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Research paper

A multi-responsive multicomponent hydrogel with micro-phase separation structure: Synthesis and special drug release

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ABSTRACT

In this article, the multicomponent hydrogel was prepared by the copolymerization of the hydrophobic silicon-containing monomer tris(trimethylsiloxy)-3-methacryloxypropyl-sliane (TRIS) with the hydrophilic monomers 2-hydroxyethyl methacrylate (HEMA) and N-vinyl pyrrolidone (NVP). The ethanol extraction experiments as well as the FTIR, DSC results showed that the copolymerization was effective. The silicone hydrogel that had hydrophilic and hydrophobic phases could be loaded with hydrophilic drug (FITC) and hydrophobic drug (Nile Red) simultaneously. The drug release properties of the hydrogel were studied by taking advantage of its innate stimuli-responsiveness to solvent and pH. The release behaviors of hydrophilic and hydrophobic drugs were found to be solvent dependent. And the release behavior of hydrophilic drug was also pH sensitive. With the characteristics above, the silicone hydrogels can be good candidates for specified materials and may have broad applications in responsiveness, drug release, contact lens, etc.

1. Introduction

Hydrogel has been generally considered as a three-dimensionally crosslinked hydrophilic polymer capable of swelling and retaining large amounts of water in the swollen state [1–6]. Over the past few decades, hydrogel that has impressive properties such as biocompatibility [7], mechanical strength [8,9], optical properties [10,11], and oxygen permeability [12–14], has been widely studied as a functional material in fields of medicine [15–17], biology [18,19], material science and engineering [20–24]. Among those properties, the responsive drug release behavior of the hydrogels has become a rising research topic.

Environmentally responsive hydrogels containing ionic groups, polar groups, hydrophilic/hydrophobic groups are usually sensitive to stimuli such as pH [25–27], temperature [28–30], ions [31], and solvents [32,33],, resulting in reversible changes in their physico-chemical properties. The environmental responsiveness is driven by the internal affinities such as Van der Waals' force, hydrogen bond, hydrophobic force and electrostatic force within the hydrogel, appearing in drastic changes of swelling volume. By taking advantage of their swelling behaviors in response to external stimuli, this environmentally responsive hydrogel is expected to have broad applications in drug delivery, bioengineering, biomaterial and biosensor [17,34–37]. Hydrogels with good biocompatibility have been used for drug delivery in human body [38–41]. For instance, the hydrogel contact lenses can be loaded with medicine to treat eye diseases [42]. Different responsive hydrogels including single and multiple hydrogels have also been applied in drug delivery for controlled drug release in response to specific environmental stimuli [18,34,43,44].

Hydrogel carriers capable of loading both hydrophilic and hydrophobic drugs have attracted increasing interests among researchers [45]. Ha et al. conjugated the hydrophobic anticancer drug camptothecin (CPT) to a class of low molecule weight poly(-ethylene glycol) (PEG) chains to synthesize an amphiphilic prodrug CPT-PEG, which further formed stable hydrogels through partial inclusion complexation. The formed hydrogels were loaded with water-soluble drug 5-FU combined with CPT to enhance their anticancer activity [46]. Zhong et al. reported a composite hydrogel made of silk fibroin and PLA-PEG-PLA copolymer, to which aspirin and indomethacin were loaded as two model drugs with different water-solubility. The drug release was mainly caused by the degradation of the composite hydrogel [30]. Up to now, very few researches studied the responsive drug release of the hydrogel

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which carried both hydrophilic and hydrophobic drugs.

On the basis of our previous results, silicone hydrogels copolymerized by a mixed formula of both hydrophilic and hydrophobic monomers possessed micro phases separation structure [33] as well as pH- and solvent-responsiveness [47,48]. The micro phases separated silicone hydrogel could be regarded as an amphiphilic gel, in which the silicone phase acted as the hydrophobic area. Thus, the silicone hydrogel has the potential to carry both hydrophilic and hydrophobic drugs. Moreover, silicone hydrogel containing HEMA and NVP monomers in response to pH and solvents is a controllable material for drug release.

In this work, the stimuli-responsive silicone hydrogels were prepared by the copolymerization of hydrophobic silicon-containing monomer TRIS with hydrophilic monomers HEMA and NVP. The obtained hydrogel was characterized through extraction experiment, FTIR, DSC, TEM and mechanical experiments. Furthermore, two model drugs (hydrophilic FITC and hydrophobic Nile Red) were used to assess the entrapment and controlled release behaviors from the silicone hydrogels.

2. Experimental section

2.1. Materials

Tris(trimethylsiloxy)-3-methacryloxypropyl-sliane (TRIS) was purchased from Alfa Aesar Chemical Co. 2-Hydroxyethyl methacrylate (HEMA) was obtained from BASF Chemical Co. N-Vinylpyrrolidone (NVP), ethylene glycol dimethacrylate (EGDMA), 2-hydroxy-2-methylbenzene acetone (D-1173) were purchased from TCI Development (Shanghai). Ethanol, hexanol, hexane and tetrachloromethane were purchased from Sino Pharm Chemical Reagent Co. Fluorescein isothiocyanate (FITC) was purchased from Aladdin Reagent Co., Ltd. Nile Red was purchased from Sigma-Aldrich Chemical Reagent Co.

2.2. Preparation of silicone hydrogel

For the synthesis of silicone hydrogels, the photo initiator D-1173 and the crosslinking agent EGDMA were added in the beaker. Then, HEMA, NVP and TRIS were added in sequence. At last, the solvent hexanol was added. The formulation mixture was stirred for 2 h in dark at room temperature (25 °C). The mixture was transferred into the double stack polypropylene molds and UV ($\geq$15 mV/cm^2) initiated for 3 h at room temperature. The newly formed silicone hydrogels were purified by extraction with ethanol for 16 h and then hydrated in boiling water for 4 h. A series of silicone hydrogels were prepared using the formula in Table 1. For all the formulations, the amounts of the cross-linking agent EGDMA and the initiator D-1173 were fixed at 1 and 0.2 wt%, respectively [33,47,48].

2.3. Measurements of extractables

The obtained hydrogel sample was dried to constant weight in vacuum oven, and the dry weight M_1 was measured. And then the dried sample was extracted with ethanol for 16 h, and dried to constant weight again. The dry weight M_2 was measured. The extractables (β) was calculated by the following equation: $\beta = [(M_1 - M_2)/M_1] \times 100\%$.

Table 1
The copolymerization formulations for the multicomponent hydrogels with different TRIS percentages (wt%).

Hydrogel	0	I	II	III	IV	V
TRIS	0	10	20	30	40	50
HEMA	70	63	56	49	42	35
NVP	30	27	24	21	18	15
D-1173	0.2	0.2	0.2	0.2	0.2	0.2
EGDMA	1	1	1	1	1	1

2.4. Differential scanning calorimetry (DSC)

The glass-transition temperatures of P(HEMA-NVP) copolymer hydrogel and the finial silicone hydrogel were measured using a modulated DSC (Modulated DSC-8230, TA Instruments) coupled with a refrigerated cooling system. The swelling equilibrium hydrogel sample was used to perform the measurements. Nitrogen was used as pure gas and cooling gas at the flow rate of 20 mL/min and 100 mL/min respectively. These samples were heated from 0 °C to 400 °C at a heating rate of 2.5 K/min.

2.5. Measurements of internal morphology

The internal morphology of the dried silicone hydrogels with 30 wt% TRIS (hydrogels III) was characterized by TEM (JEM-2100), the hydrogel was cooled down using liquid nitrogen and then grounded rapidly into powder and dispersed in water again. This mixture was stored in tube and incubated overnight. For preparing samples, the tube was shaken and then a small amount of the mixture was transferred to the copper grid using a pipet. Then, the sample was dried using an infrared lamp. This sample was characterized by TEM at an operating voltage of 200 kV in vacuum.

2.6. Measurements of swelling ratio

The dried hydrogels were immersed in different solutions/solvents until their weight became constant. Then the hydrogels were taken out and the surfaces were blotted with filter paper before measurements. The swelling ratio was calculated with the following equation:

Swelling ratio (%) = (Ws−Wd)/Wd·100%, where Ws is the weight of the swollen hydrogel and Wd is the weight of the dry hydrogel.

2.7. Hydrophilic and hydrophobic drug loading and in vitro release behavior

The hydrogels III were loaded with hydrophilic drug by immersing in 5 mL of 2 mg/mL FITC aqueous solution for 2 h. Then these hydrogels were taken out and immersed into 5 mL CCl_4 solution of Nile Red at the concentration of 2 mg/mL for 2 h (For the loading of a single drug, the hydrogel was immersed into one solution.) The loading effect could be observed by fluorescence microscope (Olympus IX71). FITC was excited by blue light and Nile Red was excited by green light.

The soaked hydrogels were rinsed with the corresponding solvent (water or organic solvent) and placed in a tube with 10 mL solvent. Then the tube was shaken at 100 rpm at 37 °C. 500 μL of the medium was taken out as samples for UV measurements and the same volume of fresh solution was supplemented. The sample was collected at time intervals of 1, 4, 7, 31, 55 and 79 h for the release evaluation. The amount of drug released from the silicone hydrogels was determined by UV-vis spectrophotometer (Shimadzu UV-2450). The ultraviolet absorption peak of FITC molecules ranged from 400 nm to 500 nm and the ultraviolet absorption peak of Nile Red molecules ranged from 200 nm to 300 nm.