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Structure and properties of cellulose/poly(*N*-isopropylacrylamide) hydrogels prepared by SIPN strategy

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ABSTRACT

Semi-interpenetrating polymer network (SIPN) strategy was employed to fabricate a kind of novel hydrogels composed of cellulose and poly(*N*-isopropylacrylamide) (PNIPAAm) in the presence of *N*,*N*′-methylenebisacrylamide (MBAAm) as the crosslinker and benzoyl peroxide (BPO) as the initiator. The results from FTIR and TGA indicated that the network indeed existed in the SIPN hydrogels. The data from experiments, those related to the swelling behavior of the hydrogels at different temperatures in particular, demonstrated the thermal sensitivity of these hydrogels. The impact of crosslinker content on the hydrogel properties was discussed as well. The swelling ratio of hydrogels decreased with increasing the content of MBAAm. Besides, the loading and releasing behavior of the hydrogels were examined using dimethyl methylene blue as a model drug. These novel hydrogels combining the advantages of natural polymer with thermal responsive behavior are of great potential to be applied to drug delivery and control release systems.

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1. Introduction

Intelligent hydrogels, which can undergo a reversible and yet discontinuous volume phase change in responsive to various external physicochemical stimuli, have evoked extensive attention worldwide because of their potential for significant technological and biomedical applications (Bradley, Vincent, & Warren, 2006; Elizabeth, Serban, & Leonidas, 2004; Han, Sang, & Sun, 2005; Liu, Fan, & Wei, 2006). Recently, much attention has been paid especially to the stimuli-responsive composite gels based on natural polymer such as chitosan, alginate, cellulose and dextran (Mani & Joao, 2006).

Cellulose has been widely studied during the past decades due to its green feature and attractive properties such as nontoxicity, biodegradation, renewable capacity and thus acceptable from an environmental point of view. Cellulose-based intelligent hydrogels exhibit unique properties such as biocompatibility, biodegradability, and biological functions which could be widely used in biomedical applications including drug controlled delivery, bioengineering or tissue engineering (Gupta & Khandekar, 2003; Kubota & Shiobara, 1998; Marsano, Bianchi, & Viscardi, 2004)

Recently, numerous interpenetrating polymer network (IPN) hydrogels have been developed (Chang, Han, & Zhang, 2011; Kim & Park, 2004; Kumar, Somashekar, & Mahesh, 2007; Yin, Fei, Tang, & Yin, 2007). Due to the physical entanglement, IPN hydrogels have exhibited more favorable mechanical strength as compared with the individual cross-linked network. In the context of cellulose based hydrogels, IPNs can be divided into two types: sequential IPN and semi-IPN. For sequential IPN, cellulose is used as the first network and the second network is formed by polymerizing other monomers in the presence of the cellulose network. But for semi-IPN, the cellulose is linear or branched and can copolymerize with other monomers in a cross-link network (Chang & Zhang, 2011). It is well known that poly(*N*-isopropylacrylamide) (PNIPAAm) is one of the most widely explored polymers for preparing temperature responsive hydrogels. PNIPAAm hydrogels in aqueous system undergo a reversible hydrophilic–hydrophobic phase transition around its lower critical solution temperature (LCST) of 32 °C, below which PNIPAAm hydrogel is in highly water swollen state. While the external temperature is above the LCST, the hydrogel collapses and expels most of the contained water (Chang, Dolbow, & Zauscher, 2007).

There are few reports about the SIPN cellulose based hydrogels, and even fewer literatures on the thermal sensitive cellulose-based SIPN hydrogels except for the work done by Williamson et al. on preparing semi-IPN hydrogel composed of cellulose and poly(*N*,*N*-dimethylacrylamide) in LiCl/*N*,*N*-dimethylacetamide (DMAc) (Williamson, Armentrout, & Porter, 1998). This literally

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Table 1
Feed compositions of SIPN hydrogels.

Sample	Cellulose (g)	NIPAAm (g)	MBAAm (g)	Cellulose:(PNIPAAm + PMBAAm)
GEL1	1	10	1	1:1.4
GEL2	1	10	2	1:2.4
GEL3	1	10	4	1:5.5
GEL4	1	10	5	1:7.4

Note: The dosage of the cellulose and NIPAAm in all samples was 1 g and 10 g, respectively.

stimulates our interest in exploring the novel hydrogels from such a system.

In this work, the cellulose-based thermal sensitive hydrogels were synthesized by SIPN strategy. The chemical structure, thermal performance and morphology of the SIPN hydrogels were characterized by FT-IR, TGA and scanning electron microscope (SEM). Their swelling properties were measured by gravimetric method. Moreover, the influence of the cross-linker content on the properties of SIPN hydrogels was also discussed. The key objective of this work was to find the potential application of SIPN hydrogels to drug delivery and control release systems.

2. Experimental

2.1. Materials

Microcrystalline cellulose (MCC) (CAS# 9004-34-6) was purchased from EHEY Co. Ltd., China. *N*-isopropylacrylamide and *N*,*N*′-methylenebisacrylamide were the products of Aladdin Reagent Co. Ltd., Shanghai, China. The other chemicals were all of reagent grade and used as received.

2.2. Preparation of the SIP hydrogels

Firstly, the cellulose in LiCl/DMAc solution at 3 wt% was prepared according to the method reported by Tosh, Chowdhury, and Narendra (2000). Then, the determined amounts of NIPAAm, MBAAm and BPO were added to the cellulose solution in the tube (diameters of 35 mm), respectively. The mixture was stirred extensively at the ambient temperature until it turned to be transparent. After being purged with N_2 for 10 min, the tube was sealed and placed in an oven at 90 °C for 24 h. At last, the gel was immersed in DMAc for 5 days and then in deionized water for another 5 days to remove unreacted reagents. The formulations for preparing SIPN hydrogels, labeled as GEL1, GEL2, GEL3 and GEL4, are listed in Table 1. The calculated weight ratios of the cellulose to monomers in the resulting dry samples ranged from 1:1.4 to 1:7.4, depending on the amount of the cross-linking agent used.

2.3. Characterization

The freeze-dried hydrogels were ground into powder and mixed with KBr for FTIR investigation in the region of 400–4000 cm^{-1}.

Thermogravimetric analyses (TGAs) of cellulose, PNIPAAm and SIPN hydrogels were performed on a TA Instruments Q500 using approximately 5–10 mg of sample under nitrogen at a heating rate of 20 °C min^{-1} from the ambient temperature to 650 °C.

Scanning electron micrograph (SEM) observation was carried out on a EVO18 microscope (ZEISS, German). The hydrogel samples were frozen in liquid nitrogen and fractured immediately, and then a thin film of gold was sprayed on their surface. The internal structure of the samples was observed under 10 kV accelerating voltage.

2.4. Swelling measurements

A gravimetric method was employed to measure the swelling ratios of the hydrogels in distilled water at different temperatures ranging from 15 to 45 °C. After the immersion of the dried hydrogels in distilled water at each predetermined temperature for about 24 h until the swelling equilibrium was reached; then the hydrogel samples were taken out and weighed after removing the excess water on the surfaces with filter paper. Each sample was measured three times, and the average value of three measurements was taken. The equilibrium swelling ratio (SR) was calculated as follows:

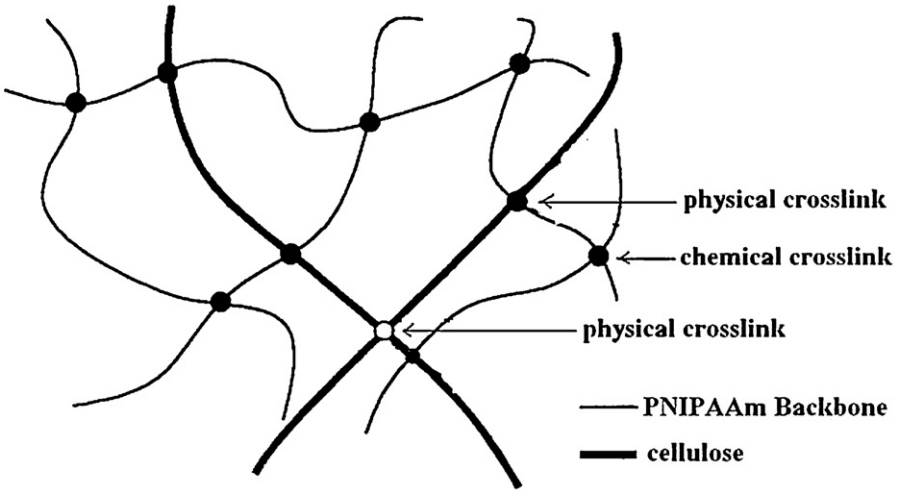

Fig. 1. The proposed structure model of the SIPN hydrogel.

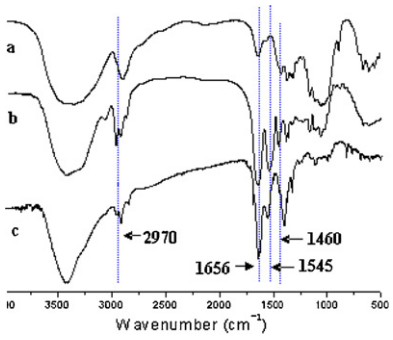

Fig. 2. FTIR spectra of cellulose (a), SIPN hydrogel (b) and NIPAAm (c).

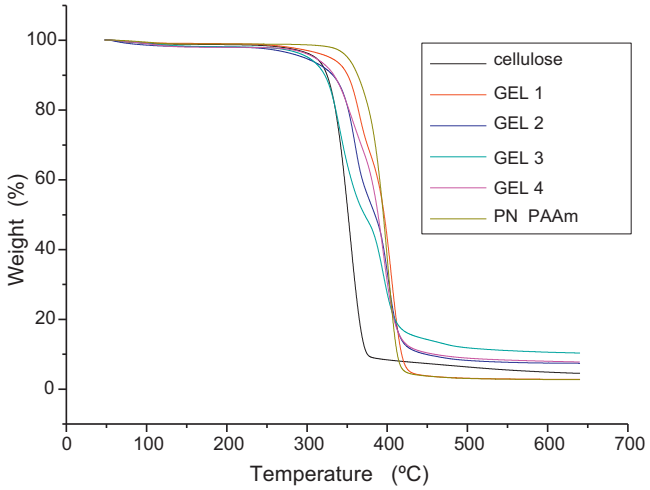

Fig. 3. TG spectra of the cellulose, SIPN hydrogels and PNIPAAm.

$SR = W_s/W_d$, where W_s is the weight of the equilibrium swollen hydrogel and W_d is the weight of the gel at the dry state.

The deswelling kinetics of the equilibrated swollen hydrogel at 45 °C (above the LCST of PNIPAAm) was measured gravimetrically in distilled water. At the predetermined time intervals, the samples were taken out from the hot water and weighed after the water on their surface was wiped with wet filter paper. The water retention of the deswelling gel was defined as follows:

$DR = [(W_t - W_d)/W_s] \times 100$, where W_t is the mass of sample at time t at 45 °C, W_s is the mass of the water content at room temperature, and W_d is the weight of dry gel sample.

The reswelling kinetics was measured gravimetrically at 15 °C in distilled water. The vacuum dried samples were immersed in water and then taken out at the determined time interval. They were weighed after removing the excess water on the surface with wet filter paper. The experiments were performed in duplicate. The water retention of the reswelling samples was defined as follows:

$RR = [(W_t - W_d)/W_s] \times 100$, where W_t is the mass of the equilibrated sample at time t at 15 °C, the other symbols are the same as defined above.

2.5. Drug loading and release

The drug loading and release property were evaluated using dimethyl methylene blue (DMB) as a model drug. The concentrations of DMB solutions were determined from the absorbance at 664 nm using a UV–vis (DU-7HS, Beckman, America) spectrophotometer.

The weighted dry hydrogel was swollen firstly in distilled water at 20 °C for 24 h, then the equilibrated swollen hydrogel was immersed in the 20 mg/L DMB solution at 20 °C for 24 h, the loading of DMB was calculated as follows:

$L_{DMB} = (C_0 - C_e) \times V/m$, where C_0 is the initial concentration of DMB solution; C_e is the remnants concentration of DMB solution; V is the initial volume of DMB solution (40 mL); and m is the weight of dry hydrogel.

The equilibrated DMB-loaded hydrogel performed at 20 °C was transferred into the distilled water at 50 °C (above LCST), and the concentration of DMB released in water was estimated at different time, t. The cumulative release was defined as follows:

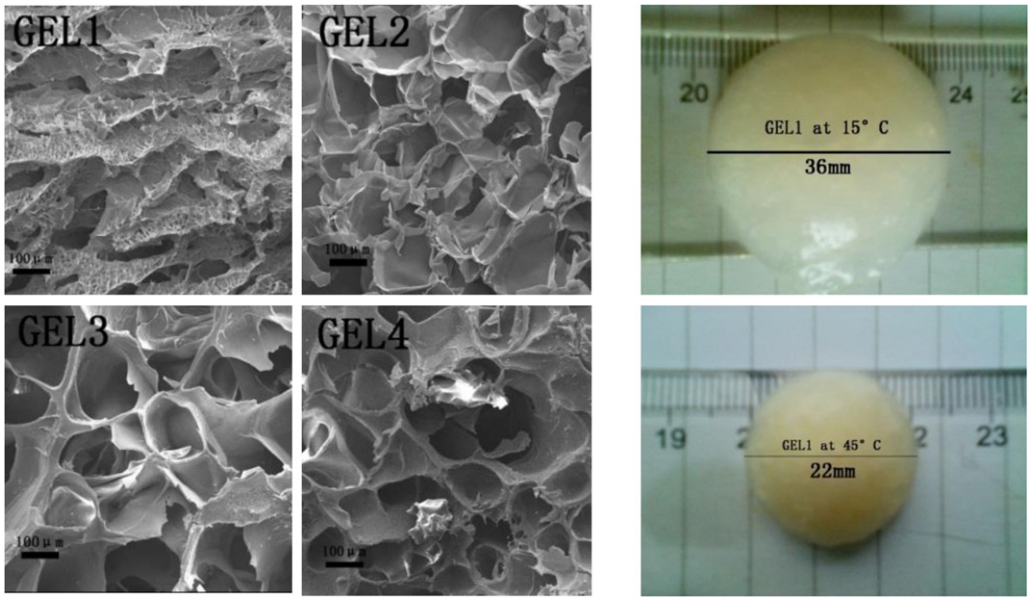

Fig. 4. SEM images of SIPN hydrogels (GEL1–4), the bars are 100 μm; optical images of GEL1 at 15 °C and 45 °C.

CR = M_t/M_0, where M_t is the mass of DMB released in water at time t; M_0 is the equilibrated loading mass of DMB in the tested hydrogel.

3. Results and discussion

3.1. Preparation and structure of SIPN hydrogels

In the late 1970s and early 1980s, it was reported that LiCl/DMAc could serve as a good solvent for cellulose, allowing a variety of the modification or derivative reactions to be conducted under homogeneous conditions (McCormick, Callais, & Hutchison, 1985). It was reported that the persistence length of cellulose was 252×10^{-8} cm in LiCl/DMAc solution, which is larger than that reported in other solvent systems. Williamson et al. approved that in the SIPN composites, cellulose acted as a fully extended, rigid rod polymer, which also has the capability to form hydrogen bond with other cellulose polymer chains and the DMAm matrix (Williamson et al., 1998). In this research, the same system was adopted but the NIPAAm substitute of DMAm to create the thermal-responsive hydrogels. Therefore, it might be deduced that the proposed structure of the SIPN hydrogel (Fig. 1).

The FTIR spectra of the SIPN hydrogel (Fig. 2b) prepared in this work, the cellulose (Fig. 2a) and NIPAAm (Fig. 2c) are shown in Fig. 2. A sharp absorption peak at 3420 cm^{-1} was assigned to —OH groups stretching vibration of cellulose in the cellulose and SIPN hydrogel. The absorption peak at 2970 cm^{-1} and 1460 cm^{-1} could be attributed to the asymmetric stretching vibration and asymmetric deformation of the $-CH_3$ groups, respectively (Liang, Rieke, Liu, & Fryxell, 2000). The typical amide I and II bands of NIPAAm at 1656 cm^{-1} and 1545 cm^{-1} could be observed in the spectrum of SIPN hydrogel. The results of FTIR indicated that the SIPN hydrogels composed with cellulose and PNIPAAm were synthesized successfully.

Thermal stability is very important for polymer materials. To investigate the intermolecular interaction within the SIPNs, the degradation properties were investigated as a function of weight percent for different types of polymer. The results (Fig. 3) from TGA revealed that the degradation of SIPN hydrogels occurred in one stage over a temperature range between cellulose (350 °C) and PNIPAAm (400 °C). This suggests strong intermolecular interaction between the NIPAAm matrix and the linear cellulose. If there were no intermolecular interaction, the resulting degradation profile would be expected to occur in two stages.

The SEM images of the gels with different contents of the crosslinker are shown in Fig. 4. It can be seen that all the hydrogel samples exhibited three-dimensional network structures. From GEL1 to GEL4, the pore size of the hydrogel was decreased and the thickness of the pore wall was increased, which might be attributed to the increase of the dosage of the cross-linker MBAm. Interestingly, a number of smaller pores were observed on the walls of macropores in GEL1, which could be caused by the low crosslinking density and incomplete coherence of the three-dimensional structure of GEL1.

3.2. Swelling properties of SIPN hydrogels

Equilibrium swelling ratios of SIPN hydrogels at various temperatures are presented in Fig. 5a. The results indicated that all the hydrogels showed a certain degree of the thermo-responsive profiles. For GEL1, there is a sharp transition of swelling ratio from 20.5 to 2.4 while the external temperature was increased from 15 °C (below the LCST) to 45 °C (above LCST). For GEL2, the swelling ratio decreased from 15.8 to 4.0 in the same external temperature range. However, the change of the swelling ratio for

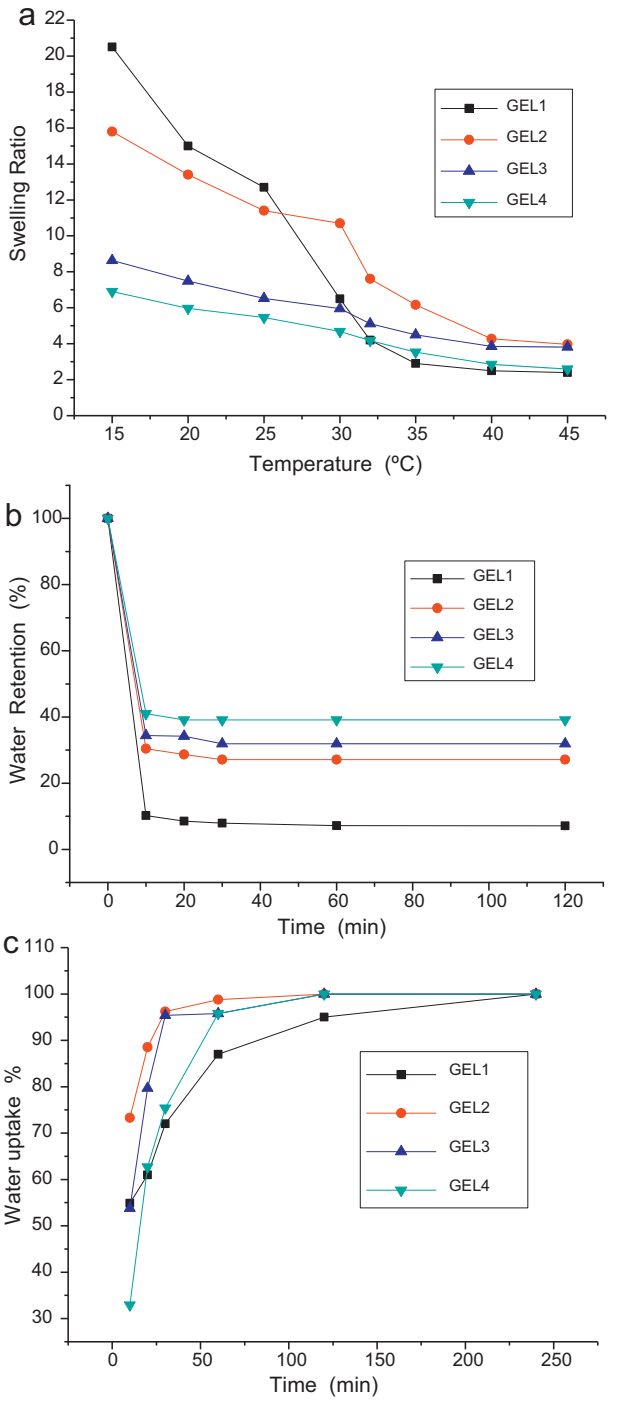

Fig. 5. Swelling properties of SIPN hydrogels. (a) Swelling ratio of hydrogels at different temperature. (b) Deswelling kinetics of hydrogels. (c) Reswelling kinetics of hydrogels.

samples GEL3 and GEL4 is less significant than those of the former ones; and the highest swelling ratio are 8.6 and 6.9 and the lowest are 3.8 and 2.6, respectively. The different thermo-responsive behavior of the gels may be attributed to the different interior morphology of the hydrogels and the degree of crosslinking at the same content of cellulose and NIPAAm. As mentioned earlier, the ratio of (PNIPAAm + PMBAm) to cellulose was increased from 1.4 to 7.4 for GEL1–4. It is well known that hydrophilicity of cellulose was higher than PNIPAAm. The average pore sizes of gels were also decreased from GEL1 to GEL4. Therefore, the corresponding water retention capacities of the hydrogels were decreased,

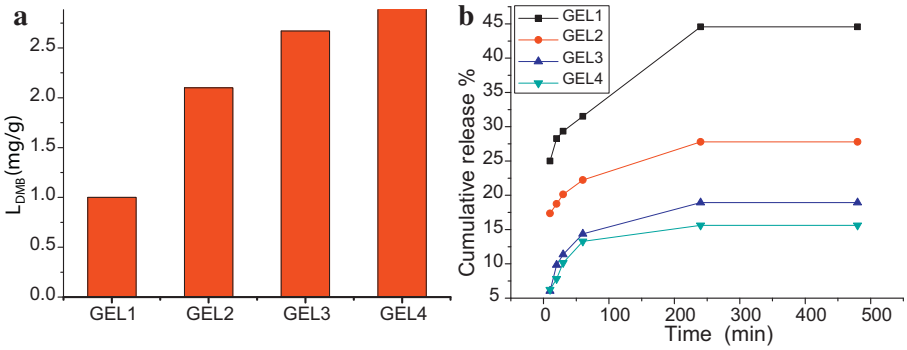

Fig. 6. Drug loading and release of SIPN hydrogels. (a) The equilibrated loading of DMB in hydrogels. (b) The cumulative release of DMB in the hydrogels.

resulting in the decreasing swelling ratio from GEL1 to GEL4. Theoretically, the higher content of PNIPAAm in gel, the better thermo-responsivity of gel. The crosslinking density of the SIPN gels is increased with the increase of MBAm content, so that the thermo-responsivity is lowered from GEL1 to GEL4. To visualize such effect, the optical images of GEL1 swollen at 15 °C and 45 °C are shown in Fig. 4. The obvious size change of GEL1 at different temperature (below or above LCST) further demonstrated that the SIPN hydrogel was thermo-responsive.

In practical applications, the temperature responsive kinetics or deswelling kinetics upon the external temperature is critically important. The deswelling kinetics of the hydrogels was investigated by transferring the equilibrated swollen samples at 20 °C (below LCST) to hot water at 45 °C (above LCST) and the results are illustrated in Fig. 5b. It was found that all hydrogels tended to shrink immediately once they were immersed into hot water at 45 °C. After 10 min, the most amount of the absorbed water in the hydrogels have been expelled, the highest amount is 90% for GEL1 and 69.6%, 65.6%, 59% for GEL2, GEL3, GEL4, respectively. The different shrinking kinetics of the hydrogels can be attributed to the different crosslinking density of hydrogels.

Fig. 5c demonstrated the reswelling behaviors of the hydrogels. From the figure, it can be seen that the reswelling rates of GEL1–4 are 54%, 73%, 53% and 33% at the same time (10 min); and all hydrogels could reach the equilibrium after 2 h, which is attributed to the high hydrophilic of SIPN hydrogels. Meanwhile, the reswelling rates of hydrogels were decreased with the increasing of cross-linker dosage. However, the GEL1 is exceptional, which might be due to fact that there are a number of small pores on the wall of the gel, as revealed by SEM observation. Such small pores potentially influence the reswelling behavior of hydrogel.

3.3. Drug loading and release

The porous structure and thermo-responsivity of the SIPN hydrogels enable them to be used as carriers for controlled drug loading and release. Using DMB as a model drug, the equilibrated loading and cumulative release of DMB in the hydrogels were measured; and the results are shown in Fig. 6.

As can be seen from Fig. 6a and b, the equilibrated loading of DMB was increased as the increasing of monomer/cellulose ratios (i.e., from GEL1 to GEL4), but the cumulative release decreased correspondingly. Such behaviors might be attributed to the difference of the PNIPAAm content in SIPN hydrogels. The interaction between DMB and PNIPAAm is stronger than that between DMB and cellulose, which allows more DMB to be included. However, the strong interaction also retards the release of DMB.

4. Conclusion

Novel hydrogels consisting of cellulose and PNIPAAm were prepared according to the SIPN strategy. The resulting SIPN hydrogels exhibited three-dimensional network structure and favorable thermosensitivity. With the increasing of cross-linker dosage, the deswelling and reswelling of hydrogels were decreased dynamically, which implied that it could be possible to control the deswelling and reswelling behavior of hydrogels by varying the dosage of cross-linker. Besides, it is found that the equilibrated loading of DMB was increased as the increasing of monomer/cellulose ratios (i.e., from GEL1 to GEL4), but the cumulative release decreased correspondingly.

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