

PARTICLE FORMATION IN THE SAS PROCESS AND ITS CORRELATION TO FLUID ATOMIZATION BY OPTICAL LASER ANALYSIS

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The supercritical antisolvent atomization process SAS is used for the production of fine powders particularly in the pharmaceutical industry. Important properties such as particle size, morphology and particle size distribution can be influenced by varying parameters such as concentration, pressure and temperature.

This particle generating process method was examined using optical laser analysis for detecting propagation, concentration and the corresponding state of phase within the injected solution atomized inside the precipitation chamber. Evaluating these results with respect to the particle size and particle size distribution of powders produced allows an highly informative insight on the particle formation process.

1 INTRODUCTION

Methods for the production of powders with defined particle properties have reached great importance in many fields since these characteristics have a direct influence on the quality of the final product [1]. The application of a drug via the respiratory system is just one example for which such high standards are required [2]: the particle size of the applied medicine must not exceed 5 μm to be respirable. Particles below 1 μm will be adsorbed within the lungs and will therefore be exhaled [3, 4]. Providing that a powder of such particle size distribution is available, a more efficient drug reception is achieved allowing a lower dosage causing fewer secondary effects and reducing costs of the application [5]. A second important aspect is a good bioavailability of the drug due to a high solubility which is improved by a larger specific surface as can be found in micronized powders.

The supercritical antisolvent (SAS) process is a high pressure precipitation method suitable for the production of fine powders with defined particle properties. Generally operated at moderate temperatures, it allows the processing of temperature sensitive products. Detailed investigations inside the injected dilution can be used to explain the interaction between the operation conditions of the precipitator and the resulting particle properties.

For an exact control of the particle synthesis and for the optimization of the process it is therefore significant to understand the correlation of process parameters and particle formation. As the injection of the drug loaded solute into the supercritical fluid and the particle formation are rapidly taking place in a high pressure system it is found challenging to monitor the process without intervention. In cooperation with the Erlangen Graduate School in Advanced Optical Technologies (SAOT) optical laser analysis methods were applied to detect propagation, concentration and the corresponding state of phase within the injected solution atomized inside the precipitation chamber. The results were compared to the particle size and particle size distribution of powders produced.

2 MATERIALS AND METHODS

The setup consists of the SAS-precipitation system and the optical measurement system.

2.1 SAS-Precipitator

The SAS-precipitation system shown in Figure 1 is constructed for chamber pressures up to 45 MPa and temperatures up to 353 K. The main component of the high pressure system used for the particle formation is a heated chamber with a volume of 350 ml. In this work, it is pressurized with the antisolvent carbon dioxide up to the desired operation pressure p_{CO_2} and heated by four heating cartridges to a temperature T_{chamber} . Paracetamol dissolved in ethanol (5 wt.-%) is dispersed into the chamber at different injection pressures p_{EtOH} . For stabilizing and controlling the required injection pressure p_{EtOH} , a bladder accumulator is installed and a back pressure regulator is used. A piezoelectric actuated injector is connected to an injection control unit and triggered by a multi-channel pulse generator. It is utilized for adjusting the duration, frequency and the overall number of the injections. In contrast to similar particle formation techniques, the duration of a single injection is hereby reduced to only 1.5 milliseconds. The nozzle is identical to a standard diesel injector nozzle but has only one capillary at the tip with a diameter of 0.1 mm and 0.2 mm length. The precipitated particles are collected by circulating the chamber content through a filter using a heated diaphragm pump ensuring constant pressure and temperature. After rinsing the system with CO_2 to avoid agglomeration and subsequent pressure release, the particles are removed from the filter. Particle size is analyzed by online extinction measurement described elsewhere in detail [6]. Particle shape was specified using scanning electron microscopy (SEM).

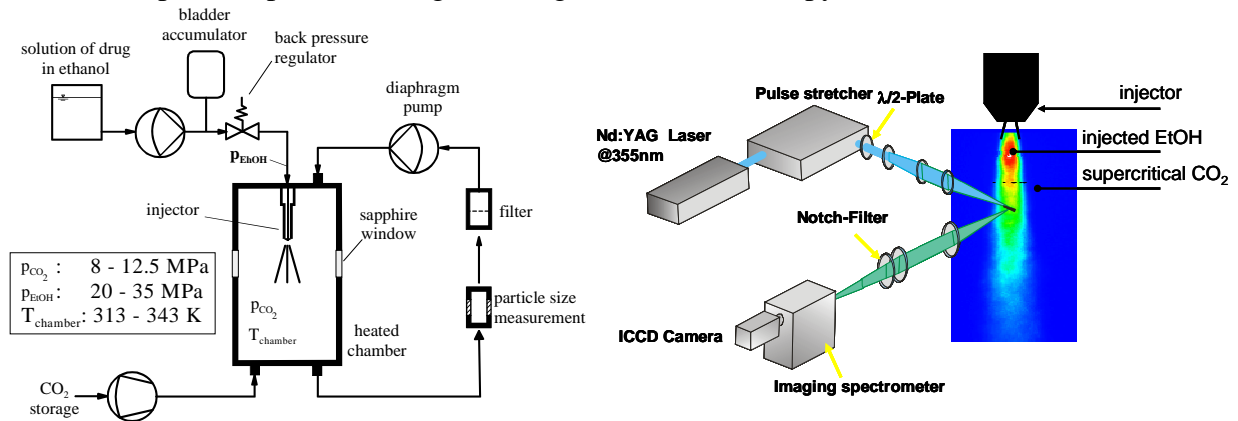


Figure 1: Schematic of the optically accessible SAS- precipitator (left) and the experimental setup of the 1-D linear Raman scattering technique (right)

For the optical observation of the injection characteristics the chamber is equipped with three sapphire windows with an inner diameter of 19 mm arranged in equal height, two opposite to another and one at 90 degree to both. Only the tip of the nozzle is visible through the window to allow a maximum size of the spray image.

2.2 Optical Measurement System

For the locally resolved acquisition of the mole fraction during the process of mixture formation the linear Raman scattering technique was applied. The experimental setup is shown on the right of Figure 1.

The laser is focused into the probe volume, which is imaged by lenses onto the 300 μm slit of the spectrometer. The spectra were acquired by one intensified CCD camera. The local resolution of this mole fraction detecting measurement technique is about 200 μm along one

line of 7 mm. In the diagrams shown in Figure 2 and 3, only the centre of this line (the middle of the apparatus ± 2 mm) is presented. As the laser ray shoots through the chamber filled with CO₂ at only one selected height (in this case $z = 5$ mm below the nozzle) it passes through the injected ethanol, where a reduction of the CO₂ mole fraction is observed followed by an increase of the CO₂ signal when leaving the centre of the dispersed solvent. A variation of process parameters can result in different mole fraction distributions along this line. Mole fraction values of 0.5 represent areas within the spray at which both supercritical and liquid ethanol was observed (preferably in the middle of the spray). A detailed explanation of the Raman scattering technique for these mole fraction and phase measurements is given elsewhere [7]. A second optical setup for two-dimensional Raman measurements applied to detect the density distribution during ethanol injection is introduced at the 11th European Meeting on Supercritical Fluids and described in detail in the current proceedings [8].

3 Results and discussion

To show that the temperature alone has an effect on particle formation, density was kept constant by adjusting the CO₂ pressure in the chamber at different temperature levels:

chamber temperature T_c [K]	chamber pressure p_c [MPa]	injection pressure p_i [MPa]	particle size \bar{x}_0 [μ m]
313	8.5	25.0	6,6
323	9.7	25.0	3,5
333	11.0	25.0	3,0
343	12.2	25.0	2,3

Table 1: Particle size dependent on temperature at constant CO₂ density (1075 kg/m³)

It is shown in table 1 that particle size is reduced by temperature increase. When regarding the mole fraction distribution of the spray, it can be noticed that it is equal at all temperature levels. This indicates that the hydrodynamic conditions stay constant with constant density. Nevertheless, particle size is affected due to higher nucleation rates at increased temperatures. The influence of the CO₂ temperature and its corresponding density at isobaric conditions was also obtained and is shown in table 2. Particle size reduced even further than in the previous experimental series when temperature was increased.

chamber temperature T_c [K]	chamber pressure p_c [MPa]	injection pressure p_i [MPa]	particle size \bar{x}_0 [μ m]
313	8.5	25.0	6,6
323	8.5	25.0	3,2
333	8.5	25.0	2,7

Table 2: Particle size dependent on temperature at varied CO₂ density

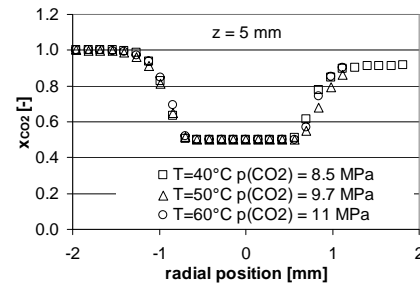


Figure 2: Mole fraction distribution dependent on temperature at constant CO₂ density (1075 kg/m³)

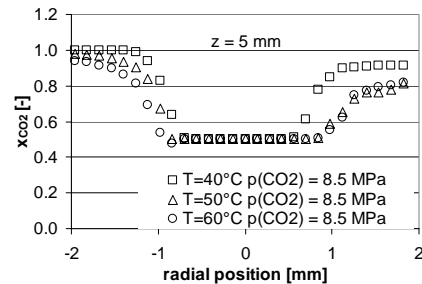


Figure 3: Mole fraction distribution dependent on temperature at varied CO₂ density

The corresponding mole fraction measurements above show that an increase of the temperature leads to lower CO₂ densities causing reduced flow resistance and broadening the distribution of the solution. Because of the higher temperature one would expect a better mass transport due to enhanced CO₂ diffusion. This is not the case. The diagram shows that the CO₂ mole fractions at 323 K and 333 K are lower than at 313 K. As described by Dowy et al. [8], the mixture critical pressure is shifted towards higher pressures by temperature increase. The mixing process at the presented higher temperatures therefore takes place in the two phase regime. It was observed by laser optical measurements, that the CO₂ density within this regime is increased by a factor of 3 compared to the surrounding pure supercritical CO₂ due to ethanol evaporation and CO₂ absorption. Further research is in progress to explain this phenomenon in detail. The effect on particle formation is a greater supersaturation causing a larger nucleation rate and therefore smaller particles.

4 Conclusion

The approach of combining laser optical investigation of the injection and online particle size measurements provides new possibilities of understanding the SAS process in detail. Published experimental results are controversial to the ones predicted according to current spray models and theories of atomization. Thus, investigations inside the injected dilution are an important step towards detailed spray models describing the interaction between the operation conditions of the precipitator and the resulting particle properties.

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