

Hole–Shell Microparticles from Controllably Evolved Double Emulsions**

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Polymeric core–shell microparticles with hollow interiors have great potential for use as microencapsulation systems for controlled load/release,^[1–3] active protection,^[4] and confined microreaction.^[5] Core–shell structures with solid shells provide effective encapsulation; however, transport of the encapsulated molecule through the shell is more difficult. Addition of holes to the shell can provide more versatility for the microparticles by facilitating mass transport through the shell based on the size or functional selectivity of the holes; this produces microparticles with porous shells for a myriad of uses including controlled capture of particles,^[1,6] controlled release of active molecules and small particles,^[7,8] and removal of pollutants.^[9] Additional uses for these microparticles can be achieved through finer control of the holes in the shell: for example, a single, defined hole can provide a very versatile structure for selectively capturing particles for classification and separation, or capturing cells for confined culture. Even more versatility can be obtained through control of the shape of the hollow core: for example, microparticles with a dimple-shaped core are useful for size-selective capture of colloidal particles, whereas microparticles with a fishbowl-shaped core are more useful for loading objects such as cells and confining a microreaction. Finally, to make these structures fully functional, it is also desirable to control the interfacial properties of the core to enable precise interactions between encapsulated molecules and the solid shell.

Colloidal-scale core–shell microparticles with a single hole in the shell are typically made with particle or emulsion-template methods: polymerization-induced buckling of silicon drops,^[10] freeze-drying solvent-swollen polymeric particles,^[11] self-assembly of phase-separated polymers,^[12] diffusion-induced escape of monomers^[13] or solvents^[14–16] from the microparticles during fabrication, selective polymerization of phase-separated drops,^[17] and other means to control the phase behavior of the templates.^[9,18,19] These microparticles provide excellent performance when sizes less than a few microns are required. By contrast, larger microparticles provide additional versatility when the size requirements are not constrained to very small particles. These microparticles are typically formed using emulsion drops as templates and have sizes of tens of micrometers or larger. Even finer control over the monodispersity of the microparticles is achieved using microfluidic techniques to produce the emulsion templates.^[20–22] The microparticle structure strongly depends on the configuration between the core-drop and shell-drop in the emulsion templates. With the shell-drop partially wetted on the core-drop, organic-biphasic Janus drops produce truncated-sphere-shaped microparticles.^[23–26] With completely wetted core–shell configurations, aqueous-biphasic drops and water-in-oil-in-water (W/O/W) double emulsions respectively produce bowl-shaped^[6] and fishbowl-shaped^[27] microparticles. Surface modification of these microparticles was recently achieved by introducing functional nanoparticles such as SiO₂ nanoparticles into the organic phase of the emulsion templates.^[23,24,27] Complete versatility of the microparticles requires accurate and independent control of the shape and size of both the single-hole and the hollow-core, as well as the functionality of the core surface; this requires precise control of the configurations and interfacial properties of the emulsion templates. However, techniques to achieve this sort of fine control do not exist.

Herein, we report a versatile strategy for fabrication of highly controlled hole–shell microparticles with a hollow core and a single, precisely determined hole, and with simultaneous, independent control of the properties of the core interface. W/O/W double emulsions from capillary microfluidics were used as the initial templates for the microparticles. By controlling the composition of the organic middle phase, we varied the adhesion energy ΔF ^[28,29] between the inner drop and outer phase to control the evolution of the emulsions from initial core–shell to the desired acorn-shaped configuration; this produces versatile emulsion templates for controllable fabrication of monodisperse hole–shell microparticles with advanced shapes. Further adjustment of the hole–shell structures can be achieved by changing the size and

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number of the inner drop through tuning the flow rates. By incorporating nanoparticles in the inner drop, we coat only the interface of the hollow core, thereby simultaneously, but independently controlling the interfacial properties. This method provides full versatility for preparation of hole-shell microparticles with a single hole in the shell.

We demonstrated the excellent controllability of our technique by starting with the preparation of hole-shell microparticles from ordinary core-shell W/O/W emulsions (see Supporting Information for all experimental details). A capillary microfluidic device was used to generate monodisperse emulsion templates (Figure 1 a). An aqueous solution with 1% (*w/v*) Pluronic F127 and 5% (*w/v*) glycerol was used

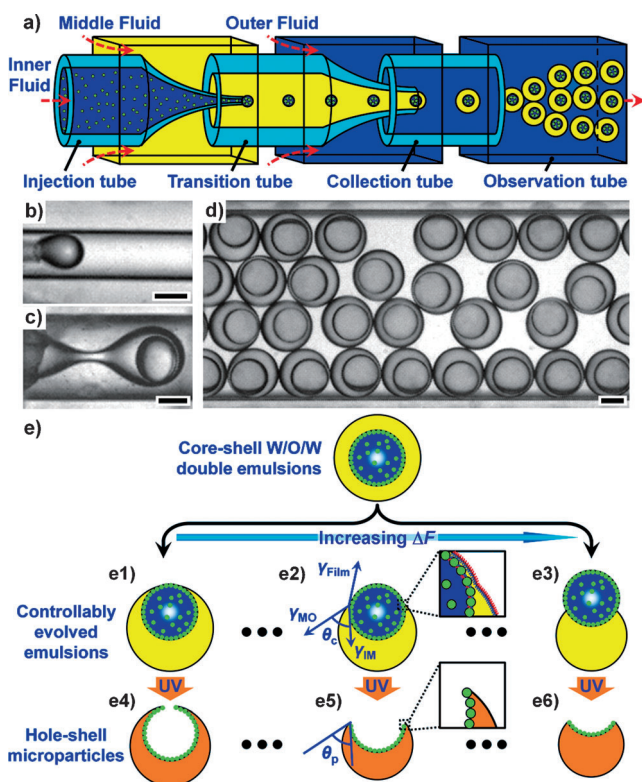


Figure 1. Strategy for fabricating the desired hole-shell microparticles from W/O/W emulsions. a) Microfluidic device used to generate monodisperse W/O/W emulsions with nanoparticle-containing inner drops. b–d) Optical micrographs showing the generation of inner drops (b) and core-shell W/O/W emulsions (c,d). e) Templated synthesis of hole-shell microparticles from W/O/W emulsions, with nanoparticles dispersed in the inner drop for modifying the core surface. Scale bars = 100 μm .

as the outer fluid (OF). Photocurable ethoxylated trimethylolpropane triacrylate (ETPTA) monomer with 1% (*v/v*) 2-hydroxy-2-methyl-1-phenyl-1-propanone was used as the middle fluid (MF). An aqueous solution containing 0.01 g mL^{-1} fluorescein-isothiocyanate-labeled poly(*N*-isopropylacrylamide-*co*-methyl methacrylate-*co*-allylamine) (FITC-PNIPAM) nanogels (see Supporting Information, Figure S1 for nanogel characterization) was used as the inner fluid (IF). Drops of IF were first generated in the transition

tube (Figure 1 b), with nanogels absorbed at the drop surface for stabilization (Figure S2). Then these water drops were encapsulated in the oil shell of MF, resulting in monodisperse core-shell W/O/W emulsions (Figure 1 c,d; Movie S1). After they were collected in vessels, the inner drops were drawn to the top of the oil shell because of a mismatch in densities between the IF and the MF (Figure 1 e1, Figure 2 b1). Polymerization of the eccentric core-shell emulsions by UV-irradiation for five minutes produced fishbowl-shaped microparticles with a large hollow core and a small single hole in the shell (Figure 1 e4, Figure 2 e; Figure S3a). The single-hole formation was due to the volume contraction and fast polymerization (within approximately one second)^[30] of the oil shell under UV light. The volume of the oil shell decreased to approximately 59.1 vol.% after polymerization (Figure S4); this squeezed the inner drop out of the oil shell, while fast in situ polymerization fixed this morphology and produced hollow microparticles with a single hole.

Controllable evolution of the W/O/W emulsions from core-shell to acorn-shaped configuration was achieved by inducing adhesion of the aqueous inner drop with the outer phase. An organic solvent benzyl benzoate with the surfactant polyglycerol polyricinoleate (PGPR) was added into the ETPTA as the MF. The poor solubility of ETPTA for PGPR reduces the solvent quality and leads to adhesion of the inner drop with the outer phase (Figure 2 a; Figure S5). The thin oil film that separates the inner drop and outer phase (Figure 2 a2) is associated with an adhesion energy:^[28,29] $\Delta F = \gamma_{\text{IM}} + \gamma_{\text{MO}} - \gamma_{\text{Film}}$, where γ_{IM} and γ_{MO} are respectively the interfacial tensions between the inner-middle and middle-outer phases, and γ_{Film} is the tension of the thin film. This ΔF is directly reflected by the contact angle θ_c between the adhesive inner drop and the outer phase (Figure 1 e2),^[31] which also defines the shape angle θ_p of the resultant hole-shell microparticles (Figure 1 e5). Thus, precise control of ΔF allowed controllable evolution of the W/O/W emulsions for synthesis of hole-shell microparticles with advanced shapes (Figure 1 e). Moreover, the core surface of the microparticles could be independently modified by introducing nanoparticles into the inner drop and fixing them at the W/O interface by polymerization.

Precise control of the evolved emulsion morphologies was studied by investigating θ_c as a function of ΔF (Figure 2 b,c). For ΔF calculation, γ_{IM} and γ_{MO} were measured by the pendent-drop method; γ_{Film} was obtained from adhesion experiments of IF and OF drops in MF phase according to force balance (see Supporting Information for detailed measurements and Table S1 for results).^[28,29] Precise manipulation of θ_c was achieved by tuning ΔF through adjustment of the ETPTA fraction. For core/shell emulsions with 100 vol.% ETPTA as shell (Figure 2 b1), $\theta_c = 0^\circ$ is observed (theoretically $\Delta F = 0$). For acorn-shaped emulsions with a mixed-oil shell, the θ_c value increased with increasing ΔF (Figure 2 b2–b5). The experimental θ_c results showed good agreement with the calculated values (Figure 2 c). With precisely manipulated θ_c values, these emulsions allowed for synthesis of hole-shell microparticles with controlled θ_p , for structure control (Figure 2 d). This produced controllable hole-shell microparticles, ranging from bowl shape (Fig-

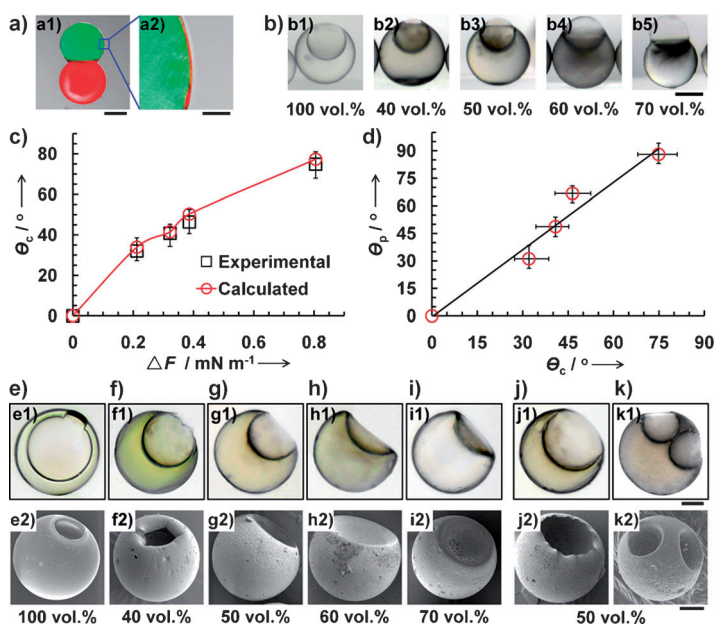


Figure 2. Templated synthesis of hole-shell microparticles from W/O/W emulsions. a) CLSM images of W/O/W emulsions with an inner drop containing FITC-PNIPAM nanogels and an oil shell containing a fluorescent dye. a1) Scale bar = 100 μm ; a2) Scale bar = 20 μm . b) Optical micrographs of side views of W/O/W emulsions with an oil phase containing different fractions of ETPTA. Scale bar = 100 μm . c) Effect of adhesion energy ΔF on the θ_c of W/O/W emulsions; the calculated θ_c values were obtained from the force balance of γ_{IM} , γ_{MO} , and γ_{FILM} using the equation $\theta_c = \arccos[(\gamma_{\text{FILM}}^2 - \gamma_{\text{IM}}^2 - \gamma_{\text{MO}}^2)/2\gamma_{\text{IM}}\gamma_{\text{MO}}]$. d) Relationship between the measured θ_p of microparticles and the measured θ_c of the emulsion templates. e–i) Optical (row 1) and SEM (row 2) images of microparticles with a fishbowl shape (e), bowl shape (f,g), or truncated-sphere shape (h,i). j) Hole-shell microparticles with a large core and hole that were fabricated by increasing the inner drop volume of the emulsions. k) Microparticles with dual hole-shell structures that were fabricated by increasing the number of inner drops. e–k) Scale bars = 50 μm .

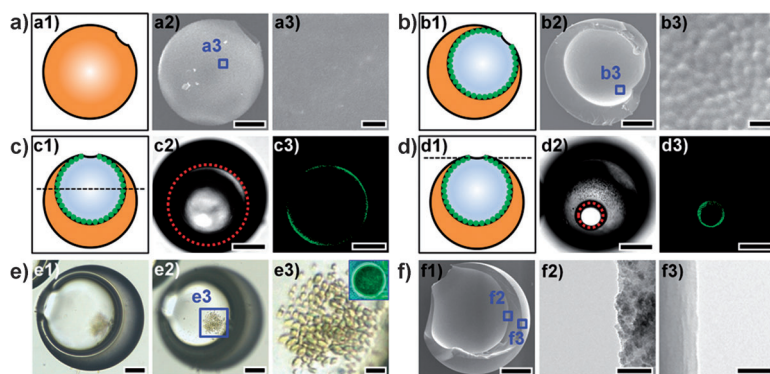


Figure 3. Hole-shell microparticles with the core surface independently modified. a,b) Schemes (a1,b1) and SEM images of smooth outer surface (a2,a3) and core surface modified with FITC-PNIPAM nanogels (b2,b3). c,d) Schemes and CLSM images focused on an equatorial cross section of the hollow core (c) and the hole mouth (d). The red circles in c2 and d2 mark the location of the FITC-PNIPAM nanogels shown in the CLSM fluorescent images (c3,d3). e) Optical micrographs of hole-shell microparticles loaded with algae cells. f) SEM (f1) and TEM (f2,f3) images of a hole-shell microparticle (f1) with a gold-nanoparticle-modified core surface (f2) and unmodified outer surface (f3). Scale bars are 500 nm in a3 and b3, 10 μm in e3, 50 nm in f2 and f3, and 50 μm for the rest.

ure 2 f,g; Figure S3 b,c), to truncated-sphere shape (Figure 2 h,i; Figure S3 d,e). The slight buckling at the hole mouth observed in Figure 2 f is due to the low mechanical strength caused by the low ETPTA fraction. The microparticles and their holes show good monodispersity; for example, the coefficient of variation (CV) values of the sizes of microparticles and their holes shown in Figure 2 g are as low as 1.35% and 2.26% (Figure S6). Moreover, besides fishbowl-shaped microparticles with a large core and a small hole, changing the inner drop volume through the flow rates created a large core and large hole within the microparticles (Figure 2 j; Figure S3 f). Meanwhile, changing the number of inner drops produced microparticles with dual hole-shell structures (Figure 2 k; Figure S3 g).

The flexibility of our strategy for independently modifying the core surface of hole-shell microparticles was demonstrated by coating the core surface with FITC-PNIPAM nanogels. As confirmed by SEM, microparticles were created with a smooth outer surface (Figure 3 a) and rough core surface with densely packed nanogels (Figure 3 b; Figure S7). The locations of the FITC-PNIPAM nanogels in the confocal laser scanning microscopy (CLSM) images (Figure 3 c,d) also showed their presence on the core surface. With thermo-responsive hydrophilic/hydrophobic transitions, these anchored nanogels allow for control of the wettability of the modified core surface by changing the temperature (Figure S8). Because cell behavior can be influenced by the surface wettability,^[32] microparticles with such a controllable wettability could potentially be used for cell capture and confined cell culture. Cell capture was demonstrated by capturing algae cells (Figure 3 e) and red blood cells (Figure S9) inside the microparticles. The versatility of our modification strategy was demonstrated using gold nanoparticles (Figure S10), with excellent catalytic properties,^[33] for modifying the core surface (Figure 3 f).

To further illustrate the uses of our hole-shell microparticles, selective capture of microspheres and confined synthesis of functional materials were performed. Under ultrasonic treatment, microspheres with a size fitting the hole and core were trapped into the hole-shell microparticles based on a “lock-key” match for 1:1 capture (Figure 4 a; Figure S11). Driven by ultrasonic vibrations, the size-screening effect of the hole allowed selective loading of microspheres smaller than the hole size (red) from larger ones in solution for size classification (Figure 4 b; Figure S12). The captured microspheres can be collected by embedding magnetic nanoparticles in the microparticle shell and separating with a magnet (Figure S13 and Movie S2). Further-

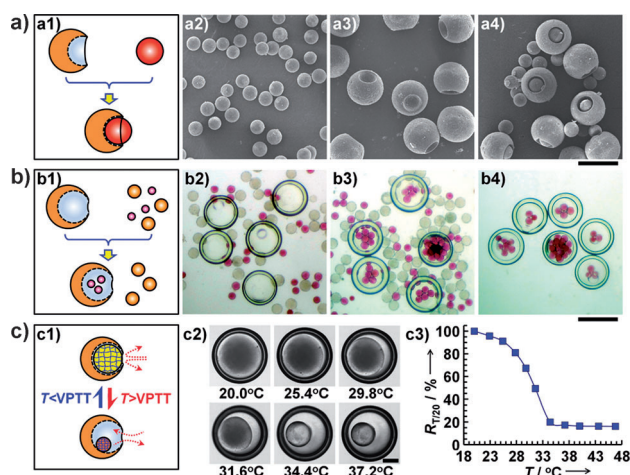


Figure 4. Hole-shell microparticles for controlled capture (a), size-classification (b), and confined microreaction (c). a) SEM images. b) Optical micrographs. c) Confined synthesis of PNIPAM microgel, in which the VPTT is the volume phase transition temperature. Optical micrographs (c2) and temperature-dependent volume-change curve (c3, $R_{T/20}$ is the ratio of the microgel volume at T to that at 20°C). Scale bars = 200 μm in (a) and (b), and 50 μm in (c).

more, we used the hole-shell microparticles as microreactors for the synthesis of thermo-responsive microgels inside the core. The microgel could then be used as a gate for opening and closing the hole (Figure 4c), providing a simple way to control the mass transfer into and out of the core.

In summary, monodisperse hole-shell microparticles with precisely controlled structures and flexibly modified core surfaces were fabricated using W/O/W emulsions as templates. We achieved control over the hole-shell structures by manipulating the adhesion-energy-dependent configuration of the W/O/W emulsions. Further control over the hole-shell structure was achieved by changing the volume and number of the inner drops. Control of the interfacial properties of the core was achieved by incorporating nanoparticles, such as thermo-responsive nanogels and gold nanoparticles, into the inner drop to coat the core surface for modification. The hole-shell microparticles allow for the capture of living cells, size-matched particle capture, size classification of microspheres, and confined synthesis of functional materials. These microparticles could be used as microcontainers for controlled capture/release, and as microreactors for catalysis. This approach based on double emulsions provides a versatile way to fabricate hole-shell microparticles with advanced shapes and specific functions.

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