

AN OPTICAL TECHNIQUE TO GAIN INFORMATION ON MIXING, NUCLEATION, AND PHASE BEHAVIOUR

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The supercritical antisolvent precipitation process (SAS) is a very fast bottom up technique for the production of nano and micro sized particles. Here we report on the application of an optical technique that is on the one hand very sensitive and on the other hand pretty fast to gain information on mixing, nucleation and phase behaviour. These three main influencing parameters for the size and shape of the manufactured particles appear on a time scale in the μs -range. Thus an in-situ optical laser based measurement technique becomes reasonable. The set-up comprises 2D-Raman concentration measurements of the solvent and the antisolvent during the whole particle formation process and the measurement of the Mie scattered light from the particles in order to obtain information on the location of particle formation. Information on the different, but nearly simultaneously appearing processes have been observed with the model substance Paracetamol by using an optical laser based Raman and Mie scattering setup.

INTRODUCTION

The supercritical antisolvent technique (SAS) is a method which is currently used for the production of fine particles in a big variety of different applications [1, 2]. The SAS process is especially advantageous for pharmaceutical products, superconductor precursors, polymers or biological sensitive substances, as the operation conditions are mild compared to conventional methods for the production of small particles [3]. In supercritical fluid technology, the properties of the produced particles can be influenced considerably by changing the process conditions just slightly. Supercritical fluid technology enables a single-step, clean and recyclable processing of small particles as the separation of the solid particles can be efficiently done by just depressurization. The drawback of this process are, that many processes like mixing of the solution and the antisolvent, jet break up, supersaturation, nucleation, growth and agglomeration are taking place nearly at the same time and are strongly influenced by each other. That is why so many researches failed to create a universal model which is valid for different solutes and solvents.

MATERIALS AND METHODS

All experiments were carried out using an optically accessible SAS chamber. The details of the setup are outlined elsewhere [4, 5]. A schematic of the experimental setup for the simultaneous detection of Raman and elastically scattered signal used for the visualization of the CO_2 mole fraction distribution and the particle formation process is shown in Figure 1.

The scattering process is excited by a pulsed frequency-doubled Nd-YAG laser at a wavelength of 532 nm with maximum single-pulse energy of 650 mJ and a pulse width of 10 ns (FWHM). By a combination of mirrors, spherical lenses and a cylindrical lens, the laser beam is focused into the centre of the SAS-chamber and formed to a light sheet with a thickness of about 200 μm and a height of 19 mm which is limited by the bore diameter of the windows. In order not to exceed the window damage threshold, a single-loop pulse stretcher and a telescope which expanded the laser beam diameter were used.

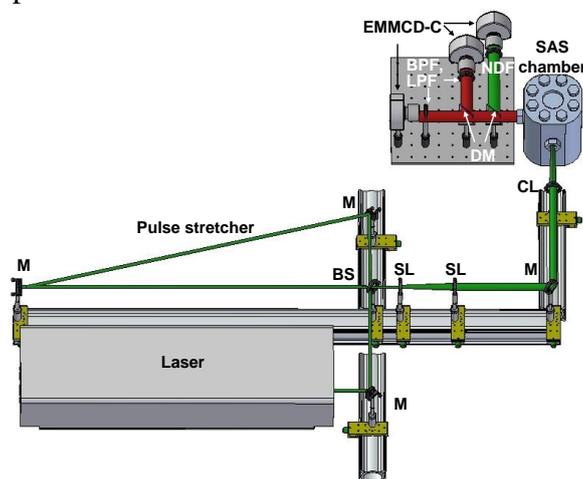


Figure 1: Schematic of the optical setup; M: Mirror, BS: Beam splitter, SL: Spherical lens, CL: Cylindrical lens, DM: Dichroitic mirror, BPF: Band pass filter, LPF: Long pass filter, EMCCD-C: Electron-Multiplying-Charge-Coupled-Devise-Camera

On the Raman detection side, perpendicular to the laser sheet, the Raman signals were detected using three electron multiplied CCD (EMCCD) cameras equipped with CCD chips of 658 x 496 pixels, each of 10 μm x 10 μm . Superpixels were formed by binning the available pixels 2 x 2 resulting in a better signal-to-noise ratio but also reducing the maximum local resolution of the cameras. The mixture and particle formation area was imaged on 128 x 134 superpixels with a local resolution of 135 μm x 135 μm which is close to the laser sheet thickness of about 200 μm . For the separation of both Raman and the elastically scattered signals, two dichroitic long pass mirrors were used. As the elastically scattering process has a much higher signal level compared to Raman scattering, the elastically scattered light had to be attenuated by neutral density filters with an optical density of 6.3 in order to not swamp the camera. The Raman signals of ethanol and CO₂ were separated by a dichroitic long pass beam splitter, which was transitive for the signal wavelength of the CH-vibration of ethanol at 630 nm and reflective for the signal wavelength of CO₂ at 574.4 nm. To guarantee the detection of pure Raman signals, the suppression of interferences particularly elastically scattered and reflected laser light onto the Raman cameras had to be carefully performed. This was realized by a combination of a long pass filter and a narrow band pass filter for the desired signal wavelength assembled directly onto the camera lens.

RESULTS

Due to previous studies on the system paracetamol, ethanol and CO₂ two important things are known. First, the MCP of the ternary system paracetamol, ethanol and CO₂ is significantly above the MCP of the binary system ethanol and CO₂ [4, 6]. Therefore the assumption to operate in the one phase region just by setting the operation pressure above the binary ethanol-CO₂ MCP does not hold as soon as paracetamol is part of the system. Second, the

partial density of CO₂ indicates, whether mixing and precipitation happens in a one phase or a multi phase system [4]. Only in multi-phase pressurized systems of organic solvents and CO₂, the partial density of CO₂ inside the liquid phase is known to be higher than in the gas phase [5]. Therefore, if the CO₂ partial density inside the penetration regime of the injected solution is higher than it is outside, multi phase mixing is indicated.

Mixture formation

Mixture formation between the solution which is injected as a liquid, and the supercritical antisolvent and thereby supersaturation of the solution is the first and most crucial step in the SAS process. For the precipitation of nanoparticles, a supercritical mixture must be generated prior to precipitation [7]. Here we show how the presence of the solute paracetamol strongly influences the mixing mechanisms between the injected solution and the antisolvent from homogeneous supercritical jet mixing to multi-phase mixing with particle precipitation from a liquid phase. At conditions above the MCP, the mixing process is in general gas-like and therefore characterized by turbulent flow and vortices in the jet structure. Figure 2 shows the mole fraction distribution x_{CO_2} at process conditions above the MCP for a 3 wt% solution of paracetamol dissolved in ethanol. The image gives information on the mixture formation process, which can be influenced by the injected solution concentration, the injected amount of solution and the CO₂ chamber pressure. Higher mole fractions in the area of injection indicate a fast mixing process with a high supersaturation, which is the driving force for particle precipitation. Above the MCP, the mole fraction distribution is shifted to higher mole fractions by increasing the solution concentration. This is due to an increase in the partial density of CO₂ in the region of solution injection [8].

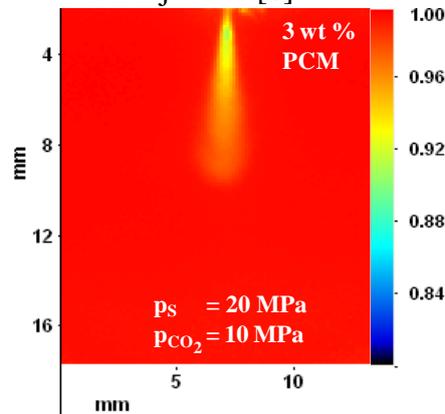


Figure 2: Mole fraction x_{CO_2} image for the injection of a 3 wt% paracetamol/ethanol solution with an injection pressure of 20 MPa into CO₂ at a chamber pressure of 10 MPa and 313 K

Partial density of CO₂ as an indicator for precipitation from a multi-phase mixture

If a paracetamol solution is injected, CO₂ gets enriched within the mixing regime. For pure ethanol injection the CO₂ partial density distribution remains local homogeneously distributed, even within the area where mixing takes place. Consequently, if the CO₂ partial density is enriched at certain locations for the injection of the 3 wt% paracetamol solution like shown in Figure 3, the resulting CO₂ mole fraction distribution must be close to $x_{CO_2} = 1$. In a previous publication [5], we were able to visualize the CO₂ partial density increase within the mixing regime of the injected spray when pure ethanol was injected into supercritical CO₂ at pressures below the MCP. The increase of CO₂ partial density can only be detected, if – due to fast CO₂ mass transfer from the bulk into the droplet – volume expansion results in a CO₂ partial density increase inside the liquid phase of the spray. Hence, for pure ethanol injection

above the MCP this effect could not be observed. Obviously and according to Figure 3, the presence of a solute can also result in an increase of the CO₂ partial density even if the set pressure exceeds the MCP of the binary mixture. Therefore, we assume that the presence of paracetamol shifts the mixing behaviour from single-phase jet mixing (pure ethanol injection) to a multi-phase mixing process with the enrichment of CO₂ in a liquid phase (injection of a paracetamol solution).

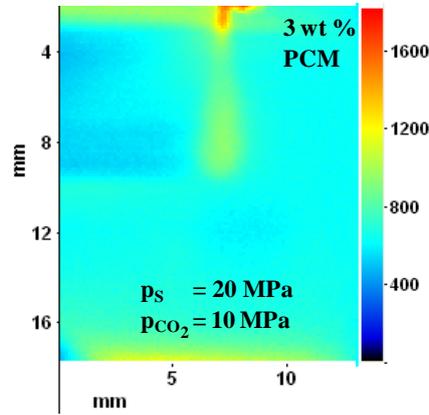


Figure 3: Partial density ρ_{CO_2} image of CO₂ for the injection of a 3 wt% paracetamol/ethanol solution with an injection pressure of 20 MPa into CO₂ at a chamber pressure of 10 MPa and 313 K

Particle nucleation and growth

For the comparison of pure solvent injection and the injection of a paracetamol solution, not only the CO₂ mole fraction distribution and the CO₂ partial density distribution were monitored, but also the appearance of phase boundaries. This was done by detecting the elastically scattered light (Mie scattering) which dominantly originates from phase boundaries. Thus wherever Mie scattering signals can be identified, there must either exist a phase boundary between fluids or a phase boundary between a solid and a fluid. In Figure 4, Mie scattering signals are obtained from phase boundaries between fluids close to the nozzle exit and from phase boundaries between solid particles and a fluid. The Mie signal directly at the nozzle exit must be assigned to the still persisting interfacial tension between the bulk CO₂ and the injected solution.

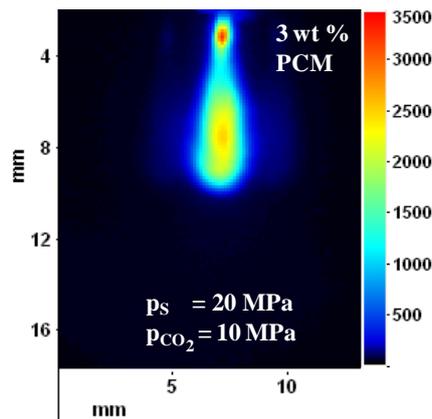


Figure 4: Mie scattering image for the injection of a 3 wt% paracetamol/ethanol solution with an injection pressure of 20 MPa into CO₂ at a chamber pressure of 10 MPa and 313 K

A comparison of the ovoid area close to the nozzle exit shows approximately the same signal intensities for the injection of pure ethanol and the 3 wt% solution concentration. This implies that particle formation does not appear directly at the nozzle exit. Otherwise, the Mie signal

intensities directly underneath the nozzle exit would be higher for the injection of a paracetamol containing solution. Further downstream, the Mie signal strength increases a second time, this mainly originates from solid phase boundaries due to nucleation from the highly supersaturated solution.

To compare particular Mie- or Raman scattering intensities, only line profiles are compared in this section. The corresponding intensities were extracted from the images shown before along the centre vertical line, starting at the nozzle exit. Therefore the intensities are all given as a function of the distance downstream of the injector nozzle. In Figure 5, considering the Mie scattered light for pure solvent (Mie 0 wt%), the intensity along the vertical axis forms a local maximum 1 mm downstream the nozzle exit and afterwards decreases to zero 4 mm downstream the nozzle exit. When injecting a 3 wt% solution (Mie 3 wt%) the same maximum at 1 mm is visible and after a small signal decrease, the Mie signal intensity increases again and forms a broad high intensity signal hill. For the pure solvent, a constant CO₂ partial density until 1 mm is obtained. This means, that at this position the partial density of CO₂ is significantly higher than it is in the bulk CO₂. Further downstream, the CO₂ partial density permanently decreases, until the value of bulk CO₂ is reached. When the 3 wt% solution is injected, the CO₂ partial density increases after the local minimum forms a broad signal hill, and then levels down to the signal intensities of the pure ethanol solution.

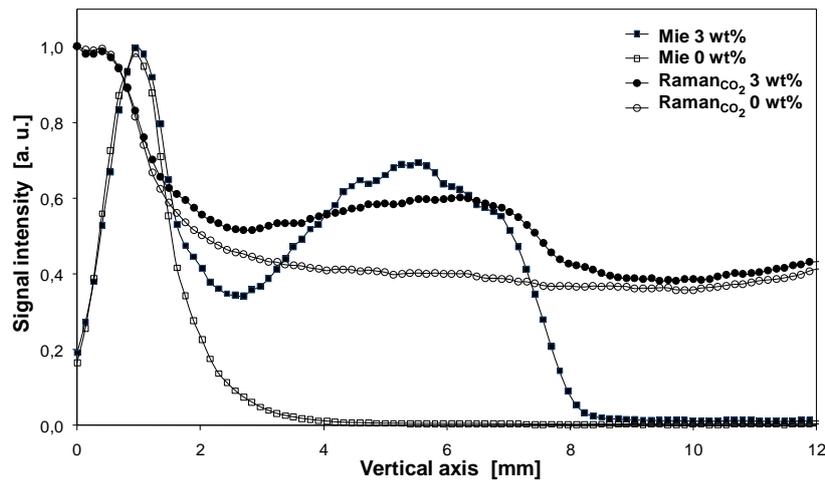


Figure 5: Normalized Mie scattered light intensity and partial density of CO₂ from the centred pixel line plotted versus the distance from the nozzle exit for a 3 wt% solution concentration at operation conditions above the MCP at an injection pressure of 20.0 MPa and a chamber pressure of 10.0 MPa

Since the intensity rise for the Mie scattered light observed at 1 mm is detected for both solutions, the Mie scattered light originates from the phase boundary between the injected liquid ethanol or the liquid solution and the supercritical CO₂ and not from particle formation. The decrease after the maximum (Mie 0 wt%) and the local maximum (Mie 3 wt%) must be in both cases ascribed to the disappearance of the transient interfacial tension. Coexistent to the relaxation in transient interfacial tension and jet breakup, an increase of the Mie scattered light for the 3 wt% solution becomes visible which is the consequence of the start of particle nucleation and growth. This intensity rise is due to an increase in the number and/or size of the particles and is accounted for as particle growth zone. The later decrease of the curve is caused by the effective dispersion of the particles in the chamber. The increase of the CO₂ partial density arises by a different process. Like already mentioned before, the CO₂ partial density can be used as an indicator for a system which is composed of at least one liquid phase. Due to the precipitation of particles, we assume that the presence of paracetamol shifts

the mixing behaviour from single-phase jet mixing (pure ethanol injection) to a multi-phase mixing process with the enrichment of CO₂ in a liquid phase [4].

CONCLUSION

We developed an in-situ optical measurement technique to obtain information on the mixture formation process, the phase state of the mixture and the location of particle precipitation. The information is obtained simultaneously with a local and temporal resolution in the μ s-range. For the system paracetamol/ethanol/CO₂, mole fractions close to one with higher mole fractions at higher solution concentrations were found for conditions above the MCP. The drawback for the injection of high solution concentrations is the reformation of a liquid phase by the start of particle precipitation. This may lead to agglomeration and larger particles. The location of particle formation is dependent on the injected solution concentration.

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