

# Tailor Made Particles by means of Supercritical Antisolvent Precipitation. “From Nanoparticles to Hollow Spheres via Microparticles”

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The supercritical antisolvent process (SAS) is used to generate particles in the micro- and nanometer scale with a defined size, morphology, polymorphism and a narrow size distribution. A liquid solution of a solvent and a solute is injected into a supercritical fluid which acts as an antisolvent. By varying the process parameters such as pressure, temperature, solvent type and solute concentration, the properties of the produced particles can be strongly influenced. The SAS process can be utilized to micronize all kind of materials from semiconductor precursors to pharmaceutical compounds.

This contribution deals with the tailored generation of nanoparticles, microparticles and hollow spheres in the SAS process. The single steps of the particle generation respectively the corresponding time scales (jet break up, liquid/supercritical interface disappearance, particle precipitation) were measured by an in situ light scattering approach, which has been developed to specially analyze this process.

The focus of this talk is on the influence of the phase equilibria, jet fluid dynamics and mass transfer on the precipitation of the generated particles. Different process routes to the desired particle properties could be identified and will be discussed.

To explain the particle generation and phase behavior of the processed mixtures, existing theories use a pseudo binary system without solute as a base framework for the SAS process. With the results presented in this contribution the empirical model is extended by substantial factors. This allows a further insight on the particle formation in the supercritical antisolvent micronization process

## INTRODUCTION

The supercritical antisolvent process is a suitable way to generate fine particles at moderate conditions, without nearly any residual solvent. Therefore it is for example ideally suited for pharmaceutical products. The produced particles have a defined size and a narrow size distribution, depending on the process parameters chosen. This makes the SAS process also advantageous for other substances like semiconductor precursors, polymers or biological

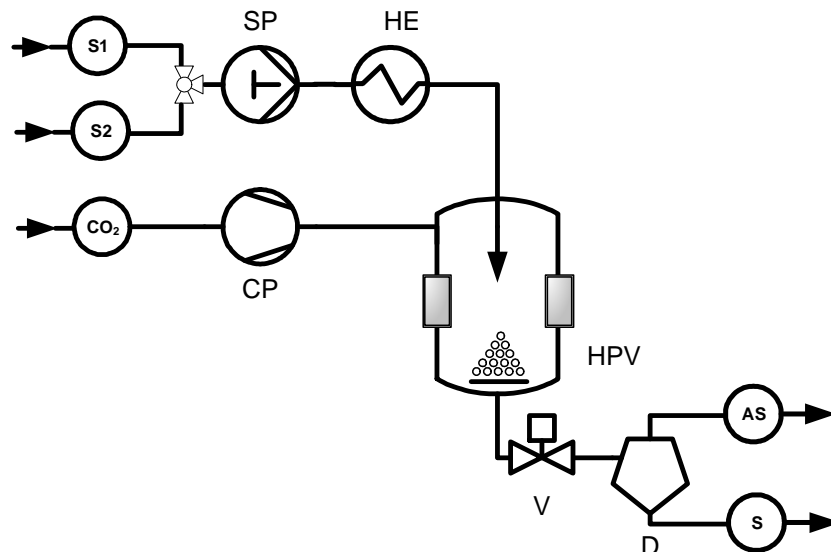
active substances[1, 2]. By just slightly varying the process parameters such as pressure, temperature, type of solvent and solute concentration, the properties of the produced particles can be strongly influenced.

Furthermore it is also possible to adjust the desired shape, e.g. crystalline or amorphous, of the generated particles. In case of crystals, even the polymorphism of the precipitate can be manipulated by changing the process parameters [3].

## MATERIALS AND METHODS

In this work, dimethylsulfoxid (ROTIDRY® 99,5%, purchased from Carl Roth) was used as solvent, yttrium acetate (99.9% META, purchased from Sigma Aldrich) as solute and CO<sub>2</sub> (99.9%, purchased from Linde) as antisolvent.

Figure 1 shows the schematic representation of the SAS-plant. The central part of the plant is the optically accessible high pressure vessel, where the precipitation occurs. The liquid solution and the supercritical antisolvent are continuously delivered to the vessel. The antisolvent is pressurized by a compressor. The liquid solution is pumped with a syringe pump and is injected into the precipitator via a nozzle with an inner diameter of 200 μm. The precipitated particles are separated at a filter within the vessel. The remaining mixture of solvent and antisolvent is depressurised via a metering valve. Liquid solvent and gaseous antisolvent are separated in a demister at ambient pressure downstream of the valve. The whole plant is fully automated and can be controlled by a single operator.

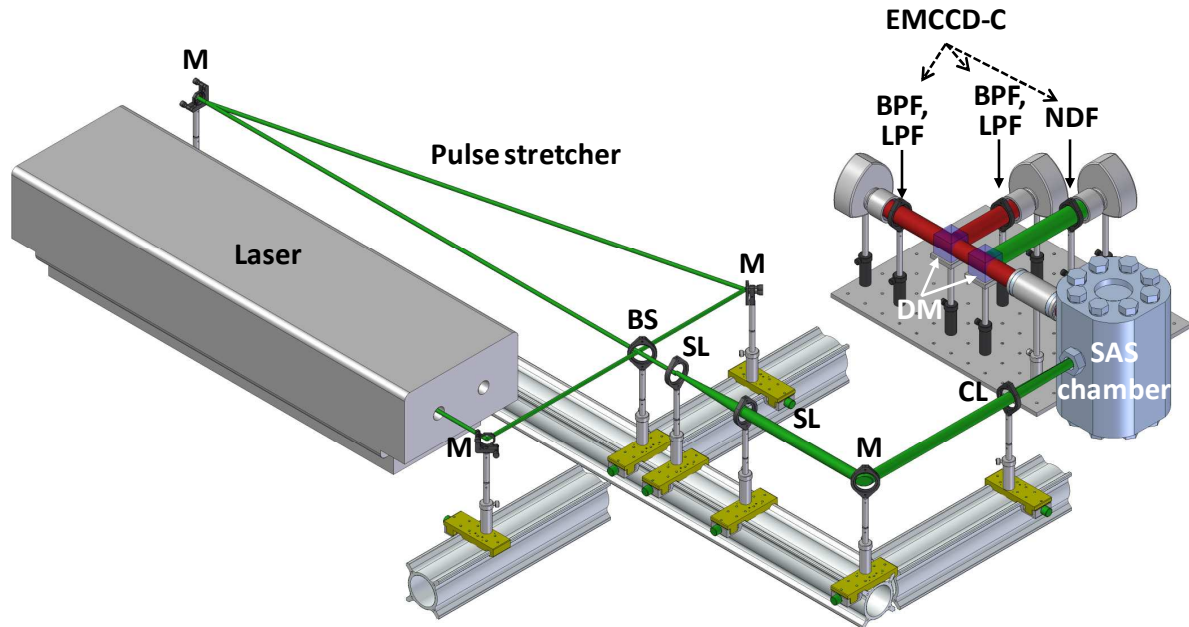


**Figure 1:** Schematic representation of the fully automated SAS plant. (SP= syringe pump; HE= heat exchanger; CP= compressor; HPV= high pressure vessel; V= valve; AS= antisolvent; S= Solvent/Solution)

An experiment usually follows the same procedure. First of all the vessel is pressurised to the desired value, and then a constant antisolvent flow is adjusted. After that, pure solvent is injected into the chamber. The ratio of solvent and antisolvent flow is set to achieve a certain molar fraction within the precipitator. Thereafter, the injection of pure solvent is stopped and the liquid solution is injected. At the end of the solution injection and the following

precipitation, the whole plant is washed with supercritical CO<sub>2</sub> to remove the residual solvent from the precipitator.

Laser optical investigations into the mixing, phase behaviour and particle formation in the supercritical antisolvent process, which are also explained in detail elsewhere[4,5], are carried out with the optical setup given in figure 2.



**Figure 2:** Schematic of the Raman and elastic light scattering setup, (M: mirror, BS: beam splitter, SL: spherical lens, CL: cylindrical lens, DM: dichroic mirror, NDF: neutral density filter, BPF: band pass filter, LPF: long pass filter, EMCCD-C: electron multiplying charge coupled device camera) [5]

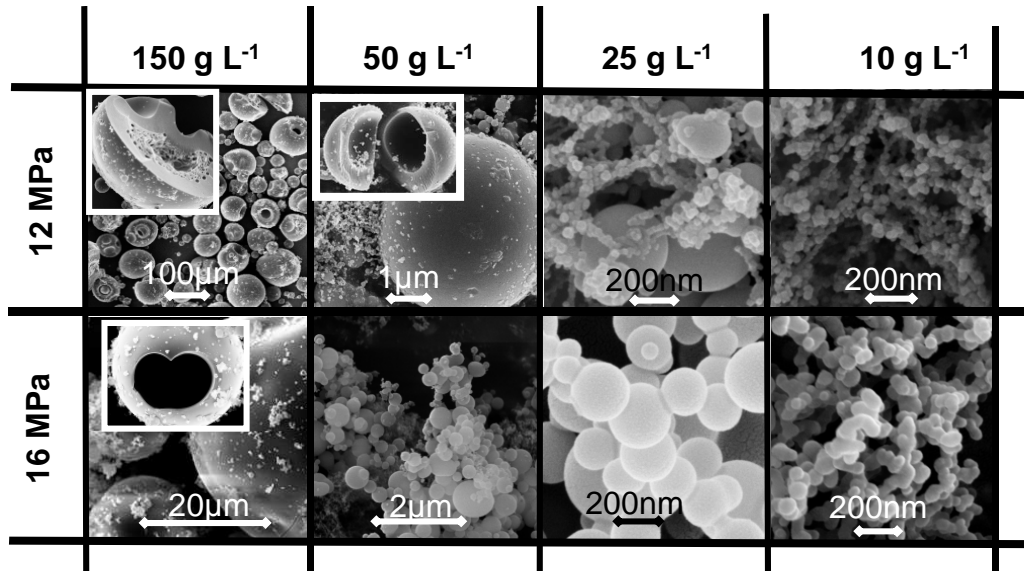
The laser optical setup consists basically of one pulsed excitation laser and three cameras for the detection of different signals. The measurement volume is set up as a light sheet within the vessel directly beneath the nozzle exit. Two cameras detect the Raman scattering signals of DMSO and CO<sub>2</sub>. The third camera is used to detect the elastic light scattered from phase boundaries, which can be either liquid/fluid (droplets) or solid/fluid (particles). With this setup, the distribution of the phase boundaries (liquid/fluid and solid/fluid), the partial densities of CO<sub>2</sub>, DMSO, and YAc, the composition of the mixture and the supersaturation can be imaged simultaneously and in situ at real process conditions[5].

## RESULTS

In this contribution, results concerning the tailored generation of nanoparticles, microparticles and hollow spheres in the SAS process will be presented. The influence of the pressure and initial solute concentration on the generated particles was investigated. This was done on the one hand by characterizing the resulting particles morphologies and on the other hand, by laser

optical investigations on the evolution of the interfaces respectively the corresponding time scales (jet break up, liquid/supercritical interface disappearance, particle precipitation).

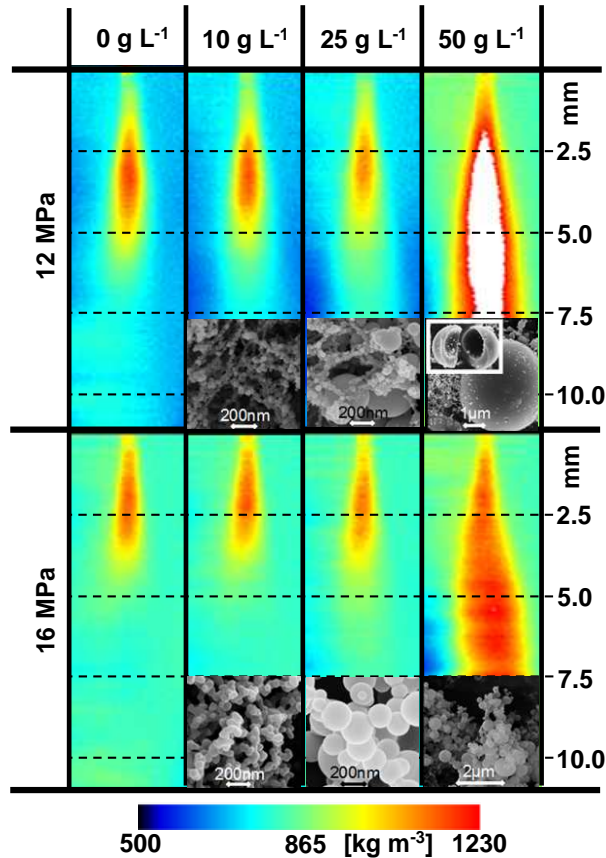
In figure 3, exemplary SEM images of YAc particles, which were generated at different pressures and initial solute concentrations, are displayed. In all the images the temperature was 313 K, the solution flow rate was 2 mLmin<sup>-1</sup> and the overall CO<sub>2</sub> mole fraction was set to 0.98. The pressure was varied between 12 MPa and 16 MPa and the solute concentration was set to 10 gL<sup>-1</sup>, 25 g L<sup>-1</sup>, 50 gL<sup>-1</sup> and 150 gL<sup>-1</sup>.



**Figure 3:** SEM images of YAc particles, which were precipitated at 12 and 16 MPa, 313 K and a solution flow rate of 2 mL min<sup>-1</sup>. The overall CO<sub>2</sub> mole fraction was 0.98.

Two possibilities of adjusting the desired properties of the generated particles can be seen in figure 3. By changing the pressure and/or the initial solute concentration, it can be switched between nanoparticle, micro particle and hollow microparticle generation [5-9].

In figure 4, the measured distribution of the CO<sub>2</sub> partial density below the injection nozzle for the injection of solutions with different initial concentrations at pressures of 12 MPa and 16 MPa are displayed in one plane. Corresponding SEM images of the generated particles are also integrated in this figure for reasons of better comparability.



**Figure 4:** Distribution of the CO<sub>2</sub> partial density for the injection of solutions with different solute concentration and corresponding SEM images of the produced particles. The solution flow rate was 2 mL min<sup>-1</sup>, and the operation conditions were 12 (upper row) and 16 MPa (lower row), 313 K and an overall CO<sub>2</sub> mole fraction of 0.98.

This figure summarizes the distribution of the CO<sub>2</sub> partial density for the injection of various concentrated solutions at 12 and 16 MPa. According to [5,] the CO<sub>2</sub> partial density is a tool to differentiate between two-phase regions (enriched CO<sub>2</sub> partial densities), where liquid/fluid interfaces still prevail, and single-phase regions (CO<sub>2</sub> partial densities are similar to the bulk), where the liquid/fluid interfaces disappeared completely.

By comparing the distribution of the CO<sub>2</sub> partial density with the obtained particles and the also determined phase boundaries and CO<sub>2</sub> mole fraction within the jet, a schematic model of the mechanisms governing particle precipitation, as given in figure 5, can be set up.

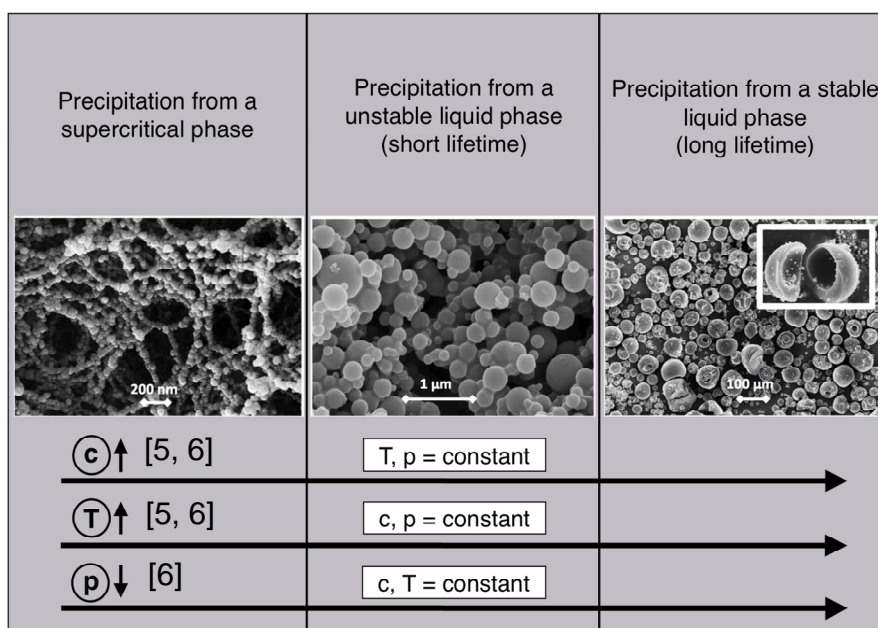


Figure 5: Schematic model of the particle precipitation process concerning the influence of initial solute concentration, temperature and pressure on the governing time scales [5, 6].

Figure 5 comprises the influence of the process parameters on the produced particles respectively on the phase where they are generated in. Nano particles precipitate from a supercritical phase, micro particles are generated from an unstable liquid phase of short lifetime and hollow micro particles origin from a precipitation from a stable liquid phase of long life time. A switch between these precipitation phases and therefore between the different particle morphologies, is possible by increasing the concentration (at constant temperature and pressure), by increasing the temperature (at constant concentration and pressure) and by decreasing the pressure (at constant concentration and temperature). This model can be seen as a substantial extension of the previously published model by other authors in the past.

## CONCLUSION

Different strategies can be applied to switch between the specific precipitation of nanoparticles, of micro particles or of expanded micro particles. The already known methods are to either tune the pressure from below the MCP, to slightly above the MCP and to far above the MCP or to vary the temperature. Another strategy is to operate above the MCP but varying the solute concentration.

The consideration of two major times, which are the time, required for the complete degradation of the liquid/fluid interface and the time required to precipitate particles, can explain the occurrence of the three different particle morphologies. Hence this time scale approach has the potential to reflect the real SAS behaviour.

## ACKNOWLEDGEMENT

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