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Mean Aspects Controlling Supercritical CO₂ Precipitation Processes

*Antonio Montes, Clara Pereyra
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Abstract

The use of supercritical CO₂ is an excellent alternative in extraction, particle precipitation, impregnation and reaction processes due to its special properties. Solubility of the compound in supercritical CO₂ drives the precipitation process in different ways. In supercritical antisolvent process, mass and heat transfers, phase equilibria, nucleation, and growth of the compound to be precipitated are the main phenomena that should be taken into account. Mass transfer conditions the morphology and particle size of the final product. This transfer could be tuned altering operating conditions. Heat transfer in non-isothermal process influences on mixing step the size of generated microparticles. In rapid expansion of supercritical solution, phenomena as the phase change from supercritical to a CO₂ gas flow, rapid mass transfer and crystallization of the compound, and expansion jet define the morphology and size of the final product. These phenomena a priori could be modulated tuning a large number of operating parameters through the experiments, but the correlations and modeling of these processes are necessary to clarify the relative importance of each one. Moreover, particle agglomeration in the expansion jet and CO₂ condensation are determinant phenomena which should be avoided in order to conserve fine particles in the final product.

Keywords: supercritical, antisolvent, rapid expansion, particle, super saturation

1. Introduction

Nowadays, particle formation technology is continuously finding out how to solve the problems that conventional crystallization finds as residues of organic solvent in final product, thermal and chemical solute degradation, heterogeneous batches, and difficult to control the particle size distribution [1]. These problems are essential and must be overcome in pharmaceutical, cosmetic, and food industries. Controlling thermodynamic and kinetic factors together with mass and heat transfer and nucleation and growth of crystal is the key to carry out successfully the crystallization phenomena. Moreover, these forces interplay between them making it difficult to establish trends about it. Anyway, supercritical fluid technology tends to reduce or remove most of the drawbacks previously cited, so active substance with controlled particle size distribution in the micro- and nanometer range and quite stable is achieved. Solvent power and selectivity of supercritical fluids can be

tuned altering the experimental conditions. Moreover, their large diffusivities result in higher mass transfer rates.

There are two main particle formation processes using supercritical fluids: rapid expansion of supercritical solution (RESS) and supercritical antisolvent (SAS) processes. The high or low solubility of the active substance in the supercritical fluid will determinate the choice between one and another process.

Numerous investigations in particle formation with supercritical fluids have been carried out to shed light the parameter to govern the crystallization mechanism using CO₂ as antisolvent (SAS) [2–15] or as solvent (RESS) [16–28].

The SAS process consists of spraying a solution of the solute to be precipitated into the vessel that contains the bulk supercritical fluid. Then, there is a rapid solubilization of supercritical fluid into the solvent causing its volumetric expansion and thus reducing the solvation capacity of the solvent. This fact causes the supersaturation of the liquid phase and the consequent generation of the particles. Thus, mass transfer of the process seems to be a key factor affecting particle morphology [29].

SAS technique has been investigated using solutes in a wide range of industrial fields with applications as polymers [30, 31], explosives [32], pharmaceutical compounds [2, 3], superconductors [33], catalysts [34], coloring matter [35], and functional food [6, 7], among others. On the other hand, the application of RESS technique has been enclosed to pharmaceutical field [19–27].

Once SAS process involves the interaction of several phenomena as thermodynamics, mass transfer, jet hydrodynamics, and nucleation kinetics, it is difficult to isolate one of them as responsible for a particle feature trend [36]. Anyway, the mass transfer which occurs between a droplet of organic solvent and a compressed antisolvent is a crucial step of the process especially below mixture critical point in partially miscible conditions. It is well known that in miscible conditions, above mixture critical point, there is no obvious way to define the interface between the two fluids. However, Dukhin et al. have evidenced the existence of a dynamic interfacial tension to the transient existence of droplets at conditions slightly above the mixture critical point (MCP) [37].

Particle size and morphology are influenced by the antisolvent-solvent mass transfer ruled by diffusion process and by the jet breakup, although it seems that the first phenomenon has often more importance [38, 39] in isothermal mixing.

Heat transfer should also be taken into account in this kind of process due to the temperature can be an effective parameter to modulate the lifetimes of the droplets [40]. Thus, there is another way to change the mixing time without pressure and temperature modifications, if the process occurs in non-isothermal conditions. The mixing time will increase if a colder solution is immersed into a warmer CO₂ and will decrease if a warmer solution is immersed in colder CO₂ [40]. Thus, size of microparticles could be tuned.

On the other hand, RESS process takes advantage of the solubility of the solute to be precipitated into supercritical fluids. In this case the supercritical solution, CO₂ plus solute, is rapidly depressurized to atmospheric pressure through a nozzle, thus causing the precipitation, extremely fast, of the solute.

With regard to RESS process, nucleation, condensation, and coagulation models for crystallization of solute have been explored [41–44]. In order to evaluate these models, it is crucial to predict the thermophysical properties and flow characteristics in the nozzle, where supercritical solution comes from the nozzle inlet to the outlet of the expansion chamber [45].

In the work SAS and RESS processes are described making incidence on the main aspects which should be controlled to get a successful precipitation of fine particles.

2. Supercritical CO₂

A supercritical fluid is defined as whatever substance above its critical temperature and pressure. In **Figure 1** a typical pressure-temperature phase diagram is shown where a singular region is shaded. Supercritical fluids have special properties as solvent power similar to liquids, but diffusivities two orders of magnitude larger than those of typical liquids, resulting in higher mass transfer rates. Moreover, solvent power and selectivity can be tuned with the modification of the density of this fluid. This one can be adjusted continuously by altering the experimental conditions of temperature and pressure.

Singularities in compressibility and viscosity, diminishing difference in liquid and vapor phases, are other exceptional characteristics that are present in this state.

CO₂ is the fluid more used in supercritical conditions due to its low danger and relative low cost. CO₂ is a solvent generally recognized as safe (GRAS), non-flammable, non-toxic, gaseous at room temperature, and easily removed from the process. Moreover, it presents relative mild conditions of its critical point (31.1°C and 71.8 bar) permitting the processing of thermolabile solutes which are primordial in pharmaceutical, cosmetic, and functional food industries.

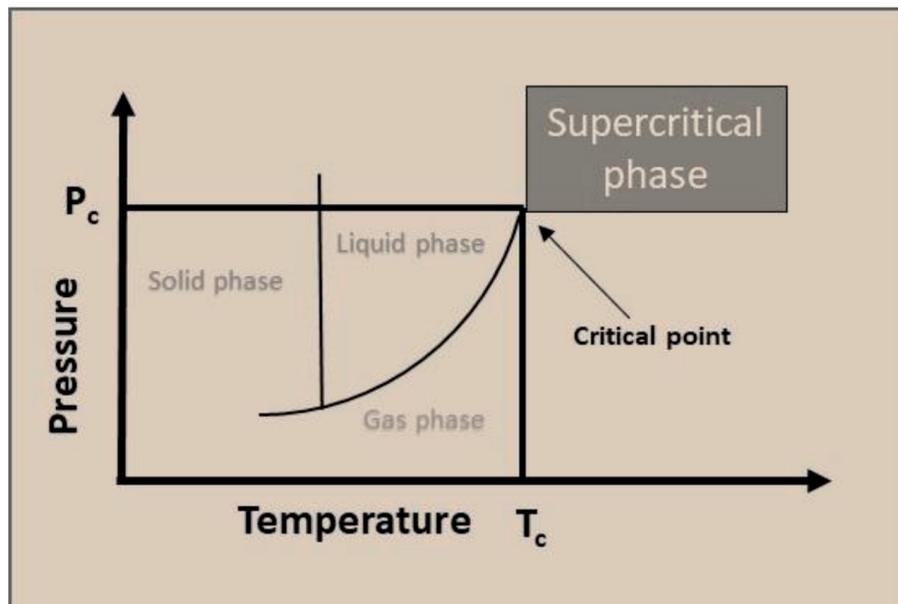


Figure 1.
Pressure-temperature phase diagram.

3. Supercritical antisolvent process

In SAS process an organic solution of the solute is sprayed through a micrometric nozzle to improve the mass transfer between CO₂ and the microdroplets of solution. CO₂ is solubilized into organic solvent and vice versa in lower degree causing a volumetric expansion of the solvent and a super saturation of the solution and the consequent precipitation.

The substances which can be processed by this technique must fulfill two main requirements: (1) It must be not soluble in supercritical CO₂ and (2) must be soluble in an organic solvent that is miscible with supercritical CO₂.

Most of the active ingredients and added value substances are not soluble in supercritical CO₂. So, the main problem is finding out the appropriate solvent to be used in the process. In **Figure 2** a scheme of the process is shown.

In a typical experiment of SAS process, CO₂ is cooled to 5°C (HE1) and posteriorly pumped by a high-pressure pump (P1) to a precipitation vessel (V). CO₂ flow rate is controlled by a Coriolis flowmeter (FM). The stream of CO₂ is heated (HE2) at the required set point. The pressure level is held with the aid of automated back pressure regulator (ABPR). The system works in a semicontinuous way, so until the operating conditions are not reached in this vessel, the organic solution is not pumped to the vessel by a solution pump (P2). This solution is put into the vessel through a nozzle with hundreds of microns to improve the mass transfer. Then, two opposed processes happen in different degrees. CO₂ is solubilized into the solvent, and solvent is evaporated into the bulk CO₂. Anyway, simulations of some systems have shown that absorption of CO₂ into the liquid phase is always faster than solvent evaporation and, consequently, the produced microdroplets swell as soon as they get into contact with CO₂ [46]. Then, CO₂ is rapidly solubilized into the small droplets of the solution provoking the loss of solvation power of solvent and generating a supersaturation of the solution and the consequent precipitation of solute in the form of micro- or even nanoparticles. CO₂ and solvent are posteriorly separated in a cyclone (CS) venting out the CO₂ for the top and collecting the liquid for the bottom. CO₂ is continuously flowing for a time, called washing time, to ensure no solvent is present into the vessel when depressurization is carried out and could redissolved into the precipitate particles.

Mass transfer, described by Fick's law, of the process will be conditioned by the situation of operating conditions on the phase equilibrium diagram solvent-solute-CO₂, thus affecting on the size and morphology of the precipitated particles. In this sense, a pseudobinary diagram (Figure 3) instead of ternary diagram often is considered by authors due to the solute having low solubility in the mixture supercritical CO₂ plus solvent, so the equilibrium would not be altered. Pressure and temperature define the situation with regard to mixture critical point (MCP). But if the concentration of the solution is high, the solute-solvent-interaction could increase significantly MCP to higher values [47]. In this sense programmed experiments above MCP (Figure 3(2)) could be in subcritical conditions as experiments

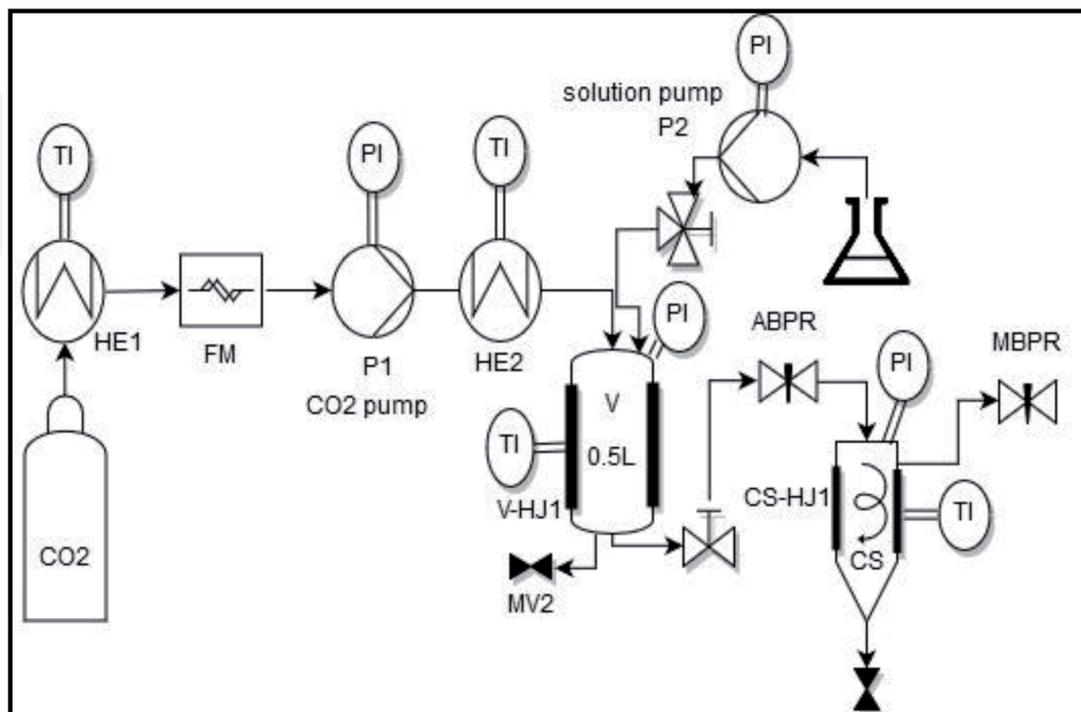


Figure 2.
Scheme of SAS process.

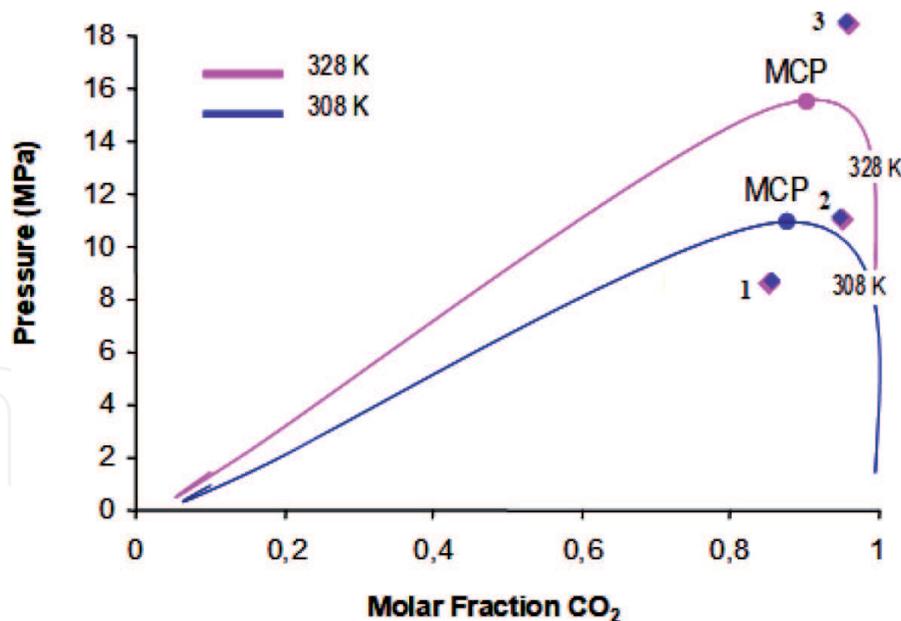


Figure 3.
Phase equilibrium diagram.

designed below mixture critical point CO₂-organic solvent where interfacial tension exists (**Figure 3(1)**). However, far above MCP (**Figure 3(3)**), there will be no interfacial tension in the system solvent-CO₂ when the sprayed solution is in contact with the bulk supercritical CO₂.

To understand this fact, kinetic and hydrodynamic factors should be taken into account. Injected solution has a surface tension as a liquid, but the vanishing of this tension solvent-CO₂ is faster than the breakup jet, so there is no interfacial tension when the solution finds bulk supercritical CO₂ at hard conditions. When supercritical CO₂ is slight above MCP (**Figure 3(2)**), there is a residual surface tension at the moment to be immersed into the bulk CO₂, so mass transfer is lower and microparticles are generated. In this case droplet lifetime is the key to observe difference in morphology and particle size of the precipitates. In this region operating conditions could be tuned to influence mass transfer. As a rule, an increase of pressure leads to a decrease of droplet lifetimes [40], so smaller particles would be precipitated. On the other hand, droplets could swell or shrink depending on the difference in density and diffusivity between the two phases [36] so that droplets shrink when the solvent's mass density is lower than those of the bulk CO₂ and swell when the CO₂ density is lower.

Not only pressure but also temperature modifies sensibly the density, so combination of pressure and temperature is an effective tool to modify the droplet lifetimes [40]. Temperature even has more influence than pressure near the MCP (**Figure 3(2)**). In this sense, the diffusion coefficients are quite sensitive to temperature, and their increase would also accelerate the transfer.

Since an increase of pressure seems to lead to a shorter droplet lifetime as a general rule, an increase of temperature might have opposite effects depending on the pressure range and the chosen solvent. For instance, using acetone or ethanol, the lifetimes will be short at relatively low pressure and larger at higher pressure [40].

On the other hand, heat transfer should be taken into account due to the solvent droplet is often immersed in bulk supercritical CO₂ at a different temperature. In non-isothermal conditions the temperature gradient can be an additional tool to tune the droplet lifetime. Thus, the immersion of colder solvent in warmer CO₂ permits to increase the mixing time that is less interesting for crystal production. In this case low supersaturation ratio can be generated by the injection of colder solution than

CO₂ due to often solubility of compounds increasing with temperature [40]. This fact merged to the less concentration of the solution that leads to larger particles. On the contrary, a warmer solvent immersed in colder CO₂ accelerates the mixing process. Thus, high supersaturation ratio can be achieved, so smaller particle size of the precipitated is generated. An additional advantage is the opportunity to inject solutions more concentrated that come in addition to the crystallization by antisolvent [40].

Mass transfer kinetics are also influenced by hydrodynamic aspect, particularly, the disintegration mode of the liquid jet into the supercritical bulk fluid. There are several main modes of disintegration that affect to mass transfer. In the dripping mode, droplets are formed in the outlet of the nozzle as consequences of lower flow rates and/or higher nozzle diameters. A laminar mode where the jet is continuous at the outlet of the nozzle device and the rupture jet is produced as monodisperse droplets symmetrically or asymmetrically. In the first one called axisymmetric mode, the breakup is produced by axially symmetric disturbances. In the asymmetrical mode, the breakup is caused by disturbances that are symmetrical about a helical axis that starts at the nozzle orifice. Then, atomization mode is achieved when the jet leaves the nozzle smoothly till the zone of highly chaotic rupture is reached. In this case a cone of atomized liquid is formed improving the mass transfer. It is possible to tune the process toward one or another mode acting on the critical atomization velocity, which is the velocity corresponding to the boundary between the asymmetrical and the atomization modes. The critical atomization velocity depends on the liquid solution flow rate and the nozzle device. Liquid solution flow rate depends in turn on viscosity and surface tension of solvent. As a general rule, relative higher flow rate and smaller nozzle diameter are recommended to achieve atomization mode.

Not only the nozzle diameter but also the length or the geometry have been evaluated in order to improve the mass transfer of the process achieving the critical atomization velocity [48, 49]. Even the nozzle relative position to CO₂ inlet modifies the mass transfer due to influences on hydrodynamics and mixing between solution and CO₂. For instance, if CO₂ is injected through the annulus, the fluid that diffuses into the jet does not have organic solvent residues increasing the supersaturation, and smaller particles are generated [50]. Modification of SAS process has been carried out to improve the mixing. In this sense solution-enhanced dispersion by supercritical fluid (SEDS) process uses a coaxial nozzle to introduce the supercritical fluid antisolvent and solution [51, 52].

4. Rapid expansion of supercritical solution process

This technique is appropriated when the active substance is soluble in supercritical fluid. In this case a supercritical solution is formed and then is expanded through a nozzle to ambient pressure provoking the fast supersaturation and the precipitation in form of nano- or microparticles. Nozzle must be thermostated due to the expansion from supercritical to ambient pressure which comes associated with a dramatic loss of heat and the consequent freezing by Joule effect. It must be taken into account that supercritical solution achieves in the nozzle the speed of sound and expands into the expansion chamber to a supersonic flow provoking an expansion jet with multiple shocks that influence the coagulation process [45].

In **Figure 4**, a general scheme of RESS technique is shown. The procedure is a batch process: on the one hand, the charge of solutes and, on the other hand, the charge of CO₂ and mixing. Solutes which are going to be micronized are weighted and placed into the solubilization chamber (V1) which is posteriorly sealed. Then, CO₂ at 5°C (HE1) of temperature is pumped to V1 after temperature set point is achieved (HE2). CO₂ and solute are held in the vessel during a contact time before

MV2 valve opening. In this point the supercritical solution is sprayed through the thermostatized nozzle to vessel V2 at room conditions. Nano- or microparticles are produced by the drop of pressure once solubility of the solute in supercritical CO₂ is drastically reduced. This fact is associated to a high supersaturation of the solution leading to the formation of fine particles with narrow particle size distribution.

Nucleation, condensation, and coagulation govern the crystallization of solute. During RESS process, properties of the fluid rapidly change from those of a supercritical fluid to those of a gas as the fluid crosses the critical pressure in the nozzle implying mass and heat transfer. Moreover, the flow is accelerated from a static condition to supersonic speeds in the expansion [45].

Solubility of solute in the supercritical CO₂ solution dominates the saturation rate in this process. This rate is the key to know where the supersaturation and the consequent nucleation of the solute will take place. This point will coincide when supercritical fluid crosses the critical pressure toward the gas phase.

Authors have studied the main experimental parameter that influences on particle size and particle size distribution as temperature and pressure of solubilization chamber, pre- and postexpansion pressure and temperature, diameter, geometry and length of nozzle, spray distance, and so on.

Solvating power depends on both temperature and pressure into the solubilization chamber, because the density of the solvent depends on these parameters. Thus, the higher the pressure, the higher the density while temperature is held constant. This increase in density is related to better solvating power of the supercritical fluid and solute concentration in supercritical fluid. Once concentration is increased, the supersaturation and the nucleation rates are increased during the expansion step causing a smaller particle size precipitation [53].

On the other hand, temperature could influence on two competing phenomena. If temperature is increased there is a decrease in the density of CO₂ (decreasing the solvent power of CO₂ and the solute saturation) but a concurrent increase of the solute vapor pressure (increasing the solubility in CO₂ and the solute saturation). Depending on which phenomena prevail, the trend on particle size will be different, and higher particles or smaller particles will be produced if the first or second phenomenon do respectively.

Corazza et al. pointed out that the supersaturation profile in the free jet region depends on the pre-expansion conditions that could have a remarkable effect on

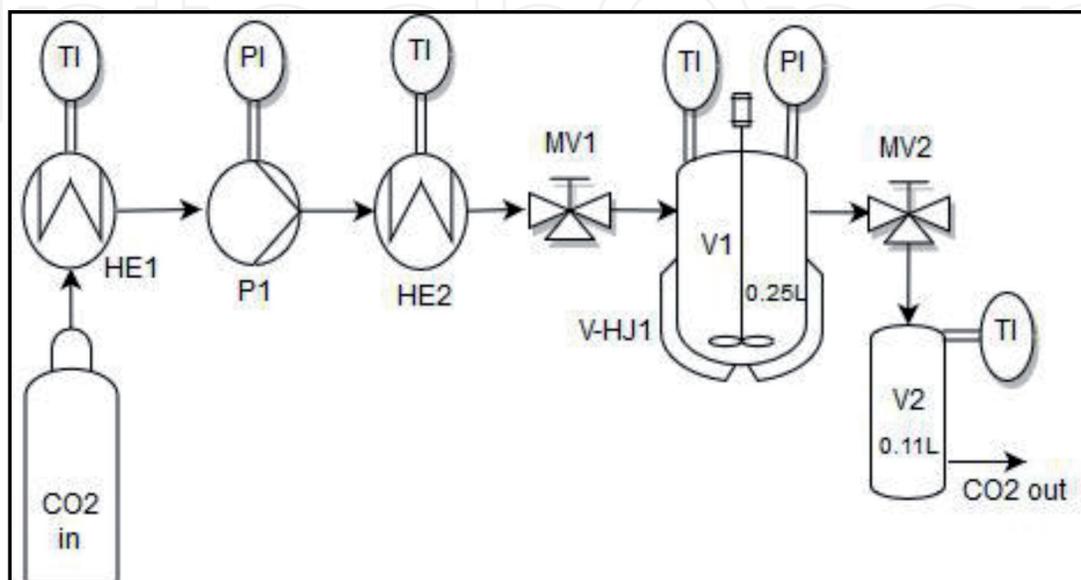


Figure 4.
Scheme of RESS process.

the characteristics of precipitated particles [17]. Higher pre-expansion pressure and lower temperatures are recommended to obtain smaller particle size of benzoic acid, cholesterol, and aspirin precipitated by RESS process [16].

The use of liquid [20] and solid [21] cosolvents to improve the solubility of the solute in supercritical fluid and modify the saturation rate has been associated to RESS process by numerous investigations.

Not only thermodynamic but also hydrodynamic aspects are quite relevant for the success of the process. In this sense, Huang et al. reduced the coalescence and particle size below the micron developing a new clearance nozzle with small exit size in a few microns [18]. Moreover, the spray distance in the expansion unit and the residence time of the precipitated particles are also important factors. Higher spray distance is equal to longer fly time of the particles which allow for their growing and to produce bigger particles [53]. This time is related to the collection distance. Thus, the coagulation of the particles that happens in the expansion region could be minimized using short residence time or short collection distance [53].

Moreover, coagulation phenomena could be drastically reduced modifying the expansion process, so stabilized separated particles were generated. Rapid expansion from supercritical to aqueous solution (RESAS) [54] and rapid expansion of supercritical solutions into liquid solvent (RESOLV) [55] processes appear as alternative to classical RESS process where the air spraying is done. In RESAS the solution is sprayed into surfactant water solution and in RESOLV process into another solvent different to water as ethanol. Thus, particle growth is minimized, and the coagulation of the powder is prevented.

In our facilities nonsteroidal anti-inflammatory drugs (NSAIDs), as ibuprofen and naproxen [22, 23] (**Table 1**) and vanillin [28] (**Table 2**), a solute more soluble in supercritical CO₂, were successfully precipitated by this technique, and parameter influence was investigated. In general, pressure and temperature were the factors which affect strongest as the particle size. Note that naproxen precipitation was aided with methanol as cosolvent due to less solubility of naproxen in supercritical CO₂ than ibuprofen. In both groups of compounds, lower particle size was obtained when pressures were increased. This can be explained due to solvating power of the supercritical fluid which is improved increasing the solute concentration in the supercritical solution, so higher super saturation induces higher nucleation rate during the expansion period provoking fine particle precipitation. In the case of vanillin, the main effects of variables on particle size were found out through a design of experiments

Sample	P (bar)	T (K)	Methanol (%)	Particle size
Naproxen	200	333	5	0.92 ± 1.16
Naproxen	300	333	5	0.22 ± 0.09
Naproxen	200	333	5	0.06 ± 0.01
Naproxen	300	333	5	0.10 ± 0.04
Ibuprofen	100	308	—	1.29 ± 0.38
Ibuprofen	150	308	—	1.26 ± 0.58
Ibuprofen	300	308	—	0.69 ± 0.31
Ibuprofen	100	318	—	1.04 ± 1.48
Ibuprofen	150	318	—	0.67 ± 0.38
Ibuprofen	300	318	—	0.22 ± 0.06

Table 1.
Operating conditions in RESS NSAID assays.

Factors	Low level	High level	Particle size effects
Pressure (bar)	100	300	-6.49
Temperature (K)	313	343	5.29
Contact time (h)	1	2	-1.37
Nozzle diameter (μm)	100	200	2.41

Table 2.
Effects of main operating conditions set in RESS process on particle size of vanillin.

of two levels. It seems particle growth may be dominant over nucleation in these operating conditions and solutes [25]. Higher temperature was recommended in the case of ibuprofen to get smaller particles. The opposite trend happened with vanillin where higher temperature led to higher particle size. Moreover, contact time or nozzle diameter had less impact on particle size recommending smaller nozzle diameter and higher contact time. Anyway, due to the multiple phenomena that interplay in this process, it is difficult sometime to establish general trends.

Modeling of RESS process could permit to shed light to the process. In this sense Moussa et al. simulated particle transport and Brownian coagulation in the expansion chamber by resolving the general dynamic equation. The results showed that postexpansion conditions are an important factor to control particle size of precipitates and demonstrated that particle growth is not completed in the supersonic free jet during the RESS process [56]. In this way Reverchon and Pallado modeled the hydrodynamics of the RESS process and concluded that most of the pressure drop and temperature decrease took place in the postexpansion chamber bringing to light the important role of the process parameters connected to the postexpansion device [57].

Thermophysical flows of RESS process were numerically simulated from the nozzle inlet to the outlet of the expansion chamber using program package for thermophysical properties of fluids (PROPATH) [58] developed at Kyushu University [59] and naphthalene as model molecule. The results indicated that the location at which the pressure crosses the critical pressure is sensitive to the pressure at the nozzle inlet and nucleation starts near that place [45].

Helfgen et al. developed a one-dimensional, steady-state flow field model based on mass, momentum, and energy balance and the Bender equation of state. In the inlet region of the nozzle, a pressure drop, friction, and heat exchange are considered for the flow along the nozzle and a possible condensation in the supersonic free jet. They resolve the general dynamic equation for simultaneous nucleation, condensation, and coagulation. The results showed a decrease of pressure and temperature at the capillary nozzle outlet, which leads to immediate precipitation of the solved substance, and most of the particle growth occurred inside the expansion chamber, but the calculated particle sizes are too high in relation to the measured ones [60]. Further investigations are needed to clarify the process and their dominant forces.

5. Conclusions

Special properties of supercritical CO₂ as solvent power similar to liquids but high diffusivities similar to gases, resulting in higher mass transfer rates. This mass transfer rate is quite important in particle formation process using CO₂ as solvent or antisolvent. In antisolvent processes mass transfer rate will influence on the size and morphology of the particles. Higher mass transfer rate is related to smaller particle size. Anyway, mass transfer of supercritical antisolvent process depends on

the one hand on the situation of phase equilibrium diagram of operating conditions and on the other hand on the hydrodynamics of the process. The hydrodynamics of the process is controlled by flow rates of CO₂ and solution and by the nozzle that forms the spray. This spray reduces the boundary between CO₂ and microdroplets of solution, improving the mass transfer of the process. Heat transfer in supercritical antisolvent process influences directly on the mixing step in non-isothermal process. If the solution is colder than bulk CO₂, the mixing time that is less interesting for crystal production will increase. However, in the opposite situation, a warmer solvent immersed in colder CO₂ accelerates the mixing process. Thus, high supersaturation ratio can be achieved, so smaller particles are precipitated.

In rapid expansion of supercritical solution, mass transfer happens in solubilization chamber and in nozzle and expansion chamber. Saturation of the solution which is governed by solubility of solute in supercritical fluid will decide the place where to start the precipitation. This location could be into the nozzle or after in the expansion chamber. Heat transfer happens at the exit of the nozzle due to the drastic change of pressure by Joule effect. Nozzle should be thermostated to prevent freezing and clogging.

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