

ANALYSIS OF THE MECHANISMS GOVERNING THE SUPERCRITICAL ANTISOLVENT MICRONIZATION

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Supercritical Antisolvent (SAS) precipitation is a semi-continuous precipitation technique developed to produce micrometric and sub-micrometric particles that are not attainable by conventional methods. Despite the fact that many works have been published on the generation of particles by SAS, only a limited number of them has been focused on the mechanisms controlling particle formation.

In this work, a study of the precipitation process has been performed to understand the role of phase behavior in controlling morphology and dimension of the precipitates. The mixture Yttrium Acetate (YAc)/Dimethylsulfoxide (DMSO), using supercritical CO₂ as the antisolvent, has been chosen as the model system. The results showed that operating above the Mixture Critical Point (MCP) sub-micronic particles are generated nearly independently from the kind of the injector. We also demonstrated that it is also possible to obtain sub-micronic particles (with an average diameter of 0.28 μm) or macro-particles (up to 50 μm) by simply changing the operating pressure and/or temperature. These results have been explained on the basis of the position of the operating point with respect to the MCP of the pseudo-binary mixture DMSO/CO₂. Particularly, we have seen that the single-phase region in the gas-rich side of the pressure-composition solubility diagram and below the MCP can be usefully explored in order to modify the particle dimensions of the precipitate.

INTRODUCTION

In the SAS process a supercritical fluid (SCF) and a liquid solution are continuously delivered to a high-pressure precipitator in which the SCF forms a solution with the liquid inducing the precipitation of the dissolved solid. The most attractive characteristics of SAS precipitation are the ability to control particle size and morphology, and to eliminate the solvent residue without post-processing the produced powders. From a thermodynamics point of view, SAS process must satisfy the following requirements: the solute must be soluble in the organic solvent at the process temperature and must be insoluble in the SCF. The solvent must be completely miscible with the SCF; otherwise, two fluid phases will form and the solute can remain dissolved or partly dissolved in the liquid rich phase.

Scientific literature contains information on several materials that have been processed by SAS using different apparatuses and conditions. For example, pharmaceuticals, superconductors, catalyst precursors, pigments and polymers have been prepared using SAS precipitation [1, 2]. The results are quite different depending on the process mode and, of course, on the nature of the material and on the fluid phase equilibria characterizing the ternary system. As a general consideration, the mean particle size that can be obtained by SAS precipitation ranges from 0.1 to several microns. For what concerns the particle shape, spherical amorphous microparticles can be obtained and in several cases crystals have been obtained.

The mechanisms controlling particle formation are related to the interplay of fluidodynamics (jet break-up), mass transfer, nucleation kinetics and thermodynamics (high pressure ternary phase equilibria). Moreover, particle morphology can be affected by many process parameters such as temperature, pressure, concentration of the liquid solution and solution to antisolvent flow rate ratio.

To date, SAS micronization is performed without a clear knowledge of the high-pressure phase behavior of the ternary system Solvent/Antisolvent/Solute and of the conditions at which the ternary mixture is supercritical. Therefore, it is difficult to correlate experimental results to phase behavior. A contribution in this direction has been given by Wubbolts et al. [3] who related the variation of particle morphology of Acetaminophen precipitated from ethanol with the position of the operating point on the phase diagram of the binary mixture Ethanol/CO₂. Particularly, it was observed that below the critical point of the binary system, a liquid-rich phase is formed from which large crystals are generated due to supersaturation, and that above the mixture critical point one phase is formed at a high level of supersaturation from which relatively small particles are formed.

The role of liquid jet break-up on the particle formation mechanism has been studied by different authors and various injection devices have been proposed in the literature [2]. However, the influence of fluidodynamics on particle morphology is not yet well understood.

Therefore, from the analysis of the works until now published, a lack of information exists in the correlation between the particle morphology and the main phenomena governing the process; particularly jet break-up, mass transfer and phase equilibria.

The aim of this work is to produce data targeted to the understanding of the role of jet break-up and phase equilibria in controlling the morphology of precipitates. Two SAS apparatuses (laboratory and pilot scale) with two injector arrangements have been used. The experiments have been performed at selected values of pressure and temperature using the mixture Yttrium Acetate/DMSO that has been chosen as a model system since its processability by SAS was previously demonstrated [4]. An effort has been made to correlate different position of the operating point in a P/x diagram with respect to the mixture critical point (MCP) of the binary system DMSO/CO₂.

EXPERIMENTAL SECTION

Materials.

Yttrium Acetate (YAc) purity 99.9% and Dimethylsulfoxide (DMSO) purity 99% were bought from Aldrich. Untreated YAc crystals ranged from about 20 to 200 μm. We measured a solubility of YAc in DMSO of about 320 mg/mL at room temperature. The powder collected in the precipitator was observed by a scanning electron microscope (SEM) Assing mod. LEO 420. Samples were covered with 250 Å of gold using a sputter coater (Agar model 108A). Particle size of each sample was evaluated measuring about 600-800 particles from different images using an image analysis software (SigmaScan Pro 5). Particle size distributions (PSD) were obtained and the mean particle size (D_n) was calculated as the number-average diameter.

APPARATUS AND PROCEDURES

The configuration of SAS 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. (I.D. 5 cm) is used as the precipitation 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. CO_2 is 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 CO_2 -organic solvent solution to pass through. A more detailed description of this apparatus and of the adopted procedures can be found in a previous paper [5].

A pilot plant (I. V. of the precipitator equal to 5.2 dm^3) and a transparent vessel are also available and have been used in some tests. A detailed description of these plants can be found in previous works [6, 7].

RESULTS AND DISCUSSION

The role of injector kind and dimensions on particle size and morphology of YAc powders has been analyzed performing a set of experiments at 150 bar, 40°C and 50 mg/mL of YAc in DMSO. The injector diameter on the bench-scale apparatus has been varied from 60 to 200 μm , whereas the modified tube-in-tube injector in the pilot scale plant has been fitted with an injector with an internal diameter of 500 μm . Submicronic particles with the same morphology and similar dimensions have been produced in all experiments; therefore, we concluded that the injector arrangement and dimension have a negligible influence on the particle diameter at least at the experimental conditions adopted. Similar results have been obtained in a previous work on the system Amoxicillin/NMP [6].

Experiments performed at 40°C .

A set of experiments has been performed at a temperature of 40°C , a liquid concentration of 15 mg/mL DMSO and varying the operating pressure from 70 to 150 bar. For pressures in the range of 70-90 bar, the material was formed only on the bottom of the precipitator. From SEM analysis we observed that the precipitate was formed by a strictly connected network of particles; i.e., YAc precipitated from a liquid phase [4].

Other experiments have been performed in the range 95-100 bar, obtaining powder with a very different macroscopic aspect: YAc was present on all the precipitation chamber and was soft. SEM analysis revealed the presence of YAc empty shells (balloons), as shown in **Figure 1**.

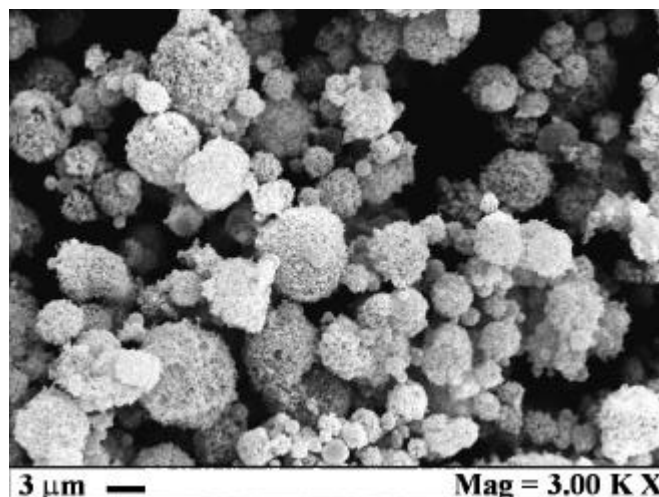


Figure 1. SEM image of micronized YAc at 95 bar, 40°C and 15 mg/mL DMSO.

A further increase of the pressure (in the range 110-150 bar) produced another morphology: a fine powder constituted by spherical non-coalescing nanoparticles. In **Figure 2**, an example of these nanoparticles obtained at 120 bar, 40°C and 15 mg/mL DMSO has been reported.

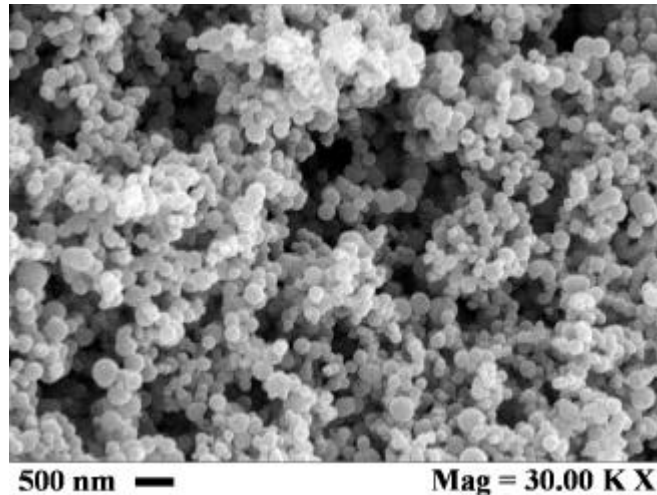


Figure 2. SEM image of micronized YAc at 120 bar, 40°C and 15 mg/mL DMSO.

Experiments performed at 50°C.

Another set of experiments has been performed at 50°C and 15 mg/mL DMSO and in the pressure range from 80 to 160 bar. We observed, again, different morphologies as in the case of the experiments performed at 40°C. In particular, in the range 80-110 bar, the material precipitated only on the bottom of the precipitation chamber and revealed a compact nanostructure; at 120-130 bar we observed the formation of large porous particles (**Figure 3**); at higher pressures the formation of nanoparticles was again observed.

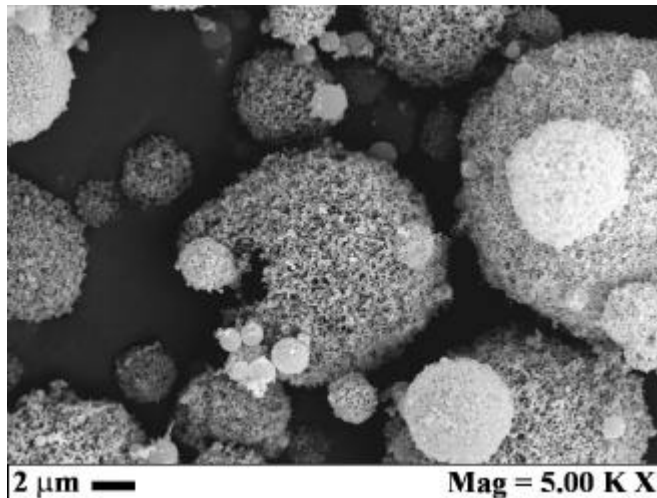


Figure 3. SEM image of micronized YAc at 120 bar, 50°C and 15 mg/mL DMSO.

Experiments performed at 60°C.

Other tests have been performed at 60°C and at the same concentration as in the previous experiments. We observed the same trend obtained at 40 and 50°C. Indeed, at about 140-150 bar, balloon-like particles were formed with diameters up to 50 µm. At pressures higher than 150 bar nanoparticles were obtained.

For each temperature tested, a pressure in correspondence of which the system shows a transition between large hollow particles and nanoparticles exists. The higher is the test temperature, the higher is the pressure at which the transition is observed. Indeed, the balloon-like morphology has been obtained for the couples pressure/temperature corresponding to 95

bar/40°C, 120 bar/50°C and 150 bar/60°C. Although we are not able to give an explanation to this experimental evidence, at all these conditions CO₂ density is similar; i.e., from 0.56 to 0.58 g/cm³.

At this point the question is: which is the relationship among morphologies and the characteristics of the process? We hypothesized a high-pressure solubility diagram of the system DMSO/CO₂ modified by the presence of YAc as reported in **Figure 4**. It has been extrapolated from the data reported by Kordikowski et al. [8] for the system DMSO/CO₂ at 25 and 30°C, and on the basis of our observations using the transparent vessel and could give an explanation of the experimental observations. In a previous paper [7], we hypothesized that the possible modification of the vapour-liquid phase behavior due to the presence of solute can consist of an increase of the mixture critical point (MCP) pressure.

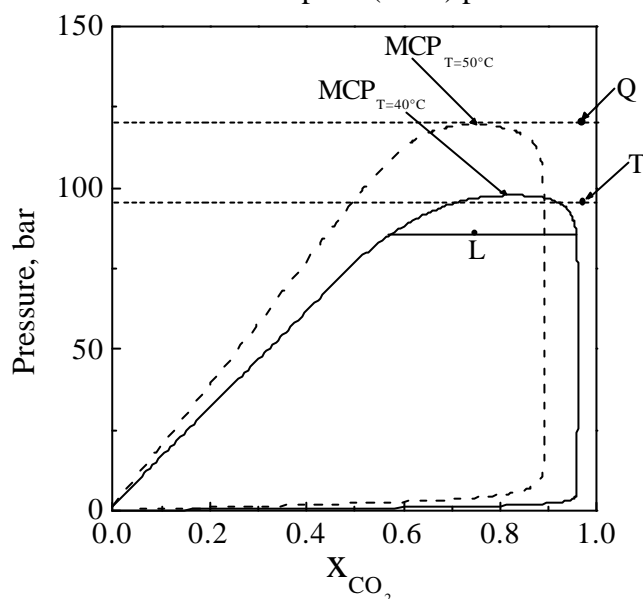


Figure 4. Hypothesized high-pressure solubility diagram of the system DMSO/CO₂ modified by the presence of YAc.

Looking at the position of the operating point of the precipitation process with respect to the MCP, we can try an explanation of the different morphologies obtained. If a L-kind mixture is formed in the precipitator, it splits in two phases: a liquid-rich phase and a CO₂-rich phase. Solute can be partitioned between the two phases and precipitation can start from both or prevalently from the liquid-rich one.

If a homogeneous supercritical phase is formed in the precipitator (Q-kind mixtures, with respect to the 40°C isotherm), particle formation results from gas phase nucleation [9] and nano or small microparticles are usually obtained. These experiments can be considered the most successful from the SAS micronization point of view. For example, YAc submicronic particles were generated from a homogeneous mixture (**Figure 2**). The very small dimension of the particles (0.28 μm mean diameter) and the slight influence of the nozzle diameter, indicate that droplets do not form because the surface tension decreases to zero before jet break-up [9].

In the one phase region below the MCP_{T=40°C}, the solvent and SC-CO₂ are still completely miscible but the mixture is subcritical. The precipitation from a T-kind mixture (for example at 95 bar and 40°C) gives place to larger particles producing balloons. These particles are formed by the expansion of the liquid droplets.

For what concerns the YAc balloons obtained at 120 bar and 50°C and at 150 bar and 60°C, we have to consider that, increasing the temperature, the ternary MCP moves to higher pressures thus, these process conditions can lead again to a subcritical homogeneous phase.

In conclusion, this work confirms that SAS micronization is a highly versatile process capable to generate particles of various dimensions and morphology, depending on the operating conditions. It is possible to obtain YAc particles from about 0.28 to 50 µm simply changing the operating pressure and/or temperature.

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