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Construction of multifunctional porous silica nanocarriers for pH/enzyme-responsive drug release

Li Qiu[a], Weirui Zhang[b,*], Shuyun Wang[b], Xu Zhang[a,b], Yanbao Zhao[a,*], Liuqin Cao[c], Lei Sun[a]

[a] Engineering Research Center for Nanomaterials, Henan University, Kaifeng 475004, China
[b] Department of Pharmaceutics, Henan University, Kaifeng 475004, China
[c] Department of Chemistry and Chemical Engineering, Henan University, Kaifeng 475004, China

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ABSTRACT

pH/enzyme-responsive nanocarriers based on porous silica ($pSiO_2$) nanospheres (NSs) were developed for controlled release of drug. The $pSiO_2$ NSs present uniform spheres and have an average diameter of 100 nm. The $pSiO_2$ NSs with high specific surface area (835 $m^2 \cdot g^{-1}$) and the pore volume (1.24 $cm^3 \cdot g^{-1}$) are suitable for drug loading and the loading capacity reaches to 29% for amoxicillin (AMX) model drug. In this system, protocatechuic acid (PCA) and L-glutamic acid (Glu) as linkers were grafting onto the surface of $pSiO_2$ NSs to conjugate the capping lids. Acid-decomposable ZnO quantum dots (QDs) were introduced to block the partial pores of $pSiO_2$ via amido bonds, which could act as gates and fluorescence probes. To minimize the premature release, hyaluronic acid (HA) was further coating on the outer surface of $pSiO_2$, which would be degraded by over-expressed hyaluronidase (Hyal-1) in the tumor microenvironment. The controlled release of the drug from the ZnO/HA-gated delivery system was realized by the acidic dissolution of ZnO QDs and enzymatic hydrolysis of HA. The obtained ZnO/HA-gated $pSiO_2$ delivery system would achieve minimized premature release and responsive release under a physiological environment.

1. Introduction

Encapsulation of drugs within nanocarriers that selectively target malignant cells has emerged as a promising tool to improve therapeutic efficacy and minimize the adverse effects of drugs [1]. For example, the use of delivery system capable of cancer cell-specific targeting and responsive drug release would improve treatment efficacy of ovarian cancer [2]. To date, a great number of nanoplatforms, including liposomes [3], polymers [4,5], hydrogels [6], supramolecular [7,8], inorganic nanoparticles [9] and mesoporous silica [10,11], have been developed to achieve a controllable delivery of drugs. For instance, thermogelling copolymer nanocarriers showed good recovery characteristics and sustained drug release [12,13]. Among them, porous silica ($pSiO_2$) nanospheres (NSs) have been the favorable choice of delivery vehicle due to their excellent high stability, good biocompatibility, large surface area and tunable pore size [14,15]. However, the practical application of $pSiO_2$ NSs in vivo still faces many critical barriers, such as nonspecific drug accumulation at tumor sites and premature release in the circulatory system. For protecting the entrapped drugs from premature release, various kinds of nanogates have been fabricated to control the opening and closing of the pores and the release of loaded drug molecules into a specific environment can be triggered by external or internal stimuli, such as pH [16,17], redox reaction [18,19], temperature [20] and enzymatic activity [21,22].

It is well-documented that the pH in tumor and inflammatory tissues is more acidic than in blood and normal tissues. ZnO quantum dots (QDs) are stable at pH 7.4 but rapidly dissolve into zinc ions at pH < 5.5, which motivates us to use ZnO QDs as gatekeepers to respond to pH signals to trigger drugs release in cancerous cells [23,24]. Furthermore, the fluorescent ZnO QDs would be used as a fluorescent label to monitor the drug release [25]. ZnO QDs also exhibit more cytotoxicity on cancer cells than normal ones, which would achieve synergistic therapy of antitumor. Hyaluronic acid (HA) is linear, naturally occurring polysaccharide that is a major extracellular constituent of connective tissues [26]. HA could be readily degraded into low molecular weight fragments by hyaluronidase (Hyal-1), whose level is known to increase in various tumors, so HA could be also used as enzyme-responsive gatekeeper for drug release [27]. In addition, HA possesses the active targeting toward tumor cells through selectively binding over-expressing CD44 receptors [28].

In this paper, we present a smart delivery platform by combining amino-functionalized porous silica ($pSiO_2$-NH_2) NSs, fluorescent ZnO

* Corresponding authors.
E-mail addresses: 10200068@vip.henu.edu.cn (W. Zhang), zhaoyb902@henu.edu.cn (Y. Zhao).

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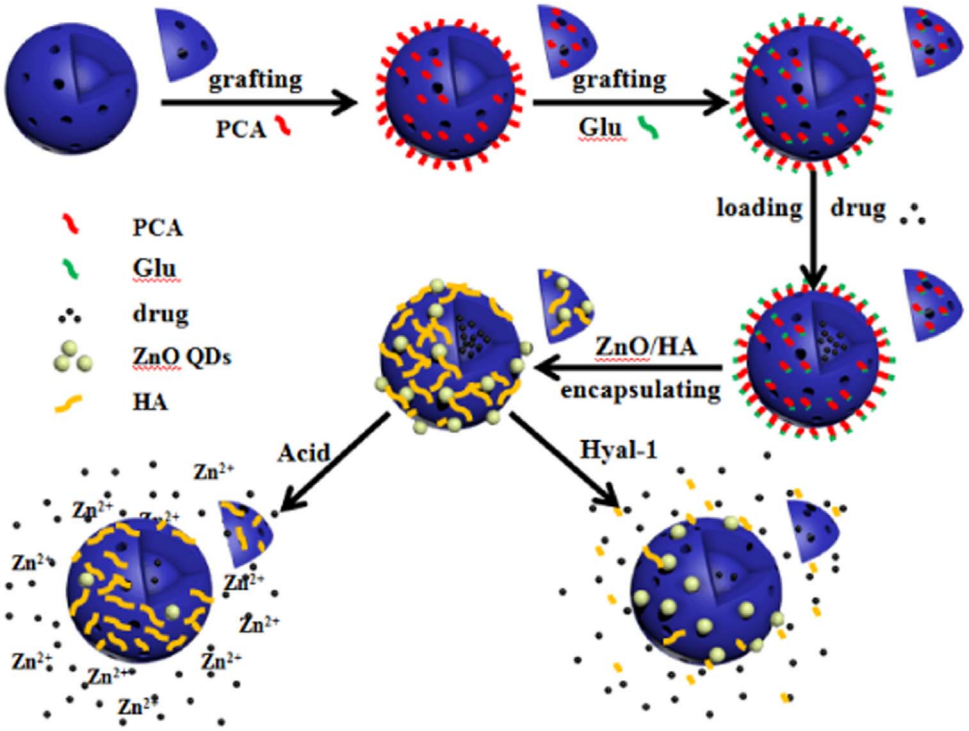

Scheme 1. Preparation of ZnO/HA gated $pSiO_2$/PCA-Glu NSs for drugs loading and releasing.

QDs and HA for pH/enzyme responsive drugs delivery (see Scheme 1). Protocatechuic acid (PCA) as a linker was grafting onto the surface of $pSiO_2$-NH_2 NSs via amido bonds. To tune the length of linker, L-glutamic acid (Glu) as co-linker was conjugated with PCA via ester bonds. Aminated ZnO QDs were used to block the drug-loaded pores of the $pSiO_2$ carriers through amido bonds. HA was further coated on the outer surface of $pSiO_2$ to minimize the premature release, which would be degraded by enzymatic hydrolysis. Amoxicillin (AMX) was chosen as a test drug to assess the drug loading and releasing behavior of the $pSiO_2$ nanocarriers. In addition, ZnO QDs can be used to monitor the drug release by fluorescent signal.

2. Experimental

2.1. Reagents

Amoxicillin (AMX), protocatechuic acid (PCA), hyaluronic acid (HA), hyaluronidase (Hyal-1), 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (EDC), *N*-hydroxysuccinimide (NHS) and 3-aminopropyltrimethoxysilane (APTMS) were purchased from Aladdin (China). L-Glutamic acid (Glu), methanol, dehydrated alcohol, tetraethyl orthosilicate (TEOS) and *N*,*N*-dimethylformamide (DMF) were purchased from Sinopharm Chemical Reagent Co. (China). Sodium citrate, disodium hydrogen phosphate ($Na_2HPO_4{\cdot}12\ H_2O$) and monopotassium phosphate (KH_2PO_4) were purchased from Deen Reagent Co. (Tianjin, China). Dimethyl sulfoxide (DMSO), hexane, zinc acetate, magnesium acetate, sodium hydroxide (NaOH) and cetyltrimethylammonium bromide (CTAB) were purchase from Tianjin Kermel Chemical Reagent Co. (Tianjin, China). Distilled water was used throughout the experiment.

2.2. Characterization

The morphology was characterized by transmission electron microscopy (TEM, JEM-2100, Japan) at 200 kV. Absorption spectra were collected on a Lambda 950 spectrometer (PE, America) at room temperature. Photoluminescence (PL) spectra were investigated using a fluorescence spectrophotometer (JY-HORIBA, France). The surface area and pore size distribution were determined from N_2 adsorption/desorption isotherms measured on a full-automatic specific surface and porosity analyzer (Quadrasorb SI, America) at 77 K. X-ray diffraction (XRD) patterns were recorded on power X-ray diffractometer (D8-ADVANCE) equipped with Cu Kα radiation (40 kV, 40 mA). Zeta potentials were measured using zeta potential analyzer (nano ZS).

2.3. Synthesis of $pSiO_2$-NH_2 NSs

APTMS-modified ZnO QDs were prepared by according to the method described in a published paper [25]. The $pSiO_2$-NH_2 NSs were prepared by sol–gel route. First, 0.6 g of CTAB was dissolved in 220 mL of distilled water and heated to 75 °C for 30 min under stirring. Then 2.0 mL of NaOH solution (2 M) was dropwise added to adjust the pH of the solution to 11. After that, the mixed solution (containing 4 mL of TEOS and 20 mL of methanol) was dropwise added into the above solution and reacted for 0.5 h under stirring. Subsequently, 1 mL of APTMS was added and reacted for another 6 h under stirring. Final, the as-synthesized $pSiO_2$-NH_2 NSs was collected by centrifugation and washed with ethanol. The CTAB surfactants were removed by heating 1.0 g of the $pSiO_2$-NH_2 NSs in 100 mL of ethanol and 6 mL of concentrated HCl solution at reflux for 10 h. The collected sample was thoroughly washed with deionized water.

2.4. Surface modification of $pSiO_2$-NH_2 NSs

200 mg of EDC and 100 mg of NHS were dissolved in 10 mL of DMSO solution with stirring for 1 h. Next, 100 mg of PCA was added into above solution to activate the carboxyl groups of PCA for 24 h. Subsequently, 100 mg of $pSiO_2$-NH_2 was added to the activated PCA solution and allowed to react for 12 h at room temperature. Finally, the $pSiO_2$/PCA NSs were collected by centrifugation and washed with ethanol.

40 mg of Glu was dissolved in 10 mL water, and then 40 mg of $pSiO_2$/PCA NSs were added to the Glu solution. After reaction at 30 °C for 15 h, the mixture was centrifuged, washed and dried to obtain $pSiO_2$/PCA-Glu sample.