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Microfluidic fabrication of photo-responsive hydrogel capsules† ‡

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We report thermo- and photo-responsive hydrogel capsules, providing controlled encapsulation and triggered release of water-soluble encapsulants. Monodisperse O/W/O (oil-in-water-in-oil) double-emulsion drops are produced in a capillary microfluidic device as templates, which transform into hydrogel capsules upon polymerization of thermo-sensitive monomers in the water phase containing gold nanorods. Controlled encapsulation and stimuli-triggered release of materials have important applications in various biological delivery systems for drugs, nutrients and cosmetics,† for example, using microcapsules which provide such properties, we can release cytotoxic drugs in local target areas without circulation of the drug in the body, thereby reducing damages or side effects. Although various conventional approaches have been studied and developed to create such capsules, resultant capsules lack controllability of size and properties and efficiency of encapsulation. Microfluidic emulsification techniques have overcome such shortcomings and provided facile double-emulsion templates to produce microcapsules,‡ which are very useful due to their core-shell geometry.‡ For example, polymeric microcapsules containing metal nanoparticles in their membrane can be prepared from double-emulsion drops, which exhibit rupture of membranes under laser irradiation;‡ however, their rupturing process is irreversible, making them non-reusable. Furthermore, active ingredients should be encapsulated during capsule formation; this makes post-encapsulation impossible, thereby limiting their long-term applications. Reversible microcapsules, consisting of a thermo-insensitive hydrogel core and a thermo-sensitive hydrogel shell, are prepared in two separate steps.‡ However, the step-by-step fabrication approach suffers from complex procedures and global temperature change is required to trigger a release, which can damage delicate biological systems. Therefore, production of uniform microcapsules which enable reversible control of permeability through facile external stimuli remains an important challenge.

In this communication, we report a microfluidic approach to create thermo- and photo-responsive hydrogel microcapsules, providing reversible loading of materials and their release. As templates of the microcapsules, we produce O/W/O double-emulsion drops whose middle phase contains a thermo-sensitive monomer and gold nanorods. The monomer in the middle layer is polymerized upon injection of a reaction accelerator into the device, leading to formation of gel networks immobilizing the gold nanorods. The resultant hydrogel capsules, whose core and continuous phase are replaced with water, exhibit reversible temperature-dependence of their size and membrane permeability. Moreover, the photothermal effect of the gold nanorods enables the local heating of the capsule membrane through irradiation of an infrared (IR) laser, thereby providing the remote control of the capsule size and membrane permeability.

To produce hydrogel microcapsules, we use a capillary microfluidic device consisting of two junctions; one is for generation of O/W/O double-emulsion drops and the other for injection of the reaction accelerator, as shown in Fig. 1a. We coaxially assemble two tapered cylindrical capillaries in a square capillary for the first junction; one left capillary is treated as hydrophobic and used for injection of the innermost oil phase, whereas the other capillary is treated as hydrophobic and used for collection of double-emulsion drops. To inject the reaction accelerator, the untapered side of the collection capillary is inserted into a second square capillary for the second junction. We use polydimethylsiloxane (PDMS) oil with kinematic viscosity of 50 cSt as an innermost oil phase and inject this through the injection capillary. As a middle phase, we use an aqueous mixture of 11.3 wt% thermo-sensitive monomer of N-isopropylacrylamide (NIPAm), 1 wt% cross-linker of NN′-methylenbisacrylamide (BIS), 0.6 wt% initiator of ammonium persulfate (APS), 0.1 wt% gold nanorods with a length of 35 nm and a width of 9 nm on average, and surfactants 0.2 wt% poly(ethylene glycol)-poly(propylene glycol)-poly(ethylene glycol) triblock copolymers (Pluronic F108, Mw 14 600) and 2 wt% poly(vinyl alcohol) (PVA, Mw 13 000–23 000). We inject this mixture through interstices between the injection and first square capillaries. We use PDMS oil containing the surfactant 2 wt% DC749 fluid (Dow Corning) as a continuous oil phase and inject this through the interstices between the collection and first square capillaries. Mono-disperse O/W/O double-emulsion drops are prepared in a mode of...
innermost-drop-triggered breakup as shown in Fig. 1b and movie S1 of the ESL. To accelerate the polymerization of NIPAAm monomers, we inject the continuous phase containing 8 wt% $N,N',N''$-tetramethyl-ethylenediamine (TEMED) through the interstices between the collection and second square capillaries; this separate injection of the reaction accelerator facilitates the stable formation of the double-emulsion drops and their polymerization, while avoiding clogging of the first junction. The double-emulsion drops are incubated in a glass vial for 12 hours at room temperature to complete the polymerization, as shown in Fig. 1c and then washed with isopropanol and finally transferred into water as shown in Fig. 1d; the core and the continuous phase are both replaced with water, resulting in highly transparent capsules. Although the hydrogel can also be prepared by photo-polymerization, fast reaction frequently induces heterogeneous morphology, and oxygen from the oil phase inhibits the photo-polymerization.

We evaluate temperature-dependence of the microcapsules composed of a water core and a pNIPAAm shell by observing them during incubation at temperatures of 27–43 °C, as shown in Fig. 2a and Fig. S2 of the ESL; because pNIPAAm has the lower critical solution temperature (LCST), capsules deswell as the temperature increases. Temperature-dependence of diameters of the core and the shell of the capsule is shown in Fig. 2b, where the diameters are measured after incubation for 5 minutes at constant temperature during step-by-step increase (filled squares and circles) or decrease (open squares and circles) in the temperature; insignificant hysteresis is observed. Both the core and the shell shrink as the temperature increases; this is different behaviour from microcapsules with a thermo-insensitive hydrogel core and a thermo-sensitive hydrogel shell, which maintain a constant core size. Dramatic changes occur at 37.5 °C which is different from the LCST of pNIPAAm, 32 °C; we attribute this increase in the LCST to trapping of surfactant molecules, Pluronic F108 and PVA, in the pNIPAAm network during polymerization, which increases hydrophobicity of the complex.

Time-dependence of the diameter upon increasing the temperature is shown in Fig. 2c, where the temperature is set to 43.2 °C at $t = 0$ from 34.3 °C; both diameters decrease for 80 seconds. Slow deswelling of the shell induces isotropic shrinkage of the hydrogel matrix, following equilibrium states; therefore, the overall size of capsules decreases.

By contrast, when the capsules are subjected to a sudden increase in temperature by adding 5 ml of water at 70 °C to 1 ml of water containing the capsules at 27 °C, the core diameter increases, while the shell diameter decreases in 2 seconds, as shown in Fig. S3 of the ESL. Fast collapse of the shell induces anisotropic shrinkage in the radial direction with insignificant lateral shrinkage, maintaining the overall capsule size with reduced shell thickness.

When the pNIPAAm hydrogel network collapses, the size of pores in the network dramatically decreases, preventing penetration of molecules through the gel. Therefore, pNIPAAm capsules can encapsulate and release water-soluble materials which are smaller than pores in the swollen network, but larger than pores in the deswollen network. We demonstrate this using fluorescein isothiocyanate (FITC)-tagged dextran molecules (Sigma-Aldrich, $M_w$ 4000). To do this, the capsules are dispersed in water containing $10^{-4}$ M FITC-dextran at 27 °C and the temperature is increased to 44.3 °C; the dextran molecules quickly diffuse through the swollen shell at 27 °C and they are trapped in the core and the shell, upon collapse of the capsules. After washing the capsules with distilled water at 45 °C several times, they are cooled to room temperature; the collapsed capsules retain the dextran molecules at $t = 0$ and then the capsules release the dextran to the continuous phase as they swell, as shown in Fig. 2d. Time-dependence of the size and fluorescence intensity in the core is shown in Fig. 2e; the capsules swell during natural cooling.
of 300 seconds. We attribute the initial increase in the fluorescence intensity in the core to migration of the dextran molecules, which are trapped in the shell during deswelling, to the core due to water flux from the continuous phase during initial expansion of the capsule; we can confirm this by the coincidence of the sudden increases in the intensity and diameters in 75 seconds as shown in Fig. 2c. By contrast, capsules incubated at a constant temperature of 44.3 °C show an insignificant decrease in the fluorescence intensity, indicating negligible leakage without temperature trigger.

The photothermal effect of gold nanorods, immobilized in the shell, enables the remote heating of the capsules by light illumination;12 gold nanorods are generally accepted as nontoxic materials. Therefore, we can externally control the deswelling and permeability of the shell, as shown schematically in Fig. 3a; this provides the novelty of our capsules compared to the previously reported thermosensitive microcapsules.9 The gold nanorods with a length of 35 nm and a width of 9 nm on average exhibit absorption peaks at 510 nm and 810 nm, as shown in Fig. S1b (ESI†). We select an IR laser with a wavelength of 810 nm to heat the capsules owing to its longer penetration depth than visible light, and illuminate the capsules in water at 25 °C with the laser. Upon the laser illumination, the capsules are deswollen due to a local temperature increase by the gold nanorods. The rate of shrinkage depends on the intensity of the laser as shown in Fig. 3b; the lasers with 50, 100, and 170 mW cm⁻² lead to complete deswelling in 240, 85, and 40 seconds, respectively, whereas the laser with 30 mW cm⁻² is incapable of inducing deswelling. The deswelling process of the capsule with illumination of the laser of 50 mW cm⁻² is shown in a series of optical microscope images in Fig. 3c, taken at 40 second intervals, and the same with 100 mW cm⁻² is shown in Fig. 3d, taken at 10 second intervals. Because the temperature locally increased by the gold nanorods, the capsules are quickly cooled to 25 °C when the laser is off; this fast cooling induces anisotropic and fast swelling, leading to deformation of the shell in the meantime, as shown in Fig. 3e, taken at 20 seconds interval. The deswelling and swelling behavior induced by laser illumination is shown in movie S2 (ESI†).

In this communication, we created the thermo- and photo-responsive hydrogel capsules using templates, O/W/O double-emulsion drops. Capillary microfluidic devices with two separate junctions facilitate the production of the double emulsion and the polymerization of the middle phase without clogging problem. The resultant capsules, consisting of a water core and a thermo-sensitive hydrogel shell, exhibit reversible temperature-dependence of their size and permeability of the shell. Moreover, gold nanorods immobilized in the hydrogel network enable the localized heating of the capsules by light illumination, potentially providing the remote control of permeability of the shell and the triggered release of encapsulants. The high controllability of this microfluidic approach of size and properties of the capsules as well as its reversible control of permeability will provide new opportunities for practical delivery systems that require local release of active ingredients such as drugs, nutrients, and cosmetics; although the large size of the current microcapsules limits circulation in the body, nanocapsules with the same structure and materials can potentially be prepared by nano-fluidics technology, providing active targeting. In addition, this approach can potentially be used to produce the hydrogel capsules with the upper critical solution temperature (UCST), which triggers the release upon heating, by contrast to the capsules with LCST; for example, poly(sulfobetaine methacrylate) with an UCST of 27 °C can be used for the capsule membrane.16

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Notes and references