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Chapter

Supercritical Fluids: Properties and Applications

Mercedes G. Montalbán and Gloria Víllora

Abstract

Currently, both humanity and the whole planet are living in a critical time, which leads us to look for more sustainable formulas to interact with the environment. One of the important changes in the design and operation of chemical processes is the search for environmentally friendly technologies. Many industrial processes are carried out under severe conditions or with reactants that involve the use of strong acids, toxic metal catalysts, organic solvents, and processes at high temperatures and/or pressures. Supercritical fluids (SCFs) and, among these, supercritical carbon dioxide (scCO\textsubscript{2}), have been revealed as promising environmentally friendly solvents, energy-efficient, selective, and capable of reducing waste, constituting an alternative to conventional organic solvents. The use of SCF, such as solvents and reaction media, makes it possible to work in less severe and more environmentally friendly conditions, even considerably increasing the efficiency of the processes. This chapter provides a brief review of the most important properties of SCF, with special emphasis on scCO\textsubscript{2}, as well as some of the most important applications.

Keywords: supercritical, critical properties, carbon dioxide, extraction, chemical reaction, nanoparticle, biocatalysis

1. Introduction

Currently, the aggregation states of the matter are solid, liquid, gas, plasma, and Bose-Einstein condensate. A supercritical fluid is a quasi-state with intermediate properties between liquids and gases.

The plasma is defined as an ionized gas, which is composed of electrons, protons, and free neutrons. It can be obtained by heating a gas or from a gas under strong magnetic fields. Although plasma is not naturally present on the Earth, the 99% of the matter of the universe is in the plasma state, with the Sun being our nearest example.

The Bose-Einstein condensate is an aggregation state, which is reached near to the zero absolute of temperature, i.e., −273°C. In this state, a macroscopic quantity of the material particles goes through the minimum energy level, which is well known as fundamental state. As a consequence of the Pauli exclusion principle, only the bosons can be in this state. Anderson et al. [1] synthesized this state at the laboratory in 1995, for the first time. For this, they cooled atoms at less than one millionth of a Kelvin above absolute zero of temperature.
In each state, matter presents differences in terms of the interaction forces between its molecules, which in the solid state are greater than in the liquid state and, in the latter, in turn, greater than in the gaseous state. This means that the molecules of a gas are less bound to each other than in the liquid and that their density is lower.

If a liquid is at rest in a closed container, inside the container an equilibrium will be established between the liquid and gaseous phases that will depend on the vapor pressure of the compound in question. If energy is applied to this system in the form of heat, the liquid will increase its temperature until it boils, and the pressure inside the contained will increase. Considering the phenomenon of thermal expansion of the liquid until it reaches its boiling temperature and the evaporation process, the density of the liquid will decrease while that of the gas will increase. If we continue with the process, we will reach a point where the densities of both phases become equal, and it is not possible to differentiate the liquid phase from the gas phase. This point is well known as critical point, and it is characterized by a critical pressure, temperature, and molar volume.

The critical temperature can be defined as the temperature above which the liquid-vapor meniscus cannot be formed when the pressure is raised at isothermal conditions. In the same way, the critical pressure can be defined as the pressure above which the liquid-vapor meniscus cannot be formed when the temperature is increased under isobaric conditions. Mathematically, the critical point is reached at a temperature and pressure at which the following is true:

\[
\left(\frac{\delta P}{\delta V}\right)_T = 0
\]

(1)

\[
\left(\frac{\delta^2 P}{\delta V^2}\right)_T = 0
\]

(2)

As can be seen on phase diagram of Figure 1, the lines represent the different equilibria that can occur between the phases. Thus, the sublimation curve (for solid-gas equilibria), the melting curve (for solid-liquid equilibria), and the vaporization curve

![Figure 1. Phase diagram including supercritical state.](image-url)
(for liquid-gas equilibria) can be defined. The cutoff point for all of them is known as the triple point and represents the conditions in which the three phases coexist. The critical point is located at the end of the liquid-gas equilibrium line, and when these conditions, i.e., pressure and temperature, are exceeded, it is said that we have a supercritical fluid.

In the supercritical state, the density can be varied by modifying the conditions (since in the supercritical zone the density increases continuously), but the change takes place through a process of gradual transition from vapor to liquid, which contrasts with the sudden transition that occurs in condensation processes. This implies that once the critical point has been exceeded, no compression process is able to allow that liquid and gas phases coexist. Therefore, it can then be said that, from the critical point, when the pressure increases, no liquefaction occurs, nor does evaporation occur when the temperature increases. Importantly, it should be seen that below and to the left of the supercritical region there are not definite boundaries and the transition from a single phase, gas or liquid, to supercritical fluid does not take place dramatically, but rather the change is gradual.

In the supercritical state, matter is compressible and behaves like a gas, although it has a density like that of liquids (0.1–1.0 g/cm$^3$). This property has led to supercritical fluids (SCFs) also being called “dense gases.”

Regarding extracting operations with SCF, SCF can be named as “gases with density-dependent solvent power.” In other words, the power as a solvent of a compound in supercritical state highly depends on its density and, therefore, on its pressure and temperature [2].

2. Properties of supercritical fluids

There are many substances commonly used as SCFs. Table 1 collects some of them and their properties. CO$_2$ is marked in yellow.

From an industrial point of view, SCF have a series of characteristics that make them very interesting for various applications. Their properties as solvents allow that they can replace water and organic solvents in numerous processes, thus reducing their consumption. This is a great benefit for the environment, not only because of

<table>
<thead>
<tr>
<th>FLUID</th>
<th>$T_c$ (°C)</th>
<th>$P_c$ (bar)</th>
<th>$\delta_c$ (g/cm$^3$)</th>
<th>Density at 400 bar (g/cm$^3$)</th>
<th>Density of the liquid (g/cm$^3$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xe</td>
<td>16.6</td>
<td>58.4</td>
<td>1.10</td>
<td>2.30</td>
<td>3.08 (sat., 111.7°C)</td>
</tr>
<tr>
<td>CHF$_3$</td>
<td>25.9</td>
<td>46.9</td>
<td>0.52</td>
<td>—</td>
<td>1.51 (sat., −100°C)</td>
</tr>
<tr>
<td>CO$_2$</td>
<td>31.3</td>
<td>72.9</td>
<td>0.47</td>
<td>0.96</td>
<td>0.93 (63.4 bar, 25°C)</td>
</tr>
<tr>
<td>N$_2$O</td>
<td>36.5</td>
<td>72.5</td>
<td>0.45</td>
<td>0.94</td>
<td>0.91 (sat., 0 °C)</td>
</tr>
<tr>
<td>SF$_6$</td>
<td>45.5</td>
<td>37.1</td>
<td>0.74</td>
<td>1.61</td>
<td>1.91 (sat., −50°C)</td>
</tr>
<tr>
<td>CCl$_2$F$_2$</td>
<td>111.8</td>
<td>40.7</td>
<td>0.56</td>
<td>1.12</td>
<td>1.53 (sat., −45.6°C)</td>
</tr>
<tr>
<td>NH$_3$</td>
<td>132.5</td>
<td>112.5</td>
<td>0.24</td>
<td>0.40</td>
<td>0.60 (10.5 bar, 25°C)</td>
</tr>
<tr>
<td>Butane</td>
<td>152.0</td>
<td>37.5</td>
<td>0.23</td>
<td>0.50</td>
<td>0.58 (sat., 20°C)</td>
</tr>
<tr>
<td>Pentane</td>
<td>196.6</td>
<td>33.3</td>
<td>0.23</td>
<td>0.51</td>
<td>0.75 (1 bar, 25°C)</td>
</tr>
</tbody>
</table>

Table 1. Physical properties (critical temperature, $T_c$, critical pressure, $P_c$, critical density, $\delta_c$, of the most commonly used SCFs.)
the water savings it implies, but also because organic solvents are consumed in large quantities and are volatile and polluting substances [3]. In particular, CO$_2$ at high pressures, in liquid or supercritical state, is drawing great attention due to its worldwide expectations [4].

In addition to being able to replace conventional solvents, SCFs have numerous advantages over them [5]:

- Its density can be modulated by adjusting pressure and temperature within the supercritical region, so the properties of the solvent can be varied just by modifying the operating conditions and without having to change the medium.
- They also have the high diffusivities inherent to gases (one or two orders of magnitude greater than those of liquids) and low viscosities (an order of magnitude lower than liquid solvents), which contribute to improving mass transfer processes.
- The supercritical processes consume less energy than those based on organic solvents, since they do not require working at high temperatures or the transitions between distillation and condensation.
- The use of SCF eliminates the environmental and safety drawbacks of organic solvents such as volatility, residue, flammability, and toxicity.
- The viscosity is much lower than that of liquids, which gives it very favorable hydrodynamic properties.
- They have high penetrability through porous solids and packed beds due to their low surface tension.

3. Supercritical carbon dioxide (scCO$_2$)

As it is widely known, CO$_2$ is a gas that is found in abundance in the Earth’s atmosphere and is the product of the respiration of animals and plants. In addition, it is produced in large quantities in combustion processes and its accumulation is leading to the greenhouse effect and global warming. From the point of view of “green chemistry” or chemistry that respects the environment, the most interesting thing to use CO$_2$ in industrial processes would be to take it from the atmosphere or from the aforementioned combustion processes (e.g., in thermal power plants); nevertheless, in practice, almost all the commercial CO$_2$ is obtained as a by-product of the ammonia manufacturing process, after being properly purified [6].

The critical parameters of CO$_2$ are 31.3°C and 72.9 bar (see Table 1), which are easily achievable. This, together with its ease of transport and not having to work at very high pressures or temperatures (which would increase the danger of the process and the price of the equipment), makes it a relatively cheap and safe option, compared with the rest of SCFs. Among all its properties, those that have made it one of the most widely used SCFs in the world are its nontoxicity, its clean nature not generating residues, and that its critical temperature makes it suitable for working with compounds that do not resist high temperatures. For this reason, CO$_2$ can be used in the food and pharmaceutical industry. CO$_2$ has also a low reactivity (a very useful property if it is to be used as a solvent), it is not flammable (it makes it safe), and it
is easy to recover and recycle. Its dielectric constant is ~1.5 for liquid and 1.1 – 1.5 for supercritical (depending on density).

In addition to the previous applications, \( \text{scCO}_2 \) is used in hydrogenations, reducing flammability and preventing fouling of the catalyst due to it can dissolve compounds that contribute to the formation of coke, in the production of polycarbonates as an alternative to the phosgene route, in the production of fine particles, in the production of certain polymers, in the foaming of thermoplastics, and as an extinguishing agent [7, 8].

Supercritical technology requires equipment with special specifications, which implies a high initial cost of the facilities, both for the main operating equipment and for the auxiliary control, prevention, and protection equipment. In addition, having a high pressure as a starting point could lead to problems when working with exothermic processes, since an increase in temperature could raise the pressure dangerously and a rigorous control of the process will be necessary. Some substances such as ammonia are toxic and flammable, and their use at high pressures and temperatures increases the risk of accidents and of their consequences. For these reasons, most governments do not authorize the creation of large industrial facilities that work with supercritical technology and that the vast majority of plants of this type are concentrated in two countries: China and India.

The low dielectric constant can be responsible of problems to dissolve polar substrates, although this can be avoided by adding a polar cosolvent such as ethanol, acetone, or water, which would increase the polarity of the solvent by hydrogen bonding. However, the presence of another compound may complicate reactions or have undesirable effects. Another option would be to complex the polar substrates with phenylboronic acid and their subsequent recovery by extraction for contact with an aqueous phase [9].

\( \text{CO}_2 \) is a Lewis acid, so it can react with strong bases such as amines, phosphines, or alkyl anions, which greatly complicates its use in reactions where these compounds are involved. Dense \( \text{CO}_2 \) produces low pH (around 2.85) if it is in the presence of water, since it leads to the formation of \( \text{H}_2\text{CO}_3 \). This can lead to problems in the field of biocatalysis because some enzymes are denatured under these conditions. This drawback can be turned into an advantage when you want to use \( \text{H}_2\text{CO}_3 \) as a reagent, since then you do not need a base to neutralize, but only to decompress. Finally, when \( \text{scCO}_2 \) is in the presence of noble metals, it can be hydrogenated producing \( \text{CO} \), which is a poison for most catalysts.

4. Applications of supercritical fluids

4.1 Extraction with supercritical fluids

One of the most interesting applications of SCFs is to use them as extraction agents, because they can be used in separation operations at much lower temperatures than distillation, avoiding the degradation and decomposition of thermolabile compounds. The interest of SCF extraction processes is due to the possibility of regeneration, solvent versatility, energy savings with respect to other processes, selectivity, sensitivity of the results to operating conditions, improved solute volatility, solvent selectivity, favorable transport properties, and environmentally acceptable [5]. Furthermore, the products thus obtained are easily recoverable and the solvent can be easily reused by depressurization at atmospheric pressure.
By means of a simple depressurization, the SCF can be turned into a gaseous state, producing a phase separation and the precipitation of the extracted compound, which can be solid or liquid. In addition, in processes that require a fractional precipitation of several products, successive stages of decompression can be carried out in series.

Supercritical CO\textsubscript{2} (scCO\textsubscript{2}) extraction is the most widespread industrial application of SCF. scCO\textsubscript{2} is applied to obtain products such as decaffeinated tea or coffee [10], nicotine-free tobacco [11], pharmaceutical products [12], aromas [13], paints [14], antioxidants [15], polymers [16], etc.

The separation with SCF requires two fundamental steps as occurs in the processes of separation, which use an auxiliary medium. Firstly, the desired extraction is carried out, and secondly, the SCF is separated from the feed, regenerated, and recirculated. The separation of the SCF from the solute is normally an easy task, which can be generally carried out by lowering the pressure, and usually accompanied by a lowering of the temperature. This can be also achieved by increasing the temperature at constant pressure.

Extraction processes using SCF can be classified into three general types. The simplest separation scheme, which is shown in Figure 2, consists of a single-stage process. It can be used to carry out the extraction of solids or liquids. For a successful extraction, very high separation factors are needed. Some examples of common industrial applications of single-stage processes are the extraction of oils, spices, and alkaloids from solids and the deoiling of lecithin [17].

Multistage processes can also be used for extraction. Their scheme is represented in Figure 3. This type of extraction is useful when the separation factors for one stage are not large enough. The main advantage of a multistage process is that the separation and/or extraction conditions can be modulated in order to improve the extraction. Examples of multistage processes include waste oil refining, edible oil fractionation, and deasphalting [17].

Finally, the third category of SCF extraction is the continuous countercurrent-flow operation, which is represented in Figure 4. This type of separation is similar to liquid-liquid extraction. Some examples of continuous countercurrent-flow operations include the enrichment of ethanol from dilute aqueous solutions, the separation of mono- and diglycerides, and the separation of fatty acids [17].
The decaffeination process is a typical example of supercritical extraction. This process provides products without caffeine or with a reduced caffeine content, such as decaffeinated coffee or decaffeinated tea. However, some processes leave a drink with low taste. Some methods use organic solvents, such as ethyl acetate, alcohol, chloroform, dichloromethane, or acetone. Other methods use water and scCO$_2$. scCO$_2$ has the advantages compared with the other methods that can retain most flavor compounds, is a nontoxic solvent, the process uses mild conditions (especially temperature), then, the energy consumption is generally lower than conventional processes, and CO$_2$ can be easily separated from the products, simply by decompression. In addition, scCO$_2$ has good dissolving capacity and good mass transfer performance. Because of that, scCO$_2$ decaffeination, despite being a relatively recent technology (was patented in Germany in 1964 and in the United States in 1974, and commercial plants went online in Germany in 1978 and in the United States in 1988), has expanded rapidly all over the world [18].
Decaffeination processes can serve to illustrate the different types of supercritical extraction from the point of view of their operating mode. One of these operating modes is by a batch process. In this case, the biomass and CO\textsubscript{2} are mixed in a fixed bed for a static time under established operating conditions (temperature and pressure). Once the determined time has elapsed, the fixed bed is depressurized and the extract and solid matrix are recovered. Generally, the batch process is carried out by a single stage due to the difficulty in handling the solids in pressure vessels by a continuous mode. Figure 5 shows a typical process.

Another operating mode is by semicontinuous or semibatch process. As can be observed in the figure, in this type of process, the biomass is placed in a fixed bed and the CO\textsubscript{2} flows continuously through the bed under the established operating conditions. The extract is retrieved at the exit of the extraction vessel and the caffeine recollected. The most commonly process used in supercritical extraction is semicontinuous because pumps can be used to pressurize fluids without containing solid particles. As presented in the scheme of Figure 6, first the CO\textsubscript{2} must be change from gas to liquid phase to avoid cavitation of the pump, then the CO\textsubscript{2} is pressurized to operating pressure by a pump, heated to the objective temperature by a heat exchanger, and fed to the extractor containing the biomass. Finally, the depleted biomass is discharged for further drying. This type of process requires short residence times of scCO\textsubscript{2} in contact with the solid and allows the use of different particle sizes [18].

In continuous operation mode (Figure 7), the CO\textsubscript{2} and the solid biomass flow continuously through the extractor, so they must be mixed and pressurized by a pump to maintain the determined operating conditions of pressure and temperature. The extract is obtained at the exit of the extractor, and the decaffeinated solid material and the caffeine are separated. The continuous process needs pumps that pressurize fluids containing solid biomass particles. As can be seen in the figure, the sequence of stages that follow each other in this type of process is: CO\textsubscript{2} cooling; mixing of CO\textsubscript{2} with crushed biomass; pressurization of the CO\textsubscript{2} mixture with the biomass to

![Figure 5](image_url)

*Figure 5.* Schematic flowchart of decaffeination by scCO\textsubscript{2} extraction in a batch process (dashed lines indicate a noncontinuous flow). Adapted from [18].
the desired pressure using a high-pressure pump; heating of the mixture to the set temperature by means of a heat exchanger; pumping of the mixture to the extractor; the collection of the extract mixed with biomass at the exit of the extraction vessel in the separators. These systems are characterized by short residence times, high solvent-biomass ratios in the feed, very small sizes of solid particles, and good process control [18].

For large extraction of caffeine processes, depressurization to atmospheric pressure makes solvent reuse more expensive, since compression processes are energy expensive. Therefore, a liquid-liquid extraction with water is preferred, so it is not necessary to reduce the pressure so much to extract the desired product. Furthermore, scCO\textsubscript{2} with recirculated water has better extraction properties than dry CO\textsubscript{2} [19].

Figure 8, adapted from [20], shows a scheme of the Kraft General Foods’ patented
process for decaffeinated green coffee beans. Saturation with water has been shown to improve caffeine extraction rates, and increased temperature and pressure improve caffeine partitioning in the supercritical phase. The extraction of scCO$_2$ from many compounds from natural substrates (plants, algae, materials of animal origin, etc.) has been investigated. Examples include extracting α acids from hops, flavors, spices, and fragrances that have been extracted and include lilac, essential oils, black pepper, nutmeg, vanilla, basil, ginger, paprika, rosemary, chamomile, and ground chili peppers.

Large-scale industrial applications require specific, single-purpose plant designs. However, multipurpose scCO$_2$ extraction plants can be designed to be used for obtaining different extracts of high added value through processes that operate at smaller scales. A common element of these plants that is important for the economy of the process is the system used to separate and recirculate CO$_2$ to the extraction unit.

The recirculation cycle may be carried out with a liquid pump or with a compressor. The recirculation cycle with a liquid pump consists of condensing the carbon dioxide at the output of the process and recirculating it using a pump for liquids. To condense carbon dioxide, the pressure must be reduced below the critical pressure and the carbon dioxide must be cooled. The pressure and temperature conditions used for condensation and recirculation must be optimized in each specific case, but pressures in the range of 40–60 bar are recommended, since the corresponding condensation temperatures are close to the ambient temperature, which allows the use of cheap refrigerants such as cooling water. When the process requires mixing an organic solvent with CO$_2$, it is necessary to take into account the separation of the same and the purification of CO$_2$. It is possible to achieve separation of the organic solvent by partial condensation of the supercritical effluent prior to CO$_2$ condensation, but if the CO$_2$ purity achieved is not high enough, more complex and expensive processes such as adsorption or cryogenic distillation may be necessary. The recirculation cycle with

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**Figure 8.**
*Scheme of semicontinuous caffeine extraction process using scCO$_2$. Adapted from [20].*
a compressor consists of recompressing and recirculating the effluent directly in a gaseous or supercritical state. If CO₂ must be purified before recycling it, it is necessary to include additional stages. The choice of using a compressor or liquid pump for the recirculation cycle depends on economic and technical reasons and will depend on the type of process. In general, the liquid pump is preferred for small installations for reasons of economy and simplicity of use [21].

Another very important factor to consider when designing an extraction process with scCO₂ is the pressure of the extractor. The most common values are in the range of 5–30 MPa. As for the container, fast-closing designs, different sizes, and (1 L-1 m³) and materials (metallic and polymeric) are available on the market.

Although the investment costs of a scCO₂ extraction plant can be high, the operating costs are usually relatively low, due to the reduction in energy consumption related to the use of temperatures close to the environment [22].

4.2 Formation of particles by supercritical technology

After more than three decades using SCF for particle formation, several techniques have been developed. Technologies currently used differ in the basic principles of operation, but they are all based on the mechanisms of nucleation, particle growth, and precipitation. In this section, we will give a brief overview of the different processes of particle formation using SCF.

Table 2 summarizes the characteristics of the different particle formation technologies using SCF.

<table>
<thead>
<tr>
<th>Process</th>
<th>Role of supercritical fluid</th>
<th>Role of organic solvent</th>
<th>Mode of phase separation</th>
</tr>
</thead>
<tbody>
<tr>
<td>RESS</td>
<td>Solvent</td>
<td>not needed or cosolvent</td>
<td>pressure/temperature induced</td>
</tr>
<tr>
<td>GAS</td>
<td>Antisolvent</td>
<td>solvent</td>
<td>solvent-induced</td>
</tr>
<tr>
<td>SAS</td>
<td>Antisolvent</td>
<td>solvent</td>
<td>solvent-induced</td>
</tr>
<tr>
<td>SEDS</td>
<td>Antisolvent</td>
<td>solvent/antisolvent</td>
<td>solvent-induced</td>
</tr>
<tr>
<td>PGSS</td>
<td>dispersing agent solute</td>
<td>not needed</td>
<td>pressure/temperature induced</td>
</tr>
<tr>
<td>PGSS-drying</td>
<td>solute/propellant</td>
<td>not needed</td>
<td>pressure/temperature induced</td>
</tr>
<tr>
<td>SAA</td>
<td>Propellant</td>
<td>solvent or not needed</td>
<td>pressure/temperature induced</td>
</tr>
</tbody>
</table>

Table 2. Summary of particle formation technologies using SCF. From reference [21] with permission of John Wiley & Sons.
fission temperature of the polymer and the degree to which these transitions may have been reduced and the path followed by the homogeneous region of a phase, particle formation may come from crossing the fluid-solid barrier (F-S), or the system may have crossed the liquid-liquid barrier (L-L), followed by solidification [23]. Then, when designing this process, the solubility of the material plays a crucial role in the formation and processing of particles, since most pharmaceutical substances, such as polymers, drugs, and proteins of high molecular weight, are polar in nature. In some cases, small amounts of organic solvents are added to improve the affinity of the polar molecules of the drugs.

RESS is the simplest and most effective method of SCF technology, but its application is limited due to its relatively high cost and, when scCO$_2$ is used, the low solubility of most solutes in non-polar scCO$_2$. To solve this problem, progress in the RESS process has been made to overcome these limitations. One of them is the RESS process in an aqueous solution containing a surfactant or other reducing agents, known as the process of rapid expansion of a supercritical solution in a liquid solvent (RESOL V), where the SCF expands into a liquid medium. This modified process inhibits the agglomeration of particles in the expansion jet. Figure 10 shows a scheme of the RESS process.

4.2.2 GAS antisolvent process (GAS)

This process is suitable for recrystallizing solids that are not soluble in SCF. This technique has been widely used with polymeric materials because most of them are not soluble in SCF or gases. In this process, the polymer is first dissolved in organic solvent and a gas is used as the anti-insolvent. The gas is injected into the airtight cell containing the solution, and precipitation of the particles takes place as the concentration of the gas in the solution increases with pressure. In this technique, it is not necessary for the anti-insolvent gas to be in supercritical conditions. The controlling principle of the process is solvent-induced phase separation, which is illustrated in Figure 11. With the introduction of the anti-dissolver, the F-S and L-L phase limits are displaced at higher temperatures or pressures, respectively. As a result, the system that was initially in a single homogeneous phase is now in a region of two phases, this separation of phases leads to the formation of particles. A significant difference between the RESS and GAS processes is that while in the first one it is treated with a binary system, material + SCF, in the second, we have a ternary system composed of...
4.2.3 Supercritical antisolvent process (SAS)

In this technique, as in the GAS process, the SCF acts as an antisolvent for a solution containing a material, but in this case the mechanism is different. The compound to be micronized is dissolved in a liquid, generally an organic solvent, and the solution is injected into a high-pressure vessel where the supercritical antisolvent is, reaching intimate contact between the two media quickly. By mixing these two currents, the solvent is extracted by the SCF phase, and the SFC is simultaneously diffused into the liquid solution. As SFC is a poor solvent for the compound, in this mixture it acts as an antisolvent. Consequently, the mixture is oversaturated, resulting in rapid nucleation and growth. This process can operate in batch or semicontinuous mode, but a continuous operation configuration can also be adopted, which is important for industrial-scale production. The process is governed by solvent-induced phase separation, as described in Figure 11. Figure 13 shows a scheme of the SAS process.
In scCO$_2$ processes, the kinetics of particle formation using a supercritical antisolvent technique is fast compared with that of liquid antisolvent techniques, due to the good transport properties of scCO$_2$. Furthermore, it is possible to accelerate the rate of the process operating under conditions above the critical point of the CO$_2$-solvent mixture, since in these conditions the solvent and CO$_2$ are completely miscible and the diffusional limitations in the mixture disappear, establishing favorable conditions to produce ultrafine particles with a narrow distribution of particle size. Even by adjusting the operating conditions (pressure, temperature, and initial concentration of solutes), the morphology of the particles can be modified [21].

**4.2.4 Solution-enhanced dispersion by supercritical fluids (SEDS)**

The SEDS process was developed by York and Hanna of Bradford University in the year 1996 [24] to improve the efficiency of the traditional SAS process. The SEDS process usually operates at a lesser time with increased mass transfer rates.
The main objective of the SEDS process is to produce uniform-sized fine particles in a single-phase equilibrium, while removing the organic solvent to obtain them in a dried form. In SEDS, the liquid solution and SCF are sprayed together using a coaxial injector. These injectors can be found in two- and three-channel versions, which are used for precipitation of one or two components respectively. In this process, the SCF is used as an antisolvent and dispersing agent of the medium. High-speed contact between the liquid and the SCF generates a finely dispersed mixture and rapid precipitation of particles. As in the GAS and SAS processes, the basic principle here is also solvent-induced phase separation. Particles are formed due to a change in composition in phases (Figure 11). The design of the nozzle, as well as its specifications, particularly internal diameters, is decisive in the particle size distribution. In addition, operating conditions such as the flow rates of compound dissolution and SFC and critical parameters must be optimized to control both particle size and morphology [25]. Figure 14 shows a scheme of the SEDS process.

4.2.5 Particles from gas-saturated solutions (PGSS)

This process is suitable to generate particles of compounds that absorb SCF in high concentrations. The PGSS process is quite similar to the RESS process. In the PGSS process, an SCF is dissolved in a molten polymer or in a liquid suspension and the mixture, which is at high pressure, is quickly depressurized through an injector leading to the formation of particles. This process has generally been used for the coating of compounds on polymer matrices. The phenomena that control this process are: the rapid changes in pressure and temperature and the solvent-induced phase separation (Figure 15).

The PGSS process has the advantage with respect to RESS that it is not necessary for the substance to be soluble in SCF, the process is simple, and low cost and technique avoid the low solubility in SCF of many molecules of pharmaceutical interest such as proteins and peptides that would be too difficult to treat with RESS. Although the applications currently developed use polymeric materials, it could be used to obtain powdered polymers or to apply coatings. Figure 16 shows a scheme of the PGSS process.

Figure 14.
Scheme of an SEDS process.
4.2.6 Particles from gas-saturated solutions drying (PGSS drying)

PGSS drying technique is a modification of the standard PGSS process, designed specifically to treat aqueous solutions (Figure 17). The process consists of pressurizing and preheating the aqueous solution and the CO$_2$ to the conditions prior to expansion. They are then vigorously mixed in a static mixer, causing partial water extraction and the saturation of the aqueous solution with CO$_2$. The resulting mixture is sprayed through a nozzle in a thermally insulated spray tower. In this tower, CO$_2$ vaporization and the expansion of gas bubbles due to depressurization occur. The water then evaporates into the CO$_2$ expansion vessel, thus producing particles. These are collected at the bottom of the tower, and CO$_2$ with evaporated water leaves the tower through its top. A cyclonic separator can be used to recover fine dust trapped in the gas effluent [26].

4.2.7 Supercritical fluid-assisted atomization (SAA)

The SAS technique is based on the solubilization of controlled amounts of scCO$_2$ in liquid solutions containing a solid solute and the atomization of the resulting solution
through a nozzle. The experimental device is shown in the Figure 18. It consists of three lines that feed scCO\textsubscript{2}, the liquid solution and an inert gas, such as N\textsubscript{2}, and three main process vessels: saturator, precipitator, and condenser. The CO\textsubscript{2} is supplied in liquid phase to a high-pressure pump and sent to a heated bath. Next, it is taken to a contactor in which the CO\textsubscript{2} is solubilized in the liquid solution. The liquid solution is pressurized in a high-pressure pump, heated, and sent to the saturator. Subsequently, a spray is produced that forms the droplets in the precipitator. The inert gas is heated in a heat exchanger and sent to the precipitation tank in order to promote the evaporation of the liquid solvent. Particles are collected in a frit located at the bottom of the precipitator, and gases are discharged into a refrigerated condenser to obtain the liquid solvent. This technique has been used with compounds such as precursors of superconductive materials and catalysts and with pharmaceutical and ceramic compounds [27].
4.3 Reactions in supercritical fluids

The application of SFC to the extraction of thermally labile compounds is the most widespread. However, recently, they have also been widely used as reaction media. The properties of SFC can be harnessed to be used as reaction media in different processes. A supercritical fluid can be used to reduce temperature in pyrolysis reactions to prevent carbon formation, improving performance, selectivity, and product separation. SFC can also be used in heterogeneous catalytic reactions that undergo catalyst deactivation as a result of coke deposition, in which coke deposits can be removed from the catalyst surface by means of SCF by reactivating the catalyst by removing low-volatility compounds. A supercritical medium can also be used in reactions where product separation using conventional techniques is difficult to achieve or very expensive. In these cases, the operating conditions can be adjusted to fractionate the reaction products. Other reasons for using SFC in chemical reactions are related to favorable mass transfer (viscosity, high diffusivity), enhanced reaction rates and process control [28].

\( \text{scCO}_2 \) has environmental (nontoxic, nonflammable), phase equilibrium (high solubility of volatile solvents, complete miscibility with gases), and chemical advantages that may be of great interest for its use as reaction medium. In this way, it can be noted that CO\(_2\) cannot be oxidized, being interesting as a medium in oxidation reactions; generally, it is not affected by free radicals, so it is an ideal solvent for reactions initiated by free radicals and is aprotic, so it can be used in cases where labile protons could interfere with the reaction.

Liquid and \( \text{scCO}_2 \) have been used in homogeneous and heterogeneous reactions, catalytic and noncatalytic, and in the synthesis and processing of polymers, including polymerization in homogeneous solution, precipitation polymerization, dispersion and polymerization in emulsion, and polycondensation [29].

4.3.1 Homogeneous catalytic reactions in supercritical carbon dioxide

Homogeneous catalysis may have certain advantages over heterogeneous catalysis, such as the possibility of carrying out the reaction under milder conditions, greater activity and selectivity, ease of spectroscopic monitoring, and controlled and tunable reaction sites. Although, heterogeneous catalytic reactions are of great importance in industries because of the easy separation of the catalyst after the reaction. Most homogeneous reactions carried out in \( \text{scCO}_2 \) are catalytic [30–33], while noncatalytic, supercritical, homogeneous reactions are generally carried out in supercritical water [5].

For homogeneous reactions, the main problem is to find an effective, CO\(_2\)-soluble catalyst, which can be achieved by adding functional groups. \( \text{scCO}_2 \) is more effective when used with nonpolar, nonionic, and low-molecular-mass compounds. However, it can be used with insoluble compounds in \( \text{scCO}_2 \) by adding cosolvents.

Homogeneous hydrogenation reactions in \( \text{scCO}_2 \) have also been developed. Jessop et al. [34] studied the hydrogenation of carbon dioxide to formic acid, methanol, and other organic substances. They described the route to formic acid based on the use of Rh organometallic catalyst in dimethyl sulfoxide and aqueous solvents and also in a supercritical mixture of carbon dioxide and hydrogen containing a ruthenium catalytic complex. They concluded that SCF represents a promising medium for homogeneous catalysis. Rhodium complexes have also been synthesized for homogeneous catalysis of 1-octene in \( \text{scCO}_2 \) from the phosphine reaction containing polymeric ligands of fluoroacrylate with an Rh complex [35].
Liu and Xiao [31] presented in 2007 a review summarizing the achievements in homogeneous and heterogeneous catalytic reactions with transition metal complexes in nonconventional media, such as ionic liquids, scCO\(_2\), and fluorinated carbons. The study includes hydrogenation, hydroformylation, carbonylation, Heck reactions, Suzuki and Stille couplings, Sonogashira reactions, allylic substitution, olefin metathesis, olefin epoxidation, and alcohol oxidation. The homogeneous hydrogenation of 1-butene to n-butane with a membrane reactor is presented for homogeneous catalysis in scCO\(_2\) with in situ catalyst separation [36].

Other homogeneous catalytic reactions using scCO\(_2\) are summarized in Table 3.

4.3.2 Heterogeneous catalytic reactions in supercritical carbon dioxide

Reactions have also been carried out in scCO\(_2\) with heterogeneous catalysts. SCFs, used as solvents or reactants, provide advantages to control and enhance heterogeneous catalytic reactions. Among these advantages can be mentioned: (i) reactants and products can be in a single phase, avoiding solubility problems and mass transfer limitations of conventional gas-liquid and liquid/liquid interfaces; ii) improve the transfer of internal mass through the pores of the catalyst, often resulting in an increase in reaction rate and selectivity; iii) enhance diffusion rate in reactions controlled by external (fluid/particle) diffusion; (iv) improve heat transfer; (v) easier product separation; (vi) inhibit deactivation of the catalyst by dissolution deposits, (vii) tune the solvent properties by changing pressure, temperature, and adding cosolvents; and (viii) thermodynamic pressure effect on rate constants [37].

scCO\(_2\) is the most widely used as a solvent in heterogeneous catalysis, probably because reactions in scCO\(_2\) have a behavior very similar to the reactions in nonpolar organic solvents (for example, n-hexane), and in practice, the replacement of these

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Catalyst</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrogenation</td>
<td>Ru, Rh complexes</td>
</tr>
<tr>
<td>Oxidation</td>
<td>Fe, Mn, Rh, Pt-Ru, Mo complexes, PdCl(_2), CuCl(_2)</td>
</tr>
<tr>
<td>Dehydrogenation</td>
<td>Rh complex</td>
</tr>
<tr>
<td>Coupling</td>
<td>Pd, Ru complexes</td>
</tr>
<tr>
<td>Diels-Alder</td>
<td>Sc, Yb, Li complexes, AlCl(_2)</td>
</tr>
<tr>
<td>Esterification</td>
<td>Yb, Pd complexes, PdCl(_2), CuCl(_2)</td>
</tr>
<tr>
<td>Allylation</td>
<td>CF(_3)(CF(_2))(_2)SO(_3)H</td>
</tr>
<tr>
<td>Hydroformulation</td>
<td>Rh, Ru, Co complexes</td>
</tr>
<tr>
<td>Carbonation</td>
<td>Re, Li, Sn, Zn, Fe complexes</td>
</tr>
<tr>
<td>Carbonylation</td>
<td>Pd, Ru complexes, PdCl(_2), CuCl(_2)</td>
</tr>
<tr>
<td>Cyclization</td>
<td>Ni, Co complexes, PdCl(_2), CuCl(_2)</td>
</tr>
<tr>
<td>Polymerization</td>
<td>Pd, Rh, Co, Sn, Ti complexes</td>
</tr>
<tr>
<td>Copolymerization</td>
<td>Zn, Cr, Al complexes</td>
</tr>
<tr>
<td>Epoxidation</td>
<td>Mo, V, Ti complexes</td>
</tr>
<tr>
<td>Transesterification</td>
<td>BF(_3)</td>
</tr>
</tbody>
</table>

Table 3. Homogeneous catalytic reactions in supercritical solvents. Adapted from reference [5] with permission of Elsevier.
solvents by scCO\textsubscript{2} does not imply important changes, from the chemical point of view. However, this fact is also a limitation, since it is not suitable for hydrophilic substances and ions. Some authors, such as Johnston and Haynes [38], have raised the possibility of overcoming these limitations, for example, by using a water microemulsion, which is kept stable by adding a surfactant, in a continuous phase of carbon dioxide.

Many heterogeneous catalytic hydrogenation reactions that have been developed using scCO\textsubscript{2} supported Pt, Pd, Ni, Mo as catalysts. Some examples are cited below. Tacke et al. [39] carried out total and partial hydrogenation of fats and oils, free fatty acids, and fatty acid esters, using supercritical CO\textsubscript{2} as a solvent. They used a continuous fixed-bed reactor with a palladium catalyst on a commercial support and obtained yields up to six times higher than in the conventional hydrogenation process with palladium catalyst supported by activated carbon. Bertucco et al. [40] studied the catalytic hydrogenation of an unsaturated ketone in scCO\textsubscript{2} using a recycle reactor with a supported palladium catalyst. More recently, catalysts of supported noble metals, such as Ru, Pd, or Pt, have exhibited high activity for the hydrogenation of bio-based carboxylic acids. Leviulinic acid and succinic acid are converted into lactones or diols depending on the nature of the catalyst and reaction conditions [41].

Other heterogeneous catalytic reactions using scCO\textsubscript{2} are summarized in Table 4.

4.3.3 Supercritical biocatalysis

The use of SCF as an alternative to conventional organic solvents in enzyme-catalyzed reactions was first investigated by Randolph et al. [42], Hammond et al. [43], and Nakamura et al. [44] in 1985. Since then, it has been a very fruitful area of research. The possibility of modifying the physical properties of the solvent by changing the pressure or temperature offers great versatility [45, 46]. The tunability of the solvent is perhaps the main characteristic of biocatalysis in SCF. In addition, the activity of enzymes in nonaqueous media depends on the properties of the solvent, so SCFs are attractive media to carry out biocatalytic reactions [47]. The low viscosities and gas-like diffusivities improve the rate of mass transfer of reactants to the active sites in enzymes disseminated in SCF, in which enzymes are insoluble. Therefore, reactions limited by diffusion rates instead intrinsic kinetic will be faster in SCF than in liquids. In addition, higher substrate concentrations can also increase the observed reaction rates and improve process yields. The density of a supercritical fluid is sensitive to temperature and pressure, so that small changes in these variables result in significant changes in density and, consequently, in the properties of the solvent.

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Catalyst</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrogenation</td>
<td>Supported Pt, Pd, Ni, Mo</td>
</tr>
<tr>
<td>Oxidation</td>
<td>Supported Pt, Pd, Ni, Co, Cu, Mn, Fe</td>
</tr>
<tr>
<td>Isomerization and rearrangement</td>
<td>Supported Pt (scCO\textsubscript{2} + cosolvent)</td>
</tr>
<tr>
<td>Cracking</td>
<td>Zeolite</td>
</tr>
<tr>
<td>Alkylation</td>
<td>Zeolite</td>
</tr>
<tr>
<td>Esterification</td>
<td>Biocatalysts, Zeolite</td>
</tr>
<tr>
<td>Hydroformulation</td>
<td>Supported Rh, Fe catalysts</td>
</tr>
</tbody>
</table>

Table 4. Heterogeneous catalytic reactions in supercritical solvents. Adapted from reference [5] with permission of Elsevier.
that are a function of density, such as the solubility parameter, the dielectric constant, and the partition coefficient [48, 49]. Such changes in properties have been frequently studied for many solvents, then the experimental environment of the biocatalytic reaction can be reasonably controlled. However, despite the advantages of SCFs over organic solvents to carry out enzymatic reactions, their use is not as widespread as might be expected.

Due to its high availability and low toxicity, as has been already mentioned, the most widely used supercritical fluid is carbon dioxide, although its use in many processes is limited by the low solubility of many reactants and products, even in supercritical conditions. Many industrial applications are hampered by this handicap and by the cost of high-pressure equipment. Despite these drawbacks, the combination of environment-friendly catalysts and solvents has attracted the attention of many researchers, and there is a huge volume of literature available on the activity, specificity, and stability of different enzymes in scCO$_2$ [44, 50–52]. Furthermore, enzymes are very specific catalysts that require mild reaction conditions to exert their activity, which reduces the synthesis of undesirable or secondary products, and its activity [53] and selectivity [54] can be tuned by modifying the pressure or temperature of the supercritical fluid.

4.3.3.1 Enzymatic reactions in supercritical carbon dioxide (scCO$_2$)

Most of the work published so far in the field of biocatalysis in SCF uses scCO$_2$ as a reaction medium for the advantages over other SCFs, such as low cost, environmentally benign nature, low toxicity, high availability, nonflammability, and low critical temperature. Furthermore, using scCO$_2$ for enzymatic reactions, the extraction of the product is not necessary since the scCO$_2$ becomes gas with depressurization to atmospheric pressure. However, other SCFs, such as fluoroform and ethane, have been shown to be even more suitable as reaction medium for some enzymatic catalysis reactions [47].

One of the first works with scCO$_2$ was carried out by Randolph et al. [42]. They found that the enzyme alkaline phosphatase was active and stable in a batch reactor using scCO$_2$ as solvent. The enzyme catalyzed the reaction of $p$-nitrophenyl disodium phosphate to obtain $p$-nitrophenol, but its activity was limited by the solubility of $p$-nitrophenyl disodium phosphate in scCO$_2$.

The enzymes mostly used with scCO$_2$ are lipases. Many authors have investigated a wide variety of reactions using this class of enzymes. Nakamura et al. [44, 55, 56] studied the acidolysis of triolein with stearic acid in scCO$_2$ in batch and continuous processes, using four lipases, one of them in free form and the rest immobilized on a support. All of them were stable in scCO$_2$, and the authors found the optimal conditions to achieve the better productivity.

scCO$_2$ has also been used to obtain optical isomers by chiral synthesis from a racemic mixture. Ikushima et al. [57] studied the transesterification of (+)-citronellol with oleic acid using the lipase Candida cylindracea. The researchers found that increasing pressure of scCO$_2$, the reaction rate increased, especially in the vicinity of the critical point. Around the critical point, the formation of the S ester was stereoselective. Endo et al. [58] also obtained chiral esters from secondary alcohols and short-chain fatty acids using two different immobilized lipases in scCO$_2$.

Almeida et al. [59] carried out the transesterification reaction of butyl acetate by $n$-hexanol in supercritical ethane, scCO$_2$, and high-pressure propane using immobilized Candida antarctica lipase B (Novozym 435). The activity of Novozyme 435
activity was found to be similar in supercritical ethane and compressed propane, but about 1 order of magnitude lower in carbon dioxide under the same operating conditions (35°C and 10,000 kPa). However, the reaction rate increased with temperature in scCO₂.

One of the most determining factors to successfully carry out a reaction in biocatalysis is the stability of the enzyme, and the conditions involved in the use of scCO₂ can aggravate the problem. It has been shown that, in most cases, pressures below 20 MPa do not denature enzyme [60]. However, many cases have also been described in scCO₂ systems in which enzyme inactivation occurs [61]. Therefore, the progress of biocatalytic reactions in scCO₂ requires the development of the stabilization techniques.

Immobilized Candida Antarctica lipase B (CALB) was successfully used as catalyst to synthesize butyl butyrate from butyl vinyl ester and 1-butanol in scCO₂ with excellent results. The catalytic behavior of the enzyme immobilized on an acrylic support was studied in a stirred tank reactor, showing that a decrease in both the water content and the scCO₂ density enhanced the synthetic activity and selectivity [3].

4.3.3.2 scCO₂/H₂O biphasic systems

Matsuda et al. [62] studied a reaction using a partially purified Geotrichum candidum alcohol dehydrogenase in a biphasic scCO₂/H₂O system and observed an inactivation of the enzyme due to the low pH in the aqueous layer because of the high density of CO₂ (H₂CO₃).

A pressurized biphasic CO₂/H₂O system with pyruvate decarboxylase has been used to catalyze a carboxylation reaction, and it has been observed that the enzyme loses 80% of its activity at 6 MPa [63]. In order to stabilize the enzyme, additives such as glycerol and trehalose have been used, and it has been immobilized on an ion exchange polymer. After the stabilization, the activity was maintained up to CO₂ pressurized at 11 MPa.

4.3.3.3 scCO₂/ionic liquid biphasic systems

The growing interest that these systems have aroused lies in the combination of the excellent properties of ionic liquids as solvents to carry out numerous reactions, together with the magnificent qualities of scCO₂ as an extraction agent; so that it allows any reaction to be carried out in an ionic liquid and recover the products dissolved in CO₂ in a similar way, fast and clean (Figure 19).

Ionic liquids have also been used frequently with scCO₂ to improve the stability of the enzymes. It has been demonstrated that some enzymes have more native, stable, and compact conformation in scCO₂/ionic liquid system than in scCO₂ [62]. Reetz et al. [64] demonstrated the possibility of carrying out biocatalytic processes in biphasic systems based on ionic liquids and SCF. As in other catalytic reactions, the success of this type of biphasic systems is based on the high solubility of scCO₂ in the ionic liquid phase, while it does not present detectable solubility in the scCO₂ phase and in the demonstrated fact that scCO₂ can extract organic substances from the ionic liquid, without contamination of the extract by the latter [65], while the enzyme, free or immobilized, can be separated from the ionic liquid by a filtration process.

The development of technologies that directly provide pure products by the integration of reaction/separation processes, product recovery, and reuse of catalyst and solvents constitutes one of the objectives of green chemical engineering. The unique
properties of ionic liquids lead, when combined with (bio)catalysts and scCO\textsubscript{2}, to improvements, not only in catalytic efficiency (activity, enantioselectivity, stability, etc.), but also in the design of integrated processes for product separation (e.g., ionic liquid/scCO\textsubscript{2} biphasic reactors, membrane reactors, nanodrop systems, microfluidic devices, supported ionic liquid phases, sponge-like ionic liquids, etc.) [66]. These systems can also operate in semicontinuous systems, consisting of carrying out the reaction within the ionic liquid, while constantly passing CO\textsubscript{2} through the system to extract the products and collect them in a cold trap [64]. Biocatalytic transformations have been carried out under flow conditions in ionic liquids and SCFs as alternative nonaqueous reaction media. Several examples are provided (e.g., KR and DKR of sec-alcohols and amines, C–C bond formation, reduction, transamination, transesterification, etc.) where the use of continuous-flow techniques enables the development of more efficient processes and multiple reaction steps to be combined into a single continuous operation [67].

Other works [68] have combined ionic liquids, scCO\textsubscript{2}, and membrane technology to perform a biocatalytic process, i.e., the synthesis of butyl propionate, from vinyl propionate and 1-butanol, in a membrane bioreactor with recirculation in a biphasic system ionic liquid/scCO\textsubscript{2}, using ceramic tubular membranes of α-microporous alumina in which Candida Antarctica lipase was immobilized (Figure 20).

Recently, a chemo-enzymatic synthesis of omega-3 monoacylglycerides was carried out in two consecutive catalytic steps; first, an enzymatic transesterification of raw fish or linseed oil with solketal for producing fatty acid solketal esters, followed by the hydrolysis of these solketal moieties catalyzed by solid acids (e.g., zeolites) in either scCO\textsubscript{2} or sponge-like ionic liquids [69].

4.4 Other applications

SCFs can be also useful for applications related to the microelectronics processing, the dyeing of textiles, dry cleaning or washing of textile garments or machine parts; although, for now, this implies certain drawbacks by having to work discontinuously. Regarding this field of application, the main efforts are being focused on getting the parts in and out of a pressure vessel without having to open it. [70].

The treatment of toxic waste (where supercritical water can be used instead of incineration) and the remediation of soils are also considered as possible applications, although less widespread [71].
scCO$_2$ has been used as an environmentally friendly medium to deliver coating systems. Significant reductions in volatile organic compounds emission can be achieved by partially or totally replacing the organic solvent with CO$_2$ in spray coatings. In addition to spray coatings on different substrates, CO$_2$ processes can be used for powder coatings and also for the coating of preformed particles, such as metal powders and pharmaceuticals for controlled drug release [72] or for delivering biocides into wood [73].

Drug-loading implants have shown numerous advantages over simple implants. Impregnation in a scCO$_2$ medium has been used to load drugs into polymeric implants, because it allows the recovery of the final implant, free of any solvent residue, and operate at a mild temperature that is suitable for processing with thermo-sensitive compounds [74].

Moreover, the sterilization of implantable medical devices is also of paramount importance to avoid complications related to surgery, such as infection and rejection. The use of scCO$_2$ for sterilization has recently been investigated. Aspects such as microorganisms that can be inactivated by scCO$_2$, operating variables, and materials sterilized by scCO$_2$ have been analyzed [75].

Recently, mold foaming process has been proposed to obtain thermoplastic polyurethane foam sheets using scCO$_2$, obtaining foams with good dimensional stability and cell morphology and excellent flexibility [76]. For applications of monolithic silica aerogels, the supercritical drying of silica aerogels using scCO$_2$ to substitute the liquid by gas has opened the possibility for a large-scale aerogel drying process [77].

Finally, another important field of research developed in the last two decades can be highlighted is the integration of SCF and ionic liquids. Reports have effectively shown the potential for combining ionic liquid and scCO$_2$ systems for product extraction and separation as well as reaction media [78].

Regarding the type of operation suitable for all these applications, it can be stated that in processes based on SCF, continuous operation is clearly advantageous compared with operation in stages. This is due to small equipment, which is much
cheaper, can be used while maintaining high productivity. In the particular case of caffeine, the industrial process works semicontinuously with two columns, i.e., one is extracting while the other is being emptied and refilled again with coffee beans.

5. Conclusions

SCFs are fluids at a pressure and temperature conditions above their critical point. Under these conditions, these substances have very interesting properties as solvents (gas-like diffusivities and densities close to liquids), which can be modulated both by the environmental conditions (P and T) and by the presence of additional cosolvents for use as solvents and as reaction media. The most used supercritical fluid is carbon dioxide, since it has relatively low critical parameters (Pc = 72.8 bar, Tc = 31.5°C), with characteristics as a solvent close to organic compounds (modulable hydrophobicity), although it has different advantages over organics as solvent and reaction medium, such as high rates of matter transfer, high diffusion coefficients, zero toxicity, non-flammability, and low cost, among others. In addition, supercritical carbon dioxide (scCO2) is especially advantageous, as it is cheap, nontoxic, and nonflammable and has a critical temperature close to room temperature and moderate critical pressure and can be reused. When used as a reaction medium, the products obtained can be easily separated since the solubility of the same in the scCO2 medium is a function of the pressure and temperature conditions of the scCO2, so its solvent capacity can be modulated. All these properties make scCO2 very attractive to be used as a “green design solvent.” As has been shown in this chapter, applications in different types of operation (extraction, reaction, obtaining nanoparticles, drying ...) and in different sectors (food and beverages, pharmaceutical, biomedical, microelectronics, textiles, forest products, petrochemicals, chemicals, environmental cleaning, production of synthetic fuels, polymers, coatings,...) have been growing since the 1980s.
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