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Thermosensitive PNIPAAm cryogel with superfast and stable oscillatory properties

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Through copolymerization/crosslinking in dimethyl sulfoxide (DMSO) at temperature below the melting point of DMSO, we demonstrated a novel poly(*N*-isopropylacrylamide) (PNIPAAm) hydrogel with regularly oriented micromatrix; the superfast/stable oscillatory hydration–dehydration character of this hydrogel would find wide applications in biomedical field.

Poly(*N*-isopropylacrylamide) (PNIPAAm) hydrogel is the most widely studied thermosensitive hydrogel with a low critical solution temperature (LCST) at around 33 °C[1] due to its unique hydration/dehydration altering and PNIPAAm hydrogel has been widely used in the biomedical field.[2] Generally, the response rate of the conventional PNIPAAm hydrogel is not as fast as required in many applications, such as artificial organs,[2a] actuators,[3] on-off switches[4] and several approaches[5] were reported to attain the fast response rate of the intelligent biomaterials. Here, we demonstrated a novel PNIPAAm hydrogel with regularly oriented micromatrix by copolymerization/crosslinking in an organic solvent (DMSO) at a temperature below its melting point. This hydrogel exhibits superfast/stable oscillatory hydration-dehydration character, which would find wide applications in biomedical field.

PNIPAAm hydrogels were prepared by free radical-redox polymerization in anhydrous DMSO and the typical preparation process is described briefly: monomer *N*-isopropylacrylamide (NIPAAm, 0.5 g), crosslinker *N*,*N*′-methylenebisacrylamide (25 mg) and initiator ammonium persulfate (10 mg) were dissolved in certain volume of anhydrous DMSO (5 ml or 10 ml) at room temperature (22 °C) in a glass bottle of 25 mm in internal diameter and 45 mm in height. 100 µl *N*,*N*′-methylenebisacrylamide were subsequently added, and the reaction glass bottles were sealed and placed at 22 or 0.5 °C for carrying out the copolymerization/crosslinking reaction for 72 h. The PNIPAAm hydrogels prepared in the liquid DMSO solvent at 22 °C was designated as the conventional hydrogels, while the one formed at 0.5 °C was designated as the cryogel. Noted, since the melting point of DMSO is 18 °C, the polymerization at 0.5 °C was carried out in a solid shape, which needs the thawing at room temperature after the preparation. All the hydrogels were cut into disc-like pieces approximately 10 mm in diameter and 4 mm in thickness for the following studies. The preparation conditions and sample ID of hydrogels are summarized in Table 1.

Based on the experiments, if the NIPPAAm monomer concentration is at 5% or below, no hydrogel was formed with the polymerization temperature at room temperature. However, if the monomer concentration increased to10 %, the hydrogel was formed at room temperature. As the polymerization temperature decreased to 0.5 °C, PNIPAAm hydrogels were generated even when the NIPPAAm monomer concentration was decreased to 5% from 10% as revealed in Table 1. The data in Table 1 suggest that the formation of the PNIPAAm hydrogel depends on the polymerization temperature as well as the monomer concentration. A reduction in the polymerization temperature with an increase in the monomer concentration may facilitate the forming of the PNIPAAm hydrogel. On the other hand, from the conversion viewpoint of the synthesized hydrogel, it seems that an optimal condition for the formation of the PNIPAAm hydrogels in DMSO exists with regard to the monomer concentration and polymerization temperature. For example, the conversion of the $Gel_{0.5\ °C–10\%}$ (58.1%) is the highest among all the formed hydrogels.

The interior morphology of these hydrogel samples was studied by using a scanning electron microscope (Hitachi S4500 SEM, Mountain View, CA) and the morphologies were shown in Figure 1. The microstructure of the cryogels ($Gel_{0.5\ °C–5\%}$ and $Gel_{0.5\ °C–10\%}$) has some very unusual characteristics, which is distinctly different from the irregular matrix of conventional hydrogel ($Gel_{22\ °C–10\%}$). For example, all pores of $Gel_{0.5\ °C–5\%}$ appear very regular and oriented along a common direction that they look like an array of high porous filaments although this

Table 1 Formation of the PNIPAAm hydrogels prepared in DMSO

Sample ID[a]	Monomer concentration (%)[b]	Temperature (°C)	Appearance	Shape features	Conversion (%)[c]
$Gel_{22°C–5\%}$	5.0	22	/[d]	/	/
$Gel_{22°C–10\%}$	10.0	22	Translucent	Rather weak	28.6
$Gel_{0.5°C–5\%}$	5.0	0.5	Opaque	Weak	19.1
$Gel_{0.5°C–10\%}$	10.0	0.5	Opaque	Rigid	58.1

[a] All reactions were carried out for 72 h under the conditions indicated above in anhydrous DMSO; [b] Monomer weight (g)/solvent volume (ml); [c] Weight percentage of the formed hydrogel from the monomer. [d] Hydrogel did not form.

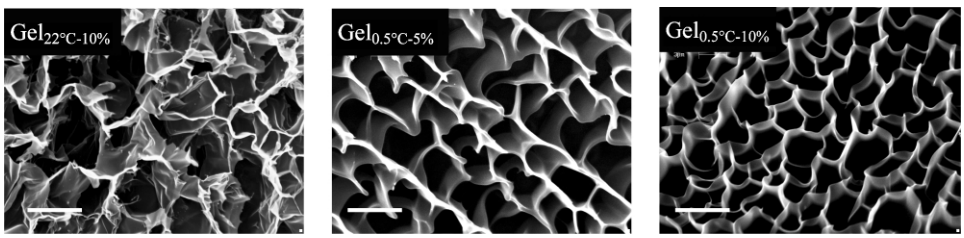

Fig. 1 SEM micrographs of the PNIPAAm hydrogels. Size of the bar is 6 µm.

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unique orientation observed in $Gel_{0.5\,°C–5\%}$ decreased in $Gel_{0.5\,°C–10\%}$ along with the reduction in the 3D depth of the pores as the polymer concentration increased to 10%. The unusually regular microstructure of cryogel was attributed to the pore-forming capability of DMSO crystals appearing during polymerization at a temperature below the DMSO melting point. Noted here, although the frozen monomer system at a temperature below the freezing point of a solvent appears homogeneous, it is composed of two phases, the solid phase and the unfrozen liquid phase dispersed within the solid phase.[6] During the polymerization of cryogel, the reaction was carried out in the liquid phase that was dispersed within the solid phase. The solid phase is composed of many DMSO crystals, which could act like the pore-forming agent during the polymerization. During thawing at room temperature after cryo-polymerization (*i.e.*, melting of DMSO crystals), many pores would be formed in the spaces that were originally occupied by DMSO. Due to the formation and orientation of DMSO solvent crystals, *i.e.*, more oriented, a regular micromatrix as observed in this cryogel would be achieved with a suitable monomer concentration and/or polymerization temperature. Thus, we suggest that the crystallization phenomenon of a solvent is the critical factor for determining the morphology of the cryogel formed below the melting temperature of the solvent.

Figure 2 shows the classical temperature dependent swelling ratios of the hydrogels over a temperature range from 22 to 50 °C, which covers the expected range of LCST of the PNIPAAm hydrogel. The swelling ratio was calculated as W_s/W_d, where W_s is the weight of water in the swollen hydrogel at each temperature (wet weight − dry weight) and W_d is the dry weight of hydrogel. The curves show that all the hydrogels exhibited the similar temperature-stimulant property, but the magnitudes of the thermo-induced swelling ratio changes of the cryogels were smaller than the conventional PNIPAAm hydrogel, which had the highest Δ swelling 57.2 (= $SR_{22\,°C} - SR_{50\,°C}$). Between the cryogels, the $Gel_{0.5°C–5\%}$ had the larger change in swelling ratio (Δ swelling 25.1) upon temperature-induced shrinkage than that of $Gel_{0.5°C–10\%}$ (Δ swelling 11.3). The possible reason for the relatively smaller magnitude of temperature-induced swelling ratio change of the cryogels than the conventional one appears to be related to the morphological difference. The oriented porous network structure along with the structured rigid cell wall observed in the cryogels may not be able to collapse as much as the morphology of conventional $Gel_{22\,°C–10\%}$ could upon heating, *i.e.*, smaller deswelling magnitude. While the smallest shrinking magnitude observed in $Gel_{0.5°C–10\%}$ sample appears to be attributed to its reduced 3D depth of the pores formed under the specified polymerization condition which, in turn, would reduce its shrinking magnitude upon heating.

The oscillatory hydration/dehydration kinetics of conventional $Gel_{22\,°C–10\%}$ and the typical cryogel $Gel_{0.5\,°C–5\%}$ over the 3 min temperature cycles between 26 (< LCST) and 37 °C (> LCST) in distilled water were presented in Figure 3. Water retention was defined as $[(W_t - W_d)/W_s] \times 100$, where W_t is the weight of the wet hydrogel at 37 °C and the other terms are the same as defined above. This 3 min cycle was continued for a total 6 cycles (36 min) in order to determine the oscillatory

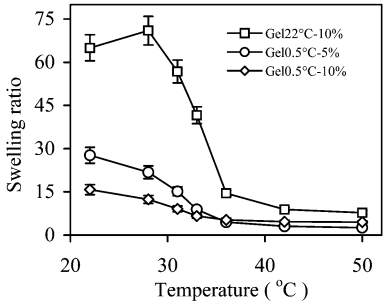

Fig. 2 Temperature dependence of swelling ratio of the PNIPAAm hydrogels in distilled water in the temperature range from 22 to 50 °C.

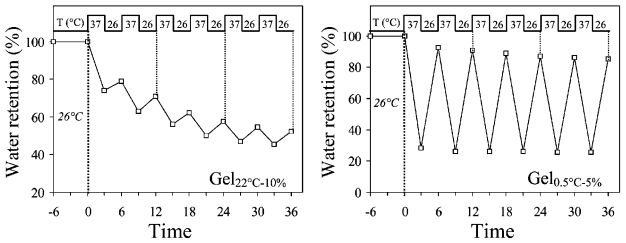

Fig. 3 Oscillatory shrinking–swelling kinetics for the PNIPAAm hydrogels over 3 min temperature cycles in distilled water between 26 and 37 °C.

hydration/dehydration kinetics of the hydrogel. It was found that, although both conventional hydrogel and the cryogel exhibited an oscillatory hydration/dehydration character upon cycling temperature between 26 and 37 °C, the cryogel exhibited much more rapid, sharp and larger magnitude hydration/dehydration changes than that from conventional hydrogel. For the conventional $Gel_{22°C–10\%}$, the shrinking and swelling cycles were accompanied by a consecutive reduction in water retention.[7] In addition, the magnitude of the oscillatory action of the conventional $Gel_{22°C–10\%}$ sample was also very small, which would damage its practical application in those areas that require a faster and larger magnitude response, such as on-off switches. As to the cryogel, the oscillatory property was significantly improved. There was nearly no loss of water retention throughout the whole 6 cycles and all the oscillatory hydration/dehydration cycles appeared identical to each other.

This very stable, rapid and larger magnitude of the oscillatory property of PNIPAAm cryogel was attributed to its special micromatrix. As discussed in the morphology above, the porous structure of the PNIPAAm cryogel was formed from the melting of the DMSO solvent crystals formed at a cryo-polymerization temperature. Under such a condition, solvent crystals would grow until they impinge each other, *i.e.*, all the solvent crystals would be connected and oriented along a specific direction. After thawing, these cavities left from the interconnected and oriented solvent crystals were also connected to each other. Therefore, the pores in the cryogel were also interconnected and oriented. During the hydration or dehydration process of cryogel, these oriented and interconnected pores with their very smooth wall interface would facilitate dramatically faster water diffusion.

In conclusion, we presented a strategy to prepare PNIPAAm cryogel with superfast, large magnitude and stable hydration/dehydration dynamic response to temperature cycling. These properties were attributed to the unique, oriented and regular porous network structure prepared during the copolymerization/crosslinking in DMSO at a cryo-temperature.

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