



A biodegradable starch hydrogel synthesized via thiol-ene click chemistry



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ARTICLE INFO

Article history:

Received 10 April 2016

Received in revised form

7 July 2016

Accepted 19 July 2016

Available online 21 July 2016

Keywords:

Starch

Hydrogel

Biodegradable

Thiol-ene click

ABSTRACT

The biodegradable polysaccharide hydrogels have attracted much attention due to its biocompatible and non-toxicity. Herein, we report a starch hydrogel synthesized via thiol-ene click reaction between thiol starch (St-SH) and allyl starch (AS). The swelling behaviors, rheological experiment and biodegradable properties of the obtained hydrogel were investigated in details. The chemical structure of functional starch was confirmed by ¹H-NMR and ¹³C-NMR. Moreover, the rheological experiment indicated that starch hydrogel possessed high mechanical strength, and its modulus could be manipulated by the thiol-ene molar ratio. Biodegradation tests revealed that the hydrogel could be biodegradable rapidly in the presence of α -amylase. The biodegradation rate could be controlled by the thiol-ene molar ratio or the concentration of α -amylase. Degradation kinetics from the hydrogel suggested that the degradation/erosion of starch hydrogel come from a combination of both the surface erosion and diffusion mechanisms.

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1. Introduction

Hydrogel is a polymeric material that exhibits the ability to swell and retain a significant fraction of water within its structure, but will not dissolve in water. Due to its significant water content, hydrogel also possesses a certain degree of flexibility which is similar to natural tissue [1–3]. Thus, its capability to localize and deliver therapeutic substance in a controlled manner, serve as delivery vehicles for cell transplantation and allow the culture of stem cells in tissue-like three dimensional microenvironments have attracted more attention for their potential applications in tissue engineering [4,5], coating [6,7], cell culture [8–10] and so on. However, for majority of the hydrogels, they were prepared from synthetic polymers. The non-degradability of synthetic polymers has limited their application in biomedical fields. Therefore, many efforts have been made aiming to improve the degradability of the hydrogels. It should be noted that, to develop optimal platforms for biomedical applications, the following major issues must be considered: 1) biocompatibility—the toxicity is a major concern for its potential applications; 2) degradability—the degradable property

can make the hydrogel hydrolysed in vivo to reduce suffering; 3) source—the price plays a key role to regulate the application; 4) reactive chemical groups—the existence of reactive chemical groups makes the monomer easily modify.

Herein we address all these issues by using starch as a single solution. Starch is a natural carbohydrate consists of two major components: amylose and amylopectin. Amylose is a primarily linear polysaccharide with α -(1–4)-linked D-glucose units, while amylopectin is a highly branched molecule with α -(1–4)-linked D-glucose as backbones and exhibits about 5% of α -(1–6)-linked as branches. As the cheapest and completely biodegradable polymer, the unique physicochemical and biological characters of starch offers great application for the utilization of hydrogel in biomedical area. For instance, Hanafi ismail et al. had reported the recent advance in starch based hydrogels [11]. Meanwhile, the development of the synthesis and characterization of starch based hydrogel was also reviewed. Elbadawy A. Kamoun et al. had described the property and application of the PVA-hydroxyethyl starch hydrogels [12].

The thiol-ene chemistry which was first reported in 1905 is an organic reaction between a thiol and an alkene to form an alkyl sulfide. Recently, it has emerged as one of the most powerful tools in drug discovery [13], chemical biology [14] and proteomic applications [15]. It has many advantages, such as modularization,

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high yields, inoffensive byproduct and stereospecific network structure. Especially at the hydrogel fields, it has become a popular method for preparing the hydrogel. Timothy M et al. had synthesized a biodegradable hydrogel library. The hydrogel displayed non-swelling equilibration and offered temporal control over material degradation and the release of biomolecules [16]. Han et al. had reported a four-arm poly (ethylene glycol) norbornene which was crosslinked with dithiol containing cross-linkers to form a hydrogel via thiol-ene click reaction [17].

Here, we reported a novel hydrogel with degradability via thiol-ene click chemistry. Then the mechanical property, swelling capacity and degradation behaviour of the hydrogel were investigated. The results showed that the hydrogel exhibits adjustable mechanical properties and swelling ability. The degradation process was a linear behaviour in the presence of α -amylase and could accelerate by increasing the concentration of the α -amylase or declining the cross-linking density. Through the observation by SEM, we concluded that the degradation process come from a combination of both surface erosion and diffusion mechanisms. The combination of feasible mechanical properties, good water uptake ability and biodegradability make the starch hydrogel have potential application in the field of biomedical and tissue engineering.

1.1. Materials and methods

1.1.1. Materials

Corn starch purchased from Changchun Dacheng Corn Development Co, Ltd (China), with macromolecular weight (M_w) of 200,000Da was obtained according to a previously published method [18]. Succinic anhydride purchased from Beijing Chemical Reagent. 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) and N-Hydroxysuccinimide (NHS) achieved from Aladdin Chemistry Co, Ltd. L-Cysteine hydrochloride achieved from Alfa Aesar Co., Ltd. 4-(2-hydroxyethoxy)phenyl-(2-hydroxy-2-propyl) ketone (Irgacure2959) purchased from TCI Co., Ltd. α -Amylase (3700IU/g) purchased from Beijing AoBoXing Bio-tech Co., Ltd. All the other chemicals obtained from Beijing Chemical Reagent and used as received.

1.1.2. Preparation of treated starch

Dry starch (30 g) was suspend in the mixture of ethanol (144 mL) and distilled water (16 mL) under mild stirring. After stirring at 70 °C for 10 min, 7 mL concentrated hydrochloric acid was added into the mixture. The reaction was performed at 70 °C for 1 h, then NaHCO_3 (8 g) was added into the system to stop reaction. After cooling to room temperature, the solution was centrifuged at $3000 \times g$ for 5 min. The precipitate was washed for four times with distilled water, and then the fifth time was washed with ethanol and dried at 45 °C air-oven. ^{13}C -NMR (DMSO- d_6): $\delta = 103$ ppm (C1), $\delta = 73$ ppm (C2, C3, C5), $\delta = 82$ ppm (C4), $\delta = 61$ ppm (C6) [18].

1.1.3. Synthesis of Allylic Starch (AS)

The AS was prepared as follow [19]: starch (9 g) was placed in a three-necked flask. Distilled water (110 mL), sodium hydroxide (7.00 g), petroleum ether (50 mL), cetyltrimethyl ammonium bromide (CTAB, 62.5 mg) and allyl chloride (12.90 g) were added and the mixture was allowed to react at 45 °C for 24 h under 250 rpm. The petroleum ether that had separated as the top layer was taken out. The polymer was then neutralized by acetic acid and precipitated in ethanol, then the product was washed several times by ethanol and dried at 40°C under vacuum.

Degree of substitution (DS_{allyl}): 0.16 (determined by bromating method) [19], AS (2 g) and distilled water (100 mL) were added into an iodine flask under stirring. KBrO_3 -KBr (molar ratio 1:5) (0.1 mol/

L, 20 mL) was added into the sample solution. After HCl (6 mol/L, 10 mL) was added, KBrO_3 reacted with KBr to produce Br_2 , and then Br_2 could react with allyl groups in the sample solution for addition reaction. 20 wt% KI (20 mL) was used to react with the residual Br_2 , and I_2 was formed from the reaction mixture. By titrating I_2 with standard solution of $\text{Na}_2\text{S}_2\text{O}_3$ and calculating the consumption of $\text{Na}_2\text{S}_2\text{O}_3$, the total allyl contents of AS could be determined by means of the interrelationships of these ingredients. ^1H -NMR (D_2O): $\delta = 4.20$ – 4.15 ppm, 5.88 ppm, 5.24 ppm (allyl H), 5.7– 4.97 ppm, 4.46– 3.24 ppm (AGU H). ^{13}C -NMR (DMSO- d_6): $\delta = 135.53$ ppm, 116.93 ppm, (allyl).

1.1.4. Synthesis of St-COOH

A typical reaction was described as follows [20]: the dried starch (3.26 g) was added in 50 mL DMSO at 70 °C under air atmosphere with a stirring speed at 200 rpm. When the solution became clear, the temperature was adjusted to 60 °C. After 10 min, imidazole (2.72 g) and succinic anhydride (1.20 g) were added into the three neck vial and keep the reaction for 6 h. Then, adjusted the temperature to room temperature and reacted for 24 h. After the reaction, the solution was poured into 250 mL isopropanol. The precipitate was washed for several times until the pure product was gained. Then put the products in vacuum oven at 45 °C for 24 h.

Degree of substitution (DS_{COOH}): 0.67 (determined by area integration from ^1H -NMR (600 MHz, Bruker Avance) spectra at ambient temperature). ^1H -NMR (D_2O): $\delta = 2.75$ – 2.40 ppm (succinic H), 3.22– 3.10 ppm (methene for L-cysteine), 4.51– 3.26 ppm, 5.75– 4.90 ppm (AGU H). ^{13}C -NMR (DMSO- d_6): $\delta = 174.20$ ppm, 172.13 ppm, (carboxylate carbon).

1.1.5. Synthesis of the St-SH

St-SH was synthesized by coupling L-Cysteine hydrochloride to the carboxylic acid moieties of St-COOH using EDC and NHS as coupling agent. In details, St-COOH (1.00 g) was dissolved in PBS (0.01 M) solutions at a concentration of 25 mg/mL at an ice water bath with a stirring speed at 250 rpm. After EDC (1.20 g) and NHS (0.71 g) were added to dissolve completely, L-Cysteine hydrochloride (1.09 g) was added (molar ratio COOH/L-Cysteine hydrochloride approximately 1:2) and the pH was adjusted to 5.5 with 1.0 M NaOH. 12 h later, the crude product was dialysis against 0.01 M PBS solutions at pH = 5.0 for three times and then against distilled water for three times. Finally, the solution was filtered and the polymers were collected after freeze-drying.

Degree of substitution (DS_{SH}): 0.16 (determined by area integration from ^1H -NMR (600 MHz, Bruker Avance) spectra at ambient temperature). ^1H -NMR (D_2O): $\delta = 2.83$ – 2.33 ppm (succinic H), 4.51– 3.26 ppm, 5.75– 4.90 ppm (AGU H). ^{13}C -NMR (D_2O): $\delta = 174.20$ ppm, 172.13 ppm, (carboxylate carbon), $\delta = 62.17$ ppm (tertiary carbon in L-cysteine), $\delta = 24.47$ ppm (methylene carbon in L-cysteine).

1.1.6. Preparation of starch hydrogel

The hydrogel was prepared according to the following process. Typically, AS (0.32 g) and St-SH (0.32 g) were added to 1mLPBS (0.01 M) solutions (pH = 7.4) respectively under strong stirring. After completely dissolved, they were mixed under mild stirring with Irgacure2959 (10 mg) for about 5 min s. Then the mixture was poured into a test tube under the UV irradiation (365 nm, 36w) for 30 min to create the hydrogel.

1.1.7. ^1H -NMR, FTIR characterization and rheological analysis

^1H -NMR and ^{13}C -NMR was performed on Bruker Avance spectra (600 MHz) at ambient temperature. FTIR characterization was performed on Perkin-Elmer Spectrum 100 spectrometer (USA) and the data were collected via 32 scans with a resolution of 2 cm^{-1} at

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