

SUPERCRITICAL ANTISOLVENT PRECIPITATION: ATOMIZATION AND PRODUCT QUALITY

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A pilot plant is presented which has been built to prepare fine particles by the Precipitation with a Compressed Fluid Antisolvent (PCA process). This technique offers interesting applications for products, which are produced in small amounts, as certain pharmaceuticals or energetic materials. In this contribution the micronization of paracetamol is presented. The mean particle size of the precipitated powder can be manipulated by changing the precipitation pressure and solvent type however the precipitation temperature has no significant influence on the particle size. It is shown that morphology and particle size is affected by the droplet size of the initial spray jet just behind the nozzle. PCA is a two step process (droplet formation and precipitation in the droplets) and both steps influence the product quality.

1 INTRODUCTION

The production of nano- and microparticles with controlled particle size and morphology is of increasing importance for several applications. But, submicronic are very difficult to be obtained using traditional methods. Therefore, supercritical fluids based techniques have been proposed in the attempt to take advantage of the solvent power and of the high diffusivity that are characteristics of supercritical fluids. Several precipitation techniques have been proposed, as recently reviewed by Jung et al. [1].

The first known precipitation process based on supercritical fluid technique is known as Rapid Expansion of Supercritical Solutions (RESS) [2, 3]. A component is dissolved in a supercritical fluid (extraction process) which expands rapidly through a nozzle. Due to this strong pressure and temperature drop the dissolved material becomes insoluble in the low pressure gas and thus a high supersaturation is created in the spray jet. Fast nucleation and growth of the crystalline particle occur.

Solids which are insoluble in a compressed gas can be processed by applying the PCA process (Precipitation with a Compressed Fluid Antisolvent). For this, a solution consisting of a solid material dissolved in an organic solvent is sprayed through a nozzle into a high pressure vessel filled with a compressed gas. The formation of the particles is based on two mechanisms which take place simultaneously. On the one hand the solvent evaporates in the compressed gas and on the other hand the compressed gas penetrates into the droplets where it acts as an antisolvent for the dissolved material so that precipitation occurs. A distinctive characteristic of supercritical fluids is the diffusivity that can be up to two orders of magnitude higher than those of liquids. Therefore, the diffusion of the supercritical fluid into a liquid solvent can produce a fast supersaturation of solute dissolved in the liquid and its precipitation in micronized particles.

Operation is either batchwise or semi-continuous with promising scale-up perspectives and particle sizes ranging from submicron to few microns. The key operating parameters are pressure, temperature, solution flow rate and initial concentration. These parameters control product quality through their effects on thermodynamics, hydrodynamics and kinetics on mass

transfer and precipitation [4-6]. A few research groups have investigated some of these effects, namely the effects of temperature and initial solution concentration [7, 8].

The objective of this study is to describe the effects of process parameters (pressure, temperature, flow rates and concentration) on the quality (e.g. particle size and morphology) of the solid product. A pharmaceutical substance (paracetamol) is precipitated from different organic solvents (e.g. methanol, ethanol, N,N-dimethylformamide) by carbon dioxide as antisolvent.

2 APPARATUS AND MATERIALS

2.1 High Pressure Pilot Plant

The experimental work was performed in a high pressure pilot plant consisting of the CO₂ supply unit including a membrane pump and a heat exchanger, the precipitation vessel (8 l internal volume) with sinter metal filter (pore size: 1 μm) and a second membrane pump which is connected with the nozzle placed at the top of the precipitation vessel (see Fig. 1). The maximum pressure in the plant is limited to 30 MPa, the precipitation temperature to 353 K. The mass flow rate of the CO₂ is limited to 30 kg/h, the maximum volume flow of the solution is 0.6 m/h.

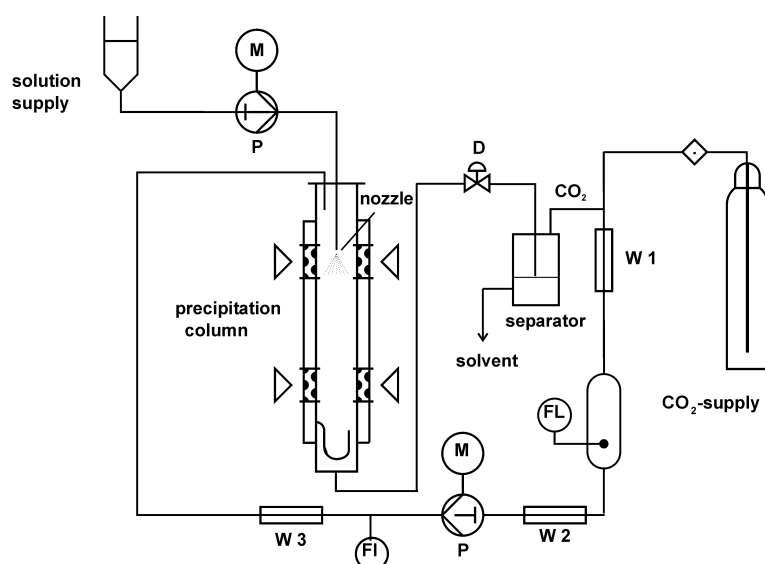


Figure 1: Flow sheet of the experimental setup: W: heat exchanger, P: membrane pump, FI: mass flow meter, FL: liquid CO₂ reservoir, D: pressure control

At the beginning of the continuous PCA process, CO₂ is fed to the precipitation vessel until the desired pressure is reached. Then, a steady antisolvent flow is set and maintained for 10 minutes before the solution is sprayed into the precipitation vessel through an atomization device. The particle formation can be observed through sapphire windows ($\varnothing = 18$ mm) which are placed at different positions in the precipitation vessel. The produced particles are collected on a sinter metal filter placed on the bottom of the precipitation vessel. To remove any residual organic solvent from the particles pure CO₂ continues to flow for at least 30 minutes through the precipitation vessel before starting the depressurization of the precipitator. If this purging step with pure CO₂ is not done, organic solvent condenses during the depressurization and partly dissolves the powder modifying its morphology and lowering the

yield. The fluid mixture (mainly CO₂ and some organic solvent) leaves the precipitation vessel and is depressurized in the separator where solvent is separated from the CO₂. The CO₂ can be recompressed and fed into the CO₂ cycle or let off.

2.2 Materials

The solubility of paracetamol in ethanol and methanol is 17.5 wt.-% and 30 wt.-%, respectively. Methanol and ethanol were used as solvents due to their complete miscibility with supercritical CO₂ at the used process conditions. The binary systems were investigated systematically and the phase behaviour is known from literature [9, 10].

3 EXPERIMENTAL RESULTS

The droplet formation process is investigated because of the properties of the droplet spectrum influence the particle formation and therefore the quality of the solid particles. A laser system was used to measure the droplet size in-situ in the high pressure vessel. Moreover, the droplet formation was visualized by a high speed camera system.

3.1 Droplet formation

The droplet formation was investigated in the same apparatus as the precipitation was carried out. The main different was that not a solution but pure solvent was spray through the nozzle into the high pressure antisolvent. The droplet size was measured by a 3-wavelength extinction laser system [11] at two different distances behind the nozzle (10 and 40 mm, respectively).

In Figure 2 the influence of the pressure and Reynolds number ($Re = (v \rho_S \cdot d_N) / \eta_S$) on the droplet size is presented. In the diagram the results measured at both measurement positions are implemented and marked with 10 and 40 mm, respectively.

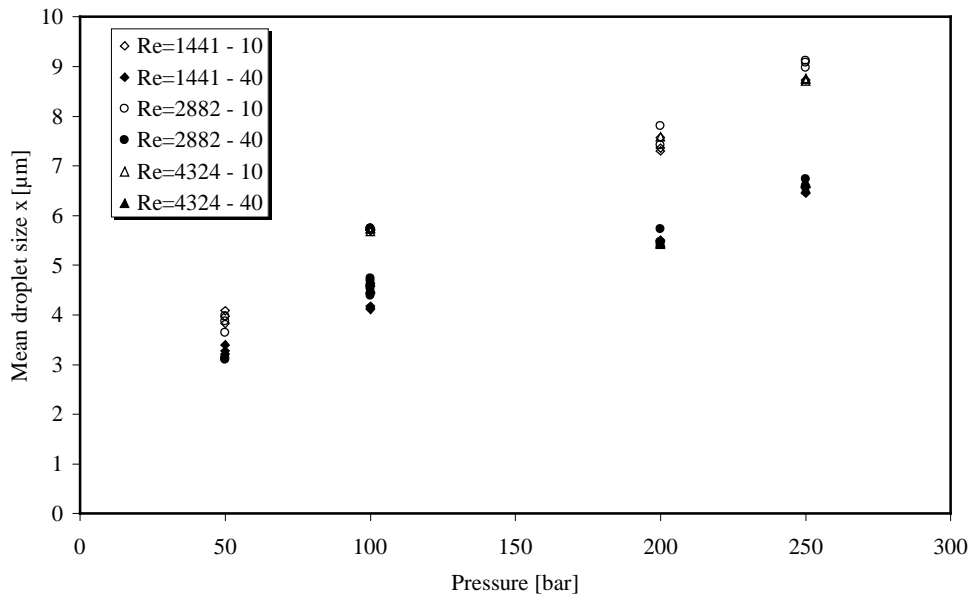


Figure 2: Mean droplet size in dependency of the antisolvent pressure (ethanol, $d_{\text{Nozzle}}=50 \mu\text{m}$, $\vartheta=45 \text{ }^\circ\text{C}$)

From these measurements three points can be seen: Increasing the antisolvent pressure larger droplets were obtained. The increase is more or less a linear function. The droplet size is independent of the Re number i.e. flow rate of the solvent through the nozzle. Nevertheless, the droplet size decreases if the distance from the nozzle is enlarged. These decrease is more significant if the pressure is elevated.

The increase of the droplet size with increasing pressure can be explained with the faster diffusion of the CO₂ into the droplet and therefore a larger volume expansion in the droplet. This phenomena is also presented by Werling et al. [12] who calculated the droplet size depending on diffusion time and pressure.

The visualization of the droplet formation was carried out with a high speed digital camera connected with a computer. In Figure 3 the disintegration of ethanol at different Re numbers in a supercritical and low pressure (0.1 MPa) atmosphere is shown. The three different spray regimes (Rayleigh breakup, sinuous wave breakup and atomization) are presented and the differences between the jet break-up in dense gases and low pressure fluids are obviously.

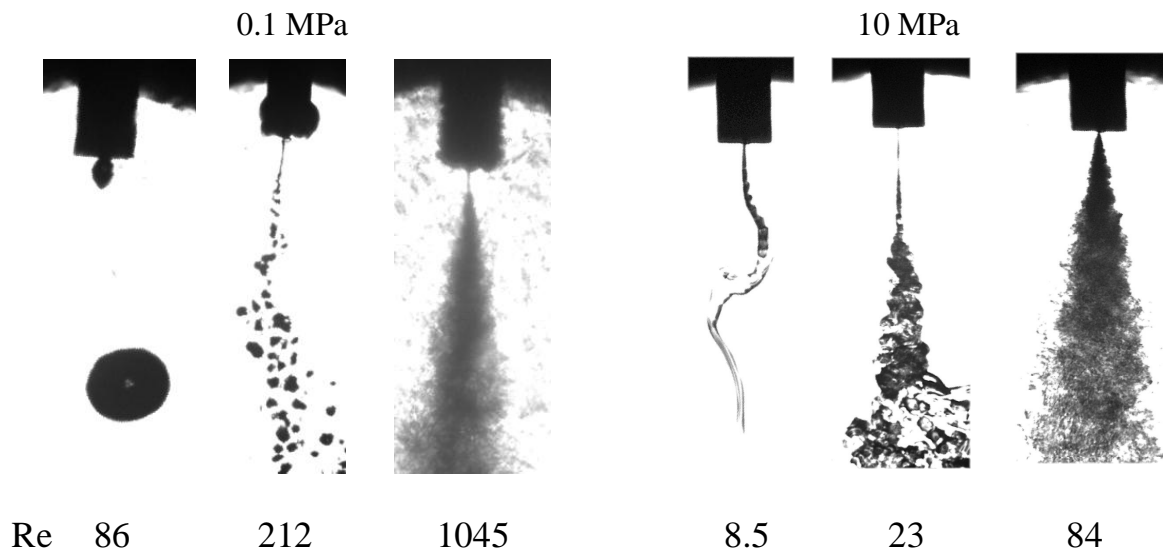


Figure 3: Dispersion of ethanol in carbon dioxide at 10 MPa, 318 K (right) and in low pressure atmosphere (left) through a capillary of 150 μm at different Re numbers (i.e. flow rates)

In a common way the evaluation of those investigations are made in a Ohnesorge-Reynolds diagram. Results of the disintegration of different liquids in supercritical CO₂ are shown in Figure 4.

In the diagram it is shown that the borders between the different spray regimes (Rayleigh breakup, sinuous wave breakup, atomization) in the Ohnesorge-Reynolds diagram were shifted to lower Reynolds numbers if the continuous phase is supercritical in contrast to the borders in the original Ohnesorge diagram at atmospheric pressure. The reason for this behaviour is the higher density and viscosity of the dense fluid in contrast to the values of atmospheric air. So, density and viscosity of the fluid have to be taken into consideration [13].

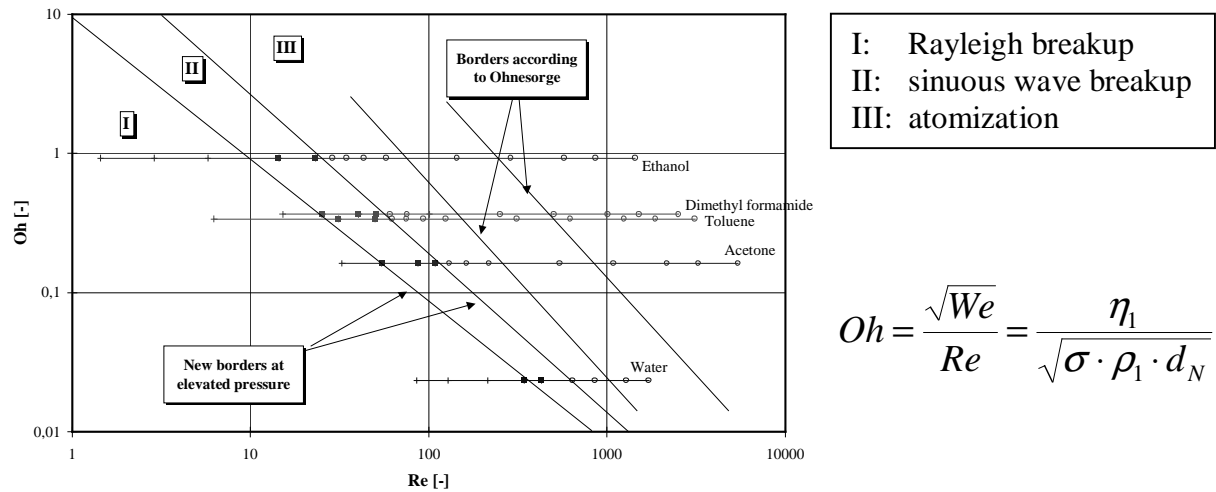


Figure 4: Oh-Re diagram for the disintegration of liquids in a supercritical atmosphere (CO₂)

3.2 Precipitation

A series of experiments with Paracetamol was performed with respect to the influence of the diameter of the capillary nozzle and precipitation pressure on the particle size. The precipitation temperature was constant at 318 K. Methanol was used as solvent, the initial solute concentration was 20 wt.-%. The ratio between antisolvent and solution flow rate was 50. Table 1 summarizes the process parameters and results.

Table 1: Precipitation of paracetamol: Influence of nozzle design and pressure

Nozzle [μm]	Pressure [MPa]	\dot{m}_{CO_2} [kg/h]	$x_{50,3}$ [μm]	$\xi = \frac{x_{84,3} - x_{16,3}}{2 \cdot x_{50,3}}$
50	15	6.2	3.32	0.638
150	15	6.1	6.24	0.598
100	10	6.2	9.81	0.736
100	12.5	6.3	7.38	0.624
100	15	6.2	5.17	0.797
100	17.5	6.1	4.93	0.977
100	20	6.2	4.68	0.781

From the measurements it becomes clear that nozzle diameter as well as precipitation pressure have an influence on the particle size. The increase of the precipitation pressure results in a decrease of the particle size. The mass transfer driving forces strongly increase at elevated pressures so that they will dominate the particle size. As shown above the droplet size increases at higher pressures but supersaturation is increased if the antisolvent penetrates faster into the droplets. A smaller nozzle diameter leads to smaller particles. In contrast to these influences the morphology of the particles is not affected by the investigated process parameters. Mainly compact particles but also a small amount of needles are generated.

The influence of the solvent was investigated in few experiments. Especially, the effect on the morphology was the objective of this study. Ethanol, N,N-dimethylformamide (DMF) and acetone were used as solvents whereas the concentration was 10 wt.-% in all experiments.

The ratio between antisolvent and solution and the precipitation temperature was constant 12.5 and 318 K, respectively. The results of these experiments are summarized in Table 2.

Table 2: Precipitation of paracetamol: Influence of solvent and precipitation pressure ($d_{\text{Nozzle}}=150 \mu\text{m}$)

Solvent	Pressure [MPa]	\dot{m}_{CO_2} [kg/h]	$x_{50,3}$ [μm]	$\xi = \frac{x_{84,3} - x_{16,3}}{2 \cdot x_{50,3}}$	Morphology
Ethanol	10	6.4	10.5	0.578	rhombic
Ethanol	15	7.2	7.15	0.879	Needles
Ethanol	20	9.2	4.32	0.745	Needles
DMF	10	8.4	5.21	0.957	Spheres
DMF	15	6.5	0.98	0.578	Spheres
DMF	20	7.1	0.86	0.501	Spheres
Acetone	10	7.4	1.24	0.465	Spheres
Acetone	15	5.8	1.94	0.578	Needles and Spheres
Acetone	20	8.2	2.24	0.487	Needles

The used solvent has an influence on the particle size as well as on the crystal morphology. The shape of the crystals precipitated from ethanol and methanol do not differ; mostly compact particles with a rhombic shape are produced. Besides of this morphology needles can be seen of which amount increases if pressure is raised. Particles with a mean size between 10 and 4 μm are produced with decreasing particle size at elevated pressures. Spherical to needle-like particles are formed if acetone is used as solvent. The mean size is in the range of 1 to 2 μm and pressure does not affect the particle size, strongly. Spherical crystals can be precipitated from DMF. At low pressure (near the critical point of the mixture) larger particles are found, increasing the pressure particles with a mean size around 1 μm are produced.

4 REFERENCES

- JUNG, J., PERRUT, M., J. Supercrit. Fluids, Vol. 20, **2001**, p. 179
- DEBENEDETTI, P.G., TOM, J.W., KWAWK, X., YEO, S.D., Fluid Phase Equilibria, Vol. 82, **1993**, p. 311
- KRÖBER, H., TEIPEL, U., KRAUSE, H., Chem. Eng. Technol., Vol. 23, **2000**, p. 763
- SUBRAMANIAM, B., RAJEWSKI, R.A., SNAVELY, K., J. Pharm. Sci., Vol. 86, **1997**, p. 885
- REVERCHON, E., J. Supercrit. Fluids, Vol. 15, **1999**, 1
- PALAKODATY, S., YORK, P., Pharm. Res., Vol. 16, **1999**, p. 976
- REVERCHON, E., DELLA PORTA, G., PACE, S., DI TROLIO, A., Ind. Eng. Chem. Res., Vol. 37, **1998**, p. 952
- KRÖBER, H., TEIPEL, U., J. Supercrit. Fluids, Vol. 22, **2002**, p. 229
- DAY, C.-Y., CHANG, C.J., CHEN, C.-Y., J. Chem. Eng. Data, Vol. 41, **1996**, p. 839
- PAGE, S.H., GOATES, S.R., LEE, M.L., J. Supercrit. Fluids, Vol. 4, **1991**, p. 109
- KRÖBER, H., TEIPEL, U., Proceedings "Spray 2001", Hamburg, Germany, **2001**, P4
- WERLING, J.O., DEBENEDETTI, P.G., J. Supercrit. Fluids, Vol. 18, **2000**, p. 11
- CZERWONATIS, N., EGGERS, R., Chem. Eng. Technol., Vol. 24, **2001**, p. 619