Novel Synthesis and Properties of Smart Core-Shell Microgels

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Summary: A new method has been developed to prepare smart microgels that consist of well-defined temperature-sensitive cores with pH-sensitive shells. The microgels were obtained directly from aqueous graft copolymerization of *N*-isopropylacrylamide and *N,N'*-methylenebisacrylamide from water-soluble polymers containing amino groups such as poly(ethyleneimine) and chitosan. The gel diameters ranged from 300 to 400 nm with narrow size distribution. The unique core-shell nanostructures exhibited tuneable responses to pH and temperature.

Keywords: core-shell microgels; graft copolymerization; pH- and temperature-sensitive polymers

Introduction

Colloidal microgels that are able to alter their volume and properties in response to environmental stimuli, such as pH, temperature and ionic strength are attractive candidates for many potential applications including drug delivery, biosensing, separation, enzyme immobilization and soft actuators.[1] Poly(*N*-isopropylacrylamide) (PNIPAM) microgel, which has a drastic and reversible volume change in water at about 33 ^{0}C, has been the most intensively studied temperature-sensitive polymer. Polymers containing ionizable functional groups that respond to change in pH have been generally utilized as pH-sensitive polymers. Recently, microgels with more complex structures, such as a multi-responsive core-shell, have received increasing attention due to the tuneable properties of the individual responsive components. Lyon *et al* prepared core-shell microgels where the cores were composed of cross-linked PNIPAM or poly(NIPAM-co-acrylic acid), and the shells were either poly(NIPAM-co-acrylic acid) or PNIPAM.[2-4] Kuckling *et al* prepared a graft terpolymer from NIPAM, poly(2-vinylpyridine) (P2VP) macromonomer and a

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chromophore monomer based on dimethylmaleimide (DMIAAm). A polymer solution with a low pH was heated above the lower critical solution temperature (LCST) of PNIPAM and irradiated to produce pH- and temperature-sensitive core-shell microgels.[5] In this paper, we present a novel synthetic approach to prepare smart core-shell microgels based on our previously developed graft copolymerization technique.[6-8] The microgels consist of well-defined poly(*N*-isopropylacrylamide) cores with cationic water-soluble polymer shells. Hence their responsiveness to pH and temperature can be manipulated individually.

Experimental Part

Materials

N-Isoproylacrylamide (NIPAM, Aldrich) was purified by repeated recrystallization of NIPAM in a mixture of toluene and n-hexane (1:5 v/v), giving spindle-like crystals. Chitosan (medium, Aldrich) was purified by dissolving it in a dilute acetic acid solution, followed by precipitating in 10% NaOH solution under stirring at room temperature. The chitosan was then filtered and washed with distilled water to neutral and dried in a vacuum oven at 60 ^{0}C. Molecular weight measurement using solution viscosity method suggested that the M_v of chitosan was approximately 80,000. Its degree of deacetylation estimated by ^{1}H-NMR was 74%.[9] Branched polyethylenimine (PEI) with an average molecular weight of 750,000 (50 wt % solution in water), *N,N'*-methylene-bisacrylamide (MBA) and *tert*-butyl hydroperoxide (70% solution in water, TBHP) were all purchased from Aldrich Chemical Co., and used without further purification. Freshly deionized and distilled water (dd H_2O) or Milli-Q water was used as the dispersion medium.

Synthesis of PNIPAM/PEI Core-Shell Microgels

For a total 50 mL of reaction mixture, PEI (0.4 g) was first dissolved in water and the pH of the solution was adjusted to 7 with 0.64 mL of 2 M of HCl solution. A mixture of purified NIPAM monomer (0.8 g) and *N,N'*-methylene-bisacrylamide (0.08 g) was charged to the PEI solution and mixed in a water-jacketed flask equipped with a thermometer, a condenser, a magnetic stirrer and a nitrogen inlet under nitrogen for 30 min at 70 ^{0}C. Dilute *tert*-butyl hydroperoxide solution (0.5 mL, 8 x10^{-3} M) was added dropwise to the mixture, and the solution was stirred at 70 ^{0}C for 2 h under nitrogen. After the reaction, the NIPAM conversion was determined gravimetrically. The dispersion of microgels was carefully purified by repeated centrifugation at 13,000 rpm for 30 min and decantation until the conductivity of the supernatant was close to that of the water used. The dispersion was further purified by placing it into a dialysis tube with a 100,000 Da molecular weight cutoff (Spectra/ Por®CE) and dialyzed against 5 L of water for one week at room temperature with daily changing of water.

Synthesis of PNIPAM/Chitosan Core-Shell Microgels

For a total 50 mL of reaction mixture, chitosan (0.25 g) was first dissolved in a 0.6% acetic acid solution. A mixture of purified NIPAM monomer (1.0 g) and *N,N'*-methylene-bisacrylamide (0.01 g) was charged to the chitosan solution and mixed in a water-jacketed flask equipped with a thermometer, a condenser, a magnetic stirrer and a nitrogen inlet under nitrogen for 30 min at 80 ^{0}C. Dilute *tert*-butyl hydroperoxide solution (0.5 mL, 1.0 x10^{-2} M) was added dropwise to the mixture, and the solution was stirred at 80 ^{0}C for 2 h under nitrogen. The NIPAM conversion was determined gravimetrically. Purification of the PNIPAM/chitosan microgels was similar to the above procedure.

Measurement and Characterization

The volume phase transition temperatures (VPTT) of the microgels were determined by measuring the light transmittance (at 500 nm) of microgel dispersion between 20 to 40 ^{0}C at a heating rate of 0.2 ^{0}C min^{-1} with an UV Spectrometer (HITACHI U-2000). Particle size and distribution were measured on a Coulter LS 230 Particle Size Analyzer. The zeta-potential of the microgels was measured with a Malvern Zetasizer 3000HS (Malvern, UK) with a 1 x 10^{-3} M NaCl aqueous solution as the suspension fluid. ^{1}H-NMR spectroscopic determinations were made on a Bruker Advance DPX 400. Concentration of the dispersion was 10 mg/mL in a deuterium oxide solution (D_2O, 99.8 atom %D) with reference peak at 4.79 ppm. The core-shell nanostructures of the microgels were observed using a scanning transmission electron microscope (STEM, *FEI* Tachai 12) at an accelerating voltage of 120 kV after treating the particles with 2% phosphotungstic acid (PTA). The morphologies of the particles were also examined by scanning electron microscope (SEM, Stereoscan 440, Leica) after coating the dried sample with a thin layer of gold to a depth of ca. 5 Å under vacuum.

Results and Discussion

Synthesis of Core-Shell Microgels

The core-shell microgels were prepared via graft copolymerization of NIPAM from either PEI or chitosan between 70 to 80 °C in aqueous media. The *tert*-butyl hydroperoxide initially interacted with the amino groups on the polymer backbone, forming amino and *t*BuO$^{\cdot}$ radicals, which then initiated both the graft copolymerization and the homopolymerization of NIPAM concurrently in the presence of a crosslinker, *N,N'*-methylene-bisacrylamide. Since the reaction was heated above the LCST of PNIPAM, the PNIPAM became hydrophobic and phase-separated during the polymerization. The amphiphilic PEI-*g*-PNIPAM or chitosan-*g*-PNIPAM generated *in situ* thus acted like polymeric surfactants, self-assembling to form micelle-like microdomains, which subsequently promoted the emulsion polymerization of the NIPAM. Stable colloidal microgels of PNIPAM/PEI and PNIPAM/chitosan were produced in the absence of surfactant. The NIPAM conversions in both systems were higher than 90%. Isolation of unreacted PEI which may be dissolved in water or physically adsorbed on the particle surface was attempted by repeated centrifugation of the microgel dispersion at 13,000 rpm for 30 min and decantation until the conductivity of the supernatant was close to that of the water used. The supernatant collected was then dried and weighted. No PEI was isolated, indicating that all PEI molecules have been converted to graft copolymers. Isolation of unreacted chitosan was carried out by Soxhlet extraction with 1 wt% acetic acid for 48 h. The PNIPAM/chitosan microgels had only 12% chitosan, which was lower than the feed composition of 20%. Dynamic light scattering measurement indicated that average volume diameters of PNIPAM/PEI particles at pH 7 and

PNIPAM/chitosan particles at pH 4.75 produced after the polymerization were 341 nm and 361 nm, respectively. The polydispersity index (D_v/D_n) was in the range of 1.1 to 1.2, indicating narrow size distribution of the microgels. SEM image of PNIPAM/PEI microgels as shown in Figure 1a, indicates that the microgels are spherical with narrow size distribution. With careful staining of the particles, the nanostructures of the microgels were clearly revealed with STEM micrographs (Figure 1b). The microgels have well-defined core-shell morphology where PNIPAM cores are coated with hairy PEI shells. Similar morphology was also observed for PNIPAM/chitosan microgels as shown in Figure 2.

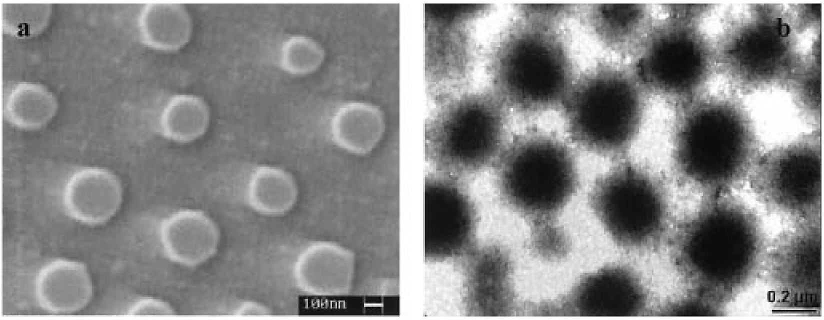

Figure 1. SEM (a) and STEM (b) micrographs of PNIPAM/PEI core-shell microgels.

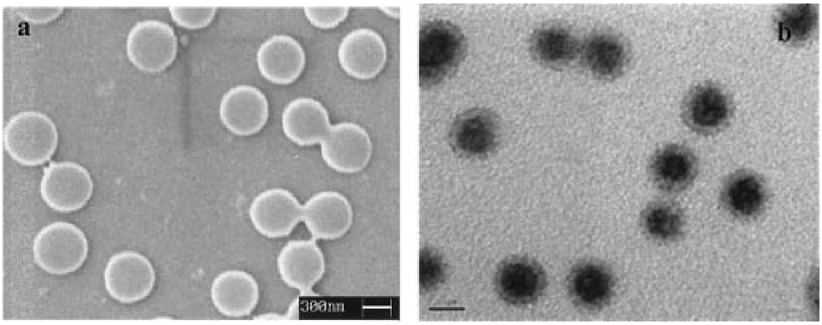

Figure 2. SEM (a) and STEM (b) micrographs of PNIPAM/chitosan core-shell microgels.

Figure 3 shows the ^{1}H-NMR spectra of the PNIPAM/PEI core-shell microgels at different temperatures. When raising the temperature from 20 ^{0}C to 40 ^{0}C, the intensity of PNIPAM peaks between 1 to 2 ppm and around 4 ppm gradually reduced, and eventually disappeared. But the PEI peaks at 2.6 to 3.3 ppm remained unchanged, indicating the presence of PEI shells. These results further confirm that the microgels have well-defined PNIPAM cores with hydrophilic PEI shells.

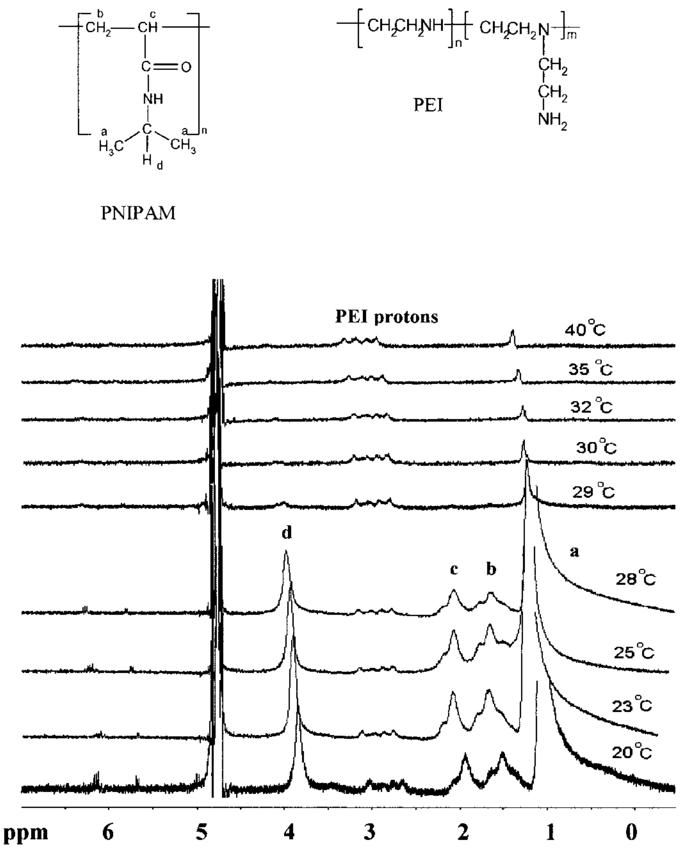

Figure 3. ^{1}H-NMR spectra of PNIPAM/PEI core-shell microgels in a D_2O solution (99.8 atom %D) at different temperatures.

Thermal-Sensitive Core

The volume phase transition temperatures of the core-shell microgels in water were examined by measuring the transmittance of the microgel dispersion as a function of temperature. Figure 4a shows that the VPTTs of the PNIPAM/PEI microgels between pH 4 to 10 were almost the same (33.5 to 33.6 ^{0}C). In other words, the increase of PEI hydrophilicity with lowering the pH of the solution had little influence on the VPTT of the PNIPAM. Similarly, little change of the VPTTs of PNIPAM/chitosan microgels was observed (between 32.9 to 33.5 ^{0}C) (Figure 4b). These results strongly suggest that the microgels have a well-defined core-shell nanostructure. Thus the properties of core and shell can be altered independently without interfering with each other.

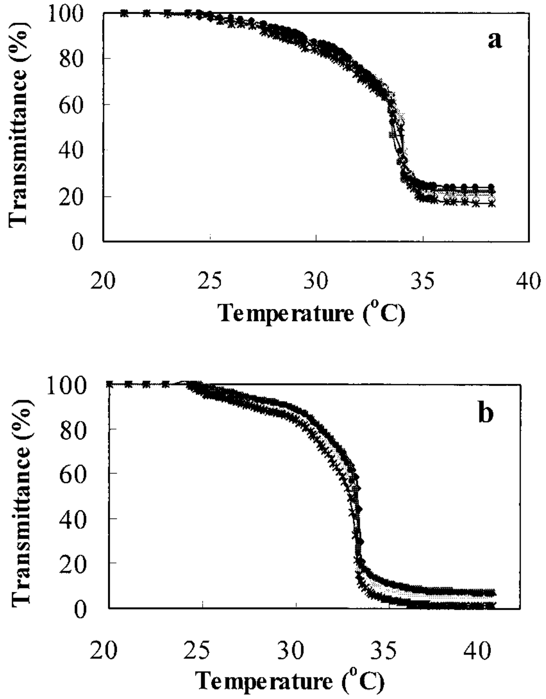

Figure 4. Effect of pH on VPTT of (a) PNIPAM/PEI core-shell microgels dispersed in dd H_2O: (+) pH 4; (●) pH 5; (*) pH 6; (×) pH 7; (▲) pH 8; (■) pH 9; (◆) pH 10; (b) PNIPAM/chitosan core-shell microgels: (□) pH 3; (■) pH 4; (▲) pH 5; (●) pH 6; (*) pH 7.

pH-Sensitive Shell

Variation of hydrodynamic sizes of PNIPAM/PEI and PNIPAM/chitosan core-shell microgels as a function of pH value was investigated with dynamic light scattering. Figure 5a shows that lowering the pH of the PNIPAM/PEI microgel dispersion from 10 to 3 significantly increased the hydrodynamic size (D_v) of the microgels from 330 to 378 nm in diameter. Since our control experiments suggested that change of pH had little influence on the particle size of PNIPAM microgels, the increase of the size was attributed to the expansion of PEI shell. A measurement of zeta-potential of the microgels indicated that positive potential increased with the decrease of pH. Therefore, the increase of particle size at a lower pH value was due to the increase of positive charges of ammonium ions and charge repulsion. Comparable size expansions of PNIPAM/chitosan microgel particles were observed when the pH was lowered from 7 to 3 (Figure 5b). These results evidently demonstrate that PEI and chitosan shells are pH-sensitive, and the thickness of the shell can be easily altered with the change of pH of the dispersing medium.

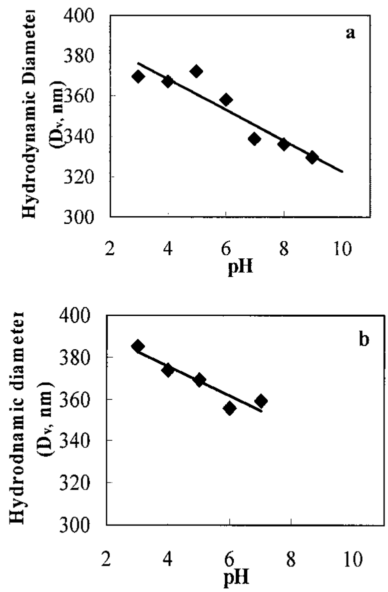

Figure 5. Effect of pH on the hydrodynamic diameter (D_v) of (a) PNIPAM/PEI, and (b) PNIPAM/chitosan core-shell microgels. Conductivity of dispersion in various pH was adjusted with 50 mM NaCl solution to approximately 10 mS.

Conclusion

A new route to prepare smart microgels that consist of well-defined temperature-sensitive cores with pH-sensitive shells has been developed. This simple and versatile method has several advantages: 1) A variety of synthetic polymers and biopolymers can be used as pH-sensitive components; 2) Well-defined core-shell microgels can be produced in the absence of surfactant; 3) Individual components can be manipulated to respond to changes in temperature and pH. Thus new smart materials prepared by this approach should be extremely useful in a wide range of applications. Detailed studies of effects of reaction variables on the particle formation and properties of PNIPAM/PEI and PNIPAM/chitosan microgels will be reported in subsequent papers.

Acknowledgment

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