven at room temperature to constant weight, finally cut with mixer and screened through a 40–80 mesh sieve to get white granule product. The preparation procedure of TMIPN was shown in Scheme 1.

The loading capacity (micrograms of drug per milligram of TMIPN xerogel) and efficiency (percent loaded as a function of amount of drug added) of triazole in TMIPN was determined by dissolving a known amount of the drug-loaded TMIPN xerogel in absolute ethanol, then sonicated under ultrasonic wave for 3–4 h, the amount of triazole in solution was determined by a UV assay at 231.2 nm on a Perkin-Elmer Lambda 35 UV/vis Spectrometer (Perkin-Elmer Instruments, USA) at room temperature. The results showed that the loading capacity of TMIPN was 4.93 μg/mg.

In order to compare the swelling/deswelling properties between TMIPNs and IPNs, the interpenetrating networks of PAA/PVA (IPNs) were prepared. The preparation procedure of the IPNs was similar to that of TMIPNs except for replacing TMPVA with PVA.

2.3. Swelling and deswelling measurements

The swelling and deswelling experiments were performed in distilled water and various solutions with pH ranged from 1.00 to



Scheme 1. The synthetic scheme for TMIPN.

12.00 (which were adjusted by 1 M HCl or 1 M NaOH) and different concentrations of NaCl aqueous solutions. The weighed (W_d) xerogel sample was immerged into the specified medium to swell to reach a constant weight (W_f) of the hydrogel. Before weighing the swollen sample, any surface water was removed with filter paper and then they were weighed on a sensitive balance.

The degree of the swelling or the deswelling was calculated on the basis of the dry and equilibrium-swollen weights (Milimouk et al., 2001).

$$\text{Equilibrium swelling degree } (SW_{eq}) = \frac{W_f - W_d}{W_d} \quad (1)$$

2.4. FTIR measurements

Fourier transform infrared spectroscopy (FTIR) was conducted on Nicolet NEXUS 670 FTIR Spectrometer (American Nicolet Corporation, USA). The samples were dried completely and ground to fine powder, then pressed pellicle with IR grade KBr. The resolution is 4.0 cm^{-1}, and the scanned wave number ranges from 4000 to 400 cm^{-1}.

2.5. Differential scanning calorimetry (DSC) analysis

The DSC analysis for samples was done on a Sapphire DSC (Perkin-Elmer Instruments, USA) with the scan rate of 10 °C/min under dry nitrogen atmosphere. The weight of the samples ranged within 8–12 mg. The second scan was taken into consideration.

2.6. Scanning electron microscopy (SEM) measurements

Two hydrogels were swollen completely in the solutions of pH 2.06, 7.05 and 10.02 at room temperature, respectively, and then were freeze-dried for 15 h with LABCONCO (England) freeze-dried system to avoid the collapse of porous structures. Then the surface morphology of xerogels was determined by using a scanning electron microscope, JSM-5600LV SEM (Japan).

3. Results and discussion

3.1. Characterization of the IPNs and TMIPNs

3.1.1. Infrared spectra

The infrared spectra of IPN and TMIPN were shown in Fig. 1. According to the IR spectra of TMIPN, the peak at 965.5 cm^{-1} should be assigned to the vibration bands of N–N=N in 1H-l, 2, 3-triazole ring, which was the same as that of our previous work (Dong and Wang, 2005). However, it was not found in the infrared spectrum of IPN. This indicated that the triazole ring had been introduced into hydrogel networks and the resultant was TMIPN.

3.1.2. Determination of glass transition temperature (Tg)

The dried IPN and TMIPN gels showed obvious glass transition process. The introduction of triazole ring into IPN decreased the number of crosslinked bond to lead to the decrease of glass transition temperature (T_g), i.e. from 146.8 to 145.0 °C for IPN and TMIPN, respectively, as shown in Fig. 2. However,

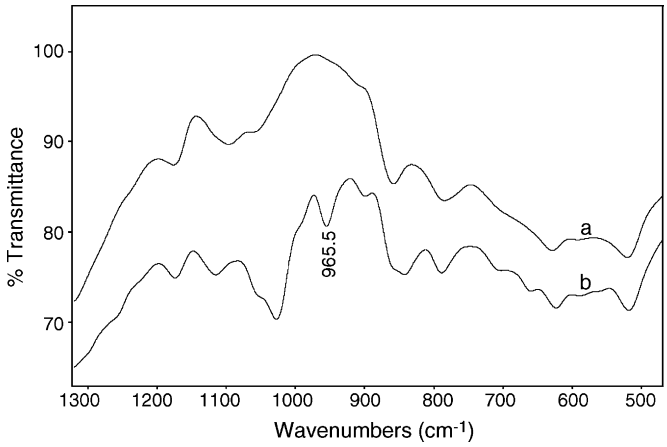


Fig. 1. FTIR Spectra of IPN (a) and TMIPN (b).

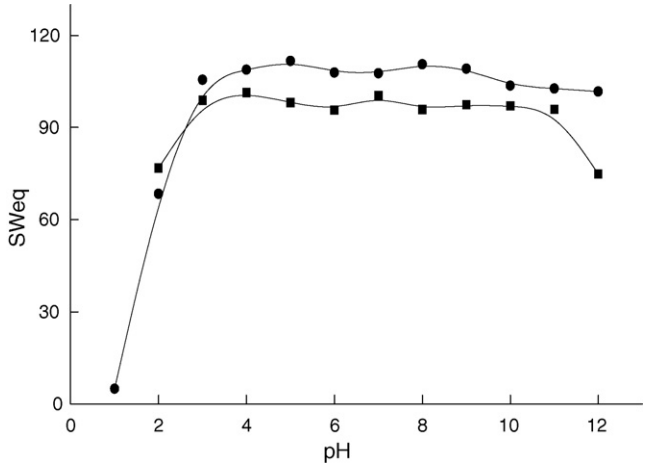


Fig. 3. Effect of pH on the equilibrium swelling degree (SWeq) for IPN and TMIPN at room temperature. (■) IPN; (●) TMIPN.

as a small molecular and small load quantity, the loaded triazole compounds could not rouse significant chain movement of crosslinked IPN, so T_g of TMIPN had little difference with that of IPN.

3.2. Swelling/deswelling properties of IPN and TMIPN

3.2.1. Swelling behavior of IPN and TMIPN in solutions with different pH

The swelling/deswelling properties of IPN and TMIPN were investigated in different pH, as shown in Fig. 3. It could be found at pH < 4.0, hydrogels showed a low swelling degree. The reason might be that the unneutralized carboxylic acid groups were undissociated and the higher concentration hydrogen bonds were formed to lead to a rather compact conformation of hydrogels. When the pH value was greater than the dissociated constant of PAA, pK_a, a fraction of the carboxylic acid groups dissociated to form carboxylate ions. In solutions with pH range from 4.0 to 11.0, the carboxylic acid groups would dissociate to form carboxylate ions, which led to the breakage of the hydrogen bond and the extension of the conformation owing to the increase of the charge repulsion. All of these resulted in a rather higher swelling degree. Obviously it was aroused by the buffer action of sodium carboxylate in acidic or basic conditions, which was also presented by Lee (Lee and Wu, 1996). At pH ≥ 11.0, a decrease for the swelling ratio of IPN was observed, which was caused by the decrease of the osmotic pressure between the hydrogel and the external solution and the increase of the hydrogel dissolution under this condition (Prazeres, 1995).

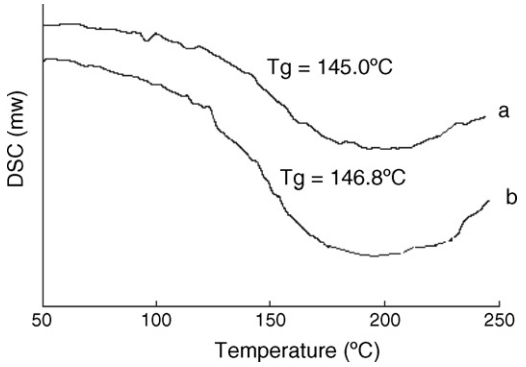


Fig. 2. DSC curves of xerogels. (a) TMIPN, T_g = 145.0 °C; (b) IPN, T_g = 146.8 °C.

3.2.2. Reversibility behavior of pH-responsive for IPN and TMIPN

In order to examine the responsive properties of IPN and TMIPN when the surroundings changed, we investigated the pH-dependent swelling reversibility of IPN and TMIPN at different pH. The typical fluctuated reversibility of the swelling behavior was displayed in Fig. 4. The curves in this figure showed that IPN and TMIPN swelled in the solution of pH 7.05 and then shrinked in the solution of pH 2.20 and the process could be repeated many times, demonstrated that the IPN and TMIPN had obvious and repeatable pH-dependent swelling reversibility.

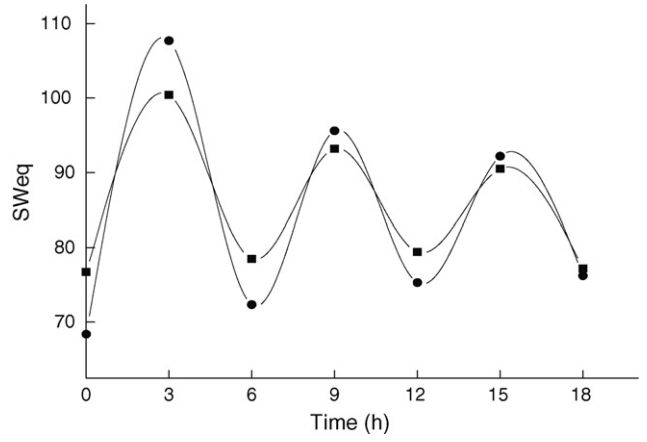


Fig. 4. Trend of the equilibrium swelling degree (SWeq) vs. swelling time (h) for IPN and TMIPN measured in varying pH solutions between 2.20 (bottom points) and 7.05 (top points) at intervals of 3 h at room temperature. (■) IPN; (●) TMIPN.

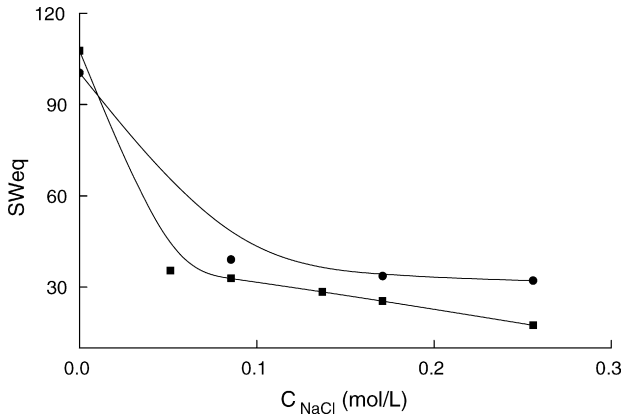


Fig. 5. Effect of the concentration of NaCl aqueous solution (C_{NaCl}) on the equilibrium swelling degree (SWeq) for IPN and TMIPN at room temperature. (pH 7.05) (●) IPN; (■) TMIPN.

3.2.3. Swelling behavior of IPN and TMIPN in NaCl aqueous solutions with different concentrations

To investigate whether the pH-sensitive IPN and TMIPN had ionic strength-sensitivity, the swelling experiments were performed in aqueous solutions with different salt concentrations (Fig. 5). The results showed that the equilibrium swelling degree of IPN and TMIPN would drop when the ionic strength was very low ($I = 0.085$ M), which indicated that IPN and TMIPN had ionic strength-sensitivity. The reason might be that the dramatic increase of the osmotic pressure would inhibit the diffusion of water from the outer to the inner of hydrogels with the increase of the concentration of NaCl (C_{NaCl}). The interaction between the confined water and hydrogels was weakened for swollen hydrogels. Furthermore, the higher the NaCl concentration (C_{NaCl}), the greater osmotic pressure was, and then the smaller the equilibrium swelling degree was (Harada et al., 2005; Suzuki et al., 2005; Muta et al., 2001).

3.2.4. Microscopic observation

The SEM images of xerogels were shown in Fig. 6. It could be seen that IPN and TMIPN were three-dimensional physical structures. The xerogels of TMIPNs, which swelled in solutions of pH 7.05 and 10.02 displayed a looser structure to show faster swelling/deswelling response rate and higher equilibrium swelling degree. These results were in good agreement with the swelling/deswelling experiments of the above mentioned. The structures of TMIPNs swelled in solution of pH 2.06 and IPN swelled in solution of pH 7.05 were shown more compact, which resulted in slower response rate and lower equilibrium swelling degree of them.

3.3. Controlled-release properties of TMIPN in vitro

3.3.1. Working curve of MMTCA

The concentration of MMTCA and the absorbency linearity were tested by the method of working curve (Fig. 7). The illustration showed the absorbency was linearly relative to the concentration of MMTCA ($r^2 = 0.996$; r, correlation coefficient). The relative standard deviation (R.S.D) of the absorbency was 3.3% for the concentration of MMTCA. That was, we could use the solution absorbency to determine MMTCA release quantity.

3.3.2. Influence of physical stimulus on the release behavior of TMIPN hydrogel

Fig. 8 showed the influence of ultraviolet ray and ultrasonic wave on the controlled release behavior of MMTCA in TMIPN hydrogel at room temperature ($25 \pm 2\,^{\circ}C$). From Fig. 8, it could

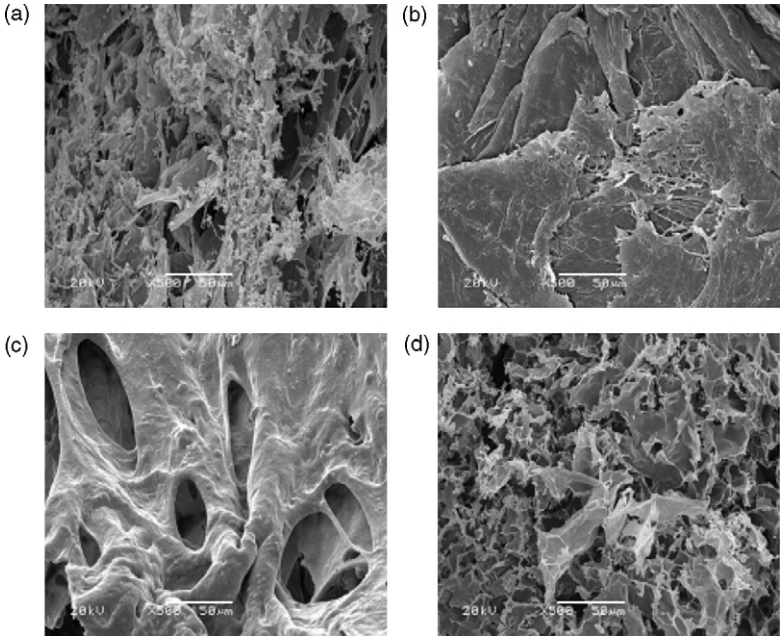


Fig. 6. SEM micrographs of xerogels. (a) TMIPN swollen in solution of pH 2.06; (b) TMIPN swollen in solution of pH 7.05; (c) TMIPN swollen in solution of pH 10.02; (d) IPN swollen in solution of pH 7.05.

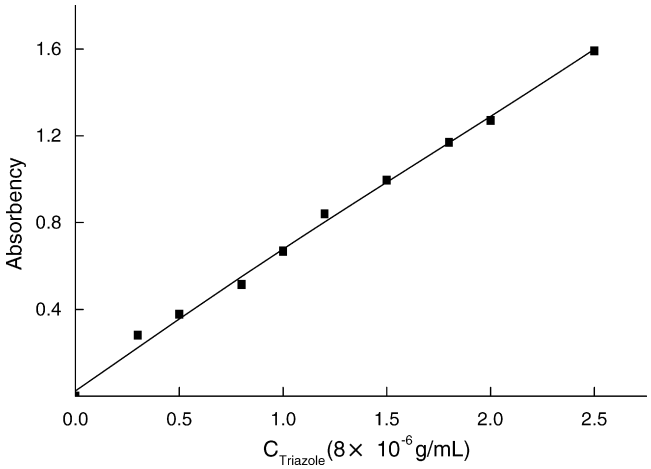


Fig. 7. Working curve of MMTCA (λ = 231.2 nm).

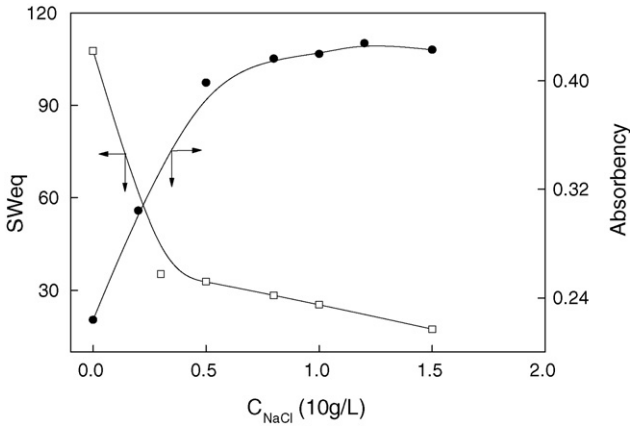


Fig. 9. Relationship between the equilibrium swelling degree (SWeq) of TMIPN hydrogel and the released amount of MMTCA relative to concentrations of NaCl.

be found that MMTCA was released very slowly at room temperature without any stimulus. However, the release rate increased obviously under the condition of wave irradiation. It might be due to the increased hydrolysis of TMIPN hydrogel under thermal and photocatalytic effect of wave irradiation (Imanaka et al., 2003). In comparison with ultraviolet ray, ultrasonic wave showed more significant thermal and cavitation effect which led to the exudation and the diffusion of the hydrolyzed MMTCA in TMIPN hydrogel (Shotipruk et al., 2001), therefore, ultrasonic wave showed more sensitive for the release rate than ultraviolet ray.

3.3.3. Relationship between the equilibrium swelling degree (SWeq) of TMIPN hydrogel and the released amount of MMTCA relative to concentrations of NaCl solutions

Fig. 9 illustrated the varying trend of the equilibrium swelling degree (SWeq) of TMIPN hydrogel and the released amount of MMTCA, shown as the absorbency of MMTCA, relative to different concentrations of NaCl solutions. With the increase of NaCl concentrations, the SWeq value dropped and the released amount of MMTCA increased constantly, and then the trends changed slowly when the NaCl concentration was greater than 5.0 g L^{-1}. The possible reason was that the dramatic increase of the osmotic pressure would inhibit the diffusion of water from the outer into the inner of hydrogels with the increase of NaCl concentrations, on the contrary, water and MMTCA in hydrogels diffused outside easily. Apparently, the release of MMTCA in TMIPN hydrogel was salt-sensitive.

3.3.4. Relationship between the equilibrium swelling degree (SWeq) of TMIPN hydrogel and the released amount of MMTCA relative to pH of solutions

Fig. 10 illustrated the varying trend of the equilibrium swelling degree (SWeq) of TMIPN hydrogel and the released amount of MMTCA, shown as the absorbency of MMTCA, relative to different pH values of solutions. It could be found that SWeq of TMIPN hydrogel increased constantly with the increase of pH value of the solution. However, the released amount of MMTCA changed wavily along with the pH value increasing. At pH < 4.0, the change increased slowly; when pH > 4.0, the released amount of MMTCA dropped rapidly and achieved the minimum at pH 6.0; thereafter it increased continually. The possible reason for this change was that the ester bond which linked to MMTCA and PVA chain might be hydrolyzed under acidic conditions and released MMTCA from TMIPN hydrogel, which further formed the hydrogen bond to make the hydrogel

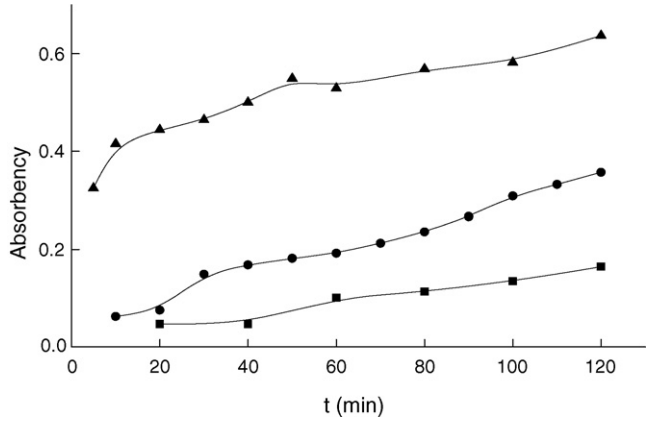


Fig. 8. Release curves of TMIPN hydrogel with different conditions. (■) Room temperature; (●) ultraviolet ray; (▲) ultrasonic wave.

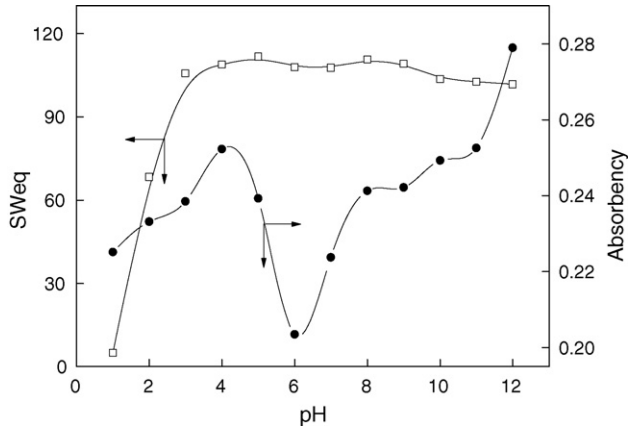


Fig. 10. Relationship between the equilibrium swelling degree (SWeq) of TMIPN hydrogel and the released amount of MMTCA relative to pH values.

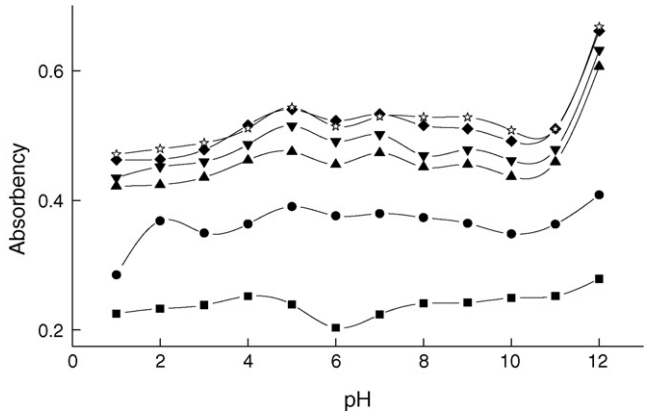


Fig. 11. Release curves of MMTCA from TMIPN hydrogel under different NaCl concentrations and pH values. (■) NaCl 0 g/100 mL; (●) NaCl 0.25 g/100 mL; (▲) NaCl 0.5 g/100 mL; (▼) NaCl 1.0 g/100 mL; (♦) NaCl 1.5 g/100 mL;(☆) NaCl 2.0 g/100 mL.

network shrink. With the pH value increasing constantly, the hydrogen bond was destroyed gradually, and then the hydrogel network opened to make MMTCA release easily (pH < 4.0). When the pH value raised from 4.0 to 6.0, the ester hydrolysis was weakened remarkably, thus caused the trough of the absorbency of MMTCA at pH 6.0. When pH > 6.0, the hydrogel network changed unconspicuously and the ester hydrolysis was strengthened gradually, the released amount of MMTCA increased correspondingly. Apparently, the release of MMTCA from TMIPN hydrogel was pH-sensitive.

3.3.5. Influence of pH values and NaCl concentrations on the release behavior of TMIPN hydrogel

Fig. 11 showed the controlled release curves of MMTCA in TMIPN at different pH values and NaCl concentrations. It could be found that the controlled release properties of MMTCA in TMIPN were influenced simultaneously by pH values and NaCl concentrations. When the NaCl concentration was low, the controlled release behavior was mainly decided by the change of the pH value, the trend of the controlled release curve was similar to that of the curve in Fig. 10. When the concentration was more than 0.5 g/l00 mL, the effect of NaCl concentration on the released behavior of TMIPN was unconspicuous. It was also found that at a higher NaCl concentration, with the pH value increased the trend of the controlled release curve was a little different from that of the curve in Fig. 10. That was to say, at pH 1.0–4.0, the released amount of MMTCA increased constantly; at pH 4.0–11.0, the released amount of MMTCA was close to a constant; at pH > 11.0, the released amount of MMTCA increased sharply. Obviously it was the result of the integrated effect of pH values and NaCl concentrations.

4. Conclusions

A series of interpenetrating polymer networks of poly(acrylic acid)/triazole modified poly(vinyl alcohol) (TMIPNs) were synthesized and characterized. The swelling/deswelling behavior of TMIPNs and the controlled release properties were also investigated by contrast method. The results showed that: (1) TMIPNs had the strong swelling capability in distilled water at room temperature; (2) TMIPNs had remarkable pH-sensitivity and salt-sensitivity; (3) the controlled release behavior of TMIPNs possessed apparent pH, salt and other physical stimulus responsibility and was concerned with the swelling/deswelling of TMIPNs. So TMIPNs have great perspective in controlled release drugs for clinic application.

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