

SUPERCritical ANTISOLVENT TECHNIQUE: PRODUCTION OF NANOPARTICLES.

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ABSTRACT

Supercritical antisolvent micronization (SAS) is a versatile technique that allows the obtainment of different morphologies and dimensions of precipitates, but only in some cases nanoparticles were produced. This work is focused on the selection of the SAS operating conditions to obtain this morphology. A series of experiments on several compounds and different solvents at 40 °C and selected pressure conditions, between 150 and 250 bar, were performed and nanoparticles with mean diameters ranging between 45 nm and 150 nm were obtained.

INTRODUCTION

Supercritical antisolvent precipitation (SAS) has been used to produce micro and/or nanosized materials of several kinds of compounds¹⁻³. The results can be quite different, depending on the process mode (batch or semi-continuous), on the nature of the material and on the high-pressure vapor liquid equilibria (VLEs) characterizing the ternary system solvent-solute-supercritical antisolvent. Crystals, spherical nano, sub-micro and microparticles with mean diameters ranging from 0.1 μm to several tenth of microns and empty shells are the most frequently observed morphologies¹⁻³.

Most of the SAS produced powders range in the micron-size region that has been the target of several studies: many industrial applications require these particle dimensions to obtain the best process performance. For example, small particles in the 1-5 μm range with a narrow particle size distribution are needed for applications in pulmonary delivery and controlled release systems⁴⁻⁵.

The production of controlled diameter nanoparticles is even more ambitious than producing microparticles of controlled dimensions.

In a recent work⁶, our research group, analysing new and literature data, demonstrated that the production of nanoparticles is a general feature of the SAS process and that it is possible to describe conditions of the SAS parameters at which nanoparticles of controlled size and distributions can be obtained.

The scope of this work is to extend the range of operative conditions in which nanoparticles are produced. We performed experiments at higher pressures (up to 250 bar) to verify if the dimensions of the nanoparticles are influenced by this process parameter.

EXPERIMENTAL SECTION

Materials.

Yttrium acetate (YAc), Samarium acetate (SmAc) and Rifampicin (Rifa) (purities 99.9%) were supplied by Sigma-Aldrich (Italy); Amoxicillin (Amoxi) and Dextran-40 (Dextr) were bought by ICN Biochemicals (USA) and their purities are higher than 98%.

Dimethyl sulfoxide (DMSO, purity 99.5%) and N-methyl 2-pyrrolidone (NMP, purity 99.5%), were supplied by Sigma–Aldrich (Italy). CO₂ (purity 99%) was purchased from SON (Italy).

The solubilities have been measured at room temperature and are respectively: Yttrium Acetate in DMSO 303 mg/mL; Samarium acetate in DMSO 213 mg/mL; Rifampicin in DMSO 122 mg/mL; Amoxicillin in NMP 195 mg/mL; Dextran-40 in DMSO 147 mg/mL.

The powder collected in the precipitator has been observed by a scanning electron microscope (SEM) Assing mod. LEO 420. Samples have been covered with 250 Å of gold using a sputter coater (Agar model 108A). Particle size (PS) and particle size distributions (PSDs) were measured using an image analysis performed using Sigma Scan Pro software (Jandel Scientific), an image processing program that counts, measures and analyzes digital images; from about 700 to 1000 particles were considered in each PSD calculation.

APPARATUS AND PROCEDURES

The SAS laboratory apparatus consists of an HPLC pump equipped with a pulse dampener used to feed the liquid solution, and a diaphragm high-pressure pump used to deliver carbon dioxide. A cylindrical vessel of 0.5 dm³ I.V. is used as the precipitation chamber. The precipitation chamber was electrically heated using thin band heaters. The pressure in the chamber was measured by a test gauge manometer and regulated by a micrometering valve located at the bottom of the chamber. The liquid mixture is sprayed in the precipitator through a thin wall stainless steel nozzle. SC-CO₂ is pumped through another inlet port located on the top of the chamber. CO₂ was heated to the process temperature before entering the precipitator. A stainless steel frit is put at the bottom of the chamber to collect the solid product, allowing the CO₂–organic solvent solution to pass through. A second collection chamber located downstream from a micrometering valve was used to recover the liquid solvent. The pressure in this chamber was regulated by a backpressure valve. At the exit of the second vessel a rotameter and a dry test meter were used to measure the CO₂ flow rate and the total quantity of CO₂ delivered, respectively. More details on this apparatus and on the procedures are given elsewhere^{1,7}.

RESULTS AND DISCUSSION

The prerequisites for successful SAS process are the complete miscibility between the liquid solvent and the antisolvent and the insolubility of the solute in the antisolvent (or, rather, in the solution solvent-antisolvent formed in the precipitator). Considering the binary system solvent-antisolvent, this condition is obtained at pressures larger than the Mixture Critical Point (MCP). However, it should be also considered that the presence of a solute can modify the binary system vapor-liquid equilibria (VLEs), as a rule, moving the MCP of the ternary system towards higher pressures than for the corresponding binary one⁸⁻¹⁰. Therefore, in the selection of the SAS operating conditions, it could be not possible to consider that the MCP of the ternary system is coincident to the one of the binary system, except from the cases in which the solute is practically not soluble in the system solvent-antisolvent. It should be advisable to select pressure relatively higher than the MCP pressure of the binary system, to avoid the risk of working at subcritical conditions.

Operating at 150 bar and 40 °C, we observed that, decreasing the concentration of the liquid solution, smaller particles were obtained. As an example, we reported in Figure 1, a SEM image of Samarium Acetate precipitated from DMSO at 150 bar, 40 °C and 17.5 mg/mL.

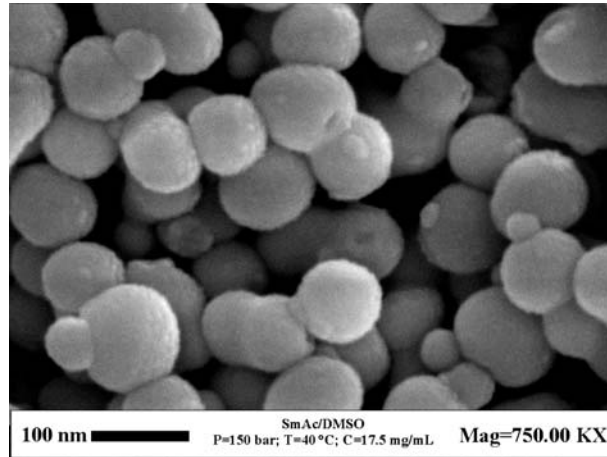


Figure 1: Samarium acetate precipitated from DMSO at 150 bar, 40 °C and 17.5 mg/mL.

Some further experiments have been performed at pressures different than 150 bar, fixed all the other process conditions as in the previous work, to analyze the influence of this process parameter on the diameter of nanoparticles. These new results are summarized in Table 1 and an example of particles obtained at 250 bar is reported in Figure 2.

In Table 1, we reported the operating conditions of the experiments and the mean diameter of the particles obtained (C_R is the reduced concentration defined as $C_R = C/C_0$, where C_0 is the saturation concentration).

Table 1: Mean diameters of the particles obtained by SAS at 40 °C and different pressures.

Material	Solvent	Pressure	Temperature	C_R	d
Amoxi	NMP	150	40	0.102	118
		180			58
Dextr	DMSO	110		0.068	180
		130			120
		150			95
Rifa	DMSO	120		0.081	150
		150			115
SmAc	DMSO	100		0.082	200
		120			180
		150			110
		180			55
YAc	DMSO	120		0.044	200
		150	82		
		250	0.017	62	
			0.044	63	

Organizing the new results in a diagram mean diameter vs. pressure (Figure 3), it is possible to observe that a non linear dependence of nanoparticle size with pressure characterizes all the materials tested. The mean diameter of nanoparticles is strongly reduced when the pressure increases from 100 to 150 bar; then, it seems to asymptotize to about 50 nm for larger pressures. This trend is somewhat expected since between 100 and 150 bar, system evolves from near-critical to completely developed supercritical conditions and because a lower limit of particles diameter is expected due to the nucleation and growth in the nanoparticle in the gaseous phase.

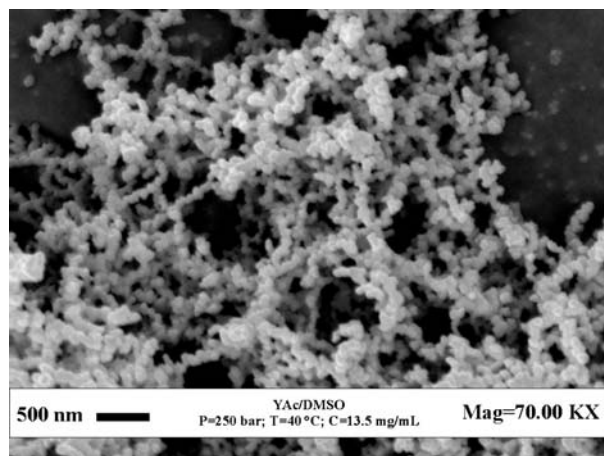


Figure 2: Yttrium acetate precipitated from DMSO at 250 bar, 40 °C and 13.5 mg/mL.

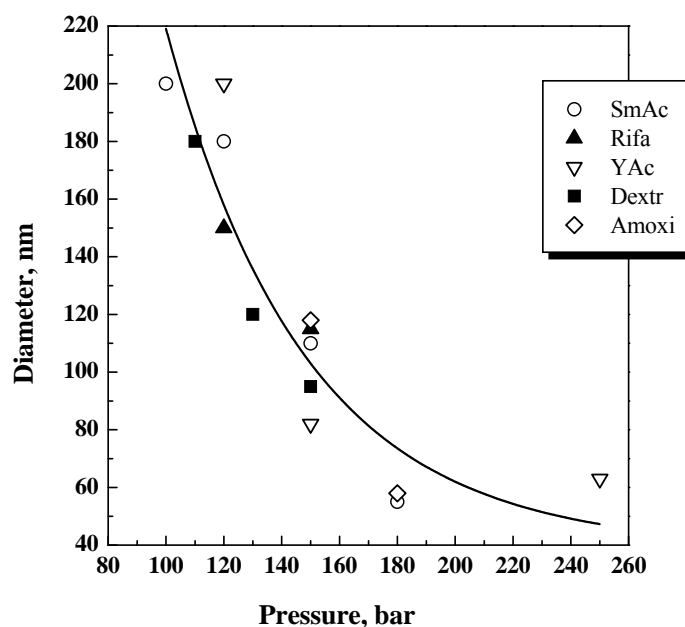


Figure 3: Mean diameter vs. pressure for some materials at 40 °C.

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