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Supercritical fluid and pharmaceutical applications. Part I: Process classification

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The supercritical fluid technology has been target of many pharmaceuticals investigations in particles production for almost 35 years. This is due to the great advantages it offers over others technologies currently used for the same purpose. A brief history is presented, as well the classification of supercritical technology based on the role that the supercritical fluid (carbon dioxide) performs in the process.

Key words: Supercritical fluid technology, supercritical carbon dioxide, pharmaceuticals.

INTRODUCTION

Caignard de la Tour (1822) discovered the critical phenomena by observation of natural mineralization. The supercritical fluid technology (SCF) is based on the discovery of this phenomenon. Although the SCF is known since late nineteenth century, the basic concept of rapid expansion of supercritical solutions (RESS) was first described by Hannay and Hogarth (1879), in a study of the solubility of metal chlorides in supercritical ethanol to understand natural mineralization, observed by Caignard de la Tour (1822), in this study the authors reported the great power of SCF solvation. However, was Worthy (1981) whom steered the study of SCF to optimize micromeritic of organic materials difficult to form powders.

For more than one hundred years the broad assortment of techniques, limitation of the equipment and specific conditions to achieve the supercritical state made an accelerated advancement scientific research difficult (Berche et al., 2009). The concept of SCF technology as said by Jung and Perrut (2001) was better understood and developed after the pioneering work of Krukonis (1984) and, especially, by the disclosure of the Battelle Institute's research (Smith, 1985; Petersen et al., 1986; Matson et al., 1987a, b), they described and modeled flow pattern and nucleation process at supercritical conditions. Since then, many methods using this technology have been published and patented.

A supercritical solvent is one that at a certain temperature and pressure, does not condense or evaporate, it exists as a fluid (Yasuji et al., 2008). This

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happens when a substance is high above its critical temperature and pressure, and passes it to a condition called “supercritical fluid state”. Under these conditions, the densities of the liquid and vapor are identical, and for this reason the meniscus, on the interface between the two phases, disappears (Moribe et al., 2008).

In SCF conditions, substances exhibit physical properties that are intermediate between gases and liquids of the start material. Thus, the density of a SCF can be altered by the variation of the pressure applied on the fluid. When the fluid is compressed at high temperatures it can have a density varying between those displayed by gases up to typical values of liquids. Likewise, a SCF maintained at a relatively high density has the ability to dissolve a variety of materials, exactly as conventional liquids do, but with the power of gases penetration (Chan and Kwok, 2011).

The use of environmentally more acceptable intermediaries, such as carbon dioxide (CO_2) and water, is an advantage of SCF technology. The SCF most used in pharmaceutical applications is the CO_2, due to its low cost and also because of its supercritical milder condition, which enables the processing of pharmaceuticals and other thermolabile raw materials (DeSimone, 2002).

Increased bioavailability of poorly-soluble molecules, development of modified release systems of drugs, and drug delivery via oral, pulmonary or transdermal - which are less invasive than the parenteral route – are the main objectives of the pharmaceutical industry. These objectives can be achieved by SCF technology which demonstrates dramatic change in the solid morphology after processing, that is, medium-size and particle size distribution, particle shape and porosity, and, consequently, surface area and dissolution rate are often quite different from those of the starting material (Perrut, 2003).

The supercritical CO_2 (SC-CO_2) is easily obtained in critical temperature (Tc) of 304K and critical pressure (pc) of 7.38 MPa (Yasuji et al., 2008) but there are other substances such as nitrogen, ethanol and water, which also have interesting solvent properties in its supercritical state. However, for reasons of cost, danger of explosion, flammability, toxicity and adverse physical properties (conditions for T_c and p_c too high), these substances are less used commercially (Maul, 1999).

Currently, the SCF technology is an alternative for application in drug release technology, in addition to meeting the principles of green chemistry, who’s most accepted definition (Anastas and Warner, 1998)is "the design, development and implementation of chemical processes and products to reduce or eliminate hazardous substances to human health and the environment". This definition has been expanded by Poliakoff et al. (2002) in 12 principles.

The traditional methods for developing drug delivery systems, either in micro or nanoscale, using technologies such as co-precipitation, coacervation and solvent evaporation polymerization, use large amounts of organic solvents and/or surfactants which, in general, are harmful to the environment (Kawashima et al., 1989; Yoshida et al., 2015). The aforementioned methods used to produce particles which commonly exhibited low rates of drug entrapment and difficulties in scaling, and most often require further treatment to remove solvent(s) and/or impurities from the particles. Although the pharmaceutical industry shows interest in innovative technologies involving production of micro and nanoparticles, the solvent disposal strongly limits the industrial production and generates increased costs (Jung and Perrut, 2001). Hence, the subject of several studies has been about the development of other technologies that minimize the problems related to pollution, toxicity and ease of production scale-up (De Zordi et al., 2012).

PROCESSES IN SCF TECHNOLOGY

The SCF technology can be classified into three broad categories according to the use of the SCF in the process: (i) as solvent, (ii) as antisolvent, and (iii) processes that do not depend on the solvent power of CO_2.

SCF used as solvent

Supercritical carbon dioxide (SC-CO_2) density is extremely sensitive to minor changes in temperature and pressure near the critical point. The density of the SC-CO_2 is closer to that of organic liquids but the solubility of solids can be 3-10 orders of magnitude higher (Motonobu et al., 2008).

The solvent strength of a SC-CO_2 can be expressed by the solubility parameter which is the square root of the cohesive energy density and is defined rigorously from first principles. A plot of the solubility parameter for carbon dioxide versus pressure would resemble that a plot of density versus pressure. This confirms that the solvation strength of a supercritical fluid is directly related to the fluid density. Thus the solubility of a solid can be manipulated by making slight changes in temperatures and pressures. Another attractive feature of SC-CO_2 is that the properties lie between that of gases and liquids. A SC-CO_2 has densities similar to that of liquids, while the viscosities and diffusivities are closer to that of gases. Thus, a SC-CO_2 can diffuse faster in a solid matrix than a liquid, yet possess a solvent strength to extract the solute from the solid matrix.

Rapid expansion of supercritical solutions (RESS)

The RESS process has been extensively investigated and involves two steps, solubilization followed by particles formation (Figure 1a). The fallout of particulate material is obtained by dissolution of the material in the

SCF to form a solution, and then this mixture is expanded and suddenly depressurized. This decompression causes a rapid increase in supersaturation, leading to rapid nucleation and generation of sub-micrometer sized particles (≤ 100 nm) (Reverchon et al., 2000). Changing the process variables, particularly the temperature and pressure of the expansion and the diameter of the nozzle, it is possible to control the average diameter of particles and their size distribution. The advantage of the RESS process is to present valuable commercial-scale applications when the solubility of material or product on SCF (preferably CO_2) is not too small (≥ 10^{-3} kg/kg or mole fraction > 10^{-4}). The application of RESS process is limited to the nonpolar compounds or of low polarity (Perrut and Clavier, 2003; Reverchon et al., 2007).

The most commonly used inputs for the development of particulate systems are not sufficiently soluble in SC-CO_2 to make the efficient production process. Thus, it is often necessary to modify the RESS process, as for example, using an organic cosolvent (Sauceau et al., 2004; Chattopadhyay et al., 2007) or a cosolvent solid (Thakur and Gupta, 2006).

Rapid expansion of a supercritical solution into a liquid solvent (RESOLV)

Sun and Rollins (1998); Sun et al., (2000) and Meziani et al. (2005) made a simple but significant modification in the RESS process, using a liquid on the receiving end of the rapid expansion (Figure 1b). This modification was developed for the production of nanoscale particles. It has been shown that the RESOLV is, potentially, a good platform for the nanonization of water-insoluble drugs (Meziani et al., 2005; Sun et al., 2005, 2006). Although both, RESS and RESOLV, appear to involve a process of particle agglomeration, one could argue that the particle growth and aggregation observed in RESOLV should not be necessarily considered as a part of the technique, because they are on a longer time scale after the initial formation of nanoparticles. On the other hand, the growth of particles and aggregation in RESS happens in jet expansion, which differentiates it from the RESOLV process (Sun et al., 2005).

Particularly, the RESOLV process makes use of a liquid to suppress the growth of particle in the jet expansion, making it possible to keep the particles in nanoscale. However, being the nanoparticles produced in suspension, these can lead to clustering and form aggregates. A critical issue in the particles nanonization of drugs through the RESOLV is to initially protect the formed particles of agglomeration using stabilizing agents (Sun et al., 2005).

Rapid expansion from supercritical to aqueous solution (RESAS)

Young et al. (2000, 2003) proposed the RESAS system (Figure 1c) to overcome the problem in the difficulty of collecting the particles that occurs in the RESS process. From theoretical calculations, the RESS process could form particles as small as 20 to 50 nm. The inability of the RESS process in approaching the theoretical limit is probably related to the growth of particles during collisions in the free jet expansion (Debenedetti, 1994).

To provide stabilization against particle growth resulting from collisions in the jet of expanding, Young et al. (2003) used an aqueous solution containing phospholipid vesicles mixed with non-ionic surfactant to obtain sub-micrometer particles with high drug loading rate.

Rapid expansion of supercritical solution with solid cosolvents (RESS-SC)

The RESS-SC process is divided into three parts, pre-extraction, extraction, and expansion (Figure 1d). In pre-extraction phase, CO_2 is pressurized until the desired pressure. In extraction phase two cylindrical vessels are used as extraction column, one for the solid cosolvent, and one for the drug. Both vessels are kept at a constant extraction temperature and pressure is monitored in this phase. In the expansion phase temperature is controlled to be less than 5°C. A filter of glass wool is usedat the end of the expansion chamber output to retain the particles produced in the process (Thakur and Gupta, 2006).

In the RESS-SC process the choice of the solid cosolvent is very important, due to its need in offering interaction to improve polar solute solubility in CO_2. The solid cosolvent must have the following properties: (i) high vapor pressure enough for easy removal by sublimation; (ii) solid output conditions of nozzles (typically – 5 at 25°C); (iii) appreciable solubility in SC-CO_2; (iv) non-reactive solute with desired or SC-CO_2; (v) non-flammable and non-toxic properties; and (vi) low cost. Menthol is a compound that meets all the requirements of solid cosolvent. Its melting point is 34 to 36°C, with high vapor pressure, good solubility in SC-CO_2 and is widely used in pharmaceutical and food industries (Thakur and Gupta, 2006).

Thakur and Gupta (2006) proposed that the solid cosolvent not only enhances the solubility of polar compounds in SC-CO_2, but also avoids particle growth by hindering agglomeration. In their work, low solubility and growth by coagulation are addressed by utilizing a cosolvent that is solid at the nozzle exit conditions.

SCF used as antisolvent

Application of SCF as antisolvent is an alternative to the technique of recrystallization to processes insoluble solids in the SCF. This method exploits the ability of gases to dissolve in organic liquids, decreasing the "solvent power" of the solvent for solution components,

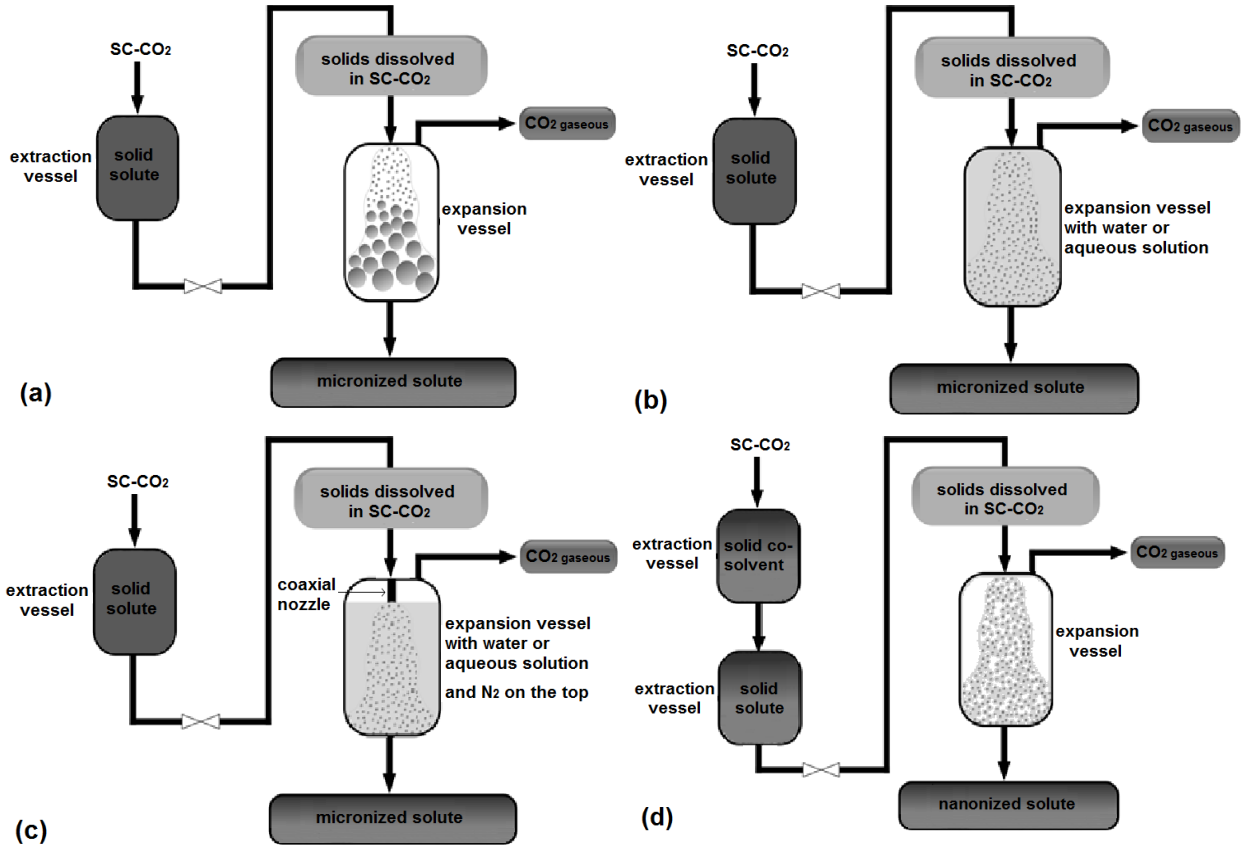

Figure 1. Schematic diagrams of the processes (a) RESS, (b) RESOLV, (c) RESAS, and (d) RESS-SC.

which causes precipitation solutes (Jung and Perrut, 2001; Knez and Weidner, 2003; Perrut et al., 2007). Processes using gas antisolvent differ in how the contact is obtained between the solution and the antisolvent (Jung and Perrut, 2001; Knez and Weidner, 2003).

Supercritical anti-solvent (SAS)

The process named SAS is based on the decrease of the solvent power from a polar organic solvent, in which the substrate(s) of interest (pharmaceutical active ingredient and/or polymer) is/(are) dissolved. The dissolution of the SCF in the solution greatly expands its volume, acting as an antisolvent, which causes the formation of crystalized solutes and precipitation of the substrate of interest. In this way, the SCF is used to extract the solvent of this solution (Jung and Perrut, 2001; De Zordi et al., 2012) (Figure 2a).

The SAS process is easily escalated and has been largely studied due to its potential of micro- and nanoparticles production, with control of the particles size and morphology (Perrut and Clavier, 2003; Shariati and Peters, 2003; Reverchon and Adami, 2006). The procedure is usually carried out at temperatures ranging between 308 K and 333 K, being useful when thermolabile compounds need to be micronized (Reverchon et al., 2010).

SAS process, with minor changes, is also known as the ASES or PCA. In these techniques, a SCF acts as antisolvent for polymer solutions, such as in the GAS process, but the contact mechanism is different than the one used in the GAS process. The polymer is dissolved in a liquid solvent and the solution is sprayed into a chamber, where anantisolvent already exists, causing rapid contact between the two means. This generates greater reason of solution supersaturation, resulting in rapid growth and nucleation, and consequently, causing smaller particles. A special advantage of this technique is its adaptability to continuous operation, which is important for large-scale production.

Gas anti-solvent (GAS)

The GAS recrystallization process or GASR (Gas Anti-Solvent Recrystallization) was patented by Krukonis et al. (1994) and was recognized as a solid material recrystallization method from systems composed of solute, suitable liquid solvent, and gaseous component in

soluble solvent, which presence makes the solvent approaches or reaches a supersaturated state, precipitating the solute. The recrystallized material properties can be controlled by the parameters adopted in the process, among them, pressure, temperature, time, and gas injection flow.

The GAS process was originally designed for recrystallizing solid compounds that are soluble in SCF, having its principle based on the solution supersaturation, gas supercritical solution and antisolvent contact-induced. The role of the antisolvent is to reduce the solubility of compounds dissolved in solution and promote breakthrough, nucleation and crystal growth (Sacha et al., 2006).

In the GAS process, after the introduction of the antisolvent gas, the boundaries of the fluid-solid and liquid-liquid phases are shifted, respectively, for higher temperature or higher pressures. As a result, the system was initially a homogeneous phase region that turns into a two-phase region, where it suffers separation, leading to the particles formation. A significant difference between the GAS and RESS processes is that the RESS process works with a binary system of polymer and SCF, while in the GAS process have a ternary system of polymer, organic solvent, and antisolvent gas (Yeo and Kiran, 2005).

The solubility is directly related to the solvent power of a particular solvent for the crystallization compound, which may affect the breakthrough degree and nucleation rate when the antisolvent is added to the solution. The solute solubility in a solvent is determined by the parameters of the solute and solvent physicochemical properties, such as, dipole moment, dielectric constant and solubility coefficient (Park et al., 2006).

Aerosol solvent extraction system (ASES)

Müller and Fischer (1989) patented the ASES process which uses the supercritical gases properties of organic solvent extraction. The $CO_{2(\ell)}$ is introduced in a cooled condenser and is pumped through a heated high pressure column, the column temperature can be adjusted with another heater and is controlled by a thermostatic cartridge, and pressure in the middle column is regulated by a magnetic valve controlled by a gauge pressure. Under these conditions the CO_2 is expanded in subcritical conditions into the separation container, where it evaporates and is transferred to the condenser, and then is liquefied again (Bleich et al., 1993) (Figure 2b).

During the time of spraying it is possible to work with CO_2 directlyin a current or static phase. To produce the drug and polymer microparticles,the drug and polymer are dissolved or dispersed in an organic solvent and sprayed through an atomizing nozzle as fine droplets inside the column with SC-CO_2. The organic solvent is soluble in SC-CO_2, and is extracted, leading to the microparticles formation. The SCF dissolution in atomized liquid droplets is accompanied by a large expansion in volume and, consequently, a reduction in the liquid solvent power causing supersaturation and formation of microparticles, submicroparticles, and uniforms liposomes (Bleich et al., 1993; Yu et al., 2008).

Many variants of the ASES technique were proposed in order to control the particles morphology and size by using special nozzles. The preparation of thin particles for pulmonary administration opens a future for new types of materials engineering. Nanoparticles (50 to 500 nm), microparticles (500 to 5000 nm) or hollow nanoballoons (5 to 50 µm), enabled a significant increase in the bioavailability of poorly water soluble drugs or microspheres preparation with drugs for sustained release (Perrut, 2000; Perrut and Clavier, 2003).

Supercritical solvent impregnation (SSI)

In the SSI process the drug is transported by a SCF and adsorbed onto a porous carrier. The polymers can be impregnated through the dissolution of the drug in SCF and, consequently, resulting in the mixture of the fluid with particles of polymers (Figure 2c).The interest in polymeric material by impregnation SCF stems from the opportunity to use high diffusivity, low surface tension and ease in solvent recovery for preparation of new polymeric materials (Kikic and Vecchione, 2003).

Supercritical anti-solvent with drug excipient mixing (SAS-DEM)

In the SAS-DEM process the drug particles are precipitated in SC-CO_2 within a vessel containing, in addition to the SC-CO_2, particles of excipient (lactose and/or microcrystalline cellulose) in suspended state (in dichloromethane), with or without a surfactant (polaxamer407 or sodium dodecyl sulfate), and under agitation (Sanganwar et al., 2010; Sathigari et al., 2011) (Figure 2d). The SAS-DEM process was effective in overcoming drug–drug particle aggregation (Sanganwar et al., 2010), but the product further undergo aggregation which can be minimized by the addition of surfactant (Sathigari et al., 2011).

Supercritical anti-solvent with enhanced mass transfer (SAS-EM)

The SAS-EM process was proposed (2001) and patented (2003) by Chattopadhyay and Gupta and can be used to fabricate micro- and nanoparticles possessing very narrow size distribution due to the increased mass transfer system (Chattopadhyay and Gupta, 2002).

In the SAS-EM apparatus, anultrasound field is

generated by the nozzle surface and also provides a velocity component in the normal direction to the buccal surface which significantly increases the turbulence and mixing potential within the supercritical phase (Figure 2e), resulting in a high mass transfer between the solution and the antisolvent. The combined effect of the rapid mixing rate between antisolvent and solution, reduce the solution droplets size due to atomization, providing approximately particles 10 times smaller than those obtained from conventional SAS process (Chattopadhyay and Gupta, 2001, 2003).

Solution enhanced dispersion with supercritical fluid (SEDS)

In SEDS the SCF is used as an antisolvent agent for polymer solutions and dispersing agent. The SEDS process is similar to the semi-continue SAS process, which consists of spraying a solution in condensate gas in a pressurized vessel. However, the design of the nozzle of both proceedings is different. The SEDS nozzle features a coaxial design with a length of mixture, in order to improve the mass transfer and get a simultaneous release of the solution and the antisolvent (York and Hanna, 1996).

The SEDS process is distinguished by three main features: (i) solution and SCF are co-introduced in a jet with high speed, (ii) SCF turbulent flow accelerates mixture and particles formation processes, (iii) solvent composition and SCF material in the jet stream, the precipitation is fixed from the mixture start point, providing conditions for particles formation in uniform and continue procedure (York and Hanna, 1996).

The SEDS process also involves the application of organic solution in SC-CO_2 to precipitate the solute. In this process the CO_2 is liquefied through cooling system and then pumped into the precipitation vessel through the piston pump and heat exchanger of the outdoor coaxial nozzle tubule. Vessel pressure is regulated and when the flow rate, temperature and pressure of SC-CO_2 in the vessel of precipitation reaches the desired values, the drug solution is released into the vessel of precipitation through the inner tubule of the coaxial nozzle (Palakodaty and York, 1999; Edward et al., 2001; Tabernero et al., 2012).

In this process, it is important to consider the different theoretical and experimental aspects, such as phases equilibrium, nucleation kinetics, hydrodynamics and mass transfer (Reverchon et al., 2010). It is essential to study the phase behavior of solids-solvent-antisolvent system, in order to determine the conditions under which this mixture lies in a single phase (supercritical phase) or vapor-liquid binary region. In this context, the critical mixing point may be defined as the pressure and temperature conditions at which the vapor-liquid mixture melts in a single supercritical phase (Franceschi et al., 2008).

Atomization of supercritical antisolvent induced suspensions (ASAIS)

In the ASAIS process the SCF is used as antisolvent and dispersion agent. Rodrigues et al. (2011) developed this process, which is a small volume of SAS process characterized by inline dissolution from antisolvent before the liquid atomization for the solvent extraction step. The antisolvent (CO_2) is mixed with a solute solution contained in a small volume mixer, immediately before the hole in the nipple, under such conditions to cause precipitation of the solutes.

The suspension generated is then treated by spray-dried for the separation of solvent. In comparison with other similar techniques of producing particle, this approach allows a more effective control of antisolvent process and reduces the volume of the high-pressure precipitator in several orders of magnitude. The particles of theophylline produced by ASAIS are the polymorph previously obtained by conventional SAS. However, the normal crystalline form (non-polymorphic) is obtained under non-antisolvent conditions (Rodrigues et al., 2011).

Precipitation with a compressed fluid anti-solvents (PCA)

In the PCA process the SCF is used as antisolvent and dispersion agent, being an alternative way for micronizationin a single-stage process.Operation is either batchwise or semi-continuous with promising scale-up perspectives and particle sizes ranging from submicron to few microns. The drug is first dissolved in organic solvent and then the solution is sprayed inside, or mixed with, the SC-CO_2 which causes the drug precipitation due to the solvent dissolve in CO_2 (Figure 2f). The operating temperature and pressure are selected so the SCF is totally miscible with the organic solvent (Snavely et al., 2002).

In order to control the acute phase transition kinetics and produce uniform particle size distribution throughout PCA processing, two conditions must be met. First, there must be uniform conditions within the nucleation medium (that is, can not exist supersaturation gradients). The uniform conditions in the nucleation medium can be performed by a perfect blend of fluid, resulting in a homogeneous level of supersaturation and nucleation rate. Secondly, each formed critical stage should experience the same amount of time for the particles growth. Variations in the particle's permanence time result in a fine particle size distribution, due to different particle growth times after primary nucleation. Mixing settings, used to optimize the gas mixture, allows control over the supersaturation'slevel and uniformity, providing control of the average residence time and distribution of the particles size (Jarmer et al., 2003).

The design of the nozzle's key feature is the combination of a swirl flow and achamber micro mix to

optimize the mixture between the solvent and compressed antisolvent gas. PCA nozzles designed to optimize the gas mixture are essentially different from conventional spray nozzles, and enable the production of particles in nano scale PLLA size distribution with a sharper than previously possible (Jarmer et al., 2003) (Figure 2).

Supercritical fluid extraction of emulsions (SFEE)

In the SFEE process the SCF is used as antisolvent and dispersion agent, producing suspension of drug nanoparticles. SFEE technology combines the advantages of using emulsion, which controls the size of the particles and the surface properties, with the continuous extraction process for SCF (Chattopadhyay et al., 2006).

Since the main control parameters are the physical properties of the emulsion, instead of drug characteristics, the development of the formula that will sustain the stable emulsion and ensure the particles' suspension must be preformulated with caution (Yasuji et al., 2008).

Processes that do not depend on the carbon dioxidesolvent power

This category comprises all operations that do not depend on the solvent potency of CO_2, but instead takes advantage of the great volume expansion and cooling effect produced when the CO_2 is depressurized, in operating condition, to the ambient pressure.

The combination of SC-CO_2 technology with othertechnologies (such as, for example, coacervation and emulsion),as well with equipment for special methods (spray drying, specialised beaks, and freeze drying) could solve the problemsfor the production of functional particles while havingcontrol of involved physicochemical variables (Yasuji et al., 2008).

Particles from gas saturated solutions (PGSS)

In the PGSS process SCF employs the function of co-solute (Nunes and Duarte, 2011), a melted substance is delivered with a pressurized gas in a static mixer (that is, the CO_2 is dissolved in organic solutions or melted compounds) and is expanded through a nozzle of ambient pressure, forming particles from saturated gas solutions (Brunner, 2010).

The PGSS process offers promising prospects of industrial development where the SC-CO_2 is used as a reducing viscosity agent (solute) (Fages et al., 2004) because it is known that an increase in viscosity and an unequal coating material distribution leads to a non-uniform mixing of carrier material and coating material, resulting in inefficient coating and particles with wide size distribution (Chattopadhyay et al., 2006). The advantages of techniques based especially in SAS and PGSS are the production of spherical nano or microparticles with smooth surfaces and with narrow size distribution (Sheth et al., 2012).

Concentrated powder form (CPF)

The products obtained with the RESS, SAS, and PGSS drying process typically comprise only solid compounds. In 1997, the so-called CPF process was proposed by Weidner et al. (1997; 2001) allowing the generation of dry, free-flowing powders, and containing a very high liquids content. The liquid to be turned into powder comes incontact with a pressurized gas and is expanded through a nozzle. A thin spray of dispersed liquid droplets is formed. A solid support material is blown into the spray through an inert gas. The expanding gas causes an high turbulence area in the case of liquid droplets and solid support material, which are intensely mixed (Weidner, 2009).

The support material is agglomerated by liquid droplets. If the spray tower is high enough, the agglomerated are formed before reaching the bottom or the wall. The clusters can contain up to 90% (w/w) (in some cases, more than liquid % (w/w)). They are continuously removed from the bottom of the spray tower (Weidner, 2009).

The CPF process was applied to more than 100 liquids and approximately 60 different solids vehicles (Grüner et al., 2003). The properties of clusters rely heavily on the support and liquid material properties. The supporting materials ability to take certain amount of fluid depends on its chemical composition and physical properties. The net uptake of transporting materials has been investigated in detail by theoretical and experimental view point (Lankes et al., 2001).

A procedure for selecting suitable support material has been developed by Otto et al. (2001). The density of support material is an adequate quantity parameter to correlate the experiments on the liquid absorption. Highly dispersed silica with a 50 $kg.m^{-3}$ density can connect to more than 90% of the liquid, while the silica, with 200 $kg.m^{-3}$ density, can connect to 60% in mass (Otto et al., 2001).

Other product properties correlated with the process parameters are: (i) Joule–Thomson effect in spray tower; (ii) inert gases are applied without oxygenation in the spray tower, and (iii) selected products (unsaturated fats) versus stability (Grüner-Richter, 2007). In addition to these data, there is lack of knowledge about the processes in the static mixer, drops formation, spray sintering process on spray tower, and behavior of product properties during long-term storage (stress) (Weidner, 2009).

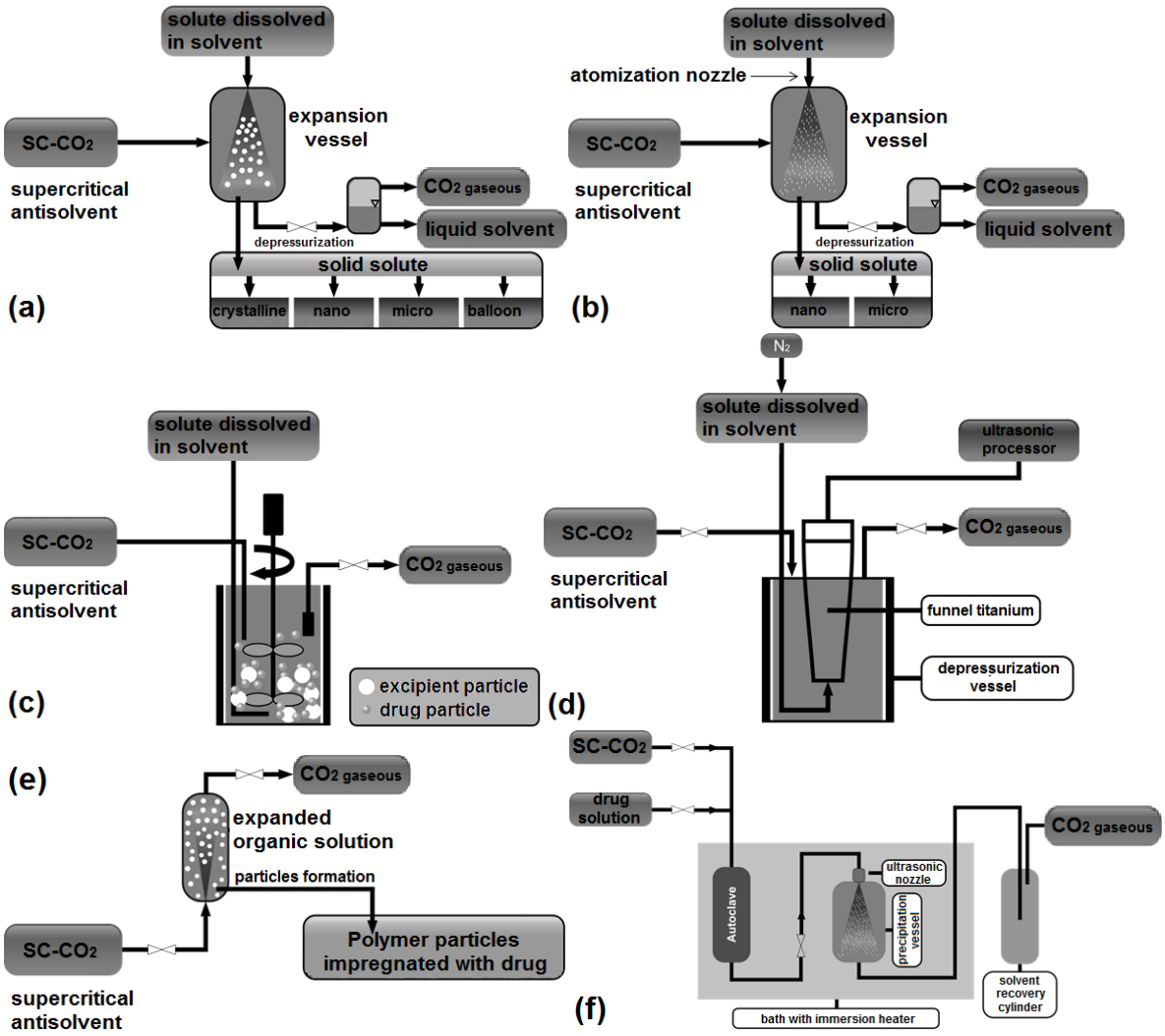

Figure 2. Schematic diagrams of some antisolvent processes (a) SAS, (b) ASES, (c) SSI, (d) SAS-DEM, (e) SAS-EM, and (f) PCA.

Continuous powder coating spraying process (CPCSP)

The CPCSP is another process derived from PGSS and was proposed by Weidner et al. (1999), as an alternative technique for the manufacture of powder coatings (Weidner et al., 2001; Petermann et al., 2003).

The continuously operated process is applicable to low-melting, fast-reacting, and conventional powder coating systems and allows coatings production with improved properties. The process uses the dense gases solubility which has solute-solute in molten coating polymers at pressures up to 220 bar. In separated tanks, the single components of a powder coating mixture are melted and are dosed to a static mixer by means of high-pressure pumps. In the mixer, the melts are homogenized and simultaneously the CO_2 compressed is dissolved. In the sequence of the process this solution is depressurized over a nozzle into a spray tower. In that way, the melt is atomized into fine droplets and cooled by the expanding gas. The drops solidify and form fine solid particles. The operating parameters on the plant modify particle size, particle size distribution, and powders morphology (Weidner et al., 2001; Petermann et al., 2003).

Supercritical enhanced atomization (SEA)

The SEA technique essentially explored the CO_2 atomization enhancement in a spray drying process and is based on the SCF ability to improve break-up of liquid jets into fine droplets when simultaneously depressurized with liquid solutions (Padrela et al., 2010; Rodrigues et al., 2012). The SCF-assisted atomization is particularly intense, mostly due to the SCFs exhibit high densities and low viscosities, causing a strong increase in the

liquid's momentum and interfacial shear forces (Rodrigues et al., 2012). The atomization of liquid jets assisted by a gas is a classical fluid mechanics process although the use of SCF for this purpose is relatively recent.

Supercritical fluid-assisted atomization (SAA)

The SAA was described by several researchers (Sievers et al., 1998; Sellers et al., 2001; Reverchon et al., 2004) as a process where the SC-CO_2 and a drug solution (in water or organic solvent) are heated separately, mixed into the saturator and then sprayed into the vessel in close conditions to atmospheric pressure at a stream of heated nitrogen to assist liquid droplets evaporation. On SAA apparatus a bottling thermostat contactor is used to obtain a dissolution nearly the equilibrium of SC-CO_2 in liquid solution (Reverchon et al., 2004).

A two-step atomization is achieved: the primary droplets on output injector are still divided into secondary droplets due to expansion SC-CO_2 from the inside of the primary. This process was used to improve the micronization of drugs through SCF, since with the SAS process for extraction some drugs presented unsatisfactory results (Sievers et al., 1998; Reverchon et al., 2004).

Carbon dioxide assisted nebulization with a bubble dryer (CAN-BD)

CAN-BD process originated from the SAA process and was patented by Sievers et al. (2003). This process has been shown to have wide applicability for small molecule, as well as for macromolecule (including therapeutic proteins) by obtaining dry powders with good stability and activity. In addition the dry powders are thin enough to be inhaled and reach the lungs (Cape et al., 2008). In this process, the drug dissolved in water or alcohol (or both) is mixed intimately with almost-critical or supercritical CO_2 for pumping both fluids through a low volume tube in 'T' to generate micro-bubbles and micro-droplets, which are are then uncompressed by a low-temperature drying chamber, where aerosol plume is dried in a few seconds. The $CO_2$and solution are mixed in the 'T' at room temperature while the micro-bubbles and micro-droplets formed are quickly dried at lower temperatures (25 to 80°C) than are used in the traditional spraying drying processes. The particles residence time inside the drying glass chamber, laboratory-scale of 750 mL, is less than 3 s (Sievers et al., 2001, 2003).

The best advantage of this process is that there is less thermally labile drug decomposition. Secondly, no high pressure vessels are required to proceedings CAN-BD, except for the syringe pump, the 1/16 inch OD stainless steel tube, the 'T' of low volume and flow limiter, which allow the fluid mixture to a moderate pressure (that is, between 80 and 100 bar), and the micro-bubbles and micro-droplets expansion at atmospheric pressure.

Thirdly, these particles are generally formed in a suitable size distribution for the release in the pulmonary alveoli (Sievers et al., 2003, 2007).

PGSS drying

In a different approach named PGSS drying, which the SCF exerts the co-soluto and propellant function,the particles need not be dried through a stream of heated N_2 as in CAN-BD and SAA processes. Instead, the solvent is removed from the spray tower along with the gas, and a free flowing powder precipitates at low temperatures (30 to 60°C) in an inert oxygen-free atmosphere which is particularly important when processing oxidation-sensitive substances (Weinreich et al., 2002; Nunes and Duarte, 2011). Such as in the PGSS process, the liquid solution to drought is intensely mixed with SC-CO_2 using a static mixer at desired temperature and pressure. The mixture is expanded in a nozzle into a spray tower, in which its conditions are adjusted in a method that the solvent is removed together with the gas. Super heating the mixture under pressure promoted adjusts in the spray tower temperature. The post-expansion temperature must at least be higher than the dew point in the gas and solvent binary system. In that case, solvent and gas form a homogeneous phase being removed from the spray tower and fine droplets are formed, due to expansion of CO_2 because atmospheric conditions. In addition, evaporation of residual solvent takes place due to the pre-selected temperature conditions in the spray tower (Weidner, 2009). If mixture as a liquid solvent is used, the equilibrium phase data of multicomponent system are required to determine the appropriate conditions to attain the precipitation (Meterc et al., 2007; 2008).

Depressurization of an expanded liquid organic solution (DELOS)

DELOS is a single-step process, being employed in direct production of micro- or sub micrometer crystalline particles. This method is based on experienced high temperature, and the fast and very evenly decremented mass of an organic solution, previously expanded with a compressed CO_2, when is depressurized. Through the process DELOS, it is possible to achieve the reduction in size of different types of organic compounds that are difficult to spray through conventional techniques, according to the Ventosa et al. (2001). This process, patented by Ventosa et al. (2002), in which the SCF act as cosolvent being completely miscible, at a given pressure and temperature, with the organic solution of the solute to be crystallized. According to authors, the role of the SCF is to produce a homogenous sub cooling of the solution with the precipitation of solid particles.

Table 1. Pharmaceutical applications of SCF.SCF category, process name, organic solvent use, process type, critical factors in the process, and type of produced particles.

SCF category	Process name	Organic solvent	Process type	Critical factors*	Type of produced particles	References
Solvent	RESS	No	Continue	a, b, c, d	Micro or nanoparticles and compound particles	Krukonis (1984), Türk et al. (2002)
	RESOLV	No	Continue	a, b, c, d, f	Nanoparticles	Meterc et al. (2008)
	RESAS	No	Continue	a, b, c	Nanoparticles	Young et al. (2000; 2003)
	RESS-SC or CSS	No	Discontinue	a, b, c, h, i	Nanoparticles	Thakur and Gupta (2006)
Anti-solvent	SAS	Yes	Semi-continue	a, e, i, j	Micro ou nanoparticlesandcompoundparticles	Yeo et al. (1993), Reverchon et al. (2003)
	GAS	Yes	Discontinue	a, e, i, j	Micro or nanoparticles and compound particles	Warwick et al. (2000)
	ASES	Yes	Semi-continue	a, b, c, e, i, j	Micro or nanoparticles and compound particles	Bleich et al. (1993), Kunastitchai et al. (2006)
	SSI	Yes	Discontinue	a, b, c, e, h, i	Polymer particles impregnated with drug	Kikic and Vecchione (2003)
	SAS-DEM	Yes	Semi-continue	a, i, e, j, m	Micro or nanocompound particles	Sanganwar et al. (2010), Sathigari et al. (2011)
	SAS-EM	Yes	Semi-continue	b, e, f, j	Nanoparticles and compound particles	Chattopadhyay and Gupta (2001; 2002)
	SEDS	Yes	Semi-continue	a, b, c, e, i, j	Microparticles and compound particles	Yorkand Hanna (1996)
	ASAIS	Yes	Semi-continue	a, c, e, i, j	Microparticles and compound particles	Rodrigues et al. (2011)
	PCA	Yes	Continue	b, e, j	Micro or nanoparticles and compound particles	Snavely et al. (2002)
	SFEE	Yes	Continue	a, e, f, i, j	Microparticles and compound particles	Yasuji et al. (2008)
Other	PGSS	No	Continue or Discontinue	c, n	Micro or nanoparticles and compound particles	Wendt (2007)
	CPF	Yes	Continue	b, e, f, j	Dried powders, free flowing and of high liquid content	Petermann et al. (2001), Weinreich et al. (2002)
	CPCSP	No	Continue or Discontinue	a, b, c, i, j, o	Coated powders	Weidner et al. (2001)
	CAN-BD	Water and/or alcohol	Continue	a, b, c, e	Nanoparticles and compound particles	Sievers et al. (2003)
	SAA	Yes	Continue	a, c, e, i, j, n, o	Microparticles and compound particles	Reverchon (2007)
	SEA	No	Continue	a, c, i, j	Microparticlesandcompoundparticles	Padrela et al. (2010)
	PGSS *drying*	Yes	Continue	a, e, f, l, o	Microparticles	Meterc et al. (2007)
	DELOS	Yes	Discontinue	a, b, c, d, e, h, i	Micro or nanoparticles	Ventosa et al. (2001)

*FSC factors for particles production: (a) material solubility on FSC, (b) pre-expansion condition, (c) spray device, (d) particulate material aggregation, (e) co-solvent type, (f) choice of plasticizer, (g) diffusion propriety, (h) eutectic propriety, (i) solvent extraction, (j) mass transfer, (l) viscosity, (m) properties of the carrier material and liquid, (n) liquid solution concentration, (o) choice of temperature.

The DELOS process includes three steps: (i) dissolution of the solute to be crystallized in conventional organic solvent, at atmospheric pressure and room temperature to form concentrated solution of solute, which is below the saturation limit. (ii) addition of CO_2 in the organic solution to obtain an volumetric expanded liquid solution at high working temperature and pressure. The solute concentration in this step must remain below the limit of saturation in the mixture expanded on conventional solvent and CO_2 (iii) rapid reduction of the expanded solution pressure, from the atmospheric pressure through a check valve (Ventosa et al., 2001; 2002). During depressurization process, the CO_2 evaporation from the expanded solution takes place producing a significant volume decrease, in a fast and extremely homogeneous temperature of the solution up to the final temperature. As a result, a sharp and homogeneousincrease of supersatu-ration ratio over the entire solution takes place and the phenomenon of catastrophic nucleation occurs causing the precipitation of submicron or micron sized crystalline particles with a narrow particle size distribution (Ventosa et al., 2001, 2002).

Table 1 shows the classification of SCF technology, in which is described the process

type of SCF, SCF process critical factors for the production of particles and possible type of particles that can be produced.

CONCLUSION

There are two basic approaches, RESS and SAS techniques, for the production of pharmaceutical micro or nanoparticles by theSCF technology, where the SCF acts as solvent or anti-solvent in the RESS and SAS processes, respectively. Changing the RESS process, particularly modifying the contents of the receiving end vessel, increasing the number of expander vessels in the process or others modifications which increases mass-transfer rate, it is possible to create a new process. However, in many cases, the SAS process is the most suitable because it does not require that the solute is soluble in the SCF as required by the RESS technique. The SAS process received incremented technological innovations generating derivatives processes, especially modifying the atomization efficiency. The SCF technology in the pharmaceuticals application process cannot depend on the SCF solvent power, but other factors, such as the volume expansion or association with other technologies, give rise to new processes. After witnessing a steady growth of this technology over the last 35 years, it is expected in a near future for major investments to happen in facilities related to the production and also the development of other innovative applications, interestingly not only for the pharmaceutical industries but also for the academia.

Conflict of Interests

The authors have not declared any conflict of interests.

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