Temperature/pH Sensitive Cellulose-based Hydrogel: Synthesis, Characterization, Loading, and Release of Model Drugs for Potential Oral Drug Delivery

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Due to their unique physical and chemical properties, hygrogels have been applied in various industrial and agricultural fields. Biomedicine is another high value-added and attractive area for the application of hydrogels. For this reason, a novel temperature/pH sensitive cellulose based hydrogel was synthesized based on the cellulose from *Phyllostachys heterocycla*. Its synthesis conditions were optimized, and its loading and release capabilities for model drugs were investigated in detail. The resultant data showed that the synthesized hydrogel exhibited the highest swelling ratio at 37 °C and pH 7.4, corresponding to the temperature and pH of the human intestinal environment. The hydrogel held excellent load performance for model drug MB and an obvious temperature dependence at 37 °C (body temperature of human) when the model drug was released from it. These positive results suggest that the synthesized temperature/pH sensitive cellulose-based hydrogel has a great potential for oral drug delivery applications.

Keywords: Cellulose; Hygrogel; Temperature/pH sensitive; Oral drug delivery; Phyllostachys heterocycla

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INTRODUCTION

Hydrogels, with three-dimensional crosslinked polymeric structure, are capable of absorbing and holding amounts of liquids tens to thousands of times their own weights due to physical and/or chemical interactions (Anirudhan *et al*. 2011; Wu *et al*. 2012). Based on these important advantages, they are used in various fields such as sanitary products (sanitary napkin and disposable diaper) (Kosemund *et al*. 2009), environmental protection (Shukla *et al*. 2012), agriculture and horticulture (Liang *et al*. 2013; Zhang *et al*. 2013), bioengineering (Lin *et al*. 2013) and biomedicine (Ma *et al*. 2009; Wu *et al*. 2008). As a high value-added industry, biomedicine is attracting more and more attention and opening up a new field of application for hydrogels.

At present, most of the hydrogel products are synthetic polymers constructed by the monomers from petrochemical processes, such as acrylic acid (AA) and acrylamide (AM). These monomers are costly, poorly biodegradable, and environmentally unfriendly (Zohuriaan-Mehr and Kabiri 2008; Wang and Wang 2010). With the increasing development of hydrogel production and consumption, the source of raw materials and waste treatment become two troublesome problems due to the non-renewability and poor

biodegradability of traditional hydrogels (Wang and Wang 2010). Rich source of raw materials and biodegradability of products are primary motivations for current studies on hydrogels (Dong *et al*. 2008; Hubbe *et al*. 2013).

Hydrogels based on natural polymers, *e.g*., cellulose, starch, chitosan, and alginate are currently of great interest due to their unique advantages of abundant sources, nontoxicity, excellent biocompatibility, and biodegrability (Peng and Chen 2010). The utilization of natural polymers for hydrogel synthesis is expected to effectively solve resource and environmental issues (Liang *et al*. 2009). Cellulose is recognized as the most abundant organic natural polymer in the world. As a renewable material, its outstanding physicochemical properties and wide applications have attracted significant interests from both research scientists and industry in recent years (Tehrani and Neysi 2013). *Phyllostachys heterocycla* is classified as long-fibered fibrous material. With the advantages of short growth period, suitable fiber morphology, and similar chemical composition to that of softwood, it is used as feedstock for many cellulose based products such as cellulose esters, cellulose ethers, paper, and textile fibers (Ma *et al*. 2014).

At present, hydrogels have been used to deliver various therapeutics such as enzyme, antibacterial, antibody, vaccine, contraceptive, and hormone (Xu *et al.* 2014). But oral drug delivery always faces challenges due to the location of drug release. Many oral drugs are easily digested, destroyed, or inactivated in the acidic environment when they go through the stomach (pH close to 1.4). As a result, the active ingredients in drugs cannot be absorbed effectively by the human body. Oral drugs are expected to be released in the intestine, in which the pH and temperature are close to 7.4 and 37 °C, respectively. The resistance to an acidic environment is necessary for oral drug deliveries.

Our attention in this work is directed towards synthesizing a temperature/pH sensitive hydrogel based on the cellulose from *P. heterocycla* for potential oral drug delivery applications. The synthesis conditions and swelling, temperature/pH sensitivity properties of the obtained hydrogel were investigated. The load and release behaviors of the hydrogel product for two kinds of model drugs (methylene blue, MB and methyl orange, MO) were evaluated especially.

EXPERIMENTAL

Materials

Bamboo pulp, derived from *P. heterocycla*, was provided by the Guizhou Chitianhua Paper Industry Co., LTD., China. The cellulose content was tested as 91.3% using the Kurschner-Hoffer cellulose method. Analytical grades of Urea, NaOH, ethanol, N,N-methylenebisacrylamide (MBA), acrylamide (AM), N-isopropylacrylamide (NIPPAm), methylene blue (MB), and methyl orange (MO) dyes were purchased from the Hangzhou Mike Chemical Agents Company, China. AA (analytical grade; Aladdin Chemistry Co. Ltd., China) was distilled under reduced pressure. Ammonium persulfate (APS, analytical grade; Aladdin Chemistry Co. Ltd., China) was recrystallized from water. Deionized water obtained from a Millipore Direct-Q 5 ultrapure water system was used throughout the experiments.

Dissolving of Bamboo Pulp Cellulose

Bamboo pulp were cut up, crushed, and screened to collect the particles between 80 and 100 mesh (0.15 to 0.25 mm). 2 ± 0.0001 g of the bamboo pulp particles were

poured into a 500 mL three-neck flask and then combined with 66 mL 7 wt% NaOH-12 wt% urea mixed solution which was pre-cooled to -20 °C. The mixture was stirred for 5 min to make the particles become dispersed adequately in the solution. The mixed solution was cooled at -60 °C for 2 h and then stirred for 5 min to obtain a transparent and ropy cellulose solution.

Synthesis of Hydrogel

The obtained cellulose solution was transferred to a thermostatic water bath equipped with magnetic stirrer, reflux condenser, and nitrogen line. The reactor was immersed in the water bath preset at 60 °C. Oxygen-free nitrogen gas was bubbled into the solution for 30 min before adding initiator. A certain amount of APS (initiator) was added. After 10 min of stirring, solutions containing specified amounts of AA (70% neutralization degree), AM, MBA, and NIPPAm were successively added to the reaction system. The whole volume of solution was controlled at 90 mL. After 2 h, the hydrogel was obtained, washed to neutral with deionized water and soaked in 500 mL absolute ethanol for dehydration. After standing for 12 h at room temperature, the hydrogel was cut into small pieces, frozen in cryogenic refrigerator at -80 °C for 12 h, and then lyophilized at -45 °C for 24 h to obtain the hydrogel products.

Water Absorbency Measurement

The classical gravimetric method was used to measure the water absorbency of the hydrogel products. The dried hydrogel was milled to prepare particles with sizes in the 40 to 60 mesh range. 0.1±0.0001 g of the particles was immersed in 500 mL phosphate buffer solution (PB) of pH 7.4 at room temperature to reach swelling equilibrium (about 2 h) (Zhang *et al*. 2013) and then filtered with a 100 mesh gauze to remove excess water. The equilibrium swelling Q_{eq} was calculated according to Eq. (1),

$$Q_{eq} = (M_2 - M_1)/M_1 \quad (1)$$

where M_1 and M_2 are the weights of the dry and swollen samples (g) respectively and Q_{eq} is the water absorbency of per gram dried sample (g/g).

Temperature Sensitivity of Hydrogel

0.1±0.0001 g of the hydrogel particles were soaked in 500 mL PB of pH 7.4 at the predetermined temperatures (ranging from 25 to 45 °C) for 2 h to reach swelling equilibrium. The swollen particles were filtered by 100-mesh gauze to remove excess water. The equilibrium swelling Q_{eq} was also used to evaluate the swelling performance of the hydrogel products at different temperatures, which was calculated by Eq. 1.

pH Sensitivity of Hydrogel

0.1±0.0001 g of the hydrogel particles were soaked in 500 mL PB of 37 °C at the predetermined pH values (ranging from 1.4 to 9.4) for 2 h to reach swelling equilibrium. The swollen particles were filtered by 100-mesh gauze. The equilibrium swelling Q_{eq} was also used to evaluate the swelling performance of the hydrogel products at different pH values, using Eq. 1 for calculations.

Structural Characterization

The lyophilized hydrogel was equilibrated in PB of pH 7.4 at room temperature and then quickly frozen in cryogenic refrigerator at -80 °C for 12 h and lyophilized at -45

°C for 24 h. The original and resultant samples were fractured in liquid nitrogen, sputter-coated with a gold layer and observed using a Hitachi S-4800 field emission scanning electron microscopy (FESEM) system using the acceleration voltage of 2 kV. The Fourier transform infrared (FTIR) spectra of the bamboo pulp and hydrogel products were recorded on a Thermo Nicolet 5700 TIFR spectrometer.

Load and Release of Model Drug

MB and MO dyes were employed as the model drugs to simulate the load and release of cationic and anionic substances into/from hydrogels.

Model drug load

0.05±0.0001 g of the hydrogel particles were soaked in phosphate buffer saline (PBS) of pH 7.4 at 25 °C for 12 h to reach swelling equilibrium. The swollen hydrogels were transferred into 100 mL 50 mg/L MB/MO solution at 25 and 37 °C for 24 h, respectively. The concentration of the MB/MO solution after removing the hydrogels was estimated using the absorbance at the maximum absorption wavelength of MB/MO, by a DU-7HS spectrophotometer. The loading capacity *LC* of MB/MO was calculated by concentration difference of the MB/MO solution before and after being soaked by Eq. 2,

$$LC = (C_1 - C_2)V / M_1 \quad (2)$$

where C_1 and C_2 are the concentrations of MB/MO solution before and after being soaked (mg/L), V is the volume of MB/MO solution (L), and M_1 is the dry weight of hydrogel (g).

Model drug release

The loaded hydrogel particles were transferred into PBS of pH 7.4 at 25 and 37 °C, respectively. At every 1 h interval, 3 mL of the buffer solution was drawn out from the release system for analysis, and another 3 mL fresh buffer solution was added to maintain constant volume of solution. The released MB/MO was determined by UV analysis as described above. The cumulative release amount Q_t of the MB/MO from hydrogel was calculated according to Eq. 3,

$$Q_t = V \times C_t + 3 \times \sum_{i=1}^{t-1} C_i \quad (3)$$

where V is the volume of release system (L) and C_t is the concentration of MB/MO in the release system (mg/L) at a certain time.

RESULTS AND DISCUSSION

Optimization of Synthesis Conditions

Hydrogels synthesized under different conditions usually have different water absorbency and retention capabilities due to their different physical structures and chemical properties. In the early synthesis process of the cellulose-based hydrogel, oxygen-free nitrogen gas was introduced to avoid the invalid decomposition of the APS and improve the grafting efficiency between the cellulose and monomers. Reaction time of 2 h ensured the adequate cross linking of the cellulose and monomers to form hydrogel. The lyophilization process was used to maintain the porous structure of the hydrogel products. In order to obtain the optimal synthesis conditions for target hydrogel products

for oral drug delivery applications, an orthogonal experiment with four factors and three levels was conducted. "A" stands for the dosage of initiator APS, which has three levels of 0.1, 0.2 and 0.3 g. "B", "C", and "D" stand for the dosage of AA+AM (AA/AM = 4:1), the dosage of crosslinker MBA, and the mass ratio of NIPPAm to bamboo pulp, respectively. According to the orthogonal array of $L_9(3)^4$ presented in Table 1, the following experiments were performed according to Table 2.

Temperature and pH sensitivity are the two most important parameters for oral drug delivery materials. The results of the orthogonal experiments were evaluated by temperature and pH sensitive of the hydrogel products. Figure 1 shows the equilibrium swelling ratios of hydrogels at different temperatures and pH in PB, respectively.

Table 1. Factors and Levels of the Orthogonal Experiment (A: Dosage of APS; B: Dosage of AA+AM (AA/AM = 4:1); C: Dosage of MBA; D: NIPPAm to Cellulose Mass Ratio)

Factor/level	A (g)	B (g)	C (g)	D
1	0.1	10+2.5	0.04	2:0.5
2	0.2	8+2	0.06	2:1.5
3	0.3	6+1.5	0.08	2:1

Table 2. The Orthogonal $L_9(3)^4$ Experiment of APS, AA+AM, MBA, and NIPPAm (A: Dosage of APS; B: Dosage of AA+AM (AA/AM = 4:1); C: Dosage of MBA; D: NIPPAm to Cellulose Mass Ratio)

Sample No.	A (g)	B (g)	C (g)	D
1	0.1	10+2.5	0.04	2:0.5
2	0.2	10+2.5	0.06	2:1
3	0.3	10+2.5	0.08	2:1.5
4	0.2	8+2	0.04	2:1.5
5	0.3	8+2	0.06	2:0.5
6	0.1	8+2	0.08	2:1
7	0.3	6+1.5	0.04	2:1
8	0.1	6+1.5	0.06	2:1.5
9	0.2	6+1.5	0.08	2:0.5

As shown in Fig. 1a, all the hydrogels displayed different temperature sensitivity. The equilibrium swelling ratios of the products increased with the rise of temperature. The hydrogel product No. 9 (green) exhibited the highest swelling ratio 47.9 at 37 °C and relatively low swelling ratio at other temperatures. This phenomenon demonstrated that No. 9 held good temperature sensitivity to the characteristic body temperature of humans. Meanwhile, No. 2 (red) also presented a similar trend. Its swelling ratio displayed the highest point as 42.4 at 37 °C and declined at other temperatures. This may be attributed to the fact that before 37 °C and with the increase of temperature, intermolecular hydrogen bonds among cellulose, AA, AM, and NIPPAm were broken and replaced by the corresponding hydrogen bonds with water molecules. This led more water to entering the hydrogel, resulting in swelling. After 37 °C, with the continued increase of temperature, intermolecular movement was accelerated and the previous hydrogel-water structure of the swollen hydrogel was destroyed. Intermolecular hydrogen bonds were reformed; shrinkage of hydrogel occurred which caused the decline of swelling ratio of the hydrogel (Wei *et al*. 2008).

With regard to pH sensitivity, Fig. 1b shows that the hydrogels had lower swelling capability in acid medium and higher swelling degree in neutral or weakly basic medium. Products No. 9 and 2 both reached their highest swelling ratio 47.0 and 43.5 at pH 7.4, respectively, in keeping with the pH value of the human intestinal environment. No. 4, 5, 6, and 8 reached their maximum swelling ratio close to pH 5.4. This is associated with the fact that the carboxyl groups and residual hydroxyl groups on the molecular chains of hydrogels as functional groups can accept or release protons in response to various pH aqueous media. A number of hydrogen bonds form in acidic environment, and the interaction of hydrogen bonds restricts the movement of gel network chains. As a result, a compact hydrogel network forms, leading to a lower swelling ratio. In neutral or alkaline media, these free functional groups are ionized to free ions, leading to a higher swelling ratio. With increased pH from 7.4 to 9.4, the swelling ratio decreases gradually because the hydrogel forms more ionic bonds, which generate the relatively increased cross-linking density of hydrogel (Wu *et al*. 2008).

Based on the fact that the pH value of human intestinal environment is 7.4 and the body temperature of humans is close to 37 °C, the synthesized hydrogels No. 2 and 9 demonstrate the potential for oral drug delivery applications according to the reference (Wang *et al*. 2013). Therefore, these two products were chosen to further investigate their properties and capabilities in loading and release of model drugs.

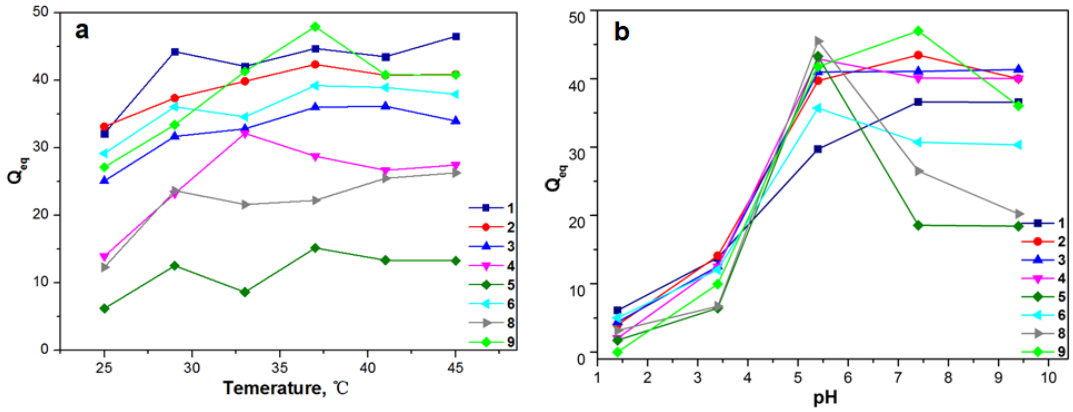

Fig. 1. Equilibrium swelling ratios of hydrogel products in PB: (a) at different temperatures; (b) at different pH values

Characterization of Hydrogel Product

The FTIR spectra of the original bamboo pulp, in addition to the hydrogel products No. 2 and 9 are exhibited in Fig. 2. The characteristic peak at 1069 cm^{-1} is attributed to β-1,4-glycosidic bonds on molecular chains of cellulose (Wu *et al*. 2012). The characteristic adsorption band at 1662 cm^{-1} appeared on account of the amide I band stretching vibrations and the overlap of C=O in the AA (Wu *et al*. 2012). The band at 1553 cm^{-1} is assigned to amide II in the AM or due to asymmetric vibrations of $-COO^-$ existing in the AA, which was also not observed in the original cellulose (Dragan *et al*. 2012). The band at 1320 cm^{-1} is attributed to amide III (C-N) in the AM (Dragan *et al*. 2012). These characteristic absorptions were detected both in the spectra of the hydrogel products No. 2 and 9, which indicated that the copolymerization among the bamboo pulp cellulose, NIPPAm, AA, and AM was achieved. The target hydrogels were synthesized successfully.

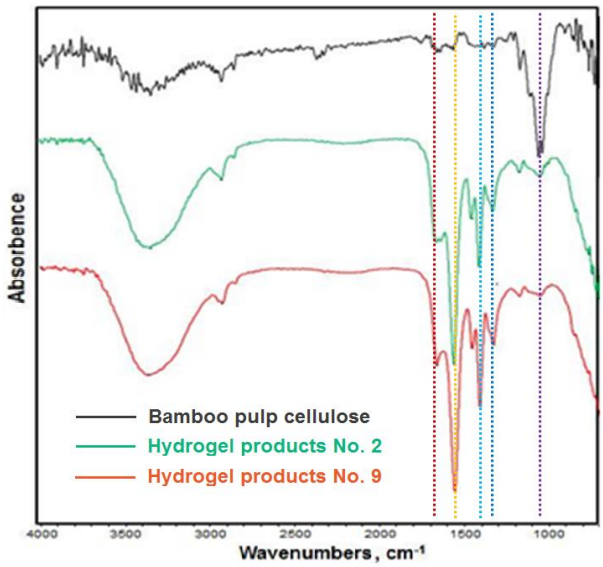

Fig. 2. FTIR spectra of the original bamboo pulp, hydrogel products No. 2 and 9

Figure 3 exhibits the FESEM and digital pictures of the bamboo pulp materials and cellulose-based hydrogel products. Figure 3a shows that the original bamboo pulp was distributed as fibers with widths in the range of 5 to 15 μm. Each fiber was aggregated with plenty of fibrils.

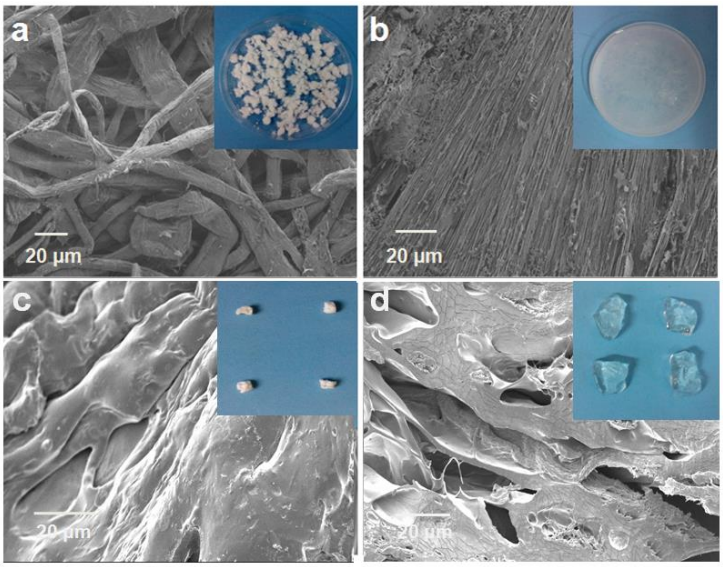

Fig. 3. FESEM and digital pictures of the (a) original bamboo pulp cellulose, (b) dissolved bamboo pulp cellulose, (c) dry and (d) swelling hydrogels (cross-section)

When the material was dissolved in cellulose solvent (NaOH/urea mixed solution) as shown in Fig. 3b, the fibrils were separated from each other and presented an amorphous status. This is attributed to the complete destruction of hydrogen bonding inside of or among cellulose molecular chains. Figure 3c and d display the cross-section morphologies of the hydrogel product No. 9 before and after swelling in PB of pH 7.4. The cross-sectional image of dry hydrogel exhibited lots of small holes which interconnect inside of the hydrogel. After swelling in PB, as shown in Fig. 3d, the small

holes became much larger. Water was filled in most of them until the hydrogel reached swelling equilibrium. This internal structure expansion of hydrogel just provides the conditions for the release of substances (like active ingredients of drugs) from the hydrogel interior.

Loading and Release of Model Drugs

The loading and release of active ingredients of drugs is the most important indicator for an oral drug delivery system. The hydrogel products No. 2 and 9 were screened out to investigate their adsorption and release capabilities to model drugs MB and MO, which represented cationic and anionic substances respectively. The load of model drugs onto hydrogels was carried out at 25 and 37 °C, respectively. The loading results are presented in Fig. 4. The loading amount of MB into hydrogels was significantly more than that of MO whether at 25 or 37 °C in solutions with the same initial concentration. A possible reason is that the interaction between cationic MB and anionic carboxyl groups as well as residual hydroxyl groups on the hydrogel molecular chains contributes to the strong adsorption between the MB and hydrogel. On the other hand, the loading amount of both MB and MO at 37 °C was higher than that at 25 °C. The reason is that the swollen hydrogel can allow diffusion of the model drugs into its polymer matrix, thus increasing the loading amount of drugs. When the temperature of absorbed solution rises, hydrogels swell easier and are accompanied by higher adsorption of drugs into it.

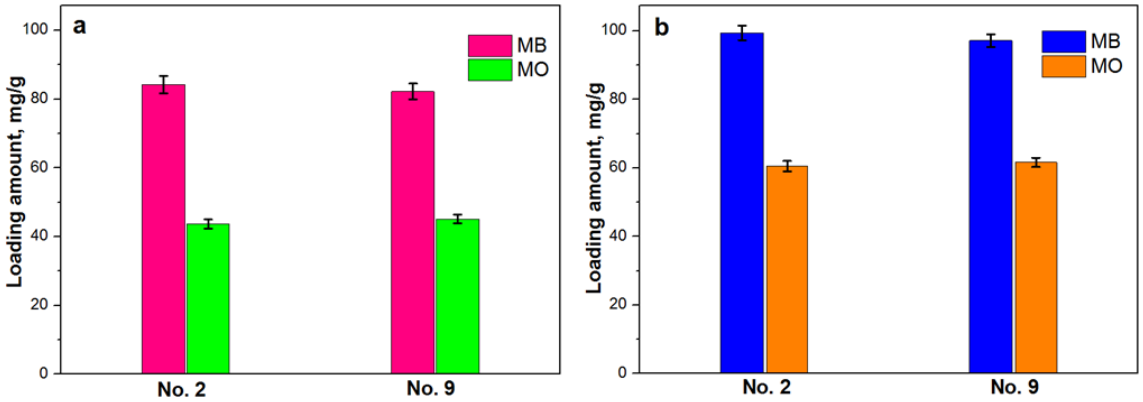

Fig. 4. Loading amount of model drugs MB and MO into the hydrogel products No. 2 and 9 at (a): 25 °C and (b): 37 °C, respectively

The release of model drugs MB and MO from the hydrogel products No. 2 and 9 was carried out at 25 and 37 °C in PBS (pH=7.4), which simulated the human intestinal environment. Figure 5 depicts the cumulative releases of MB and MO from hydrogels at different time intervals. In Figure 5a, the cumulative release amounts of MB and MO from the hydrogel No. 2 within the first 1 h were 106.8 and 1004.1 ug at 37 °C, and 93.8 and 1027.4 ug at 25 °C. The cumulative releases of MB and MO within 12 h were 139.5 and 1079.3 ug at 37 °C, and 114.1 and 1135.3 ug at 25 °C. In Figure 5b, the cumulative releases of MB and MO from the hydrogels No. 9 within the first 1 h were 95.6 and 708.2 ug at 37 °C, and 68.9 and 622.9 ug at 25 °C. The cumulative releases of MB and MO within 12 h were 122.2 and 755.9 ug at 37 °C, and 116.6 and 689.3 ug at 25 °C. Both the release rate and the cumulative release amount of MO were evidently higher than that of MB. This is mainly attributed to the strong adsorption of the negatively charged hydroxyl

groups on cellulose and amide bonds on AM and NIPPAm to the cationic MB, which slows its release from the hydrogels. On the other hand, 25 °C is a key temperature, at which the hydrogels can keep the loaded drugs inside of them even in neutral or weakly basic aqueous solution. This guarantees that the obtained hydrogel products can achieve targeted release for oral drugs in human intestine (37 °C, pH 7.4). As shown in Fig. 5, the hydrogel No. 9 achieved better release of both MB and MO at 37 °C, which is more suitable for drug release in the human intestinal environment. Relative to some other temperature- or pH-sensitive hydrogel products, it achieved equivalent temperature sensitivity (Xu *et al*. 2013), more excellent pH response (Xu *et al*. 2007), and greater biodegradability (Constantin *et al*. 2014) for the loading and release of drugs. These results suggest that the synthesized temperature/pH sensitive hydrogel No. 9 is more suitable for oral drug delivery applications.

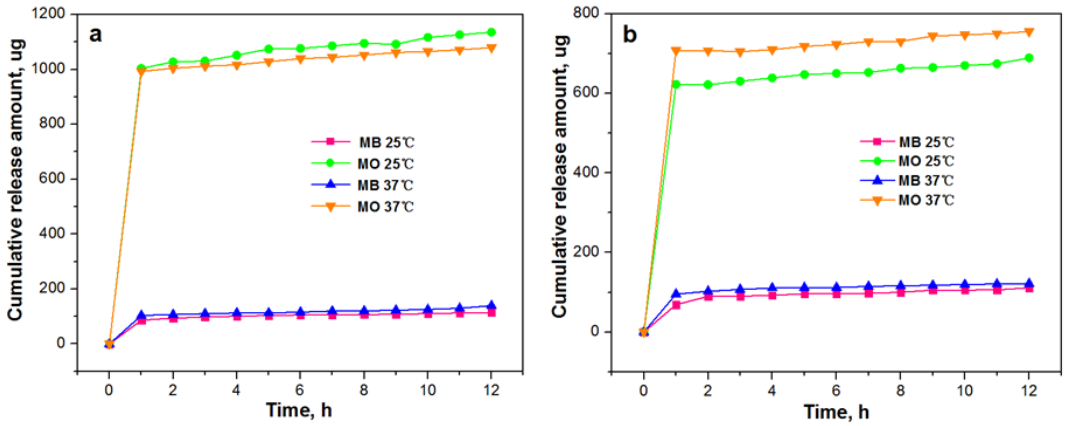

Fig. 5. Cumulative release amounts of model drugs MB and MO from the hydrogel products (a): No. 2 and (b): No. 9 at 25 and 37 °C in PBS (pH=7.4)

CONCLUSIONS

1. A temperature/pH sensitive hydrogel was successfully synthesized and characterized based on the cellulose from *P. heterocycla*. Its optimal synthesis conditions (reagent dosages) were summarized as: APS at 0.2 g, AA and AM at 6 and 1.5 g, MBA at 0.08 g, and NIPPAm to cellulose mass ratio at 2:0.5. The synthesized hydrogel held the highest swelling ratio in PB at 37 °C and pH 7.4, which were consistent with the temperature and pH of human intestinal environment.
2. The hydrogel product exhibited relatively higher loading amount to cationic MB than anionic MO due to its interaction with the hydrogel molecular chains. The release of model drug from hydrogel No. 9 showed its temperature dependence at 37 °C, corresponding to body temperature of humans. These positive results suggest that the synthesized temperature/pH sensitive cellulose-based hydrogel (No. 9) has a great potential for oral drug delivery applications.

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