568 *Macromolecules* **2010**, *43*, 568–571
DOI: 10.1021/ma902058b

Macromolecules
NOTE

Synthesis of Thermo-Sensitive Nanocapsules via Inverse Miniemulsion Polymerization Using a PEO−RAFT Agent

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Received September 15, 2009; Revised Manuscript Received November 2, 2009

Introduction

Polymeric nanocapsules (NCs) have wide potential applications in the areas of drug delivery,[1−3] as contrast agents,[4] catalysis protection or carrier,[5,6] etc. Many innovative techniques have been developed to do encapsulation of inorganic solids or hydrophobic liquids via block copolymer assembly,[7] layer-by-layer polyelectrolyte deposition,[8] shell polymerization of particles,[9] and miniemulsion polymerization.[10−13] Miniemulsion polymerization is a feasible and efficient technique in scale-up synthesis of NCs with the size around 50−500 nm. Landfester et al. have used direct miniemulsion polymerization to encapsulate $CaCO_3$, which was made hydrophobic by surface adsorption of stearic acid prior to the introduction in monomer phase.[12] Interfacial polycondensation inverse miniemulsion to synthesize NCs with a hydrophilic liquid as the core was also reported.[13] Luo[14] also synthesized hydrophobic liquid and polystyrene core/shell particles via direct miniemulsion process. However, encapsulation of hydrophilic materials (such as inorganic salts, hydrophilic dyes or pigments) by radical inverse miniemulsion polymerization has not been reported. This communication is the first to report the synthesis of temperature responsive nanoencapsulation of inorganic salts via reversible addition−fragmentation transfer (RAFT) interfacial confined inverse miniemulsion polymerization using a poly(ethylene oxide)−MacroRAFT (PEO−RAFT) agent.

Recently, amphiphilic MacroRAFT agents have been reported frequently to be applied in (mini)emulsion polymerization. Hawkett's group first carried out RAFT controlled/living ab initial emulsion polymerization by amphiphilic MacroRAFT self-assembly.[15] They also encapsulated hydrophobic or hydrophilic pigments by emulsion polymerization using butyl acrylate/acrylic acid random MacroRAFT copolymers.[16] Poly(ethylene oxide) MacroRAFT agent used as both a stabilizer and a control agent in styrene polymerization in aqueous dispersed system was also reported by Santos et al.[17,18] Luo et al. have proposed a newly facile way to carry out nanoencapsulation via RAFT confined interfacial miniemulsion polymerization.[19,20] They used amphiphilic SMA−RAFT (poly(styrene-*co*-maleic anhydride)-*b*-polystyrene−RAFT) agent to confine the polymerization to the interface of the oil droplets to form a polystyrene shell and encapsulated the hydrophobic liquid $C_{19}H_{40}$.[19] Well-defined monodisperse NCs were also synthesized via this method.[21] However, the MacroRAFT agent used in inverse miniemulsion was never reported.

Poly(*N*-isopropylacrylamide) (PNIPAM) has wide applications in medical and bioengineering fields because of the biocompatible and intriguing thermo-sensitive properties.[22] Poly(NIPAM) microgel particles are usually attractive by researchers due to the rapid and reversible swelling/deswelling transitions. The preparation of poly(NIPAM) microgel particles was first reported by Pelton,[23] who pointed out the lower critical solution temperature (LCST) was around 32 °C. Their group also reported the synthesis of highly pH and temperature microgels based on poly(NIPAM) and functionalized with vinylacetic acid.[24] Deng[25] has synthesized hollow microspheres due to the immiscibility of PNIPAM above the LCST with either water or toluene and the cross-linking polymerization was confined on the interface of droplets. However, the particle size was always large and the wall thickness was not easily controlled because of the low shear force and molecule diffusion reaction.

In the current work, an amphiphilic PEO−RAFT agent ($PEO_{17}{-}SC({=}S)SC_{12}H_{25}$, MacroRAFT) is investigated to confine the polymerization of NIPAM on the outer shell of miniemulsion droplets to encapsulate hydrophilic inorganic salt sodium sulfate, which was usually used as the costabilizer to prevent Ostwald ripening in inverse miniemulsion and also as the core materials in this research system.[26,27] The mechanism of interfacial polymerization is suggested in Scheme 1A. The amphiphilic PEO−RAFT agent would self-assemble on the interface of droplets and cyclohexane. The radical within the droplets would quickly transfer to the PEO−RAFT agent anchored on the interface. The new formed radical with poly(ethylene oxide) as the R group of MacroRAFT would propagate NIPAM monomer and become surface active to stay on the interface preferably, because PNIPAM is not miscible with water or cyclohexane above the LCST. Thus, the polymerization controlled by the MacroRAFT is confined to the interface. PNIPAM grows outward to form the polymer shell in situ and polymeric nanocapsules (NCs) were obtained. The size of NCs was about 100−250 nm. Theoretically, the functionality and thickness of the polymer shell should be easily "controlled" via RAFT polymerization.

Experimental Section

Materials. *N*-Isopropylacrylamide (NIPAM, 97%, Aldrich) was twice recrystallized from a 60:40 toluene:hexane mixture before use. The costabilizer anhydrous sodium sulfate (Na_2SO_4, 99%, Mallinckrodt Baker) and cyclohexane (>99.5%, Aldrich), were used as received. 2,2′-Azobis[2-(2-imidazolin-2-yl) propane]dihydrochloride (VA-044, >98%), which is shown in Figure 1, was purchased from Wako and used without further purification. Water used was deionized. The PEO−RAFT agent, $PEO_{17}{-}SC({=}S)SC_{12}H_{25}$ (Figure 1), which was synthesized according to the literature and the detail was shown in the Supporting Information. The nonionic surfactant B246SF, which is of a

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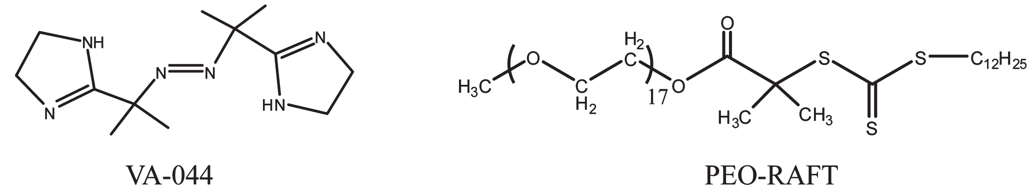
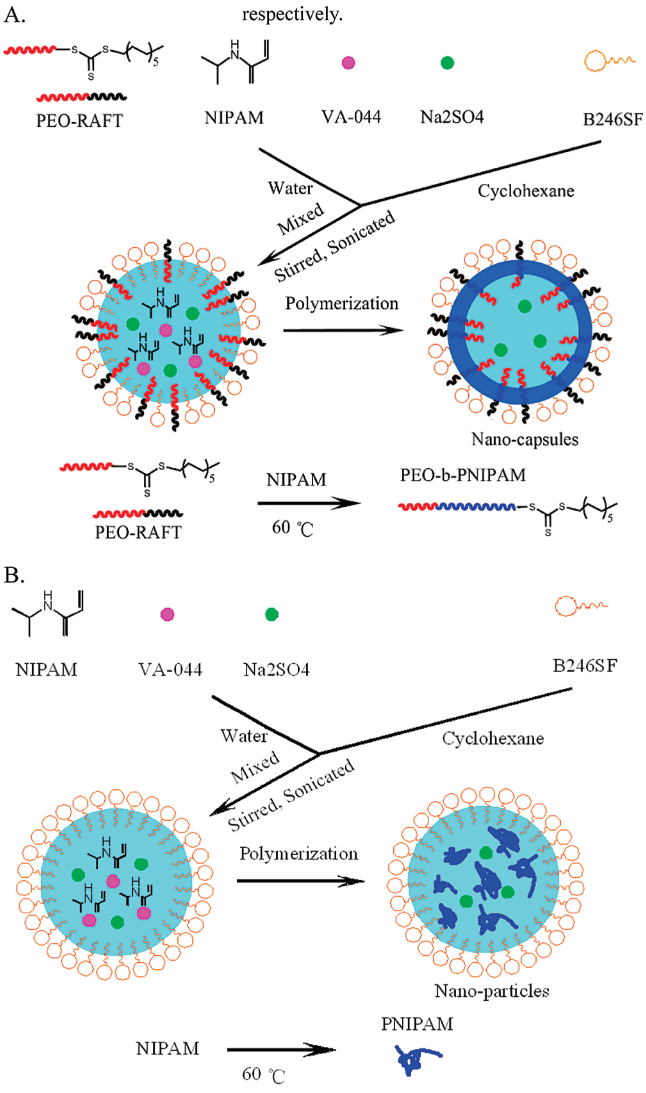


Figure 1. Chemical structure of the initiator (VA-044) and MacroRAFT agent (PEO−RAFT).

Scheme 1. Suggested Mechanisms of RAFT Interfacial inverse Miniemulsion Polymerization and Free Radical Inverse Miniemulsion Polymerization with NIPAM as the Monomer As Illustrated in Parts A and B, Respectively



ABA triblock copolymer structure with block A as poly(12-hydroxystearic acid) and block B as poly(ethylene oxide),[28] was kindly supplied by Uniqema. The number-average molar weight of the surfactant was around 3500 g mol^{-1}.

Inverse Miniemulsion Polymerization. The RAFT interfacial inverse miniemulsion polymerization was prepared as follows: the nonionic surfactant B246SF (0.6 g) was dissolved in 40g cyclohexane as the continuous phase of the inverse miniemulsion. The RAFT agent, $PEO_{17}-SC(=S)SC_{12}H_{25}$ (0.052 g, 0.046 mol) was added into 10 g deionized water, followed with the costabilizer sodium sulfate (0.12 g, 0.8 mmol), the monomer NIPAM (1.5 g, 13.3 mmol) and the initiator VA-044 (0.015 g, 0.046 mmol) to prepare the dispersed phase. Then these two phases were mixed together and stirred under nitrogen at 10 °C for 30 min to be pre-emulsified. The coarse inverse emulsion was subject to an Omni-Ruptor 250 ultrasonic homogenizer operated at a 70% power output and a 30% duty cycle for 6 min. During the sonication, the emulsion was in an iced bath to prevent the polymerization. The free radical inverse miniemulsion was prepared in the same way, but no PEO−RAFT agent was added into the dispersed phase.

The prepared inverse miniemulsion was transferred to a three-neck 100 mL flask with a reflux cooler, a rubber plug and nitrogen inlet. The polymerization was carried out in an oil bath set at 60 °C under magnetic stirring. The polymerization lasted 3 h and the final latex was collected.

Results and Discussions

The morphology of the final colloids and the encapsulated inorganic salts were observed via images and electrical diffraction in TEM, respectively. The detail of the TEM observation is represented in the Supporting Information. A TEM image of the final latex for the RAFT interfacial inverse miniemulsion polymerization is shown in Figure 2a. Well-defined core−shell nanocapsules were clearly observed. But few solid particles were present. It confirmed the mechanism of NCs formation well, which is shown in Scheme 1A. The diameter of the capsules was around 100−250 nm as determined by TEM, which was close to the diameter of initial droplets (d = 125 nm, determined by dynamic light scattering, DLS). The wall thickness of the NCs was about 30 nm. A great deal of black seed-like microaggregates was found to be encapsulated on the inside of the polymer shell. These microaggregates were confirmed to be crystalline structures from the electrical diffraction via TEM, as shown in Figure 3A. In this system, the core material sodium sulfate should be the only crystals. Therefore, the encapsulated microaggregates should be sodium sulfate, which was salted out from the aqueous phase during the preparation of TEM copper sample.

It was well-known that poly(NIPAM) would translate from hydrophilic to hydrophobic above its LCST (around 32 °C), which was recognized as the temperature responsive property.[29] The diameter of NCs at different temperature was determined by DLS. The final latex diluted with cyclohexane to about 0.1 wt % was measured at 25 °C first, then the temperature of DLS was set at 40 °C and the size of NCs was determined again. The NCs would shrink from d = 188 nm at the temperature of 25 °C to d = 140 nm at 40 °C, as shown in Table 1. Because the polymer chains of poly(NIPAM) as the NCs shells will stretch out into the dispersed water phase at 25 °C(below LCST) but curl or cross at 40 °C(above LCST). This indicates that these NCs with poly(NIPAM) polymer shells were temperature sensitive.

The molecular weight of the final poly(NIPAM) was determined by gel permeation chromatography (GPC) relative to polystyrene standards to be approximately 53,200. This is a little higher than the theoretical value of 35,000 attributing to the existence of little impurity in PEO−RAFT agents, which was found in NMR spectrum shown in the Supporting Information. The polydispersity of the final poly(NIPAM) was low (PDI = 1.3), indicating that the polymerization was well controlled by the PEO−RAFT agent based on the narrow molecular weight distribution.

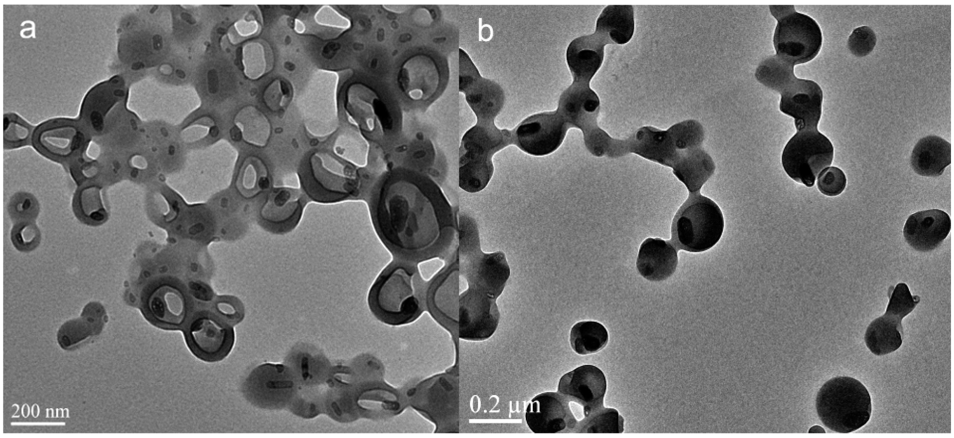


Figure 2. TEM images for the final latex: (a) RAFT interfacial inverse miniemulsion polymerization of NIPAM; (b) free radical inverse miniemulsion polymerization of NIPAM.

Table 1. Particle Size (D_v) and Polydispersity Index (PI) of the Final Latex for RAFT Interfacial Inverse Miniemulsion Polymerization at 25 and 40 °C Measured by DLS

temperature (°C)	D_v (nm)	PI[a]
25	188	0.41
40	140	0.58

[a] PI is defined as an estimate of the width of the distribution of the particle size, which is obtained via fitting a multiple exponential to the correlation function. The detail is defined in International Standard ISO 13321 Methods for Determination of Particle Size Distribution Part 8: Photon Correlation Spectroscopy, International Organization for Standardization (ISO), 1996.

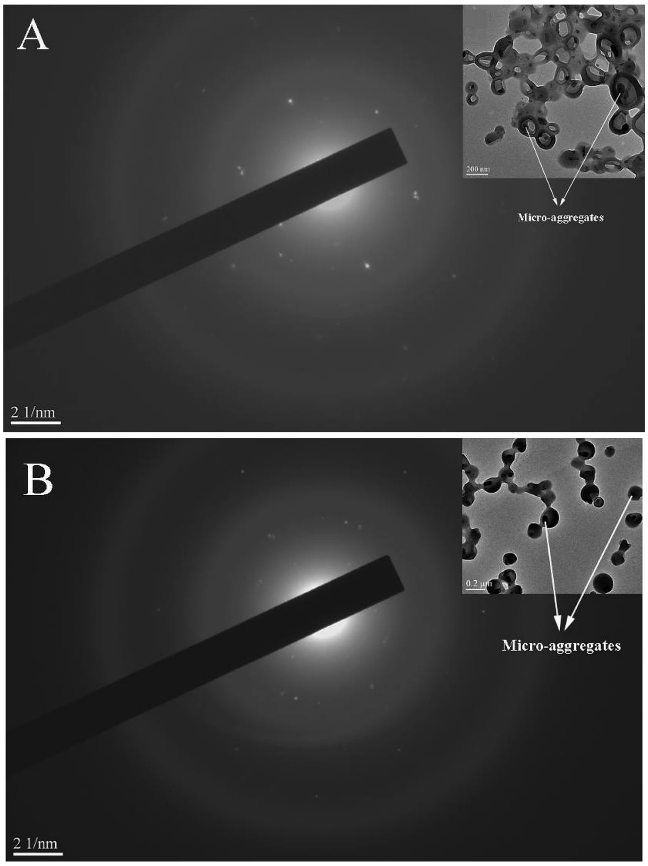


Figure 3. TEM diffraction for the microaggregates in the NCs or particles: (A) NCs from the RAFT interfacial inverse miniemulsion polymerization; (B) particles of the free radical inverse miniemulsion.

The mechanism of NIPAM free radical inverse miniemulsion polymerization is shown in Scheme 1B. Comparing with RAFT interfacial inverse miniemulsion polymerization, the poly(NIPAM) would precipitate to form aggregates inside of particles in free radical inverse miniemulsion due to the reaction temperature above the LCST of poly(NIPAM). As the poly(NIPAM) precipitated more and more, finally, the droplets nucleated into solid particles. The costabilizer sodium sulfate should still stay in the particles. But it is also definitely different from the acrylamide (AM) free radical inverse miniemulsion polymerization reported previously.[30] Solid nanoparticle morphology was found by TEM imaging of the final latex, as shown in Figure 2b. TEM diffraction shown in Figure 3B confirmed that the inorganic salt sodium sulfate was dispersed inside the particles well as the suggested mechanism.

Conclusion

A new and flexible method to synthesize temperature responsive NCs to encapsulate inorganic salt or other hydrophilic materials has been demonstrated. The method uses PEO−RAFT interfacial inverse miniemulsion polymerization to synthesize the NCs in a one-step process. The size of the NCs is about 100−250 nm and the thickness is around 30 nm. The hydrophilic core material in this case was a salt, but could be inorganic contrast agents, magnetic materials or hydrophilic pigments. The NCs could be applied in medical diagnose or pharmaceuticals therapy because of the thermo-sensitive polymer shell, which will release the core contents of the NCs around the body temperature. As the polymerization is a radical living/controlled polymerization confined in the interface, the polymer shell could be functionally modified via post reaction. The strength of the polymer shell can be increased by cross-linking polymerization to obtain rigid hollow NCs. Work is ongoing on the cross-linking polymerization of the polymer shell.

Acknowledgment. The authors would like to acknowledge the support of the National Science Foundation (Grant CTS-0553516) for this work.

Supporting Information Available: Text giving experimental details and preparation for the TEM observation of particles morphology and electrical diffraction and DLS measurements and figures showing NMR data and GPC chromatograms. This material is available free of charge via the Internet at http://pubs.acs.org.

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