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Smart Microgel Capsules from Macromolecular Precursors

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Abstract: Microgel particles and capsules which consist of multiple layers can be fabricated using droplet microfluidics, but in existing methods, emulsion templating forms layers of dissimilar polarity. In this paper, we fabricate functional microgel capsules that consist of two *miscible* yet distinct layers. We use microfluidic devices to template micrometer-sized drops that are loaded with prepolymerized precursors and solidify them through a polymer-analogous reaction. This allows the particle morphology to be controlled and prevents pronounced interpenetration of the different layers despite their miscibility. We use polyacrylamide and poly(*N*-isopropylacrylamide) precursors to form thermoresponsive core−shell microparticles and demonstrate their utility for encapsulation and controlled release applications.

Introduction

Droplet microfluidics is a powerful method to form monodisperse double and higher order emulsions of controllable size, morphology, and composition.[1−9] These drops-in-drops emulsions are useful for encapsulation and controlled release purposes;[5] they can also serve as templates for the synthesis of microparticles by solidifying their different phases.[1,3,4,9] Since the fluids which form them are necessarily immiscible, complex microstructures such as hollow shells[1,3−5] or bipolar microparticles[9] can be created and used for applications such as microcapsules or interfacial stabilizers. However, it is impossible to create distinct core−shell particles that consist of very *similar* materials with this technique, because their miscibility allows rapid interpenetration of the different layers in the preparticle droplets. Thus, there is no simple means of creating these valuable structures using droplet microfluidics.

In this paper, we present a method to fabricate multilayered hydrogel particles with sizes in the micrometer range, using droplet microfluidics to control their morphology with high precision. We prevent marked interpenetration of the miscible layers by gelling them from prepolymerized precursors, which do not intermix on the time scale of our experiments. This allows us to produce microparticles which consist of distinct layers of poly(*N*-isopropylacrylamide) (pNIPAAm) and related polymers. These microgels are thermosensitive,[10] allowing us to use them for the encapsulation and controlled release of hydrophilic actives.

Results and Discussion

To produce core−shell particles, we proceed in a stepwise manner. First, we create monodisperse microgel particles that serve as the core material. Then, we wrap them into monodisperse polymer shells using a microfluidic device that consists of two cross-junctions in series, as sketched in Figure 1a. In the first junction we add a semidilute solution of cross-linkable pNIPAAm chains as a shell phase. In the second junction we add oil to form bilayered pregel drops. We then lock these structures by cross-linking the pNIPAAm chains in the shell phase via a rapid polymer-analogous photoreaction as shown in Scheme 1.[11−13] Finally, we remove the oil phase and transfer the core−shell particles into water.

We conduct our experiments using poly(dimethylsiloxane) microfluidic devices made by soft lithography.[14] We start our stepwise particle production using a single cross-junction to fabricate monodisperse water in oil emulsions. We produce aqueous droplets of ∼100 μm diameter which are loaded with a 100 g L^{-1} solution of NIPAAm, along with 1 mol % (rel. to the amount of NIPAAm) of *N*,*N*-methylenebisacrylamide (BIS) as a cross-linker, 0.1 mol % (rel. to the amount of NIPAAm) of *N*-(3-aminopropyl)-methacrylamide (NAPMAAm), which is an amine-functionalized comonomer to be used for subsequent fluorescence labeling, and 10 mmol L^{-1} ammonium persulfate

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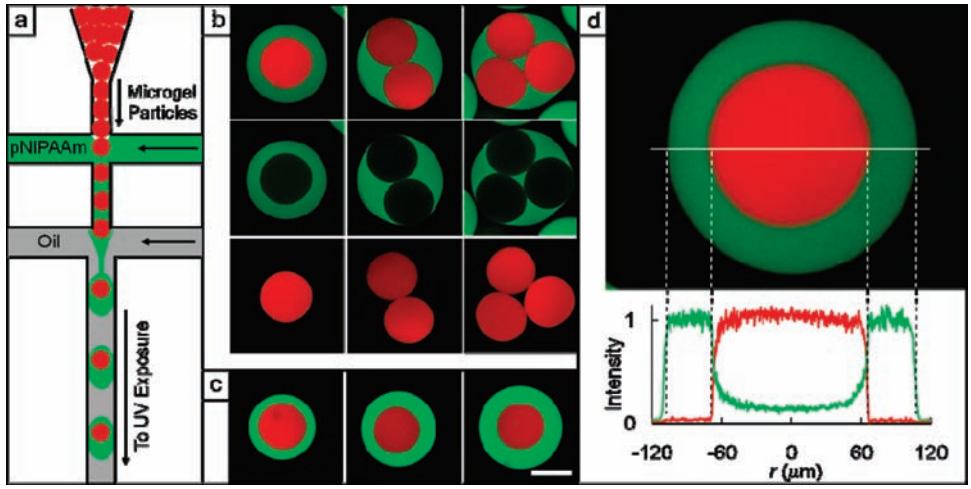
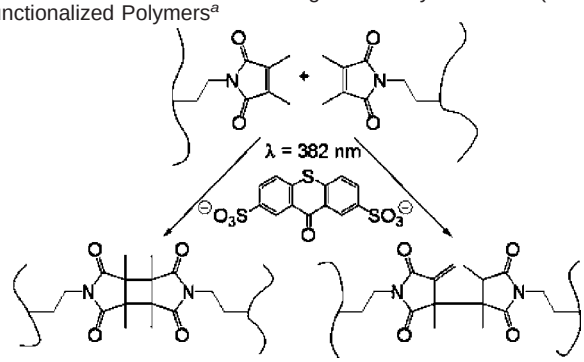


Figure 1. Microfluidic fabrication of microgel capsules that consist of two miscible yet distinct layers. (a) Schematic of a microfluidic device forming aqueous poly(*N*-isopropylacrylamide) (pNIPAAm) droplets that are loaded with a well-defined number of prefabricated particles of a similar material, pNIPAAm or polyacrylamide. Subsequent gelation of the pNIPAAm phase leads to microgels with a distinct core−shell architecture. (b, c) Adjusting the flow rates of the inner particle phase (red-tagged pNIPAAm), the middle polymer phase (green-tagged pNIPAAm), and the outer oil phase controls the number of core particles in each shell (b) as well as the shell thickness (c).[15] Pictures in the upper row of panel b show an overlay of the micrographs in the middle and lower row, which depict separate visualizations of the green-tagged pNIPAAm shell and the red-tagged pNIPAAm core. (d) Spatially resolved intensity profiles of the red and green fluorescence in the single-core particle shown in panel b, evidencing only very little interpenetration of its two phases. The scalebar denotes 100 μm and applies to all micrographs in panels b and c.

Scheme 1. UV-Induced Crosslinking of Dimethylmaleimide (DMMI) Functionalized Polymers[a]



[a] Two isomeric DMMI-dimers are formed in aqueous media if the reaction is mediated by a triplet sensitizer, thioxanthone-2,7-disulfonate, each constituting a covalent junction between the precursor chains.[11,12]

(APS) as a radical initiator. The continuous phase is a fluorocarbon oil (HFE-7500, 3M) containing 1.8 wt % of surfactant Krytox 157 FSL (Dupont) as well as 1 vol % of *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TEMED). Upon emulsification, TEMED penetrates into the aqueous droplets and triggers a free-radical cross-linking copolymerization of the monomers. This produces monodisperse pNIPAAm microgels which are then transferred into water, whereupon they swell to a size of 130 μm at ~25 °C. Before using them as core particles in subsequent experiments, we tag them by attaching a rhodamine dye to the pendant primary amine moieties imparted by the NAPMAAm comonomer.

After preparing the core microgels, we densify them using a centrifuge (Eppendorf MiniSpin Plus, 1000 rpm., 30 s). We inject the resulting paste into a microfluidic device with a double cross-junction geometry as sketched in Figure 1a. We use an injection channel which gradually narrows to a width of 100 μm, thus forcing the particles into a single-file flow; we also ensure the formation of a single particle layer by employing channels with a uniform height of 100 μm. As the particles are close-packed, they enter the first cross-junction with high periodicity. This allows us to load them into preshell droplets

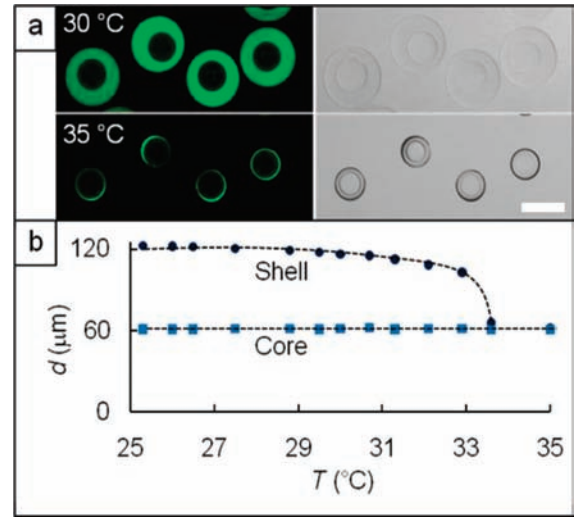


Figure 2. Thermoresponsive behavior of pAAm−pNIPAAm core−shell microgels. (a) Fluorescence images (left column) and bright field micrographs (right column) of microgels consisting of a 60 μm nontagged pAAm core encapsulated in a green-tagged pNIPAAm shell. At ambient temperatures (upper row), the shell is swollen, whereas it collapses at elevated temperatures (lower row). By contrast, the core dimension remains unaffected by the same changes of temperature. (b) Detailed plot of the particle diameter, *d*, as a function of temperature, *T*. Dark blue circles represent the diameter of the entire particle, i.e., pAAm core plus pNIPAAm shell, whereas light blue squares represent the sole pAAm core. The dotted lines are guides to the eye. The scalebar denotes 100 μm.

with precise control over the number of particles in each droplet.[15] Our shell phase consists of an aqueous, semidilute solution of a pNIPAAm precursor containing 0.75 mol % of pendant dimethylmaleimide (DMMI) groups. These moieties can be selectively transformed into dimers by a photochemical reaction (Scheme 1),[11−13] thus cross-linking the pNIPAAm chains.

To distinguish the shell from the core, we dope our shell phase with a photo-cross-linkable tracer polymer that is tagged with a green fluorescent dye, as opposed to the red labeling of the

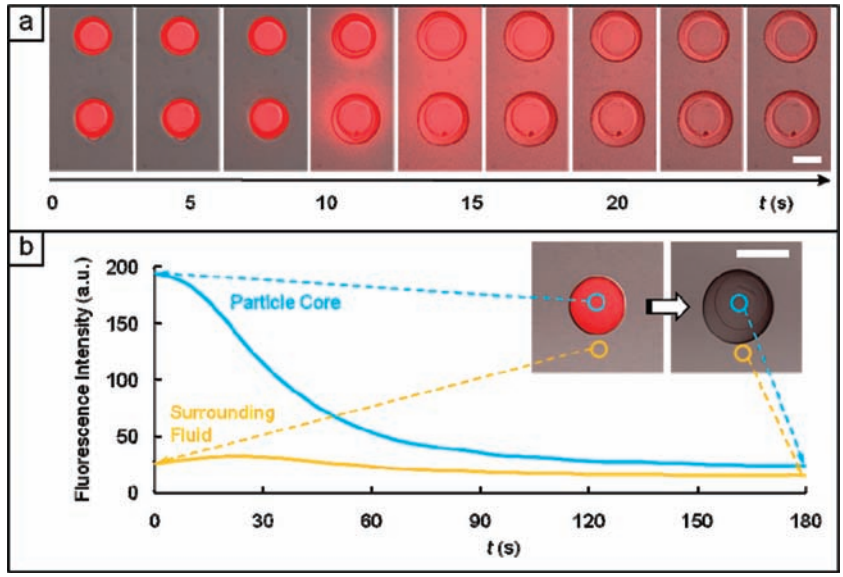


Figure 3. Controlled release applications of pAAm−pNIPAAm core−shell microgels. (a) Release of RITC-dextran (M = 10 000 g mol^{-1}) loaded into the particles shown in Figure 2a. In the course of the first 10 s, the temperature remains above 33 °C, and the particles remain sealed (left three pictures). As the temperature decreases further, a spontaneous release of the active incorporated in the particles is triggered by the reswelling of the pNIPAAm shells. (b) Average fluorescence intensity in the particle core (blue curve) and in the surrounding fluid (orange curve) as a function of time during a similar experiment on the controlled release of rhodamine B, a low molecular weight fluorescent dye. The scalebars denote 50 μm.

core particles. Immediately after adding the shell phase, the aqueous stream is dispersed into droplets in an oil phase using the second cross-junction of our microfluidic device, as indicated in Figure 1a. We use a viscous paraffin oil (η(1 rad s^{-1}) = 130 mPa s) containing 2 wt % of a modified polyether−polysiloxane surfactant (ABIL EM 90, Evonik Industries, Germany). The resultant emulsion exits the device through a piece of polyethylene tubing which is exposed to strong UV light. This induces an irreversible interconnection of the precursor chains in the shell droplets, thus creating a permanent core−shell structure. The resultant particles are collected in a vial. After transferring them into plain water, we image them on a confocal laser scanning microscope (Leica TCS SP5) which can be operated in fluorescence and bright field mode. We excite the red and green labels with the 543-nm line of a HeNe laser and the 488-nm line of an Ar-ion laser, respectively. Fluorescence detection takes place in two separate channels in the wavelength range of 650−800 nm (red channel) and 493−538 nm (green channel).

We control the number of core particles in each shell as well as the shell thickness by adjusting the flow rates of the inner particle stream, the aqueous middle phase, and the continuous oil phase, as shown in Figure 1b and c and detailed in ref 15. The size of the core particles can be independently adjusted by the flow conditions in the first microfluidic device. Thus, the two-step microfluidic production allows custom-made core−shell morphologies to be fabricated.

A crucial aspect for the formation of *distinct* core−shell structures is to prevent pronounced intermixing of the two phases; this is exacerbated because we use miscible materials in the different layers. Our strategy to solve this problem is to use prepolymerized precursors in the shell phase which encapsulates the cross-linked core particles. Since the diffusivity of polymer chains in semidilute solutions and networks is generally low,[16] there is no marked interpenetration of the shell material into the core on the time scale of our experiments. This is evidenced when inspecting the middle and lower row of micrographs in Figure 1b, which show separate visualizations of the green-labeled shells and the red-labeled cores of the microgels in the upper row. To substantiate this finding, we estimate spatially resolved profiles of the fluorescence intensity from the micrographs shown in the left column of Figure 1b, as plotted in Figure 1d. These profiles show that the red-tagged core material and the green-tagged shell material are well separated. There is only a small amount of penetration of the green shell polymer into the red core, reflecting the small degree of diffusion of short precursor chains into the core before gelation occurs.

If both the core and the shell of the particles consist of pNIPAAm, they are both thermoresponsive,[10] and the swelling and shrinking of these core−shell particles is not very different from the swelling and shrinking of a simple pNIPAAm microsphere. However, our method allows us to fabricate particles which consist of a non-thermoresponsive core nested in a thermoresponsive shell. We accomplish this by incorporating non-thermoresponsive polyacrylamide (pAAm) particles of ~60 μm diameter into thermoresponsive pNIPAAm shells with an average thickness of ~30 μm. Once again, the shell is green fluorescently tagged for greater clarity. The behavior of these pAAm−pNIPAAm particles upon increase of the temperature to 35 °C is visualized in Figure 2a and detailed in Figure 2b: while the green-tagged shell collapses due to the volume phase transition of pNIPAAm, the colorless core remains unaffected.

Due to this selective sensitivity, pAAm−pNIPAAm core−shell particles are applicable for encapsulation and controlled release purposes. When the pNIPAAm shell is swollen, it is porous and permeable, whereas it becomes nonporous and impermeable when it collapses. By contrast, the core remains unaffected by temperature, providing stability of shape. Thus, when the shells are swollen, the particles can be loaded with any low molecular weight or mesoscopic material consisting of molecules or aggregates which are smaller than the mesh size of the polymer network, which is ~10 nm, as determined from measurement

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of the elastic modulus using a macroscopic sample. Upon increase of the temperature above the lower critical solution temperature of pNIPAAm, the thermo-responsive shell collapses and encapsulates the active in the pAAm core, which supports the collapsing shell and prevents any of the encapsulated active from escaping. After sealing the particles, all surrounding feed material can be removed and the loaded particles can be stored at elevated temperatures. However, as soon as the temperature is again decreased, the encapsulated actives are rapidly released.

This interesting application is substantiated in Figure 3a, which shows a sequence of images obtained from an experiment where RITC-tagged dextran ($M = 10\,000$ g mol^{-1}) is released. This material is mesoscopic ($r_{hydr} \approx 2-5$ nm) and can penetrate both the core and shell of the pAAm−pNIPAAm particles as long as they are swollen. However, as soon as the temperature is raised, the collapsing shell seals the particles and dextran is trapped within the pAAm cores. Upon removal of all residual RITC-dextran in the surrounding material, fluorescence is detected only in the particle cores. Only a recooling step is able to trigger a spontaneous release of the labeled material as shown in Figure 3a.

The same principle is also applicable to the encapsulation of low molecular weight species. The release characteristics of rhodamine B, a low molecular weight fluorescent dye, from a similar experiment is shown in Figure 3b. The time axis starts at the point where the temperature of the system falls below 33 °C, which is close to the lower critical solution temperature of pNIPAAm in aqueous media.[10] This leads to a rapid loss of fluorescence intensity in the particle cores since the fluorophores are released, as represented by the blue curve. By contrast, the intensity in the direct neighborhood of the particles, as represented by the orange curve, exhibits a slight increase, before it redecreases due to rapid spatial equilibration of the dye concentration. The encapsulation of such small substances requires an environmentally sensitive shell which is absolutely nonporous. This is another important reason to create the outer pNIPAAm layer through a photochemical polymer-analogous process rather than polymerizing it from monomers. In fact, the application or evolution of heat, which typically accompanies polymerization reactions, would lead to pronounced micrometer-scale porosity during this step.[17,18]

Conclusion

The step-by-step approach presented in this article allows multilayered particles that consist of very similar materials to be created. As the materials used to form the core and the shell can be pre-engineered in independent syntheses, "smart" microcapsules sensitive to different external stimuli such as temperature, pH, ionic strength, or specific chemical environments can be easily fabricated and used for controlled release applications. Moreover, our multistep approach represents a general alternative to the use of double or higher order emulsion templates for producing multilayered particles. This is of potential value for commercial applications, which require parallelized production at high rates, not easily achieved by multiple emulsification.

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Supporting Information Available: Full experimental details and movies showing the controlled release of RITC-dextran ($M = 10\,000$ g mol^{-1}) from pAAm−pNIPAAm microgel particles. This material is available free of charge via the Internet at http://pubs.acs.org.

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