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Micronization processes by supercritical fluid technologies: a short review on process design (2008-2012)

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ABSTRACT. Several micronization processes based on supercritical fluids have been developed. These processes can be classified according to the role of the supercritical fluid in the process: solvent, solute or co-solvent, and anti-solvent. Application of supercritical fluids as alternative to traditional micronization methods and the growing demand of the industrial sector for new technologies motivated this review. In this context, the objective of this work was to present the operating principles of the micronization process by means of supercritical fluids and the effects of the main process variables on particles characteristics. The review continues with an update of current experimental data presented in the literature in the period from 2008 to 2012.

Keywords: supercritical fluids, micronization process, review.

Processos de micronização utilizando tecnologia supercrítica: uma breve revisão sobre projeto de processos (200-2012)

RESUMO. Vários processos de micronização baseados na tecnologia supercrítica têm sido desenvolvidos. Tais processos podem ser classificados conforme o papel do fluido supercrítico no processo: solvente, soluto ou co-solvente e anti-solvente. O presente trabalho de revisão foi motivado pela cresecnte demanda do setor industrial por técnicas alternativas e também devido a aplicabilidade dos fluidos supercríticos. Neste contexto, o principal objetivo deste trabalho é apresentar os princípios operacionais referentes a micronização com fluidos supercríticos e os efeitos das principais variáveis de processo nas características das partículas produzidas. O presente trabalho de revisão cobre os avanços experimentais reportados na literatura no período de 2008-2011.

Palavras-chave: fluído supercrítico, processo de micronização, revisão.

Introduction

Micronization processes are characterized by the reduction of particle sizes in order to provide changes in their structures, surface areas and functional properties. These processes are applied to several different materials (e.g., metal oxides, metal salts and organic compound) and as a consequence, motivate the researches in academic world as well as in the industry (CHAU et al., 2007).

Conventional techniques for micro/nanoparticles production (spray drying, mechanical comminution, solute recrystallization, coacervation, freeze-drying, interfacial polymerization) present drawbacks such as excessive use of solvent, thermal and chemical solute degradation, high residual solvent concentration, and mainly, difficulty in controlling the particle size (PS) and particle size distribution (PSD) during processing (HE et al., 2004). These techniques may also change the crystal structure of the precipitated powder, leading to products with undesirable characteristics (FRANCESCHI et al., 2008a). To minimize the undesirable effects caused by conventional techniques different methods using supercritical fluids have been developed by means of exploiting the peculiar properties of these fluids.

Micronization process of compounds using supercritical fluids (SCF) is not recent. In the late 19th century, Hannay and Hogarth (1879) reported that a substance homogeneously dissolved in a SCF, under a certain pressure, may precipitate in 'snow' form by pressure decrease. Then, microencapsulation development, for instance, began in the 1930s with the preparation of paper capsules incorporated with dyes for copying purposes and carbon paper assemble, commercially used for the first time in 1954. Tavana and Randolph (1989) proposed to crystallize benzoic acid from SC-CO_2 by simultaneously reducing temperature and pressure in an autoclave (WEIDNER, 2009). The end of the 1980s was characterized by a considerable increase in reports in literature concerning the application of supercritical fluid technology for particle processing.

The properties that make SCF particularly attractive, in general, are the gas-like diffusivities, the continuously adjustable solvent power/selectivity and the possibility of its complete elimination at the end of the process (REVERCHON; ADAMI, 2006). Several precipitation methods take advantage of the possibility of modulate the SCF properties, or suddenly change these properties by means of pressure and temperature changes to achieve homogeneous supersaturation conditions, which leads to the production of fine powders with a narrow particle size distribution (MARTÍN; COCERO, 2008a).

Carbon dioxide (CO_2) is the most widely used supercritical fluid because it is cheap and non pollutant and presents middle critical properties. However, ammonia, alcohols, light hydrocarbons and water have also been proposed as supercritical media, among other materials, for nanoparticle production (REVERCHON; ADAMI, 2006).

The CO_2 supercritical region can be achieved at moderate pressures and temperatures (Tc = 304.2 K, Pc = 7.38 MPa); therefore, working with SC-CO_2 it is possible to carry out the process at near-ambient temperatures, avoiding the degradation of thermolabile substances, SC-CO_2 also provides an inert medium suitable for processing easily oxidable substances (COCERO et al., 2009).

Another important advantage is the easy and efficient separation between the micronized solute and SCF. Additionally, the high solubility of most organic solvents in SCFs allows the recovery of the organic solvent and also the production of solvent-free particles.

In this context, this review is focused in process design data for micronization processes by means of SCF for the period from 2008 to 2012. The manuscript is divided in three sections. The first section discuss about the various micronization techniques based on the role of SCF in the process (MARTÍN; COCERO, 2008a): solvent, solute or co-solvent, and antisolvent. In the second section, we discuss some process parameters which affect the particle size and morphology of composites and encapsulated materials. Finally, in the third section, are listed and organized the applications of the methods based on the SCFs.

Micronization process with supercritical fluids as solvent

Rapid Expansion of Supercritical Solutions (RESS): The RESS process explores variations in solvency of the fluid with the pressure changes and consists in expanding the solution (solute dissolved in supercritical fluid) to ambient conditions of temperature and pressure leading to decrease in solvent power and consequent solute precipitation due to supersaturation of the solution caused by a significantly decrease in solvent density Jung and Perrut (2001). The high supersaturation ratios and a rapidly propagating perturbation are distinctive characteristics of the RESS process (MISHIMA, 2008). The Figure 1 shows a RESS unit according to Jung and Perrut (2001), clearly dividing the process in two-step: (1) first, the extraction process where the SCF is saturated with the substrates of interest; (2) second, the extraction is followed by a sudden depressurization through a nozzle, producing a drastic decrease in the solvent power and the temperature of the fluid, therefore causing the precipitation of the solute (TÜRK et al., 2002).

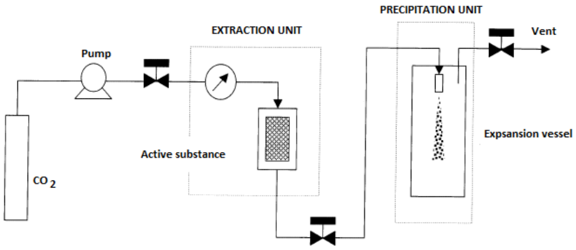

Figure 1. RESS equipment concept.
Source: Jung and Perrut (2001).

The major limitation of the RESS technique is the low solubility in the SCF of the most attractive compounds required for precipitation (SHARIATI; PETERS, 2002). This limitation is, evidently, more severe for co-precipitation/encapsulation applications because not only the active substance but also the carrier (encapsulate material) have to be soluble in SC-CO_2 (COCERO et al., 2009). It is also possible to overcome the limitation of low solubility in CO_2 by employing alternative organic solvents (PESTOV et al., 2003) Another alternative to eliminating the solubility limitation is the RESS-non-solvent process (RESS-N) where a liquid antisolvent for the polymer is used as a cosolvent in order to improve the solubility in the SCF (COCERO et al., 2009).

An interesting variation of the RESS process is the Rapid Expansion of a Supercritical Solution into a Liquid Solvent (RESOLV), represented by the spray of the supercritical solution into a liquid, which allows the reduction of the particles growth in the precipitator and therefore improving the RESS performance. Moreover, the interaction between the nucleating solid particles and the compounds contained in the liquid phase suggest that a chemical reaction step is also involved (REVERCHON; ADAMI, 2006).

Another modification of the RESS technique is the use of substances to enhance the solubility or improve the dispersion of the solute, i.e., the Supercritical Solvent Impregnation (SSI), which requires the dissolution of the solute in the SCF. According to Braga et al. (2008), several properties of pharmaceutical product such as drug loading or drug depth penetration can be modified by adjusting process parameters such as the rate of the depressurization step, the time of impregnation or solvent density. The solution is subsequently put in contact with a polymer and, if the polymer swells due to the addition of the SCF, it is possible (after a subsequent depressurization) to impregnate the polymer with the drug, obtaining therefore a drug release system (ALESSI et al., 2003).

Micronization process with supercritical fluids as solute or co-solvent

Depressurization of an Expanded Liquid Organic Solution (DELOS): The DELOS process consists of a saturation of the SCF with the solution formed by the substance of interest in an organic solvent followed by the expansion through a nozzle and resulting in fine particle formation (MARTÍN; COCERO, 2008a). The SCF such as supercritical CO_2, plays the role as co-solvent during the components mixture and as anti-solvent and viscosity reduction during the spray step (HAKUTA et al., 2003). Then, the driving force for the DELOS precipitation is the intense cooling effect produced by the CO_2 vaporization (MARTÍN; COCERO, 2008b). This process can only be applied for substances where the anti-solvent effect of CO_2 is small, as otherwise the solute precipitates in the saturator and not in the expansion vessel. The main advantages of this process are the reduced consumption of CO_2 and the possibility to operate at atmospheric pressures in the precipitator (MARTÍN; COCERO, 2008a e b). The Supercritical Assisted Atomization process (REVERCHON, 2002) is similar to the DELOS process except that SAA uses an aqueous solution as solvent (HAKUTA et al., 2003).

Particles from Gas Saturated Solutions (PGSS): The PGSS method is used for micronizing solids immiscible in the SCF, although they can be swell by the SCF addition, such as esters or fats (TABERNERO et al., 2012). The PGSS requires low gas demand and reduced operating pressure. The principle differs from the RESS technique because the supercritical solvent is dissolved in a melted solid to create a saturated solution. After that, a depressurization is performed at atmospheric pressure, and the expansion causes the vaporization of the dissolved fluid (MARTÍN; COCERO, 2008a). Because the SCF is more soluble in the liquid than vice versa, less amount of SCF is required to obtain particles, avoiding the use of an organic solvent to saturate the solution (TABERNERO et al., 2012). The Figure 2 shows the PGSS equipment according to Jung and Perrut (2001).

The atomization of the PGSS process can be improved by using a second gas such as air in the atomization and precipitation vessel, generating the Gas Assisted Melting Atomization process (GAMA) (SALMASO et al., 2009). However, the most used PGSS variation is the PGSS-drying process, which was developed by Meterc et al. (2008) for drying aqueous compounds from green tea extracts. In this process, an aqueous solution is contacted with the compressed fluid in a static mixer with several mixing elements, promoting the mass transfer between the SCF and the solution, which is then depressurized (TABERNERO et al., 2012).

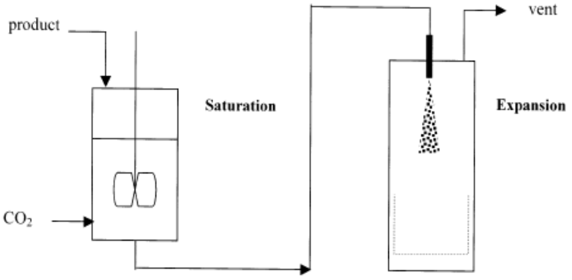

Figure 2. PGSS equipment concept.
Source: Jung and Perrut (2001).

Micronization process with supercritical fluids as antisolvent

Several techniques belong to this category, which is based on the immiscibility or very low miscibility of the solute of interest in the SCF, the anti-solvent effect, complemented by the complete miscibility of the solvent in the SCF. The processes from this category differ mainly by the configuration, i.e., by the contact between the solution (solute + solvent) and the anti-solvent, and also by the anti-solvent state, as detailed below.

Gas AntiSolvent (GAS): The GAS technique (GAS), characterized as a discontinuous or batch process, was first described by Gallagher et al. (1989)

for explosive recrystallization. The GAS method consists of the addition of SCF into a solution formed by organic solvent and the solute of interest and ‘steels’ the solvent from the solution with a consequent solid pressurization. This transfer occurs because the SCF is highly soluble in the solvent while the solid is not (TABERNERO et al., 2012). Figure 3 shows the GAS equipment according to Jung and Perrut (2001). Briefly, the solution is introduced into a temperature controlled chamber followed by the antisolvent addition through the bottom to the chamber by a filter disperser, at a predetermined constant rate and temperature causing the expansion of the liquid solution and precipitation of the solid material (FRANCESCHI et al., 2008b).

Supercritical AntiSolvent (SAS): the SAS method is based on the same principles as the GAS process but in a continuous or semi-continuous operation. The SAS process starts with introducing the pure liquid solvent until the steady state condition is obtained. Then, the solution containing the solute of interest is sprayed through the nozzle at a given flow rate into a flow of antisolvent. Due to the high solubility of the solvent in the antisolvent, the precipitation of the solute occurs and, when the given quantity of solution is injected, the liquid pump is stopped and the formed particles collected (REVERCHON et al., 2008).

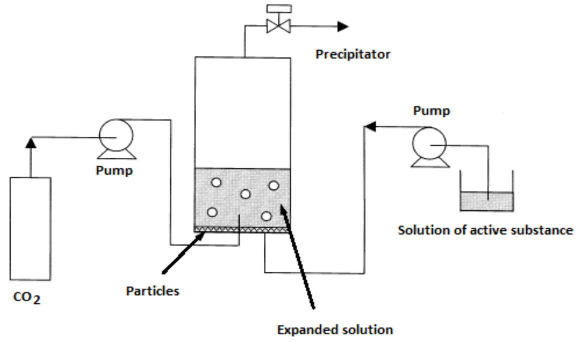

Figure 3. GAS equipment concept.
Source: Jung and Perrut (2001).

In the last decade the SAS method has been improved by many researchers to allow the production of fine particles with narrow particle size distribution. This development generated the following processes which are detailed in the sequence: Supercritical AntiSolvent with Enhanced Mass transfer (SAS-EM), Aerosol Solvent Extraction System (ASES), Precipitation with Compressed Antisolvent (PCA), the Solution Enhanced Dispersion by Supercritical Fluids (SEDS) and the Supercritical Fluid Extraction of Emulsions (SFEE) (HAKUTA et al., 2003).

Supercritical AntiSolvent with Enhanced Mass transfer (SAS-EM): Chattopadhyay and Gupta (2002) proposed the SAS-EM method in order to reduce the size of the particles formed during precipitation and improve the mixing of SAS method. The SAS-EM process uses ultrasonication at the injection nozzle for improving dispersion of the solution into fine droplets (JIN et al., 2012).

Aerosol Solvent Extraction System (ASES): In the ASES process the organic solution with the active substance is sprayed through a nozzle into a precipitator chamber filled with the antisolvent in the supercritical state. Mass transfer between the solvent and supercritical CO_2 is enhanced and fine particles are obtained (HAKUTA et al., 2003). The ASES has been considered a suitable process for the formation of pharmaceutical compounds.

Precipitation with a Compressed Antisolvent (PCA): The complex phase behavior of some compounds in supercritical fluids has a crucial influence on the performance of the precipitation processes. A liquid–liquid phase split may be observed when antisolvent pressure is increased, where one of the two liquid phases in equilibrium is solute-rich, while the other is antisolvent- and solvent-rich (PÉREZ DE DIEGO et al., 2005). Based on this phase behavior, the PCA process was proposed to improve the ASES technique and consists of separating the liquid–liquid phases in a first step and followed by solute drying and precipitation.

Solution Enhanced Dispersion by Supercritical fluids (SEDS): The SEDS process is a modification of the SAS method and the main difference is the contact of the solution mixture or solvent(s) with the antisolvent. In SEDS process, intense mixing of SCFs with solution/solvent(s) is done via coaxial nozzle, increasing mass transfer rate at the interface (TABERNERO et al., 2012). Figure 4 shows a summarized schematic diagram of the micronization process that using supercritical fluids as antisolvent, specifically, the SEDS and ASES techniques.

Supercritical Fluid Extraction of Emulsions (SFEE): The application of SCFs in particle technology with emulsions appears to be a natural decision to avoid problems from each method separately. Usually large amount of organic solvents are associated with the use of emulsion technique, requiring the inconvenience of the separation downstream procedures, which normally involves high temperatures.

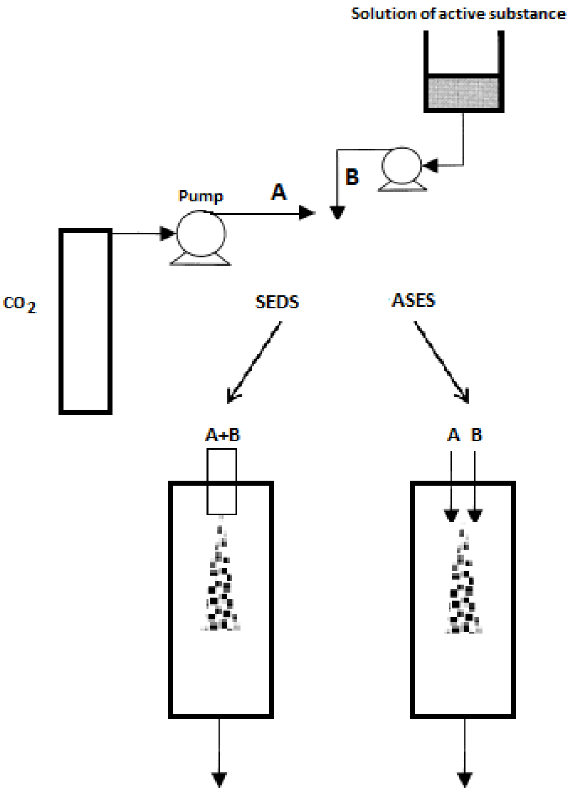

Figure 4. Schematic diagram of the micronization process that using supercritical fluids as antisolvent.
Source: Adapted from Jung and Perrut (2001).

Complementarily the high pressure micronization methods normally produce particle in the micrometric range or with agglomerate aspects. The SFEE technique, a combination of both methods (emulsion and SCF) to produce micro/nanoparticles, may compensate the above mentioned drawbacks. In SFEE method each emulsion droplet (disperse phase) behaves as a miniature GAS precipitator and the final product consists of a micro/nano-suspension of the solute in water. The use of emulsions for encapsulation may provide model morphology for the microcapsule (i.e. 'costume made' particles) if the active solution is dissolved in the disperse phase and the carrier in the continuous phase (COCERO et al., 2009).

The SFEE processes can be performed in a batch mode or in continuous form, and the equipments involved in the precipitation process are very alike to the GAS batch system and to the SAS semi continuous process, respectively. The differences from GAS and SAS processes are: (a) an emulsion containing the desired substance to be precipitated dissolved in its dispersed phase is injected instead of a simple solution of the substances ; (b) a liquid product is formed, allowing the continuous extraction of the product but requiring additional steps to produce a powdery product, (c) the preparation of the initial solution requires the use of surfactants, high energy dispersion techniques, (d) the emulsion droplet size distribution is an additional controlling parameter besides the usual ones from GAS and SAS processes (pressure, temperature, flow rates, and concentrations) (COCERO et al., 2009).

The above mentioned techniques are compared in terms of the role of the SCF in the process. Table 1 also accounts the present survey object, which is the list of publications registered in two important database, the ISI Web of Knowledge and the Scopus, from the period 2008 to the end of the first semester in 2012. The survey was performed using the following words: 'Rapid Expansion of Supercritical Solutions'; 'Rapid Expansion of a Supercritical Solution into a Liquid Solvent'; 'RESS non-solvent'; 'Supercritical Solvent Impregnation'; 'Depressurization of an Expanded Liquid Organic Solution'; 'Particles from Gas Saturated Solutions'; 'Gas Assisted Melting Atomization'; 'PGSS drying'; 'Gas Anti Solvent'; 'Supercritical Anti Solvent'; 'Supercritical Anti Solvent with Enhanced Mass transfer'; 'Aerosol Solvent Extraction System'; 'Precipitation with a Compressed Antisolvent'; 'Solution Enhanced Dispersion by Supercritical fluids' and 'Supercritical Fluid Extraction of Emulsions'.

It is possible to observe from Table 1 that the year 2010 was, in general, the most productive year with a total of 42 from ISI Web of Knowledge and 180 from Scopus publications. GAS process presented the highest number of publications generated in the Scopus, 231 published materials of last five years. This observation can be anchored by the fact of this technique is especially suitable for polymers because majority of polymers are not soluble in supercritical fluids or gases (YEO; KIRAN, 2005), and the most used cover materials in the encapsulation process are polymers. However, for ISI Web of Knowledge, the SAS process presented more publications, with a total of 55 published materials of last five years. This process notably is applicable for solvents with relatively high solubility in the SCF. A special advantage of this technique is its adaptability for continuous operations, which is important for large-scale mass production of particles (YEO; KIRAN, 2005).

Table 1. Classification according to the role of the supercritical fluid in the process, and number of publications in the ISI Web of Knowledge and Scopus database (2008-2012).

Database		ISI Web of Knowledge	Scopus
Classification	Process	All publications (2012) (2011) (2010) (2009) (2008) Sum of publication of 5 last years	
Solvent	RESS	126 (12) (3) (8) (5) (6) 34	334 (25) (20) (27) (21) (20) 113
	RESS-n	4 (0) (0) (0) (0) (0) 0	5 (0) (0) (1) (0) (0) 1
	RESOLV	13 (0) (0) (0) (0) (1) 1	13 (0) (1) (0) (0) (1) 2
	SSI	11 (1) (2) (4) (1) (2) 10	110 (6) (11) (8) (10) (11) 46
Solute or Co-Solvent	DELOS	5 (1) (1) (0) (0) (0) 2	6 (1) (0) (1) (0) (1) 3
	PGSS	43 (4) (6) (6) (3) (2) 21	205 (7) (15) (20) (17) (18) 77
	GAMA	1 (0) (0) (0) (1) (0) 1	2 (0) (0) (0) (1) (0) 1
	PGSS drying	9 (2) (2) (3) (1) (1) 9	11 (2) (1) (4) (1) (1) 9
AntiSolvent	GAS	52 (3) (3) (2) (2) (2) 12	550 (34) (70) (47) (38) (42) 231
	SAS	96 (15) (17) (7) (6) (10) 55	374 (46) (52) (46) (38) (38) 220
	SAS-EM	2 (0) (0) (1) (0) (0) 1	7 (1) (1) (2) (1) (1) 6
	ASES	51 (2) (3) (1) (4) (9) 19	122 (3) (13) (7) (9) (14) 46
	PCA	17 (0) (2) (2) (1) (0) 5	86 (1) (3) (7) (2) (8) 21
	SEDS	50 (4) (2) (4) (4) (7) 21	93 (5) (8) (6) (8) (11) 38
	SFEE	13 (3) (0) (4) (2) (1) 10	18 (3) (2) (4) (2) (3) 14

Effects on particle size and morphology

A review published by Martín and Cocero (2008a) discuss about some micronization processes using supercritical fluids. The authors pointed that the commercial application of supercritical fluids precipitation technologies requires predictability and consistency of the characteristics of the product, especially because there are many variables involved in the systems. This remark involves a detailed understanding of the influence of all relevant process parameters. The effect of the main process parameters on the micronization processes with SCFs that have an effect on the particle size and morphology are discussed in the sequence.

Effect of temperature: In general, lower temperature implicates less agglomeration and less growth of crystals. The agglomeration of the crystals might be due to a more favorable redissolution of these at higher temperatures (COCERO; FERRERO, 2002; YOUN et al., 2011). The preparation of ursolic acid nanoparticles using the SAS process was studied by Yang et al. (2012). In this case, the authors observed that, the mean particle size reduces with the increase in temperature from 318 K to 338 K. According to the authors, this tendency may be explained by the particle size behavior which is directly related to the solubility of the compound in the supercritical phase. At constant pressure, the temperature increase above 318 K result in decrease in density of the SC-CO_2 leading to a reduction in the ethanol (co-solvent) and ursolic acid solubility in the supercritical phase. Therefore, lower solubility allows higher degree of supersaturation and particles with a smaller mean particle size.

Effect of pressure: Franceschi et al. (2008b) investigated the effect of processing parameters on the precipitation of pure β-carotene and poly(3-hydroxybutirate-co-hydroxyvalerate) (PHBV) and co-precipitation of them using the SEDS technique. According the authors, the mean particle size enhanced with the pressure increased, while the morphology of β-carotene precipitated also changed with pressure, modifying from plate-like to a leaf-like form of particles. In this sense, pressure effects can be explained in terms of solubility, since the supersaturation is defined by the ratio between the solute concentration in the solvent + anti-solvent mixture and the saturation concentration of the solute in the mixture. As the solvent + antisolvent mixture stands above the mixture critical point, an increase in pressure leads to a decrease in solute concentration in the mixture, hence reducing the supersaturation. Already, Reverchon et al. (2008) revised general characteristics of SAS for production of spherical microparticles which can be successfully produced at near critical pressure conditions up to completely developed supercritical conditions. In some cases a pressure decrease causes a small increase of particle size and an enlargement of the particle size distribution. In some other cases, the influence of pressure produced the opposite effect. Spherical microparticles were sometimes obtained operating at liquid CO_2 conditions.

Effect of nozzle design: The particle size decreases with decreasing the nozzle diameter which increases the dispensing shear forces inside the nozzle. Asghari and Esmaeilzade (2012) evaluated the formation of ultrafine deferasirox particles by RESS process and the results show that the average particles sizes can be reduced by lowering the nozzle diameter. Nozzle obstructions can occur in experiments, which may to cause instability in the process and reductions of the amount of product which could be sprayed into the precipitation vessel (DE PAZ et al., 2012), and it is usually necessary to interrupt the process after obstruction.

Effect of solute concentration: An initial study for the knowledge of the saturation concentration of solute in possible solvents is very necessary. Therefore, a supercritical precipitation process like RESS and SSI techniques requires the determination of the solubility of the substance in SCF at high pressure, and also for systems with an organic solvent (MARTÍN; COCERO, 2008a). The concentration of solute also affects the crystal form. Li et al. (2012) observed a probable reorganization in a different solid phase of puerarin drug by GAS technique with the change of concentration of drug dissolved. Priamo et al. (2010), studying the β-carotene precipitation by SEDS technique, verified that the increase in the solute concentration at constant pressure and temperature led, in most cases, to a reduction in the particle size. On the other hand, when applying SAS process with fixed conditions of pressure, temperature and CO_2 molar fraction, an increase of solute concentration produces, in general, an increase in spherical microparticles diameter (REVERCHON et al., 2008).

Effect of solvent: Lin et al. (2010) evaluated the solvating power of toluene, tetrahydrofuran, acetone and nitromethane for a polymer since it depends on their solubility parameter and observed the effect on the particles morphology, taking into consideration that the addition of compressed CO_2 to a polymer solution would increase the difference in the solubility parameter between the solvent and polymer. The results showed that spherical, submicrometer-sized polymer particles without coalescence could be generated only from the toluene solution. According to the authors (LIN et al., 2010), the reason for the superiority of toluene over the other solvents was due to its solubility parameter value, which is the lowest, and in general, a large affinity between a solute and a solvent exists when their solubility parameter values are sufficiently close. For recrystallization of puerarin using the GAS process, ethanol, acetone and methanol were employed as solvent (LI et al., 2012). The new crystal form of puerarin was generated with ethanol at the optimal condition, presenting particles of 30.34 mm with needle-like shape. The authors mentioning that, the most important factor was the physico-chemical properties of the solvent from which the solute is precipitated. Solvent properties such as dipole moment, dielectric constant and the presence of hydrogen bonding may influence the crystal growth mechanism.

Effect of antisolvent addition rate: The increase in the antisolvent flow rate enhances the turbulence inside the precipitation chamber, promoting an intense mixture between the solution and anti-solvent. An increase in this variable induces a decrease in mean particle size (FRANCESCHI et al., 2008b, 2009). Similar flow rate influence was observed by Fusaro et al. (2009) in the GAS process, emphasizing that the antisolvent rate is the key parameter to control the product particle size, since it directly controls the supersaturation build-up in the system, where enhancing the flow rates mostly implies in smaller particles.

Effect of agitation: De Paz et al. (2012) evaluated the formulation of β-carotene with poly-(ε-caprolactones) by PGSS process and observed that a longer mixing time allows obtaining a more homogeneous and stable mixture with a higher saturation with CO_2, which improves the performance of the process and permits producing smaller particles. Regarding the β-carotene content in the sample, it was considerably increased when the homogenization time decreased. Jin et al. (2012) discuss in their work that the major factor regarding particle size reduction in the SAS-EM technique is the ultrasonication power supply at the injection nozzle, due to ultrasonic atomization and the increased mixing. However, these authors note that higher power supply produced smaller particles but also increased the agglomeration of them due to the improved van der Waals attraction of the smaller particles.

Therefore, the literature suggests that many of the above cited parameters have a simultaneous influence on different process steps, producing, sometimes, difficulties in process interpretation, or even contradictory experimental results obtained by different researchers. Therefore, the development of a process often requires an extensive experimental study with different combinations of process parameters. It is necessary to have some knowledge of the process mechanism allowing performing a deeper interpretation and analysis of the experimental results for posterior applicability and validity of the process (MARTÍN; COCERO, 2008a). An interesting review of patents related to supercritical precipitation technologies was presented by Martín and Cocero (2008b), as well as the aspects of the processes and the features to improve or to solve the technical problems.

Some applications of the micronization methods based on the SCF are listed in Table 2 (Anexo), for the period previously cited (2008 to August 2012). The interested readers are addressed to consult the papers cited in the present work for additional details regarding process parameters such as the effect of solvent, antisolvent addition rate, solute concentration, agitation, operating temperature, system pressure, nozzle design etc., on PS, PSD and morphology.

Conclusion

As described in this review, the analysis of literature results has confirmed that the supercritical micronization technologies are well established. Depending of the desired objective, the technique and operating conditions can be properly selected. The possibility to generate new products, technically and economically feasible, without additional steps, as drying, typically required by traditional techniques, is the attractive for developing the micronization technologies from SCFs. Although nowadays there are some industrial-scale plants, already in operation, several academic research still need to be scaled-up in order to be introduced industrially. For this, the knowledge of the phenomena occurring at high pressures using data from phase equilibrium of these generally complex systems is crucial for further development of engineering design and construction of pilot and industrial scale units.

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ANEXO

Table 2. Applications of the methods based on the supercritical fluids.

Method	Components	Results and Observations	References
RESS	- with / without acetone; - deferasirox (DFS); - CO_2.	Reduction in the size of the precipitated particles of DFS (50 nm-5 μm) via RESS process compared with the original particles of DFS 5-500 μm; The optimum for micronization: 17 MPa, 313 K, effective nozzle diameter of 1200 μm and using acetone.	Asghari and Esmaeilzadeh (2012)
	- with / without ethanol; - L-menthol; - CO_2.	With higher ethanol concentration, the micronized L-menthol changes from needle-like to quasi-spherical morphology with smaller particle size. The optimum for micronization: 303 K, 10 MPa, CO_2 with the presence of 10 wt % ethanol, and average size was 0.4 μm with a smaller variance of 0.2.	Suankaew et al. (2012)
	- ethanol, acetone and dichloromethane (DCM); - coenzyme Q10 (coQ10); - poly-(lactic acid) (PLA) and poly(ethylene glycol) (PEG); - CO_2.	More important effect of the ratio polymer / coQ10, compared with the effect of type of co-solvent, on morphology and size of microcapsules, however, it has an influence on the particle size and the coenzyme solubility. Using ethanol as co-solvent smaller particles are obtained.	Vergara-Mendoza et al. (2012)
	- polyaniline (PANI); - dodecyl benzene sulphonic acid (DBSA); - CO_2.	RESS technique applied to sensor coating with conducting polymer PANI. Pressure of carbon dioxide was kept at 10 MPa with flow rate of 30 mL minutes^{-1}. Sensors prepared were sensitive to organic vapors and less sensitive to moisture.	Steffens et al. (2010, 2009)
RESS-n	- aluminum; - CO_2 + cyclotrimethylentrinitramine (RDX).	Aluminum-RDX particles (ALEX®) were produced by heterogeneous nucleation, at pre-expansion pressures up to 34.5 MPa and pre-expansion temperatures up to 353 K.	Essel et al. (2010)
RESOLV	- polyacrylonitrile (PAN); - dimethylformamide (DMF) + CO_2	PAN fibers with size range of 50–300 nm in diameter were obtained when a solution of supercritical SC-CO_2 and DMF mixture containing PAN was rapidly expanded into an ambient aqueous NaCl solution, at a pre-expansion pressure and temperature of 20.7 MPa and 333 K, respectively. PAN nanofibers were exclusively obtained at higher polymer concentrations whereas aggregated nanoparticles were produced by lower concentrations of PAN in the supercritical solution.	Kim et al. (2008)
SSI	- ethanol; - acetazolamide (ACZ); - silicone-based soft contact lenses (SCLs); - CO_2.	SCLs drug-loading was studied at (313 and 323) K, from (15 MPa up to 20) MPa, and time of the loading (1, 2 and 3) hours. *In vitro* drug release kinetics studies were performed and can be potentially employed as combined biomedical devices for simultaneous therapeutic and correction of refractive deficiencies purposes.	Braga et al. (2011)
	- ethanol; - quercetin; - thymol; - n-carboxybutylchitosan (CBC); - agarose (AGA); - CO_2.	CBC and AGA were loaded with quercetin and thymol, separately or as a mixture, at 10 and 20 MPa, and at 303 and 323 K. Ethanol (10%, v v^{-1}) was employed whenever quercetin was used. Higher amounts of quercetin and/or thymol were loaded when higher pressures and temperatures were employed.	Dias et al. (2011)
	- piroxicam; - poly(vinylpyrrolidone) (PVP); - CO_2.	Various PVP / drug systems at different polymer molecular weights (PVP K-15, K-30, K-90) were tested. Good results in terms of acceleration in the drug release were obtained only for the PVP K-15 / piroxicam system. The best result was obtained for the impregnated sample containing a piroxicam amount equal to 11.3%, which released the 94.7% of the drug after 10 minutes.	Banchero et al. (2009)
DELOS			
PGSS	- abimono 90 N (emulsifier); - deionized water; - hydrogenated castor oil (HCO); - CO_2.	Maximum operating pressure and temperature are 35 MPa and 373 K. The mean particle size is in the range 3-22 μm, and morphologies vary between agglomerates, foam-like structures and spheres. Open as well as closed structures are found. In some pictures, pinholes can be seen on the surface.	Hanu et al. (2012)

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Method	Components	Results and Observations	References
	- poly-(ε-caprolactones) (PCLs); - β-carotene; - CO$_2$.	Particle sizes in the range of 110-130 ìm with a â-carotene content of up to 340 ppm were obtained using PCL with a molecular weight of 4000 g mol^{-1}. The highest â-carotene concentrations were obtained at high pressures and temperatures (343 K and 15 MPa, respectively) and with short homogenization times (60 minutes).	De Paz et al. (2012)
	- liposomes produced with commercially available lecithins and cholesterol; - lavandin (Lavandula hybrida) essential oil; - CO$_2$.	Dry and fine but aggregated soy lecithin particles were produced, with a particle size in the range 1.4-24.8 μm and a poor efficiency of incorporation of essential oil ranging from 3 to 14.5%. These particles could be dispersed in water, producing liposomes whose size ranged between 0.5 and 1.5 μm.	Varona et al. (2011)
GAMA	- homogeneous dispersions of insulin in lipid mixtures: (1) tristearin, Tween-80, phosphatidylcholine and 5 kDa PEG (1:0.1:0.9:1 and 1:0.1:0.9:2 weight ratio); and (2) tristearin, dioctyl sulfosuccinate and phosphatidylcholine (1:1:0.5 weight ratio); - dimethylsulfoxide (DMSO); - CO$_2$.	High product recovery (70%, w w^{-1}) were achieved in optimized process conditions. Two size fractions of particles, with 80–120 and 200–400 nm diameters were produced. In all final products, DMSO used to prepare the insulin/lipid mixture was below 20 ppm. Protein encapsulation efficiency increased up to 80% as the DMSO content in the insulin/lipid mixture increased.	Salmaso et al. (2009)
PGSS drying	- lavandin (lavandula hybrida) essential oil; - linalool - n-octenyl succinic (OSA)-modified starches	The efficiency of encapsulation of lavandin oil and linalool in OSA-starch microcapsules varies in the ranges 6–52 and 9–85%, respectively, decreasing when the initial oil/starch ratio is increased, and increasing when pre-expansion temperature is decreased. The residual moisture content, measured in samples obtained, was in the range 6.7–4.1% (w w^{-1}), similar to the water content in unprocessed OSA-starch. Particle size decreases when pre-expansion temperature is decreased, when pre-expansion pressure is increased and when the gas/liquid ratio is increased.	Varona et al. (2010)
	- polyethylene glycol (PEG) from aqueous solutions; - CO$_2$.	Spherical PEG particles with average particle size of 10 μm and residual water content below 1 wt% were produced. Smaller particles were obtained when CO$_2$ solution^{-1} ratio, pressure and temperature were increased. The residual humidity in the product decreased when CO$_2$ solution^{-1} ratio and temperature were increased and when pressure was decreased.	Martín et al. (2010)
	- poly(ethylene oxide) (PEO) 6000 in water (50%, w w^{-1}); - CO$_2$.	It was possible to separate solvents and to micronize the polymer in only one process step. Powders with different residual solvent contents are obtained. The condensation of solvent in the spray tower could be avoided, and that the high pressure phase behavior upstream the decompression step shows significant influence on the remaining amount of solvent in the powder.	Pham et al. (2012)
GAS	- polymeric scaffolds; - hyaluronic benzyl esters (HYAFF11); - poly-(lactic acid) (PLA); - Sodium chloride (NaCl); - CO$_2$.	10-15 w w^{-1} solutions of a HYAFF11 and PLA were used to fill packed beds of 0.177-0.425 mm NaCl crystals. Maximum operating pressure and temperature are 16 MPa and 313 K. Uniform porosity (~70%) and a high interconnectivity between porous. The polymeric walls were porous themselves counting for 30% of the total porosity.	Flaibani and Elvassore (2012)
	- polycaprolactone (PCL); - rosemary extract; - CO$_2$.	Operating pressure and temperature are 30 MPa, 313 K, exhibited a narrow particle size distribution, a lower mean particle size and higher encapsulation efficiency (254.5 nm, 82.8%).	Yesil-Celiktas and Cetin-Uyanikgil (2012)
	- ethanol, acetone and methanol; - puerarin (Pur); - CO$_2$.	Maximum operating pressure and temperature are 14 MPa and 316 K. The optimal condition was size of 30.34 μm. When the solvent was ethanol, it exhibited the similar needle like appearances, for acetone, it exhibited as long need les with brushes and for methanol, the crystals were prolonged markedly and appeared as long columns.	Li et al. (2012)

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Method	Components	Results and Observations	References
SAS	- ethanol; - ursolic acid (UA); - CO$_2$.	The optimal conditions were 338 K and 12.5 MPa. Particles with mean particle size ranging from 139.2 ± 19.7 to 1039.8 ± 65.2 nm were obtained by varying the process parameters.	Yang et al. (2012)
	- ethanol and dichloromethane; - proliposomes (PL); - lutein; hydrogenated soya phosphatidylcholine (HPC); - CO$_2$.	The optimal conditions were 308 K, 8 MPa and the solution flow rate of 1 mL minutes^{-1} - the lutein loading of the PL reached 55 mg g^{-1}. The lower temperature, higher pressure and a higher liquid flow rate favored smaller and more regular PL spheres. The encapsulation efficiency of lutein reached 90.0%.	Xia et al. (2012)
	- acetone; - shrimp extract; - Pluronic F127; - CO$_2$.	The highest efficiency in astaxanthin encapsulation (74%) was obtained at 10 MPa, 308.15 K and ratio between solution and CO$_2$ flow rate of 1 (mL minutes^{-1}) (kg h^{-1}) $^{-1}$. All particles produced obtained better color preservation compared to the crude extract.	Mezzomo et al. (2012)
SAS-EM	- dimethyl sulfoxide (DMSO) and acetone; - thalidomide; - CO$_2$.	The size of the particles decreased with increasing ultrasound power supply but also increased agglomeration of particles. The optimum condition of the SAS-EM process was 225 W at 303 K and 15 MPa. Modification the crystal formation of thalidomide from an original state of a â-polymorph to the amorphous state á-polymorph.	Jin et al. (2012)
	- methanol; - methylene chloride; - poly-lactic acid (PLA); - CO$_2$.	The operating pressure and temperature are 8 MPa and 308 K. The particle size was able to be controlled in the range of 0.4-1.0 μm, by adjusting the power supply, the system pressure and temperature. With the power supply ultrasonic field of 200 W, spherical PLA particles smaller than 1 μm were obtained.	Park et al. (2010)
	- methylene chloride; - itraconazole; - CO$_2$.	The process was conducted at a pressure of 10 MPa and a temperature of 313 K and ultrasound amplitude of 25% (the total ultrasonic power rating is 750 W at 100% amplitude). Itraconazole particles were observed as lakes ranging from submicrometer to 14 μm.	Sanganwar and Gupta (2008)
ASES	- dichloromethane and methanol; - poly(L-lactide) (PLLA), and the block length of methoxy poly(ethylene glycol)-b-poly(L-lactide) (mPEG-PLLA); - leuprolide acetate (LA); - CO$_2$.	The operating pressure and temperature are 13 MPa and 308 K. The processed LA had an agglomerated spherical morphology with size of 100-200 nm. The PLLA particles had a sphere-like morphology and were smaller than 5 μm in size. LA-loaded mPEG-PLLA particles with different mPEG block lengths had spherical morphologies with smooth surfaces. An increase in PEG length of mPEG-PLLA from 2 to 10% leads to an increase in the mean particle size from 2.86 to 5.63 μm.	Jung et al. (2012)
	- ethyl acetate (EA); - valsartan; - CO$_2$.	Ultra fine valsartan particles with a mean diameter of 0.1 μm were obtained without excessive agglomeration at the subcritical CO$_2$ of 7 MPa and 278 K. When the supercritical CO$_2$ was at 10 MPa and 313 K, valsartan was precipitated to fine particles that tended to agglomerated.	Youn et al. (2011)
	- methanol; - prednisolone, - polyethylene glycol (PEG); sodium dodecyl sulfate (SDS); - CO$_2$.	The process parameters, pressure and the temperature of the reaction vessel, were adjusted to 8.0 MPa and 308 K, respectively. Prednisolone/PEG 4000/SDS at the weight ratio of 1:6:2 with a solution concentration of 0.5% (w v^{-1}) yielded the smallest particle size of prednisolone of approximately 230 nm.	Moribe et al. (2009)
PCA	- acetone; - poly(D,L-lactide-co-glycolide) (PLGA); - Gentamicin (GEN); - bis(2-ethylhexyl) sulfosuccinate sodium salt (AOT); - CO$_2$.	The operating pressure and temperature are 10 MPa, 298 K. The micronization complex GEN-AOT yielded a particulated material with a higher surface area than the non-precipitated complex, while PLGA nanoparticles within a size range of 250-330 nm. GEN encapsulation efficiency values of approximately ~100% were achieved for the different formulations.	Imbuluzqueta et al. (2011)
	- Toluene, tetrahydrofuran, acetone and nitromethane; - poly(methyl methacrylate) (PMMA); - CO$_2$.	More uniform submicrometer-sized PMMA particles were obtained at PMMA concentrations equal to or less than 1.0 wt% in the toluene solution. The optimal conditions were 298 K and 6.41 MPa. A narrower particle size distribution was observed for precipitating PMMA with a molecular weight of 85,000 versus PMMA with a molecular weight of 36,000.	Lin et al. (2010)

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Method	Components	Results and Observations	References
	- dimethyl sulfoxide; - lysozyme; - CO_2.	In the vapor liquid coexistence region of the solvent-antisolvent mixture, particles between 100 and 200 nm were obtained, whereas at supercritical and liquid conditions studied in the 298-313 K and 10-15 MPa ranges, particle sizes were reproducibly below 100 nm.	Fusaro et al. (2009)
SEDS	- ethanol; - acetaminophen; - tretinoin; - CO_2.	The best results for spherical microparticles without aggregates and with a size around 0.5-0.75 ìm, are obtained just above the mixture critical point (approximately 7.5 MPa for 313 K and 8 MPa for 318 K) of the mixture antisolvent– solvent.	Tabernero et al. (2012)
	- Dichloromethane (DCM); - trans-â-carotene; - poly(3-hydroxybutirate-co-hydroxyvalerate) (PHBV); - CO_2.	The smallest particle size of â-carotene (1.29 μm) and largest particle size of PHBV (1.10 μm) was obtained at the same pressure of 8 MPa, for â-carotene and PHBV concentrations of 8 and 30 mg mL^{-1}, respectively, and the encapsulation results showed that at this condition and at 313 K presented the highest encapsulation efficiency (55.54%).	Priamo et al. (2011, 2010); Franceschi et al. (2009, 2008b)
	- ethanol and dichloromethane; - theophylline; - CO_2.	Experimental condition 333.15 K and 11 MPa led to the smallest mean particle size (3×1 μm) and particle size distribution (1×0.8 μm to 5×2 μm). The reduction in particle size was quite significant, very close to nanometric sizes, from 244×38 μm for the unprocessed theophylline to 3×1 μm for the processed one.	Franceschi et al. (2008a)
SFEE	- ricinoleic acid; - poly(lactic-co-glycolic); acid (PLGA); - dicloromethane; - CO_2.	Stable suspension of magnetite–PLGA composite nanoparticles in water was produced. Narrower size distributions are obtained with larger amounts of emulsifier and lower amounts of magnetite. The morphology of the particles tends to be of Janus type, with the magnetite accumulated on one hemisphere of the particle. The proposed approach is suitable for the preparation of large quantities of high-quality magnetite–PLGA composite nanoparticles for biomedical applications.	Furlan et al. (2010)
	- β-carotene; - lycopene; - n-Octenyl succinic anhydride (OSA)-modified starch; - dicloromethane; - CO_2.	Sub-micrometer particles of carotenoids suspended in aqueous media were produced. Suspensions containing stabilized carotenoids with final particle size of 344–366 nm and encapsulation efficiency of 34–89% were obtained. Independently of the type of carotenoid used, emulsion flow rate influenced the production of suspensions of carotenoids, particularly the encapsulation efficiency and the degree of isomerization. Higher encapsulation efficiencies, but also higher degradations were obtained when β-carotene was employed instead of lycopene. The concentration of surfactant/carrier material was the only process parameter that influenced the final particle size, while the encapsulation efficiency and degree of isomerization were influenced also by the concentration of surfactant/carrier material and by pressure.	Santos et al. (2012)
	- phenanthrene; - ethyl acetate (99.5%); - poly(vinyl alcohol); - CO_2.	Phenanthrene crystals are formed either by self-nucleation of single emulsion droplets, or through contact of emulsion droplets with already existing crystals. On the other hand, emulsion droplets are mainly consumed by the growth of phenanthrene crystals, involving mass transfer through the continuous water phase. When increasing the temperature, the average median x_{50} of the particle size distribution increased from 15 μm at 293 K to 103 μm at 333 K. The study demonstrates that this process exhibits good reproducibility and enables controlling the particle size in a rather wide range, thus further underlining the potential of this technique for industrial and research applications.	Kluge et al. (2012)