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Preparation of mechanically-tough and thermo-responsive polyurethane-poly(ethylene glycol) hydrogels

Kewen Li[a], Chao Zhou[a], Shunli Liu[a], Fang Yao[a], Guodong Fu[a,*], Liqun Xu[b,*]

[a] School of Chemistry and Chemical Engineering, Southeast University, Nanjing, Jiangsu Province 211189, PR China
[b] Institute of Clean Energy and Advanced Materials, Faculty of Materials and Energy, Southwest University, Chongqing, PR China 400715

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ABSTRACT

Hydrogels have been considered as promising materials in tissue engineering and biomedical areas. However, the weak and brittle nature of common synthetic hydrogels largely hinders their potential applications. Therefore, it is challenging to fabricate tough hydrogels for biomedical applications. In this manuscript, well-defined and thermo-responsive polyurethane-poly(ethylene glycol) (PU-PEG) hydrogels were prepared via thermally-induced copper-catalyzed 1,3-dipolar azide-alkyne cycloaddition (CuAAC) using azido-pendent PU-PEG and dialkynyl PEG as the gel precursors. The physical properties of the as-formed hydrogels were investigated by swelling ratios and mechanical tests. The PU-PEG hydrogels not only possess thermo-responsive and excellent mechanical properties, but also exhibit good biocompatibility.

1. Introduction

Common synthetic hydrogels exhibit poor mechanical properties [1,2], which largely hinder their potential applications such as tissue engineering and structural biomaterials [3–7]. They are brittle with little possibility for extension or compression under stress, and can be damaged by stress concentration crack extension, leading to the rupture of the entire body [8]. This phenomenon may be due to the adsorbed water molecules occupy the space of chain movement and make the network chain rigid and difficult to slack [3,9]. To solve this problem, one possible solution is to increase the hydrophobic segment in the network, providing sufficient slack to the network strands.

Polyurethane (PU) consists of the flexible segment contributed by the oligodiol and the rigid component composed of carbamates (urethane) [10,11]. Due to its good mechanical properties, tunable chemical structures and superior biocompatibility, PU has been widely used in biomedical applications [12–19]. PU has also been integrated with hydrophilic components such as PEG [20,21], silk fibroin [10], polyacrylic acid [22], polyvinyl acetate [23], and polyacrylamide [24] to form hydrogels via either chemical or physical interactions. Among them, PU-PEG gels are particularly interesting due to their good biocompatibility and excellent molecular tailorability [25–27]. Xue et al. investigated the mechanical properties of biodegradable PU-PEG hydrogels prepared from toluene dicyanate, linear PEG and three-armed poly(L-lactic acid) [28]. Divakaran et al. synthesized curcumin-incorporated PU-PEG hydrogels with antibacterial and anticancer properties using PEG, curcumin, 1,2,6-hexanetriol and 4,4′-methylenebis(cyclohexyl isocyanate) as the starting materials [17]. These PU-PEG hydrogels were cross-linked from the precursors in suitable organic solvents, followed by immersing in water to remove the organic solvents. The solvent exchange process is time-consuming, and the residual organic solvents exhibit noticeable cytotoxicity for future biomedical applications [29–30]. Furthermore, the solvent exchange process may be difficult to remove the cross-linkers and catalysts used for the formation of polymeric networks. Thus, the synthesis of PU with suitable functionality for the cross-linking with PEG in the aqueous medium is highly demand for the preparation of PU-PEG hydrogels.

In this paper, the azido-pendant PU-PEG was first synthesized via chain extension between α,ω-diazido PEG (DAPEG) and hexamethylene diisocyanate (HMDI). The PU-PEG hydrogels were then prepared using the azido-pendant PU and α,ω-dialkynyl PEG (DAKPEG) as the precursors via thermally-induced copper(I)-catalyzed azide-alkyne cycloaddition (CuAAC, Scheme 1). The as-prepared PU-PEG hydrogels not only exhibit controllable gelation time and high mechanical strengths, but also show good biocompatibility with low/negligible toxicity to normal cell line.

2. Experimental section

2.1. Materials

N,*N*-dimethylformamide (DMF, AR), tetrahydrofuran (THF, AR) and

* Corresponding authors.
E-mail addresses: fu7352@seu.edu.cn (G. Fu), xulq@swu.edu.cn (L. Xu).

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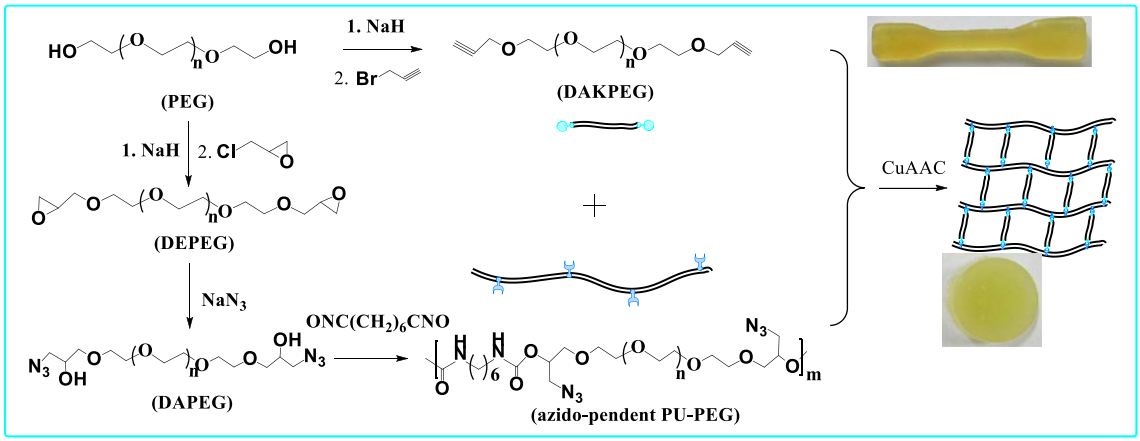

Scheme 1. Synthesis of DAKPEG and azido-pendent PU-PEG, and preparation of PU-PEG hydrogels via thermally-induced CuAAC.

dichloromethane (DCM, AR) were purchased from Chemical Reagent Company of National Pharmaceutica Group. Sodium azide (99%), pentamethyldiethylenetriamine (PMDETA, 99%), propargyl bromide (80%) and copper(II) bromide ($CuBr_2$, 98%) were purchased from Shanghai Chemical Reagent Plant. Epichlorohydrin (ECH, 99%), HMDI (99%), dibutyltin dilaurate (DBTDL, 99%), *tert*-butyl benzoperoxoate (TBPB, AR), bibenzoylperoxide (BPO, AR), ammonium persulfate (APS, AR) and PEG (M_n = 2000, 1000 and 500 g/mol) were purchased from Aladdin Industrial Corporation. THF was dried by refluxing over sodium and benzophenone and distilled before use. DCM was distilled after being stirred with CaH_2. PEG was dried by azeotropic distillation with toluene. Propargyl bromide was distilled before use. The preparation of *α*, *ω*-dialkynyl PEG (DAKPEG) and *α*, *ω*-diazido PEG (DAPEG) [31,32] was shown in the Supplementary data.

2.2. Synthesis of gel precursors

2.2.1. Synthesis of PU with pendent azido groups (PU-PEG$_{2000}$-N$_3$) [33,34]

PU-PEG_{2000}-N_3 was synthesized by step addition polymerization using HMDI and DAPEG in the presence of DBTDL catalyst. $DAPEG_{2000}$ (11.0 g, 5.0 mmol), DBTDL (3.15 mg, 0.01 Eq. of DAPEG) and 60 mL of dry THF were added to a 250 mL round bottom flask. The solution was purged by N_2, and a stoichiometric amount of HMDI (HMDI:diol = 0.95:1) dissolved in 80 mL of dry THF was slowly added. The reaction mixture was kept at 75 °C for 6 h, followed by dialysis against ethanol for 72 h. The solvent was removed by rotary evaporation, and the residual liquid was precipitated into excessive diethyl ether (100 mL). The filtered precipitate was dried under vacuum at room temperature, resulting in a white powder (14.8 g, Yield = 95.5%). ^{1}H NMR ($CDCl_3$, *δ*): 1.38–1.52 ppm (−CONHCH$_2$(C***H$_2$***)$_6$CH$_2$NHCO−), 3.11 ppm (−CONHC***H$_2$***(CH$_2$)$_6$C***H$_2$***NHCO−), 3.38 ppm (−C***H$_2$***N$_3$), 4.02 ppm (−COC***H***(CH$_2$)$_2$) and 3.62 ppm (−OCH$_2$CH$_2$O−).

PU-PEG_{1000}-N_3 was synthesized using HMDI, $DAPEG_{1000}$ and PEG_{1000} as the reactants and DBTDL as the catalyst. The stoichiometric molar ratio of $DAPEG_{1000}$:PEG_{1000}:HMDI:DBTDL was kept at 1:1:0.97:0.01. PU-PEG_{500}-N_3 was synthesized using HMDI, $DAPEG_{500}$ and PEG_{500} in the presence of DBTDL catalyst. The stoichiometric molar ratio of $DAPEG_{500}$:PEG_{500}:HMDI:DBTDL was kept at 1:3:0.98:0.01. The synthetic procedures of PU-PEG_{1000}-N_3 and PU-PEG_{500}-N_3 were similar to that of PU-PEG_{2000}-N_3.

2.2.2. Synthesis of PU-PEG hydrogels via thermally-induced CuAAC [32]

The formation of PU-PEG hydrogels via thermally-induced CuAAC was studied using varied thermal initiators (BPO, TBPB and APS) to Cu^{2+} and Cu^{2+} to alkyne (or azide) molar ratios at different reaction times. In a typical run, PU-PEG_{2000}-N_3 (0.2 g), $DAKPEG_{2000}$ (0.2 g), 1 mL of H_2O, $CuBr_2$ (1.12 mg, 0.005 mmol), PMDETA (1.73 mg, 2 equiv. of $CuBr_2$) and APS (1.14 mg, 0.005 mmol) were added into a small vial. The reaction mixture underwent three successive freeze-pump-thaw cycles to eliminate oxygen. The vial was then sealed under nitrogen atmosphere and placed in an oil bath at 60 °C. Gelation time was determined by the vial-inversion method [35–37]. The resulting PU-PEG hydrogel was referred to as PU-PEG_{2000} hydrogel.

For comparison, PU-PEG_{1000}-N_3 and PU-PEG_{500}-N_3 were also used to synthesize the PU-PEG hydrogels using APS as the radical source at 60 °C, resulting in PU-PEG_{1000} and PU-PEG_{500} hydrogels, respectively.

2.3. Characterization

FT-IR spectra were obtained on a Bruker Vector 22 IR spectrometer. ^{1}H NMR spectra were performed on a Bruker ARX300 MHz spectrometer in $CDCl_3$ using tetramethylsilane as internal standard. Gel permeation chromatography (GPC) was measured on a Waters 1515 system equipped with two PL Mixed-C columns using THF as the eluent at a flow rate of 1.0 mL/min at 40 °C against commercial polystyrene standards (Waters ShodexVR). The mechanical property of PU-PEG hydrogels were measured on a MCR102 modular compact rheometer (Anton Paar). Differential scanning calorimetry (DSC) measurements were carried out on a Perkin Elmer DSC 7 calorimeter under a nitrogen atmosphere. All samples were heated to 120 °C at a heating rate of 10 °C min^{-1} to erase the thermal history, and cooled to −70 °C at a cooling rate of 10 °C min^{-1}. The samples were heated again to 120 °C at a heating rate of 10 °C min^{-1}. The presented data were determined from the cooling curve and the second heating curve.

2.4. Swelling degree testing

The swelling ratio (SR) of PU-PEG hydrogels was measured in buffered solution at 37 °C. The freeze-dried gels were weighed (W_d) first. At a predetermined time, the swollen samples were taken out to remove the adsorbed water with filter paper and weighed (W_t). SR was calculated using the following equation:

$$SR = (W_t - W_d)/W_d \times 100 \quad (1)$$

The temperature effect on the SRs of PU-PEG hydrogels was studied in the range of 15–70 °C.

2.5. Mechanical tests

The compression testing experiments of the PU-PEG hydrogels were carried out on a CMT 4503 electron universal testing machine. The compression measurements were performed using a universal mechanical tester at a crosshead speed of 0.5 mm min^{-1} at room temperature. The hydrogel