Polymer 51 (2010) 1648–1653

Contents lists available at ScienceDirect

Polymer

journal homepage: www.elsevier.com/locate/polymer

A novel stimuli-responsive hydrogel for K^+-induced controlled-release

Peng Mi [1], Xiao-Jie Ju, Rui Xie, Han-Guang Wu, Jiang Ma, Liang-Yin Chu*

School of Chemical Engineering, Sichuan University, Chengdu, Sichuan 610065, China

ARTICLE INFO

Article history:
Received 10 November 2009
Received in revised form
17 January 2010
Accepted 9 February 2010
Available online 16 February 2010

Keywords:
Hydrogels
Ion-recognition
Controlled-release

ABSTRACT

A novel family of stimuli-responsive smart hydrogel is developed in this study for K^+-induced self-regulated controlled-release, which is featured with isothermally K^+-induced pulse-release mode at a certain temperature due to the isothermally K^+-induced shrinking behavior of the hydrogel by recognizing the increase of K^+ concentration in the environment. The proposed poly(*N*-isopropylacrylamide-*co*-benzo-15-crown-5-acrylamide) hydrogel is composed of crown ether 15-crown-5 as ion-signal sensing receptor and poly(*N*-isopropylacrylamide) as actuator. The selective formation of stable 2:1 "host-guest" complexation between the crown ether 15-crown-5 and potassium ion drives the polymeric network of the hydrogel to shrink; as a result, the hydrogel exhibits especial and selective response to potassium ions. A K^+-recognition pulse-release performance of loaded drug from the fabricated hydrogel is achieved by using the K^+-induced isothermal shrinkage property of the hydrogel. The proposed hydrogel provides a new mode of K^+-recognition volume change for stimuli-responsive smart actuators, which is highly attractive for targeting drug delivery systems, biomedical devices, and sensors and so on.

1. Introduction

Stimuli-responsive smart hydrogels that can respond to environmental physical and chemical stimuli, such as temperature [1–7], pH [6–9], light [10,11], electric field [12], magnetic field [13,14], and substance species [15–21], have attracted great interests in recent years due to their versatile applications such as controlled drug and gene delivery systems [22–28], chemical-/bio-separations [21,29,30], adaptive liquid microlenses [31], soft machines [32], and sensors and/or actuators [33,34], and so on. Among those smart hydrogels, ion-responsive hydrogels that can selectively respond to certain metal ions are of special interests and importance, because heavy metal ions show serious toxicity to human beings and other living organisms whereas some metal ions such as potassium and sodium ions are very important for chemical signal transduction in biological systems. Potassium ion plays an important role in biological systems, not only involves in the maintenance of extracellular osmolarity but also regulates the concentration of other ions in the living cell. The concentration of potassium ion inside of cell is about 30 times as high as that outside of cell due to the active function of ion channels across the cell membrane [35,36]. An unbalance of potassium ion concentration is always associated with certain diseases. For example, serious cytoclasis or disabled K^+-Na^+ pumps in the cell membrane could result in abnormal increase of extracellular K^+ concentration at some pathological sites in the body [37–39]. Therefore, the abnormal increase of K^+ concentration could be taken as a stimulus for self-regulated targeted drug delivery at corresponding pathological sites.

Recently, some bio-inspired K^+-recognizable hydrogels and polymeric systems have been developed successfully by introducing the cooperative action of thermo-responsive poly(*N*-isopropylacrylamide) (PNIPAM) and ion-recognizable crown ether 18-crown-6, in which the crown ether 18-crown-6 is used as an ion-signal sensing receptor and PNIPAM acts as an actuator [20,21,25,38–47]. When the pendant crown ether 18-crown-6 receptors capture specific ions such as potassium ions, the lower critical solution temperature (LCST) of the poly(*N*-isopropylacrylamide-*co*-benzo-18-crown-6-acrylamide) (P(NIPAM-*co*-B18C6Am)) copolymers shift to a higher temperature due to the enhancement of hydrophilicity of the copolymer when specific ions (for example, potassium ions) are captured [48]. Therefore, when the environmental temperature is settled between the two LCSTs before and after the crown ether receptors capture specific ions, all these P(NIPAM-*co*-B18C6Am)-based smart hydrogels or polymers swell isothermally when they recognize potassium ions in environments [20,21,25,38–47]. However, to achieve a smart hydrogel system for self-regulated drug delivery by recognizing abnormal increase of K^+ concentration, an isothermally K^+-induced shrinking mode of the K^+-recognizable hydrogel is necessary. Unfortunately, until very recently [49,50],

* Corresponding author.
E-mail address: chuly@scu.edu.cn (L.-Y. Chu).
[1] Present address: Department of Bioengineering, Graduate School of Engineering, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8656, Japan.

0032-3861/$ – see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.polymer.2010.02.018

little attention has been paid to the negative shift mode of the LCST of K^+-recognizable polymers. Up to now, there has not been any report concerning K^+-recognizable smart hydrogels with isothermally K^+-induced shrinking mode for controlled-release by recognizing the increase of environmental K^+ concentration.

In this study, we report on a novel family of K^+-recognizable smart hydrogels for self-regulated controlled-release, which is featured with isothermally K^+-induced pulse-release mode at a certain temperature due to the isothermally K^+-induced shrinking behavior of the hydrogel by recognizing the increase of K^+ concentration in the environment.

2. Experimental section

2.1. Materials

N-isopropylacrylamide (NIPAM, kindly provided by Kohjin Co., Ltd., Japan) was purified by recrystallization with a hexane/acetone (v/v, 50/50) mixture solution. Amino-benzo-15-crown-5 (97%) was purchased from Fluka. *N*,*N*′-Methylene-bis-acrylamide (BIS, Chengdu Kelong Chemical Reagent Co.) was used as crosslinker. 2,2′-Azobisisobutyronitrile (AIBN, Shanghai Reagent Fourth Factory) was recrystallized with ethanol and used as initiator. All other chemicals were of analytical grade. Deionized water (18.2 MΩ at 25 °C) from a Milli-Q Plus water purification system (Millipore) was used throughout the experiments.

2.2. Hydrogel fabrication and characterization

Benzo-15-crown-5-acrylamide (B15C5Am) monomer was synthesized from amino-benzo-15-crown-5 according to previously reported procedures [51,52]. The P(NIPAM-*co*-B15C5Am) hydrogel was synthesized by thermally initiated free-radical crosslinking polymerization. Briefly, 0.046 g of B15C5Am and 0.356 g of NIPAM monomers, 0.01 g of crosslinker BIS and 0.005 g of initiator AIBN were dissolved in 3 mL of pure water/tetrahydrofuran (THF) (v/v, 4/1) mixture solution. The molar ratios of B15C5Am, AIBN and BIS to NIPAM monomer were 4.5%, 1%, and 2%, respectively. N_2 gas was bubbled into the solution for at least 15 min to remove dissolved oxygen. The solution was then immediately transferred into a glass tube with an inner diameter of 6 mm and the tube was sealed immediately. The glass tube was then immersed into a constant-temperature water bath at 70 °C for 8 h to carry out the polymerization. After the polymerization was complete, the prepared cylindrical hydrogel was pushed out from the tube and immersed into deionized water to remove residual unreacted chemicals. The water was replaced with fresh water every 6 h and the wash was lasted for 7 days. The washed P(NIPAM-*co*-B15C5Am) hydrogel was cut into thin discs and then separately equilibrated in deionized water and salt solutions at 20 °C. PNIPAM hydrogels were also prepared as reference samples using the same procedure and ingredient ratios but without any addition of B15C5Am. The obtained hydrogels were characterized by Fourier Transform Infrared Spectrometer (FT-IR, Nicolet 560) to make sure that the B15C5Am groups were successfully introduced into the hydrogel networks.

2.3. Isothermally K^+-induced shrinking behaviors of the hydrogel

The volume phase transition behaviors of P(NIPAM-*co*-B15C5Am) hydrogels responding to temperature and metal ions were carried out by measuring the diameter change of hydrogel discs in different solutions and at various temperatures ranging from 20 to 38 °C. The hydrogel discs were separately immersed in deionized water, $LiNO_3$, $NaNO_3$ and KNO_3 solutions with the salt concentrations of 0.1 and 0.2 mol L^{-1} in glass culture dishes with calibrated scale. The glass culture dishes were placed in a temperature-controlled water bath with temperature fluctuation of ±0.1 °C. The diameter of the hydrogel discs was measured by taking photos using a digital camera (Sony T-20, Japan) when the hydrogel reached to the equilibrium state at each temperature. The photos of the hydrogel discs with scale bar were analyzed by graph-processing software to determine the diameters of the hydrogel discs. At least three different pictures of each hydrogel sample at the same temperature were analyzed to reduce the errors in measurements.

The dynamic isothermal volume shrinkage of the P(NIPAM-*co*-B15C5Am) hydrogel responding to K^+-recognition was investigated using similar method as mentioned above. P(NIPAM-*co*-B15C5Am) hydrogel disc was firstly immersed in deionized water in the glass culture dish at 30 °C until reached to equilibrium state. Then, the P(NIPAM-*co*-B15C5Am) hydrogel disc was immediately transferred to another glass culture dish filled with 0.2 mol L^{-1} KNO_3 solution and the diameter change of the hydrogel disc was simultaneously measured by taking photos using a digital camera at fixed time intervals. This process was repeated at least three times using different hydrogel samples to ensure the accuracy of results.

2.4. K^+-induced controlled-release of model drug from the hydrogel

VB_{12} was used as the model drug in the controlled-release experiment. The K^+-induced release of the loaded drug from P(NIPAM-*co*-B15C5Am) hydrogel was carried out at 30 °C by measuring the increased VB_{12} concentration in the surrounding medium at fixed time intervals during the release process. The controlled-release experiment included two procedures, the drug loading and the K^+-induced drug release. In the drug loading procedure, the prepared P(NIPAM-*co*-B15C5Am) hydrogel with a length of 4 cm at 20 °C was cut into 8 pieces of hydrogel discs, and then these hydrogel discs were immersed into 0.2 mmol L^{-1} VB_{12} solution at 0 °C for at least 72 h to make the hydrogel swell enough and load drug molecules adequately. The VB_{12} solution was refreshed periodically until that the VB_{12} concentration of the surrounding solution did not change anymore to ensure the sufficient loading of VB_{12} solutes into the hydrogel. For the drug-releasing procedure, a 100 mL beaker containing 50 mL deionized water was placed in a constant-temperature water bath at 30 °C. Another 100 mL beaker containing the drug-loaded hydrogel discs in 0.2 mmol L^{-1} VB_{12} solution was also placed in the constant-temperature water bath at 30 °C. The drug-loaded hydrogel discs were transferred into the beaker with 50 mL deionized water at 30 °C and timed immediately. At fixed time intervals, the VB_{12} concentration was determined using a UV–visible recording spectrophotometer at a wavelength of 361 nm. During the drug release process, the water around the hydrogel discs was stirred gently to eliminate the effect of concentration polarization near the hydrogel surface on the drug release. The amount of released drug from the hydrogel was calculated from the VB_{12} concentration and the solution volume. In the treatment of drug release data, the VB_{12} concentration change in the surrounding solution in the first minute was subtracted in order to exclude the portion of drug that was from the extra drug solution on the hydrogel sample surface but not released from the inside of hydrogel sample. The controlled-release experiment was carried out for at least three times to verify the repeatability.

To examine the K^+-induced pulse-release performance of the hydrogel, an experiment was carried out as follows. After the drug release from the drug-loaded P(NIPAM-*co*-B15C5Am) hydrogel and PNIPAM hydrogel have been carried out for 10 min in pure water, KNO_3 was immediately added into the surrounding aqueous solutions to make K^+ concentration up to 0.2 M, and then the drug release rate was measured continuously.

To check the reversibility and repeatability of P(NIPAM-*co*-B15C5Am) hydrogel in K^+-induced controlled-release, the hydrogel samples that have been used in the release experiments were washed adequately to remove the captured guest ions and loaded drug molecules, and then these hydrogels were reused for the release experiment again. Three runs of release experiments were carried out with the same hydrogel samples in this study.

3. Results and discussion

3.1. Strategies for fabrication and K^+-induced controlled-release function of hydrogel

The concept of the proposed K^+-recognizable smart hydrogel for K^+-induced controlled-release is schematically illustrated in Fig. 1. The hydrogel is composed of three-dimensional crosslinked copolymer networks of poly(*N*-isopropylacrylamide-*co*- benzo-15-crown-5-acrylamide) (P(NIPAM-*co*-B15C5Am), Fig. 1a), in which the crown ether 15-crown-5 is used as an ion-signal sensing receptor and PNIPAM acts as an actuator. The crown ether 15-crown-5 is a well-known host molecule in supramolecular "host-guest" systems to selectively recognize sodium ion by forming "host-guest" complex, and it has been reported that the 15-crown-5 molecules can also recognize potassium ions by forming "sandwich" (crown ether:cation = 2:1) structural complexes [53,54]. By the cooperative action of thermo-responsive PNIPAM and crown ether 15-crown-5, K^+-induced negative shift of the LCST for phase transition of P(NIPAM-*co*-B15C5Am) has been discovered in our group recently [50].When there is no potassium ions appearing in the environmental solutions, the LCST of P(NIPAM-*co*-B15C5Am) is located in $LCST_b$ (Fig. 1b); however, when potassium ions present in the environmental solutions, the LCST of P(NIPAM-*co*-B15C5Am) shifts significantly to a lower temperature at $LCST_a$ (Fig. 1b) as a result of the change of hydrophobicity when the 15-crown-5 cavities capture potassium ions via forming stable 2:1 (crown ether:cation = 2:1) "sandwich" complexes [50]. This significant negative shift behavior of the LCST of P(NIPAM-*co*-B15C5Am) is selectively triggered by K^+-recognition, and can not be induced by some other alkali metal ions, such as sodium ions, lithium ions or cesium ions [50]. Therefore, when the operation temperature is selected between the $LCST_a$ and the $LCST_b$, the proposed hydrogel can isothermally shrink from swollen state to shrunken state by selectively recognizing potassium ions. By using such an isothermal shrinking function induced by K^+-recognition, an isothermally K^+-triggered pulse-release of loaded substance from the proposed hydrogel can be achieved (Fig. 1c), which can be aimed at self-regulated targeted drug delivery with the above-mentioned abnormal increase of K^+ concentration as a stimulus.

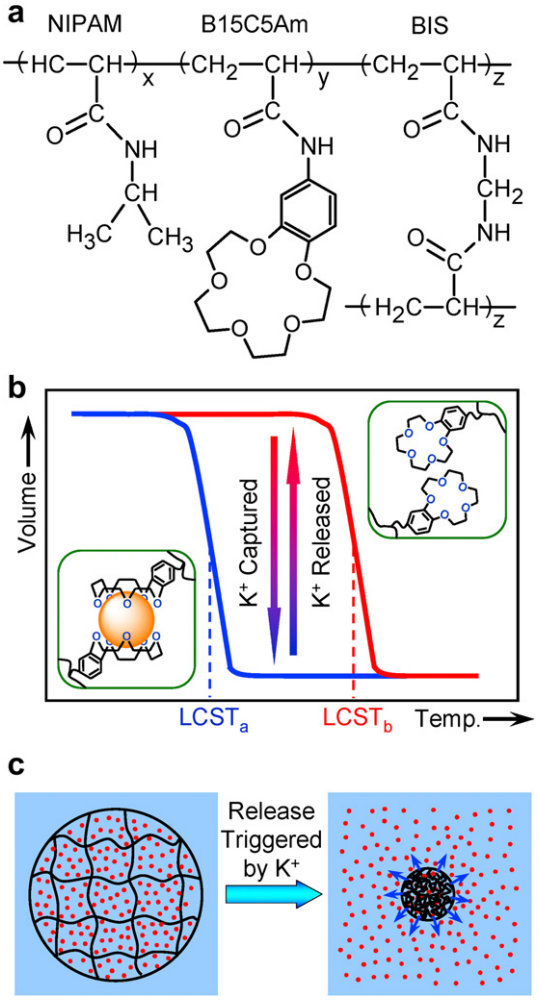

Fig. 1. Schematic illustration of the proposed ion-recognizable hydrogel and K^+-induced controlled-release. a) The chemical structure of P(NIPAM-*co*-B15C5Am) hydrogel. b) Thermo-responsive volume change behavior of the P(NIPAM-*co*-B15C5Am) hydrogel in response to potassium ion. c) The K^+-induced controlled-release from the P(NIPAM-*co*-B15C5Am) hydrogel due to K^+-induced isothermal shrinkage of the hydrogel.

3.2. Componential analyses of the hydrogel

Fig. 2 shows FT-IR spectra of B15C5Am and NIPAM monomers and crosslinked P(NIPAM-*co*-B15C5Am) hydrogel. The characteristic peaks of the B15C5Am monomer, including a strong peak at 1516 cm^{-1} for C=C skeletal stretching vibration of the phenyl ring, a peak at 1228 cm^{-1} for C–O asymmetric stretching vibration in Ar–O–R, a peak at 1132 cm^{-1} for C–O asymmetric stretching vibration in R–O–R′, and a peak at 1055 cm^{-1} for C–O symmetric stretching vibration in Ar–O–R, are all found in the spectrum of the crosslinked P(NIPAM-*co*-B15C5Am) hydrogel. At the same time, the characteristic peaks of the NIPAM monomer, such as peak at

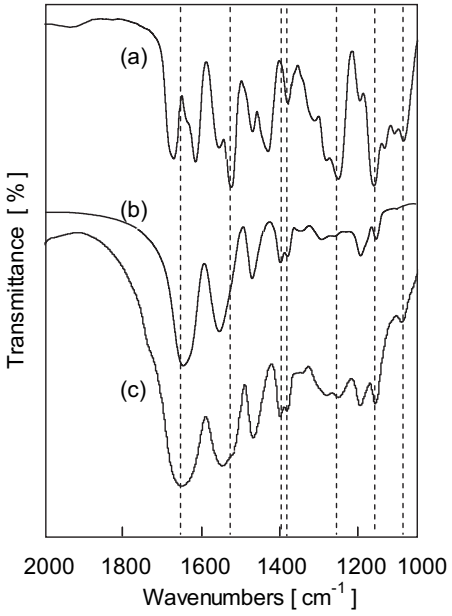

Fig. 2. FT-IR spectra of a) B15C5A monomer, b) NIPAM monomer, and c) crosslinked P(NIPAM-*co*-B15C5Am) hydrogel.

1647 cm^{-1} for C=O stretching vibration of the amidogroup and the characteristic double peaks at 1388 and 1366 cm^{-1} for isopropyl group of NIPAM, also appear in the spectrum of the crosslinked P(NIPAM-*co*-B15C5Am) hydrogel. The results confirm the successful fabrication of P(NIPAM-*co*-B15C5Am) hydrogel, *i.e.*, both B15C5Am and NIPAM components are proven to be constructed in the crosslinked hydrogel.

3.3. Isothermally K^+-induced shrinking behaviors of the hydrogel

The thermo-responsive and ion-recognition characteristics of the P(NIPAM-*co*-B15C5Am) hydrogel are studied by detecting the volume change of the hydrogel in water and in aqueous solutions containing different metal ions. Fig. 3 shows thermo-responsive volume change of P(NIPAM-*co*-B15C5Am) hydrogels in solutions containing different alkali metal ions. The hydrogels undergo thermo-responsive volume shrinkage due to the phase transition when the environmental temperature increases across the corresponding LCST. Just as expected, when potassium ions present in the solution, the LCST of the P(NIPAM-*co*-B15C5Am) hydrogel shifts

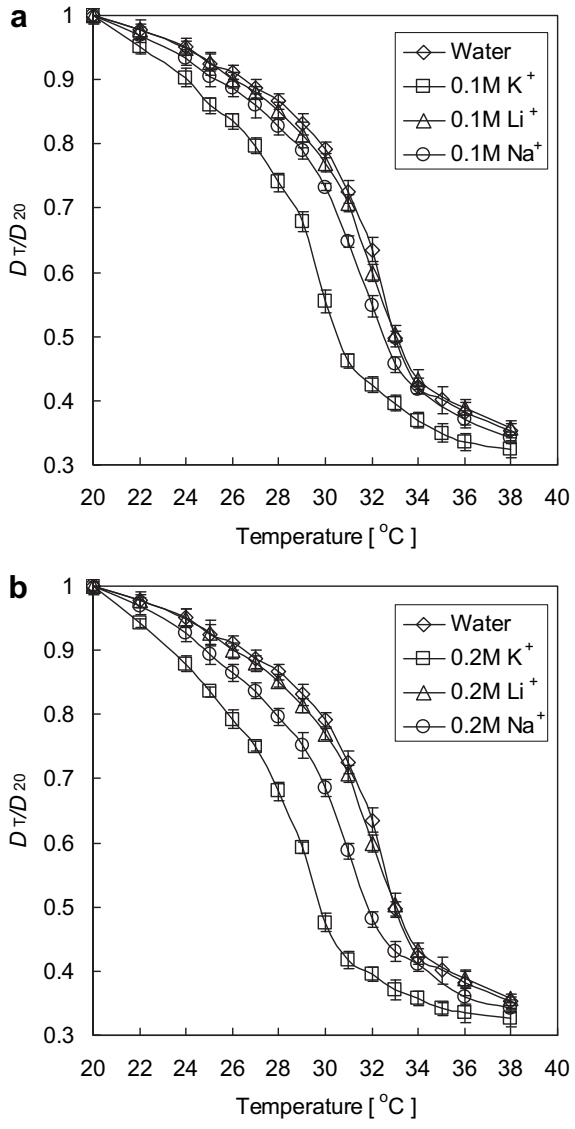

Fig. 3. Thermo-responsive volume change of P(NIPAM-*co*-B15C5Am) hydrogels in solutions containing different alkali metal cations. D_T represents the diameter of the hydrogel disc at each test temperature T, and D_{20} represents that at 20 °C.

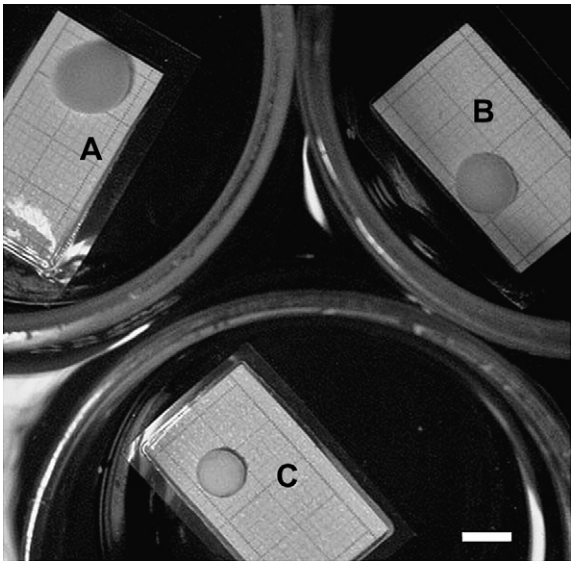

Fig. 4. K^+-induced shrinkage of the P(NIPAM-*co*-B15C5Am) hydrogel at 30 °C. Sample A is in deionized water, sample B is in 0.1M K^+ aqueous solution, and sample C is in 0.2M K^+ aqueous solution. Scale bar is 5 mm.

to a lower temperature than that in water. However, when lithium and sodium ions appear in the solutions, the LCST shifts of the hydrogels are not so significant. Although Na^+ has been reported to easily form complexation with crown ether 15-crown-5 at a ratio of 1:1 because of their size fitness [52], K^+ stably forms complexation with crown ether 15-crown-5 at a ratio of 2:1 (crown ether:cation) [52], which may drive the polymer to shrink much more effectively and cause the LCST shift more significantly than that in the case of Na^+. The presence of Li^+ nearly does not affect the LCST for phase transition because the diameter of Li^+ is very small comparing with the cavity size of crown ether 15-crown-5. In other words, Li^+ cannot effectively form stable complexation with the crown ether

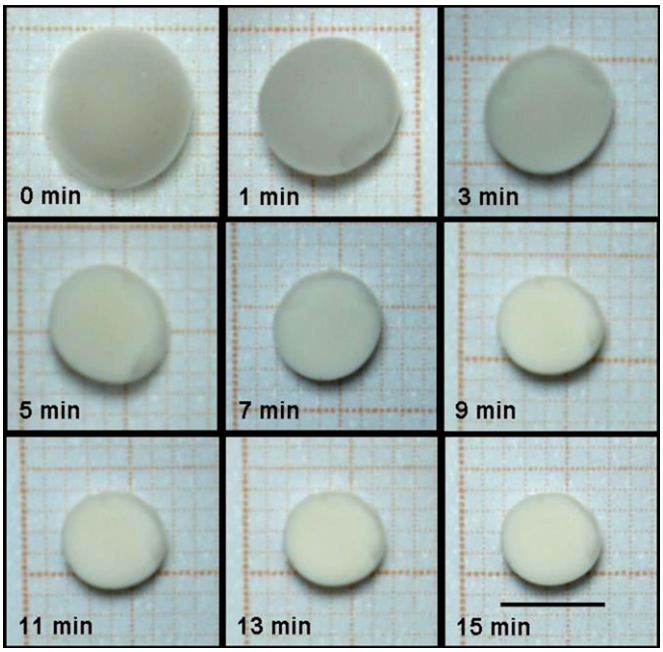

Fig. 5. Dynamic process of the K^+-induced shrinkage of P(NIPAM-*co*-B15C5Am) hydrogel in 0.2M K^+ aqueous solution at 30 °C. Scale bar is 5 mm.

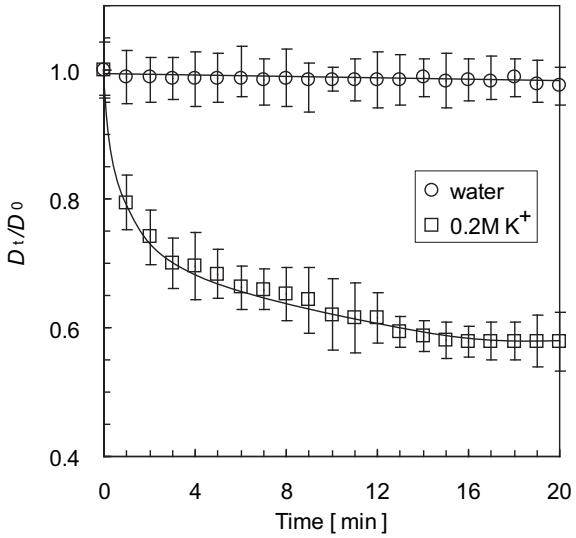

Fig. 6. Dynamic K^+-induced volume-shrinking behavior of the P(NIPAM-*co*-B15C5Am) hydrogel in 0.2M K^+ aqueous solution at 30 °C. The hydrogel does not shrink in pure water. D_t represents the diameter of the hydrogel disc at time t, and D_0 represents the initial diameter of the hydrogel disc at $t = 0$ min.

15-crown-5. Therefore, the prepared P(NIPAM-*co*-B15C5Am) hydrogel is especially and selectively sensitive to potassium ions.

From the results shown in Fig. 3, it is expected that isothermally K^+-induced significant shrinkage of the prepared P(NIPAM-*co*-B15C5Am) hydrogel can be achieved at an environmental temperature of 30 °C. The optical picture in Fig. 4 vividly shows the K^+-induced shrinkage of the P(NIPAM-*co*-B15C5Am) hydrogel at 30 °C. The three hydrogel samples in Fig. 4 are of the same diameters originally in water at 30 °C. Comparing with the situation in water, the hydrogels immersed in K^+ solutions exhibit obvious isothermal shrinkage, and the shrinkage in 0.2 M K^+ solution is larger than that in 0.1 M K^+ solution at this temperature.

The dynamic behavior of the isothermal shrinkage of P(NIPAM-*co*-B15C5Am) hydrogel triggered by K^+-recognition are studied by transferring the hydrogel from pure water at 30 °C to 0.2 M K^+ aqueous solution at the same temperature promptly and then measuring the dynamic volume change of hydrogel in 0.2 M K^+ aqueous solution at this temperature. As shown in Figs. 5 and 6, the K^+-triggered volume shrinkage of P(NIPAM-*co*-B15C5Am) hydrogel is rapid and remarkable. The diameter of the hydrogel disc in 0.2 M K^+ aqueous solution decreases to about 50% of that in pure water within a few minutes.

3.4. Isothermally K^+-induced controlled-release of model drug from the hydrogel

The isothermally K^+-induced release characteristics of VB_{12} as a model drug from both the P(NIPAM-*co*-B15C5Am) hydrogel and the PNIPAM hydrogel (as a reference) have been investigated by measuring the released VB_{12} amount to ambient solution at fixed time intervals at 30 °C. In pure water, the VB_{12} release characteristics from both hydrogels are resulted from concentration-driven diffusion and have almost the same release rates (Fig. 7a). However,

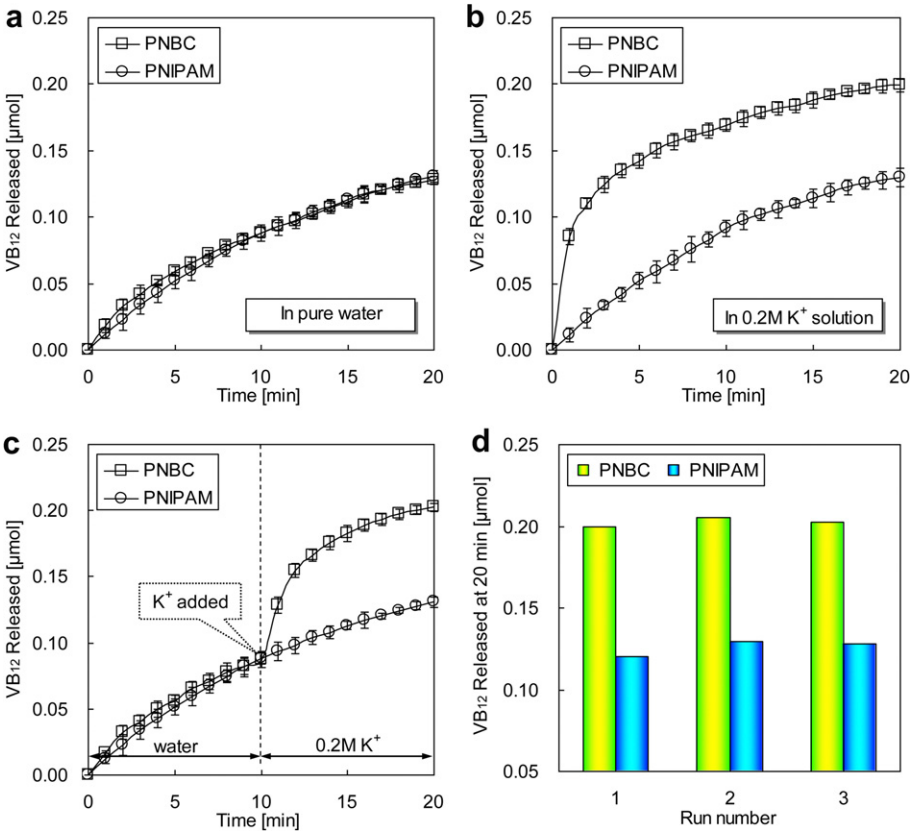

Fig. 7. K^+-induced controlled-release of model drug VB_{12} from the P(NIPAM-*co*-B15C5Am) hydrogel. PNBC is the abbreviation of P(NIPAM-*co*-B15C5Am), and PNIPAM hydrogel is used as a reference. a) Dynamic release behavior of VB_{12} from PNIPAM and P(NIPAM-*co*-B15C5Am) hydrogels in pure water, b) dynamic release behavior of VB_{12} from PNIPAM and P(NIPAM-*co*-B15C5Am) hydrogels in 0.2 M K^+ aqueous solutions, c) K^+-induced controlled-release of VB_{12} from P(NIPAM-*co*-B15C5Am) hydrogel by adding 0.2 M K^+ into the surrounding aqueous solution, and d) reversible and repeatable characteristics of K^+-induced controlled-release of VB_{12} from the P(NIPAM-*co*-B15C5Am) hydrogel (all the release experiments in Fig. 7d are performed the same as those shown in Fig. 7c). All the release experiments are carried out at 30 °C.

in 0.2 M K^+ solutions, the dynamic release behavior of VB_{12} from the P(NIPAM-*co*-B15C5Am) hydrogel is significantly different from that from the PNIPAM hydrogel (Fig. 7b). Both the release rate within the first 3 min and the total release amount within 20 min of VB_{12} from the P(NIPAM-*co*-B15C5Am) hydrogel are higher than those from the PNIPAM hydrogel. The drug release from the P (NIPAM-*co*-B15C5Am) hydrogel in K^+ aqueous solution is resulted from both the concentration-driven diffusion and the K^+-induced shrinkage of the hydrogel. Because of the K^+-induced volume shrinkage of the P(NIPAM-*co*-B15C5Am) hydrogel, the loaded model drug VB_{12} inside the hydrogel is squeezed out when potassium ions present in the environment.

The dynamic behavior of K^+-induced drug release from the P (NIPAM-*co*-B15C5Am) hydrogel by adding K^+ to the surrounding aqueous solution during the release process is also examined. The results demonstrate that the addition of potassium ions to the environment can trigger a pulse-release of loaded drug from the P (NIPAM-*co*-B15C5Am) hydrogel due to the K^+-induced isothermal shrinkage of the hydrogel (Fig. 7c). However, the PNIPAM hydrogel does not show such a performance. The fabricated P(NIPAM-*co*-B15C5Am) hydrogel is highly potential to be used as materials candidate for smart targeted drug delivery system that can recognize abnormal increase of potassium ions.

The K^+-induced controlled-release of model drug VB_{12} from the P(NIPAM-*co*-B15C5Am) hydrogel shows reversible and repeatable characteristics, just as the PNIPAM hydrogel does (Fig. 7d). After each run of the release experiment, both the P(NIPAM-*co*-B15C5Am) hydrogel and the PNIPAM hydrogel are washed thoroughly and then used again for the release experiment. After three runs, the total release amount of model drug VB_{12} from the P (NIPAM-*co*-B15C5Am) hydrogel within 20 min is almost the same as that in the first run. That is, the fabricated P(NIPAM-*co*-B15C5Am) hydrogel can be used repeatedly for K^+-induced controlled-release.

4. Conclusions

In summary, a novel family of stimuli-responsive hydrogel for K^+-induced self-regulated controlled-release, which is featured with isothermally K^+-induced pulse-release mode at a certain temperature due to the isothermally K^+-induced shrinking behavior of the hydrogel by recognizing the increase of K^+ concentration in the environment, has been successfully developed. The crown ether 15-crown-5 is introduced in the crosslinked three-dimensional hydrogel as an ion-signal sensing receptor and the PNIPAM is designed as an actuator for the hydrogel, and the P (NIPAM-*co*-B15C5Am) hydrogel is fabricated by thermally initiated free-radical polymerization of monomers NIPAM and B15C5Am. The selective formation of stable "host-guest" complexation between the crown ether 15-crown-5 and potassium ion at a ratio of 2:1 (crown ether:cation) drives the copolymer network to shrink, and as a result the fabricated P(NIPAM-*co*-B15C5Am) hydrogel is especially and selectively sensitive to potassium ions. The experimental results demonstrate that the addition of potassium ions to the environment can trigger a pulse-release of loaded drug from the P(NIPAM-*co*-B15C5Am) hydrogel due to the K^+-induced isothermal shrinkage of the hydrogel. Although the operation temperature for the K^+-triggered controlled-release of model drug from the hydrogel is 30 °C in this study, this temperature can be easily adjusted to physiological temperature around 37 °C by simply introducing some hydrophilic components into the hydrogel networks [55]. The proposed P(NIPAM-*co*-B15C5Am) hydrogel provides a new mode of K^+-recognition volume change for stimuli-responsive smart actuators, which is highly attractive for targeting drug delivery systems, and sensors and so on.

Acknowledgements

The authors gratefully acknowledge support from the National Science Fund for Distinguished Young Scholars (20825622), the National Basic Research Program of China (2009CB623407), the National Natural Science Foundation of China (20674054), the Key Project of the Ministry of Education of China (106131), and Sichuan Youth Science and Technology Foundation for Distinguished Young Scholars (08ZQ026-042). The authors thank the Kohjin Co., Ltd., Japan, for kindly supplying the *N*-isopropylacrylamide.

References

[1] Yoshida R, Uchida K, Kaneko Y, Sakai K, Kikuchi A, Sakurai Y, et al. Nature 1995;374:240.
[2] Hu ZB, Chen YY, Wang CJ, Zheng YY, Li Y. Nature 1998;393:149.
[3] Chu LY, Kim JW, Shah RK, Weitz DA. Adv Funct Mater 2007;17:3499.
[4] Ju XJ, Chu LY, Zhu XL, Hu L, Song H, Chen WM. Smart Mater Struct 2006;15:1767.
[5] Xiao XC, Chu LY, Chen WM, Wang S, Li Y. Adv Funct Mater 2003;13:847.
[6] Zhang J, Chu LY, Li YK, Lee YM. Polymer 2007;48:1718.
[7] Zhang J, Xie R, Zhang SB, Cheng CJ, Ju XJ, Chu LY. Polymer 2009;50:2516.
[8] Qu JB, Chu LY, Yang M, Xie R, Hu L, Chen WM. Adv Funct Mater 2006;16:1865.
[9] Kim SJ, Spinks GM, Prosser S, Whitten PG, Wallace GG, Kim SI. Nat Mater 2006;5:48.
[10] Juodkazis S, Mukai N, Wakaki R, Yamaguchi A, Matsuo S, Misawa H. Nature 2000;408:178.
[11] Tatsuma T, Takada K, Miyazaki T. Adv Mater 2007;19:1249.
[12] Kwon IC, Bae YH, Kim SW. Nature 1991;354:291.
[13] Satarkar NS, Hilt JZ. J Control Release 2008;130:246.
[14] Wang W, Liu L, Ju XJ, Zerrouki D, Xie R, Yang L, et al. ChemPhysChem 2009;10:2405.
[15] Holtz JH, Asher SA. Nature 1997;389:829.
[16] Brahim S, Narinesingh D, Guiseppi-Elie A. Biosens Bioelectron 2002;17:973.
[17] Chu LY, Li Y, Zhu JH, Wang HD, Liang YJ. J Control Release 2004;97:43.
[18] Ehrick JD, Deo SK, Browning TW, Bachas LG, Madou MJ, Daunert S. Nat Mater 2005;4:298.
[19] Zhang SB, Chu LY, Xu D, Zhang J, Ju XJ, Xie R. Polym Adv Technol 2008;19:937.
[20] Ju XJ, Chu LY, Liu L, Mi P, Lee YM. J Phys Chem B 2008;112:1112.
[21] Ju XJ, Zhang SB, Zhou MY, Xie R, Yang L, Chu LY. J Hazard Mater 2009;167:114.
[22] Qiu Y, Park K. Adv Drug Deliv Rev 2001;53:321.
[23] Hoffman AS. Adv Drug Deliv Rev 2002;54:3.
[24] Soppimath KS, Aminabhavi TM, Dave AM, Kumbar SG, Rudzinski WE. Drug Dev Ind Pharm 2002;28:957.
[25] Chu LY, Yamaguchi T, Nakao S. Adv Mater 2002;14:386.
[26] Thornton PD, Mart RJ, Ulijn RV. Adv Mater 2007;19:1252.
[27] Hamidi M, Azadi A, Rafiei P. Adv Drug Deliv Rev 2008;60:1638.
[28] Cheng H, Zhu JL, Sun YX, Cheng SX, Zhang XZ, Zhuo RX. Bioconjug Chem 2008;19:1368.
[29] Yang M, Chu LY, Wang HD, Xie R, Song H, Niu CH. Adv Funct Mater 2008;18:652.
[30] Xie R, Zhang SB, Wang HD, Yang M, Li PF, Zhu XL, et al. J Membr Sci 2009;326:618.
[31] Dong L, Agarwal AK, Beebe DJ, Jiang H. Nature 2006;442:551.
[32] Calvert P. Adv Mater 2009;21:743.
[33] Beebe DJ, Moore J, Bauer J, Yu Q, Liu RH, Devadoss C, et al. Nature 2000;404:588.
[34] Eddington DT, Beebe DJ. Adv Drug Deliv Rev 2004;56:199.
[35] Stryer L. Biochemistry. New York: Freeman; 1988.
[36] Kuo HC, Cheng CF, Clark RB, Lin JJC, Hoshijima M, Nguyen-Tran VTB, et al. Cell 2001;107:801.
[37] Clausen T. Physiol Rev 2003;83:1269.
[38] Okajima S, Yamaguchi T, Sakai Y, Nakao S. Biotechnol Bioeng 2005;91:237.
[39] Okajima S, Sakai Y, Yamaguchi T. Langmuir 2005;21:4043.
[40] Yamaguchi T, Ito T, Sato T, Shinbo T, Nakao S. J Am Chem Soc 1999;121:4078.
[41] Ito T, Hioki T, Yamaguchi T, Shinbo T, Nakao S, Kimura S. J Am Chem Soc 2002;124:7840.
[42] Ito T, Sato Y, Yamaguchi T, Nakao S. Macromolecules 2004;37:3407.
[43] Ito T, Yamaguchi T. J Am Chem Soc 2004;126:6202.
[44] Ito T, Yamaguchi T. Angew Chem Int Ed 2006;45:5630.
[45] Ito T, Yamaguchi T. Langmuir 2006;22:3945.
[46] Hara N, Hidenori O, Ito T, Yamaguchi T. Macromolecules 2009;42:980.
[47] Ju XJ, Liu L, Xie R, Niu CH, Chu LY. Polymer 2009;50:922.
[48] Irie M, Misumi Y, Tanaka T. Polymer 1993;34:4531.
[49] Ju XJ, Chu LY, Mi P, Song H, Lee YM. Macromol Rapid Commun 2006;27:2072.
[50] Mi P, Chu LY, Ju XJ, Niu CH. Macromol Rapid Commun 2008;29:27.
[51] Ungaro R, El Haj B, Smid J. J Am Chem Soc 1976;98:5198.
[52] Yagi K, Ruiz JA, Sanchez MC. Makromol Chem Rapid Commun 1980;1:263.
[53] Lin SY, Liu SW, Lin CM, Chen CH. Anal Chem 2002;74:330.
[54] Yamauchi A, Hayashita T, Nishizawa S, Watanabe M, Teramae N. J Am Chem Soc 1999;121:2319.
[55] Xie R, Li Y, Chu LY. J Membr Sci 2007;289:76.