IMPINGING JETS APPLIED TO SULFATHIAZOLE CRYSTALLIZATION USING SUPERCRITICAL ANTISOLVENT (SAS) PROCESS

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ABSTRACT: The aim of this study is to improve mixing in supercritical antisolvent process (SAS) with impinging jets in order to form finer particles. The influence of several process parameters variations upon sulfathiazole crystallization, a poorly water-soluble drug, is studied. Parameters are jets velocity (0.25 m/s to 25.92 m/s), temperature (313K to 343K), pressure (10 MPa to 20 MPa) and sulfathiazole concentration in the organic solution (0.5% to 1.8 %). Crystallized powders show that particle size, size distribution and morphology are different from the ones obtained with classical SAS introduction device in similar conditions. The mean particle size and the size distribution are significantly smallest than results obtained with classical SAS. Different polymorphs are obtained, including the pure stable one.

INTRODUCTION

The Supercritical AntiSolvent process (SAS) is commonly used for drug micronization [1-6]. The principle of this process is to inject, through a capillary tube, an organic solution containing a dissolved solute into a continuum of supercritical CO_2. The solvent is evaporated into the CO_2 rich phase, this latter diffuses into the liquid solution, hence the solution is supersaturated and the solute crystallizes.

Several different processes have been developed upon the antisolvent principle. Often, the introduction mode of fluids is the only difference with classical SAS. For example, the SEDS process (Solution-Enhanced Dispersion with Supercritical fluids) uses a coaxial nozzle which causes a tangential impingement of the solution and the antisolvent, which allows a better dispersion and mixing of solutions [4,7,8]. The resulting powders formed are finer than the ones obtained with traditional SAS process. In this work, a new introduction mode is studied: the impinging jets technology.

This technology has already been used in liquid crystallization. Some authors [9] underlined that confined impinging jets devices are obstructed by the solid particles when they are used for precipitation and the free-impinging jets device is proposed as a promising alternative. The mixing zone is not confined and then obstruction problem cannot occur. Industrial two-impinging-jets precipitators are used to obtain pharmaceutical products since 1983 [9] and patents illustrates the use of this device for the production of some pharmaceutical compounds [10].

A previous work [11] studied the application of these impinging jets for the micronization with supercritical fluids. With griseofulvin, this technology allows a particle size reduction from a few millimeters to 10 µm.

The aim of this work is to study the effect of operating parameters of impinging jets in supercritical conditions on the crystallization of a pharmaceutical solute: the sulfathiazole, an antibiotic which exhibits five different polymorphic forms. The stable one is the form IV. This molecule is a poorly water soluble drug so improving its bioavailability by decreasing the mean particle size is of great interest. Moreover, for a good industrialization, the powders must have good flowability and a certain (not too low) apparent density, so the particles are expected to have a near spherical homogenous morphology. Finally, properties of the active

pharmaceutical ingredient, such as solubility, dissolution rate, density, physical stability and melting point, are depending on the type of crystalline form. The polymorphism is hence an important powder characteristic.
The studied process parameters are pressure, temperature, inlet jets velocity, and massic concentration of the solute in the solution. Mean particle size, particle size distribution, morphology/habit and polymorphism are the powder characteristics which will be taken into account as results. The objective is to prove that this new process is able to form particles which targeted characteristics.

MATERIALS AND METHODS

The impinging jets SAS process (figure 1) was performed using the experimental equipment previously described [11]. Briefly, it is composed of a 750 ml jacket reactor (ESPOSITO, Italy) manufactured to resist a maximum pressure of 25 MPa and a maximum temperature of 100°C. It is equipped with pressure and temperature sensors. The fluids are fed 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 reactor, 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, on the bottom of the autoclave.

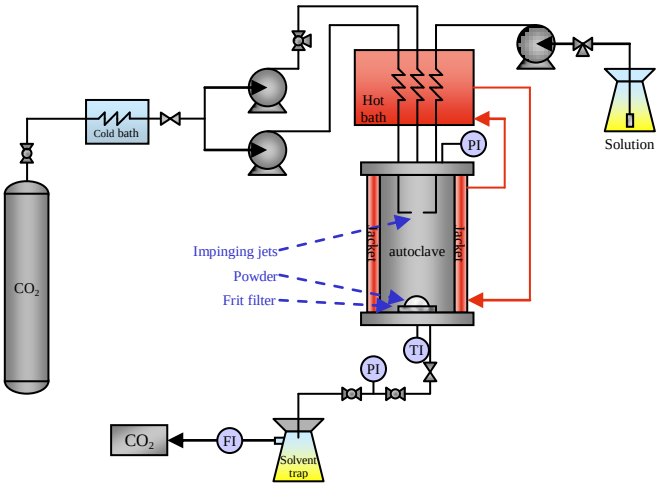

Figure 1: Impinging jets SAS Process

For the particles size and the morphology, the powders are observed using a Hitachi S-3000 (Hitachi, Japan) Scanning Electron Microscope (SEM). In order to identify the different polymorphic forms, solid-state ^{13}C NMR spectra have been studied, obtained with 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 are placed in zirconium dioxide rotors of 4-mm outer diameter and spun at a Magic Angle Spinning rate of 10 kHz. The CP technique is applied with a ramped ^{1}H-pulse starting at 100% power and decreasing until 50% during the contact time (2ms) in order to circumvent Hartmann-Hahn mismatches. To improve the resolution, a dipolar decoupling GT8 pulse sequence is applied during the acquisition time. To obtain a good signal-to-noise ratio in ^{13}C CPMAS experiment 6000 scans are accumulated using a delay of 5s.

RESULTS

Several experiments have been carried out to study the influence operating parameters' variations upon crystallization. The impinging jets velocity (from 0.25 $m.s^{-1}$ to 25.92 $m.s^{-1}$), the temperature (from 313K to 343K), the pressure (from 10 MPa to 20 MPa) and the concentration of the solute in the solution (from 0.5% to 1.8%) have been varied.

Effect of jets velocity

Experiments with impinging jets are performed at six different velocities: 0.25 $m.s^{-1}$, 2.5 $m.s^{-1}$, 3.24 $m.s^{-1}$, 6.48 $m.s^{-1}$, 12.96 $m.s^{-1}$ and 25.92 $m.s^{-1}$. Except for the first one, all these velocities are higher than the atomization velocity threshold, which has been determined for the studied system in previous works [13] and which is approximately 0.4 $m.s^{-1}$. It can be seen in the table 1 that this parameter has a great influence upon the characteristics of powders.

For jets velocities higher than the atomization threshold, increasing this parameter allows decreasing significantly particle size and size distribution; the morphology becomes more homogeneous. For the smallest velocities, the powders obtained exhibit different habits for a same batch while from the value of jets velocity of 6.48 $m.s^{-1}$, powders are only composed of near spherical particles. On the other hand, when the velocity is below the atomization threshold, the mean particle size is approximately 1.55 µm and it is interesting to notice that it is as small as the one obtained with a 6.48 $m.s^{-1}$ velocity. Only the morphology is less homogeneous: the powder is a mix of near spherical particles and platelet-like.

First, the powder characteristics can be explained by the effect of the velocity on the jet dispersion. Figure 1 shows the jets that can be observed below (a) and above the atomization threshold (b). The axisymmetrical jets observed for the lowest velocities exhibit a long plain jet while an atomised jet, rapidly broken up, has a short length. Impingement is hence more strengthened when the jets are not atomized. On the other hand, for the atomized jets, when the velocity increases, the impingement is strengthened.

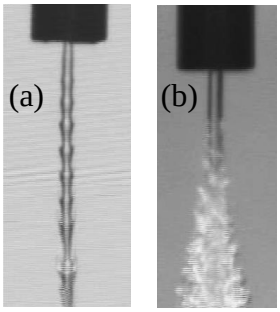

Fig. 1: (a) axisymmetrical jet, (b) atomized jet [13]

As concerns polymorphism, when velocities are above the atomization, pure form I is always obtained. It is interesting to notice that the stable form is obtained only for a velocity below the atomization threshold. This experiment allows crystallizing a powder composed of 75% of the form IV and 25% of the form I. This result is due to the influence of the fluids velocity on the nucleation kinetic. Metastable polymorphs are kinetically favoured. For the studied system, a velocity below the atomization threshold leads to the obtention of the stable polymorph. This result is of great interest.

Table 1: Effect of jets velocity at 10 MPa, 313 K, x_{solv} = 10 mol% and x_{solute} = 1.8 wt%

Velocity ($m.s^{-1}$)	0.25	2.5	3.24	6.48	12.96	25.92
Morphology	T + S	N + S	TA	S	S	S
Mean particle size (µm)	T: 1.8 S: 1.31	N: 70.71 S: 0.78	2.45	1.56	1.63	1.07
Standard deviation (µm)	0.56 / 0.49	36.87 / 0.36	1.23	0.83	0.72	0.6
Polymorphism	25% I + 75% IV	I	I	I	I	I

Notation: S: near Spherical; N: Needle-like; P: Platelets; T: Tablets; A: Agregates

Effect of temperature

We have carried out experiments of sulfathiazole crystallization at three different temperatures: 313K, 328K and 343K, at 15 MPa and with jets velocities of 0.25 $m.s^{-1}$. The chosen pressure corresponds to conditions for which CO_2 and acetone are miscible in all proportions.

The results show that the effect of temperature on the powders is very significant. Indeed, when temperature increases, morphology of the particles becomes more heterogeneous with appearance of large aggregated platelets which increases the mean particles size and enlarges the size distribution. It is because at high temperature the solute solubility in the solution is higher and so, for a same initial concentration, the supersaturation value is lower. Hence, the nucleation kinetic is lower.

Table 2: Effect of temperature at 0.25 $m.s^{-1}$, 15 MPa, x_{solv} = 10 mol% and x_{solute} = 1.8 wt%

Temperature (K)	313	328	343
Morphology	S + P	S + PA	S + PA
Particle size (µm)	3.63	S: 1.99 / PA ≈ 10.	S: 1.25 / PA ≈ 15.
Standard deviation (µm)	2.53	S: 1,04	S: 0,71
Polymorphism	15% I + 85% IV	IV	79% IV + 21%V

Effect of pressure

Experiments have been performed at 0.25 $m.s^{-1}$ and three pressures: 10 MPa, 15 MPa and 20 MPa. The results show that above 10 MPa, the particle size is two times higher, from approximately 1.5 µm to approximately 3.5µm. The effect on the particle size distribution is more significant: the PSD increases with pressure. This behaviour can be explained regarding the solubility of solute in the continuous phase (composed of acetone and CO_2) which increases with pressure. The concentration gradient between the dispersed phase and the continuous phase is smaller and then, kinetic is slower. Those conditions favoured the formation of the stable polymorph.

Table 3: Effect of pressure at 313 K, 0.25 $m.s^{-1}$, x_{solv} = 10 mol% and x_{solute} = 1.8 wt%

Pressure (MPa)	10	15	20
Morphology	T + S	T + S	T + S
Particle size (µm)	T: 1.8 / S: 1.31	3.63	3.40
Standard deviation (µm)	0.56 / 0.49	2.53	3.10
Polymorphism	25% I + 75% IV	15% I + 85% IV	IV

Effect of sulfathiazole concentration in the solution

The effect of the concentration have been studied for three massic ratios: 0.5%, 1% and 1.8%. The mean particle size decreases significantly when the concentration increases. Indeed, for the two lower concentrations, the morphologies are heterogeneous and there are a lot of large particles, as needles or platelets. This behaviour is due to the supersaturation value which increases when the concentration increases. As for temperature, the increasing of supersaturation has a significant effect on the morphology and the habit but it has no significant influence on the polymorphism.

Table 4: Effect of the massic ratio at 10 MPa, 313K, 0.25 $m.s^{-1}$ and x_{solv} = 10 mol%.

Massic ratio (%)	0.5	1	1.8
Morphology	S + TA + PA	S + T + P	T + S
Particle size (µm)	/	/	T: 1.8 S: 1.31
Standard deviation (µm)	/	/	T: 0.56 S: 0.49
Polymorphism	IV	IV	25% I + 75% IV

Comparison with SAS process

Three experiments performed with impinging jets process have been carried out with classical SAS. Even if the morphology is not always more homogeneous with impinging jets, the results show that powders are significantly different. Indeed, it can be seen that with impinging jets, the particle size is from approximately 5 times to 50 times smaller than with classical SAS and the particle size distribution is more narrow.

These results are in agreement with what was expected. The impingement of the jets allows improving the mixing which decreases the particle size.

Table 5: Comparison of classical and impinging jets processes at 6.48 $m.s^{-1}$ and a concentration of 1.8wt%

Experience	313K, 10 MPa		313K, 20 MPa		343K, 20 MPa	
Process	Impinging jets	SAS	Impinging jets	SAS	Impinging jets	SAS
Morphology	S	S + T	N+T+S	T+S	T+S	T+S
Mean particle size (µm)	1.56	7.66	3.06	T: 159.7 S: 4.18	1.67	13.09
Standard deviation (µm)	0.83	11.14	2.84	T: 80.28 S: 2.44	0.66	5.08

CONCLUSION

In conclusion, it has been observed that different jets velocities lead to significantly different powder characteristics. Working with a velocity lower than the threshold of atomisation gives probably the most interesting results since it allows forming small particle, almost 1.6 µm, with a narrow size distribution and a powder mainly composed of the stable polymorphic form. At this velocity, the pressure has been identified to be an influent parameter on the polymorphism and the pure stable polymorph has been formed at 20 MPa. Concerning the particle size, the most influent parameters are temperature and sulfathiazole concentration. All these results show how this process allows a good polymorphic control with particles smaller than classical SAS ones.

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