

**Role of hydrodynamics on powder characteristics  
in Supercritical Anti-Solvent recrystallization processes**

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**ABSTRACT:** A drug molecule (sulfathiazole) has been recrystallized using Supercritical Anti-Solvent (SAS) process under different experimental conditions. In these conditions, hydrodynamics of the fluid phase in the autoclave has been first characterized. When the introduction device is a capillary tube and for flow rates commonly used in SAS processes, the solution -containing the solute to be crystallized- is dispersed forming a laminar jet that can be atomized or not. For an experimental domain corresponding to complete miscible conditions of the fluid phases (P: 9-12 MPa; T: 308-313 K) and for five different organic solvents (acetone, acetonitrile, methylene chloride, dimethyl formamide and ethanol), the mode of jet dispersion and the critical jet atomization of the pure organic solvent have been determined. The main result is that this critical atomization velocity is similar whatever the solvent and the experimental conditions. Crystallization experiments were carried out at 308 K and 9 MPa, for a solvent-antisolvent molar ratio of 0.08 and for different capillary internal diameters (150; 254; 510  $\mu\text{m}$ ). Each crystallization experiment has been carried out in two different flow conditions: for a jet velocity lower than the atomization threshold and for a jet velocity corresponding to an atomized jet. The different crystals obtained were characterized in terms of crystal size, habit and polymorphic nature. Platelet-like crystals, tablets and micron-sized spherical polycrystalline particles were formed depending on the crystallization operating conditions.

The results show that the mode of jet dispersion influences the powder characteristics. Nevertheless, in order to interpret all the results, it is also necessary to take into account other parameters as local supersaturation or mixing efficiency.

## **I Introduction**

Lots of experimental works dealing with Supercritical Anti-Solvent (SAS) precipitation processes have been described in literature the last twenty years. These processes, applied to active pharmaceutical ingredients, polymers, explosives, pigments or precursors of semi-conductors, allow the formation of nanoparticles or microparticles with a good control of their characteristics such as particle size, morphology and habit [Reverchon, 1999, 2002, 2007; Yung, 2001; Charbit, 2004; Yeo, 2005]. This last decade, those techniques were proved to be also efficient for polymorphic control [Edwards, 2001; Kordikowski, 2001, Charbit 2004]. Indeed, lots of experimental parameters can be tuned on in order to vary the thermodynamic conditions and the kinetics of crystallization leading to the formation of different polymorphic forms for a given compound. For a good interpretation of SAS results, the different phenomena involved like phase behaviour, hydrodynamics, mixing, kinetics of mass transfer as well as kinetics of nucleation and growth have to be further studied.

This paper focuses on the role of hydrodynamics in SAS processes and on its influence upon powder characteristics. The basic principle of SAS process is to put into contact the organic solution containing the solute to be precipitated with the supercritical fluid which acts as an anti-solvent of precipitation. In most cases, the organic solution is dispersed through a capillary tube forming a liquid jet which is dispersed into a supercritical continuum. The first part of this work is dedicated to the characterization of the jet dispersion for various experimental conditions. In a second part, crystallization experiments are performed in similar conditions for which hydrodynamics has been characterized. Each crystallization experiment has been carried out in two different flow conditions:

for a jet velocity lower than the atomization threshold and for a jet velocity corresponding to an atomized jet. The different characteristics of the powders obtained have been then interpreted referring to hydrodynamics considerations. The study has been carried out under experimental conditions corresponding to complete miscibility for the systems solvent-antisolvent.

## II Materials and methods

### II.1 Materials

Carbon dioxide (molar assay: 99.7 %) was supplied from Air liquide (France). Methylene chloride and dimethyl formamide were purchased from SDS (France) whereas acetone and ethanol were respectively supplied by Fluka (Germany) and Carlo Erba (Italy). The solvent molar assay is higher than 98.0 %. Sulfathiazole (SFZ) - a drug for pulmonary diseases treatment used here as solute – was provided by Fluka (Germany). Its molar assay is higher than 98.0 %.

### II.2 Jet dispersion visualization

The experimental set-up used for direct jet dispersion visualization is shown on figure 1. Supercritical carbon dioxide is first introduced into the autoclave of 0.763 L volume equipped with two facing borosilicate windows (NWA, Germany) and with a frit filter at the bottom. When the desired pressure is reached, the valve is opened at the outlet of the autoclave. When a constant carbon dioxide flow rate is obtained at the working pressure, the pure organic solvent is introduced into the autoclave through a capillary tube. The dispersion of the solvent is recorded by the video for different liquid flow rates. The films are then viewed in order to determine the critical atomization velocity for the different experimental conditions studied.

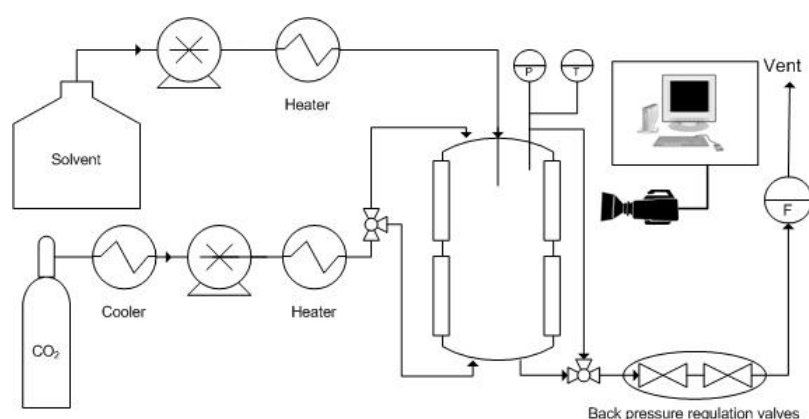


Figure 1: Schematic diagram of the experimental apparatus dedicated to jet visualization

### II.3 Crystallization study

Crystallization experiments have been carried out with an experimental set-up similar than the one presented in figure 1. The only difference concerns the autoclave; which is in this part of 0.48 L volume without windows (Top Industrie, France). At the beginning of the experiment, the procedure is similar to the jet visualization one. The pure solvent is replaced by an organic solution composed of an organic solvent with sulfathiazole. When the desired quantity of powder is obtained, a washing step is carried out with pure carbon dioxide during the time required to renew the content of the autoclave and then to avoid the condensation of organic solvent during the last depressurization step. The powder is then recovered and observed with a Scanning Electron Microscope (SEM) to determine the particles size and the habit of the crystals. The polymorphic nature is determined by X-Ray Diffraction (XRD) analysis. Sulfathiazole crystals can exhibit five different polymorphic forms: forms I to V. The most stable form is the form IV.

The crystallization experiments have been performed in experimental conditions for which hydrodynamics has been characterized in the first part of this study.

### III Results and discussion

#### III.1 Jet dispersion

The dispersion of the five following organic solvents has been studied: acetone, acetonitrile, ethanol, methylene chloride and dimethyl formamide. The tested experimental conditions correspond to complete miscibility conditions for the system solvent-antisolvent. The pressure was varied from 9 to 12 MPa and the temperature from 308 to 313 K. One part of the experiments of liquid dispersion was carried out in pure carbon dioxide while an other part was carried out in steady state conditions with a fixed molar ratio of organic solvent varying from 2 to 8 %. Two different flow configurations were tested: co and counter-current flows. Lastly, the different capillary IDs used are: 150, 254 and 510  $\mu\text{m}$ . All those data are grouped in table 1.

The flow rates of the liquid solutions have been varied from 0.1 to 7.5  $\text{mL}\cdot\text{min}^{-1}$  which are values commonly used for SAS process applications. The flow rate of carbon dioxide has been varied from 0.05 to 3.2  $\text{kg}\cdot\text{h}^{-1}$ .

Table 1: Tested experimental conditions

Solvent	P / MPa	T / K	$d_c / \mu\text{m}$	X / % mol	Flow configuration
Acetone	9-12	308 - 313	150 ; 254	0 ; 2 ; 5 and 8	co-current counter-current
Acetonitrile	9 - 11		150		
Ethanol					
Methylene Chloride	9 - 11				
Dimethyl Formamide	9-12		150 ; 254 and 510	0	

For all the different solvents and upon the range of flow rates studied, different jet dispersion modes have been observed: axisymmetrical, asymmetrical and directly atomized jets. The characteristics of those different modes in dense media have been discussed elsewhere [Czerwonatis, 2001; Carretier, 2003; Badens, 2005].

The objective of this study is to determine the value of velocity jet which corresponds to the transition from an asymmetrical jet (see figure 2a) to an atomized jet (see figure 2b). This value is the *critical atomization jet velocity* named  $u_{CA}$ .

It appeared that for all the tested conditions and for all the solvents, similar values of critical atomization jet velocity were obtained. The different values are listed in table 2. Even if the different solvents exhibit different viscosities and densities, no significant changes in atomization conditions can be quoted. It can be underlined that for different values of capillary ID, the values of critical atomization jet velocity are also similar. Since atomization conditions correspond to better mixing conditions and then enhanced mass transfer, this study shows that for a jet velocity roughly higher than  $0.4 \text{ m}\cdot\text{s}^{-1}$ , crystallization will take place in better mixing conditions.

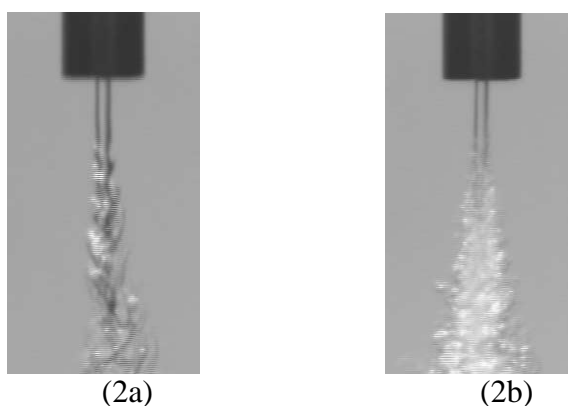


Figure 2: Jets of acetone formed from a 254 $\mu\text{m}$  ID capillary at 308 K and 12MPa

(2a) asymmetrical jet (2b) atomized jet.

Table 2: Critical atomization velocities for different experimental conditions

Solvent	$d_c / \mu\text{m}$	P / MPa	T / K	X / % mol	$u_{CA} / \text{m.s}^{-1}$	
					Co - current	Counter current
Acetone	150 - 254	9-12	308 - 313	0 - 8	0.33 - 0.42	
Acetonitrile	150	9-11		0	0.33 - 0.42	
Ethanol	150	8-11		0 - 8	0.38 - 0.42	
Methylene Chloride	150				0.33 - 0.38	
Dimethyl Formamide	150 - 510	9-12		0	0.36 - 0.42	

### III.2 Crystallization

Sulfathiazole has been recrystallized from acetone solutions. Each crystallization experiment has been carried out in two different flow conditions: for a jet velocity  $u_j$  lower than the atomization threshold ( $u_j = 0.25 \text{ m.s}^{-1}$ ) and for a jet velocity corresponding to an atomized jet ( $u_j = 0.5 \text{ m.s}^{-1}$ ). Three different capillary IDs have been used ( $d_c$ : 150, 254 and 510  $\mu\text{m}$ ). The different operating conditions are grouped in table 3.

Table 3: Operating conditions tested for crystallization experiments

	<b>Operating conditions</b>
$u_j / \text{m.s}^{-1}$	<b>0.25; 0.5</b>
Solvent	Acetone
P / MPa	9
T / K	308
[sulfathiazole] / g per g	0.02
X / mole per mole	0.08
$d_c / \mu\text{m}$	<b>150 ; 254 ; 510</b>

Crystallization experiments carried out for velocity jets lower than the atomization velocity:

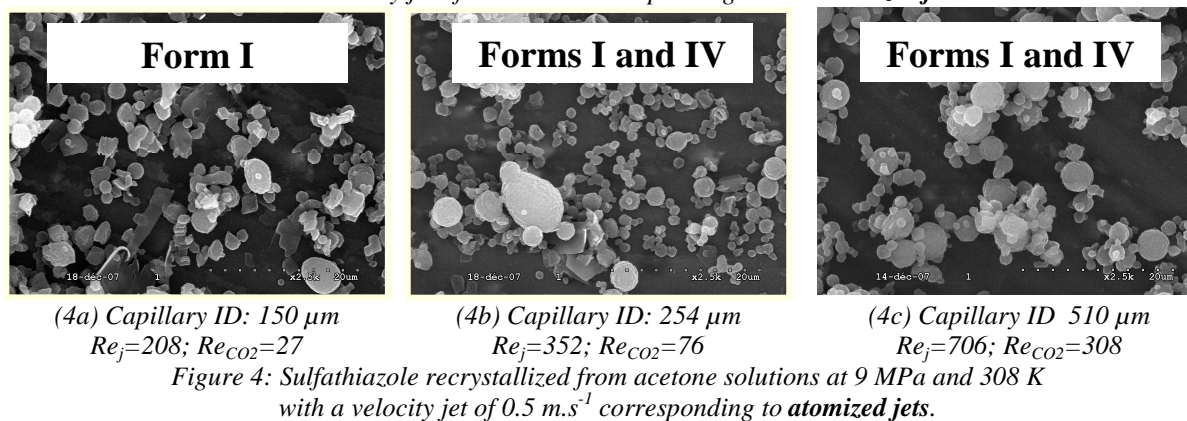
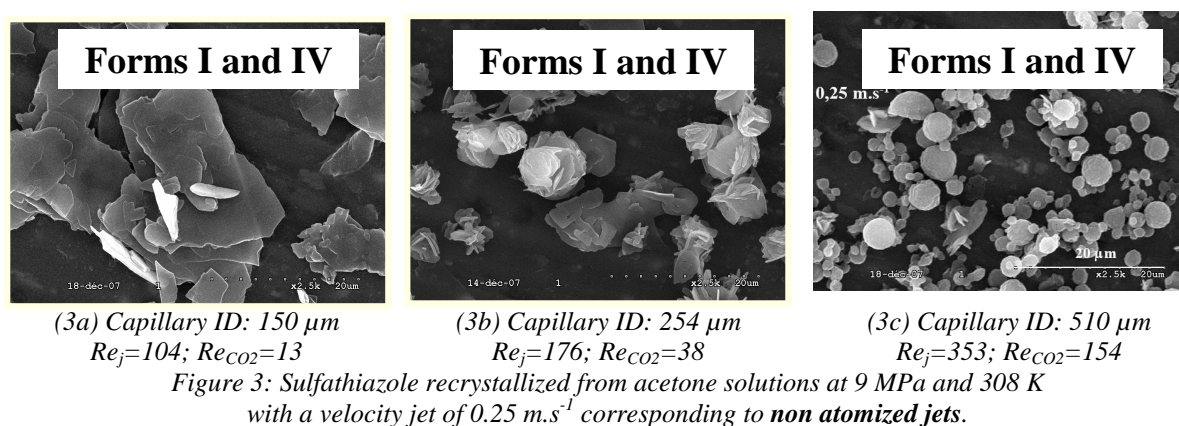
The crystals obtained for velocity jets of  $0.25 \text{ m.s}^{-1}$ , corresponding to non atomized jets, exhibit different characteristics depending on the capillary ID. Figure 3 shows the crystals obtained for capillary IDs of 150  $\mu\text{m}$  (figure 3a), 254  $\mu\text{m}$  (figure 3b) and 510  $\mu\text{m}$  (figure 3c). In this figure (as well as in figure 4)  $Re_j$  stands for the Reynolds number of the organic solution calculated at  $u_j$ . For the smallest value of capillary diameter (150  $\mu\text{m}$ ), the crystals are platelet like with an average dimension in length of 18.7  $\mu\text{m}$  ( $\pm 1.2 \mu\text{m}$ ). For the capillary ID of 254  $\mu\text{m}$ , the crystals are smaller (tablet or platelet-like) showing an average dimension of 2.5  $\mu\text{m}$  ( $\pm 1.1 \mu\text{m}$ ) and are aggregated. For the highest capillary ID (510  $\mu\text{m}$ ), polycrystalline casi-spherical particles are obtained. In each case, a mixture of the form IV (the most stable polymorphic form) and of the form I has been obtained.

Even if the velocity jet is the same in each case, the jet dimensions (length and diameter) are different. This implies different mixing conditions and then different local supersaturations which obviously have a significant influence upon the crystals size and habit.

### Crystallization experiments carried out for velocity jets higher than the atomization velocity:

The results obtained for velocity jets of  $0.5 \text{ m.s}^{-1}$ , corresponding to atomized jets, exhibit quite similar characteristics in terms of crystals size and habit whatever the capillary ID used. Figure 4 shows the crystals obtained for capillary diameters of  $150 \mu\text{m}$  (figure 4a),  $254 \mu\text{m}$  (figure 4b) and  $510 \mu\text{m}$  (figure 4c). The only difference that can be noted is that for the lowest capillary ID, only one polymorphic form was obtained: the form I. This form is a kinetically favoured one.

Those results show that the velocity jet has a preponderant influence on crystals characteristics for the lowest capillary ID studied while the crystals obtained with a capillary ID of  $510 \mu\text{m}$  have the same characteristics in terms of size, habit and polymorphic nature whatever the velocity jet, i.e. whether the jet is atomized or not. It can be then concluded that to correlate the crystals characteristics to the jet hydrodynamics, other parameters than the velocity jet have to be considered. The hydrodynamics in the crystallization autoclave has to be characterized through the mixing state and the knowledge of local supersaturation.



## IV Conclusion

This study shows that for the operating conditions commonly used in SAS applications, the liquid solutions which is dispersed in the precipitation autoclave can be atomized or not. Under the experimental domain studied and for different solvents, the critical atomization velocity jet is similar and is roughly about  $0.4 \text{ m.s}^{-1}$ . The crystals formed in conditions for which the jet is atomized or not can have different characteristics depending on the capillary ID used. In order to fully interpret crystallization results, the mixing state as well as the local supersaturation have to be considered.

## V References

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