Preparation of Microspheres with Silicone Oil Cores and Poly(N-isopropylacrylamide) Shells by Physical Coating

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ABSTRACT: Surfactant-free thermoresponsive microspheres with a silicone oil cores surrounded by poly(N-isopropylacrylamide) shells have been successfully prepared by physical coating method for the first time. The influences of reaction temperature, N-isopropylacrylamide (NIPAM) dosage, and stirring rate on the formation, morphology, particle size, and monodispersity of microspheres were experimentally studied. In the preparation of microspheres, when reaction temperature was above the lower critical solution temperature of poly(N-isopropylacrylamide), products had higher yield of particles and narrower size distribution. With increasing NIPAM dosage, the particle diameter became larger and the shell layer thickened and the monodispersity became better. With increasing stirring rate, the particle diameter and the monodispersity decreased obviously. © 2006 Wiley Periodicals, Inc. J Appl Polym Sci 102: 5571–5576, 2006

Key words: physical coating; thermoresponsive microspheres; formation of microspheres

INTRODUCTION

Thermoresponsive polymeric hydrogels attract increasing attention due to their potential applications in numerous fields,[1–3] including, controlled drug delivery,[4–9] chemical separations,[10,11] sensors,[12–14] catalysis,[15] and enzyme immobilization.[16] Because microgel particles have a high surface-to-volume ratio that is several orders of magnitude larger than that of a comparable macrogel,[17] and the characteristic time of gel swelling has been reported to be proportional to the square of a linear dimension of the hydrogels,[18] in recent years much attention has been focused on small-sized thermoresponsive hydrogel microspheres.[2,3,19–30]

As the main material of thermoresponsive hydrogel, poly(N-isopropylacrylamide) (PNIPAM) exhibits a reversible phase separation in aqueous media at its lower critical solution temperature (LCST) around 32°C. That is, it swells below 32°C and shrinks above 32°C. Because its LCST is close to physiological temperature, PNIPAM-based hydrogel microspheres have been studied heavily[2,3,19–27] and most are with core-shell structure[2,3,19–26] and are prepared by copolymerization[2,3,19–20,23,24,27] or graft method.[21,22,26,27]

For drug-delivery system, the invariant of size and shape of the core limits the loading or releasing of drug. And in some case, it is necessary that drug be enclosed inside particles. So we explored to use PNIPAM chains and oil phase including drug by physical coating to prepare core-shell microsphers and expected such microspheres can keep drug from releasing before arriving at target and its interior provides larger space for drug, which has not been any reports. Because surfactant heavily affects on thermosensitive characteristics of hydrogel particles,[1] in this work, we adopted to silicone oil to act as oil phase and N-isopropylacrylamide (NIPAM) monomer to prepare core-shell microspheres without surfactant. Its schematic illustration of physical coating mechanism is shown in Figure 1. After prepared by free radical polymerization, PNIPAM chains were absorbed on the surface of silicone oil droplets to form shell layer. Absorbed PNIPAM chains acted as surfactant to stabilize microspheres. Experimental investigations were carried out on formation, morphology, the particle size, and monodispersity of microspheres. The objective of this work was to provide some valuable guidance for the preparation of small-sized core-shell thermoresponsive hydrogel microspheres.

EXPERIMENTAL

Materials

The NIPAM was kindly provided by Kohjin (Tokyo, Japan), and was used after purifying by recrystallization in hexane and acetone and then drying *in vacuo* at room temperature. A silicone oil, polydimethylsiloxane,
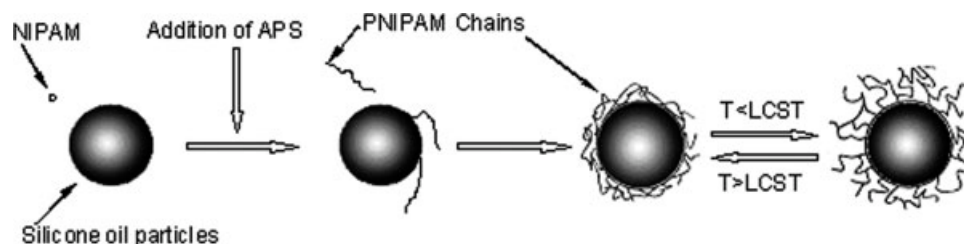
Figure 1 Schematic diagram of preparation of core-shell microshperes by physical coating method.

of type H201 with viscosity of 9.78 Pa s and density of 0.968–0.978 g cm^{-3}, manufactured by Changzhou Longchen Organosilicon (Changzhou, China) was selected as oil phase without any further purification. Silicone oil was chosen because it is transparent, chemically inert with respect to gels and the solvents used and sufficiently viscous, enabling to exert the stresses necessary to deform the gel particles. The initiator ammonium persulfate (APS), the accelerator N,N,N′,N′-tetramethylethylenediamine (TEMED), and the crosslinker N,N′-methylenebisacrylamide (MBA) were of analytical grade and used as received without any further purification. Double-distilled water was used in all the synthesis processes.

Preparation of microspheres with PNIPAM shell layer

A mixture of NIPAM, MBA (1 mg), hydrophobic silicon oil, double-distilled water (50 mL), and a few TEMED was sheared at some rate in a 150-mL round-bottom flask equipped with a condenser, a nitrogen inlet, and a stirrer. Nitrogen was bubbled into the solution to remove oxygen in all the synthesis processes. After the emulsification continued for 30 min, the polymerization was initiated by slowly adding 5 mL of an aqueous solution containing 0.014 g APS and was allowed to proceed for 4 h at some reaction temperature. After APS aqueous solution was added, the stirring rate was kept at 200 rpm. Experimental parameters are listed in Table I.

Morphological analysis

Morphology is a critical factor to analyze final result. In this work, the morphology of core-shell microspheres was observed by a JEM-100CX II-type transmission electron microscope (TEM) operating at 100 kV. All samples were stained by phosphate–tungstic acid.

Determination of mean diameter and size distribution of microspheres

The size distribution of dry microspheres was determined using a digital image analysis system on the basis of the TEM photographs of the microspheres. In the analysis, the particle number of each sample was always more than 300. To describe the monodispersity of microspheres quantitatively, an index named particle size dispersal coefficient, δ, is defined as:

$$\delta = \frac{D_{90} - D_{10}}{D_{50}} \tag{1}$$

where D_n ($n = 10$, 50, and 90) denotes the cumulative number percentage of particles with diameter up to D_n is equal to $n\%$. The smaller the value of δ, the narrower the size distribution, that is, the better the monodispersity.[27,29]

Determination of thermoresponsive characteristics of the core-shell microspheres

The hydrodynamic diameters of the prepared core-shell hydrogel microspheres at different temperatures were determined by temperature-programmed photon correlation spectroscopy (TP-PCS; Brookhaven BI-9000AT). This technique has been applied extensively to the characterization of such material, as it allows for *in situ* size characterization of soft material that cannot be reliably sized by electron microscopes due to deformation and/or dehydration under vacuum.[2] The dispersed particles in water were allowed to equilibrate thermally for 10–15 min before measurements were taken at each temperature. The hydrodynamic diameters of particles were calculated from diffusion coefficients by the Stokes–Einstein equation, and all correlogram analyses were performed using the manufacturer-supplied software. In the data presented in this study, each data point at a given temperature rep-

TABLE I
Experimental Parameters for the Preparation of Core-Shell Microspheres

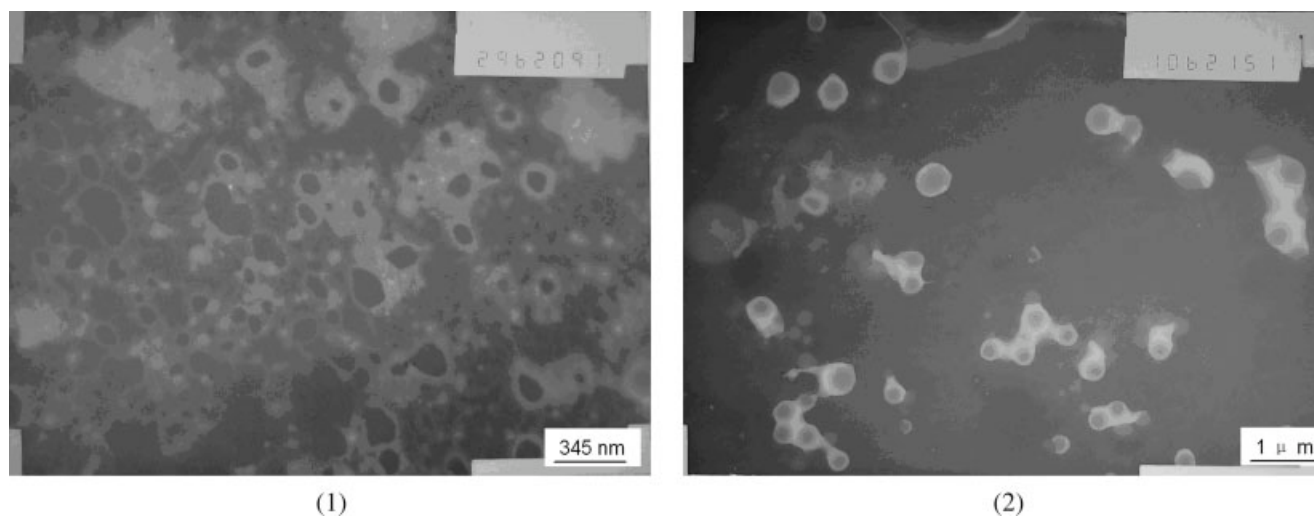| Sample number	NIPAM dosage (g)	Volume of silicone oil (mL)	Reaction temperature (°C)	Stirring rate (rpm)
1	0.15	0.10	27	600
2	0.15	0.10	40	600
3	0.15	0.10	40	600
4	0.20	0.10	40	600
5	0.15	0.50	40	600
6	0.15	0.50	40	1000

Figure 2 TEM micrographs of microspheres prepared at different polymerization temperatures. Scale bar: (1) 345 nm; (2) 1 μm. The sample code is defined in Table I.
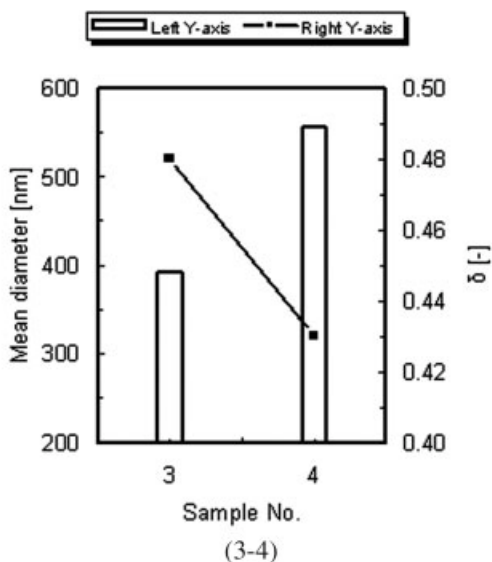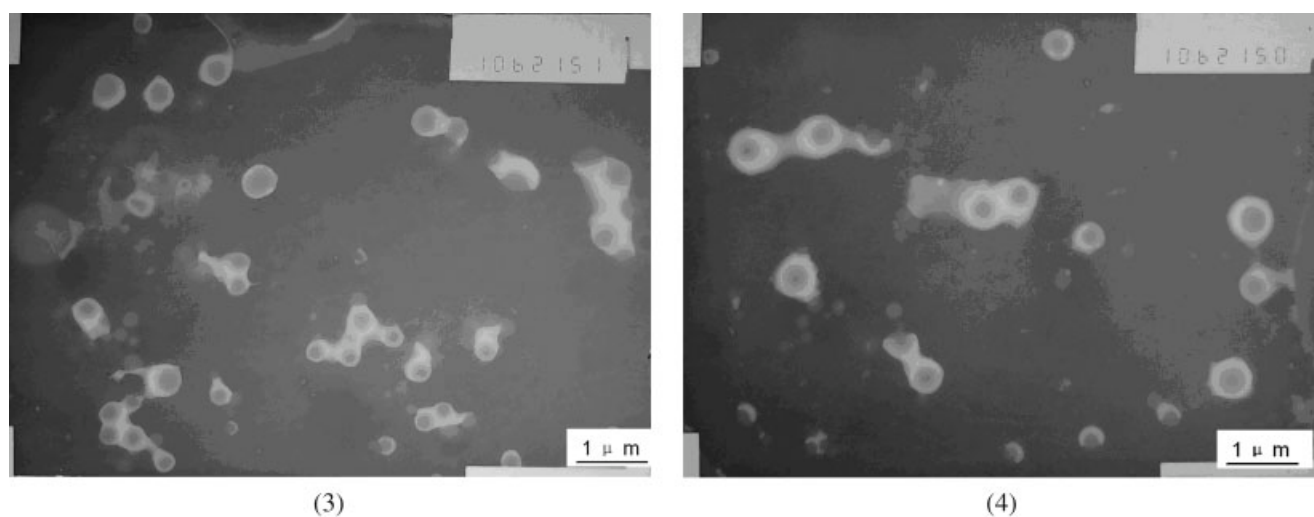

Figure 3 TEM micrographs of microspheres prepared with different NIPAM dosages and the effect of NIPAM dosages on the size and monodispersity of microspheres. Scale bar: (3) and (4) 1 μm. The sample code is defined in Table I.

resents the average valve of 15–20 measurements, with a 20-s integration time for each measurement.

RESULTS AND DISCUSSION

Effect of reaction temperature on formation of microspheres

Figure 2(1, 2) shows the TEM photographs of PNIPAM microspheres prepared at different reaction temperatures. The TEM micrographs show that the resulting microspheres at 40°C are satisfactorily spherical with core-shell structure. While under lower temperature (27°C), microspheres have very lower yield and larger monodispersity. This is because PNIPAM chains are hydrophilic and exist in aqueous media, then it is difficult that these chains are absorbed on surface of silicone oil droplets when reaction temperature is below the LCST of PNIPAM, and when stirring rate decreasing after adding APS, the silicone oil droplets will be unstable and aggregate together to form larger droplets. The final will result in phase separation, few microspheres and the worse monodispersity. When reaction temperature is above LCST, however, hydrophobic character of PNIPAM chains has larger affinity to silicone oil and PNIPAM chains are absorbed easily on the surface of silicone oil droplets. In the following experiment, the adopted reaction temperature is at 40°C.

Effect of NIPAM dosage on formation of microspheres

To prepare microspheres with core-shell structure, we explored different phase ratios of NIPAM dosages and volumes of silicone oil. The conclusion is that the
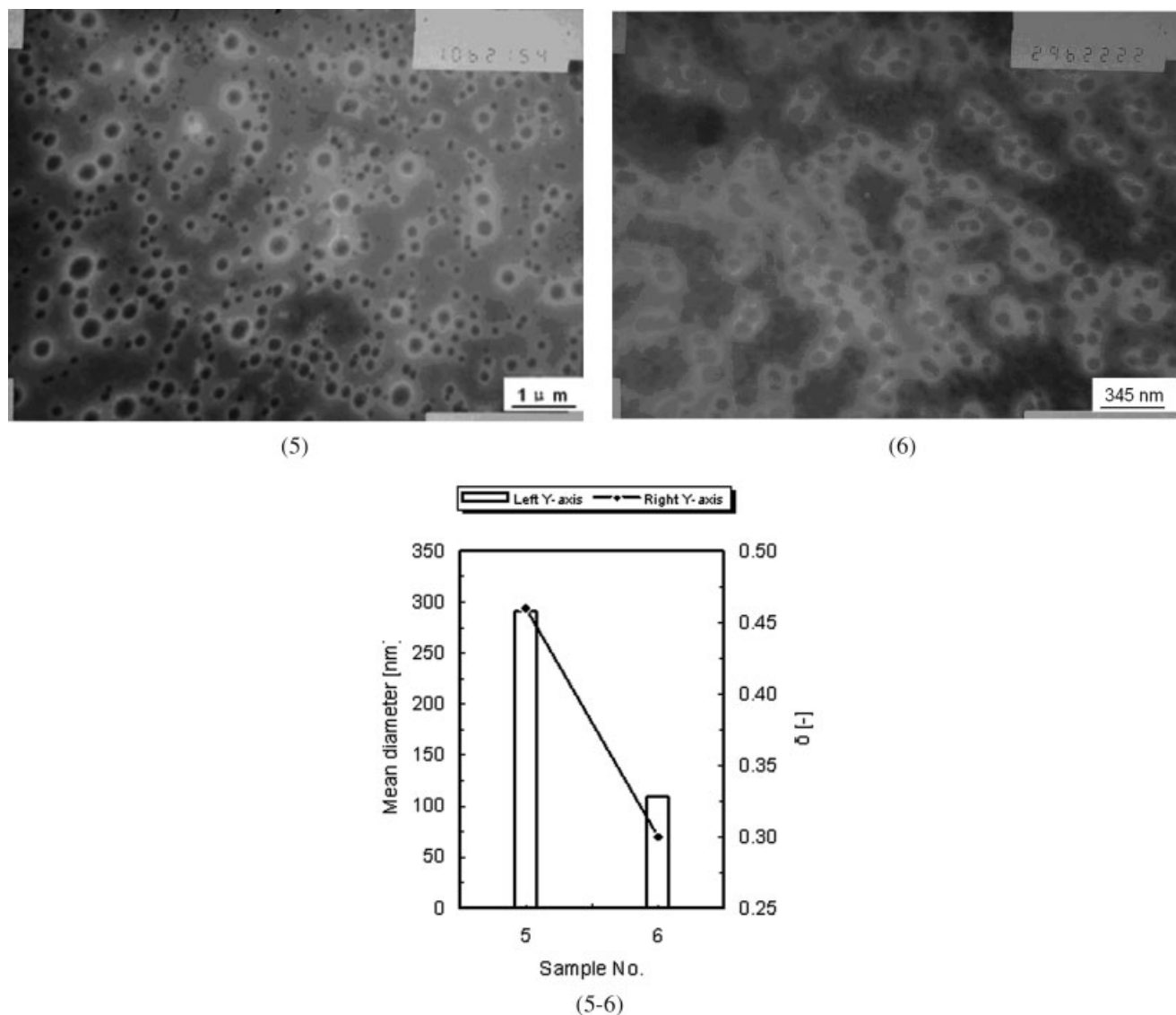

(5)

(6)

(5-6)

Figure 4 TEM micrographs of microspheres prepared with different stirring rates and the effect of stirring rates on the size and monodispersity of microspheres. Scale bar: (5) 1 μm; (6) 345 nm. The sample code is defined in Table I.
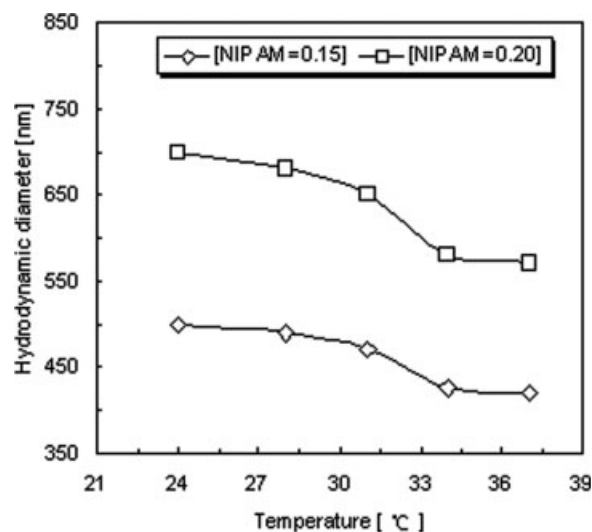
Figure 5 Effect of NIPAM dosages on temperature-sensitive characteristics of core-shell microspheres.

microspheres could not be prepared when the phase ratio is less than about 15% (g mL^{-1}). Figure 3(3, 4) illustrates the TEM photographs of microspheres prepared with different NIPAM dosages and the effect of NIPAM dosages on the size and monodispersity of PNIPAM microspheres. With the NIPAM dosage increasing, the diameter of the prepared microspheres became larger and the shell thickness increased and the monodispersity became better. The increase in monomer amount provided more materials for the particles growth. For this study, PNIPAM chains were located on the surface of silicone oil droplets, therefore the diameters of the microspheres became larger and the shell thickened with increasing NIPAM dosage correspondingly. In the surfactant-free emulsion polymerization of this study, monomer NIPAM and its polymers are hydrophilic, so its polymers played the role of stability and scattering action during the course of reaction.[1] When NIPAM dosage was lower, the precursor particles had no enough PNIPAM chains to act as stabilizers, the particles aggregated and could not grow normally, which lead to worse monodispersity of particles size.

Effect of stirring rate on formation of microspheres

Figure 4(5, 6) shows the TEM micrographs of microspheres prepared with different stirring rates and the effect of stirring rates on the size and monodispersity of PNIPAM microspheres. With increasing stirring rate, the particle diameter and the monodispersity decreased obviously. Because droplets of silicone oil acted as template, in fact in this study, the size and monodispersity of droplets affect inevitably these of final product. The droplets formation required me-

chanical stirring. With increasing stirring rate, the shear forces in fluids increased, with the results that the droplets of silicone oil became smaller and the monodispersity became better; correspondingly, the produced microspheres became smaller in size and better in size distribution.

Thermoresponsive characteristics of the core-shell microspheres

Figure 5 shows the effect of NIPAM dosages on the thermoresponsive swelling characteristics of the core-shell microspheres. With increasing the NIPAM dosage, the thermoresponsive swelling ratio of the hydrodynamic diameters of the core-shell microspheres at temperatures below the LCST of PNIPAM to those above the LCST increased. The hydrophilic groups of PNIPAM chains on the core-shell microsphere surfaces formed hydrating layers by hydrogen bond with water. The longer the PNIPAM chains, which resulted from increasing the NIPAM dosage, the thicker the hydrating layer, and then the larger the hydrodynamic diameter. The thickness of the hydrating layer decreased because of the breakage of hydrogen bonds with increasing temperature. When temperature approached to the LCST, hydrogen bonds were broken seriously, which led to the thickness of hydrating layer decreased rapidly, and then the PNIPAM polymer chains collapsed quickly, resulting in a rapid decrease in the hydrodynamic diameters of the core-shell microspheres. Figure 5 displays the microspheres are thermosensitive and are stable in water.

CONCLUSIONS

In this study, soap-free thermoresponsive hydrogel microspheres with silicone oil cores and PNIPAM shells were successfully prepared by physical coating method for the first time. The influence of reaction temperature, NIPAM dosage, and stirring rate on the formation, morphology, particle size, and monodispersity of microspheres were experimentally studied. In the preparation of microspheres, when reaction temperature was higher than the LCST of PNIPAM, microspheres had higher yield of particles and narrower size distribution. With increasing NIPAM dosage, the diameter became larger and the shell layer thickened, and monodispersity became better. With increasing stirring rate, the particle diameter and the monodispersity decreased obviously.

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