

POWER DISSIPATED IN AN IMPINGING JET DEVICE IN SAS PROCESS

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ABSTRACT

This work is dedicated to the impinging jet technology applied to the Supercritical Anti-Solvent (SAS) crystallization of a drug. In the precipitation autoclave, two capillaries are placed face to face. In the first one, the organic solution (acetone + dissolved sulfathiazole) is injected. In the other one, supercritical CO₂ is injected. The other parts of the process are the same as for more traditional SAS processes. For a better control of this process, the first objective is the determination of the power dissipated in the two flows mixing zone between the two capillaries. This power is calculated taking into account the speed of injection of the two flows (varied from 0.25 to 6.48 m.s⁻¹) and the volume of the mixing zone which is determined with a direct visualization in the high pressure autoclave equipped with two borosilicate windows. The other varied parameters are the following: pressure (10 - 15 MPa) and the temperature (313 – 328 K). The results indicate a variation of the dissipated power from 0.1 to 158 W.kg⁻¹. The characteristics (crystal size, habit and polymorphic nature) of the crystals obtained are different depending on the operating conditions and particularly on the mixing efficiency.

INTRODUCTION

Particle generation using Supercritical Anti-Solvent (SAS) process has been widely described for the last twenty years. It has been demonstrated that the mixing conditions may have a significant influence upon the characteristics of the formed crystals or particles. The characterization of mixing efficiency during SAS process is useful for a better understanding of this technique. The impinging jet technology is known to improve mixing and has already been applied in supercritical media [1 - 3]. The study presented here deals with the SAS drug crystallization using impinging jets device as the introduction device of the supercritical anti-solvent (CO₂) and of the organic solution containing the solute to be precipitated (sulfathiazole). First results obtained in our laboratory have been yet proposed [2, 3], dealing on the research of optimal functioning conditions and have proved the efficiency of the impinging jets to form finer particles than with conventional SAS process. The originality of

the study presented here relies on the estimation of the power dissipated in the two flows mixing zone between the two capillaries for different operating conditions.

This power has been calculated taking into account:

1- The velocity of injection of the two flows. One value is lower than the critical atomization velocity (evaluated by [4, 5]): 0.25 m s^{-1} . In this case, two free plain jets are impacted. The other velocities studied are higher than this critical velocity: 2.5, 3.24 and 6.48 m s^{-1} . In this case, atomised jets are injected.

2- The volume of the mixing zone. This volume is determined by direct visualization in a high pressure autoclave equipped with two borosilicate windows.

The influence of the variation of jet velocities and of some experimental parameters as pressure (10 - 15 MPa) or temperature (313 – 328 K) upon dissipated power and upon the crystal characteristics has been studied.

MATERIALS AND METHODS

Materials

Carbon dioxide (purity 99.7%) was purchased from Air Liquide (France). Sulfathiazole (polymorph III, purity > 98%) and acetone (purity > 99.5%) were purchased from Sigma-Aldrich (Germany).

Experimental set-up

Experiments of the impinging jets SAS process (Figure 1) were performed using the experimental equipment previously described [3]. Two different autoclaves have been used: an autoclave equipped with windows for the visualization of the impinging jets (a 763 mL autoclave from New Ways of Analytics, Germany) and an autoclave without windows for the crystallization experiments (a 750 mL jacket autoclave from ESPOSITO, Italy). Both are equipped with pressure and temperature sensors. The fluids are fed, through two capillaries with an inlet diameter of $127 \mu\text{m}$, by GILSON 307 pumps and the global CO_2 feeding is made thanks to a DOSAPRO MILTON ROY pump (Saint-Pierre Bridge, France). At the bottom of the vessel, the fluid goes through degassing valves, the solvent remains in the solvent trap while the CO_2 is evacuated. The crystallized drug is collected on a frit filter, at the bottom of the autoclave. The video recording the jet dispersion is realized by a high speed camera, connected to a computer using Virtual Dub software.

Experimental procedure

The experimental procedure consists in feeding first the autoclave with CO_2 , until the desired pressure is reached. Then, the output valves are opened in order to create a constant

flow rate of CO₂ at constant pressure and temperature. It has to be noted that there is two feeding lines of CO₂, the main one at the top of the autoclave and one in the impinging jet. The solution containing the solute is then impinged with the other CO₂ feeding, via the impinging jet. Thus the solute crystallizes.

After crystallization, there is a washing composed of two steps. First, an injection of 5 mL of pure solvent is made in order to purge the injection loop. Then, pure CO₂ is introduced during a given time in order to evacuate the organic solvent from the autoclave and remove the residual solvent contained in the powder. The washing time is fixed at 5 times the residence time.

Then, the autoclave is depressurized to atmospheric pressure in order to collect crystallized powders.

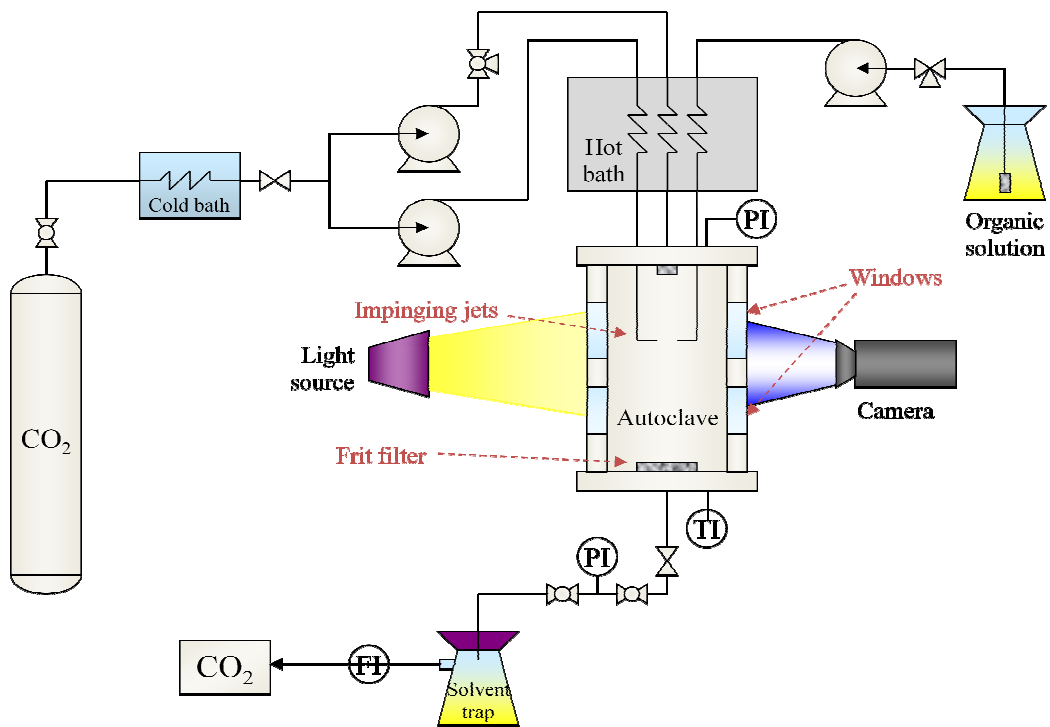


Figure 1: Experimental set-up for SAS precipitation and impinging jets visualization.

Determination of the dissipated power in the impinging jets

The dissipated power corresponds to the power introduced in the system divided by the mass in which it is dissipated. This mass is the product of the mixing volume V_m and of the mixture density ρ_3 .

So, the dissipated power per mass unit and the available power can be calculated as following:

$$\bar{\varepsilon} = \frac{P_{\max}}{\rho_3 V_m} \quad \text{Eq. (1)}$$

With $V_m = (\pi/4) d^2 h$
d and h are respectively the diameter and the thickness of the assimilated disk (see figure 2).
Indeed, in the impact zone, the mixing volume is considered to be the volume of a disk.

$$P_{\max} \propto \frac{1}{2} m_1 u_1^2 + \frac{1}{2} m_2 u_2^2 - \frac{1}{2} m_3 u_3^2 \quad \text{Eq. (2)}$$

In this study, the velocity of the mixture CO_2 – solvent (u_3) can be neglected since it is smaller in comparison with the jet velocity of CO_2 and of the solvent jet velocity, u_1 and u_2 .
The available power can be thus estimated using the following relation where m_1 and m_2 are the massic flow rates:

$$P_{\max} \propto \frac{1}{2} m_1 u_1^2 + \frac{1}{2} m_2 u_2^2 \quad \text{Eq. (3)}$$

Since the jet velocities (u_1 and u_2) and the capillary diameters (d_1 and d_2) are equal, the following relation can be written when each flow is stable:

$$\frac{m_1 u_1}{\rho_1} = \frac{m_2 u_2}{\rho_2} \quad \text{Eq. (4)}$$

With ρ_1 and ρ_2 , respectively the densities of CO_2 and of the organic solvent.

The following relation can thus be used for the estimation of the dissipation available power:

$$P_{\max} \propto \frac{\pi}{8} d_1^2 u_1^3 \rho_1 \left(1 + \frac{\rho_2^2 m_1}{\rho_1^2 m_2} \right) \quad \text{Eq. (5)}$$

Combining Eq. 1 and Eq. 5, the following equation is obtained:

$$\text{[Blank Equation Box]} \quad \text{Eq. (6)}$$

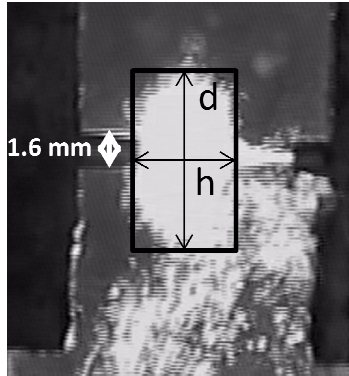


Figure 2: Impact zone assimilated to a disc (diameter: d and thickness: h)

Particle observations

The powders were observed with a Hitachi S-3000 (Hitachi, Japan) Scanning Electron Microscope (SEM). Each sample was prepared with a SC7620 Sputter Coater (Quorum Technologies, England) which deposits a 2 nm layer of gold and palladium in order to optimize the image resolution.

Polymorphs analysis

The Solid-State Nuclear Magnetic Resonance (NMR) has been used for the characterization of the polymorphic nature of the crystalline powder obtained by SAS process.

The solid-state ^{13}C NMR spectra were obtained on a Bruker Avance-400 MHz NMR spectrometer operating at a ^{13}C resonance frequency of 106 MHz and using a commercial Bruker double-bearing probe. About 100 mg of samples were placed in zirconium dioxide rotors of 4 mm outer diameter and spun at a Magic Angle Spinning rate of 10 kHz. The CP technique was applied with a ramped ^1H -pulse starting at 100 % power and decreasing until 50 % during the contact time (2 ms) in order to circumvent Hartmann-Hahn mismatches. To improve the resolution, a dipolar decoupling GT8 pulse was applied during the acquisition time. To obtain a good signal-to-noise ratio in ^{13}C CPMAS experiment 6000 scans were accumulated using a delay of 5 s.

RESULTS

For each operating conditions used for SAS crystallization, the phase mixing in the impact zone (of the impinging jets) has been characterized by direct visualization and by the estimation of the dissipated power.

The following experimental conditions have been studied:

- Anti-solvent: CO_2
- Solvent: acetone
- Drug: Sulfathiazole
- Pressure: 10 and 15 MPa
- Temperature: 313 and 328 K
- Solvent/ CO_2 molar ratio: 10 %
- Solute concentration: 1.8 wt%
- Jet velocity: 0.25 to 6.48 $\text{m}\cdot\text{s}^{-1}$.

Reproducibility tests

The first experiments have been focused on reproducibility aspects of the crystallization. Four experiments have been carried out twice and we have characterized the polymorphic nature of the powders obtained. Depending on the experimental conditions, the pure form I of sulfathiazole (experiments 1 and 3) or a mixture of the most stable form IV with the form I have been obtained. As it can be seen in table 1, when a mixture of two forms has been obtained, the proportion of each polymorph has the same order of magnitude when the experiment is doubled. So, it can be concluded that the experiments are reproducible.

Table 1 : Reproducibility tests

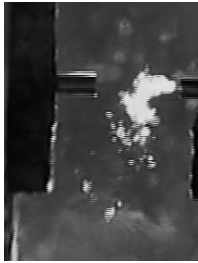
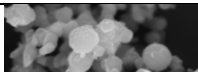
Experiment	1	1'	2	2'	3	3'
Operating conditions	Solvent: acetone P=10 MPa, T=313 K $u_{jet}=12.96 \text{ m.s}^{-1}$ solv. /CO ₂ : 10 mol% [solute]=1.8 wt%		Solvent: acetone P=15 MPa, T=313 K $u_{jet}=0.25 \text{ m.s}^{-1}$ solv. /CO ₂ : 10 mol% [solute]=1.8 wt%		Solvent: acetone P=10 MPa, T=313 K $u_{jet}=12.96 \text{ m.s}^{-1}$ solv. /CO ₂ : 10 mol% [solute]=1 wt%	
Polymorphic composition	Form I	Form I	Form IV (91%) + Form I (9%)	Form IV (96%) + Form I (4%)	Form I	Form I
Deviation	-		5 %		-	

Influence of jet velocity

One experiment has been conducted with a jet velocity corresponding to a non atomized jet ($u = 0.25 \text{ m.s}^{-1}$) and three experiments with jet velocities corresponding to atomized jets [4-5] ($u: 2.5 - 6.48 \text{ m.s}^{-1}$). The impact zones (of the impinging jets) observed for each jet velocity are shown in table 2. The mixing volume (V_m) has been estimated for each case. The dissipated power has been calculated using the equation (6). The mixing volume as well as the dissipated power increase when the jet velocities increase. A value of dissipated power smaller than 1 W.kg^{-1} has been calculated for a jet velocity of 0.25 m.s^{-1} while the dissipated power increases from 25 to 158 W.kg^{-1} when the jet velocity increases respectively from 2.5 to 6.48 m.s^{-1} . It is worth noting that the chosen conditions of jet hydrodynamics correspond to significant variations of the dissipated power.

The corresponding powders obtained exhibit different crystal sizes and habits. The effect of mixing conditions upon crystal characteristics is obvious. The most stable form IV has been obtained only for the less efficient mixing conditions.

Table 2: Influence of jet velocity

Jet velocity	0.25 m.s ⁻¹
	
Dissipated power	0.1 W.kg ⁻¹
	
Polymorphic nature	Form IV (75 % + Form I (25 %

Influence of pressure

Two different conditions are studied to observe the effect of the pressure variation (0.1 W.kg⁻¹).

As concerns the polymorphic nature, form IV increases when pressure increases in the supercritical phase increase supersaturation and then a high

Table 3: Influence of pressure

Pressure
Dissipated power
Polymorphic nature

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