Engineering Powder Properties By Supercritical Fluid for Optimum Drug Delivery

Part Two: Supercritical-Assisted Atomization

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Supercritical fluid (SCF) methods promise the control of particle size (PS) and size-distribution (PSD) in the micrometric and nanometric ranges. These expectations derive from a continuous, adjustable solvent power and selectivity obtained at varying pressures and temperatures. Diffusivity is about two orders of magnitude greater than for liquids. So SCF-based processes can quickly transfer mass and offer performance unobtained using conventional solvents.

SCF-based processes, including successful micronization of different drugs, are described in scientific literature (**1–3**). The aim of this two-part review is to discuss results obtainable using the supercritical antisolvent precipitation (SAS) and supercritical-assisted atomization (SAA) techniques. Particular emphasis is given to the production of particles of controlled size and with sharp size distribution in the micrometric and nanometric ranges. Interpretation of the two processes is incomplete, and information is available on a limited number of compounds. Last month, we examined SAS; this month we conclude with a discussion of SAA.

PRODUCT FOCUS: PROTEINS, PEPTIDES, ANTIBIOTICS, AND SOME VACCINES

PROCESS FOCUS: DOWNSTREAM (FORMULATION)

WHO SHOULD READ: FORMULATION AND PROCESS SCIENTISTS

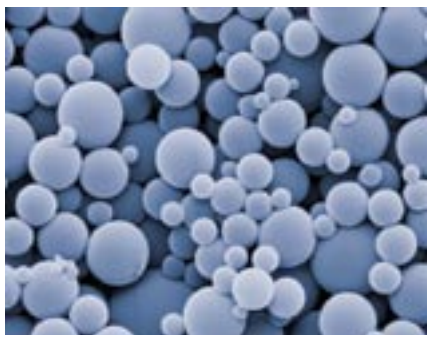
KEYWORDS: SUPERCRITICAL FLUIDS, MICRONIZATION, DRUG DELIVERY, POWDER FORMULATIONS

LEVEL: ADVANCED

SUPERCRITICAL-ASSISTED ATOMIZATION

Recently, atomization processes assisted by supercritical CO_2 have been proposed. These are based on the mixing and/or solubilization of supercritical CO_2 (SC-CO_2) in a liquid solution, with subsequent atomization of the resulting mixture. Such techniques allow drug micronization using water as a liquid solvent — but they can work using organic solvents as well.

Sievers and coworkers proposed supercritical CO_2-assisted nebulization bubble-drier (CAN-BD) using a 1-µL tee to minimize time of contact between the two phases (liquid and supercritical). Various capillary injectors have been suggested for CAN-BD, with microparticles formed mainly by a pneumatic effect. Sievers et al.



Cefonicid and DMSO micronized at 150 bar pressure, 60 °C, 10 mg/mL (colorized)

used solutions of water, ethanol, or water–ethanol mixtures to produce aerosols with very small droplets rapidly expanded by supercritical CO_2 and then dried by warm nitrogen (**19–21**).

Reverchon (**22**) proposed a technique called *supercritical assisted atomization* (SAA), in which a thermostated, packed contactor is used to obtain continuous near-equilibrium solubilization of CO_2 in the liquid solution. The contactor has the opposite function of the near–zero volume tee described above (**19**); it is designed to provide a large contacting surface and adequate residence time to allow efficient dissolution of supercritical CO_2 in the liquid solution. The solution formed there is then sent to a thin-wall injector and sprayed

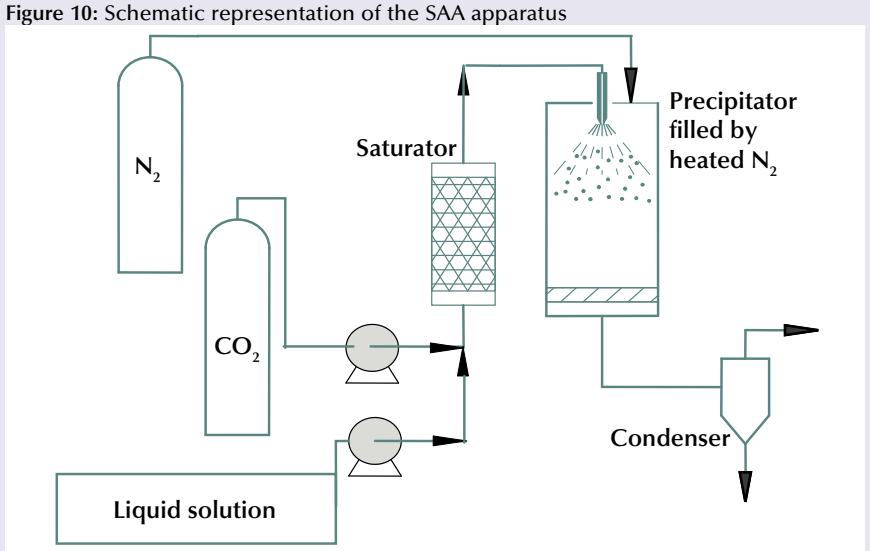
into a precipitator. Figure 10 is a schematic representation of the apparatus used. More details are reported elsewhere (**22–23**).

SAA process performance is strictly related to CO_2 solubilization in a liquid solution, which dictates the efficiency of atomization. The amount of CO_2 solubilized depends on the type of solvent as well as temperature, pressure, and residence time in the contacting device (saturator). CO_2 solubility in the liquid solvent should be accurately measured before setting pressure and temperature conditions in the saturator and selecting the relative quantities of CO_2 and liquid solution to use. When too much CO_2 is used, the liquid in that CO_2 also solubilizes: Part of the solute precipitates in the saturator, and the process fails. Moreover, liquid and CO_2 flow rates must be set to provide adequate residence time together in the contacting device. High-pressure vapor–liquid equilibria (VLE) data for different organic solvents and water in supercritical carbon dioxide can be found elsewhere (**24**).

Operating conditions are selected by first considering the binary system VLE and assuming that the solute's presence does not modify the miscibility behavior of the solvent–CO_2 system — or only slightly modifies the boundaries of the miscibility region. Saturator operating conditions can be set based on the liquid solvent used in the ranges of 90–120 bar and 70–90 °C, with the goal of assuring high CO_2 solubility in the liquid solution. To prevent thermal degradation of processed compounds, the precipitation chamber temperature is maintained at 50–70 °C. Preheated nitrogen (N_2) is added to efficiently evaporate the liquid droplets. Thin-wall injectors are used with internal diameters of 80 and 100 µm.

Examples of SAA Results: In most cases, at the optimum operating SAA conditions observed morphologies were represented by spherical particles. Several drugs were successfully processed, with particle sizes controlled in the micronic and submicronic ranges (**25–28**).

Figure 10: Schematic representation of the SAA apparatus



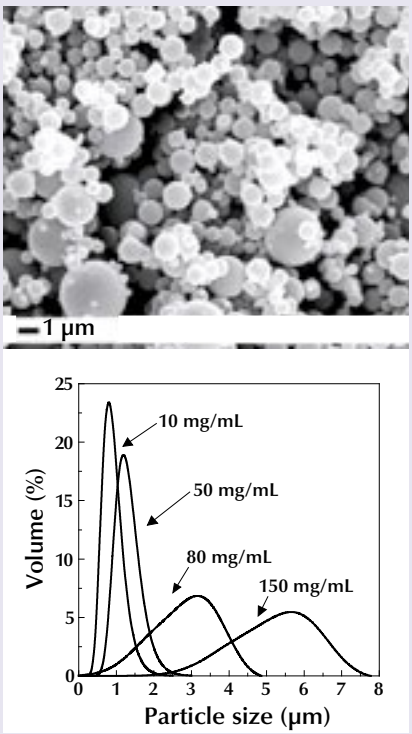
For example, ampicillin particles precipitated from buffered water in the saturator (120 bar, 90 °C), with sizes varied by changing the solute concentration in the solution injected (**28**). The precipitator temperature was maintained at 60 °C with a flow rate ratio (R) of 1.8. Precipitated ampicillin in all experiments were well-defined spherical micrometric particles in morphology. Their mean size varied from 0.5 to 5 µm, and an enlarged distribution was observed when the solute concentration was increased from 10 to 150 mg/mL. Figure 11 shows an SEM image of the precipitated particles, with PSDs obtained at the different solute concentration.

Terbutaline particles precipitated from water in the saturator at 95 bar, 80 °C (**26**). The temperature was maintained at 70 °C, with 1.8 *R*. In all cases, regular and homogenous particles were obtained (Figure 12). Figure 13 compares particle size distribution curves (based on volume) for terbutaline produced by SAA from water at 80 mg/mL and a micronized commercial sample. Nearly 30% of the commercial sample consists of particles larger that 5 µm, whereas the SAA-processed sample ranges 1–4 µm.

Ultraviolet–visible detected high-pressure liquid chromatographic (HPLC–UV-vis) analyses performed on the micronized powders revealed that no chemical modifications occurred during the SAA process — except when distilled water was used. In such cases, using buffered water prevented drug degradation. When organic solvents were used, flame-ionization detected gas chromatography (GC-FID) head-space analysis revealed an organic solvent residue of >300 ppm for all solvent used.

Process Parameters Control Particle Formation: Precipitation chamber temperature is a critical parameter in an SAA process. High temperatures must be avoided to prevent thermal degradation of the drug. With water solutions, particle coalescence was observed when chamber temperature was lower than 60 °C. Such low precipitator temperatures induce a partial water recondensation on the particles. At micrometer/nanometer scales, the presence of liquid solvent (even in small proportions) on particle surfaces affects interparticle forces by smoothing surface imperfections and reducing interparticle distances.

Figure 11: SEM images of ampicillin precipitated by SAA from buffered water and PSDs obtained varying the solute concentration in water from 10, 50, 80 and 150 mg/mL (adapted from ref. **28**).



Strong boundary forces are caused by the solvent surface tension to draw particles together, causing the observed coalescence.

To compare SAA results obtained with different solvents, it is useful to define relative concentrations as the ratio of an injected solute concentration to its solubility in the considered solvent. When water is used, larger particles are obtained, whereas at the same solute relative concentration, organic solvents (e.g., methanol or ethanol) produce smaller particles. In ampicillin precipitation, for example, particles with a mean size of 1 µm were obtained using a solute relative concentration of 0.4 in water, whereas 0.5-µm particles were produced in methanol. The same behavior was observed for other active ingredients studied.

The influence of *R* (defined as the mass flow ratio between CO_2 and the liquid solution) on particle size operating at a fixed relative concentration was also studied (**27**). Three R values were used (0.7, 1.3, and 1.8 w/w) in an erythromycin–ethanol system. In all tests, spherical particles were the observed morphology, but their size decreased with increasing *R* values (Figure 14, both images at the same enlargement). Quantitative analysis provides the same results (Figure 15, showing particle size distributions as the percentage of particles with a given diameter): Particles were smaller when the *R* value was higher. At $R > 1.8$, the liquid solution was partially solubilized in CO_2. That causes solute to precipitate in the saturator, so the SAA process fails.

Figure 12: SEM images of terbutaline precipitated by SAA from buffered water (adapted from ref. **26**)

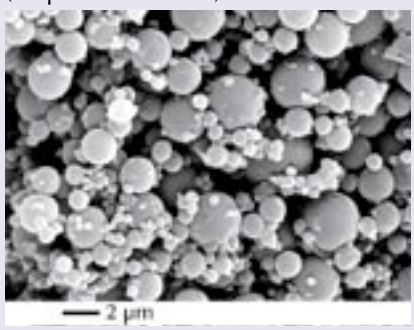


Figure 14: SEM images of erythromycin precipitated by SAA from ethanol operating at *R* values of 0.7 (top) and 1.8 (bottom)

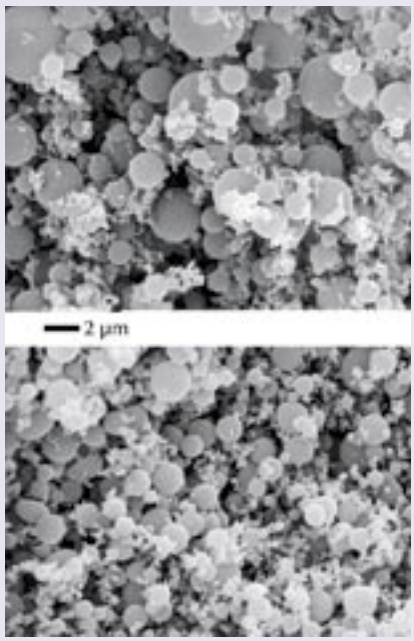


Figure 13: Comparing particle size distribution curves (based on particle volume) of terbutaline produced by SAA at 80 mg/mL and of the micronized commercial sample (adapted from ref. **26**)

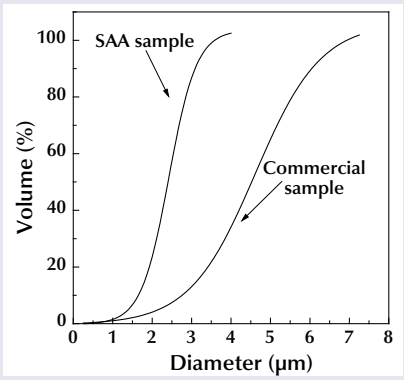
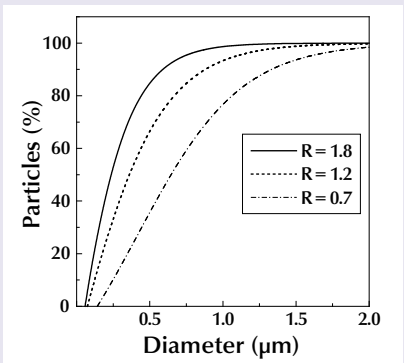
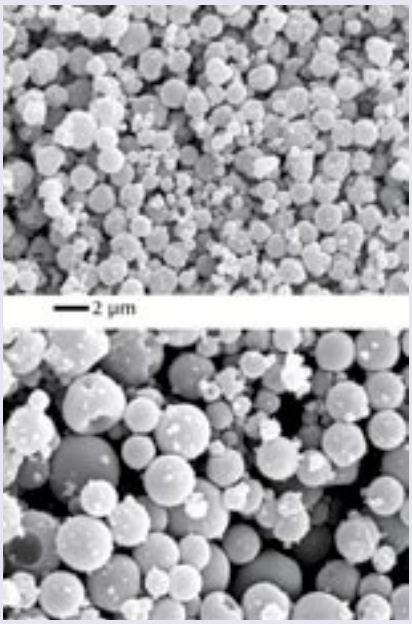


Figure 15: Particle size distributions (number of particles) for erythromycin precipitated by SAA from ethanol at different R values (adapted from ref. **27**).



In all systems studied, we observed that precipitate particle sizes increase at higher relative concentrations. In the case of tetracycline, for example, drug particle morphology was spherical in all experiments, with single particles having well-defined boundaries (**25**). At 25 mg/mL solute concentration, over 90% of the particles fell in the 0.2–1 µm range, with a mean value of 0.5 µm. If the solute concentration was increased to 200 mg/mL, particles fell in the 0.5–2.5 µm range, with a mean size of 1.4 µm. This behavior is confirmed by Figure 16, where SEM images of the precipitated particles are reported with the same enlargement for the two different solute concentrations. In the case of rifampicin, an increase of mean particle size from 0.7 to

Figure 16: SEM images of Tetracycline precipitated by SAA from water operating at 97 bar 85 °C in the saturator and at 63 °C in the precipitator, solute concentration in liquid solution of 25 (top) and 200 mg/mL (bottom), respectively (adapted from ref. **25**)



1.7 µm occurred when the solute concentration was increased from 10 to 40 mg/mL. Particle size distribution also increased (Figure 17).

The SAA process also successfully micronizes enzymes and proteins that are solubilized in water. Figure 18 shows SEM images of lysozyme precipitated by SAA from water. The particle morphology was spherical, with well-defined and noncoalescing micronic and submicronic particles. Enzyme activity was retained for 95% of the protein after SAA processing.

Efficient particle size control is possible with SAA because of its probable process mechanism (**22**): We think that SAA involves formation in the atomization device of "primary droplets" that rapidly release CO_2 to form "secondary droplets" see Figure 19. The secondary droplets are rapidly dried by warm N_2, one particle to each droplet. This mechanism also explains why larger particles are obtained when water is used than with organic solvents. Different strengths of the cohesive forces operating on the primary droplets — surface tension and viscosity — affects their behavior. Although water and organic solvents can have similar viscosities at these operating temperatures, the surface tension is threefold higher than for methanol. Moreover, dissolution of a gas in a liquid reduces viscosity and surface tension; therefore, the larger the amount of gas dissolved, the greater the reduction of those cohesive forces. The amount of CO_2 dissolved in an organic solvent, as deduced from the literature, is higher than that dissolved in water at the same operating conditions. Therefore, the SAA process using CO_2 and organic solvents offers a further advantage in surface tension reduction compared with a CO_2–water SAA process.

Perspectives

SAA produces nanometric and micrometric particles of controlled size and distribution at mild operating conditions that are compatible with the stability of thermolabile compounds. Selection of solvent, feed ratio, and solute concentration allows precipitation of powders in the size range required for a specific application. Moreover, the SAA process allows precipitation of water-soluble proteins and enzymes together with excipients and stabilizing agents. So this technique can be used not only for classical drug micronization but also for protein precipitation and micronization.

Further experimentation and mathematical modeling is still needed for development of comprehensive and possibly predictive tools that simplify application of these processes to wider ranges of products. Meanwhile, pilot and small

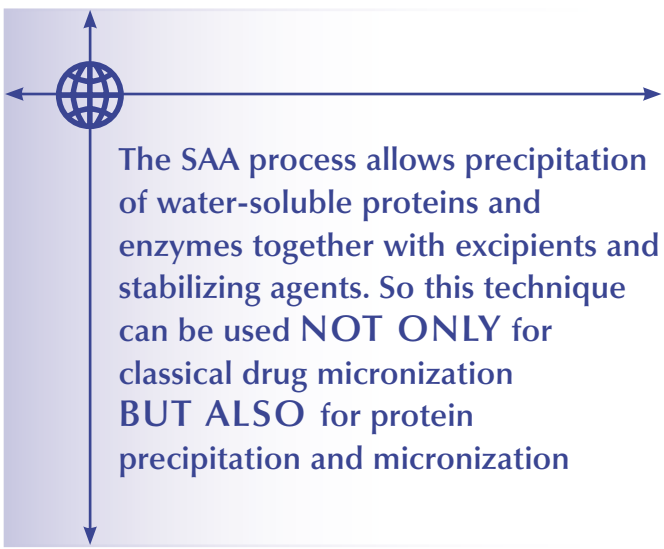


Figure 19: Hypothezed SAA process mechanism

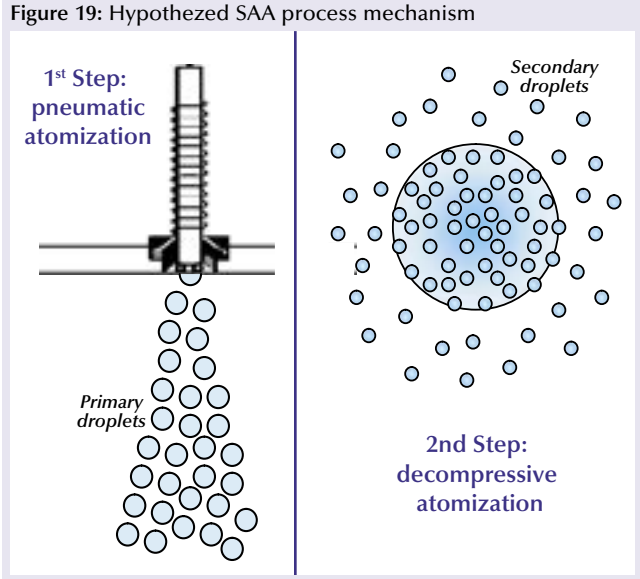


Figure 17: Particle size distribution curves (based on particle volume) of rifampicin produced by SAA from methanol operating at 97 bar 85 °C in the saturator and at 60 °C in the precipitator and varying the solute concentration in the solution from 10 to 40 mg/mL (adapted from ref. **25**)

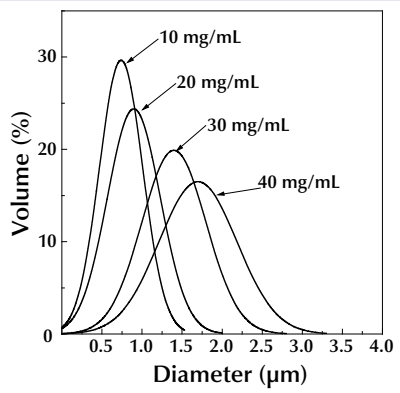
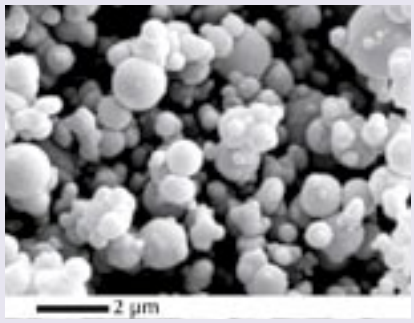


Figure 18: SEM image of lysozyme precipitated by SAA from water



industrial scale micronization plants will allow industrial use of supercritical fluids in production of powder formulations.

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