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A new route to fabricate biocompatible hydrogels with controlled drug delivery behavior

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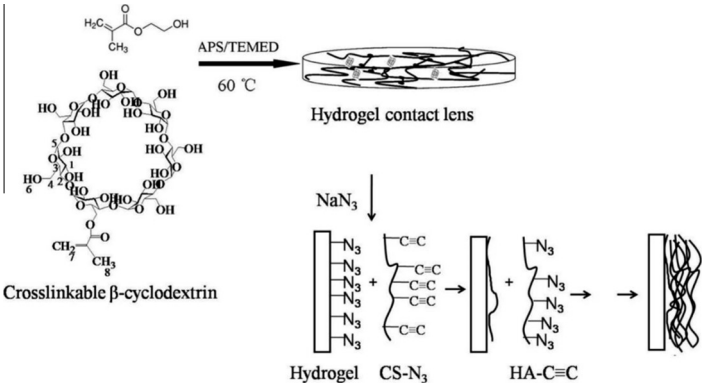
GRAPHICAL ABSTRACT

Biocompatible hydrogel contact lenses with controlled drug delivery behavior were fabricated using copolymer hydrogels and Layer-by-Layer (LbL) surface modification technique through click chemistry.



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ABSTRACT

Hydrogels for drug delivery have attracted extensive interests since they can be used for biomaterials such as contact lenses. Here, we report that biocompatible hydrogels for contact lenses with controlled drug delivery behavior can be fabricated using copolymer hydrogels and Layer-by-Layer (LbL) surface modification technique. Methyl acrylic anhydride (MAA) modified β-cyclodextrin (β-CD) (MA-β-CD) was synthesized and copolymerized with hydroxyethyl methacrylate (HEMA) to form copolymer hydrogel. The introduction of second monomer of MA-β-CD would accelerate the polymerization of hydrogel, leading to increase of residual C=C groups. The structure of copolymers was characterized by differential scanning calorimetry (DSC). Transparence, equilibrium swelling ratio and contact angle of copolymer hydrogel were also detailed discussed in the work. *In vitro* drug release results showed that copolymer hydrogel with higher MA-β-CD content exhibited a better drug loading capacity and drug release behaviors could be tuned by MA-β-CD/monomer ratio. Finally, alkynyl functional hyaluronic acid (HA-BP) and nitrine functional chitosan (CS-N_3) were synthesized and covalently cross-linked to copolymer hydrogel surface using LbL technique through click chemistry. The successful LbL multilayers were confirmed by X-ray Photoelectron Spectroscopy (XPS). Results of cytotoxicity experiment revealed that the hydrogels were biocompatible since they could support the growth of cells.

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1. Introduction

Recently, new drug delivery materials have been developed to control the release of ophthalmic drugs in order to cure the eye disease [1–3]. One of the biggest challenges is how to control drug delivery and optimize bioactivity of materials. Soft contact lenses made of hydrogels are one of the most suitable materials to achieve this because they can prolong the residence time of drugs and improve bioavailability [4–10]. Traditional hydrogels are composed of poly-hydroxyethyl methacrylate (pHEMA). Hydrophilic monomers are often copolymerized with HEMA to improve the hydrophilicity of contact lenses [11]. Although these copolymer hydrogels could partially meet the requirement of soft contact lens applications in eyesight correction and cosmetology, they lack ligands to immobilize drug. As a result, the loaded drug amount in hydrophilic copolymer hydrogel is limited and burst release of the loaded drug from hydrogels often occurs within 1 h [11].

To date, some methods have been used to enhance interactions between drugs and hydrogel network including copolymerization with ionic monomers, introduction of nanoparticles or colloids and usage of molecularly imprinted technology [5–9]. In order to improve the drug loading capacity and avoid burst release, a few systems have been designed [12–14]. However, these systems still have limitations.

As we know, a group of cyclic oligosaccharides with hydrophobic cavities can complex with small molecules [15,16]. β-CD is one of cyclic oligosaccharides, which has been used to prepare hydrogels to control drug loading and releasing [17,18]. The hydrophilicity and biocompatibility [19] of hydrogels are also crucial to the application of soft contact lenses because soft contact lenses inevitably contact with cornea. Moreover, good hydrophilicity of hydrogel is critical to the comfort for wear of contact lenses. Therefore, it is necessary to improve the hydrophilicity of hydrogels by surface modification. Hyaluronic acid (HA) is a linear anionic polysaccharide, which plays an important role in the organization and stabilization of ECM, and maintains a high level of hydration [20]. Another polysaccharide, chitosan (CS), has properties of biodegradability, good biocompatibility and antibacterial property [20,21]. Layer-by-Layer (LbL) approach is a facile technique to construct multilayers by circularly alternatively dipping a surface in two interactive polymer solutions [22–25]. A covalent LbL protocol based on "click" chemistry can be employed to functionalize surface [26], which shows some advantages such as high stability and good control over the quantity and thickness [27].

In this study, β-CD was first modified by double carbon groups to improve the ability of drug loading and retarded drug release in and from the hydrogel. Then cross-linkable β-CD was copolymerized with HEMA to form hydrogel contact lenses. Because orfloxacin and puerarin are commonly used drugs to cure the infection of eyes and alleviate glaucoma (or ocular hypertension), the two drugs were chosen as model drugs to be loaded into hydrogels. The drug loading and releasing behavior of orfloxacin and puerarin were investigated to evaluate the drug delivery property of p(HEMA-CD) copolymer hydrogel, and results showed drug delivery behavior could be tuned by MA-β-CD/monomer ratio. LbL assembly based on "click" chemistry was used to construct HA/CS multilayers on the hydrogels for surface modification. Finally, the cytotoxicity of hydrogels was evaluated, and results proved that the hydrogels were biocompatible since they could support the growth of cells.

2. Experimental

2.1. Materials

Chitosan (Mg < 600 kDa) was purchased from Haidebei Marine Bioengineering Company, Ji'nan, China. Hydroxyethyl methacrylate (HEMA), methyl acrylic anhydride (MAA), and 3-bromo-1-propyne (BP) were obtained from Shanghai Jingchun Industries Co. Ltd., China, and distilled under vacuum before use. β-cyclodextrin, sodium azide, 2-propanol, ammonium persulphate (APS) and N,N,N′,N′-tetramethylethylenediamine (TEMED) were obtained from Shanghai Chemical Industries Co. Ltd. (China). Hyaluronic acid, trypsin, Dulbecco's modified Eagle's medium (DMEM), fluorescein diacetate (FDA) and 3-(4,5-dimethyl)thiazol-2,5-dime thyl tetrazolium bromide (MTT) were obtained from Sigma. Orfloxacin and puerarin were purchased from Jinling Pharmac Industries Co. Ltd., China. All other reagents and solvents were of analytical grade and used as received.

2.2. Synthesis of MA-β-CD

MA-β-CD was primarily synthesized according to Ref. [20]. In brief, 8.0 g dry β-CD (105 °C, 24 h) solubilized in 36 mL dry pyridine together with 40.0 mg BHT, into which 19.8 g MAA was carefully added. The mixture was stirred at room temperature for 2 h and then at 50 °C for 5 h. Then, the reaction solution was poured into 300 mL cold distilled water and kept at 4 °C for 12 h. The MA-β-CD was precipitated and isolated by filtration, which was following purified by dissolution in MeOH and subsequent precipitated in cold distilled water. The white solid obtained was freeze-dried and characterized the nuclear magnetic resonance hydrogen spectrum (^{1}H NMR, Bruker AV500) in DMSO-d_6 solution and fourier-transformed infrared spectroscopy (FTIR, Nicolet IS10).

2.3. Synthesis and characterization of p(HEMA-CD) copolymer hydrogel

MA-β-CD was dissolved into 5 mL HEMA by stirring and the final concentration of MA-β-CD reached 0%, 10%, 20%, 50% w/w. 2.7 mL of water was added into monomer mixture, into which certain amount of APS and TEMED with equal molar ratio were respectively added with final initiator concentration at 0.5%. 500 μL of the above mixture was injected into a circle model (200 μm thickness), which was then input into oven at 60 °C. 1 h later, the formed hydrogel was obtained. The gelation time was evaluated by differential scanning calorimetry detection (DSC, STA 449). Hydrogels were characterized by UV spectroscopy (Cary 50). Hydrogels were dried in oven at 40 °C, and then weighed (W_0). The dry hydrogels were submerged in water at 37 °C for 4 h, and then weighed (W_1). The equilibrium swelling ratio of the hydrogels was defined as ESR (%) = $(W_1 - W_0)/W_1 \times 100\%$. The dried hydrogels were characterized by FTIR, DSC, and contact angle measurement system (Kruss, DSA100). At least three positions of a film were characterized for the final results of contact angle. The β-CD content was detected using 3-methylbenzoic acid (3-MBA) method. Briefly, dried hydrogels were immersed in 10 mL alcohol for 24 h to extract unreacted MA-β-CD. The 3-MBA concentration was spectrophotometrically determined (Cary 50) at 281 nm. The number of β-CD cavities was estimated from the amount of absorbed 3-MBA, which was calculated as the difference between the initial and the final amount in the solution.

2.4. Drug loading and releasing behavior

Orfloxacin and puerarin were loaded into hydrogels as model drugs. Hydrogels were submerged in 3 mL 1 mg/mL drug solution to load drugs. After 24 h, 50 μL of drug solution was diluted into 5 mL. The absorbance of diluted drug solution at 270 nm for orfloxacin, or 255 nm for puerarin was recorded by UV spectroscopy. The diluted drug concentration was obtained by referring to a calibration curve, which was constructed from known concentrations of drug solutions. The drug concentration after loading was then obtained. The loaded drugs in hydrogel were calculated by a differ-