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Polymer Micronization using Batch Supercritical Antisolvent Process

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In this paper, different polymers were processed using a Batch Supercritical AntiSolvent precipitation (BSAS) to evaluate the possibility of producing nanoparticles and microparticles of controlled size and distribution. Liquid solutions of a polymer in dimethylsulfoxide (DMSO) or acetone were charged in a vessel; then, supercritical CO_2 with the role of antisolvent was pumped up to the desired pressure. The process was performed in two steps: in batch mode for a time t_1 and in continuous mode for a time t_2, with a constant CO_2 flow rate. All the experiments were carried out at a final pressure of 100 bar and a final temperature of 40 °C, whereas the concentration of the liquid solution was varied from 0.1 to 5 mg/mL.

SEM images of the processed material were used to study morphology, mean particle size and particle size distribution. Amorphous particles were obtained at all successful BSAS conditions, whereas crystals were sometimes observed when the micronization process failed. Polymers solubilized in acetone, such as cellulose acetate, ethyl cellulose, polymethyl methacrylate (PMMA) and Poly(vinylidene fluoride-co-hexafluoropropylene) (PVDF-HFP) prevalently precipitated in form of nanoparticles in the range 50-200 nanometers, whereas polymers solubilized in DMSO, such as Poly-vinyl-alcohol (PVA), dextran and inulin precipitated in form of nanoparticles at lower concentrations (in the range 100-200 nanometers) and in form of microparticles at higher concentrations (in the range 0.7-2 μm).

1. Introduction

Batch supercritical antisolvent precipitation (BSAS) and continuous supercritical antisolvent precipitation (SAS) have been frequently used to produce micro and/or nanosized polymers, as reported in some experimental papers for different polymers (Perez de Diego et al., 2005; Perez de Diego et al., 2006; Duarte et al., 2006) and in some reviews (Hakuta et al., 2003; Shariati and Peters, 2003; Reverchon and De Marco, 2011) . Using the SAS process, crystals, spherical nanoparticles, and microparticles with mean diameters ranging from 0.1 µm to several tenth of microns are the most frequently observed morphologies. In some cases, hollow micrometric particles have been obtained.

Different explanations have been proposed to justify the obtainment of the different morphologies. Considering the thermodynamic aspect of the process, a correlation between particles dimension and the position of the operating point in the high pressure vapor–liquid equilibria diagram has been proposed. A general trend has been observed: at pressures far above the mixture critical point (MCP), nanoparticles are precipitated (Reverchon et al., 2007); near above the MCP, microparticles can be obtained (Reverchon et al., 2008a); whereas, operating at subcritical conditions, expanded microparticles (in some cases called balloons) (Reverchon et al., 2008b) are produced.

It has been also observed that the continuous sequence of morphologies of amorphous particles (expanded hollow microparticles, microparticles and nanoparticles) has been obtained only using a particular solvent, dimethylsulfoxide (DMSO), whereas, using other solvents, like acetone, only some morphologies have been obtained (Reverchon et al., 2010; De Marco et al., 2012). In the case of the SAS process, this result has been correlated to the different mixing behavior of these two solvents in contact with supercritical CO_2: in the case of acetone, there is sharp transition from two-phase mixing to single phase jet mixing at pressures larger than the mixture critical pressure of the binary system solvent–carbon

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dioxide; in the case of other solvents, like DMSO, a large transition range between the two-phase mixing regime below the mixture critical pressure and the completely developed one-phase mixing regime above the mixture critical pressure has been observed.

In this paper, using the BSAS, a simpler process with respect to SAS, considering that there is not a jet of a liquid solution, the possibility of producing nanoparticles and microparticles of various polymers using two different solvents (acetone or DMSO) has been explored. The aims of this work are:

- the production of the micro and nanoparticles using the batch process;
- the confirmation of the SAS obtained results, in terms of morphologies, using the BSAS process.

2. Experimental section

2.1 Materials

Cellulose acetate (CA, degree of substitution = 2.5, MW 50,000), ethyl cellulose, polymethyl methacrylate (PMMA, MW 120,000), Dextran (MW 40,000), Inulin (MW 5,000) Polyvinyl alchool (PVA, MW 30,000–70,000), dimethyl sulfoxide (DMSO, purity 99.9 %) and acetone (AC, purity 99.8%) were supplied by Sigma–Aldrich (Milan, Italy).

Poly(vinylidene fluoride-co-hexafluoropropylene) (PVDF-HFP, MW 353,000, density 1.78 g cm^{-3}) was kindly supplied by Solvay S.A. (Ixelles, Belgium).

2.2 Apparatus and procedures

BSAS apparatus scheme is represented in Figure 1. It consists of an HPLC pump (Gilson, model 305) used to deliver the supercritical CO_2. A 316 stainless steel cylindrical high-pressure vessel with an internal volume of 80 mL is used as precipitation chamber in which SC-CO_2 contacts the polymer solution in a single pass.

The polymer was dissolved in the solvent (acetone or DMSO) and the solution was placed in the formation cell (steel caps with a diameter of 25 mm and heights of 300-500 μm). The cell was rapidly (ca. 30 seconds) put inside the precipitation vessel to avoid the evaporation of the solvent. Then, the vessel was closed and filled from the bottom with SC-CO_2, up to the desired pressure. Before entering the precipitator, CO_2 is heated at the process temperature. The precipitator is electrically heated using thin band heaters (Watlow, model STB3J2J1) and the pressure in the chamber is measured using a test gauge manometer (Salmoiraghi, model SC-3200). The vessel was then filled from the bottom with supercritical CO_2, up to the desired pressure using the HPLC pump. We operated in batch mode for a time t_1; then, a micrometric valve (Hoke, model 1315G4Y) was opened at the bottom of the vessel and the operation was performed in continuous mode; i.e., at a constant CO_2 flow rate of 1.5 kg/h for a time t_2. This valve is heated by a cable heater (Watlow, model 62H24ASX) connected to a controller. Pressure and temperature were hold constant. Then, the vessel was slowly depressurized for 30 min.

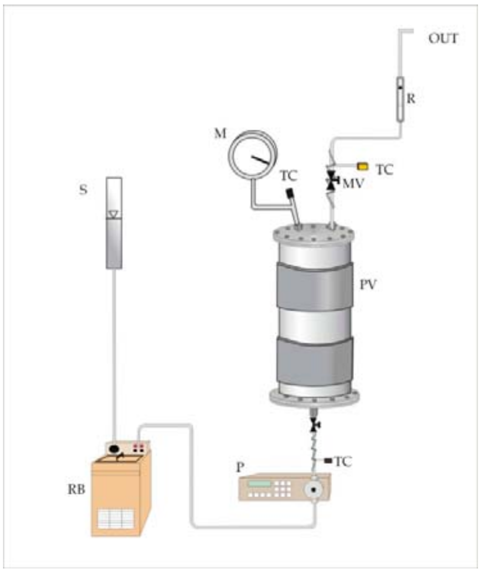

Figure 1: Schematic representation of BSAS apparatus. S: CO_2 supply; RB: refrigerating bath; P: pump; PV: precipitation vessel; MV: micrometering valve; R: rotameter; TC: thermocouple; M: manometer.

Samples of the precipitated powder were observed using a Scanning Electron Microscope (SEM) (Assing, mod. LEO 420). SEM samples were covered with 250 Å of gold using a sputter coater (Agar, mod. 108A). The particle size (PS) and the particle size distributions (PSDs) were measured using an image analysis performed with Sigma Scan Pro 5.0 software (Jandel Scientific, San Rafael, Canada), an image processing program to count, measure and analyze digital images; about 1000 particles were considered in each PSD calculation. Then, Origin 6 software (Microcal, Northampton, USA) was used to determine the particle size and the particle size distribution.

3. Results and discussion

The range of operating conditions used in this work was initially selected on the basis of previous experiences on the SAS and BSAS processes. The pressure was fixed at 100 bar and the temperature at 40 °C. These values of pressure and temperature correspond to supercritical conditions; the operating pressure (100 bar) is slightly higher than the mixture critical point pressure of the binary systems AC/CO_2 and DMSO/CO_2. Table 1 reports a summary of the experiments performed on the different polymers, with the indication of the solute, the solvent, the concentration of the liquid solution, the process characteristic times and the obtained morphology.

Table 1: List of experiments. NP: nanoparticles; MP: microparticles; CP: crystalline powders;

Polymer	Solvent	concentration, mg/mL	t_1, min	t_2, min	morphology
Cellulose acetate	AC	0.1	60	30	NP
		1	30	30	NP
		5	60	30	NP
Ethyl cellulose	AC	0.1	60	30	CP
		1	30	30	CP
		5	60	30	CP
PMMA	AC	0.1	60	30	NP
		1	30	30	NP
		5	60	30	Connected NP
PVDF-HFP	AC	0.1	60	30	CP
		1	30	30	CP
		5	60	30	Connected NP
PMMA	DMSO	5	120	30	MP
Dextran	DMSO	5	120	30	MP
Inulin	DMSO	5	120	30	MP
PVA	DMSO	1	90	30	NP
		5	90	30	MP

3.1 Particles obtained from acetone

The first set of experiments was performed using acetone as the liquid solvent. Cellulose acetate, ethyl cellulose, PMMA and PVDF-HFP were dissolved in acetone and BSAS processed at different polymer solution concentration and at different process times.

In the case of cellulose acetate, spherical nanoparticles were systematically produced at 100 bar and 40°C. No significant differences were revealed varying the liquid solution concentration from 0.1 to 5 mg/mL. As an example, in Figure 2, the SEM image and the corresponding particle size distribution of the powder obtained at 100 bar, 40°C, 5 mg/mL are reported.

From Figure 2, it is possible to observe that the obtained particles are spherical (from the SEM image) and in the nanometric dimensions range. Indeed, the mean diameter is equal to 0.148 μm and the standard deviation is equal to 0.028 μm.

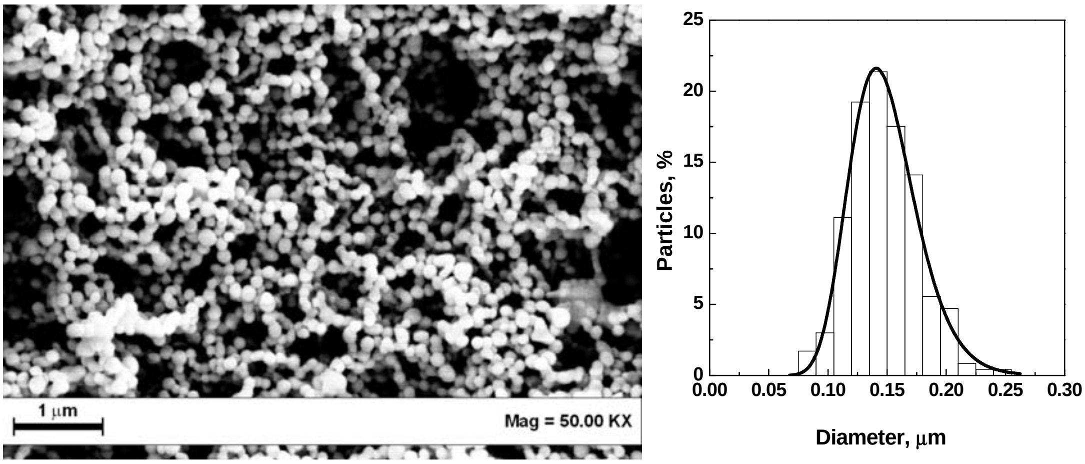

Figure 2: Cellulose acetate micronized from acetone at 100 bar, 40°C, 5 mg/mL; left: SEM image; right: particle size distribution.

Ethyl cellulose and PVDF-HFP particles, in correspondence of all the operating conditions, precipitated in form of crystalline non spherical particles, as it is possible to observe from the SEM images of Figure 3.

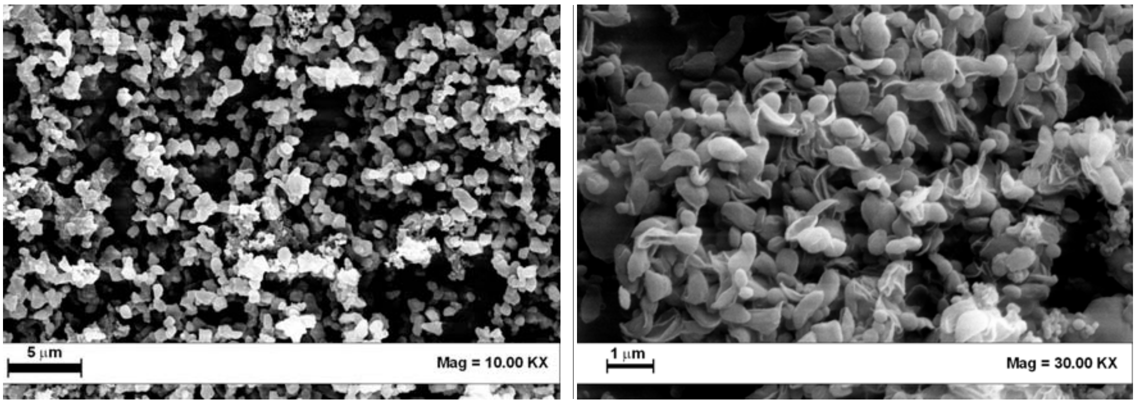

Figure 3: SEM images of non-spherical polymeric particles precipitated from acetone; left: ethyl cellulose; right: PVDF-HFP.

PMMA precipitated in form of nanoparticles in correspondence of the lower concentrations (0.1 and 1 mg/mL), whereas increasing the polymer solution concentration the nanoparticles formed a network and were not well discernable.

The BSAS results obtained for the different polymers confirmed the semi-continuous SAS results obtained in the literature. Microparticles were not obtained at 100 bar and 40°C, even increasing the concentration of the liquid solution. Therefore, the explanation given for the SAS process in terms of different jet mixing may be applied to this batch case, where a real jet of solvent is not present. Indeed, in the BSAS process, there is an interface between the liquid solvent and the supercritical carbon dioxide, but not a jet of liquid solution. The explanation given in De Marco et al. (2012) in terms of viscosities, in any case, can be applied also to the BSAS batch process.

3.2 Particles obtained from DMSO

Other experiments were performed using DMSO as the liquid solvent. In this case, PMMA, Dextran, Inulin and PVA were BSAS processed at different process times. From Table 1, it is possible to observe that the time t_1, for the BSAS tests performed using DMSO as the liquid solvent is, in general, higher with respect to the time t_1 in the case of the tests performed using Acetone as the liquid solvent. For all the solutes, spherical microparticles were systematically produced at 100 bar and 40 °C.

Examples of SEM images of these particles with the corresponding particle size distribution are reported in Figure 4 in the case of PVA microparticles and in Figure 5 in the case of Dextran microparticles.

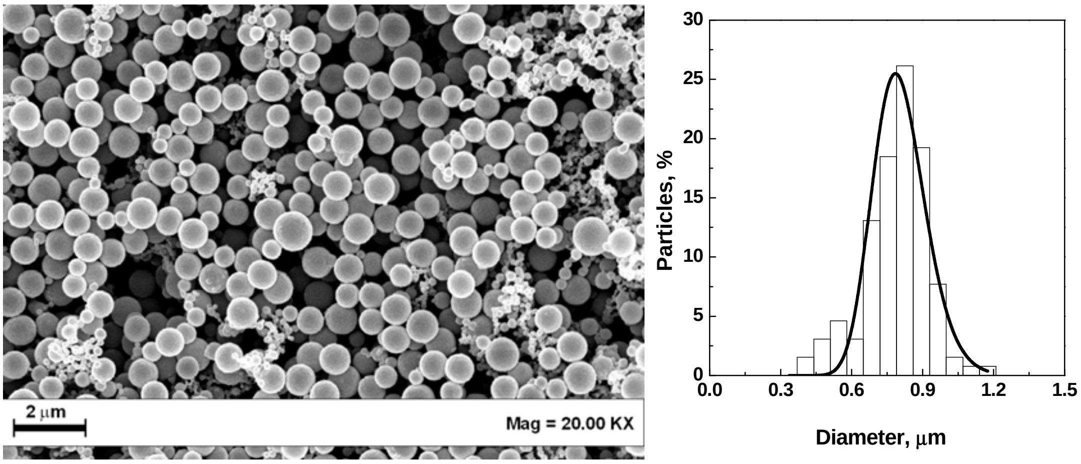

Figure 4: PVA microparticles obtained from DMSO at 100 bar, 40°C, 5 mg/mL; left: SEM image; right: particle size distribution.

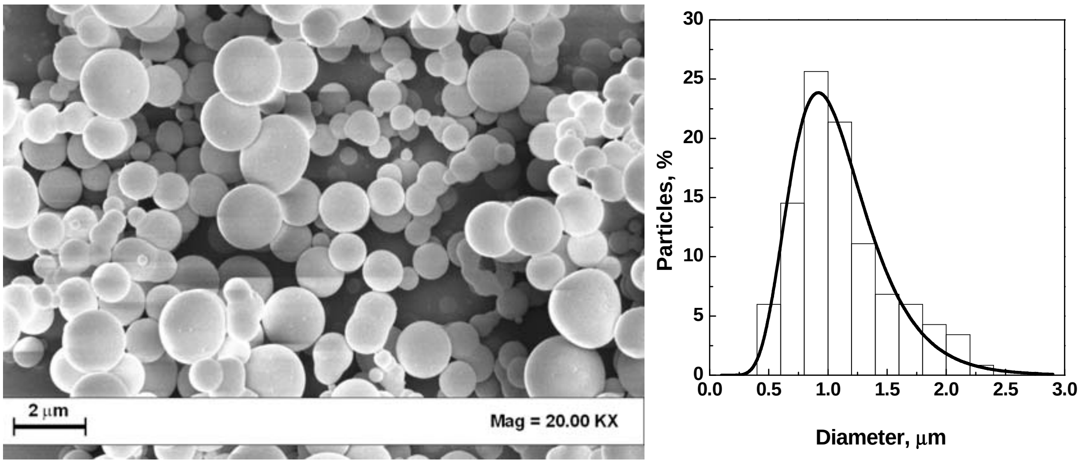

Figure 5: Dextran microparticles obtained from DMSO at 100 bar, 40 °C, 5 mg/mL; left: SEM image; right: particle size distribution.

In the case of PVA (Figure 4), the mean diameter is equal to 0.792 μm and the standard deviation is equal to 0.138 μm, whereas, in the case of dextran (Figure 5), the mean diameter is equal to 1.116 μm and the standard deviation is equal to 0.412 μm.

Also in the case of DMSO soluble polymers, the BSAS results obtained for the different polymers confirmed the semi-continuous SAS results. In this case, operating at 100 bar and 40 °C, microparticles were systematically obtained.

4. Conclusions

Different polymers were successfully micronized using the batch supercritical antisolvent process. Therefore, we demonstrated that also with the simple batch process, it is possible to obtain micro and nanoparticles of polymeric solutes. Moreover, different morphologies have been obtained: crystals, nanoparticles and microparticles, depending on the used organic solvent. In particular, we observed that, at all the tested operating conditions, it is not possible to obtain microparticles using acetone as the liquid solvent. On the contrary, it is possible to obtain microparticles (in the range 1-5 μm) using DMSO as the liquid solvent.

References

De Marco I., Knauer O., Cice F., Braeuer A., Reverchon E., 2012, Interactions of phase equilibria, jet fluid dynamics and mass transfer during supercritical antisolvent micronization: The influence of solvents, Chem. Eng. J. 203, 71-80.

Duarte A.R.C., Gordillo M.D., Cardoso M.M., Simplicio A.L., Duarte C.M.M., 2006, Preparation of ethyl cellulose/methyl cellulose blends by supercritical antisolvent precipitation, Int. J. Pharm. 311, 50-54.

Hakuta Y., Hayashi H., Arai K., 2003, Fine particle formation using supercritical fluids, Curr. Opin. Solid State Mater. Sci. 7 (4–5), 341–351.

Perez de Diego Y., Pellikaan H.C., Wubbolts F.E., Witkamp G.J., Jansens P.J., 2005, Operating regimes and mechanism of particle formation during the precipitation of polymers using the PCA process, J. Supercrit. Fluids 35, 147–156.

Perez de Diego Y., Pellikaan H.C., Wubbolts F.E., Borchard G., Witkamp G.J., Jansens P.J., 2006, Opening new operating windows for polymer and protein micronisation using the PCA process, J. Supercrit. Fluids 36, 216–224.

Reverchon E., De Marco I., Torino E., 2007, Nanoparticles production by supercritical antisolvent precipitation: a general interpretation, J. Supercrit. Fluids 43 (1), 126–138.

Reverchon E., Adami R., Caputo G., De Marco I., 2008a, Spherical microparticles production by supercritical antisolvent precipitation: interpretation of results, J. Supercrit. Fluids 47 (1), 70–84.

Reverchon E., De Marco I., Adami R., Caputo G., 2008b, Expanded micro-particles by supercritical antisolvent precipitation: interpretation of results, J. Supercrit. Fluids 44 (1), 98–108.

Reverchon E., Torino E., Dowy S., Braeuer A., Leipertz A., 2010, Interactions of phase equilibria, jet fluid dynamics and mass transfer during supercritical antisolvent micronization, Chem. Eng. J. 156 (2), 446–458.

Reverchon E., De Marco I., 2011, Mechanisms controlling supercritical antisolvent precipitate morphology, Chem. Eng. J. 169, 358-370.

Shariati A., Peters C.J., 2003, Recent developments in particle design using supercritical fluids, Curr. Opin. Solid State Mater. Sci. 7 (4–5), 371–383.