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In situ optical monitoring of the solution concentration influence on supercritical particle precipitation

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ABSTRACT

We report a novel approach for the measurement of the location of particle formation in the supercritical antisolvent process (SAS). The measurement strategy is based on in situ Raman and elastic light scattering. In the SAS process, paracetamol was used as the solute, ethanol as the solvent and carbon dioxide as the antisolvent. Experiments were performed under miscible conditions for the binary system ethanol and carbon dioxide at 313 K and pressures between 10 MPa and 17.5 MPa. For high paracetamol concentrations in the injected ethanol solution, particles were found to start precipitating after jet breakup in a multi-phase flow. For low paracetamol concentrations, precipitation starts later in a one-phase flow, when the transient interface (phase boundary) between the injected solution and the supercritical carbon dioxide has diminished.

1. Introduction

There is growing interest in the application of supercritical fluid technologies in material design due to various advantages of using supercritical fluids as solvents or antisolvents [1–3]. Compared to particle formation via conventional routes, supercritical carbon dioxide ($scCO_2$) facilitates the generation of pure products at mild operation conditions. CO_2 is a non-flammable, non-toxic, inexpensive, and environmentally benign substance whose thermodynamic properties can easily be influenced by manipulating the operation conditions around its critical parameters of 304 K and 7.4 MPa [1]. In the downstream process, the solid product can be separated from the solvent and the antisolvent to be recovered by simply reducing the pressure [2].

In 1879, Hannay and Hogarth first discovered that compressed gases can dissolve particular solids [3]. Today, several supercritical fluid technologies for the production of fine and uniform particles are available [4]. Some of them use CO_2 as a solvent, but CO_2 is also frequently used as an antisolvent to overcome the drawback of the poor solubility of a variety of solids in pressurized CO_2. An additional organic solvent is then required to dissolve the solute before it is precipitated due to interaction with the antisolvent CO_2. One precipitation technique which applies this principle is the supercritical antisolvent (SAS) process. The solute to be micronized is dissolved in the liquid organic solvent to form a solution. In best case the solute is totally insoluble in the antisolvent/solvent mixture (CO_2/organic solvent) [4–6] while the solvent is completely miscible with the antisolvent. When the solution is injected into the $scCO_2$ mixing induces a high supersaturation of the injected solution and nucleation appears to overcome the metastable mixture.

The SAS precipitation technique has been used for the production of many different materials and a considerable variety of particle morphologies have been observed. The first experiments were used for the production of explosive materials and solid propellants which are difficult to handle using conventional methods [7,8]. Several researchers have produced polymers [9–13] or biologically active proteins [14,15]. The SAS process is most suitable for high-value-added pharmaceutical products because of its mild operation conditions [16]. The mean particle size of the powder produced range from 50 nm up to several microns [17]. Some general reviews on nanomaterials [18], nanoparticle formation [19], microparticle formation [17,20], nanoparticle synthesis towards biomedical applications [21], nanoparticles synthesis in pharmaceutics and the different ways of delivery [22] and investigations dealing with the specific processes involved in particle formation [23–29] can be found in the literature.

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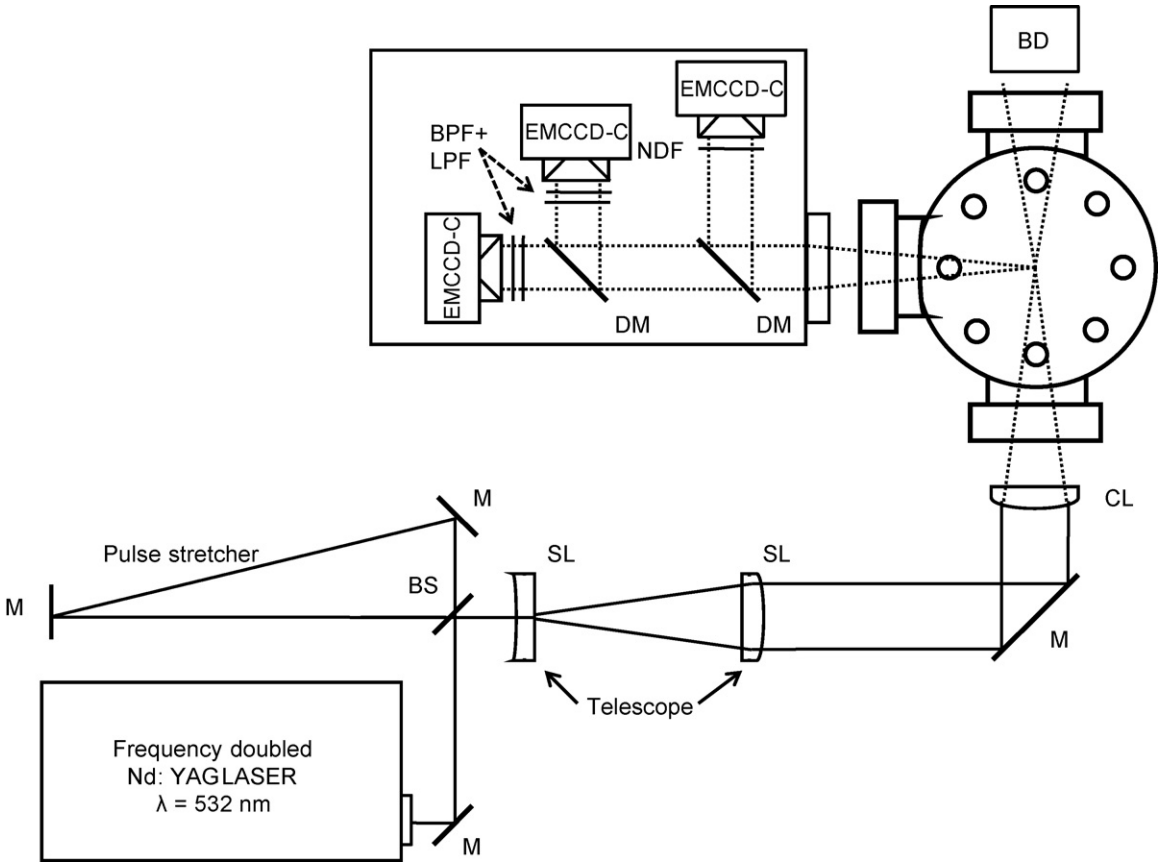

Fig. 1. Schematic of the experimental setup, (M: mirror, BS: beam splitter, SL: spherical lens, CL: cylindrical lens, BD: beam dump, DM: dichroitic mirror, NDF: neutral density filter, BPF: band pass filter, LPF: long pass filter, EMCCD-C: electron multiplying charge coupled device camera).

Optical measurement techniques have rarely been used for investigating the SAS process. Nevertheless, some very interesting literature on this topic is available. A general introduction into spectroscopy and its potentials for supercritical fluid phases is given by Poliakoff et al. [30]. Some attempts to in vestigate the jet breakup have been made using Shadowgraphy or light scattering techniques [23,27]. The influence of the dynamic interfacial tension and jet breakup near the critical point was studied by Dukhin et al. [31]. Sun and Shekunov [32] conducted a comparison between equilibrium and dynamic interface tension and found a dynamic interface tension that was twice as large as the equilibrium interface tension and a significantly higher mixture critical pressure (MCP) for the dynamic case. A comprehensive overview on the hydrodynamics of the injected solution, phase equilibria and a comparison with the resulting particles by means of elastic light scattering is given in Reverchon et al. [33]. Measurements and calculations of the characteristic time scales for mass transfer and nucleation at process conditions below the MCP are reported by Chavez et al. [34]. The time for mass transfer is larger than the development of the hydrodynamic instability of the jet. They conclude that just little antisolvent has diffused into the liquid spray by the time the jet breaks up into droplets. Furthermore, they divide the nucleation process into diffusion limited or nucleation limited regime, depending on the desolvation energy, the interfacial tension and the supersaturation.

The objective of our work is to investigate the influence of different solution concentrations and process conditions on the obtained supersaturation and the location of particle precipitation. Time scales for the different processes that take place during particle formation are estimated from the measured data and a comprehensive explanation on mixture formation, jet breakup, phase behaviour and particle nucleation is given. The optical results are compared with particle size distributions from the micronized drug paracetamol. Experiments with the solute paracetamol dissolved in ethanol were conducted at process conditions above the MCP of the binary mixture ethanol and CO_2, from $p_{CO_2} = 10$ MPa up to $p_{CO_2} = 17.5$ MPa and injection pressures from $p_S = 20$ MPa up to $p_S = 35$ MPa. The main focus of this work is the influence of the concentration of solute in the solution on the particle nucleation process. Paracetamol has been previously used in several investigations, e.g. micronization was studied by Fusaro et al. [35] in a gas antisolvent (GAS) recrystallization technique where they obtained different crystal habits and particle sizes in the range from 50 μm to 250 μm. Bristow et al. [36] and Shekunov et al. [37] produced smaller irregular crystals of paracetamol in the solution enhanced dispersion by supercritical fluids (SEDS) process with particle diameters ranging from 3 μm to 20 μm. Irregular crystals (2 μm) and small elongated crystals (30 μm) were precipitated in the precipitation with compressed antisolvent (PCA) process by Wubbolts et al. [38].

2. Experimental and analytical method

2.1. Experimental apparatus, materials and optical setup

The experimental setup comprises a SAS plant for particle precipitation and an optical Raman and Mie scattering setup for the in situ investigation of the particle precipitation process. A sketch of the experimental setup is shown in Fig. 1. The SAS chamber volume for particle production is 350 ml. Pressurization was created using a Sulzer compressor up to the design limit of the precipitation vessel of 20.0 ± 0.1 MPa. To maintain a constant, set temperature,