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Preparation and Characterization of Thermo-Sensitive Poly(vinyl alcohol)-Based Hydrogel as Drug Carrier

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ABSTRACT: Poly(vinyl alcohol)s (PVA) with high and low molecular weights were chemically modified by introducing acetaldehyde onto the polymer backbone to induce thermal-responsive properties. The influence of both molecular weight ($\overline{Mw}$) and acetalization degree on the lower critical solution temperature (LCST) of thermo-sensitive polymer was investigated. Moreover, a temperature responsive hydrogel was prepared by controlled cross-linking of acetalized poly(vinyl alcohol) (APVA) and glutaraldehyde. As a model drug, ciprofloxacin was introduced into the prepared thermal sensitive hydrogel to reveal the drug loading and release behaviors. The structure, thermo-sensitivity, swelling/deswelling kinetics, morphology, and drug loading/release behaviors were also investigated. The results indicated that the APVA polymer solution exhibited temperature responsivity, and APVA with high acetalization degree showed low LCST, whereas those with high $\overline{Mw}$ PVAs showed high LCST. Meanwhile, morphology study was identical with the swelling/de-swelling behavior. The loading and release of ciprofloxacin were controllable. © 2013 Wiley Periodicals, Inc. J. Appl. Polym. Sci. 000: 000–000, 2013

KEYWORDS: drug delivery systems; morphology; stimuli-sensitive polymers; gels; swelling

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INTRODUCTION

Stimuli-responsive polymers and hydrogels, such as pH, thermal sensitive, antigen responsive, have been extensively investigated.[1–3] Particularly, thermal sensitive polymers have been proved to be very attractive from a scientific point of view because of high demand in pharmaceutical and biomedical areas.[4–6] For example, temperature responsive hydrogels can be utilized to switch the drug release ON and OFF due to their characteristic like swelling/collapse transition state at different temperatures.[7]

Temperature responsive polymers undergo a quick and reversible volume change when the temperature is increased from low temperature (below the lower critical solution temperature (LCST)) to high temperature (above the LCST). Below the LCST, the polymer aqueous solution is transparent because most of its hydrophilic groups are exposed to water. Above the LCST, alternatively, hydrogen bonds between hydroxyl groups are broken and polymer chains are hydrophobic and folded as a result of dehydration and assemble to form a phase separation state.[8]

Poly(vinyl alcohol) (PVA) is a hydrophilic polymer extensively used in pharmaceutical applications because of its biodegradability, biocompatibility, nontoxic, and noncancerous nature.[9] PVA is produced by the polymerization of vinyl acetate (PVAc), followed by hydrolysis of PVAc to PVA.[10] Various commercial PVAs of different molecular weights ($\overline{Mw}$) are available in highly hydrolyzed grades (degree of hydrolysis above 99.0%). Like low $\overline{Mw}$ alcohols, PVA is reactive and very useful as a precursor of a broad class of materials undergoing physical/chemical modification reactions via its hydroxyl groups. Up to now, cross-linking with bi-functional groups containing chemical agents (e.g., glutaraldehyde,[10,11] maleic anhydride, succinyl,[12] and toluene diisocyanate[13]) by radical polymerization is a frequently used method. To the best of our knowledge, PVA-based thermal-sensitive hydrogels have not been reported until now.

Hydrogels have been used for the development of controlled drug delivery systems for a long time. A water-insoluble drug incorporated into hydrogels can be controllably released when the solute migrates to the medium surrounding the system via molecular diffusion. Ciprofloxacin is the third generation fluoroquinolone with a broad spectrum of antibacterial activity and good prevention and treatment of infections in bone and soft tissues (Figure 1).[14] Ciprofloxacin possesses small particle size, hydrophobicity, and ability in deactivating various bacteria; thus, it has been chosen as a model drug of many different studies.[15,16]

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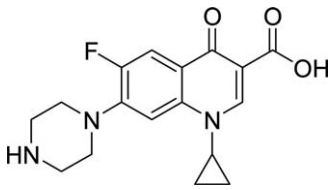

Figure 1. Chemical structure of ciprofloxacin.

This work describes the behavior of ciprofloxacin loading and release by PVA-based hydrogels. Two different PVAs with low/high $\overline{Mw}$ and highly hydrolyzed degree (99+ %) were acetalized using different dosages of acetaldehyde to create a range of temperature responsive polymers. The influence of $\overline{Mw}$ and acetalization degree on the LCST of the acetalized poly(vinyl alcohol) (APVA) was systematically monitored. A thermo-sensitive three dimensional network hydrogel was also prepared by cross-linking glutaraldehyde with APVA. The behaviors of swelling and deswelling were studied in addition to the controlled loading via impregnating and release of ciprofloxacin.

EXPERIMENTAL

Materials

Poly(vinyl alcohol) with molecular weights of 89,000–98,000, 124,000–186,000 and degree of hydrolysis of 99+ %, acetaldehyde, glutaraldehyde, 25% (v/v) in water, and Ciprofloxacin were purchased from Sigma-Aldrich. 1.0*N* hydrochloric acid solution was obtained from Fisher Scientific. Buffer solution of pH 6.86 containing monosodium phosphate was purchased from VWR Scientific. PVA and other reagents were used as received.

Synthesis of Thermal Sensitive APVA with Controlled Degree of Acetalization

The temperature responsive APVAs were prepared based on a procedure described earlier.[17] 7.0 g PVA were dissolved in 210 mL distilled and deionized water (DD water) at 95°C for 30 min in a three-neck flask, equipped with a condenser and a dropping funnel. The homogenous solution was then allowed to cool down naturally to room temperature. Subsequently, 1.5 mL of the catalyst HCl (1.0*N*) were added to adjust the pH of the solution to 2 ± 0.05, and the solution was thermostated at 15°C for 10 min. Various amounts of acetaldehyde were then added dropwise into the flask with vigorous stirring for 30 min. The temperature was raised to 40°C gradually, and the reaction system was left to proceed for 4 h. The samples were then precipitated by increasing the temperature to 80°C. Finally, the precipitates were collected and freeze-dried. Figure 2(a) shows the proposed acetalization reaction to prepare APVA.

Synthesis of Thermal-Sensitive Acetalized PVA-Based Hydrogel (APVG)

A controlled cross-linking degree of PVA-based hydrogel was prepared by mixing 50.0 g 5.0 wt % of the APVA(the acetalization degree = 27%, LCST=37°C) aqueous solution with a calculated amount of 25.0% (v/v) glutaraldehyde corresponding to 30% of theoretical cross-linking degree [Figure 2(b)].[10] The mixed APVA/GA solution was shaken vigorously in an ultrasound scope for 10 min and degassed with a vacuum pump. The sample was then placed in a refrigerator for 30 min and then moved to an oven to induce favorable reaction by holding the temperature at 55–60°C for 5 h. The resulting hydrogel was equilibrated with DD water for 72 h so that the unreacted monomers and chemicals were leached out. The swollen hydrogel was equilibrated in DD water in a refrigerator, flash frozen with liquid nitrogen, moved to a freezer (−80°C) for 12 h and finally freeze-dried (model: micromodulyo, thermofisher) at −45°C for three days to remove water. For examining the properties of swelling and deswelling, drug loading and release study, the dried hydrogel was cut into cubes of 1.0 cm length.

Characterization

Fourier transform infrared spectroscopy (FTIR) spectra were recorded in KBr pellets in a range of 4000–400 cm^{-1} using an S-100 FIIR spectrometer (Perkin Elmer). ^{1}H-NMR spectra were recorded in dimethyl sulfoxide-d_6 (DMSO-d_6) using an Oxford spectrometer operating at 400 MHz. Both PVA and APVA were soluble in DMSO-d_6. Scanning electron microscopy (SEM) was taken on a JEOL (Japan) model JSM-6400 instrument, and the freeze-dried hydrogels were fractured carefully in liquid nitrogen and then sputtered with gold to make it conducting and placed on a copper stub. Thermo-gravimetric analysis (TGA) was recorded at a heating rate of 10.0°C/min in nitrogen between room temperature and 600.0°C using thermo-gravimetric analyzer (SDT Q600 TA Instrument).

Lower Critical Solution Temperature Characterization

The LCST was determined by measuring the percent transmittance of the APVA polymer solutions as a function of temperature using Ultraviolet/Visible (UV-Vis) spectrophotometer (Genesys 10S, Thermo Electron Co.) at 550 nm. The APVA samples in 0.02 wt % were put into a cuvette and immersed from 7°C to 70°C in increments of 1°C.[8] The samples were kept in a water bath for 10 min at each temperature, and then taken out and dried quickly before inserting into UV-Vis[8]. The transmittance was then recorded at the corresponding temperature.

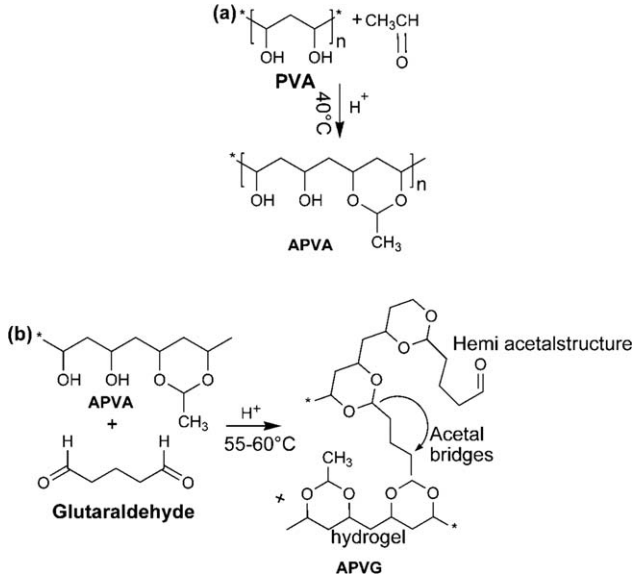

Figure 2. (a) Chemical reaction of the PVA polymer with acetaldehyde. (b) Chemical reaction of the APVA polymer with glutaraldehyde.

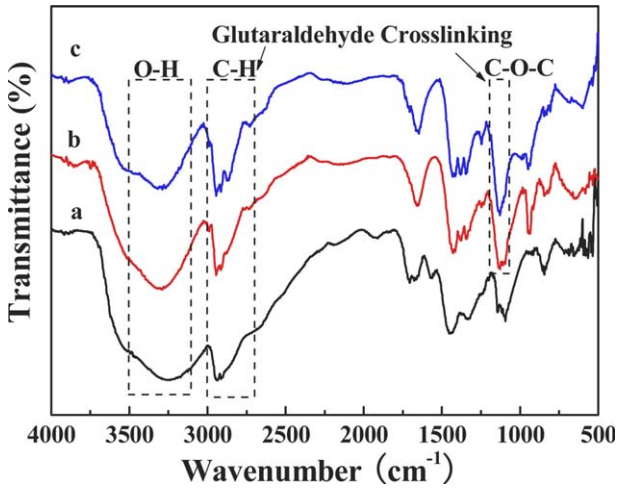

Figure 3. FTIR spectra of (a) the pure PVA, (b) APVA, and (c) APVG. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Swelling and Deswelling Studies of Hydrogels

For the swelling behavior, the dried hydrogel samples (1.0 g) were immersed in a buffer solution of pH 6.86. The dynamic and equilibrium swelling experiment was carried out in 100 mL of solution at three predetermined temperatures, 5, 37, and 45°C. The hydrogel samples were then taken out at regular time intervals and weighted after wiping off the surface water by blotting using moist filter paper. Three replicates were conducted and the average values were presented. The swelling ratio (*SR*) was determined by the following equation:[18]

$$\%\mathrm{SR} = \frac{W_s - W_d}{W_d} \times 100\% \quad (1)$$

where W_s and W_d are the weights of wet and dry samples, respectively.

For the dynamic deswelling behavior, the hydrogel samples were equilibrated in pH 6.86 buffer solutions at predetermined temperatures ranging from 30 to 70°C, with increments of 1°C. The hydrogels were immersed for a holding time of 40 min at each temperature; after the holding time is complete, the samples were taken out and weighted after removing excess surface water by blotting using moist filter paper. The equilibrium swelling ratio (ESR) was determined using the following equation:[19]

$$\mathrm{ESR} = \frac{W_e - W_d}{W_d} \times 100\% \quad (2)$$

where W_e is the weight of hydrogel after establishment of equilibrium, W_d is the weight of dry hydrogel.

Kinetic Study of Drug Loading

To perform the study of ciprofloxacin loading model via impregnating, the APVG hydrogels and a mixture of 20 mL ciprofloxacin/HCl (0.1*N*) solution (0.3 mg/mL) were kept at three temperatures, 5, 37, and 45°C. After a certain incubation period, the amounts of drug incorporated into the APVG hydrogels were estimated by taking the difference between the initial and final drug concentrations. The change in the concentration of the drug loading solution was monitored periodically by the UV-Vis absorbance of the dialysate at 355 nm. The standard calibration curve was obtained from the linear relationship between the UV absorbance and the ciprofloxacin concentration. The experiment was carried out in triplicate to minimize experimental errors, and the average values were recorded. The entrapment efficiency is expressed as follows:[20]

$$\text{Entrapment efficiency}\,(\%) = \frac{\text{Practical drug loading}}{\text{Theoretical drug loading}} \times 100\% \quad (3)$$

In Vitro Drug Release from APVG Hydrogel

Drug-bearing hydrogels were wiped using moist filter paper to remove its surface excess solution, followed by drying under vacuum at ambient temperature. Therefore, the ciprofloxacin loaded hydrogels were placed into three vials containing 20 mL of 0.1 N HCl solution for about 67 h. One vial was placed in a fridge at 5°C, and the second and the third in water bath at temperatures of 37°C and 45°C, respectively. At regular time intervals, 1.0 mL of the released solution was withdrawn and at the same time 1.0 mL of the fresh solution was replenished. The cumulative drug release was calculated using the following equation:

$$\text{Cumulative drug release}\,(\%) = \frac{\text{The amount of drug release from hydrogel}}{\text{The amount of drug loaded in hydrogel}} \times 100\% \quad (4)$$

All release measurements were done in triplicate to minimize experimental errors and the average values are presented.

RESULTS AND DISSCUSION

FTIR Spectroscopy

The FTIR spectra of the pure PVA, APVA, and APVG are analyzed and presented in Figure 3. In the three spectra, the large O—H bands were observed between 3550 and 3200 cm^{-1}, which were due to the stretching of intermolecular and intramolecular hydrogen bonds.[10] Additionally, typical strong hydroxyl bands for free O—H stretching band at$v$= 3600–3650 cm^{-1}. In comparison, the spectral intensity of O—H bonds showed decrease in magnitude as follows: pure PVA> APVA >APVG. This result suggests that the hydroxyl groups on the PVA polymer backbone were significantly cross-linked by acetaldehyde and glutaraldehyde.

In addition, the spectral intensity also shows strong evidence that the reaction of PVA with acetaldehyde and/or glutaraldehyde had occurred by formation of aldehyde bridges among the pendant hydroxyl groups.[10] Furthermore, the strong band between 1710 and 1740 cm^{-1} was verified from the carbonyl group. As shown in Figure 2, one aldehyde group on the bi-functional cross-linker glutaraldehyde may react with the OH

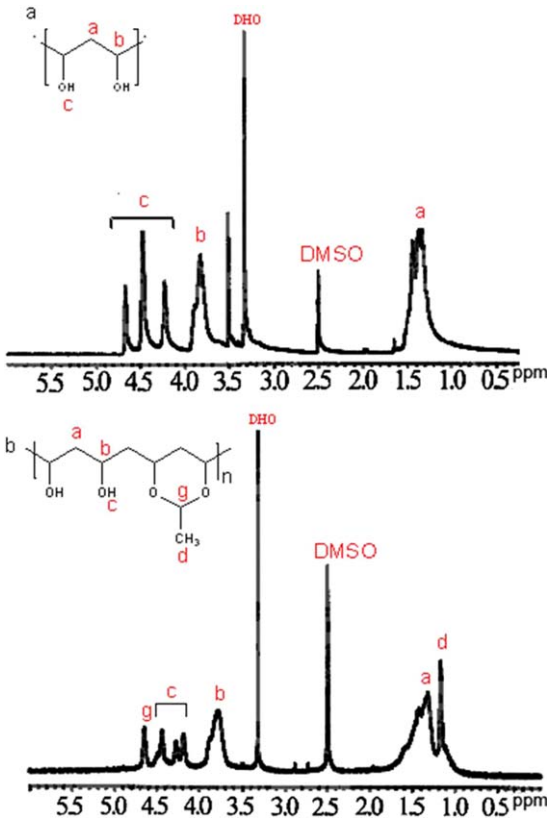

Figure 4. ^{1}H-NMR spectra of (a) the pure PVA and (b) APVA. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

groups of the PVA polymer chain, consequently only one hemiacetal structure is formed and the other one does not react which is associated with some conformation or kinetics limitation. For this reason, the intensity of the peak was weaker for the PVA polymer than for the APVG hydrogel.

The spectral peaks between 2840 and 3000 cm^{-1} corresponded to the stretching vibration of C—H bonds on the PVA backbone.[10] As evidence, the two important bands of C—H stretching related to the aldehyde groups appeared at $v = 2850$ and 2750 cm^{-1} because of the duplet absorption with peaks attributed to the alkyl chain. The region from 1200-1050 cm^{-1} represents the C—O—C stretching bands related to the acetal bridges of acetaldehyde.[10] According to the precursors' work, the crystallinity of the PVA polymer contributes to this vibrational band, which is related to carboxyl stretching band (C—O).[21] In summary, the FTIR spectra showed in Figure 3 have confirmed the formation of the APVA/glutaraldehyde hydrogel networks. The glutaralhyde has acted as a crosslinking agent among the APVA polymer chains.

^{1}H-NMR Spectroscopy

Figure 4 shows the ^{1}H-NMR spectra of the pure PVA (a) and the APVA (b). The amount of acetaldehyde reacted with PVA corresponded to the acetalization degree, which was equal to the ratio of the integrated area of proton in the methyl group to that of the methylene group in the ^{1}H-NMR method where DMSO-d_6 was used as a solvent.

The proton resonance of the methylene group in the PVA backbone was between 1.0 and 1.6 ppm. In fact this is broad because of the combination of spin-spin coupling and configurationally splitting of orbital electrons.[8] The resonance of the methine protons in the PVA main chain appeared at 3.7-3.9 ppm. The presence of the three distinct hydroxyl resonance signals at 4.20, 4.45, and 4.65 ppm was mainly attributed to the syndiotactic, heterotactic, and isotactic triad sequences, respectively.[9] The resonance peaks at 2.5 and 3.3 ppm belongs to the remnant protons from DMSO-d_6 and water.

In comparing the ^{1}H-NMR of the pure PVA and APVA, Figure 4(b), the resonance peak of the methylene group in the main chain of APVA appeared at 1.3–1.7 ppm, the methine protons at 3.7–3.9 ppm, and the resonance of the methyl protons at 1.1–1.3 ppm. In the APVA polymer, the methine proton shift could be seen at 4.7–5.1 ppm, due to the bridge between the two oxygen atoms at pendant position.[9] Three distinct resonance signals of the hydroxyl protons appeared at 4.1–4.6 ppm. The difference shown in the two ^{1}H-NMR spectra indicated that after acetalization two or more methyl and methine protons are incorporated. Moreover, the strength of the APVA backbone hydroxyl groups was much weaker than that of unmodified PVAs, due to the partial hydroxyl groups reacting with acetaldehyde.[8]

Effect of Molecular Weight and AD on the LCST of APVA

The LCST of the two series of APVAs with low/high $\overline{Mw}$ and various acetalization degrees was analyzed using UV-Vis spectrophotometer. The influence of the acetalization degree on the LCST of the APVAs is presented in Figure 5. The acetalization degree significantly affected the LCST of the prepared APVA solutions.

As shown in Figure 5(a), the LCST increased with decreasing the acetalization degree; however there is no LCST when the acetalization degree is as low as 16% for the low $\overline{Mw}$ APVA. The LCST of the high $\overline{Mw}$ APVA solution changed from 45°C to 18°C due to the change of the acetalization degree between 31 and 61%.

The temperature dependence of the LCST on the acetalization of different $\overline{Mw}$ PVAs is shown in Figure 6. The temperature responsibility of all the APVA polymer solutions is affected by the LCST, $\overline{Mw}$, acetalization degree and their interactions. For example, when the LCST was close to 37°C, the acetalization degree of the high $\overline{Mw}$ APVA was higher than that of the low $\overline{Mw}$ APVA. All the APVAs polymers exhibited linear relationship between the LCST and the acetalization degree. This result provides an opportunity to study the relationships among the acetalization degree, $\overline{Mw}$ and LCST, following the previous work.[17]

Swelling and Deswelling Conditions

It is of crucial importance for hydrogels to have high water swelling ratios for their application in controlled drug release field, especially for unique thermal sensitive hydrogels. Here, the swelling kinetics was evaluated gravimetrically by monitoring the water imbibed by hydrogels at three temperatures: 5, 37, and 45°C, at various time intervals. Figure 7(a) illustrates the

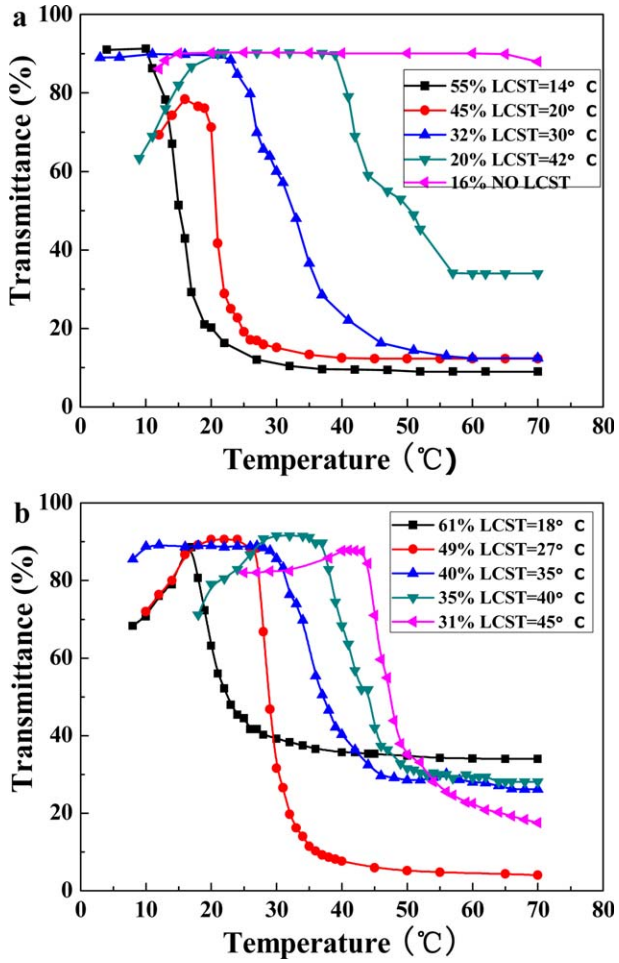

Figure 5. LCST of different $\overline{Mw}$ APVAs as a function of the acetalization degree. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

temperature dependence of the swelling kinetics of the APVG hydrogels. Thermo-sensitive hydrogels demonstrated large-scale volumetric changes in response to incremental temperature

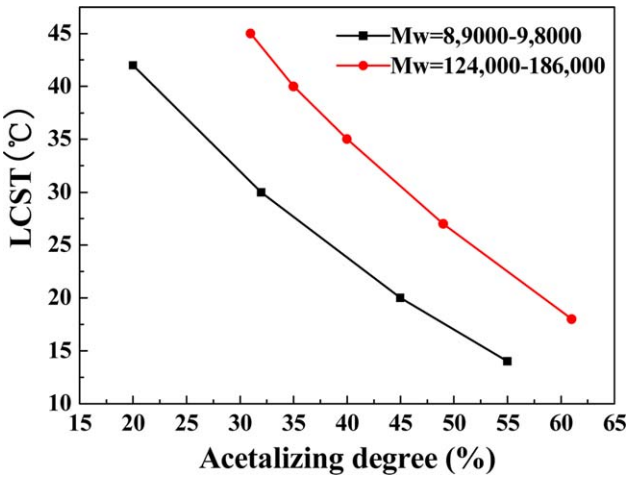

Figure 6. Different acetalization degrees of APVA and its effect on LCST for corresponding $\overline{Mw}$ range. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

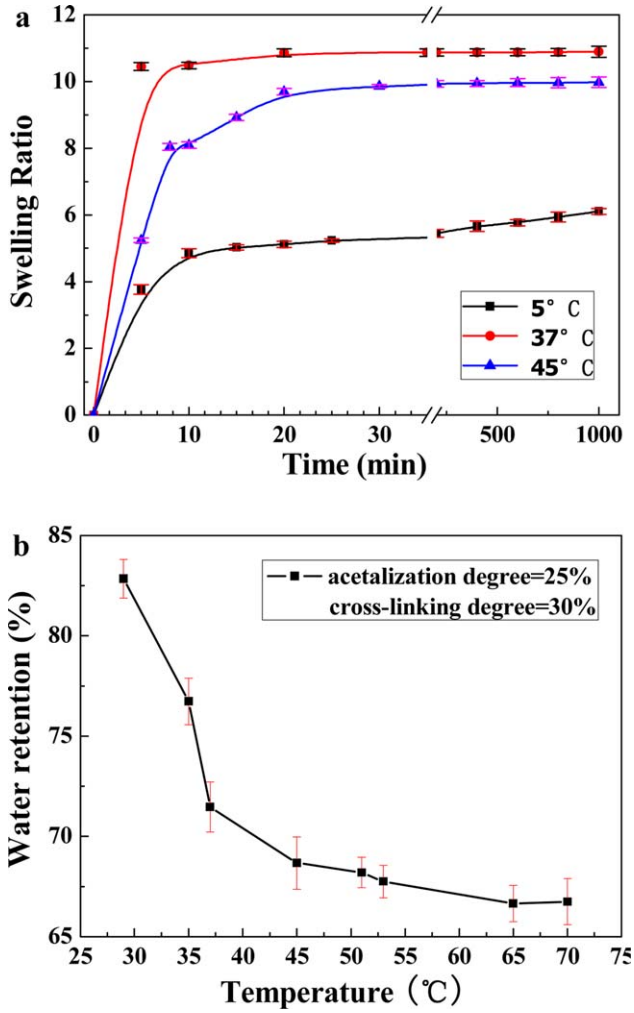

Figure 7. (a) Temperature dependence of swelling ratio of APVG hydrogel (b) Deswelling kinetics of the APVG hydrogel. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

stimuli, and this is obviously of practical interest and more important in commercial applications.[22,23]

In every sample, the water uptakes were very fast in the beginning, and then leveled off to specific amounts. The highest water uptake quantity was at 37°C, and the lowest was at 5°C. This is because the hydration of the hydroxyl groups on the surface of the APVG hydrogel leads to a quick diffusion of water molecules into the hydrogel pores,[24] and this hydration can be reversed quickly by increasing temperature. The structure of the hydrogel polymer main chains shows dual configuration such as hydrophilic nature by the hydroxyl groups or hydrophobic nature attributed to the aldehyde rings.[25] The reason that the swelling ratio at 5°C was lower than at 45°C might be because the hydroxyl groups cannot fully swell at low temperatures which may be similar to the case of PVA dissolving better at high temperature.

The deswelling kinetics of the hydrogel were studied after the hydrogel attained equilibrium-swelling conditions at 5°C. The hydrogel was transferred quickly into a vial which contains a buffer solution of pH 6.86 at 29°C. Figure 7(b) shows the

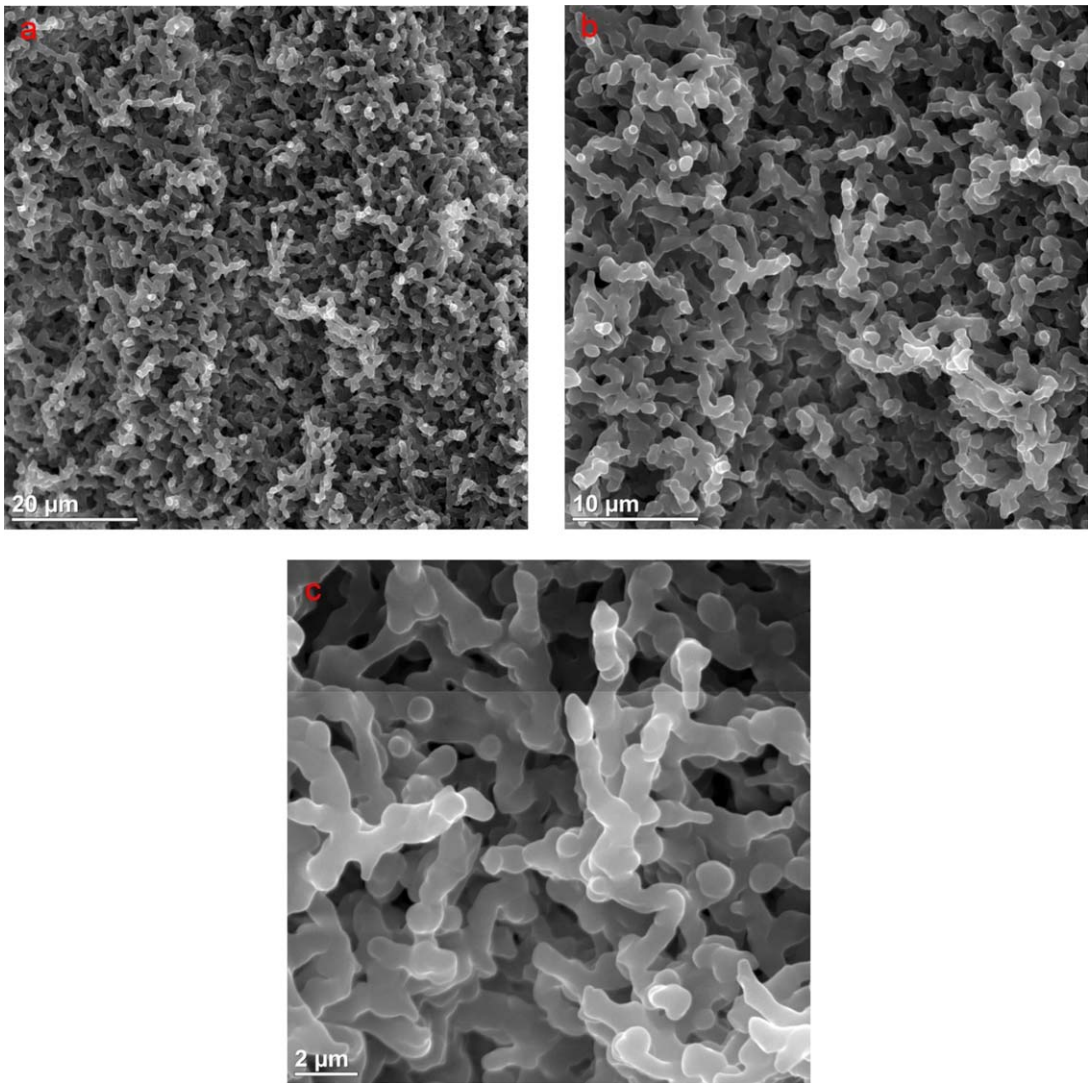

Figure 8. SEM micrographs of the freeze-dried APVG hydrogel.

temperature dependence of equilibrium swelling ratio of the APVG hydrogel over a temperature range of 29−70°C. As the temperature was increased, the water retention decreased, leading to drastic dehydration around 37°C. In general, the key factor for such a phenomenon can be attributed to the unique and rapid alternation of the hydrophilic and hydrophobic states.[23] Most pendants of the PVA main chain are hydroxyl groups, which contribute to weak hydrogen bonds. At temperature below the LCST, a stable hydration shell formed by hydrogen bonds acts as a blanket around the hydrophobic groups thus resulted in a larger swelling ratio.[23] Conversely, when the temperature is suddenly increased above the LCST (37°C), most entrapped water molecules are diffused out of the hydrogel and a new balance of the hydrophobic and hydrophilic forms. As a result, the water retention is sharply decreased. In other words, as the external temperature increases, the hydrophobic groups were totally exposed to the environment and the hydrogen bonds are broken, therefore, water molecules entrapped by the associative interactions among the hydrophobic groups are released from the hydrogel networks.[22]

Morphology Analysis

The internal morphology of the freeze-dried hydrogel prepared using the 30% cross-linking degree is shown in Figure 8. The cross-sectional view is shown at three magnifications: 500×, 1000×, and 5000×. A definite three dimensional (3D) structural pattern arose in the sample of APVG, and the interlocking of the chain resulted in a comparative network structure. As shown, the microstructure of the APVG hydrogel was mostly unique because it seemed like a branched blend polymer instead of the common honey comb style.[26,27]

Thermo-Gravimetric Analysis (TGA and DTG)

Figure 9(a−c) shows the typical TGA thermo gram of weight loss as a function of temperature for the samples PVA, APVA, and APVG hydrogel. The initial decomposition temperature (IDT), the final decomposition temperature (FDT), and the decomposition temperature per 10% weight loss with for each sample are presented in Table I. In each case, the initial weight loss due to the loss of moisture has been ignored and the IDT

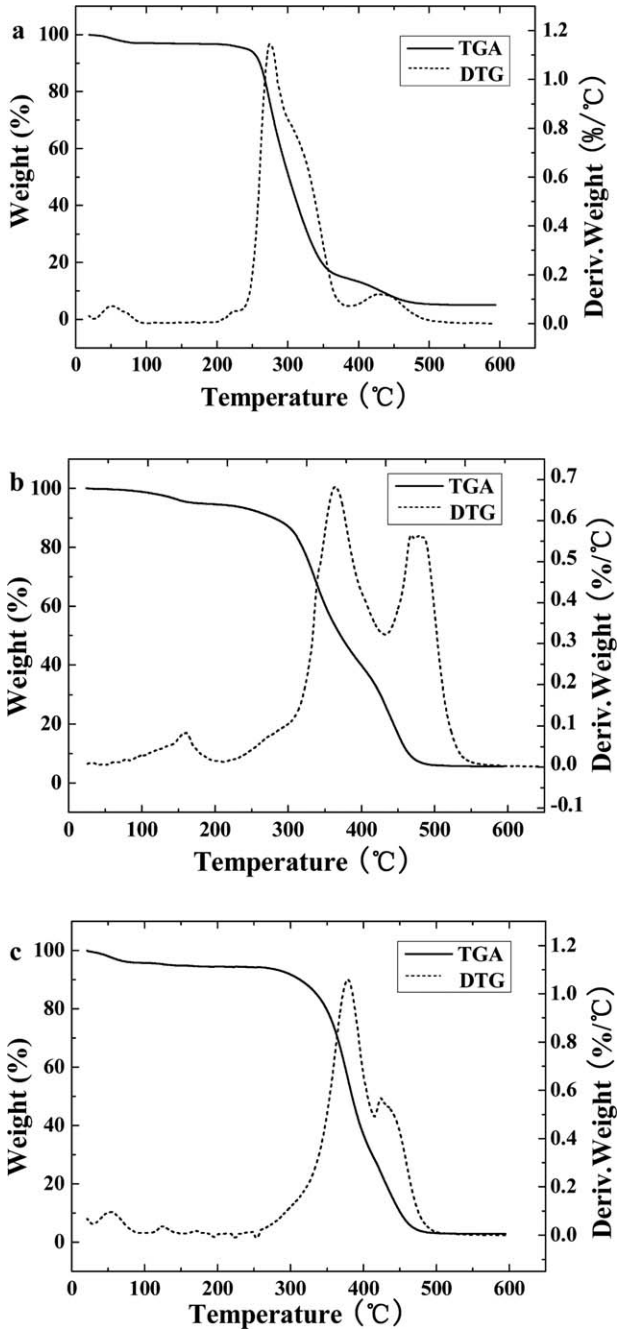

Figure 9. Thermo-gram (TGA and DTG) of (a) the pure PVA, (b) APVA, and (c) APVG.

was taken as the temperature where the actual degradation of the polymers started.

In Figure 9(a), there are two distinct and well-separated turns (230−350°C and 350−550°C) in the thermo-gravimetric curve and two corresponding weight-loss peaks in the DTG curve for the pure PVA. Therefore, the thermal degradation of PVA can be roughly regarded as a two-step-degradation. The IDT and FDT for PVA were observed at 229°C and 485°C (residue left = 5%), respectively.[28] The second decomposition stage started at 357°C (residue left=18.3%). About 90% PVA degradation occurred at 428°C.

In the APVA polymer, the IDT and FDT were obtained at 217°C and 500°C (residue left = 7.8%), respectively. As with PVA, a two-stage decomposition mechanism was observed for the decomposition of the APVA polymer [Figure 9(b)]. The first stage started at 217°C (residue left=92.2%); the second stage started at 438°C. More than 60% of the polymer decomposition occurred during the first stage of decomposition.

In the APVG hydrogel, 6.25% loss of initial weight occurred at 200°C due to both its bonded water and hygroscopic property. The IDT and FDT were obtained at 267°C and 500°C (residue left=2.4%), respectively. A two-stage decomposition mechanism was observed for the decomposition of the APVG hydrogel [Figure 9(c)]. The first stage started at 267°C (residue left=93.75%); the second stage started at 415°C (residue left=30%). It is noted that the peak temperature of the main degradation step is shifted to higher temperatures compared to the pure PVA, APVA. This is an indication that the chemical structure plays an important role in the thermal decomposition process. Additionally, the decomposition of the pure PVA happened at higher temperature than that of APVA, but lower than that of the APVG hydrogel. This implies that the cross-linking reaction could improve the stability of modified PVA and the uncross-linked acetal bridge bond in the APVA polymer is easier to be broken than that cross-linked in the APVG hydrogel.

Loading of Ciprofloxacin into Hydrdogels

In this study, ciprofloxacin was employed as a model drug to investigate the loading and release performance of the APVG hydrogels. The loaded drug content and entrapment efficiency of hydrogels are shown in Table II. The dried APVG hydrogel was immersed into 20 mL ciprofloxacin/HCl (0.1*N*) solution (0.3 mg/mL, pH 4.0) under three temperatures, 5, 37, and 45°C, for 48 h. The dynamic loading process of ciprofloxacin into the APVG hydrogel is presented in Figure 10. The loaded amounts of ciprofloxacin depended upon the water uptake and the temperature conditions. The ciprofloxacin entrapment efficiency and the drug loading content were the highest at 37°C and the lowest at 5°C. At high temperature, there are fewer bonded water molecules inside of the APVG hydrogels than at low temperature. In addition, the hydroxyl groups on the APVG surface are exposed to the ciprofloxacin mixture; therefore, it is easy to form hydrogen bonds between the ciprofloxacin molecules and the hydroxyl groups. At low temperature, swollen hydrogels are full of water inside of their pores, and most ciprofloxacin are entrapped because of the concentration gradient. In the first few minutes, most ciprofloxacin molecules are moved from the regions (external environment) of high concentration to the regions (hydrogel meshes) of low concentration by this natural flow down a concentration gradient. The larger the mesh size, the higher the concentration gradient, and thus more ciprofloxacin goes into the hydrogel meshes. When equilibrium is reached, the concentration gradient becomes small, and the driving force is weak because the 3D hydrogel network is likely saturated with ciprofloxacin.

Release Behavior

The influence of temperature on the ciprofloxacin release from hydrogels was studied at 5, 37, and 45°C, Figure 11. At each

Table I. Thermo-Gravimetric Analysis of the Pure PVA, APVA, and APVG Hydrogel

			DT[c] at every 10% weight loss										
Sample	IDT[a]	FDT[b]	10	20	30	40	50	60	70	80	90	100	Residue left/%
PVA	229	485	260	270	280	288	300	311	327	349	428	485	5.0
APVA	217	500	295	323	339	351	374	400	427	442	463	500	7.8
APVG	267	500	313	350	367	380	387	399	415	433	450	500	2.4

[a] The initial decomposition temperature(°C).
[b] The final decomposition temperature(°C).
[c] Decomposition temperature(°C).

temperature, the release was fast at the beginning and then reached a plateau, which implied that the residual amount remains within the hydrogel. At 37°C, the release of the ciprofloxacin from the hydrogel showed a pronounced burst behavior in the first 2 h, during which 65% of the ciprofloxacin was released. The release rate of the ciprofloxacin at 37°C was much higher than those at 5°C or 45°C. As shown, less than 50% of the ciprofloxacin was released in the first 16 h at 5°C. Also, a continuous release still occurred for more than 48 h exhibiting a sustained release. At equilibrium, 54%, 90%, and 79% of the loaded ciprofloxacin were released at 5, 37, and 45°C, respectively. The amount of the ciprofloxacin released at 37°C was much higher than at temperatures of 5°C and 45°C. A possible reason is the formation of hydrogen bonds between the carboxyl group of the ciprofloxacin and the hydroxyl groups of the PVA chains. Therefore, it is not easy to break the hydrogen bonds and release the ciprofloxacin from the APVG hydrogel at a low temperature, and the ciprofloxacin cannot be heavily loaded at 45°C because the pores of the APVG hydrogel are clogged. As 37°C is the temperature close to the LCST of the APVG hydrogel (Figure 7), the ciprofloxacin could be loaded easily and released quickly.

Table II. Loading of Ciprofloxacin for the APVG Hydrogel

Temperature (°C)	Drug content (mg/mg)	Entrapment efficiency (%)
5	0.214	40.6
37	0.445	87.4
45	0.405	76.7

CONCLUSIONS

A series of thermal-sensitive polymers of APVA with different $\overline{Mw}$ and acetalization degrees was successfully prepared and the APVG hydrogel was made by further cross-linking the APVA polymer with the glutaraldehyde. The ciprofloxacin was employed to study the drug loading and release behavior of the APVG hydrogel under different conditions. The effects of the structure, morphology, temperature responsivity, drug loading, and release were investigated. The FTIR and ^{1}H-NMR spectra revealed the existence of aldehyde rings between PVA and acetaldehyde and/or glutarldehyde. LCST of the APVA solution showed correlation between LCST and acetalization degree, the LCST was directly proportional to the PVA $\overline{Mw}$ but inversely proportional to the aceltalization degree. The swelling and deswelling kinetics of the APVG hydrogels showed that the sample could absorb the largest amounts of buffer solution when the temperature was around the LCST (37°C). The morphology

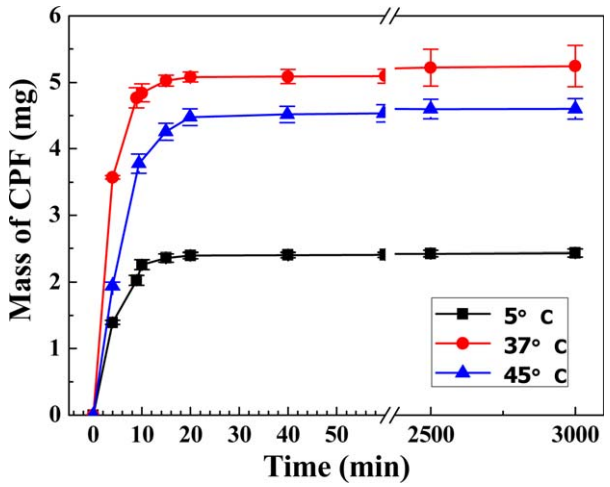

Figure 10. Ciprofloxacin loading assays at different temperatures. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

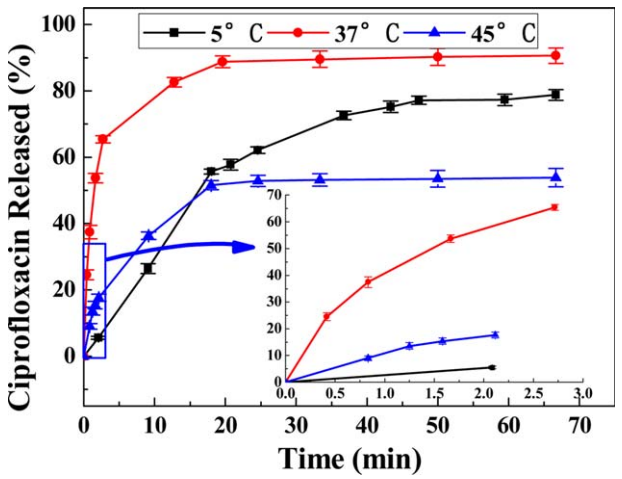

Figure 11. Release of ciprofloxacin from the APVG hydrogel at various temperatures. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

study showed a unique 3D polymer network which favored controlled drug loading and release. The drug loading and release behavior showed that more ciprofloxacin could be entrapped into meshes of the APVG hydrogel at 37°C, as well as more ciprofloxacin was released quickly at 37°C. This confirmed that the drug loading and release of the PVA-based hydrogels could be triggered by temperature.

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