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Stimulus-responsiveness and methyl violet release behaviors of poly(NIPAAm-*co*-AA) hydrogels chemically crosslinked with β-cyclodextrin polymer bearing methacrylates

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ABSTRACT

To fabricate thermo- and pH-sensitive hydrogels functionalized with β-cyclodextrin (β-CD) moieties, β-CD polymer bearing methacrylate (CDP-*g*-GMA) used as a reactive and functional crosslinker was synthesized, and then copolymerized with *N*-isopropylacrylamide (NIPAAm) and acrylic acid (AA) in aqueous solution via UV-initiated free radical polymerization. The stimulus-responsiveness of the resultant hydrogels has been carried out by measuring the swelling ratio at different temperatures and pH values. The results showed that the thermo- and pH-sensitivities of the produced hydrogels were significantly dependent on the compositions of the hydrogels, and the dual sensitivities exhibited good reversible process. The interior morphology observed by SEM exhibited that the pore size of the hydrogels could be tailored by pH of the local medium. Using a water-soluble cationic dye methyl violet (MV) as a model drug, MV loading and release profiles of the hydrogels as potential drug controlled release carriers were evaluated. The MV release rate from CD-functionalized hydrogels was much slower than that from the hydrogel without β-CDs at both pH 2.0 and pH 7.4. The release of MV from CD-functionalized hydrogels at pH 2.0 was faster than that at pH 7.4, the release kinetics of MV from the CD-functionalized hydrogels displayed a sustained release profile, and the release mechanism followed Fickian diffusion.

1. Introduction

Intelligent polymeric hydrogel systems have gained great interest in biomedical fields due to the modulation of their structure and function in response to various external stimuli such as temperature, pH, ionic field, light and so on.[1–3] Up to date, thermo- and/or pH-responsive hydrogels as drug delivery carriers have been dominantly investigated, owing to their temperature and/or pH-dependent swelling behaviors in physiological media, which could efficiently regulate the drug release profiles from the hydrogel matrices.[4,5] Among these stimuli-responsive hydrogels, poly(*N*-isopropylacrylamide) (PNIPAAm) and poly(acrylic acid) (PAA) are typical thermo- and pH-responsive hydrogels as feedback-regulated drug delivery systems, respectively.[6,7]

β-Cyclodextrin (β-CD) is a macrocyclic oligosaccharide consisting of seven α-1,4-linked D-glucopyranose units with an internal hydrophobic cavity, which provides pharmaceutically useful complexation characteristics for the widest range of drugs.[8–10] However, its application is limited in formulations due to low aqueous solubility and toxicity. An effective approach is to incorporate β-CD into the crosslinked network of the hydrogel; the CD-functionalized hydrogels display the synergic properties of β-CD and hydrogels in pharmacotherapy: the hydrophilic network structure enhances the biocompatibility and increases the stability of the inclusion complexes in the physiological medium, while β-CD finely tailors the mechanical features and provides affinity-based regulation of drug loading and release.[11–13] Such multifunctional materials open creative approaches to drug delivery systems (DDS) for hydrophobic as well as hydrophilic drugs via almost any route in a single material, expanding the scope of applications of the hydrogels.[14]

Until now, different strategies have been developed to construct CD-based hydrogels. Such hydrogel systems are frequently fabricated via condensation reaction using pristine β-CDs as building blocks and bi(multi)functional condensing molecules as crosslinking agent, such as epichlorohydrin (EPI), diisocyanates (2,4-diisocyanate (TDI) or hexamethylene diisocyanate (HDMI)), ethyleneglycol diglycidylether (EGDE), etc.[15–17] Chemical or physical interpenetration with poly(methacrylic acid) (PMAA) or poly(*N*-isopropylacrylamide) (PNIPAAm) into the resultant CD-based hydrogel network enables the stimuli-sensitive hydrogels the function of forming inclusion complexes with guest molecules.[18,19] However, the type of condensing agents and the versatility of the

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direct cross-linking methods are limited. An alternative to obtain CD-based hydrogels is to transform the β-CDs in monomers with one or more reactive double bonds that can be subsequently copolymerized with other vinyl/acrylic monomers via free radical polymerization. The preparation of monofunctionalized CD monomers is quite challenging, since the large amount of hydroxyl groups are available in each CD molecule.[20,21] A multifunctional β-CD derivative (MAH-β-CD) was designed via condensation reaction of β-CD with maleic anhydride (MAH); copolymerization of MAH-β-CD with NIPAAm resulted in thermo- and pH-responsive hydrogels, such hydrogels have been proposed to uptake chlorambucil and released it at pH-dependent rate. However, MAH-β-CD displayed a relatively weak reactive character.[22]

In the present study, a feasible approach was developed to prepare β-CD-functionalized thermo- and pH-sensitive hydrogels. First of all, preferentially linear β-CD polymer (CDP) was prepared according to previously reported method.[23] Second, β-CD polymer bearing methacrylates (CDP-*g*-GMA), used as photopolymerizable and functional crosslinker, was prepared via the ring-opening reaction between the resultant β-CD polymer and glycidyl methacrylate (GMA). Third, UV-photo-crosslinking of *N*-isopropylacrylamide (NIPAAm), acrylic acid (AA) and CDP-*g*-GMA was then carried out in aqueous solution to produce β-CD-functionalized poly(NIPAAm-*co*-AA) hydrogels. The temperature and pH dependence of the resultant hydrogels and their reversibility were investigated under variation of temperature and pH of the local medium. Using a water-soluble cationic dye methyl violet (MV) as a model drug, loading and release profiles of MV from the hydrogels as potential drug controlled release carriers were also evaluated.

2. Experimental

2.1. Materials

β-Cyclodextrin (β-CD), epichlorohydrin (EPI), toluene, acrylic acid (AA), obtained from Shanghai Reagent Corp. (China), were of analytical purity grade; β-CD was recrystallized twice from water prior to use and dried under vacuum at 90 °C; AA was distilled before use. *N*-isopropylacrylamide (NIPAAm, 97%), obtained from Aldrich (USA), was recrystallized with hexane. Glycidyl methacrylate (GMA, 97%) was imported from Aldrich (USA) and 4-dimethylaminopyridine (DMAP, 99%) was provided from TCI (Japan). *N*-vinyl-2-pyrrolidone (NVP, 97%) and 2,2-dimethoxy-2-phenyl acetophenone (DMPA) as the photoinitiator were supplied by Fluka (Switzerland) and used as received. Poly(ethylene glycol) dimethacrylate ($M_n \approx 550$) was purchased from Aladdin (Shanghai, China). The other chemicals were of analytical grade and used without further purification.

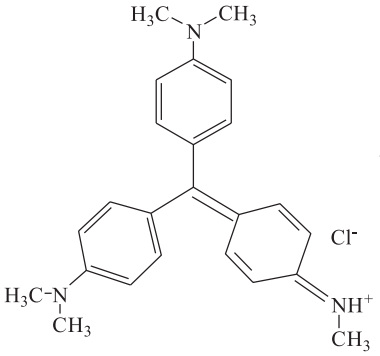
Dye methyl violet (MV) was purchased from Shanghai Reagent Corp. (China), and its chemical structure and characteristics are exhibited in Table 1.

2.2. Synthesis of β-CD polymer (CDP) and CDP-g-GMA

Mainly linear β-CD polymer (CDP) was prepared as reference described.[23] Briefly, 15 g of β-CD was dissolved by stirring in 23 mL of 18 wt% NaOH aqueous solution. The mixture was stirred for 4 h at 35 °C, and 1.22 g of toluene was added and stirred continually for 3 h, and then 6.14 g of EPI was added to the mixture. After stirring for 3 h at 35 °C, the crude product was precipitated in an excess of acetone. The precipitation was dissolved in water, neutralized by dilute hydrochloric acid and dialyzed against distilled water for 7 days (MWCO = 8,000); a white powder was obtained via lyophilization. Yield: 65%. M_n (SEC): 4.46×10^5, $M_w/M_n = 1.64$.

CDP-*g*-GMA was synthesized via the ring-opening reaction of the hydroxyl groups of CDP with epoxy group of GMA using DMAP as a catalyst, similar to previously reported method.[24] Twelve grams of above-mentioned CDP was dissolved in 100 mL of dried DMF in a 250-mL round-bottomed flask; 0.25 g of GMA and 0.15 g of DMAP were added to the solution. The mixture was stirred at room temperature for 48 h. The crude product was precipitated in an excess acetone, and then filtered, dried, washed three times with acetone. The precipitate was dried under vacuum at room temperature for 48 h.

Table 1
Chemical structure and characteristics of methyl violet (MV) in this study

Name	Chemical structure	Molar mass (g mol^{-1})	Color index number	λ_{max} (nm)
Methyl violet (MV)		407.99	42535	584

2.3. Preparation of the CD-functionalized poly(NIPAAm-co-AA) hydrogels

To prepare the CD-functionalized dual-sensitive hydrogels, NIPAAm, AA monomers and CDP-*g*-GMA as a crosslinker were dissolved in 15 g of distilled water at room temperature. Then a certain amount of photoinitiator solution of DMPA in NVP (100 mg mL^{-1}) was added to the solution. The mixture was added to a Teflon model and exposed to a 365 nm LWUV lamp of 16 W (ZF-7A type, Shanghai Jinhui Scientific Instrumental Co., Ltd.) for 15 min to produce the crosslinked polymeric network. The feed compositions and the illustration for preparation of the hydrogels in this study are shown in Table 2 and Scheme 1, respectively. In order to evaluate the effect of β-CD moieties in the copolymerized hydrogels on MV loading and release profile, Gel-0 hydrogel sample was also prepared according to the feed composition of Gel-1 sample using poly(ethylene glycol) dimethacrylate ($M_n \approx 550$) as a crosslinker instead of CDP-*g*-GMA.

The just obtained hydrogels were punched into disks with 10 mm diameter and 2 mm thickness. To remove the unreacted monomers and other impurities, the samples were immersed in distilled water for 3 days at 15 °C, and the distilled water was refreshed every day. The purified samples were first dried at room temperature for 2 days, and then dried at 80 °C under vacuum to constant weight.

Table 2
The feed compositions for synthesis of dual-sensitive hydrogels in the study

Sample code	Feed compositions			
	AA (g)	NIPAAm (g)	CDP-g-GMA (g)	H_2O (g)
Gel-0	0.12	3.6	0.35[a]	15
Gel-1	0.12	3.6	0.65	15
Gel-2	0.41	3.6	0.65	15
Gel-3	0.99	3.6	0.65	15

[a] Gel-0 sample using poly(ethylene glycol) dimethacrylate ($M_n \approx 550$) as the crosslinker instead of CDP-*g*-GMA.