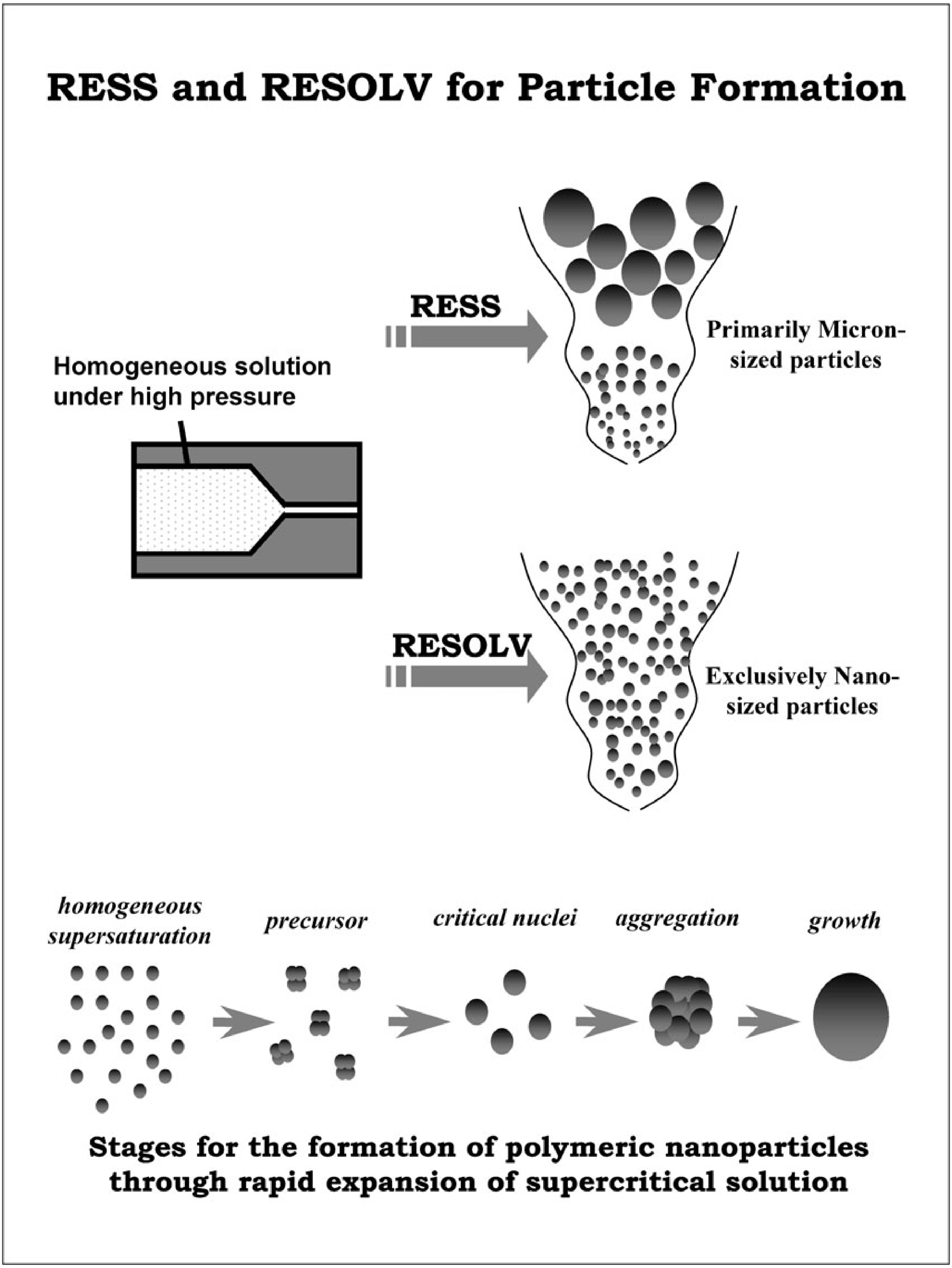

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Polymeric Nanoparticles from Rapid Expansion of Supercritical Fluid Solution

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Abstract: In this concept paper we highlight applications of supercritical fluid technology in particle formation and production, especially some recent advances in the rapid expansion of supercritical solutions (RESS) processing technique. We also highlight the simple but significant modification to the traditional RESS by using a liquid solvent or solution at the receiving end of the supercritical solution expansion, or the rapid expansion of a supercritical solution into a liquid solvent (RESOLV), and applications of the technique to the preparation of nanoparticles. In particular, successes and challenges in the use of RESOLV for nanoscale (<100 nm) polymeric particles and the subsequent protection of the suspended nanoparticles from agglomeration are discussed.

Keywords: nanostructures · polymers · supercritical fluids

Introduction

Great advances have been made in the synthesis and production of nanoparticles (i.e., particles of 100 nm or less) from a variety of materials, though most of which are based on metals or other inorganic elements.[1] There has been considerably less progress in the development of reliable and versatile techniques for the preparation of well-dispersed organic and polymeric nanoparticles. The available methods for micron-sized and nanoscale polymeric particles include those in which the particles are formed in situ in the polymerization of monomers under emulsion, suspension, dispersion, and precipitation conditions. These different polymerization methods are developed to make polymeric particles in specific size ranges. For example, the emulsion polymerization is used for particles in the size range of 100–1000 nm,[2,3] the miniemulsion polymerization for particles of 50–200 nm, and the microemulsion polymerization for particles of 20–50 nm.[3,4] Other methods for the formation of particles from made polymers include solvent-in-emulsion evaporation, phase separation, and spray drying.[5] Among widely discussed disadvantages for all of these methods are an excessive use of surfactant and solvent, the presence of unwanted residues, and insufficient colloidal stability, etc.[5]

Supercritical fluid technology has played a significant role in the particle formation applications. A supercritical fluid is loosely defined as a solvent at a temperature above the critical temperature, at which the fluid remains a single phase regardless of pressure. However, for practical purposes such as high density for solubility considerations, fluids of interest to materials processing are typically at near-critical temperatures. Among the most important properties of a supercritical fluid are the low and tunable densities, which can be easily varied from gaslike to liquidlike through a simple change in pressure at constant temperature, and the unusual solvation effects at densities near the critical density (often discussed in terms of solute–solvent and solute–solute clusterings). Numerous investigations have been conducted on supercritical fluids,[6,7] and the results have demonstrated the unique advantages of using supercritical fluids as alternative media for both chemical reactions and materials processing. Examples of the applications and related advantages are the use of supercritical fluids (CO_2 and water, in particular) as environmentally benign solvents,[7a] the ability to tune selectively chemical reactions or processes,[8,9] the enhancement of reaction rates due to the low viscosities or high diffusivities in the fluids,[9] the ability to solvate or precipitate solutes selectively,[10] and the production of fibers and powders through rapidly expanding the supercritical fluid solutions.[11,12] In this paper, we focus on the recent advances in the application of supercritical fluid processing to particle

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production, and we also highlight our newly developed rapid expansion technique for the preparation of exclusively nanoscale polymeric particles.

Supercritical Fluid Processing of Particles

Applications of supercritical fluids in materials processing have received considerable attention since the mid-1980 s. A number of reviews on the subject have appeared in the literature.[13–22] One area of focus has been on particle formation. Among the most widely investigated processing techniques are those involving precipitation processes in supercritical solutions known as SAS (supercritical antisolvent)[14b,23] and RESS (rapid expansion of supercritical solutions).[14c,24,25] SAS generally refers to the precipitation for particle formation in a compressed fluid at supercritical as well as subcritical conditions. The process is also called PCA (precipitation with compressed antisolvent) or GAS (gas antisolvent). As with any precipitation process, the antisolvent can be added to the solution (normal-addition precipitation) or the solution can be added to the antisolvent (reverse-addition precipitation). The method requires that the supercritical antisolvent be miscible with the solution solvent and that the solute be insoluble in the supercritical antisolvent. In the normal-addition SAS, a solute is dissolved in a liquid solvent, and a supercritical antisolvent is added to the solution in a partially filled, closed container that is initially at ambient pressure. With the addition of the supercritical antisolvent, both the volume of the solution/antisolvent mixture and the pressure of the closed container increase. The decrease in solubility of the solute with increasing antisolvent fraction in the mixture results in precipitation of the solute. The precipitate is then washed with the antisolvent to yield the desired particles. The size and size distribution of the particles are dependent on the selection of the solution/antisolvent system, the solution concentration, the relative solution and antisolvent quantities, the rate of the antisolvent addition, and the degree of mixing.[23a] In the reverse-addition SAS, a liquid solution is sprayed through a nozzle into a supercritical antisolvent. The rapid diffusion of the solvent from the solution droplets sprayed into the bulk supercritical fluid results in the solute precipitation. The precipitate is then washed with the antisolvent and filtered to obtain the desired particles.

The SAS methods have been used for preparing a variety of particles and fine powders from proteins, pharmaceuticals, pigments, polymers, and even explosives. For example, fine particles of trypsin, lysozyme, and insulin proteins with diameters ranging from 1 to 5 μm were produced by spraying the protein solution in DMSO through a small orifice into supercritical CO_2.[26] Increases in the particle sizes could be achieved by decreasing the pressure or increasing the temperature of the antisolvent or by increasing the expansion-nozzle diameter. For polymers, Johnston and co-workers used antisolvent precipitation to prepare both microparticles and fibers of polystyrene by varying the CO_2 density and temperature.[27] The product morphology (particles vs fibers) was found to be dependent on the polymer solution concentration, with a higher concentration (1–5 wt %) promoting the formation of fibers. A significant advantage of the SAS and related supercritical fluid processing methods over a liquid solution-based technique is the ability to prepare dry powders in a single step.[16a] The preparation of dry powders at low temperature is particularly important for pharmaceuticals and protein samples, as well as other materials that are thermally labile or shock sensitive. Because many compounds of interest have higher solubility in liquid solvents than in low-temperature supercritical fluids, the SAS method generally allows higher through-puts than the RESS method.

The RESS process for particle production has been studied extensively[14f,25c,25d,28–37] since the pioneering investigation by Krukonis.[24] It differs from the SAS process in that in RESS the solute is dissolved in a supercritical fluid and then the solution is rapidly expanded through a small nozzle or orifice into a region of lower pressure.[13,14a–c] A typical RESS apparatus for particle preparation is illustrated in Figure 1. The rapid reduction in pressure—and, therefore, density—results in rapid precipitation of the solute. Experimentally, the supercritical solution can be generated either by heating and pressurizing a solution from room temperature or by continuously extracting the solute by using an extraction column.[13] The RESS process is driven by the decrease in pressure, which can propagate at speeds up to the speed of sound in the expansion nozzle. Because solubilities in supercritical fluids can be up to a million times higher than those under ideal gas conditions, the rapid expansion from supercritical pressure to ambient pressure results in extremely high supersaturation—and, consequently, homogeneous nucleation of the solute—leading to narrow size distributions in the products. The RESS technique has been used for particle formation from a variety of materials. For example, supercritical water was used in the RESS preparation of iron oxide (Fe_2O_3) particles,[38] and the expansion was at 500 °C and 100 MPa through 50–200 μm diameter orifices into an evacuated chamber. The Fe_2O_3 particles thus obtained were small and exhibited exceptional reactivities. In addition to inorganic oxides, several neutral metal carbonyls (chromium hexacarbonyl, dimanganese decacarbonyl, and triiron dodecacarbonyl) were processed through

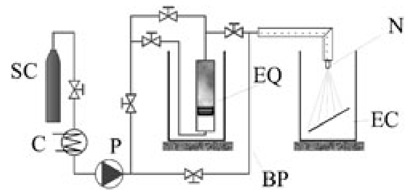

Figure 1. Adapted from reference [12]: Schematic of RESS apparatus. SC, solvent cylinder; C, solvent cooler; P, solvent pump; EQ, equilibrium cell; BP, bypass line for solvent; N, Nozzle; EC, expansion chamber.

RESS to form micron-sized particles.[39] The solubility of these compounds allowed the use of supercritical CO_2 in the RESS processing.

Smith and co-workers carried out a series of RESS experiments aimed at not only processing of various materials, but also evaluation of the effects of processing conditions on product morphology, size, and distribution.[25,40,41] The results from these experiments and others suggest that the RESS process generally produces micron- or submicron-sized particles.[12,14f,33c,34,35] For nano-sized particles, we made a simple but significant modification to the traditional RESS by using a liquid solvent or solution at the receiving end of the supercritical solution expansion, or the rapid expansion of a supercritical solution into a liquid solvent (RESOLV). The RESOLV process produces exclusively nanoparticles from a variety of materials.[1] For example, cadmium sulfide (CdS) nanoparticles of ~3 nm in average diameter were prepared by means of RESOLV by rapidly expanding a supercritical ammonia solution of $Cd(NO_3)_2$ into a room-temperature solution of Na_2S in water or ethanol.[42a,b] The nanoparticles produced in the process could be prevented from aggregating by the presence of a polymeric or other protection agent in the receiving solution.[42a,b] It should be noted that there was a precipitation reaction accompanying the rapid expansion process in the formation of CdS nanoparticles.[42a,b] The same RESOLV process with a similar reaction scheme has been applied to the production of many other semiconductor and metal nanoparticles. These nanoparticles are all small, on average less than 10 nm in diameter, and are protected to form stable suspensions.[1,42,43] As recognized by us, the RESOLV process for nanoparticle production has a unique feature in that it does not require nanoscale templating agents for the 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.[43c,d] For example, we have demonstrated recently that the semiconductor and metal nanoparticles coated directly with natural protein species could be prepared in the RESOLV process. Shown in Figure 2 are transmission electron microscopy (TEM) and atomic force microscopy (AFM) images of the silver sulfide (Ag_2S) nanoparticles conjugated with bovine serum albumin protein.[43d]

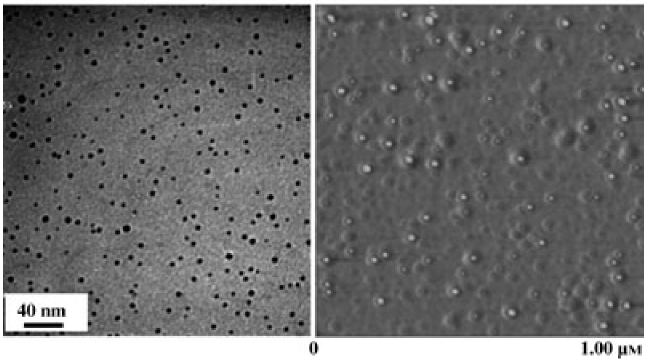

Figure 2. TEM (left) and AFM (right) images of the BSA-conjugated Ag_2S nanoparticles prepared via RESOLV (adapted from reference [43d]).

While most of these processes are still at the stage of laboratory development, some scale-up efforts have been made. For example, Thies and Muller developed a scaled SAS process capable of producing 200 g of biodegradable polymer microparticles.[44] In addition to the technical benefits, these processes evidently have regulatory advantages for industrial scale-up, because of their environmentally friendly nature.

Polymeric Nanoparticles

The traditional RESS process has been particularly popular in the processing of polymeric materials. According to the original report by Krukonis,[24] the rapid expansion of a solution of polypropylene in supercritical propylene resulted in the formation of fiberlike particles. Since then, particle formation in RESS from a large number of polymeric materials has been reported.[25b,32,40,41,45–48] For example, Smith and co-workers used RESS to prepare a variety of micron-sized polymer particles, including polystyrene, polypropylene, poly(carbosilane), poly(phenyl sulfone), poly(methyl methacrylate), and cellulose acetate.[25b,40,41,45] However, formation of nano-sized particles has apparently not been a focus of the community. Instead, much effort has been on an understanding of the RESS process for different products, particles versus fibers. In addition to Smith and co-workers, several other research groups also investigated the effect of RESS processing conditions, such as nozzle geometry and pre-expansion temperature and pressure, on the product size and morphology. For example, Shine[46] and later Mawson and co-workers[32] reported that the formation of particles is more favorable over fibers at a low polymer concentration, low pre-expansion temperature, high pre-expansion pressure, and small length/diameter ratio for the nozzle. The results were explained on the basis of the location of phase separation in the nozzle: particles are formed if the precipitation of polymer-rich phase occurs late in the nozzle and fibers are produced if the precipitation occurs up-stream in the nozzle.[32,46] Thies and co-workers[47] also reported the impact of polymer concentration on product size and morphology for cellulose acetate in supercritical methanol and fluoroacrylate in supercritical CO_2. They found a transition from continuous fibers to particles as the polymer concentration decreased from higher than 5 wt% to less than 1 wt%.[47]

In the application of the traditional RESS process the production of micron-sized polymeric particles is generally observed, with only a few exceptions.[25b,32,40,41,45–47] Mechanistically, however, several theoretical studies suggest that the traditional RESS should facilitate the formation of primarily nanoscale particles, and that agglomerations during the rapid expansion process are responsible for the growth of the initially formed particles beyond the nanoscale and, thus, for the observation of micron-sized particles as major products.[12,35] Ginosar and co-workers[49] have shown experimentally that both nano- and micron-sized particles are present in the expansion jet and that the particle sizes increase with the distance from the expansion nozzle, consistent with the theoretically predicted agglomeration mechanism (Figure 3). For example, they found that the nanosized particles increased in size from an average diameter of 10 to 22 nm as the distance from the expansion nozzle increased from 0.26 to 5 mm, while micron-sized particles maintained a relatively constant average diameter of ~0.7 μm.[49] These theoretical and experimental results suggest that nanoscale polymeric particles could be obtained from the RESS process if the nanoparticles could be effectively “captured”. The RESOLV process, with a significant modification to the traditional RESS, enables the capture and stabilization of polymeric nanoparticles.[50]

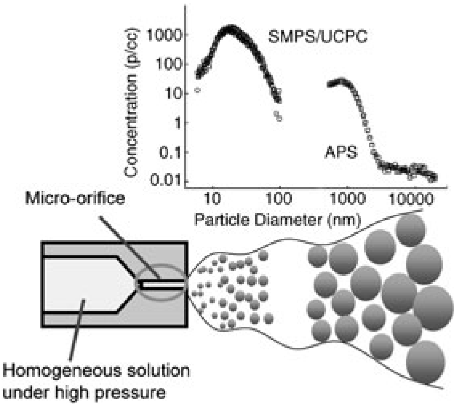

Figure 3. Experimental particle size scans of phenanthrene taken at the centerline of expansion jet and 2 mm from the expansion orifice, and a cartoon illustration of the process (adapted from reference [49]).

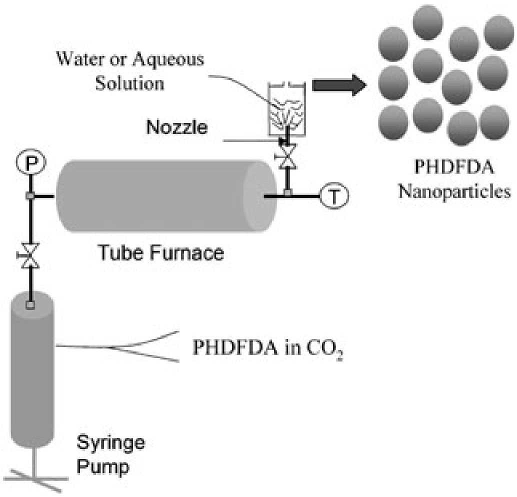

Figure 4. From reference [50]: Experimental setup for the preparation of polymeric nanoparticles via RESOLV.

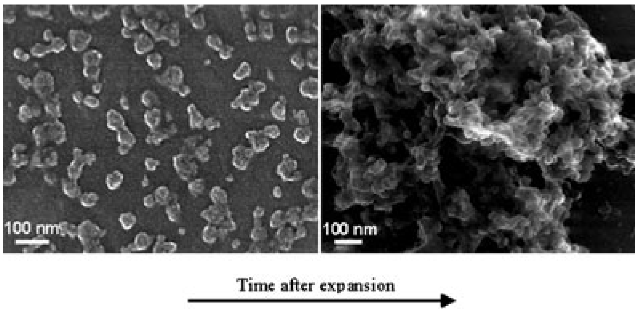

Figure 5. SEM images of PHDFDA nanoparticle specimens prepared 5 min (left) and 15 min (right) after the start of the rapid expansion process (from reference [50]).

In RESOLV, the liquid at the receiving end of the rapid expansion apparently suppresses the particle growth in the expansion jet, making it possible to yield exclusively nanoscale (less than 100 nm) polymeric particles. We have used a CO_2-soluble polymer poly(heptadecafluorodecyl acrylate) (PHDFDA) as model solute to demonstrate the production of polymeric nanoparticles by means of RESOLV. The experimental setup for RESOLV, illustrated in Figure 4, is similar to a typical RESS apparatus, except that the rapid expansion is into a chamber containing a liquid solution. For PHDFDA specifically, the CO_2 solution in the syringe pump was pressurized and heated to the desired pre-expansion pressure and temperature and then rapidly expanded through a capillary nozzle into an ambient aqueous medium. The process apparently resulted in the intrinsic formation of nanoparticles.[49] For example, when the expansion was into neat water, the suspensions obtained in different time intervals (5 min, 15 min, etc.) from the start of the rapid expansion process were analyzed. The results shown in Figure 5 are consistent with the initial formation of PHDFDA nanoparticles and then the agglomeration of the nanoparticles into aggregates that grow in size with time. The RESOLV process has been applied to other polymers such as poly(L-lactic acid) (PLA). The same initial formation of PLA nanoparticles and the subsequent particle agglomeration were observed when neat water was used at the receiving end of the rapid expansion.[51]

The rapid expansion in both RESS and RESOLV should probably produce nanoscale particles in the absence of any secondary processes. Theoretical modeling of the traditional RESS process has predicted the formation of sub-50 nm particles upstream of the Mach disk in the supersonic free jet region and that the typically observed micron-sized particles are from the particle growth processes of condensation and coagulation that occur downstream of the Mach disk in the transonic and subsonic free jet regions.[12] A similar conclusion was reached according to the computational fluid dynamics calculation for the RESS processing of a perfluoropolyether diamide oil, though the final product was a liquid instead of solid particles.[37b] In this context, the use of a liquid at the receiving end of the rapid expansion in RESOLV probably inhibits or disrupts the condensation and coagulation in the expansion jet, thus effectively quenching the rapid particle growth processes. In highlighting the RESOLV production of nanoscale polymeric particles, Lavine correctly characterized the technique as "capturing polymer nanoparticles".[52]

While both RESS and RESOLV appear to involve a particle agglomeration process, one may argue that the observed particle growth and aggregation in RESOLV should not necessarily be considered as a part of the technique, because they are on a longer timescale following the initial formation of the nanoparticles. On the other hand, the particle growth and aggregation in RESS happen in the expansion jet, thus hardly separateable from the RESS process itself.

Another important difference between RESOLV and RESS is that in RESOLV the initially formed nanoparticles are suspended in a liquid medium, providing opportunities to protect and stabilize the suspended nanoparticles from agglomeration. For PHDFDA nanoparticles, as an example, we have evaluated various stabilization strategies.[50] We tried a substantial increase of ionic strength in the receiving aqueous solution by adding NaCl (0.5 M). It worked to some degree, but the PHDFDA nanoparticles still agglomerated to form larger aggregates and then precipitates. We have had much success with the use of surfactants and polymers as stabilization agents. The initially formed PHDFDA nanoparticles can be protected by anionic surfactant sodium dodecyl sulfate (SDS) at a relatively low concentration (20 mM) to form a stable aqueous suspension.[50] According to the SEM images of the specimen prepared from such a suspension (Figure 6), the protected PHDFDA nanoparticles remain nanoscale, with an average particle size of ~40 nm in diameter when approximated as spheres.

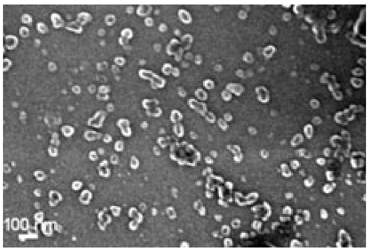

Figure 6. An SEM image of SDS-protected PHDFDA nanoparticles produced via RESOLV (from reference [50]).

Polymers can also be effective in the protection of the suspended polymeric nanoparticles. Again with PHDFDA nanoparticles as an example, the RESOLV experiment was carried out with poly(vinyl alcohol) (PVA) as a protection agent in the aqueous receiving solution.[51] The PVA-stabilized aqueous suspension of PHDFDA nanoparticles was found to remain homogeneous without precipitation for at least several days. An additional advantage with polymer as a protection agent is the ready preparation of polymeric nanocomposites, in which the polymer matrix is embedded with polymeric nanoparticles. Shown in Figure 7 is an SEM image of the PVA film after the embedded PHDFDA nanoparticles are removed through CO_2 extraction; nanoscale pores in the film are observed.[51]

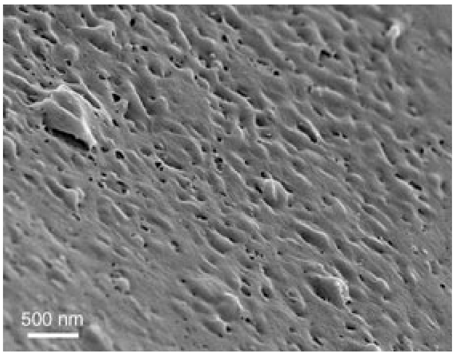

Figure 7. An SEM image of the PVA film with nanoscale pores after the removal of embedded PHDFDA nanoparticles.

The production of polymeric nanoparticles through RESOLV may conceptually be divided into two somewhat related processes. One is the initial formation of nanoparticles in the rapid expansion, and the other is the stabilization of the suspended nanoparticles. Evidently, the protection of initially formed polymeric nanoparticles represents a different set of technical challenges, which are largely independent of the rapid expansion process itself, especially if the protection agent is added immediately after the expansion. The good news is that many methods for stabilizing nanoparticle suspensions are already available in the literature,[5c,53] some of which have shown promise in use with RESOLV.[50]

In summary, supercritical fluid processing techniques can play a significant role in the particle formation and production. In particular, the RESOLV technique offers a unique way to prepare clean and narrowly distributed polymeric nanoparticles. Since the nanoparticles obtained in RESOLV are suspended, they may be protected from agglomeration by using existing stabilization methods and agents. These stable nanoparticle suspensions may find many interesting and important applications, as already discussed in the literature.[5,53]

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