Materials Science and Engineering C 75 (2017) 829–835

Contents lists available at ScienceDirect

Materials Science and Engineering C

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

Template-etching route to construct uniform rattle-type Fe_3O_4@SiO_2 hollow microspheres as drug carrier

Lin Cheng [a], Yuanyuan Liu [c], Bingfang Zou [b,*], Yong Yu [a], Weimin Ruan [c], Yongqiang Wang [a,*]

[a] Key Laboratory for Special Functional Materials of the Ministry of Education, Henan University, Kaifeng 475004, PR China
[b] School of Physics and Electronics, Henan University, Kaifeng 475004, PR China
[c] School of Life Sciences, Henan University, Kaifeng, 475004, PR China

ARTICLE INFO

Article history:
Received 8 October 2016
Received in revised form 20 December 2016
Accepted 21 February 2017
Available online 24 February 2017

Keywords:
Template-etching route
Rattle-type
Fe_3O_4@SiO_2
Hollow microspheres
Drug carrier

ABSTRACT

Template-etching strategy was put forward to synthesize rattle-type magnetic silica (Fe_3O_4@SiO_2) hollow microspheres in a controlled way. During the experiment, monodisperse Fe_2O_3 microspheres were fabricated as physical template to generate uniform Fe_2O_3@SiO_2 with controlled shell thicknesses through sol-gel method, and the subsequent Fe_2O_3 template etching process created variable space between Fe_2O_3 core and SiO_2 shell, and the final calcination process transformed rattle-type Fe_2O_3@SiO_2 hollow microspheres into corresponding Fe_3O_4@SiO_2 product in hydrogen/nitrogen atmosphere. Compared with traditional physical template, here template-etching synthesis of rattle-type hollow microspheres saved the insertion of middle shells and their removal, which simplified the synthesis process with controllable core size and shell thickness. The rattle-type Fe_3O_4@SiO_2 hollow microspheres as drug carrier show efficient doxorubicin (DOX) loading, and the release rate of DOX loaded the rattle-type Fe_3O_4@SiO_2 hollow microspheres exhibit a surprising shell-thickness-dependent and a pH responsive drug release features. Additionally, MTT assays in HeLa cells demonstrated that the Fe_3O_4@SiO_2 nanocarriers were non-toxic even at the concentration of 250 μg mL^{-1} for 48 h. Thus, our results revealed that the Fe_3O_4@SiO_2-DOX could play an important role in the development of intracellular delivery nanodevices for cancer therapy.

1. Introduction

With the advantages like the nontoxic nature, adjustable pore diameter, and very high specific surface area, amorphous mesoporous silica materials are a kind of satisfactory drug carrier which were widely investigated in the past few years, and more and more researches on mesoporous silica based drug delivery systems have been reported [1–9]. Among them, the mesoporous silica spheres with hollow core/mesoporous shell were found to provide much higher drug loading capacity than the conventional mesoporous silica such as MCM-41 and SBA-15, and also have the sustained release property [10,11]. Furthermore, the mesoporous silica hollow microspheres are widely accepted as useful drug delivery systems because they can be ingested or injected and present a homogeneous morphology [12–14]. However, mesoporous silica suffer from some inherent limitations, such as how to carry a drug to the target organs or locations in the body. Lately, mesoporous silica functionalized by magnetic nanoparticles can carry the drugs and be guided to the targeted organs or locations inside the body, which will facilitate the therapeutic efficiency and avoid the damage of normal organs or tissues due to the drug toxicity before targeting the desired positions [15–25]. Therefore, the magnetic nanoparticles together with mesoporous silica represent a significant advance in the field of drug delivery.

Until now, many strategies were developed to combine magnetic nanoparticles and mesoporous silica spheres for drug delivery. Generally speaking, there are three kinds of structures which were designed for magnetic silica composite microspheres. One is the magnetic silica core shell structure [26–29]. For example, Zhao and Jiang et al. reported the uniform magnetic nanocomposite spheres with a magnetic core/mesoporous silica shell structure, where the porous silica shell was used to uptake drug molecules [26,27]. The other is the encapsulation of magnetic nanoparticles in the channels of mesoporous silica [30,31]. For example, Yiu et al. encapsulated magnetic nanoparticles into silica mesoporous spherical materials via temperature-programmed reduction of an iron oxide-SBA-15 composite [30]. Although the above two methods realized the combination of magnetic nanoparticle and silica microsphere, there are very few drug molecules loaded in the mesoporous channels. Recently, the rattle-type magnetic core/mesoporous shell silica microspheres were developed which not only realized high drug loading in the hollow interior but also showed the magnetic targeting delivery.

Obviously, rattle-type microspheres, as an important extension of core/shell particles, possessed a cavity between the shell and the inner

* Corresponding authors.
E-mail addresses: bfzou@henu.edu.cn (B. Zou), wangyq@henu.edu.cn (Y. Wang).

http://dx.doi.org/10.1016/j.msec.2017.02.105
0928-4931/

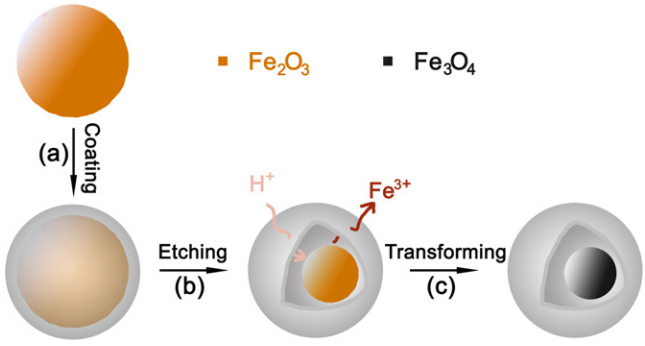
core [32,33]. Thus, to combine the magnetic nanoparticles and hollow mesoporous silica spheres, simple template method was developed involving the preparations of middle layer and outer shell on preformed inner core and subsequent removal of the middle layer [34–36]. For example, Zhao et al. have synthesized rattle-type hollow magnetic mesoporous spheres as drug delivery carriers by using Fe_2O_3 particles as template and calcination, where the usage of Fe_2O_3 could avoid aggregation by direct using Fe_3O_4 particles as template [37]. However, although rattle-type Fe_3O_4@SiO_2 hollow mesoporous spheres were obtained, the insertion and subsequent removal of middle layer for the formation of cavity was rather complex. Zhang et al. demonstrated the preparation of hollow mesoporous organosilica with Fe_3O_4 nanocrystals in the hollow cores by using oil-in-water microemulsion strategy [38]. Zhu et al. developed an efficient route to prepare rattle-type Fe_3O_4@SiO_2 hollow mesoporous spheres with large cavities and excellent monodispersity by using carbon spheres as templates [39–41]. However, the magnetization saturation was very low since very few iron precursors were absorbed into carbon spheres. Therefore, how to develop a facile, efficient and controllable way become the major aims for the fabrication of magnetic rattle-type hollow microspheres.

Herein, a template-etching route was developed to synthesize the rattle-type Fe_3O_4@SiO_2 hollow microspheres with controlled parameters including shell thickness and void space, where uniform Fe_2O_3 microspheres were used as template as seen in Scheme 1. (a) By using monodisperse Fe_2O_3 microspheres as template, the mesoporous silica shell was firstly coated easily through sol-gel method with the shell thickness being adjusted by TEOS precursor. (b) After silica shell coating, the void between core and shell could be generated through etching Fe_2O_3 template, where H^+ ions entered into the core to dissolve Fe_2O_3 and Fe^{3+} ions diffused outward. Obviously, the size of the core could be controlled by etching time or concentration of hydrogen ions. (c) After heating in reducing atmospheres, rattle-type Fe_3O_4@SiO_2 hollow microspheres was obtained. This kind of etching strategy for rattle-type hollow microspheres was obviously simpler than traditional insertion and removal of middle layer, and the size of the core and thickness of the shell could be easily controlled during the coating and etching procedure. Using DOX as a model drug, the influences of the parameters including shell thicknesses and void space on the drug uptake and release was investigated systematically, which demonstrated the advantages of template-etching route for rattle-type hollow spheres.

2. Experimental section

2.1. Preparation of Fe_2O_3@SiO_2 microspheres

The monodisperse Fe_2O_3 microspheres with diameter about 160 nm were prepared through a previously hydrothermal reaction, where 0.8 g $FeCl_3 \cdot 6H_2O$ were used [42]. The as-obtained Fe_2O_3 microspheres (0.1 g) were dispersed in 35 mL ethanol solution by sonication for 30 min at 20 °C in a water bath to produce a homogeneous solution, then a solution of TEOS in ethanol and $NH_3 \cdot H_2O$ solution (5 mL) were dropped into the above solution under magnetic stirrer in turn. After 2 hours' reaction, the product was collected by centrifugation and washed thoroughly with water and ethanol, and finally dried in a vacuum oven at 60 °C overnight.



Scheme 1. Schematic illustration of the template-etching route for uniform rattle-type Fe_3O_4@SiO_2 hollow microspheres.

2.2. Preparation of rattle-type Fe_3O_4@SiO_2 hollow microspheres

The above Fe_2O_3@SiO_2 core shell microspheres were etched by HCl solution to create void between core and shell. Typically, 0.1 g Fe_2O_3@SiO_2 microspheres were dispersed in the 20 mL HCl solution with different concentrations under vigorous stirring for 8 h. The particles were separated by centrifugation and washed thoroughly with deionized water and ethanol, and dried in vacuum oven at 60 °C for 12 h. Finally, the product was calcined in 8% H_2/92% N_2 at 350 °C for 2 h, black powder was obtained and could be easily collected by a magnet.

2.3. Drug loading and release in vitro

Typically, rattle-type Fe_3O_4@SiO_2 hollow microspheres (10 mg) were added to 10 mL of 0.2 mg mL^{-1} DOX solution and the mixture was kept in a shaker (SK-O180-Pro) for 24 h. After the DOX-loaded rattle-type Fe_3O_4@SiO_2 hollow microspheres were collected by magnet, they were washed three times with deionized water to remove the unbound drug molecules and dried at room temperature. The absorbance of the supernatant fluid at 480 nm was monitored by UV–Vis spectrophotometer. The DOX-loaded rattle-type Fe_3O_4@SiO_2 hollow microspheres was dispersed in 10 mL phosphate buffered saline (PBS) at 37 °C with gentle shaking. The release medium was withdrawn at predetermined time intervals and an equal amount of fresh PBS was added at the same time to maintain the total solution volume constant. The samples were analyzed by UV–Vis spectroscopy after separation to determine the amount of DOX released.

2.4. In vitro cytotoxicity of Fe_3O_4@SiO_2 against HeLa cells

Firstly, HeLa cells were seeded in 96-well plates (5×10^3 cells/well) in 200 μL of the medium and cultured in 5% CO_2 at 37 °C for 24 h. After that, Fe_3O_4@SiO_2 particles with different concentrations were added to the medium, and the cells were incubated in 5% CO_2 at 37 °C for 24 h or 48 h. Cell viability was determined by MTT assay.

2.5. Characterization

The size and morphology of the as-synthesized materials were measured using a Hitachi S-5500 Field-emission scanning electron microscope (FE-SEM, Tokyo, Japan), JEOL JEM-2010 high-resolution transmission electron microscope (HRTEM, Kyoto, Japan). The composition of products were analyzed by X-ray diffraction (XRD, Philips X'pert diffractometer), in a 2θ range from 20° to 80° and Infrared Fourier Transform Spectrometer (FT-IR, AVATAR360, Nicolet, U.S.). Magnetic measurements were performed with a superconducting quantum interference device (SQUID, Quantum Design MPMS) magnetometer at room temperature (300 K). To determine the specific surface area of the samples, nitrogen sorption isotherms were obtained at 273 K with a Quadrasorb TM SI Four Station Surface Area Analyzer and Pore Size Analyzer (Quantachrome Instruments, Boynton Beach, FL). UV–Vis spectra were recorded using a Beckman DU 800 nucleic acid/protein analyzer (Beck-man Instruments, Inc., Rosemead, CA).

3. Results and discussion

The monodisperse Fe_2O_3 microspheres used as template were synthesized through a typical hydrothermal method in our previous report