Polymer Nanoparticles

Supercritical-Fluid Processing Technique for Nanoscale Polymer Particles[**]

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It remains a challenge to develop reliable and versatile techniques for the production of well-dispersed organic and polymeric nanoparticles (that is, particles of 100 nm or less) for various applications (e.g., drug delivery).[1,2] Several supercritical-fluid processing methods have been identified as being promising for such a purpose.[3–7] In particular, particle formation via the rapid expansion of a supercritical solution (RESS) has been studied extensively.[8–23] In traditional RESS, the solute is dissolved in a supercritical fluid to form a solution, followed by the rapid expansion of the solution across an orifice or a capillary nozzle into ambient air. The high degree of supersaturation accompanying the rapid pressure reduction in the expansion results in homogenous nucleation and thereby the formation of well-dispersed particles.[24,25] Results from mechanistic studies of different model solutes by the RESS process indicate that both nanometer- and micrometer-sized particles are present in the expansion jet, though microparticles are generally obtained as primary products.[9,17,18,24,25]

We have made a simple but significant modification to the traditional RESS process by expanding the supercritical solution into a liquid solvent instead of ambient air, or the *r*apid *e*xpansion of a supercritical solution into a liquid *solv*ent (RESOLV).[7,26] The liquid solvent apparently suppresses the particle growth in the expansion jet, thus making it possible to obtain primarily nanosized particles. We have applied RESOLV to the preparation of small nanoparticles (less than 10 nm) with relatively narrow size distributions from a variety of inorganic materials, which include nanoscale semiconductors, metals, and metal oxides.[7,26–32] In addition, a unique feature of the RESOLV method is that it requires no nanoscale templating agents for nanoparticle formation because the templating effect is provided by the "supercritical fluid rapid expansion process", thus offering a clean way to directly couple the nanoparticles with biological species.[31,32]

In this paper we report the application of RESOLV to the preparation of nanoscale (on average less than 50 nm) polymeric particles. The selected polymer poly(heptadecafluorodecylacrylate) (PHDFDA) is highly soluble in supercritical CO_2 (under various conditions such as a pressure of 130–210 bar and a temperature of 35 °C) but insoluble in water, amenable to the RESOLV processing by rapidly expanding a supercritical CO_2 solution of the polymer into an aqueous medium. The results from characterizations of the polymeric nanoparticles produced under various experimental conditions are presented and discussed.

A RESOLV setup for the preparation of polymeric nanoparticles is shown in Figure 1. In a typical experiment, a CO_2 solution of the polymer PHDFDA (0.3 wt %) was pressurized in a syringe pump and pushed through the heating unit (a copper block wrapped with a stainless steel tube) to attain the desired supercritical temperature (35 °C) before reaching the expansion nozzle. The expanded solution (pre-expansion pressure of 207 bar) was passed through the nozzle (fused silica capillary hosted in stainless steel tubing) into a chamber containing ambient water. Since the polymer is insoluble in water, it precipitated to form nanoscale particles. The expansion of the supercritical CO_2 solution (60 mL) took about 30 min. In the first 5 min of the rapid expansion, the aqueous nanoparticle suspension appeared clear and stable. An aliquot of the clear suspension was used to prepare a specimen for scanning electron microscopy (SEM) analysis.

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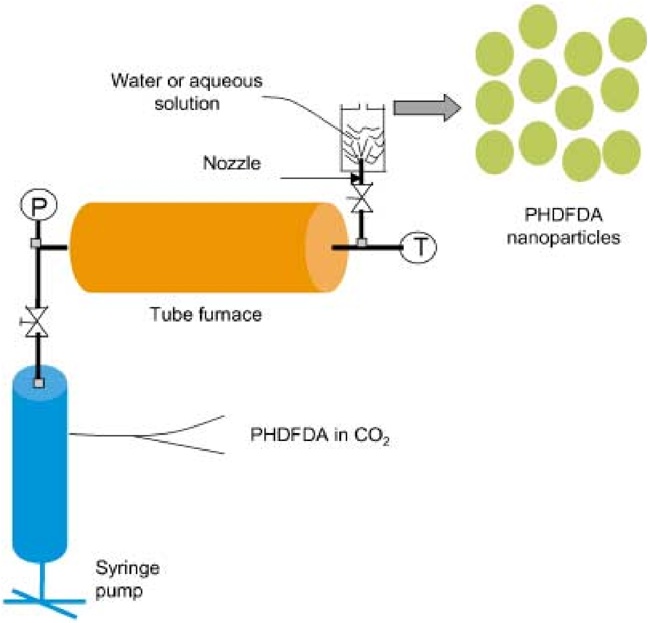

Figure 1. Experimental setup for the preparation of polymeric nanoparticles using the RESOLV process. PHDFDA = poly(heptadecafluorodecylacrylate)

The SEM image thus obtained exhibits dispersed small aggregates of nanoparticles (Figure 2). The result from an energy dispersive X-ray (EDX) analysis of the specimen confirms the presence of C, O, and F in compositions consistent with those of PHDFDA. As the rapid expansion progressed (about 15 min and longer), larger objects were seen to form in the aqueous suspension. According to SEM analyses, these suspended objects are larger aggregates of PHDFDA nanoparticles (Figure 2). It seems reasonable to suggest that the RESOLV process intrinsically produces small PHDFDA nanoparticles suspended in water and that these initially produced nanoparticles of high surface areas agglomerate to form larger aggregates in the absence of any stabilization agents in the aqueous suspension.

In an effort to prevent agglomeration of the initially formed PHDFDA nanoparticles, an aqueous NaCl solution (0.5 M) was used instead of water at the receiving end in the rapid expansion process. The increased ionic strength in the initially formed nanoparticle suspension had some stabilization effect, slowing down the agglomeration process by some degree. As shown in Figure 3, the initially formed PHDFDA nanoparticles have an average diameter of 43 nm, with a standard deviation of 8.5 nm. However, even in the presence of NaCl, the nanoparticles began to agglomerate to form visible larger aggregates during the RESOLV process. An SEM image of the nanoparticle aggregates is also shown in Figure 3.

A highly basic aqueous solution of NaOH (pH ≈ 11–12) was also evaluated for use at the receiving end in the rapid expansion process. The purpose was to test an idea, taken from inorganic nanoparticle research, of attaching OH^- ions to the surfaces of the initially formed PHDFDA nano-

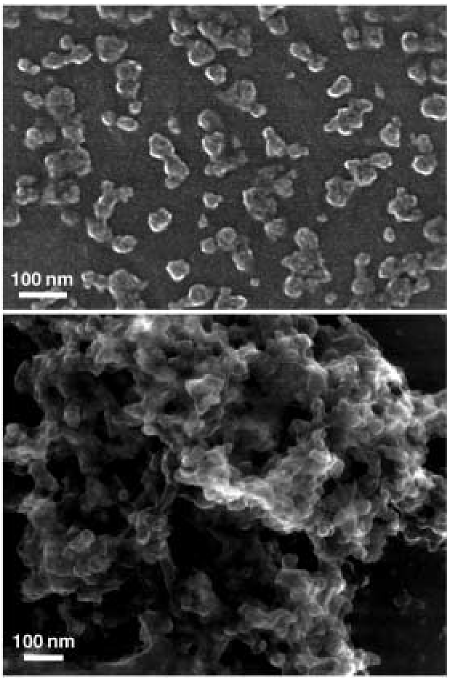

Figure 2. SEM images of PHDFDA nanoparticle specimens from aqueous suspension, obtained about 5 min (top) and 15 min (bottom) after the start of the rapid expansion process.

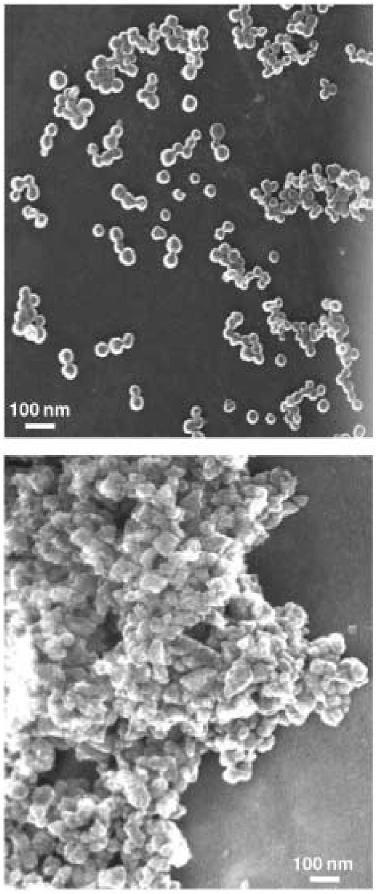

Figure 3. SEM images of PHDFDA nanoparticle specimens prepared from an aqueous suspension containing NaCl (0.5 M), obtained about 5 min (top) and 15 min (bottom) after the start of the rapid expansion process.

particles, to prevent agglomeration due to attractive interparticle interactions. Experimentally, however, the high pH value did not stabilize the initially formed nanoparticles to a greater degree than with NaCl, as discussed above.

The PHDFDA nanoparticles formed in the RESOLV process could be protected from agglomeration by adding a surfactant such as sodium dodecyl sulfate (SDS) to a basic aqueous solution (pH ≈ 11) at the receiving end in the rapid expansion process. In the presence of SDS (20 mM), the aqueous suspension of PHDFDA nanoparticles remained stable for an extended period of time (at least several days). The dispersion of the nanoparticles in a stabilized aqueous suspension was confirmed by SEM analyses (Figure 4). SEM images of the specimen prepared from the suspension following the RESOLV experiment exhibit no large nanoparticle aggregates. The result from an EDX analysis of the sample indicates the presence of C, F, O, S, and Na, consistent with the SDS protection of PHDFDA nanoparticles. According to a statistical analysis of the SEM images, these nanoparticles have an average diameter of 41 nm when approximated as spheres, with a standard deviation of 8.5 nm.

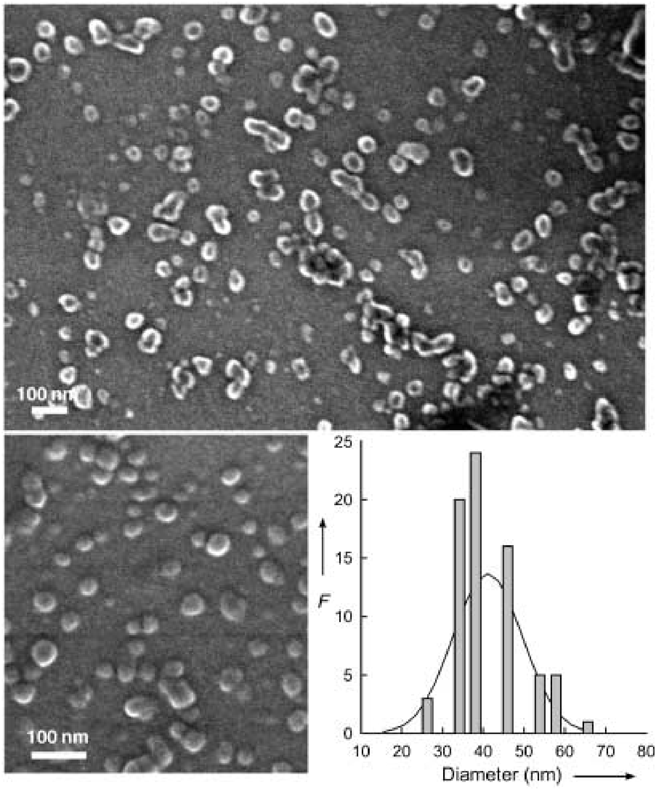

Figure 4. SEM images of a PHDFDA nanoparticle specimen prepared from a basic (pH ≈ 11) aqueous suspension containing SDS (20 mM) as a stabilization agent. A statistical analysis of the particle sizes is shown (bottom right; F = frequency).

The results presented here show that the RESOLV process yields nanoscale polymer particles of less than 50 nm and that the nanoparticles can be obtained as primary products if the subsequent agglomeration of the nanoparticles is suppressed or eliminated.[33] According to reported modeling efforts on RESS,[25] the rapid expansion process itself should intrinsically produce small nanoparticles. Theoretical calculations have predicted the formation of nanoparticles much less than 50 nm in diameter for RESS (upstream of the Mach disk in the supersonic free-jet region).[25] The experimental observation of primarily micrometer-sized particles in traditional RESS has been attributed to the particle growth processes of condensation and coagulation during the rapid expansion (downstream of the Mach disk in the transonic and subsonic free-jet regions).[19,20,24] In this context, the use of a liquid at the receiving end of the rapid expansion process in RESOLV probably interferes or disrupts condensation and coagulation in the expansion jet, thus effectively quenching rapid particle-growth processes. After the initial formation of polymeric nanoparticles in RESOLV, the observed agglomeration of nanoparticles in aqueous suspension occurs over a longer time scale. This agglomeration process is absent in traditional RESS because there the particles are in the solid state following the expansion. While it presents a different set of technical challenges to protect the as-formed polymeric nanoparticles in RESOLV, many methods for stabilizing nanoparticle suspensions are already available.[1,2] One such method is the use of surfactant molecules, as demonstrated in this work on the effective protection of the PHDFDA nanoparticles by SDS to form a stable aqueous suspension. Thus, it is safe to conclude that RESOLV, coupled with a post-nanoparticle-formation strategy, should be further developed to become a reliable and versatile technique for the production of well dispersed polymeric and organic nanoparticles.

Experimental Section

Carbon dioxide (high-purity SFC grade) was supplied by Air Products. The monomer 3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecyl acrylate was obtained from Aldrich. PHDFDA was prepared from the monomer via solution polymerization, as reported elsewhere.[34] The polymer is semicrystalline, with a melting point of 78 °C, no glass-transition observed above room temperature, and stable up to 275 °C. According to results from gel permeation chromatography (hexafluoroisopropanol with 0.1M sodium trifluoroacetate as mobile phase), the polymer has an average molecular weight M_W of 254 000 g mol^{-1} and a polydispersity index of ≈ 3.

A Hitachi HD-2000 STEM system was used in the SEM mode for the imaging of the polymeric nanoparticles. The specimen for the SEM imaging was prepared by depositing a few drops of a dilute nanoparticle aqueous suspension onto a carbon-coated copper grid, followed by drying under ambient conditions. Energy dispersive X-ray (EDX) analysis was performed in situ on the same STEM system.

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