Microporous and Mesoporous Materials 123 (2009) 107–112

Contents lists available at ScienceDirect

Microporous and Mesoporous Materials

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

Magnetic SBA-15/poly(*N*-isopropylacrylamide) composite: Preparation, characterization and temperature-responsive drug release property

Yufang Zhu [a,*], Stefan Kaskel [b], Toshiyuki Ikoma [a], Nobutaka Hanagata [a]

[a] International Center for Young Scientists (ICYS), National Institute for Materials Science (NIMS), 1-2-1 Sengen, Tsukuba, Ibaraki 305-0047, Japan
[b] Institut für Anorganische Chemie, Technische Universität Dresden, Mommsenstrasse 6, Dresden 01069, Germany

ARTICLE INFO

Article history:
Received 16 December 2008
Received in revised form 11 March 2009
Accepted 22 March 2009
Available online 28 March 2009

Keywords:
Mesoporous materials
Magnetic
Controlled release
Temperature-responsive

ABSTRACT

A novel magnetic targeting and temperature-responsive drug delivery system based on poly(*N*-isopropylacrylamide) (PNIPAM) modified mesoporous SBA-15 containing magnetic γ-Fe_2O_3 nanoparticles has been successfully prepared. The structure and morphology of the magnetic SBA-15/PNIPAM composite was characterized by X-ray diffraction, scanning electron microscopy (SEM), transmission electron microscopy (TEM), Differential scanning calorimetry (DSC) and N_2 adsorption–desorption technique. This composite shows superparamagnetic behavior with the magnetization strength of 2.1 A m^2 kg^{-1} at 377 A m^{-1}. Using gentamicin as a model drug, in vitro testing of gentamicin release exhibits a temperature-responsive controlled release property. Therefore, this magnetic SBA-15/PNIPAM composite could be applied in targeting and stimuli-responsive drug delivery.

1. Introduction

Progresses in mesoporous silica materials over the last decade offer exciting opportunities in the development of promising materials for biomedical applications, such as drug (or gene) delivery, diagnosis and hyperthermia [1–5]. These materials have high surface areas, tunable pore sizes and volumes, and well-defined surface properties for modification, which provides a robust framework for coating or the incorporation of guest molecules or nanoparticles to give multifunctional capabilities [6].

Magnetic mesoporous silica materials have attracted much attention as promising carriers for drug delivery [5–19], because magnetic mesoporous silica materials provide the ability to selectively target the desired organs or tissues inside the body in the presence of an external magnetic field. To date, the research relating to magnetic mesoporous silica materials for drug delivery has been reported by many groups [5–19]. For example, Shi's group reported uniform magnetic nanocomposite spheres with a magnetic core/mesoporous silica shell structure and uniform rattle-type hollow magnetic mesoporous spheres as drug delivery carriers. These systems have sustained-release property and show a possibility for potential application in targeted drug delivery [7,8]. Vallet-Regí's group demonstrated the synthesis of spherical silica-based mesoporous materials encapsulating magnetic γ-Fe_2O_3 nanoparticles by using an aerosol-assisted route, and evaluated their potential to be magnetically guided for drug targeting [9]. Hyeon's group developed a magnetic fluorescent delivery vehicle using uniform mesoporous silica spheres embedded with monodisperse magnetic and semiconductor nanocrystals [10]. Shul's group prepared mesoporous Fe/SiO_2 as a carrier for magnetic drug targeting by using the sol-gel route and a chemical reduction method, and the release of ibuprofen from the mesoporous Fe/SiO_2 was described as a diffusion-controlled process [18]. These examples indicated the potential application in targeted drug delivery. However, they only can realize the sustained-release pattern, which may be result in the damage of normal organs or tissues due to the drug toxicity before targeting the desired positions.

Compared to the sustained-release system, the stimuli-responsive controlled release system can realize the controlled release pattern, which can improve the therapeutic efficacy. Recently, much effort has been devoted to the development of stimuli-responsive delivery systems based on mesoporous silica materials [20–28]. Lai et al. and Giri et al. claimed the stimuli-responsive controlled release of water-soluble drugs from MCM-41 using chemically removable CdS or Fe_3O_4 nanoparticle as caps for mesoporous channels and disulfide bond-reducing molecules as release triggers [20,21]. Mal et al. have successfully realized, for the first time, photo-controlled reversible release of drug molecules from coumarin-modified MCM-41 [22]. Zhu et al. developed a novel pH-responsive controlled drug delivery system based on hollow mesoporous silica spheres and polyelectrolyte multilayer (PAH/PSS) coatings [23,24]. pH-Controllable drug release systems based on poly(acrylic acid) (PAA) hydrogel encapsulated SBA-15 and carboxylic-acid-modified SBA-15 also have been reported by Song et al. and Yang et al. [25,26].

* Corresponding author. Fax: +81 29 8592200.
E-mail address: zjf2412@163.com (Y. Zhu).

1387-1811/$ - see front matter © 2009 Elsevier Inc. All rights reserved.
doi:10.1016/j.micromeso.2009.03.031

It is well known that poly(*N*-isopropylacrylamide) (PNIPAM) represents one of the most widely investigated temperature-responsive polymers, and can undergo a hydrophilic–hydrophobic transition at a "lower critical solution temperature" (LCST) of about 32 °C [29,30]. Recently, PNIPAM has been widely used as a material for controlled drug release. However, reports on mesoporous silica/PNIPAM composites are few [31–35]. Fu et al., Zhou et al. and You et al. reported the temperature-responsive controlled release systems based on PNIPAM-modified MCM-41 and mesostructure cellular foam materials (MCFs), respectively [31–33]. Chung et al. have synthesized a series of PNIPAM-coated MCM-41 by a surface-initiated living radical polymerization with a reversible addition-fragmentation chain transfer reaction, and these core-shell materials showed the temperature-dependent solution partition behavior in a biphasic toluene/water solution [34]. However, these mono-stimuli-responsive mesoporous silica systems could not be applied for the site-specific drug delivery due to the lack of agents for targeting. Although Zhang's group demonstrated a responsive carrier system based on SBA-15 with Fe_3O_4 nanoparticles and PNIPAM, [35] this system shows ferromagnetic property with a very low saturation magnetization (M_s) of 0.40 emu/g. Actually this kind of ferromagnetic system is not suitable for bio-related applications.

In this paper, we have successfully prepared a mesoporous SBA-15 carrier system combined with maghemite (γ-Fe_2O_3) nanoparticles and PNIPAM polymers. The superparamagnetic behavior of γ-Fe_2O_3 nanoparticles and temperature-responsive PNIPAM together with the high surface area and large mesoporous channels allow this composite to realize the potential of magnetic targeting and temperature-responsive controlled drug release.

2. Experimental

2.1. Synthesis of magnetic mesoporous SBA-15

Mesoporous SBA-15 was prepared following a previously reported method [36]. Four grams of Pluronic P123 ($EO_{20}PO_{70}EO_{20}$) was added to a mixture of 30 g of H_2O and 120 g of 2 M HCl aqueous solution in a Teflon-lined container, which was stirred at 35 °C usually overnight. Then, 8.50 g of TEOS was added to this solution under vigorous stirring. After 5 min of stirring, the mixture was kept under static conditions at 35 °C for 20 h, followed by 24 h at 100 °C. The solid products were collected by filtration, washed with water, dried, and calcined at 550 °C in flowing air. The synthesis process of magnetic mesoporous SBA-15 was similar as described previously [37]. 1.0 g of acetylferrocene was first dissolved in 1 ml of furfuryl alcohol. This solution was then introduced into 1.0 g of SBA-15 to achieve incipient wetness, and subsequently polymerized in air at 150 °C. The sample was finally calcined in air at 800 °C for 3 h to form magnetic mesoporous SBA-15. The sample was named as γ-Fe_2O_3/SBA-15.

2.2. Modification of γ-Fe_2O_3/SBA-15 with methacryloxypropyltrimethoxysilane (MPS)

0.5 g of γ-Fe_2O_3/SBA-15 was added to 100 ml ethanol solution containing 1.0 ml of methacryloxypropyltrimethoxysilane. After being stirred at 40 °C for 24 h, the mixture was extensively washed with ethanol and air-dried. The sample was named as γ-Fe_2O_3/SBA–MPS.

2.3. Preparation of magnetic SBA-15/PNIPAM composite

PNIPAM synthesis was carried out by a conventional emulsion polymerization, as described elsewhere [38,39]. In a typical synthesis, a solution of 1.132 g of *N*-isopropylacrylamide (NIPAM) and 0.078 g of *N,N*-methylenebisacrylamide (BIS) dissolved in 50 ml of H_2O and 50 ml of ethanol was prepared in a three-neck flask equipped with a reflux condenser and a magnetic stirrer. The solution was heated to 40 °C to obtain an emulsion. 0.1 g of γ-Fe_2O_3/SBA–MPS was then added. The mixture was heated to 70 °C and kept under a nitrogen atmosphere to remove oxygen. After 1 h of intense stirring at 70 °C, 1 ml of potassium peroxodisulfate (KPS, 1 mg/ml) solution was then rapidly added. The colorless emulsion became turbid 10 min after the KPS addition and the polymerization proceeded for 4 h at 70 °C. The turbid solution was then cooled to room temperature and stirred overnight. Finally, the prepared products were cleaned by centrifugation and dispersed in H_2O several times. The sample was named as γ-Fe_2O_3/SBA–PNIPAM.

2.4. Loading and in vitro release of gentamicin

Here, gentamicin (Biochemika, Sigma), a wide spectrum antibiotic, was used as the model drug. 0.5 g of γ-Fe_2O_3/SBA–PNIPAM particles was added to 10 ml of gentamicin aqueous solution (10 mg/ml) and stirred at 45 °C for 24 h. Then, the mixture was rapidly cooled below 20 °C, washed quickly and thoroughly with H_2O. Finally, the products were dried under vacuum at 40 °C. The sample was named as γ-Fe_2O_3/SBA–PNIPAM–Gen. The estimation of gentamicin loaded in γ-Fe_2O_3/SBA–PNIPAM was carried out through an indirect method, by determining the difference in gentamicin concentration before and after loading using UV/Vis spectrometer.

In vitro release of gentamicin from γ-Fe_2O_3/SBA–PNIPAM–Gen (0.2 g) was carried out in 50 ml of phosphate buffer (pH 7.4) under stirring at 100 rpm in a flask. The temperature of the suspension was kept at 10 ± 0.5 °C or 40 ± 0.5 °C. The concentration was determined by UV/Vis spectroscopy. The analysis was determined by measuring the absorbance values at the absorbance of gentamicin at the wavelength of 256 nm [40]. Before determination, a calibration curve was recorded. The release medium was withdrawn at the predetermined time intervals, and replaced with fresh soaking medium each time. The in vitro release at various temperatures was controlled as follows: 0.2 g of γ-Fe_2O_3/SBA–PNIPAM–Gen was added in 50 ml of phosphate buffer (pH 7.4) at different temperature (10, 20, 30, 40, 50, and 60 °C) under stirring at 100 rpm in a flask, and then kept for 6 h before the measurement.

2.5. Characterization

The small angle X-ray diffraction (SAXRD) patterns were measured on a Bruker AXS Nanostar using Cu$K\alpha_1$ radiation (1.5405 Å)

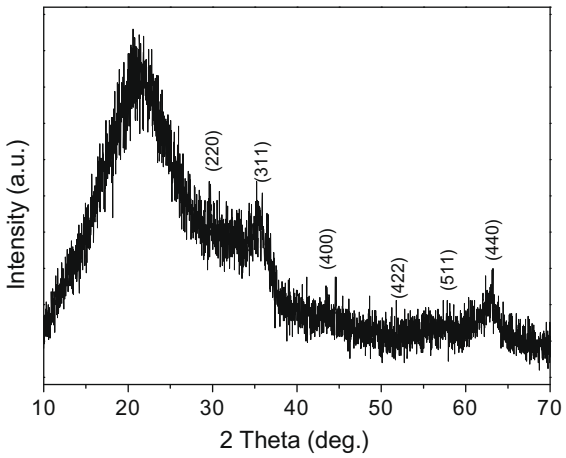

Fig. 1. WAXRD pattern of the sample of γ-Fe_2O_3/SBA-15 (the hkl indices indicate the γ-Fe_2O_3 phase in this sample).