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Fabrication of poly(ethylene glycol)-based cyclodextrin containing hydrogels via thiol-ene click reaction

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ABSTRACT

A simple and efficient methodology for the fabrication of poly(ethylene glycol) (PEG) based chemically cross-linked hydrogels containing discrete β-cyclodextrin (β-CD) units is outlined. Hydrogels were synthesized using homo-bifunctional linear PEGs containing allyl groups and heptavalent thiol-functionalized β-CD as crosslinkers via the radical-induced thiol-ene click chemistry. Various hydrogels comprising of different molecular weight PEGs and varying crosslinker feed were investigated in terms of their physical properties such as water uptake capacity, surface morphology and rheological behaviors. Uptake and controlled release of a poorly water-soluble drug, namely, puerarin was demonstrated using these hydrogels. The drug uptake and release was found to be depended on the hydrogels composition. Benefiting from the photochemically induced gel formation, the methodology was extended to fabricate hydrogel micro-structures on solid substrates.

1. Introduction

Three-dimensional cross-linked hydrophilic polymeric networks, often referred as hydrogels, are indispensible materials for various biomedical applications such as drug delivery formulations, scaffolds for tissue regeneration, support for biocatalysts, biomolecular sensors and implant coatings [1,2] The porous hydrophilic network structures of hydrogels allows pronounced water uptake while retaining their viscoelastic behavior [3]. This ability to swell, high biocompatibility and tunable mechanical properties make hydrogels suitable materials for use as controlled drug delivery platforms. The voids in hydrogel interior serve as reservoirs to load the drugs and release them in a sustained manner through different mechanisms such as diffusion, erosion, matrix relaxation and degradation [4,5]. Various approaches have been developed to increase the loading efficiency of hydrogels through covalent, hydrophobic, ionic interactions with drug molecules as well by employing the molecular imprinting [6]. Hydrogels are also suitable platforms in immobilization of biomolecules and development of immunoassays. Due to their high surface area and ability of tailoring network structure for functionalization with receptor ligands, hydrogels play an important role in biomolecular immobilization [7]. Development of efficient methodologies for controlling the hydrogel network structure via covalent or non-covalent interactions as well as controlling encapsulation and/or attachment of bioactive compounds for aforementioned applications is an important area in soft material design.

In recent years, various efficient and versatile click reactions have been utilized to prepare and functionalize hydrogels for a wide range of applications [8]. Various click reactions, predominantly including the copper-catalyzed

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and copper-free azide-alkyne cycloaddition [9], the Diels–Alder reaction [10], and the thiol-ene reactions [11] have been successfully employed in crosslinking of monomers and polymers. Due to the highly effective and selective nature of click reactions, hydrogels prepared in this way possess near-ideal networks that results in materials with improved physical properties [12].

Among the various available click reactions, the metal-free conjugation strategies are attractive for fabrication of materials intended for biological applications. In particular, reaction of a thiol with an alkene functional group under radical-initiated conditions i.e. the radical thiol-ene reaction has been proven as a versatile methodology for preparation of cross-linked networks [13]. Using the photochemically induced radical thiol-ene reaction, spatial and temporal regulation during network formation can be achieved. The reaction can also proceed in the presence of air or in aqueous environment thus providing a powerful technique for fabrication of hydrogels for biomedical applications. Recently, Lin and co-workers reported the synthesis of visible light-mediated thiol-ene hydrogels using eosin-Y, a Type II initiator, as the only photo-initiator [14]. The hydrogels were formed using PEG-4-norbornone and dithiothreitol precursor within 4 min. using a visible light source (400–700 nm). Thiol-ene hydrogels obtained by this new strategy were highly cytocompatible as demonstrated by the encapsulation of human mesenchymal stem cells (hMSCs) and MIN6 β-cells.

Cyclodextrins (CDs), a family of cyclic oligosaccharides consisting of 1,4-linked D-glucopyranose units are torus shaped molecules that posses hydrophilic outer shell and a hydrophobic interior cavity. This unique structure of CDs enables the incorporation of hydrophobic molecules into their inner cavity through inclusion complex formation in aqueous environment [15]. The interaction of cyclodextrins with hydrophobic molecules is a dynamic equilibrium, rendering the formation and dissociation of inclusion complex dependent on environmental conditions [16]. In the presence of a competitive host molecule or dilution of the aqueous environment, the molecule included in the cavity can be released. Because of this behavior, cyclodextrins are extensively studied in the design of polymer/hydrogel based sustained drug delivery systems to modify the release kinetics [17]. Common strategies for incorporating cyclodextrin units into hydrogels network include the polymerization of cyclodextrin containing monomers with other hydrophilic monomers or by reacting hydroxyl groups with isocyanate or epoxide containing polymers [18]. In the latter approach, the multivalent chemical structure of cyclodextrins allows them to be used as multifunctional crosslinking reagents. For example, Katime and co-workers utilized isocyanate end-capped poly(ethylene glycol) (PEG) polymers to obtain hydrogel networks [19]. Hydrogels were obtained through the reaction of the hydroxyl groups of cyclodextrin with the isocyanate groups at polymer chain-ends. Although, efficient hydrogel formation is obtained in the abovementioned studies, the crosslinking occurs through participation of hydroxyl groups from both the top and bottom rim hydroxyl groups of the cyclodextrin in a random fashion that leads to heterogeneity in the binding sites.

Microstructured hydrogels are actively investigated since it is well documented that relief size and shape affects how these materials interact with their environment. For example, it is known that micropatterns on hydrogel surfaces modulate cellular proliferation and adhesion [20]. Hydrogel based micro-needles allow sustained drug delivery over prolonged period to time [21]. Due to its operational simplicity, efficiency and high selectivity, photo-chemically governed radical thiol-ene click reaction is an ideal method for obtaining micropatterned hydrogels.

In the present study, facile synthesis of poly(ethylene glycol) (PEG) based cyclodextrin containing hydrogels through radical thiol-ene reaction is disclosed. The strategy involves the utilization of alkene end-functionalized poly(ethylene glycol)s as the hydrophilic matrix and thiol functionalized β-cyclodextrin (β-CD(SH)$_7$) as multifunctional crosslinker. Structurally well-defined hydrogels were obtained in high conversions through rapid gelation reactions under mild conditions. In order to tailor the physicochemical properties of hydrogels, polymer molecular weight as well as crosslinking degrees were varied. The resulting hydrogels were characterized by their water uptake properties and morphology, as well as their dynamic rheological behavior. These cyclodextrin embedded hydrogels were investigated for uptake and release of a poorly water-soluble (0.011 M at 25 °C) [22] drug puerarin used in the treatment of glaucoma. Additionally, hydrogel microstructures were fabricated to highlight the advantage of the photochemically induced gelation process.

2. Experimental section

2.1. Materials and characterization

Poly(ethylene glycol)s (PEG 2 kDa, 4 kDa, 8 kDa), allyl bromide, 2,2-Dimethoxy-2-phenylacetophenone (DMPA), (5,5'-dithio-*bis*-(2-nitrobenzoic acid) (DTNB) and (trimethylsilyl) methacrylate (TMSMA) were obtained from Aldrich Chemical Co. Puerarin was obtained from TCI Chemicals. Other chemicals and solvents were purchased from Merck and used as obtained without further purification unless otherwise noted. Synthesis of thiol functionalized β-cyclodextrin [23] and α,ω-diallyl PEGs [24] were conducted according to reported procedures. All thiol-ene reactions were performed at 365 nm using a handheld UV lamp (Blak-Ray UVP model B-100AP/R high intensity UV lamp with a 100-watt spot bulb and 7° beam width).

2.2. Methods

2.2.1. Representative synthesis of Hydrogel via radical thiol-ene reaction

PEG polymer (0.050 g, 12.2×10^{-3} mmol for *diallyl*-PEG$_{4000}$) was placed in a vial and dissolved in DMF (100 μl). A calculated amount of β-CD-(SH)$_7$ and photoinitiator, DMPA (0.2 eq. per thiols) were then added to this solution. The mixture was irradiated under UV for 30 min at 365 nm. After hydrogel formation, unreacted gel precursors were removed by washing the gel with DMF,

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