Materials Science and Engineering C 33 (2013) 2879–2884

Contents lists available at SciVerse ScienceDirect

Materials Science and Engineering C

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

Folic acid-functionalized magnetic $ZnFe_2O_4$ hollow microsphere core/mesoporous silica shell composite particles: Synthesis and application in drug release

Dandan Yang [a], Kaiwei Wei [a], Qi Liu [a,*], Yong Yang [a], Xue Guo [a], Hongren Rong [a], Mei-Ling Cheng [a], Guoxiu Wang [b]

[a] School of Petrochemical Engineering and Key Laboratory of Fine Petro-chemical Technology, Changzhou University, Changzhou, Jiangsu 213164, PR China
[b] Centre for Clean Energy Technology, School of Chemistry and Forensic Science, University of Technology Sydney, Broadway, Sydney, NSW 2007, Australia

ARTICLE INFO

Article history:
Received 24 August 2012
Received in revised form 21 February 2013
Accepted 3 March 2013
Available online 14 March 2013

Keywords:
Magnetic particles
Mesoporous silica
Drug delivery
Folic acid

ABSTRACT

A drug delivery system was designed by deliberately combining the useful functions into one entity, which was composed of magnetic $ZnFe_2O_4$ hollow microsphere as the core, and mesoporous silica with folic acid molecules as the outer shell. Amine groups coated magnetic $ZnFe_2O_4$ hollow microsphere core/mesoporous silica shell (MZHM-MSS-NH_2) composite particles were first synthesized by a one-pot direct co-condensation method. Subsequently a novel kind of folic acid-functionalized magnetic $ZnFe_2O_4$ hollow microsphere core/mesoporous silica shell (MZHM-MSS-NHFA) composite particles were synthesized by conjugating folic acid as targeted molecule to MZHM-MSS-NH_2. Ibuprofen, a well-known antiphlogistic drug, was used as a model drug to assess the loading and releasing behavior of the composite microspheres. The results show that the MZHM-MSS-NHFA system has the higher capacity of drug storage and good sustained drug-release property.

1. Introduction

Since the MCM-41 silica was discovered by Mobile company scientists in 1992 [1], mesoporous silica (MS) microspheres have offered a wide range of applications in catalysis, separation, sensors, and dye lasers due to their high surface areas, well-defined pore structures, and tunable pore sizes [2,3]. As a result of their large surface areas and pore volumes, MS microspheres could also serve as ideal carriers for large quantities of biogenic agents and subsequently deliver them to target sites. With the development of preparation and application of MS materials, increasing interest has been devoted to the exploration of MS materials which control the drug release rate as drug carrier [4–8]. For satisfying the need of controlling drug release rate, it has been well established that surface functionalized MS materials (MCM-41 and SBA-41) are applied as vehicles in the drug delivery–release systems [9]. Now it is also reported that many magnetic MS nanomaterials containing/not containing functional groups have been synthesized for the targeted drug delivery [10–15]. But the saturation magnetization of some mesoporous composites is weak due to the lower proportion of magnetic materials in them, and some preparation processes are complex [10,16]. Thus, these materials suffer from some inherent limitations in biomedical applications.

To overcome these drawbacks, it is essential to develop new and simple methods for the preparation of magnetic core/mesoporous silica shell composite nanomaterials with surface functionalization and higher magnetization.

There have been reports that folic acid (FA) can specially bind with folate receptor overexpressed in the surface of many types of tumor cells, such as ovarian carcinomas, endometrial cancer, brain tumor and other human tumors [17,18]. Thus, the magnetic nanoparticles with surface modified by FA can be used in targeted drug delivery system and magnetic resonance imaging agent [19–21].

On the other hand, nano/micro-sized hollow spheres have received considerable attentions, due to its potential applications in the fields of catalysis, drug delivery, and optic–electric materials and so on [22,23]. Compared with conventional MS, hollow MS can store more drug molecules [24,25].

Therefore, if one could combine the advantages of magnetic hollow microspheres, MS and FA molecules to synthesize FA-functionalized magnetic hollow metal oxide/MS composite microspheres with high surface area and magnetization, a new targeted drug delivery system should be obtained.

Based on the above considerations and the reports that MnZn ferrite nanoparticles and silica-coated $Mn_{0.5}Zn_{0.5}Fe_2O_4$ nanoparticles have good biocompatibility [26,27], by using magnetic $ZnFe_2O_4$ hollow microspheres as core, tetraethyl orthosilicate (TEOS) as silica source and aminopropyltriethoxysilane (APS) molecules as amine groups (–NH_2) source, we first synthesized the magnetic $ZnFe_2O_4$ hollow microsphere core/MS shell with amine (MZHM-MSS-NH_2) composite particles via one-pot direct co-condensation method, then FA-functionalized magnetic $ZnFe_2O_4$ hollow microsphere core/MS shell composite particles (MZHM-MSS-NHFA) via the bonding of

* Corresponding author. Tel./fax: +86 519 83288656.
E-mail address: liuqi62@163.com (Q. Liu).

0928-4931/$ – see front matter © 2013 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.msec.2013.03.006

MZHM-MSS-NH_2 and FA molecules. Furthermore, ibuprofen, a typical anti-inflammatory drug, was used as a model drug to assess the loading and controlled-releasing behavior of this kind of novel core/shell composite microspheres (MZHM-MSS-NHFA).

2. Experimental section

2.1. Materials

$FeCl_3 \cdot 6H_2O$, sodium acetate (NaAc), $ZnCl_2$, ethylene glycol (EG), absolute ethanol, N, *N*-dimethylformamide (DMF), FA, EG, dimethyl sulfoxide (DMSO), *N*-hydroxysuccinimide (NHS) and polyoxyethylene (20) sorbitan monolaurate (Tween-20), TEOS, 3-APS, hexadecyl trimethyl ammonium bromide (CTAB) were purchased from Shanghai Guoyao Chemical Reagents Company, China. Dicyclohexylcarbodiimide (DCC) was purchased from Shanghai Sheshan Chemical Plant, China. Ibuprofen was purchased from Zhejiang Juhua Pharmaceutical Factory, China. All the reagents were used directly without further purification. Phosphate buffered saline (PBS, pH 7.4) was prepared according to the documented procedure.

2.2. Preparation of magnetic $ZnFe_2O_4$ hollow microspheres (MZHM)

$FeCl_3 \cdot 6H_2O$ (0.676 g, 2.5 mmol) and $ZnCl_2$ (0.17 g, 1.25 mmol) were dissolved in EG (20 mL) to form a clear solution, followed by the addition of NaAc (1.8 g, 21.95 mmol) and Tween-20 (2.0 mL). The mixture was stirred vigorously for 30 min and then sealed in a Teflon-lined stainless-steel autoclave (30 mL capacity). The autoclave was heated and maintained at 200 °C for 6 h, and allowed to cool to room temperature. The black products were washed several times with water and absolute ethanol and dried at 60 °C for 6 h in vacuum [28].

2.3. Synthesis of magnetic $ZnFe_2O_4$ hollow microsphere core/MS shell with amine group (MZHM-MSS-NH_2) composite particles

CTAB (1.17 g) was dissolved in a solution containing water (180 g), EG (30 mL) and ammonia aqueous solution (7.2 mL, 25%). Then 0.2 g magnetic $ZnFe_2O_4$ hollow microspheres was added. After vigorous stirring for about 30 min at 50 °C, TEOS (1.43 mL) and APS (0.263 mL) were rapidly added to the mixture. The final molar composition in the solution was 1 TEOS:0.18 APS:0.50 CTAB:13.2 NH_3:84 EG:1561.1 H_2O. The resulting mixture was stirred for another 2 h at 50 °C and was then kept statically at the same temperature for 20 h. Samples were collected by centrifugation at 10,000 rpm for 10 min, washed, and redispersed several times with deionized water and ethanol. The synthesized MZHM-MSS-NH_2 containing CTAB were dried at 60 °C in a centrifuge tube. Then the synthesized MZHM-MSS-NH_2 containing CTAB (0.1 g) and NH_4NO_3 (0.3 g) were dissolved in ethanol (40 mL), heated at 60 °C three times to remove the surfactant CTAB, and separated by centrifugation to obtain the product MZHM-MSS-NH_2 containing no CTAB [29,30].

2.4. Synthesis of FA-modified $ZnFe_2O_4$ hollow microsphere core/MS shell (MZHM-MSS-NHFA) composite particles

FA (0.3 g) was first activated by using DCC (0.093 g) and NHS (0.077 g) dissolved in DMF/DMSO (27 mL, 3:1, v/v) solution with stirring for 24 h. The precipitated side product of dicyclohexylurea was removed by filtration. MZHM-MSS-NH_2 (0.2 g) before surfactant removal were added to the filtrate and allowed to react with stirring 12 h under anhydrous conditions at room temperature. After the reaction, the mixture was centrifuged at 800 rpm and washed with water and ethanol several times to give MZHM-MSS-NH_2 modified with FA (MZHM-MSS-NHFA). The synthesized MZHM-MSS-NHFA containing CTAB were dried at 60 °C in a centrifuge tube. Then the synthesized MZHM-MSS-NHFA containing CTAB (0.1 g) and NH_4NO_3 (0.3 g) were dissolved in ethanol (40 mL), heated at 60 °C for 6 h three times to remove the surfactant CTAB, and separated by centrifugation to obtain the product MZHM-MSS-NHFA without CTAB.

2.5. Drug loading procedure

The ibuprofen, a typical anti-inflammatory drug, was used as a model drug to assess the drug loading and controlled release behavior of the novel core/shell composite microspheres. Ibuprofen was dissolved in hexane at a concentration of 5 mg/mL. MZHM-MSS-NH_2 (0.0300 g)/MZHM-MSS-NHFA (0.0300 g) were added into this hexane solution (10 mL) at room temperature. The mixture sealed in a vial was shaken for 24 h at 200 rpm to reach the equilibrium state. Then, the ibuprofen-loaded microspheres (named as ibuprofen-loaded MZHM-MSS-NH_2 or ibuprofen-loaded MZHM-MSS-NHFA) and the supernatant solution were collected respectively via magnetic separation of the dispersions. The ibuprofen-loaded microspheres were dried for 6 h at 55 °C in a vacuum, and ibuprofen-loaded MZHM-MSS-NH_2/ibuprofen-loaded MZHM-MSS-NHFA were obtained. The amount of loaded drug in MZHM-MSS-NH_2/MZHM-MSS-NHFA was determined by measuring the absorbance of ibuprofen in the supernatant solution on a UV–vis photospectrometer (absorption at $\lambda_{max} = 264$ nm for ibuprofen). By comparing the absorbance of ibuprofen in the supernatant solution with the calibration curve of ibuprofen absorbance with known concentrations, the loading amount of ibuprofen was calculated using the following formula:

$$\text{Loading content}\ (\%) = \frac{\text{initial weight of ibuprofen} - \text{weight of ibuprofen in supernatant solution}}{\text{weight of the ibuprofen loaded microspheres}} \times 100\%$$

2.6. Drug release procedure

The ibuprofen-loaded microspheres were redispersed in 10 mL PBS (pH 7.4) immediately. The dispersion was then transferred into a conical flask and the conical flask was shaken at 100 rpm at 37 °C. At timed intervals, after the dispersion was magnetically separated, 1 mL supernatant solution was collected from the solution and the amount of released drug was estimated spectrophotometrically. The volume of the release medium was kept constant by adding 1 mL fresh PBS buffer solution after each sampling.

2.7. Characterization

The X-ray powder diffraction (XRD) pattern of the as-prepared products was collected on a D/max 2500 PC diffractometer with Cu Kα radiation ($\lambda = 1.54056$ Å). Transmission electron microscopy (TEM) images and selected area electron diffraction patterns (SAED) were obtained by employing JEOL JEM-200CX transmission electron microscope, using an accelerating voltage of 200 KV. Scanning electron microscopy (SEM) images were taken on a Hitachi-S-4800 scanning electron microscope. A Lake Shore 7307-9309 vibrating sample magnetometer performed room-temperature magnetic characterization of the as-prepared products. Nitrogen sorption isotherms were obtained on a Micromeritics ASAP2010C pore analyzer at 77 K under continuous adsorption conditions. Brunauer, Emmett, and Teller (BET) and Barrett, Joyner, and Halenda (BJH) analyses were used to calculate the surface area, pore size, and pore volume. Fourier transform infrared (FTIR) spectra were recorded on a Nicolet 460 spectrophotometer in the form of KBr pellets. Zeta potentials were measured by a Zeta potential analyzer (ZEN 3600).