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Short communication

Effect of amine functionalization of SBA-15 on controlled baicalin drug release

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Abstract

In this paper, we present the release of baicalin from hexagonal periodic mesoporous silica SBA-15 and amino-functionalized mesoporous SBA-15 (A-SBA-15), which serve as drug delivery systems (SBA-15/baicalin and A-SBA-15/baicalin). The modified and drug loaded mesoporous materials were characterized by XRD, SEM, TEM, N_2 physisorption, IR, TG and HPLC. The results demonstrated that slightly higher amount of baicalin was loaded in APS-SBA-15, and the dissolution rate of baicalin from the A-SBA-15/baicalin was much faster than from the SBA-15/baicalin. A-SBA-15/baicalin as baicalin delivery system was better than SBA-15/baicalin because the faster dissolution rate compared with SBA-15/baicalin was more conducive to drug absorption.

Keywords: A. Sol–gel processes; D. SiO_2; E. Functional applications; E. Biomedical applications

1. Introduction

SBA-15 mesoporous silica has been investigated as the potential drug carrier material due to large surface area, large pore size, thick walls and easy surface modification [1,2]. Some insoluble drugs, such as ibuprofen, nimodipine, itraconazole, and so on, have been applied to control the delivery from SBA-15 into simulated biological fluids [3–5]. Then, the introduction of appropriate organic compounds into SBA-15 has presented excellent results regarding drug release control. The choice of appropriate functionalizing agent can generate the inner channel surface acidic [6], basic [7] as well as hydrophobic [8]. Furthermore, the functionalized surface groups can interact via ionic interactions with desired drug. For example, mesoporous materials modified with amine groups were applied as carriers for adsorption of drugs with acidic character [9]. In the contrary, modification of the surface of SBA-15 or MSU with acids (e.g. with carboxylic groups) increases the adsorptive properties of drugs with basic properties [10,11].

Baicalin (baicalein 7-O-h-glucopyranuronoside, BG) is a bioactive flavonoid isolated from Chinese herbal medicine *Scutellaria baicalensis Georgi*. Pharmacological studies reveal that baicalin has many biological activities, such as antibacterial, anti-viral, anti-inflammatory, anti-pyretic [12,13]. However, poor solubility of the currently marketed oral preparations including tablets and capsules has resulted in poor dissolution and bioavailability. It can be noted in the baicalin structure shown in Fig. 1 that the 2-OH, 3-OH or 4-OH of glucuronide in baicalin molecules may serve as proton donors to form hydrogen bonds with carriers [14]. Therefore, mesoporous SBA-15 material may be a good candidate for baicalin adsorption because of its relatively large pore size, abundant hydroxyl groups and easily modified surface with silanes. In this work, a simple and effective approach has been developed for controlled drug delivery carrier through local surface modification in mesoporous silica SBA-15 with aminopropyl groups. The released amount of baicalin represented 15.2% from

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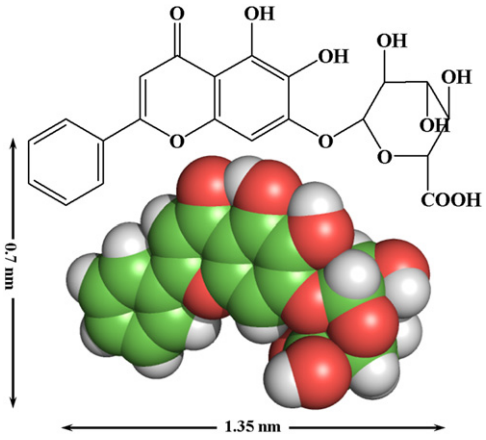

Fig. 1. Molecular structure of baicalin.

the unmodified SBA-15 in 72 h, while from the sample A-SBA-15/baicalin the released amount represented about 98.4% in 72 h. A-SBA-15/baicalin have shown more improvement in dissolution capability because it increases the solubility of baicalin by drug-matrix interactions.

2. Experimental

2.1. Preparation procedure

SBA-15 was synthesized according to the methods described in the literatures [1,2]. Amino-functionalized SBA-15 was prepared using a procedure similar to that described by Mckittrick and Jones [15]. 1.0 g of calcined SBA-15 was added to 100 mL of dry toluene in a 250 mL flask, and the flask was flushed with nitrogen for 20 min. Then 0.54 mL of 3-aminopropyltriethoxysilane (APTES) was added and stirred. After 24 h, the solid was filtrated, washed with toluene and ethanol, and dried in air. The received solids were denoted as A-SBA-15.

2.2. Loading of baicalin

0.30 g of parent SBA-15 and modified A-SBA-15 were soaked by the solutions of baicalin in methanol (concentration 30 mg mL^{-1}). The solid products were filtered off, gently washed with methanol and dried at room temperature. The respective samples were denoted as SBA-15/baicalin and A-SBA-15/baicalin. Filtrates (1.0 mL) were sucked and properly diluted to determine the loading amount by HPLC spectrophotometer.

2.3. Baicalin release

The release of the drug was received by shaking 0.2 g samples of SBA-15/baicalin and A-SBA-15/baicalin in 250 mL of simulated body fluid (SBF). SBF with ion concentrations similar to those in human blood plasma as prepared according to the method described by Kokubo and Takadama [16]. The released amounts of the drug from samples were monitored in selected time intervals: 1 h, 3 h, 5 h, 7 h, 24 h, 30 h, 48 h and 72 h by HPLC method.

2.4. HPLC system

The HPLC system consisted of a 6005 pump, 7725 dosing valve and a 2487 UV–vis double-wavelength detector (Waters Co., USA). A Hypersil-C18 column (4.6 mm × 150 mm) (Dalian elite, China) was used. The mobile phase was methanol-water-formic acid (49:51:0.2, v/v/v), filtered through a 0.45 μm filter and degassed prior to use. The flow-rate was 0.8 mL min^{-1}. Detection was performed at a wavelength of 275 nm at room temperature. The injection volume was 10 μL and the column temperature was 30 °C. Output data from the detector were integrated using millenium32 chromatographic workstation (Waters Co., USA).

3. Characterization

Power X-ray diffraction (PXRD) measurements were obtained through a Siemens D5005 diffractometer. A Hitachi X-650B scanning electron microscope was used for SEM measurements. Transmission electron microscope (TEM) for materials was carried out by a JEM1200EX. N_2 physisorption isotherms were recorded at 77 K with a Micromeritics ASAP 2010. Infrared spectra (IR) were obtained using Avatar FT-IR spectrometer. Powder samples were prepared in KBr pellets for IR analysis. Thermogravimetric (TG) was carried out at heating rate of 10 °C min^{-1} in the air atmosphere under dynamic conditions, using a STA Netzch 409 PC instrument.

4. Results and discussion

The powder XRD patterns of the samples are shown in Fig. 2. Fig. 2a pattern displays an intense peak at $2\theta = 0.82°$ and two weak peaks in a 2θ range of 1.3°–1.8°, which matches well with the pattern of SBA-15 silica reported in the literature [1,2]. The prominent peak should be indexed as (100) diffraction peak, and other two as (110) and (200) diffraction peaks, respectively. After the introduction of 3-aminopropyl groups and baicalin, the powder XRD patterns of parent SBA-15 silica are still kept very well (Fig. 2b), indicating that the introduction of these organic functionalities does not destroy the mesoporous structure of parent SBA-15. However, due to the contrast matching between the organic functional groups and inorganic framework, a decrease in the intensity of diffraction peaks is observed [2]. The scanning electron microscopy image (SEM) of A-SBA-15/baicalin shows rope-like domains aggregated to wheatlike macrostructure (Fig. 3a). From transmission electron microscope (Fig. 3b), sample was classified as 2D hexagonal, p6mm structures with relatively uniform pore widths to adequately accommodate baicalin.

From N_2 adsorption-desorption analysis (Fig. 4), typical IV isotherms with H1 type of hysteresis loops for SBA-15, A-SBA-15, SBA-15/baicalin and A-SBA-15/baicalin are observed [3]. The pore size distribution suggests that the four samples have uniform mesoporous channels. Some changes, however, can also be observed. With the introduction of organic functional groups, the BET surface areas gradually decrease from 923.12 $m^2 g^{-1}$ of SBA-15 to 619.17 $m^2 g^{-1}$ of A-SBA-15, and further to 462.53 $m^2 g^{-1}$ of SBA-15/baicalin and 271.48 $m^2 g^{-1}$ of A-SBA-15/baicalin (Table 1). Meanwhile, the pore diameters and pore volumes are also reduced correspondingly.

Infrared spectra of all samples were recorded and are shown in Fig. 5. For the pure SBA-15 and A-SBA-15, the typical Si-O-Si bands around 1220, 1086, 802, 460 cm^{-1} associated with the formation of a condensed silica network are present, and weak peaks associated with noncondensed Si-OH groups in the range 940–960 cm^{-1} are also present [17]. The spectrum of SBA-15/baicalin and A-SBA-15/baicalin showed, some IR signals such as 1730, 1668, 1609, 1572, 1489, 1362 and 690 cm^{-1} respectively, similar to those of baicalin [14], can be clearly observed. These bands give a direct demonstration of the loading of baicalin molecules into SBA-15 framework and baicalin in the amorphous or the molecular state dispersed to a high degree in pure SBA-15 and A-SBA-15.

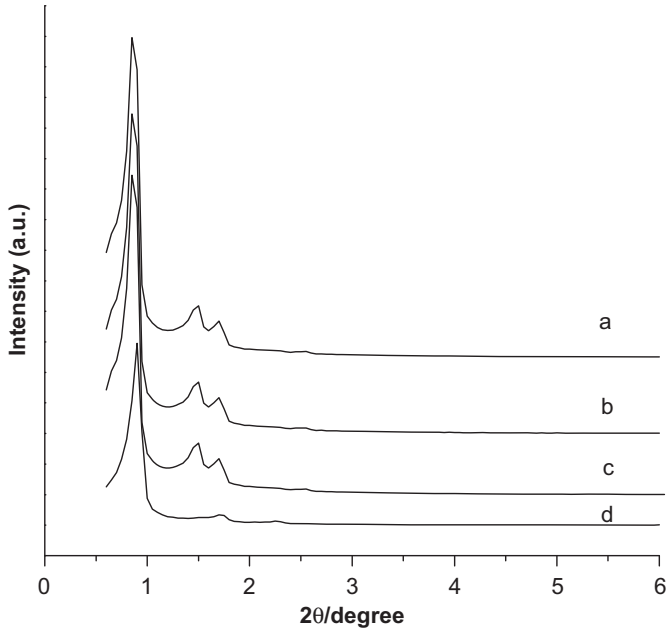

Fig. 2. XRD patterns of (a) pure SBA-15, (b) A-SBA-15, (c) SBA-15/baicalin, (d) A-SBA-15/baicalin.

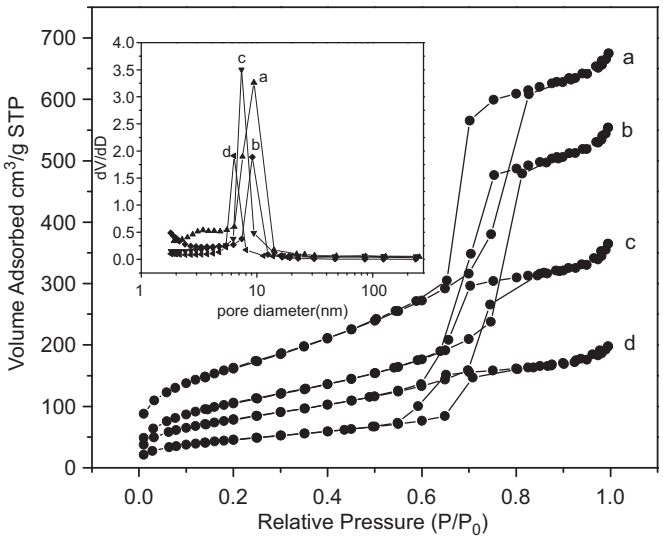

Fig.4. N_2 adsorption-desorption isotherms (a) pure SBA-15, (b) A-SBA-15, (c) SBA-15/baicalin, (d) A-SBA-15/baicalin.

Table 1
Physical properties of pure siliceous SBA-15 and related samples.

Sample	Cell parameters (nm)	BET surface area ($m^2 g^{-1}$)	Pore volume ($cm^3 g^{-1}$)	Pore diameter (nm)
SBA-15	12.3	923.12	1.01	9.37
A-SBA-15	12.1	619.17	0.82	9.07
SBA-15/baicalin	11.8	462.53	0.52	7.35
A-SBA-15/baicalin	11.6	271.48	0.28	6.36

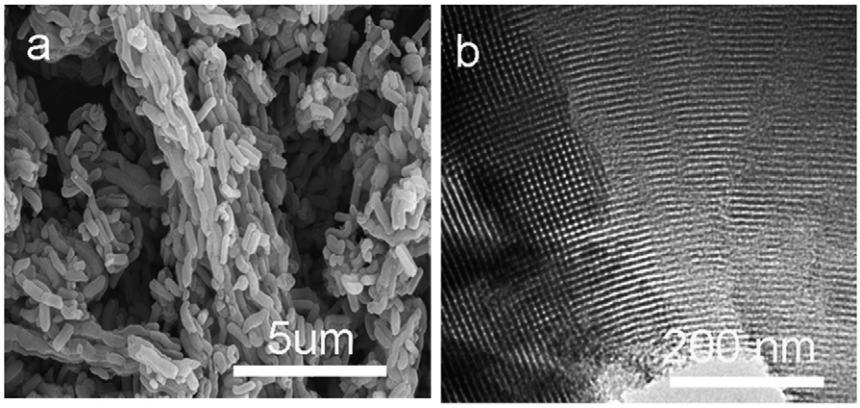

Fig. 3. A representative SEM image of (a) pure SBA-15, (b) A-SBA-15/baicalin.

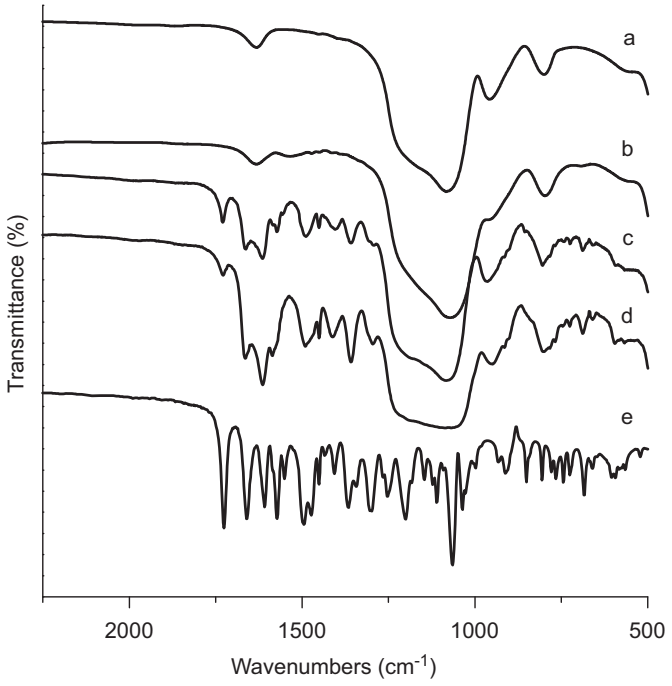

Fig. 5. FT-IR spectra (a) pure SBA-15, (b) A-SBA-15, (c) SBA-15/baicalin, (d) A-SBA-15/baicalin, (e) baicalin.

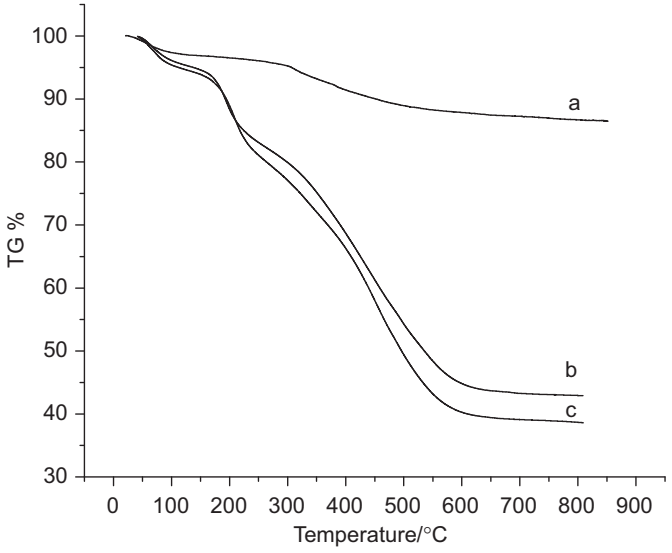

Fig. 6. Thermoanalytical curves (TG) of the samples (a) A-SBA-15, (b) SBA-15/baicalin, (c) A-SBA-15/baicalin.

To calculate the amount of baicalin loaded into the parent and amine-modified mesoporous materials, thermogravimetric analyses were made. The results are displayed in Fig. 6. The different thermal behavior was observed for amine modified sample A-SBA-15 (Fig. 5a). The mass loss step, observed above 200 °C, corresponds to the thermal decomposition of aminopropyl chains anchored on the surface of SBA-15. The total mass loss recorded for the sample A-SBA-15 in the range 200–850 °C represented 10.7%. The sample loaded with baicalin SBA-15/baicalin (Fig. 6b) showed two mass loss steps after dehydratation. The mass loss was observed between the temperatures 300–700 °C and corresponds to the baicalin decomposition and release. The total mass loss observed in the temperature range 300–700°C was 36.3%, which corresponds to the loading of 363 mg of the drug in 1 g of the sample SBA-15/baicalin. The mass loss was 39.1% between the temperatures 300–700 °C and corresponds to the baicalin decomposition and release in A-SBA-15/baicalin. As can be seen from TG results, the functionalization increases the interactivity between carboxyl groups of drug and amines on the silica surface, which may increase the amount of the drug loaded into porous matrix [18,19]. Similar results were also observed by Rosenholmand Lindén, who reported small differences between salicylic acid loaded in modified and unmodified mesoporous silica materials [20]. After loading drugs, filtrates (1.0 mL) were sucked and properly diluted to determine the loading amount by HPLC spectrophotometer. The results of TG were in accordance with the HPLC results of filtrates.

Fig. 7 shows the curves of the percentage of drug release as a function of time, it can be seen that the total amount of the drug released after 72 h was 15.2% in the case of sample SBA-15/baicalin and 98.4% in the case of the sample A-SBA-15/baicalin. This confirms the trends that the modification with amino groups increases the delivery rate of the drug from mesoporous material. Generally, in the case of the porosity matrix, release of the impregnated drug occurs through penetration of solvent into the pores of the matrix, and then the drug slowly dissolves into the permeating fluid phase and diffuses from the system along the solvent-filled channels. The delayed drug delivery from the SBA-15/baicalin and A-SBA-15/baicalin could be explained a strong barrier effect, by hydrogen bonds can be formed between the drug and carrier. However, for the modified samples (A-SBA-15/baicalin), besides the influence by the baicalin diffusion process through the mesoporous channels, the observed increase of the release

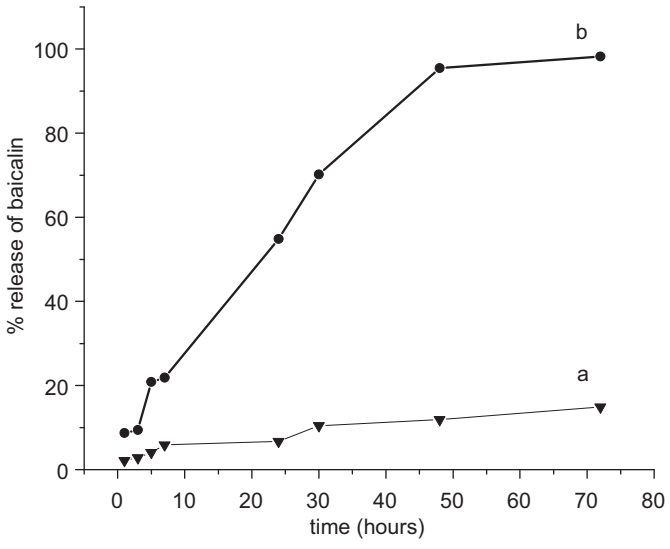

Fig. 7. Cumulative release rates of (a) SBA-15/baicalin, (b) A-SBA-15/baicalin.

rate may be mainly due to the property of aminopropyl groups on the mesoporous silica surface. At this stage, the basic aminopropyl groups would accelerate the solubility of acidic baicalin in the mesoporous channels. It is crucial to maximize the dissolution of drugs in the body within a limited time to improve absorption. The Noyes–Whitney equation: $dc/dt = KS(Cs - C)$, where dc/dt is the dissolution rate, K is the dissolution rate constant, S is the dissolving boundary area, Cs is the drug solubility, and C is the concentration of drug in solution, indicates that the dissolution rate of drugs from solid dosage forms is proportional to K, S and Cs [14]. Higher drug solubility is related to a higher dissolution rate that lay the ground work for the fact that the dissolution of the A-SBA-15/baicalin was higher than that of the SBA-15/baicalin. The remarkably improved dissolution rate of baicalin created an opportunity for absorption within a limited time.

5. Conclusions

In the present work, we studied the amine-modified and unmodified hexagonal mesoporous silica SBA-15 loaded with antibacterial drug baicalin. The obtained results show that the drug could be successfully loaded into SBA-15 mesoporous matrix as well as the amine-modified silica A-SBA-15, and subsequently released from the samples SBA-15/baicalin and A-SBA-15/baicalin into the physiological solution. We also observed that A-SBA-15/baicalin was more suitable for sustained release of baicalin, because it had greater drug loading and faster drug dissolution rate.

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