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Novel temperature-sensitive, β-cyclodextrin-incorporated poly(*N*-isopropylacrylamide) hydrogels for slow release of drug

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Abstract Novel temperature-sensitive poly(*N*-isopropylacrylamide) hydrogels containing water-soluble β-cyclodextrin polymer were prepared by forming semi-interpenetrating polymeric networks. Compared to the conventional poly(*N*-isopropylacrylamide) gel, the β-cyclodextrin-incorporated hydrogels showed the same lower critical solution temperature due to the independence of the β-cyclodextrin polymer in the networks. The release time of ibuprofen from the novel gel was significantly prolonged, which was presumably attributed to the formation of the inclusion complexes between the cyclodextrin groups and the drug molecules.

Keywords Temperature-sensitive · Poly(*N*-isopropylacrylamide) · β-Cyclodextrin · Hydrogel · Drug delivery system

Introduction

Due to the special phase transition property, i.e. the gel constituents becoming insoluble below or above a particular temperature, called the lower or upper critical solution temperature (LCST or UCST), temperature-sensitive hydrogels have been widely investigated to design the drug delivery systems in the past decades [1–5]. Poly(*N*-isopropylacrylamide) (PNIPA) hydrogel shows a LCST at ~33°C [6], and the gels swollen at room temperature become aggregated when the temperature is increased above LCST. As used in biomedical applications, conventional PNIPA hydrogel exhibits some limitations, such as the weak mechanical strength, slow response rate to temperature stimulus and the fast release dynamics of small-molecule drugs. Many efforts have been made to improve the properties of the normal PNIPA hydrogel. For example, interpenetration of another network into PNIPA or increasing the hydrophobicity of the hydrogel could enhance the mechanical strength [3, 7]. Additionally, many kinds of PNIPA hydrogels with fast responsive kinetics to temperature changes have been prepared by different methods [8–13]. However, to our knowledge, little attention has been paid to investigate the prolonged release of small-molecule drugs from PNIPA hydrogel at room temperature.

Cyclodextrins (CDs), a group of cyclic oligosaccharides consisting of several glucopyranose units, have the polar hydrophilic outer shell and relatively hydrophobic cavity, which are good host molecules and can form inclusion complexes with some drug molecules through the host–guest interactions. Recently, the usefulness of the α-, β- and γ-CDs in the drug delivery systems has

been studied considering the stabilization, improvement in release and bioavailability of many drugs, and many advanced dosage forms have been designed [14, 15]. In this study, thermal-sensitive, β-CD-incorporating PNIPA hydrogels are prepared by interpenetrating water-soluble β-cyclodextrin-epichlorohydrin (EP-β-CD) polymers into the PNIPA hydrogels to form semi-interpenetrating polymeric networks (semi-IPN). Ibuprofen (IBU), as a model drug, was loaded into the hydrogels to investigate the release properties. We found that in contrast to that of normal PNIPA hydrogel, the release rate of the model drug from the β-CD containing gel was slower and the release time was greatly prolonged, which is probably due to the formation of inclusion compounds between the CD groups and the drug molecules.

Experimental

Materials

N-isopropylacrylamide (NIPA, Aldrich Chemical Co., Inc., USA) was purified by re-crystallization from a mixed solvent of benzene and *n*-hexane. β-cyclodextrin (β-CD), epichlorohydrin (EP), *N*,*N*′-methylene-bis(acrylamide) (BIS), ammonium persulfate (APS), *N*,*N*,*N*′,*N*′-tatramethylethylenediamine (TEMED) and sodium hydroxide (NaOH), all of analytical grade, were used without further purification as supplied by Shanghai Chemical Co (China). Ibuprofen (IBU) was kindly donated by Prof. Z.X. Shan (Department of Chemistry, Wuhan University).

Synthesis of the water-soluble β-cyclodextrin-epichlorohydrin (EP-β-CD)

EP-β-CD was synthesized according to the literature [16]. First, 5 g β-CD and 8 ml aqueous NaOH solution (33 wt%) were mixed at 30°C and stirred to allow β-CD to dissolve completely. Then, 3.45 ml EP was added rapidly and the reaction was kept at 30°C for 8 h. After adding acetone, the polymerization was stopped. Then, acetone was removed and the pH value of the solution was adjusted to 12 with hydrochloric acid (6 M). The temperature was increased to 50°C overnight. After cooling, the solution was dialyzed against double-distilled water for 4 days (molecular weight cut off 8,000–10,000). The polymer solution was freeze dried in a freeze-dry system (LANCONCO) for the following use. The average number molecular weight and the polydispersity of the polymer were determined by the light scattering measurement and their values are 259,000 and 1.14, respectively.

Synthesis of β-cyclodextrin-incorporated PNIPA hydrogel

NIPA, BIS and EP-β-CD were dissolved in 1.2 ml double-distilled water at room temperature. After adding 20 μl APS (33 wt%) and 20 μl TEMED as a pair of rodex initiators, the polymerization was carried out at 20°C for 12 h. Then, the gels were cut into discs (25 mm in diameter and 3 mm in thickness). Gel discs were immersed in double-distilled water at room temperature for 3 days, during which the water was replaced repeatedly to wash off the monomers and other chemicals. The feed composition of monomers and sample code are listed in Table 1.

Measurement of swelling ratio

The hydrogels were incubated in double-distilled water at least 24 h at each temperature point, and then the weight of the hydrogels was measured gravimetrically at temperature ranging from 24 to 41°C after blotting the excess water on the surface of the gels with moistened filter paper. Swelling ratio (SR) is defined as $SR = Ws/Wd$, where Ws is the weight of the water in the swollen hydrogels at a given temperature and Wd is the weight of the dried hydrogels.

Reswelling kinetics and drug-release study

EP40 gel was chosen as a typical representative to carry out the drug-delivery study, and the reswelling kinetics was also determined during the release experiment. EP0 and EP40 swollen at room temperature were dried under ambient conditions first and then under vacuum. The dried gels were immersed in IBU alcohol solution (2 mg/ml) for 3 days to reach equilibrium. The drug-loaded gels were placed at room temperature and 1 atm for three days, and then dried completely in vacuum.

Dried EP0 and EP40 hydrogels with the drug were put into 20 ml 0.1 M phosphate buffer solution (PBS, pH = 7.4) to carry out the release studies. At fixed time intervals, the concentrations of released IBU were measured and calculated by the absorption at 223 nm

Table 1 Feed composition of the β-CD-incorporated PNIPA hydrogels

Component	Sample code				
	EP0	EP10	EP20	EP30	EP40
NIPA (mg)	100	100	100	100	100
EP-β-CD (mg)	0	10	20	30	40
BIS (mg)	3	3	3	3	3
H_2O (ml)	1.2	1.2	1.2	1.2	1.2

using a UV-spectrometer (PERKIN ELMER, Lamda Bio40), and the drug solution was replaced by 20 ml fresh PBS. At the same time, the weight of the gel was noted to get the reswelling kinetics. The water uptake (WU) of the hydrogel is defined as follows: WU = Wt/Wd, where Wt is the weight of the water in gels at a particular time and Wd is the same as above.

Results and discussion

Figure 1 shows the equilibrium SR versus temperature, which illustrates the LCST behavior of the novel β-cyclodextrin-incorporated PNIPA hydrogels. It is clearly observed that the normal PNIPA hydrogel (EP0) and the β-CD-contained hydrogels exhibit similar SRs below the LCST. As the temperature is increased, the SRs of the gels decrease and a sharp reduction in SRs of all the gels occurs at ~33°C, which is regarded as their LCSTs. The hydrophilicity of the EP-β-CD is probably similar to that of the PNIPA, and the increase of EP-β-CD in PNIPA network does not increase the hydrophilicity of the gel system. Therefore, the SRs of all the gels are alike at the temperature below LCST. When phase transition takes place, the delicate hydrophilic/hydrophobic balance in the PNIPA network is broken and dehydration in the PNIPA network appears, which results in the aggregation of the PNIPA chains and the sharp volume change [17, 18]. The EP-β-CD polymer chains are interpenetrated into the PNIPA network, but are independent of the PNIPA backbone, and the hydrophilic/hydrophobic balance in the PNIPA chains determines the LCST, so the LCSTs of the hydrogels containing β-CD are the same as that of normal PNIPA gel.

Figure 2 displays the reswelling kinetics of the EP0 and EP40 in PBS at 25°C, as a function of the time. We found that the reswelling rate of EP40 is faster than that of EP0. In this process, three steps are proposed to occur in succession [19]: first, water molecules diffuse into the polymer system; second, the hydrated polymer chains become relaxed; and third, the polymeric network expands into the solution. Due to the existence of EP-β-CD polymers, which act as water-moving channels, water molecules might easily diffuse into the gel matrix, and hydration and expansion of the polymer chains might easily occur; therefore, the reswelling kinetics of EP40 is faster than that of EP0.

Figure 3 illustrates the cumulative release of IBU from the normal PNIPA gel (EP0) and β-CD contained hydrogel (EP40) as a function of time in PBS at 25°C. As shown in Fig. 3, there is a 'burst' release of IBU from both EP0 and EP40 gels in the first stage, and almost all of the IBU loading in the normal PNIPA gel (EP0) can be released out within 12 h. While for the hydrogel containing β-CD, the release rate is slower than that of conventional PNIPA gel, and the release time can be retarded to 48 h. When the dried drug-loaded gels were immersed in PBS, the drug molecules located on the surface during the drying process first diffused into PBS, so there is a 'burst' release for both gels, just as displayed in Fig. 3. For the dried glassy gels, the process of reswelling may control the release results, and the drug molecules diffuse by the exchange with the water molecules when the gels reswell in PBS. In this study, the reswelling rate of EP40 is faster than that of EP0 as discussed above; if reswelling dynamics completely dominates the drug release, the release rate of IBU from EP40

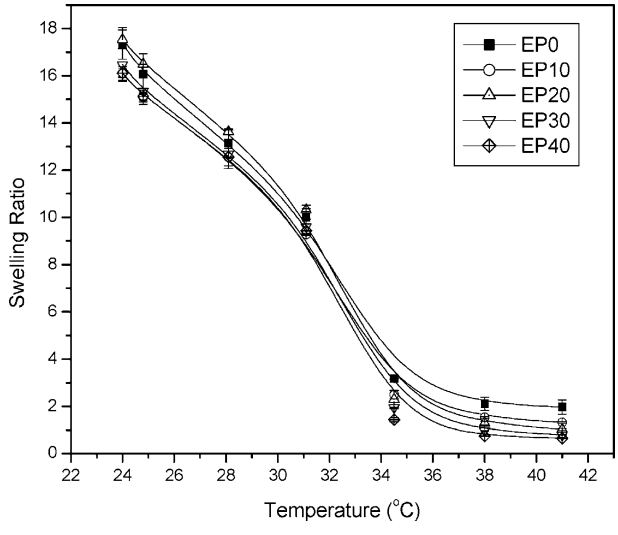

Fig. 1 Temperature dependence of the SRs of the PNIPA/EP-β-CD interpenetrating polymer network hydrogels in the temperature ranging from 24 to 41°C

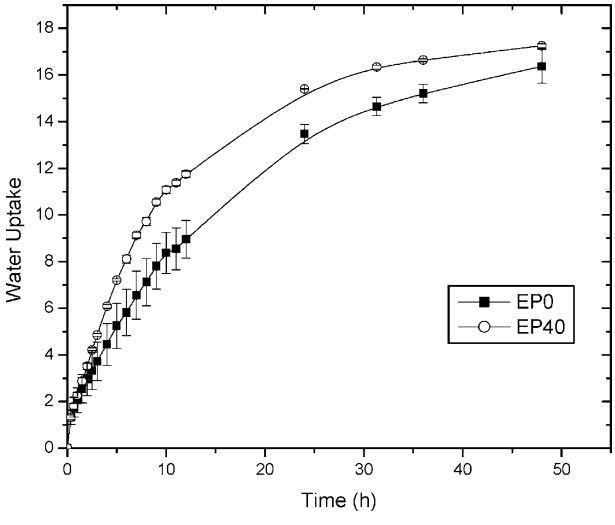

Fig. 2 Reswelling kinetics of the PNIPA/EP-β-CD interpenetrating polymer network hydrogel (EP40) and the normal PNIPA gel (EP0) as a function of the time in PBS at 25°C

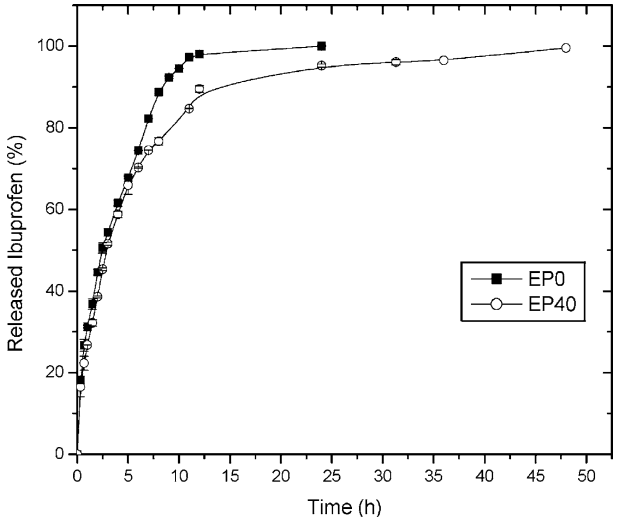

Fig. 3 Cumulative release of IBU from the normal PNIPA gel (EP0) and β-CD containing hydrogel (EP40) as a function of time in PBS at 25°C

should be quicker than that of normal PNIPA hydrogel (EP0). On the contrary, the release rate of IBU from EP40 is slower, suggesting that the β-CD groups within the EP40 gel network greatly influence the release kinetics. It is presumed that the inclusion complexes between β-CD and drug molecules may be formed during the drug-loading process, which decreases the exchange possibility between drug and water molecules and leads to the slow release of IBU from β-CD incorporated PNIPA hydrogel.

Conclusions

The newly synthesized PNIPA/EP-β-CD semi-interpenetrating polymeric networks exhibited temperature sensitivity similar to normal PNIPA hydrogel due to the PNIPA constituent. The release time of IBU from the dried β-CD-incorporated hydrogel (EP40) in PBS was markedly prolonged, which may be attributed to the other component, EP-β-CD, which can form the inclusion complexes with drug molecules through the host–guest interactions.

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References

1. Bromberg LE, Ron ES (1998) Adv Drug Deliv Rev 31:197
2. Ramkissoon-Ganorkar C, Liu F, BaudyŠ M, Kim SW (1999) J Control Release 59:287
3. Bae HB, Okano T, Hsu R, Kim SW (1987) Makromol Chem Rapid Commun 8:481
4. Zhang XZ, Zhuo RX, Cui JZ, Zhang JT (2002) Int J Pharm 235:43
5. Park TG (1999) Biomaterials 20:517
6. Hirokawa Y, Tanaka T (1984) J Chem Phys 81:6379
7. Muniz EC, Geuskens G (2001) Macromolecules 34:4480
8. Wu XS, Hoffman AS (1992) J Polym Sci Part A Polym Chem 30:2121
9. Zhang XZ, Zhuo RX (2000) Eur Polym J 36:2301
10. Zhang JT, Cheng SX, Huang SW, Zhuo RX (2003) Macromol Rapid Comunn 24:447
11. Zhang XZ, Zhuo RX (2000) Eur Polym J 36:643
12. Zhang JT, Cheng SX, Zhuo RX (2003) J Polym Sci Part A Polym Chem 41:2390
13. Zhang JT, Cheng SX, Zhuo RX (2003) Colloid Polym Sci 281:580
14. Hirayama F, Uekama K (1999) Adv Drug Deliv Rev 36:125
15. Loftsson T, Masson M (2001) Int J Pharm 225:15
16. Renard E, Deratani A, Volet G, Sebille B (1997) Eur Polym J 33:49
17. Otake K, Inomata H, Konno M, Saito S (1990) Macromolecules 23:283
18. Feil H, Bae YH, Feijen J, Kim SW (1993) Macromolecules 26:2496
19. Yoshida R, Okuyama Y, Sakai K, Okano T, Sakurai Y (1994) J Membr Sci 89:267