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Versatile Triggered Release of Multiple Molecules from Cyclodextrin-Modified Gold-Gated Mesoporous Silica Nanocontainers

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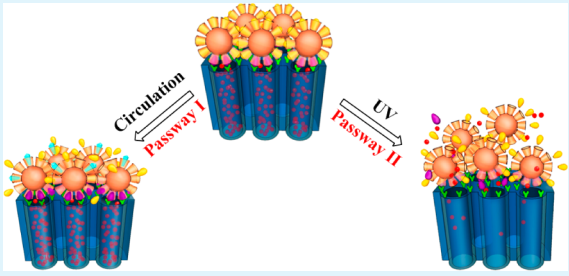
Supporting Information

ABSTRACT: A versatile triggered release system by capping the cyclodextrin-modified gold nanoparticle onto the mesoporous silica was fabricated. The as-designed nanocontainers combine the merits of multiple molecules loading and sequential release by natural circulation manner and light initiation.



KEYWORDS: *mesoporous silica, stimuli responsive, controlled release, gold nanoparticles, cyclodextrin, light initiation*

Mesoporous silica (MS) is considered to be attractive nanocontainer for a wide field of applications, including catalysis,[1] drug delivery,[2] sensing,[3] imaging,[4] and separation.[5] In the area of drug delivery, MS has been employed as a versatile and useful solid support for constructing various controlled-release systems because of its unique features such as uniform and tunable pore structure, and great diversity in surface functionalization.[6,7] Several sophisticated systems based on MS have been designed, using a concept of gatekeeping that keeps guest molecules in the pore until they are released by external stimuli. A series of stimuli, including light,[8,9] competitive binding,[10] redox,[11] pH,[12] temperature,[13] and enzyme,[14] have been developed in these nanosystems to modify target molecules release behavior. Forthermore, fine-tuned release of molecules by well designed nanosystems that are sensitive to several external impulses have been investigated to achieve on-demand molecule regulation.

Up to now, reports on the gatekeepers on the surface of the MS containers for the control of release of guests using different kinds of pore blockers, including supramolecular,[15] magnetic nanoparticles,[16] gold nanoparticles,[17] quantum dots,[18] biomolecule,[19] and polymer.[20] The combination of MS and supramolecular assemblies as gatekeepers has resulted in novel organic/inorganic hybrid materials with improved functionalities. Cyclodextrin (CD), a well-known and readily available molecular host in supramolecular chemistry, which comprises seven α-1,4-linked D-glucopyranosyl units with top and bottom cavities of 6.0 and 6.5 Å, respectively, has been employed as a gatekeeper in drug delivery systems.[21] Moreover, CD has been proven as excellent drug carriers with the ability to improve various drug properties, such as solubility, dissolution rate, stability, bioavailability, and prevent drug−drug and drug−excipient interactions through the formation of inclusion complexes.[22] Unfortunately, CD as a functional gatekeeper cannot exhibit its ability of carrier drug that was a great loss to stimuli-responsive assembles. In this regard, the development of a hybrid MS-supramolecular assembly with hydrophobic cavity and porous solid support is of considerable significance, which could solve the problem of single delivery approach and provide separated compartments to load multiple molecules.

Combination of two or more functional compounds in nanomaterials may lead to synergistic effect. For example, in the field of biology, codelivery two or more drugs has been proven to be a simple and efficient approach to shorten the duration of treatment and prevent emergence of drug resistance.[23] However, less effort has been made to produce multiple compounds delivering nanocontainers which able to controlled release of two or more agents by different stimulate behavior. Therefore, a major challenge is how to engineer hybrid nanocontainers with integrated functionalities by controlling the release behavior of each agent individually.

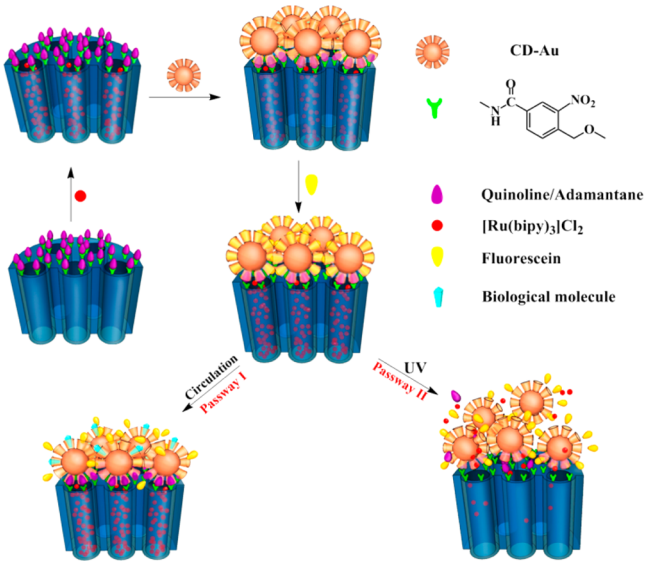
Herein, we report a versatile triggered release system by capping the cyclodextrin-modified gold nanoparticle (CD-Au) onto the mesoporous silica (CD-Au-MS), which combines the merits of multiple molecules loading and sequential release by natural circulation manner and light initiation. The natural circulation manner includes biomolecules competition, dissociation due to dilution and cyclodextrin elimination mainly contributes for more strongly bound molecules.[22,24] In addition, CD-Au is useful carrier of hydrophobic anticancer drugs and the intracellular glutathione concentration significantly influences the release of drugs.[25] The light initiation

Received: April 24, 2014
Accepted: May 30, 2014
Published: May 30, 2014

   dx.doi.org/10.1021/am502463h | ACS Appl. Mater. Interfaces 2014, 6, 9932−9936

realized by a photoactive *o*-nitrobenzyl bromide linkage. The basic principle of this CD-Au-MS hybrid nanoassembly is shown in Scheme 1 and Figure S1 in the Supporting Information. The surface of MS was decorated with specific guest molecules that selectively bound CDs by host−guest interaction. The *o*-nitrobenzyl bromide groups are used as linker between MS and specific guest molecules that was carefully selected as model molecule I (quinoline/adamantane). Furthermore, model molecule II ($[Ru(bipy)_3]Cl_2$ (bipy = 2,2′-bipyridine)) could be locked into the pores of MS by the blocking caps (CD-Au), which also could provide abundant hydrophobic cavity to load model molecule III (fluorescein).[22] Fluorescein can be escaped in a natural circulation manner and quinoline/adamantane and $[Ru(bipy)_3]Cl_2$ can then be irreversibly released by irradiation through light-induced photoisomerization of the *o*-nitrobenzyl caged derivatives into *o*-nitrobenzaldehyde.

Scheme 1. Schematic Illustration of Versatile Triggered Release of Multidrug from Mesoporous Silica-Based Nanocontainers



To create these MS-based nanocontainers, we introduced an amino group on the outlet of MS (denoted as MS-NH_2) using established methods.[26] The honeycomb-like structure of MS-NH_2 was confirmed by scanning electron microscopy (SEM) and transmission electron microscopy (TEM) analysis (see Figure 1(a) and Figure S2 in the Supporting Information). The MS nanoparticles displayed a BET surface area of 1050 m^2/g and an average pore diameter of 3.0 nm, as determined by Powder X-ray diffraction (XRD) and nitrogen sorption isotherms analysis (see Figures S3 and S4 in the Supporting Information). The IR spectrum of MS-NH_2 shows a peak at 1465 cm^{-1} is indicative of the presence of a primary amine group, which leads to the conclusion that the amine modification has taken place (see Figure S5 in the Supporting Information). Then, the photoactive *o*-nitrobenzyl bromide linker was grafted by the reaction of excess 4-bromomethyl-3-nitrobenzoic acid with amino groups on the particle surface,[8] which was confirmed by the characteristic peaks of acrylamide at 1650 cm^{-1}. Quinoline-6-carboxylic acid is selected as a model molecule which can react with *o*-nitrobenzyl bromide group functionalized MS. Quinoline-grafted on MS (denoted as MS-Q) was confirmed by fluorescence spectra and unreacted quinoline-6-carboxylic acid was removed thoroughly by centrifugation (see Figure S6 in the Supporting Information). It should be noted that further functionalization with light-responsive linker and quinoline has not damaged the mesoporous 3D structure (see Figure S3 in the Supporting Information) for the value and intensity of the d_{10} peak in this pattern are still strong. A negligible fluorescence signal from silica nanoparticles without *o*-nitrobenzyl bromide groups excludes the possibility of nonspecific interactions of quinoline-6-carboxylic acid with the particle surface.

SH-*β*-CD was synthesized according to published literature procedures[27] (see Figure S7 in the Supporting Information) and then utilized as thiolated capping agents to prepare CD-Au nanoparticles via previously established methods.[28] The particle size was also examined by TEM with a diameter of ∼3 nm and exhibit a sharper and more intense plasmon absorption band close to 512 nm (see Figure S8 in the Supporting Information). CD-Au was then formed inclusion complexes with quinoline and as the capping agent onto the MS. Figure 1(a) and (b) inset show TEM images of MS before and after capping with CD-Au. The hexagonally packed mesoporous channels could be clearly visualized (inset in Figure 1(a)) before capping. In contrast, the TEM of CD-Au-MS (see inset in Figure 1(b) and Figure S9 in the Supporting Information) shows dark spots on the exterior surface of the mesoporous silica, representing the aggregation of CD-Au nanoparticles around MS. The CD-Au was also confirmed by the appearance of (111), (200), and (220) diffraction peaks of Au nanoparticles in the powder XRD

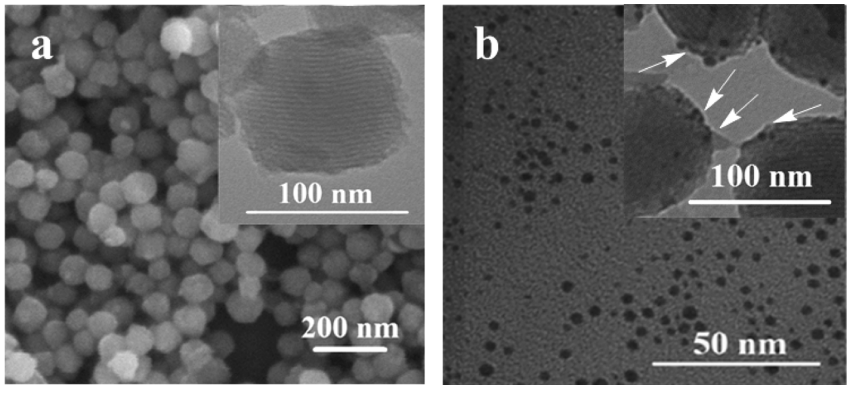


Figure 1. (a) SEM of MS-NH_2 and (b) TEM of CD-Au. Inset in a is the TEM of a; inset in b is the assembly of MS-Q: CD-AuNPs.

dx.doi.org/10.1021/am502463h | ACS Appl. Mater. Interfaces 2014, 6, 9932−9936

(see Figure S10 in the Supporting Information). N_2 sorption measurement of MS-NH_2 exhibited the typical type IV isotherms of mesoporous materials while CD-Au-MS showed an isotherm characteristic of nonporous materials (see Figure S4 in the Supporting Information).

To investigate the versatile triggered release behavior of MS-Q: CD-Au association, we selected $[Ru(bipy)_3]Cl_2$ as model molecule loaded into the MS. The loading of $[Ru(bipy)_3]Cl_2$ was determinned to be 1.6 μmol/g of MS-Q: CD-Au nanocontainers. $[Ru(bipy)_3]Cl_2$ loaded mesoporous silica-based nanocontainers were collected and redispersed in PBS buffer to test their release profile. The gate-like effect can then be straightforwardly studied via the release of the $[Ru(bipy)_3]Cl_2$ from the pore voids to the aqueous solution through monitorization of the metal-to-ligand charge-transfer transition band of the $[Ru(bipy)_3]^{2+}$ complex centered at 459 nm in the PBS buffer. As shown in Figure 2, without the application of

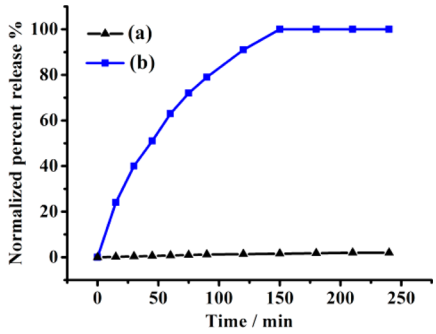


Figure 2. Controlled release of $[Ru(bipy)_3]Cl_2$ from MS-Q: CD-Au nanoparticles (1.0 mg) in 1 mL of PBS solution (100.0 mM, pH 7.4). (a) No noticeable release was observed without external stimuli; triggered by (b) UV.

external stimuli, only 2% leakage of the entrapped $[Ru(bipy)_3]Cl_2$ molecules was observed after 5 h. When the UV light was focused on the releasing solution, the significant release of the $[Ru(bipy)_3]Cl_2$ was observed because of photolysis of MS-Q resulting from the light-induced photoisomerization of the *o*-nitrobenzyl caged derivatives into o-nitrobenzaldehyde. Accordingly, the quinoline was released. Nearly 100% release could be achieved by 3 h (Figure 2, curve b), which was rapid more than the reported light responsive polymer-based drug release system for the catalysis of Au nanoparticles.[9]

To prove it is possible to control the release individual molecules, 1-adamantaneacetic acid selected as drug molecules which contains one active carboxylic acid group can react with surface *o*-nitrobenzyl bromide group of MS (denoted as MS-A). Fluorescein was utilized as another drug model molecule and was carried by stirring with $[Ru(bipy)_3]Cl_2$ loaded MS-A:CD-Au nanoparticles in a pH 7.4 PBS solution for 4 h. Fluorescein can be embedded into the cavities of CDs and has a lower binding capacity compared with adamantane according to the binding constant available,[29] and thus will not destroy the MS-A:CD-Au association. The excess fluorescein was removed by centrifugation and repeated washing with PBS buffer. The MS-A:CD-Au with dyes loaded nanoparticles was dispersed in PBS buffer exhibit different emissions under different excitation wavelengths, which confirmed multiple moleculars loading. Fluorescein and $[Ru(bipy)_3]Cl_2$ have two distinct maximum emission wavelengths with fluorescein at 510 nm and $[Ru(bipy)_3]Cl_2$ at 605 nm. When excited at 490 nm (the absorption maximum of fluorescein), the emission spectrum of nanoparticles showed a dominated peak (Figure 3, curve a) at

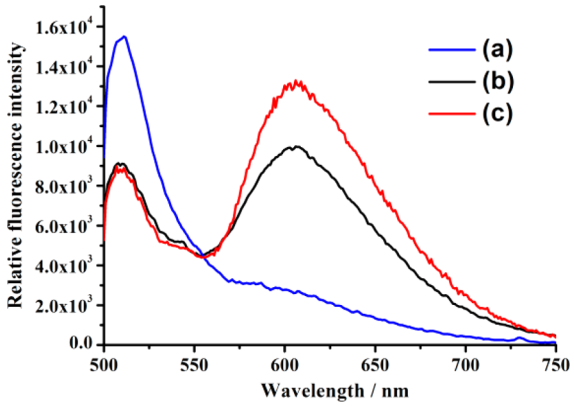


Figure 3. Fluorescence emission spectra of the MS-A: CD-Au NPs with loaded fluorescein and $[Ru(bipy)_3]Cl_2$ nanoparticles (a) excited at 490 nm, (b) excited at 450 nm, and (c) excited at 450 nm with exposure to UV light.

510 nm which is typical emission spectrum of fluorescein. Under excitation at 450 nm (the absorption maximum of $[Ru(bipy)_3]Cl_2$), the peak around 510 and 610 nm is comparative. Most significantly, UV irradiation of these MS-A:CD-Au association for 30 min, the release of $[Ru(bipy)_3]Cl_2$ was observed and indicated the ability of the CD-Au nanoparticles, uncap the silica, and allow guest release. It is worth mentioning that the fluorescence spectra of the fluorescein were not affected seriously with continuous UV irradiation because of the enhanced photostability by formation of inclusion complexes between fluorescein and cyclodextrin.[30] The release of fluorescein depends on their biological environment, which includes biomolecules competition, glutathione concentration, etc.

Finally, MCF-7 cells were incubated with fluorescein and $[Ru(bipy)_3]Cl_2$ loaded MS-A:CD-Au nanoparticles for 2 h on a plate and then washed with PBS buffer to remove the noninternalized nanoparticles. The results evaluated the biological compatibility and intracellular light-triggered release property of the hybrid nanoparticles. Fluorescence microscopy images of the incubated cells are shown in Figure 4. After MCF-7 was incubated with the hybrid nanoparticles, a strong green fluorescence signal for fluorescein, a weak red fluorescence signal for $[Ru(bipy)_3]Cl_2$ were observed under confocal laser scanning microscopy (CLSM). However, enhanced red fluorescent was observed after UV irradiation for 5 min (Figure 4d–f), which suggests the light-triggered release of $[Ru(bipy)_3]Cl_2$ from the nanoparticles and its diffusion into the cell. These results confirmed that the hybrid nanoparticles are cell permeable and biocompatible so they are suitable for intracellular light-controlled drug delivery.

In conclusion, we have described a light/competition triggered release system by capping the cyclodextrin-modified gold nanoparticle onto the MS. It was shown that the nanopores of silica and the cavity of CD can be loaded different cargoes to realize multimolecules loading and sequential release. Model molecule quinoline/adamantine connects with MS by light responsive linkage, which is used to lock CD-Au nanoparticle on the basis of strong host–guest interaction. In addition, actual drug such as ibuprofen, cisplatin, and curcumin can be respectively chosen as molecule I, II, and

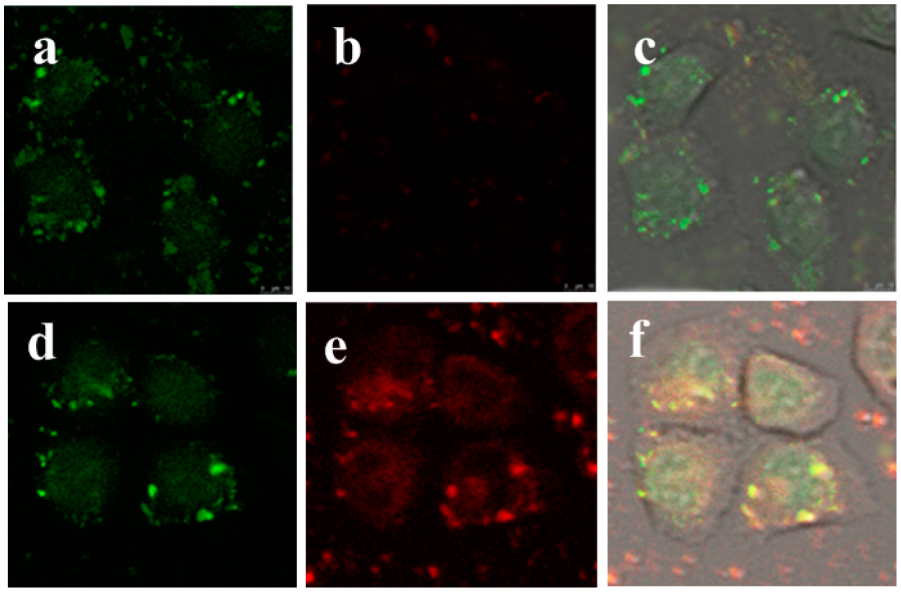


Figure 4. Confocal microscopy images of MCF-7 cells incubated with fluorescein and $[Ru(bipy)_3]Cl_2$ loaded MS-A: CD-Au nanoparticles 20 μg/mL (a–c) before and (d–f) after UV irradiation. (a, d) emissions of fluorescein excited at 488 nm; (b, e)emissions of $[Ru(bipy)_3]Cl_2$ excited at 405 nm; (c, f) overlay images.

III to fulfill the needs of multiple drug therapy, which could improve the effectiveness of cancer treatment. The results make the hybrid nanocontainer reported here a promising candidate in multiresponsive nanogated ensembles. This approach could also provide a general route to graft other supramolecular-modified materials for a wide range of applications.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental section and materials characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by 973 Program (2013CB933800), National Natural Science Foundation of China (21227005, 21390411, 91313302, 21035003, and 21205074) and Program for Changjiang Scholars and Innovative Research Team in University.

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