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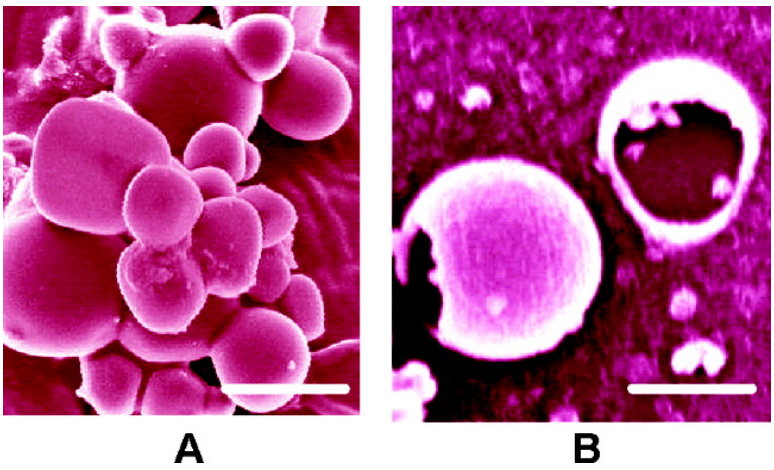

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In Situ Synthesis of Temperature-Sensitive Hollow Microspheres via Interfacial Polymerization

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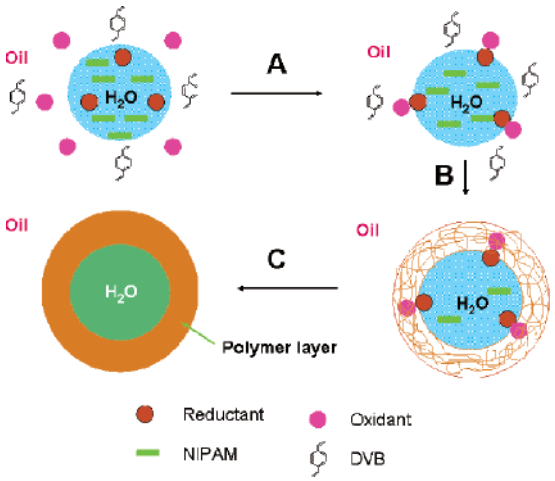
In recent years, hollow microspheres have attracted intense research attention because of its wide variety of applications, such as in delivery vesicles for drugs, dyes, or inks, microcontainers for artificial cells, protection shield for proteins, enzymes, or DNA, and for catalysis applications as well.[1−3] Both inorganic and polymeric hollow microspheres have been reported. Templating method is one of the most common methods for preparing hollow spheres, but the application of this approach is limited because in most cases the materials that need to be encapsulated in the microspheres are not suitable templates.[4] Hubert and co-workers reported an approach with a hydrophobic monomer entrapped between the liposome bilayer and followed by polymerization in situ, and Landfester et al. reported a miniemulsion process immediately followed by hydrophobe removal.[4d,5] The shortcoming of these two methods is that only limited bilayer systems or hydrophobe−polymer pairs can be found. To the best of our knowledge, there have been no reports of one-pot polymerization to prepare temperature-sensitive hollow microspheres via an interfacial polymerization approach under mild reaction conditions.

Poly(*N*-isopropylacrylamide) (PNIPAM) and its derivatives have attracted increasing research interests due to their intriguing temperature-sensitive performance.[6−9] Among the wide applications of the PNIPAMs, microspheres are of particular interest in terms of the state-of-the-art applications in controlled drug release,[7] biosensors and actuators,[8] and bioengineering material applications[9] as well. Nevertheless, most of the studies are focused on the physical and chemical performances around its lower critical solution temperature (LCST), also called coil-to-globule transition.[6] To date, little work was done using this transition in polymer reaction engineering to develop novel material architectures and functions. In this study, the transition of PNIPAM from hydrophilic to hydrophobic above its LCST was adopted in a designed unique interfacial polymerization process by which the temperature-sensitive hollow microspheres could be synthesized in situ.

As depicted in Scheme 1, the NIPAM monomer was first dissolved in an aqueous phase and then emulsified with toluene to form a water-in-oil (W/O) emulsion in the presence of a low HLB surfactant, such as sorbitan monooleate (commercial name Span-80, with HLB value of 4.3). The emulsion droplets with a diameter of 1−3 μm could be obtained. To conduct an interfacial polymerization at the oil/water interface, a redox initiation system containing benzoyl peroxide (BPO) in oil phase and tetraethylenepentamine (TEPA) in water phase was used as the interfacial initiator.[10] During the reaction process A, as described in Scheme 1, the reductant TEPA and the oxidant BPO will diffuse to the oil/water interface first to generate free radicals. After that, the polymerization of NIPAM will start spontaneously at the interface. If the polymerization is carried out at the temperature above the LCST of PNIPAM, the PNIPAM will be neither water-soluble (hydrophobic) nor oil-soluble (toluene as oil phase), as shown in process B in Scheme 1. For this reason, the formed PNIPAM layer will be restricted at the oil/water interfacial area at the temperature above its LCST. At the same time, the cross-linking agent (divinylbenzene, DVB) in oil phase will also diffuse to the interface and participate in the polymerization. As the polymerization continues, all monomers and cross-linkers are reacted and an insoluble cross-linked PNIPAM network is formed at the interface with a hollow microspheric structure, as shown in process C of Scheme 1.

Scheme 1. In Situ Synthesis of Temperature-Sensitive Hollow Microspheres via an Inverse Emulsion Polymerization Approach



As can be seen in Figure 1 A and Figure S1, the microspheres formed via the proposed approach have a quasi-spherical morphology, with separated particles and microspheres with diameters of ca. 1−3 μm, in accordance with the particle size scale in an inverse emulsion process in our previous studies.[11,12] The polydispersity of the particle size distribution of the microspheres, as shown in Figure 1 and other experiments (data not shown here), suggests that (1) the emulsion stability and drop size distribution are important for controlling the final product particle size distribution; (2) the agitation rate is important because the formation of an initial shell may be destroyed if too high a quantity is used; and (3) the concentrations of cross-linker and monomer should not relatively high. Otherwise, the final product is not strong enough to be a hollow sphere. Our preliminary experiments indicated that a plethora of broken and twisted microspheres were formed when insufficient or inappropriate surfactants were used. The interior morphology of the microspheres, as shown in Figure 1B and Figure S1B, exhibited a truly hollow structure, with a wall thickness of ca. 100 nm, further supporting the feasibility of the concept proposed.

It has been well-known that cross-linked PNIPAM is a temperature-sensitive polymer network in water that will swell at a temperature lower than its LCST and deswell at a temperature higher than its LCST.[13,14] This is really the case when the PNIPAM

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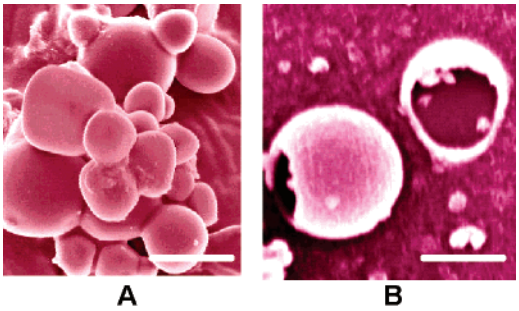

Figure 1. SEM images of PNIPAM microspheres. (A) Overview picture; (B) cross section. Scale bar: (A) 2.0 μm; (B) 1.0 μm.

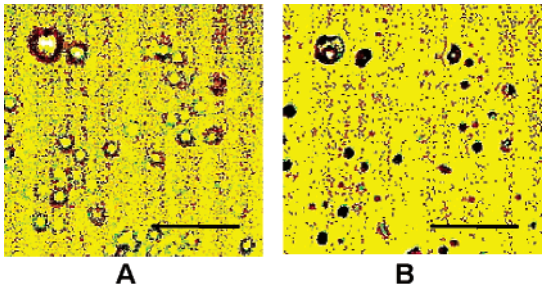

Figure 2. Optical microscope images of the microsphere particles at (A) increased temperature (>LCST) and (B) room temperature. Scale bar: 10.0 μm.

constructed a hollow-structured microsphere. As expected, the size of the hollow-structured microspheres changed dramatically upon temperature variation, approximately one time around the LCST, as demonstrated in Figure 2. The particles changed from transparent spots to dark spots upon temperature increase and vice versa, indicating the reversibility and reproducibility of the swelling and deswelling processes of the as-prepared hollow microspheres in the temperature changing process.[15,16]

In conclusion, a novel one-pot synthetic strategy to prepare hollow-structured PNIPAM microspheres via an interfacial polymerization approach at the interface of an inverse W/O emulsion has been demonstrated. The results show that the prepared PNIPAM microspheres have a real empty core and a polymer shell structure, with a wall thickness of ca. 100 nm and a size range of ca. 1−3 μm. The hollow-structured microspheres experienced a reversible swelling and deswelling process via mediating the temperature below and above the LCST. The particle size and the thickness of the wall depend on the emulsion stability, the network formation rate, and the polymer concentration in the emulsion droplet. Too high shear force will prevent the formation of polymer shell at the surface. Because of the flexibility in choosing substances being dissolved in the water phase, this approach revealed interests in encapsulating bioactive materials or drugs requiring mild encapsulation conditions within a temperature-sensitive polymer shell. The methodology revealed in the study not only provided a unique technical pathway in hollow microsphere construction with a one-pot approach under mild reaction conditions but also opened a platform to better understand the diffusion and migration mechanism of PNIPAM at an oil/water interface above its LCST and the polymer layer formation mechanism as well. Ongoing work is underway.

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Supporting Information Available: Preparation and cryo-breaking procedures for the PNIPAM microspheres, and supplementary SEM images before and after cryo-sonication-broken processes. This material is available free of charge via the Internet at http://pubs.acs.org.

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