Pressure drop particle precipitation from a quasi-incompressible, ternary and liquid mixture

Mirko D’Auria\textsuperscript{a}, Miriam Willger\textsuperscript{a}, David Piña\textsuperscript{b,c}, Nora Ventosa\textsuperscript{b,c}, Andreas S. Braeuer\textsuperscript{a,1,}\textsuperscript{*}

\textsuperscript{a} Institute of Thermal-, Environmental-, and Resources’ Process Engineering (ITUN), Technische Universität Bergakademie Freiberg (TUBAF), 09599 Freiberg, Germany
\textsuperscript{b} Instituto de Ciencia de Materiales de Barcelona, ICMAB-CSIC, Campus UAB, 08193 Bellaterra, Spain
\textsuperscript{c} CIBER de Bioingeniería, Biomateriales y Nanomedicina (CIBER-BBN), Nanomol Group, Campus UAB, 08193 Bellaterra, Spain

HIGHLIGHTS

\begin{itemize}
\item Pressure drop can cause crystallization also in quasi-incompressible liquid mixtures.
\item Ibuprofen shows a pressure sensitive solubility in mixtures of water and acetone.
\item The solubility was quantified as a function of mixture composition and pressure.
\item Pressure decrease of saturated solutions results in supersaturated solutions.
\item Solubility behaviour can be exploited for the precipitation of particles.
\end{itemize}

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ABSTRACT

We found a quasi-incompressible and liquid mixture of ibuprofen, water and acetone, that enables the crystallization of ibuprofen particles by decreasing the pressure from 15MPa to ambient pressure (~0.1MPa). We measured the solubility of ibuprofen in the mixture as a function of the acetone/water-ratio for pressures of 0.1MPa, 5.5MPa and 15MPa and at 308K using the cloud point method. Based on the solubilities, binodal compositions of the ternary system were modelled using the NRTL-SAC model. The solubility of the drug in the mixture increases with increasing pressure at constant acetone/water-ratio. This pressure sensitive solubility can be exploited for the crystallization of ibuprofen particles via a pressure-drop approach. A pressure-drop from 15MPa to ambient pressure (~0.1MPa) can result in a supersaturation of up to 1.43.

1. Introduction and state of the art

The crystallization or precipitation of particles from liquid solution is one essential operation in chemical engineering processes with huge relevance for separation and purification processes in the industries of nutrition (sugar or salt) [1,2], pharmacy (drugs) [3] and electronics ((semi)-conducting nanoparticles) [4–6].

Crystallization or precipitation of particles can be initiated by (i) changing the temperature of the solution [7], such as in the case of heating or cooling crystallization [8,9], (ii) changing the composition of...
the solution [7,9–12], such as in the case of antisolvent- [13], evaporation- or reactive crystallization, (iii) changing the flow conditions [14], (iv) changing the pressure [15–18] or by a combination of several changes [19–23]. With respect to particle precipitation from solutions, attempts that make use of a pressure variation are usually inherent to solutions that feature a rather high compressibility [20,24–26]. This implies that the pressure variation has a huge influence on the specific volume, which is known to be inversely proportional to the solvation power [27]. Therefore, a pressure drop in a compressible solution results in an increase of the specific volume. This in turn, results in a decrease of the solvation power and can lead to a supersaturation of the solution. The supersaturation can be degraded by the formation of particles [21,23,28–32]. For reasons of completeness it should be mentioned here that the pressure variation also can be accompanied by a temperature drop or rise, depending on (i) the pressure level, (ii) the pressure-drop range and the (iii) depressurization path (isenthalpic, isotropic….) [33,34]. Micronization processes, in which compressed CO₂ is utilized for the modification of the viscosity [35], for assisting the atomization [36] or for cooling the system [19,37] are not further regarded here.

We here present a pressure-drop strategy for the generation of ibuprofen particles from a ternary mixture of ibuprofen, water and acetone. The compressibility of the liquid solution is rather small. A pressure-drop from 15MPa to ambient pressure results for example in a marginal increase of the specific volume of only 2%. However, the pressure-drop can drive a sub-saturated ternary solution under quasi isothermal conditions into supersaturation, where particle precipitation occurs. In order to show and proof the pressure drop strategy for the generation of ibuprofen particles, we here present solubility data of ibuprofen at 308K in the ternary system ibuprofen/water/acetone at 0.01MPa, 0.1MPa and 15MPa.

2. Experimental setup and procedure/material and methods

The materials used for the experiments were ibuprofen (Fagron, Germany, purity 99.7%), deionized water (KERNDL, conductivity <10mScm⁻¹, Germany), and acetone (Merck LiChrosolv®, purity > 99.9%, Germany). Fig. 1 shows a sketch of the high-pressure variable volume view cell (HPVVVC) with accessories, which we used for the determination of the solubility of ibuprofen in the ternary liquid mixture of ibuprofen, water and acetone. This HPVVVC is equipped with four quartz glass windows that allow the visual observation of the system and a double-wall heating or cooling jacket which allows temperature conditioning of the ternary mixture inside. The internal volume of the HPVVVC can be adjusted between 30 and 60mL, depending on the penetration depth of the piston. The current penetration depth of the piston can be read from the number of thread pitches. The temperature inside the HPVVVC is measured with a PT100 resistance thermometer class AA with a resolution of 0.05K. A pressure sensor type PAA – 3XXX from Keller with a precision of 0.01MPa (according to manufacturer specification) indicates the pressure.

2.1. Cloud point method

The solubility of ibuprofen in the ternary mixture of ibuprofen, water and acetone was measured isothermally at 308K, isobarically at various pressures of ambient pressure (0.1MPa), 0.5MPa and 15MPa and determined via the cloud point method [38,39]. The volume of the cell is set to 35mL. Before the addition of the ibuprofen/acetone solution, the cell contains air. The cell is completely filled with the initial binary solution of acetone and ibuprofen through a valve V (Fig. 1). The added solution displaces all the air through a third valve, which is connected to the very top of the volume of the cell and which is not shown in Fig. 1. As soon as the cell is filled, the valve V to the syringe and the air-release valve are closed. The known amount of liquid inside the HPVVVC is continuously agitated with a magnetic fish stirrer. The magnetic bar rotates with ~350 rotations per minute. The desired pressure is adjusted by driving the piston into the chamber. Then the syringe pump (model 260D from Teledyne, Lincol, NE) containing the water is operated in a constant pressure mode at exactly the pressure of the HPVVVC and the valve between both devices is opened. Water is fed in incremental amounts in an isobaric and isothermal manner by increasing step by step the internal volume of the HPVVVC by rotating the shaft that drives the moveable piston. The amount of water fed into the HPVVVC can be read from the indication panel of the syringe pumps as the difference between the amount of substance contained inside the syringe pump before and after the feeding process.

After the addition of each incremental amount of water, the turbidity of the system is checked. The experiment stops when the mixture turns permanently cloudy. The solubility point represents the composition of the system at which - after the addition of another small incremental amount of water – the system for the last time was transparent. The following addition of a small incremental amount of water turned the stirred system at the set pressure permanently turbid (cloudy). Turbidity is caused by the precipitated particles. The precipitated particles settle at the bottom of the chamber once agitation is stopped. Each experiment was triplicated in order to test its reproducibility.

2.2. NRTL-SAC model

The Non-random Two-Liquid Segment Activity Coefficient (NRTL-SAC) model [40,41] was applied to fit the solubility data. According to
the literature, this model is suitable for predicting drug solubility in mixtures of solvents. Nevertheless, it cannot reflect the influence of pressure, as it does not contain pressure sensitive parameters. As a consequence, the parameters have to be fitted for each pressure separately and are only applicable for this respective one.

In the NRTL-SAC model applied in this study, each compound is composed of potentially four segments; one hydrophobic segment X, one hydrophilic segment Z, one polar attractive segment Y- and one polar repulsive segment Y+. In our specific case, there would be four segments for the compound water, four segments for the compound acetone and four segments for the compound ibuprofen. Unlike in the common NRTL-model, not the compounds interact with each other, but the segments interact with each other. Chen and Song [42] built the NRTL-SAC model on constant segment-specific binary NRTL segment interaction parameters \( \gamma_{\text{segment1}, \text{segment2}} \) which we show in Table 1.

According to Table 1 the segment interaction parameters \( \gamma_{\text{segment1}, \text{segment2}} \) on depend only on the interacting segments, not on the molecules the segments are assigned to. In other words and giving an example, the interaction parameters for the interaction between the Z-segment of water and the X-segment of acetone and between the Z-segment of water and the X-segment of ibuprofen are identical. Finally, it has to be addressed, which segment (X, Z, Y+, Y-) contributes to which extend to the molecule of the compound. The relevance of one of these segments to the molecule is represented by the so called “segment number”. The segment numbers for the compounds water and acetone are taken from [40] and are listed in Table 2.

Table 2 shows for example that the hydrophilic liquid water can be represented by only one Z-segment. For the representation of the acetone, three segment types are required. The summation of the four segment numbers in one compound can be non-unity. The segment numbers can be derived for each molecule as fit-parameter in the NRTL-SAC model from vapour-liquid-equilibria, from liquid-liquid-equilibria or from solid-liquid-equilibria of mixtures. Though they are derived from mixtures, they are molecular properties and do not rely on the other mixture constituents. In other words, the segment numbers of acetone do not depend on whether acetone is in a mixture with water or with ibuprofen. Now the charm of the NRTL-SAC model compared to the NRTL model becomes obvious. For the NRTL model one would need the binary interaction parameters \( r \) and \( a \) for the binary systems water/acetone, water/ibuprofen and acetone/ibuprofen. For the NRTL-SAC model the binary segment interaction parameters are all known from Table 1 and also the segment numbers are known for water and acetone from Table 2. Therefore, the segment numbers for ibuprofen are the only unknown parameters. We used them as fit-parameters in order to be able to replicate the experimentally measured solubility data of ibuprofen in the ternary mixtures of ibuprofen, acetone and water with the NRTL-SAC model derived activity coefficients. The fitting was accomplished using the Aspen Solubility Modeler, a specific tool in Aspen. It mathematically minimizes the deviation between the experimentally measured binodal compositions and the modelled binodal compositions using the activity coefficients computed via the NRTL-SAC model. It is assumed that the precipitated solid phase is pure ibuprofen featuring an ibuprofen activity of unity.

3. Result and discussion

Fig. 2 quantifies the solubility of ibuprofen in the ternary mixture for three pressures and at 308 K. In this rectangular diagram the compositions of the binary mixtures (ibuprofen and acetone) fed into the HPVVVC before the addition of water correspond to the left ordinate where \( x_{\text{water}} = 0 \). The saturation ibuprofen fraction in acetone at 308K is \( x_{\text{IBU}}^{\text{sat}} = 0.311 \) [43] and is indicated in Fig. 2 as Asterix. We measured the same value with respect to the first two decimals. When water is added to the mixture, the molar fraction of ibuprofen \( x_{\text{IBU}} \) decreases in the mixture while \( x_{\text{Water}} \) increases, until after the addition of an infinite amount of water the entire mixture is quasi pure water. Then \( x_{\text{IBU}} \to 0 \) and \( x_{\text{Water}} \to 1 \). Therefore, the grey dashed lines represent the overall composition of the mixture inside the HPVVVC along the mixing path during the dilution with water, irrespectively of whether it is still a single homogeneous liquid phase or a dispersion containing already precipitated ibuprofen particles. The starting points of the various grey dashed mixing-path-lines at \( x_{\text{Water}} = 0 \) are chosen arbitrarily. The cloud-point experiments are conducted along such mixing-path lines (see previous section). As long as during the addition of the water the saturation fraction exceeds the overall ibuprofen fraction, the mixture remains transparent. Once the saturation fraction is reduced below the overall ibuprofen fraction, the mixture gets cloudy due to the formation of particles. The data points in Fig. 2 represent the measured ibuprofen saturation molar fractions \( x_{\text{IBU}}^{\text{sat}} \).

One can see that for water molar fractions \( x_{\text{Water}} < 0.4 \) the saturation molar fraction of ibuprofen \( x_{\text{IBU}}^{\text{sat}} \) are above the grey dashed mixing-path-line starting as saturated ibuprofen/acetone solution \( x_{\text{IBU}} = 0.31 \) & \( x_{\text{Water}} = 0 \). On the contrary, for water molar fractions \( x_{\text{Water}} > 0.4 \) the saturation molar fraction of ibuprofen \( x_{\text{IBU}}^{\text{sat}} \) are below the grey dashed mixing-path-line starting as saturated ibuprofen/acetone solution \( x_{\text{IBU}} = 0.31 \) & \( x_{\text{Water}} = 0 \). We therefore conclude that water acts as a co-solvent for \( x_{\text{Water}} < 0.4 \) and as an antisolvent for \( x_{\text{Water}} > 0.4 \) [44]. The error bars in the rectangular diagram in Fig. 2 represent the standard deviation after the triplication of the experiments.

According to the experimental results, the solubility of ibuprofen increases with increasing pressure. For water molar fractions between \( x_{\text{Water}} = 0.35 \) and \( x_{\text{Water}} = 0.50 \) the solubility of ibuprofen features the highest sensitivity with respect to pressure (Fig. 2).

Fig. 3 shows the experimentally determined solubility points in a ternary Gibbs diagram as data points. Additionally, we included the binodal composition curves which we modelled based on the experimental data using the NRTL-SAC model derived activity coefficients. The segment numbers we used for acetone and water irrespectively of pressure are tabulated in Table 2. In order to being able to reflect the pressure sensitive solubility behaviour of ibuprofen in the ternary

Table 1
Binary NRTL segment interaction parameters (from [42]).

| \( \gamma_{\text{X}, \text{Y}} \) | \( \gamma_{\text{X}, \text{Z}} \) | \( \gamma_{\text{Y}, \text{Z}} \) |
|-----------------------|-----------------------|-----------------------|
| 1.643                 | 6.547                 | 2.000                 |
| 1.834                 | 10.949                | 0.35 Water            |
| \( \alpha_{\text{X}, \text{Y}} \) | \( \alpha_{\text{X}, \text{Z}} \) | \( \alpha_{\text{Y}, \text{Z}} \) |
| 0.2                   | 0.2                   | 0.2                   |

Table 2
Segment numbers for the compounds acetone and water (from [40]).

| Segment numbers for water | Segment numbers for acetone |
|---------------------------|-----------------------------|
| \( r_{\text{X}, \text{Water}} \) | \( r_{\text{X}, \text{Acetone}} \) |
| 0.131                     | 0.109                       |
| \( r_{\text{Y}, \text{Water}} \) | \( r_{\text{Y}, \text{Acetone}} \) |
| 0                         | 0.513                       |
| \( r_{\text{Z}, \text{Water}} \) | \( r_{\text{Z}, \text{Acetone}} \) |
| 1                         | 0                           |
mixture, we fitted the segment numbers for ibuprofen for each pressure separately. The obtained segment numbers are tabulated in Table 3.

Below the binodal curve the system is heterogeneous. Above the binodal curve the system is homogeneous, it features a single liquid phase and it is transparent. For example, it can be seen that the point A represents a mixture that at 15MPa is stable, because the point A is above the binodal curve at this pressure. After a depressurization to 0.1MPa, point A is below the 0.1MPa binodal and thus occupies the two-phase region where ibuprofen precipitates.

Fig. 2. Solubility of ibuprofen in the mixture of ibuprofen, water and acetone at 308K and at three different pressures in a rectangular diagram. The error bars represent the standard deviation of the triplication of the experiments. The saturation molar fraction of ibuprofen in the binary ibuprofen/acetone mixture is provided as Asterix.

Table 3
NRTL-SAC parameters X (hydrophobic segment), Y− (polar-attractive segment), Y+ (polar-repulsive segment) and Z (hydrophilic segment) for ibuprofen at three different pressures obtained with data regression of experimental solubility values via Aspen solubility modeler at 308K.

| p/MPa | X_{Ibu} | Y_{Ibu}^- | Y_{Ibu}^+ | Z_{Ibu} |
|-------|---------|-----------|-----------|---------|
| 0.1   | 0.8844  | 0.0314    | 0         | 0       |
| 5.5   | 0.8596  | 0.0339    | 0         | 0       |
| 15.0  | 0.8686  | 0.0484    | 0         | 0       |

Fig. 3. Solubility in a ternary diagram of the mixture ibuprofen, water and acetone at 308K at three different pressures, including the measured solubilities (in dots) and the computed binodal curves using the NRTL-SAC model.
Fig. 4 shows the degree of supersaturation

\[ S = \frac{x_{\text{IBU}}(15 \text{ MPa})}{x_{\text{IBU}}(0.1 \text{ MPa})} \]  

(1)

defined as the ratio between the solubility at 15 MPa and at 0.1 MPa over the molar fraction of water. The values taken for \( x_{\text{IBU}} \) are the solubility data modelled along the binodal composition curves. In other words, the supersaturation is computed as the ratio of the green 15 MPa binodal and the black 0.1 MPa binodal in Fig. 3.

According to Fig. 4, a pressure-drop from 15 MPa to 0.1 MPa can result in degrees of supersaturation up to \( S \approx 1.43 \) at \( x_{\text{Water}} \approx 0.45 \). Anticipating that the solubility of ibuprofen in the ternary system increases with pressure also for pressures above 15 MPa, even larger degrees of supersaturation can be expected when the pressure drop is realized from a solution saturated at larger pressures down to ambient pressure.

Fig. 5 shows two photographs of the same ternary mixture (\( x_{\text{IBU}} = 0.07, \ x_{\text{Water}} = 0.55 \)) and \( x_{\text{Acetone}} = 0.38 \), on the left side as turbid system at 0.1 MPa and at the right side as transparent system at 15.0 MPa. From Fig. 4 it can be extracted that a pressure-drop of a saturated solution from 15 MPa to 0.1 MPa at \( x_{\text{Water}} = 0.55 \) will result in a supersaturation of \( S \approx 1.2 \). The pressure-increase from 0.1 MPa (Fig. 5 left) to 15.0 MPa (Fig. 5 right) is achieved by decreasing the volume of the mixture from 35 mL to 34.3 mL, which corresponds to a relative volume decrease of only \( \sim 2\% \). Therefore, we consider the mixture as rather incompressible. For changing the volume from 35 mL to 34.3 mL and vice versa, the rotating shaft that drives the piston either into or out of the HPVVVC has to be rotated by only half of a complete rotation. As a consequence, one can switch between the high-pressure and the low-pressure level quasi instantaneously.

As pressure perturbations propagate with the speed of sound through the system, the pressure within the system can be assumed to be instantaneously changed with the volume change and homogeneously distributed all over the solution.

Due to the low compressibility of the system, neither the pressurization from 0.1 MPa to 15 MPa nor the depressurization from 15 MPa to ambient pressure requires or releases large amounts of energy.

We replicated the pressure-drop particle precipitation experiment, which we have shown in Fig. 5 in the Freiberg (Germany) HPVVVC, another time in the Barcelona (Spain) HPVVVC, which has different

![Fig. 4. Degree of supersaturation obtainable for a depressurization from 15 MPa to 0.1 MPa as function of the water fraction \( x_{\text{Water}} \).](image)

![Fig. 5. Ternary system ibuprofen \( x_{\text{IBU}} = 0.07 \), water \( x_{\text{Water}} = 0.55 \) and acetone \( x_{\text{Acetone}} = 0.38 \) at 308K and ambient pressure on the left side and after isothermal pressurization to 15MPa the right side within the high-pressure variable volume view cell (HPVVVC).](image)
dimensions (for details see [45]). We adjusted the same mixture composition, the same temperature and we also varied the pressure between 15MPa and 0.1MPa. The system in Barcelona showed the same behaviour, being transparent at 15MPa and being turbid at 0.1 MPa.

Furthermore, we repeated the pressure-drop experiment with mixtures that are sub-saturated at both pressures, 15MPa and 0.1MPa. As expected, the mixtures remained transparent at both pressures.

4. Prospect on a potential process

A potential process that puts the pressure drop particle precipitation concept into practise is shown superficially in Fig. 6. The process is separated into a low-pressure and a high-pressure section. The solvent is pressurized through a pump from the low-pressure section to the high pressure section. The pressurized solvent dissolves the solute when it passes through the saturator and turns to a saturated solution. The solution moves from the high-pressure section through a throttle to the low pressure section and becomes a suspension. Particles are formed as a consequence of the sudden pressure drop. The precipitating particles are filtered from the suspension. The permeate is then pressurized again through the pump.

5. Conclusions

Within this work we showed the pressure dependence of ibuprofen solubility in the ternary system composed of ibuprofen, water and acetone. We found this system and its pressure-response by serendipity. Yet we do not know, why the pressure-drop particle precipitation works with the ternary system ibuprofen/acetone/water. This also explains why we currently cannot forecast for which alternative solutes or alternative organic solvents it might work, too. So far, we also have not yet characterized the emerging particles, as we had severe difficulties separating them from the suspension using filters. The particles either blocked the filter immediately or simply passed through it. Most probably, in situ particle characterization methods can help characterize the produced particles and their long-term stability.

We have to admit that the mixture composition \((x_{\text{Ibu}} = 0.07, x_{\text{Wate}} = 0.55\) and \(x_{\text{Ace}} = 0.38\)) we considered in Fig. 5 for demonstrating the pressure-drop particle precipitation potential of such systems is not chosen ideally. We nevertheless show this pressure-drop particle precipitation potential for this composition, as exactly this mixture composition by serendipity draw our attention onto the pressure sensitive solubility behaviour of ibuprofen in mixtures of ibuprofen, acetone and water. Fig. 4 shows that the maximum achievable supersaturation for \(x_{\text{Wate}} = 0.55\) and a pressure-drop from 15MPa and 0.1MPa is approximately 1.2. The maximum supersaturation of 1.43 can be achieved when making the pressure-drop experiment with a mixture of the following composition \(x_{\text{Ibu}} = 0.17, x_{\text{Wate}} = 0.45\) and \(x_{\text{Ace}} = 0.38\).

The aim of the work involved the description of the ternary system with the characterization of the solubility and the stability of the above-mentioned system for accessing of a potential pressure drop particle generation strategy.

In fact, the idea of a pressure-drop induced particle-generation-process can be advantageous due to the low compressibility of the system. Neither the pressurization nor the depressurization from 15 MPa (or higher pressures) to ambient pressure requires or releases large amounts of energy. Furthermore, and depending on the starting conditions at the high-pressure level, the system can be on purpose driven to different degrees of supersaturation. This might probably influence the polymorphisms, polymorph or particle size distribution of the precipitated particles and will be subject of future investigations.

Declaration of Competing Interest

The authors declare no competing financial interest.

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References

[1] A.M. Umo, S.B. Alabi, Advances in super-saturation measurement and estimation methods for sugar crystallisation process, Int. J. Food Eng. 2 (2016) 108–112, https://doi.org/10.18178/ijfe.2.2.108-112
[2] M.T. Gomes, Á.L. Santana, D.T. Santos, M.A.A. Meireles, Trends on the rapid expansion of supercritical solutions process applied to food and non-food industries, Recent Pat. Food, Nutr. Agric. 10 (2019) 82–92, https://doi.org/10.2174/2212798410666180925160459
[3] D. Zhang, S. Xu, S. Du, J. Wang, J. Gong, Progress of pharmaceutical continuous crystallization, Engineering 3 (2017) 354–364, https://doi.org/10.1016/J.ENG.2017.03.023
[4] A. Merzmann, Crystallization Technology Handbook, CRC Press, 2001.
[5] J.W. Mullin, Crystallization, Butterworth-Heinemann, 2001.
[6] Y.-P. Sun, R. Guduru, F. Lin, T. Whiteside, Preparation of nanoscale semiconductors through the rapid expansion of supercritical solution (RESS) into liquid solution, Ind. Eng. Chem. Res. 39 (2000) 4663–4669, https://doi.org/10.1021/ie9901114
[7] K. Sattler, Thermische Trennverfahren: Grundlagen, Auslegung, Apparate, 3rd ed., VCH, Weinheim, Chichester, 2001.
[8] N. Sanzida, Z.K. Nagy, Strategic evaluation of different direct nucleation control approaches for controlling batch cooling crystallisation via simulation and experimental case studies, Comput. Chem. Eng. 130 (2019) 106559, https://doi.org/10.1016/j.compchemeng.2019.106559
[9] O.L. Watson, A. Galindo, G. Jackson, C.S. Adjiman, Computer-aided Design of Solvent Blends for the Cooling and Anti-solvent Crystallisation of Ibuprofen, 29th European Symposium on Computer Aided Process Engineering, Elsevier, Amsterdam, 2019, pp. 949–954.
[10] U. Fritsching, Process-Spray: Functional Particles Produced in Spray Processes, Springer International Publishing, Cham, 2016.
[11] P.M. Gallagher, M.P. Coffey, V.J. Krukonis, N. Klasutis, Gas antisolvent recrystallization: new process to recrystallize compounds insoluble in supercritical fluids, in: K.P. Johnston, J.M.L. Penninger (Eds.), Supercritical Fluid Science and Technology, 1989.
A. Martín, M.J. Cocero, Numerical modeling of jet hydrodynamics, mass transfer, and crystallization kinetics in the supercritical antisolvent (SAS) process, J. Supercri. Fluid 52 (2004) 203–219, https://doi.org/10.1016/j.supflu.2004.02.009

T. Jaouhari, F. Zhang, T. Tassaing, S. Fery-Forgues, C. Aymonier, S. Marre, A. Erriguible, Process intensification for the synthesis of ultra-small organic nanoparticles with supercritical CO₂ in a microfluidic system, Chem. Eng. J. 397 (2020) 125333, https://doi.org/10.1016/j.cej.2020.125333

G.J. Dunderdale, S.J. Davidson, A.J. Ryan, O.O. Mykhaylyk, Flow-induced crystallization of polymers from aqueous solution, Nat. Commun. 11 (2020) 3372, https://doi.org/10.1038/s41467-020-17167-8

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