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Nanovalve-Controlled Cargo Release Activated by Plasmonic Heating

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Supporting Information

ABSTRACT: The synthesis and operation of a light-operated nanovalve that controls the pore openings of mesoporous silica nanoparticles containing gold nanoparticle cores is described. The nanoparticles, consisting of 20 nm gold cores inside ∼150 nm mesoporous silica spheres, were synthesized using a unique one-pot method. The nanovalves consist of cucurbit[6]uril rings encircling stalks that are attached to the ∼2 nm pore openings. Plasmonic heating of the gold core raises the local temperature and decreases the ring−stalk binding constant, thereby unblocking the pore and releasing the cargo molecules that were preloaded inside. Bulk heating of the suspended particles to 60 °C is required to release the cargo, but no bulk temperature change was observed in the plasmonic heating release experiment. High-intensity irradiation caused thermal damage to the silica particles, but low-intensity illumination caused a local temperature increase sufficient to operate the valves without damaging the nanoparticle containers. These light-stimulated, thermally activated, mechanized nanoparticles represent a new system with potential utility for on-command drug release.

Multifunctional drug delivery systems are currently being studied intensively because of their potential to combine multiple essential properties in a single nanovehicle.[1−4] The ability to control the location, time, and amount of drug released are important in nanomedicine.[5,6] In the specific case of photothermal control of the release, multifunctional nanoparticles combining the photothermal heating of metal particles that have plasmonic properties with core or shell nanoparticles that have drug-carrying capability with specific remote-triggered release have been exploited with bare gold nanoparticles,[7,8] core@shell Au@liposome,[9,10] Au@polyelectrolyte multilayers@lipid,[11] polymer@Au,[12] and silica nanorattle@mesoporous silica@Au.[3] None of these systems are robust nanocarriers that prevent premature release because of drug leakage through phospholipid membranes, polymer irregularities, and shell imperfections, respectively. Very recently, gold nanorods were coated with mesoporous silica to enable photothermal release of doxorubicin electrostatically trapped in the pores, but premature leakage from the uncapped pores before irradiation was severe.[13]

Mesoporous silica nanoparticles (MSNs) have been shown to be nontoxic,[14,15] are taken up (endocytosed) by cells,[16−18] and are able to transport various drugs.[19−21] Many gate-keeping mechanisms have been developed and attached to MSN pore openings to trap the drug payload.[4,22] As a result, a remarkable variety of mesoporous silica nanocarriers has been designed with both autonomous activation (pH or redox opening of nanovalves)[23−25] and external (light or magnetic field) control.[26−28] It should be noted that in most of these on-command release systems, precise spatial control cannot be achieved.

In this communication, we report the synthesis and successful operation of nanovalves on MSNs that are remotely controlled by light through a photothermal mechanism involving the plasmonic properties of a gold nanoparticle core. During the course of this study, we discovered a facile one-pot synthesis of gold nanoparticles embedded in the mesoporous silica matrix, Au@MSN, through the autoreduction of tetrachloroaurate ions in the presence of cetyltrimethylammonium bromide (CTAB), which also induces the template-directed assembly. This one-pot synthesis is a faster and greener preparation of such nanovehicles than the multistep methods previously reported.[15,29] Irradiation of nanovalve-mechanized Au@MSNs at wavelengths corresponding to the plasmon resonance of the gold core causes internal heating and subsequent opening of the nanovalves, allowing the contents of the pores to escape. Investigation of the state of the particles after release showed that they remained intact at moderate light intensities but that some degradation occurred at high intensity.

The nearly monodisperse Au@MSN nanoparticles (Figure 1) were obtained through the condensation of tetraethoxysilane on freshly prepared gold nanoparticles (21 ± 4 nm) in a basic water/ethanol mixture. The formation of the gold nanoparticles was surprising because no additional reducing agent was provided. The reduction of the gold precursor was sensitively dependent on the precise experimental conditions [basic pH, order of introduction of the reactants, and temperature; see Table 1 in the Supporting Information (SI)]. Interestingly, the injection of sodium hydroxide was found to be necessary to obtain the gold nanoparticles. Previous studies reported the reduction of tetrachloroaurate ions via quaternary ammonium ions under γ irradiation[30] and the encapsulation of gold nanoparticles via a similar autoreduction in the presence of a cross-linked tertiary amine polymer.[31]

The mechanism of operation of the molecular machine involves temperature-dependent noncovalent interactions between the stalk and the cucurbit[6]uril ring (Figure 2).[28]

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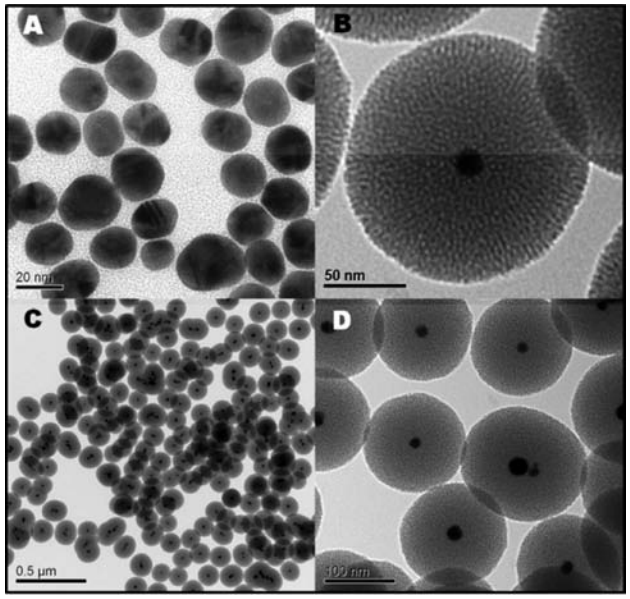

Figure 1. TEM images of (A) gold nanoparticles prepared by the CTAB-mediated autoreduction of tetrachloroaurate ions and (B–D) the final Au@MSN from the one-pot synthesis.

The two ammonium groups of the stalk interact with the carbonyl groups of the cucurbituril via hydrogen bonds, while the alkyl chain of the stalk interacts with the hydrophobic cucurbit[6]uril core through London forces. The stalk–ring binding constant decreases exponentially with increasing temperature, so that at 25 °C the cucurbit[6]uril rings dwell on the stalks but at 60 °C these rings slip off and open the pores (Figure 2A).

The molecular mechanization was performed by condensing *N*-(6-aminohexyl)aminomethyltriethoxysilane stalks on the porous silica surface in dried toluene (see the ^{13}C and ^{29}Si solid-state NMR (ssNMR) spectra in Figure S5 in the SI). The rhodamine B cargo was then loaded by soaking the CTAB-extracted Au@MSN-Stalk nanoparticles in a concentrated aqueous solution. Finally, the pores were closed by complexing cucurbit[6]uril on the stalks (Figure S1). This step was performed by adding cucurbit[6]uril (and NaCl to increase its solubility) to the previous rhodamine loading solution in order to avoid the loss of cargo molecules during the pore-capping process.

The thermal operation of the machine was assessed in a control experiment (without light) by heating the solution. The dye-loaded Au@MSN@Valve nanomachines were placed in the bottom of a glass cuvette filled with water and heated on a hot plate. The release of cargo molecules was monitored by using a probe diode laser (448 nm, 18 mW) to irradiate the upper part of the cuvette and a CCD detector to measure the fluorescence of the dye that escaped from the pores. This experiment showed that a temperature of 60 °C or higher was required to induce the release by disrupting the temperature-dependent supramolecular stalk–ring interactions (Figure 2). At room temperature, the release profile exhibited a flat baseline characteristic of a nonleaky carrier, which validates the usefulness of these nanomachines as a robust drug delivery system without premature leakage of the cargo.

Operation of the system by photoinduced internal heating was studied in a similar manner except that no external heating of the solution occurred. Figure 3A illustrates schematically the

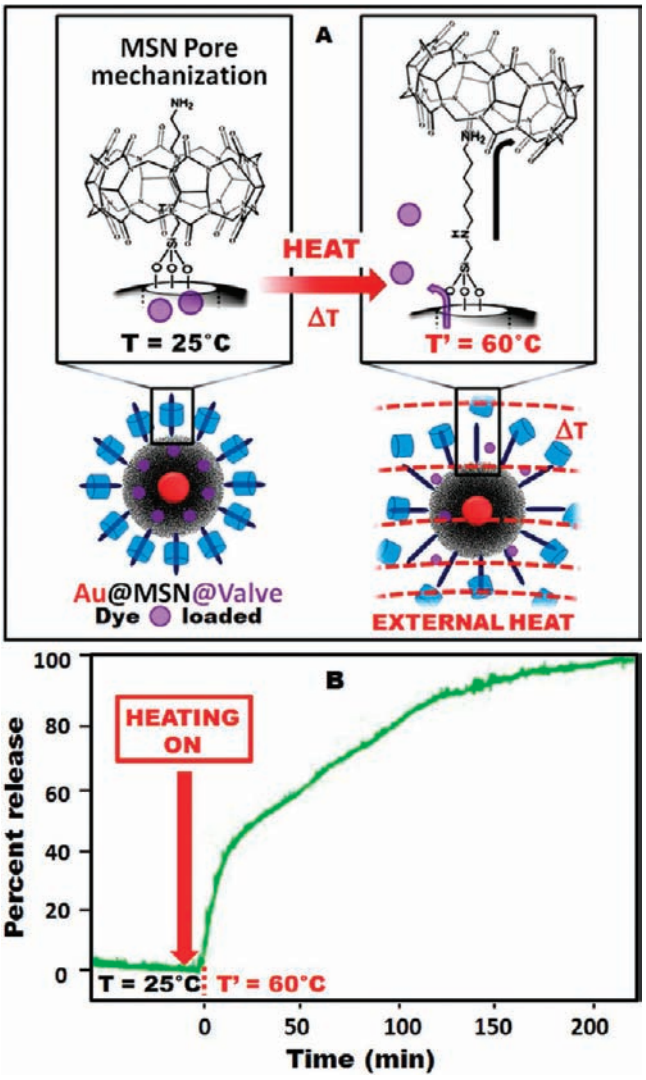

Figure 2. (A) External heating of a suspension of Au@MSN@Valve to 60 °C causes dissociation of the cucurbituril caps from the stalks and release of the cargo molecules from the pores. (B) Release profile caused by bulk thermal activation of the nanomachines.

surface plasmon effect induced by appropriate laser irradiation of the Au@MSN@Valve, which produces a photothermal conversion of the laser energy. The mechanism involves the internal temperature increase inside the particle that is produced by the photothermal effect, which disrupts the stalk–ring interactions and releases the cargo. The dye-loaded particles were placed in a corner of a glass cuvette, as was done in the bulk external heating control experiments, but the sample was irradiated at 514 nm (100 mW) to excite the gold cores at their plasmon band maximum at 530 nm (measured by the extinction spectrum shown in Figure S3C). The release of cargo molecules was monitored by using a probe diode laser (448 nm, 18 mW) to irradiate the upper part of the cuvette and a CCD detector to measure the fluorescence emission of the dye. The release profile (Figure 3B) displays the laser-triggered instantaneous release of rhodamine B, thus demonstrating the control of a temporal remote-photothermal release of cargo molecules encapsulated in Au@MSN nanocarriers.

To verify that the local temperature increase in the nanoparticles (rather than an increase of the temperature of the bulk solvent) was responsible for the cargo release, the

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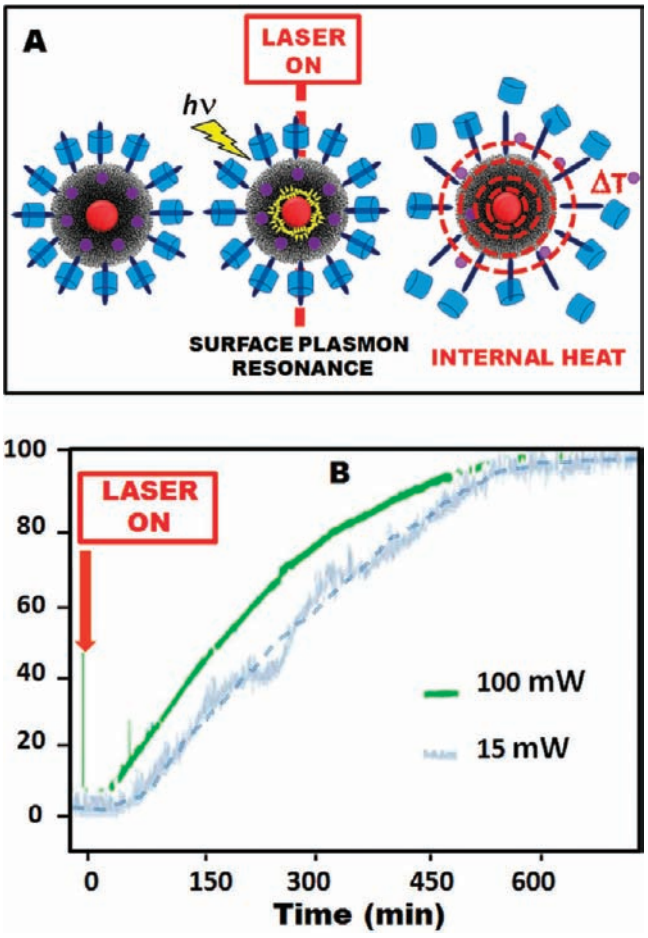

Figure 3. Photothermal-induced internal heating of Au@MSN@Valve through the surface plasmon effect of the gold cores releases dye molecules under power-dependent laser actuation. The release profiles were normalized to the plateaus representing the maximum amount of released dye. The maximum (2.5 wt %) varied according to the geometry of the experiments and the laser power. The rate of release increased with laser power.

solvent temperature was monitored during the photothermal-induced release experiment. The solution temperature remained unchanged within experimental error during experimental runs as long as 10 h. These results show that the heat necessary for uncapping the pore and releasing the cargo was provided by the very localized heating of the nanoparticles by photothermal conversion of the laser electromagnetic energy. Local temperatures in the vicinity of the stalk and cap had to reach at least 60 °C. Such a local temperature increase should be very useful in applying these nanomachines for spatially controlled dual therapy involving delivery of the cargo to cells and necrosis through hyperthermia. This dual use of plasmonic heating distinguishes this light-sensitive nanomachine from others based on chromophores alone and may be advantageous for increasing the killing efficiency.[32,26,27]

An alternative mechanism for releasing the cargo could be thermal damage to the silica shell itself. The nanocarriers were analyzed after photoirradiation and cargo release by transmission electron microscopy (TEM) (Figure 4). Under the highest irradiation intensity (100 mW), some of the particles were severely degraded. Thus, some of the cargo release could have been produced by cracking the silica rather than by opening of the nanovalves. As a control, bare MSN nanoparticles (no gold core) were irradiated at 514 nm (100 mW for 14 h), and no silica damage was observed, confirming that only the nanoparticles with embedded gold were light-sensitive (Figure S4). Notably, the addition of NaOH aliquots at the end of this laser irradiation both confirmed that the nanoparticles were loaded and capped with Stalk−CB[6] nanomachines. Release experiments were carried out at lower power (15 mW) with equal irradiation times, and the release profiles were characterized similarly (Figure 3B). The release was slower at lower power, as expected, but the particles were undamaged (Figure 4B). Thus, it is clear that plasmonic heating at high light intensities produces enough heat or a rapid enough temperature change to degrade the silica, while lower powers do not damage the silica but do cause enough of a local temperature change to open the valves and release the contents.

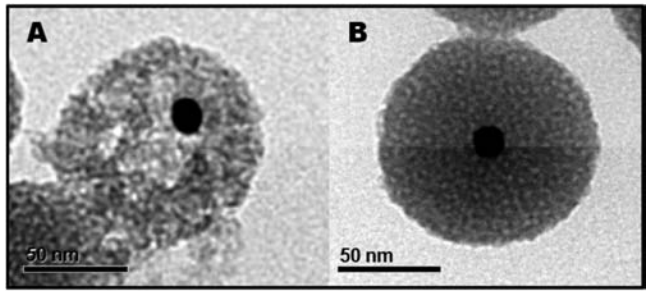

Figure 4. TEM images of nanoparticles irradiated at (A) 100 and (B) 15 mW.

In summary, we have demonstrated that novel gold-core mesoporous silica nanoparticles are effective in actuating a thermosensitive nanovalve under exposure to laser irradiation. The release mechanism was demonstrated to be caused by local internal heat produced via photothermal conversion of the light energy rather than by a bulk temperature increase. A novel one-pot synthesis of the Au@MSN nanoparticles was presented. The mechanized Au@MSN nanoparticles enabled remotely controlled triggered release of the cargo molecules "on command" via a robust matrix without premature leaking. This novel nanocarrier fulfills the strict criterion of controlled release of cargo molecules at a desired time in a specified spatial location that is a significant advancement for nanomedicine. It is envisioned that Au@MSN nanomachines could efficiently kill cancer cells through hyperthermia as well as synergistically enhance the cytotoxicity of drugs such as docetaxel.[33]

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental details, UV−vis spectra of Au@MSN compounds, ^{13}C and ^{29}Si ssNMR spectra of Au@MSN-Stalk compounds, TEM images of MSN irradiated under 200 mW, and the MSN@Valve control laser experiment. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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