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Thermoresponsive hydrogel with rapid response dynamics

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Intelligent hydrogels, particularly poly(N-isopropylacrylamide) (PNIPAAm)-based hydrogels, have attracted extensive interest because the soft wet hydrogels can change their shapes in response to the small changes of environmental factors like temperature. In order to fully make use of this unique property of PNIPAAm-based hydrogels, the response rates of the PNIPAAm hydrogels have to be improved since the dynamics property is critical to certain applications of this material. In this paper, the thermo-sensitive PNIPAAm hydrogels were successfully synthesized by carrying out the polymerization of N-isopropylacrylamide monomer in vacuum (− 100 kPa) at room temperature (22 °C). The resultant hydrogel has tremendously improved shrinking rate as well as the large volume changes upon temperature stimulation when comparing with the normal PNIPAAm hydrogel. The SEM micrographs revealed that the improved properties were attributed to the macroporous network structure generated during the synthesis under vacuum.

Introduction

In recent years, a lot of interests have been focused on the design of new and improved biomedical materials, especially the smart or intelligent polymeric materials, which can respond in shape or volume changes to small external stimuli, such as temperature, pH, electric fields, antigen and radiation forces [1–4]. Among all these intelligent polymeric materials, poly(N-isopropylacrylamide) (PNIPAAm) is the most widely studied thermoresponsive polymer. PNIPAAm has a phase transition temperature (T_{tr}) or lower critical solution temperature (LCST) at about 32 °C [5]. The aqueous solution of PNIPAAm exhibits a unique hydration–dehydration change in response to temperature. Correspondingly, the polymer chains of the crosslinked three-dimensional PNIPAAm hydrogel undergo a coil-globule transition when the external temperature cycles exceeds the LCST (~ 33 °C) [6].

The phase separation property of PNIPAAm hydrogels makes them especially useful for biomedical and bioengineering applications, such as tissue engineering [7], protein-ligand recognition [8], on–off switches [9] or artificial organs [10]. Since the rapid response rate and large volume changes due to temperature variation is the essential function for intelligent hydrogels' applications, there is a clear need for thermoresponsive hydrogel with improved response rate and larger volume changes to an external temperature stimulus.

The response rate and volume changes of the PNIPAAm hydrogel is generally regarded as a diffusion-dominant process and determined by the collective diffusion coefficient of water through the hydrogel matrix. In this regard, several attempts [11–17] have been proposed to achieve fast responsive thermoresponsive PNIPAAm hydrogel. For instance, Kabra *et al.* [11] utilized the phase separation technique to yield fast responsive PNIPAAm hydrogels. Then, Wu *et al.* [12] modified the phase separation technique: the polymerization was conducted at a temperature above the LCST (50 °C) and the reactor was evacuated near the end of polymerization. They suggested that a two-phase system (e.g. aggregated polymer particles suspended in the liquid solution of monomer) occurred when the polymerization temperature was above the LCST, and thus the termination of the growing polymer chains would be retarded. This resulted in a macroporous structure and a fast response rate was achieved. Yoshida *et al.* [13] found that introducing the freely mobile and grafted polymer chain to the network of PNIPAAm gel could improve the deswelling rate of the gel matrix during the shrinking process owing to the increased channels for water diffusion. Recently, several strategies [14–17] were also reported by Zhang *et al.* that the improved response rate of the gels could be obtained through incorporating siloxane linkage, cold polymerization and using the pore-forming agent, etc.

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In this paper, the thermoresponsive PNIPAAm hydrogels with macroporous network structure were successfully synthesized by carrying out the polymerization in vacuum oven (− 100 kPa) at room temperature (22 °C). The resultant hydrogel has tremendously improved shrinking rate as well as large volume changes upon temperature stimulus when comparing with the normal PNIPAAm hydrogel.

Materials and methods

Materials

N-isopropylacrylamide (NIPAAm, Aldrich Chemical Company, Inc., USA) was purified from benzene/*n*-hexane by recrystallization. N,N′-methylenebisacrylamide (MBAAm, Bio-Rad Laboratories, USA), ammonium persulfate (APS, Bio-Rad Laboratories, USA), N, N, N′, N′-tetramethylethylenediamine (TEMED, Bio-Rad Laboratories, USA) were used as received.

Synthesis of hydrogels

For the synthesis of the macroporous, fast responsive PNIPAAm hydrogel (VGel), 100 mg NIPAAm monomer was dissolved in 2.5 ml de-ionized (DI) water in the presence of 2.0 mg crosslinker MBAAm. APS (0.5 wt % based on the NIPAAm) was used as the initiator and TEMED (2.0 wt % based on the NIPAAm) were used as an accelerator. Polymerization was carried out in vacuum (− 100 kPa) at room temperature (22 °C) for 12 h, and the produced hydrogel was then immersed in DI water at 22 °C for at least 24 h for reaching swelling equilibrium for the subsequent characterization studies. During this period, the DI water was replaced with fresh DI water every several hours in order to leach out the unreacted chemicals. The synthesis of the normal PNIPAAm hydrogel (NGel) was carried out the same way as VGel, except in an atmospheric pressure (100 kPa).

Surface morphology

The scanning electron microscope (SEM, XL Series-30, Philips, USA) was employed to study the surface morphology of the freeze-dried hydrogels. Before the SEM examination, the hydrogel samples were immersed in the DI water for at least 48 h at room temperature to reach the equilibrated swelling. The equilibrated swollen hydrogel samples were frozen quickly by using liquid nitrogen and then, the frozen hydrogel samples were rapidly transferred to a freeze-dryer to be freeze-dried (− 48 °C, 38×10^{-3} mbar) for at least 24 h. Finally, the freeze-dried specimens were coated with gold in SEM coating equipment (JFC-1200 Fine Coater, Japan) for 30 s for the following SEM studies.

Equilibrium swelling ratio

The hydrogel samples synthesized above were allowed to swell in DI water for at least 24 h at various temperatures from 22 to 50 °C. The water temperature was controlled up to ± 0.1 °C by a thermostated water bath (Grant Precision Stirred Bath, Grant Instruments Ltd, Cambridge, England). The swelling ratio of the hydrogels was measured gravimetrically after blotting the excess water on the surfaces of the wet hydrogels with filter papers. Swelling ratio was calculated from the weight of water in the swollen hydrogel (W_s) per weight of the corresponding dried hydrogel (W_d) at each temperature. Equilibrium–swelling ratio was obtained over an extent period of time when there was no further change in weight with time at each special temperature.

Thermal analyses of hydrogels

The hydrogel samples were first immersed in DI water at an ambient temperature (22 °C) for at least 24 h to reach equilibrium. After wiping off the excess water on the surface, the swollen hydrogel samples were analyzed using a Perkin Elmer 7-Series differential scanning calorimeter (DSC) (Model DSC 4, Perkin-Elmer, CT, USA). The thermal analyses were carried out without reference at a heating rate of 3.0 °C/min in the temperature range from 25 to 50 °C under a nitrogen atmosphere (40 ml/min).

Deswelling kinetics

The hydrogel samples were first immersed in DI water at an ambient temperature till equilibrium. The equilibrated gel samples were then quickly transferred into de-ionized water with a temperature of 50 °C. At predetermined time intervals, the samples were taken out from the hot water and weighted after wiping off the excess water on the surface with filter papers. Water retention was defined as $[(W_t - W_d)/W_s] \times 100$, where W_t is the weight of the wet hydrogel at 50 °C and the other symbols are the same as above.

Oscillating deswelling–swelling kinetics over temperature

The oscillating deswelling–swelling kinetics of both the VGel and NGel over the 1-min temperature cycles between 30 °C (below the LCST) and 35 °C (above the LCST) in DI water was further investigated. The hydrogel samples were first immersed in DI water at 30 °C till it reached equilibrium swelling. After equilibrium, the hydrogel sample was rapidly transferred to the DI water at 35 °C for one minute and the sample would exhibit shrinking or deswelling behavior. After 1 min, the sample was removed from the hot water (35 °C) and its wet weight after blotting the excess water on the gel surface by a wet filter paper was recorded. The sample was then transferred to the DI water at 30 °C for swelling to occur for another 1 min, and weighted and recorded as mentioned above. These deswelling–swelling cycles were conducted for up to 12 min for determining the oscillating deswelling–swelling kinetics of the hydrogels.

Results and discussion

Fig. 1 illustrates the surface morphology of freeze dried, swollen VGel and NGel. It was found that the pore size of VGel is much bigger than that of the normal hydrogel,

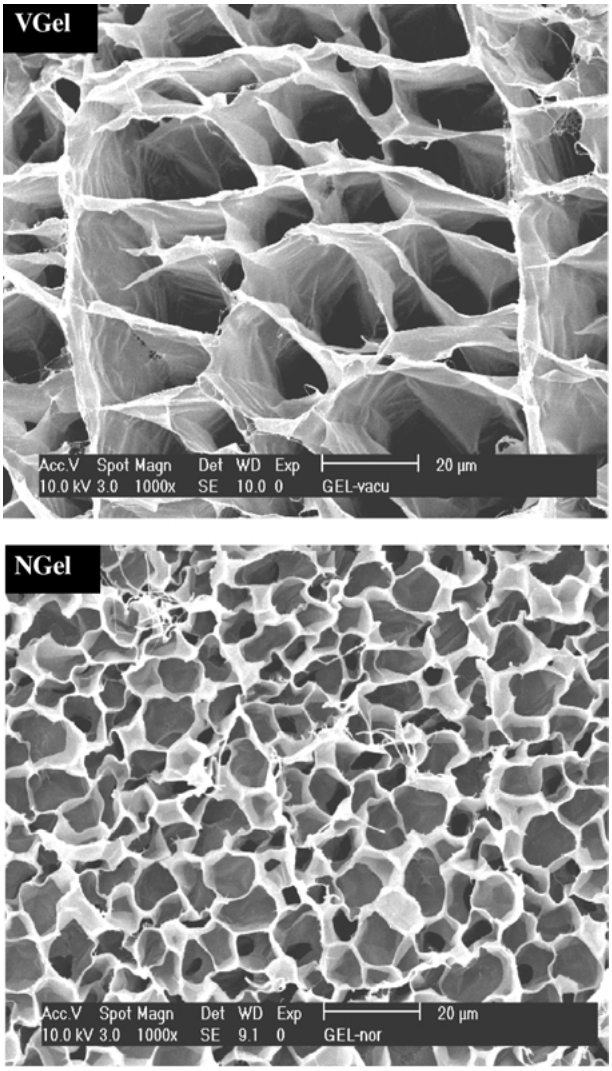

Figure 1 SEM micrographs of the normal (NGel) and macroporous (VGel) PNIPAAm hydrogels after reaching equilibrium swelling in water at room temperature.

which demonstrates that the vacuum-synthesis can enlarge the network of the hydrogel significantly. During the polymerization process in vacuum, the volume of the reactive system was enlarged due to the low pressure, and the resulting polymer chains were also expanded, which lead to the enlarged network of the hydrogel synthesized. On the other hand, because of the polarity of the monomer, the conformation of the synthesized polymer chains and their network was also changed accordingly when comparing with the hydrogel synthesized in the atmospheric pressure. For example, there exists a hydrophilic/hydrophobic balance in the PNIPAAm polymer chains, and there are many hydrogen bonds between the hydrophilic groups in the side chains of the PNIPAAm and water molecules [18–21]. Due to the fact that the nature of hydrogen bonds is anisotropic [22], the conformation of the resulting polymer chains in vacuum should be different from that synthesized in the atmospheric pressure. This effect is complicated and further investigations are needed. As we know that the hydrogel structure has the memorizing capability to its forming history and the molecular conformation [23–25]. So, the expanded network with a certain conformation would be kept after the polymerization.

Fig. 2 illustrates the effect of temperature (22–50 °C), particularly at the LCST, on the equilibrium–swelling ratio of both VGel and NGel. As the temperature increases, the swelling ratios of both hydrogels decrease. It is well known that the distinctive property of the PNIPAAm hydrogel is attributed to its unique alteration between hydrophilicity and hydrophobicity upon external temperature stimulation. At a temperature below its LCST, the hydrogen bonds in the PNIPAAm hydrogel act cooperatively to form a stable hydration shell around the hydrophobic groups, which leads to the high water-solubility characteristics of the PNIPAAm hydrogel. However, as the external temperature increases, the hydrogen bond interactions become weakened or destroyed, thus the hydrophobic interactions among the hydrophobic groups become stronger which subsequently induce the freeing of the entrapped water molecules from the hydrogel network. When the temperature reaches or is above the LCST, the hydrophobic interactions become fully dominant. Along with the water release, the polymer chains in the hydrogel collapse abruptly and the phase separation of the PNIPAAm hydrogel system occurs.

At the temperature below LCST, the equilibrium–swelling ratio of the macroporous VGel is much larger than that of the normal hydrogel NGel. This is because the macroporous PNIPAAm VGel provides greater space for water uptake. In addition, Fig. 2 indicates that the VGel has stronger temperature sensitivity due to its higher phase-separation-degree (i.e., the ratio of the changes of the swelling ratio (ΔSR) vs. temperature changes (ΔT) around the transition temperature, $\Delta SR/\Delta T$), and the volume changes of VGel are also much greater than that of NGel during the phase transition process.

The data in Fig. 2 also suggest that the LCST of VGel has no obvious shift from the LCST of NGel. This lack of shift in LCST due to different synthesis routes is further confirmed by the DSC data shown in Fig. 3. The temperature at the onset point of the DSC endotherm is generally referred as the LCST [26], and our DSC data show almost the same LCST between VGel and NGel at around 35 °C.

The rapid response of the VGel to temperature is also demonstrated in Fig. 4, in which the deswelling kinetics

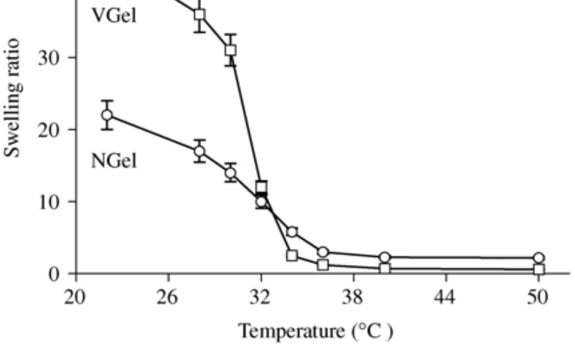

Figure 2 Temperature dependence of the equilibrium swelling ratio of the normal (NGel) and macroporous (VGel) PNIPAAm hydrogels over the temperature range from 22 – 50 °C.

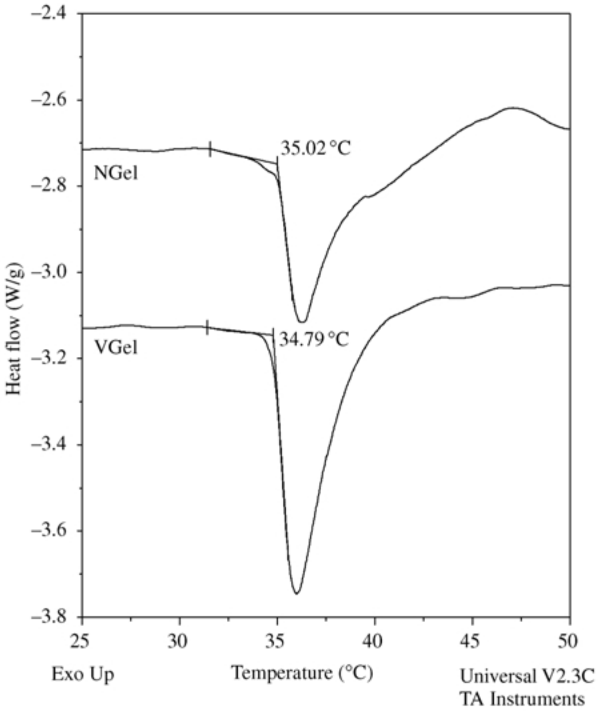

Figure 3 DSC thermograms of the normal (NGel) and macroporous (VGel) PNIPAAm hydrogels over the temperature range from 25 – 50 °C at a heating rate of 3 °C/min for determining lower critical solution temperature (LCST).

of both VGel and NGel at a temperature (50 °C) higher than their LCST are presented. It is clear that the macroporous hydrogel (VGel) can dramatically shrink, and rapidly reach its equilibrated water content and lose over 98% water within 5–7 min. But the dehydration rate of the normal hydrogel (NGel) is much slower than that of the macroporous hydrogel. All the hydrogels whether norm or vac type became opaque after placing into the hot water. However, there were no bubbles appeared on the surface of VGel hydrogel, whilst many bubbles were found on the NGel surface.

This observed difference in response to hot water between VGel and NGel could be explained as follows. During the shrinking process of these hydrogels, lots of freed water molecules appear and these water molecules had to diffuse out from the hydrogel network. The diffusion rate of water is controlled by the collective diffusion coefficient and hydrogel morphology. Due to the appearance of a collapsed dense skin layer [27, 28] of the normal hydrogel at the beginning of the shrinking process, the diffusion rate of water was greatly inhibited. The existence of this collapsed dense skin layer was responsible for the appearance of the surface bubbles during the shrinking process. The macroporous hydrogel (VGel), however, did not have surface bubble appearance as NGel did during the same shrinking process. This was attributed to the lack of formation of the collapsed dense skin layer in VGel. This is because the VGel had more even heat and mass transfer capability due to their enlarged macroporous network structures. Heat transfers from hot water to the innermost hydrogel matrix occurred rapidly, which resulted in a rapid but homogeneous phase separation throughout the matrix at almost the same time. In addition, this macroporous network can provide connected channels for the freed water molecules to diffuse out promptly. Thus, a large amount of the freed water could diffuse out quickly once the VGels were immersed in the hot water (50 °C).

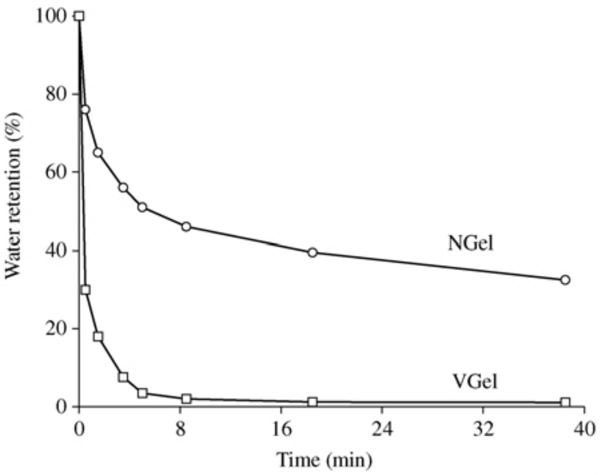

Figure 4 Deswelling kinetics of the normal (NGel) and macroporous (VGel) PNIPAAm hydrogels at 50 °C.

The kinetics of the temperature-dependent oscillatory swelling–deswelling properties of thermoresponsive hydrogels is important for determining the feasibility of this class of hydrogels in a variety of practical applications. Fig. 5 summarizes the kinetics of this macroporous hydrogel over the 1-min temperature cycles between 30 and 35 °C in DI water. Generally, the largest volume changes of the PNIPAAm hydrogel take place at around 32–33 °C; in this study, we chose 30 °C (2° below 32 °C) and 35 °C (2° above 33 °C) to compare the oscillatory swelling–deswelling dynamics of the normal and vacuum synthesized PNIPAAm hydrogels. The data in Fig. 5 show both VGel and NGel exhibited rapid and thermoreversible transparent–opaque changes once the temperature was cycled between 30 and 35 °C. At the

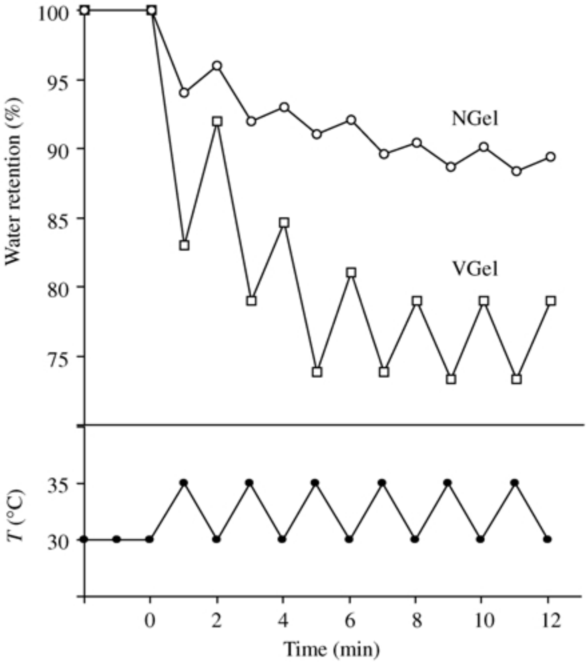

Figure 5 Oscillatory swelling–deswelling kinetics for normal (NGel) and macroporous (VGel) PNIPAAm hydrogels over the 1-min temperature cycles between 30 and 35 °C.

same time, we found both the swelling–deswelling cycles are accompanied by a slight decrease of the swelling ratio due to the relatively slower reswelling rate of the hydrogels when comparing with the deswelling rate [12]. However, it was clear that the VGel had more rapid and larger magnitude swelling–deswelling changes than the smaller swelling–reswelling kinetics of NGel. Although both VGel and NGel exhibited a continuous reduction in water retention upon temperature cycling, VGel showed stable dependence of water retention with time after the first three temperature cycles, while NGel shows a continuous but smaller reduction in water retention with time upon additional temperature cycles.

Conclusion

A novel macroporous PNIPAAm hydrogel was prepared by carrying out the polymerization in vacuum (-100 kPa) at room temperature (22 °C). The equilibrium swelling ratio was significantly increased when comparing with NGel at a temperature below the LCST, and the deswelling rate of VGel at hot DI water (50 °C) was also dramatically accelerated. Furthermore, this macroporous PNIPAAm hydrogel exhibited large magnitude of volume changes and reproducible oscillations as the external temperature cycled within a small temperature range in short time intervals. This macroporous PNIPAAm hydrogel accompanied with the above advantages would be more favorable for the applications in many fields including biomedical and biotechnology fields and we believe the results reported here represent an interesting contribution to the design of the smart hydrogel systems.

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