Chem. Mater. **2007,** *19,* 5839–5841 5839

Synthesis of Thermosensitive Hollow Spheres via a One-Pot Process

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Received May 23, 2007
Revised Manuscript Received October 16, 2007

In recent years, functional hollow spheres have attracted intense research interest because of the variety of potential applications, such as drug delivery systems,[1–3] protection of biological active agents,[4,5] water treatment,[6] and catalysis.[7–9] To control the transport and delivery of guest materials into the hollow spheres under particularly demanding conditions, "smart" hollow spheres, which are sensitive to temperature,[10–12] pH,[13–15] and ions,[16] have been reported. For the construction of "smart" hollow spheres, poly(*N*-isopropylacrylamide) (PNIPAM) has been widely investigated because of its sharp thermosensitive phase transition at the lower critical solution temperature (LCST) around 32 °C.[17] As shown in recent studies, a variety of strategies, including precipitation polymerization onto templates,[10,12,18] layer-by-layer techniques,[11,19,20] and emulsion/interfacial polymerization strategies,[21–23] have all been employed to prepare polymeric hollow spheres. Among these strategies, the method of precipitation polymerization onto templates is the most popular. In a typical procedure, a sacrificial core is introduced as a template onto which a polymer shell is formed. This core then degrades, leaving behind a hollow sphere. For instance, Zha et al.[10] synthesized silica particles with polymerizable units on the surface, which were further reacted with PNIPAM via polymerization. Hollow spheres were then obtained after dissolving the silica particles in HF solution. There are a number of shortcomings associated with this synthetic strategy. First, the multistep process needed for the preparation of the core/shell particles, e.g., the synthesis of core particles, the modification of the particles, the coating of the shell materials, and degradation of the cores, is both complicated and time-consuming. Second, the introduction of an etching agent and the dissolved byproducts during the degradation process pollute the hollow spheres, thereby limiting the application of these hollow spheres in some biological and medical fields. The emulsion/interfacial polymerization strategies provide an in situ way to produce the hollow structure.[21] However, organic solvents and a large amount of surfactant are necessary. Therefore, the development of facile and green methods for the preparation of thermosensitive hollow spheres remains a great challenge.

Herein, we propose a novel synthetic strategy to prepare thermosensitive hollow spheres via a one-pot process, such that the formation of the shells and dissolution of the cores are fulfilled in the same medium. Furthermore, all of the processes are carried out in aqueous condition, without the use of organic solvents or etching agents. As is well-known, the polymerization of the PNIPAM in aqueous solution above the LCST could be considered as a precipitation polymerization method. A typical precipitation polymerization process consists of two major stages: a nucleation stage and a nucleus-growing stage.[24] In the nucleation stage, the formed oligomers coagulate to form nuclei. After the nucleation stage, the quantity of nuclei remains constant. During the following nucleus-growing stage, the sizes of the formed nuclei increase by capturing the oligomers being formed in solution until all of the monomer is consumed. On the basis of the mechanism of the precipitation polymerization mentioned above, the one-pot process illustrated in Scheme 1 is proposed. The whole synthetic procedure is composed of three stages. The first one is the nucleation stage. When the polymerization is initiated above the LCST, the formed hydrophobic PNIPAM oligomers precipitate from the aqueous medium and aggregate to form nuclei, which could be considered as non-cross-linked templates. In the following nucleus-growing stage, as the nuclei grow, cross-linked shells

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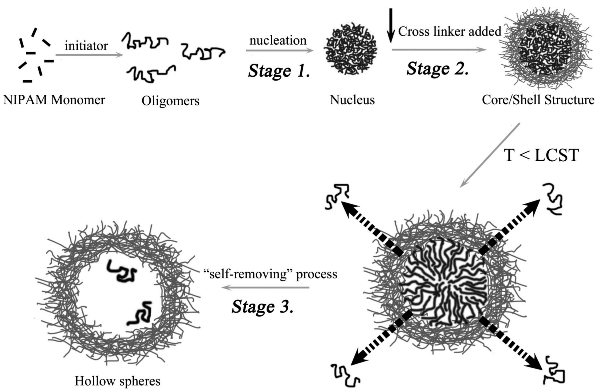
10.1021/cm071391k CCC: $37.00

Scheme 1. Schematic Illustration of the Preparation Route To Form PNIPAM Hollow Spheres



can be formed on the nuclei by adding a cross-linking agent to give a core–shell structure with a non-cross-linked core and a cross-linked shell. The final stage involves a “self-removing” process in which the dissolution of the core takes place spontaneously without the addition of an etching agent. However, by reducing the temperature below the LCST, it is possible to change the PNIPAM from a hydrophobic to hydrophilic polymer. Thus, the PNIPAM in the non-cross-linked cores is considered to penetrate through the cross-linked shells into the aqueous phase to form cross-linked PNIPAM hollow spheres.

To make a comparison, a sample, namely, N1, was synthesized as the conventional microgels. For the synthesis of sample N1, a cross-linker material was added to the solution before the polymerization was initiated.[25] Another sample, namely, N2, was prepared by the suggested strategy.

TEM analysis gave direct evidence for the synthetic mechanism. A typical TEM image of sample N1 (Figure 1A). indicates that the particles are solid spherical microgels with a netlike fine structure. In contrast, the TEM image of sample N2 before the “self-removing” treatment (Figure 1B) shows that the particles clearly display core–shell structures. The core–shell particles are composed of non-cross-linked PNIPAM cores and cross-linked shells. As the non-cross-linked core is more shrinkable than the cross-linked shell, it could be seen that there is a region with low density formed between the core and shell due to drying in the process of TEM sample preparation. The obvious difference between the TEM images of the two samples confirms that the nuclei formed in the polymerization stage act as non-cross-linked templates, whereas the residual NIPAM (in the presence of an added cross-linker) is polymerized onto the templates to form the cross-linked shells. The TEM image of sample N2 after the “self-removing” treatment (proceeded at about 25 °C) is shown in Figure 1C. It could be seen that the core (the gray part in the center of the particle) in the Figure 1B is disappeared and left behind a hollow structure. The clearly hollow structure in Figure 1C compared with the core–shell structure in Figure 1B indicated that the “self-removing” process does indeed occur and the process is near complete. It can also be seen that, before the “self-removing” process (Figure 1B), the shells of sample N2 are fairly compact, whereas after the “self-removing” process (Figure 1C), the shells became a little less compact because of the diffusion of the PNIPAM in the core. Further evidence for the hollow structures was obtained by SEM and freeze−fracture TEM investigation of the N2 hollow spheres (see the Supporting Information).

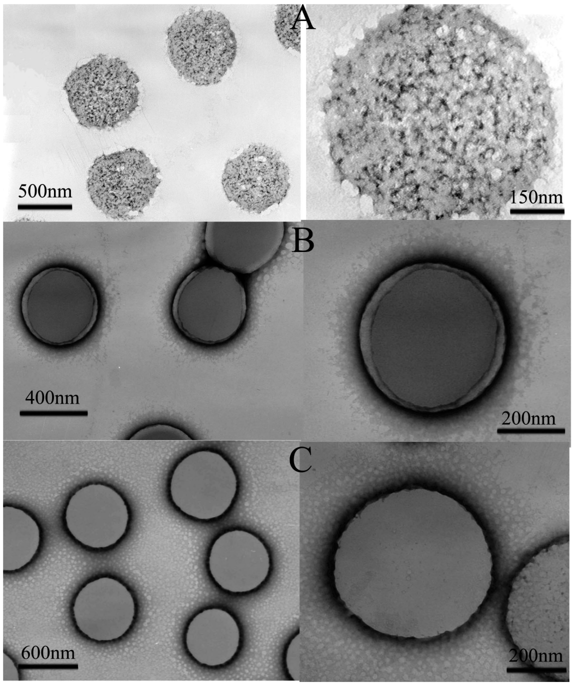


Figure 1. TEM images of sample N1 (A), and sample N2 before (B) and after (C) the self-removing process.

It is found that introducing additives, such as surfactant (e.g., sodium dodecyl sulfate) and electrolytes (e.g., NaCl), into the reaction solution, has significant influence on the size of finally obtained hollow spheres. The size of the hollow spheres decreases with the increasing content of the sodium dodecyl sulfate (SDS) or the decreasing of the NaCl concentration. Through modulating the content of SDS between 0% and 0.15% (mole ratio of SDS to *N*-isopropylacrylamide), a series of PNIPAM hollow spheres with the diameter ranging from 838 to 280 nm were obtained, whereas controlling the concentration of the NaCl between 0 and 0.015 M led to a series of PNIPAM hollow spheres with diameter ranging from 838 to 1467 nm was obtained (Figure 2). The results were also supported by the TEM analysis (see the Supporting Information). However, when the SDS content and the NaCl concentration were relatively high, for example, 0.15% SDS or 0.015 M NaCl, some solid spherical microgels were also observed. As we all know, the size of the hollow spheres is dependent on the size of the templates. In our strategy, the nucleus, which is used as the non-cross-linked template, is stabilized by electrostatic repulsion originating from sulfate groups that come from the persulfate initiator.[26] A stable nucleus should contain a certain number (called average aggregation number) of oligomers to mentain adequate surface charge density. These electrostabilized particles were senitive to the surfactants and electrolytes. The

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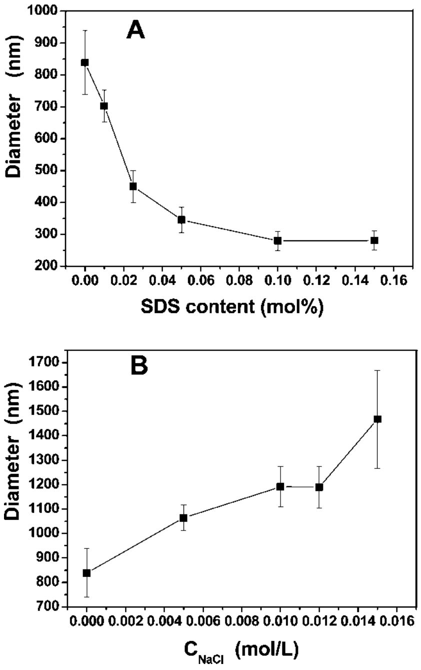

Figure 2. Influence of SDS content (A) and NaCl concentration (B) on the diameter of PNIPAM hollow spheres.

surfactants can participate in the nucleation process and stabilize these formed nuclei so that the average aggregation number of the nuclei can be reduced; in other words, the size of the nuclei could be decreased. The electrolytes can weaken the electrostatic repulsion among the nuclei, so that the average aggregation number should be increased in order to mentain sufficient surface charge density. The detailed work on the stability and size control of the self-assembled PNIPAM particles has been reported by Pelton et al.[26] Consequently, through controlling the size of the nuclei, we could modulate the size of the hollow spheres.

The hollow spheres composed of PNIPAM showed temperature sensitivity as a basic property. The temperature-induced volume transition of the N2 hollow spheres was investigated with photon correlation spectroscopy, determined to be a useful technique for characterization of such materials.[27] As shown in Figure 3, the volume phase transition takes place around 32 °C. As the temperature increased from 25 to 43 °C, the hydrodynamic diameter of the N2 hollow spheres decreased from 1022 to 319 nm, which means that the volume of the hollow spheres decreases by about 30 times.

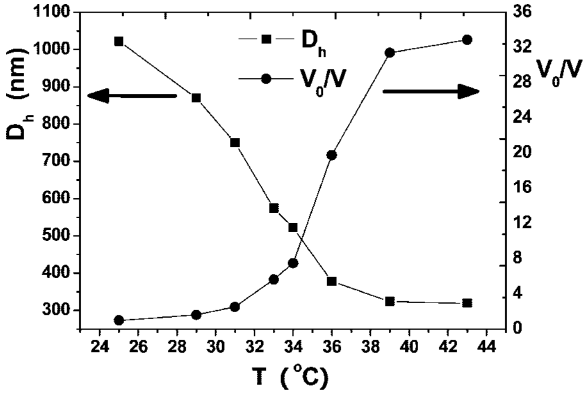

Figure 3. Variation in D_h and V_0/V (V_0 corresponds to the volume of the hollow spheres at 25 °C) of PNIPAM hollow spheres as a function of temperature.

In conclusion, a novel approach to prepare thermosensitive PNIPAM hollow spheres based on a precipitation polymerization method has been demonstrated. The formed nuclei in the nucleation stage played the role of non-cross-linked templates, on which cross-linked PNIPAM shells were formed by adding a cross-linker to the aqueous solution during the following nucleus-growing stage. A “self-removing” process was found to take place when the temperature of the reaction solution was reduced below the LCST, where the non-cross-linked PNIPAM spontaneously penetrated through the cross-linked shells to form the hollow spheres. All of these synthetic processes including the synthesis of the core, the formation of the shell, and last the dissolution of the core, occurred in the same media, water, and neither organic solvent nor etching agent was needed. Further more, the size of the hollow spheres could be easilily controlled ranging from the submicrometer scale to the micrometer scale by modulating the surfacatant content and the electrolyte concentration. On the basis of this technique, we also also prepare other PNIPAM hollow spheres with pH sensitivity by introducing a second monomer (e.g., acrylic acid, methyl acrylic acid, vinyl imidazole, etc.), and the related result will be reported in the near future.

Supporting Information Available: Synthesis details and summaries of the various characterization studies (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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