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Reinforcement of phenylalanine-based supramolecular hydrogels by hybridizing poly(*N*-isopropylacrylamide) nanogels

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In an aqueous solution of a L-phenylalanine derivative-based gelator, the addition of a proper amount of thermosensitive poly(N-isopropylacrylamide) nanogel particles leads to the formation of hybridized supramolecular hydrogels. Due to the presence of the nanogel particles, the gelation ability of the gelator can be improved as shown by the decrease of the critical gelation concentration (CGC) of the gelator from 2.5 wt% to 0.8 wt% when 1 wt% of nanogels were employed. Meanwhile, the thermostability of the hybridized system was also improved. For instance, the phase transition temperature (T_{GS}) increased from 48 ºC to 61 ºC. Rheological studies indicated that the supramolecular hydrogels can be significantly reinforced by hybridizing 0.6 wt% nanogels. When used as a drug carrier, the drug release behavior from the hybridized system can be controlled by changing the content of nanogels as well as the temperature.

Introduction

Based on the unique feature of thermal reversibility and environmental sensitivity, supramolecular hydrogels formed by self-assembly of low-molecular-weight gelators exhibit great potential applications, for example, in the fields of biomedicine, sensing and nano-materials. Thus, supramolecular hydrogels have received much attention in the last two decades.[1-5] Similar to conventional polymer hydrogels with three-dimensional (3D) network structures, supramolecular hydrogels also consist of 3D networks formed from the entangled, fiber-like aggregates of the gelator. However, the content of gelator in the resultant supramolecular hydrogels is rather low, even less than 0.5 wt% in certain systems.[6] In other words, supramolecular hydrogels consist of a large amount of water. Therefore, a serious disadvantage of supramolecular hydrogels is their poor mechanical strength, greatly limiting their application. How to improve the mechanical strength of supramolecular hydrogels has become a research focus.[7]

Since the driving force of gelator self-assembly is non-covalent interaction, such as hydrogen bonding, one of the strategies to improve the strength of supramolecular gels is to construct gelators possessing the ability to form multiple hydrogen bonds. For instance, the quadruple hydrogen bonds formed between pyrimidine and carboxylic acid derivatives provide an example. The resultant trapezoid and network structures possess relatively high strength and directionality.[7,8] The gelators based on organic dendrimers and dendrons[9] or nature's building blocks (α-amino acids)[10] were also employed to improve the strength of supramolecular gels. Similar to the reinforcement of polymers, some inorganic nano-materials, such as Au nanoparticles,[11] CdSe/ZnS quantum dots[12] and nanocarbons like graphene, carbon nanotubes and fullerene,[13,14] were added to supramolecular gels. The addition of these rigid nano-additives improved the mechanical strength of supramolecular gels to a certain extent, and also endowed the gels with some new attractive properties such as light, thermal and electrical sensitivity. However, there is a problem with the compatibility between rigid inorganic nano-materials and gel matrices. Other methods, involving the use of so-called dual network systems, have also been reported, namely some polymers like polysaccharides[15] or poly(acrylic acid)[16] were directly added into supramolecular gels. Although the interfacial compatibility between polymer chains and the gel matrix can be improved, the hybridized systems have a high viscosity in the sol state, leading to an inconvenient use.

We note that the above reinforcement strategies mainly focus on the supramolecular organogels.[12,13,17] Less attention has been paid to the reinforcement of supramolecular hydrogels.[15,16,18] Since supramolecular hydrogels have excellent biocompatibilities and potential applications, particularly for scaffolding materials of tissue engineering, the reinforcement

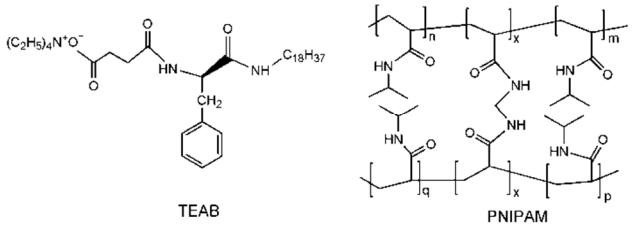
by supramolecular hydrogels appears to be more significant in comparison with supramolecular organogels.

In this work, we propose a novel strategy to reinforce the supramolecular hydrogels through a hybridization of poly(*N*-isopropylacrylamide) nanogels (denoted as PNIPAM nanogels). Herein, tetraethylammonium 3-{[(2R)-2-(octadecylamino)-3-phenylpropanoyl] amino}butyrate (denoted as TEAB)[19,20] was used as a hydrogelator. The supramolecular hydrogels based on α-amino acid derivatives possess the advantages of low toxicity and biodegradability. PNIPAM nanogels are a typical thermosensitive nanomaterials with good biocompatibility and have been extensively studied as biomaterials.[21-24] It is noteworthy that aqueous dispersions of PNIPAM nanogels show quite low viscosities[25] and reversible sol-gel phase transition temperatures near the human body temperature.[26] Therefore, PNIPAM nanogels can be used as injectable embolic materials [27] and as controlled drug-delivery carriers.[28] Based on both the rigidity of nanoparticles and the flexibility of the polymer, PNIPAM nanogels were used as reinforcement additives to improve the strength of supramolecular hydrogels.

Experimental section

Materials

Tetraethylammonium 3-{[(2R)-2-(octadecylamino)-3-phenyl propanoyl] amino} butyrate (TEAB) was synthesized according to the method described in our previous report.[19] The chemical structure of TEAB (Scheme 1) was further identified *via* their IR and ^{1}H NMR spectra. The melting point was 88~90 ºC. PNIPAM nanogels (Scheme 1) were prepared according to the method described in our previous report with *N,N′*-methylenediacrylamide as crosslinker at a concentration of 1 mol% to monomer NIPAM.[26,28] The obtained nanogel particles were dialyzed in ultra-pure water and subsequently lyophilized for further use. The hydrodynamic diameter of the PNIPAM nanogel was found to be ~230 nm at 25 ºC and ~50 nm at 35 ºC, measured by using dynamic light scattering (Nano-ZS 90, Malvern) equipped with a He-Ne laser (λ=633 nm). The polydispersity index of the size distribution was found to be ~0.06, i.e. close to monodispersity.[26] Salicylic acid (SA, AR, Sinopharm Chem. Reagent Co. Ltd) was used as a model drug.



Scheme 1. Chemical structures of TEAB and PNIPAM nanogels.

Preparation of nanogel-hybridized supramolecular hydrogels

A designed amount of lyophilized PNIPAM nanogel powder was dispersed in water with stirring overnight to obtain a transparent suspension for further use. A designed amount of TEAB was added into water and the mixture was stirred and heated in a water bath of 60 ºC until a transparent solution was obtained. Subsequently, a designed amount of the nanogel suspension was mixed with the TEAB aqueous solution. A series of the mixtures with varied concentration of nanogels and TEAB were sonicated for approximately 30 min in a water bath of 60 ºC to obtain uniform hybridized systems. The hot solutions were allowed to cool to room temperature to form a series of stable hybridized supramolecular hydrogels which exhibited no gravitational flow on inversion of the test tube. As reference, non-hybridized supramolecular hydrogels were prepared in the absence of nanogels. A required minimum concentration of TEAB for the formation of hydrogel is defined as the critical gelation concentration (CGC).[29] The temperature for the phase transition of the above system from gel to sol is defined as the gel-sol transition temperature (T_{GS}), which was determined in a water bath by the vial inverting method in the range of 10–80 ºC with a heating rate of 0.5 ºC/min and was also characterized by using differential scanning calorimetry (DSC, Q2000, TA) using a heating rate of 5 ºC/min.

Morphology of the supramolecular hydrogels

The morphologies of the resultant supramolecular hydrogels were characterized by using a field-emission scanning electron microscope (FE-SEM, Sirion 200, FEI). The samples were prepared by depositing a small amount of the heated solutions of TEAB with/without nanogels onto the pre-heated glass slides and allowing them to cool to room temperature. The obtained gel samples were freeze-dried (Freezone 6, Labconco) by liquid nitrogen and coated by gold. The accelerating voltage was 5 KV. Similarly, the gel samples without freeze-drying were used for atomic force microscopic measurements (AFM, SPI 3800, Seiko).

Rheological measurements

A strain-controlled rheometer (ARES 2000, TA) equipped with a parallel plate (Φ25 mm) was employed to measure the rheological behavior of the supramolecular hydrogels. The distance between the parallel plates was set at 1 mm. The heated solutions of TEAB with/without nanogels were spread on the measuring plate and sealed with silicon oil. In order to establish the linear viscoelastic region, the rheological parameters, elastic modulus G′ (also defined as storage modulus) and viscous modulus G″ (also defined as loss modulus) were measured as a function of stress (0–100 Pa) at an angular frequency of 1 Hz at 25 ºC. Subsequent measurements were conducted at a fixed stress (5 Pa) within the linear viscoelastic region. The rheological parameters were measured at a fixed frequency of 1 Hz and a fixed stress of 5 Pa in the temperature range of 10–80 ºC. The heating rate was 3 ºC/min.

Drug release from supramolecular hydrogels

The aqueous solution of salicylic acid (SA) with a concentration of 200 mg.L^{-1} was prepared and then used as solvent. In a colorimetric tube, a designed amount of TEAB and

PNIPAM nanogels were dissolved and dispersed in the aqueous solution of SA in a water bath of 60 ºC. The hot mixtures were allowed to cool to room temperature to form a series of stable hybridized supramolecular hydrogels with SA. Subsequently, 10 mL of DI water was added into the colorimetric tube as a release medium. At designed time intervals, 1 mL of the upper solution was removed for testing the amount of released SA. Simultaneously, 1 mL of fresh water was replenished into the tube. The sample solution was filtrated using a microporous membrane (0.45 μm) and then the absorbance at 296 nm was measured using a UV-vis spectrophotometer (UV-2600, Shimadzu). The accumulative release ratios were calculated from a standard absorbance curve. All experiments were performed in triplicate.

Results and discussion

The critical gelation concentration (CGC) is an important parameter to characterize the gelation ability of a gelator. According to our previous results,[18] the CGC of TEAB in water is approximately 2.5 wt%, i.e. one TEAB molecule can gelatinize approximately 200 water molecules. The transition temperature from gel to sol (T_{GS}) is approximately 48 ºC. Therefore, TEAB is a highly efficient hydrogelator for water. To further improve its gelling ability, we attempted to add PNIPAM nanogels into the aqueous solution of TEAB. Interestingly, the presence of the nanogels significantly affected the CGC of TEAB as shown in Table 1. The CGC of the TEAB decreased with an increase of the nanogel content. For example, the CGC was decreased from the initial 2.5 wt% to 0.8 wt% when 1 wt% of nanogels was added. We note that the added nanogels are in the state of a water-swollen equilibrium, rather than of xerogels. Therefore, the decrease of CGC cannot be attributed to the water absorption of xerogels. Because of the hydrophilicity of PNIPAM nanogels, we submit that it may be ascribed to the hydrogen-bonding interaction between amide groups of the nanogels and water molecules surrounding the nanogels. Although we do not give any experimental evidence about the hydrogen-bonding interaction, this speculation is based on the general theory of hydrogen-bonding formation. Similar result was also reported by N. C. Woodward et al. [30] In this case, the nanogels can "solidify" some water molecules. In other words, PNIPAM nanogels play a synergistic role together with TEAB for the gelation of water, resulting in decreased CGC of TEAB. This result is important for discussing the reinforcement of supramolecular hydrogels hereinafter.

Table 1. Effect of nanogel content in the hybridized systems on the CGC of TEAB

nanogel content (wt%)	0	1	2	3	4
CGC (wt%)	2.5	0.8	0.7	0.6	0.5

The above results indicate that the presence of nanogels is beneficial for decreasing the CGC of TEAB. However, it is unclear whether it also affects the stability of the supramolecular hydrogel. We note that the T_{GS} is usually measured to characterize the thermal stability and applicability of the supramolecular gels. In general, the T_{GS} of supramolecular hydrogels depends upon the concentration of gelator. Fig.1a shows that T_{GS} still increases with an increase of the TEAB concentration although the systems contain varied amounts of nanogels. For instance, the T_{GS} of supramolecular hydrogels formed by using 2.5 wt% of TEAB was found to be 48 ºC in the absence of nanogels. Yet, when the concentration of TEAB was 2 wt%, the T_{GS} of the system increases to 55~61 ºC in the presence of 1~3 wt% nanogels. This could be attributed to the hydrogen-bonding between nanogel particles and the surrounding water molecules as mentioned above. The synergistic effect of these non-covalent interactions and the self-assembly of TEAB promotes the gelation of hybridized system. It is notable that the addition of 3 wt% nanogels resulted in a decrease of T_{GS} in comparison with the addition of 2 wt% nanogels. This phenomenon may be ascribed to the fact that more nanogel particles interfere with the self-assembly of TEAB and the resultant 3D network structure formed by the TEAB fibers. It is well-known that this 3D network structure in supramolecular hydrogel plays an important role to support the stability of the gels. In order to further evaluate the effect of nanogels on the T_{GS}, as shown in Fig. 1b, the T_{GS} also exhibits a tendency to increase with an increase of the nanogel content in the case of a fixed concentration of TEAB. The result indicates that the presence of nanogels, for instance, 2 wt% of nanogels significantly improves thermal stability of the hydrogels.

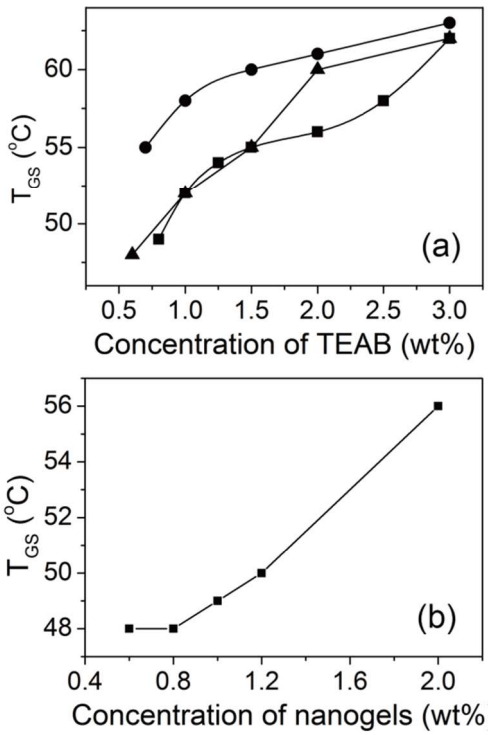


Fig. 1 (Plot a) Gel-sol phase transition temperature (T_{GS}) of hybridized hydrogels versus the concentration of TEAB in the presence of 1 wt% (▯), 2 wt% (●) and 3

wt% (■) of nanogels. (Plot b) T_{GS} of hybridized hydrogels versus the concentration of nanogels in a fixed concentration of TEAB (0.8 wt%).

To further investigate the thermodynamic behavior of the sol-gel phase transition, we measured the DSC thermograms of these hybridized systems. Fig. 2a shows the DSC thermogram of the supramolecular hydrogel formed by using only 3 wt% of TEAB. The endothermic peak at 70 ºC implies that the 3D network of the hydrogel collapsed and the gel became a sol at this temperature. Fig. 2b shows the DSC thermogram of the nanogel aqueous dispersion. The observed endothermic peak at 31.5 ºC is attributed to the volume phase transition temperature (VPTT) of PNIPAM nanogels because of their thermosensitivity.[24,31-33] When the temperature is below its VPTT, PNIPAM nanogel particles swell and absorb water. While the temperature is higher than its VPTT, the nanogel particles shrink and expel water. As shown in Fig. 2c, two endothermic peaks at 31.5 and 61.9 ºC were found in the DSC thermogram of the hybridized system composed of 3 wt% TEAB and 3 wt% nanogels. They can be attributed to the VPTT of the nanogels and the T_{GS} of the supramolecular hydrogel, respectively. In comparison with the system without nanogels, the presence of nanogels apparently resulted in a decrease of T_{GS} from 70 ºC to 61.9 ºC. This result is in accord with the discussion based on Fig.1, i.e., an excess of nanogels in the hybridized system is not beneficial to improve the thermal stability of the gels.

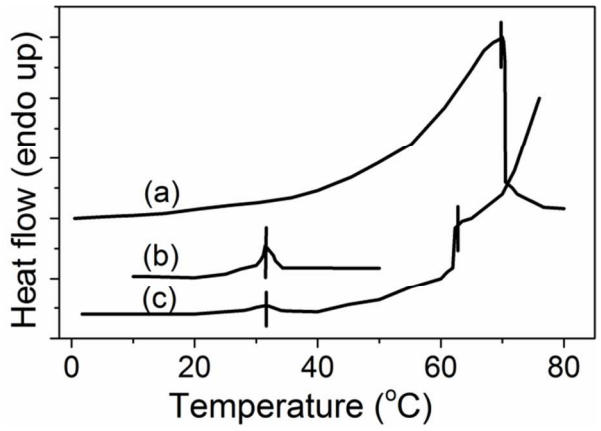


Fig. 2 DSC thermograms of the hydrogel formed by 3 wt% TEAB in water (a), 3% nanogel aqueous dispersion (b) and hybridized hydrogel formed by 3 wt% TEAB and 3 wt% nanogels (c).

Rheological techniques are usually used to characterize the phase transition and mechanical properties of complex systems. Fig. 3 shows the storage modulus (G', Fig. 3a) and loss modulus (G'', Fig. 3b) of the supramolecular hydrogels in the presence of a varied content of PNIPAM nanogels at temperatures ranging from 10 to 80 ºC. Except for the sample without nanogels, the G' and G'' of all other samples with nanogels show a turning points at about 32 ºC. This phenomenon can be attributed to the volume phase transition of PNIPAM nanogels. When the temperature is lower than the VPTT, G' and G'' show a tendency to decrease which may be ascribed to the cracks formed inside the hydrogel matrix because the swollen nanogel particles begin to shrink as mentioned above. With an increase of temperature, the mobility of the TEAB supramolecular fibers is also enhanced. This is beneficial to form a 3D network structure. In this case, G' and G'' were increased again. When the temperature was higher than ~60 ºC, both modulus show a significant decline. This temperature is the T_{GS} of the hybridized hydrogel, implying the collapse of the hydrogel matrix which is caused by the disassembly of TEAB aggregates. This result is in accord with the DSC discussion of Fig. 2.

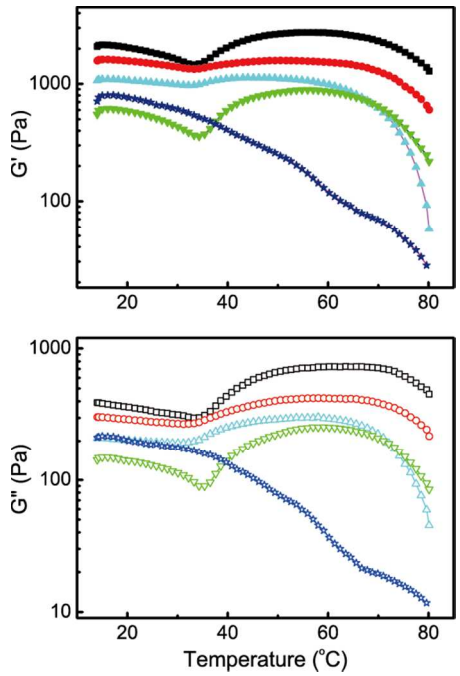


Fig. 3 Variation of G′ (filled symbols) and G″ (hollow symbols) as a function of temperature. Samples were prepared by using 2 wt% TEAB and 0.6 wt% (■, □), 1 wt% (●, ○), 2 wt% (▲,△) and 3 wt% (▼,▽) of PNIPAM nanogels, respectively. Samples were prepared by using 3 wt% TEAB only (★, ☆).

As a reference, both modulus of supramolecular hydrogels without nanogels show a continuous tendency to decrease with an increase of temperature. In addition, Fig. 3 also indicates that the G' and G'' of the hybridized systems are distinctly higher than that of supramolecular hydrogels without nanogels. The sample with 0.6 wt% nanogel shows the highest modulus. In other words, more nanogels (such as 3 wt%) do not increase the modulus of the system because excessive nanogels interfere with the self-assembly of TEAB, leading to a decrease of the gel strength. This conclusion is in accord with the discussion of the thermal stability of the hybridized hydrogels.

The mechanism of nanogels-reinforced supramolecular hydrogels can be also studied based on the microscopic structures of the hybridized systems. Fig. 4a–d show SEM images of xerogels obtained from a 2 wt% PNIPAM nanogel aqueous dispersion, the hydrogel formed by 3 wt% of TEAB only, the hybridized hydrogel formed by 3 wt% of TEAB and 0.5 wt% of nanogels and the hybridized hydrogel formed by 3

wt% TEAB and 3 wt% nanogels, respectively. Fig. 4e–f show AFM images of the corresponding samples. As shown in Fig. 4a and 4e, the size of the nanogel particles is quite uniform and the diameter was found to be ~100 nm. The supramolecular fibers formed by the self-assembly of TEAB and the resultant 3D network structure can be clearly observed in Fig. 4b and 4f. The size of the fibers was found to be 100~200 nm. By contrast, it was found that the supramolecular fibers in the hybridized systems become shorter and sparser depending upon the content of nanogels (Fig.4c, 4d, 4g and 4h). In general, the self-assembly behavior of the gelator in a solvent is similar to a crystallization process including a nucleation and a succeeding growth.[16,34-36] A certain amount of nanogel particles in the hybridized system may act as physical dopping reagent, providing additional supramolecular interactions between nanogel particles and gelator molecules. This physical dopping and supramolecular interaction plays an important role to improve strength of the hydrogels. However, excessive nanogel particles, like 3 wt%, may interfere the self-assembly of TEAB, resulting in the formation of shorter supramolecular fibers as shown in Fig.4d and 4h. In this case, the strength of the hydrogels cannot be improved. This result is in accord with the discussion of the rheological data.

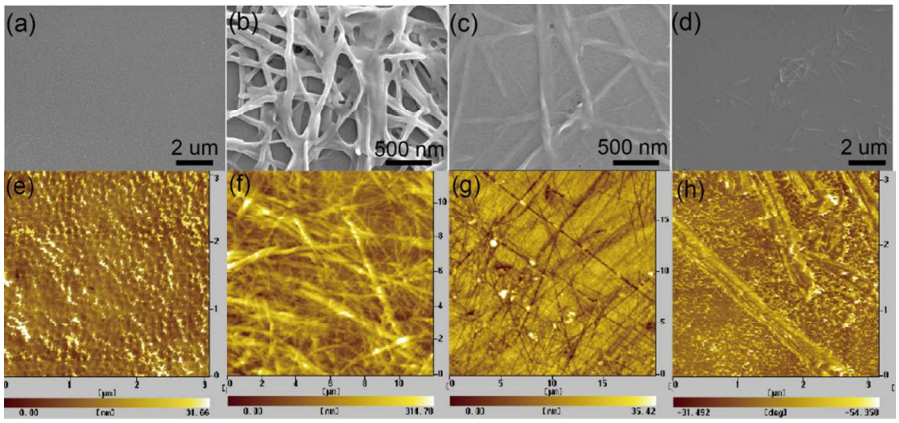
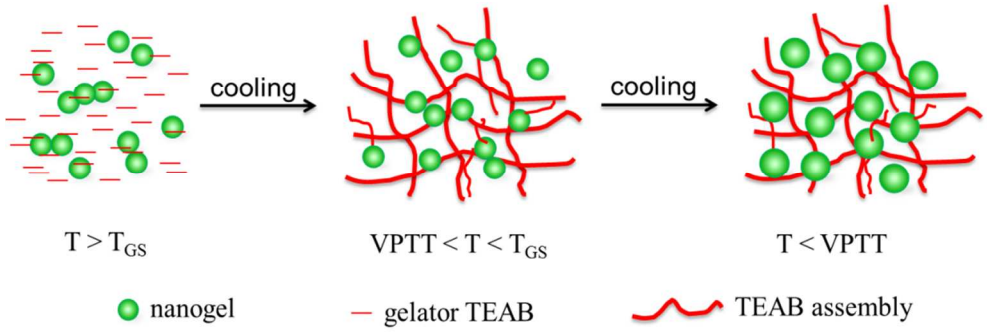


Fig. 4 (a–d) SEM images of 2% nanogel particles, supramolecular hydrogels formed by 3% TEAB only, hydrogels with 0.5 wt% of nanogels, and hydrogels with 3% nanogels, respectively. (e–h) AFM images of the corresponding samples.

Based on the above discussion, we suggest a reinforcement mechanism of supramolecular hydrogels by inducing nanogel particles as shown in Scheme 2. In the preparation of supramolecular hydrogels, TEAB is first dissolved in water at a temperature of 60~70 ºC, and then a specific amount of a PNIPAM nanogel aqueous dispersion is added. Here, PNIPAM nanogel particles are in the state of hard shrunk because the temperature is higher than the VPTT of PNIPAM. In this case, the hydrophobic groups on the surface of the nanogel particles may interact with the long hydrophobic chains of TEAB. With a decrease of temperature, TEAB molecules start to self-assemble into the supramolecular fibers in the presence of hard nanogel particles. When the temperature is lower than the VPTT (~32 ºC), the nanogel particles are transformed into the swollen state. When the temperature decreases to room temperature, TEAB ultimately self-assembles into a 3D network structure, resulting in the formation of stable hybridized hydrogels. Similar to the fillers-reinforced polymers, the swollen nanogel particles also act as fillers to reinforce the strength of supramolecular hydrogels. Generally, a serious problem with fillers-reinforced polymers is interfacial compatibility between inorganic fillers and the polymer matrix. We note that organic nanogels are essentially compatible with the supramolecular hydrogels. This may be one of the reasons why supramolecular hydrogels can be reinforced by nanogel particles.



Scheme 2. Schematic illustration of PNIPAM nanogel-hybridized supramolecular hydrogels formed by TEAB.

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In addition to play a role of reinforcement, PNIPAM nanogel particles themselves possess thermosensitivity. It suggests us to employ this feature to endow new functions of hybridized hydrogels. For example, we can use the hybridized hydrogels as drug-delivery carriers. For this purpose, salicylic acid (SA) was used as a model drug and loaded in the hybridized hydrogels. As shown in Fig. 5, the release rates of SA from the hybridized hydrogels are distinctly lower than that from the hydrogel without nanogels. Such low release rates may be due to the presence of nanogel particles, hindering the diffusion of SA inside the system. Furthermore, the PNIPAM nanogel particles are in the swollen state at 25 ºC (lower than its VPTT). Part of SA may be adsorbed within the swollen nanogels. In comparison with the SA directly released from the gel matrix, a part of SA take part in both diffusion from nanogel particles as well as from the matrix of supramolecular hydrogels. Therefore, the SA release behavior from the hybridized hydrogels is similar to a typical sustained-release. In addition, considering the temperature sensitivity of nanogels, we speculate that the SA release rate at the physiological temperature (37 ºC, higher than VPTT) may increase (data not show). This may be caused by the fact that the nanogel particles are in the shrunk state at 37 ºC. In this case, the SA encapsulated within the nanogels is quickly released together with expelling of water. Therefore, the drug release behavior can be modulated by altering the nanogel content in the hybridized system and the temperature-sensitivity of the nanogel itself.

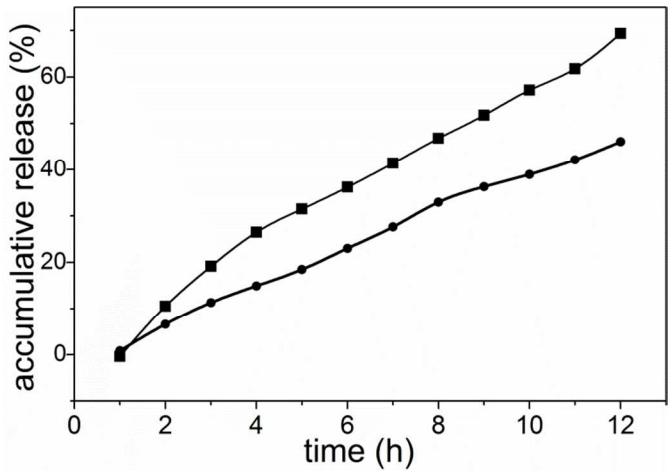

Fig. 5 Release profiles of SA from the supramolecular hydrogels without nanogels (■) and with nanogels (●) at 25 °C.

Conclusions

In this work, a new strategy to reinforce supramolecular hydrogels was proposed by inducing thermosensitive PNIPAM nanogels. The presence of nanogels can significantly improve the gelation ability of TEAB. Rheological studies indicate that the strength of the supramolecular hydrogel can be distinctly reinforced by adding a certain amount of nanogels. The resulting hybridized hydrogels can be used as a sustained-release drug carrier. The release behavior can be modulated by changing the nanogel content in the hybridized system as well as the thermosensitivity of the nanogel itself.

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