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Surface functionalization of hydrogel by thiol-yne click chemistry for drug delivery

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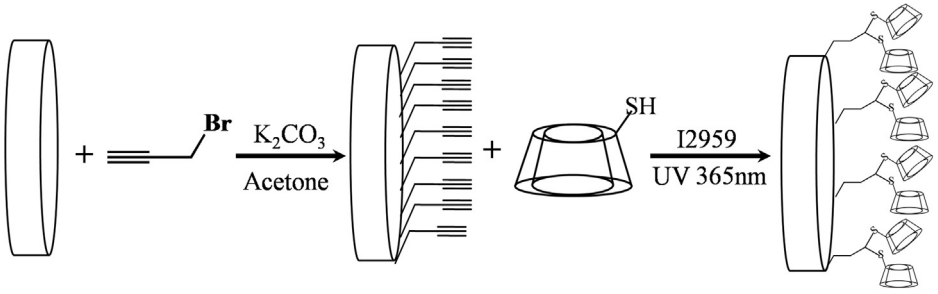
HIGHLIGHTS

- β-CD functionalized hydrogel was obtained by thiol-yne click chemistry.
- Synthesis was verified and analyzed by semiquantitative analysis of FTIR spectra and XPS results.
- β-CD functionalization resulted in better properties.
- The drug delivery performance was improved for hydrogel after β-CD functionalization.

GRAPHICAL ABSTRACT



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ABSTRACT

Although hydrogel has some outstanding performance, traditional hydrogel still has some drawbacks in the application of drug delivery field. Herein, we attempted to utilize the thiol-yne photopolymerization, which had advantages of high efficiency, mild reaction condition and low toxicity as a type of click chemistry, to realize β-cyclodextrin (β-CD) functionalized hydrogel in order to improve its performance for drug delivery. As a prerequisite, alkynylation was conducted on the per-formed hydrogel. The above-mentioned synthesis was verified by the results of atomic concentration from X-ray Photoelectron Spectroscopy (XPS) characterization and semiquantitative analysis of Fourier-transformed infrared spectroscopy (FTIR) spectra. Similarly, the optimum reaction condition including optimal reaction time and feeding molar ratio were also determined by semiquantitative analysis of FTIR spectra and XPS results. The alkynylation resulted in higher contact angle, lower equilibrium water and coarser surface. Then, β-CD functionalization was beneficial to the hydrophilicity and protein resistant property of hydrogel. With respect to drug delivery performance, an increasing drug concentration and β-CD molecules that grafted onto hydrogel benefited to aggregating orfloxacin molecules in hydrogels. The loading drug concentration as well as β-CD content on hydrogel exerted influences upon drug release behaviors.

1. Introduction

Since hydrogel was discovered and applied as a soft contact lens, the semi-solid material, which is composed of hydrophilic polymer network and enormous embedded water, attracts intensive attention, especially in the field of tissue engineering and drug delivery [1–3]. This solid–liquid structure endows hydrogel a number of flexible properties like adjustable swelling property along with solution surroundings, stimuli-responsive properties with temperature, pH, ions and/or certain chemicals, drug biocompatibility on account of aquatic environment, molecule accommodation and affixation due to hydrogel mesh structure [1–9]. Moreover, it is

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reported that aquatic environment of hydrogel can protect cells, maintain the bioactivity of susceptible drugs, benefit the ions and molecules exchange between polymer network and outside environment [1,2]. The above-mentioned properties lay the foundation of drug carrier for hydrogel. As for ideal drug carriers, further drug encapsulated capacity and drug controlled-release properties are also required for hydrogel [10,11]. However, hydrophilic polymer network of traditional hydrogel had limited drug encapsulated capacity and drug controlled ability, which also had been discovered in our previous research [12–16].

Cyclic oligosaccharides (CDs), which have exerted a profound influence upon the field of drug delivery, are considered as ideal intermediates to hold drug molecules and control its release on account of host-guest interaction between hydrophobic cavity of CDs and drug molecules [17,18]. Therefore, they have been incorporated into nanoparticles, micelles, colloids, films, hydrogel, and the like, either through crosslinking or through copolymerization [3,9,17–21]. In the case of traditional hydrogel, bulk copolymerization may deteriorate the mechanical properties of hydrogel including strength, toughness, elasticity, and so on. For this purpose, surface functionalization is an efficient and effective way to improve certain performance of materials with the advantage of maintaining the original properties of materials [13,14]. Therefore, the aim of this study is to provide an efficient and effective approach to functionalize the hydrogel surface with β-CD for drug delivery.

When it comes to surface functionalization for biomaterials, an ideal approach should have features of rapid reaction speed, low toxicity, site-selective functionalization. Undeniably, a recently highlighted reaction with click-like characteristics and mild reaction condition, named as click chemistry, can mainly satisfy the requirement of surface functionalization for biomaterials [22–24]. Though Cu^+-catalyzed azide–alkyne cycloaddition, widely-used click chemistry, has been proven to be an efficient and effective approach toward surface engineering, the biotoxicity of Cu^+ is still an unsolved issue that is to be improved [25]. Based on the above-mentioned, another similar method for surface modification with low toxicity is needed for further investigation of surface engineering. Therefore, another type of click chemistry, the thiol-yne photopolymerization, was applied to realize the hydrogel surface modification with β-CD in this work. In particular, the practicality of this approach for surface engineering was demonstrated in this research.

Although a similar reaction, thiol-ene reaction, has been verified to be a viable approach in areas of macromolecular design, postpolymerization, surface modification and bioconjugation, the thiol-yne photopolymerization has not yet been explored in hydrogel surface engineering for the purpose of drug delivery in spite of many merits including room temperature reaction, high efficiency, no consideration of oxygen/water, no expensive and potentially toxic catalysts, highly tolerance of functional groups, temporal and spatial control of the reaction site and the like [26–30]. Additionally, the utility of postmodification approach of hydrogel for drug delivery is still to be evaluated.

2. Material and methods

2.1. Materials

Hydroxyethyl methacrylate (HEMA) and 3-Bromo-1-propyne (BP) were obtained from Shanghai Jingchun Industries Co., Ltd., China, and distilled under vacuum before use. Mercapto-β-cyclodextrin (Mercapto-β-CD) was obtained from Shandong Binzhou Zhiyuan Bio-Technology Co., Ltd., Ammonium persulphate (APS) and *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TEMED) were obtained from Shanghai Chemical Industries Co., Ltd. (China). 2-Hydroxy-1-[4-(hydroxyethoxyphenyl]-2-methyl-1-propanone (Irgacure2959) was obtained from Sigma. Orfloxacin was purchased from Zhengzhou Andrew Biological Engineering Co., Ltd., China. All other reagents and solvents were of analytical grade and used as received.

2.2. Hydrogel fabrication

pHEMA hydrogel was formed by previous method [12]. Briefly, 500 μL of 65% HEMA monomer solution, which contained 0.5% initiators of APS and TEMED (equal molar ratio), were injected into a circle model (200 μm thickness), and then formed at 60 °C after 1 h later.

2.3. Alkynylation of hydrogel surface

Initially, surface modification was conducted by bromination reaction using 3-Bromo-1-propyne (BP). Briefly, certain BP was added into hydrogel/acetone solution (5 piece of dried hydrogel in 20 mL acetone) under stirring. At the same time, certain amount of K_2CO_3 with equal molar ratio of BP was added into the above mixture. After the reaction had lasted for 2 h, the hydrogel was washed by fresh acetone several times. Then alkynylated hydrogel, which was denoted by pHEMA-BP hydrogel in the following section, was obtained after dried.

2.4. Surface functionalization with β-CD

Secondly, β-CD was grafted onto hydrogel surface by thiol-yne click chemistry, which was specified as follows. The dried pHEMA-BP hydrogel was put into tetrahydrofuran (THF)/water mixture solvent (1:1), into which certain amount of mercapto-β-CD was added under stirring. After the mercapto-β-CD was completely dissolved, 0.05% w/v Irgacure2959 was added into the above mixture. The final mixture was then irradiated by 365 nm UV light with a power of ~10 mW/cm^2 for some time. Finally, the mercapto-β-CD functionalized hydrogels, named as pHEMA-CD hydrogels in the following section, were washed with water.

2.5. Hydrogel characterization

Hydrogels were characterized by Fourier-transformed infrared spectroscopy (FTIR, Nicolet IS10), contact angle measurement system (Kruss, DSA100), element analysis (Eager 300), X-ray Photoelectron Spectroscopy (XPS, Kratos AXIS Ultra DLD). The grafting ratio (G_{BP}) of pHEMA-BP hydrogel was calculated by weight of pHEMA-BP hydrogel ($W_{pHEMA\text{-}BP}$) and weight of pHEMA hydrogel (W_{pHEMA}), which was defined as $G_{BP} = [(W_{pHEMA\text{-}BP} - W_{pHEMA}) \times 130/(W_{pHEMA} \times 38)] \times 100\%$. Hydrogel was dried naturally in the atmosphere at room temperature. After dried, the hydrogels were observed by scanning electron microscopy (SEM, S-8100). The dry hydrogels (W_0) were submerged in water at 37 °C for 12 h and weighed (W_1). The equilibrium swelling ratio of the hydrogels was defined as ESR (%) = $[(W_1 - W_0)/W_1] \times 100\%$.

2.6. Drug loading and releasing

Hydrogels were submerged in 3 mL orfloxacin solution with different concentration to load drugs for 24 h. The orfloxacin concentration was spectrophotometrically determined (cary 50) at 270 nm [6]. The loaded drugs in hydrogel were calculated by a difference of drug concentration before and after loading. The drug loaded hydrogels were submerged in 4 mL PBS at 5 mL centrifugal tube. At regular intervals, 1 mL of released solution was moved from the centrifugal tube and 1 mL of fresh PBS was added at the