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Nanosizing Drug Particles in Supercritical Fluid Processing

Pankaj Pathak, Mohammed J. Meziani, Tarang Desai, and Ya-Ping Sun*

Department of Chemistry, Howard L. Hunter Chemistry Laboratory, Clemson University, Clemson, South Carolina 29634-0973

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The poor aqueous solubility of drug candidates presents a significant problem in drug development and related requirements such as bioavailability and a normal absorption pattern.[1,2] Among various strategies to address the solubility issue, reducing the drug particle sizes has emerged as an effective and versatile option.[2−5] Complementary to traditional methods for the particle size reduction is the development of several supercritical fluid-processing techniques that overcome some of the limitations associated with the traditional methods and offer advantages in clean and nontoxic drug formulation.[5−7] In particular, rapid expansion of supercritical solution (RESS) has been widely studied as a promising technique for particle production.[7−17] In RESS, a 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 rapid reduction of pressure in the expansion is accompanied by high degree of supersaturation, resulting in the homogeneous nucleation and thereby the formation of well-dispersed particles. RESS generally produces micrometer-sized particles as primary products, despite the prediction of theoretical calculations for nanoscale particles and occasional experimental observations of submicrometer-sized particles.[12,13,18]

We have modified the traditional RESS by expanding the supercritical solution into a liquid solvent instead of ambient air, or the rapid expansion of a supercritical solution into a liquid solvent (RESOLV).[7] This processing technique produces exclusively nanoscale particles from a variety of materials including metals and semiconductors.[19,20] Mechanistically, the liquid at the receiving end of the rapid expansion in RESOLV probably suppresses the particle growth in the expansion jet, making it possible to obtain only nanoscale particles. We have recently demonstrated the use of RESOLV in the production of nanoscale particles (less than 50 nm in average diameter) from a CO_2-soluble polymer.[21]

The development of versatile methods for the preparation of homogeneously distributed nanoscale drug particles and their stable aqueous suspension is still a major challenge, despite the extensive effort based on traditional techniques. Here we report the application of RESOLV to the production of drug nanoparticles. The drugs selected for demonstration are Ibuprofen and Naproxen,[22] which are somewhat soluble in supercritical CO_2 and practically insoluble in water. The RESOLV processing yielded aqueous suspensions of homogeneously distributed Ibuprofen and Naproxen nanoparticles.

Before the RESOLV experiments, the drug solubility in the selected supercritical solvents under different temperature and pressure conditions was evaluated spectroscopically by using a high-pressure optical cell with quartz windows. In a typical RESOLV experiment for Ibuprofen,[22] a solution of the drug in liquid CO_2 (0.25 mg/mL) was prepared in the syringe pump. The solution was pushed through the heating unit to attain the desired supercritical temperature of 40 °C before reaching the expansion nozzle. The rapid expansion was carried out at a preexpansion pressure of 200 bar through a 50-μm orifice into ambient water or aqueous solution. In the case of neat water at the receiving end of the rapid expansion, the aqueous suspension appeared homogeneous initially, but there was soon (after 15 min) precipitation in the suspension. The SEM imaging of the precipitate (Figure 1) seems to suggest that the RESOLV process produces intrinsically nanoscale drug particles, and then these nanoparticles agglomerate to form larger aggregates on a longer time scale. The results agree well with those from the RESOLV processing of polymeric nanoparticles.[21]

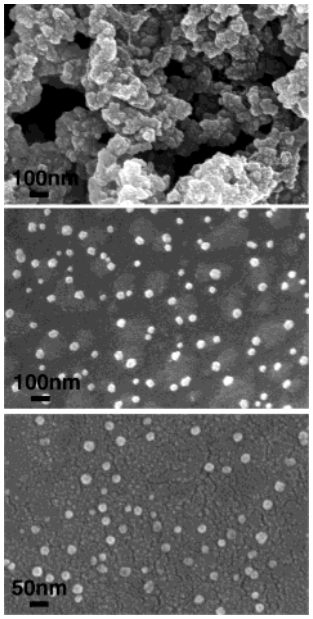

Figure 1. SEM images of the Ibuprofen nanoparticle samples obtained from RESOLV with neat water (top), aqueous PVP solution (middle), and aqueous SDS solution (bottom) at the receiving end of the rapid expansion.

The initially formed drug nanoparticles in RESOLV could be protected from agglomeration by the presence of a stabilization agent in the aqueous suspension. For example, when an aqueous solution of poly(*N*-vinyl-2-pyrrolidone) (PVP, M_W ~40000, 0.5 mg/mL) instead of neat water was used at the receiving end of the rapid expansion, the aqueous suspension of Ibuprofen nanoparticles from the same RESOLV process remained stable without precipitation (for at least several days). A small drop of the stable suspension was used to prepare a specimen for SEM analysis. As shown in Figure 1, the Ibuprofen nanoparticles in the specimen are homogeneously distributed. According to a statistical analysis of the SEM images, these nanoparticles have an average size of 40 nm in diameter and a size distribution standard deviation of 8.5 nm.

PVP is a commonly used and relatively effective stabilizer in drug formulation. The PVP-protected aqueous suspension of Ibuprofen nanoparticles was stable at a drug/polymer weight ratio up to 4. A variation of the ratio from 0.3 to 4 in the RESOLV experiments resulted in no significant changes in the average particle

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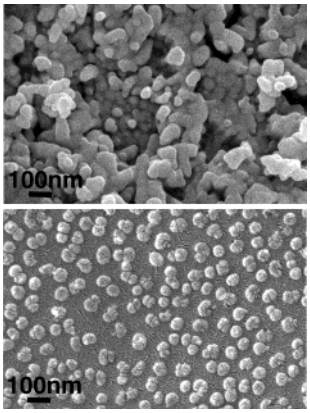

Figure 2. SEM images of the Naproxen nanoparticle samples obtained from RESOLV with neat water (top) and aqueous PVP solution (bottom) at the receiving end of the rapid expansion.

size of the Ibuprofen nanoparticles. Other stabilizers could also be used with RESOLV to protect the produced drug nanoparticles from agglomeration in aqueous suspension. For example, the use of sodium dodecyl sulfate (SDS, 3.3 mg/mL) instead of PVP in the receiving solution of the rapid expansion also yielded a stable aqueous suspension of Ibuprofen nanoparticles (Figure 1), where the average particle size and size distribution standard deviation are 25 and 5 nm, respectively.

The same RESOLV processing technique was applied to produce nanoparticles of another water-insoluble drug, Naproxen.[22] Since the solubility of Naproxen in neat supercritical CO_2 is relatively low, methanol was used as a cosolvent.[23] In a typical experiment, a solution of Naproxen in CO_2 containing 2 wt % methanol was rapidly expanded (40 °C and 200 bar) into an ambient aqueous solution of PVP (0.5 mg/mL). The aqueous suspension of Naproxen nanoparticles thus produced appeared homogeneous and remained stable for an extended period of time (at least days). Shown in Figure 2 is an SEM image of the Naproxen nanoparticles, where the average size and size distribution standard deviation are 64 and 10 nm, respectively. Again, the particle sizes of Naproxen are insensitive to changes in the Naproxen/PVP weight ratio (from 0.3 to 2).

There are some changes in the physical properties of the nanosized drug particles from the starting drug samples. According to differential scanning calorimetry (DSC) results, the melting point decreases by 2.5 °C for Ibuprofen and 5.6 °C for Naproxen upon their nanosizing, indicative of a significant reduction in the degree of crystallinity. This is supported by the X-ray powder diffraction results. It is widely discussed that a reduction in the crystallinity of drug particles increases their bioavailability.[24]

Some exploratory experiments were performed to examine the effects of RESOLV processing conditions on properties of the produced drug nanoparticles. For example, the increases in the loading of Ibuprofen from 0.25 to 0.83 mg/mL or in the PVP concentration from 0.5 to 3.3 mg/mL resulted in no significant changes to the sizes of Ibuprofen nanoparticles. However, a change in the preexpansion temperature from 40 to 120 °C increased the average Ibuprofen nanoparticle size from 40 to 52 nm. The sizes of the Ibuprofen nanoparticles are also sensitive to changes in the molecular weight of PVP. For example, the use of high-molecular weight PVP ($M_W \approx 360000$) as stabilizer reduced the average Ibuprofen nanoparticle size to 30 nm. Similarly, the Naproxen nanoparticles obtained with the use of the high-molecular weight PVP are only about half the sizes of those with the use of low-molecular weight PVP. These obvious effects offer opportunities to the manipulation of the drug particle properties via altering and controlling the RESOLV experimental parameters.

In summary, the RESOLV processing of the selected drugs produces exclusively sub-100 nm nanoparticles. These drug nanoparticles are suspended in aqueous solutions, and the suspensions can be stabilized against agglomeration and precipitation in the presence of PVP or other stabilization agents. The technique may serve as a "clean" way in the nanosizing of drug particles and the preparation of stable suspensions of drug nanoparticles for formulation and other delivery-related requirements.

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