Journal of Materials Chemistry

Cite this: *J. Mater. Chem.*, 2011, **21**, 7882

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# Controlled release using mesoporous silica nanoparticles functionalized with 18-crown-6 derivative†

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***Received 30th March 2011, Accepted 15th April 2011***
**DOI: 10.1039/c1jm11334h**



**Mesoporous silica nanoparticles were functionalized with an 18-crown-6 group as a gate molecule and the releasing capacity as a drug delivery system was controlled by the exchange reaction of "host–guest complex" with alkaline metal ions.**

The goal of drug delivery is to administer medicinally active molecules with high specificity to diseased cells in a targeted and controlled manner.[1,2] Recently, mesoporous silica nanoparticles were described as an appealing class of drug delivery vehicles, due to their sophisticated design and mode of action.[3] Increasing evidence has shown that the nanoparticles are not cytotoxic and that those on the order of 100–200 nm in diameter can be taken up by cellular endocytosis and transported into acidic lysosomes.[2]

Recently, in the field of gated nanochemistry, photochemically, electrochemically and ionically controlled gate-like elements have been incorporated into 3D MCM-41 scaffolds *via* tethering molecular or supramolecular gating ensembles on the pore outlets of the mesopores.[4–7] For instances, Stoddart and Zink *et al.* presented supramolecular redox-controlled nanovalves containing grafted pseudorotaxanes and bistable rotaxanes in the pore outlets of mesostructured silica thin films and they reported pH-driven systems containing dialkylammonium threads anchored to MCM-41 and capped with dibenzo-24crown-8.[4] Some other release stimuli involve coordination features, auto-modulated systems and specific irreversible reactions such as cleavage of specific bulky groups or taps.[8–10] For instance, in a recent publication operational controlled hydrolysis was demonstrated by taking advantage of enzyme specificity through rupture of an ester-like stopper.[8]

From these examples, it is apparent that most of the guest-release controls on gate-like scaffolding have been reported by using light-redox or pH-driven systems. In contrast, it is clear from the literature that examples of guest release controlled in response to cations in aqueous solution have still never been reported. However, the design of such systems for certain cation species could be of interest for the design of complex functional materials driven by the presence of cations. In relation to this field, the combination of mesoporous supports with suitable coordination is a promising starting point for applying the versatility of supramolecular ideas to the design of nanoscopic devices and a method for bringing molecular and supramolecular concepts to new advances in the field of nanosciences.

With these ideas in mind, we describe the mesoporous silica immobilized with 18-crown-6 derivative as a cation-responsive release system. Since the stoichiometric ratios of 18-crown-6 derivative complexed with cations is strongly dependent on the size of cations, the 18-crown-6 derivative was selected as the gate molecule. The release rate of the curcumin cargo molecule from mesoporous silica nanoparticles immobilized with 18-crown-6 derivatives could be efficiently controlled by using different stoichiometries of coordination complexes with $Cs^+$ and $K^+$ ions. In the current study, the selected model drug was curcumin (or diferuloylmethane), one of the best-characterized chemopreventive agents. Since curcumin has strong absorption and fluorescent emission properties,[11] we can monitor the operation of the controlled release by following the changes in its luminescent property. This system is not only quite simple compared to previous reported methods, but it also allows easy control of the release rate of a cargo molecule by change in the concentration of $K^+$ ion.

Scheme 1 shows the strategy of the cation-responsive release system on the mesoporous silica surface. Mesoporous silica nanoparticles were uniformly covered with 18-crown-6 functional groups (**1**), as coordination binding sites for $Cs^+$ and $K^+$, and attached to the surface by covalent bonds. The 18-crown-6 moiety of **1** formed the sandwich-type complex with $Cs^+$ by a 2 : 1 ratio.[12] On the other hand, the 18-crown-6 moiety of **1** forms a complex with $K^+$ by a 1 : 1 ratio.[12] $Cs^+$ ions readily bind to the 18-crown-6 groups on the mesoporous surface to form a "host–guest" coordination bond, in which the mesopores are closed. Subsequently, $K^+$ can be exchanged with the $Cs^+$ ion, because the stability constant of $K^+$ ion is much higher than that of $Cs^+$ ion. The 18-crown-6 moiety of **1** forms a 1 : 1 complex with $K^+$; this causes the mesopores to open. Thus, curcumin molecules harbored within the mesoporous silica nanoparticles can be released into the solution phase with $K^+$ ion.

The synthetic procedure for the preparation of the 18-crown-6 derivative **1** (Scheme S1†) functionalized mesoporous silica nanoparticles is as follows; the mesoporous silica particles were prepared through the sol–gel process by the previously reported method.[13] Before removal of a template, the 18-crown-6 group, used as a gate, was attached to the external surface of mesoporous silica nanoparticles in a sol–gel grafting reaction. The surfactant template was

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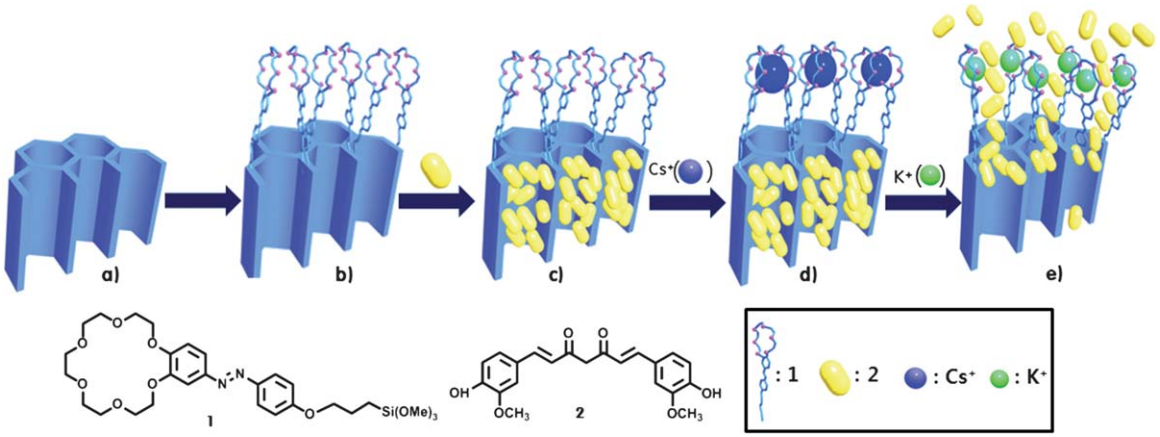
† Electronic supplementary information (ESI) available: Spectroscopic data and experimental conditions. See DOI: 10.1039/c1jm11334h




**Scheme 1** Schematic representation for the drug delivery system by using mesoporous silica nanoparticles: (a) preparation of mesoporous silica nanoparticle, (b) immobilization of **1** as gate molecule, (c) encapsulation of curcumin (**2**), (d) complex formation of 18-crown-6 moiety with $Cs^+$ ion and (e) release of curcumin (**2**) upon addition of $K^+$ ion.

removed by ethanol extraction; then, the silica particles obtained in the sol–gel reaction were characterized by transmission electron microscopy (TEM), $^{13}C$ cross-polarization magic-angle-spinning (CP-MAS) solid-state NMR spectroscopy, BET isotherms, TOF-SIMS, X-ray photoelectron spectroscopy (XPS) and powder X-ray diffraction (PXRD).

Fig. 1 shows the TEM image of silica particles after 18-crown-6 derivative (**1**) immobilization with a covalent bond. The 18-crown-6-immobilized mesoporous silica nanoparticles (C-MS) exhibited a typical mesopore structure of 4.48 nm with 100–500 nm of particle size, which had hexagonal structure. The nanoparticles also show XRD patterns typical of the hexagonal mesoporous silica. An interplanar spacing ($d_{100}$) of ~4.48 nm was calculated from these patterns (Fig. S1†).

The spectroscopic observations provide direct evidence for the attachment of 18-crown-6 derivative (**1**) onto the external surface of silica nanoparticles. The IR and TOF-SIMS results were consistent with bond formation; the IR spectrum of C-MS showed strong new bands at 3010, 2970, 1350 and 1250 $cm^{-1}$, which originated from molecule **1**. This was consistent with **1** residing on the silica particle (Fig. S2†). The TOF-SIMS spectrum of C-MS displayed fragments attributable to **1** ($m/z$ = 473.25), thereby providing evidence that **1** was anchored onto the surface of the silica particles (Fig. S3†). After immobilization of **1**, examination of the $^{13}C$ CP-MAS solid NMR spectrum of C-MS (Fig. S4†) shows that (i) the signals resonating around 70 ppm can be attributed to the characteristic peak of the ethyl ether 1, 2 and 3; (ii) the signal resonating around 20–60 ppm can be assigned to the characteristic peaks of carbon on the alkyl chain;

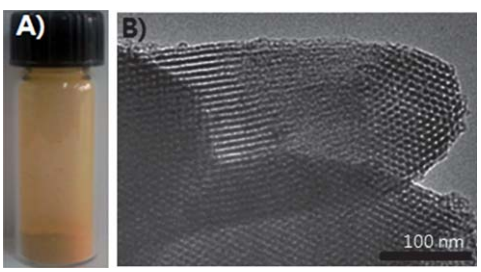



**Fig. 1** (A) Photograph and (B) TEM image of 18-crown-6 derivative (**1**) attached onto mesoporous silica particles (C-MS).

(iii) the signals resonating around 100, 115, 125 and 148 ppm can be attributed to the characteristic carbon peaks of azobenzene moiety. Mesoporous silica nanoparticles before and after functionalization of **1** were further confirmed by XPS (Fig. S5†). The XPS spectrum of mesoporous silica nanoparticles before immobilization of **1** shows Si2P and O1S binding energy (Fig. S5a†), whereas C1S and N1S for carbon and nitrogen appeared for C-MS (Fig. S5b†). The absorption and emission bands of C-MS in the solid state appeared at 350 nm; this resulted in a yellow color (Fig. S6†). In addition, the $N_2$ adsorption–desorption isotherms obtained at 77 K (Fig. S7†) showed a typical type IV isotherm; in this, the observed step could be related to nitrogen condensation inside the mesopores by capillarity. The pore size and surface area of the silica nanoparticles before immobilization of **1** were determined to be 4.48 nm and 1157.20 $m^2g^{-1}$, respectively (Fig. S7a†). After immobilization of **1**, the pore size and surface area of the silica nanoparticles were determined to be 4.48 nm and 960.66 $m^2g^{-1}$, respectively (Fig. S7b†). These were slightly smaller than those observed before immobilization of **1**. From the above experimental data, we clearly concluded that the 18-crown-6 derivative (**1**) was attached onto the external surface of mesoporous silica nanoparticles by covalent bonding. In addition, we measured the density of **1** attached to the external surface of mesoporous silica nanoparticles by TGA. 30% of **1** was attached onto the external surface of mesoprous silica nanoparticles (Fig. S8†).

In order to determine the binding affinity and stoichiometry of **1** complex with $Cs^+$ and $K^+$, $^1H$ NMR titrations of the 18-crown-6 derivative (**1**) were carried out upon the addition of $Cs^+$ and $K^+$ ions in DMSO-$d_6$ (Fig. S9 and S10†). The formation constant ($K_f$) for **1** complex with $Cs^+$ is *ca.* 1.25 × $10^4$ $M^{-1}$,[14] which shows 2 : 1 stoichiometry. On the other hand, the value of $K_f$ for **1** complex with $K^+$ is *ca.* 5.20 × $10^4$ $M^{-1}$,[14] which has 1 : 1 complex structure. These results suggest that C-MS complex with $Cs^+$ is exchangeable with $K^+$ in aqueous solution.

To include a model drug molecule, curcumin (10 mM) was added to a dispersed solution of C-MS (10 mg) and stirred for 1 h. The final curcumin-loaded C-MS (C-C-MS) solid was isolated by centrifugation and washed with ethanol to eliminate the residual curcumin. C-C-MS was characterized by TGA, fluorometry, FT-IR and solid $^{13}C$ NMR. The emission band of the C-C-MS solid appeared at 530 nm by fluorometry. The IR spectrum of C-C-MS showed new bands at

3300, 3050 and 1700 $cm^{-1}$, which originated from curcumin (Fig. S11†). In addition, the $^{13}C$ CP-MAS spectrum of C-C-MS included new peaks at 40, 58, 90, 104, 118, 142, 158,182 and 195 ppm (Fig. S12†). The estimated loading was 20% of curcumin per gram of C-MS by TGA observation (Fig. S13†).

As mentioned above, the 18-crown-6 moiety of **1** formed a complex with $Cs^+$ by a 2 : 1 stoichiometry. Thus, we selected $Cs^+$ as a stopper ion. C-C-MS (10 mg) was suspended in $Cs^+$ solution (0.7 equiv.). Then, the solid product was isolated by centrifugation and washed with water to remove the free $Cs^+$. The physically adsorbed curcumin on the external surface of the mesoporous silica nanoparticle would be removed for precise releasing experiments. In addition, our previous experiments confirmed that the curcumin loaded on the inside of mesoporous silica was not released to the outside of the mesopore.

To investigate the delivery system of C-C-MS, we used luminescence spectroscopy to monitor the release of the cargo molecule, curcumin (**2**), upon the addition of $K^+$ ion in aqueous solution. The emission intensity of cargo **2** was negligible before the triggered release from this system. When the concentration of $K^+$ was adjusted from 0 to ~3.0 equivalents, the emission intensity of curcumin in solution gradually increased, indicating that cargo molecule **2** had been released into the aqueous phase (Fig. 2). In addition, we measured the luminescence properties of curcumin in the presence of $K^+$ and $Cs^+$. However, we could not find any influences in curcumin with $K^+$ and $Cs^+$, because we used a small amount of $K^+$ and $Cs^+$ in compared to curcumin. In addition, most of $K^+$ was bound to **1** attached onto mesoporous silica particles. Thus, the $Cs^+$ bound to the 18-crown-6 group on the external surface of C-C-MS was de-complexed by $K^+$, in which the $K^+$ ion became coordinated to the 18-crown-6 group by 1 : 1 complex structure, and opened the pores on the surface of the C-MS.

Finally, we investigated the releasing capacity of the hollow silica particles at different concentrations of $K^+$ ion. The amount of curcumin (**2**) released from C-C-MS was determined by measuring the fluorescence emission intensity of the supernatant before and after the addition of $K^+$ ion. The release profiles were expressed in weight percentages of cargo **2** at different concentrations of $K^+$ (Fig. 3). The release of cargo **2** was negligible for 210 min in the absence of $K^+$ ion; this indicated that cargo **2** remained in the pores of the silica nanoparticles. However, upon the addition of 1.0 equivalent of $K^+$, up to 45% of cargo **2** was gradually released over 170 min. Upon the addition of 3.0 equivalent of $K^+$ in compared to the concentration of $Cs^+$, approximately 100% of cargo **2** was efficiently released into the aqueous phase over 90 min. The results indicate that the rate of the release of cargo **2** depends directly on the concentration of $K^+$ ion, with higher release rates occurring at larger concentrations of $K^+$ ion.

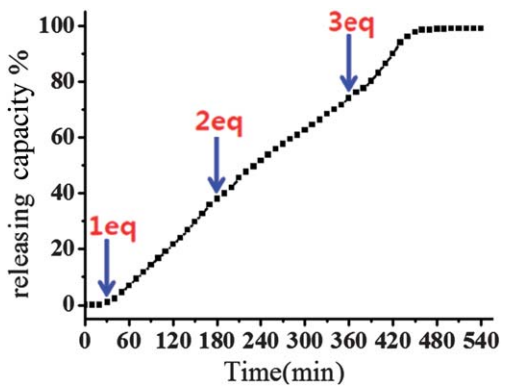



**Fig. 2** Controlled release profile of cargo molecule **2** from C-MS (10 mg) in the presence of $Cs^+$ (0.7 equiv.) upon addition of $K^+$ ion (0–3 equivalents) in aqueous solution.

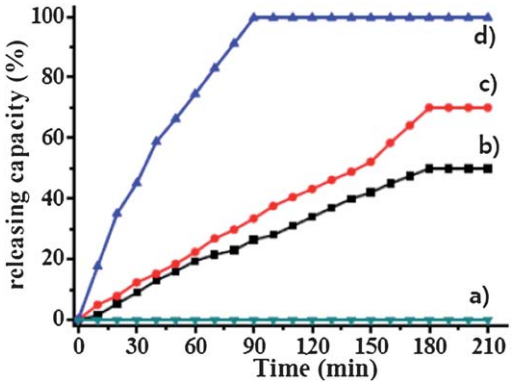



**Fig. 3** Concentration dependence of $K^+$ ion for the release profiles of cargo molecule **2** from C-MS upon (10 mg) in the presence of $Cs^+$ (0.7 equiv) upon addition of KCl; (a) 0, (b) = 1.0, (c) = 2.0 and (d) = 3.0 equivalents in aqueous solution.

In conclusion, we developed a mesoporous silica-based cation responsive release system, based on the "host–guest" concept. The curcumin molecules loaded into pores of C-MS were effectively released by de-complexation of the coordination bonds between the 18-crown-6 group of C-MS and $Cs^+$ upon the addition of $K^+$. Therefore, this system, based on the complexation of host and guest molecules, may be a promising method for developing custom-made controlled-delivery devices specifically triggered by target molecules.

## Acknowledgements

This work was supported by a grant from the NRF (grant no. 2010-0016306) and the World Class University (WCU) Program (R32-2008-000-20003-0) supported by Ministry of Education, Science and Technology.

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