Materials Science & Engineering C 82 (2018) 284–290

Contents lists available at ScienceDirect

Materials Science & Engineering C

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

Multi-responsive hydrogels with UCST- and LCST-induced shrinking and controlled release behaviors of rhodamine B

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A B S T R A C T

By using a disulfide-functionalized crosslinker, a pH- and thermo-responsive 2-(dimethylamino) ethyl methacrylate (DMAEMA) monomer and a zwitterionic sulfobetaine methacrylate (SBMA) monomer were conjugated to fabricate a multi-responsive P(DMAEMA-SS-SBMA) copolymeric hydrogel. Apparent UCST and LCST volume transitions were observed in the P(DMAEMA-SS-SBMA) hydrogels with equivalent weight fractions of monomers. Different pore size and response sensitivity of shrunken structures below UCST and above LCST were visualized by SEM images. The hydrogel exhibited a highly swollen state with a swelling ratio of 17.8 and a pore size of 106 μm at 45 °C, they deswelled unequally at 5 °C with a compact surface with pore size of 30 μm and a loose bulk with pore size of 83 μm, while they deswelled uniformly at 65 °C with dense shrunken structure with small pore size of 12 μm. The dual-thermoresponsive hydrogel was promising in controlled drug release. The initial drug release was predominantly controlled by diffusion, and the long-term release was influenced by the swelling ratio. Below UCST, the relatively hydrophilic shrunken structure and slow diffusion had a synergistic effect on the sustained release. Above LCST, the fast diffusion and the rapid "off" effect of hydrophobic skin layer resulted in a burst release. Additionally, pH-tunable swelling and redox-sensitive degradation were also observed.

1. Introduction

Hydrogels are crosslinked hydrophilic polymer networks with three-dimensional structures. Due to their high water retention, excellent biocompatibility, high permeability for water-soluble drugs and particular biomimetic mechanical strengths [1,2], hydrogels are promising biomaterials for tissue-engineering scaffolds [3,4], wound dressing [5–7], cell culture matrix [8], drug delivery [9,10] and gene transfection [8]. Stimuli-responsive hydrogels can respond to external stimuli such as temperature [11], pH [12], salt [13], light [14], redox [15] and magnetic field [16]. In which, thermoresponsive hydrogels are the most commonly studied ones, which are usually composed of (*N*-isopropylacrylamide) (NIPAM), *N*-vinylcaprolactam (VCL), 2-(2-methoxyethoxy)ethyl methacrylate (MEO_2MA) and 2-(Dimethylamino)ethyl methacrylate (DMAEMA). Physically and chemically crosslinked thermoresponsive hydrogels can respectively undergo reversible gel–sol phase transitions and volume phase transitions around the lower critical solution temperature (LCST) of polymer systems. Based on the sol-gel phase transition of thermoresponsive polymers, Loh's group [17–20] has designed various injectable gels to be used in drug delivery [21–23] and tissue engineering [24], which is of great significance to the clinical development. Also, the volume phase transitions of thermoresponsive hydrogels with good mechanical properties are intensively studied and used in controlled drug release. Hydrogels with LCST volume phase transitions are often modified by the incorporation of pH-responsive monomers [25,26], hydrophobic monomers [27] and zwitterionic monomers [28,29] to obtain more versatile functions or enhanced mechanical strength [29,30]. However, hydrogels with the upper critical solution temperature (UCST) volume phase transitions are scarcely reported. Sulfobetaine methacrylate (SBMA) [31–33] is a UCST-type monomer and is usually incorporated into LCST-type hydrogels, which could decrease the swelling ratios of LCST-type hydrogels and suppress the thermosensitivity of the LCST volume phase transitions [25,30,31]. However, UCST volume transition was not observed in the copolymeric hydrogels composed of LCST and UCST monomers, presumably because of the slight swelling of PSBMA segment.

The reversible volume transition of stimuli-responsive hydrogel will achieve drug release at a specific site and time [34], avoiding repeated dosage and toxic side effects for other tissues [35]. LCST-type hydrogels usually exhibited an "on-off" effect on drug release [36]. Drug molecules diffused from the hydrogel at low temperatures, while they were trapped in the hydrogel by the "skin layer" resulted from the surface

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http://dx.doi.org/10.1016/j.msec.2017.08.067
Received 5 July 2017; Received in revised form 13 August 2017; Accepted 16 August 2017
Available online 18 August 2017
0928-4931/

shrinkage above LCST. However, it was also reported that drugs could be squeezed out above LCST because of the shrinkage of gels [37]. Some believed it was the lagged shrinkage between the bulk and the surface that resulted in the initial release. The incorporation of hydrophobic monomers into LCST-type hydrogels contributed to the rapid formation of "skin layer" and the complete "off" effect, while the incorporation of hydrophilic monomers resulted in incomplete "off" effect [27]. Yet no visualized evidence of the "skin layer" and the lagged shrinkage between the surface and the bulk was reported. Few reports were found about the drug release using UCST volume transition of hydrogels because the swelling and volume transition of PSBMA moiety were tiny. Wang [38] reported that poly(acrylic acid)/polyacrylamide hydrogel, an UCST-type hydrogel driven by hydrogen bonding, exhibited an obvious deswelling and slower release below UCST. In this paper, DMAEMA and SBMA were crosslinked by a crosslinker containing disulfide bonds. The obtained P(DMAEMA-SS-SBMA) hydrogels exhibited LCST/UCST/pH-sensitive swelling behaviors and biodegradable structures. It is apparent that different shrunken structres can be observed induced by the UCST and LCST volume transitions of the (PSBMA-SS-SBMA) hydrogels via scanning electron microscopy (SEM). The dual-thermoresponsive hydrogel was promissing as a wound dressing with "on-off" switching effect near UCST or LCST. And the difference in polarity and response sensitivity of the deswelled hydrogels below UCST and above LCST could resulted in different "off" effect on long-term drug release. Furthermore, the hydrogel can be degraded by glutathione (GSH) and reform in-situ with DMAEMA monomer.

2. Experimental section

2.1. Materials

2-(Dimethylamino)ethyl methacrylate (DMAEMA, 98%), [2-(methacryloyloxy)ethyl]dimethyl-(3-sulfopropyl) ammonium hydroxide (sulfobetaine methacrylate, SBMA, 97%), *N*,*N*′-bis(acryloyl)cystamine (BAC, 99%), ammonium persulfate (APS, 98%), *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TEMED, 99%), L-Glutathione reduced (GSH, 98%) and rhodamine B (RhB, 98%) were from Sigma-Aldrich. DMAEMA monomers were passed through a basic aluminum oxide column to remove the acidic inhibitors, and other materials were used as received.

2.2. Hydrogel preparation

P(DMAEMA-SS-SBMA) copolymeric hydrogels were prepared by free-radical cross-linking random polymerization using the feed ratios given in Table S1. A total of 50 wt% of different mass ratios of DMAEMA to SBMA was cross-linked by CBA (1.2 wt% to monomers) and initiated by APS (1.6 wt% to monomers). The samples with different monomer ratios of SBMA to DMAEMA were abbreviated as S#100, S#80, S#50 and S#20. After monomers and cross-linker dissolved and the solution bubbled with N_2, the initiator and the catalyst was added. After vortexing for several seconds, the solution was poured into two glass slides enclosed by a rubber spacer with a thickness of 1 mm and sealed with parafilm. Twelve hours later, the gel was punched into disks with diameter of 7.2 mm and immersed in a large amount of water to remove the chemical residues.

2.3. Characterization of P(DMAEMA-SS-SBMA) hydrogels

The swelling kinetics of the P(DMAEMA-SS-SBMA) hydrogels were measured gravimetrically. The disks were air dried to a constant weight (m_d) and then immersed in swelling media. After wiped superficially with blotting paper, the average weights (m_t) at certain moments were obtained. The swelling ratio (Q_t) was determined by the equation $Q_t = (m_t - m_d) / m_d$. The equilibrium weight (m_∞) of the swollen gel was considered to be the weight which kept constant after several measurements. And the equilibrium swelling ratio (Q_∞) was obtained similarly. The stimuli-responsive phase transition behaviors of the hydrogels were characterized by equilibrium swelling ratios in different swelling media. The swollen hydrogel (m_s) was air dried at room temperature and weighed (m_t) before equilibrium (m_d), and the water retention (WR) at different time points were calculated as: $WR = (m_t - m_d) / m_s$. The swollen hydrogels at different temperatures were freeze-dried and observed by scanning electron microscopy (SEM; JSM-6360LV). The pore sizes in SEM images were statistically counted by Nano Measurer 1.2.

2.4. Loading and release of rhodamine B

Rhodamine B (RhB) was used as a model drug to investigate the controlled release of the P(DMAEMA-SS-SBMA) hydrogel. A certain amount of RhB was dispersed in the polymerization system and loaded in the network during polymerization. The as-prepared hydrogels were punched into disks and immersed in the water at different temperatures. The concentration of RhB was monitored by the UV–Vis spectrophotometer and calculated from the standard curve of RhB (Fig. S1). The correlation equation was $A = 0.00434C - 0.00577$ ($R^2 = 1$). After the drug release reached the plateau, GSH was added to reach the concentration of 10 mM. Three hours later, the network was degraded and the total amount of RhB was determined. The loading efficiency and the cumulative release were defined as follows:

$$\text{Loading efficiency (\%)} = \frac{\textit{tatal amount of RhB}}{\textit{weight of dried hydrogel disk}} \times 100\%$$

$$\text{Cumulative release (\%)} = \frac{\textit{amount of RhB}}{\textit{total amount of RhB}} \times 100\%$$

The average loading efficiency was calculated to be 18.1%. The in vitro drug release kinetics (cumulative release vs time profiles) at different temperatures and pHs are plotted and compared.

3. Results and discussion

The swelling of hydrogel is codetermined by physical and chemical process. First, water molecules enter the matrix and hydrate the most polar and hydrophilic groups. Second, the polymer chains begin to stretch due to the hydrogen bond and the network becomes loose. The osmotic driving force promotes the network to absorb more water. Finally, the fully stretched polymer network tends to shrink due to the structural stress. The balance between the retraction force and the infinite dilution force make a swelling equilibrium. Therefore, the swelling behavior of hydrogels is influenced by the properties and composition of monomers, crosslinking density and swelling condition (temperature, pH and ionic strength).

3.1. Composition-dependent swelling kinetics

As shown in Fig. 1, the swelling properties of the hydrogels with different compositions differed greatly in deionized water at room temperature. PSBMA hydrogel (S#100) showed slight swelling with a remarkable overshoot. The overshoot was attributed to the formation of ionic pairs due to the hydration and approaching of zwitterionic PSBMA chains, which behaved as physical cross-linking points and expelled the water molecules out of the network. This phenomenon was also observed in the systems in which hydrogen bond [39,40] and ion interchange [41] existed. By incorporating of the DMAEMA monomer, the equilibrium swelling rate of the hybrid hydrogels increased and the overshooting effect disappeared. At the initial 2.5 h, the swelling kinetics of P(DMAEMA-SS-SBMA) disc can be well described by Fickian equation (Fig. S2), indicating a diffusion-controlled swelling at the early stage. With time went by, the hydrogel did not suitable for Fickian equation because of the increasing stress from the loose polymeric