

# **-SUBMICRON POLY(VINYLLIDENE FLUORIDE) PARTICLES FROM RAPID EXPANSION OF SUPERCRITICAL SOLUTION**

M. Imran-ul-haq,<sup>1)</sup> E. Breininger,<sup>2)</sup> S. Beuermann,<sup>1)</sup> M. Türk<sup>2)</sup>

<sup>1)</sup>Institut für Chemie, Universität Potsdam, Karl-Liebknecht Str. 24-25,  
D-14476 Golm / Potsdam

<sup>2)</sup>Institut für Technische Thermodynamik und Kältetechnik, Universität Karlsruhe (TH),  
Engler-Bunte-Ring 21, D-76131 Karlsruhe

Email: [sabine.beuermann@uni-potsdam.de](mailto:sabine.beuermann@uni-potsdam.de), [tuerk@ttk.uni-karlsruhe.de](mailto:tuerk@ttk.uni-karlsruhe.de)

## **ABSTRACT**

Micronisation results of poly(vinylidene fluoride) by Rapid Expansion from Supercritical Solution (RESS) are presented. The polymers were obtained from surfactant-free polymerizations in solution with supercritical carbon dioxide (sc-CO<sub>2</sub>). In a typical RESS experiment, the polymer is dissolved in sc-CO<sub>2</sub> and then the supercritical mixture is expanded through a nozzle down to atmospheric conditions. In all RESS experiments, small polymer particles in the range from 45 to 120 nm were produced and a strong correlation between particle size and molar mass was found.

## **1 INTRODUCTION**

Numerous thermally labile substances have been processed with supercritical fluids. In particular, biocompatible and / or biodegradable polymers of pharmaceutical interest and significance were considered, since submicron polymer particles may be used as a carrier for drugs or proteins and for controlled release applications (e. g. see review articles [1-3]). In pharmaceutical applications size and morphology of the particles are important, because they affect the bioavailability of the drug particles. Particle size reduction is one of the methods, which can improve the bioavailability, as the dissolution rate can be enhanced by decreasing particle size. Experimental investigations show, that the RESS-process enables the formation of submicron drug particles with improved dissolution behaviour [4-6].

The feasibility of producing submicron L-poly(lactic acid) and DL-poly(lactic acid) particles by RESS has been demonstrated by Türk et al. [7]. Recently, Sane and Thies have shown that RESS products from poly(L-lactide) (PLLA) consisted predominantly of nanoparticles with 30 - 100 nm in diameter [8]. However, investigations on the application of RESS on fluorinated polymers are scarce. Particularly interesting are polymers with piezoelectric properties, as for example poly(vinylidene fluoride) (PVDF). Chernyak et al. [9] have reported experimental results on the formation of perfluoropolyether diamide droplets during the RESS process. For the system CO<sub>2</sub> + poly(heptadecafluorodecylacrylate) the relationship between RESS process conditions and product morphology was investigated by Blasig et al. [10]. Sane and Thies have demonstrated that RESS can be used to produce nanoparticles (45 - 88 nm) of a fluorinated tetraphenylporphyrin (TBTPP) [11,12]. Matsuyama et al. [13,14] used ethanol as co-solvent (up to 30% ethanol in CO<sub>2</sub> by weight) to dissolve different polymers in CO<sub>2</sub>, and the mixtures were rapidly expanded to form microspheres. More details about the formation of polymer particles with supercritical fluids are summarized by Yeo and Kiran [1].

In the present work, the micronisation of PVDF from sc-CO<sub>2</sub> solutions and the influence of the polymer molar mass on particle size and size distribution were investigated.

## 2 EXPERIMENTAL

### 2.1 MATERIALS AND METHODS

CO<sub>2</sub> (Linde AG; Germany) was chosen as supercritical solvent since it is a non-flammable, inexpensive, and non-toxic solvent. Due to the low critical temperature, sc-CO<sub>2</sub> allows processing at moderate temperatures.

PVDF samples were obtained from solution polymerization of vinylidene fluoride in sc-CO<sub>2</sub> at 393 K and 150 MPa. Polymerizations were carried out in optical high-pressure cells allowing for in-line Fourier Transform Near Infrared (FT-NIR) spectroscopy. FT-NIR spectra indicated that almost complete monomer conversions were reached in homogeneous phase. Experimental details were reported previously [15,16]. Molecular weight control was achieved by chain transfer to perfluorinated hexyl iodide. <sup>1</sup>H-NMR and electrospray ionization - mass spectrometry revealed that predominantly polymer end groups originating from perfluorinated hexyl iodide were obtained [16]. Polymer molecular weights were measured via size-exclusion chromatography (SEC) using N,N'-dimethylacetamide containing 0.1 % LiBr as eluent. The SEC set-up was calibrated using low polydispersity polystyrene standards (PSS), since PVDF standards were not available. Further details were reported elsewhere [15]. Number average molecular weights,  $M_n$ , and polydispersities, PDI, of the samples applied to the RESS procedure were as follows: PVDF-A:  $M_n = 2040$  g/mol, PDI = 1.4; PVDF-B:  $M_n = 4360$  g/mol, PDI = 1.5. Differential scanning calorimetry (DSC 2010, TA Instruments) was applied to determine melting temperatures of the PVDF samples. The temperature was varied from 273 to 473 K with a heating rate of 10 K per minute. For each sample 3 heating – cooling cycles were measured. The melting temperature of sample PVDF-A is 424.1 K and of sample PVDF-B 435.9 K. Scanning electron microscopy (SEM) images were recorded using a Field Emission Scanning Electron Microscope (Hitachi S-4800) at accelerating voltage of 2.0 kV. The polymer sample was placed on a sample holder (from Hitachi SEM) sputtered with gold/palladium in a sputter coater SCO 050 from Balzers.

The average particle size ( $d_{50}$ ) and particle size distribution (PSD, expressed as  $d_{10}$ ,  $d_{50}$ , and  $d_{90}$ ) were statistically determined from SEM images using image analysis (ImageJ Version 1.38). The  $d_{50}$  is defined as the diameter where 50 % of the particles have a larger diameter, and the other 50 % have a smaller diameter.  $d_{10}$  ( $d_{90}$ ) is the diameter where 10% (90%) of the particles have a smaller diameter and hence the remaining 90% (10) a larger diameter. As a rule, about 600 particle diameters were considered in each PSD calculation.

### 2.2 PARTICLE FORMATION

The RESS process involves two steps and two units: the first one for dissolution, and the second for expansion, particle formation, and collection. In Fig. 1 a schematic flow sheet of the RESS set-up is shown. The apparatus consists of an extraction unit connected with a capillary nozzle, which enables experiments in the temperature range from 270 to 370 K and pressures up to 25 MPa. In the first step, polymer and glass beads were mixed to prevent solute caking and added to the extractor. To minimize the unsteadiness of the flow and to accelerate thermal equilibrium, pure CO<sub>2</sub> flows through the thermostated bypass section into the thermostated high-pressure vessel and is expanded through a heated capillary nozzle (50  $\mu$ m inner diameter,  $L/D = 10$ ) into the expansion chamber. In order to prevent cavitation in the pump, firstly the fluid was cooled in a chiller. After equilibrium conditions (as indicated by constant pressure and temperature) were obtained, the bypass section was closed and supercritical CO<sub>2</sub> flow through the extractor and became enriched with the polymer. The sc-CO<sub>2</sub> + polymer mixture in the tubing leading to the nozzle was heated to the desired pre-expansion temperature using cable heaters. The mixture was expanded through a nozzle,

heated at the pre-expansion temperature ( $T_0$ ), into the expansion chamber ( $V = 2.6 \text{ dm}^3$ ) at ambient conditions. Samples were collected onto SEM stages located on the sampling device.

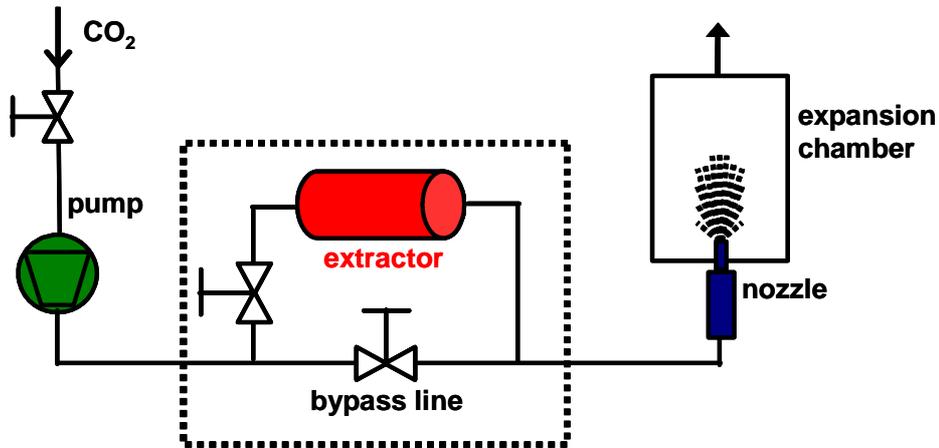


Fig. 1: Schematic diagram of the RESS apparatus.

### 3 EXPERIMENTAL RESULTS

In a typical experiment, the polymer is dissolved in sc- $\text{CO}_2$  at  $p_E = 20 \text{ MPa}$  and  $T_E = 323 \text{ K}$  and then the supercritical mixture is expanded through the nozzle ( $T_0 = 333 \text{ K}$ ,  $p_0 = 20 \text{ MPa}$ ) down to atmospheric conditions ( $300 \text{ K}$ ,  $0.1 \text{ MPa}$ ). Usually, during the experiments, the nozzle temperature was equal to the pre-expansion temperature. In these experiments the influence of the polymer molar mass on particle size and size distribution were investigated. The SEM images of the unprocessed ( $M_n = 2040 \text{ g/mol}$ ) and micronized PVDF are shown in Figure 2 a, and b, respectively. These pictures are typical examples of the obtained product and indicate that the small primary particles are strongly agglomerated and coagulated.

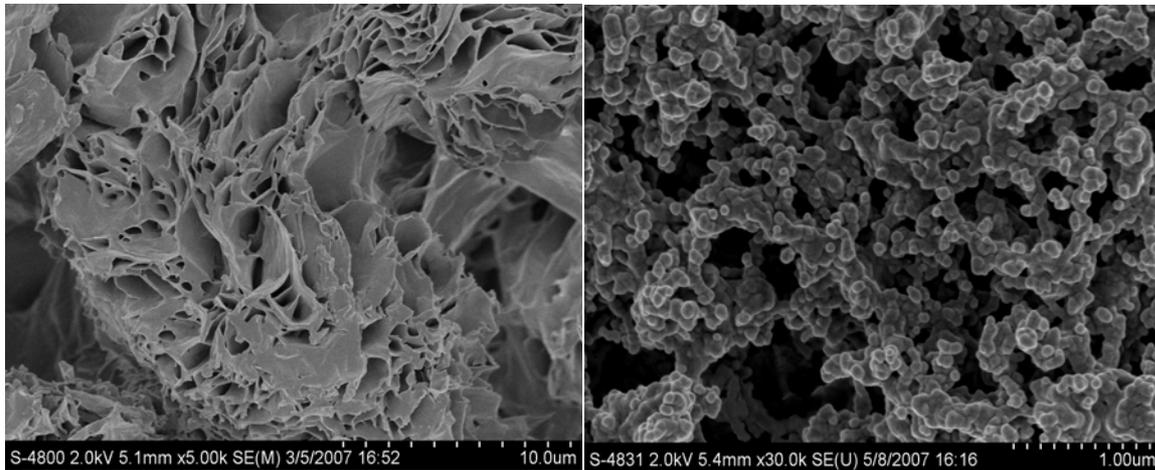


Figure 2: Typical SEM of unprocessed PVDF-A (left) and of PVDF-A particles obtained from RESS experiments at  $T_E = 323 \text{ K}$ ,  $p_0 = p_E = 20 \text{ MPa}$  and  $T_0 = 333 \text{ K}$  (right).

The PSD obtained by image analysis showed that in case of the lower molar mass, the RESS precipitated PVDF powders are formed by particles ranging between  $58 \text{ nm}$  ( $d_{10}$ ) and  $119 \text{ nm}$  ( $d_{90}$ ), with  $50 \%$  of the particles smaller than  $82 \text{ nm}$  ( $d_{50}$ ). Increasing the molar mass from  $M_n = 2040$  to  $M_n = 4360 \text{ g/mol}$  leads to a PSD ranging from  $46 \text{ nm}$  ( $d_{10}$ ) to  $100 \text{ nm}$  ( $d_{90}$ ) with  $50 \%$  of the particles smaller than  $69 \text{ nm}$  ( $d_{50}$ ). The observed increase of particle size with decreasing

polymer molar mass can be explained as follows: the increase of molar mass leads to a lower solubility of the polymer in sc-CO<sub>2</sub> and the lower solubility results in noticeably lower number concentrations and therewith to smaller particles [17]. Thus, the observed relationship between molar mass and particle size is consistent with classical nucleation theory, since particle collision rate is directly proportional to the square of particle concentration. In addition, the experimental results are consistent with our modelling results. These calculations show that a lower solubility and hence a higher dilution of the particles in the expansion chamber inhibit post-expansion particle growth and results in smaller particles [18]. Comparing our results obtained for the system CO<sub>2</sub> + PVDF with data published in literature, we note that the average diameters of our polymer nanoparticles are in the same range as the TBTPP and the PLLA nanoparticles produced by Sane and Thies [8,11,12].

#### 4 CONCLUSION

We have demonstrated that RESS can be used to produce PVDF nanoparticles with diameters less than 100 nm without the use of liquid solvents, surfactants, or other agents. In particular, the rapid expansion of the sc-CO<sub>2</sub> + polymer mixture enables the formation of nanoparticles with diameters of 82 nm and 69 nm at a polymer molar mass of  $M_n = 2040$  g/mol and  $M_n = 4360$  g/mol.

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