HOLLOW MICROMETRIC PARTICLES PRODUCTION BY SUPERCRITICAL ANTISOLVENT PRECIPITATION

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Supercritical Antisolvent (SAS) precipitation is a semi-continuous micronization technique used to produce micrometric and nanometric particles. However, in correspondence of given values of pressure and temperature, hollow micrometric particles (balloons) can be obtained. The analysis of the high pressure phase behavior of the ternary system organic solvent-CO_2-solute allows to select the Pressure – temperature – molar fraction region in which this kind of particles can be obtained.

In this work, Yttrium Acetate, Dextran and Cefonicid solubilized in Dimethylsulfoxide (DMSO) and Poly(methyl methacrylate) (PMMA) solubilized in Methyl methacrylate (MMA) have been precipitated in form of micrometric hollow particles ranging from about 5 to 100 μm in diameter. Carbon dioxide has been used as the supercritical antisolvent. The hollow particle morphology, according to the general model, has been attributed to the precipitation of the solute from a subcritical gas phase located near the ternary mixture critical point.

INTRODUCTION

Some micronization processes based on the use of supercritical antisolvents have been suggested during the last ten years as alternatives to traditional liquid antisolvent techniques [1]. The results obtained are quite different depending on the process mode (batch or semi-continuous), on the nature of the material and on the high-pressure equilibria characterizing the ternary system. Crystals, spherical nano- and microparticles from 0.1 μm to several μm and empty shells can be obtained [2].

In the semicontinuous antisolvent (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.

The SAS has been applied by various research groups to pharmaceutical compounds, superconductors, catalyst precursors, coloring matters, explosives, polymers and biopolymers [1-3]. Despite the fact that many works have been published on SAS precipitation, only a limited number of them has been focused on the mechanisms controlling particle formation and on the role of the process parameters on the morphology and on the dimensions of the powder precipitated [4].

In some recent works, our research group has pointed out the relationship between high pressure phase equilibria and the morphology of SAS precipitated materials. The observed morphologies and the position of the process operating point with respect to the mixture critical point have been correlated for some compounds [5-6]. In some cases, vapor-liquid equilibrium (VLE) behaviour is substantially the same of the corresponding liquid – supercritical fluid (binary) system [5]. In some other cases, we observed substantial modifications of the binary VLE behavior when a third component was added [6].

In this work, we have focused our attention on the generation of hollow micrometric particles (balloons). Particularly, we have tried to produce balloons of Yttrium Acetate, Dextran and Cefonicid solubilized in Dimethylsulfoxide (DMSO) and of PMMA solubilized in MMA, using a laboratory plant and a pilot plant.

I - EXPERIMENTAL SECTION

Materials.

Yttrium Acetate (YAc) purity 99.9%, PMMA purity 99.9%, MMA purity 99% and DMSO purity 99% have been purchased from Aldrich. Dextran purity 99.9% has been purchased from ICN Biomedicals Inc. Cefonicid sodium salt has been kindly supplied by Farmabios Spa (Italy). CO_2 (purity 99%) has been purchased from SON (Naples, Italy). The solubilities of YAc, PMMA, Dextran and Cefonicid have been measured at room temperature. They are equal to 320 mg/mL for YAc, 20 mg/mL for Dextran, 100 mg/mL for Cefonicid in DMSO. The solubility of PMMA in MMA is very large.

Untreated YAc and Cefonicid are formed by irregular crystals with particle size ranging between 20 and 200 μm. Dextran and PMMA are amorphous polymers with molecular weights equal to 40000 in the case of Dextran and 100000 in the case of PMMA.

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 of each sample has been evaluated measuring about 1000 particles from different images using an image analysis software (SigmaScan Pro 5). Particle size distributions (PSD) have been obtained and the mean particle size (D_n) has been calculated as the number-average diameter.

II - APPARATUS AND PROCEDURES

The configuration of 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 dm^3 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 (d = 200 μm). SC-CO_2 is pumped through another inlet port located on the top of the chamber. 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 previous papers [7-8].

The pilot plant is a closed loop plant consisting of a water-jacketed precipitator with an I.V. of 5 dm^3 and a L/D ratio of 9.4. The liquid solution and SC-CO_2 are fed to the precipitation chamber through a tube-in tube injection system. The generation of small liquid droplets is ensured by the presence of a 500 μm nozzle fitted on the tip of the internal tube. The injector has been designed to produce a fast contact between the two streams at the outlet of the tubes, where a turbulent flow is generated. A more detailed description of the pilot plant can be found in a previous work [9]. The experimental procedure has been described in previous works [7-8] and is similar for laboratory and pilot scale plant.

III - RESULTS AND DISCUSSION

In previous works [5-6] we tried to give a general interpretation of the morphologies observed during SAS precipitation on the basis of the high pressure VLEs of the ternary (liquid + solute + supercritical fluid) systems. The basis of this approach is that, due to the very fast mass transfer that characterizes SCF processes, near-equilibrium conditions can be attained even in continuous processes. Using pseudo-binary equilibrium diagrams, the phase equilibria involving the solute are neglected and only modifications in the binary diagram due to the presence of solute are considered.

Some compounds do not interfere with the binary VLEs; therefore, the one-phase region is the same as in the binary system (at temperatures and pressures higher than mixture critical point; i.e., the pressure at which the ternary mixture is supercritical). In general, we observed that the presence of the solute modifies the binary VLEs even at low solute concentrations. The simplest modification that can be presented by ternary systems, with respect to the corresponding binary system, consists of the shift of the mixture critical point (MCP) towards higher pressures. This effect could also be a function of the concentration of solute in the liquid solution; i.e., the higher is the concentration, the larger is the pressure increase of the MCP. However, the shift of the MCP towards higher pressures is only the simplest possible modification of the VLEs. More complex interactions among the three components may occur [6]. We hypothesized these modifications, starting from general thermodynamic considerations. In particular, the so-called cosolvency effect can occur when a mixture of two components solvent + solute is better soluble in a supercritical solvent than each of the pure components alone. In contrast to this behavior, a ternary system can show poorer solubility compared with the binary systems antisolvent + solvent and antisolvent + solute; a system with these characteristics is called a non-cosolvency (antisolvent) system [10-11]. In particular, in the case of the SAS process, we hypothesized that the solute does not induce cosolvency effects due to the antisolvent effect of the CO_2. The simplest modification of the VLEs in the case of ternary non-cosolvency systems, with respect to the corresponding binary system, consists of the movement of the MCP towards higher pressures.

Once hypothesized how the solute can modify the VLEs, we tried to relate the different morphologies obtained to the position of the process operating point with respect to the MCP. In particular, we assumed that sub-microparticles are produced when precipitation occurs from a supercritical ternary phase (point S in **Figure 1**); balloons (hollow large particles) are produced when precipitation occurs from a gaseous subcritical phase (point V).

To confirm the general validity of this framework, in this work we performed various sets of experiments aimed at the obtainment of balloons (point V in **Figure 1**).

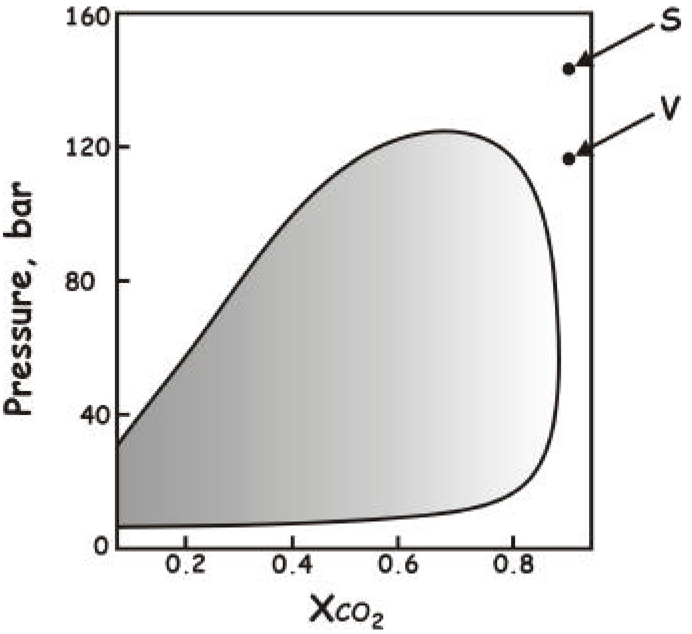

Figure 1. Position of the operating points with respect to the miscibility hole in a pseudo-binary diagram at a fixed concentration of solute.

In the case of the system Yttrium Acetate – DMSO, once fixed the temperature, we performed a set of experiments at pressures that starting from point S move towards point V, until the balloon-like morphology has been obtained. Particularly, the balloons have been obtained at the following couples pressure/temperature: 95bar/40°C, 120bar/50°C and 140bar/60°C. In **Figure 2**, an example of balloons of YAc precipitated from DMSO at 140 bar, 60°C and 15 mg/mL has been reported. The balloons ranged between about 2 and 10 μm, had a hollow core and a discontinuous surface: they are constituted by strictly connected nanoparticles. In correspondence of all these couples pressure/temperature, the density of supercritical CO_2 is in the range 0.55-0.60 g/cm^3; whereas, at higher densities, nanoparticles have been obtained (see, for example, **Figure 3**).

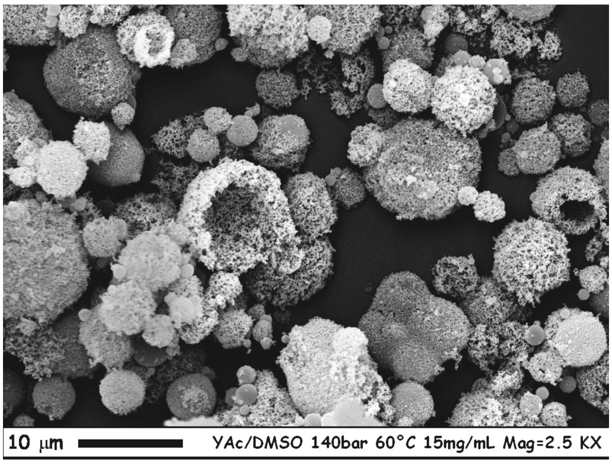

Figure 2. Balloons of YAc precipitated from DMSO at 140 bar, 60°C and 15mg/mL.

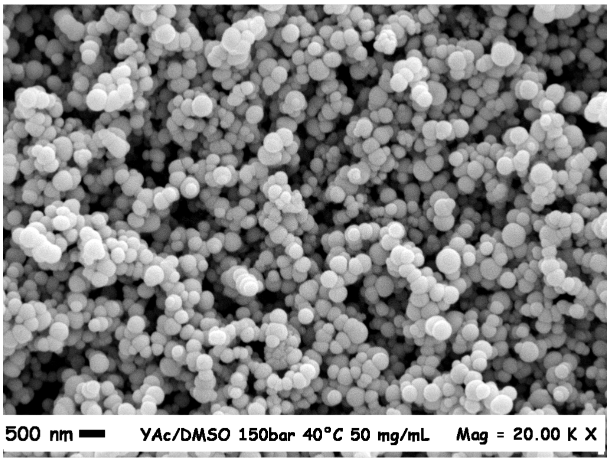

Figure 3. YAc nanoparticles precipitated from DMSO at 150 bar, 40°C and 50 mg/mL.

In the case of the system Dextran – DMSO, the experimentation has been performed both on the laboratory and on the pilot plant. Balloons have been obtained at 60°C for pressures set in the range 135-150 bar (at the same CO_2 density values of YAc), whereas in correspondence of 40°C, we have not been obtained the balloon-like morphology.

The system PMMA/MMA is completely different from the all the ones previously tested, since in this case PMMA has been precipitated from its monomer. In analogy with the other systems, we obtained PMMA balloons at 85 bar and 40°C. An example of these balloons has been reported in **Figure 4**.

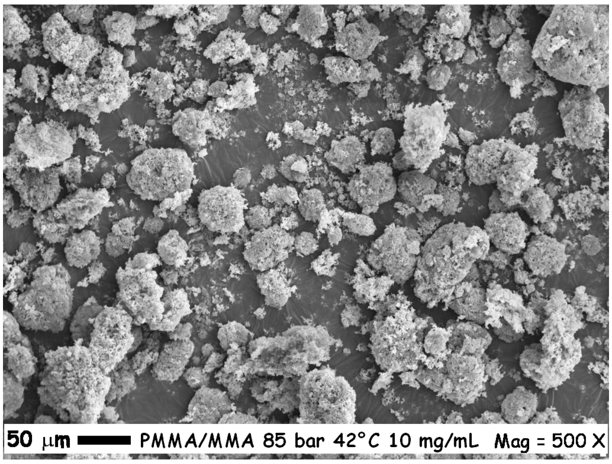

Figure 4. Balloons of PMMA precipitated from MMA at 85 bar, 42°C and 10mg/mL.

The fourth system explored has been Cefonicid in DMSO. In this case, the variation of morphology has been induced by the increase of concentration. Indeed, we fixed the operating conditions at 150 bar and 40°C and varied the concentration of the Cefonicid in DMSO from 10 to 90 mg/mL. SEM analysis of the powders precipitated in these experiments showed that Cefonicid has been precipitated in form of sub-microparticles in correspondence of liquid concentrations up to 50 mg/mL; whereas, balloons with continuous surface and hollow core have been obtained in correspondence of concentrations higher than 75 mg/mL. An example of these balloons has been reported in **Figure 5**. We hypothesized that, in this case, the increase of solute concentration amplifies also the interactions with the system DMSO – CO_2, and the higher is the concentration of the liquid solution, the higher is the increase of the pressure at which MCP is located. We also verified this hypothesis performing some SAS experiments on a quartz windowed precipitator.

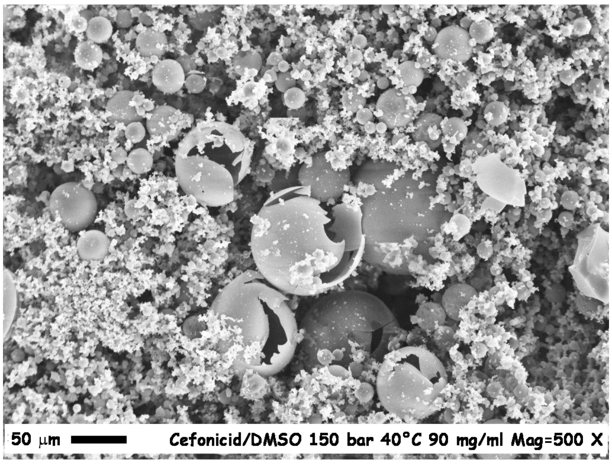

Figure 5. Balloons of Cefonicid precipitated from DMSO at 150 bar, 40°C and 90mg/mL.

CONCLUSIONS

Balloons have been obtained for all the systems tested in this work. They always have a hollow core, whereas their surface is continuous in the case of some materials and discontinuous in the case of other.

Moreover, in three cases (YAc/DMSO – Dextran/DMSO – PMMA/MMA), the balloons have been obtained in correspondence of about the same CO_2 density conditions. In the case of the system Cefonicid/DMSO, the increase of concentration moved the MCP towards higher pressures until subcritical conditions have been obtained.

REFERENCES

[1] JUNG, J., PERRUT, M., J. Supercrit. Fluids, Vol. 20, **2001**, p. 1.
[2] REVERCHON, E., J. Supercrit. Fluids, Vol. 15, **1999**, p. 1.
[3] FOSTER, N., MAMMUCARI, R., DEHGHANI, F., BARRETT, A., BEZANEHTAK, K., COEN, E., COMBES, G., MEURE, L., NG, A., REGTOP, H. L., TANDYA, A., Ind. Eng. Chem. Res., Vol. 42, **2003**, p. 6476.
[4] WUBBOLTS, F. E., BRUINSMA, O. S. L., VAN ROSMALEN, G. M., J. of Crystal Growth, Vol. 198/199, **1999**, p. 767.
[5] REVERCHON, E., CAPUTO, G., DE MARCO, I., Ind. Eng. Chem. Res., Vol. 42, **2003**, p. 6406.
[6] REVERCHON, E., DE MARCO, I., J. Supercrit. Fluids, in press.
[7] REVERCHON, E., DELLA PORTA, G., PACE, S., DI TROLIO, A., Ind. Eng. Chem. Res. Vol. 37 (3), **1998**, p. 952.
[8] REVERCHON, E., DELLA PORTA, G., CELANO, C., PACE, S., DI TROLIO, A., J. Material Res., Vol. 13 (2), **1998**, p. 284.
[9] REVERCHON, E., DE MARCO, I., CAPUTO, G., DELLA PORTA, G., J. Supercrit. Fluids, Vol. 26, **2003**, p. 1.
[10] SCHEIDGEN, A. L., SCHNEIDER, G. M., Fluid Phase Equilib., Vol. 194-197, **2002**, p. 1009.
[11] BECKER, F., RICHTER, P., Fluid Phase Equilib., Vol. 49, **1989**, p. 157.