Review

Supercritical fluids for pharmaceutical particle engineering: Methods, basic fundamentals and modelling

Antonio Taberneró, Eva M. Martín del Valle*, Miguel A. Galán

Department of Chemical Engineering, University of Salamanca, P/Los Caños 5/N, 37008, Spain

A R T I C L E   I N F O

Article history:
Received 3 May 2012
Accepted 18 June 2012
Available online 26 June 2012

A B S T R A C T

The interest of the use of supercritical fluids, especially supercritical CO₂, for particle engineering over the last years has received attention from the pharmaceutical industry. Supercritical fluids can be used in different clean technologies to achieve high supersaturation, and consequently small crystalline particles with a narrow particle size distribution can be produced. This article aims to provide a compilation of old and new supercritical fluid as solvent or antisolvent techniques for drug processing and their fundamentals in terms of crystallization, thermodynamics and modelling results.

© 2012 Elsevier B.V. All rights reserved.

Contents

1. Introduction ................................................................................................................................. 9
  1.1. Requirements of pharmaceutical industry ................................................................................. 9
  1.2. Supercritical fluids and their properties .................................................................................... 10
  1.3. Supercritical CO₂ .................................................................................................................. 10
  1.4. Particle engineering and sc-CO₂ ............................................................................................ 11
  2. Relation between crystallization and supersaturation ............................................................. 11
  3. Phase equilibrium ..................................................................................................................... 12
  4. Processes with SCFs .................................................................................................................. 13
  4.1. RESS and its modifications (RESOLV and RESSAS) ............................................................. 13
  4.2. GAS ..................................................................................................................................... 14
  4.3. SAS, ASE, PCA, SEDS, SAS-EM and ARISE ...................................................................... 15
  4.4. DELOS, PPRGEL, PGSS and PGSS-drying ....................................................................... 17
  4.5. CAN-BD and SAA ............................................................................................................... 20
  4.6. SFEE ................................................................................................................................... 20
  4.7. Miscellaneous ..................................................................................................................... 21
  5. Conclusions .............................................................................................................................. 21
  Acknowledgment ......................................................................................................................... 22
  References .................................................................................................................................... 22

1. Introduction

1.1. Requirements of pharmaceutical industry

Over the last decades, research in advanced drug delivery and targeting have increased drastically due to the requirements of the pharmaceutical industry. As a matter of fact, in mid-90s, several products based on drug delivery had worldwide sales with more than 10 million dollars [1]. Inside the pharmaceutical industry, around 90% are in crystalline form [2].

Particle engineering for drug delivery needs methodologies that can provide control of particle size and polymorphic purity. Particle size affects the delivery route of the drugs, “deciding” what specific organ can be targeted. Particles should be around 0.1–0.3 μm for intravenous delivery, 1–5 μm for inhalation delivery, and 0.1–100 μm for oral delivery [3]. Small size also implies a greater percentage of drug absorbed by the human body and a reduction of the doses number. On the other hand, crystallinity affects the physical and chemical stability, whereas organic and inorganic impurities indicate toxicity [2].
In spite of these facts, conventional micronization techniques for pharmaceutical industry do not give the option to control or modify these previous characteristics.

Specifically, regarding size and distribution, milling and grinding produce a broad particle size distribution (PSD). Jet milling, a technique that uses impact forces between the particles to break up the products into smaller pieces consumes energy, and in addition does not provide a uniform PSD. Another method like freeze-drying usually requires a subsequent milling due to the broad PSD. Particles with controllable size might be obtained using a spray-drying process, but the required high temperatures to drive the droplets evaporation can damage the pharmaceutical. Finally, if a conventional precipitation process with organic solvents is used, traces of the organic solvent might be remained in the precipitated particles [4–7].

As an example, Fig. 1 shows different techniques and the particle size that can be obtained with them. It can be seen how supercritical fluids (SCFs) technologies can provide a particle size less than 1 μm, offering in addition a clean technology.

1.2. Supercritical fluids and their properties

A SCF can be defined as any fluid which is at conditions above its critical point (Fig. 2). SCFs present gas–liquid transport properties. As it can be observed in Fig. 2, SCFs have liquid-like density, but viscosity and diffusivity remain between liquid-like and gas-like values. In addition, SCFs exhibit almost zero surface tension. Due to these transport properties, SCFs have been introduced in different fields for different applications, such as extractions, chromatography, or particle generation.

1.3. Supercritical CO2

A variety of compounds might be used as SCFs. However, as it can be observed in Table 1, the critical properties are usually extremely high except for a few compounds. These compounds, such as light hydrocarbons, are usually in addition inflammable and toxic products. On the other hand, it seems that carbon dioxide is the only compound that can be used as a “green solvent” with acceptable critical properties. That is the main reason why supercritical CO2 (sc-CO2) is the most used SCF.

Furthermore, CO2 is non-flammable and inert. Its threshold limit value (TLV) is around 5000 ppm. It is as a consequence less toxic than acetone (750 ppm) or pentane (600 ppm). Its TLV and high vapour pressure implies that residual CO2 is not harmful to human health [9].

Regarding solubility, CO2 is considered a non-polar solvent, in spite of its quadrupole moment. However, as happens with other supercritical gases, the dielectric constant of the CO2 increases with pressure. These two opposite effects make difficult to predict the solubility behaviour of different molecules in sc-CO2. According to Stahl et al. [10], sc-CO2 is a good solvent for lipophilic compounds with low polarity such as epoxides, ethers or esters at low pressure range.

Nevertheless, molecules constituted by strong polar groups (e.g. —COOH) are less soluble in sc-CO2. Regarding benzene derivatives, it is important to consider different aspects. It seems that compounds with three phenolic hydroxyls or one carbonyl and two hydroxyl groups can be solubilized in sc-CO2. The opposite effect, however, has been found for molecules with one carbonyl and three or more hydroxyl groups [10].

Nevertheless, if it is required, the solubility of any polar solid in sc-CO2 can be enhanced by using different co-solvents. Finally, polar solvents like short alcohols and short-chain hydrocarbons (ethanol, acetone) are miscible with sc-CO2 at relatively moderate pressures. This solubility decreases directly with the number of carbon atoms in the chain. In this context, different works and reviews have been done regarding the solubility of solids in SCF with and without cosolvents [11,12].

### Table 1

<table>
<thead>
<tr>
<th>Compound</th>
<th>Tc (K)</th>
<th>Pc (MPa)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ammonia</td>
<td>405.7</td>
<td>11.3</td>
</tr>
<tr>
<td>Benzene</td>
<td>562.2</td>
<td>4.9</td>
</tr>
<tr>
<td>Carbon dioxide</td>
<td>304.3</td>
<td>7.4</td>
</tr>
<tr>
<td>Chlorotrifluoromethane</td>
<td>384.9</td>
<td>3.9</td>
</tr>
<tr>
<td>Ethane</td>
<td>305.6</td>
<td>4.9</td>
</tr>
<tr>
<td>Ethylene</td>
<td>282.5</td>
<td>5.1</td>
</tr>
<tr>
<td>Methanol</td>
<td>513.7</td>
<td>7.9</td>
</tr>
<tr>
<td>n-Propane</td>
<td>367.0</td>
<td>4.3</td>
</tr>
<tr>
<td>Water</td>
<td>647.6</td>
<td>22.1</td>
</tr>
<tr>
<td>Xenon</td>
<td>562.9</td>
<td>5.84</td>
</tr>
</tbody>
</table>

**Fig. 2.** Phase diagram of a compound and physicochemical properties for liquids, gases and SCFs.
with their main innovation. It should be specified that the corresponding acronyms will be explained in section 4. It must be also highlighted the issue 3, volume 60 (2008) of the journal Advanced Drug Delivery Reviews. That issue is dedicated to supercritical fluid technologies for drug delivery and pharmaceutical applications (some of them exposed in Table 2).

These previous reviews focus in the use of SCFs for different pharmaceuticals applications, and occasionally for modelling/foundations of these types of processes.

Our present review aims to cover a more extended number of SCFs (as solvents or antisolvents mainly) processes for solid particle engineering. Their corresponding modifications and modelling results for the most used processes are also included.

Small crystalline particles with a narrow PSD are obtained because the use of SCFs can provide great and fast supersaturations. Since the supersaturation depends on the phase equilibrium of the system, this review should start therefore with the corresponding fundamentals of the crystallization kinetics and phase equilibria.

2. Relation between crystallization and supersaturation

Get a great and a fast supersaturation is the main objective of the SCFs processes for particle formation. From a thermodynamic point of view, this can be explained due to the difference between the chemical potential of the solute in the fluid ($\mu_i$) and at equilibrium ($\mu^*$). This difference is the driving force of the precipitation (Eq. (1)).

When the concentration ($x_i$) is higher than the equilibrium concentration ($x^*$), the solute will precipitate up to the difference between the corresponding chemical potentials became null, and the equilibrium is achieved [42]. The activity coefficient of the solute ($\gamma_i$), and the solute at equilibrium ($\gamma_i^*$), the gas constant $R$ and the temperature $T$ are included in Eq. (1).

$$\mu_i - \mu_i^* = RT \ln \left( \frac{\gamma_i x_i}{\gamma_i^* x^*} \right)$$

On the other hand, the supersaturation ($S$) is directly related to the difference between the respective chemical potentials (Eq. (2)).

$$\ln(S) = \frac{\mu_i - \mu_i^*}{RT} = \ln \left( \frac{\gamma_i x_i}{\gamma_i^* x^*} \right)$$

The previous equation justifies the precipitation of the solid for great values of supersaturation. By using different methodologies, the equilibrium concentration $x^*$ can be reduced drastically, and the solute should precipitate to reach the equilibrium for the system [3].

The supersaturation also establishes the nucleation kinetics. These kinetics can be primary heterogeneous and primary homogeneous. The homogeneous (and the optimal) nucleation occurs without the existence of a solid surface, and it is explained by means of the classical nucleation theory. This theory assumes that clusters or embryos are produced due to a combination process [43]. Eq. (3) shows the embryo free energy for a particle for a given radius $r$. The term $\lambda$ is referred to the energy for surface unit ($J \cdot m^{-2}$), $a$ is the area of a spherical particle ($m^2$) with a radius $r$ ($m$), $k_B$ is the Boltzmann’s constant (J K$^{-1}$), whereas $v$ and $v$ are molecular volume of the precipitated embryo ($m^3$) and the volume of a spherical particle ($m^3$) with a radius $r$.

$$\Delta G = - \left( \frac{v}{r^3} \right) k_B \cdot T \cdot \ln(S) + 2a$$

According to Eq. (3), nuclei are only formed when the value of the supersaturation is higher than the unit because the free energy is negative. This can be also observed in Fig. 3 which shows the energy change against the radius. For supersaturations greater than the unit, the energy increases until a maximum that corresponds

### Table 2: Different published reviews and their main subject.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Main subject</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subra and Jestin, 1999 [17]</td>
<td>RESS y SAS. Applications and fundamentals of solid formation.</td>
</tr>
<tr>
<td>Palakodaty and York, 1999 [18]</td>
<td>Phase behaviour for SCFs as antisolvents.</td>
</tr>
<tr>
<td>Vemavarapu et al., 2005 [25]</td>
<td>General review and design of processes for particle formation at laboratory scale.</td>
</tr>
<tr>
<td>Yeo and Kiran, 2005 [26]</td>
<td>General review and polymer and microencapsulation with SCFs.</td>
</tr>
<tr>
<td>Reverchon and Adam, 2006 [27]</td>
<td>SCF techniques for nanomaterials.</td>
</tr>
<tr>
<td>Nalawade et al., 2006 [28]</td>
<td>Applications of sc-CO$_2$ as a processing solvent for polymer applications. Fundamentals.</td>
</tr>
<tr>
<td>Tandya et al., 2007 [29]</td>
<td>General review and drug/polymer formulation with different techniques.</td>
</tr>
<tr>
<td>Byrappa et al., 2008 [31]</td>
<td>General review and different biomedical applications.</td>
</tr>
<tr>
<td>Pasquali et al., 2008 [33]</td>
<td>General review. Control of the solid state of drugs.</td>
</tr>
<tr>
<td>Pasquali and Bettini, 2008 [34]</td>
<td>General review and SCFs for pharmaceutical applications.</td>
</tr>
<tr>
<td>Cocero et al., 2009 [35]</td>
<td>General review and fundamentals of encapsulation and coprecipitation processes with SCFs.</td>
</tr>
<tr>
<td>Reverchon et al., 2009 [36]</td>
<td>General review. SCFs for polymer processing for pharmaceutical applications (scaffolds, microencapsulation).</td>
</tr>
<tr>
<td>Kikic, 2009 [37]</td>
<td>Interactions between polymer and SCFs.</td>
</tr>
<tr>
<td>Kiran, 2009 [38]</td>
<td>Modelling solubility of polymers in SCFs.</td>
</tr>
<tr>
<td>Skeger et al., 2011 [40]</td>
<td>RESS and modifications. Modelling and its fundamentals.</td>
</tr>
<tr>
<td>Beh et al., 2012 [41]</td>
<td>Solubility of solids in SCFs. Modelling.</td>
</tr>
</tbody>
</table>

### 1.4. Particle engineering and sc-CO$_2$

The use of sc-CO$_2$ provides therefore several advantages in comparison with the previous conventional techniques. The sc-CO$_2$ can be used as a solvent, antisolvent, as extracting agent for the organic phase of oil in water emulsions or even to improve the spraying process in different techniques.

These processes and/or their fundamentals have been discussed in different reviews. Table 2 shows reviews for the last two decades
with a specific radius (critical radius $r^*$). Particles higher than $r^*$ are considered nuclei, but if the particles are smaller than the critical radius, they will redissolve (embryos). Finally, after the maximum, the free energy decreases until the equilibrium is reached. At this value, the nuclei will be stable with their corresponding size [43].

The number of nuclei per volume and time $B$ can be calculated with the knowledge of the supersaturation (Eq. (4)). According to this equation, the term $B$ is strongly non-linear with $S$. $B$ tends to 0 if the supersaturation is close to 0. However, the number of nuclei increases when the supersaturation is higher than 1:

$$B = A \exp \left[ \frac{16\pi \lambda^2}{3kT (\ln S)^2} \right]$$  \hspace{1cm} (4)

The time to get the supersaturation is important. Fast supersaturation highlights that nucleation is the main phenomenon over crystal growth. On the other hand, there is a competition between both phenomena, with larger crystals and wider PSD for slower supersaturation time.

3. Phase equilibrium

In order to guarantee a proper process design, it is crucial to know the phase behaviour and solubility of the system of interest. In fact, the driving force of any precipitation process is the supersaturation, which is defined as the ratio of the real concentration and the saturation concentration.

Therefore, it would be very important to make a previous theoretical calculation of the saturation concentration. In order to do that, different types of equations can be used to determine concentrations at equilibrium.

**Cubic equations of state (EOS)**, such as Peng–Robinson (PR) for instance (Eq. (5)):

$$P = \frac{R \cdot T}{v-b} - \frac{a}{v^2 + 2bv - b^2}$$  \hspace{1cm} (5)

This type of equations establishes a relation between pressure ($P$), temperature ($T$) and molar volume ($v$). In order to take into account the non-ideal behaviour, energetic parameters ($a$) and co-volume ($b$) must be introduced [44].

These EOS can be used to calculate fugacities. This fact is very important because equilibria are usually calculated based on an iso-fugacity approach for the different phases. This procedure can be used for binary or multicomponent equilibria (liquid–vapour, solid–vapour, solid–liquid–vapour). For solids, the solid phase should be assumed as pure solute, and it would be necessary to use the solid sublimation pressure to calculate the fugacity of the solid. There are few data for sublimation pressure of pharmaceuticals, but this fugacity might be also calculated as a function of a reference sub-cooled liquid state [45].

One of the main limitations of this procedure is the requirement of different properties, such as critical properties or the sublimation pressure of the solid [46]. Although there are different contribution groups or methodologies to estimate these properties [47–52], but the deviation can be increased by the use of these estimations because they have been developed in some occasions for only a specific type of compounds.

Moreover, to get a better fit for the phase equilibria, mixing rules are needed. These mixing rules modify the energetic parameter and the volume by introducing binary interaction parameters, taking into account deviations due to the interactions. In fact, the “predictive power” of the equation is given by the mixing rules.

The most common mixing rules were established by Van der Waals, and have one or two binary interaction parameters [53,54]. Since then, different works have been published in order to create new mixing rules, even with three interaction parameters, in order to improve the fit [55,56].

Although a proper fit for vapour–liquid equilibria can be obtained using one single binary interaction parameter in the mixing rule, usually two parameters are used [57–59]. However, if there is a solid involved, at least two parameters are needed to get an accurate result with polar solids [56,60,61]. Furthermore, if the system contains a polymer, these equations do not provide a good fit, due to the difficulties for cubic equations to take into account strong interactions.

These parameters should be calculated by regressing experimental data of binary systems against theoretical data. This fact highlights the semiempirical character of the EOS. Moreover, if it would be necessary to estimate a solid–liquid–vapour equilibrium with more than two components (multicomponent and multiphasic equilibria), experimental data for solid–vapour and vapour–liquid equilibria must be previously determined to calculate the corresponding interaction parameters.

Therefore, the EOS might not be a suitable tool for predicting equilibria data at high pressure, given that experimental data are required for obtaining these interaction parameters.

**Semiempirical equations** are emerging as a good way to fit solubility data of solids in SCFs. These equations do not need solid properties and they include different semiempirical parameters that must be calculated for each solid. These parameters are based on simple error minimization, avoiding therefore the required iterative computational methods for iso-fugacity approaches. One of the first semiempirical equations was published by Chrastil in the 80s (Eq. (6)). This equation [62] is based on the solvato complex formed between solute and SCF at equilibrium, proposing a relation between the solubility ($S$ in kg.m$^{-3}$) and the density of the SCF ($\rho_1$ in kg.m$^{-3}$). It can be seen, how three parameters ($k$ is the association factor, $A$ and $B$) must be determined for this equation by regressing experimental against theoretical data:

$$S = \rho_1^k \exp \left( \frac{A}{\rho_1} + B \right)$$  \hspace{1cm} (6)

Since then, several modifications of Chrastil’s equation and new (and numerous) semiempirical models have been developed, some of them even with 6 adjustable parameters, in order to reduce the deviation [63–70]. Among them, it is possible to find either solubility–density relations or empirical correlations based on the effect of the different experimental parameters ($P$, $T$, $\rho$) in the solubility of the solid. Due to this big number of semiempirical equations, different articles have been published in order to perform a comparison between them (and with cubic EOS) [71–74]. According to some works, semiempirical models usually give a more accurate result in terms of deviation than cubic EOS.

The main drawbacks of these equations are their semiempirical character and their only application for solid–SCFs systems.
However, semiempirical models have been proposed to correlate the solubility of solid–cosolvent–sc-CO$_2$ and solid–cosolute–sc-CO$_2$ [75,76].

**Molecular-based equations**, are non-cubic EOS and can fit properly these solubility data. Lattice-based Sánchez–Lacombe (SL) EOS [77] or off-lattice based theory Perturbed Hard Sphere Chains (PHSC) [78] can be included in this classification. This type of equations needs the use of mixing rules and different molecular properties that should be calculated with different contribution groups [79]. In comparison with other equations, SL-EOS fits successfully the equilibrium with polymers, but fails to predict vapour–liquid equilibria or solid–vapour equilibria (in comparison with PHCT-EOS or PR-EOS). On the other hand, PHCT-EOS fits properly polymeric systems and provides in general a better fit that PR-EOS for vapour–liquid, solid–vapour equilibria and solid–liquid–vapour equilibria, but can fail with high polar molecules [80].

Although it is proved that there are different equations to fit solubility data of binary and multicomponent systems at high pressure, it seems that all the previous methodologies present an important shortcoming.

Solubility data is always required to calculate the interaction parameters for the different equations in order to get a better fit. Therefore, there is not a suitable tool to perform a reasonable and accurate prediction of this type of equilibria without experimental data.

This is the reason why new methodologies to predict these equilibria without experimental data (only with solid properties) are being developed. As an example, De Zordi et al. [81], recently published an article in which solid–vapour equilibria could be estimated by calculating the activity coefficient at infinite dilution of the solute in the dissolution using a linear free energy correlation.

4. **Processes with SCFs**

There are several processes that use SCFs for particle production. These methods will be explained with more detail after this classification. Depending on the characteristics, these techniques can be divided into different groups:

**SCFs as solvents**. In this case, the solute must be dissolved in the SCF. Rapid expansion of supercritical solution (RESS), rapid expansion of a supercritical solution into a liquid solvent (RESSOL), rapid expansion of supercritical solution into an aqueous solution (RESSAS) and rapid expansion of supercritical solution with a nonsolvent (RESS-N) are in this group.

**SCF as antisolvents**. The SCF is put in contact with a solution of the solute. Processes such as gas antisolvent (GAS), supercritical antisolvent (SAS), aerosol solvent extraction system (ASES), solute enhanced dispersion by supercritical fluids (SED), particles by compressed antisolvent (PCA) or atomized rapid injection for solvent extraction (ARISE) can be defined in this group.

**SCFs as cosolvents or as a compound to reduce the melting point**. Techniques in which the solution (or only the solute) is solubilized in the SCF, followed by a rapid depressurization to exploit the Joule–Thomson effect. Particles from gas saturated solutions (PGSS), PGSS-drying, gas assisted melting atomization (GAMA) and depressurization of an expanded liquid organic solution (DELOS) can be included in this group. Similar to DELOS is the process called precipitation by pressure reduction of gas-expanded liquids (PPRGEL).

**SCFs as a nebulization compound**. The SCF is used to assist the nebulization of the solution, such as carbon dioxide assisted nebulization with a bubble dryer (CAN-BD) and supercritical fluid-assisted atomization (SAA). In SAA, the SCF plays also the role of a cosolvent.

**SCFs as an extracting and antisolvent compound**. Supercritical fluid extraction of emulsions (SFEE) combines the extraction and the antisolvent power of the SCFs.

**Miscellaneous processes**. Techniques to take advantage of different aspects of the SCFs to obtain compounds for pharmaceutical applications.

4.1. **RESS and its modifications (RESSOL and RESSAS)**

RESS was patented in 1986 [82], and exploits the ability of the sc-CO$_2$ to solubilize different compounds. The mixture is expanded subsequently to a vessel at atmospheric pressure by using a nozzle. This fast depressurization provides great supersaturation values because the solvent power of the SCF decreases drastically, and the nucleation takes place only in the gas phase. That means good size and distribution. The schematic of the RESS technique can be observed in Fig. 4.

The particle size and morphology might be controlled by changing different parameters [83,84]. The pre-expansion pressure and nozzle design (greater nozzle diameters give higher flow rates) can be controlled to modify the residence time, because the SCF flow rate is strongly dependent on these parameters [85]. Even the structure of the compound might be modified by changing the operation conditions, as occured with the carbamazepine [86].

Formulation of liquid droplets should be avoided in this process. It is required to perform a previous thermodynamic study to get a knowledge of the variation of the solid (or polymer) melting temperature with the pressure (knowing the solid–gas equilibrium), and to determine the solubility of the compound in the SCF [86].

The melting point depression should also be considered when a microencapsulation is performed, that is another application for the RESS process [85]. Inclusion complexes with cyclodextrins can be also produced using this technique [87].

Sonic velocities are produced at the exit of the nozzle due to the difference between the pre-expansion pressure and the expansion pressure. As a consequence, the pressure drop at the exit of the nozzle causes a temperature decrease (freezing process). Nozzle design can therefore affect the fluid mechanics of this technique [13,14]. Freezing/condensation is the main reason why the temperature must be kept constant in the nozzle and in the vessel.

RESS process is well-studied and different works regarding their modelling have been published, and many of them have been
reviewed by Turk, 2009 [39]. According to different studies, (very well explained in Turk’s article), the smallest particles are produced for short residence times and a relative low solubility of the solute in the SCF. RESS provides a uniform PSD and in addition its application for small scale is relatively simple. Moreover, particles are solvent free and do not require post-processing.

On the other hand, the great SCF/solution rate requirement and the limited solubility (the solubility should be $10^{-4}$ for a reasonable outcome) of pharmaceuticals in sc-CO$_2$ due to the difference in polarity are important drawbacks. Another shortcoming is the probability of damaging sensitive high stress products, such as proteins. However, problems concerning solubility might be solved using a liquid [88,89] or even a solid (e.g. menthol) cosolvent [90].

RESS process is not easy to scale-up due to the possibility of nozzle blockage, and in addition, the obtained small particles are difficult to use in proper pharmaceutical form due to the possibility of adhesion/aggregation [39]. Therefore, to the previous reasons, several modifications have been implemented for the RESS process.

One of these RESS variations is called RESS-N. Polymer microparticles or microcapsules of proteins have been produced with this process. The main characteristic of this technique is the use of a cosolvent to enhance the solubility of the solid in the sc-CO$_2$. This cosolvent must not neither dissolve the polymer in its pure form nor produce the polymer swelling [89]. This process provides in addition the ability to control the thickness and the PSD of the particles by changing the feed composition of the solid. But, liquid cosolvents are usually organic liquids that can produce undesired organic traces.

RESSOLV is a simple RESS modification. Although different simulations prove that particles with 10–50 nm diameter range can be obtained with RESS [13,14] as long as there is a subsonic expansion, these particles are usually in the micron-sized due to different collisions mechanisms. RESOLV uses a liquid solvent in the expansion vessel to avoid the growth of the particles in the expansion jet, and therefore, particles less than 100 nm are obtained. However, it is required the use of a stabilization agent [91,92]. The use of the stabilization agent can complicate the understanding of this process, but this fact might be employed to modify the crystallinity and properties of the solute.RESSAS is a simple modification of RESOLV, using a water solution with a surfactant as a stabilizing agent [93,94]. For RESOLV and RESOLV, more experimental parameters should be taken into account, such as surfactant properties (surface tension and dynamic interfacial tension) or the solute solubility in the aqueous surfactant solution [39].

4.2. GAS

As it was explained before, one of the main limitations for RESS application is the poor solubility of compounds with high polarity, such as several pharmaceuticals, in sc-CO$_2$. Therefore, the sc-CO$_2$ (or another SCF) was started to use as an antisolvent.

GAS consists of the addition of the SCF to a solution. If the SCF is highly soluble in the solvent, and at the same time the solid is not soluble in the SCF, the SCF exerts a high antisolvent effect. Great supersaturations can be therefore achieved.

Fig. 5 illustrates a schematic of a GAS process. GAS is a batch process in which the antisolvent is added to a solution of the targeted compound. Due to the dissolution of the SCF in the solvent, it is produced a volume expansion [59,95], which reduces the solvent density and consequently its “solvent power”.

GAS is a well-known process, being the most important parameter the relative volume molar expansion (Eq. (7)) [96]. Although this expansion can be used as the key parameter, different articles established the relative partial molar volume reduction as a better criterion [97,98].

$$\frac{\Delta v}{v} = \frac{v_1(T, P, x_1)}{v_2(T, P_0)} - 1$$  (7)

The knowledge of this expansion provides the ability to manipulate the supersaturation and the PSD. In fact, the minimum relative volume molar expansion corresponds with the maximum attainable supersaturation [96]. The solvent and the thermodynamic conditions are chosen therefore depending on this minimum.

In this process it is very important to take into account how the solubility of the solid decreases. In order to get a proper micronization, the solubility of the solute in the ternary system should decrease sharply to get a fast supersaturation [Fig. 6] [96]. Otherwise it might be produced a cosolvent effect by the use of the SCF. This cosolvent effect has been applied by DELOS to produce microparticles, and it is explained in Section 4.4.

The main advantage of the GAS process is the ability to micronize polar compounds (particles between 0.5 and 500 μm) and to obtain microcapsules [99–101]. However, there is a batch process and an organic solvent is used, and solvent traces can be obtained in the final particles.

---

**Fig. 5.** GAS process.

**Fig. 6.** Suitable conditions to get a succesful micronization with GAS.
4.3. SAS, ASES, PCA, SEDS, SAS-EM and ARISE

In order to overcome the previous limitations, new antisolvent processes were applied for particle formation. SAS, PCA and ASES processes are basically identical (Fig. 7), and they are constituted by a vessel in which it is placed a fluid in supercritical state. After that, the solution of the compound is sprayed through a nozzle in that supercritical atmosphere. Due to the solution spraying, the mass transfer is enhanced due to the droplet formation, and consequently small particles with good distribution can be obtained.

Since the solution is sprayed in the vessel, there is the possibility to use different nozzle configurations to achieve different objectives. Hanna and York patented the SEDS process in order to micronize proteins or different sugars, avoiding solubility problems [102]. They designed a two (or three) coaxial passages nozzle to provide a simultaneous introduction of the solution/suspension and different solvents in order to overcome solubility drawbacks (Fig. 8A).

However, the most common strategy is to use a coaxial nozzle with two passages, sometimes with a mixing length at the end of the nozzle to provide a premixing between the SCF and the solution (Fig. 8B). The solution is introduced along the inner surface, whereas the SCF is pumped along the outer surface. This allows a closest contact and the mass transfer is enhanced. Particles with a size around 1–5 μm have been obtained with this nozzle configuration [103].

SAS-EM (supercritical antisolvent precipitation with enhanced mass transfer) is another variation of SAS process. It consists of a high-pressure ultrasound precipitation vessel to provide a different methodology to create the jet break-up. This ultrasonic field enhances the mass transfer and turbulence, and another way to tune particle size and morphology by changing the ultrasonic frequency. Although SAS-EM might be classified into enhanced atomization processes, this technique uses the SCF for providing an antisolvent effect [104,105].

However, semicontinuous antisolvent processes can provide shortcomings related to nozzle blockage, what may require the use of low flow solution rate. This fact hinders the possibility of scaling-up.

In order to overcome this limitation, ARISE was developed to eliminate the capillary nozzle (using a 1 mm of internal diameter), avoiding blockages. In this case, the solution is placed in a pressurized vessel with an inert compound (nitrogen for instance), and then by means of a depressurization the solution is injected into a vessel with a SCF (that should be at lower pressure than the vessel with the inert compound) which will act as antisolvent. The first depressurization improves in addition the subsequent atomization process [106].

SCFs antisolvents (and semicontinuous) processes are influenced by different parameters, such as fluid mechanics, thermodynamics, intra-droplet nucleation, crystallization kinetics, and heat and mass transfer.

The most studied antisolvent techniques are SAS and SEDS. Although a lot of works have studied the influence of different experimental parameters on particle size, PSD and morphology, contradictory results have been found in terms of the best conditions to get the smallest particles with a narrow PSD [107–110].

Because of that, we only consider here the influence of the position of the experimental conditions with respect to the mixture critical point (MCP) of the system antisolvent–solvent. The position of the MCP has been introduced as a crucial parameter due to different peculiarities, such as theoretical surface tension vanishing, what affects the mass transfer and the atomization process of the technique.

• The MCP for semicontinuous supercritical antisolvent processes

The position of the MCP of the system antisolvent–solvent is very important in supercritical antisolvent processes. When the temperature is above the critical temperature of the SCF, the MCP can be defined as the pressure at which the mixture antisolvent–solvent is in one supercritical phase.

Different works [103,111] have established that the MCP of antisolvent–solvent systems matches with the conditions at which the molar fraction of the solute is the minimum in the ternary systems SCF + solvent + solute (as long as the initial solution is diluted). Therefore, according to these works, pressure and temperature conditions at which the supersaturation is the maximum in the ternary systems might be known using only binary equilibria diagrams antisolvent–solvent. The explanation lies in the antisolvent effect of the SCF. The maximum molar fraction of the CO2 in the liquid phase (and consequently maximum antisolvent effect) is reached just in the MCP. At these conditions, the maximum attainable supersaturation for the ternary system is reached. Above the MCP, there is only one single supercritical phase, and the solubility of the solid in the ternary system can increase [103–111].

The MCP is usually determined by means of an EOS, neglecting often the effect of the solute because the solutions are diluted. However, several authors have suggested that the effect of the solute should be taken into account. The solute can produce the apparition of immiscibilities liquid–liquid which can hinder the respective mass transfer pathways between the solution and the SCF. The solute can also change the effect of the SCF, acting sometimes this SCF as a cosolvent due to the addition of the solute [112–114].

Surface tension plays an important role in relation with the MCP. Above the MCP, the surface tension reaches a null value, what means that in these semicontinuous processes there is no droplet formation existing only one single supercritical phase. However, under the MCP there is droplet formation. Therefore, the precipitation mechanism, particle size and morphologies are different above or under the MCP [108–115].

Several works try to elucidate how the position of the experimental conditions with respect to the MCP can influence the PSD and morphology. However, different results were obtained. The best particle size has been found obtained close to the MCP.
Nevertheless, Reynolds, 16 of [121].

In order to get a complete understanding of the precipitation mechanism, more phenomena should be taken into account, mainly hydrodynamic jet conditions and mass transfer. That is the reason why different investigations have been done regarding modelling supercritical antisolvent processes in order to place together all these fundamentals.

- Modelling supercritical antisolvent processes

In order to explain the particle diameter, particle morphology and the precipitation mechanism, many models based on different assumptions have been proposed.

These semicontinuous processes start with the atomization of the solution–liquid jet under a high pressure atmosphere. The different disintegration regimes at atmospheric pressure are well-known, and are classified according to empirical correlations, based on Reynolds, Weber and Ohnesorge numbers. These correlations provide a method to identify different breakup regimes depending on the velocity or viscosity of the liquid jet [122].

However, these “classical” definitions are not suitable for atomization regimes at high pressure. Specifically, the influence of the gas atmosphere increases with pressure because the gas might be dissolved in the liquid and in addition the “theoretical” vanishing of the surface tension above the MCP should be considered [123].

In order to overcome the previous anomalies, several studies have investigated the different jet disintegration regimes at high pressure [124,125]. Under the MCP, dripping, axisymmetric, asymmetrical and atomization regimes are produced [124], and correlations have been proposed in order to distinguish between atomized and non-atomized regimes at high pressure [126].

However, near and above the MCP, although the surface tension is null, there is droplet formation due to the existence of a dynamic surface tension and even an interphase can be observed [115,127]. Nevertheless, once the equilibrium is reached, the droplets disappear. On the other hand, far above the MCP, there is no droplet formation, and the liquid jet behaves like a gas-like jet (composed of gaseous plumes).

Atomization theories were used therefore to establish a relationship between the initial theoretical droplet size (calculated with Jasuja’s equation) and the final particle size [120]. The initial droplet size correlated better (although roughly) the particle diameter under the MCP than above the MCP [120]. This is mainly due to the difficulty to estimate the surface tension above the MCP and the existence of a secondary atomization. Those deviations highlight that the mechanism one particle-one droplet cannot be applied for these processes, and more phenomena should be taking into account to explain particle size and morphology, such as mass transfer and jet hydrodynamics.

After the solution is atomized in the supercritical atmosphere, there is a two-way mass transfer between the droplet and the surrounding atmosphere. There is a competitive process between the absorption of the SCF inside the droplet, and the solvent evaporation.

However, two different mechanisms should be considered depending if the conditions are under or above the MCP.

These two mechanisms were mathematically studied considering the two-way mass transfer for a stagnant droplet of toluene under sc-CO2 atmosphere at isothermal conditions [128,129]. The different interfacial fluxes and the behaviour (swelling/shrinking) of the droplet with the droplet flying time in a high pressure atmosphere were determined using Fick’s law and PR-EOS.

Under the MCP the droplet always swells (showing in addition a non-monotonic pressure and temperature dependence) because the flux is inside the droplet. Swelling finishes near the MCP because the diffusion is zero, and consequently the flux becomes also zero. When the droplet is saturated, the droplet shrinks because the mass transfer is out of the droplet [128].

This studio also states that droplets with short lifetimes are not necessarily the fastest to reach supersaturation. Droplet lifetime diverges near the mixture critical point, but far from the critical point the lifetime decreases increasing pressure, showing a non-monotonic temperature dependence.

On the other hand, droplet was defined above the MCP using a “cutoff” value of the density of the system. Droplet can swell (toluene density > CO2 density) or shrink (CO2 density > toluene density) depending on the density difference. When the respective densities are similar no droplet was defined [129].

According to these couple of studies, mass transfer under supercritical conditions is faster than under subcritical conditions, but more parameters should be taken into account in this type of processes to confirm this statement, as might be the droplet velocity.

Droplet velocity was considered by Pérez de Diego et al. [130] to perform a mass transfer study with Maxwell-Stefan approach for the system CO2–DCM (dichloromethane) at subcritical and isothermal conditions. They proved droplet swelling (absorption faster than solvent evaporation) and the strong influence causing by the initial droplet diameter in its lifetime (if the diameter is duplicated, lifetimes increases by four). This fact highlights that pressures just under the MCP are the best to reduce the droplet lifetime because the evaporation process is enhanced with a vapour phase high density.

Tavares-Cardoso et al. [131] added the buoyancy effect to jet hydrodynamics, mass transfer and phase equilibrium for above-MCP conditions. According to their results, at low Reynolds number

\[103,107,111,116\], far above the MCP [117–119] and under the MCP [120]. There have also been cases in which the precipitation was not successful under the MCP due to the existence of a liquid phase [121].

![Fig. 8. (A and B) Different SEDS nozzle schematics.](image-url)
(the \(k\)–\(\omega\) turbulence model was used in its simulation) the fast produced supersaturation prevents to get the real supersaturation and therefore the initial solution concentration does not affect particle size.

The effect of the solute in the evaporation effect was considered by Lora et al. [122], who developed one of the first models at isothermal conditions for SAS process, accounting the previous hydrodynamic, mass transfer (Fick’s law) and thermodynamics. They concluded that the supersaturation is reached very fast (50–100 ms) and provides the required strong antisolvent effect to precipitate the solid. However, sometimes antisolvent effect should be coupled with evaporation to get a precipitation. Particle size and morphology can change due to this phenomenon. Therefore, there are cases in which the solid precipitates only due to a strong antisolvent effect (phenanthrene), but for other solids, like naphthalene, an antisolvent–evaporation effect is required.

Heat transfer between droplet-supercritical atmosphere was taken into account by Fadli et al. [133], performing a simulation to study heat and mass transfer with Fick’s law and PR-EOS above the MCP. They suggested the possibility of controlling the droplet lifetime by changing the temperature gradient at non-isothermal conditions. According to their results, the injection of cold solvent into warm \(\text{CO}_2\) increases the droplet lifetime. On the other hand, warm solvent into colder \(\text{CO}_2\) increases the mixing process and decrease the droplet lifetime.

Mukhapadhyay and Valdi [134] studied the temperature changes in SAS process. The temperature variation above the MCP is very small for high flow rates, because of the small droplet size. That indicates a steady temperature profile at these conditions. However, under the MCP there is a 1–3 K variation followed by an stabilization.

The most complete study for SAS was developed by Martin and Cocero [135]. Thermodynamics, hydrodynamics (\(k\)–\(\omega\) turbulence model), mass transfer and crystallization kinetics were simultaneously considered. This work concluded that the supersaturation is the most important parameter to obtain the best particle size, and consequently the experimental parameters should be modified to get the maximum attainable value. Pressure and temperature are the main parameters, but high solution concentrations, high flow rates and high turbulence improves the mixing. Best conditions are near and above the MCP.

All these models are useful to explain the precipitation mechanism and what is happening when a solution is introduced by means of a nozzle in a supercritical atmosphere. However, there are not able to explain the different particle size and morphology, depending on the experimental conditions.

In order to overcome this shortcoming, Reverchon et al. [115] published a complete article based on experimental observations, which conjugated mass transfer, phase equilibria and jet hydrodynamics (observing the gas–liquid boundaries with an optical set-up).

They made a general interpretation to explain particle size and morphology depending on the break-up time \(t_b\) for breaking the jet and the time for the complete disappearance of the surface tension \(t_s\). If \(t_s\) is less than \(t_b\), there is a gas to solid nucleation (nucleation followed by a size reduction), and nanoparticles are obtained (conditions far above the MCP).

On the other hand, if \(t_s\) is greater than \(t_b\) (under the MCP), there is a droplet growth due to the solubilization of the \(\text{CO}_2\) and then the droplet evaporates. In this case, the obtained microparticles present different morphologies, depending on the mass transfer mechanism of the precipitation inside the droplet.

A mixture between microparticles and nanoparticles can be produced due to a competition between the previous times.

Recently, this theory was numerically explained by calculating \(t_b\) and \(t_s\) for the system \(\text{CO}_2\)-dimethyl sulfoxide-\(\text{Yttrium acetate}\) for different concentrations and pressure conditions [136]. \(t_b\) and \(t_s\) decrease with pressure, and increase with concentration due to the viscosity increase. If both time curves are plotted, a cross point can be observed (Fig. 9). Two different precipitation mechanisms, surface tension vanishing mechanism (nanoparticles), and jet break-up mechanism (microparticles) are distinguished depending on the situation of this point.

Although this last work explains particle size and morphology of the supercritical antisolvant experiments, this work is not able to predict the particle size. The difficulty to obtain a model to predict the PSD is basically due to aggregation mechanisms, phenomena such as secondary nucleation or particle coalescence or even the different behaviour for each solid. Stratified areas because of mixing problems, and the excess volume due to the behaviour of the antisolvent–solvent mixture should be taken into account, and maybe the change of the entrance of the CO might improve the process [131].

Different phenomena such as vessel design or Brownian motion (modified for the different published works) can be also the reasons why different experimental results have been obtained in literature with respect to the best conditions to obtain the smallest PSD.

4.4. **DELOS, PPRGEL, PGSS and PGSS-drying**

These processes consist of a previous solution of the solution in the SCFs followed by a depressurization.

**DELOS** was developed and patented by Ventosa et al. [137]. This process can be used as long as the solution (with the solute to be precipitated) is miscible with the SCF. After this solubilization process, a depressurization at atmospheric pressure is performed. That entails a temperature decrease (Joule–Thomson phenomenon) and uniform supersaturations. The general steps are described in Fig. 10.

The temperature decrease and the supersaturation are enhanced by the capacity of the solution to solubilize \(\text{CO}_2\) or another SCF (R-134a has been also used [138]). However, this technique is similar to GAS, and it is important to distinguish the conditions when the SCF is acting as antisolvent or as a cosolvent.

A thermodynamic study of the solubility should be performed to do that. Fig. 11 shows the standard behaviour of a batch process when a SCF is added.

In this figure, \(S_r\) is the supersaturation ratio of the initial solution, defined as the ratio of the actual concentration and the saturation concentration. It can be seen that the left part of the chart indicates that the SCF acts as cosolvent because the working line lies above the equilibrium curve. However, after the molar fraction \(x_L\) is reached, the situation changes, and the equilibrium curve is
under the working curve. That means that the SCF is acting as an antisolvent and a GAS process will be produced [139].

That fact can be an advantage, because it would be possible to modify the type of process by changing the initial supersaturation ratio. However, this modification should be performed cautiously, because the precipitation yield decreases when the supersaturation ratio is reduced. According to Ventosa et al. [137], the stirring system is not crucial, and the pressure does not affect the temperature reduction in a great extent. Therefore, lower pressures can be used for an optimum precipitation. Moreover, DELOS has been used to produce polymorphs that cannot be obtained with other crystallization techniques. For instance, polymorph E of the stearic acid has been precipitated with DELOS, whereas with GAS, only polymorph C was produced [140].

Temperature decrease due to the Joule–Thomson effect is exploited by PPRGEL. This process use fluids in subcritical state to obtain microparticles. Temperature reduction can be even 70 °C and strongly depends on the SCF (in this case subcritical) released moles from the mixture SCF–solvent [141,142]. Therefore, the key point is to choose a great solvent for the CO₂.

**PGSS** (Fig. 12) was patented by Weidner et al. [143]. This process is used for micronizing solids that are not miscible in the SCF, but they can swell by the SCF addition, such as esters [144] or fats [145]. This process has been also employed for encapsulating β-carotene in poly(ε-caprolactone), taking advantage of the low glass transition of the polymer [146].

PGSS entails a melting point depression to create a saturated solution. In this step, viscosity reduction, swelling or plasticization effects by the use of the SCF help the subsequent spraying process. After that, a depressurization is performed at atmospheric pressure to cool-down the solution by the Joule–Thomson effect. Therefore, solid particles are formed. That highlights the importance of controlling the temperature of the spray tower and the hydrodynamic conditions regarding morphology [147].

Since the gas is more soluble in the liquid that vice versa, a less amount of SCF is required to obtain particles, and in addition it is avoided the use of an organic solvent.

It is very important to study previously the solid–liquid–gas equilibria frontiers (and the possibility of the existence of liquid–liquid equilibria) to know the influence of the high pressure on the solid melting temperature [144,148,149]. Furthermore,
differences can be observed between solid–liquid and liquid–solid transitions in this type of processes. That means the existence of hysteresis, and consequently polymorphic transitions should be taken into account [149].

The atomization of the PGSS process can be improved by using a second gas (in this case air) in the atomization and precipitation vessel [150] (GAMA process).

However, the most used PGSS variation is called PGSS-drying, which was developed by Meterc et al. [151] for drying aqueous compounds (specifically green tea extracts).

Basically, an aqueous solution is contacted with the compressed fluid in a static mixer with several mixing elements. Mass transfer SCF–solution is provided by this mixing. Afterwards, depressurization is performed in a tower at atmospheric pressure and at temperatures above the dew line of the mixture CO2–water. Knowing the VLE diagram of this mixture, different strategies can be followed for compound drying, such as higher temperatures (although softer than temperatures for conventional extraction processes) with a small amount of CO2, or lower temperatures and higher mass flow of CO2. This process provides an inert atmosphere (CO2 atmosphere without oxygen), avoiding the possibility of the oxidation [151]. Thermal stability of the compound should be taken into account to select a suitable temperature for the spray tower. The ternary equilibrium CO2 + solid + water should be also considered, given that the knowledge of the solubility of the CO2 in the liquid phase (and the liquid phase in the CO2) can be very useful.

Furthermore, the water can be absorbed by the particles surface due to the existence of an atmosphere of carbon dioxide and water [152].

PGSS-drying can be used for micronizing hydrophilic compounds as well as sensitive substances such as essential oils [153]. As an example, a complete study of the micronization of the polyethylene glycol with a PGSS-drying pilot plant was performed by Martín et al. [154]. They found that an increase of the gas/liquid ratio reduces the particle size and the residual moisture because the atomization and the drying process are enhanced. This moisture is given by thermodynamic considerations (mainly the gas–liquid ratio).

The morphology changes with the final humidity, obtaining with high water content a kind of undesirable “paste”. On the other hand, low water content produces spherical particles [152,154].

Finally, the obtained particles with PGSS-drying are similar to those obtained with SCF techniques without water. However, regarding microcapsules, the microencapsulation efficiency is lower than the obtained with PGSS process [153,154].

• Modelling PGSS

PGSS was thermodynamically analyzed by Elvassore et al. [155] by calculating the enthalpic changes along the process with the perturbed-hard-sphere-chain-theory EOS. This enthalpic change gives information about the nature of the final product (liquid or solid–liquid). In this way, P–T charts were depicted to predict if depending on the initial conditions the outcome would be either solid or solid–liquid mixture.

Li et al. [156,157] published two articles for PGSS modelling for the system CO2 and hydrogenated palm oil (HPO). They considered an annular mist flow at the exit of the nozzle with an existing equilibrium between the CO2–rich gas phase and the mixed CO2–HPO liquid phase. They used mass, momentum and energy conservation coupled with crystallization equations and PR-EOS (for fluid properties and phase equilibrium) to calculate different parameters profile inside the nozzle [156]. However, they took the mass conservation for the CO2–rich phase as a homogeneous model (HPO particles can be found in this phase). Only trends in particle size are predicted by the simulation, giving the model always a smaller particle size (the reason might be that the calculations are only in the nozzle). At the same time, the model cannot explain the mechanism by which bimodal PSD were sometimes experimentally produced.

In the second article and with the same system (CO2–HPO), they studied independently the governing equations for the CO2 and the HPO for the CO2–rich phase. Their results indicated that at the exit of the nozzle the PSD is narrower with a smaller particle size because the particles are formed by melt crystallization, but if the particle formation is due to an atomization process, PSD is larger and wider. A bimodal PSD is explained with this theory [157].

However, both models were only focused on droplet diameter and PSD, without entering in the fluid dynamics of a generated droplet by the PGSS.

In this context, Strumendo et al. [158] studied mass and heat transfer for a saturated and stagnant droplet of tristearin in CO2 until the particle is generated (solid–liquid equilibrium (SLE is reached). Equilibrium is computed with PHSC–EOS and Stefan equations are used. However, convective motion, gravity and droplet interactions are not taken into account.

Faster heat transfer than mass transfer is obtained according to the results. The time for getting the SLE is calculated for different CO2 initial mass fractions and initial droplet temperatures. The SLE time goes to zero when the temperature is close to the melting point, and an increase in temperature increases the SLE time. However, the opposite effect was obtained if the initial CO2 mass fraction is increased. These SLE time results correlate well with the trend of the PSD, which increases with temperature and decreases with initial mass fraction of CO2. The droplet shrinks for all the investigated conditions, although this shrinking is very small because of the shorter times to reach the equilibrium.

This model does not take into account nozzle hydrodynamics, crystallization or the effect of the drying because bubble formation inside the droplet. However, it highlights the importance of the equipment design in terms of get the correct time to get the particle formation.

• Modelling PGSS-drying

Martin and Weidner [159] published a model for PGSS-drying for the system CO2–water–PEG. They performed a mass balance and enthalpic balance (with experimental adsorption results water–PEG) to predict the gas–liquid ratio to get a complete evaporation, the moisture concentration in the outcome and the expansion temperature as function of the pre-expansion conditions. They used a PC-SAFT equation to take into account the non-idealities and to calculate the corresponding equilibrium and mass transfer limits in the system.

These mass transfer limits provide information to determine the extracted water to the gas phase in the static mixer as function of the gas–liquid ratio. The authors found out that the water can be totally extracted in the static mixer by changing the gas liquid ratio and the pre-expansion temperature (first proposed mechanism). Then, by using global mass transfer coefficients, the different profiles of molar flux CO2–liquid phase were determined as function of the static mixer length [159].

Furthermore, water can be extracted with a second mechanism after the depressurization. In this case, the water should be transported to the CO2 atmosphere. Therefore, pre-expansion temperature and gas–liquid ratio might be modified to obtain a perfect drying using a mixture between these two mechanisms [152].

Two simultaneous types of atomization for PGSS-drying process were proposed by Martin and Weidner [159]: flash-boiling [160] (a superheated liquid is expanded through a nozzle) and effervescent [161] (a biphasic mixture is expanded through a nozzle, taking advantage of the formed bubbles).
4.5. CAN-BD and SAA

Both techniques were developed with the aim of using the SCF (mainly sc-CO₂) to improve the atomization process.

**CAN-BD** (Fig. 13) was used to micronize hydrophilic compounds. Solution and sc-CO₂ are put in contact during short time in a low-dead-volume tee. A quantity of CO₂ is solubilized in water and an emulsion is formed [162]. Subsequently, this emulsion is atomized by using a restrictor to a drying chamber where a N₂ inert flux help the drying process. CO₂ solubilization in water provides an atomization enhancement, differing from the complete saturation occurring in PGSS or PGSS-drying. Droplet diameter might be controlled varying temperature, pressure, flow rates and diameter restrictor. Drawbacks related to the blockage nozzle (Joule–Thomson effect) are avoided because nozzle, tee connection and chamber are heated.

On the other hand, relatively high temperatures to perform the droplets drying process are required, and might damage the active substance.

At our knowledge, a mechanism for this process has not been established yet, but an effervescent atomization might take place.

**SAA** process was developed by Reverchon [163] in order to avoid the big pressure drop in the tee. A packed tower to mix the CO₂ with the liquid (water or other solvents) at high pressure and temperature was used. Their objective was to saturate the mixture with CO₂ by adding therefore an excess of sc-CO₂ at conditions above the MCP. This saturation is the main difference with PGSS-drying (last technique uses the minimum amount of CO₂). CO₂ acts therefore as a cosolute, improving the atomization at the same time. Subsequently, an atomization of the mixture at atmospheric pressure is performed in a heated precipitator with N₂ to evaporate the droplets.

SAA (like CAN-BD) provides a more efficient atomization because after the primary atomization, the release of CO₂ produces a secondary atomization. Smaller droplets are produced due to this phenomenon.

However, it is important to consider the limitation of this process with respect to several thermolabile compounds due to the high required temperatures. This can be solved by applying a vacuum in the precipitator [164]. This fact highlights the easy tunability of this process to produce particles and/or microcapsules [165].

As occurs with other techniques with SCFs, the previous thermodynamic study can play an important role regarding morphology or PSD. In this case, the experiments should lie in a single liquid phase (with respect to the antisolvent–solvent diagram) to produce the same morphology, avoiding biphasic areas. The temperature should be enough to produce the solvent evaporation, and at the same time the glass transition temperature must not be reached (if the solid is a polymer) [166].

SAA has not been modelling yet and the mechanism is complicated, because the antisolvent effect of the sc-CO₂ should be considered. Rodrigues et al. [167] precipitated lysozyme with SAA, obtaining two different morphologies, what indicated that antisolvent and atomization crystallizations might be produced at the same time. Same authors precipitated the same compound using high nitrogen-solution ratios, obtaining a one single morphology with a similar PSD. Therefore, it seems that a strong and intensive mixing could be enough to precipitate particles [167].

The main mechanism of particle nucleation in this process was clarified by using a population balance. It was shown that SAA process produces mainly a primary nucleation [168].

4.6. SFEE

One of the main limitations for the previous techniques is the particle size. Except for a few occasions (mainly with RESS or RESOLV), particles are usually in a micrometric range. Nevertheless, sub-micron particles can be required for different applications. In this context, methodologies using w/o emulsions can be very useful. **SFEE** mixes the efficiency of the SFE and the ability of the emulsion processes to obtain nanoparticles. Basically, the SCF is put in contact with water in oil emulsions (w/o) or oil in water emulsions (o/w), and the SCF extracts oil-organic phase in which it is solubilized the water-insoluble drug. The drug remains therefore in a suspension that should be established by using a surfactant that at the same time avoids aggregation phenomena. In addition, this technique provides “clean” particles with low concentration (ppm) of the solvent [169].

Different compounds were successfully processed with **SFEE** [170]. Those compounds can have similar structure to the backbone of many steroids, can presented mechanical micronization difficulties or they can be even water-insoluble.

Polymers can be also processed with SFEE. In this case, it is very important to take into consideration the equilibrium CO₂–water–polymer. This fact can decrease the glass transition to form plasticized polymer beads, although this phenomenon can be even beneficial for the emulsion stabilization and solvent removal [171].

The use of emulsions and SCF can be used together for w/o emulsion reaction assisted by sc-CO₂. This technique has been employed to produce metal oxides [172]. In this case, the sc-CO₂ extracts the organic phase and at the same time it is produced a reaction in the aqueous phase with the CO₂ as a reactant to produce nanoparticles.

Pharmaceutical compounds can be encapsulated with SFEE process by creating an emulsion of a drug–polymer mixture. Capsules are formed inside the emulsion droplet [171].

At the beginning, this process was considered only as a discontinuous process. However, high pressures with large time increase the surface tension, and the emulsion might be destabilized. A packed tower was used therefore to perform a continuous process. Although these towers might be blocked if solids are involved, this blockage can be avoided due to existence of a suspension
with low residence time and a surfactant. A continuous process provides greater drug/polymer recovering (with similar particle distribution) and less residuals (better contact between the different phases). Moreover, the extraction is six times faster [173].

Therefore, the main limitation for the SFEE is the control of the emulsion. The emulsion should be stable, avoiding coalescence phenomenon (more possible with double emulsions). A phase equilibria study of the complete system should be performed to know the proper operation conditions. Experiments should be carried out in the biphasic zone, to create a stable emulsion (in the one-phase area the emulsion is not stable and the particles are aggregates) [174].

As long as the droplet corresponds to a stable emulsion, it is assumed droplet-particle theory. However, the results not always agree with this theory, and particle size larger than droplet size have been obtained, due to the existence of interactions.

For instance, higher concentration of the drug/polymer solutions increases the viscosity in the oily phase, getting emulsion droplets bigger [175].

The mechanism for the SFEE is explained taking into account the mass transfer routes. It is assumed that there is a direct extraction between the SCF and the organic phase inside the droplet. At the same time, due to the equilibrium between the solvent-aqueous phases there is a diffusion of the organic solvent in water following for its extraction from the aqueous phase [173]. The first step is known as direct supercritical extraction whereas the second step is known as indirect supercritical extraction.

• Modelling SFEE

In order to get a complete understanding of this process, it would be necessary to see the evolution of a single droplet during the precipitation process. That was illustrated by Mattea et al. [176,177]. They studied in a high pressure visual cell the evolution of a single droplet of the organic solvent for the system CO2–DCM–water taking into account the volume and surface tension changes, and calculating the concentration profiles of the droplet. It was showed (using a sessile drop and taking advantage of the change of the refractive index) that droplet undergoes a swelling/shrinking process depending on the experimental conditions. Under the MCP, the droplet swells up to a maximum value, followed by a droplet shrinking. Equilibrium CO2–DCM and the solubility of CO2 in water explain this phenomenon. Based on these considerations, under the MCP there is a point in which the DCM diffusion out of the droplet turns out faster than the diffusion towards the droplet. This theory can explain the swelling phenomenon over the shrinking process that occurs above the MCP, conditions at which the equilibrium does not establish a barrier for the diffusion [176].

On the other hand, applying a pendant droplet methodology, it was observed an increase of the surface tension of the organic phase, meaning that the emulsion becomes unstable with time. That is one limitation of a batch process (greater times are required).

It was shown that the CO2 addition does not affect the surfactant properties, as long as the surfactant concentration is not very high (higher concentrations can involve the precipitation of the surfactant). Finally, by adding beta-carotene it was shown that each droplet behaves as a single GAS process, theory that applied to calculate the different molar flux inside/out of the droplet [177].

4.7. Miscellaneous

The previous processes usually employ sc-CO2. However, more fluids in supercritical or subcritical state can be employed for drug processing.

Water, for instance, can be used in subcritical state to produce particles of hydrophobic compounds [178,179]. This process consists of heating the water up to 200 °C at high pressure to maintain the water in liquid state. At this temperature, the dielectric constant of the water decreases, and therefore the water can solubilize hydrophobic compounds. However, cosolvents should be used to reduce the dielectric constant and get a complete solubilization. The use of cosolvents also offers the possibility of controlling particles morphology [178]. Then, as happens with the rest of SCFs techniques, a fast supersaturation can be achieved if the solution is cooling down, and the solid precipitates. It is required a subsequent drying process because the particles are suspended in an aqueous medium.

A carrier/excipient can be used in the precipitation chamber [178]. Drug agglomeration can be avoided by the use of this carrier, as it was appointed by Sanganwar et al. [180], to design the SAS-DEM process (supercritical antisolvent-drug excipient mixing). This is a typical SAS process, but with lactose as a suspended excipient in the vessel, inducing the co-mixing.

Different (antisolvent and solvent) techniques can be employed at the same time. RESS and SEDS were used together for the crystallization of a triblock polymer PLA–PEG–PLA. This polymer is partial soluble in sc-CO2, what indicates that it could not be processed with RESS or SEDS. In order to overcome this drawback, a SEDS process of the polymer solution was performed, and after that the resulting mixture was sprayed in a vessel at atmospheric pressure (RESS). The polymer was then precipitated using two techniques simultaneously [181].

A variation of the PGSS can be applied to produce powder coatings [182]. Coatings are formed by two components (binder and hardener). Continuous powder coating spraying process (CPCSP) melts the components in two different vessels, and subsequently those components are mixed in a static mixer with compressed CO2. The mixture is subsequently sprayed in a tower, and the gas is removed by using a cyclone. This process provides a control of morphology and particle size depending on the viscosity of the mixture.

The use of SCFs can produce valuable techniques to obtain different complex formations or to impregnate polymers with pharmaceuticals. Controlled particle deposition (CPD) can provide complex formations of a soluble drug in sc-CO2 in a porous solid carrier. The carrier is non-soluble in sc-CO2. This drug is dissolved in the SCF, and by a subsequent permeation of the supercritical solution into the carrier, the drug is precipitated into the porous, forming a complex [183].

On the other hand, supercritical solvent impregnation (SSI) requires the dissolution of the drug in the SCF. The solution is subsequently put in contact with a polymer. If the polymer swells due to the addition of the SCF, it is possible (after a subsequent desorption) to impregnate the polymer with the drug, obtaining therefore a drug release system [184]. As happens with other techniques that use sc-CO2, the key point of this process is the solubility of the different compounds in the SCF and the polymer swelling. This technique has been even applied to impregnate intraocular [185] or contact lens with drugs [186,187] and different starches with essential oils [188,189].

5. Conclusions

Supercritical fluids techniques are a good alternative for conventional methods for drug processing. They can be employed (specifically sc-CO2) as “green” technologies to obtain crystalline pharmaceuticals with a narrow particle size distribution. In this context, an extensive research has been performed over these last 20 years to increase the possibilities of these techniques.
Nowadays, it is possible to process different compounds in spite of their characteristics, by only changing the methodology, or the used supercritical fluid (the use of water for instance has been proposed). Moreover, the supersaturation, and consequently the particle size, can be controlled by modifying the experimental conditions.

However, prior to the use of these techniques, it is usually required to perform a thermodynamic study in order to know the solubility behaviour of the system and the corresponding phase frontiers. Nevertheless, at present time, there is not a general equation to provide a proper estimation of this solubility and/or equilibria data.

Same occurs with the particle size and the morphology of the final product. A general model to predict the particle characteristics has not been developed yet. Nevertheless, many of the mechanisms for the most employed processes have been established. Based on these works, it is possible to get a qualitative prediction of the effect of the parameters in particle size, and have a previous knowledge of the general characteristics of the produced particles.

Acknowledgment

This research was supported by funds from the Ministerio de Ciencia e Innovación (Spain), project CTQ2009-08222 (PPQ Sub-program).

References

Z. N. supercritical (2012)
semiempirical of a
critical CO2–organic
dissolution in methanol, and acetone mixtures.
A. Tabernero et al. / Chemical Engineering and Processing 60 (2012) 9–25


