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Controlled drug release from bifunctionalized mesoporous silica

Wujun Xu [a,c], Qiang Gao [a,c], Yao Xu [a,*], Dong Wu [a], Yuhan Sun [a], Wanling Shen [b,c], Feng Deng [b]

[a] State Key Laboratory of Coal Conversion, Institute of Coal Chemistry, Chinese Academy of Sciences, Taiyuan 030001, PR China
[b] State Key Laboratory of Magnetic Resonance and Atomic and Molecular Physics, Wuhan Institute of Physics and Mathematics, Chinese Academy of Sciences, Wuhan 430071, PR China
[c] Graduate University of the Chinese Academy of Sciences, Beijing 100049, PR China

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ABSTRACT

Serial of trimethylsilyl-carboxyl bifunctionalized SBA-15 (TMS/COOH/SBA-15) have been studied as carriers for controlled release of drug famotidine (Famo). To load Famo with large capacity, SBA-15 with high content of carboxyl groups was successfully synthesized by one-pot synthesis under the assistance of KCl. The mesostructure of carboxyl functionalized SBA-15 (COOH/SBA-15) could still be kept even though the content of carboxyl groups was up to 57.2%. Increasing carboxyl content could effectively enhance the loading capacity of Famo. Compared with pure SBA-15, into which Famo could be hardly adsorbed, the largest drug loading capacity of COOH/SBA-15 could achieve 396.9 mg/g. The release of Famo from mesoporous silica was studied in simulated intestine fluid (SIF, pH = 7.4). For COOH/SBA-15, the release rate of Famo decreased with narrowing pore size. After grafting TMS groups on the surface of COOH/SBA-15 with hexamethyldisilazane, the release of Famo was greatly delayed with the increasing content of TMS groups.

1. Introduction

In 2001, a new property of drug release based on mesoporous silica was disclosed by Vallet-Regi [1]. Subsequently, many groups have shown their interest in this new application of mesoporous silica [2–7]. It was found that drug loading and release rate could be well-adjusted by organic functionalization of mesoporous materials. Song et al. [2] found that aminopropyl-modified SBA-15 showed larger drug loading capacity than that of pure SBA-15 materials. In our group, it was observed that the release rate of ibuprofen could be obviously delayed by grafting trimethylsilyl (TMS) groups onto MCM-41 material [6]. Up to now, these achieved developments were mainly focused on single-organic-functionalized drug carriers. As we know, any kind of organic group possesses its distinct characteristic, and simultaneously has certain limitations. For example, hydrophobic alkyl groups could effectively reduce the release rate of ibuprofen, but these groups could not enhance its loading capacity of ibuprofen; though NH_2–Pr groups could enhance the loading capacity of ibuprofen, its reduction to the release rate of ibuprofen was worse than hydrophobic alkyl groups. Therefore, sometimes, single-functionalized mesoporous carriers were not able to meet the multiplicate demands of complicated human body.

Multi-functionalization should be a good method to make mesoporous silica possesses demanded multiplicate surface properties. New surface properties of mesopores could complement or promote with each other. Because of the confinement of mesopore structure, it is difficult to simultaneously functionalize three or more kinds of organic groups on the surface of mesoporous silica. Luckily, it was an easy thing to obtain bifunctionalized mesoporous silica materials, which have shown better behaviors than single-organic-functionalized materials in the fields of catalysis [8] and separation [9]. But, there were few reports about drug release system based on bifunctionalized mesoporous silica. Recently, Pasqua et al. [10] synthesized named "bifunctionalized" mesoporous silica for tumor-specific drug delivery by grafting aminopropyl group and folic acid on mesoporous silica. In this drug delivery system, the aminopropyl groups only acted as a bridge between mesoporous silica and folic acid, and it did not play a direct role in controlling drug loading capacity or drug release rate. So, though the mesoporous silica functionalized with two different groups, the obtained material did not possess true bifunctional properties. To some extent, the method should be a complex single-functionalization.

Famotidine (Famo) is a histamine H2-receptor antagonist for treatment ulcers in the stomach and intestine, whose molecule structure is presented in Fig. S1 (see supporting information). In 1985, Takabatake et al. [11] studied the pharmacokinetics of Famo and found its half-life of elimination was only 2.6 h in normal subjects. And later, Yeh et al. [12] found the bioavailability of oral

* Corresponding author. Fax: +86 351 4041153.
E-mail address: xuyao@sxicc.ac.cn (Y. Xu).

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Famo (40 mg/times) just reached 43.0% and the blood concentration of Famo showed a severe peak-to-trough fluctuation. In order to void the disadvantages mentioned above, controlled release of Famo was developed for clinical application [13–15]. For example, Değim et al. [13] fabricated a biodegradable Famo microspheres of poly(lactide-*co*-glycolide) polymer by using multiple emulsion technique. It was found that the penetration of the Famo molecule could be controlled in this system, which might be useful for long-term treatments with Famo. Recently, the controlled release of Famo on inorganic porous materials was extended to mesoporous silica [16]. It was found that Famo could not be adsorbed into pure MSU, and the amount of Famo adsorbed into mesopores related with the surface COOH groups. However, there were still some unsolved problems in the system. In Ref. [16], the loading capacity of Famo was very low (only 160.4 mg/g), and it was unclear how the carboxyl groups affected the release rate of Famo. As we know, both of these questions were crucial for a drug release system. In order to further answer these questions, a novel TMS-carboxyl bifunctionalized drug release system was synthesized, in which these two kinds of organic groups complement with each other. To load Famo with large capacity, carboxyl groups were firstly functionalized on mesoporous SBA-15. Then TMS groups were grafted on the surface of mesoporous silica to control the release of Famo.

2. Experimental section

2.1. Preparation of carboxyl functionalized SBA-15 (COOH/SBA-15)

In a typical synthesis, 2-cyanopropyltriethoxysilane (CPTES) was introduced to HCl solution containing triblock copolymer Pluronic P123 ($EO_{20}PO_{70}EO_{20}$) and KCl. After hydrolyzed for 0.5 h under stirring at 40 °C, tetraethoxysilane (TEOS) was added into the mixture slowly. The molar composition of the mixture was (1.0−*x*) TEOS:*x* CPTES:0.015 P123:6.1 HCl:1.2 KCl:170 H_2O, where $x = 0$–0.50. Next, the resultant mixture was stirred at 40 °C for 20 h, followed by aging at 90 °C for 24 h under static condition. The solid product was recovered by filtration and dried at 60 °C. At last, according to the method of Yang et al. [17], the dried product was treated with 48.0% H_2SO_4 solution at 95 °C to eliminate the template and produce carboxyl functionalized SBA-15. Table 1 lists the detailed reactant compositions of the above samples.

2.2. TMS functionalization to COOH/SBA-15 after Famo loading

A total of 0.5 g dried COOH/SBA-15 and 0.75 g Famo were added to 500.0 mL mixed solvent of methanol and water (mass ratio of methanol:water = 0.8:1). After soaked for 8 h under stirring, the drug-loaded mesoporous powder was recovered by filtration. To measure the loading amount of Famo, 2.0 mL of filtrates was diluted to 50 mL and then analyzed using UV/Vis spectroscopy at the characteristic adsorption wavelength of Famo at 266.0 nm. Subsequently, the Famo-loaded samples were dried under vacuum at 50 °C for 24 h to remove residual solvent from obtained materials. The amount of Famo loaded in mesoporous silica was calculated by using

$$\text{wt\%} = \frac{m_1 - \frac{50}{v}CV}{m_2 + \left(m_1 - \frac{50}{v}CV\right)} 100\% \quad (1)$$

where m_1 and m_2 correspond to the initial mass of Famo and mesoporous silica added into the mixed solvent of water and methanol, respectively. C is the concentration of filtrates diluted in 50 mL volumetric flask, v is sampled volume from filtrates, and V is the volume of mixed solvent for drug loading.

Hexamethyldisilazane (HMDS) was used to silanize the drug-loaded COOH/SBA-15 in vapor phase. A 0.50 g drug-loaded C-15 sample was homogeneously spread on a piece of filter paper, which was put on a bracket in a beaker containing 1.0 mL HMDS. The beaker was closed and put in an oven at 50 °C. After determined treating time, the samples were taken out and dried under vacuum at 50 °C. These samples were designated as C-15M-A1 and C-15M-A2 corresponding to the different treating time of 0.5 and 3.0 h, respectively.

2.3. TMS functionalization to COOH/SBA-15 before Famo loading

In order to study the effect of silylation procedure on Famo loading and Famo release, the bifunctionalized SBA-15 was also prepared before Famo loading. A 0.50 g C-15 without loading drug was homogeneously spread on a piece of filter paper, which was put on a bracket in a beaker containing 1.0 mL HMDS. The beaker was closed and put in an oven at 50 °C. After determined treating time, the samples were taken out and dried under vacuum at 50 °C. The TMS-COOH bifunctionalized SBA-15 materials (TMS/COOH/SBA-15) were, respectively, assigned as C-15M-B1 and C-15M-B2 corresponding to the HMDS-treating time of 0.5 and 3.0 h.

The obtained TMS/COOH/SBA-15 samples were immersed into 500.0 mL mixed solvent of methanol and water to load Famo (mass ratio of methanol:water = 0.8:1). After soaked for 8 h, the drug-loaded mesoporous powder were recovered by filtration. To measure the loading amount of Famo, 2.0 mL of filtrates was diluted to 50 mL and then analyzed using UV/Vis spectroscopy. The loading amount of Famo was calculated based on Eq. (1).

2.4. In vitro drug release

The release profile of Famo was obtained by soaking drug-loaded powder in simulated intestine fluid (SIF, phosphate buffer solution, pH = 7.4). The release experiment was performed at 37 °C under stirring rate of 100 r/min. A 2.0 mL of release fluid was sampled at a predetermined time interval, and another 2.0 mL of fresh SIF was supplied immediately. The drug concentration in the sampled fluid was measured by UV–Vis spectrophotometer. Because some amount of Famo was sampled from the release fluid and this part of Famo could not be reflected in the latter sampling point. Therefore, a corrected method was used to calculate the actual amount of Famo released from mesoporous carriers. The calculation was based on the following equation [18]:

$$C_{t-\text{corr}} = C_t + \frac{v}{V}\sum_{0}^{t-1} C_t \quad (2)$$

where $C_{t-\text{corr}}$ is the actual concentration of Famo released at time t, C_t is the drug concentration in release fluid at time t measured on UV/Vis spectrometer, v is the sampled volume taken at a predetermined time interval, and V is the total volume of release fluid.

Table 1
The molar ratio of reactants for synthesis of carboxyl functionalized SBA-15

Sample	CPTES	TEOS	P123	KCl	$\frac{\text{CPTES}}{\text{CPTES+CPTES}}$
SBA-15	0.0	1.0	0.015	1.2	0.0
C-15	0.15	0.85	0.015	1.2	0.15
C-25	0.25	0.75	0.015	1.2	0.25
C-40	0.40	0.60	0.015	1.2	0.40
C-50	0.50	0.50	0.015	1.2	0.50