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Heat shock responsive drug delivery system based on mesoporous silica nanoparticles coated with temperature sensitive gatekeeper

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ABSTRACT

Mesoporous silica nanoparticles (MSN) have several advantages as carriers for drug delivery, including high drug loading capacity, good biocompatibility, excellent stability, and easily tailorable surface properties. This study describes the design of an MSN-based carrier for use in a heat shock responsive drug delivery system. MSN were functionalized with the temperature-sensitive PEG/PCL multiblock copolymer, as gatekeepers, allowing the release of entrapped drugs in response to heat shock stimuli (MBC-MSN). In the absence of heat shock, doxorubicin (Dox)-loaded MBC-MSN showed very low cytotoxicity, as PEG/PCL inhibited the premature release of Dox from MBC-MSN. In response to heat-shock stimuli, however, these Dox@MBC-MSN showed significant cytotoxicity, similar to that of free Dox. Dox release was due to the loosening of the structure of the gatekeeper, PEG/PCL, in response to the heat shock stimuli. Taken together, these findings suggest that MBC-MSN are a strong candidate to act as a carrier in heat shock responsive drug delivery.

1. Introduction

Mesoporous silica nanoparticles (MSN) have several advantages as carriers for drug delivery systems responsive to stimuli, especially exogenous stimuli [1,2]. Among these advantages are high drug loading capacity, good biocompatibility, low apparent cytotoxicity, uniform size, high surface areas, excellent stability, and easily tailorable surface properties [3,4]. Drug molecules loaded into MSN may be released immediately after administration, but this may induce severe side effects due to the nonspecific uptake of released drugs by healthy organs, including the liver, kidneys, bone marrow and heart, before reaching the targeted organs [5–7]. Therefore, it is highly desirable to develop functionalized MSN with stimulus-responsive gatekeepers, thus preventing any premature release. To date, studies have investigated the response of several types of gatekeepers, such as nanoparticles, macrocyclic molecules, liner molecules and polymeric multilayers, to a variety of stimuli, including magnetism, temperature, pH, redox molecules and photochemical changes [8–11]. Sensitivity to pH is especially important in cancer therapy because of the specific pH conditions of tumor tissues [12,13]. Recent studies have evaluated temperature sensitivity, because temperature is an exogenous stimulus, whereas pH is an endogenous stimulus [14–16]. Heat shock is a response is exogenous changes in temperature induced by, for example, thermal therapy in cancer patients as well as inflammation-associated infrared therapy.

This study describes the development of a smart MSN carrier covered with temperature sensitive multiblock copolymer as gatekeepers, allowing the release of entrapped drug in response to heat shock stimuli. The system consists of a drug entrapped MSN and a temperature sensitive poly(ethylene glycol)/poly(epsilon-caprolactone) (PEG/PCL) multiblock copolymer (MBC-MSN), which has a dense, crystalline structure. The gate remains closed in the absence of heat shock stimuli, whereas, in their presence, the gate opens due to the melting of PCL crystals, resulting in the heat shock responsive drug release drug (Fig. 1). In aqueous solution, PEG/PCL is swollen, but its compact crystalline structure restricts the penetration of water. Heating of the copolymers to around 45 °C

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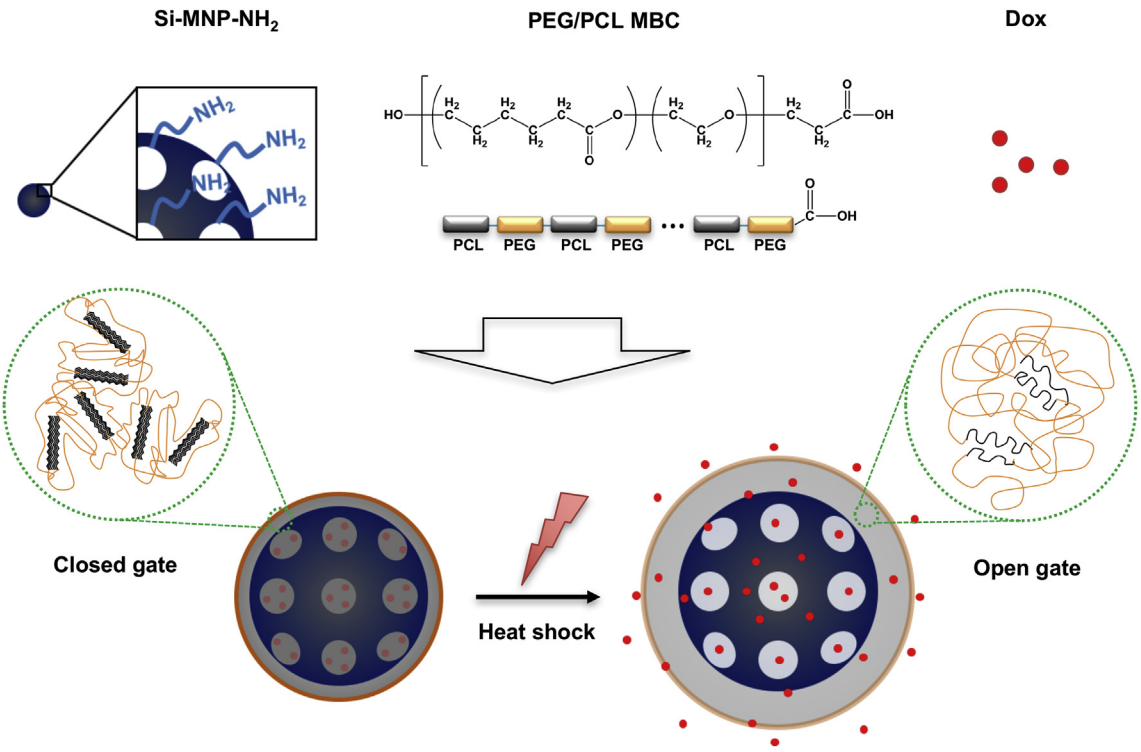

Fig. 1. Schematic illustration of heat shock responsive drug delivery system with MBC-MSN. In the absence of heat shock, PEG/PCL has a dense structure including PCL crystals (closed gate). In the presence of heat shock, PEG/PCL shows a looser structure due to the amorphous state of PCL (open gate).

causes the crystalline structure of PCL to disappear. Reduction to room temperature results in a swollen state alone, owing to a reduction of interactions between the PCL chains - PCL cannot form a crystalline structure in its swollen state because water prevents the regular structure from forming [17]. These findings suggest that PEG/PCL MBC can act as a gatekeeper for MSN, resulting in temperature sensitive release of therapeutic drugs.

2. Material and methods

2.1. Materials

Amine functioned mesoporous silica nanoparticles (MSN, propylamine functionalized silica, 200 nm particle size, pore size 4 nm) was purchased from Aldrich Chemical Co. (Milwaukee, WI, USA). Polyethylene glycol bis carboxyl methyl ether, dicarboxylated PEG (PEG, Mw 600 Da), polycaprolactone diol, dichydroxylated PCL (PCL, Mw 530 Da), 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC), N-hydroxybenzotriazol (HoBt), 4-dimethyl aminopyridine (DMAP), and doxorubicin hydrochloride (Dox) were obtained from Aldrich Chemical Co. (Milwaukee, WI, USA).

2.2. Synthesis of PEG/PCL multiblock copolymers

Dicarboxylated PEG and equimolar dihydroxylated PCL were dissolved in methylene chloride. Pre-determined amounts of EDC, and equimolar DMAP and HoBt (Table S1) were added and stirred overnight at room temperature under nitrogen purge. Methylene chloride removed from reaction mixture with rotary evaporator and then distilled water added. After lyophilization, PEG/PCL multiblock copolymers (MBC) obtained. To evaluate the molecular weight of synthesized PEG/PCL MBC, they were dissolved in THF and were analyzed by high-performance liquid chromatography system (Agilent 1260 infinity series) equipped with a gel permeation chromatography analysis mode (Agilent Technologies, Santa Clara, CA, USA).

2.3. Temperature sensitivity of PEG/PCL MBC

To evaluate the temperature sensitivity of PEG/PCL MBC, their size and crystallinity were measured. Heat shock was performed with 30 min incubation at 45 °C. The average mean diameter of PEG/PCL MBC were determined using dynamic light scattering (90 Plus Particle Size Analyzer, Brookhaven Instruments Corporation, Holtsville, NY, USA) at 632 nm. WAXD analysis for measurement of crystallinity was conducted with a Rigaku X-ray diffractometer using Cu Kα source (0.154 nm). All samples were scanned at a rate 0.6°/min between $2\alpha\theta = 10°$ and 35° in transmission mode (40 kV and 200 mA).

2.4. Preparation of MBC-MSN

MSN (propylamine functionalized silica, 40 mg) was dispersed in 20 mL methanol/chloroform (v/v = 1/1). 10 mL methanol/chloroform including 2.2 g PEG/PCL MBC, equimolar EDC and HoBt added stirred overnight at room temperature under nitrogen purge. Organic solvents removed from reaction mixture with rotary evaporator and then distilled water added. After lyophilization, MBC-MSN obtained.

2.5. Characterization of MBC-MSN

To confirm surface modification, the surface charge of these MSN was measured using a Zeta-potential meter (90 Plus Particle Size Analyzer, Brookhaven Instruments Corporation, Holtsville, NY, USA). The morphology of MBC-MSN was verified using a 200 kV Tecnai F20 TEM (FEI Company, Hillsboro, OR, USA). To measure cytotoxicity of MBC-MSN, A549 cells were seeded at 1×10^4 cells/

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