

# CONVERTING SPRAY DRYERS INTO SUPERCRITICAL MACHINES BY ATOMIZATION OF SUPERCRITICAL ANTISOLVENT INDUCED SUSPENSIONS

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The Atomization of Supercritical Antisolvent Induced Suspensions (AS AIS) is a small volume supercritical antisolvent process characterized by the inline dissolution of the antisolvent before the liquid atomization for the solvent extraction step. The antisolvent (CO<sub>2</sub>) is mixed with the solute-containing solution in a small volume mixer immediately before the nozzle orifice in conditions such that cause the precipitation of the solutes. The generated suspension is then spray-dried for solvent separation. Compared to most supercritical antisolvent techniques, this approach allows a more efficient control of the antisolvent process and reduces the volume of the high-pressure precipitator by several orders of magnitude, typically into a 1 cm<sup>3</sup> mixer.

Theophylline (TPL) was processed into micrometric particles by AS AIS using different processing conditions with either an antisolvent fluid (CO<sub>2</sub>) or a non-antisolvent fluid (N<sub>2</sub>). The TPL particles obtained by AS AIS turned out to be TPL polymorph, the same form that is also obtained by conventional SAS. Yet, the normal (non-polymorph) crystal form was obtained under non-antisolvent conditions, either by using non-antisolvent fluid (N<sub>2</sub>) or at conditions that favor the TPL dissolution in the supercritical phase.

**Keywords:** supercritical, atomization, anti-solvent, AS AIS, Polymorphism, Spray-drying

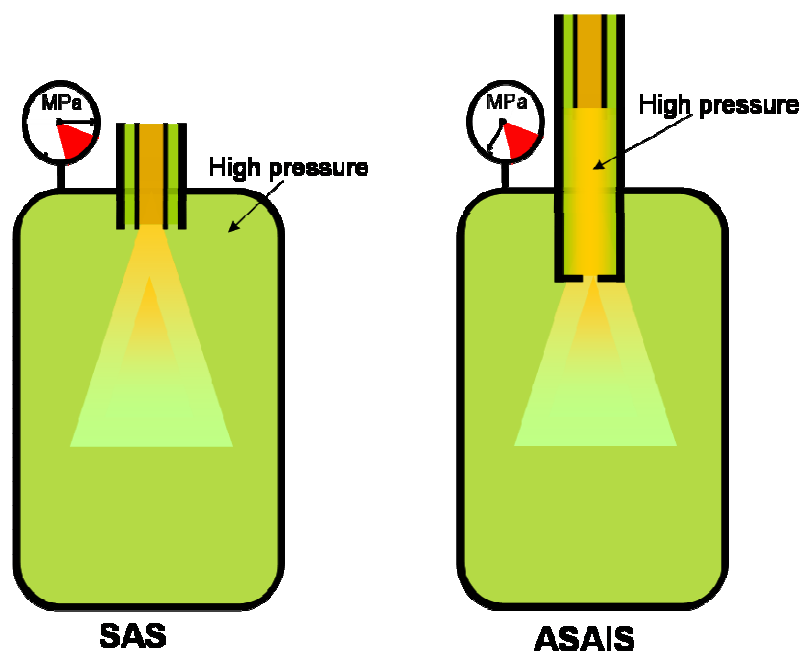
## INTRODUCTION

The properties of supercritical carbon dioxide (SC-CO<sub>2</sub>) have been explored for the production of particles by many authors [1-2]. SC-CO<sub>2</sub> anti-solvent properties are in the basis of the supercritical anti-solvent (SAS) that has been applied, in the last two decades, to comminute substances to micrometric and sub-micrometric sizes, with some control of morphology and size distribution, at moderate temperature and mechanical stress [2]. SAS has also gained interest due to its potential to control the crystalline form of pharmaceutical substances. Due to the singularity of the supercritical anti-solvent mechanism, it induces polymorphism in substances that it is otherwise difficult to reproduce with other techniques. It is well-known the importance of polymorphs to the pharmaceutical industry, where it constitutes leverage tool to conquer a market share, but most importantly, because it also has the potential to transform physical-chemical characteristics of powders. Polymorphism has impact in the melting point, bulk density, chemical reactivity, apparent solubility and dissolution rate. In other words, polymorphism can affect drug stability, manipulation, and bioavailability. [3-4]

Despite the SAS potential, the process has yet to obtain widespread industrial acceptance. Complex mass transfer has been considered one of the major limitations regarding SAS scale-up. In SAS, the antisolvent precipitation, the solvent extraction and the particle harvest occur simultaneously in the same unit (the high-pressure precipitator). Some issues on mass transfer related to the scale-up of high pressure supercritical precipitators, together with complex particle recovery by filtration, could explain the difficulties to expand the industrial applications [5].

Recently, we have developed a new version of SAS that restricts the use of CO<sub>2</sub> at supercritical conditions (high-pressure) to a small volume - the atomization of anti-solvent induced suspensions (ASAIS). This process consists in mixing the solution with SC-CO<sub>2</sub> in a mixer prior to atomization to generate a suspension. This suspension is immediately sprayed for solvent extraction by spray-drying at normal pressure. By restricting the high pressure exclusively to where it is indispensable (to induce precipitation), the installation is simplified and becomes compatible with existing spray-drying equipment. In ASAIS the supercritical conditions are restricted to a small volume mixer, conversely to SAS, where everything happens in supercritical media (atomization, anti-solvent crystallization, solvent extraction and particle separation), as Fig. 1 illustrates. This strategy avoids the highvolume equipment at high pressure and complex particle harvesting in filters, which is incompatible with continuous regime operation.

In this work, we converted a spray-drying setup to ASAIS by assembling an ASAIS nozzle in typical spray-drying components. Consequently, this strategy allowed us to perform a supercritical antisolvent process in a continuous regime operation. Herein we discuss several variables associated to ASAIS processing in order to understand the mechanisms leading to polymorphism of TPL by SC-CO<sub>2</sub> and optimal process conditions for production of the TPL polymorph. We also delineate some pros and cons of ASAIS comparing to spray-drying and SAS.



**Figure 1** – Conceptual differences between SAS and AS AIS techniques. In AS AIS antisolvent precipitation occurs before the jet dispersion into a small volume equipment. In AS AIS high-pressure is confined to a small equipment and the suspension spray is dried at normal pressure.

## MATERIALS AND METHODS

### *Materials*

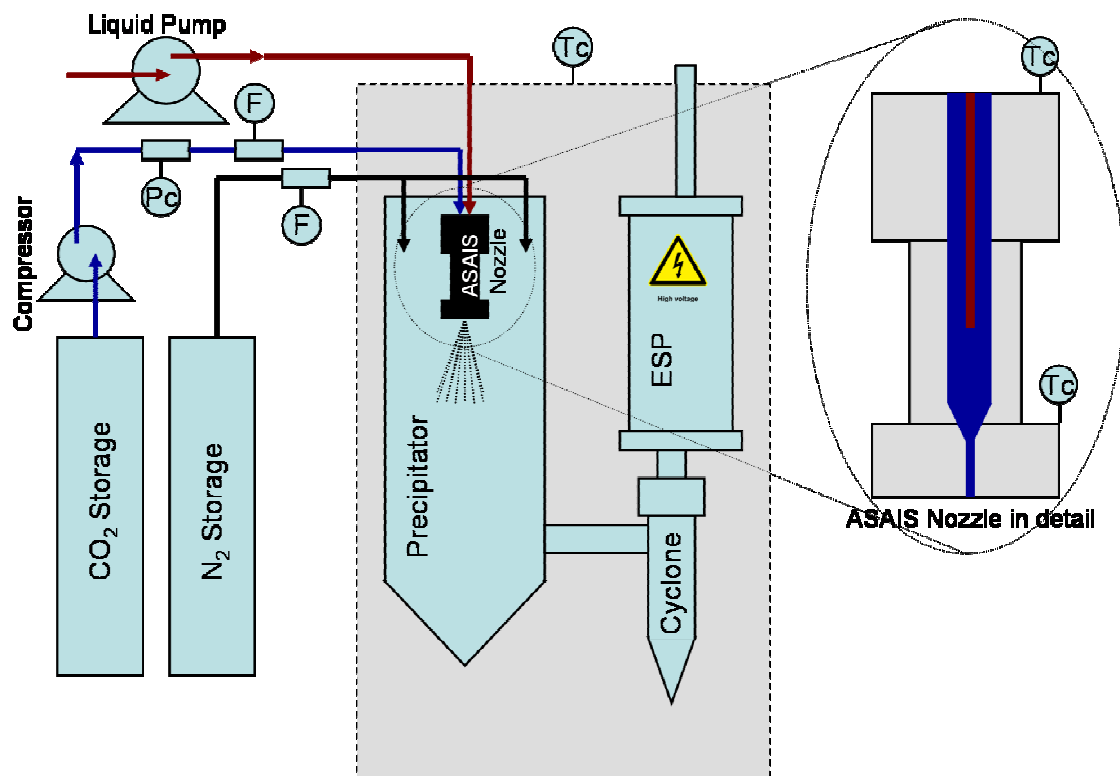
Theophylline (TPL) with a purity of  $\geq 99\%$ , mp 545 K, was supplied by BioChemika (USA). Tetrahydrofuran (THF) was obtained from Panreac with a purity of 99.5% (wt.) and was used as received. Carbon dioxide 99.98% and nitrogen 99% pure were supplied by Air Liquide (Portugal).

### *Experimental setup*

Figure 2 shows schematically the AS AIS setup. The liquid solution was pumped by a LKB metering pump (model 2150) into the AS AIS nozzle where it was mixed with a gaseous or supercritical fluid ( $\text{CO}_2$  or  $\text{N}_2$ ). The gas ( $\text{N}_2$  or  $\text{CO}_2$ ) was compressed by a compressor (Newport, model 46-13421-2). The nozzle flow (between 10 g/min and 20 g/min) was measured by a mass flowmeter (Rheonik, model RHM007). Pressures were measured by transducers (Omega, model PX603) and temperatures were controlled, in the air chamber and in the water bath, by T-type thermocouples and Ero Electronic controllers (model LDS). Nozzle orifice diameter ranged from 100  $\mu\text{m}$  to 150  $\mu\text{m}$ . All nozzle discs (provided by Lenox Laser, USA) were 250  $\mu\text{m}$  thick and the orifices were laser drilled.

The mixing volume was set by the height of the liquid solution in a 1/16 inch tube inside the nozzle. A drying N<sub>2</sub> flow at 353 K was set at approximately 30 normal liter per minute. The particles were collected in a Buchi™ cyclone and in an electrostatic precipitator (ESP) assembled in a single-stage tubular configuration and powered by a EMCO DX high voltage with 10 kV to 15 kV.

A spray-drying-like run was carried replacing the CO<sub>2</sub> flow across the ASAIS nozzle by N<sub>2</sub>. Spray drying conditions were: pressure: 10MPa; initial TPL concentration in the THF solution: 0.2% mass; mixer volume: 1 cm<sup>3</sup>; flow rate ratio of the solution and the N<sub>2</sub>: 0.01.



**Figure 2** – Schematic representation of the experimental setup.

### *Particles Characterization*

The particles' morphologies were analyzed by a Scanning Electron Microscope (SEM) Hitachi S2400. Particle samples were coated prior to measurement with a gold film by electrodeposition in vacuum.

### *Powder X-ray Diffraction (PXRD)*

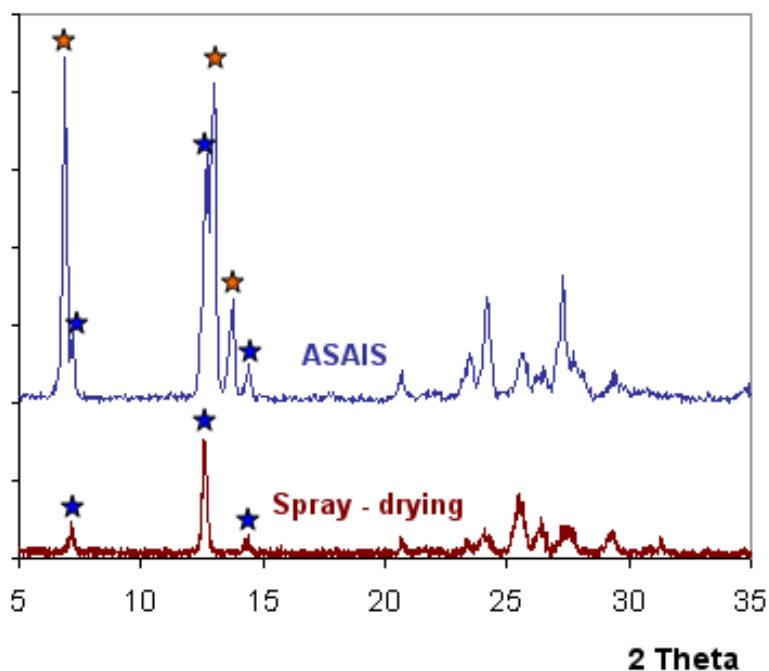
The patterns for different samples were collected on a Bruker D8 Advance powder diffractometer using Cu K $\alpha$  radiation (1.54056 Å) in Bragg Brentano geometry. The tube voltage and amperage was 40 kV and 40mA, respectively. The divergence slit and antiscattering slit settings were variable for illumination of the 20 mm sample. Each

sample was scanned with  $2\theta$  between  $5^\circ$  and  $40^\circ$  with a step size of  $0.02^\circ$  and 0.5 s at each step.

The areas of the peaks at the angles ( $2\theta$ ) 13.9 and 14.8 were measured for relative quantification analysis i.e. polymorph proportion to normal form.

## RESULTS AND DISCUSSION

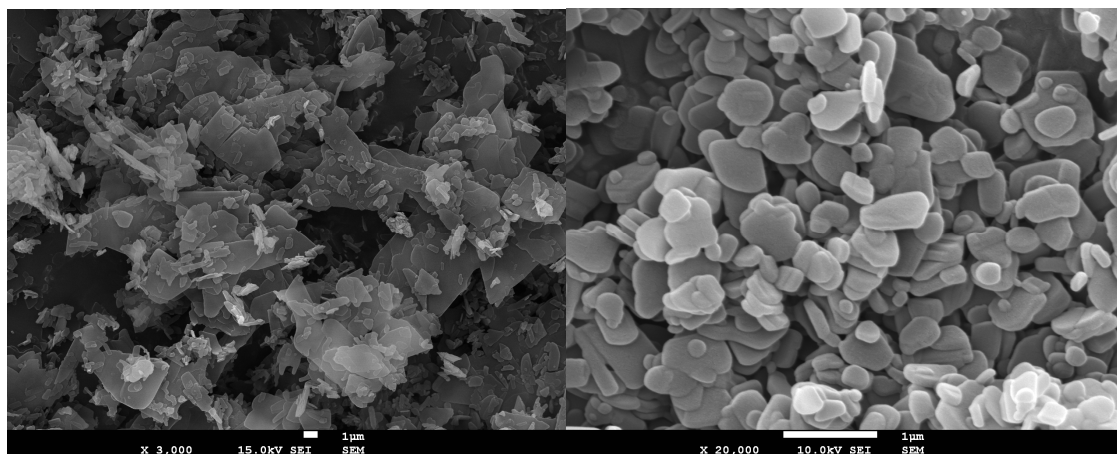
The diffractograms in Fig. 3 show the two TPL crystalline forms addressed in this work: the normal crystal form, herein obtained by spray-drying (the same form of the unprocessed TPL) and the polymorph induced by SC- $\text{CO}_2$  obtained by ASAIS. Figure 3 reveals that ASAIS was able to produce the supercritical TPL polymorph and it is therefore a continuous regime alternative to the SAS process. The PXRD of ASAIS powders reveal intense polymorph peaks (marked in Fig. 3) and more crystallinity than that produced by spray drying. The higher crystallinity may result from the larger size of ASAIS particles as Fig. 4 shows. This distinct size and morphology also evidence the fact that TPL precipitated by distinct mechanisms despite the experimental set-up and conditions were the same, at the exception of the fluid used -  $\text{N}_2$  causes spray-drying and  $\text{CO}_2$  causes ASAIS. Because  $\text{N}_2$  does not promote anti-solvent precipitation, the mechanism for particle formation is therefore a fast supersaturation by solvent extraction, while in ASAIS supersaturation happens in the liquid phase due to the dissolution  $\text{CO}_2$ .



**Figure 3** – PXRD of TPL produced by ASAIS (Run 5 in Table 1) and by spray drying. Orange and blue stars evidence respectively the polymorph and the normal TPL form.

Figure 3 also shows that the polymorph is contaminated with the normal crystalline form - this also happens in conventional SAS [6]. This dual crystallinity of TPL powders may

result from the TPL solubility in the SCF phase, which concurs with the anti-solvent effect of the SC-CO<sub>2</sub> in the liquid, as discussed below.



A

B

**Figure 4** – A: TPL polymorph produced by ASAIS (Run 5 in Table 1); B: TPL produced by spray drying.

**Table 1** – Experimental conditions used in ASAIS runs. *P*: pressure at the mixer; *C*<sub>0</sub>: TPL concentration in the THF solution; *C*: TPL concentration in the mixer; *V*: volume of the mixing chamber; *t*: flow residence time in the mixer; *R*: mass flow-rate ratio of the solution to the supercritical fluid; *Y*: ratio of diffraction area of the polymorph and normal form selected peaks.

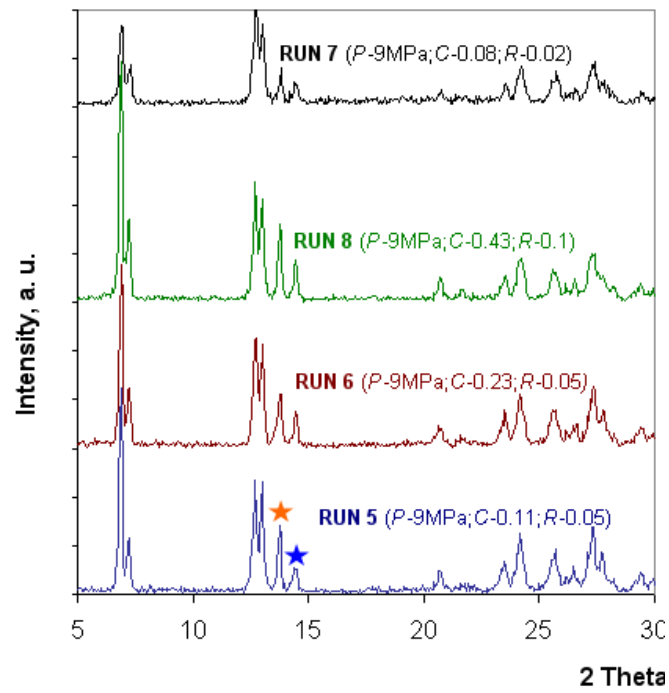
	<i>P</i> (MPa)	<i>V</i> <sub>mixer</sub> (cm <sup>3</sup> )	<i>C</i> <sub>0</sub> [TPL] mg/g	<i>C</i> [TPL] mg/g	<i>t</i> Residence time (s)	<i>R</i> <sub>flow ratio</sub> Liquid/SCF	<i>Y</i> <sub>Polymorph/normal</sub> diffraction area ratio
Run 1	15	0.9	2	0.07	1.1	0.05	0.0
Run 2	11	0.9	2	0.12	1.3	0.09	0.3
Run 3	14	0.3	1	0.02	0.4	0.02	0.0
Run 4	10	0.3	2	0.07	0.7	0.04	0.9
Run 5	9	0.3	2	0.11	0.3	0.06	2.2
Run 6	9	0.3	4	0.23	0.2	0.06	2.2
Run 7	9	0.3	4	0.08	0.2	0.02	1.3
Run 8	9	0.3	4	0.43	0.2	0.12	2.2

Several ASAIS runs were carried out to find trends that may lead to improvement of the control of the crystalline form and the purity of TPL polymorphs. The process conditions and results are summarized in Table 1. Pressure revealed to be the most important variable affecting polymorph formation. The ratio between the areas of selected characteristic peaks “Y” (signaled on Fig. 5A), shows that less polymorph is produced as pressure is increased. This is also evident comparing Fig. 5A with Fig. 5B. Figure 5A shows similar diffractograms, despite other conditions than pressure (9 MPa) were different. The increase of pressure, as in the runs of Fig. 5B, produced almost pure normal crystalline form. This can be explained by the dissolution of TPL in the supercritical phase. Johannsen and Brunner [7] reported a constant solubility (0.044 mg/g) of TPL in SC-CO<sub>2</sub> (at 313 K) in the range of 20 MPa to 30 MPa. The pressure used in this work [15 MPa] is below the values reported by Johannsen and Brunner, although, THF acts as a co-solvent improving TPL solubility. It is therefore reasonable to expect that the solubility of TPL to be of similar magnitude for 15 MPa (318 K). Increasing the pressure in the ASAIS process also increases the CO<sub>2</sub> density and the flow-rate, causing the dilution of TPL (observable in Table 1). This implies that a considerable fraction of the TPL may dissolve in the SC phase. The TPL dissolved in the SC-phase precipitates only after the depressurization – following the mechanism of the process Rapid Expansion of Supercritical Solution (RESS) – and not by the anti-solvent process.

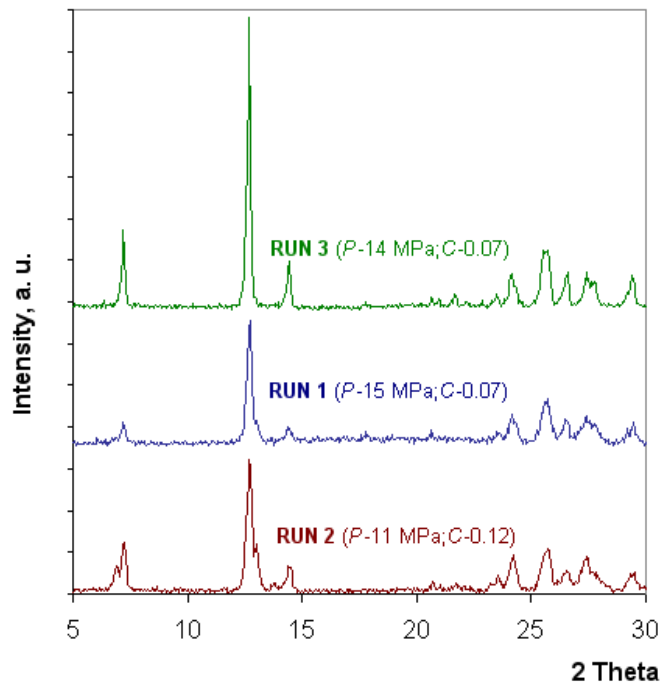
Contrarily to our observation, several authors noticed inconsistent polymorph yield with pressure using the conventional SAS process [6]. In conventional SAS the soluble fraction of theophylline does not crystallize inside the supercritical precipitator - it remains in the SC phase and it is flushed out through the filter. Thus, the TPL particles that result from the depressurization of the SC phase are not collected. In ASAIS, all substances precipitate after the atomization, because the precipitator is at normal pressure, and therefore it is difficult to compare both processes without accounting for the fraction of theophylline that is lost in conventional SAS.

Table 2 outlines a few comparative notes of ASAIS, SAS and spray-drying based on our experience in the processing of TPL in THF solutions using these processes [4, 8].

The most important feature of ASAIS is its ability to induce the polymorphism of TPL like SAS, while drying particles at normal pressure and working in continuous regime, like a spray dryer. This is achieved by using a high pressure mixing chamber before the nozzle, that is 3 orders of magnitude smaller than the SAS precipitator (as shown in Table 2). This is possible because the dimensioning of the high pressure unit in ASAIS is completely different from SAS. In SAS, the precipitator is dimensioned for complete dissolution of the organic solvent in the supercritical CO<sub>2</sub> – therefore, in the case of THF, it requires a 0.98 molar fraction of CO<sub>2</sub> (at 9 MPa 318 K). In contrast, in ASAIS the high pressure mixer is dimensioned to achieve anti-solvent composition in the liquid phase, that has been shown to be 0.4 (molar fraction of CO<sub>2</sub> in liquid) for a 5mg/g THF solution [4]. ASAIS also enables better control over the crystallization process because the crystallization time is constant - it consists in the residence time in the mixer.



**A**



**B**

**Figure 5** –PXRD of powders produced by ASAIS at different conditions. The stars refer to the peaks selected for relative-quantification; orange and blue stars mark respectively the polymorph and the normal form.



**Table 2** – Comparative notes on AS AIS, SAS and spray-drying regarding the production of TPL particles from THF solutions. The anti-solvent conditions used in AS AIS and SAS were 9 MPa, 318 K.

	AS AIS	SAS	Spray-drying
Induce polymorphism	yes	yes	no
Crystallinity	+	+	- +
Control of crystallization	++	-	-
High pressure volume per g/min of liquid solution	0.1 cm <sup>3</sup>	100 cm <sup>3</sup>	-
Particle recovery	Cyclone	Filter	Cyclone
Regime of operation	Continuous	Semi-continuous	Continuous
Gas (CO <sub>2</sub> /N <sub>2</sub> ) per g solution	20 g	50 g	20 g
Process control difficulty	++	+	-

The advantages of AS AIS come with the downside of requiring an extended understanding of the thermodynamics and kinetics of the anti-solvent process, order to achieve nucleation while limiting crystal growth below nozzle orifice dimensions, as discussed elsewhere [4].

## CONCLUSION

A typical spray-drying setup was transformed into a continuous supercritical antisolvent process – AS AIS. The AS AIS setup was able to reproduce TPL polymorph crystals reported previously by conventional SAS processing. The polymorphism of TPL is disfavored by increasing pressure due to the solubility of TPL in the supercritical phase, which counter-acts the anti-solvent effect. AS AIS hybrid nature between SAS and spray-drying confers it several advantages compared to conventional SAS. While being able to induce TPL polymorphism (as SAS), it extracts the solvent at normal pressure (discarding big high-pressure vessels) and works in continuous regime like a spray dryer. AS AIS split-up between crystallization and particle harvest also enables a better control of the crystallization, although, it requires extended knowledge of process thermodynamics and kinetics and a more demanding process control.

## ACKNOWLEDGMENTS

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