

Supercritical fluids-assisted micronization techniques. Low-impact routes for particle production*

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Abstract: Micronized powders are of interest in many industrial fields; pharmaceuticals, catalysts, pigments, and biopolymers, for example, are some categories of products that can be used as micro-sized particles. Traditional techniques used to produce micronic powders are based on high-temperature reactions that require high energies, on jet milling that is characterized by low efficiencies and mechanical stress, and on liquid solvents precipitation that has a poor control on particle size and can pollute the product. Generally, the control of the powder size and the span of its distribution are still very approximate.

In the last few years, several supercritical fluids-based techniques have been proposed for the production of micronic and nanometric particles. These processes try to take advantage of some specific properties of gases at supercritical conditions such as enhanced solubilization power and its modulation, large diffusivities, solventless or organic solvent reduced operation, and the connected possibility of controlling powder size and distribution. Techniques like the rapid expansion of supercritical solutions (RESS), supercritical antisolvent precipitation (SAS), particle generation from gas-saturated solutions (PGSS), and new atomization processes have been critically reviewed in this work.

INTRODUCTION

During the last few years, the possibility of application of supercritical fluids has received an increasing attention from the scientific community with the aim to develop new technologies for the production of materials or to substitute the traditional technologies based on the use of organic solvents. Solid material properties at micro- and nano-size level are connected to their chemical composition as well as to their particle size. The production of solid materials with specific properties is very important for many industries, for example, catalysts, coatings, electronics, ceramics, superconductors, dyestuff, pigments, and pharmaceuticals.

In these fields, research is very active in improving the properties of these materials by proposing new processes and technologies that can be “green technologies”, as well. Indeed, organic solvents are process fluids currently used in these industries. They produce pollution not only of the process products, but also of the processed material and of the environment with relevant social and industrial costs. The supercritical fluids, instead, can produce new and improved products with new and advanced processes. Moreover, they have the advantage that they do not pollute the extracts, residues, and, in many cases, the environment.

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Supercritical fluids are characterized by a continuous adjustable solvent power/selectivity obtained by varying pressure and temperature. Therefore, the same supercritical solvent can be used in different sections of the plant to obtain different extraction/separation performances. At last, the diffusivity of supercritical fluids is similar to that of gases (they are gases, indeed); thus, it is about two orders of magnitude larger than that of liquid solvents. As a consequence, process times can be greatly reduced, and no wastes are produced.

Among all the possible supercritical fluids, it is largely used carbon dioxide that performs like a lipophilic solvent, it is nontoxic, nonflammable, nonpolluting (it is not produced during the process and is used many times before discharge), and very cheap; its critical parameters of pressure and temperature are readily accessible on the industrial scale ($T_c = 31.1\text{ }^\circ\text{C}$; $P_c = 73.8\text{ bar}$). Particularly, critical temperature is very near the room one and allows the treatment of thermolabile compounds.

Various supercritical fluids-based processes for microparticles generation have been developed for taking advantage of supercritical fluid properties. In this work, we review the most interesting and promising techniques and analyze the major results obtained. The sources we used are the scientific literature, the proposed patents, and our direct experience in some of these processes. Comprehensive references on materials processed by supercritical techniques, their particle sizes and particle size distributions can be found in two recent reviews written by Reverchon [1] and Jung and Perrut [2].

RAPID EXPANSION FROM SUPERCRITICAL SOLUTION TECHNIQUE (RESS)

The rapid expansion of supercritical solutions (RESS) consists of saturating a supercritical fluid with a solid substrate, then this solution is depressurized through a heated nozzle into a low-pressure chamber in order to cause an extremely rapid nucleation of the substrate in the form of very small particles or fibers or films that are collected from the gaseous stream [3–6].

RESS concept can be implemented in relatively simple equipments, although particle collection from the gaseous stream is not easy. However, the applications are limited since many attractive substrates are not soluble enough into the supercritical fluid to lead to profitable processes; a cosolvent may be used to improve this solubility, but its elimination from the resulting powders is not simple and cheap.

SUPERCRITICAL ANTISOLVENT PRECIPITATION TECHNIQUE (SAS)

Different acronyms were used by the various authors to describe the supercritical antisolvent-induced precipitation of solids from a liquid solution. We will refer to this technique as *supercritical antisolvent precipitation* (SAS). Since the results can be heavily influenced by the process arrangement, a short presentation of the most common SAS-related processes follows.

Batch operation

The precipitation vessel is loaded with a given quantity of the liquid solution, and then the supercritical antisolvent is added until the final pressure is reached. The rate of supercritical antisolvent addition can be an important parameter in controlling the morphology and size of solid particles. The antisolvent can be added from the bottom or from the top of the chamber; we will refer it as *liquid batch SAS*.

Semicontinuous operation

The liquid solution and the supercritical antisolvent are continuously delivered to the precipitation vessel in co-current or counter-current mode. Flow rates and their ratio can be important for the evolution of the precipitation process.

A key role in the semicontinuous operation is played by the liquid solution injection device. The injector is designed to produce liquid jet break-up and the formation of small micronic droplets that expand in the precipitator. The solid solute is released when its local concentration exceeds the saturation limit. Various injection devices have been proposed in the literature. Some authors proposed the adoption of a nozzle or internal diameter capillaries. Coaxial devices in which two or more capillary tubes continuously deliver the liquid solution and the supercritical antisolvent have also been proposed.

SAS thermodynamics, jet break-up, and mass transfer

When a solution is studied, as in the case of SAS experiments, the modification of the binary behavior of the system solvent/antisolvent due to the presence of solute has to be taken into account. Indeed, the presence of a solute can induce the formation of complex vapor–liquid equilibria (VLE). However, in various cases the liquid-supercritical fluid system is insensitive to the presence of solute as in the case reported for Dextran-DMSO-CO₂ [7]. In conclusion, the analysis of ternary diagrams solute-solvent-supercritical antisolvent is generally required to assess the feasibility of SAS precipitation.

For a successful semicontinuous processing, other constraints have also to be considered. The first is the proper selection of the atomization device and of the process conditions to obtain the liquid break-up and droplets formation. Indeed, if droplets are not formed at the exit of the injection device, the precipitation will develop from a continuous liquid phase and fibers more than particles will be generated. After the droplets formation, mass transfer in and out of the droplet will be responsible for the process evolution. Experimental observations [1,8–9] converge in indicating the droplet expansion followed by solute precipitation on the dried droplet surface as the major steps of the precipitation process. Dried droplet destruction will generate nano- and/or microparticles (single droplet, many particles model).

Using SAS, particle dimensions from 30 nm to several hundreds of microns and many morphologies have been observed [1]; however, only the production of single or connected spherical particles can be strictly related to the previously described precipitation process. All the other morphologies can be due to precipitation by multiphase systems formed in the precipitation chamber or by further interactions between the precipitate and the fluid phases.

Several precursors of superconductors have been successfully micronized by semicontinuous SAS producing nano- and microparticles of controlled particle size (PS) and particle size distribution (PSD) by precipitation from DMSO using supercritical CO₂ as antisolvent [8–9]. Studies were also oriented to the understanding of the effect of some SAS process parameters on PS and PSD of produced powders. In all cases, PS and PSD increased with the starting concentration of the liquid solution injected in the precipitation chamber. The increase of the mean particle size and the enlargement of the PSD were attributed to the superposition of growth mechanisms on the nucleation ones when more concentrated solutions were injected.

Many pharmaceutical compounds have also been successfully processed. Among these, antibiotics [10–12], corticosteroids [13–15], biopolymers [7,16], and proteins [17–18] have been successfully processed by SAS. The effect of solute concentration on particle size and particle size distribution was demonstrated also for these compound families: larger particles have been produced at the higher solute concentration in the liquid solution injected. An SEM image of the rifampicin microparticle obtained is reported in Fig. 1. The particle size distributions of Rifampicin powders precipitated from DMSO at different solute concentration are also shown.

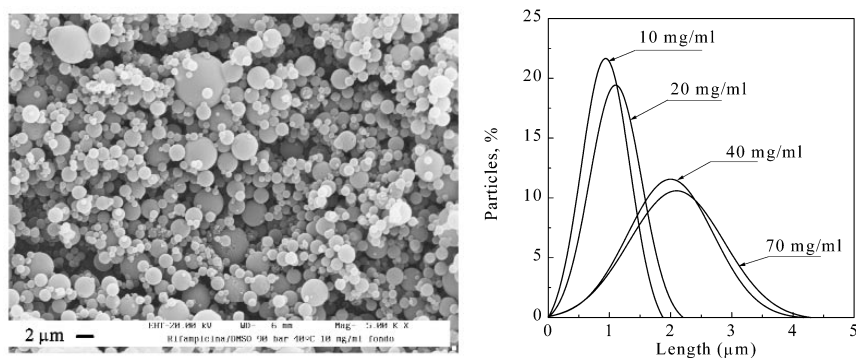


Fig. 1 An SEM image of the micronized Rifampicin at 90 bar, 40 °C, and 10 mg/ml and particle size distributions of Rifampicin powders precipitated from DMSO at different solute concentrations.

PARTICLES FROM GAS-SATURATED SOLUTIONS TECHNIQUE (PGSS) AND ATOMIZATION

Since the solubility of compressed gases in liquids and some polymers is usually high, and, as a rule, larger than the solubilities of such liquids and solids in the compressed gas phase, this process consists of the solubilization of supercritical carbon dioxide in melted or liquid-suspended substances, leading to a so-called gas-saturated solution/suspension that is then expanded through a nozzle with the formation of solid particles [19–20]. This process can produce particles from a great variety of substances that need not be soluble in supercritical carbon dioxide, especially with polymers that generally absorb a large concentration (10 to 40 wt %) of CO₂ that either swells the polymer or melts it at a temperature much below (~10 to 50 °C) its melting/glass transition temperature. This process can also be used with suspensions of active substrate(s) in a polymer or other carrier substance leading to composite microspheres.

A marked similarity with PGSS characterizes also supercritical-assisted spray process. This process involves the use of supercritical carbon dioxide both as an atomization vector and as a viscosity reducer solvent. Smooth and high-quality coatings or powders can be attained with this technology. Limitations for PGSS application are solute thermal stability up to liquefaction conditions and the smallest particle size obtainable that has been until now reported as to several microns.

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