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Synthesis of photoresponsive hybrid alginate hydrogel with photo-controlled release behavior

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ABSTRACT

A photoresponsive hybrid alginate hydrogel was successfully prepared by Ca^{2+}-mediated crosslinking reaction with a mixture of β-cyclodextrin-grafted alginate (β-CD-Alg) and diazobenzene-modified poly(ethylene glycol) (Az_2-PEG). The water-soluble Az_2-PEG exhibits efficient *trans*-to-*cis* isomerization of the terminal azobenzene moieties under UV-light irradiation and readily switched back to the initial *trans* state under visible light. Because of low affinity between β-CD and *cis*-Az, the host–guest inclusion complex formed by β-CD and *trans*-Az gradually dissociates under UV-light exposure. Accordingly, the bulk gel exhibits substantial photo-induced transformation in gel morphology by the appearance of significant comb-like cavities. This photosensitive behavior accompanied by the structural degradation enables the rapid release of entrapped dye molecules under UV light stimulus. Moreover, an incident light with higher power and mild acidic environment are capable of accelerating the photo-triggered release, thus allowing the potential applications toward acute wound healing.

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1. Introduction

Alginate, which is commonly isolated from brown algae, is an anionic linear polysaccharide composed of two saccharides: epimeric β-D-mannuronate (M) and α-L-guluronate (G). The M and G monomers are covalently bonded through 1,4-glycosidic linkages and arranged into either homopolymeric blocks (MM and GG) or alternating blocks (MGMG) along the polymeric backbone (Martins, Sarmento, Souto, & Ferreira, 2007; Gattás-Asfura & Stabler, 2009; García-González, Alnaief, & Smirnova, 2011; Gong et al., 2011; Goh, Heng, & Chan, 2012). According to the "egg-box" model, two facing GG blocks can be coordinated with divalent ca^{2+} ions, resulting in interchain crosslinking and hydrogel formation (Sikorski, Mo, Skjåk-Bræk, & Stokke, 2007; Coleman et al., 2011; Narayanan, Melman, Letourneau, Mendelson, & Melman, 2012; Cui et al., 2013).

Alginate hydrogels have high water content, elasticity, and the ability to maintain a physiologically moist microenvironment in the wound bed; therefore, they are widely applied in tissue engineering (Patterson, Martino, & Hubbell, 2010; Sun & Tan, 2013; Bozza et al., 2014). Moreover, alginate wound dressings can accommodate drugs and gradually release the drugs during the process of gel swelling to prevent wound infection (August, Kong, & Mooney, 2006; Bencherif et al., 2012; Pereira et al., 2013). However, alginates especially rich in GG blocks can incorporate more ionic interactions between chains and usually form a gel with high mechanical integrity. Therefore, during the controlled release of drugs, a bulk alginate hydrogel is less responsive to external stimuli such as temperature, pH level, and mechanical force. Recently, Han et al. (2012) presented a pH-sensitive shape-memory alginate hydrogel prepared by crosslinking a β-cyclodextrin (β-CD)-modified alginate and a diethylenetriamine-modified alginate. Ariga and co-workers reported a controlled release system containing a β-CD-crosslinked alginate gel triggered by a mechanical stimulus (Izawa et al., 2013). The release of drugs from this gel system was enhanced through mild mechanical compression because of a change in the host–guest inclusion ability of CD moieties for accommodating drug molecules.

Semiinterpenetrating networks (semi-IPNs) that are composed of one crosslinked polymer system in which free polymer chains are dissolved are capable of modulating the bulk properties of gel networks (Matricardi, Pontoriero, Coviello, Casadei, & Alhaique, 2008; Pescosolido et al., 2011). In semi-IPN systems, both crosslinked and free polymers synergistically contribute to the physicochemical properties of hybrid gels. Based on this concept, we developed a photoresponsive hybrid alginate semi-IPN that contains crosslinked β-CD-grafted alginate (β-CD-Alg) and

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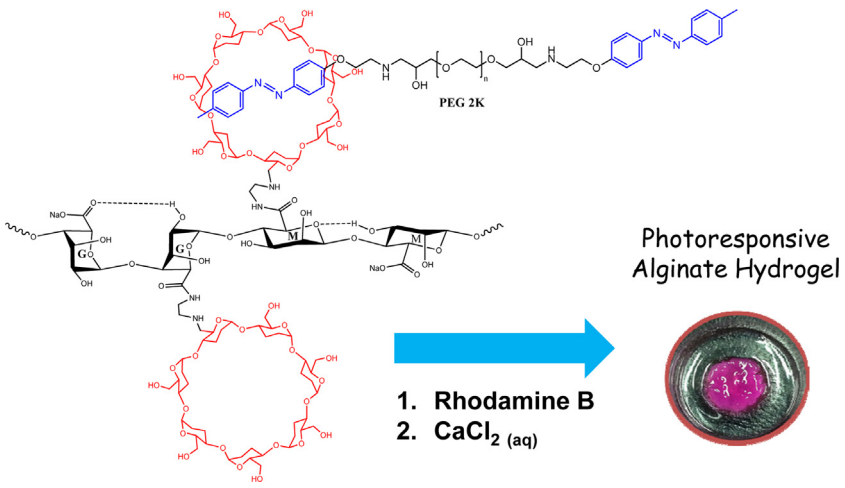


Scheme 1. Preparation protocol of a photoresponsive hybrid alginate hydrogel that contains crosslinked β-CD-grafted alginate (β-CD-Alg) and interpenetrating diazobenzene-terminated poly(ethylene glycol) (Az_2-PEG). Red-colored rhodamine B (RhB) is the mimic of entrapping drug molecules.

interpenetrating diazobenzene-terminated poly(ethylene glycol) (Az_2-PEG), as shown in Scheme 1. Because of the size and shape of the CD cavity, *trans*-Az and β-CD can form a favorable inclusion complex through host–guest affinity, whereas *cis*-Az is excluded from the complexation (Yuen & Tam, 2010; Tan et al., 2012). Therefore, the hybrid gel network features Ca^{2+} ions as cross-linkers as well as numerous junction points composed of β-CD and *trans*-Az inclusion complexes. Moreover, UV light irradiation induces efficient *trans*-to-*cis* isomerization (Peng, Tomatsu, & Kros, 2010; Tamesue, Takashima, Yamaguchi, Shinkai, & Harada, 2010; Meng et al., 2011). Accordingly, the hybrid alginate hydrogel is sensitive to the UV light used to facilitate *trans*-to-*cis* photoisomerization, which results in the dissociation of the inclusion complex and partial gel degradation. Thus, a light trigger can accelerate the release rate of small molecules entrapped within the gel. In addition to causing spontaneous drug release during gel swelling, this strategy entails using a bulk alginate hydrogel as a photocontrollable release system.

2. Experimental

2.1. General methods

All reactions were carried out under a nitrogen atmosphere. All solvents were dried following standard procedures. Sodium alginate (M_w = 1.2–1.4 × 10^5 Da) and *poly(ethylene glycol) diglycidyl ether* (M_n = 2 × 10^3 Da) were purchased from Sigma-Aldrich, and other chemical reagents were obtained as *high-purity reagent-grade* from commercial suppliers and used without further purification. Flash column chromatography was performed on spherical silica gel with 75-200 um particle dimensions. ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra were recorded on a Varian Mercury Plus 400 MHz spectrometer *at room temperature*. Spectral processing (Fourier transform, peak assignment and integration) was performed using MestReNova 6.2.1 software. *Trans*/*cis* photoisomerization for the azobenzene-containing polymers dissolved in organic solvents was carried out under the exposure of light-emitting diodes (LEDs) at 365 and 470 nm and an output power of 10 W. Ultraviolet–visible (UV–vis) absorption spectra were performed on a Thermo Genesys 10S UV–vis spectrometer equipped with a thermostatic cuvette holder. Field emission scanning electron microscopy (FE-SEM) was performed on a Jeol JSM-6700F instrument equipped with a cold-cathode field emission gun. The UV–vis measurement was carried out under a constant temperature. The relative viscosity (η_r) measurement was performed on an Ostwald–Fenske viscometer using distilled water as a standard.

The hydrogel samples containing rhodamine B (RhB) with a strong fluorescence at λ_{max} = 580 nm were irradiated with 365 nm LED, and the reflective emission from the samples were collected and induced by a fiber bundle into a CCD imaging spectrometer (USB-4000, Ocean Optics) for the spectra recording. To carry out *trans*-to-*cis* photoisomerization, the samples were also excited by 365 nm LED for a specific time interval and in situ analyzed by the same experimental apparatus (see Fig. S1 in Supporting information).

2.2. Materials synthesis and characterization

2.2.1. Synthesis of (E)-4-(p-tolyldiazenyl)phenol (**1**)

An aqueous solution of $NaNO_2$ (1.91 g, 27.7 mmol) was slowly added into a solution of p-toluidine (1.52 g, 14.2 mmol) in 30 mL of 3 M HCl, and then the mixture was stirred under 0 °C for 30 min, followed by adding an aqueous buffer solution containing phenol (1.71 g, 18.2 mmol), NaOH (0.73 g, 18.2 mmol), and Na_2CO_3 (1.93 g, 18.2 mmol). After stirred at 0 °C for 30 min, the mixing solution was extracted by ethyl acetate for 3 times. The combined organic phase was dried over anhydrous magnesium sulfate, and rotary evaporation to dryness afforded the crude product. Further purification was performed on flash column chromatography (SiO_2, ethyl acetate/hexane = 2:8, R_f = 0.4) to yield the final product **1** as orange solid (2.41 g, 80%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.84 (d, J = 8.8 Hz, 2*H*), 7.78 (d, *J* = 8.3 Hz, 2*H*), 7.29 (d, *J* = 8.3 Hz, 2*H*), 6.91 (d, *J* = 8.8 Hz, 2*H*), 5.74 (bs, 1*H*), 2.42 (s, 3*H*).

2.2.2. Synthesis of (E)-1-(4-(2-bromoethoxy)phenyl)-2-(p-tolyl)diazene (**2**)

To a anhydrous THF solution of **1** (1.5 g, 7.1 mmol), K_2CO_3 (6.8 g, 49 mmol), and 18-crown-6 (20 g, 75 mmol), 1,2-dibromoethane (27 g, 0.14 mol) was added dropwisely over 30 min under N_2 atmosphere. The mixture was stirred at 45 °C for overnight and then extracted by ethyl acetate for 3 times. The combined organic phase was dried over anhydrous magnesium sulfate, and rotary evaporation to dryness afforded the crude product. Further purification was performed on flash column chromatography (SiO_2, ethyl acetate/hexane = 2:8, R_f = 0.6) to yield the final product **2** as orange solid (1.9 g, 84%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.90 (d, *J* = 9.1 Hz, 2*H*), 7.79 (d, *J* = 8.3 Hz, 2*H*), 7.30 (d, *J* = 8.3 Hz, 2*H*), 7.01 (d, *J* = 9.1 Hz, 2*H*), 4.36 (t, *J* = 6.3 Hz, 2*H*), 3.67 (t, *J* = 6.3 Hz, 2*H*), 2.43 (s, 3*H*).

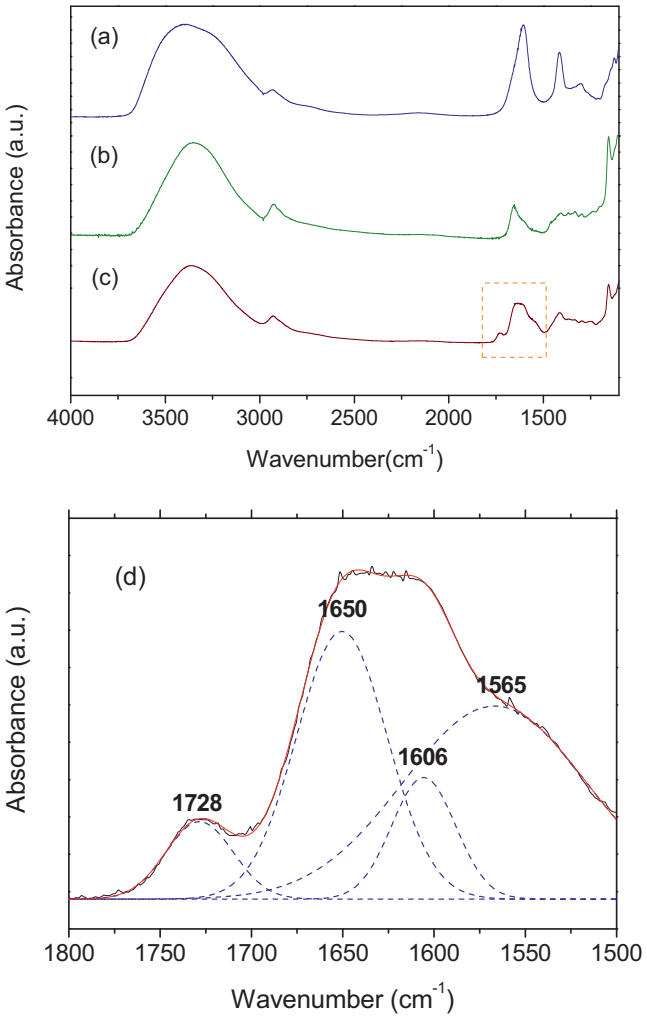


Fig. 1. FT-IR spectra of (a) sodium alginate, (b) mono-6-amino-β-CD, and (c) β-CD-Alg. (d) Peak deconvolution in the selected region shows the characteristic amide stretching at 1650 and 1565 cm^{-1}, and carboxylate stretching at 1606 cm^{-1}.

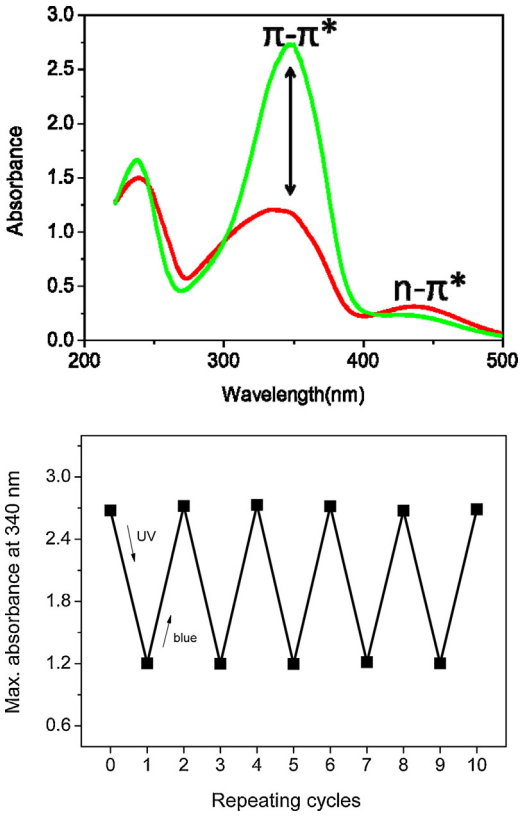


Fig. 2. (a) The absorbance change in π–π* and n–π* transitions of *Az_2-PEG* solution upon 365-nm LED excitation. (b) Reversible change in π–π* absorbance by alternating 365-nm and 470-nm light irradiation.

2.2.3. Synthesis of (E)-1-(4-(2-azidoethoxy)phenyl)-2-(p-tolyl)diazene (**3**)

An anhydrous DMF solution of **2** (1.5 g, 4.7 mmol) and NaN_3 (3.2 g, 49 mmol) was stirred at 100 °C for overnight under N_2 atmosphere. The DMF was removed under vacuum, and then the mixture was extracted by ethyl acetate for 3 times. The combined organic phase was dried over anhydrous magnesium sulfate, and rotary evaporation to dryness afforded the final product **3** (1.1 g, 83%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.91 (d, J = 9.1 Hz, 2*H*), 7.79 (d, J = 8.3 Hz, 2*H*), 7.30 (d, J = 8.3 Hz, 2*H*), 7.02 (d, J = 9.1 Hz, 2*H*), 4.22 (t, J = 6.3 Hz, 2*H*), 3.64 (t, J = 6.3 Hz, 2*H*), 2.43 (s, 3*H*).

2.2.4. Synthesis of (E)-2-(4-(p-tolyldiazenyl)phenoxy)ethanamine (**Az**)

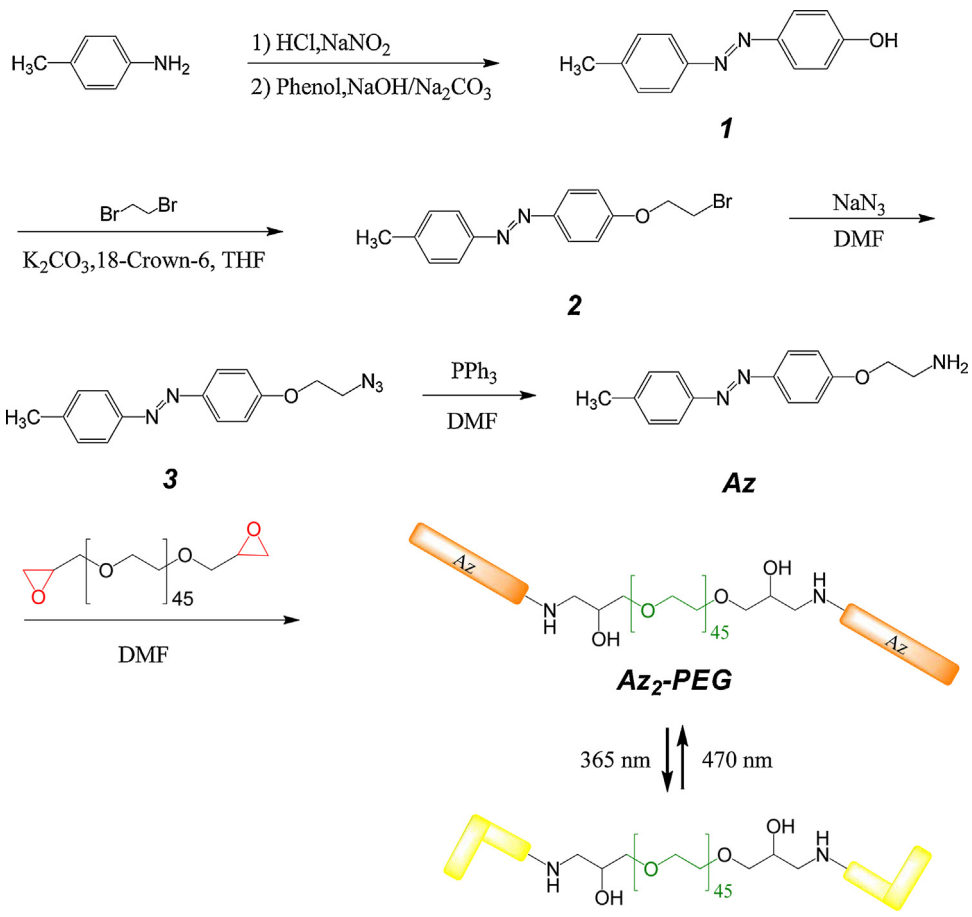
An anhydrous DMF solution of **3** (1.5 g, 5.3 mmol) and PPh_3 (6.3 g, 24 mmol) was stirred at room temperature for 2 h under N_2 atmosphere, followed by adding 5.3 mL of water and then stirred at 90 °C for another 3 h. The DMF was removed under vacuum, and then the mixture was extracted by ethyl acetate for 3 times. The combined organic phase was dried over anhydrous magnesium sulfate, and rotary evaporation to dryness afforded the crude product. Further purification was performed on flash column chromatography (SiO_2, methanol, R_f = 0.3) to yield the final product **Az** as orange solid (1.1 g, 81%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.90 (d, J = 9.0 Hz, 2*H*), 7.79 (d, J = 8.5 Hz, 2*H*), 7.29 (d, J = 8.5 Hz, 2*H*), 7.01 (d, J = 9.0 Hz, 2*H*), 4.06 (t, J = 5.1 Hz, 2*H*), 3.12 (t, J = 5.1 Hz, 2*H*), 2.42 (s, 3*H*) 1.39 (bs, 2*H*).

2.2.5. Synthesis of diazobenzene-terminated poly(ethylene glycol) (***Az_2*-PEG**)

An anhydrous DMF solution of **Az** (0.13 g, 0.51 mmol) and poly(ethylene glycol) diglycidyl ether (0.5 g, 0.25 mmol) was stirred at 100 °C under N_2 atmosphere until the complete disappearance of **Az**. The DMF was removed under vacuum, and then the mixture was extracted by ethyl acetate for 3 times. The combined organic phase was dried over anhydrous magnesium sulfate, and rotary evaporation to dryness afforded the crude product. Further purification was performed on flash column chromatography (SiO_2, methanol, R_f = 0.6) to yield the final product **Az_2-PEG** as dark-yellow solid (0.4 g, 80%).

2.2.6. Synthesis of β-cyclodextrin-grafted alginate (β-CD-Alg)

The mono-6-amino-β-CD was synthesized following the published procedure (Lin, Tsai, Tu, Jeng, & Chu, 2013). An aqueous buffer solution containing sodium alginate (108 mg, 2.4 mmol of COOH) and *N*-hydroxysuccinimide (1.61 g, 13.9 mmol) was slowly added by another aqueous solution of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (2.67 g, 13.9 mmol). The reaction mixture was stirred at 4 °C for 10 min, followed by adding an aqueous solution of mono-6-amino-β-CD (2.82 g, 2.4 mmol). After reacting for another 12 h, the mixture was purified by membrane dialysis (molecular weight cut-off = 12,000–14,000 Da) against water for 3 days until complete removal of all the reagents, and lypophilization yields the final product as white powder. The ^{1}H NMR spectra are shown in Fig. S1. Based on the integral peak area (S1) of characteristic H-1 proton of β-CD (δ = 5.1 ppm) and the integral peak area (S2) of alginate protons from δ = 3.5–4.0 ppm,



Scheme 2. Synthetic route of diazobenzene-terminated poly(ethylene glycol) (Az_2-PEG).

degree of substitution (DS) of β-CD along the polymer was determined following the relationship of DS = (S1/7)/[(S2-4S1)/4] (Han et al., 2012).

2.2.7. *Preparation of hybrid alginate hydrogel*

An aqueous solution containing β-CD-Alg (15 mg), Az_2-PEG (7 mg), and RhB (10^{-2} M, 0.5 mL) was blended thoroughly by vortex mixer, and the hydrogel was immediately formed as the mixture was added into 10% of $CaCl_2$ solution through a syringe. The bulk hydrogel was repeatedly rinsed with water until free red-colored dye molecules was completely removed from the gel network.

3. Results and discussion

Alginate polymers with varying degrees of β-CD substitution were first synthesized through carbodiimide-promoted amidation by using a commercially available sodium alginate and mono-6-amino-β-CD in various feeding ratios with respect to the carboxylate groups in an 2-(*N*-morpholino)ethanesulfonic acid (MES) buffer (pH = 5.8) (Yang, Xie, & He, 2011). The resulting polymers were purified through dialysis to remove unreacted β-CD derivatives and then characterized using ^{1}H NMR and FT-IR analysis. Although the proton resonance exhibited by the polysaccharides on the β-CD ring and the alginate backbone substantially overlapped in the range of δ = 3.5 – 4.0 ppm, the appearances of the characteristic anomeric protons at δ = 5.1 ppm clearly indicated that β-CD was functionalized onto the alginate (Fig. S2) (Han et al., 2012; Izawa et al., 2013; Lin et al., 2013). Moreover, IR peak deconvolution in the selected region, confirming that an amide bond (I: 1650 and II: 1565 cm^{-1}) joined the alginate and β-CD, and free carboxylate stretching was 1606 cm^{-1} (Fig. 1).

The relative viscosity (η_r) measurement for 1 wt% aqueous solutions of pristine alginate and β-CD-Alg indicated that the η_r values of the polymer solutions decreased as the β-CD feeding ratios increased (Fig. S3). This result confirmed that β-CD-Alg with various β-CD grafting ratios was synthesized and that the dangling β-CD moieties along the alginate backbone effectively reduced the viscosity of the polymer solution. In preparing an alginate hydrogel, the viscosity of the alginate solution is critical, and therefore the degree of β-CD substitution was optimized. In addition, because the alginate crosslinking was mainly attributed to the coordination of Ca^{2+} ions with the carboxylate groups of two facing GG blocks, nonselective β-CD functionalization onto either M or G units exerted a substantial influence on the crosslinking property of the hydrogel. We discovered that higher β-CD grafting ratios along the backbone prohibited the crosslinking of each polymer chain and, thus, formed hydrogels may lose their mechanical integrity. Therefore, for preparing a crosslinkable hydrogel with a suitable mechanical strength, the feeding molar ratio of β-CD to the carboxylate groups were determined to be 1, and the average degree of substitution was approximately 0.17 according to NMR analysis.

The Az_2-PEG, which acted as the second component in the semi-IPN gel system, was simply prepared through a substitution reaction of diepoxy PEG with amine-modified Az (Scheme 2). The photoisomerization of the Az molecules at PEG chain ends was analyzed using UV–vis absorption spectra. As shown in Fig. 2a, the decrease in π–π* absorbance from 2.6 to 1.2 at λ_{max} = 340 nm clearly confirmed that *trans*-to-*cis* isomerization occurred upon UV light irradiation, and alternating UV and visible light

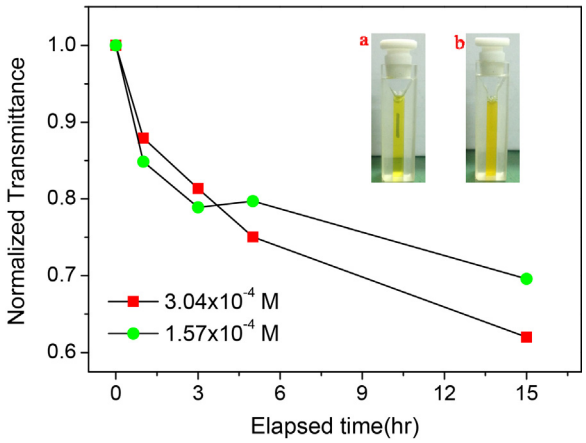


Fig. 3. The change in transmittance at λ = 630 nm for an aqueous mixture containing *Az_2-PEG* and *β-CD*. The image shows a transparent solution (a) becomes opaque (b), indicating the formation of host–guest inclusion complex of these two components.

exposure resulted in a rapid, reversible photoswitch between the *trans* and *cis* states (Fig. 2b). Moreover, the host–guest reaction between Az_2-PEG and β-CD was characterized according to the turbidity of the complex solution by using an incident beam at 630 nm (Ikeda, Ooya, & Yui, 1999). As shown in Fig. 3, the initial transparent solution became turbid after the two components were mixed for 1 h, and the transmittance decreased to approximately 65%. This result confirmed that inclusion complexes formed.

The hybrid alginate hydrogel was prepared through the dropwise addition of the β-CD-Alg (15 mg/mL) and Az_2-PEG (7 mg/mL) mixtures into an aqueous $CaCl_2$ solution. To mimic the release of small drug molecules, red-colored rhodamine B (RhB) with a strong fluorescence at λ_{max} = 580 nm was incorporated into the hybrid gel. Fig. 4a shows images and fluorescence spectra of an RhB-containing hydrogel stored in the dark. A slight decrease in fluorescence intensity within 60 min indicated the spontaneous release of RhB molecules into the surrounding water during gel swelling. Studies have reported that alginate hydrogels release hydrophobic curcumin molecules over a period of up to 20 days (Dai et al., 2009). By contrast, in the current study, the hybrid gel exhibited a substantial decrease in fluorescence intensity after 365-nm LED light irradiation, and it was almost colorless after UV light exposure for 60 min, as shown in Fig. 4b. Moreover, we examined the light-triggered release of a control hydrogel that contained only β-CD-Alg and RhB. Fig. 4c shows the results of a quantitative analysis of the change in fluorescence intensity of the control gel and hybrid gel systems upon light exposure. Only a slight decrease in the fluorescence intensity of the control gel precluded the photobleaching effect of RhB dyes produced through UV light irradiation and thus confirmed that the phototriggered rapid release of RhB molecules from the hybrid gel was successful. According to our thorough review of relevant research, this is the first report of the photocontrolled release of a bulk alginate hydrogel through a photoresponsive Az and β-CD inclusion complex.

We speculated that UV-light-induced *trans*-to-*cis* photoisomerization results in the dissociation of the host–guest complex of β-CD and *cis*-Az, thus agitating the IPN framework of the hybrid gel system. Consequently, the RhB molecules could be released from the bulk hydrogel more quickly upon UV light irradiation. As shown in Fig. 5a, our assumption was supported by two controlled experiments: (1) The release rate was increased by increasing the power of a UV lamp because more efficient photoisomerization yields more *cis* isomers; and (2) 470-nm LED light irradiation did not induce accelerated RhB release because *trans*-to-*cis* isomerization can be conducted only at a specific wavelength. In addition, we

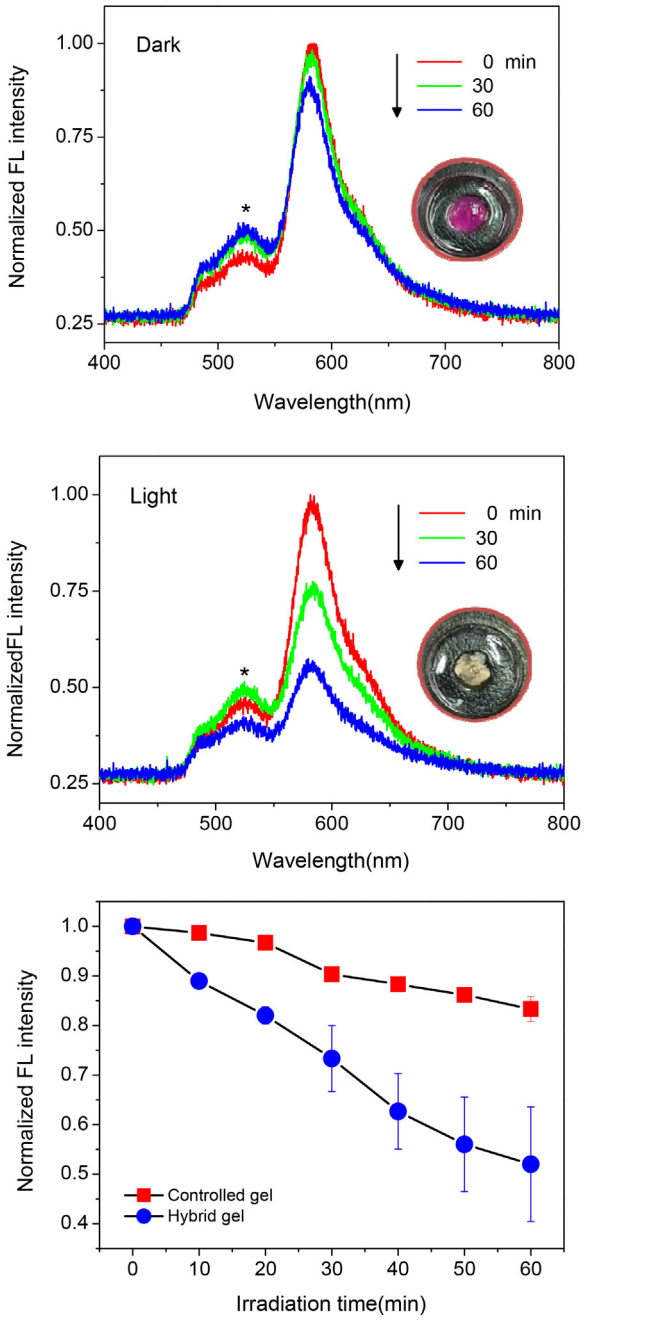


Fig. 4. Fluorescence spectra (λ_{ex} = 365 nm) and images of an RhB-containing hybrid hydrogel (a) stored in the dark and (b) upon UV-light exposure. (c) Quantitative analysis of the change in fluorescence intensity of the control gel (●) and hybrid gel (■). The control gel contains only β-CD-Alg and RhB.

compared hybrid hydrogels with contents of Az_2-PEG ranging from 0.04 to 7 mg/mL. As shown in Fig. 5b, the release rate increased as the content of photoresponsive moieties increased, clearly suggesting that greater Az_2-PEG contents engendered faster drug release upon UV light irradiation.

The change in the morphology of the photoresponsive hybrid hydrogels upon light stimulus was analyzed using scanning electron microscopy. Fig. 6a shows the β-CD-Alg hydrogel before and after UV light irradiation. The surface morphology was almost unchanged under light exposure, suggesting that the controlled hydrogel was insensitive to the UV light. This result confirmed that the accumulative heat during LED light exposure exerted no influence on the gel structure. Compared with a pristine Alg

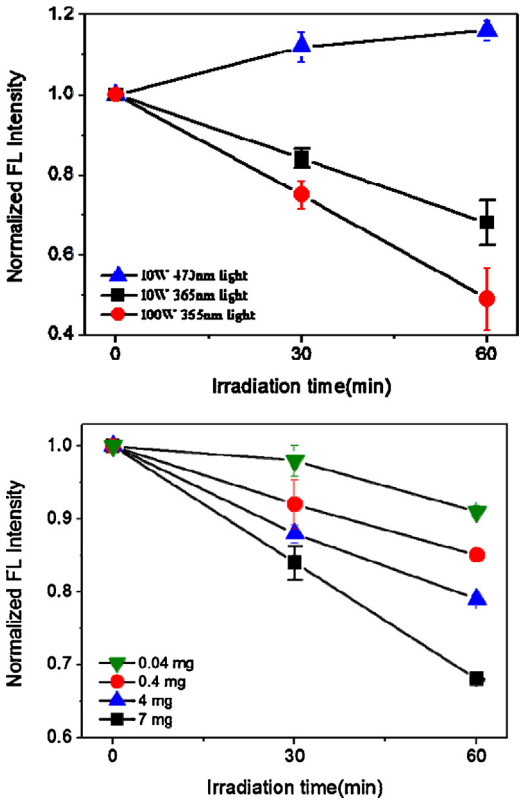


Fig. 5. (a) The change in fluorescence intensity of the hybrid hydrogels exposed to 365-nm light with lower (10 W) and higher (100 W) output energy and to 470-nm LED (10 W). (b) The change in fluorescence intensity of the hybrid hydrogels composed of an increasing amount of Az_2-*PEG*.

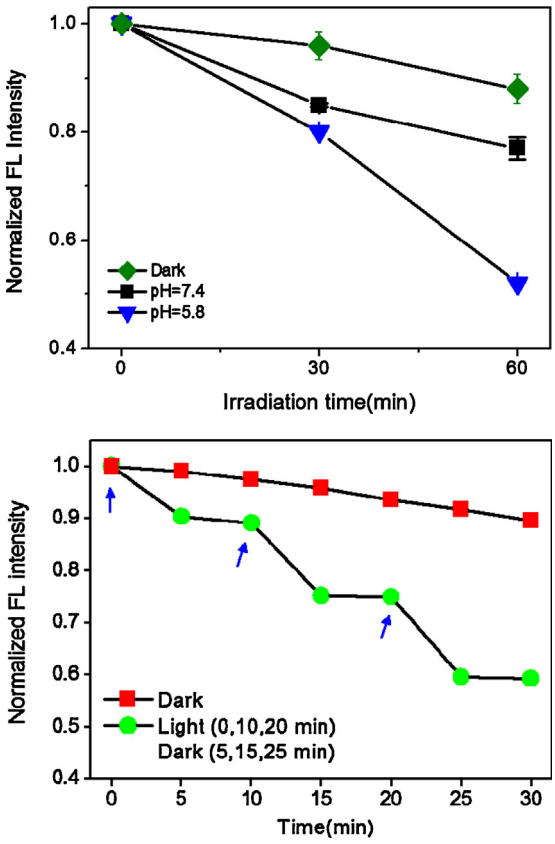


Fig. 7. (a) A pH-dependency of RhB releasing from hybrid hydrogel upon UV-light irradiation. (b) A stepped RhB releasing by alternating phototriggered and spontaneous processes. The hydrogel was irradiated with UV light at 0, 10, 20 min and exposed to darkness at 5, 15, 25 min.

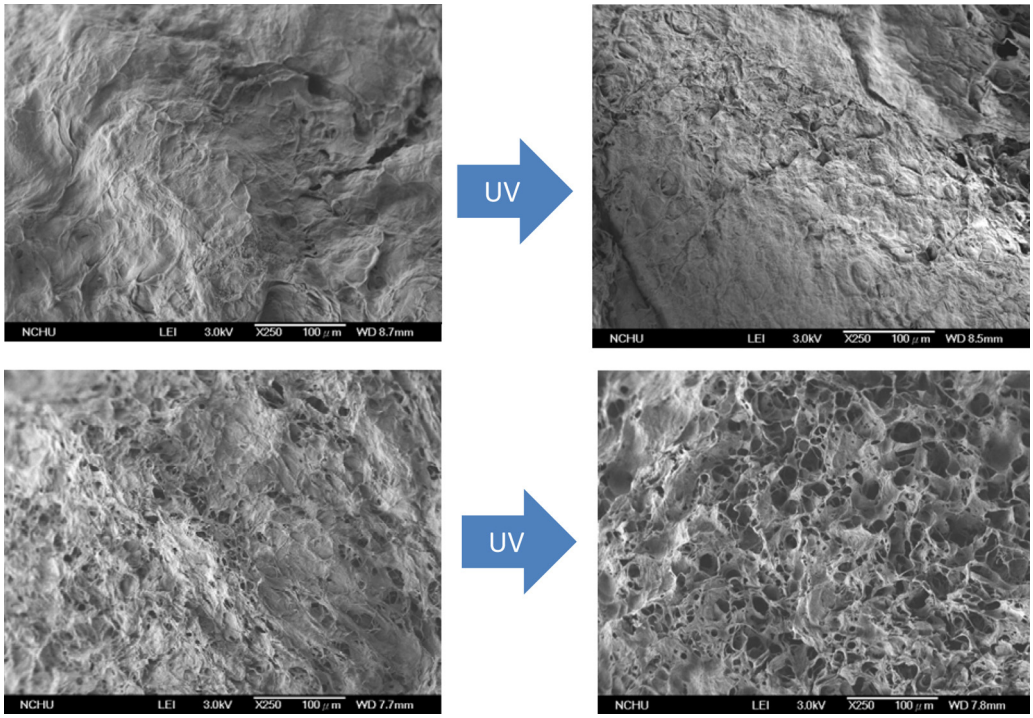


Fig. 6. Scanning electron microscopy (SEM) images of (a) β-CD-Alg hydrogel and (b) hybrid hydrogel before and after UV-light irradiation.

hydrogel exhibiting a smoother surface (Fig. S4), the structural integrity of the β-CD-Alg hydrogel with cracks on the surface was slightly lower. The loss of structural integrity may moderately enhance the release of RhB from the β-CD-modified hydrogel; this speculation is consistent with the fluorescence profile shown in Fig. 4c. Regarding the hybrid hydrogel system composed of Az_2-PEG and β-CD-Alg, Fig. 6b shows a substantial change in morphology upon UV light irradiation. The formation of comb-like cavities on the surface clearly indicated phototriggered structural degradation, which is mainly due to the photosensitive properties of the β-CD and Az inclusion complexes. Because of efficient *trans*-to-*cis* photoisomerization, the disassembly of *cis*-Az and β-CD may agitate the gel network, thus leading to a noticeable influence in structural integrity of the bulk hydrogel. Accordingly, gradual gel decomposition caused by UV light irradiation accounted for the accelerated release of entrapped RhB from the hybrid hydrogel.

In addition, the hybrid gel system exhibited pH dependency; the release rate in a mild acidic environment was greater than that in a physiological pH environment (Fig. 7a). Generally, both acute and chronic wounds gradually reach an acidic state as healing occurs (Tsukada, Tokunaga, Iwama, & Mishima, 1992; Gethin, 2007; Sikareepaisan, Ruktanonchai, & Supaphol, 2011). Therefore, this hybrid alginate hydrogel is applicable to photocontrollable delivery systems used in acute wound healing when rapid drug release is typically necessary. To provide a proof of concept of the photocontrolled accelerated release, the light exposure experiment was divided into three cycles repeated within 30 min. The hydrogel was irradiated with UV light for 5 min and then exposed to darkness for another 5 min. Fig. 7b shows a stepped release profile, according to which the RhB molecules were expeditiously released from the hydrogel after exposure to UV light but only gently released when the gel was exposed to darkness. This result suggested that alternating phototriggered and spontaneous release constitutes a well-controlled process and that rapid drug release in acute wound healing can be achieved through light stimulation.

4. Conclusion

In conclusion, we demonstrated a smart hybrid alginate hydrogel from which entrapped small molecules were rapidly released through UV light irradiation. The hybrid gel was prepared based on a semi-IPN structure composed of a crosslinked β-CD-grafted alginate and interpenetrating Az_2-PEG. In addition to crosslinking with the carboxylates along the alginate backbone induced by Ca^{2+} ions, the additional junctions formed by the host–guest complex between β-CD and *trans*-Az provided multiple photoresponsive sites within the bulk gel system. UV light irradiation induced efficient *trans*-to-*cis* photoisomerization, leading to the dissociation of the *cis*-Az from β-CD. Moreover, this photosensitive behavior was accompanied by substantial structural degradation of the hybrid gel, enabling the rapid release of entrapped molecules. Because biocompatible alginate hydrogels are widely applied in tissue engineering, in vitro and in vivo biological study of the applications of this photoresponsive hybrid gel in wound healing is currently being conducted.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.carbpol.2014.11.043.

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