pH-Responsive Carrier System Based on Carboxylic Acid Modified Mesoporous Silica and Polyelectrolyte for Drug Delivery

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An efficient pH-responsive carrier system has been constructed by oppositely charged ionic interaction between carboxylic acid modified SBA-15 silica rods and polyelectrolyte. Active molecules such as vancomycin can be stored and released from the pore voids of SBA-15 by changing pH values at will. The amount of vancomycin stored in the pores of sample based on carboxylic acid modified SBA-15 rods and poly(dimethyldiallylammonium chloride) is up to 36.4 wt % at pH 6.8. When the pH is at mild acidity, vancomycin is steadily released from the pores of SBA-15. Both nitrogen adsorption−desorption isothems and X-ray diffraction patterns show that this system possesses stable mesostructure, which will be considered an interesting alternative to a polymeric delivery system.

Introduction

In the past decade, controlled carrier systems have attracted much attention because of their most important application in high-performance drug delivery, which requires precise spatial and temporal delivery of therapeutic agents to the target site.[1] Generally, controlled drug delivery systems can maintain the concentration of drugs in the precise sites of the body within the optimum range and under the toxicity threshold, which improve the therapeutic efficacy and reduce toxicity.[1] Recently, research on controlled drug delivery has been greatly advanced, not only in the typical polymeric systems[2] but also in novel inorganic materials-based systems.[3]

Ordered mesoporous silica materials[4,5] with stable mesostructure,[6,7] large surface areas, good biocompatibility,[8] and tailorable size of mesopores on the nanometer scale have equipped chemists with ideal carriers to construct new carrier systems. Recently, a number of successful carrier systems based on mesoporous silica for release of guest molecules have been reported,[9,10] such as release of drugs from a series of mesoporous silicas with different pore characteristics,[9] sequestration, and release of proteins by modified mesoporous silica.[10] More recently, studies in mesoporous silica-based delivery were extended to responsive carrier systems in which delivery can be controlled at will by certain external stimuli.[8,11,12] For example, Lin et al. presented modified mesoporous silica nanospheres with chemically removable caps for release of drugs or gene,[8] Fujiwara et al. reported photocontrolled release of guest molecules from coumarin modified MCM-41,[11] and Stoddart et al. described redox-controlled nanovalves based on mesostructured thin films for release of luminescent molecules.[12]

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It is well-known that certain tissues of the body have a pH slightly more acidic than the blood and normal tissue.[13,14] Therefore, the carrier system based on mildly acidic pH[15] provides a safe and efficient way for drug release targeting specific sites in the body, such as tumor and inflammatory tissues (pH ∼ 6.8),[13] endosomes (pH ∼ 5.5−6), and lysosomes (pH ∼ 4.5−5.0).[14] Recently, a few successful examples of a pH-controlled carrier system based on mesoporous materials have been reported.[16,17] Martínez-Máñez et al.[16] showed pH-controlled molecular-gate-based modified MCM-41 for mass transport from the solution to the mesopores, but the release of guest molecules from the mesopores was not discussed. Huddersman et al.[17] discussed the drug uptake and release from the surface adsorption of mesoporous Al−MCM-41 influenced by pH value, but the uptake of drug is relatively low (3−17 wt %).

We report here a smart pH-responsive carrier system based on carboxylic acid modified SBA-15 silica rods[18] and poly(dimethyldiallylammonium chloride) (PDDA)[19] for storage and release of drug molecules from pore voids. This system can be described as a drug delivery device that contains drug reservoirs and environment-sensitive orifices, and the state of the orifices (closed or opened) can be controlled by pH value. As depicted in Figure 1, polycations (PDDA) absorbed to anionic SBA-15 by oppositely charged ionic interaction are acting as closed gates for storage of drugs in the mesopores. When ionized carboxylic acid species (COO^-) are transformed into protonated groups (COOH) by changing of the pH value, polycations are separated from the surface of modified SBA-15, leading to opening of the gates for release of drugs from the mesopores. In contrast to recently reported mesoporous silica-based carrier systems, this system has higher drug-loading capacity and larger mesopores for the storage of bulky active molecules.

Experimental Section

Synthesis of 11-Triethoxysilanylundecanoic Acid Ethyl Ester.[20] $H_2PtCl_6 \cdot 6H_2O$ (0.2 mmol) was dried under vacuum (2 h, 180 °C) in a 100 mL round-bottom flask, which was followed by addition of ethyl undec-10-enoate (21.6 g, 0.106 mol) and ethyltriethoxysilane (24.6 g, 0.15 mol) under nitrogen. After stirring at ambient temperature for 24 h, unreacted triethylsilane was removed in vacuo, and the residue was distilled at 0.1 Torr and 120 °C to give the product as a colorless oil. Yield: 30.6 g (77%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.11 (q, J = 7.4, 2 H), 3.80 (q, J = 6.8, 6 H), 2.27 (t, J = 7.8, 2 H), 1.70−1.54 (m, 2 H), 1.46−1.15 (m, 26 H), 0.61 (q, J = 8.3, 2 H).

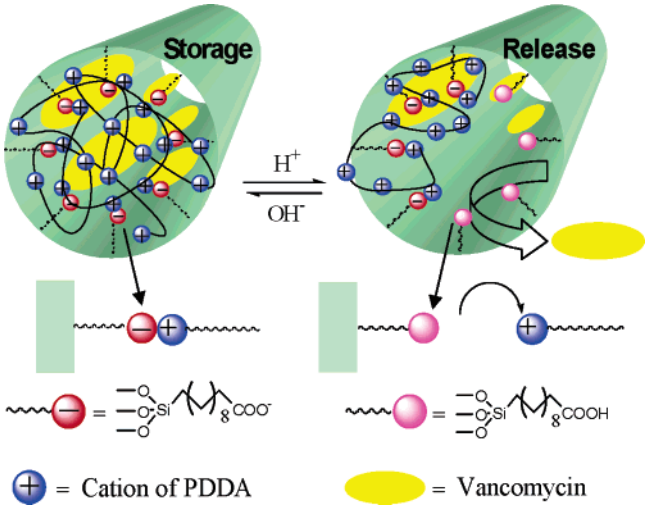

Figure 1. Schematic representation of pH-responsive storage-release drug delivery system. This pH-controlled system is based on the interaction between negative carboxylic acid modified SBA-15 silica rods with polycations (PDDA).

Synthesis of Carboxylic Acid Modified SBA-15 Rods. A typical run for synthesis of carbonxylic acid modified SBA-15 silica rods is as follows: (1) 2 g of as-synthesized SBA-15 silica rods[18b] were dried under vacuum at 150 °C for 3 h, followed by addition of 20 mL of dry toluene and 0.35 g of 11-triethoxysilanylundecanoic acid ethyl ester under stirring at ambient temperature for 15 min. Toluene was evaporated by a rotary evaporator at 80 °C for 2 h, and the resulting material was dried under vacuum at 150 °C for 12 h. (2) A total of 2 g of the SBA-15 silica rods obtained in step 1 were placed in a round-bottom flask containing a magnetic stirring bar, equipped with a reflux condenser under nitrogen, followed by addition of dry CH_3CN (60 mL) and AlI_3 (0.2 g). After heating at 85 °C for 4 h, the mixture was cooled to ambient temperature, followed by filtration, washing with fresh acetonitrile, and stirring with 10% HCl for 1 h. (3) The solid product was mixed with 50 mL of ethanol and then heated at 80 °C for 40 h to remove the surfactant of P123. After filtration, washing, and drying at ambient temperature for 24 h, carboxylic acid modified SBA-15 rods were obtained, which are designated as sample **A-1**.

pH-Controlled Storage-Release Experiments. (1) A total of 0.5 g of sample **A-1** in 10 mL of water was mixed with 0.5 g of vancomycin hydrochloride under stirring at ambient temperature for 24 h. After addition of PDDA (20 wt % in water, 2.5 g, Aldrich), the pH value of the solution was adjusted to 7.8 and the solution was stirred for 3 h at room temperature. After filtration, washing with water four times (removal of vancomycin outside of mesopores), and drying under vacuum at room temperature for 4 h, the vancomycin loaded sample was obtained, which was designated as sample **A-2**. (2) A total of 50 mg of sample **A-2** was suspended in 10 mL of water, with stirring for 240 min at various pH values from 6.5 to 2.0. After stirring for 240 min at pH 2.0, filtrating, washing with water, and drying at room temperature for 24 h, the released sample was obtained, which was designated as sample **A-3**.

In comparison, sample **B** was prepared from carboxylic acid modified SBA-15 silica rods in the absence of PDDA; sample **C** was prepared from unmodified SBA-15 silica rods and PDDA; sample **D** was prepared from carboxylic acid modified MCM-41

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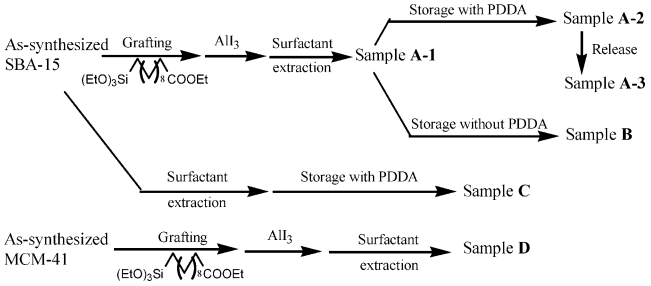

Figure 2. Preparation procedures of various samples.

and PDDA. The storage procedures of these samples (sample **B**, sample **C**, and sample **D)** were similar to those of sample **A-2**.

The procedures for preparation of various samples used in this work are shown in Figure 2.

Characterization. X-ray diffraction (XRD) patterns were obtained with a Siemens D5005 diffractometer using Cu Kα radiation. Fourier transform infrared (FT-IR) spectra were recorded on Nicolet Impact 410 FT-IR spectrometer. Scanning electron microscopy experiments were performed on a JSM-6700F electron microscope (JEOL, Japan). The isotherms of nitrogen were measured at 77 K using a Micrometeritics TriStar 3000 system. The pore size distributions were calculated from adsorption branches of N_2 adsorption/desorption isotherms based on the BJH model. The content of vancomycin in aqueous solution was analyzed by HPLC (Shimadzu SPD-10A, LCD-10AT). The amount of vancomycin stored inside of the mesopores was approximately equal to the decreasing amount of vancomycin in aqueous solution. Similarly, the released amount of vancomycin for the samples was approximately equal to the increasing amount of vancomycin in aqueous solution.

Results and Discussion

As observed in Experimental Section, sample **A-1** is prepared through the procedures of grafting of 11-triethoxysilanylundecanoic acid ethyl ester with as-synthesized SBA-15 rods, refluxing in CH_3CN in the presence of AlI_3, and heating at 80 °C in ethanol. During the procedure of grafting, as-synthesized SBA-15 rods are necessary for the functional group to attach to the pore outlets rather than their inside walls.[11] After interaction between surface silanol of as-synthesized SBA-15 rods with 11-triethoxysilanylundecanoic acid ethyl ester, the acid ethyl ester species attached on the pore outlets of as-synthesized SBA-15 rods are formed, as evidenced by an IR band at 1739 cm^{-1} assigned to C═O species of ether (Figure 3a). After refluxing in CH_3CN and AlI_3, a new band at 1712 cm^{-1} appears, which is associated with C═O species of the acid (Figure 3b).[21] These results indicate that the acid ethyl ester groups modified on as-synthesized SBA-15 rods are cleaved to carboxylic acidic groups. After heating at 80 °C in ethanol, the polymer surfactant of P123 in SBA-15 rods is almost removed, and carboxylic acid modified SBA-15 silica rods with a large amount of pore volume (sample **A-1**) are successfully prepared.

Scanning electron microscopy images (Figure 4) of sample **A-1** show the monodispersed rods with sizes of about 0.70 $\times$ 0.25 μm. As a typical guest molecule, vancomycin,[22] with the size of 2.3 nm (interatomic distances calculated by the program of Cerius 2) is used to study the efficiency of this pH-responsive carrier system. After the PDDA solution is mixed with the carboxylic acid modified SBA-15 and vancomycin, the drug loaded sample (sample **A-2**) is obtained.

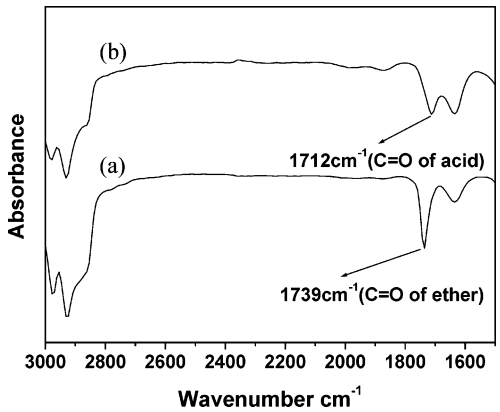

Figure 3. FT-IR spectra of 11-triethoxysilanylundecanoic acid ethyl ether modified SBA-15 silica rods (a) and reflux of the SBA-15 silica rods in CH_3CN in the presence of AlI_3 (b).

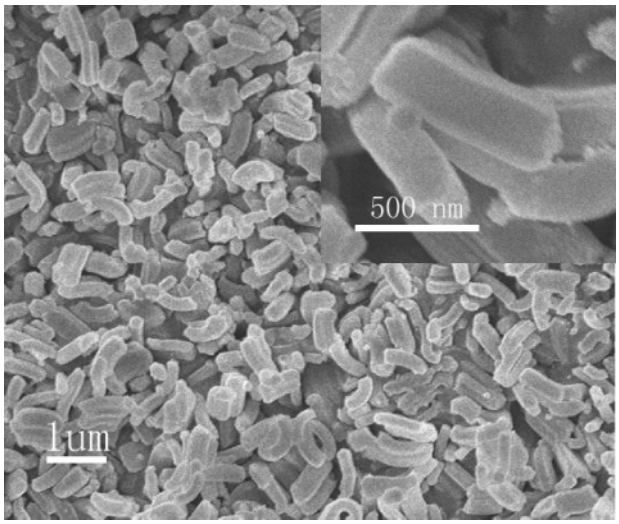

Figure 4. SEM micrograph of monodispersed carboxylic acid modified SBA-15 silica rods (sample **A-1**) with sizes of about 0.70 $\times$ 0.25 μm.

Table 1. Texatural Parameters and Vancomycin Storages of Various Samples

sample	d_{100} (nm)	S_{BET}[a] ($m^2\ g^{-1}$)	pore size[b] (nm)	V_P[c] ($cm^3\ g^{-1}$)	drug storage[d] (wt %)
A-1	10.8	544	7.2	1.02	0.0
A-2	10.8	190	5.9	0.40	36.4
A-3	10.8	497	7.2	0.83	2.4
B	10.8	528	7.2	0.97	5.0
C	10.8	534	7.2	1.00	2.2
D	4.2	977	2.3	0.89	6.9

[a] BET specific surface area. [b] Calculated from the adsorption branches of N_2 adsorption/desorption isotherms based on the BJH model. [c] Primary mesopore volume. [d] The amount of vancomycin stored inside of the mesopores was approximately equal to the decreasing amount of vancomycin in the aqueous solution.

Table 1 presents the amounts of vancomycin stored in various mesoporous silica-based systems. Notably, the amount of vancomycin stored in the pores of sample **A-2**

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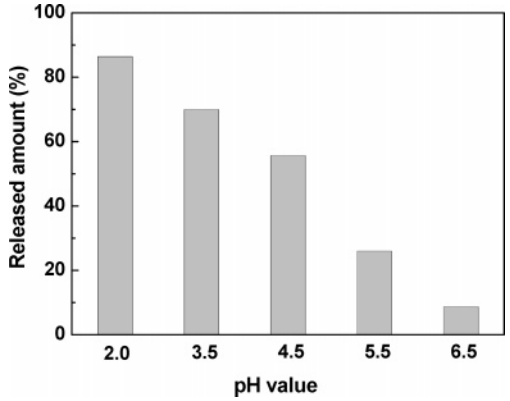

Figure 5. Released amounts of vancomycin from sample **A-2** at various pH values for 30 min.

based on carboxylic acid modified SBA-15 rods and PDDA is up to 36.4 wt % (vancomycin/silica, w/w). To the best of our knowledge, this drug loading is very high in mesoporous silica-based carrier systems, which may be related to the large pore volume of SBA-15 rods.[18] In contrast, sample **B** based on only modified SBA-15 rods fails to retain vancomycin (5.0 wt %, Table 1). Sample **C** based on unmodified SBA-15 rods and PDDA also has difficulty uptaking vancomycin (2.2 wt %, Table 1). These results indicate that the interaction between polycations of PDDA with anionic COO^- groups attached on SBA-15 plays a crucial role in the storage of vancomycin. In addition, sample **D** based on PDDA and carboxylic acid modified MCM-41 also exhibits very low storage of vancomycin (6.9 wt %, Table 1), which is assigned to the limitation of a relatively small mesopore size of 2.3 nm in sample **D**. These results indicate that relatively large mesopores in SBA-15[5] are very important for the storage of bulky medical molecules such as vancomycin.

To investigate pH-responsive release of this system, the vancomycin-loaded sample (sample **A-2**) is immersed in water at different pH values and the mass transport from mesopores to the solution was detected by HPLC. Figure 5 shows the level of vancomycin released from sample **A-2** at pH values from 2.0 to 6.5 over the same time period (30 min). Obviously, the released amounts of vancomycin from sample **A-2** are stepwise from 8 to 86% by adjusting the pH values from 6.5 to 2.0, which suggests that the environment-sensitive orifices in this system are gradually opened. Actually, interaction between polycations and anionic SBA-15 is weakening with increasing acidity, which is in good agreement with the balance between ionized carboxylic acid (COO^-) and protonated groups (COOH).[23]

Figure 6 shows the dependence of the released amount for vancomycin in sample **A-2** on time at pH values of 2.0, 4.5, and 6.5, respectively. Notably, the release rate is very fast at pH 2.0, and the amount basically reaches a maximum value of 90 wt % at 30 min. Possibly, in this case, there is not any negative charge on carboxylic acid modified SBA-15 silica rods.[21b] Therefore, PDDA with a positive charge will be separated from the surface of SBA-15 and then the state of the gates around the mesopores is completely opened. On the contrary, at pH 6.5, the release amount is quite low

(23) $pH = pK_a + \log [COO^-]/[COOH]$.

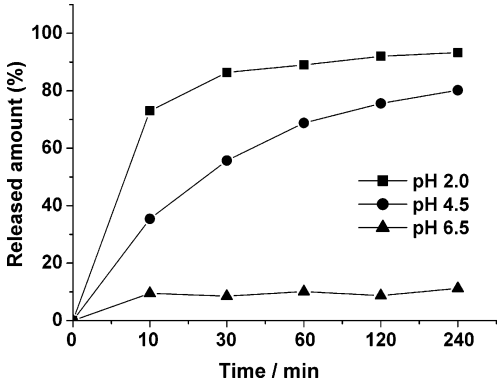

Figure 6. Dependence of released amounts of vancomycin on time from sample **A-2** at pH values of 2.0, 4.5, and 6.5.

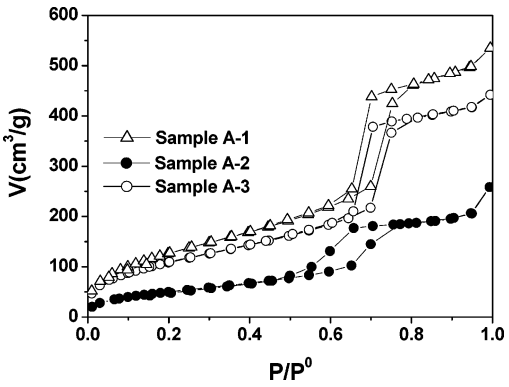

Figure 7. Nitrogen adsorption/desorption isotherms of samples **A-1**, **A-2**, and **A-3**.

and remains essentially constant (~8.0 wt %), which suggests that the state of the gates around the mesopores is almost closed, as a result of a strong interaction between the negative group of COO^- and the positive group of PDDA. It is very interesting to note that there is a steady release with stepwise increasing from 35.4 to 80.2 wt % during 4 h when at pH 4.5. This result indicates that drug delivery in our system at a mildly acidic pH value such as pH 4.5 may be long-lived and continuous, which is helpful for maintaining the concentration of drugs in the certain sites of the body within the optimum range. All mentioned above confirms that the level of vancomycin release from this system is strongly dependent on the pH value.

Nitrogen adsorption−desorption isothems (Figure 7) also provide direct evidences of storage-release efficacy of the pH-controlled carrier system. Sample **A-1** exhibits a typical IV isotherm, giving a large pore volume (1.02 $cm^3\ g^{-1}$) and narrow pore size distribution (7.2 nm, Table 1). After loading of vancomycin, sample **A-2** still shows a IV isotherm, but its pore volume (0.40 $cm^3\ g^{-1}$), surface area (190 $m^2\ g^{-1}$), and pore size distribution (5.9 nm) are drastically decreased, compared with those (1.02 $cm^3\ g^{-1}$, 544 $m^2\ g^{-1}$, and 7.2 nm) of sample **A-1**, which should be attributed directly to vancomycin stored in the mesopores of the sample **A-2**. Very interestingly, after vancomycin has been released (sample **A-3**), the sample still shows a typical IV isotherm, and its pore volume (0.83 $cm^3\ g^{-1}$), surface area (497 $m^2\ g^{-1}$), and pore size distribution (7.2 nm) are close to those of sample **A-1** (Table 1). All results mentioned above further demonstrate that this system is efficient for storage and release of

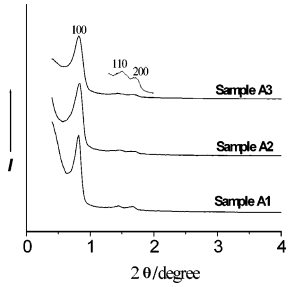

Figure 8. XRD patterns of samples **A-1**, **A-2**, and **A-3**.

vancomycin and the mesostructure in this system is stable for drug delivery.

Figure 8 shows XRD patterns of samples **A-1**, **A-2**, and **A-3**. Obviously, these samples almost retain the same value and intensity of the d_{100} peaks, which indicates that vancomycin storage and release do not damage the ordered hexagonal structure of mesostructure in this system. It is well-known that ordered mesoporous silica materials of SBA-15 type have good hydrothermal and chemical stability. Therefore, the carrier system based on the ordered mesoporous silica of SBA-15 will be considered an interesting alternative to the polymeric delivery system which suffers from limitations including poor thermal and chemical stability.[3a]

Conclusion

In summary, an efficient responsive carrier system has been successfully constructed by oppositely charged ionic interaction between polycations and anionic SBA-15. This intelligent system is efficient for storage and release of drug controlled by the pH value at will. Moreover, this system with attractive features of high drug-loading capacity, mild storage-release conditions, and stable mesostructure will be considered as an interesting alternative to the polymeric delivery system. Although there still remains challenges, recent progress in interdisciplinary aspects of pharmaceutical science and mesoporous materials, such as preparation of ordered mesoporous materials with nanoscale particle sizes,[24] increases their potential for drug delivery application. More significantly, artificial molecular gates around mesopores switched on and off by the pH value are of great importance for other potential applications including sensors and molecular machines,[25] and further studies in this area are being pursued in our laboratory.

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