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Gated mesoporous carbon nanoparticles as drug delivery system for stimuli-responsive controlled release

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ABSTRACT

Mesoporous carbon nanoparticles (MCNs) show low toxicity suitable for drug delivery carriers but are limited to strong hydrophobic property. Carboxylation and subsequent amination of MCNs were beneficial to drug delivery and release. Gated channel-interconnected MCN vehicles were constructed to realize stimuli-responsive controlled release of drugs. *N*-(3-Trimethoxysilylpropyl)ethylenediamine triacetate-functionalized ZnO quantum dots (QDs) as gatekeepers were covalently linked with carboxylated MCNs (ca. 115 nm in diameter and 3–3.5 nm in pore size) via dual amide linkages encapsulated drugs within the interconnected channels. The gating of the MCN vehicles not only improved the drug loading capacity but also introduced the stimuli-responsive performance. The controlled release of the drugs could be achieved by lowering pH (acidic microenvironment of tumor cells) to dissolve the ZnO QD gatekeepers and further promoted at elevated temperatures. The ZnO-gated MCN drug delivery system exhibits prospective applications for tumor therapy.

1. Introduction

A variety of nanoparticle-based drug delivery systems have been developed for improvement of therapeutic efficacy and minimum of side effects of drugs [1]. Mesoporous silica nanoparticles (MSNs) possess the features of biocompatibility, high specific surface area, tunable mesopore size, and ease of surface modification and make them as potential drug vehicles [2]. Extensive efforts have been devoted to MSN drug delivery systems for stimuli-responsive controlled release. A number of capping scaffolds, such as inorganic nanoparticles, polymers, and biomacromolecules, function as MSN gatekeepers to realize drug's controlled release in response to endogenous stimuli (such as pH, redox, enzymes, and specific analytes) and exogenous stimuli (such as light, ultrasound, temperature changes, and magnetic fields) [3–13]. Mesoporous carbon nanoparticles (MCNs) have the similar structural features and properties to MSNs and show lower toxicity than MSNs [14,15]. To date, a few MCN drug delivery systems have been reported [16–20], however, gated MCN drug delivery systems are still lacking for stimuli-responsive controlled release.

Herein, a gated MCN drug delivery system was constructed for stimuli-responsive controlled release. MCNs were synthesized [17] using MCM-48 type MSNs [21], with the cubic $Ia\bar{3}d$ porous morphology, as the templates. The mesoporous channels of MCNs are interconnected because they are the replication of the MCM-48 mesostructure consisting of two interpenetrating continuous frameworks of chiral channels [22,23]. Drug leakage can be unavailable for the MCM-41 type MSN based drug delivery systems even in the case that not all of the parallel-arranged channels (without interconnection) were capped [2] because the loss of the loaded drugs only occurs for the uncapped pores [24]. However, absence of gating of the interconnected MCN pores would lead to the loss of loaded drugs in principle and the stimuli-responsive performance is unavailable. Thus, it is a challenge to construct stimuli-responsive drug delivery systems based on the channel-interconnected MCNs.

ZnO quantum dots (ZnO QDs) benefit from their ease of synthesis, cheap, biocompatibility, and ease of functionalization and were selected as gatekeepers to construct gated MCN delivery system (Fig. 1). The surfaces of the carboxylated MCNs were covalently linked with carboxylated ZnO QDs via dual amide bonds to improve drug loading capacity and to minimize premature release of drugs. ZnO QDs are stable at neutral pH but undergo a rapid dissolution into zinc ions when pH is lower than 5.5 [25,26]. It has

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been found that zinc ions play vital roles in functions of human bodies, such as growth, metabolism, immune, and healing [27]. Moreover, zinc is also of importance to the reduction of cardiovascular and cancer diseases [28] and resistance to ultraviolet light [29]. It is known that tumor and inflammatory tissues develop more acidic microenvironments than blood and normal tissues. The early endosomes and late endosomes/lysosomes in the tumor cells are at approximately pH 6.0 and pH 5.0, respectively [30]. It is clear that the ZnO-gated MCN delivery system has prospective applications thanks to the acidic microenvironments of tumor cells.

2. Experimental

2.1. Materials

Triblock copolymer Pluronic F127 ($EO_{106}PO_{70}EO_{106}$), 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (EDC), *N*-hydroxysuccinimide (NHS), and 1,6-diaminohexane were obtained from Aladdin, and tetraethylorthosilicate (TEOS, 99%) was from Sigma–Aldrich. Aminopropyltrimethoxysilane (APTMS), magnesium acetate tetrahydrate, zinc acetate dehydrate, rhodamine 6G (Rh6G), and concentrated H_2SO_4, and ammonium persulfate ($(NH_4)_2S_2O_8$) were purchased from Sinopharm Chemical Reagent Co., Ltd. (China), and cetyltrimethylammonium bromide (CTAB) and aqueous ammonia solution (25 wt%) were from Shanghai Chemical Reagent Co., Ltd. (China). Mitoxantrone hydrochloride (MIT, 98%) was obtained from Adamas Reagent Co., Ltd. (China), and *N*-(3-trimethoxysilylpropyl)ethylenediamine triacetate trisodium salt (TSP-DATA, 45%) in water was from Fluorochem Ltd. Unit. The buffer solution (10 mM) was prepared from 4-(2-hydroxyerhyl) piperazine-1-erhaesulfonic acid (HEPES), and hydrochloric acid (HCl) or sodium hydroxide (NaOH) was added to the buffer to adjust pH. All of the chemicals used were of analytical grade, and water used was double-distilled.

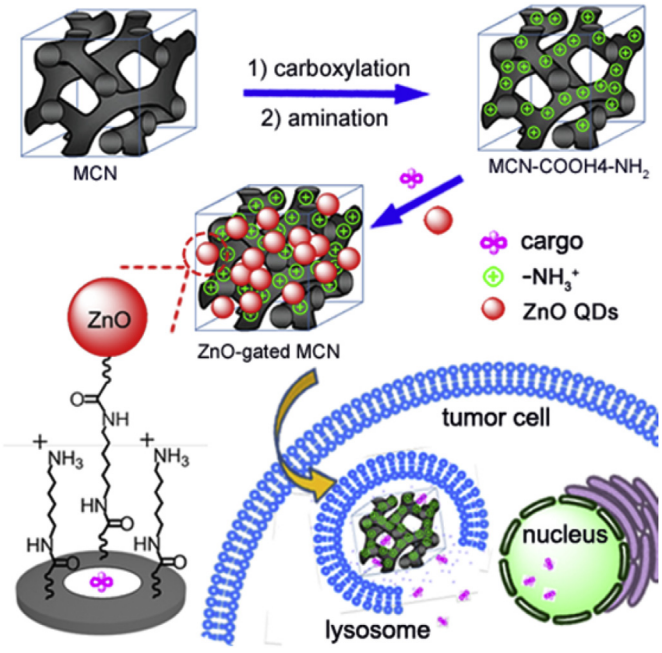

Fig. 1. Schematic illustration of construction of ZnO-gated MCN delivery system and controlled release of encapsulated cargo. (A colour version of this figure can be viewed online.).

2.2. Instruments and measurements

A Hitachi S-4800 scanning electron microscope (SEM) and a JEM-2100 transmission electron microscope (TEM) were used to record the corresponding images of MSNs and MCNs. Small-angle X-ray diffraction (XRD) patterns were measured on a Philips X'Pert Pro diffractometer with a Cu-Kα radiation ($\lambda = 0.15405$ nm), and nitrogen adsorption-desorption isotherms were performed on an ASAP2020 porosimeter at 77 K. A VECTORTM22 spectrometer was used to collect FTIR spectra, and a Lambda35 UV–vis spectrometer (PerkinElmer) was to record UV–vis spectra. A zeta potential analyzer (ZetaPALS, Brookhaven Instruments Co.) was employed to measure zeta potentials, and a 90Plus particle size analyzer (Brookhaven Instruments Co.) was used to determine hydrodynamic diameters. The confocal microscopy images of cells were acquired on an MD ImageXpress microscope (BL-KJ0A0048, USA).

2.3. Synthesis of MCNs

CTAB (500 mg) and F127 (2.0 g) were dispersed in 250 mL of $NH_3 \cdot H_2O$/ethanol/water solution (12:43:95, v/v/v) under stirring at room temperature for 10 min. TEOS (1.9 mL) was added to the dispersion under vigorous stirring for 1 min, and then the dispersion was left for aging up to one day. The as-synthesized silica nanoparticles were centrifugally separated and washed with water and ethanol, followed by drying in vacuum. The dry nanoparticles were extracted with methanol (100 mL) and concentrated HCl solution (6.0 mL) under refluxing for 24 h to remove the surfactant templates. MCM-48 nanoparticles were finally obtained after separation, washing with methanol, and drying.

The MCM-48 nanoparticles (430 mg) was dispersed in 50 mL of anhydrous toluene, then 1 mL of APTMS was added, and the solution was refluxed under nitrogen at 80 °C for 12 h. Aminated MCM-48 nanoparticles were separated by centrifugation followed by washing with methanol and drying in a desiccator.

The aminated MCM-48 nanoparticles (500 mg) were dispersed in 40 mL of aqueous solution containing glucose (9.9 g) under sonication for 20 min, and then the mixture reacted in an autoclave at 180 °C for 3 h. The as-synthesized brown solids were separated and washed with water and ethanol followed by drying at 100 °C. The dry solids were carbonized at 900 °C and then added to aqueous hydrofluoric acid (HF) solution (10%) in a plastic container to etch silica at 80 °C for 4 h. The black MCNs were collected by centrifugation, washed with water and methanol up to neutral pH, and dried in vacuum.

2.4. Carboxylation of MCNs

MCNs were carboxylated according to the method in the literature [31]. In brief, MCNs (200 mg) were added to 120 mL of aqueous solution containing 27.4 g of $(NH_4)_2S_2O_8$ and 13 mL of concentrated H_2SO_4 under stirring at room temperature for 2, 4, 6, and 8 h. The black carboxylated MCNs were separated by centrifugation and thoroughly washed with water and ethanol up to neutral pH. The carboxylated MCNs were denoted as MCN-COOH*n* ($n = 2$, 4, 6, and 8), where *n* represents carboxylation time in hour.

2.5. Amination of MCNs

MCN-COOH4 (200 mg) was dispersed in 30 mL of dimethyl sulfoxide (DMSO), and then 200 mg of NHS, 400 mg of EDC, and 200 mg of 1,6-diaminohexane were added under stirring at 30 °C for 24 h. The resulting MCN-COOH4-NH_2 was collected by centrifugation and washed with ethanol.