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Short communication

Dendritic porous SnO_2/SiO_2@polymer nanospheres for pH-controlled styptic drug release

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ABSTRACT

Dendritic porous tin oxide/silica (DTS) nanospheres (NSs) were prepared by emulsion-condensation route. DTS NSs have an average diameter of 80 nm and possess accessible center-radial large pore channels, which endow them high surface area, less drug diffusion resistance and more mass transport. SnO_2 quantum dots (QDs) embedded in silica skeleton can be used to track the drug release behavior. DTS NSs were coated by chitosan/polymethacrylic acid and polymer shell would make them achieve great loading capacity and pH-sensitive release for aminomethylbenzoic acid (AMBA).

Introduction

Dendritic silica nanospheres with easy-functional surfaces have been proved enormous potential as efficacious drug delivery carriers for small drug molecules, genes, and proteins [1–4]. In particular, apart from the established series of nanosilica materials, like mesoporous and hollow structures [5,6], dendritic silica nanospheres were developing as favorite drug carriers, owning to their partial interconnected pores in the nanometer range and relatively small matrix particle size, which can reduce drug diffusion resistance and enhance mass transport.

To date, many efforts have been focused on the silica-based "smart" drug carriers [7,8]. For example, polyethyleneimine modified mesoporous silica nanoparticles display excellent pH-responsive release [9]. However, the process of drug delivery cannot be monitored *in vivo* using the pure silica materials because of the lack of detectable signals. Therefore, the development of silica-based delivery system with the capacity of controlling and monitoring drug release is highly desirable.

SnO_2 is a metal oxide semiconductor used in sensors, solar cells and photocatalysis [10,11]. Especially, SnO_2 quantum dots (QDs), unlike organic fluorescence dye, are biocompatible and display drug-dependent fluorescence [12,13]. In this work, we present a smart delivery platform by combining fluorescent SnO_2 QDs, porous silica and polymer layer. SnO_2 QDs were used to monitor drug release by recording the fluorescent change. The porous silica NSs possess accessible center-radial large pores for drug loading and polymer shell (chitosan/poly methacrylic acid) would endow the nanocarriers pH-responsiveness [14–16]. Aminomethylbenzoic acid (AMBA) is a potent synthetic inhibitor of plasmin, which has been used for treating all kinds of bleeding with the advantage of distinct hemostasis effect on oozing of blood. Additionly, chitosan can be used in medical and surgical procedures by its direct application to a bleeding surface using the various physical forms, so DTS@CS–PMAA applied in AMBA release can achieve the synergistic effect of hemostasis. Here, AMBA is used as a model drug to evaluate the release behavior of the nanocarriers [17]. The nanocarriers exhibit an excellent pH-controllable release property. We believe that this study will provide important information for the rational design of dendritic silica based nanocarriers with improved biological effects and stimuli responsive drug delivery features.

Experimental

Materials

All chemical agents used in these experiments were of analytical grade and used without further purification. Tetraethyl orthosilicate (TEOS, 98%), cetyl trimethyl ammonium bromide

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(CTAB, 99%), cyclohexane (C_6H_6), ammonium persulfate $(NH_4)_2S_2O_8$), glutaraldehyde (≥25%) and methacrylic acid (MAA, 99%) were purchased from Tianjin Kermel Chemicals (Tianjin, China); 3-triethoxysilylpropylamine (APTES, 98.0%) was from Aladdin (China); Chitosan (CS, 98.0%) was from Sinopharm Chemical Reagent (Shanghai, China); Ammonium hydroxide (NH_4OH, 28%), hydrochloric acid (HCl, 35%) and absolute ethanol were obtained from Luoyang Chemicals (Luoyang, China); Phosphate buffer saline (PBS; 0.1 mol/L; pH 7.4, 5.5 and 6.8) was purchased from Sigma-Aldrich, America. Aminomethylbenzoic acid (AMBA, 99%) was obtained from Ningbo Doulebe Sun Pharmaceutical Co. Ltd. (Ningbo, China).

Synthesis of DTS NSs

SnO_2 QDs were previously prepared by hydrothermal process [12]. DTS NSs were prepared by sol–gel route. First, water (70 mL), cyclohexane (15 mL), ethanol (5 mL) and CTAB (0.5 g) were added into round-bottom flask to form homogenous emulsion at 25 °C, and its pH was tuned to 8.0. Then, 40 mg of SnO_2 QDs were dispersed in the emulsion. After that, the mixture of TEOS (3.5 mL) and APTES (0.1 mL) was quickly dripped into the above solution and vigorously stirred at 25 °C for 4 h. Finally, 1 mL of HCl (37%) was added to stop the reaction and the white precipitate was centrifuged to get DTS sample.

Polymer modification

140 mg of DTS, 80 mg of MAA and 50 mg of CS were dissolved in 75 mL of water and heated to 80 °C. Then, 40 μL of $(NH_4)_2S_2O_8$ solution was injected into it and sonicated for 2 h. After that, the reaction solution was cooled down to 50 °C and 100 μL of glutaraldehyde was also added to react for another 2 h. Last, DTS@CS–PMAA NSs were obtained by centrifuged, washed and dried.

Characterization

The morphology and composition were characterized by transmission electron microscopy (TEM, JEM-2010, Japan), flourier transform infrared (FT-IR, AVATAR360, America), X-ray diffraction (XRD, X-Pertpro, Holland), fluorescence spectrometer (FL, fluoroSENS, Britain), full-automatic specific surface and porosity analyzer (Specific surface, Quadra orb SI, America). The UV absorption spectra were investigated using a UV–vis spectrophotometer (PE-Lambda 35, America). Raman spectrum of AMBA was measured by confocal laser Raman spectrometer (RM-1000, British Renishaw), and the samples (about 50 mg) to be measured was pressed evenly on the slide.

Drug loading and release

AMBA was used as a model drug to estimate the drug loading capacity and release behavior of DTS@CS–PMAA NSs. First, ABMA was dissolved in phosphate buffer solution (PBS, pH = 4.0) with a concentration of 12 mg/mL. Then 90 mg of the DTS@CS–PMAA NSs was soaked with ABMA solution for 4 h at 25 °C. The ABMA-loaded DTS@CS–PMAA NSs were collected by centrifugation and washed with PBS for several times.

For *in vitro* drug release, the ABMA-loaded sample (15 mg) was dispersed in 10 mL of phosphate buffer solution with different pH values (pH 5.5, 6.8 and 7.4), and gently stirred at 120 rpm and 37 °C. At predetermined time intervals, 1 mL of the solution was withdrawn, and an equal volume of fresh medium was added to keep the volume constant. The amount of released ABMA was analyzed by UV/vis spectroscopy at a wavelength of 295 nm.

Result and discussion

Fig. 1a gives the XRD patterns of DTS and DTS@CS–PMAA samples. In XRD pattern of DTS, the characteristic diffraction peaks

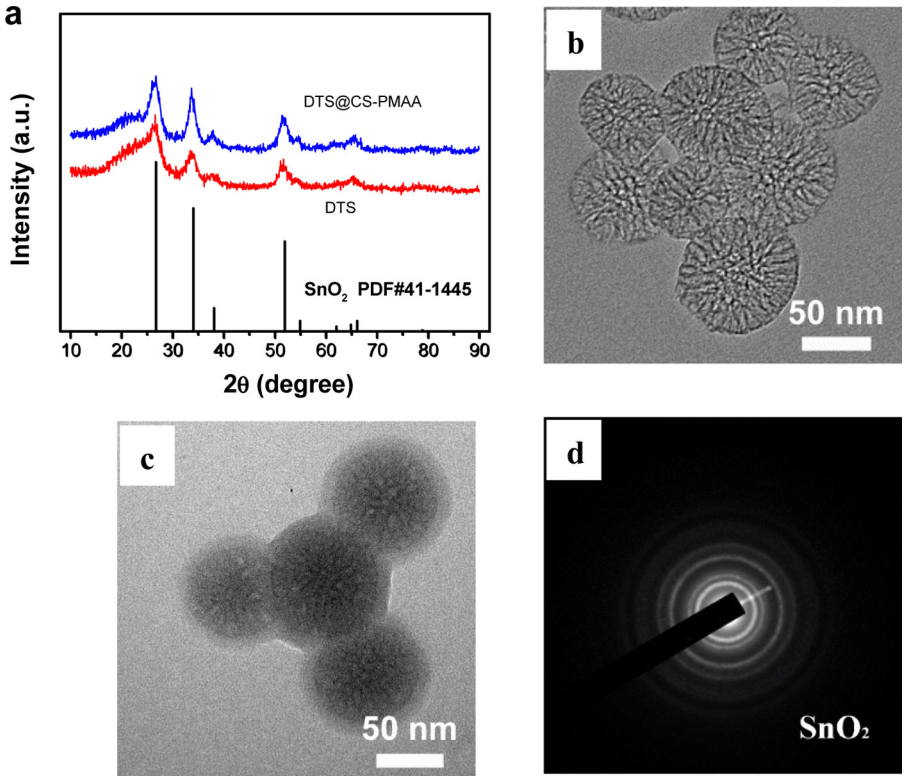

Fig. 1. XRD patterns of as-prepared samples (a), TEM images of DTS (b) and DTS@ CS–PMAA (c), ED patterns of SnO_2 QDs (d).