Materials Science & Engineering C 82 (2018) 25–28

Contents lists available at ScienceDirect

Materials Science & Engineering C

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

Short communication

α-Cyclodextrin concentration-controlled thermo-sensitive supramolecular hydrogels

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ARTICLE INFO

Keywords:
Thermo-sensitivity
Inclusion complex
Base-pairing interaction
Supramolecular hydrogel
Biomedical application

ABSTRACT

Supramolecular hydrogels (SHGs) built from inclusion complex of macrocyclic compound α-cyclodextrin (α-CD) and poly(ethylene glycol) (PEG) have attracted much interest due to their excellent biocompatibility and great potential for biomedical applications. In this work, the hydrogen bond of nucleic acid was introduced into the above-mentioned SHG by syntheses of nucleobase guanine/cytosine (G/C)-terminated PEG (G-PEG-G/C-PEG-C). The base-pairing interaction between G and C as an additional network junction effectively enhanced storage moduli (*G*'s) of the hydrogels. Moreover, the prepared hydrogels exhibited excellent cytocompatibility and property for controlled drug release, outlining the potential of thermo-sensitive construct for biomedical applications, such as local chemotherapy of cancers.

Hydrogels, as three-dimensional (3D) cross-linked networks of water-soluble polymers, have been widely utilized in drug delivery [1–3], tissue engineering [4], cell immobilization, and so forth, mainly attributed to their abundant water contents, biocompatible properties, as well as tunable degradation and release performances [5–7].

Since 1994, α-cyclodextrin (α-CD) with specific truncated cone structure has been introduced in preparation of hydrogels by inclusion complex formation with poly(ethylene glycol) (PEG) [8]. During this process, α-CDs were threaded onto the PEG chain like beads on the line, for which the inclusion complexes (ICs) were vividly named “sliding gels”. The physical junction between the two molecules created a supramolecular network that induced formation of the poly(pseudo)rotaxane hydrogel, which showed promising utilization in multi-drug delivery [9–11].

Among them, supramolecular hydrogels (SHGs) based on noncovalent interactions of various building blocks, including host-guest interactions [12], hydrophobic interactions, hydrogen bonding, stereocomplexation, van der Waals forces, and so on, have exerted tremendous fascination as promising injectable drug delivery systems [13–15], or cell-encapsulation vehicles with distinguished biocompatibility [16]. In such SHG, drug loading can simultaneously occur during the gelation process, which not only enhances drug-loading efficiency but also avoids structural changes of the system. Yu et al. synthesized a reduction-sensitive SHG based on α-CD/polymer inclusion [17]. The formation of the inclusion complex of α-CD and PEG provided a major force in the gelation of SHG. Lin et al. introduced various amounts of α-CD into a gene delivery SHG and found that the highest concentration of α-CD at 8 wt% was most outstanding in accelerating the gelation process and reducing the release rate [18].

As a viscoelastic material, the applications of SHG are to a large extent affected by rheological properties [10,19], usually symbolized by the magnitude of storage modulus (*G′*). *G′* is decided by solid concentration, CD/polymer ratio, and guest polymer parameters [20,21]. Thus, it is reckoned that the introduction of multiple hydrogen bonds into the CD-polymer SHGs as network junctions would be an effective way to enhance the rheological properties.

Biologically, the adenine–thymine (A–T), guanine–cytosine (G–C), and adenine–uracil (A–U) base pairs form 2 or 3 hydrogen bonds along the Watson–Crick edge, a particular hydrogen binding pattern of DNA and RNA [22]. The highly specific interactions between the nucleobases can be employed to design drugs, molecular sensors, functional structures, and so on [6]. The use of base-pairing hydrogen binding force to increase *G′* of SHG has been proved in previous studies [23]. It was shown that nucleobase pair A and T in SHG led to sustained and controlled release profile of antitumor drug [6]. As three hydrogen bonds were formed between two pyrimidine rings instead of two in purine's bicyclic structure, G–C base pair was chosen to fabricate SHG [22].

Herein, G–C base pair was explored as a network junction to expectantly improve the rheological properties of CD–polymer SHGs. The terminal nucleobase (G/C)-functionalized PEGs (G-PEG-G/C-PEG-C)

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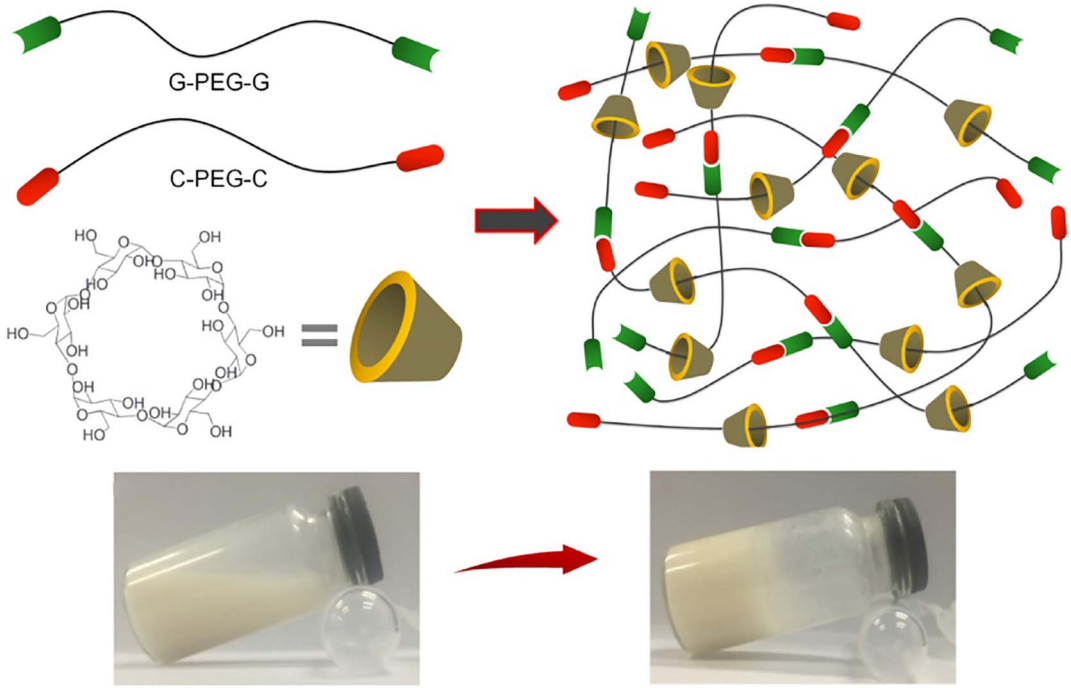
http://dx.doi.org/10.1016/j.msec.2017.08.045
Received 29 May 2017; Received in revised form 3 August 2017; Accepted 10 August 2017
Available online 12 August 2017



Scheme 1. Schematic illustration of the gelation mechanism of SHG.

were synthesized. And then, SHGs were obtained by mixing G-PEG-G/C-PEG-C with α-CD in aqueous solution, as shown in Scheme 1. The gelation properties of SHGs with different ratios of α-CD were indicated by the determination of gelation times, rheological behaviors, and *in vitro* DOX release profiles. The acquired hydrogels exhibited excellent cytocompatibility *in vitro*.

G-PEG-G and C-PEG-C were synthesized through the coupling reactions between PEG and nucleobases, as shown in Supplementary Scheme S1. The chemical structures of G-PEG-G and C-PEG-C were confirmed by proton nuclear magnetic resonance (^{1}H NMR) spectra. As for G-PEG-G in Fig. 1A, the newly appeared peak at 8.90 ppm belonged to guanine and the one at 3.97 ppm was assigned to PEG. As depicted in Fig. 1B, the peaks at 7.36 and 5.83 ppm were the characteristic signals of cytosine, and the one at 3.53 ppm stood for PEG. The results demonstrated the successful syntheses of both G-PEG-G and C-PEG-C.

When equimolar G-PEG-G and C-PEG-C were mixed with α-CD, physical gelation was instantly accomplished and SHG was acquired. The gelation speed could be controlled by altering the concentrations of α-CD in the initial solution. Specifically, four concentrations of α-CD, that is, 10, 15, 20, and 30 wt%, were used in SHG1, SHG2, SHG3, and SHG4, respectively, when the concentration of PEG was kept at 10.0 wt %. As shown in Table 1, a higher concentration of α-CD resulted in a faster speed of hydrogel formation under mild condition. In addition,

Table 1
Gelation times of SHGs with different α-CD concentrations at 25 and 37 °C.

Sample	Concentration of α-CD (wt%)	Gelation time at 25 °C (min)	Gelation time at 37 °C (min)
SHG1	10	52	75
SHG2	15	40	56
SHG3	20	28	42
SHG4	30	19	33

the temperature was another decisive factor during gelation. As expected, the viscosity of polymer solution decreased with rising temperature, leading to an extended gelation time. It was worth noting that when SHG4 was further heated to above 45 °C, it converted from hydrogel to sol state (Fig. 2A), indicating good thermo-sensitivity. Therefore, the prepared SHG could be expected to be a thermo-controlled drug delivery system for cancer treatment.

Wide-angle X-ray diffraction (WAXD) was utilized to investigate the threading process of PEG into α-CD and the following aggregation into poly(pseudo)rotaxane. As exhibited in Fig. 2B, the XRD spectra of lyophilized hydrogel samples showed clear diffraction peaks at $2\theta = 19.9^{\circ}$, which symbolized the channel-type structure of a crystalline–necklace-like complex of α-CD and PEG [24]. SHG1, SHG2, SHG3,

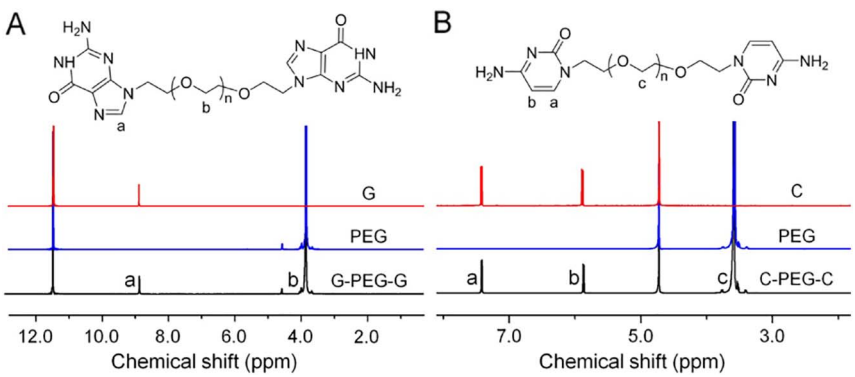


Fig. 1. Chemical structure confirmation. ^{1}H NMR spectra of (A) G, PEG, and G-PEG-G and (B) C, PEG, and C-PEG-C with deuterated trifluoroacetic acid (TFA-d) and water (D_2O) as solvents, respectively.