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Near-infrared light-responsive supramolecular nanovalve based on mesoporous silica-coated gold nanorods†

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We constructed a novel cancer theranostic hybrid platform, based on mesoporous silica-coated gold nanorods (AuNR@MSN) gated by sulfonatocalix[4]arene (SC[4]A) switches, for bio-friendly near-infrared (NIR) light-triggered cargo release in a remote and stepwise fashion. The advantages of supramolecular switches, mesoporous silicas, and AuNRs were combined in one drug delivery system. Mesoporous silicas coated on AuNRs guarantee a high drug payload and can be easily post-functionalized. Significantly, the plasmonic heating from the NIR light-stimulated AuNR cores can decrease the ring-stalk binding affinity, leading to the dissociation of SC[4]A rings from the stalks, thus opening the nanovalves and releasing the cargos. The NIR light-responsive mechanized AuNR@MSN offers exciting prospects for non-invasive controlled drug delivery, being more effective and safer than other techniques.

Introduction

The past few years have witnessed the revolutionary impact of nanotechnology on modern (nano)medicine, ranging from more reliable diagnostic techniques to enhanced therapeutic efficacy.[1–3] In particular, as an important beneficiary of nanotechnology, smart and multifunctional drug delivery systems have made great developments in terms of their targeting, low toxicity, excellent intracellular biostability and biocompatibility, and multidrug delivery and theranostics.[4–7] Mesoporous silica nanoparticles (MSNs) that are functionalized with molecular and supramolecular nanovalves to yield mechanized MSNs have attracted substantial attention. They can effectively solve the problem of premature leakage by using elegant designs of nanovalves.[8–11] Meanwhile, a variety of stimuli have been applied to activate the nanovalves, thereby realizing controlled cargo/drug release, including redox-activation,[12–15] pH,[11,16–19] light,[20–24] competitive binding,[9,11] enzymes,[25,26] an oscillating magnetic field,[27] and so on.

However, the most desirable course is to explore benign activation mechanisms that can be applied to biological systems or to make the best of the natural biochemistry inside cells. For example, glutathione from the cell cytosol can be used as a chemical reductant to activate the release of cargos from disulfide-containing [2]rotaxanes-functionalized MSNs by the reductive cleavage of the disulfide bonds.[12] pH-Responsive MSN-based nanovalves have also been designed where biologically relevant pH changes are employed to trigger the release of cargo molecules.[16] Our research group recently reported arene-based biocompatible supramolecular nanovalves that can be specifically triggered by enzymes[26] or neurotransmitters.[9] Among various kinds of stimuli, light activation is a more promising approach owing to its advantages of remote control and reduced invasiveness. Specifically, compared to ultraviolet-visible (UV-vis) light-stimulated mechanized MSNs,[20–24] a near-infrared (NIR) light stimulus enables deeper penetration and less risk of damage to body tissues.[28–32] So far, NIR light-responsive supramolecular nanovalves based on MSNs have not yet been reported.

Herein, we designed and synthesized a biocompatible NIR light-responsive nanovalve system on the surface of a mesoporous silica-coated gold nanorod (AuNR@MSN) using sulfonatocalix[4]arene (SC[4]A) supramolecular switches (Fig. 1). The plasmon wavelength of the longitudinal mode of gold nanorods (AuNRs) can be made to cover the NIR regions by tailoring their aspect ratios.[33] Thus, AuNRs can absorb NIR light and convert it into heat to realize the plasmonic photothermal conversion.[33–35] In the mechanized drug delivery hybrid platform, the negatively charged SC[4]A rings encircle the quaternary ammonium salt (QAS) stalks on the surfaces of AuNR@MSN *via* host–guest

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† Electronic supplementary information (ESI) available: Experimental details, FTIR spectra, SEM and TEM images, the characterization and controlled release experiments, the experimental setup of the NIR laser, ITC. See DOI: 10.1039/c4sc00198b

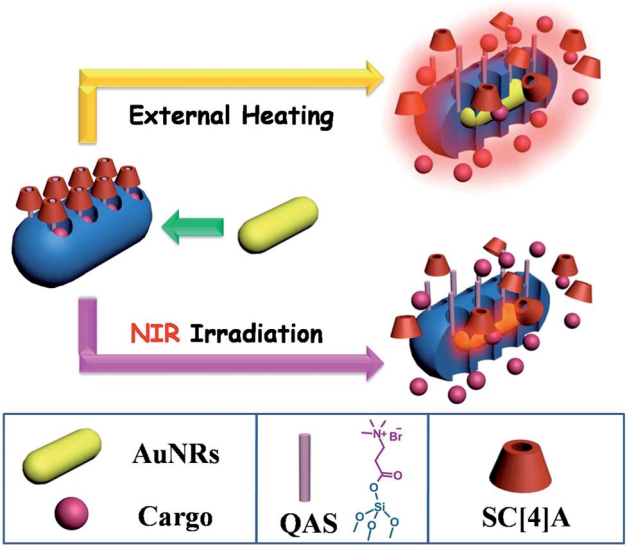

Fig. 1 Schematic representation of SC[4]A-QAS nanovalves based on AuNR@MSN. The nanovalves can be operated by either NIR light irradiation or external heating to regulate the release of a model drug, *i.e.*, rhodamine B (RhB).

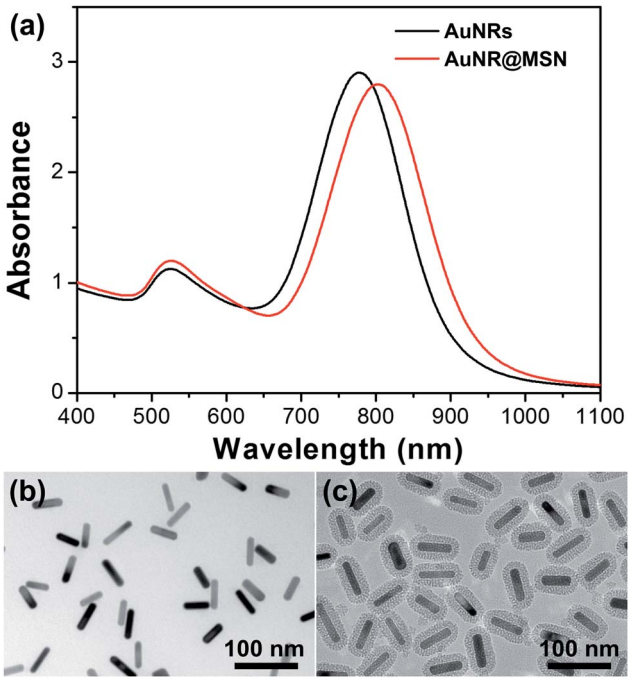

Fig. 2 (a) Ultraviolet-visible (UV-vis) spectra of AuNRs and AuNR@MSN. Transmission electron microscopy (TEM) images of (b) AuNRs and (c) AuNR@MSN.

complexation.[36–38] Upon NIR light irradiation, hyperthermia from AuNRs can efficiently kill cancer cells.[33–35] Meanwhile, the plasmonic heating from the AuNR cores can decrease the ring-stalk binding affinity,[39] leading to the dissociation of SC[4]A rings from the stalks, thus opening the nanovalves and releasing the cargos. A pulsed controlled-release based on NIR light was also successfully achieved.

Results and discussion

AuNR@MSN nanoparticles were prepared according to the literature reports with some modifications (see ESI†).[32,40] In the silica-coating process, cetyltrimethylammonium bromide (CTAB) on the surface of AuNRs as a stabilizing agent can serve as the organic template for the formation of the silica layer *via* base-catalyzed hydrolysis of tetraethylorthosilicate (TEOS). Empty pores were obtained by the removal of the CTAB template with acidified MeOH. From the Fourier transform infrared (FTIR) spectra, the presence of Si–O–Si peaks (~1090 and ~802 cm^{-1}) and –OH (~3415 cm^{-1}) indicated the formation of the silica layer with hydroxyl on the surfaces of AuNRs (Fig. S13b†), and the loss of the C–H peak at ~2900 cm^{-1} compared to the absorption bands of CTAB-stabilized AuNRs indicated the removal of the CTAB template (Fig. S13a and b†).[22] The UV-vis spectra show the characteristic longitudinal absorbance peak of AuNRs at ~780 nm (Fig. 2a). After silica shell coating, the absorbance peak underwent a red shift to ~800 nm (Fig. 2a) due to the refractive index changes around the AuNRs.[41] The corresponding transmission electron microscopy (TEM) image (Fig. 2b) of the AuNRs shows the average length and width of AuNRs to be 46.5 ± 4.1 nm and 12.9 ± 0.9 nm, respectively (about a 3.6 : 1 aspect ratio). Nearly monodisperse and uniform mesoporous AuNR@MSN nanoparticles with a AuNR core coated by a silica layer of 13.6 ± 0.9 nm in thickness (Fig. 2c, S15 and S16†) were successfully synthesized. They can be used as drug carriers and further incorporated with supramolecular switches to construct supramolecular nanovalves.

The fabrication of the mechanized AuNR@MSNs (Fig. 1) is summarized in the ESI.† First, the QAS stalks were tethered to the surfaces of AuNR@MSNs, and then luminescent rhodamine B (RhB, 0.5 mM) as a model drug was loaded in their mesopores at room temperature for 6 h. Finally, a sufficient amount of SC[4]A was introduced to encircle the stalks on the surface of AuNR@MSN *via* host–guest complexation to form supramolecular switches, thereby realizing the drug encapsulation. The successful surface functionalization of AuNR@MSN was confirmed by FTIR spectroscopy. The C=O stretching band at ~1726 cm^{-1} and the reappearance of the C–H peak at ~2900 cm^{-1} (Fig. S13c†) indicated the successful surface-modification of AuNR@MSN with QAS. After loading and capping, the peak moved from 1600 cm^{-1} to 1450 cm^{-1} (Fig. S13d†), representing the characteristic absorption of aromatic rings of SC[4]As. A series of control experiments have also been done to prove the functionalization of SC[4]A supramolecular switches on AuNR@MSN surfaces by comparing the difference of the release performance of materials with and without the attachment of SC[4]As (Fig. S3 and S5–8†). The availability of nanovalves and the release capacity of RhB-loaded, SC[4]A-capped AuNR@MSNs were evaluated by competitive binding-triggered release and UV-vis spectroscopy was employed to monitor the cargo release. Excess ethanediamine was added to induce sufficient release of RhB.[9,26,42] As shown in Fig. 3a, an immediate release of cargo molecules was

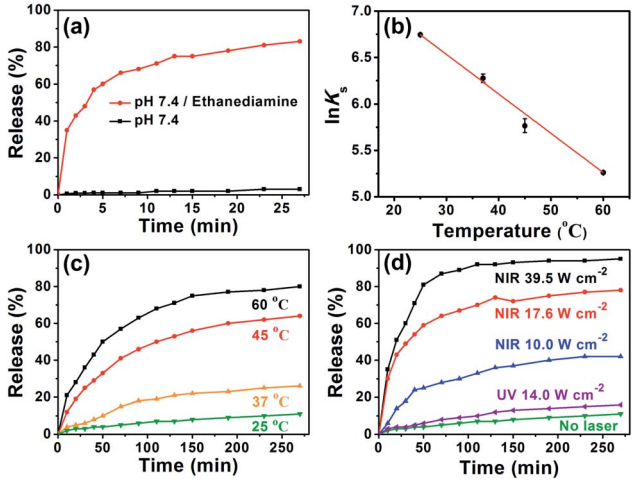

Fig. 3 Release profiles of the RhB-loaded, SC[4]A-capped AuNR@MSNs caused by (a) competitive binding, *i.e.*, ethanediamine, (c) varying temperatures (25, 37, 45 and 60 °C, respectively), (d) an 808 nm-NIR laser with different power densities (10, 17.6 and 39.5 W cm^{-2}, respectively), a 355 nm-UV laser (14 W cm^{-2}) and no laser light irradiation. (b) The changes in SC[4]A-QAS association constants (ln K_S) as a function of temperature that are obtained by isothermal titration calorimetry (ITC). All the above experiments were performed in sodium phosphate buffer solution (PBS buffer, pH = 7.4).

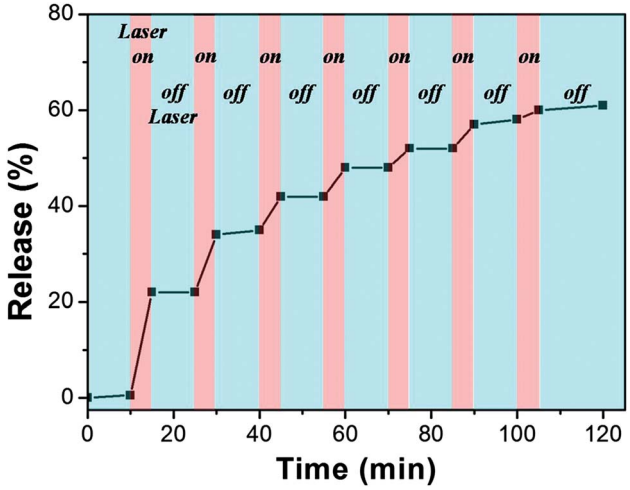

Fig. 4 "Ladder" pulsatile release profile of RhB from nanovalves in PBS buffer (pH = 7.4) with periodic NIR laser ON/OFF irradiation (808 nm laser with a power density of 17.6 W cm^{-2}).

observed as a result of ethanediamine-induced opening of nanovalves. Using Beer's Law, it can be calculated that for 1 mg of nanoparticles, 0.04 μmol of RhB molecules can be released (Fig. S3a†).

To better understand that NIR light causes the internal heating of AuNRs cores leading to subsequent opening of the nanovalves, the inherently thermal response of the SC[4]A-QAS inclusion complex-based nanovalves was tested first. With increasing temperature, the supramolecular interactions between the SC[4]A rings and the QAS stalks are weakened, as confirmed by isothermal titration calorimetry (ITC) (Fig. S19–26 and Table S1†). ITC allows for the accurate determination of complex stability constants (K_S) and also provides thermodynamic parameters for complexation. Calorimetric titration of SC[4]A sodium salts (2 mM) with QAS (40 mM) was conducted at different temperatures in sodium phosphate buffer solutions (PBS buffer, pH = 7.4) to avoid the influence of different cations for K_S.[36] Elevated temperature caused a significant decrease in binding. All the data are listed in Table S1† and Fig. 3b. The observed decrease in binding stabilities was largely due to the increased $-T\Delta S^o$ (more positive) with elevated temperatures, which agrees with other host–guest systems.[43,44] The external heating-triggered *in vitro* cargo release of RhB-loaded, SC[4]A-capped AuNR@MSNs was studied at varying temperatures. The sample (1 mg) was placed in the corner of a cuvette filled with PBS buffer (pH = 7.4, 3 mL) and heated in a water bath (at 20, 37, 45, and 60 °C). The amount of cargo release gradually increased with rising temperature, which resulted in lower K_S, which is in good agreement with the ITC data (Fig. 3c).

Finally, we investigated the NIR-induced controlled release properties of RhB-loaded, SC[4]A-capped AuNR@MSNs. The experimental setup (Fig. S10–12†) of the 808 nm-NIR laser and controlled-release experiments is shown in detail in the ESI.† An 808 nm-NIR laser with different power densities (10.0, 17.6, 39.5 W cm^{-1}) was employed as a stimulus, and RhB was used as a probe molecule. Cargo release experiments were performed in PBS buffer (pH = 7.4, 3 mL) and the release process was monitored by UV-vis absorption spectroscopy. As shown in Fig. 3d, the adjustment of laser irradiation power and time is the key to delicately activate the release of the model drug from AuNR@MSNs. The amount of RhB released can reach 95 wt% in 2.5 h under 808 nm laser light irradiation of 39.5 W cm^{-2}, while less than 10 wt% of RhB was released in 4.5 h in a control experiment without NIR light irradiation. And, as another control, a 355 nm-UV laser that mismatches with the surface plasmon resonance (SPR) peak of AuNRs cannot induce the release of the model drug either (Fig. 3d). In order to prove that the opening of nanovalves occurs because of the plasmonic photothermal effect of gold cores rather than the heating effect of the light itself, traditional mechanized MSNs without gold cores (Fig. S6, S8, S14, S17 and S18†), that can respond to external heating due to the weakened host–guest complexation at higher temperatures, were stimulated with an 808 nm laser (17.6 W cm^{-2}) under the same experimental conditions (Fig. S9†). Only a negligible amount of the model drug was released due to the heating effect of the light itself. Another important feature (advantage) of photoswitching is that "ladder" triggered-release can be realized by using periodic NIR laser ON/OFF irradiation (Fig. 4). This "initial-burst-then-sustained-release" manner of controlled drug release is very powerful in controlling the drug dose, minimizing the drug side effects, prolonging the drug action period, and reducing the administration frequency, which meets urgent needs in current therapeutics.

Conclusions

In conclusion, we designed and synthesized a novel NIR light-responsive hybrid platform using SC[4]A-based supramolecular

switches on the surface of AuNR@MSN that is able to trap cargo molecules and then release them upon exposure to NIR light. Each component in our system is biocompatible,[8,29,34,45] and NIR light is more bio-friendly due to its reduced damage to biological specimens and deeper tissue penetration for disease therapy.[28] The plasmonic photothermal conversion of AuNRs is a key feature which causes the internal heating, leading to the disassociation of SC[4]A rings from the QAS stalks. A series of control experiments were conducted to check the accessibility of the gold core and NIR light. Neither NIR light-stimulated traditional mechanized MSNs (no gold cores) nor AuNR@MSNs exposed to UV light could give an efficient release of cargo molecules. Both remote continuous release and "ladder" pulsatile release upon NIR exposure were successfully demonstrated. We envision that this new hybrid nanomaterial, which combines physical and chemical treatment in one pot, will prove to be a novel drug delivery system for cancer therapy in the near future.

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