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Water-actuated microcapsules fabricated by microfluidics†

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We found a new water-actuated feature of poly(*N*-isopropylacrylamide) microgels and fabricated microcapsules with this feature based on microfluidic double emulsions. The microcapsules would release encapsulated actives by simple hydration, while forming biphasic hybrid microparticles by gradual dehydration. More complex microcapsules and hybrid microparticles could be produced by varying flow rates and inner oil types. These novel microcapsules could potentially be used for controllable storage or release of chemicals, fabrication of complex microparticles and applications in biochemical fields.

Poly(*N*-isopropylacrylamide) (PNIPAM) microgels are representative intelligent microparticles in response to temperature changes, which swell in water below their lower critical solution temperature (LCST), but shrink dramatically above LCST.[1–3] Due to this unique temperature-actuated feature, microparticles made of PNIPAM have been considered as vigorous candidates for controllable macromolecules release, microsensing and photonic devices.[3,4] However, most reports regarding PNIPAM microparticles have to employ external thermostats to control the surrounding temperature.[3–9] In addition, for the reported PNIPAM microparticles with encapsulated actives (also called "microcapsules"[10,11]), it is difficult for them to release the actives completely when increasing temperature, and this is mainly due to the denser hydrogel shells and hydrophobic interactions, thus, preventing the encapsulated actives from being released[12,13] (see ESI S1†). Herein, we firstly report a new water-actuated feature of the PNIPAM microgels, and apply this feature in the fabrication of novel microcapsules based on microfluidic double emulsion technology. The synthesized microcapsules could release their encapsulated actives simply by hydration process without temperature stimulus. In addition, the PNIPAM microcapsules could also be transformed to biphasic hybrid microparticles (analogous to "Janus" particles[14,15]) by gradual dehydration. Moreover, by varying flow rates of the fluids and types of the inner oils during the synthesizing process, the microcapsules could encapsulate different inner oil actives and would form diverse hybrid microparticles. These new kinds of microcapsules expand the PNIPAM application and will be of great potential for storage and pulsed release of drugs, development of microsensing and fabrication of complex microparticles.

To generate monodisperse PNIPAM microcapsules, we constructed a PDMS microfluidic device consisting of T-junction and flow-focusing geometries, which enabled the generation of pre-gel droplets as templates. The device consisted of a PDMS slab with microchannels and a glass substrate coated by a thinner layer of PDMS membrane, both of them were assembled by plasma treatment. The schematic of the whole device was shown in Fig. 1A. Three immiscible phases: Fluorous oil (FC-40), NIPAM aqueous solution (20%, wt %, with 1% N,N′-methylenebisacrylamide as cross-linker) and mineral oil were used as outer continuous phase, middle hydrogel shell phase and inner oil core phase to generate double emulsions. After spherical double emulsion droplets were formed, UV light was employed to solidify the hydrogel shell to form microcapsules with inner oil actives. When the fabricated microcapsules were added into

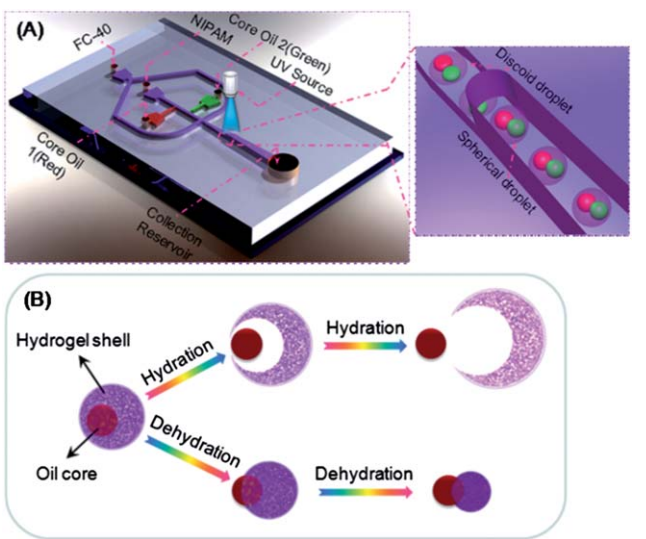

Fig. 1 (A) Schematics of the microfluidic device used to form double emulsion templates and fabricate PNIPAM microcapsules. The inset denotes the expanded microchannel where discoid double emulsions come into spherical droplets and then are solidified by UV irradiation to form microcapsules. (B) Sketches of the new water-actuated feature of PNIPAM microcapsule, illustrating the release of the inner oil active by hydration and formation of biphasic hybrid microparticle by dehydration.

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water, they would release the inner active quickly by hydration process, meanwhile, the microcapsules would form biphasic hybrid microparticles if they were dehydrated gradually. The mechanism behind this process is sketched in Fig. 1B. During the hydration process, the PNIPAM shell would absorb water molecules and became soluble when added into water, leading to the swelling of PNIPAM chains.[1,3,16,17] As more and more water was absorbed, a hole around the inner oil active would be generated and become larger and larger, and eventually, the PNIPAM shell would be broken and the inner oil would be released into water surrounding with floatage. On the other hand, if the synthesized microcapsules were exposed in the atmosphere, the water molecules in the hydrogel networks would evaporate naturally, resulting in continuous shrinking of the microcapsules with the loss of water. The inner active would be gradually squeezed out by interaction forces between the hydrophobic groups of mineral oil (hydrocarbon chain) and hydrophilic groups of PNIPAM chains, forming biphasic hybrid microparticles, which is also sketched in Fig. 1B. (See also ESI S2†).

In order to release the inner actives by hydration and produce biphasic hybrid microparticles by dehydration, it is considered important to firstly synthesize asymmetrical microcapsules with a thinner side of the hydrogel shells. As the fluid parameters such as viscosities and densities of the aqueous solution and the mineral oil were quite different, it was hard to keep the mineral oil core staying in the exact centre of the NIPAM shell droplet after the formation of double emulsion. Conversely, the oil core would stay aside during the movement, resulting in a thinner adjacent side of the PNIPAM microcapsule after UV solidification, and thus, forming the necessarily asymmetrical geometry. Fig. 2A showed that once the asymmetrical microcapsule contacted with water, the thinner side of the microcapsule was broken and the oil actives would be released immediately. Meanwhile, Fig. 2B showed the formation of biphasic hybrid microparticle by dehydration in the atmosphere. The PNIPAM microcapsule shrunk continuously with evaporation of the water molecules in the hydrogel shell, and the oil active was then gradually squeezed out from the thinner side of the shell and adhered to it, but not released, forming biphasic hybrid microparticle with one hydrogel face and the other oil face. It is noteworthy that a thin layer of FC-40 existed between microcapsules and flat substrate during the formation of hybrid microparticles, avoiding collapses of the oil actives when they were squeezed out.

To fabricate complex microcapsules and hybrid microparticles, flow rates of the three immiscible fluids were adjusted. The microcapsules with multiple inner actives could be generated from double emulsions with multiple oil cores by tuning the flow rates. Similar to single-active microcapsules, when contacted with water, the oil actives in the microcapsule would also be released quickly by hydration of the PNIPAM hydrogel, with multiple holes left on the surface of the hydrogel shell. Fig. 3A showed microcapsules with two or three encapsulated oil actives and the corresponding hydration results. The hydrated hydrogel shell presented non-spherical shape, thus, by varying the number and size of the oil cores during the formation of double emulsions, the microcapsules can be transformed to various kinds of non-spherical microparticles[18,19] easily and controllably. On the other hand, by dehydration, the double- or triple-active microcapsules would gradually form ternary or quadruple biphasic hybrid microparticles with one hydrogel face and two or three oil faces (Fig. 3B).

Furthermore, more complex microcapsules and hybrid microparticles could be fabricated by varying both the types of the inner oil phase and the flow rates of fluids. Fig. 4A showed microcapsules with composite oil actives, while Fig. 4B showed hybrid microparticles with complex faces. The synthesized microcapsules in Fig. 4A indicated good compatibilities of the different actives, which avoided the risk of cross-contamination. More importantly, the distinct actives could be released at the same time by hydration as well. For the complex microparticles shown in Fig. 4B, the hybrid microparticles with two or three oil faces of different types and sizes were formed by gradual dehydration of the corresponding microcapsules, which was similar to biphasic ternary and quadruple hybrid microparticles mentioned above. This technology might be useful for multiplex molecules storage and pulse release, as well as composite microparticle fabrication.

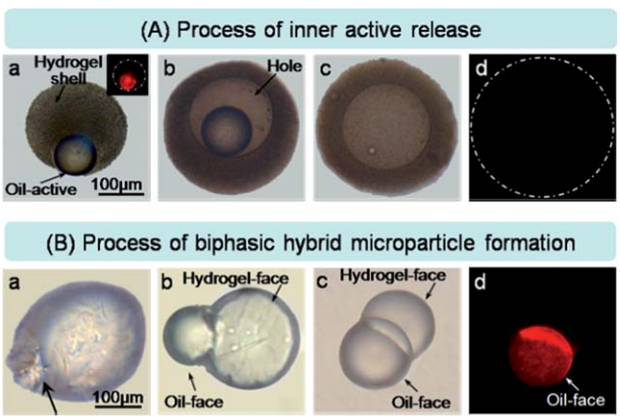

Fig. 2 (A) Images of hydration process of microcapsule. (a) Microcapsule with inner oil active. (b) A hole is generated around the active by hydration. (c) Release of the inner active with floatage. (d) Fluorescence of the released microcapsule, the dashed circle denotes the profile of hydrated microcapsule in (c). (B) Sequences of dehydration process of microcapsule. (a) Inner active starts to break the hydrogel shell, the black arrow demonstrates the broken location. (b–c) The active is gradually squeezed out to produce biphasic hybrid microparticle. (d) Fluorescence of the oil face of formed hybrid microparticle.

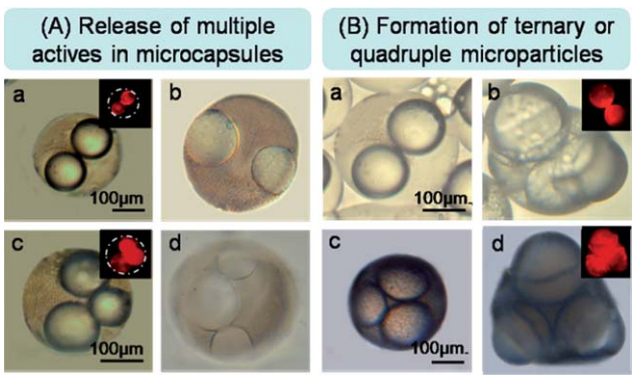

Fig. 3 (A) Release of two or three oil actives encapsulated in microcapsules by hydration. (a) and (c) demonstrate microcapsules with two and three actives, respectively. The insets show the fluorescent images. (b) and (d) denote the corresponding hydration results. (B) Formation of ternary or quadruple biphasic hybrid microparticles by dehydration. (b) and (d) illustrate the formed microparticles by dehydrating microcapsules in (a) and (c) correspondingly. The insets show fluorescence of oil faces of the hybrid microparticles.

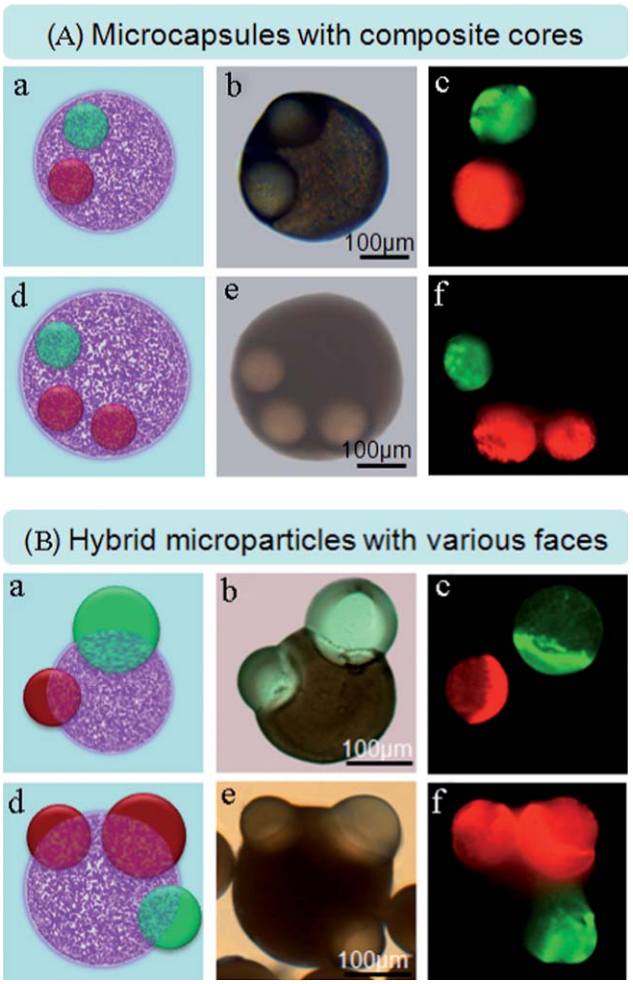

Fig. 4 (A) Microcapsules with two or three distinct oil actives. (a) and (d) reveal the schematics of composite microcapsules. (b) and (e) are optical while (c) and (f) are fluorescent images of the microcapsules. (B) Complex hybrid microparticles with two or three distinct oil faces and one hydrogel face. (a) and (d) denote schematics, (b) and (e) are optical while (c) and (f) are fluorescent images.

In principle, the swelling and shrinking of the PNIPAM hydrogel is proportional to the absorption and exclusion of water molecules, it is believed that the water percentage in the hydrogel also affects the hydration and dehydration results of synthesized microcapsules. In our experiments, it was found harder to release the inner actives by hydration when the microcapsules were synthesized using 10% (with 0.5% N,N′-methylenebisacrylamide) NIPAM monomer solution (as shown in the ESI S3A†). This was due to the higher ratio of water that was reserved in the cross-linked hydrogel network, and thus, a smaller amount of water was absorbed to force the hydrogel to swell, which was not enough to break up the hydrogel shell completely. For the higher concentration of NIPAM (30%, with 1.5% N,N′-methylenebisacrylamide), a lower ratio of water was held in the PNIPAM shell. The microcapsules would release the oil actives quickly by absorbing lots of water molecules, however, these microcapsules showed much less transparency in bright field. The optical density of microcapsules as a function of NIPAM concentrations were plotted in the ESI S3C,† which revealed that lower concentration of NIPAM led to higher transparency. Additionally, for the dehydration process, water drops appeared on the surface of the hydrogel face if the microcapsules were synthesized with 10% NIPAM monomer, (ESI S3B†). This was explained as that the excessive water molecules excluded from the shell could not evaporate immediately. Nevertheless, for the microcapsules of 30% NIPAM monomer, it took a longer time to squeeze the oil active to form biphasic hybrid microparticles. This was due to the occurrences of more hydrogen bonds and harder loss of the water molecules in the cross-linked hydrogel networks. Furthermore, it was found that 30% NIPAM could not dissolve completely in water without solubilizing agent. By comparisons, it is believed that 20% NIPAM with 1% N, N′-methylenebisacrylamide is the suitable concentration for fabrication of microcapsules and hybrid microparticles.

In conclusion, we presented a new water-actuated feature of PNIPAM microgels independent of typical temperature controlling, and fabricated novel microcapsules with this feature based on a microfluidic approach. The microcapsules could release their inner oil actives quickly by simple hydration process and enable to further produce biphasic hybrid microparticles by gradual dehydration. By varying the flow rates and types of inner oil phases, microcapsules with different composite actives and hybridized microparticles with complex faces could be fabricated as well. It is envisioned that this new approach paves a way for controllable fabrications of novel microcapsules and hybridized microparticles, thus, providing the potential for application in the areas of water-actuated microsensing, multiplex molecules delivery or pulse release, complex microparticle fabrication and other biochemical fields.

Experimental section

Microfluidic chip fabrication

The microfluidic chip was fabricated using PDMS by well-established soft lithography.[20] Briefly, approximately 50 μm thick × 120 μm wide SU8 3035 channels on glass substrate were used as a mold to stamp microfluidic designs on PDMS, the size of the T-junction orifices was 40 μm wide × 200 μm long, while the flow focusing orifice was 150 μm × 500 μm. Noticeably, the sizes of the formed double emulsions was larger than the square microchannel, thus it was compressed like discoid droplets. In order to form spherical microcapsules, the downstream part of the microchannel adjacent to collection reservoir was expanded to 500 μm wide × 300 μm high, where UV light was also used to solidify the microcapsules.

Surface modification of the microchannels

In order to produce double emulsion droplets, the surface of microfluidic channels was spatially modified. For the o/w droplets formation, the two T-junctions were grafted poly(acrylamide) (PAA) *via* photomask assisted to induce hydrophilic surface.[21] For the o/w/o double emulsions generation, the flow-focusing junction was patterned hydrophobic and fluorophilic using perfluorooctyltrichlorosilane immersed for 10 min and followed by ethanol washing for 30 s. Lastly, the whole device was baked at 80 °C for 30 min to remove the solvent residues.

Hydrogel microcapsules synthesis

The middle NIPAM aqueous phase contained 4% sodium dodecyl sulfate (SDS) as surfactant and 0.12% 2,2-Dimethoyl-2-phenyl-acetophenone as UV initiator, the outer FC-40 oil phase contained

2% EA (RainDance Technologies) as surfactant, UV spot light source (UVATA, Shanghai, China) was used to solidify the double emulsions once they entered the expanded microchannel to form spherical microcapsules. For the fluorescence in oil actives, two quantum dots of CdSe/ZnS (Red and Green fluorescence emissions due to the different particle sizes) were added separately in the two inner oil phases. To generate double emulsions with multiple oil cores, the flow rates of the three fluids were tuned as follows: core oil phase 0.01∼0.1μL min^{-1}, hydrogel shell phase 0.3∼0.9 μL min^{-1}, and continuous phase 1∼5 μL min^{-1}.

Image analysis

A fluorescent microscope with CCD camera (Olympus IX71) was used for real-time image acquisitions when the microcapsules were added into water or gradually dehydrated at room temperature. Image-Pro 6.0 was used for image analysis.

Acknowledgements

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