Microporous and Mesoporous Materials 264 (2018) 151–158

Contents lists available at ScienceDirect

Microporous and Mesoporous Materials

journal homepage: www.elsevier.com/locate/micromeso

pH-sensitive polymer-gated multifunctional upconversion $NaYF_4$:Yb/Er@$mSiO_2$ nanocomposite for oral drug delivery

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ARTICLE INFO

Keywords:
pH-responsive
Upconversion
Mesoporous
Polymer-gated
Oral drug delivery

ABSTRACT

Multifunctional nanocomposite have received much attention due to their potential applications in controlled drug delivery systems. Herein, multifunctional UCNPs@$mSiO_2$-PAA nanocomposite with UCNPs as core and poly (acrylic acid) (PAA)-gated mesoporous silica as shell were fabricated for oral drug delivery. The results demonstrated that the mesoporous silica shell (~20 nm) uniformly coated on the UCNPs, and the PAA brushes were covalently attached on the pore mouths of mesoporous silica shell. The *in vitro* drug release results exhibited that the doxorubicin (DOX) molecules were almost encapsulated in the locked pores in simulated gastric fluid (SGF, pH = 1.2) due to the capping effect of PAA brushes, while the DOX could easily diffuse from the opened pores in phosphate buffer solution (PBS, pH = 7.4) due to the removing of the capping. These results indicating that the PAA brushes can be employed as gatekeepers to control the drug transport in and out of the pore channels of UCNPs@$mSiO_2$-PAA. Moreover, the drug release process can be monitored by the changes of fluorescence intensity under the NIR light laser excitation. We anticipate that the multifunctional nanocomposite can be used as nanocarrier for control and tracking of drug release in oral drug delivery systems.

1. Introduction

Development of multifunctional nanostructures for disease therapy has attracted considerable attention over the past several decades. Lanthanide-doped upconversion nanoparticles (UCNPs) have been widely explored and used as drug carriers or therapy agents in cancer therapy due to their attractive features such as weak autofluorescence background, good photostability and strong penetration ability under near-infrared radiation, *etc* [1–4]. Moreover, UCNPs can be employed as luminescence labels to track and evaluate the drug release process in living system [5,6]. Yb/Er or Yb/Tm co-doped $NaYF_4$ nanocrystals are generally considered to be the most efficient host materials to date [7,8]. However, the currently used $NaYF_4$ nanoparticles still suffer from several drawbacks for biological applications such as the poor water-solubility, poor biocompatibility and low specific surface area. Thus, much effort has been devoted to solving these problems by surface modification or silica coating of surface of UCNPs [9–12].

Mesoporous silica nanoparticles (MSN) have been recognized as suitable candidates for drug carriers due to their remarkable features, including the huge specific surface area, excellent biocompatibility and the ease of surface modification and so on [13–15]. Thus, mesoporous silica-coated UCNPs has been studied extensively for biological applications in recent years [16–19]. Because the porous silica shell not only enhance the biocompatibility of UCNPs, but also can store drug molecules to improve the drug loading capacity. What is more, the pore channels of mesoporous silica can be capped with intelligent gatekeepers for controlled release of drug when triggered by external stimuli such as temperature [20–22], pH [23–27], enzymes [28–30], *etc*. The gatekeeper-capped mesoporous silica can deliver the drug molecules to the targeted site on demand. In particular, pH is the most popular stimulus because it can be triggered by different physiological pH in a body instead of extra stimulus. For example, the pH values are different in stomach (pH = 1.0–3.0) and colon (pH = 7.6–8.0) tissue [31]. Smart polymer have been demonstrated to be suitable gatekeepers

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https://doi.org/10.1016/j.micromeso.2018.01.029
Received 11 November 2017; Received in revised form 6 January 2018; Accepted 19 January 2018

to control the transport of drugs in and out of the pore channels [32–34], since they have excellent biocompatibility and good biodegradation [35]. Thus, integration of the merits of UCNPs and polymer modified mesoporous silica to develop multifunctional nanocarriers have gained much interest for controlled release of drug in the past years [36–39].

Oral chemotherapy is regarded as the most preferred route for the treatment of cancer disease because it is convenient and compliant to the patient, and can decrease the side effects [40]. However, most of the anticancer drugs, such as doxorubicin (DOX), prematurely release in strong acidic stomach before reaching the cancer disease site, resulting in the drastically decrease of the drug bioavailability. Thus, it is of great significance and highly desirable to design a pH-controlled oral drug delivery system to enhance the drug bioavailability by oral route. Up to date, however, previous studies mainly focused on the targeted drug release in the acidic conditions which is not favourable for oral drug delivery systems. To the best of our knowledge, the combination of upconversion nanoparticles and polymer-gated mesoporous silica for oral drug delivery have been rarely reported. Previously, we fabricated a multifunctional nanocarrier composed of dense silica-coated UCNPs and modified with poly (methacrylic acid) (PMAA) for targeted release in weak basic condition [38]. However, the dense silica shell is almost not available for drug loading and controlled release. Subsequently, we demonstrated that the pores of mesoporous silica can be capped with polymer *via* a facile graft-onto method for oral targeted drug release of DOX [41].

Hence, in this work, we design a multifunctional UCNPs@$mSiO_2$-PAA nanocomposite with UCNPs as core and poly (acrylic acid) (PAA)-capped mesoporous silica as shell for controlled release of DOX by oral route. The results showed that the loaded DOX molecules in the pore channels of the UCNPs@$mSiO_2$-PAA can be encapsulated in the locked pores in simulated gastric fluid (SGF, pH = 1.2) due to the capping effect of PAA brushes. Thus, these findings indicated that the resultant multifunctional nanocarrier have potential applications in oral drug delivery systems.

2. Experimental

2.1. Synthesis of UCNPs@$mSiO_2$-PAA nanocomposite

2.1.1. Synthesis and surface modification of UCNPs@$mSiO_2$

Upconversion $NaYF_4$:Yb/Er nanospheres (UCNPs) were prepared according to the previous literature [42]. The silica-coated UCNPs was prepared *via* a modified sol-gel process [43]. In a typical procedure, 100 mg of obtained UCNPs nanosphere was dispersed in 80 mL of ethanol and treated with ultrasonicator for 30 min. Afterward, 20 mL of deionized water, 1.0 mL of concentrated ammonia aqueous solution (28 wt%), and 50 μL of TEOS was added to the above solution. After stirring for 6 h, the product was separated and washed with ethanol, and then redispersed in a mixed solution containing 0.3 g of cetyltrimethylammonium bromide (CTAB), 80 mL of deionized water, 60 mL of ethanol and 1.5 mL of concentrated ammonia aqueous solution. After stirring for 1 h, 300 μL of TEOS was added dropwise to the solution with vigorous stirring. After reaction for 6 h, the product was collected and washed with abundant water and ethanol, respectively. The CTAB-containing product nanospheres were denoted as UCNPs@$mSiO_2$-CTAB.

In order to modify the external surface of UCNPs@$mSiO_2$ nanospheres with amino groups, the above UCNPs@$mSiO_2$-CTAB was added into 20 mL of toluene containing 0.5 mL of (3-aminopropyl) triethoxysilane (APTES). After being stirred at 80 °C for 8 h, the structure-directing agent CTAB was removed by refluxing in NH_4NO_3/ethanol (10 wt%) solution at 80 °C for 4 h, and then collected by centrifugation and washed several times with ethanol and dried in vacuum oven at 60 °C for 12 h.

2.1.2. Synthesis of UCNPs@$mSiO_2$-PAA nanocomposite

The pH-sensitive polymer PAA was grafted on the surface of UCNPs@$mSiO_2$ *via* a grafted-onto method. In a typical procedure, the obtained amino modified UCNPs@$mSiO_2$ was redispersed in 15 mL of ethanol containing 10 mg of N-(3-dimethylaminopropyl)-N-ethylcarbodiimide hydrochloride (EDC) and 10 mg of triethylamine. Then 0.4 g of PAA in 15 mL ethanol was added to the above solution under ultrasonication for 30 min. The reaction kept at 45 °C for 2 h with stirring. Finally, the resulting UCNPs@$mSiO_2$-PAA nanocomposite were collected by centrifugation and washed with ethanol and dried in vacuum at 60 °C for 12 h.

2.2. Drug loading and release

DOX was chosen as a model drug to investigate the drug release behavior from the UCNPs@$mSiO_2$-PAA nanocomposite. Typically, 40 mg of nanocomposite was dispersed in 10 mL of phosphate buffer solution (PBS, pH = 7.4) with a DOX concentration of 1.0 mg/mL and under stirring for 24 h at room temperature. Then the solution was centrifuged to collect DOX-loaded UCNPs@$mSiO_2$-PAA sediments and washed for two times with PBS to remove the surface adsorbed DOX. The supernatant solutions were collected, the amount of DOX loaded into the nanocomposite and entrapment efficiency were determined by UV-vis spectrophotometer at the wavelength of 500 nm. Finally, the sample was dried at 60 °C for 12 h, which was denoted as DOX-UCNPs@$mSiO_2$-PAA.

The release test of DOX *in vitro* was performed as follows: 20 mg of DOX-UCNPs@$mSiO_2$-PAA sample was dispersed in 10 mL of dilute hydrochloric acid solution (pH = 2.0) or PBS (pH 7.4) and gently shaken at 37 °C. At selected time intervals, 2.0 mL of the solution was taken and replaced with 2.0 mL of fresh buffer solutions, and the amounts of released DOX were analyzed by UV-vis spectrophotometer.

2.3. Cytotoxicity assay

The cytotoxicity of UCNPs@$mSiO_2$-PAA nanocomposite was measured by MTT assay on Caco-2 cells. Cells with a density of 10000 cells per well were cultured in a 96-well plate in 5% CO_2 at 37 °C for 24 h. Then the cells were incubated with different concentrations of UCNPs@$mSiO_2$-PAA, DOX-loaded UCNPs@$mSiO_2$-PAA or free DOX in the Dulbecco's Modified Eagle Medium (DMEM) medium for 24 h. Then, 20 μL of 3-(4, 5-dimethyl-2-thiazolyl)-2, 5-diphenyl-2-H-tetrazolium bromide solution (MTT, 5.0 mg/mL) was added to 96-well plates and incubated for another 24 h. The solution was removed and 100 μL of dimethyl sulfoxide (DMSO) was added to each well and shaken slowly for 10 min at room temperature and the absorbance was measured at 490 nm.

2.4. Characterization

Powder XRD patterns were performed on a Bruker D8 Focus diffractometer using Cu Kα radiation (λ = 0.15406 nm). Transmission electron microscope (TEM) was performed on JEOL-2100F with a field emission gun operating at 200 kV. Nitrogen adsorption/desorption analysis was measured at a liquid nitrogen temperature (77 K) using a Micromeritics ASAP 2020 HD88 instrument. The specific surface areas were calculated by the Brunauer–Emmett–Teller (BET) method. The pore size distribution was calculated from the adsorption branch using the BJH model. The zeta-potential of nanoparticles were obtained on Zetasizer Nano ZS90 (Malvern instrument, UK) at 25 °C. FT-IR spectra were recorded on a Nicolet 5700 FT-IR spectrophotometer using the KBr pellet technique. Thermogravimetric analysis (TGA) was performed on a Perkin–Elmer STA-6000 from 30 to 800 °C under N_2 atmosphere at a heating rate of 10 °C min^{-1}. The UC emission spectra were obtained on an FLS920P Edinburgh Analytical Instrument (Edinburgh Instrument, UK) equipped using a 980 nm laser as the excitation source.