STUDY OF SULFATHIAZOLE RECRYSTALLISATION USING THE IMPINGING JETS TECHNIQUE

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ABSTRACT

In this work the recrystallization of sulfathiazole is considered by using a special fluid feed device apparatus. The general principle is the same as for the Supercritical Anti Solvent process (SAS), being its particularity the introduction device. In the SAS process, the organic solution (organic solvent + dissolved sulfathiazole) is simply introduced in a continuum of supercritical phase through a capillary, while in this work a capillary faces another one where the supercritical CO2 is injected. The two facing capillaries are spaced by 8 mm, and have the same internal diameter. As the flow rates are identical, the velocities of injection are also the same. The impact is located between the two capillaries, leading to a high turbulence and a good mixing between the two flows. Another carbon dioxide flow is introduced in the reactor in order to preserve a constant CO2/solvent molar ratio. The sulfathiazole is used as a so called model compound, as it leads to different morphologies and polymorphisms depending on the operating conditions.

The purpose of this work is to test the potential of this device for the success of sulfathiazole recrystallization in terms of size, size distribution, habit and polymorphism control. For that purpose, the main parameter which is considered in this study is the velocity of injection of the two flows. However, the initial sulfathiazole massic concentration (1 and 1.8 wt %) and the ratio organic solvent / CO2 flows (10 and 20 %) are also investigated. All the experiments are conducted under 10 MPa and 40 °C. In order to study the results, powders obtained are analyzed using DSC and X ray diffraction analysis, and habit and particle size are observed from MEB pictures.

The main results show that habit, particle size and particle size distribution are influenced by the velocity of injection. A comparison with the results obtained from other processes using supercritical carbon dioxide shows that this device allows significant reduction of particle size.

To conclude, the experimental device used in this study gives interesting results for the formulation of a sulfathiazole powder. The comparison between the results obtained with different introduction devices (and consequently the mixing conditions) should also give some information on the crystallization mechanism.

INTRODUCTION

In the pharmaceutical processes, the polymorphic control of a powder is a key point. A determined one must be obtained, as pure as possible. The control of the particles size and particles size distribution is also an important point. Among the different processes used for the recrystallization of an active principle, the one using supercritical CO2 presents some interests. In this study, the process used is derived from the SAS (Supercritical Anti Solvent) type [1]. In the SAS process, the organic solution containing the solute to be precipitated is introduced through a capillary in a continuous flow rate of supercritical CO2. The latter plays the role of an antisolvent, leading to the supersaturation and crystallization of the compound. The SAS process can give some interesting results, but for some cases it could be interesting to increase the mixing between the two phases. For that purpose, the use of an impinging jet is proposed. Two jets are injected at the same velocity face to face: one with the organic solution and another with supercritical CO2. This should enhance the mixing and it very interesting to look at its influence on the powder characteristics.

Few studies have been presented on the application of the impinging jets technique, some in liquid solution and others in supercritical fluids. In the case of results obtained in liquid solution, Lindrud *et al.* [2] have for instance produced submicronic particles combining the effect of the impinging jets and a sonic probe. In the case of experiments conducted in a supercritical CO2 medium, Pellikan *et al.* [3] have patented the production of nanoparticles made of a carbohydrate polymer and a biopolymer. They tried a classical SAS, the impinging jets and the confined impinging jets. They show that increasing the energy dispersed in the medium decreases the particle size.

These few results encourage us to develop and test an impinging jets technique in supercritical CO2. In order to make an interesting comparison with other results, we have decided to choose sulfathiazole as compound to be recrystallized, as it has been widely used in studies dealing with supercritical CO2. The first interest of this molecule is because of its different polymorphic forms. Four main forms have been identified [4]. The order of stability is the following form III > form IV > form II > form I [5]. It must be noticed that the order of stability of form III and IV can be changed as their solubility is very close and depends on the organic solvent used. Besides, an interesting study dealing with the polymorphic forms obtained with respect to the solvent used [5] indicates that with acetone (the solvent used in this study) forms I and IV are usually obtained. As far as particle size obtained in previous results, authors using the GAS process obtained large needles, from 300 to 6000 μm [6] [7]. More sophisticated systems are required if one want to decrease particles size. Some authors use the SEDS process [8] [9], leading to particle sizes from 1 to 70 μm. Caputo *et al.* [10] use a traditional SAS process, but they put an additive (urea) in their organic solution. The results are interesting, as particle sizes obtained ranged from 0.45 to 20 μm, but only a mixture of form I and amorphous form is obtained. Those results indicated that is interesting to test another device that could at the same time decrease particle size and lead to the most stable form (IV).

MATERIALS AND METHODS

The following components have been used for the experimental work:

- Sulfathiazole (purity >98 %) supplied by Sigma Aldrich (France).
- CO2 (purity 99.5%) purchased from Air Liquid company (Paris, France)
- Acetone (analytic purity 99.8%) from Fluka Company (Buchs, Switzerland).

The experimental apparatus is represented in Figure 1. The general system is very close to the SAS process. The autoclave (ESPOSITO, Italy) is cylindrical and has an internal diameter of 70 mm and a

height of 195 mm leading to a volume of 750 mL (1). It is manufactured to resist a maximum pressure of 25 MPa and a maximum temperature of 100°C. It is composed of a double jacket where the preheated water circulates, allowing to control temperature at about 0.5 °C in the reactor. This last one is equipped with a temperature and pressure sensor. The reactor is composed of three entries, one exit and a rupture disc in case of overpressure. The carbon dioxide is initially cooled in the cold bath n°1 then pumped by a high pressure pump DOSAPRO MILTON ROY (Saint-Pierre Bridge, France) thus allowing the circulation of a supercritical CO_2 continuum (central entry, 2). The flow rate is adjusted in order to maintain a constant organic solution / CO2 ratio. Two other entries connected to two high pressure liquid pumps (GILSON, model 307) are used to introduce the organic solution and the CO2. Those two feedings are made with two capillaries (internal diameter 127 µm) placed face to face inside the vessel (3). The distance between the two capillaries can be easily adjusted. The three feeders are preheated at desired temperature. The pressure and the flow of the CO2 continuum are controlled by means of two degassing valves in series, allowing an accurate constant flow rate.

Particle size estimation for each samples was carried out by means of an optical microscope MOTIC B2 (Motic Wetzlar, Germany) equipped with a digital camera. Some observations were carried out with a Hitachi S-3000 Scanning Electron Microscope (Hitachi, Japan). Each sample was passed in a SC7620 Sputter Coater (Quorum Technologies, England) depositing a very fine layer (2 nm) of gold and palladium in order to optimize the image resolution. The size of the particles and their standard deviation are obtained with at least two hundred measurements taken from photographs, using ImageJ software.

DSC measurements were performed using Setaram 92 differential scanning calorimeter. Between 8 and 10 mg per sample of sulfathiazole was weighted in aluminium pans and sealed. Under nitrogen gas purge (flow rate: 20 $mL.min^{-1}$) the samples were equilibrated at 293 K and then heated up to 523 K at ramp rates of 10 $K.min^{-1}$. The identification of polymorphism forms from the curves obtained is made with comparison with the work of Zeitler *et al.* [11].

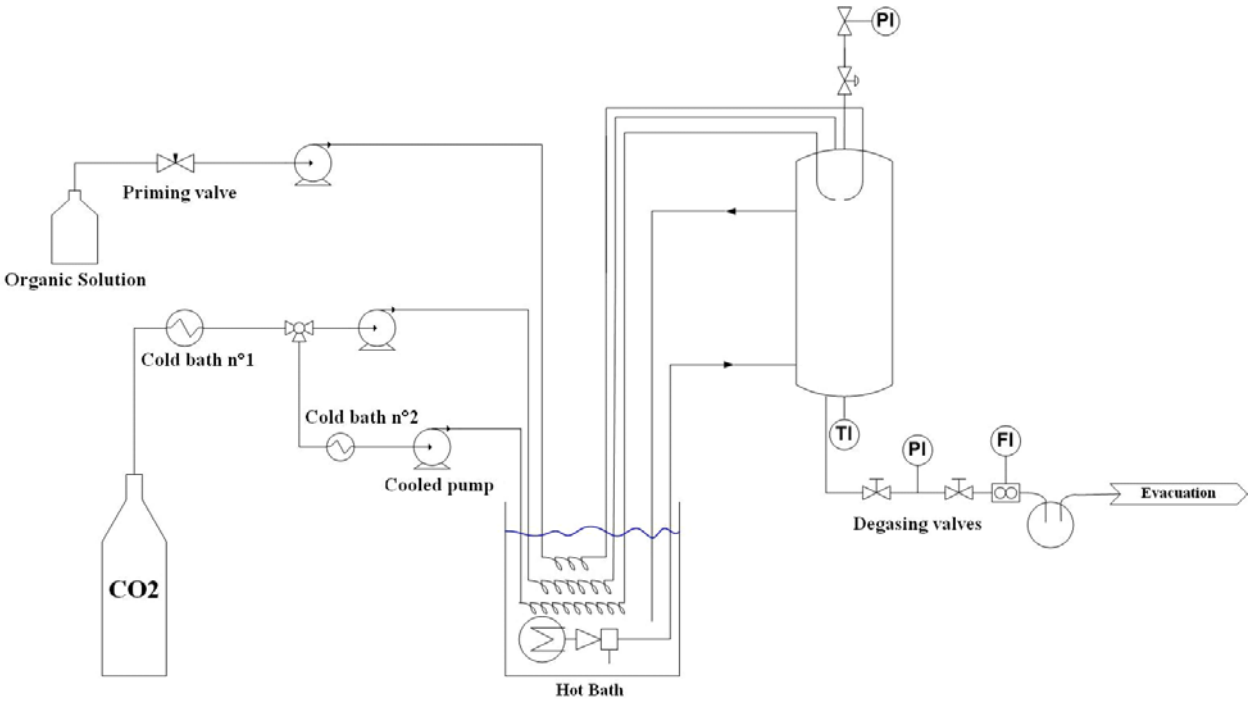

Figure 1 Experimental device

RESULTS

The different results obtained are presented in Table 1. Flow rate 1 stands for the organic solution and the CO2 injected in the impinging jets, and flow rate 2 stands for the global flow of CO2 at the exit of the reactor (CO2 injected in the impinging jet + CO2 injected at the top of the reactor). All the experiments were conducted under a pressure of 10 MPa and a temperature of 40 °C. Figure 2 provides an example of the particles obtained for experiment 4.

Table 1: Experimental results (solvent: acetone, Pressure: 10 MPa, Temperature: 40°C)

Exp.	Flow rate 1 $mL.min^{-1}$	Velocity $m.s^{-1}$	Flow rate 2 $g.h^{-1}$	Molar ratio %	Solute fraction wt %	Yield %	Habit	Size μm	Polym.
1	2.5	3.24	881.6	10	1.8	89.3	Platelets	3.6 (0.8)	I
2	2.5	3.24	881.6	10	1	88.4	Platelets	2.1 (0.5)	I
3	5	6.48	1550	10	1.8	90	Balloons	1.8 (0.7)	I
4	10	12.96	3100	10	1.8	86.7	Balloons	1.3 (0.5)	I et IV
5	10	12.96	3100	10	1	88	Balloons	1.11 (0.24)	I
6	20	25.92	6200	10	1.8	85	Balloons	1.2 (0.6)	I et IV

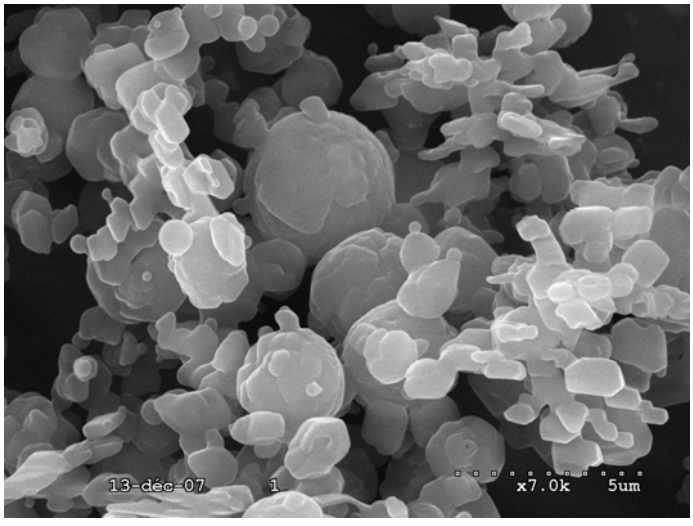

Figure 2 MEB photography of particles obtained in experiment 6

The first general remark on the results obtained is that the morphology changes with the injection velocity, from platelets to balloons. However, the two morphologies give a high specific surface area. As for the particle size, it can be noticed that increasing the injection velocity decreases the average particle size. This decrease is significant: from experience 1 to 5, the injection velocity is multiply by 8 and the average particle size divided by 3. This decrease is regular with the increase of the injection velocity. The first purpose of this injection device, *i.e.* the influence of the injection velocity on the particle size, is hence reaches in a very satisfactory way: the smallest particles obtained have an average size of 1 μm, which is very competitive with the results previously obtained.

Two polymorphic forms are obtained: form I and form IV. This result is coherent with the fact that acetone is used as solvent. At slower flow rates, pure form I is obtained, *i.e.* the less stable form. When the flow rate increase, a mixture of polymorphic forms I and IV is obtained. Let's remind that form IV is the more stable form. That's mean that increasing flow rate allow to obtain the most stable form, which is not the expected result. The explanation could be the following: increasing flow rate increases the micromixing and then the nominal supersaturation is rapidly reached leading partly to the formation of the most stable polymorph. For the lowest flow rates, because of a less efficient micromixing, high local supersaturation can be reached and lead to the formation of the unstable polymorph.

In comparison with the results obtained in literature, the particles we obtained are nearly as small as the smallest obtained previous studies. For instance, Caputo and Reverchon [10] obtained particles which smallest size is 0.5 μm. The powder obtained is a mixture of form I and amorphous form. Authors who obtained form IV (mixed with polymorph I) ([8], [9]) have bigger particles (few 10 μm). With the device used in this study, it is possible to obtained small particles with the right polymorph.

CONCLUSION

The results presented in this article first indicate that the impinging jets technique is viable to produce a controlled powder with controlled characteristics. Indeed, the system allows a control of the particle size and, in a certain extend, a control of polymorphic form. It is possible to obtain a very fine powder, with the stable polymorphic form, even if for the moment it is mixed with another form. However, a comparison with previous results obtained by other researches indicates that this process is very competitive. The next objective is to obtain the pure stable polymorph, playing with the injection velocity and with the global flow of supercritical CO2.

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