Particle Formation Depending on Nozzle Geometry, Injection and Antisolvent Pressure in a SAS Process Monitored by Online Particle Size Measurement

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ABSTRACT

A **s**upercritical **a**nti**s**olvent (SAS) batch process was studied applying both nozzle and capillary as injection devices. An ethanol solution of the model drug Paracetamol (acetaminophen) was dispersed into supercritical CO_2. The influence of injection pressure and vessel pressure on the hydrodynamics (especially spray angle and velocity) and the resulting effects on the particle size and shape were measured. It is shown that variation of hydrodynamic conditions affects particle properties and that the used online particle size measurement technique is applicable for determining the alteration.

I. INTRODUCTION

The particle formation in a SAS process is influenced by thermodynamics, fluid mechanics and precipitation kinetics. In addition to the phase behaviour of the ternary system, consisting of solute, solvent and antisolvent, the particle properties can also depend on the mixing intensity induced by the injection device. The mixing of the drug solution with the antisolvent leads to a local supersaturation, which is reduced by nucleation of the solute.
The intention of the presented work is not only to influence the phase behaviour of the antisolvent by varying the operation pressure and temperature but also to modify the mixing of solvent and antisolvent by changing the injection pressure and the geometry of the nozzle. Thus the particle formation can be controlled successfully in shape and size.

II. EXPERIMENTAL METHOD

The SAS batch plant shown in Figure 1 has been applied to crystallize the model compound Paracetamol from ethanol solution and to observe the injection characteristics of different injection devices. The particle formation vessel (volume 700 ml) is heated by four heating cartridges. The vessel is equipped with three sapphire windows (diameter 19 mm). Pressure and temperature of the experiments were kept between 100-200 bar and at 313 K. At these operation conditions ethanol and CO_2 are completely miscible. The ethanol solution was dispersed by two different injection devices (nozzle and capillary) and at differential pressures ($\Delta p=p_2-p_1$) varying between 50 and 200 bar. The required injection pressure is stabilized and controlled by a bladder accumulator and a back pressure regulator. The duration of the injection period (typically 2 s) is controlled by a pneumatic actuated valve. To characterize the hydrodynamics previous to the particle crystallization experiments the behaviour of all injection devices (orifice diameter D: 0.1 mm, 0.2 mm) was observed by spraying pure water and ethanol in supercritical CO_2. Photographs of the spray process were made using a high-speed camera system (HSC, Weinberger Vision/ Speed Cam Visario) with a sample frame rate of 10.000 fps and an image resolution of 512 x 196 pixel. The spray angle θ and the

penetration velocity u of the visible spray front were analysed using image processing software.

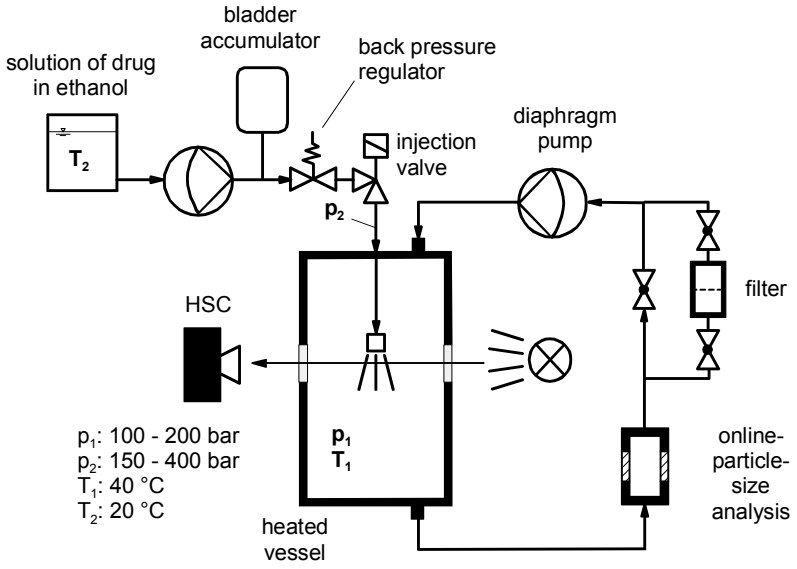

Figure 1: Plant Setup of the SAS Batch Process with Circulation Loop

After characterization of the spray and the mixing parameters Paracetamol particles were crystallized from ethanol solution (5 wt.-%). For injection both capillary and nozzle (each 0.1 mm diameter) were used. The crystallized particles were circulated by a diaphragm pump passing an optical cell for online particle size analysis based on dynamic and spectral extinction measurement (Aello in-line sensors) and then collected in a filter (typical quantity approx. 100 mg). Particle shape and crystal structure were analysed using scanning electron microscopy (SEM) and X-ray diffraction (Philips/X´Pert).

III. RESULTS

III.1. Hydrodynamics

According to the spray pattern and classification of the disintegration modes all nozzles and capillaries showed a turbulent disintegration of the liquid in the scCO2 [1]. An increase of differential pressure Δp leads to a velocity increase of the spray front. Comparing the velocity at varying differential pressures the injection of water showed a dependency approximate to the Bernoulli law (Eq. 1).

$$\frac{u(\Delta p_1)}{u(\Delta p_2)} = \sqrt{\frac{\Delta p_1}{\rho_{l1}} \cdot \frac{\rho_{l2}}{\Delta p_2}} \qquad (1)$$

The experimental results of water injection in scCO2 were also used for verification of numerical simulations. A 2-D capillary model was set up using the commercial CFD-software Star-CD (Version 3.2). Applying different multi-phase and turbulence models the best match was achieved using a free surface model combined with a modified k-ε turbulence model (Chen-model) [2]. The simulated velocity at the outlet of the capillary u_{CFD} is almost equal to a theoretically predicted velocity u_{th} (Equation 2).

$$u_{th} = c_D \cdot \sqrt{\frac{2\Delta p}{\rho_l}} \qquad (2)$$

The discharge coefficient c_D is calculated using empirical expressions given in [1]. Due to disintegration of the jet the velocity u is decreasing versus time until an approximately stable value is reached (Figure 2). This end value is close to the experimental measured value (u=9 m/s), whereas the difference between experimental and numerical values at the beginning result from mechanical and fluid mechanic inertia effects, not included in the simulation.

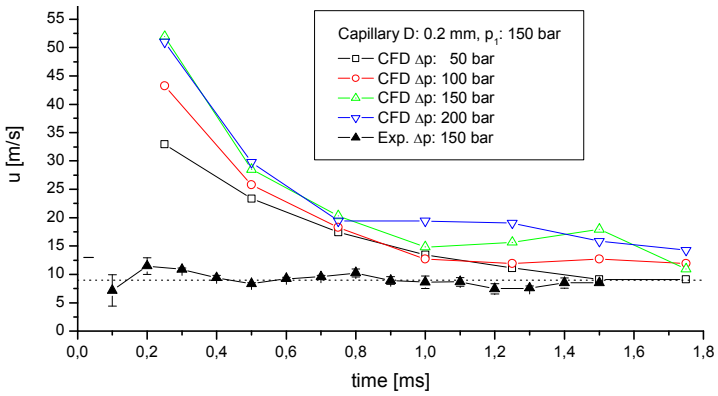

Figure 2: Comparison of numerical simulation and experimental results (water)

The dissolution of ethanol in scCO2 influences the velocity of the visible ethanol spray front. Therefore the mean velocity $\bar{u}$ of the ethanol spray front is smaller than the compared spray of water injection. Equation 1 is therefore not valid for ethanol injection (Figure 3).

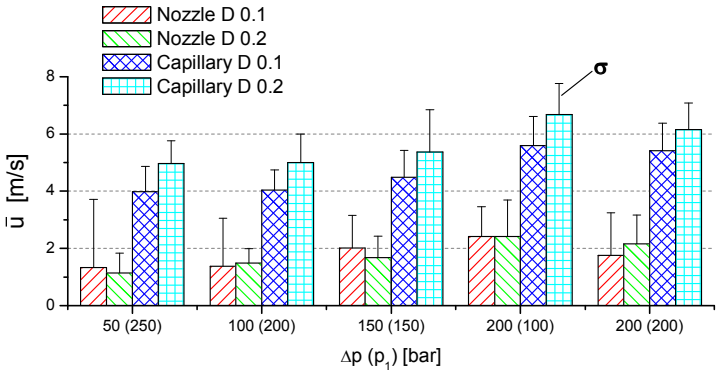

Figure 3: Influence of differential pressure Δp on the velocity $\bar{u}$ of the spray front, ethanol injection at different vessel pressures p_1, σ standard deviation

Beside the difference concerning the velocity $\bar{u}$ water and ethanol spray also showed a different behaviour concerning the spray angle. The spray angle θ of the capillary jet was 21 to 24° for water and 14 to 21° for ethanol. Injection of water through the nozzle showed an angle in the range of 49 to 65° whereas ethanol injection leads to an angle between 29° and 39°. Regarding ethanol injection an increasing differential pressure led to an increased angle for the capillary jet and to a decreased spray angle of the nozzle spray. For water injection the influences of Δp on the angle were negligible.

The characteristic time constant of mixing was estimated based on the theory of turbulent jets which has been previously used for describing mixing in a SEDS process [3, 4]. The mixing model assumes interaction between mixing on meso- and microscale. Micromixing is a molecular process realized by molecular diffusion and engulfment of one fluid by another. The equations for calculation of the characteristic time scales for molecular diffusion t_{mD},

engulfment t_{mE} and mesomixing t_M are given by Baldyga et al. [5,6]. The rate of turbulent energy dissipation ε and the integral scale of turbulence L_t is calculated at distance y=7D, where ε reaches its maximum value [5]. The fluid viscosity ν_f is taken from references [8, 9] and the diffusivity D_m is calculated using empirical approaches given in [8]. The range of the estimated time scales is given in Table 1.

time constant	lower bound	upper bound
$t_{mD} = 2 \cdot \left(\frac{\nu_f}{\varepsilon} \right)^{1/2} \cdot arc\sinh\left(0{,}05 \cdot \frac{\nu_f}{D_m} \right)$	0,11 x 10^{-4} s	2,39 x 10^{-4} s
$t_{mE} = 12 \cdot \left(\frac{\nu_f}{\varepsilon} \right)^{1/2}$	0,45 x 10^{-4} s	7,0 x 10^{-4} s
$t_M = \frac{3}{2} \cdot \left(\frac{5}{\pi} \right)^{2/3} \cdot L_t^{2/3} \cdot \varepsilon^{-1/3}$	0,43 x 10^{-4} s	4,2 x 10^{-4} s
$\varepsilon_{\max}(y = 7D) = \frac{110}{2401} \cdot \frac{u_D^{\,3}}{D}; \quad L_t(y = 7D) = 0{,}2695 \cdot D$		

Table 1: Estimated time scales of mixing

Due to the minor difference between the time constants no mixing effect is dominating. Therefore both micro- and mesomixing effects are influencing the mixing process of solvent and antisolvent. An increase in velocity with increasing differential pressure leads to a decrease of mixing time. As the nucleation time constant of acetaminophen ($t_N=10^{-4}$ s) [4] and the mixing time constants have the same order of magnitude the particle formation is influenced by the hydrodynamics of the process.

III.2. Particle formation

Crystallization of Paracetamol particles lead to different particle shapes and sizes dependent on operation and differential pressure and injection device (Figure 4 and 5). The noticeable effects can be summarized as follows: Increasing operation pressure leads to formation of larger and elongated particles.

The effect of differential pressure variation is dependant on the injection device. Using the nozzle an increase of Δp lead to the formation of agglomerated particles (p_1: 100 bar) and enforced production of needle like particles (p_1: 200 bar). In contrast raising Δp using the capillary promotes the formation of prismatic particles while at lower differential pressures acicular (p_1 100 bar) and planar particles (p_2: 200 bar) are crystallized. The mean value of the online particle measurement technique $\bar{x}$ indicates an enlargement of the particles with increasing operation pressure and differential pressure. This alteration also results from changes in particle shape and agglomeration of particles. The diffraction pattern of the x-ray diffraction analysis showed no modification of the monoclinic crystal structure.

IV. DISCUSSION

The precipitation of particles is always affected by the molecular structure of compounds. According to Baldyga et al. [7] the particle crystallinity is the higher and the nucleation time constant is the smaller the simpler the molecule structure. For relatively small molecules, like acetaminophen, the particle shape is often defined by periodic chains of the strongest

intermolecular bonds, resulting in different relative growth rates of the crystal faces. Blocking or slowing down the growth rate of crystal faces leads to anisometric or needle like shapes and is often caused by low supersaturation and local differences in kinetic mechanism and diffusion conditions [7]. Therefore the formation of isometric prisms can be judged as an indication for an appropriate hydrodynamic mixing in the SAS process.
Using a capillary the mixing conditions are improved by increasing the differential pressure and thus enhancing the turbulent dissipation rate, leading to prismatic particles. In contrary applying a differential pressure of 50 bar to the nozzle is sufficient for desired particle formation and an increase of Δp worsens the mixing conditions. This can possibly be traced back to a decrease of the spray angle which narrows the mixing zone.
In both cases the increase of operation pressure p_1 leads to an increase in particle size due to alteration of the CO2 fluid properties. The diffusivity is decreased and solubility of Paracetamol is increased [7].

V. CONCLUSION

In the present work the influence of injection device and injection pressure on the particle shape in a SAS process have been investigated. A change in particle size could be determined using a new online measurement technique. An effect of increasing the differential pressure on particle shape has been determined which is different for capillary and nozzle. This effect is explained by changes in the fluid mixing behaviour. Using a high speed camera the general spray parameters (spray angle and velocity of the spray front) were determined and used for describing the fluid mixing. In future laser measurement techniques will be used for a more detailed investigation of the concentration distribution and mixing intensity in the vicinity of the visible mixing zone.

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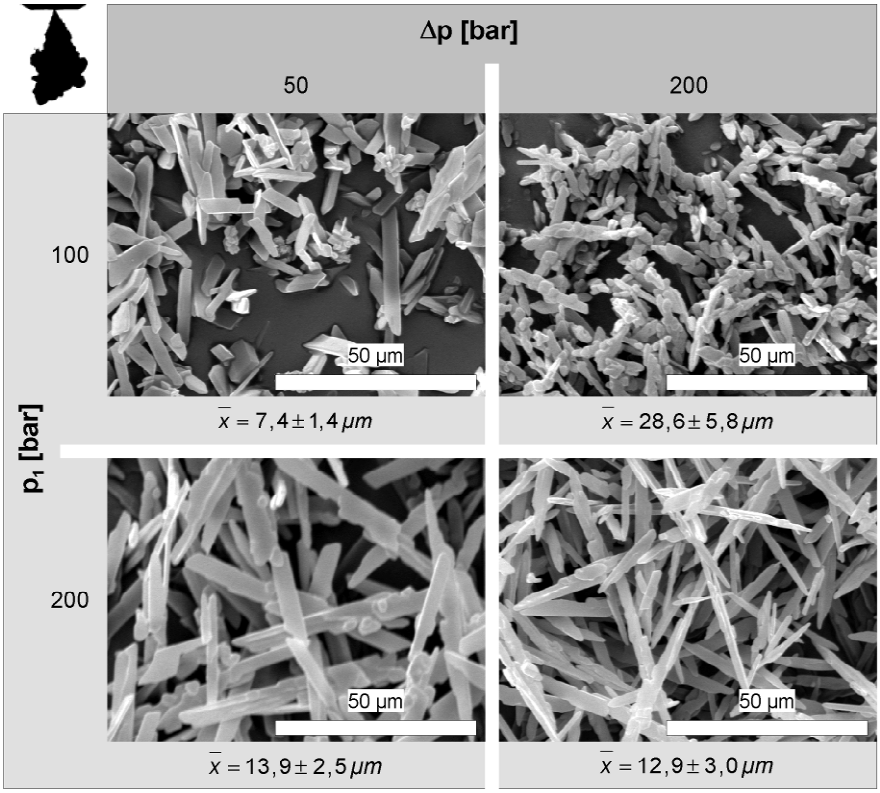

Figure 4: SEM photographs of parcacetamol particles obtained at different pressures, injection device: nozzle 0.1 mm, concentration 5 w.-%

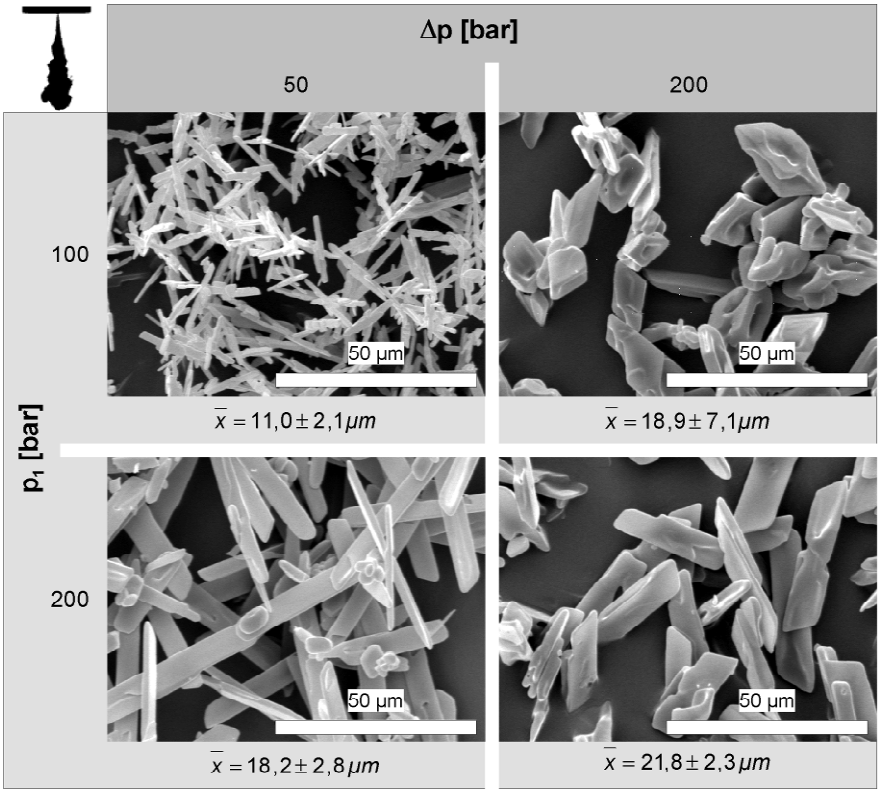

Figure 5: SEM photographs of parcacetamol particles obtained at different pressures, injection device: capillary 0.1 mm, concentration 5 w.-%