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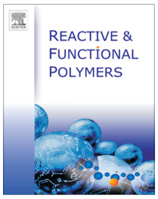

Suprarmolecular hydrogels driven by the dual host–guest interactions between α-cyclodextrin and ferrocene-modified poly(ethylene glycol) with low-molecular-weight

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ABSTRACT

In general, α-cyclodextrin (α-CD) and low-molecular weight poly(ethylene glycol) (low-MW PEG) (M_w = 400–10,000) cannot construct supramolecular hydrogels but easily form crystalline precipitates. In this study, low-MW PEG (M_n = 2000, PEG-2000) was functionalized by ferrocene as mono-end-group. The obtained ferrocene-modified PEG-2000 (FcPEG-2000) further self-assembled into supramolecular hydrogel with α-CD even at low concentration ($C_{FcPEG-2000}$ = 17 mg/ml), driven by dual host–guest interaction between α-CD and FcPEG-2000. Interestingly, the hydrogel was still observed even when hydrophobic Fc group was oxidized to hydrophilic ferrocenium (Fc^+) or included into the cavity of β-CD. In the former case, the existence of Fc^+ end groups is considered to decrease the probability of PEG de-penetration from α-CD cavity, so that α-CDs have more location and opportunities to aggregate into more channel-type crystalline domains as physical cross-linking points. While in the later case, the synergistic effect of host–guest interaction between β-CD and ferrocenyl groups and host–guest interaction between α-CD and PEG chains are considered to be the main reason. The resultant FcPEG-2000 based hydrogels showed the property of shear-thinning.

1. Introduction

Biocompatible supramolecular hydrogels are physical networks self-assembled by biocompatible gelators via noncovalent interactions including hydrogen bonding, hydrophobic interaction, host–guest recognition, π–π stacking interaction and so on [1–3]. They have been extensively explored for applications in biological medicine, genetic engineering and biomedical materials due to easy operation, thixotropic reversibility and good biocompatibility [4–6]. Therefore, the construction of biocompatible supramolecular hydrogels has attracted wide attention in recent years. Biocompatible cyclodextrins (CDs) are a series of cyclic oligosaccharides composed of 6, 7, and 8 glucose units linked by α-1,4-linkages and named α-CD, β-CD, and γ-CD, respectively. CD has a unique architecture of truncated cone possessing hydrophilic outer surface and hydrophobic cavity with the ability to encapsulate different guest molecules, which makes CD a suitable backbone to build one-dimensional, two-dimensional or three-dimensional supramolecular network structures [7–10].

Harada and Kamachi [11] first reported in 1990 that linear poly(ethylene glycol)s (PEGs) with different molecular weights (MWs, M_w = 400–90,000) could penetrate the inner cavity of α-CDs to form polymer inclusion complexes (PICs) with necklace-like supramolecular structures called *polypseudorotaxanes*. α-CDs threaded onto PEG chains can further assemble into "channel-type" crystals, and crystalline precipitates were obtained when PEG with low MW (M_w = 400–10,000) was used. The driving forces contain hydrogen bonding, size matching between the host and guest molecules and hydrophobic effect. Li et al. [12] first reported a hydrogel made of high molecular weight PEG and α-CD. Since then, such physical hydrogels have also been prepared from PEG-containing block copolymers, star or branched polymers [13–21].

In contrast to these extensive investigations on supramoleclar hydrogels made of α-CD and high-MW PEG homopolymer (M_n > 10,000) or PEG-based copolymers with different topologies, only a little work has been conducted on the inclusion complexes of α-CD and low-MW PEG and their ability to form gel [11,12,22,23]. In general, crystalline precipitates have been obtained when PEG with low MW (M_w = 400–10,000) was used. Water-soluble PEG is known to be biocompatible and has been widely used in bioengineering and pharmaceutics. Compared with high molecular-weight (high-MW) PEG, low-MW PEG has better biocompatibility, which is very important to hydrogels for biomed-

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ical applications [24]. Therefore, developing a new method of preparing supramolecular hydrogels based on α-CD and low-MW PEG has more practical prospects.

Ferrocene, consisting of one Fe (II) and two cyclopentadienes, is of particular research interest in designing supramolecular assemblies due to its unique sandwich structure, hydrophobic character and redox property [25–26]. It is well known that hydrophobic ferrocene not only can be oxidized to hydrophilic ferrocenium utilizing mild oxidants such as hydrogen peroxide and cerium (Ce^{4+}) salts, but also undergoes reversible oxidation and reduction via electrochemical means [27–28]. At the same time, hydrophobic ferrocene can also form hydrophilic complexes with different CDs and the structures of the complexes are dependent on the sizes of the CDs' hydrophobic cavity. One molecular ferrocene was fitly included into the cavity of β-CD, however it was included by two molecular α-CDs to form molecular capsule [8]. Although ferrocene and its derivatives are strongly bound under uncharged state, the complexes dissociate when they are oxidized. The hydrophobicity–hydrophilicity transition has been employed in designing supramolecular assemblies [29–34]. However, studies on supramolecular hydrogels based on ferrocene-modified polymer are very limited [33].

Herein, in the present work, the inclusion complexes between α-CD and low-MW PEG mono-end-functionalized by ferrocene (FcPEG-2000) were systematically investigated and a kind of supramolecular hydrogels was obtained that is still stable whenever hydrophobic ferrocenyl group was reduced, or oxidized, or included into the cavity of β-CD. The resulting supramolecular hydrogel retained the basic characteristics of supramolecular physical hydrogels, especially the shear-thinning property. The research provides a new idea of constructing biocompatible supramolecular hydrogels which should be useful as functional biomaterial for drug delivery.

2. Experimental section

2.1. Materials

The α-cyclodextrin (α-CD) was purchased from TCI shanghai. Methoxy poly(ethylene glycol) ($M_n = 2000$, PEG-2000) (Aldrich, 99%) was dried by azeotropic distillation in the presence of toluene. Dicyclohexylcarbodiimide (DCC, Alfa Aesar, 99%, USA), 4-dimethylaminopyridine (DMAP, Alfa Aesar, 98%, USA) and ferrocenecarboxylic acid (FcA, Acros Organics, 99%, USA), were utilized as received. All solvents were used as received.

2.2. Synthesis of FcPEG-2000

FcPEG-2000 was synthesized by reaction between the hydroxyl end of PEG-2000 and FcA according to the literature [35]. The degree of end-functionalization reached 99%, determined by ^1H NMR.

FT-IR (KBr, powder, cm^{-1}): 2886 (C—H), 1736 (C═O), 1620 (C═C in ferrocene), 1157 (C—O). ^1H NMR (600 MHz, $CDCl_3$, δ, ppm): 4.8 (2H, ═CHC(COOH)CH═), 4.4 (2H, —CH═CH—), 4.2 (5H, another cyclopentyl), 3.7 (178H, —OCH_2CH_2O—), 3.4 (3H, terminal CH_3O—).

2.3. Preparation of hydrogels

A certain amount of α-CD, PEG-2000 and FcPEG-2000 was dissolved in water to form solution, respectively. Then, each of the aqueous solution of PEG-2000 or FcPEG-2000 with various concentrations was added dropwise to the aqueous solution of α-CD with various concentrations. The mixed solutions were ultrasonically treated for 2 min and then were left to stand at room temperature.

2.4. Measurements

Scanning electron microscope (SEM) was performed on a TECNAI T20 electron microscope. For SEM observations, the specimens were freeze-dried *in vacuo*. The dried specimens were ground into fine powder, placed on conducting glue, and then coated with gold vapor and analyzed on a TECNAI T20 electron microscope. Differential scanning calorimeter (DSC) measurements were carried out with an EXTAR SII-600 system (Seiko Instruments Inc.). Each sample capsulated in a metal pan (5 mm in diameter) was first heated from room temperature to 140 °C, then cooled to −15 °C and finally heated to 140 °C again under a nitrogen flow. The heating and cooling rate was 10 °C/min. The melting temperature (T_m) and crystallization temperature (T_c) were recorded. X-ray diffraction (XRD) patterns were performed on an X-ray diffractometer (MSAL-XD2) with Cu Kα radiation ($\lambda = 0.1541$ nm, 30 kV, 30 mA). The XRD data were collected with 2θ values in the range of 5–50° with a 0.01° step. The steady and dynamic rheological measurements were carried out on a Physica MCR-300 rheometer with 12-mm parallel-plate geometry. All tests were performed at 25 °C. The electrochemical experiments were performed on a CHI 660A electrochemical work station (Shanghai CH Instruments Co., China) with a conventional three-electrode system consisted of a modified glass carbon electrode as working electrode, a platinum wire as auxiliary electrode, and a saturated calomel electrode (SCE) as reference electrode.

3. Results and discussion

It is reported that low-MW PEG ($M_n < 10{,}000$) could form stoichiometric whole complexes with α-CDs in which two ethylene glycol units of PEG were bound in a single α-CD cavity, however only partial PEG chain units that were close to both ends could penetrate into α-CD, even if α-CDs were excessive when high-MW PEG was used. In the previous reports on the complexes of α-CD and PEG with various MWs, low MW PEG with a low concentration was mostly used to interact with α-CD with a high concentration, which mainly formed precipitates [11,12,22]. So in this study, the inclusion complexes between α-CD and PEG as well as their ability to gel were investigated through the variation of polymer concentration (called ***C***) or the feeding molar ratio of PEG repeat unit to α-CD (called ***R***). Two kinds of low-MW PEG as guest molecules were chosen for contrast. One is low-MW PEG without end-functionaization (PEG-2000) and the other is low-MW PEG mono-end-functionalized by ferrocene group (FcPEG-2000).

3.1. Hydrogels assembled by inclusion complexes of PEG-2000 and α-CD

As reported, precipitate S_1 (Table 1 and Fig. 1A-1) rather than a homogeneous hydrogel was obtained when low concentration PEG-2000 (10 mg/ml) was mixed with a saturated α-CD solution (145 mg/ml) [11]. To solve this problem, a PEG chain partially covered by α-CDs was adopted. With PEG-2000 repeat unit to α-CD (***R***) kept at 6.3, and increasing the concentration of PEG-2000 in water ($C_{PEG-2000}$), a series of inclusion complexes were obtained and the results are shown in Table 1 and Fig. 1A. The mixture of α-CD and PEG-2000 with a low concentration (5 mg/ml) was a transparent aqueous solution and the solution became gradually turbid and sticky with increasing the $C_{PEG-2000}$. Unstable gel C_2 turning into sol after 6 h was observed when $C_{PEG-2000}$ reached 15.6 mg/ml (Fig. 1A-2 and A-3). Only at high $C_{PEG-2000}$ (40 mg/ml) could a stable hydrogel C_4 be obtained (Table 1 and Fig. 1A-4).

The formation of stable hydrogel C_4 was traced by rheological measurement. As shown in Figs. 2 and Fig. 3a and b, the modulus